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A thesis entitled

STUDIES OF NUCLEOPHILIC DISPLACEMENT

AT PHOSPHORUS IN HETEROARYLPHOSPHORUS

COMPOUNDS

presented by

MALCOLM THOMAS JOHN MELLOR A.R.I.C.

in part fulfilment of the requirements

for the degree of

DOCTOR OF PHILOSOPHY
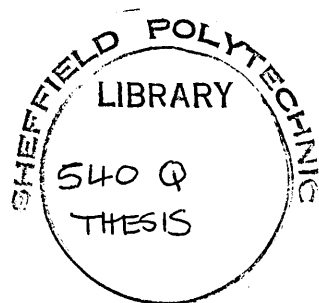
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February 1975.

# SUMMARY

The course of the alkaline hydrolysis of methyl-2-(1-methylpyrrolyl)-diphenylphosphonium iodide proceeds with exclusive loss of 1-methylpyrrole whilst in the corresponding alkaline hydrolysis of benzyltri-2-(1-methyl-pyrrolyl)phosphonium bromide cleavage of the heterocyclic substituent occurs to a minor extent; both toluene and 1-methylpyrrole are formed in a 3 : 2 molar ratio. These results indicate that the stabilities of the forming carbanions are in the order benzyl $>$ 2-(1-methylpyrrolyl) $>$ phenyl, in contrast with earlier studies on related 2-furyl and 2-thienyl systems which have shown the heteroaryl carbanions to be more stable than either benzyl or phenyl carbanions. The ability of the heterocyclic systems to stabilise the forming negative charge in the 2-position is discussed in terms of the $\sigma$-inductive effect of the heteroatom and the $\pi$-electron moment of each ring system and is further related to the direction of the dipole moment of each heteroaryl group.

The rates of alkaline hydrolysis of methyltri-2-(1-methylpyrrolyl)-phosphonium iodide and triphenyl(1-methylpyrrol-2-yl)methylphosphonium iodide have been determined and compared with the corresponding data for 2-furyl-and 2-thienylphosphonium salts. The findings are discussed in terms of the stabilities of the forming carbanions in the rate-determining step of the reaction, and also with regard to the electronic effect of the substituent on the position of the equilibria which precede the rate-determining step. Studies of the $^{31}$P n.m.r. spectra of the salts have been made, and the results are discussed in relation to the apparent electronic effects of the heteroaryl substituents on the adjacent phosphonium centre.

The effect of the 2-(1-methylpyrrolyl) substituent at phosphorus on the course of the Wittig reaction in protic solvents has been investigated. The reaction of methyltri-2-(1-methylpyrrolyl)phosphonium iodide and methyl-2-(1-methylpyrrolyl)diphenylphosphonium iodide with benzaldehyde in alcoholic-

alkoxide media proceed with loss of 1-methylpyrrole and the formation of di-2-(1-methylpyrrolyl)-β-styrylphosphine oxide and diphenyl-β-styrylphosphine oxide respectively, indicating that these reactions involve vinylphosphonium intermediates. In contrast, the reactions of the corresponding 2-furyl-phosphonium salts proceed via collapse of the cyclic oxaphosphetan and yield normal Wittig products. Since loss of the 1-methylpyrrolyl substituent from the intermediate vinylphosphonium salt takes place rather than migration from phosphorus to $\alpha$-carbon, a steric effect by the 1-methyl group is suspected. This is supported by results obtained for related t-butyl and o-tolyl systems.

Diethyl and Diphenyl esters of 2-furyl-, 2-thienyl-, 2-(1-methylpyrrolyl)- and phenylphosphonic acids have been synthesised and a study of the kinetics of alkaline hydrolysis has been made. The results are discussed in relation to the electronic effect of the heteroaryl substituent on the approach of the nucleophile and also on the departure of the leaving group in the reaction. The results for the hydrolysis of the corresponding carboxylic acid esters are introduced into the discussion together with infrared and $^{31}$P n.m.r. spectroscopic data for the phosphonate esters.

In view of the possibility of a $p\pi - d\pi$ interaction between the $p\pi$ orbitals of the heterocyclic ring and the d orbitals of phosphorus in the above compounds, the diethyl esters of 2-furylmethyl-, 2-thenyl-, and benzylphosphonic acids have been prepared and the rate data for the alkaline hydrolysis reactions obtained, since in the heteroarylmethyl derivatives the electron-withdrawing $\sigma$-inductive effect exerted by the heteroaryl group is more easily recognised. The diethyl esters of 2-, 3-, and 4-pyridylmethylphosphonic acids together with diethylchloromethylphosphonate and diethylmethylphosphonate have also been prepared; the kinetics of alkaline hydrolysis have been studied, and a comparison of these results and $^{31}$P n.m.r. data with those obtained for the 2-furylmethyl, 2-thenyl and benzyl systems is made.

The effects of $\sigma$-inductive electron-withdrawal and $\pi$-mesomeric electron-

donation on the rates of alkaline hydrolysis of a series of diethyl substituted phenylphosphonate esters is further investigated in the form of a structure-reactivity (Hammett) correlation. A linear correlation has been obtained for a plot of $\log (k/k_o)$ versus the Hammett substituent constant $(\sigma)$ giving a correlation coefficient of $0\cdot99$ and a reaction constant $(\rho)$ of $1\cdot88$. The result confirms the involvement of $p_\pi - d_\pi$ interactions in the transition of the alkaline hydrolysis reaction.

Finally, di-(2-furyl)phosphinic acid, di-(2-thienyl)phosphinic acid and (2-furyl)phenylphosphinic acid have been obtained from the alkaline hydrolysis of heteroarylphosphine oxides. Ethyldi-(2-furyl)phosphinate, ethyldi-(2-thienyl)phosphinate and ethyldiphenylphosphinate have been prepared and the kinetics of alkaline hydrolysis studied. The kinetic results, together with $^{31}$P n.m.r. data are discussed in relation to the possible disturbance of conjugation between the $\pi$-electrons of the aromatic systems and the phosphinyl bond when two aryl groups are attached to phosphorus.

The anomalous chemistry of 2-(1-methylpyrrolyl) derivatives in comparison with the 2-furyl and 2-thienyl analogues is indicated throughout this study and it is suggested that these results support current theories regarding the direction of the dipole moment in these systems.

# ACKNOWLEDGEMENTS

# CONTENTS

# INTRODUCTION

By virtue of their chemical reactivity furan, thiophen and pyrrole are appropriately grouped as "electron-rich aromatics." This classification implies a pronounced ability to stabilise an electron-deficient transition state or intermediate, as in electrophilic aromatic substitution and side-chain carbonium ion reactions. A recent paper[1] has summarised much of the available data on the relative reactivities of these systems in electrophilic substitution, the observed order of reactivity being pyrrole $>$ furan $>$ thiophen $>$ benzene. It has been suggested, however, that the ease of electrophilic substitution of these compounds is not of necessity an indication of an increased ground-state electron density at the ring carbon atoms, since the reactivity data refers to both the reactants and transition states. Much of the reactivity has thus been attributed to the low localisation energies of these systems, and also as suggested by Dewar[2] to the fact that the Wheland intermediate in the electrophilic substitution reaction has the same number of covalent bonds as the starting molecules.



(I)             (II)
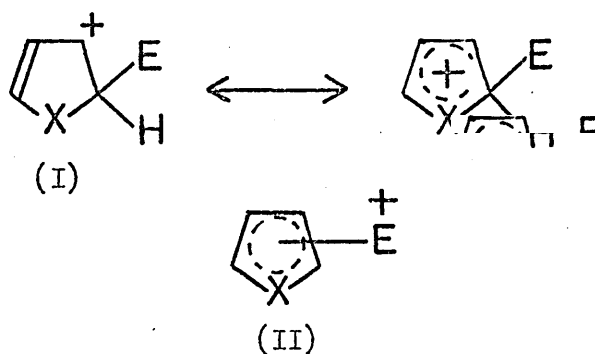
The most widely accepted mechanism for electrophilic substitution involves a change from $sp^2$ to $sp^3$ hybridisation of the carbon under attack, with the formation of an intermediate (the Wheland or $\sigma$-complex (I) ). Prior to and perhaps also after the formation of the $\sigma$-complex, a $\pi$-complex (II) (with the aromatic ring behaving as an electron-donor) can form, although it has not been proved that the formation of the $\pi$-complex is a necessary step in the reaction path[3].

The ability of the heterocyclic ring systems of furan, thiophen and pyrrole to direct electron density to an electron-deficient site is illustrated by the ready hydrolysis of their halogenomethyl derivatives (i.e. analogues of benzyl halides), and their migratory behaviour in the pinacol-pinacolone rearrangement. In the former reaction the stability of the intermediate carbonium ion (III) can be understood in terms of $p_\pi$—$p_\pi$ overlap between the $\pi$-system of the ring and the vacant p-orbital of the carbonium ion centre.[4]


(III)
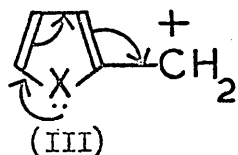
A consequence of the resonance stabilisation of the carbonium ion is the formation of a mixture of 2-furylacetonitrile (V) and 2-cyano-5-methylfuran (VI) in the reaction of furfurylchloride (IV) and cyanide ion, for which the following mechanism has been suggested[4] (Scheme A).
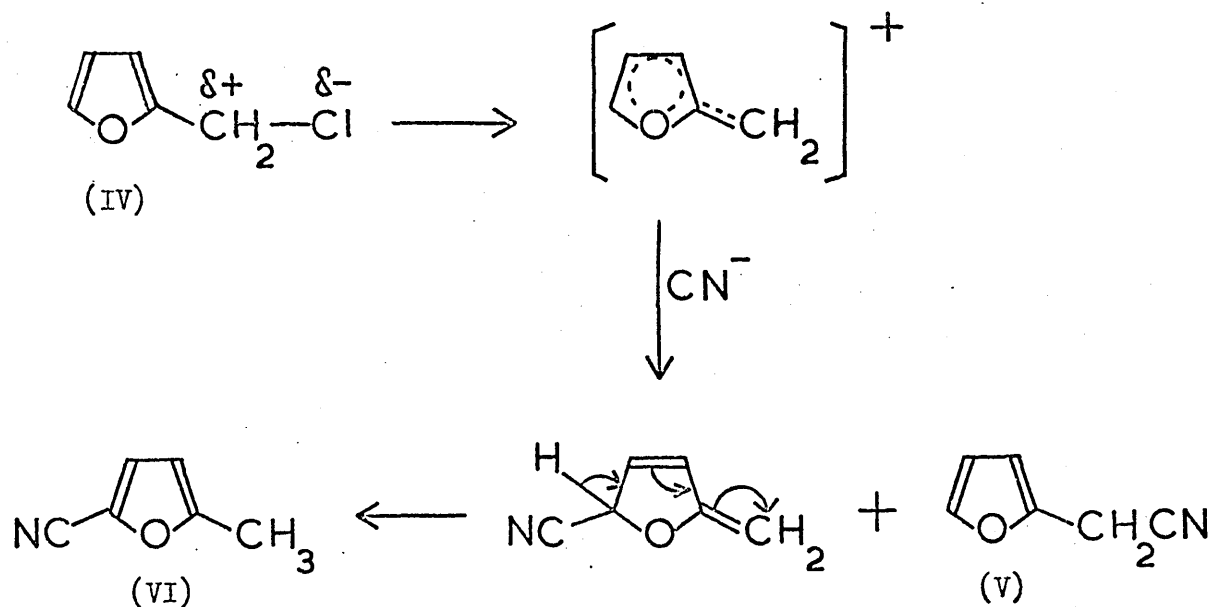


Scheme A

Kegelman et al[5] have studied the course of the pinacol-pinacolone rearrangement of the mixed pinacols 1,2-di-(2-thienyl)-1,2-diphenylethane-1,2-diol (VII) and 1,2-di-(2-furyl)-1,2-diphenylethane-1,2-diol (VIII) both of which proceed with exclusive migration of the heterocycle to give the ketones

(IX) and (X) respectively.



(VII)

(VIII)

(IX)

(X)
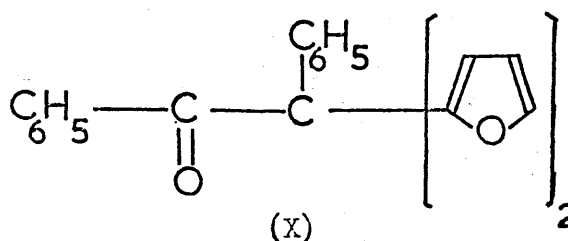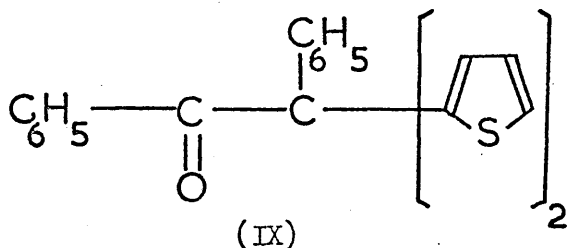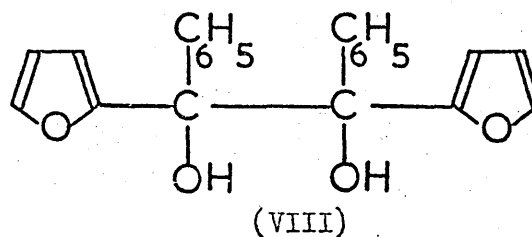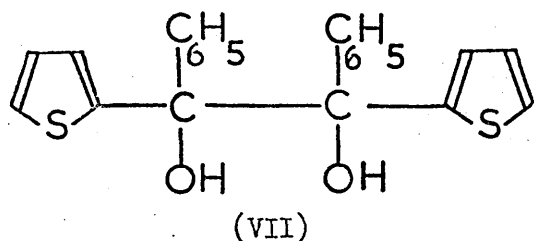
The preferential migration of the 2-furyl or 2-thienyl group thus indicates the ability of the "$\pi$-excessive" heterocycles[6] to stabilise the non-classical carbonium intermediate (XI) in the reaction to a greater extent than the phenyl group. In contrast the rearrangements of mixed pinacols bearing 2-, and 3-pyridyl substituents[7] (XII) proceeds with preferential migration of phenyl, since the "$\pi$-deficient"[6] pyridyl group is less able to stabilise the intermediate than phenyl.



(XI)

(XII)
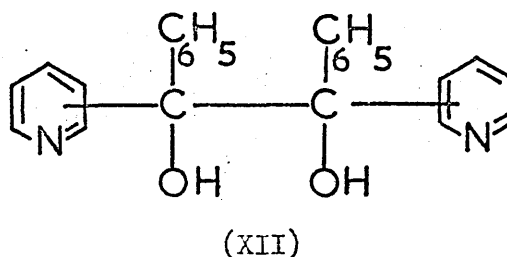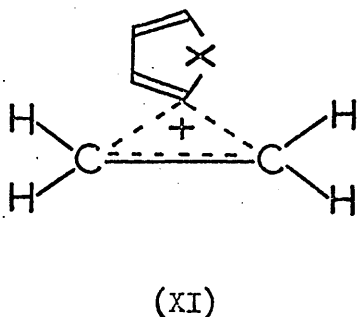
Recently a number of workers have examined the capabilities of heteroaryl groups to promote reactions involving electron-deficient transition states by studying the rates of solvolysis of a variety of derivatives of thiophen and furan. Noyce et al[8] studied the solvolysis of 1-(2-furyl)ethyl-p-nitrobenzoate (XIII) in 80% ethanol. The reaction proceeds via a carbonium ion intermediate (Scheme B) to give 1-(2-furyl)ethanol (16%) (XIV) and its ethyl ether (84%) (XV) at a rate which was estimated to be some $10^4$ times faster than for phenylethyl-p-nitrobenzoate.[9] Further work by Noyce et al[10] has revealed that

the solvolysis of 2-furylethyl-p-nitrobenzoate proceeds at a rate some five times faster than for the 2-thienyl analogue.



OPNB = p-nitrobenzoate



Scheme B
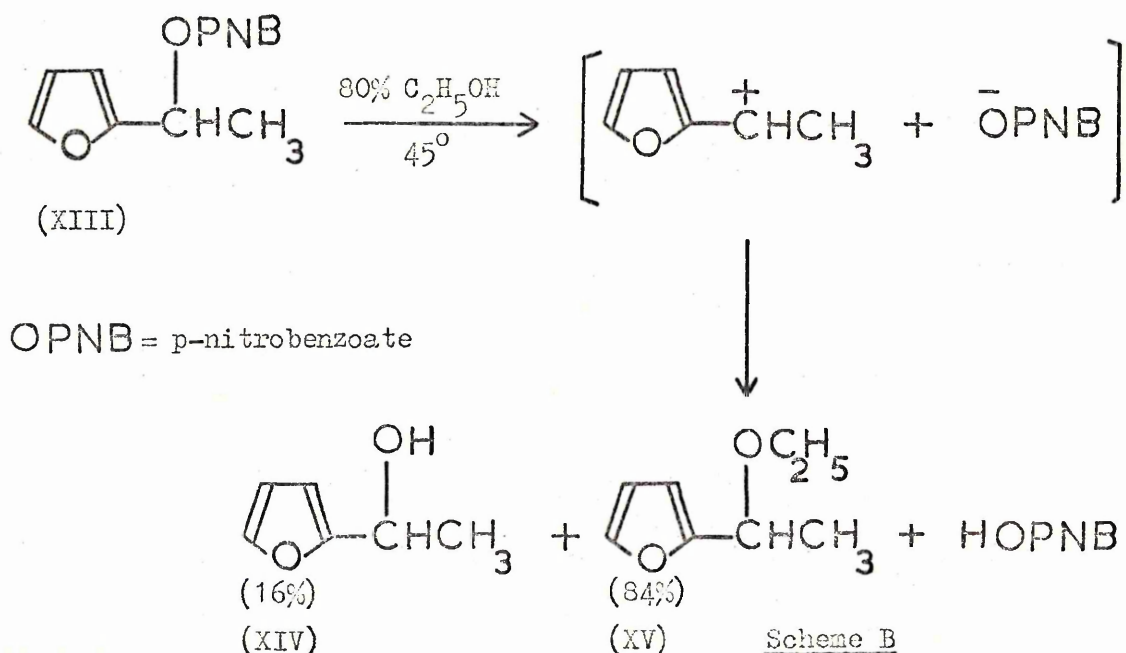
In contrast an extension of the study to the solvolysis of arylethyl tosylates[11] has revealed that the solvolysis of 2-(2-furyl)ethyl tosylate (XVI) shows a modest increase in the rate compared with 2-phenylethyl tosylate (XVII), whereas 2-(2-thienyl)ethyl tosylate (XVIII) shows a somewhat greater rate acceleration. Separation of the observed rate constants into direct substitution constants $(k_s)$ and a constant for a participating rearrangement mechanism $(k_\Delta)$ in which the substituent contributes to an unsymmetrically bridged transition state (XIX) revealed that both the 2-thienyl- and 2-furyl-tosylates show a greater proportion of participating rearrangement than does 2-phenylethyl tosylate.



(XVI)



(XVII)



(XVIII)
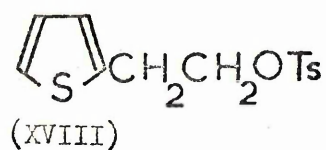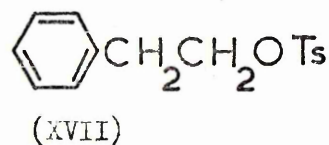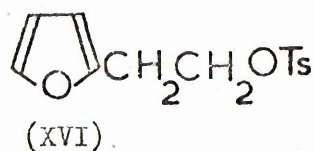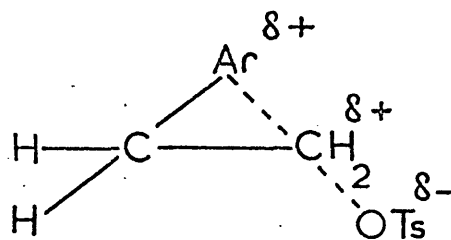
(XIX)

The rate of solvolysis via the participating rearrangement pathway $(k_\Delta)$ is greater for 2-thienyl than for the 2-furyl system. However, the ratio of participating rearrangement to direct substitution solvolysis $\left(\frac{k_\Delta}{k_s}\right)$ is higher for the 2-furyl system, a situation more in accord with the generally greater susceptibility of furan to electrophilic attack. Noyce[11] suggested that some explanation of the apparent deviation of these results from the behaviour expected on the basis of normal electrophilic reactivities is possibly obtained from the fact that in the transition state (XIX) for the reaction, an appreciable proportion of carbonium ion properties are maintained, and the stabilising influences of the aromatic moiety are not fully developed.

From a study of the solvolysis of a number of substituted t-cumylchlorides, Brown et al[12] obtained substituent $(\sigma^+)$ constants which had proved quite successful in correlating rate and equilibrium constants for a wide variety of reactions involving electron-deficient transition states or intermediates.

In order to obtain a similar set of $(\sigma^+)$ constants for a number of "electron-rich aromatics" other than substituted benzenes, and to examine their applicability to available data in the published literature, Hill et al[13] studied the solvolysis of a series of 1-arylethyl acetates $(XX; X = O, S, N-CH_3)$.
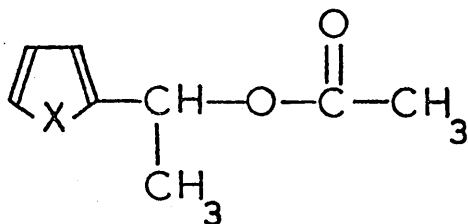


(XX)
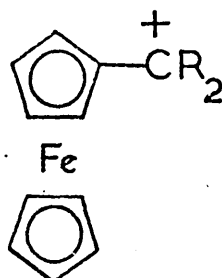


(XXI)

Earlier studies[14] of the solvolysis of 1-ferrocenylethyl acetate had demonstrated that the reaction occurs via a carbonium ion intermediate (XXI), formed as a result of alkyl-oxygen fission rather than alternative mechanisms of acyl-oxygen fission or direct displacement solvolysis. Evidence for the mechanism was obtained from azide trapping experiments.

The rates of solvolysis of the arylethyl acetates were found to decrease in the order 2-(1-methylpyrrolyl) > 2-furyl > 2-thienyl > phenylethyl acetate, the relative rates being $6 \times 10^{10}$ : $2 \times 10^{5}$ : $5 \times 10^{4}$ : 1, and $\sigma^{+}$ constants of -1·96, -0·94 and -0·84 respectively, were derived for the heteroaryl substituents. Attempts to correlate the solvolysis derived ($\sigma^{+}$) constants with kinetic data obtained for other similar "electron-deficient" reactions, received a limited degree of success when viewed on a broad scale of aromatic reactivity. Significant deviations from $\sigma^{+}$ correlations were, however, apparent in reactions where minor effects may obscure the broad trend of aromatic electron-release. In particular, the solvent is important in determining the exact relative reactivities in a given reaction.

The substituent ($\sigma^{+}$) values derived from the above reactions were, however, in reasonable agreement with those obtained by Taylor[15] from the gas-phase pyrolysis of heteroarylethyl acetates (XX; X = 0,S); a reaction taking place in the absence of solvent. The rates of the reaction were found to decrease in the order 2-furyl > 2-thienyl > phenyl, and substituent ($\sigma^{+}$) values of -0·89 for the 2-furyl substituent, and -0·79 for the 2-thienyl substituent were derived. Since the pyrolysis reaction of 1-arylethyl acetates proceeds via a partial carbonium ion on a carbon atom adjacent to the aromatic ring, increased stabilisation of the electron-deficient centre due to conjugative electron-release by the heterocycle is important in the determination of the order of reactivity. Thus the observation[16] that 1-phenylethyl acetate (XXII) undergoes pyrolysis more quickly than 2-, 3-, and 4-pyridylethyl acetates (XXIII) appears as further evidence of the major difference in the electronic character of the 5-, and

6-membered heterocycles.
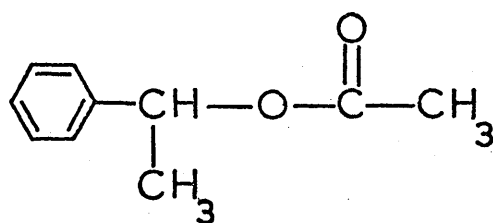


(XXII)
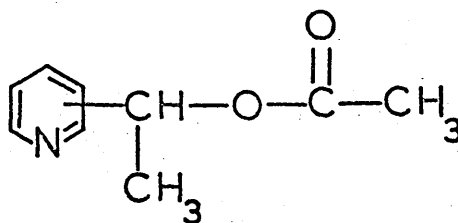
(XXIV)

(XXIII)
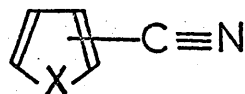
As an extension to a detailed study of substituent effects on the intensity of the C≡N infrared stretching vibration of a series of benzo-nitriles, Deady et al[17] investigated the 2-, and 3-cyanoderivatives of furan, thiophen and pyrrole (XXIV; X = O,S,NH). A series of substituent $(\sigma^+)$ constants were obtained from this study and compared with $\sigma^+$ constants obtained from electrophilic substitution and the above pyrolysis reactions. It was shown that in each case the heterocycle acts as an electron-donor. For the 2-, and 3-pyrrolyl groups the effect is very strong in accordance with the ease of electrophilic substitution in pyrrole. Electron-donation by the 2-, and 3-thienyl substituents is, however, greater than for the corresponding furyl systems, a reversal of their ease of electrophilic substitution. The substituent $(\sigma^+)$ values of −1·33, −0·44 and −0·13 for the 2-pyrrolyl, 2-thienyl and 2-furyl groups respectively were found to be much smaller than those derived from previous data in accord with the reduced electron demand. It was thus suggested that resonance electron-donation by the furyl and thienyl substituents depends on the particular reaction, and that donation by a furyl group will be less than for thienyl, in reactions in which the conjugative electron-release by the heterocyclic substituent is small.

In addition to their ability to function as "electron-rich" species, furyl, and thienyl groups are capable of acting as electron-withdrawing substituents, due to the effect of the electronegative heteroatom withdrawing

electrons by an inductive mechanism. Thus although nucleophilic substitution of a proton in pyrrole, furan and thiophen is unknown, Manly et al[18] observed the rate of nucleophilic displacement of halogen in halofurans to be some ten times faster than for the corresponding phenyl compounds. For substituted heterocyclic halogen compounds the effect is increased, and displacement of halogen in 5-chloro-2-furoyl-piperidide[18] (XXV) by piperidine is 500 times faster than for the corresponding phenyl analogue, whilst in substitutions activated by nitro groups[19,20] the relative rates of piperidino-debromination are 1-bromo-4-nitrobenzene, 1; 2-bromo-5-nitrothiophen, $4 \cdot 7 \times 10^2$; 2-bromo-5-nitrofuran, $8 \cdot 9 \times 10^4$.
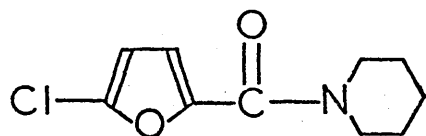


(XXV)

The slightly increased reactivity of the unsubstituted halofurans compared to the unsubstituted halobenzene was attributed to the increase in positive character of the carbon bearing the halogen, due to the inductive effect of the heteroatom. The overall effect is small because of the opposed $\pi$-moment of the heterocycle. In the substituted compounds, however, the relative reactivity is increased, since the carboxypiperidide and nitro groups reduce the effect of the $\pi$-electron transfer and the $\sigma$-inductive effects of the heteroatom become more important.

Further evidence that the 2-furyl and 2-thienyl substituents are more electron-withdrawing than phenyl in their inductive effect is obtained from carboxylic acid $pK_a$ data, and the relative rates of alkaline hydrolysis of the corresponding carboxyethyl esters. The $pK_a$ data presented in Table I reveals that while the pyrrolecarboxylic acids are weaker, thiophen and furancarboxylic acids are stronger than unsubstituted benzoic acid.

Table I

Ionisation Constants of the Carboxylic Acids in Water, at 25°

| Acid | $pK_a$ | Ref. |
|---|---|---|
| Benzoic acid | 4·21 | 21 |
| 2-Furoic acid | 3·16 | 22 |
| 3-Furoic acid | 3·95 | 23 |
| 2-Thiophencarboxylic acid | 3·53 | 22 |
| 3-Thiophencarboxylic acid | 4·10 | 24 |
| 2-Pyrrolecarboxylic acid | 4·45 | 22 |
| 3-Pyrrolecarboxylic acid | 5·07 | 25 |

Hill et al[13] suggested that the values in Table I lead to Hammett $\sigma$ values for the 2-furyl and 2-thienyl groups of +1·02 and +0·65 respectively.
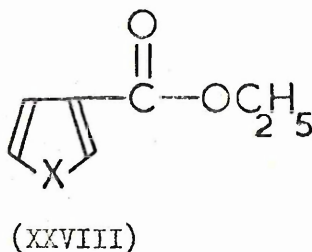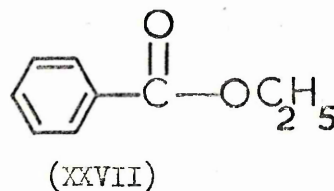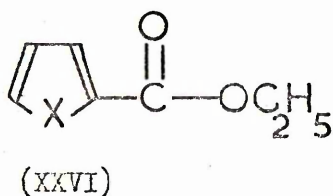


(XXVI)          (XXVII)

(XXVIII)

The kinetics of alkaline hydrolysis of the corresponding carboxyethyl esters (XXVI; X=O,S) and (XXVII) have been studied by a number of workers. Oae and Price[26] reported the rates of reaction in 70% dioxan to decrease in the order ethyl 2-furoate > ethyl 2-thenoate > ethyl benzoate, the relative rates being 4·65 : 1·03 : 1. In contrast, for the reaction in 85% ethanol, Imoto et al[27] showed the relative order of reactivity to be ethyl 2-furoate > ethyl benzoate > ethyl 2-thenoate, the relative rates being 4·35 : 1·08 : 1.

Application of the Hammett equation to this data[26] gave substituent ($\sigma$) values

of 0•24 and −0•01 for the 2-furyl and 2-thienyl groups respectively.

Subsequent attempts by Imoto[28] to correlate these results and the corresponding

data for the 3-heteroarylcarboxylic acid esters (XXVIII; X = 0,S) with the

dissociation constants of the acids, proved successful for the 3-carboxylates

but not for the 2-carboxylates. It was thus suggested that there may be a

steric effect by the adjacent heteroatom on reactions of the carboxylate

group in the 2-position.

The literature contains conflicting opinions with regard to the direction

of the dipole moments of furan, thiophen and pyrrole[29-31]. It has been

generally accepted[4] that the dipole moments are directed from the heteroatom

towards the $C(3) - C(4)$ bond, the main argument in favour of this proposal

being based on the high reactivity of these compounds toward electrophilic

substitution. It has been suggested very recently[29], however, on the basis of

much of the above data, together with results of calculations of electron

distribution[32-36], that whilst the direction of the dipole in pyrrole (XXIX)

is from the heteroatom to the ring, in furan (XXX) and thiophen (XXXI) the

dipole is in the opposite direction.



| | | |
|---|---|---|
| 1•8D | 0•71D | 0•52D |
| (XXIX) | (XXX) | (XXXI) |
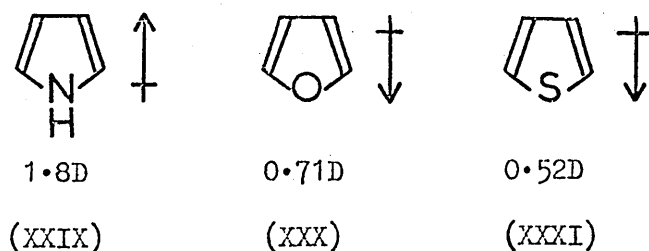
Evidence in support of this suggestion has been obtained[36-40] from dipole

moment studies of a number of substituted thiophen and furan derivatives, and

from n.m.r. solvent shift studies by Barton[41] who investigated the

orientational influence of the heterocycles as solutes on aromatic solvents,

to determine the direction of their respective dipoles.



(XXXII)    (XXXIII)    (XXXIV)
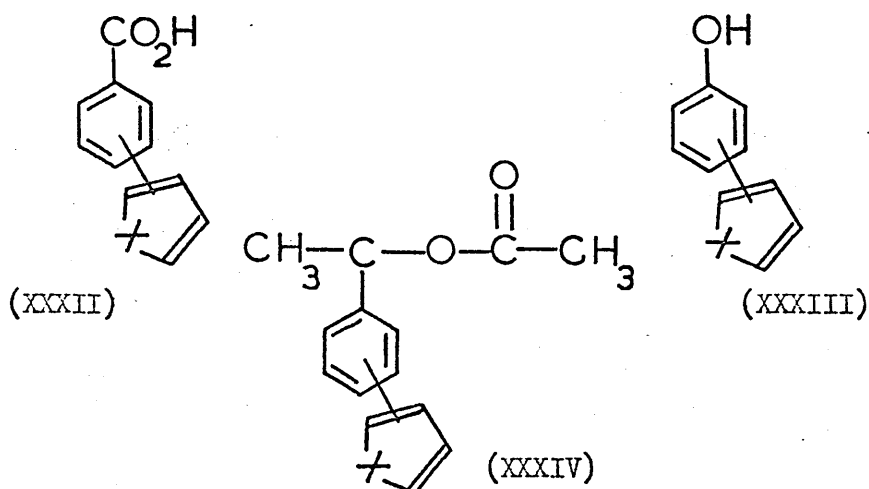
In view of the ability of the heteroaryl systems to either withdraw or release electrons according to the type of reaction considered, Marino et al[42-45] devised a series of experiments in which the interaction of substituent heteroaryl groups with the reaction site in transition states of different types was investigated.

The ionisation of heteroaryl substituted benzoic acids (XXXII, X=O,S) was chosen as the "standard" reaction in which only weak resonance interactions would be possible between the reaction centre and the substituent, whereas the ionisation of phenols (XXXIII; X=O,S) and the solvolysis of 1-phenyethyl acetates (XXXIV; X=O,S) were selected as reactions in which the substituent interacts with a negative and positive charge, respectively. A series of substituent constants $(\sigma, \sigma^- \text{ and } \sigma^+)$ were calculated from the results, and their sign and magnitude discussed in relation to the electronic properties of the heterocycle and its effect upon the respective reaction.

The ionisation constants of the benzoic acids[42,44] reveal that both the 2-thienyl and 2-furyl substituents in the meta position of the benzene ring, exert a weak inductive electron-withdrawing effect. This is reflected by decreases in the $pK_a$ of meta-2-thienylbenzoic acid and meta-2-furylbenzoic acid when compared to unsubstituted benzoic acid; para-heteroaryl substituted benzoic acids were found to be less acidic than meta, and the value $\sigma_p - \sigma_m$

was negative for both the 2-furyl and 2-thienyl substituents, thus possibly

reflecting the importance of such resonance structures as (XXXV).

$$\text{(XXXV)}$$
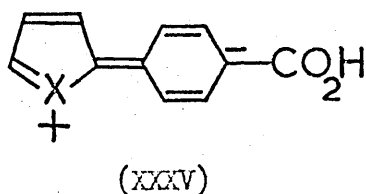
The stability of the phenate anion[42,44] increases on introduction of the

heteroaryl substituent into the benzene ring, possibly due to the ability of

the substituent to increase delocalisation of the negative charge (Mechanism A).

Thus the effect is greater for para- substituted phenols than for meta-, where

decreases in $pK_a$ relative to phenol solely reflect electron-withdrawal by the

inductive effect of the substituents. The greater acidity of p-(2-furyl)phenol

compared with p-(2-thienyl)phenol indicates an increase in the magnitude of

the resonance interaction (Mechanism A) of the 2-furyl substituent compared

with the 2-thienyl substituent.
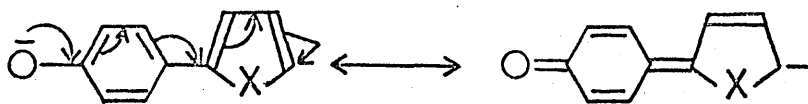
Mechanism A

The ability of the 2-furyl and 2-thienyl groups to stabilise a positive charge

was again illustrated[44,45] by an increase in the rate of solvolysis of suitably

substituted 1-phenylethyl acetates (XXXIV; X=O,S). The order of relative

reactivity p-(2-furyl)phenyl $>$ p-(2-thienyl)phenyl $>$ phenyl $>$ m-(2-furyl)phenyl

$>$ m-(2-thienyl)phenyl, indicates both resonance stabilisation of the "electron-

deficient centre" by heteroaryl substituents in the para- position and

destabilisation of the centre by the inductive electron-withdrawal of the

substituent in the meta- position.

$$\underset{\text{C}}{\overset{\text{O}}{\|}}-\text{CH}_3$$
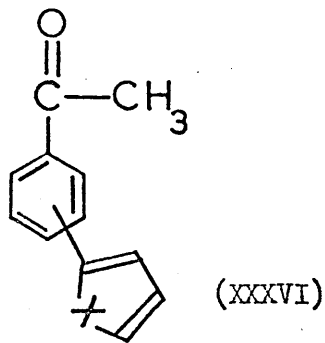
(XXXVI)

Marino[45] extended the work to investigate the effect of heteroaryl substituents on the frequency of the infrared stretching vibration of the carbonyl bond in substituted acetophenones (XXXVI; X=O,S). In keeping with the results of Deady et al[17] who observed the 2- and 3-furyl and 2- and 3-thienyl groups to act as electron-donors to the infrared probe of the cyano group in cyanoheteroaryl derivatives, Marino found that 2-furyl and 2-thienyl groups in the para- position in (XXXVI; X=O,S) act as electron donors and decrease the carbonyl stretching frequency relative to the unsubstituted acetophenone. In contrast, electron-withdrawal by the heterocyclic substituents in the meta- position in (XXXVI;X=O,S) results in slight increases in the frequency of the carbonyl infrared stretching mode relative to acetophenone.

The general conclusions reached from the above work were therefore that:-
(i) the 2-furyl and 2-thienyl groups are inductively electron-withdrawing and this is reflected in the positive sign of the $\sigma_m$ constants,
(ii) the electronic effect of the substituent in the meta- position is practically constant and thus there are only small differences in the values of $\sigma_m$, $\sigma^+_m$, $\sigma^-_m$,
(iii) the 2-furyl and 2-thienyl groups exhibit strong resonance effects for both the release and withdrawal of electrons, depending on the type of reaction. The ability to release electrons, however, is greater than the ability to withdraw electrons,
(iv) the electronic effects of the groups are variable in cases where conjugation is possible and cannot be represented by a single substituent constant valid for all cases.
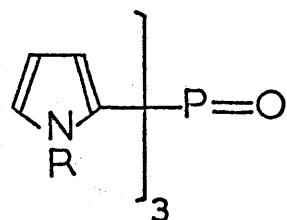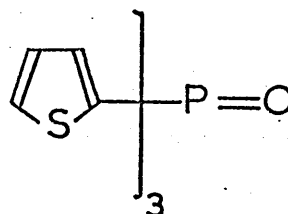
(XXXVII)    (XXXVIII)
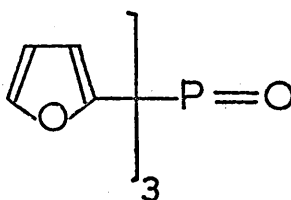
(XXXIX)

The investigation of the effect of heteroaryl substituents on the chemistry of a second row element such as phosphorus has also created some interest. Griffin et al[46] examined the ultraviolet absorption spectra of tri-(2-pyrrolyl)phosphine oxide (XXXVII; R=H), tri-2-(1-methylpyrrolyl)-phosphine oxide (XXXVII; R=CH$_3$), tri-(2-thienyl)phosphine oxide (XXXVIII) and tri-(2-furyl)phosphine oxide (XXXIX) and observed bathochromic shifts relative to the parent heteroarene of 32,30,7 and 33m$\mu$ respectively, indicating the existence of a p$_\pi$—d$_\pi$ conjugative interaction between the heterocyclic rings and the phosphacyl group which is much more appreciable than in phenyl phosphacyl systems[47]. In the corresponding 2-formyl derivatives of pyrrole, thiophen and furan, however, the bathochromic shifts are 78·5, 47·5 and 67m$\mu$ respectively, clearly indicating the weaker nature of the phosphacyl group as an electron-acceptor compared with the carbonyl group.
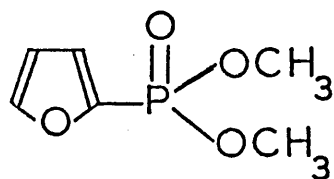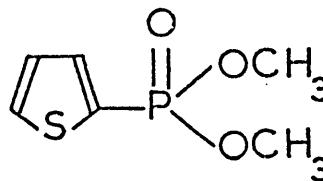


(XL)    (XLI)

This work was extended[48] to analysis of the ^{1}H nuclear magnetic resonance spectra of the above heteroarylphosphine oxides (XXXVII), (XXXVIII) and (XXXIX),

and also of the related esters, dimethyl-(2-furyl)phosphonate (XL) and dimethyl-(2-thienyl)phosphonate (XLI). The deshielding of certain of the ring protons in these compounds was interpreted as indicating $p_\pi - d_\pi$ bonding between the ring and phosphorus, the effect decreasing in the order thiophen $>$ furan $>$ pyrrole in contrast to the earlier u.v. studies.
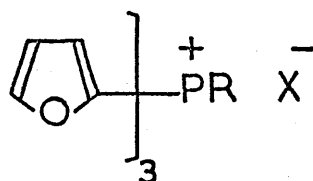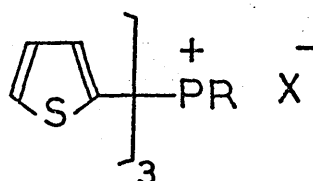


(XLII)          (XLIII)
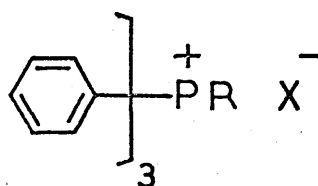
(XLIV)

Allen et al[49,50] have shown that the alkaline hydrolysis of the triheteroarylphosphonium salts (XLII; $R = CH_3$ or $C_6H_5CH_2$, X = I or Br) and (XLIII; $R = CH_3$ or $C_6H_5CH_2$, X = I or Br) proceeds more rapidly than the hydrolysis of analogous triphenylphosphonium salts (XLIV; $R = CH_3$ or $C_6H_5CH_2$, X = I or Br). The increase in rate was explained in terms of the electron-withdrawing inductive effect of the heteroaryl groups which influenced the pre-rate determining step equilibria involved in the reactions, together with increased stability of the forming 2-thienyl and 2-furyl carbanions in the rate-determining step. The effects of $p_\pi - d_\pi$ bonding between the ring systems and the phosphonium centre appeared to be of little consequence in influencing the rates of reaction.
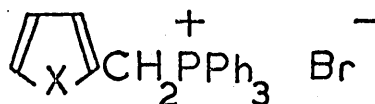


(XLV)

This study has been extended[51] to heteroarylmethyltriphenylphosphonium salts (XLV) and also to a study of the effects of 2-furyl substituents at phosphorus

on the fate of phosphobetaines in Wittig reactions in protic solvents[52].

This thesis describes an extension of this work on heteroarylphosphorus compounds to a study of the effects of 2-(1-methylpyrrolyl) substituents on the alkaline hydrolysis of heteroaryl- and heteroarylmethyl- phosphonium salts and on the fate of phosphobetaines in alcoholic solution.

In addition, a number of heteroarylphosphonates, heteroarylmethyl-phosphonates and heteroarylphosphinates have been synthesised and the effect of heteroaryl substituents on the rate of nucleophilic attack (specifically $^-$OH) at phosphorus has been studied. Rate data for the alkaline hydrolysis of a series of meta- and para- substituted phenylphosphonates have been obtained and a structure-reactivity correlation attempted in order to gain a clearer indication of the operation of electronic effects in the reaction.

In addition $^{31}$P nuclear magnetic resonance spectra of the above compounds have been obtained and are discussed in relation to current theories on the factors influencing $^{31}$P chemical shifts.

## REFERENCES

1. G. Marino, Adv. Heterocyclic Chem., 1971, 13, 235.

2. M.J.S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford, Clarendon Press, London, 1949.

3. E. Berliner, Prog. Phys. Org. Chem., 1964, 2, 253.

4. M.H. Palmer, "The Structure and Reactions of Heterocyclic Compounds," E. Arnold Ltd., London, 1967.

5. M.R. Kegelman and E.V. Brown, J. Amer. Chem. Soc., 1953, 75, 5961.

6. A. Albert, "Heterocyclic Chemistry" Athlone Press, London, 1968.

7. M.R. Kegelman and E.V. Brown, J. Amer. Chem. Soc., 1953, 75, 4649.

8. D.S. Noyce and G.V. Kaiser, J. Org. Chem., 1969, 34, 1008.

9. S. Winstein and A.H. Fainberg, J. Amer. Chem. Soc., 1957, 79, 1597.

10. D.S. Noyce, C.A. Lipinski, R.W. Nichols, J. Org. Chem., 1972, 37, 2615.

11. D.S. Noyce and R.L. Castenson, J. Amer. Chem. Soc., 1973, 95, 1247.

12. H.C. Brown and Y. Okamoto, J. Amer. Chem. Soc., 1958, 80, 4979.

13. E.A. Hill, M.L. Gross, M. Stasiewicz and M. Manion, J. Amer. Chem. Soc., 1969, 91, 7381.

14. E.A. Hill and J.R. Richards, J. Amer. Chem. Soc., 1961, 83, 3840.

15. R. Taylor, J. Chem. Soc. (B), 1968, 1397.

16. R. Taylor, J. Chem. Soc., 1962, 4881.

17. L.W. Deady, R.A. Shanks and R.D. Topsom, Tet. Lett., 1973, 1881.

18. D.G. Manly and E.M. Amstutz, J. Org. Chem., 1957, 22, 133.

19. R. Motoyama, S. Nishimura, Y. Murakami, K. Hari, and E. Imoto, Nippon Kagaku Zasshi, 1957, 78, 950; Chem. Abstr., 1960, 54, 14224.

20. D. Spinelli, G. Guanti and C. Dell'Erba, Boll. Sci. Fac. Chim. Ind. Bologna, 1967, 25, 71; Chem. Abstr. 1968, 68, 2389; C. Dell'Erba, A. Salvemini, and D. Spinelli, Ann. Chim. Rome, 1962, 52, 1156.

21. G. Kortum, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solutions," p.352, Butterworth, London, 1961.

22. P.O. Lumme, _Suom. Kemistilehti. B._ 1960, _33_, 87; _Chem. Abstr._, 1961, _55_, 5104.

23. W.E. Catlin, _Iowa State Coll. J. Sci._ 1935, _10_, 65; _Chem. Abstr._, 1936, _30_, 935.

24. J.M. Loven, _Z. Phys. Chem._, 1896, _19_, 456.

25. H. Rapoport and C.D. Willson, _J. Org. Chem._, 1961, _26_, 1102.

26. S. Oae and C.C. Price, _J. Amer. Chem. Soc._, 1957, _79_, 2547.

27. E. Imoto, Y. Otsuji, T. Hirai, and H. Inoue, _J. Chem. Soc. Japan_, 1956, _77_, 804, 809.

28. E. Imoto, Y. Otsuji, and M. Kubo, _Bull. Osaka. Pref. Ser. A. 7_, 1960, _61_; _Chem. Abstr._, 1960, _54_, 24796.

29. G. Marino, _J. Heterocyclic Chem._, 1972, _9_, 817.

30. M. Martin-Smith and S.T. Reid, _J. Med.Pharm. Chem._, 1959, _1_, 507.

31. L. Felloni and F. Pulidoric, _Ann. Chim._, 1961, _51_, 1027.

32. B. Bak, D. Christensen, L. Hansen-Nygaard and J. Rastrup-Andersen, _J. Mol. Spectrosc._, 1961, _7_, 58.

33. P. Chiorboli and P. Manaresi, _Gazz. Chim.Ital._, 1954, _84_, 248.

34. W. Adam and A. Grimison, _Theor. Chim. Acta._, 1967, _7_, 342.

35. F. Momicchioli and G. Del Re, _J. Chem. Soc. (B)_, 1969, 674.

36. A.J.H. Wachters and D.W. Davies, _Tetrahedron_, 1964, _20_, 2841.

37. E.J. Lien and W.D. Kumler, _J. Pharm. Sci._, 1970, _59_, 1685.

38. L. Felloni and F. Pulidoric, _Ann. Chim._, 1961, _51_, 1027.

39. H. Lumbroso and C. Carpanelli, _Bull. Soc. Chim. France_, 1964, 3198.

40. C. Pigenet, J. Morizur, Y. Pascal and H. Lumbroso, _Bull. Soc. Chim. France_, 1969, 361.

41. T.J. Barton, R.W. Roth, and J.G. Verkade, _J. Amer. Chem. Soc._, 1972, _94_, 8854.

42. F. Fringuelli, G. Marino and A. Taticchin _J. Chem. Soc. (B)_, 1970, 1595.

43. F. Fringuelli, G. Marino and A. Taticchi, _J. Chem. Soc. (B)_, 1971, 2302.

44. F. Fringuelli, G. Marino and A. Taticchi, *J. Chem. Soc. (B)*, 1971, 2304.

45. F. Fringuelli, G. Marino and A. Taticchi, *J. Chem. Soc. Perkin II*, 1972, 158.

46. C.E. Griffin and R.A. Polsky, *J. Org. Chem.*, 1961, 26, 4772.
    C.E. Griffin, R.P. Peller, K.R. Martin, and J.A. Peters, *J. Org. Chem.*, 1965, 30, 97.

47. H.H. Jaffe and L.D. Freedman, *J. Amer. Chem. Soc.*, 1952, 74, 1069, 2930.

48. C.E. Griffin, R.H. Kemp, W.A. Thomas and M. Gordon, *J. Chem. Soc. (B)*, 1969, 527.

49. D.W. Allen, *J. Chem. Soc. (B)*, 1970, 1490.

50. D.W. Allen, B.G. Hutley and M.T.J. Mellor, *J. Chem. Soc. Perkin II*, 1972, 63.

51. D.W. Allen, B.G. Hutley, *J. Chem. Soc. Perkin II*, 1972, 67.

52. D.W. Allen, B.G. Hutley and T.C. Rich, *J. Chem. Soc. Perkin II*, 1973, 820.

## The Alkaline Hydrolysis of Phosphonium Salts.

### 1.1 Introduction.

The alkaline hydrolysis of a quaternary phosphonium salt to give a phosphine oxide and a hydrocarbon, is one of the best known nucleophilic displacement reactions at phosphorus. The mechanism of the reaction has been extensively studied[1,2,3] and is thought to involve the steps (i) – (iv).

$$R_4P^+ + OH^- \xrightleftharpoons{rapid} R_4P \cdot OH \qquad (i)$$

$$R_4P \cdot OH + OH^- \xrightleftharpoons{rapid} R_4P \cdot O^- + H_2O \qquad (ii)$$

$$R_4P \cdot O^- \xrightarrow[k_S]{slow} R_3P{=}O + R^- \qquad (iii)$$

$$R^- + H_2O \xrightarrow{fast} RH + OH^- \qquad (iv)$$
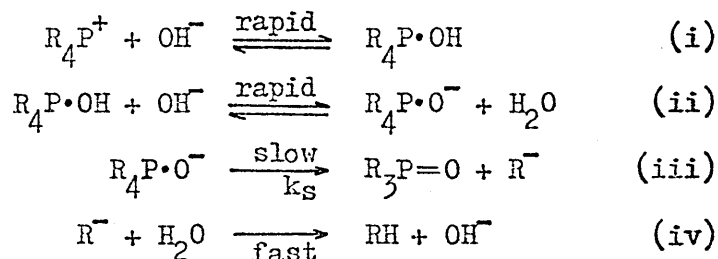
The extent to which the carbanion is developed in the transition state of the rate-determining step (iii) of the phosphonium salt hydrolysis has recently been investigated by Trippett et al[4] who observed a kinetic isotope effect, $kH/_{kD}$ of $\approx 1 \cdot 2$ in the alkaline hydrolysis of phenyl- and cumyl-phosphonium salts carried out in $H_2O - D_2O$ (1:1). The results were interpreted as indicating that in the transition state (I), little cleavage of the phosphorus-carbon bond occurs, and there is correspondingly little transfer of a proton to the forming carbanion.



$(I)$
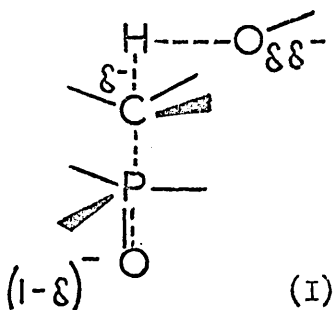
As required by the above mechanism, investigations of the kinetics of the reaction have established that a third-order rate law is followed, with a first-order dependence on the concentration of phosphonium cation and a second-order dependence on the concentration of hydroxide ion. Furthermore, the overall rate constant, $k_{obs}$, for the hydrolysis of a phosphonium salt,

although governed by the slow step (iii), is composite, and can be expressed as the product of the equilibrium constants of steps (i) and (ii), $K_1$ and $K_2$ respectively, and the rate constant of step (iii), $k_s$.

The inversion of configuration at phosphorus observed in the alkaline hydrolysis of acyclic phosphonium salts is usually interpreted in terms of a pentacovalent intermediate in which the geometry is probably that of a trigonal bipyramid, having the entering and leaving groups colinear and diapical.

From the accurate rate and product ratio data recorded for the alkaline hydrolysis of a series of mixed phosphonium salts, McEwen et al[1,2] established that the relative ease of departure of the group R in the rate-determining step (iii) parallels its stability as a carbanion. Thus a benzyl group departs more readily than a methyl[1], ethyl[1], phenyl[1], p-methoxybenzyl[2] or methylbenzyl[2] group and less rapidly than a m-bromobenzyl[2], p-chlorobenzyl[2] or nitrobenzyl[2] group. In addition to the carbanionic stability of the leaving group, the relative ease of departure of a given group is influenced by the nature of the non-departing groups. Thus the presence of electron-withdrawing substituents at phosphorus accelerates the reaction, whereas electron-donating substituents tend to retard the reaction. This effect has been attributed to the availability of the d orbitals of phosphorus for bonding during the formation of the pentacovalent intermediate; thus Craig et al[5] have shown that substituents having a (+I) effect make the d orbitals of phosphorus more diffuse and therefore less suitable for bonding. The opposite situation holds for an electron-withdrawing (-I) substituent. Thus the presence of (+I) substituents at phosphorus will lead to a decrease in $K_1$ and $K_2$, the pre-equilibrium constants, whereas a (-I) substituent will cause an increase in $K_1$ and $K_2$.

$$[C_6H_5 \!-\! \overset{+}{P}(CH_3)_3]\ Br^-$$

(II)

$$[(C_6H_5)_2 \!-\! \overset{+}{P}(CH_3)_2]\ Br^-$$

(III)

$$[(C_6H_5)_3 \!-\! \overset{+}{P}CH_3]\ Br^-$$

(IV)

$$[(C_6H_5)_4 \!-\! \overset{+}{P}]\ Br^-$$
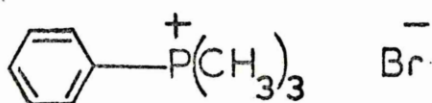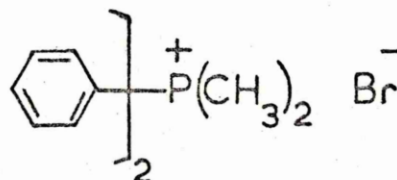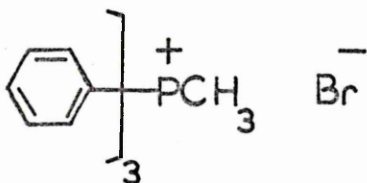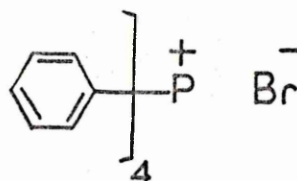
(V)

Until recently, steric effects on the rate of alkaline hydrolysis of phosphonium salts have been held to be unimportant. Aksnes et al[6] studied the kinetics of alkaline hydrolysis of a number of phenylphosphonium salts (II)-(V), and from the results calculated the energies of activation and the frequency factor (log A) for the reactions. The data revealed that the frequency factor was remarkably high and enabled the hydrolysis to proceed at measurable rates in spite of unfavourable activation energies. Differences between the frequency factors for the hydrolysis of the different salts were small, showing steric hindrance to play a minor role. Further calculations on interionic distance between the phosphonium cation and hydroxyl ion during the reaction revealed that this distance remained the same, independent of the substituents linked to phosphorus.

McEwen et al[7] obtained evidence in support of this theory, from a study of the rates of alkaline hydrolysis of a series of ortho- and para-tolylphosphonium salts. The general conclusions of the study were that the 2·2 - 2·6 fold difference, between the rates of reaction of the para-substituted versus the ortho-substituted phosphonium salts in each of the related pairs, cannot be

explained adequately in terms of steric effects, and that the results indicate
the electronic effect of the substituents to predominate. McEwen suggested
that the absence of a major steric influence on the rate of the reaction can
be attributed to a cancellation of effects. In the first step of the reaction,
addition of hydroxide ion to the salt (VI) takes place to form an intermediate
(VII) in which the geometry is probably trigonal-bipyramidal. Owing to the
greater relief of $\beta$-strain, sterically crowded tetrahedral compounds will
form the intermediate more rapidly. The rate-determining step of the reaction,
step (iii), however, involves the collapse of the intermediate back to the
more crowded tetrahedral phosphine oxide (VIII). Thus as a result of the
steric interaction caused by this change, whatever rate enhancement is gained
from the pre-equilibria, steps (i) and (ii), for the sterically crowded
systems, is lost in the rate-determining step (iii).
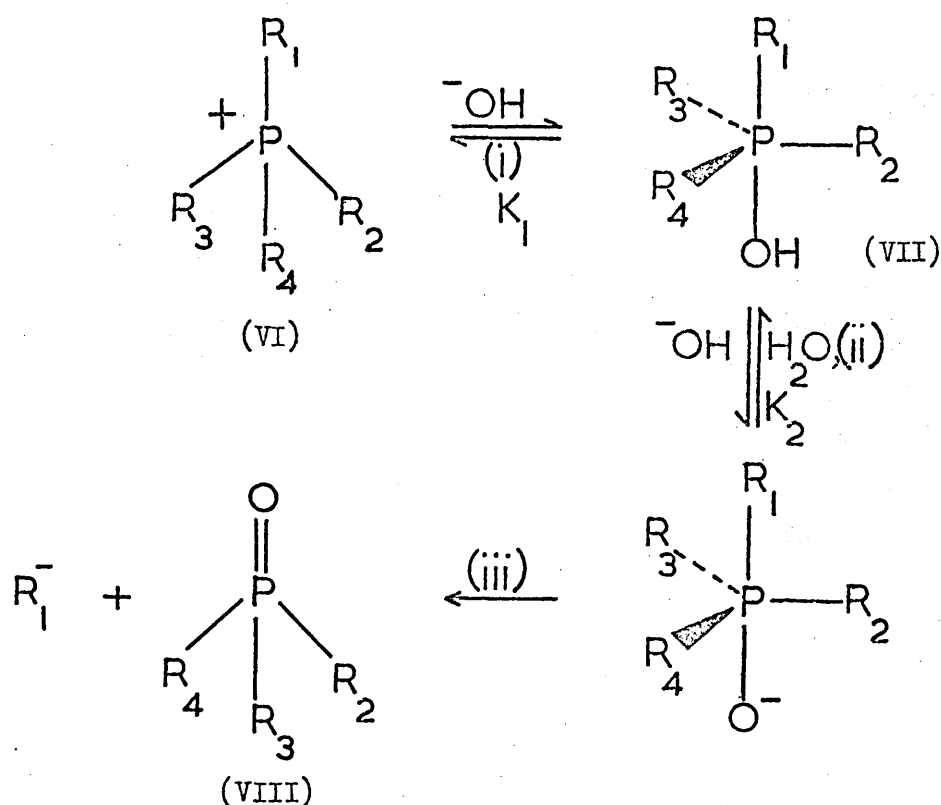


Trippett et al[8], however, obtained evidence that in extreme cases the rate
of alkaline hydrolysis of sterically crowded phosphonium salts is greatly
reduced, and may take place with possible expulsion of groups other than those
which are most stable as the carbanion. Thus di-t-butylmethylphenylphosphonium

iodide (IX) is extremely resistant to alkaline hydrolysis, while benzyldi-
t-butylphenylphosphonium bromide (X) is only slightly less resistant, yielding
benzyl-t-butylphenylphosphine and isobutene as the major products resulting
from Hoffmann elimination.  Furthermore, benzyl-t-butyl-α-naphthylphenyl-
phosphonium bromide (XI) undergoes hydrolysis to give only 45% of the expected
t-butyl-α-naphthylphenylphosphine oxide formed by expulsion of the benzyl group.
Phosphine oxides corresponding to the loss of the phenyl and α-naphthyl
carbanions are also produced.  In contrast, hydrolysis of benzyl-t-butylmethyl-
phenylphosphonium iodide (XII) gives the expected product (i.e. with loss of
benzyl) with predominant retention of configuration at phosphorus.

$$CH_3—\overset{+}{P}—\left[C(CH_3)_3\right]_2 \quad I^-$$

(IX)

$$\langle\ \rangle CH_2—\overset{+}{P}—\left[C(CH_3)_3\right]_2 \quad Br^-$$

(X)

$$\langle\ \rangle CH_2—\overset{+}{P}(C(CH_3)_3)(\text{phenyl})(\text{naphthyl}) \quad Br^-$$

(XI)

$$CH_3—\overset{+}{P}(C(CH_3)_3)(\text{phenyl})—CH_2\langle\ \rangle \quad I^-$$

(XII)
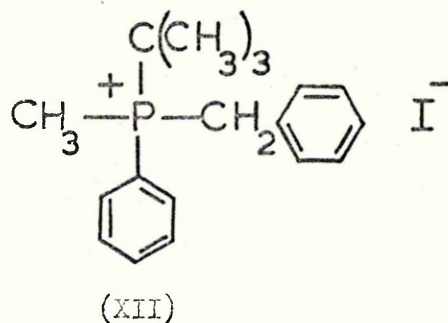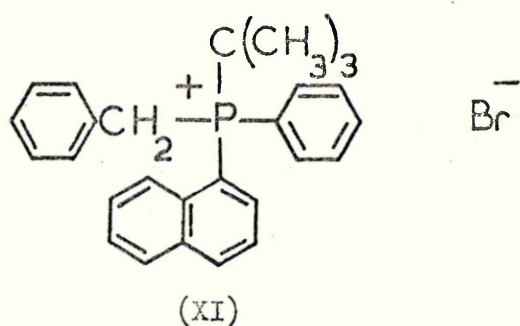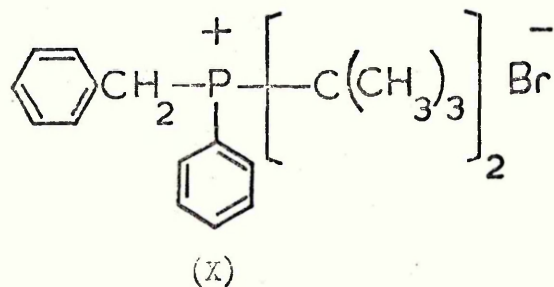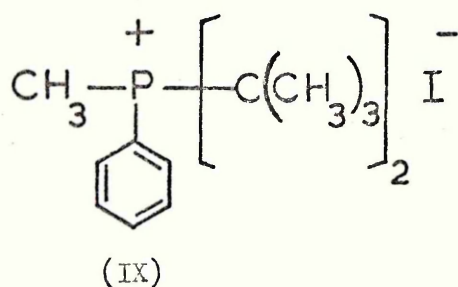
Trippett[8] suggested that the loss of a group other than that which is the most
stable as the anion, may be due to steric hindrance preventing initial attack
by hydroxide ion at a position which is colinear and opposite the group which
forms the most stable carbanion.  Alternatively, steric crowding of the
pentacovalent intermediate may prevent the expected leaving group from
attaining the correct conformation for maximum stabilisation of the departing
anion.  The problem is further complicated by the possibility of pseudorotation

of the intermediate, since it has not yet been established whether the

hydrolysis of acyclic phosphonium salts having leaving groups poorer than

benzyl are stereospecific. Thus if the intermediate has time to pseudorotate,

it is possible that attack by hydroxide ion at any point of a phosphonium salt

could lead to loss of any of the groups attached to phosphorus.
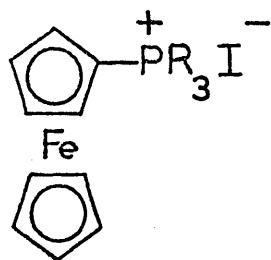
(XIII)
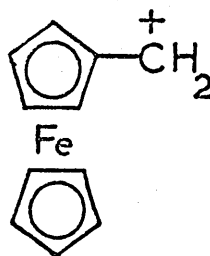
(XIV)

The effect of stabilisation of the phosphonium cation by overlap of $d\pi$

orbitals of phosphorus with electron-rich $\pi$-orbitals of a substituent, on the

rate of alkaline hydrolysis of phosphonium salts has been studied. McEwen

et al[9] observed that the presence of a ferrocenyl group bonded to phosphorus in

the salt (XIII) causes a significant decrease in the rate of alkaline hydrolysis

when compared with the corresponding phenyl substituted compounds. A strong

interaction between the non-bonding electrons of the ferrocenyl group and the

3d orbitals of the phosphorus was therefore suggested. The interaction serves

to decrease the positive charge on the phosphorus and hence reduces the

susceptibility towards nucleophilic attack. The stability of the ferrocenyl

carbonium ion (XIV) is similarly explained[10] by the overlap of either filled

iron 3d orbitals or cyclopentadienyl $p\pi$ orbitals with the vacant p orbital on

the carbonium ion carbon.

(XV)

(XVI)

(XVII)

$$\left[ \underset{O}{\text{furyl}} \right]_2 \overset{O}{\underset{}{P}}R$$

(XVIII)

$$\left[ \underset{S}{\text{thienyl}} \right]_2 \overset{O}{\underset{}{P}}R$$
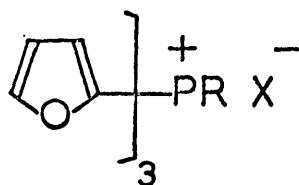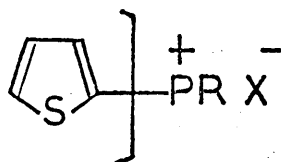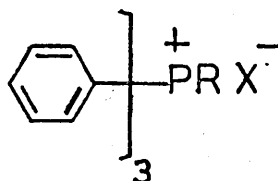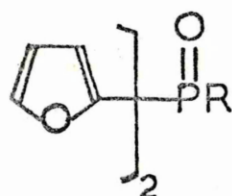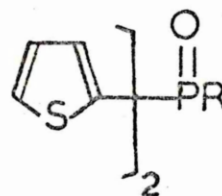
(XIX)

The possibility of a similar stabilisation of heteroarylphosphonium salts by $p\pi - d\pi$ overlap between the ring $\pi$-system and the phosphorus 3d orbitals has been investigated by Allen et al[11,12] who studied the course and rates of hydrolysis of a series of heteroarylphosphonium salts in which the heterocyclic ring is directly attached to phosphorus. It was shown that tri-(2-furyl)-methylphosphonium iodide (XV; $R=CH_3$, $X=I$) undergoes alkaline hydrolysis with loss of furan to give di-(2-furyl)methylphosphine oxide (XVIII; $R=CH_3$) some $10^{11}$ times faster than the analogous hydrolysis of methyltriphenylphosphonium iodide (XVII; $R=CH_3$, $X=I$). Furthermore the 2-furylphosphonium salt undergoes hydrolysis some $10^2 - 10^3$ times faster than the corresponding 2-thienyl-phosphonium salt (XVI; $R=CH_3$, $X=I$), which similarly yields thiophen and the oxide (XIX; $R=CH_3$). A similar order of relative reactivity was noted in the hydrolysis of the corresponding benzyltri-(2-furyl)- and benzyltri-(2-thienyl)-phosphonium salts (XV, XVI; $R=C_6H_5CH_2$, $X=Br$, respectively) which again proceed with exclusive loss of furan or thiophen to give the oxides (XVIII, XIX; $R=C_6H_5CH_2$, respectively).

The greater rate of hydrolysis of the heteroarylphosphonium salts compared with the phenyl analogues has been attributed to the greater electron-withdrawing inductive effect of the heteroaryl substituents, which lead to increases in the equilibrium constants $K_1$ and $K_2$ for the pre-equilibria involved in the hydrolysis reactions. In addition, the stability of the forming heteroaryl carbanion in the transition state of the rate-determining step is greater than for the phenyl analogues. It was concluded that the effect of $p\pi - d\pi$ bonding between the $\pi$-electron system of each heterocyclic

ring and the phosphorus 3d orbitals appears to be of little consequence in influencing the rate of the reaction.

The relative rates of hydrolysis of the 2-furyl and 2-thienyl compounds were also discussed with regard to the role of the heteroatom. The 2-furyl substituent has been shown to be more electron-withdrawing than 2-thienyl due to the greater electronegativity of the oxygen atom, and hence the pre-equilibria, steps (i) and (ii), will lie further to the right for the furyl-phosphonium salts than for the corresponding thienyl compounds[12]. Simple inductive arguments would also suggest that the 2-furyl carbanion will be more stable than the 2-thienyl carbanion. This approach, however, neglects the possibility of involvement of the sulphur 3d orbitals in stabilising the forming 2-thienyl carbanion.



(XX)
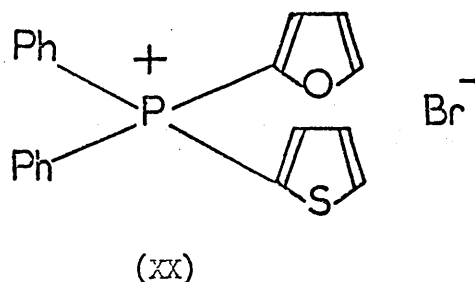
In order to investigate the relative stabilities of the transition states leading to the formation of the 2-furyl and 2-thienyl carbanions, Allen et al[13] studied the hydrolysis of 2-furyldiphenyl(2-thienyl)phosphonium bromide (XX). It was considered that the relative proportions of furan and thiophen liberated on hydrolysis of this salt would reflect the relative stabilities of the forming carbanions, since the course of the reaction is determined by carbanion formation, and electronic effects of the substituents in the pre-equilibria would not be expected to influence the overall course. The results revealed that the above salt (XX) undergoes hydrolysis with expulsion of both furan and thiophen in a 1 : 3 ratio, indicating that preferential cleavage of the phosphorus — (2-thienyl) bond takes place due to the greater stabilisation (presumably by sulphur 3d orbitals) of the forming 2-thienyl carbanion in the

transition state. The greater rate of hydrolysis of the furylphosphonium salts compared with thienylphosphonium salts must therefore be due to the inductive effect of the 2-furyl substituents on the magnitude of the pre-equilibrium constants $K_1$ and $K_2$.

The extent to which the heteroaryl carbanions develop in the transition state was also investigated, and a kinetic isotope effect, $kH/kD=1 \cdot 2$, for the formation of both furan and thiophen was observed in the alkaline hydrolysis of the salt (XX) in $H_2O - D_2O$ (1:1). It was therefore concluded that although the 2-heteroaryl carbanions would seem to be more stable than both the phenyl, benzyl and presumably cumyl carbanions, the extent of carbanion formation in the transition state for the hydrolysis of heteroarylphosphonium salts would appear to be the same as for the formation of less stable carbanions.



(XXI)          (XXIII)

(XXII)          (XXIV)
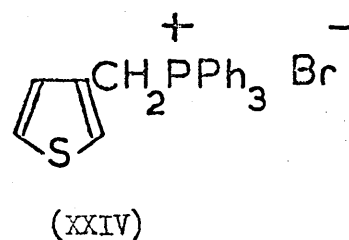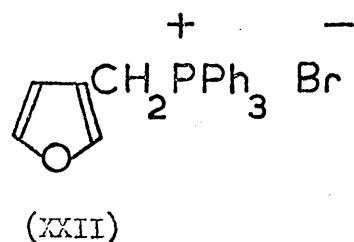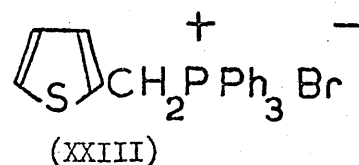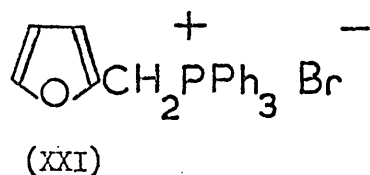
In order to extend the study to the influence of heterocyclic substituents on the stability of an adjacent carbanionic carbon, Allen et al[14] studied the kinetics of alkaline hydrolysis of a series of heteroarylmethyltriphenyl-phosphonium bromides (XXI) - (XXIV), which yield triphenylphosphine oxide and the respective methyl substituted heterocyclic compound. The relative reactivities of the salts were found to decrease, with reference to benzyl, in the order 2-furylmethyl-$>$ 2-thenyl-$>$ benzyl-$>$ 3-thenyl-$>$ 3-furylmethyl-
t-the order 2-furylmethyl-$>$ 2-thenyl-$>$ benzyl-$>$ 3-thenyl-$>$ 3-furylmethyl-
the electron-withdrawing nature of the heteroarylmethyl substituent, and the

relative stabilities of the forming heteroarylmethyl carbanions. It was

concluded that the observed rate differences between the 2-furylmethyl-,

2-thenyl-, and benzylphosphonium salts could still be due to the relative

electronegativities of the heteroatoms and the corresponding relative positions

of the pre-equilibria. As for the above 2-furyl- and 2-thienylphosphonium

salts (XV) and (XVI) respectively, however, the relative rate data does not

necessarily indicate the relative order of stability of the forming 2-furyl-

methyl, 2-thenyl and benzyl carbanions.

With regard to the 3-heteroarylmethylphosphonium salts, although it is

reasonable to assume that the pre-equilibria will lie further to the right on

passing from benzyl-, to 3-thenyl-, to 3-furylmethyltriphenylphosphonium

bromide, the stability of the transition state leading to the carbanions

clearly predominates in determining the relative rates of reaction. From the

rate data, the transition state leading to the formation of the benzyl carbanion

must be more stable than that for the formation of the 3-heteroarylmethyl

carbanions. Thus it would appear that the extensive delocalisation of the

negative charge possible in the benzyl carbanion overshadows the more restricted

delocalisation possible for the 3-heteroarylmethyl carbanions and the inductive

stabilisation by electronegative heteroatoms. In addition, possible $p_\pi - d_\pi$

participation by the 3d orbitals of sulphur would appear to increase the

stability of the forming 3-thenyl carbanion compared with the forming 3-furyl-

methyl carbanion.



(XXV)
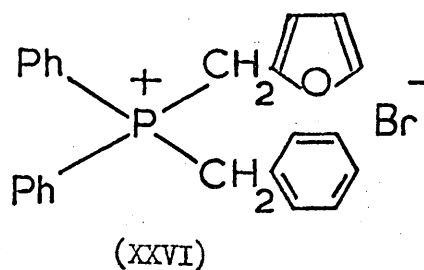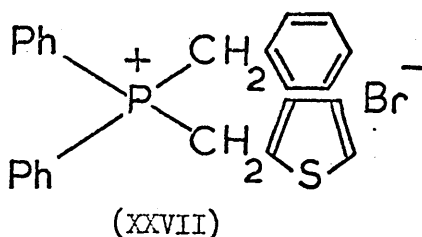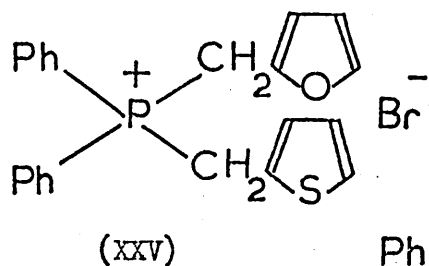
(XXVI)

(XXVII)

In order to ascertain the relative stabilities of the forming 2-furylmethyl, 2-thenyl and benzyl carbanions, Allen et al[13] also investigated the products of hydrolysis of the phosphonium salts (XXV) - (XXVII). Hydrolysis of 2-furylmethyldiphenyl(2-thenyl)phosphonium bromide (XXV) gave 2-methylfuran and 2-methylthiophen in a 1.3 : 1 mole ratio, thus indicating the 2-furylmethyl carbanion to be marginally more stable than the 2-thenyl carbanion. The inductive stabilisation by the more electronegative oxygen atom thus outweighs any contribution by the sulphur 3d orbitals in stabilising the forming 2-heteroarylmethyl carbanion. Alkaline hydrolysis of benzyl(2-furylmethyl)-diphenylphosphonium bromide (XXVI) and benzyl(2-thenyl)diphenylphosphonium bromide (XXVII) gave the heteroarylmethyl compound and toluene in the mole ratio of 7 : 1 and 5 : 1 respectively. Thus the effect of the electronegative heteroatoms in the 2-heteroarylmethyl carbanions (together with the possibility of 3d orbital participation in the 2-thenyl case) completely outweigh the greater possibilities of mesomeric delocalisation in the benzyl case. It was concluded therefore that observed rate differences between the 2-heteroaryl-methylphosphonium salts and the benzyl analogue are due to both pre-equilibrium inductive effects and the greater stability of the forming carbanions.

1.2 The Alkaline Hydrolysis of 2-(1-Methylpyrrolyl)- and 2-(1-Methylpyrrolylmethyl)-phosphonium Salts.

Because of current interest in the substituent effects of heterocyclic ring systems, it was of interest to extend the above study to investigate the effect of 1-methylpyrrolyl substituents at phosphorus and at carbon adjacent to phosphorus in heteroaryl-, and heteroarylmethylphosphonium salts.

In the first instance the relative stability of the forming 2-(1-methylpyrrolyl) carbanion was investigated by studying the course of hydrolysis of methyl-2-(1-methylpyrrolyl)diphenylphosphonium iodide (XXVIII) and benzyltri-2-(1-methylpyrrolyl)phosphonium bromide (XXIX).

$$\left[(C_6H_5)_2\overset{+}{P}(CH_3)(\text{1-methylpyrrol-2-yl})\right] I^-$$

(XXVIII)

$$\left[(\text{1-methylpyrrol-2-yl})_3\overset{+}{P}CH_2C_6H_5\right] Br^-$$

(XXIX)

$$(C_6H_5)_2P(=O)CH_3$$
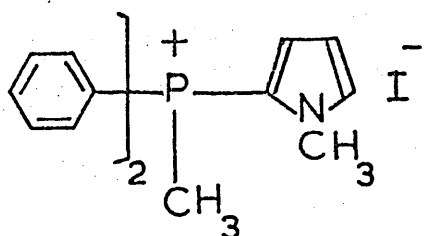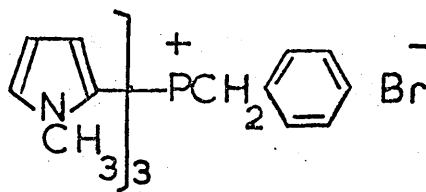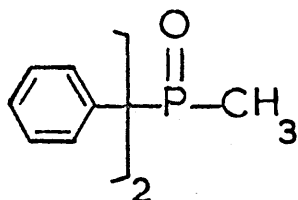
(XXX)

The alkaline hydrolysis of the salt (XXVIII) was found to take place with exclusive loss of 1-methylpyrrole to give methyldiphenylphosphine oxide (XXX); benzene was not detected in the hydrolysis mixture. However, in the alkaline hydrolysis of the salt (XXIX), cleavage of the heterocyclic substituent occurs only to a minor extent; both toluene and 1-methylpyrrole are formed in a 3 : 2 molar ratio. Allowing for statistical effects, it would appear that the relative stabilities of the forming benzyl and 2-(1-methylpyrrolyl) carbanions are of the order of 4 : 1. The course of the latter reaction contrasts with the hydrolysis of benzyltri-(2-furyl)phosphonium bromide (XV; $R = C_6H_5CH_2$, X = Br) and benzyltri-(2-thienyl)phosphonium bromide (XVI; $R = C_6H_5CH_2$, X = Br) which proceed with exclusive loss of furan and thiophen respectively to give triphenylphosphine oxide. The above reactions thus indicate that the forming 2-(1-methylpyrrolyl) carbanion is more stable than the forming phenyl carbanion, but less stable than the forming benzyl carbanion. The order of cleavage of the heteroaryl substituents with reference to benzyl, is therefore 2-thienyl > 2-furyl > benzyl > 2-(1-methylpyrrolyl) > phenyl.

In comparing the ability of the heterocyclic systems to stabilise the forming negative charge in the 2-position, it is necessary to consider both the $\sigma-$, and $\pi-$electron systems of each ring. For each heterocyclic carbanion the adjacent electronegative atom will stabilise the forming negative charge by a $\sigma$-inductive effect, and the observed differences in carbanionic stability

must have their origin in the $\pi$-electron systems. It has been suggested recently[15,16] that in furan and thiophen the $\sigma$-electronic inductive effect of the heteroatom outweighs the $\pi$-electron moment (which increases electron-density on the ring carbon atoms) and that the dipole moment in furan and thiophen is towards the heteroatom. In contrast in pyrrole systems, the $\pi$-moment predominates and the direction of the dipole moment is from the heteroatom to the ring. Indeed, it would appear that in the forming 2-furyl and 2-thienyl carbanions the $\sigma$-inductive effect predominates to stabilise the negative charge to a greater extent than for the resonance stabilisation of the forming benzyl carbanion. In contrast, in the case of the forming 2-(1-methyl-pyrrolyl) carbanion, the $\pi$-moment of the heterocycle directs electron density to the 2-position thereby decreasing the stability of the forming negative charge at that position. The fact that the 2-(1-methylpyrrolyl) carbanion is more stable than the phenyl carbanion, however, can only be due to the inductive effect of the nitrogen atom. The magnitude of the inductive effect in the 2-(1-methylpyrrolyl) system, however, must be less than for 2-furyl and 2-thienyl, since the more extensive delocalisation of the negative charge possible in the benzyl carbanion is sufficient to stabilise the latter relative to the 2-(1-methylpyrrolyl) carbanion.

Chemical evidence to support the suggestion of the contrasting electronic character of the 2-(1-methylpyrrolyl) substituent and the 2-thienyl and 2-furyl substituents is obtained from a number of sources. In the Introduction, it was pointed out that while pyrrolecarboxylic acids, like the alkoxy-and amino-substituted benzoic acids, are weaker than the unsubstituted benzoic acid, thiophen-, and furancarboxylic acids, like the chloro-, and bromobenzoic acids are stronger. This evidence together with dipole moment data for the saturated heterocyclics was used to discuss the possibility that the direction of the dipole moment in pyrrole is opposite to that of furan and thiophen.

Furthermore, in reactions where the heterocyclic substituent is donating

electrons, the enhanced reactivity of pyrrole is observed. Pyrrole, furan and

thiophen are characterised by their ease of electrophilic substitution, and

relative rates of bromination compared with benzene[17] are $3 \times 10^{18}$ : $6 \cdot 1 \times 10^{11}$ :

$5 \cdot 1 \times 10^{9}$ : 1, respectively. Isomer distribution and $\alpha : \beta$ ratios depend strongly

on the electrophilic reagent. It is of interest, however, that while furan is

substituted exclusively in the $\alpha$-position, in pyrrole the $\alpha$- and $\beta$-positions

are of similar reactivity. Thus although data for comparison under strictly

equivalent experimental conditions are not available, the existing data seems

to confirm that the order of $\alpha$-directing ability is furan $\gg$ thiophen $\gg$

pyrrole[18].

In a recent paper, Marino et al[19] examined the effect of substituents in

the ring on the rate of eletrophilic substitution of pyrrole, furan and

thiophen, and observed that in furan the rate of substitution is greatly

influenced by structural changes, indicating that the transition state for the

reaction resembles the Wheland intermediate ($\sigma$-complex). In pyrrole, however,

the sensitivity to substituents is less than for both furan and thiophen,

favouring the hypothesis that the transition state for substitutions at the

pyrrole ring will occur at a point along the reaction coordinate far removed

from the Wheland intermediate; it will therefore have more $\pi$-character.
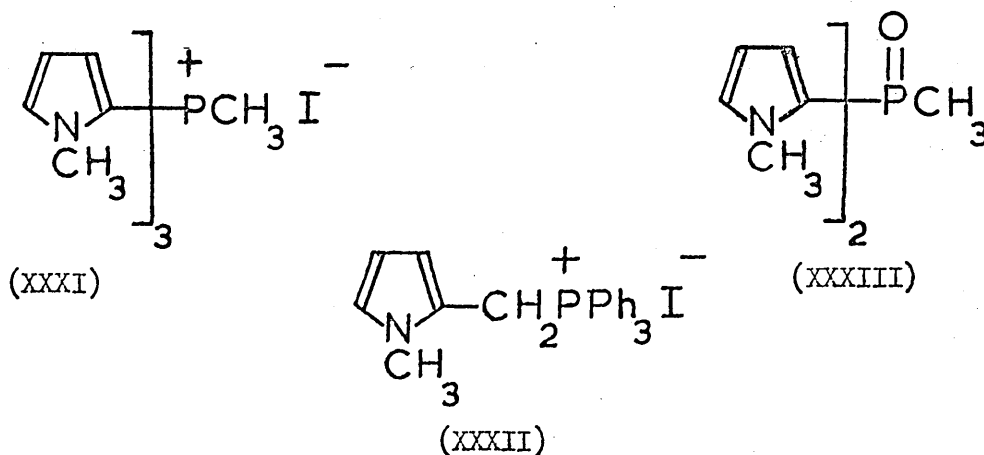


(XXXI)

(XXXII)

(XXXIII)

The kinetics of alkaline hydrolysis of methyltri-2-(1-methylpyrrolyl)-

phosphonium iodide (XXXI) and triphenyl(1-methylpyrrol-2-yl)methylphosphonium

iodide (XXXII) in 50% aqueous ethanol have been studied using a titrimetric procedure. Methyltri-2-(1-methylpyrrolyl)phosphonium iodide was found to undergo hydrolysis with loss of 1-methylpyrrole to give di-2-(1-methylpyrrolyl)-methylphosphine oxide (XXXIII); the course of the reaction is thus analogous to the hydrolysis of methyltriphenylphosphonium iodide in which a phenyl group is cleaved to give methyldiphenylphosphine oxide. The alkaline hydrolysis of triphenyl(1-methylpyrrol-2-yl)methylphosphonium iodide proceeds with loss of 1, 2-dimethylpyrrole to give triphenylphosphine oxide and is thus analogous to the hydrolysis of benzyltriphenylphosphonium bromide, which gives triphenyl-phosphine oxide and toluene. The hydrolyses of both salts follow a third-order rate law, in accordance with the generally accepted mechanism for the hydrolysis of phosphonium salts.

### Table 1.1.

Third-Order Rate Constants and Activation Parameters for the Alkaline Hydrolysis of Phosphonium Salts in Aqueous ethanol (50% v/v).

| Salt $R_3PCH_3^+ \ I^-$ | Temperature ($^\circ$C) | $k_{obs}(l^2mol^{-2}min^{-1})$ | $E_A$/kJmol$^{-1}$ |
|---|---|---|---|
| R = 2-(1-methylpyrrolyl) | 70 | 3·21 | |
| | 60 | 1·29 | 86·3 |
| R = phenyl | 60 | 0·27[*] | 131·2 |
| R = 2-thienyl | 60 | $8·3 \times 10^{7}$[*] | 60·8 |
| R = 2-furyl | 60 | ca $10^{10}$[‡] | |

[*] calculated from data in reference 11

[‡] calculated from data in reference 12

The kinetic data (Table 1.1.) reveals several features of interest. Methyltri-2-(1-methylpyrrolyl)phosphonium iodide is found to undergo alkaline hydrolysis ca 5 times more quickly than methyltriphenylphosphonium iodide, the increase in rate being accompanied by a decrease in energy of activation for the reaction. A comparison with the rate data for the corresponding 2-furyl-

and 2-thienylphosphonium salts shows that the overall rates of hydrolysis for the above series of phosphonium salts decrease in the order 2-furyl $>$ 2-thienyl $\gg$ 2-(1-methylpyrrolyl) $>$ phenyl, the relative rates being of the order of $10^{11} : 10^8 : 5 : 1$.

The rapid rate of hydrolysis of the 2-furyl- and 2-thienylphosphonium salts compared with the phenyl analogue has been attributed[11,12] to the greater electron-withdrawing (inductive effect) of the 2-furyl and 2-thienyl substituents which serves to increase $K_1$ and $K_2$ for the pre-rate determining step equilibria, and also to the greater stability of the forming 2-furyl and 2-thienyl carbanions. A similar explanation for the increased rate of hydrolysis of the tri-2-(1-methylpyrrolyl) salt compared with phenyl would, however, seem inappropriate.

The general chemistry of pyrrole would suggest that in the ground state, the inductive effect of the 2-(1-methylpyrrolyl) substituent would in fact be less than for phenyl. Thus in the hydrolysis reactions of methyltriphenyl-phosphonium iodide and methyltri-2-(1-methylpyrrolyl)phosphonium iodide the pre-equilibria, steps (i) and (ii), should lie further to the right for the triphenyl salt than for the tri-2-(1-methylpyrrolyl) analogue. Therefore, since it has been shown that the forming 2-(1-methylpyrrolyl) carbanion in the transition state is more stable than the phenyl carbanion, this factor alone must be dominant in the determination of the relative rates of hydrolysis of the respective salts. The difference in activation energy for the hydrolyses of tri-2-(1-methylpyrrolyl)- and triphenylphosphonium salts is large enough to suggest that differences in pre-equilibria will have a minimal effect on the relative rate of alkaline hydrolysis of triphenyl- and tri-2-(1-methylpyrrolyl)-phosphonium salts. Previous workers[12] have shown that it is only for the tri-(2-furyl)phosphonium salts that the pre-equilibria may lie substantially in favour of the products. It is likely therefore, that for the above salts the position of the steps (i) and (ii) will lie predominantly to the left.

The vast increase in rates of hydrolysis of the 2-furyl- and 2-thienyl phosphonium salts relative to the phenyl analogue ($10^{11}$ : $10^8$ : 1) compared with the increase in rate of the 2-(1-methylpyrrolyl) salt (5 : 1) serves to emphasize the composite nature of the observed rate constant and the importance of the inductive effect and position of the pre-equilibria upon the relative rates of hydrolysis. Further evidence of the importance of inductive effects of substituents upon rates of alkaline hydrolysis of phosphonium salts has recently been discussed by McEwen et al[20], who showed that the cyclopentadienylphosphonium salt of tricarbonylmanganese (XXXIV) undergoes hydrolysis faster than benzyltriphenylphosphonium bromide (XVII; $R = C_6H_5CH_2$, $X = Br$) which in turn is hydrolysed faster than the ferrocenylphosphonium salt (XXXV). It was suggested that the electron-withdrawing effect of the carbonyl groups in the cymantryl group promoted attack at phosphorus, in contrast with the "electron-rich" ferrocenyl group. The relative electron-withdrawing nature of the above organometallic substituents was further supported by a comparison of the $pK_a$ values of the carboxylic acid derivatives.
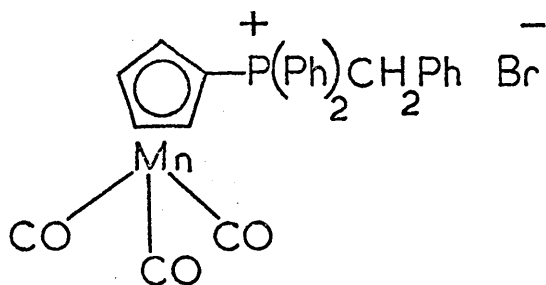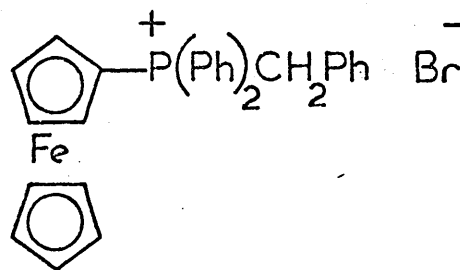


(XXXIV)                              (XXXV)

The alkaline hydrolysis of triphenyl(1-methylpyrrol-2-yl)methylphosphonium iodide (XXXII) in aqueous ethanol (50% v/v; 0·1M in KCl to maintain a constant ionic strength) was observed to proceed more slowly than that of benzyltriphenylphosphonium bromide, the relative rates being 1 : 1·2 respectively (Table 1.2.). Thus the rates of hydrolysis of 2-heteroarylmethyltriphenylphosphonium salts relative to the benzyl analogue decrease in the order 2-furylmethyl > 2-thenyl > benzyl > 2-(1-methylpyrrolyl)methyl, the decrease

in rates being accompanied by a steady increase in the energies of activation.

## Table 1.2.

Third-Order Rate Constants and Activation Parameters for the Alkaline

Hydrolysis of Heteroarylmethyltriphenylphosphonium Salts in Aqueous Ethanol

(50% v/v: 0·1M in KCl).

| Salt $Ph_3PR\ X^-$ | Temperature ($^\circ$C) | $k_{obs}$ ($l^2mol^{-2}min^{-1}$) | $E_A/kJmol^{-1}$ |
|---|---|---|---|
| R = 2-(1-methylpyrrolyl)methyl; X = I$^-$ | 50 | 16·6 | 80·6 |
|  | 40 | 6·0 |  |
| R = benzyl; X = Br$^-$ | 40 | 7·2 | 76·2[*] |
| R = 2-thenyl; X = Br$^-$ | 40 | 183·3 | 70·3[*] |
| R = 2-furylmethyl; X = Br$^-$ | 40 | 356·5 | 64·3[*] |

[*] data taken from reference 14

The increased rate of alkaline hydrolysis of the 2-furylmethyl- and
2-thenylphosphonium salts, compared with the benzyl analogue, have been
discussed in terms of the relative positions of the pre-equilibria and relative
stabilities of the forming carbanions[14]. The rate of hydrolysis of the
2-(1-methylpyrrolyl)methyl- salt relative to the above salts may be discussed
similarly. Simple inductive effects based on $pK_a$ data for pyrrole-2-carboxylic
acid and benzoic acid would suggest the benzyl substituent to be more electron-
withdrawing than the 2-(1-methylpyrrolyl)methyl substituent, and therefore the
position of the pre-equilibria, steps (i) and (ii), would lie further to the
right for the benzyl salt. On the basis of the available data, however, it is
not possible to decide unambiguously on the relative stabilities of the forming
2-(1-methylpyrrolyl)methyl and benzyl carbanions.

In the case of the 2-furylmethyl and 2-thenyl carbanions the inductive
effect of the heteroatom together with the limited resonance delocalisation
about the heterocyclic ring contribute to stabilise the carbanion to a greater

extent than for the benzyl anion where the extent of possible delocalisation of the negative charge is greater. For the 2-(1-methylpyrrolyl)methyl carbanion, however, the magnitude of the inductive effect of the electronegative nitrogen atom is difficult to assess, since the $\pi$-moment of the heterocyclic ring (which is in the opposite direction to the inductive effect) appears to predominate and increases electron density at the ring carbons. Furthermore the $\pi$-moment of the heterocycle would be expected to oppose movement of the forming negative charge from the exocyclic carbon into the ring, hence restricting any possible resonance stabilisation. Previous workers[11-13] have shown that the 2-furyl and 2-thienyl carbanions are more stable than their respective heteroarylmethyl carbanions as a result of inductive effects. However, where inductive effects are absent, the benzyl carbanion is more stable than the phenyl analogue, and thus it is possible that the delocalisation of the negative charge in the 2-(1-methylpyrrolyl)methyl carbanion will increase its stability relative to the 2-(1-methylpyrrolyl) carbanion. Since the benzyl carbanion has been shown (from the alkaline hydrolysis of benzyltri-2-(1-methylpyrrolyl)phosphonium bromide) to be only four times more stable than the 2-(1-methylpyrrolyl) carbanion, the relative stabilities of the benzyl and 2-(1-methylpyrrolyl)methyl carbanions is open to question. Indeed, if it is argued that since the inductive effects are small the rate-determining factor is the stability of the forming carbanions, the rate difference (1·2 : 1) for the alkaline hydrolysis of the benzyl- and 2-(1-methylpyrrolyl)methylphosphonium salts could be explained by the forming benzyl carbanion being slightly more stable than the 2-(1-methylpyrrolyl) carbanion. In order to resolve this point, it would be of interest to study the course of the alkaline hydrolysis of benzyldiphenyl-(1-methylpyrrol-2-yl)methylphosphonium iodide (XXXVI). Thus the relative proportions of toluene and 1,2-dimethylpyrrole liberated on the alkaline hydrolysis of this salt, should reflect the relative stabilities of the forming carbanions.

$$Ph \underset{Ph}{\overset{+}{\diagdown}} P \diagup \overset{CH_2}{\diagdown} \diagup \quad I^-$$
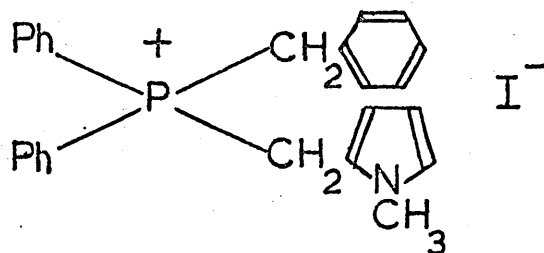
(XXXVI)

## 1.3 Studies of [31]P n.m.r. Spectra of Heteroarylphosphonium Salts.

Evidence of the electron-withdrawing ability of substituents attached to phosphorus may be obtained from [31]P n.m.r. chemical shift data. Recent studies[21,22] of the [31]P n.m.r. spectra of a series of substituted phenylphosphonic acids have shown the chemical shifts are affected by substituents on the phenyl ring in a direction opposite to that expected from the electron-withdrawing ability of the substituents. Thus for the phenylphosphonic acids, the more electron-withdrawing the substituent, the more shielded is the phosphorus. While such behaviour would appear to be anomalous in comparison with the trends observed in ^{1}H and [19]F n.m.r. spectra, it has been shown that it follows directly from quantum mechanical theory[23].

Allen et al[12,14] obtained evidence of the electron-withdrawing nature of the 2-furyl, 2-thienyl, 2-furylmethyl, 2-thenyl, phenyl and benzyl groups from [31]P n.m.r. spectra of phosphonium salts. It was shown that for heteroarylphosphonium salts, shielding of the phosphorus is in the order 2-furyl $>$ 2-thienyl $>$ phenyl and similarly in the heteroarylmethyl series the order 2-furylmethyl $>$ 2-thenyl $>$ benzyl is observed. [31]P chemical shift data for 2-(1-methylpyrrolyl)- and 2-(1-methylpyrrolyl)methylphosphonium salts are given in Table 1.3.. Data for 2-furyl-, 2-thienyl- and phenylphosphonium salts are also given for comparative purposes.

Table 1.3.

$^{31}$P Chemical Shift Data for Heteroaryl- and Heteroarylmethylphosphonium Salts.

| Salt | $\delta\,^{31}$P/p.p.m. (rel. to 85% $H_3PO_4$) | Solvent |
|---|---|---|
| $R_3\overset{+}{P}CH_3\ I^-$ | | |
| R = 2-(1-Methylpyrrolyl) | +17·8 | $CHCl_3$ |
| | +18·5 | $CF_3CO_2H$ |
| R = 2-Furyl | +15·4 | $CF_3CO_2H$* |
| R = 2-Thienyl | − 2·25 | $CF_3CO_2H$* |
| R = Phenyl | −18·8 | $CF_3CO_2H$* |
| $R_3\overset{+}{P}CH_2C_6H_5\ Br^-$ | | |
| R = 2-(1-Methylpyrrolyl) | +14·6 | $CF_3CO_2H$ |
| R = 2-Furyl | +12·8 | $CF_3CO_2H$* |
| R = 2-Thienyl | − 3·9 | $CF_3CO_2H$* |
| R = Phenyl | −19·9 | $CF_3CO_2H$* |
| $Ph_2\overset{+}{P}RCH_3\ I^-$ | | |
| R = 2-(1-Methylpyrrolyl) | − 6·2 | $CF_3CO_2H$ |
| R = 2-Furyl | − 7·7 | $CF_3CO_2H$Ɨ |
| R = 2-Thienyl | −13·0 | $CF_3CO_2H$Ɨ |
| $Ph_3\overset{+}{P}R\ I^-$ | | |
| R = 2-(1-Methylpyrrolyl)methyl | −17·8 | $CHCl_3$ |
| | −17·0 | $CF_3CO_2H$ |
| $Ph_3\overset{+}{P}R\ Br^-$ | | |
| R = 2-Furylmethyl | −17·45 | $CF_3CO_2H$⌐ |
| R = 2-Thenyl | −18·25 | $CF_3CO_2H$⌐ |
| R = Benzyl | −19·9 | $CF_3CO_2H$* |

\* Data for compounds so marked is from reference 12.

Ɨ Data for compounds so marked is "unpublished".[24]

⌐ Data for compounds so marked is from reference 14.

The results in Table 1.3. reveal a trend to a greater shielding of the phosphorus on passing from phenyl, to 2-thienyl, to 2-furyl to 2-(1-methylpyrrolyl) substituents, thus indicating the increasing electron-withdrawing character of the heteroaryl ring in that order. A similar trend is obtained from the $^{31}$P chemical shift data for diphenylheteroarylphosphines given in Table 1.4..

## Table 1.4.

$^{31}$P Chemical Shift Data for Heteroaryl- and Arylphosphines in Chloroform.

| Compound | $\delta^{31}$P/p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| $RP(C_6H_5)_2$ | |
| R = 2-(1-Methylpyrrolyl) | +25·75[I] |
| R = 2-Furyl | +23·88[I] |
| R = 2-Thienyl | +17·6[I] |
| R = Phenyl | + 4·7[I] |

[I] Data for compounds so marked is "unpublished".[24]

The apparent anomaly between the rates of alkaline hydrolysis of 2-(1-methylpyrrolyl)- and 2-(1-methylpyrrolyl)methylphosphonium salts and the $^{31}$P chemical shift data is possibly explained by considering the factors which affect $^{31}$P chemical shift. Letcher and Van Wazer[23] noted the chemical shift to be greatly affected by what may be termed asymmetric loading i.e. a summation of (i) the total occupation of the $d_\pi$ orbitals of the phosphorus, (ii) the unbalance of the $\sigma$-bonds as determined by the difference in electronegativities of various substituents and (iii) the deviations in geometrical symmetry.

From the results of a detailed study of the $^{31}$P chemical shifts of a number of quaternary phosphonium salts[25] together with comparable data compiled by Grim et al,[26] Letcher and Van Wazer[25] suggested that there was little or no $\pi$-character in the P—C bond between a phenyl group and phosphorus, since little change in $\Delta\delta$ is observed for a given group R, when Z is changed from phenyl to n-butyl or ethyl in compounds of the type $RP\overset{+}{Z}_3$. It would appear

therefore, that whilst the extent of $\pi$-bonding and the concomitant effect upon $^{31}$P chemical shift is uncertain when 2-(1-methylpyrrolyl), 2-furyl, and 2-thienyl substituents are directly bonded to phosphorus, variations in $\Delta\delta$ for triphenylheteroarylmethylphosphonium salts are mainly attributable to the difference in the average amount of charge residing in the $\sigma$-orbitals of the R—P bond, without complication from $\pi$-bonding. Thus the apparent electronegativities of the heteroarylmethyl substituents relative to benzyl are in the order 2-(1-methylpyrrolyl)methyl $>$ 2-furylmethyl $>$ 2-thenyl $>$ benzyl.

This approach, however, neglects the possibility of the involvement of steric effects. The possibility that the 1-methyl group in the 1-methylpyrrolyl substituent could lead to a possible steric effect due to deviations in geometrical symmetry, have been investigated by the effect of introducing an ortho-methyl group into phenyl on the $^{31}$P chemical shift of phenylphosphines. The results are given in Table 1.5..

### Table 1.5.

$^{31}$P Chemical Shift Data for Arylphosphines in Chloroform.

| Compound | $\delta^{31}$P/p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| Triphenylphosphine | + 4·7[I] |
| Diphenyl-o-tolylphosphine | +11·25[I] |
| Di-o-tolylphenylphosphine | +18·0[I] |
| Tri-p-tolylphosphine | + 6·75[I] |

[I] Data for compounds so marked is "unpublished".[24]

A study of the data in Table 1.5. reveals a shift to higher field on passing from triphenylphosphine to diphenyl-o-tolylphosphine ($\Delta\delta = +6\cdot55$p.p.m.) and a further positive shift ($+6\cdot75$p.p.m.) on passing to di-o-tolylphenyl-phosphine. Such shifts indicate increased shielding of the phosphorus nuclei on substitution of phenyl for o-tolyl. However, since o-tolyl is expected to be more electron-donating than phenyl it is not possible to explain the observed shielding in terms of "withdrawal" of electrons, furthermore the

additivity of the chemical shift indicates the absence of $\pi$-bonding. The evidence therefore suggests the effect to be steric in nature. This theory is supported by the comparatively small difference in $^{31}P$ chemical shift on passing from triphenylphosphine to tri-p-tolylphosphine $(\Delta\delta = +2\cdot05\text{p.p.m.})$ in which steric effects of the methyl group would be minimal, such that the electronic effect of the methyl group need only be considered.

From the above results, therefore, it is possible that the seemingly anomalous $^{31}P$ chemical shifts of the above 2-(1-methylpyrrolyl), and 2-(1-methylpyrrolyl)methyl phosphorus compounds may be due to a steric effect. It should be noted, however, that the 1-methyl group in the 2-(1-methylpyrrolyl) and 2-(1-methylpyrrolyl)methyl substituents may not have the same effect on the $^{31}P$ chemical shift as is obtained on passing from a phenyl substituent to o-tolyl. The $^{31}P$ chemical shift data for analogous phosphorus compounds containing 2-pyrrolyl and 2-pyrrolylmethyl substituents would therefore be of interest.

As an alternative to the above, if the 2-(1-methylpyrrolyl) substituent is more electronegative than the 2-furyl substituent as indicated by the $^{31}P$ chemical shift, the lack of correlation with the rate of alkaline hydrolysis may possibly be explained by the formation of a highly stable pentacovalent intermediate in the initial step of the reaction. Hence rapid nucleophilic attack at phosphorus could be followed by slow departure of the 2-(1-methylpyrrolyl) carbanion. If this was the situation, then it would enable observation of the formation of the pentacovalent phosphorane by $^{31}P$ n.m.r. techniques as used by Allen et al[12] to observe the formation of a comparable intermediate in the equilibrium between methoxide and methyltri-(2-furyl)phosphonium ions. However, no evidence for the formation of such a pentacovalent intermediate could be obtained for the analogous reaction between ethoxide ion and methyl-tri-2-(1-methylpyrrolyl)phosphonium iodide in dry ethanol.

Finally in this discussion of the apparent electronic effects of

2-(1-methylpyrrolyl) substituents at phosphorus, it is of interest to consider the rates of quaternisation of diphenylheteroarylphosphines with phenacyl bromide to form the corresponding phosphonium bromides,[27] (Table 1.6.).

## Table 1.6.

### Second-Order Rate Constants for the Quaternisation of Aryl- and Heteroaryldiphenylphosphines with Phenacyl Bromide in Nitromethane at $30^{\circ}C$.[*]

| Compound | $k_{obs}$ $(1 \text{ mol}^{-1} \text{sec}^{-1})$ | Relative Rate |
|---|---|---|
| $RPPh_2$ | | |
| R = 2-Furyl | 0·0082 | 0·128[*] |
| R = 2-Thienyl | 0·0207 | 0·323[*] |
| R = 2-(1-Methylpyrrolyl) | 0·0286 | 0·447[*] |
| R = Phenyl | 0·0640 | 1·000[*] |

[*] Rate Data obtained from reference 27.

Since the reaction involves displacement of bromide ion by the nucleophilic tertiary phosphine, the rate is dependent upon the electron-availability at phosphorus. Thus the results revealed in Table 1.6. are important since they show that the order of "electronegativity" of heteroaryl substituents when attached to phosphorus to be 2-furyl > 2-thienyl > 2-(1-methylpyrrolyl) and thereby support the suggestion of the role of steric effects on the $^{31}P$ chemical shift of phosphorus compounds containing 2-(1-methylpyrrolyl) substituents.

The possibility of steric hindrance in the quaternisation reaction is also of interest. In a recent study McEwen et al[28] observed the relative rates for the reaction between p-tolyldiphenyl-, triphenyl-, and o-tolyldiphenylphosphine with benzyl chloride to be 1·3 : 1 : 0·3 respectively, indicating that the effect of steric hindrance is to give a 4-fold decrease in the rate of reaction. It is thus possible that but for steric hindrance, the rate of quaternisation of diphenyl-2-(1-methylpyrrolyl)phosphine with phenacyl bromide would take place more quickly than that of triphenylphosphine. A study of the rate of

quaternisation of diphenyl-(2-pyrrolyl)phosphine with phenacyl bromide would
be of interest in this connection.

# EXPERIMENTAL

Compounds are colourless unless otherwise described. Operations involving phosphines or organolithium reagents were conducted under nitrogen.

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

[1]H Nuclear magnetic resonance spectra were determined at normal temperatures for deuterochloroform or trifluoroacetic acid solutions containing tetramethylsilane as an internal standard, using a JEOL C-60 HL high resolution 60 MHz instrument.

[31]P Nuclear magnetic resonance spectra were determined at normal temperatures for chloroform or trifluoroacetic acid solutions containing 85% phosphoric acid in a sealed capillary tube as an internal standard, using a JEOL C-60 HL high resolution 24 MHz instrument.

Mass Spectra were recorded using an AEI MS-30 spectrometer.

G.l.c. analyses were carried out with a Pye series 104 chromatograph equipped with a 5ft PEGA column and a flame ionisation detector.

Microanalyses were carried out by Dr. F. B. Strauss, Microanalytical Laboratory, 10 Carlton Road, Oxford.

Preparation of Phosphines and Phosphonium Salts.

2-(1-Methylpyrrolyl)diphenylphosphine – n-Butyl-lithium (0·2 mol) in hexane (200 cm³) was added dropwise, with stirring under nitrogen, to 1-methylpyrrole[29] (27·0 g, > 0·2 mol) in ether (200 cm³) during 20 minutes. The resulting solution was heated under reflux for 2 h, before cooling in ice. Diphenyl-phosphinous chloride (22·0 g, 0·1 mol) in benzene (50 cm³) was then added slowly. The mixture was then heated under reflux for 1 h, cooled in ice, and then hydrolysed by the addition of ammonium chloride solution (10% w/v; 100 cm³). The organic layer was separated, dried ($Na_2SO_4$) and evaporated; the residue was distilled to give 2-(1-methylpyrrolyl)diphenylphosphine (10·5 g, 40%), b.p. 149° at 0·15 mmHg. The phosphine, on treatment with methyl iodide, gave methyl-2-(1-methylpyrrolyl)diphenylphosphonium iodide (XXVIII), m.p. 181-2° (ex MeOAc-EtOH) (Found: C, 53·15; H, 4·65. $C_{18}H_{19}INP$ requires C, 53·05; H, 4·65%); $\tau$ ($CF_3CO_2H$) 2·0 – 2·6 (10H, m), 2·62 – 2·82 (1H, m), 3·2 – 3·4 (1H, m), 3·48 – 3·70 (1H, m), 4·42 (3H, s), and 7·23 (3H, d, $^2J_{PCH}$ 13·5 Hz); $\delta$ $^{31}P$ ($CF_3CO_2H$) –6·2 p.p.m.

Tri-2-(1-methylpyrrolyl)phosphine – n-Butyl-lithium (0·6 mol) in light-petroleum (b.p. 40-60°) was added dropwise, with stirring under nitrogen, to 1-methyl-pyrrole[29] (52 g, > 0·6 mol) in ether (200 cm³). The resulting solution was heated under reflux for 14 h before being cooled in ice. Phosphorus trichloride (13·8 g, 0·1 mol) in ether (100 cm³) was then added slowly. The mixture was then heated under reflux for an additional 3 h, before being cooled in ice and hydrolysed by the addition of ammonium chloride solution (10% w/v; 100 cm³). The organic layer was separated, the aqueous layer extracted with ether, and the combined organic layers dried ($Na_2SO_4$). Evaporation of the solvent gave a brown oil which was distilled to give tri-2-(1-methylpyrrolyl)phosphine (10·9 g, 40%), b.p. 132-140° at 0·04 mmHg, m.p. 121-2° (ex EtOH) (Found: C, 66·25; H, 6·65; N, 15·55. $C_{15}H_{18}N_3P$ requires C, 66·40; H, 6·65; N, 15·5%); $\tau$ ($CDCl_3$) 3·2 (3H, m), 3·8 –4·1 (6H, m), and 6·4 (9H, s). The phosphine, in solution in

benzene, with benzyl bromide gave <u>benzyltri-2-(1-methylpyrrolyl)phosphonium</u> <u>bromide</u>, (XXIX), m.p. 264° (ex EtOAc – EtOH) (Found: C, 59·65; H, 5·55; N, 9·25. $C_{22}H_{25}BrN_3P$ requires C, 59·75; H, 5·70; N, 9·5%); $\tau$ (CDCl$_3$) 2·6 – 3·3 (11H, m), 3·65 (3H, m), 5·27 (2H, d, $^2J_{PCH}$ = 14·25 Hz), and 6·67 (9H, s); $\delta^{31}P$ (CF$_3$CO$_2$H) +14·6 p.p.m.. The phosphine, in benzene solution when treated with methyl iodide gave <u>methyltri-2-(1-methylpyrrolyl)phosphonium iodide</u>, (XXXI), m.p. 215° (ex EtOAc – EtOH) (Found: C, 46·7; H, 5·2; N, 10·0. $C_{16}H_{21}IN_3P$ requires C, 46·5; H, 5·1; N, 10·15%); $\tau$ (CDCl$_3$) 2·65 (3H, m), 3·35 (3H, m), 3·6 (3H, m), 6·3 (9H, s), and 7·07 (2H, d, $^2J_{PCH}$ = 13·5 Hz); $\delta^{31}P$ (CHCl$_3$) +17·8 p.p.m.; $\delta^{31}P$ (CF$_3$CO$_2$H) +18·5 p.p.m..

<u>Triphenyl(1-methylpyrrol-2-yl)methylphosphonium Iodide</u> (XXXII). Dimethyl-ammonium chloride (42·5 g, 0·52 mol) in 40% formalin (39·5 g) was added, with constant stirring to 1-methylpyrrole[30] (40·5 g, 0·5 mol), at such a rate that the temperature did not exceed 60°. Stirring was continued for 2 h after the addition was complete, and the mixture was allowed to stand overnight before being poured into sodium hydroxide solution (25% w/v; 100 cm$^3$). The mixture was extracted with ether (3 x 100 cm$^3$), and the combined ether extracts were washed with water (2 x 20 cm$^3$) and dried (Na$_2$SO$_4$). The solvent was evaporated and the residue distilled to give <u>2-(dimethylaminomethyl)-1-methylpyrrole</u> (48 g, 67%), b.p. 55° at 10 mmHg (lit.,[30] 63° at 12 mmHg); $\tau$ (CDCl$_3$) 2·5 (1H, m), 4·0 (2H, m), 6·47 (3H, s), 6·73 (2H, s), and 7·85 (6H, s). This compound, in ether solution when treated with methyl iodide gave <u>trimethyl(1-methylpyrrol-2-yl)methylammonium iodide</u>, m.p. 143° (decomp.) (ex EtOH) (lit.,[30] 143° decomp.); $\tau$ (CDCl$_3$) 3·15 – 3·28 (1H, m), 3·4 – 3·57 (1H, m), 3·75 – 3·9 (1H, m), 5·03 (2H, s), 6·15 (3H, s), and 6·62 (9H, s). The above salt (0·9 g, 0·0032 mol) was added to a solution of triphenylphosphine (1·05 g 0·004 mol) in ethanol. The resulting solution was heated under reflux for 12 h. After cooling the precipitated <u>phosphonium salt</u>, (XXXII), was filtered (1·1 g, 65%), m.p. 204° (ex EtOAc – MeOH) (Found: C, 59·4; H, 4·75; N,2·9. $C_{24}H_{23}INP$ requires C, 59·6;

H, 4•8; N, 2•9%);$\tau$ (CDCl$_3$) 2•05 – 2•7 (15H, m), 3•4 – 3•55 (1H, m), 3•96 – 4•15 (1H, m), 4•25 – 4•45 (1H, m), 4•96 (2H, d, $^2J_{PCH}$ = 12 Hz), and 6•93 (3H, s); $^{31}$P (CHCl$_3$) –17•8 p.p.m.; $\delta^{31}$P (CF$_3$CO$_2$H) –17•0 p.p.m..

### Hydrolysis of Phosphonium Salts.

A. <u>Methyl-2-(1-methylpyrrolyl)diphenylphosphonium Iodide</u> (XXVIII). To a solution of the salt in ethanol (1•5 cm$^3$) was added sodium hydroxide solution (2M, 2 cm$^3$) and the resulting solution heated under reflux for 12 h. The presence of 1-methylpyrrole in the reaction mixture was confirmed by g.l.c. analysis; benzene was not detected. The reaction mixture was evaporated, and the residue extracted with water (5 cm$^3$) and chloroform (2 x 10 cm$^3$). The chloroform extract was dried (MgSO$_4$) and evaporated to give methyldiphenyl-phosphine oxide, (XXX), m.p. 112–113$^\circ$ (ex hexane-benzene) (lit.,$^{31}$ m.p. 111–112$^\circ$); $\tau$ (CDCl$_3$) 2•0 – 2•7 (10H, m), and 8•0 (3H, d, $^2J_{PCH}$ 13•5 Hz).

B. <u>Methyltri-2-(1-methylpyrrolyl)phosphonium Iodide</u> (XXXI). The salt was decomposed as described in (A) above, and the products extracted into chloroform to give <u>methyldi-2-(1-methylpyrrolyl)phosphine oxide</u> (XXXIII), m.p. 124$^\circ$ (ex hex-ane-benzene), (Found: C, 58•8; H, 6•8; N,11•95. C$_{11}$H$_{15}$N$_2$OP requires C, 59•45; H, 6•75; N, 12•6%); (m/e 222, M$^+$); $\tau$ (CDCl$_3$) 3•05 – 3•45 (2H, m), 3•5 – 3•7 (2H, m), 3•75 – 3•95 (2H, m), 6•21 (6H, s), and 8•03 (3H, d, $^2J_{PCH}$ = 14•2 Hz). The presence of 1-methylpyrrole in the reaction mixture was confirmed by g.l.c. analysis.

C. <u>Benzyltri-2-(1-methylpyrrolyl)phosphonium Bromide</u> (XXIX). The salt (0•22 g), in ethanol (1 cm$^3$), was treated with sodium hydroxide solution (2M, 2 cm$^3$) and the resulting solution allowed to stand in a stoppered flask at room temperature for 1 week. The mixture was then centrifuged to separate the precipitated phosphine oxides. The supernatant liquid was then analysed by g.l.c. and shown to contain both toluene and 1-methylpyrrole in a 3 : 2 mole ratio. $^1$H n.m.r. analysis of the precipitated phosphine oxides confirmed that loss of benzyl and 2-(1-methylpyrrolyl) substituents had occurred in the above ratio.

D. _Triphenyl(1-methylpyrrol-2-yl)methylphosphonium Iodide_ (XXXII). The salt
(0·2 g) was dissolved in sodium hydroxide solution (2M, 10 cm$^3$), and the
solution heated under reflux for 24 h. The mixture was then distilled to give
an emulsion, which was extracted with ether (2 x 10 cm$^3$). The ether extract,
after drying over MgSO$_4$, was evaporated to give 1,2-dimethylpyrrole; $\tau$ (CDCl$_3$)
2·4 - 2·6 (1H, m), 3·4 - 3·53 (1H, m), 3·9 - 4·22 (1H, m), 6·53 (3H, s), and
7·83 (3H, s). The residue in the distillation flask was extracted with
chloroform (2 x 10 cm$^3$), and the chloroform extract dried (MgSO$_4$), before
evaporation to yield triphenylphosphine oxide, m.p. 157-158$^\circ$ (ex hexane-
benzene), identical with an authentic specimen.

Kinetic Studies.

The hydrolyses were carried out in aqueous 50% (v/v) ethanol (0·1 M in KCl
in the case of the heteroarylmethyl salt), at initial concentrations of
phosphonium salt and sodium hydroxide of 0·01 M, and were followed by a
conventional back-titration procedure, in which the decrease in sodium hydroxide
was monitored. The solutions were in a thermostatted bath controlled to $\pm$0·1$^\circ$.
The reactions were followed for at least one half-life, and the data were
evaluated by the method of integration. In all cases a plot of $1/\left[\text{OH}\right]^2$ vs time
was linear confirming a third-order rate law.

$^{31}$P N.m.r. Studies of the Reaction between Methyltri-2-(1-methylpyrrolyl)-
phosphonium Iodide and Sodium Ethoxide.

The salt (0·2065 g, 1 mol. equiv.) was dissolved in dry ethanol (2 cm$^3$)
and the $^{31}$P chemical shift recorded. Addition of sodium ethoxide (0·25 cm$^3$,
0·5 mol. equiv.) (from sodium (0·23 g) in dry ethanol 10 cm$^3$) caused no shift
of the $^{31}$P resonance due to the phosphonium ion. Similarly, increases in the
proportion of ethoxide ion had no effect. No other $^{31}$P resonance could be
detected, thus indicating the absence of appreciable amounts of pentacovalent
phosphorane.

## REFERENCES

1. W.E. McEwen, G. Axelrad, H. Zanger, and E.A. VanderWerf, _J. Amer. Chem. Soc._, 1965, _87_, 3948.

2. W.E. McEwen, K.F. Kumli, A. Blade-Font, M. Zanger, and C.A. VanderWerf, _J. Amer. Chem. Soc._, 1964, _86_, 2378.

3. H. Hoffmann, Ann., 1960, _1_, 634.

4. J.R. Corfield and S. Trippett, _Chem. Comm._, 1970, 1267.

5. D.P. Craig, A. Maccoll, R.S. Nyholm, L.E. Orgel, and L.E. Sutton, _J. Chem. Soc._, 1954, 332.

6. G. Aksnes and L.J. Brudvik, _Acta Chem. Scand._, 1963, _17_, 1616.

7. R.U. Pagilagan and W.E. McEwen, _Chem. Comm._, 1966, 652.

8. J.R. Corfield, N.J. De'ath, and S. Trippett, _J. Chem. Soc. (C)_, 1971, 1930.

9. A.W. Smalley, C.E. Sullivan, and W.E. McEwen, _Chem. Comm._, 1967, 5.

10. M.L.H. Green, "Organometallic Compounds", Methuen and Co., London, 1968, vol.2, p.142, and references therein.

11. D.W. Allen, _J.Chem. Soc. (B)_, 1970, 1490.

12. D.W. Allen, B.G. Hutley, and M.T.J. Mellor, _J. Chem. Soc. Perkin II_, 1972, 63.

13. D.W. Allen, S.J. Grayson, I. Harness, B.G. Hutley, and I.W. Mowat, _J. Chem. Soc. Perkin II_, 1973, 1912.

14. D.W. Allen and B.G. Hutley, _J. Chem. Soc. Perkin II_, 1972, 67.

15. G. Marino, _J. Heterocyclic Chem._, 1972, _9_, 817.

16. T.J. Barton, R.W. Roth, and J.G. Verkade, _J. Amer. Chem. Soc._, 1972, _94_, 8854.

17. P. Lindo and G. Marino, _J. Chem. Soc. (B)_, 1968, 392.

18. G. Marino, _Adv. Heterocyclic Chem._, 1971, _13_, 235.

19. S. Clementi and G. Marino, _J. Chem. Soc. Perkin II_, 1972, 71.

20. G.J. Reilly and W.E. McEwen, _Tet. Lett._, 1968, 1231.

21. C.C. Mitsch, L.D. Freedman, and C.G. Moreland, J. Magnetic Resonance, 1970, _3_, 446.

22. C.C. Mitsch, L.D. Freedman, and C.G. Moreland, J. Magnetic Resonance, 1971, 5, 140.

23. J.R. Van Wazer and J.H. Letcher, "$^{31}$P Nuclear Magnetic Resonance," "Topics in Phosphorus Chemistry Series," eds. M. Grayson and E.J. Griffith, Interscience, New York, 1967, vol.5, p.179.

24. D.W. Allen, unpublished results.

25. J.G. Riess, J.R. Van Wazer and J.H. Letcher, J. Phys. Chem., 1967, 71, 1925.

26. S.O. Grim, W. McFarlane, E.F. Davidoff, and T.J. Marks, J. Phys. Chem., 1966, 70, 581.

27. D.W. Allen and J.R. Chorlton, unpublished results.

28. W.E. McEwen, V.L. Kyllingstad, D.N. Schulz, and Younn-Ing Yeg, Phosphorus, 1971, 1, 145.

29. D.A. Shirley, B. Gross and P.A. Roussel, J. Org. Chem., 1955, 20, 225.

30. A. Treibs and A. Deitl, Ann. 1958, 619, 80.

31. A. Michaelis and W. La Coste, Ber., 1885, 18, 2109.

Studies of the Mechanism of the Wittig Reaction.   The Effect of Substituents

at Phosphorus on the Fate of Phosphobetaines in Protic Solvents.

## 2.1 Introduction.

The reaction of an alkylidene phosphorane (I) with a carbonyl compound to

give phosphine oxide and olefin[1], which is now universally known as the Wittig

reaction, was originally discovered by Hans Staudinger in the 1920s and

developed into a useful synthetic method by Georg Wittig in the 1950s.   The

reaction has been applied with outstanding success in many fields e.g. in the

synthesis of carotenoids,  polyenes, and the D Vitamins.   The reaction has

several advantages; it proceeds under very mild conditions, the carbonyl

compound may contain a wide range of functional groups (e.g. halogen, ester,

acetal, ether, hydroxyl) and, in contrast to syntheses involving dehydration

of alcohols, there is no ambiguity in the position of the double bond.

$$R^1{}_3\overset{+}{P} - CHR^2R^3X^- \xrightarrow{\text{Base}} R^1{}_3P = CR^2R^3$$

(I)
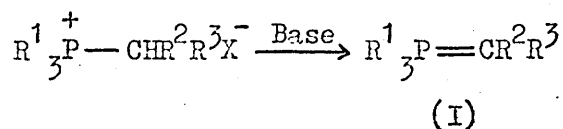
Alkylidenephosphoranes are obtained from alkylphosphonium salts by the

action of a suitable base.   The strength of the base depends on the acidity of

the $\alpha$-hydrogen and varies from aqueous sodium carbonate for some diphosphonium

salts[2] to alkyl-metals in non-polar solvents for unsubstituted alkylphosphonium

salts.   Bases and solvents commonly employed include butyl- and phenyl-lithium

in ether, benzene, or tetrahydrofuran, and sodium or lithium alkoxides in the

corresponding alcohol or in dimethylformamide.   The use of dimethyl sulphoxide

metallated by sodium hydride i.e. $MeSO \cdot CH_2^- Na^+$, with dimethyl sulphoxide as

the solvent has also been described[3], and high yields of olefins are claimed.

The mechanism of the Wittig reaction[1,4,5] is thought to be a two stage

process involving the collapse of an intermediate betaine (II), (Scheme I).

$$R^1_3P = CR^2R^3$$

$$\updownarrow$$

$$R^1_3\overset{+}{P}\!\!-\!\!\overset{-}{C}R^2R^3 \quad \underset{}{\overset{R^4COR^5}{\rightleftharpoons}} \quad R^1_3\overset{+}{P}\!\!-\!\!CR^2R^3 \quad \rightleftharpoons \quad R^1_3P\!\!-\!\!CR^2R^3$$

$$\text{(I)} \qquad\qquad \underset{\overset{|}{\overline{O}-\!CR^4R^5}}{} \qquad\qquad \underset{\overset{|}{O-\!CR^4R^5}}{} \quad \text{(III)}$$

$$\text{(II)}$$

$$R^1_3PO \;+\; \overset{R^2}{\underset{R^3}{}}C = C\overset{R^4}{\underset{R^5}{}}$$
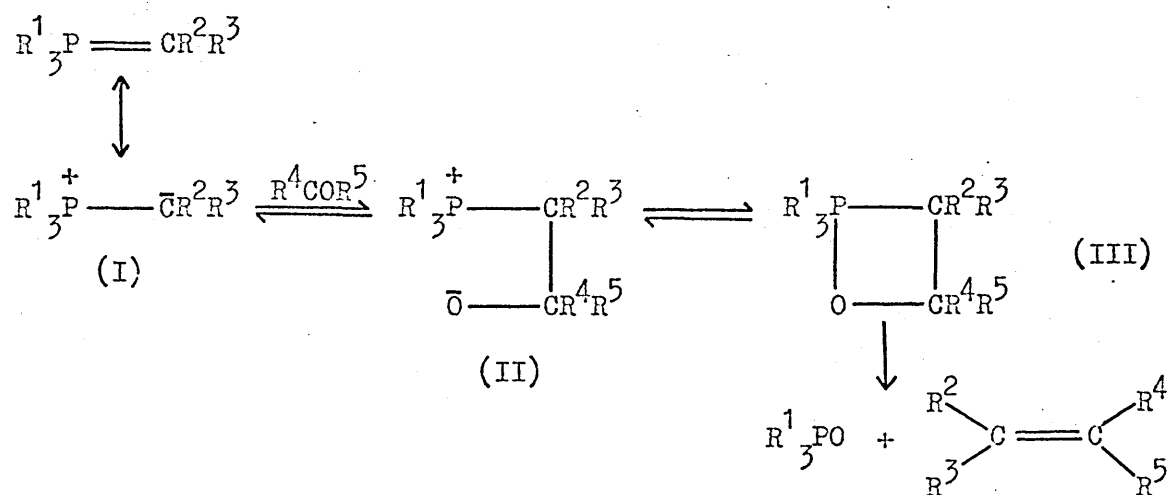
### Scheme I

The rate-determining step may be either the formation or decomposition of the
betaine. If it is assumed that betaine formation involves nucleophilic attack
by the $\alpha$-carbon of the phosphorane (I) on the carbonyl group, the rate will
depend upon the nucleophilicity of the $\alpha$-carbon, and on the susceptibility of
the carbonyl group to nucleophilic attack. Substituents at phosphorus which
decrease the positive character of that atom will increase the reactivity of
the phosphorane (I) by stabilising the contributing dipolar form, while
delocalisation of the negative charge on the $\alpha$-carbon (e.g. by substituents
$R^2$ and $R^3$ having electron-withdrawing properties) will considerably reduce the
reactivity. Thus while fluorenylidenetriphenylphosphorane (IV; R = Ph), in
which the negative charge is delocalised throughout the fluorene nucleus, reacts
with neither aldehydes or ketones, the trialkylphosphoranes (IV; R = Me, Bu)
react with aldehydes and with the more reactive ketones e.g. 4-nitroaceto-
phenone[6].
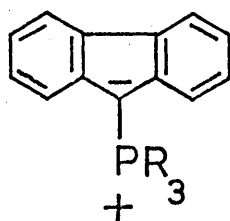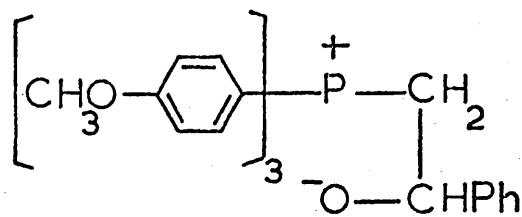


$$\text{(IV)} \qquad\qquad\qquad\qquad \text{(V)}$$

Decomposition of the betaine (II) to phosphine oxide and olefin will be retarded by electron-donating substituents $R^1$ which decrease the positive character and hence the oxygen affinity of the phosphorus, and the involvement of the betaine intermediate in the reaction is supported by the isolation of a number of betaines, e.g. (V), from the reaction between methylenetri-(p-anisyl)-phosphorane[7] and benzaldehyde in ether solvent; the electron-donating p-methoxy groups so reduce the positive charge on the phosphorus that nucleophilic attack by oxygen is prevented. Substituents $R^2 - R^5$ which can conjugate with the forming double bond in the transition state will accelerate the decomposition of the betaine (II).
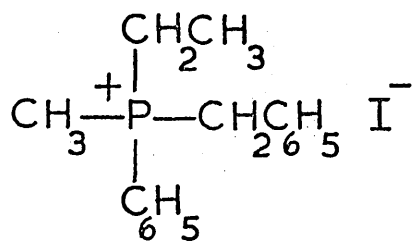


(VI)
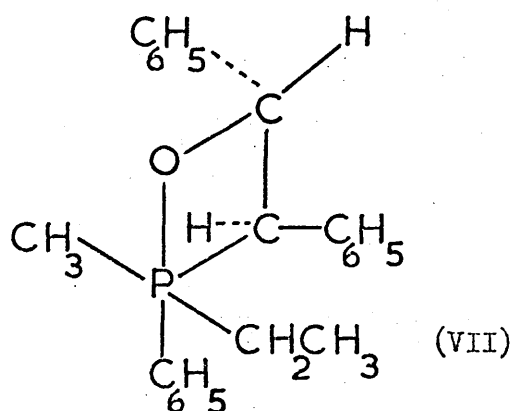


(VII)
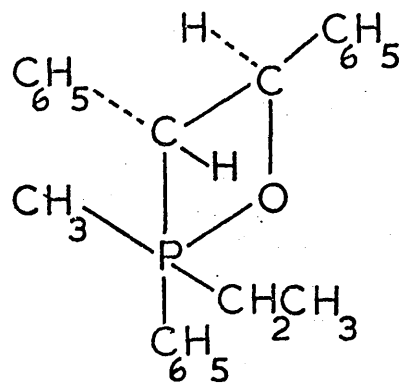


(VIII)
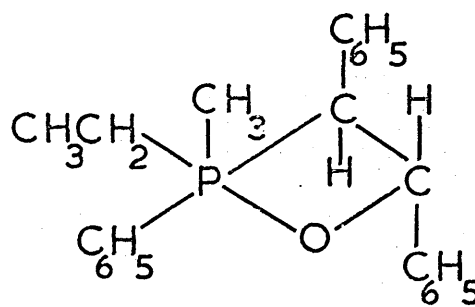


(IX)
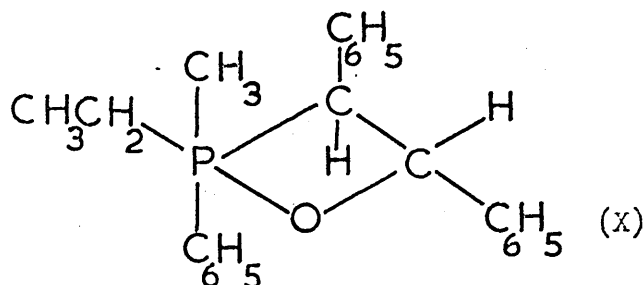


(X)

That the Wittig reaction involves complete retention of configuration at phosphorus was demonstrated by McEwen et al[8], who from the reaction between benzaldehyde and the phosphorane derived from (+)-benzylethylmethylphenyl-phosphonium iodide (VI) by the action of phenyl-lithium in ether, obtained

stilbene (predominantly as the trans isomer) and optically pure (+)-ethylmethyl-phenylphosphine oxide. In order to explain the observed retention of configuration at phosphorus during the Wittig reaction, McEwen suggested that there are four conceivable types of intermediate (VII), (VIII), (IX) and (X). It was proposed that in any of the intermediates of type (VII), (VIII) and (IX), there is no new type of angular strain about any of the bonds. The internal angles of the 4-membered rings are $90^{\circ}$ in (VII) and (VIII), and the bond angles between phosphorus and the atoms which occupy the basal positions of the trigonal bipyramid are $120^{\circ}$; whilst in (IX) the bond angles between the phosphorus and the atoms which occupy the basal positions of the square pyramid are the normal $90^{\circ}$. In a structure of type (X), however, there is much angular strain. The internal angles of the 4-membered ring cannot be $90^{\circ}$ if the bond angles between phosphorus and the atoms occupying the basal positions of the trigonal bipyramid are the normal $120^{\circ}$, and vice versa, thus it is unlikely that an intermediate of type (X) would be formed. On the basis of the arguments of Haake and Westheimer[9], intermediates (VII), (VIII) and (IX) would collapse to give products with retention of configuration at phosphorus, while the intermediate (X) would collapse to give the products of the Wittig reaction, but with inversion of configuration at the phosphorus atom. Therefore, since angular strain inhibits the formation of (X) the only intermediates which can be readily formed are those which lead to retention of configuration at phosphorus in the formation of ethylmethylphenylphosphine oxide.

Trippett et al[10] noted that while benzyltriphenylphosphonium halides give high yields of stilbenes in Wittig olefin syntheses with aromatic aldehydes in alcoholic alkoxide, methyltriphenylphosphonium halides which do not undergo alcoholysis[11], give only poor yields of olefins under the same conditions. It was therefore suggested that reactions which are not alcoholysis must be competing with the olefin synthesis from methylphosphonium salts. Thus in an investigation of the products of the reaction between benzaldehyde and

methyltriphenylphosphonium halides in ethanolic sodium ethoxide, Trippett et al showed that in addition to the normal Wittig products (11%), the rearrangement product 1,2-diphenylethyldiphenylphosphine oxide (XI; $R^1$ = Ph) is also formed (68%). The mechanism suggested by Trippett for the formation of (XI; $R^1$ = Ph) involved the simultaneous migration of a phenyl group from phosphorus to the $\alpha$-carbon, and of hydrogen (as hydride ion) from the $\alpha$-to the $\beta$-position in the intermediate betaine (XII; $R^1$ = Ph), (Scheme II).

$$Ph_3\overset{+}{P}CH_3 \underset{\overline{O}Et}{\rightleftharpoons} Ph_3\overset{+}{P}\!\!-\!\!\overline{C}H_2 \underset{R^1CHO}{\rightleftharpoons} \begin{array}{c} Ph \\ | \\ Ph_2\overset{+}{P}\!\!-\!\!CH\!\!-\!\!H \\ | \quad | \\ \overline{O}\!\!-\!\!CH\!\!-\!\!R^1 \end{array} \longleftarrow Ph_3P + CH_2\!\!-\!\!CHR^1 \text{(epoxide, O)}$$

$$(XII)$$

$$\downarrow$$

$$Ph_2P(O)CHPh\cdot CH_2R^1$$

$$(XI)$$

Scheme II

In addition to the above, the related reaction between triphenylphosphine and styrene oxide (in which the betaine (XII; $R^1$ = Ph) is the expected intermediate) in refluxing ethanolic solution, also gives the rearranged oxide (XI; $R^1$ = Ph) in high yield. The migratory aptitudes of substituted phenyl groups in the above rearrangement were investigated using both the reaction of the phosphonium salts $MePh_2\overset{+}{P}C_6H_4X$ $I^-$ with benzaldehyde in ethanolic sodium ethoxide, and the reaction of the phosphines $Ph_2PC_6H_4X$ with styrene oxide in refluxing ethanol. In all reactions, the order of migration m-chlorophenyl$>$ phenyl$>$ p-anisyl is observed, and thus the group which migrates is most stable as the carbanion.

Reactions involving aryl migration from phosphorus to the $\alpha$-carbon of an aliphatic chain have also been observed by other workers. Tebby et al[12,13] showed that 1,2-diphenylethyldiphenylphosphine oxide (XI; $R^1$ = Ph) may be

obtained from triphenylphosphine and phenylacetylene in the presence of water, the reaction involving triphenyl-$\beta$-styrylphosphonium hydroxide (XIII; $R^1$ = Ph) as the intermediate. Similarly, Brophy et al[14] obtained the same oxide (XI; $R^1$ = Ph) from the action of dilute alkali on triphenyl-$\beta$-styrylphosphonium bromide (XIV; $R^1$ = Ph), this reaction also proceeding via triphenyl-$\beta$-styryl-phosphonium hydroxide (XIII; $R^1$ = Ph). Zbiral et al[15] reported phenyl migrations arising from the alkaline hydrolysis of some $\beta$-acylvinylphosphonium salts (XIV; $R^1$ = COPh, COalkyl) and related oximino compounds[16]; a reaction pathway which again involved the corresponding vinylphosphonium hydroxides was suggested. In view of these results Tebby et al[17,18] proposed that the reaction between triphenylphosphine and styrene oxide may also pass through a vinylphosphonium hydroxide intermediate, and the following Scheme III was suggested.

$$Ph_3P + CH_2\overset{O}{\triangle}CHR^1 \qquad Ph_3P + HC\equiv CR^1 \xrightarrow{H_2O} \qquad \overset{+}{Ph_3}PCH=CHR^1\ Br^- \ (XIV) \downarrow Ag_2O\ or\ dil.\ NaOH$$

$$\overset{+}{Ph_3}PCH_2\overset{O^-}{\underset{}{C}}CHR^1 \underset{}{\overset{R^2OH}{\rightleftharpoons}} \overset{+}{Ph_3}PCH\overset{OH}{\underset{R^2O^-\ H}{C}}CHR^1 \underset{}{\overset{-R^2OH}{\rightleftharpoons}} \overset{+}{Ph_3}PCH=CHR^1\ OH^-$$

(XII) (XV) (XIII)

$$\uparrow R^2ONa$$

$$Ph_3P=CH_2 + R^1CHO \qquad \overset{+}{Ph_3}PCH_2\overset{OH}{\underset{Br^-}{C}}CHR^1 \qquad Ph_2\overset{O}{\underset{}{P}}CHPh\underset{}{CH_2R^1}$$

(XVI) (XI)

Scheme III

Thus the 2-hydroxyethylphosphonium salt (XV) is formed on protonation of the original betaine (XII; $R^1$ = Ph) in preference to the formation of the oxaphosphetan (cf Scheme I). The reaction then proceeds with the formation of the vinylphosphonium hydroxide (XIII) and hence the rearrangement oxide.

Evidence that the 2-hydroxyalkylphosphonium salt (XV; $R^1$ = Ph) is an intermediate in the rearrangement reactions reported by Trippett[10] was obtained

by Tebby from the action of base on the 2-hydroxyalkylphosphonium bromide
(XVI; $R^1$ = Ph). Thus treatment of (XVI; $R^1$ = Ph) with dilute aqueous alkali
or ethanolic sodium ethoxide at $0^o$ gives the phosphine oxide (XI; $R^1$ = Ph) in
yields of 60% and 30% respectively. Wittig[1] had previously detected benzal-
dehyde on warming the salt (XVI; $R^1$ = Ph) with aqueous sodium hydroxide.
Furthermore the intervention of the vinylphosphonium hydroxide (XIII; $R^1$ = Ph)
which should undergo oxygen exchange with water was indicated by the isolation
of the phosphine oxide (XI; $R^1$ = Ph) incorporating labelled oxygen, from the
reaction between triphenylphosphine and styrene oxide in the presence of $H_2O^{18}$;
the reaction between triphenylphosphine and styrene oxide is little affected
by the presence or rigorous exclusion of water.
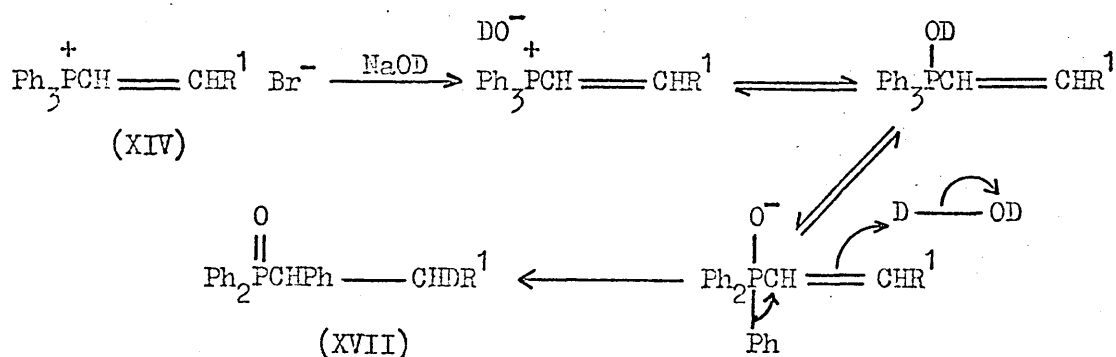


Scheme IV

The intermediate undergoing rearrangement was identified by deuteriation studies.
Thus the hydrolysis of the vinylphosphonium bromides (XIV; $R^1$ = Ph or $CO_2Me$) by
sodium deuterioxide gave mono-$\beta$-deuteriated phosphine oxides (XVII; $R^1$ = Ph or
$CO_2Me$). Mass spectral analysis of compound (XVII; $R^1$ = $CO_2Me$) showed it to be
96% monodeuteriated, in accordance with the rearrangement of a vinylphosphorus
compound (Scheme IV).

Hydrolyses of phosphonium salts are usually second-order with respect to
hydroxide ion, a fact interpreted in terms of a base-catalysed decomposition
of an intermediate, containing quinquecovalent phosphorus. That the

rearrangement reaction is base catalysed is indicated by the observation of the inhibition of the reaction by salts which have a buffering effect. Thus the presence of sodium acetate in the hydrolysis of the bromides (XIV; $R^1$ = Ph or $CO_2Me$) and in the reaction of triphenylphosphine with styrene oxide drastically reduce the yields of the rearranged phosphine oxides.

Support for the vinylphosphonium salt intermediate was given by Schweizer et al[19] who proposed an alternative mechanism (Scheme V) to that of Wittig and Schollkopf[1] (Scheme I) for reactions between phosphoranes and carbonyl reagents in alcoholic (protic) media which lead to the 'normal' Wittig products. It was suggested that in such solvents the intermediate betaine (II) is protonated (thereby preventing formation of the cyclic oxaphosphetan ) to give the $\beta$-hydroxyethylphosphonium salt (XV). The latter eliminates water to form the vinylphosphonium salt (XIII) which then undergoes alkaline hydrolysis on reaction with hydroxide ion (derived from the water eliminated in the previous step) to form with loss of the vinyl group, the 'normal' Wittig products.
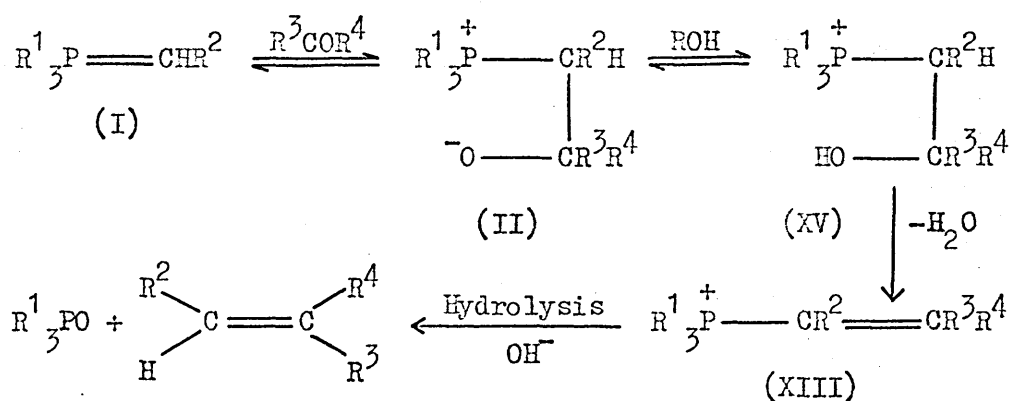
Scheme V

The sine qua non of this reaction pathway is the presence in the system of protic solvents which may protonate the intermediate betaine (II). There must also be a proton $\alpha$- to the phosphonium moiety in the betaine (II), and one of the substituents $R^2$ - $R^4$ must be capable of conjugation with the incipient double bond, in order to produce the vinylphosphonium salt (XIII) by

loss of water. It was noted that the mechanism did not extend to compounds of formula (I) where $R^2$ is H i.e. methylenephosphoranes and also to compounds which form $\alpha$-, and $\beta$-substituted vinylphosphonium salts in which the substituents $R^2$, $R^3$, and $R^4$ do not conjugate with the double bond, since previous evidence[20,21] has shown that the alkaline hydrolysis of such compounds will give $\alpha$-, and $\beta$-alkyl substituted phosphine oxides.

The Schweizer mechanism[19] (Scheme V) differs slightly from that proposed by Tebby[17,18] (Scheme III) in that the dehydration of the 2-hydroxyalkyl-phosphonium salt intermediate (XV) is irreversible. It was considered that under anhydrous conditions the possibility of the vinylphosphonium salt recombining with water to reform the 2-hydroxyalkylphosphonium salt is extremely unlikely and so this step is essentially irreversible.



(XVIII)                    (XIX)
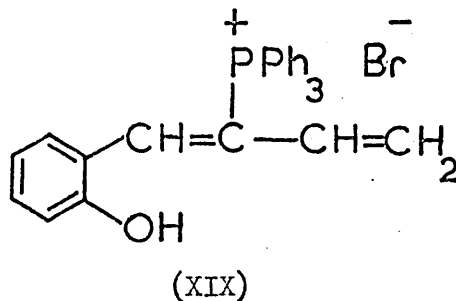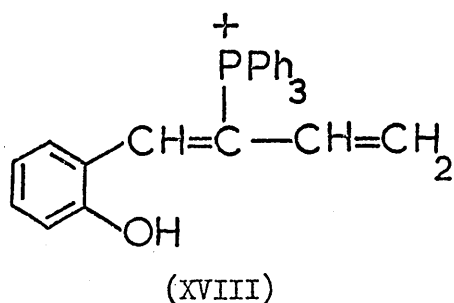
In support of the mechanism Schweizer[19] suggested that under the conditions used in most normal Wittig reactions in alcoholic solvents, the vinylphosphonium intermediates could never be isolated because of the presence of hydroxide ion which would immediately cause hydrolysis to give the olefin. However, a number of vinylphosphonium salts have been isolated under certain conditions. For example, in the reaction of salicylaldehyde with allyltriphenylphosphonium bromide in ethanol[22], the phenolic group in the intermediate (XVIII) consumes the base ($OH^-$) which would normally attack the triphenylphosphonium moiety, thus allowing the isolation of the salt (XIX) after acidification. The isolation of several other vinylphosphonium salts[23,24] were also given as supporting evidence.

The intermediacy of a vinylphosphonium salt has also been suggested by

Rakshys and McKinley[25] in order to account for a number of unexpected products in the reaction of 2-hydroxyalkyltriphenylphosphonium salts with base in protic solvents.

Trippett[26] suggested that since the mechanism proposed by Schweizer[19] involved alkaline hydrolysis of a vinylphosphonium salt intermediate to give the observed olefins and phosphine oxides, such olefin syntheses should proceed with inversion of configuration at phosphorus. Thus in an investigation of the generality of the Schweizer mechanism, Trippett et al[26] studied the steric course of the Wittig reaction between optically active (+)-benzylethylmethyl-phenylphosphonium iodide (VI) and benzaldehyde in ethanolic sodium ethoxide solution. It was shown that the reaction occurs with retention of configuration at phosphorus to give (+)-ethylmethylphenylphosphine oxide and stilbene. The result is consistent with the collapse of the cyclic oxaphosphetan, and not with the involvement of a vinylphosphonium salt intermediate, since the enantiomeric phosphine oxide is obtained from (VI) on alkaline hydrolysis. Trippett suggested that routes via oxaphosphetans and vinylphosphonium salts are competitive, the preferred course depending on the nature of the substituents on the carbon $\alpha$- to phosphorus.



(XX)

(XXI)

(XXII)

(XXIII)

(XXIV)
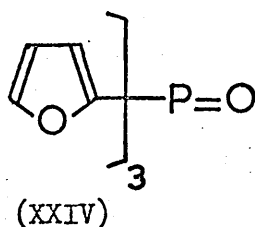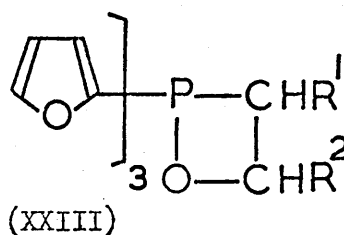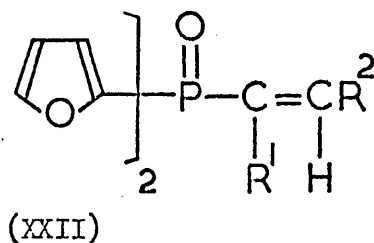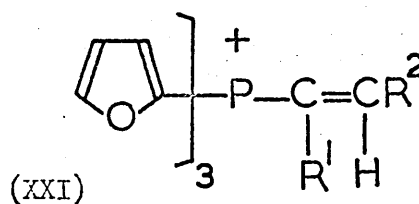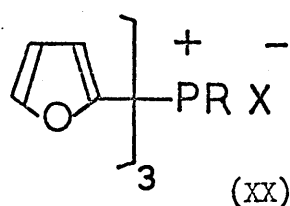
In a study of the influence of electron-withdrawing heterocyclic substituents at phosphorus on the preferred course of the Wittig reaction in protic solvents, Allen et al[27] investigated the reactions of a series of phosphonium salts bearing heteroaryl substituents, with benzaldehyde in alcoholic-alkoxide media. It was considered that if the alternative mechanism of Schweizer[19] is generally operative, then the Wittig reaction between benzyltri-(2-furyl)-phosphonium bromide (XX; $R^1 = C_6H_5CH_2$, X = Br) and benzaldehyde in anhydrous methanol containing sodium methoxide should lead to the vinylphosphonium salt (XXI; $R^1 = R^2 = C_6H_5$). Therefore on the basis of the established order of cleavage of heteroaryl, and benzyl groups from phosphorus[28], i.e. 2-furyl $>$ 2-thienyl $>$ benzyl $>$ phenyl, it was considered that the salt (XXI; $R^1 = R^2 = C_6H_5$) should undergo hydrolysis with loss of furan to give (XXII; $R^1 = R^2 = C_6H_5$). Alternatively if the mechanism predominantly involved intramolecular collapse of the oxaphosphetan (XXIII; $R^1 = R^2 = C_6H_5$) the reaction would give tri-(2-furyl)phosphine oxide (XXIV) and stilbene. Since the above reaction led to the formation of trans-stilbene and tri-(2-furyl)phosphine oxide (XXIV) with no other phosphine oxides being detected, and similar results were obtained for the corresponding reaction of the ethylphosphonium salt (XX; $R^1 = C_2H_5$, X = Br), it was suggested that a vinylphosphonium salt intermediate did not appear to be involved, the reactions following the normal Wittig course involving the collapse of the oxaphosphetan intermediate.



(XXV)

(XXVI)

(XXVII)

(XXVIII)
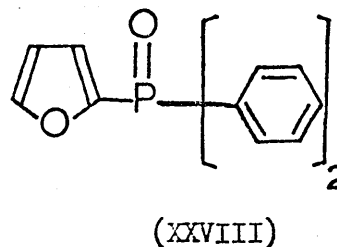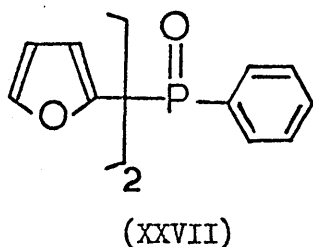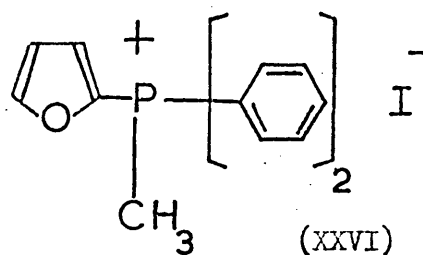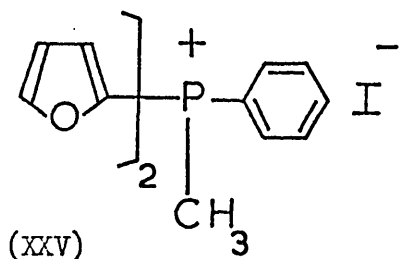
Allen et al[27] also studied the reactions of a series of methylphosphonium

salts bearing 2-furyl substituents (XX; R = $CH_3$, X = I), (XXV) and (XXVI) with

benzaldehyde in ethanolic sodium ethoxide solution. It was suggested that

should a vinylphosphonium salt intermediate be involved in these reactions, it

would be expected that migration of the 2-furyl group from phosphorus to carbon

would occur, since in the pinacol-pinacolone rearrangement[29] (where the

electronic situation is similar in that the migrating group is effectively

carbanionic), it has been shown that a 2-furyl group migrates in preference to

a phenyl group.

It was observed, however, that in marked contrast to the reaction of

methyltriphenylphosphonium iodide with benzaldehyde in ethanolic sodium ethoxide,

which occurs to give predominantly the rearrangement product 1,2-diphenylethyl-

diphenylphosphine oxide (XI; $R^1$ = Ph) the corresponding reaction of tri-(2-furyl)-

methylphosphonium iodide (XX; $R^1$ = $CH_3$, X = I) gives the normal Wittig products,

styrene and tri-(2-furyl)phosphine oxide (XXIV). The rearrangement product was

not detected. Similarly in the reactions of di-(2-furyl)methylphenylphosphonium

iodide (XXV) and (2-furyl)methyldiphenylphosphonium iodide (XXVI) with

benzaldehyde under the same conditions, the normal Wittig products di-(2-furyl)-

phenylphosphine oxide (XXVII), and (2-furyl)diphenylphosphine oxide (XXVIII),

together with styrene, were isolated.

On the basis of these results Allen et al[27] supported the suggestion made

by Trippett[26] that routes via the oxaphosphetans and vinylphosphonium salts

are competitive. The course taken, however, depends not only on the nature of

the substituents on the carbon $\alpha$- to phosphorus, but also on the nature of

the substituents at phosphorus.

2.2 The Steric and Electronic Effects of 2-(1-Methylpyrrolyl) Substituents at

Phosphorus on the Course of the Wittig Reaction in Protic Solvents.

A possible explanation for the lack of involvement of a vinylphosphonium

salt intermediate in the Wittig reaction of phosphonium salts bearing 2-furyl

substituents is that since the 2-furyl group exerts a marked electron-withdrawing

effect, rapid intramolecular nucleophilic attack at phosphorus (resulting in

the formation of the oxaphosphetan) will take place. Thus the route via the

oxaphosphetan will be favoured, rather than the alternative route involving

protonation of the betaine to the hydroxyethylphosphonium salt, followed by

dehydration to form the vinylphosphonium salt. It was of interest therefore,

in view of the apparent difference in the electronic properties of the

2-(1-methylpyrrolyl) and 2-furyl substituents, to extend the above study to

phosphonium salts bearing 2-(1-methylpyrrolyl) substituents.



(XXIX)   (XXX)

(XXXI)   (XXXII)
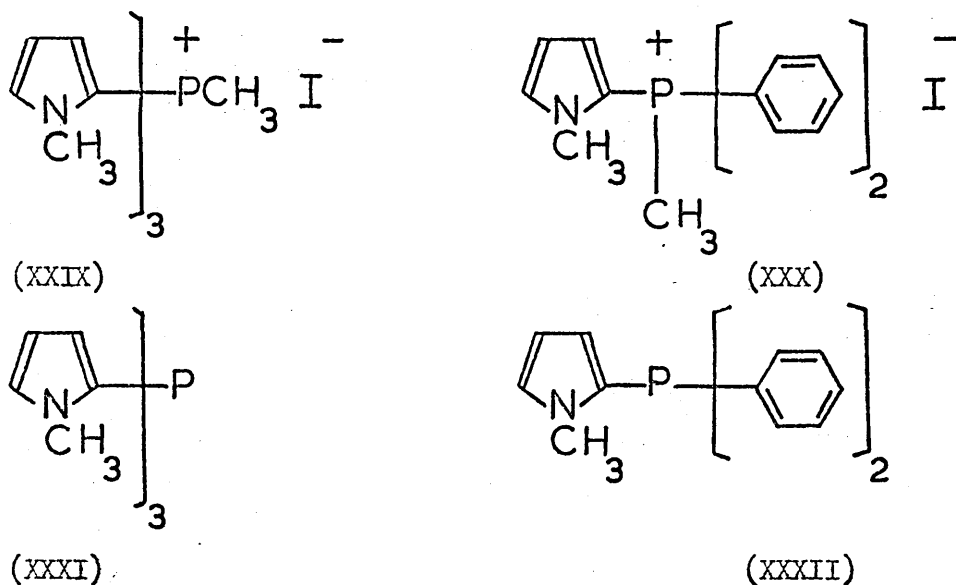
Thus the reactions of methyltri-2-(1-methylpyrrolyl)phosphonium iodide

(XXIX) and methyl-2-(1-methylpyrrolyl)diphenylphosphonium iodide (XXX) with

benzaldehyde in alcoholic-alkoxide media have been studied, together with the

reactions of tri-2-(1-methylpyrrolyl)phosphine (XXXI) and 2-(1-methylpyrrolyl)-

diphenylphosphine (XXXII) with styrene oxide in refluxing ethanol.

It was considered that since the 2-(1-methylpyrrolyl) group is much less

electron-withdrawing than the 2-furyl group, rapid intramolecular nucleophilic

attack at phosphorus is unlikely, and therefore the route via the oxaphosphetan

would be less favoured than in analogous reactions involving 2-furylphosphonium

salts. Thus if the Schweizer mechanism[19] is generally operative, protonation of the betaine followed by dehydration to the vinylphosphonium salt may occur, and on the basis of the reactions reported by Trippett[10] migration from phosphorus to α-carbon might be expected.
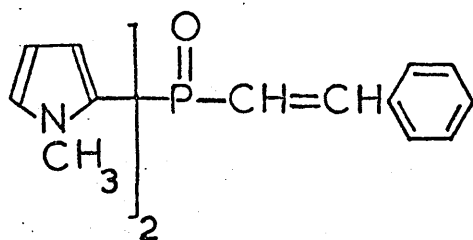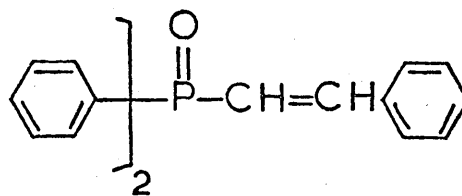
(XXXIII)                    (XXXIV)

In marked contrast to the reactions reported by Trippett[10] which give predominantly the rearrangement product, and also the corresponding reactions of methylphosphonium salts bearing 2-furyl substituents[27] which lead to 'normal' Wittig products, the reactions between methyltri-2-(1-methylpyrrolyl)-phosphonium iodide (XXIX) and methyl-2-(1-methylpyrrolyl)diphenylphosphonium iodide (XXX) and benzaldehyde in ethanolic sodium ethoxide take place with loss of 1-methylpyrrole to give di-2-(1-methylpyrrolyl)-β-styrylphosphine oxide (XXXIII) (70%) and diphenyl-β-styrylphosphine oxide (XXXIV) (53%) respectively, in addition to small amounts of the 'normal' Wittig products. Similarly, diphenyl-β-styrylphosphine oxide (XXXIV) was also obtained from the reaction between 2-(1-methylpyrrolyl)diphenylphosphine (XXXII) and styrene oxide.

The isolation of a β-styrylphosphine oxide product from the reaction clearly indicates the formation of a vinylphosphonium salt intermediate, which is subsequently hydrolysed with loss of 1-methylpyrrole to give the corresponding vinylphosphine oxide. Since decomposition of the salt to 'normal' Wittig products would not be expected on the grounds of carbanion relative stabilities, the above results are unusual in view of the rearrangement reactions reported by Trippett[10], in that migration of the 2-(1-methylpyrrolyl) group from phosphorus to the α-carbon did not take place.
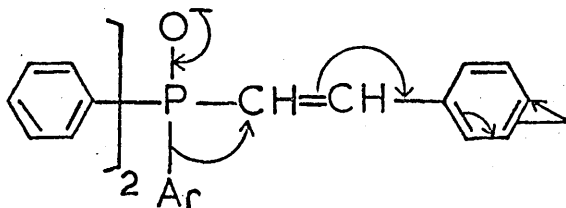
Mechanism A

Brophy et al[14] suggested that for transfer of the departing carbanion from phosphorus to the adjacent carbon during the alkaline hydrolysis of phosphonium salts, the carbon atom should carry an appropriate electron sink (i.e. a good leaving group or electron-delocalising substituent). Since the phenyl group in the styryl salt is capable of delocalisation of the displaced electron pair (Mechanism A) it would appear that factors other than the electronic character of the substituents are important in deciding the course of the above reactions. It is thus of interest to consider the observations made by other workers on related systems.
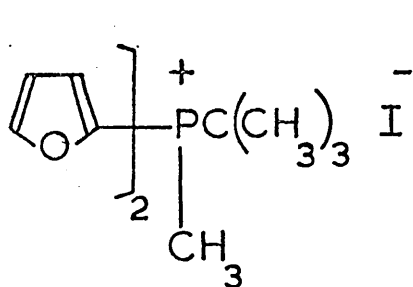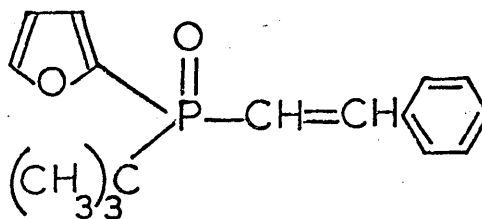
(XXXV)                                   (XXXVI)

From the reaction between t-butyldi-(2-furyl)methylphosphonium iodide (XXXV) and benzaldehyde in ethanolic sodium ethoxide, Allen et al[30] isolated t-butyl-2-(furyl)-$\beta$-styrylphosphine oxide (XXXVI) as the major product. Thus it would appear that in a reaction similar to the above, a vinylphosphonium salt is formed and is subsequently hydrolysed with loss of furan to give the $\beta$-styrylphosphine oxide (XXXVI). Since previous results involving 2-furyl-phosphonium salts indicate a reaction via the 'normal' Wittig route, this result is important since substitution of a t-butyl for a phenyl, or 2-furyl group appears to alter the mechanism for the reaction between benzaldehyde and phosphoranes derived from 2-furylphosphonium salts in protic media. The change

in mechanism can be the result of two possible effects, (i) electron-donation by the t-butyl group which will reduce the positive nature of the phosphorus atom, thus making rapid intramolecular nucleophilic attack (to form the oxaphosphetan) less favoured or alternatively, (ii) steric hindrance by the t-butyl group, which again will reduce the possibility of rapid oxaphosphetan formation. On the basis of the results reported by Trippett[31] for the alkaline hydrolysis of t-butylphosphonium salts it is likely that of the two possible effects, steric hindrance will be the more important. It is possible therefore, that in the alkaline hydrolysis of the vinylphosphonium salt intermediate a steric effect by the t-butyl group will prevent migration of the 2-furyl group to the $\alpha$-carbon, thus resulting in the loss of furan to give the $\beta$-styryl-phosphine oxide. It would therefore seem reasonable to propose that a similar steric effect is exerted by the 1-methyl group of the 2-(1-methylpyrrolyl) substituents, which also serves to prevent heteroaryl migration.



(XXXVII)

(XXXVIII)

(XXXIV)

(XXXIX)

(XL)

(XLI)
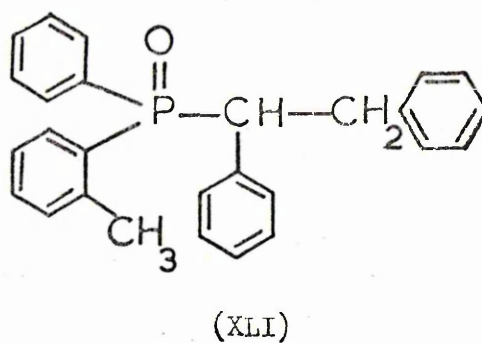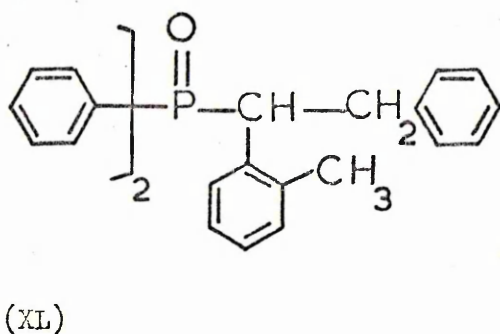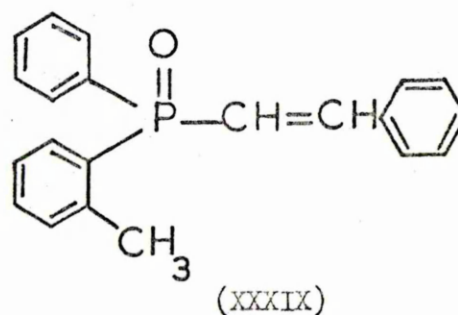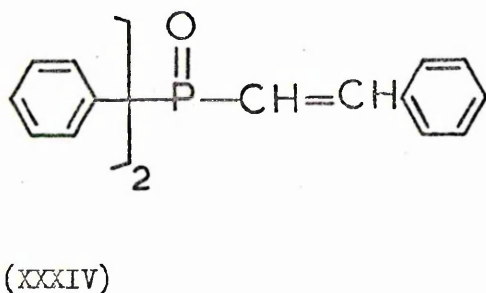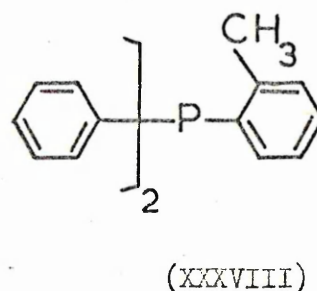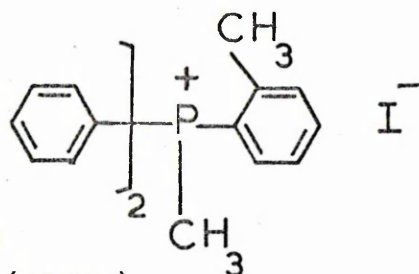
In order to further investigate steric effects in the Wittig reactions of phosphonium salts, the reactions between o-tolylphosphonium salts and benzaldehyde in alcoholic-alkoxide media have been studied[32]. Thus the reaction between methyldiphenyl-(o-tolyl)phosphonium iodide (XXXVII) and benzaldehyde in ethanolic sodium ethoxide gives a mixture from which diphenyl-β-styryl-phosphine oxide (XXXIV) and phenyl-(o-tolyl)-β-styrylphosphine oxide (XXXIX) were isolated, together with the rearrangement products 1-(o-tolyl)-2-phenyl-ethyldiphenylphosphine oxide (XL) and 1,2-diphenylethylphenyl-(o-tolyl)phosphine oxide (XLI). The same products were isolated from the reaction between diphenyl-(o-tolyl)phosphine (XXXVIII) and styrene oxide in ethanol.

In the reaction between phenyldi-(o-tolyl)phosphine (XLII) and styrene oxide[32], a mixture of phenyl-(o-tolyl)-β-styrylphosphine oxide (XXXIX) together with the rearrangement products 1-(o-tolyl)-2-phenylethylphenyl-(o-tolyl)phosphine oxide (XLIII) and 1,2-diphenylethyldi-(o-tolyl)phosphine oxide (XLIV) is formed.
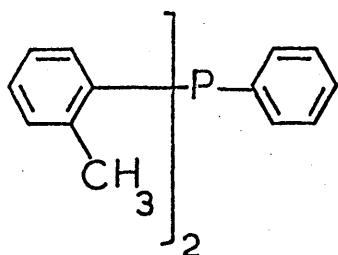


(XLII)
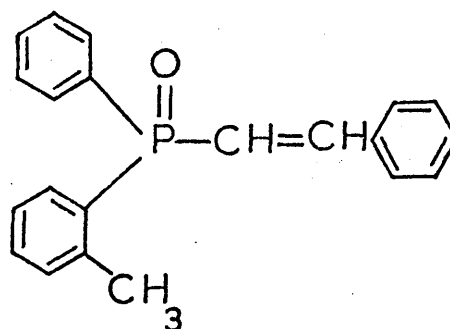


(XXXIX)
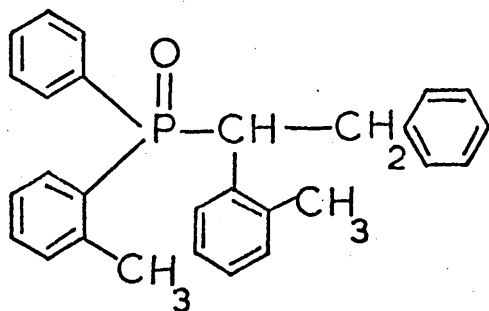


(XLIII)
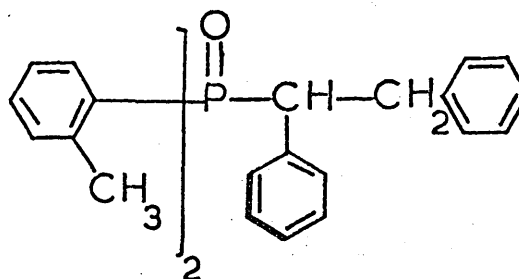


(XLIV)

These results are also important since they confirm the involvement of a vinylphosphonium salt in reactions between benzaldehyde and phosphoranes, and also between triarylphosphines and styrene oxide, which lead to rearrangement products. They are also of interest since in addition to the loss of the leaving group in the alkaline hydrolysis of the phosphonium salt, some migration from phosphorus to $\alpha$-carbon has taken place. Thus it would appear that although there is a steric effect exerted by the o-tolyl group, the effect is not sufficient to demand exclusive loss of the departing carbanion, as appears to be the case for 1-methylpyrrolyl- and t-butylphosphonium salts.

The migration or loss of both phenyl and o-tolyl groups is probably explained by the similarity in the stability of the corresponding carbanions. In addition, the o-tolyl group may be lost since a greater relief from steric crowding will be obtained on the collapse of the pentacovalent intermediate. In view of the results obtained, it is not at all clear why o-tolyl systems migrate to some extent whereas 1-methylpyrrolyl systems do not. It could be argued that the exclusive loss of the 2-(1-methylpyrrolyl) carbanion may be due to its greater stability compared to the phenyl and o-tolyl carbanions. On the basis of the results reported by Allen et al[33] the extent of carbanion formation, in the transition state of the hydrolysis reaction of phosphonium salts, would appear to be the same regardless of stability. It is possible, however, that carbanions of moderate stability such as phenyl may require the additional stability of the negative charge afforded in the transition state of the rearrangement, whereas for carbanions of greater stability, such as 2-heteroaryl carbanions, simple cleavage of the leaving group can occur.
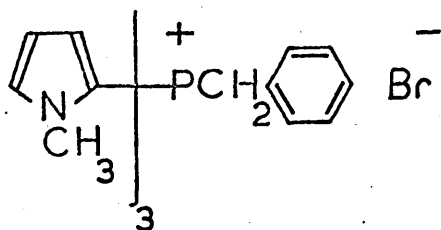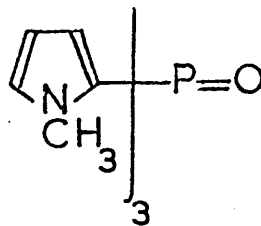


(XLV)                    (XLVI)

In view of these observations it is of interest to consider the reaction

of benzyltri-2-(1-methylpyrrolyl)phosphonium bromide (XLV) and benzaldehyde in

ethanolic sodium ethoxide, which proceeds with formation of the 'normal' Wittig

products of trans-stilbene and tri-2-(1-methylpyrrolyl)phosphine oxide (XLVI).

On the available evidence, it is not certain whether this reaction proceeds

via the 'normal' Wittig route involving the oxaphosphetan, or by the alternative

mechanism involving the hydrolysis of the vinylphosphonium salt. On the basis

of the results obtained from the reactions of the methylphosphonium salts

bearing 2-(1-methylpyrrolyl) substituents, however, it would seem likely that

the Schweizer mechanism[19] would be favoured.
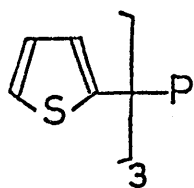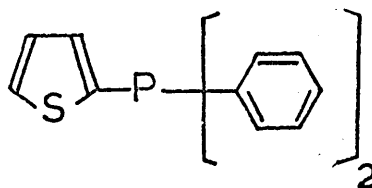


(XLVII)               (XLVIII)

In conclusion, the reactions between tri-(2-thienyl)phosphine (XLVII) and

diphenyl-(2-thienyl)phosphine (XLVIII) with styrene oxide have been shown to

proceed with the formation of 'normal' Wittig products. As for the 2-furyl-

phosphonium salts[27], it would seem that the involvement of a vinylphosphonium

salt is also unlikely in these reactions. Thus it would appear that following

the formation of a phosphobetaine, the routes via the oxaphosphetan and the

vinylphosphonium salt are competitive. The course taken may depend upon the

substituents attached to the carbon chain, but more important is the nature of

the substituents at phosphorus. In cases where rapid intramolecular attack at

phosphorus is favoured by the presence of strongly electron-withdrawing

substituents, the reactions proceed via the oxaphosphetan. However, where

rapid nucleophilic attack at phosphorus does not take place, due to the presence

at phosphorus of less electronegative or bulky substituents, the alternative

route via the vinylphosphonium salt appears to be favoured.

G.l.c. analyses were carried out using a Pye series 104 chromatograph, equipped with a 5 ft column of Apiezon L on Celite, and a flame ionisation detector.

T.l.c. separations were carried out on a preparative scale using a 0·5 mm thickness of Kieselgel HF 256 as adsorbent and ethyl acetate as solvent.

Wittig Reactions of Methylphosphonium Salts. — These reactions were carried out in duplicate according to the following general procedure. The salt (0·001 mol) and freshly distilled benzaldehyde (0·106 g, 0·001 mol) in dry ethanol (4 cm$^3$) were treated with ethanolic sodium ethoxide (1 cm$^3$) prepared from sodium (0·23 g, 0·01 mol) in dry ethanol (10 cm$^3$) and the resulting solution set aside at room temperature, under nitrogen, for 14 days. The yield of styrene, and the amount of unreacted benzaldehyde were then determined by comparison of the peak area on g.l.c. with a calibration graph obtained under the same conditions. The mixture was then neutralised with dilute hydrochloric acid, and extracted with chloroform. The extract was dried (MgSO$_4$) and concentrated to give a mixture which was separated by preparative t.l.c.. The compounds identified in the individual reactions, together with their yields, are given below.

Methyl-2-(1-methylpyrrolyl)diphenylphosphonium iodide-benzaldehyde. G.l.c. analysis showed the presence of styrene ( 5%) and unreacted benzaldehyde (15%) in the reaction products. A third volatile product was identified as 1-methyl-pyrrole, by comparison with authentic material.

Thin-layer chromatography of the concentrated chloroform extract revealed the presence of several minor components, together with a major component which was extracted into warm methanol. Removal of the solvent yielded an oil which solidified on trituration with n-hexane. The compound was recrystallised from n-hexane-benzene to give crystals, m.p. 168° (0·16 g, 53%) which were shown to be trans-β-styryldiphenylphosphine oxide (XXXIV) (lit.,[34] m.p. 168-169°) (Found:

C, 79·10; H, 5·85. Calc. for $C_{20}H_{17}OP$: C, 78·95; H, 5·60); $\tau$ (CDCl$_3$) 1·9 – 3·2 (17H, m). The mass spectrum revealed a molecular ion (m/e 304, M$^+$), and a fragmentation pattern consistent with trans-β-styryldiphenylphosphine oxide.

Methyltri-2-(1-methylpyrrolyl)phosphonium iodide-benzaldehyde. G.l.c. analysis showed the presence of styrene ( 5%), unreacted benzaldehyde ( 10%) and 1-methylpyrrole in the reaction product.

Thin-layer chromatography of the concentrated chloroform extract revealed several minor components, together with a major component which was extracted into warm methanol. Removal of the solvent yielded a brown oil (0·22 g, 70%) which could not be induced to crystallise; $\tau$ (CDCl$_3$) 2·20 – 3·25 (9H, m), 3·47 – 3·95 (4H, m), and 6·14 (6H, s). The mass spectrum revealed a molecular ion (m/e 310, M$^+$), and a fragmentation pattern consistent with di-2-(1-methyl-pyrrolyl)-β-styrylphosphine oxide (XXXIII).

The Reaction between 2-(1-Methylpyrrolyl)diphenylphosphine and Styrene Oxide.

A solution of 2-(1-methyl)pyrrolyldiphenylphosphine (XXXII) (0·26 g, 0·001 mol) and styrene oxide (0·12 g, 0·001 mol) in ethanol (3 cm$^3$) was heated under reflux for 70 h. The mixture was then cooled and water added to give a brown oil. The mixture was extracted with chloroform, and the extract dried (MgSO$_4$). Removal of the solvent yielded an oil which solidified on trituration with n-hexane. The compound was recrystallised from n-hexane-benzene to give crystals, (0·12 g, 40%), m.p. 168°, which were identified as trans-β-styryldiphenyl-phosphine oxide (XXXIV) (lit.,[34] m.p. 168–169°).

The Reaction between Tri-2-(1-methylpyrrolyl)phosphine and Styrene Oxide.

A solution of tri-2-(1-methylpyrrolyl)phosphine (XXXI) (0·27 g, 0·001 mol) and styrene oxide (0·12 g, 0·001 mol) in ethanol (3 cm$^3$) was heated under reflux for 70 h. The mixture was then cooled and water added to give a yellow solid. The compound was filtered and recrystallised from n-hexane to give crystals, (0·25 g, 95% recovery), m.p. 120°, which were identified by comparison of n.m.r. and i.r. spectra to be unchanged phosphine (XXXI), (m.p. 122°).

## REFERENCES

1. G. Wittig and U. Schollkopf, Chem. Ber., 1954, 87, 1318.

2. F. Ramirez, N.B. Desai, B. Hansen, and N. McKelvie, J. Amer. Chem. Soc., 1961, 83, 3539.

3. R. Greenwald, M. Chaykovsky, and E.J. Corey, J. Org. Chem., 1963, 28, 1128.

4. A. Maerker, Organic Reactions, 1965, 14, 270.

5. A.W. Johnson, "Ylid Chemistry", Academic Press, New York, 1966.

6. A.W. Johnson and R.B. La Count, Tetrahedron, 1960, 9, 130.

7. G. Wittig, H.D. Weigmann, M. Schlosser, Chem. Ber., 1961, 94, 676.

8. W.E. McEwen, K.F. Kumli, A. Blade-Font, M. Zanger, and C.A. VanderWerf, J. Amer. Chem. Soc., 1964, 86, 2378.

9. P.C. Haake and F.H. Westheimer, J. Amer. Chem. Soc., 1961, 83, 1102.

10. S. Trippett and B.J. Walker, J. Chem. Soc. (C), 1966, 887.

11. M. Grayson and P.T. Keough, J. Amer. Chem. Soc., 1960, 82, 3919.

12. D.W. Allen, J.C. Tebby, and D.H. Williams, Tet. Lett., 1965, 2361.

13. D.W. Allen and J.C. Tebby, Tetrahedron, 1967, 23, 2795.

14. J.J. Brophy, K.L. Freeman, and M.J. Gallagher, J. Chem. Soc. (C), 1968, 2760.

15. E. Zbiral and E. Werner, Annalen, 1967, 707, 130.

16. E. Zbiral and L. Berner-Fenz, Tetrahedron, 1968, 24, 1363.

17. E.M. Richards and J.C. Tebby, Chem. Comm., 1969, 494.

18. E.M. Richards and J.C. Tebby, J. Chem. Soc. (C), 1971, 1059.

19. E.E. Schweizer, D.M. Crouse, T. Minami, and A.T. Wehman, Chem. Comm., 1971, 1000.

20. E.E. Schweizer and A.T. Wehman, J. Chem. Soc. (C), 1971, 343.

21. F.T. Welch and H.J. Paxton, J. Polymer Sci., 1965, A, 3, 3439.

22. E.E. Schweizer, E.T. Shaffer, C.T. Hughes, and C.J. Berninger, J. Org. Chem., 1966, 31, 2907.

23. E.E. Schweizer and A.T. Wehman, unpublished results.

24. E.E. Schweizer, T. Minami, and D.H. Crouse, J. Org. Chem., 1971, 36, 4028.

25. J.W. Rakshys and S.V. McKinley, Chem. Comm., 1971, 1336.

26. D.J.H. Smith and S. Trippett, Chem. Comm., 1972, 191.

27. D.W. Allen, B.G. Hutley, and T.C. Rich, J. Chem. Soc. Perkin II, 1973, 820.

28. D.W. Allen, B.G. Hutley, and M.T.J. Mellor, J. Chem. Soc. Perkin II, 1972, 63.

29. M.R. Kegelman and E.V. Brown, J. Amer. Chem. Soc., 1953, 75, 5961.

30. D.W. Allen, P. Heatley, B.G. Hutley, and M.T.J. Mellor, Tet. Lett., 1974, 1787.

31. J.R. Corfield, N.J. De'ath and S. Trippett, J. Chem. Soc. (C), 1971, 1930.

32. D.W. Allen, unpublished results.

33. D.W. Allen, S.J. Grayson, I. Harness, B.G. Hutley, and I.W. Mowat, J. Chem. Soc. Perkin II, 1973, 1912.

34. A.M. Aguiar and D. Daigle, J. Org. Chem., 1965, 30, 2826.

# CHAPTER THREE

## Studies of Nucleophilic Displacement in Phosphacyl Compounds.

### 3.1 Introduction.

Nucleophilic displacement reactions at phosphorus have recently received considerable attention and the formal similarity between displacement reactions at carbonyl and phosphacyl* centres have been discussed in terms of the basic theoretical concepts of physical organic chemistry. However, whilst the reaction mechanisms for nucleophilic displacement at tetrahedral and trigonal carbon are quite well understood[1], the mechanistic details for displacement at phosphacyl centres remain unclear, since the situation is made more complex due to the following:-

(a) phosphorus has available d- as well as s- and p-orbitals of the same principal quantum number (3), whereas carbon is only able to utilise the 2s- and 2p-orbitals,

(b) the greater polarisability of the phosphorus atom compared with the carbon atom may lead to larger inductive effects in phosphorus compounds,

(c) the influence of $p\pi - d\pi$ bonding is not known, and is variable. Since the energies concerned are much less than $p\pi - p\pi$ bond energies, conjugation will will play a much smaller part in the determination of the reactivity of organo-phosphorus compounds, and the differentiation between $\sigma$ (inductive) and $\pi$ (conjugative) effects will be particularly difficult,

(d) the different stereochemistry leads to greater steric effects for phosphorus compounds than for their carbon analogues, though this effect is reduced by the greater radius of the phosphorus atom.

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* A phosphacyl centre is any $X(Y)P(=O)$ grouping. The term phosphacyl therefore includes phosphoryl, $RO(OR')P(=O)$, phosphonyl, $RO(R')P(=O)$, and phosphinyl, $R(R')P(=O)$.

(I)                  (II)

    (1)

(III)                  (IV)
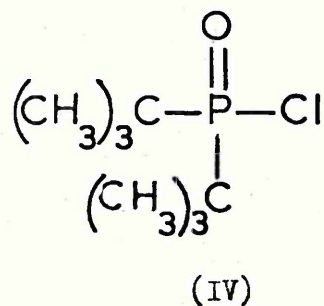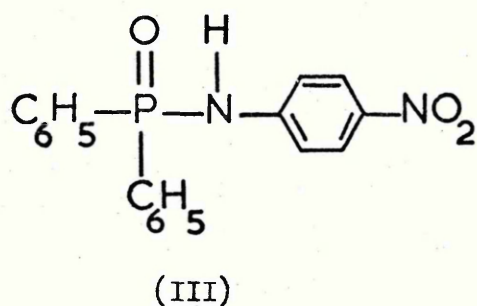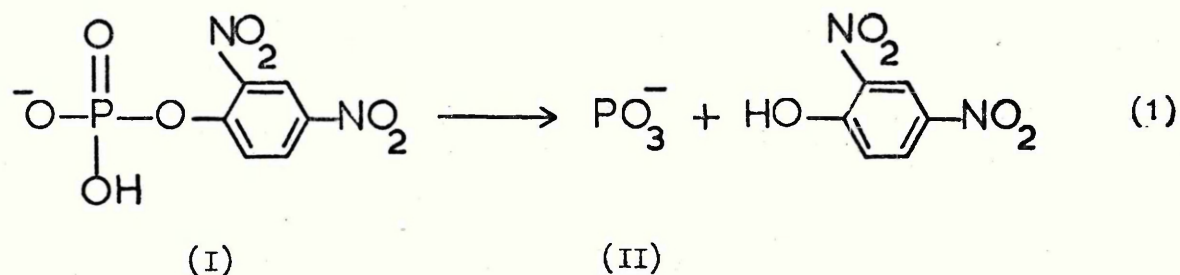
Although displacement reactions at tetrahedral phosphorus can proceed by a dissociative pathway, reliably authentic examples are few[2-4] and largely confined to phosphate derivatives where the intermediate of reduced coordination number can be stabilised by delocalisation as in the generation of metaphosphate (II) from aryl phosphates[5] (equation 1). In addition, evidence has been presented by Haake et al[6,7] for a dissociative mechanism in the acid catalysed hydrolysis of N-p-nitrophenyldiphenylphosphinamide (III) and in the solvolysis of di-tert-butylphosphinyl chloride (IV).

(V)      (VI)      (VII)      (VIII)

(IX)      (X)      (XI)
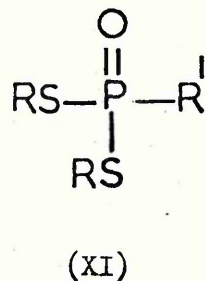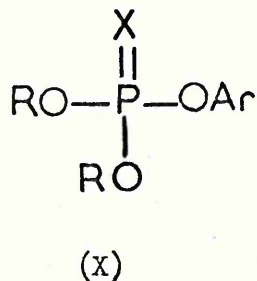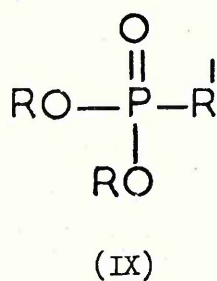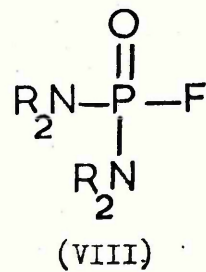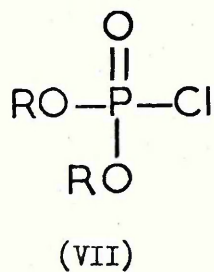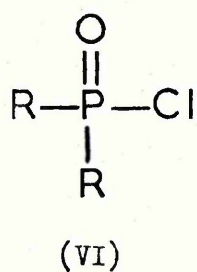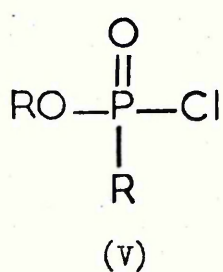
Displacement reactions at tetrahedral phosphorus with nucleophile are, however, predominantly bimolecular and are first-order in nucleophile and first-order in phosphorus compound. These reactions include the displacement of halide ion in phosphonochloridates[8] (V) and phosphinyl chlorides[9] (VI), by amine; the displacement of halide ion in phosphonochloridates[10,11] (V), phosphinyl chlorides (VI), phosphorochloridates (VII) and phosphorodiamidic fluorides[12] (VIII) by hydroxide or aryloxide ion, and the hydrolysis of esters[13-15] (IX), (X;X = S), and thiolesters (XI) by water or hydroxide ion[16].



$$(XII) \longrightarrow (XIII)$$
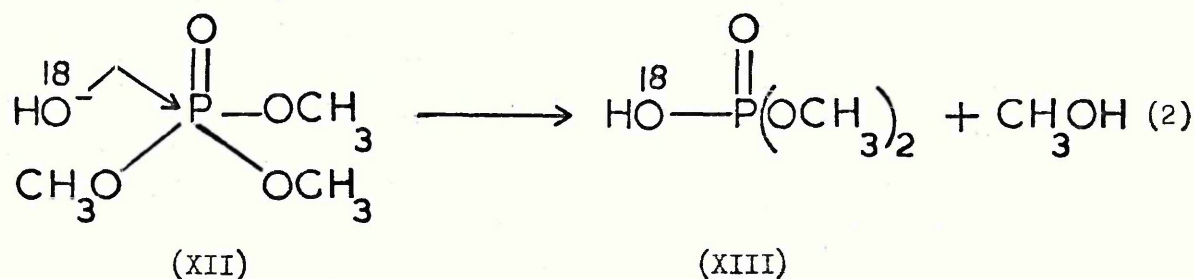
The observation by Blumenthal et al[17], that one atom of $^{18}O$ is incorporated into the dimethylphosphate (XIII) produced in the alkaline hydrolysis of trimethylphosphate (XII) in water enriched in $^{18}O$, established that the hydrolysis reaction proceeded by way of phosphorus-oxygen bond cleavage following nucleophilic attack at phosphorus (equation 2), whereas the absence of $^{18}O$ in dimethylphosphate (XIV) produced in the acid catalysed hydrolysis of trimethyl-phosphate (XII) in $H_2O^{18}$ indicated attack by water at carbon (equation 3).



$$(XII) \longrightarrow (XIV)$$
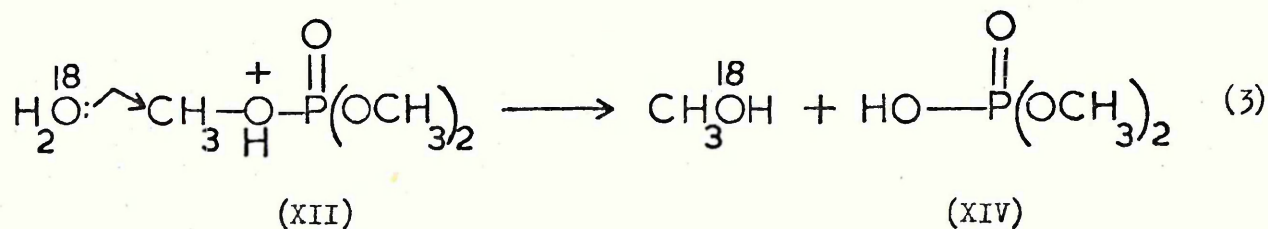
The absence of $^{18}O$ exchange into the phosphoryl oxygen during the alkaline hydrolysis of phosphates is in contrast to results obtained by Bender[18] which established an intermediate in the alkaline hydrolysis of carboxylic esters. The stability of pentacoordinate phosphorus compounds[19], however, would suggest

that addition intermediates may be present in a number of displacement reactions at phosphorus. Much recent interest in phosphorus chemistry concerns the possibility of pentacoordinate trigonal-bipyramidal intermediates in substitution reactions at tetrahedral phosphorus, and the question of pseudorotation.

$$HO_2^* + \overset{(XV)}{\underset{}{\text{[cyclic phosphate]}}} \xrightarrow{H^+} HOCH_2CH_2OP\overset{*}{O}O_2H \quad (4)$$

$$\xrightarrow{H^+} \text{[cyclic phosphate]} + H_2O \quad (5)$$
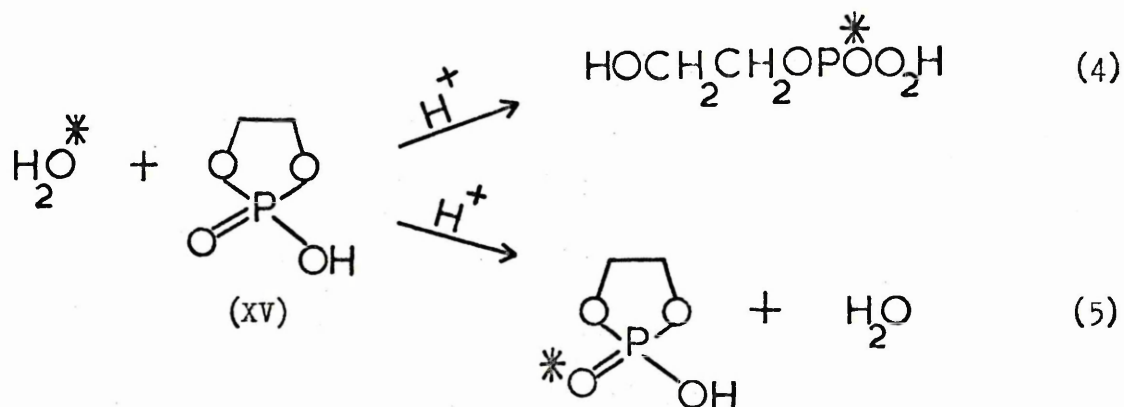
The possibility of the formation of a pentacoordinate intermediate, and the pseudorotation of this intermediate in the mechanism of hydrolysis of phosphate esters was introduced by Westheimer et al in order to explain certain experimental data. It was observed that the acid catalysed hydrolysis of ethylenephosphate[20] (XV) in $H_2O^{18}$ (equations 4 and 5) proceeds by P-O fission at a rate $10^8$ faster than that of the acyclic analogue (trimethylphosphate, equation 3), with accompanying exchange of $^{18}O$ into the phosphoryl bond, and that the acid catalysed hydrolysis of methylethylenephosphate[21] (XVI) (equations 6 and 7) takes place $10^6$ times faster than that of trimethylphosphate, and is accompanied by cleavage of the methoxyl group. Similar relative rates were observed for the corresponding alkaline hydrolysis reactions, but in contrast to the acid catalysed hydrolyses, $^{18}O$ exchange into the phosphoryl bond of the unreacted ethylenephosphate was not observed[20], and the hydrolysis of methyl-ethylene phosphate[21] took place with exclusive ring opening.

$$H_2O \ + \ \text{(XVI)} \ \xrightarrow{H^+} \ \text{(30\%)} \ + \ CH_3OH \quad (6)$$

$$\xrightarrow{H^+} \ HOCH_2CH_2OPOCH_3 \ \text{(70\%)} \quad (7)$$
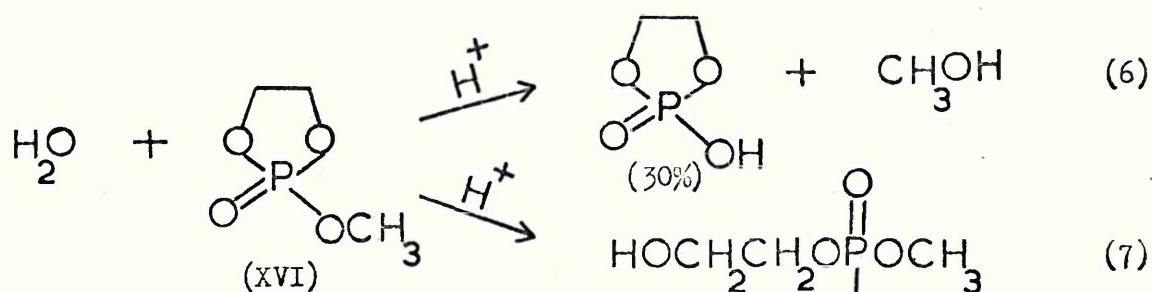
Westheimer proposed[20,22] that although ring strain may account for the enhanced rate of hydrolysis of cyclic phosphates, which proceed with ring opening (and hence the relief of strain as a result of the hydrolytic reaction), the exchange of $^{18}O$ into unchanged ethylenephosphate (in which strain is still present) (equation 5), and the rapid hydrolysis of methylethylenephosphate which takes place external to the ring (equation 6), suggests that a mechanism exists in which ring strain is relieved in the transition state. Thus the hydrolyses proceed by way of a trigonal bipyramid in which the ring is constrained to span one apical and one equatorial position, allowing a O—P—O bond angle of $90°$ and relief from angular strain.
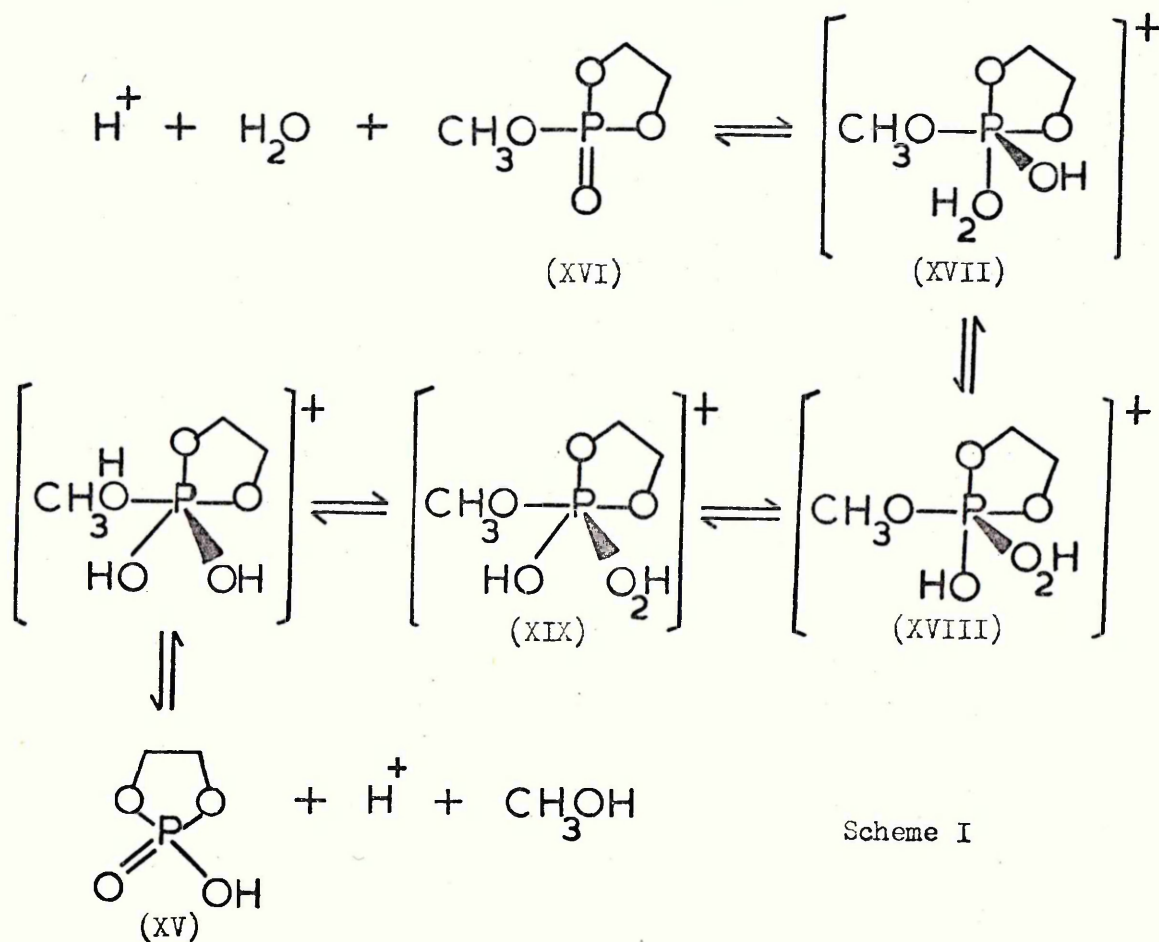


Scheme I

It was suggested[22] that in the acid catalysed hydrolysis of methylethylene-phosphate (XVI) to produce methanol and ethylenehydrogenphosphate (XV) (Scheme I), water adds to the molecule to occupy an apical position in a trigonal bipyramid (XVII). In order that the methoxyl group may leave from an apical position, the mechanism must involve pseudorotation of the trigonal-bipyramidal intermediate, analogous to the pseudorotation that has been postulated[23] to explain the rapid interchange of fluorine atoms in $PF_5$ and $RPF_4$. The shift of the proton produces an equatorial water molecule which can serve as a "pivot" for pseudorotation. The pseudorotation places the methoxyl group in the apical position of a second trigonal bipyramid (XIX), and after a proton shift, the methanol molecule can leave from this apical position. In both the trigonal bipyramids (XVIII) and (XIX), the five membered ring spans one apical and one equatorial position with reduced ring strain. The corresponding hydrolysis with ring opening can occur from the original trigonal bipyramid (XVII) with a proton shift, but without pseudorotation.

(XX)

(XXI)
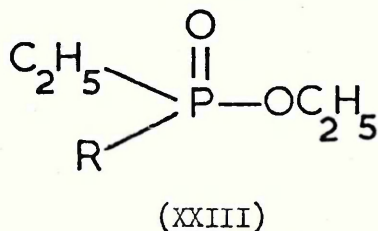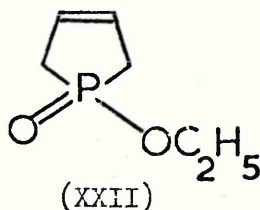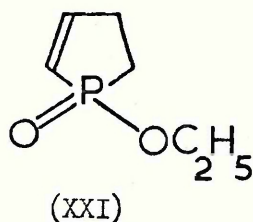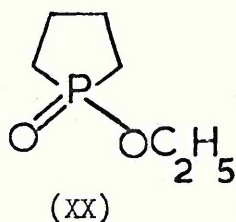
(XXII)

(XXIII)

In connection with this theory, Westheimer et al[24] observed that five-membered cyclic phosphinic acid esters (XX), (XXI) and (XXII) undergo acid and alkaline hydrolysis at rates comparable to those of their open chain analogues (XXIII; $R = C_2H_5$, $CH_2{=}CH$, $CH_2{=}CH \cdot CH_2$). It was thus suggested[24] that relief from angular strain in forming a trigonal-bipyramidal intermediate for the hydrolysis of (XX), (XXI) and (XXII) is insufficient to place an alkyl group

in an apical position, whilst angle strain prevents placing the ring in a
diequatorial position. Although neither of these intermediates is forbidden
the formation of either will necessarily be accompanied by an increase in .
energy. Thus it would appear that with phosphorus compounds, a strong preference
obtains for placing oxygen in apical positions and alkyl groups in the equatorial
positions of a trigonal bipyramid; the restrictions parallel those discovered
by Schmutzler[25] for the structures of stable alkylfluorophosphoranes ($R_n PF_{5-n}$)
where alkyl groups occupy equatorial positions.
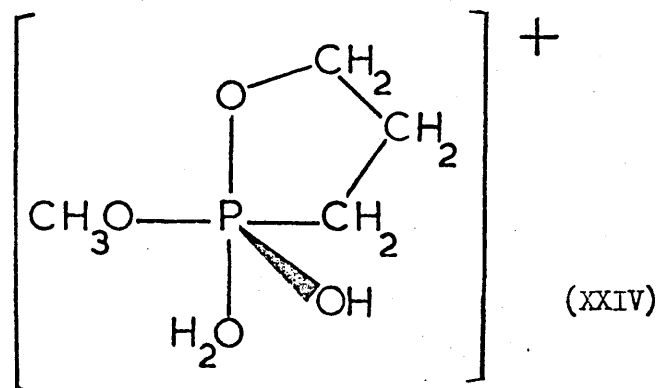


(XXIV)

Similarly pseudorotation of the trigonal bipyramid (XXIV) formed from methyl-
propylphostonate by the addition of water and a proton must be energetically
unfavourable, since the methoxyl group cannot assume an apical position in a
situation allowing the ring to occupy apical-equatorial positions. Hydrolysis
thus occurs[22] with ring opening and retention of the methoxyl group in the
product.



(XXV)                    (XXVI)
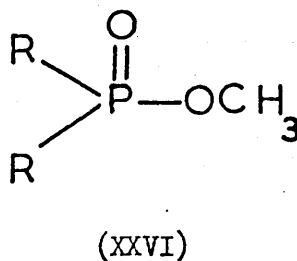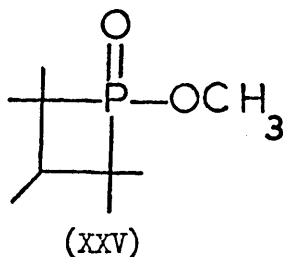
Haake et al observed the alkaline hydrolysis of methyl-2,2,3,4,4-pentamethyl-
trimethylenephosphinate (XXV) to proceed with displacement at phosphorus[26] at
a rate comparable to the much less hindered methyldiethylphosphinate[26] (XXVI;
$R = C_2H_5$) and $10^5$ faster than the similarly substituted (but probably more
hindered) methyldi-t-butylphosphinate[27] (XXVI; $R = (CH_3)_3C$). It was suggested[7,28]

that this result supported the involvement of a pentacoordinate intermediate in the reaction, on the basis that in reactions proceeding through a penta-coordinate intermediate, ring strain can be relieved in the intermediate, leading to an increased rate of reaction. Reactions which proceed via a direct displacement mechanism, however, must pass through a transition state in which the entering and leaving groups are colinear with phosphorus, and in this case ring strain causes a decreased rate of reaction.

$$
\text{HO}^- \rightarrow \overset{\displaystyle \overset{O}{\parallel}}{\underset{\underset{R}{\overset{\displaystyle R'}{|}}}{P}}\text{OCH}_3 \; \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \; \underset{\underset{OCH_3}{|}}{\overset{\overset{OH}{|}}{\underset{R'}{R\,}P}}\text{—O}^- \; \overset{k_2}{\longrightarrow} \; R_2PO_2^- + CH_3OH \quad (8)
$$

(XXVI)                          (XXVII)
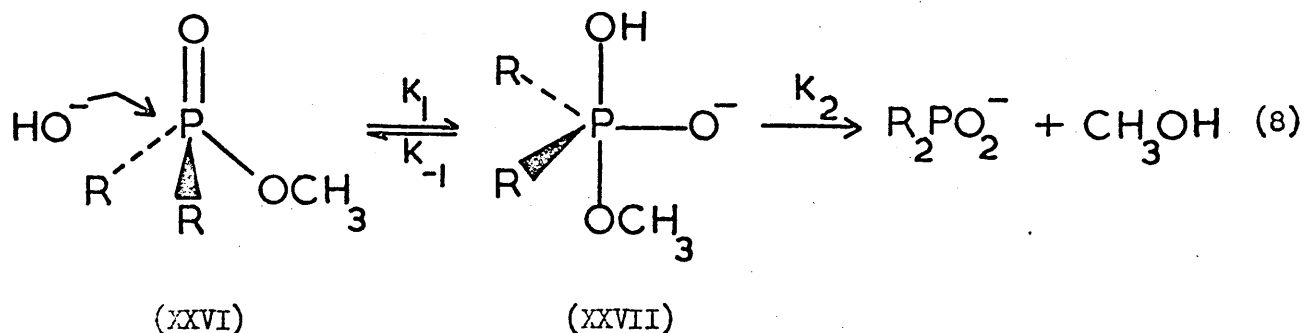
Additional, more direct, evidence for an associative intermediate[28,29] (XXVII) was obtained from the alkaline hydrolysis of methyldiisopropylphosphinate (XXVI: $R = (CH_3)_2CH$), in which an induction period was observed to precede good second-order kinetics. This result was interpreted[28,29] as indicating the accumulation of the pentacoordinate intermediate (XXVII; $R = (CH_3)_2CH$) and rate-determining breakdown of the intermediate to products. The kinetic observation of a possible intermediate was attributed to the steric effect of the isopropyl substituents, which would decrease $k_1$, because of $^-$OH-isopropyl interactions in the transition state. The rate of generation of (XXVII; $R = (CH_3)_2CH$) would thus be slower than for less hindered phosphinates. In the fully formed intermediate (XXVII; $R = (CH_3)_2CH$) the $120^o$ C—P—C angle enables relief of steric interactions between the two isopropyl groups, which are tetrahedrally disposed in the ground state, and thus amounts of (XXVII; $R = (CH_3)_2CH$) present at equilibrium should be greater for methyldiisopropyl-phosphinate than for other less hindered phosphinate esters. The induction period may therefore be due to the combination of the kinetically slower

formation of the intermediate and the need to accumulate more intermediate before second-order kinetics can be observed.

Despite the proposed rate-determining breakdown of the intermediate to products, Haake et al did not observe $^{18}O$ exchange into the phosphinyl bond during the alkaline hydrolysis of a series of phosphinate esters[28,30] in $H_2O^{18}$ enriched solvents. It was thus suggested[28] that since displacement at phosphorus appears to require that groups enter and leave at apical positions of a trigonal bipyramid, the lack of $^{18}O$ exchange into these compounds is evidence for a high barrier to any process which would make $O^-$ and OH equivalent in (XXVII).
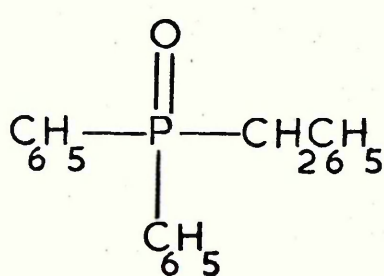


(XXVIII)          (XXIX)          (XXX)
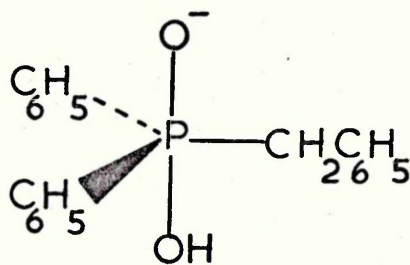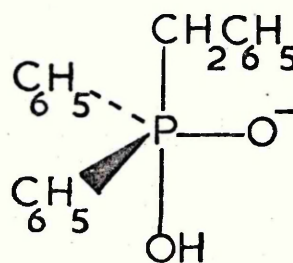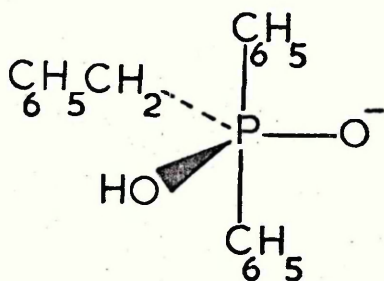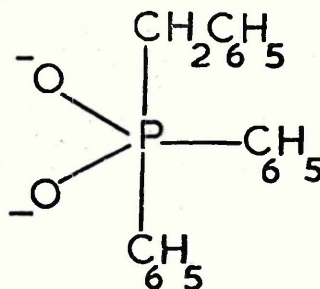
(XXXI)          (XXXII)

Thus the lack of $^{18}O$ exchange into phosphinate esters during the alkaline hydrolysis reaction may be rationalized by the geometry of the intermediate (XXVII), in which OH and the leaving group occupy apical positions and the $O^-$ occupies an equatorial position, since the more electronegative atoms appear to occupy apical positions in phosphoranes. Haake thus suggested[31] that the alkaline hydrolysis of a phosphine oxide (XXVIII) may take place with an

accompanying $^{18}O$ exchange. It was considered that since there are three P-C bonds, it is possible that the preferred geometry of an addition intermediate would have OH and $O^-$ in apical positions as in (XXIX), and rapid proton transfer would then cause identity of the oxygen atoms. Furthermore, a mechanism of direct displacement could be rejected on the assumption that the benzyl anion would be reasonably difficult to displace from benzyldiphenylphosphine oxide (XXVIII). The alkaline hydrolysis of (XXVIII) in homogeneous solution containing $H_2O^{18}$, however, was observed to proceed with the incorporation of one solvent oxygen into the resulting phosphinate anion and negligible exchange into unreacted (XXVIII). Thus, if a symmetrical intermediate such as (XXIX) exists along the reaction pathway, the collapse to products must take place at least 200 times faster than to reactants. Haake proposed two possible explanations, (i) that $O^-$ may be the pivot atom for pseudorotation. On the basis of electron repulsion theory[32], the $O^-$ would be strongly electron-repelling and possibly occupy a position where it interacts least with the other ligands and bonding electrons. Therefore, there should be a strong preference for the $O^-$ atom to be equatorial in a trigonal-bipyramidal geometry as in (XXX); and there should be a considerable barrier to pseudorotation unless $O^-$ is the pivot group. If $O^-$ must be the pivot and (XXX) is preferentially formed, the only possible pseudorotation would yield (XXXI). This would have a high energy geometry, and it is possible that it would not be formed rapidly enough to allow $^{18}O$ exchange. Alternatively, the presence of $O^-$ may cause sufficient distortion in a pentacoordinate geometry to make the identity of OH and $O^-$ impossible; (ii) with the strong activity of $OH^-$ necessary to effect displacement in (XXVIII), the predominant state of ionisation of the addition intermediate may be (XXXII). If so, loss of benzyl may be fast compared with the reversal to (XXVIII) even if (XXXII) is reasonably stable and the oxygens are equivalent. If this were the case, providing (XXXII) is predominant and the addition of $OH^-$ to (XXVIII) is rate-determining, the observed kinetics will

still be first order in $^-$OH.

$$R_2P(O)NH_2 \;(XXXIII) + HO^{18-} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (XXXIV) \rightleftharpoons (XXXV) \overset{k_2}{\longrightarrow} R_2PO_2^- + NH_3^+$$

$$(XXXIV) \rightleftharpoons (XXXVI) \underset{k'_{-1}}{\overset{k'_1}{\rightleftharpoons}} R_2P(O^{18})NH_2 + HO^- \qquad (9)$$
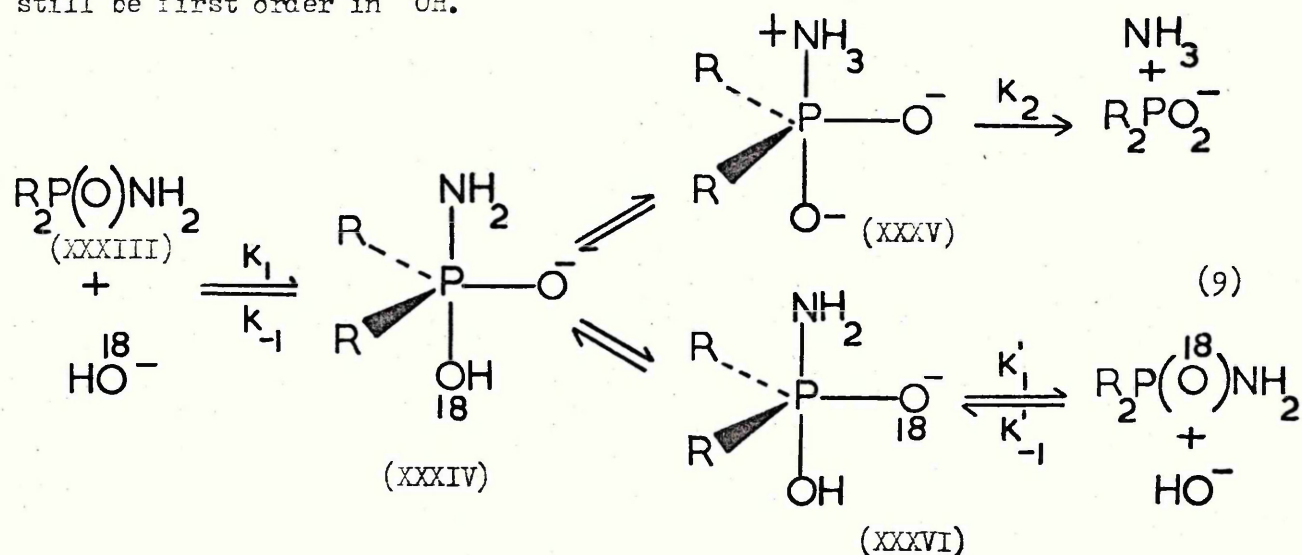
Finally Haake et al[33] observed the acid catalysed hydrolysis of phoshin-amides (XXXIII) to proceed $10^5$ faster than the corresponding benzamide. The reaction was considered to involve rate-determining nucleophilic attack by water at phosphorus in the phosphinamide which is protonated on the nitrogen atom, and a mechanism of direct displacement excluding the formation of a pentacovalent intermediate.

In contrast the alkaline hydrolysis of phosphinamides[33] proceeded slowly with rates similar to carboxylic amides, and with a small amount of $^{18}$O exchange into unhydrolysed amide in solvents enriched with $H_2O^{18}$. A mechanism (equation 9) was suggested involving intermediates of trigonal-bipyramidal geometry. Thus due to polarity effects (XXXIV) would be expected to be formed initially. Hydrolysis requires a proton transfer to generate (XXXV) which would decompose to products more readily than (XXXIV) would decompose to starting materials, since $NH_3$ is a better leaving group than $OH^-$, and thus $k_2 > k_{-1}$. Alternatively $^{18}$O exchange into the amide requires both proton transfer and pseudorotation for (XXXIV) $\rightarrow$ (XXXVI). The large ratio of hydrolysis to exchange (k(hydrolysis)/k(exchange) = 70) was explained by the fact that $k_2 > k_{-1}$, and also that there is possibly a barrier to pseudorotation, as indicated by the lack of $^{18}$O exchange observed in the alkaline hydrolysis of phosphinic acid esters in solution enriched in $^{18}$O.

Haake et al suggested[33] the possibility of a continuous spectrum of
mechanisms for reactions at phosphorus, ranging from reactions proceeding
through a stable intermediate produced by association of nucleophile with the
substrate, to unimolecular dissociation of the leaving group. The former
extreme involves cases where one has a poor leaving group, and the intermediacy
of a pentacoordinate species is advantageous to the pathway of lowest energy
between reactants and products. The latter extreme involves a species so
reactive that the leaving group dissociates in a unimolecular reaction, since
the activation energy for the formation of a pentacoordinate species is possibly
higher than the activation energy for the unimolecular reaction. It is also
reasonable that there should be a mechanism intermediate between these two
extremes.
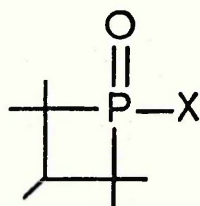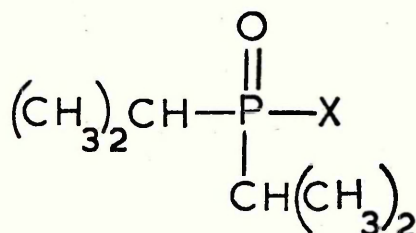


(XXXVII)                    (XXXVIII)

As a criterion of whether the mechanism of a reaction at phosphorus was a
direct displacement or involved an intermediate with sufficient stability to be
detected, Haake suggested[7] a comparison of relative rates of substitution of
strained cyclic trimethylenephosphinates (XXXVII), and unstrained acyclic
analogues (XXXVIII). The availability of a $90^{\circ}$ C—P—C angle in a penta-
coordinate intermediate and the possibility of pseudorotation enables a strained
ring to cause rate acceleration if an intermediate is involved; but in direct
displacement the strained ring should cause rate retardation, because of the
need to expand the C—P—C right angle in the transition state. Thus whilst
(XXXVII; X = $OCH_3$) undergoes alkaline hydrolysis more rapidly than the
diisopropylphosphinate (XXXVIII; X = $OCH_3$)[28] indicating an associative inter-
mediate, the reduction in the rate of solvolysis of the phosphinyl chloride

(XXXVII; X = Cl)[7] and the acid catalysed hydrolysis of the amide (XXXVII;

X = N(CH$_3$)$_2$)[7,33] compared with the acyclic analogue (XXXVIII; X = Cl, N(CH$_3$)$_2$)

is indicative of a direct displacement with entering and leaving groups colinear

with phosphorus. Additional evidence[7] involving the rates of solvolysis of

2,2,3,4,4-pentamethyltrimethylenephosphinyl chloride (XXXVII; X = Cl) in

solvents of approximately equal ionising power but vastly differing nucleo-

philicity was presented to support this theory.



(XXXIX)                                          (10)



(11)

(XL)            (XLI)
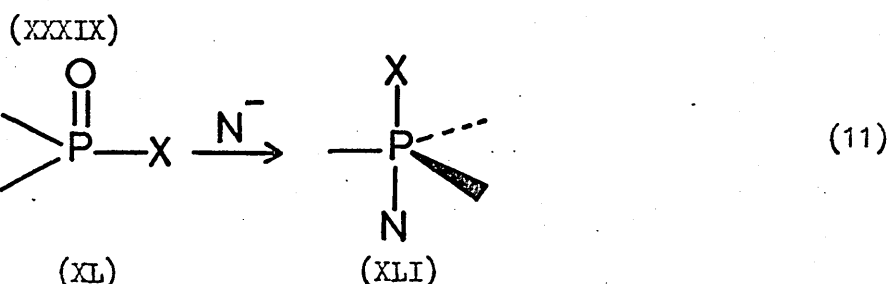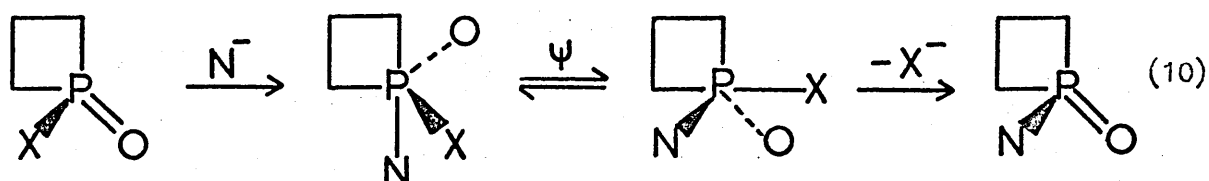
Trippett et al[34] presented an alternative explanation which assumed that

all such substitutions involve the formation of an intermediate (XXXIX) in

which the 4-membered ring is apical-equatorial. In comparison with the similar

situation of an acyclic compound (XL) which involves an intermediate (XLI),

the substitution of the phosphetan ester is accelerated by relief of ring strain

in (XXXIX) but is retarded[24] by the fact that whereas (XLI) has two electro-

negative groups in apical positions, (XXXIX) has only one. The more

electronegative is X (i.e. in general, the better it is as a leaving group) the

greater will be this retardation and when X = Cl or $\overset{+}{N}$H(CH$_3$)$_2$, the net effect

(when compared with the acyclic analogues) is a retardation. With the less

electronegative ethoxy group, the effects almost balance.

Furthermore, the colinear theory for substitutions of (XXXVII; X = Cl,

N(CH$_3$)$_2$) predicts that such substitutions will involve inversion of configuration

at phosphorus, in contrast to the retention observed with (XXXVII; X = OCH$_3$)[35]

and (XXXVII; X = OC$_2$H$_5$)[36]. However, the reaction of (XXXVII; X = Cl) with

phenyl-lithium is known[36,37] to proceed with retention of configuration at phosphorus, and if one assumes that the corresponding reaction with benzyl-lithium has the same stereochemistry, then the reactions shown in Scheme II establish that reactions of the chloride (XXVII; X = Cl) with aniline and with N-lithioaniline also involve retention of configuration at phosphorus.
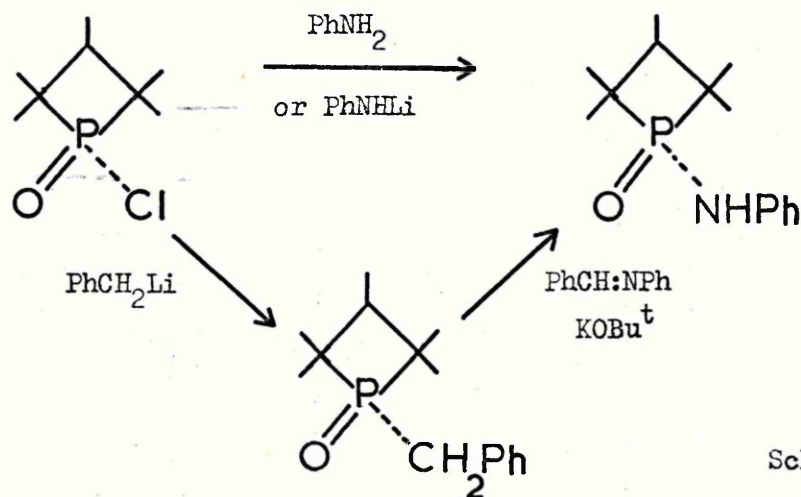


Scheme II

Many phosphorus acid esters are of great importance in biological chemistry, and the existence in living matter of sugar phosphates and phosphorus-containing lipids and nucleic acids has been known for nearly a century. A further stimulus for the investigation of phosphorus compounds, however, is the toxicity of certain phosphorus acid esters and their potential use as pesticides.

$$CH_3COCH_2CH_2\overset{+}{N}(CH_3)_3$$
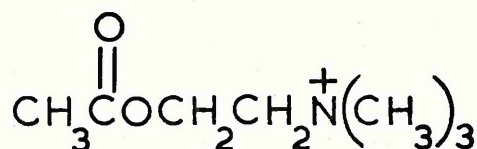
(XLII)

The insecticidal action of organophosphorus compounds is generally attributed to the inhibition of several ester-splitting enzymes present in living organisms[38]. They are particularly effective against cholinesterase which hydrolyses the acetylcholine generated in myoneural junctions during the transmission of motor commands from the central nervous system to vital muscles and organs in the body. The acetylcholine (XLII) is released by an incoming

stimulus from the central nervous system, to stimulate either an organ effect or initiate events leading to a fresh impulse. If acetylcholine were allowed to persist it would continue the stimulation and destroy the required proportionality between input stimulus and event. In practice, the acetylcholine is promptly destroyed by cholinesterase, the enzyme which is present in a large excess. If the cholinesterase should be prevented from acting (e.g. by inhibition by an anticholinesterase agent) acetylcholine will accumulate, causing excessive stimulation and finally complete disruption of the cholinergic system.

$$RO-\underset{\underset{O}{\|}}{\overset{\overset{OR}{|}}{P}}-X \;+\; EOH \;\rightleftharpoons\; \left[ RO-\underset{\underset{O}{\|}}{\overset{\overset{OR}{|}}{P}}-OE \right] \;+\; HX \qquad (XLIII)$$

$$\downarrow H_2O \;\big|\; H^+$$

$$HO-\underset{\underset{O}{\|}}{\overset{\overset{OR}{|}}{P}}-OE \;+\; ROH \qquad (12)$$
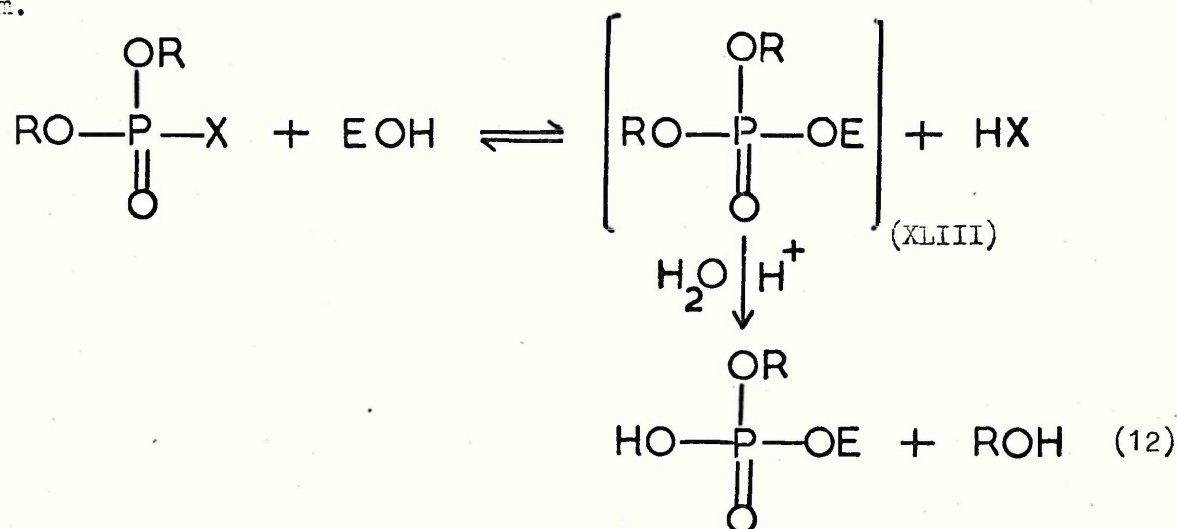
In the first instance, nucleophilic attack on the phosphorus atom by a high electron density portion of the enzyme takes place to produce the alkyl-phosphate ester (XLIII)[39]. The formation of this ester is reversible, but dephosphorylation of the enzyme is slow in comparison with the phosphorylation step (equation 12) and inhibited enzyme accumulates. Enzyme activity may be recovered, however, by nucleophilic attack with compounds such as hydroxylamine[40] and oximes[41]. Alternatively, dealkylation of the enzyme-phosphate may occur[42], a process known as ageing[43], and the covalent link between the enzyme and phosphate is stabilised.

$$\text{(XLIV)}$$

The structure shows a phenyl ring with X substituents, connected through O to a P atom bearing =O, and two OC$_2$H$_5$ groups.

(XLIV)
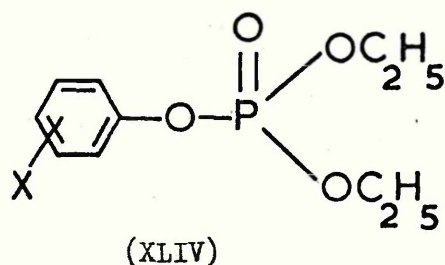
On the basis of the proposed mechanism it is apparent that the enzyme-inhibiting ability of the organophosphorus compound is related to the lability of the P—X bond. Thus it becomes possible to correlate structure and reactivity. Fukuto and Metcalf[44] observed the contact toxicity ($LD_{50}$) for the common housefly, greenhouse thrips, and citrus red mite, and the molar concentration for 50% inhibition ($I_{50}$) of fly-brain cholinesterase for a series of diethyl substituted-phenylphosphates (XLIV). These properties were then compared with the lability of the P-O-aromatic bond as measured by the rates of alkaline hydrolysis of the phosphate, infrared stretching frequency of the P-O-aromatic bond, and the Hammett sigma ($\sigma$) values of the substituents on the phenyl ring. Examination of the data revealed the degree of inhibition ($I_{50}$) to be a direct function of the electron-withdrawing capacities of the substituents on the benzene nucleus. Thus a plot of $-\log I_{50}$ against Hammetts $\sigma$ constants for the substituents revealed that most of the points lay along a straight line, with $-\log I_{50}$ increasing with increasing values of $\sigma$. A similar correlation was also observed for the rates of alkaline hydrolysis of the phosphate esters, and a straight line plot of $\log k$ (hydrolysis) against Hammetts' substituent constants was obtained, suggesting the cholinesterase inhibition and the rates of alkaline hydrolysis to be interrelated. The degree of inhibition ($-\log I_{50}$) was also found to be linearly related to the P-O-aromatic infrared stretching frequency, further suggesting that cholinesterase inhibition by phosphorus compounds is dependent upon the electronic character of the substituent in the phenyl ring and its effect upon the lability of the P-O-aromatic bond. A plot of $\log LD_{50}$ against $-\log I_{50}$ revealed that factors other than the lability of

the P—X bond are also important in the determination of the toxicity of

phosphate esters. For example, the rate of cholinesterase inhibition of

diethyl-(m-dimethylaminophenyl)phosphate methiodide (XLIV; X = m-$\overset{+}{N}(CH_3)_3$ I$^-$)

and diethyl-(p-methylmercaptophenyl)phosphate methosulphate (XLIV; X = p-$\overset{+}{S}(CH_3)_2$

CH$_3$SO$_4^-$) gave a good correlation with Hammett $\sigma$ values but a low contact

toxicity was observed. It was thus suggested that penetration through the

insect cuticle is an important factor and that polar compounds (ions) are poor

in this respect. Moderate stability to aqueous hydrolysis is another factor

which must be considered, and the low toxicity of diethyl-(2,4-dinitrophenyl)-

phosphate is probably due to the hydrolytic degradation before reaching the

reaction site.

The relationship between the rate of alkaline hydrolysis of phosphate

esters and the rate of cholinesterase inhibition had also been demonstrated by

Aldridge et al[45], who for a series of diethyl substituted-phenylphosphates

observed a linear correlation between the logarithm of the bimolecular rate

constant for cholinesterase inhibition and the logarithm of the hydrolysis

constant, implying that reactions between nucleophilic reagents and enzymes

with phosphate, proceed by a similar mechanism.



(XLV)
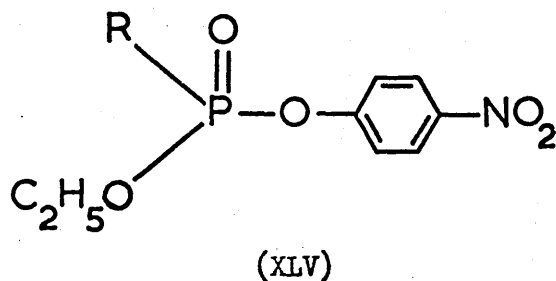
As an extension to the studies of the structure-activity relationship of

organophosphorus anticholinesterases, Fukuto and Metcalf[46,47] investigated the

effect of variation in the group R on the lability of the P-O-nitrophenyl bond

in a series of ethyl-p-nitrophenylalkylphosphonates (XLV). In this case,

however, although a general trend relating the anticholinesterase activity and

the rate of alkaline hydrolysis was observed, a linear correlation was not

obtained. The rate of inhibition of the enzyme by (XLV) was observed to be greatest when R = $CH_3$, $C_2H_5$ and $n-C_3H_7$. However, increases in chain length from 3 to 6 carbon atoms caused a rapid decrease in the rate of inhibition, for straight chain compounds. Branching at the 1-, or 2-carbon atoms also greatly reduced enzyme-substrate activity, possibly as a result of steric factors relating to the steric "fit" at the reactive site on the enzyme surface. Branching at the 3-, and 4-carbon atoms was observed to enhance the rate of inhibition, possibly because of the similarity in the over-all spatial configuration to the natural cholinesterase substrate, acetylcholine (XLII).

The presence of unsaturation in the group R, such as in allyl and phenyl, favours increased toxicity over the corresponding saturated groups. This was explained by increased reactivity caused by electron-withdrawal by the unsaturated systems. Thus allyl was nearly twice as effective as n-propyl and phenyl several hundred times more effective than cyclohexyl. The introduction of a chlorine atom in the group R, however, considerably reduced effectiveness, the relatively low activity being explained by repulsion between the chlorine atom and the anionic site on the enzyme surface.

Increases in the chain length of the alkyl group R had comparatively little effect on the stability of the ethyl-p-nitrophenylalkylphosphonate (XLV) towards alkaline hydrolysis. Rate decreases were observed with increases in chain length, and relative rates of methyl$>$ethyl$>$n-propyl = n-butyl$>$n-pentyl = n-hexyl of 1 : 0·2 : 0·17 : 0·15 were given. These results contrast with those obtained earlier by Hudson[48] for the alkaline hydrolysis of diethyl and diisopropyl esters of methyl-, ethyl-, n-propyl-, and n-butylphosphonic acids, the relative rates of reaction of these compounds with hydroxide ion in water being given as methyl (1)$>$ethyl (0·16)$>$n-propyl (0·062)$>$n-butyl (0·039) for the diisopropylalkylphosphonates, and methyl (1)$>$ethyl (0·5)$>$n-butyl (0·1) for the diethylalkylphosphonic acid esters. The stability of the p-nitrophenate anion as the leaving group in the series studied by Fukuto et al[46,47] possibly

accounts for the above differences in relative rates for esters of given phosphonic acids. Branching of the alkyl chain, particularly at the 1-carbon atom, greatly reduced the hydrolysis rate, probably as a result of steric factors. The relative hydrolysis rates of ethyl-p-nitrophenylisopropyl-phosphonate, cyclohexylphosphonate, and t-butylphosphonate compared with ethyl-p-nitrophenylmethylphosphonate were observed as 0·044, 0·013 and 0·0013, respectively. Branching of the 2-, 3-, and 4-carbon atoms, however, had little effect on the hydrolysis rate, although steric factors still appeared to be operating in view of the slight increases in rate as the methyl group was placed farther from the phosphorus atom. Rate increases were registered on substitution of a phenyl group at phosphorus and also by the presence of halogen in the alkyl chain.

The effect of structure on the rate of alkaline hydrolysis of phosphonate esters had previously been examined by Hudson et al[48]. In this investigation, both the effect of the ester group and the effect of the substituent at phosphorus on the rate of acid and alkaline hydrolysis were studied. It was observed that increases in the size of the ester group resulted in decreases in the rate of the alkaline hydrolysis reaction, and the following relative rates for a series of methylphosphonate esters $(CH_3PO_3R'_2)$ were obtained: methyl (600) $>$ ethyl (40) $>$ isopropyl (1) $>$ neopentyl (0·33). It was suggested that the decrease in the rate of reaction with increasing substitution at the ester carbon was a result of increased conjugation of the alkoxy group with the phosphonyl group $R'-\overset{\curvearrowleft}{C}\overset{\curvearrowright}{=}P\overset{\curvearrowleft}{=}O$, and also possibly increasing steric hindrance by the alkoxy group $(R')$, the latter effect being indicated by the reduced reactivity of the neopentyl ester. It was also suggested that the lack of an observed increase in activation energy for the hydrolysis of the dineopentyl-methylphosphonate (in contrast to reactions of neopentyl halides) and the activation energies for the series in general (56 – 63 kJ mol$^{-1}$) are indicative of attack at phosphorus, since higher values are normally observed in reactions

of water and hydroxyl ion at a saturated carbon atom e.g. in the hydrolysis of alkyl halides[49].

Rate changes of a different order of magnitude were observed for the acid catalysed hydrolysis of these compounds. The observed rate sequence was explained by a mechanism involving protonation of the phosphonate (the rate of which is assumed to increase with basicity of the alcohol), followed by a bimolecular reaction between water and the protonated ester, the rate of which increases in the same order as in alkaline hydrolysis. The intervention of an $SN_1P$ mechanism in the reaction was also suggested, in agreement with the extensive racemisation observed in the acid catalysed hydrolysis of phosphonates of optically active alcohols[50]. Substitution at the phosphorus atom produced little effect on the rate of the acid catalysed reaction, and relative rates of 1 : 0·5 : 0·5 : 0·33 : 0·33 were observed for the acid hydrolysis of diisopropyl esters of methyl-, ethyl-, n-propyl-, n-butyl and t-butylphosphonic acids respectively.

Finally the reactivities of aliphatic and aromatic phosphonates were compared. In agreement with Fukuto and Metcalf[46,47], a slight increase in the rate of alkaline hydrolysis was observed with a phenyl substituent at phosphorus (kPh/kMe = 1·8 : 1). The reverse has been observed in the case of carboxylic esters[51], in agreement with spectroscopic observations which suggest that phenyl groups do not conjugate significantly with the phosphorus atom[2]. The high lability of the aromatic ester group compared with the aliphatic ester group was indicated by increases in the rate of alkaline hydrolysis and also by exclusive release of p-nitrophenol from ethyl-p-nitrophenylmethylphosphonate in alkaline solution. The analogous reaction in acid solution leads to the release of ethanol at a rate similar to the acid catalysed hydrolysis of diethyl-methylphosphonate.

$$X-C_6H_4-\overset{\overset{\displaystyle O}{\|}}{C}CH_2O\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle CH_3}{|}}{P}}O-C_6H_4-NO_2$$

(XLVI)
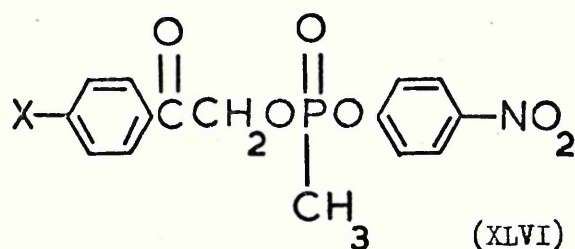
In continuation of studies[52,53] relating to the large increase in the rate of phosphonate ester hydrolysis, which results from the incorporation of a suitably placed ketonic group in the molecule, Lieske et al[54] investigated the effect of substituents on the rate of alkaline hydrolysis and toxicity of a series of substituted phenacyl-p-nitrophenylmethylphosphonates (XLVI). Increase in the rates of alkaline hydrolysis with increasing electron-attracting ability of the substituents was observed and a linear correlation between the rates of alkaline hydrolysis and the Hammett sigma $(\sigma)$ values obtained, $(\rho = 1 \cdot 43)$. Results of biological testing indicated an apparent correlation with the hydrolysis data. In this case, however, in contrast to the observations reported by Fukuto and Metcalf[44,46,47], the toxicity of the compound (as indicated by $LD_{50}$ values) decreased with increase in the rate of alkaline hydrolysis. Lieske[54] suggested that in view of the ready susceptibility of phenacylphosphonates to alkaline degradation, the compounds are possibly hydrolysed before reaching vital centres.

Aksnes et al[55] observed that electronegative substituents exhibited a much greater influence on the rate of nucleophilic reaction in carbonyl compounds than in phosphonyl compounds. Thus the relative rates for the alkaline hydrolysis of various diethylphosphonates $(RP(O)(OC_2H_5)_2)$ with $R = CH_3$ as reference are $C_2H_5$ : 0·13, $CH_3$ : 1, $ClCH_2$ : 15·6, and $Cl_2CH$ : 108, whilst for comparison, the relative rates for the corresponding carboxylic acid esters $(RCO_2C_2H_5)$ were estimated as $C_2H_5$ : 0·9, $CH_3$ : 1, $ClCH_2$ : 258, $Cl_2CH$ : 5000. Aksnes thus suggested that electron-withdrawing substituents which make the phosphorus atom more positive, hence assisting the approach of a nucleophile, also have the effect of increasing $p\pi - d\pi$ overlap between the leaving group

and phosphorus, and as the hydrolysis reaction involves bond-breaking as well as bond-formation in the transition state, the two effects almost cancel. The increase in the dative $\pi$-bonding by the ethoxy groups and by the phosphonyl oxygen on chlorination are further indicated in the rise of the frequency of the infrared stretching vibration of the phosphonyl group.

A comparison of the energies and entropies of activation for the alkaline hydrolysis reactions of the corresponding phosphonyl and carbonyl esters revealed that whilst the activation energies are almost identical, the activation entropies are more positive for the carboxylic esters. Aksnes[55] proposed that the reason for this difference is most likely the greater restriction laid upon the transition state for the alkaline hydrolysis of the phosphonate esters, which must satisfy the requirements for the synchronous movements of the incoming nucleophile as well as the leaving group. By contrast, in the intermediate for the carboxylic ester hydrolysis, fully developed $\sigma$ bonds are formed and all the degrees of freedom are left undisturbed.



solvolysis                      alkaline hydrolysis

(XLVII)
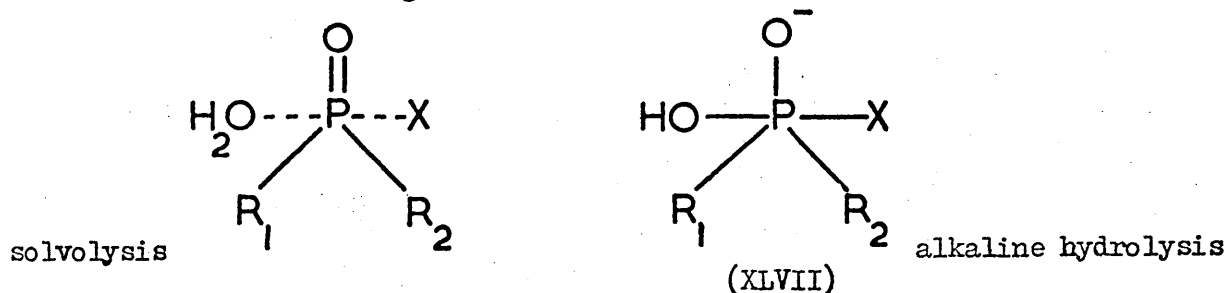
Work by Hudson et al[11] also established an increase in the rate constant and a corresponding decrease in activation energy for the alkaline hydrolysis of diethylchloromethylphosphonate compared with the corresponding alkyl-phosphonates $(RP(O)(OC_2H_5)_2)$. The influence of a $\beta$-chlorine atom on the rate of solvolysis of the corresponding chloridates $(R(C_2H_5O)P(O)Cl)$, however, was found to be considerably less and moreover the activation energy is increased. Hudson therefore suggested that in contrast to reactions at the carbonyl centre, in which the changes in reactivity correspond to changes in bond-forming energies, in phosphorus compounds bond-breaking becomes more important. Furthermore, the bonding is more variable. In solvolysis, bond-breaking and

bond-making are quite comparable, but in the alkaline hydrolysis reaction, the transition state structure is probably similar to that of an addition intermediate (XLVII). Consequently bond-forming influences are stronger in (XLVII) than in solvolysis.

Many workers[9,10,12,56,57] have demonstrated that alkoxy groups reduce the rates of reaction of phosphoryl, phosphonyl, and phosphinyl chlorides with nucleophilic agents, and have postulated a deactivating $p\pi-d\pi$ conjugation with the phosphorus atom in the ground state acting in opposition to the inductive effect[9,10,12]. Thus rate data reveals that a methoxy group reduces the rate of solvolysis of methylethylphosphonochloridate by a factor of 15 - 20 times, compared with diethylphosphinyl chloride, whilst a factor of $3 \times 10^3$ is observed for the relative reactivities of the analogous acetyl chloride and ethyl chloroformate[58]. The large difference in effects was attributed to the greater $p\pi-p\pi$ bond energy in carbonyl compounds compared with $p\pi-d\pi$ bond energy in phosphacyl compounds. Haake[7] suggested that the rate reduction is indicative of an associative mechanism, since the conjugation between the alkoxy groups and phosphorus appears to stabilise the ground state more than the transition state. Evidence for associative displacement in phosphacyl chlorides includes (i) rate enhancement on addition of nucleophilic agents[9], (ii) rate dependence on the size of the nucleophile[9], (iii) steric retardation by large substituents at phosphorus[10] and (iv) rate inhibition due to angle strain at phosphorus[7]. Rate comparisons in isosolvolytic[59] media also indicate the predominance of an associative mechanism, for example the solvolyses of phosphoryl and phosphonyl chlorides are $10^3$ times slower in formic acid than in the isosolvolytic but more nucleophilic aqueous ethanol[9,60].

The rate of alkaline hydrolysis of phosphacyl fluorides is also reduced significantly by the substitution of alkoxy groups as shown by the following relative reactivities[61]: $(C_2H_5)_2P(O)F$ (450), $C_2H_5(CH_3O)P(O)F$ (11), and $(CH_3O)_2P(O)F$ (1). Thus the situation resembles that for the solvolysis of

chlorides[10].

The replacement of alkoxy groups by alkylamino groups also has the effect of decreasing reactivity[10]. Since nitrogen is less electronegative than oxygen, the observed order is in agreement with the formation of stronger multiple bonds with nitrogen. There is some evidence[62], however, that bond-breaking becomes increasingly important in the hydrolysis of phosphorochloridamidates, owing to this conjugation.

Hudson et al[63] observed the alkaline hydrolysis of phosphacyl esters to be only slightly affected by alkoxy groups, and the following esters are hydrolysed by hydroxide ion at the relative rates per methoxyl group as shown.

$$(C_2H_5)_2 \overset{\overset{O}{\|}}{P}OCH_3 \qquad C_2H_5 \overset{\overset{O}{\|}}{P}(OCH_3)_2 \qquad (CH_3O)_3P{=}O$$

$$5{\cdot}9 \qquad\qquad\qquad 4{\cdot}2 \qquad\qquad\qquad 1{\cdot}0$$
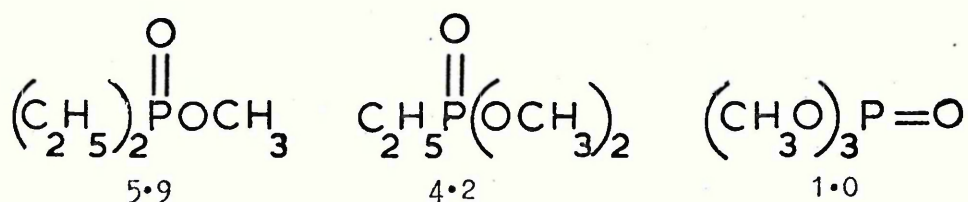
The effect of structure on the rate of alkaline hydrolysis of phosphinate esters has been studied by Haake[7,26,28-30,64]. Hydrolyses in oxygen-18 enriched media[26,28,30] have shown the reactions to proceed exclusively with attack of hydroxide ion at phosphorus, whilst variations in the concentrations of ester and base have demonstrated that the rates of hydrolysis are first-order in ester and first-order in base. The single exception, tert-butyldiphenyl-phosphinate, was observed to hydrolyse with first-order kinetics, the rate being independent of the concentration of base.



(XLVIII)

(L)

(IL)
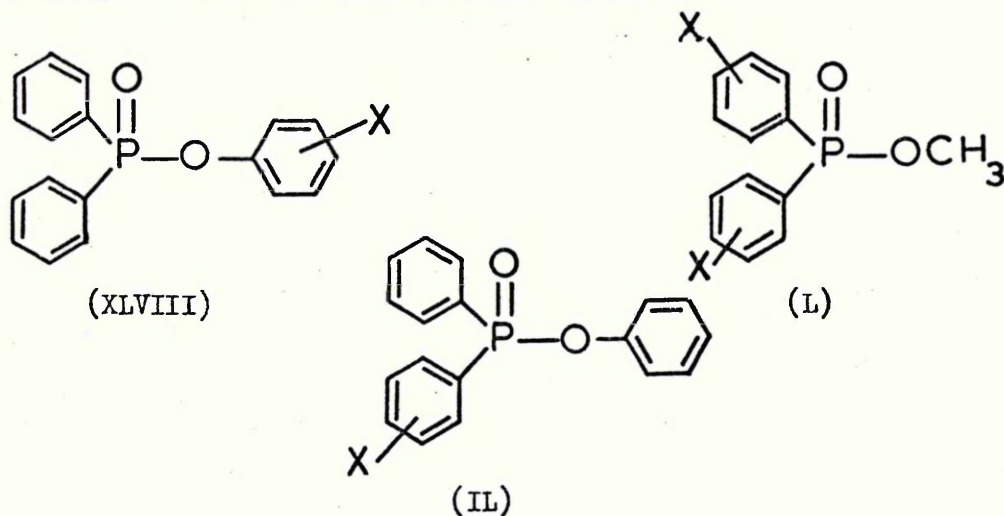
The plot of log k(hydrolysis) for (XLVIII) versus Hammett sigma $(\sigma)$

values[64] for the substituent X revealed a linear correlation $(\rho = 2 \cdot 2)$.

A similar plot of log k(hydrolysis) versus the $pK_a$ of the corresponding phenols,

however, revealed a significant deviation for the p-acetyl compound from a good

straight line defined by the remaining compounds (slope = $1 \cdot 0$). It was

suggested that the deviation of the p-acetyl compound indicated that a

significant charge is not developed on the phenolic oxygen in the transition

state i.e. the structural change from the ground state of the phosphinate to

the transition state does not resemble the structural change from phenol to

phenoxide ion for ArOH.

The linear correlation[64] of $\sigma$ values with log k(hydrolysis) for (IL)

$(\rho = 0 \cdot 7)$ (which includes the p-methoxy compound) indicated a resonance type

interaction in the reaction. Similarly the linear correlation[64] of log k(rela-

tive) for the alkaline hydrolysis of (L) relative to methyldiphenylphosphinate

with $\sigma$ parameters included data for the para-dimethylamino compound. The rate

data for the alkaline hydrolysis of ethyl benzoates was also shown to correlate[65]

with log k or log k(relative) of (IL) and (L) respectively, and thus Haake

suggested substituent effects to be similar for nucleophilic displacement

reactions of benzoates and arylphosphinates.



(LI)          (LII)          (LIII)
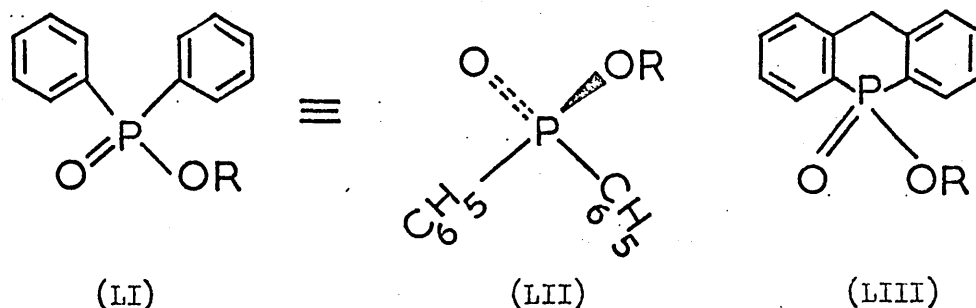
In order to investigate the nature of the $\pi$-interactions between the

phenyl rings and the phosphinyl phosphorus, the effect of changing the angular

relation between the planes of the phenyl rings and the O—P—O plane, on the

rate of alkaline hydrolysis was examined[30]. Crystal structure analysis[66] shows the diphenylphosphinates (LI) to have the "A-frame" conformation (LII) of the two phenyl rings, whilst in diphenylmethane-2,2-phosphinic acid (LIII; R = H) the phenyl rings are turned towards a more planar arrangement. The relative rates of alkaline hydrolysis of (LI; R = $CH_3$) and (LIII; R = $CH_3$) revealed the change in orientation of the phenyl rings to have a negligible effect, indicating the $\pi$-interaction to be independent of the angle between the phenyl ring and phosphinyl phosphorus. Haake thus suggested[30] that the $\pi$-bonding involved orbitals at phosphorus with considerable d-character since d-orbitals should be able to accomodate any orientation of the phenyl rings.

Cook et al[67] extended this study to include the heterocyclic phosphinic acid ester (LIV; R = $CH_3$), the structure of which corresponds to the best conformation for phenyl-3d-orbital interaction. The difference in rate, however, between (LIII; R = $CH_3$) and (LIV; R = $CH_3$) was found to be almost equal to that predicted from the $\sigma_p$ value of the methyl group. Cook[67] therefore concluded that the size of the d-orbitals of phosphorus allow them to overlap with the p-orbitals of benzene in spite of the non-planarity of the system.
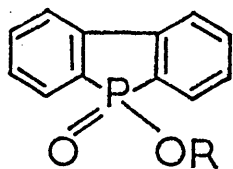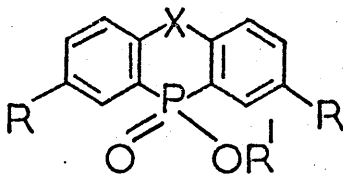


(LIV)                    (LV)

The alkaline hydrolysis of compounds of the type (LV; R' = $CH_3$) in which X and R are varied were also studied by Cook et al[67], to determine if there are across-the-ring field effects on the reactivity at phosphorus. A plot of log k(hydrolysis) versus $\sum \sigma$ values produced a reasonable straight line with the exception that (LV; R' = $CH_3$, X = CO, R = H) hydrolysed considerably faster than the value would predict. The plot of $\sum \sigma$ against the $pK_a$ of the phosphinic

acids (LV; R' = H) gave an excellent straight line for all the compounds, indicating the absence of any special effect for the carbonyl compound. Cook[67] thus postulated the mechanism for hydrolysis of (LV; R' = $CH_3$, X = CO, R = H) to involve attack of hydroxide at carbonyl carbon to form a ketal anion, which would attack phosphorus intramolecularly. The attack at carbon is favoured on steric grounds, and the pentacovalent intermediate formed after intramolecular attack would have a dibenzbicycloheptane-like structure.

The effects of varying the alkyl substituents (R)[26,28,29] on the rate of alkaline hydrolysis of methyldialkylphosphinates ($R_2PO_2CH_3$) revealed a distortion of the rate order from that predicted by $\sigma^*$. Rate constants decreased in the order: methyl $>$ benzyl $\sim$ ethyl $>$ n-butyl $\gg$ isopropyl. Application of the Taft equation, which combines both steric and polar effects[68] (equation 13)

$$\log (k/k_{CH_3}) = \sigma^* \rho^* + \delta E_s \qquad (13)$$

in the form $[\log (k/k_{CH_3})]/\sigma^* = \delta E_s/\sigma^* + \rho^*$ to the data produced a poor correlation, giving $\rho^* = 2 \cdot 5$ and $\delta = 2 \cdot 5$ per substituent. Haake[28] proposed that a comparison with the analogous data for carboxylates ($RCO_2C_2H_5$), which gives $\rho^* = 2 \cdot 48$, demonstrates that the attack of hydroxide at phosphorus in phosphinate esters is about as dependent on the electronic effects of the acyl substituents as the analogous reaction in carboxylates. Acyl substituents in phosphinates, however, cause large steric effects. Using Taft $E_s$ values, $\delta = 1$ for $RCO_2C_2H_5$[68] but $\delta = 2 \cdot 5$ per acyl substituent for $R_2PO_2CH_3$. The steric compression on the addition of $^-OH$ to tetrahedral phosphorus must therefore be larger than for the addition of $^-OH$ to trigonal carbon, and must resemble the effects of carbon substituents in SN2 reactions.

$$Bu^t\!-\!\!\overset{\overset{\displaystyle Bu^t}{|}}{\underset{\underset{\displaystyle X}{|}}{P}}\!\!\cdots Y \quad (LVI)$$

$$\overset{\overset{\displaystyle Bu^t}{|}}{\underset{X\quad O}{P}}\!\cdots Y,\quad Bu^t\!\!\!\nearrow^{\theta} \quad (LVII)$$

$$O^-\!\!-\!\!\overset{\overset{\displaystyle Bu^t}{|}}{\underset{\underset{\displaystyle X}{|}}{P}}\!\!\diagdown Y \quad (LVIII) \qquad \Longrightarrow \qquad O^-\!\!-\!\!\overset{\overset{\displaystyle Bu^t}{|}}{\underset{\underset{\displaystyle X}{}}{P}}\!\!-\!Y \quad (LIX)$$
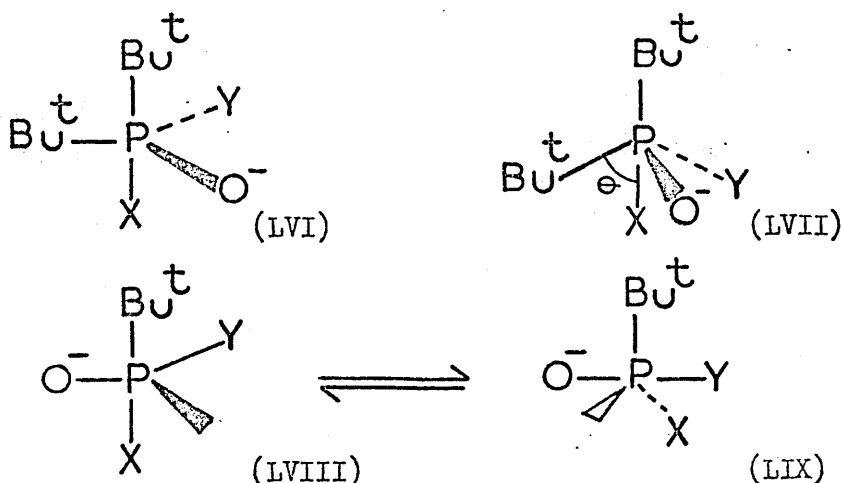
The increased effect of steric hindrance in the alkaline hydrolysis of phosphinate esters has also been observed by other workers. Trippett et al[27] found that whilst one t-butyl group attached to phosphorus in the phosphonate series $(RP(O)(OC_2H_5)_2)$ produces little steric hindrance[48] to attack of $^-OH$ on phosphorus, in the phosphinate series[27] $(R_2P(O)OC_2H_5)$ there is a sharp fall in the rate of alkaline hydrolysis between $R = Pr^i$ and $R = Bu^t$. This retardation is also observed in other substitution reactions, e.g. while dialkylphosphinyl chlorides normally react exothermically with ethanolic sodium ethoxide at room temperature, di-tert-butylphosphinyl chloride, however, is essentially unchanged after refluxing for 24 hours with this reagent.

Trippett[27] proposed that with two t-butyl groups attached to phosphorus, one must occupy an equatorial position in the first intermediate trigonal bipyramid (LVI). In the transition state (LVII) leading to this intermediate, the angle $\theta$ is less than $90^\circ$ and despite a P–C bond length of $\sim 1 \cdot 87$ Å, substantial hindrance from the "equatorial" t-butyl group to attack of the nucleophile is apparent at this point. With only one t-butyl group on phosphorus, there is little hindrance to attack of the nucleophile, as the t-butyl group can occupy an apical position in the first intermediate trigonal bipyramid (LVIII). Pseudorotation to the trigonal bipyramid (LIX) then occurs before expulsion of the group Y from an apical position.
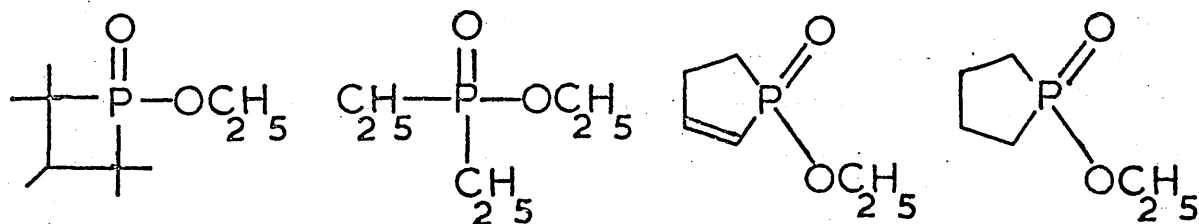
| Relative Rate | 2·9 | 1·0 | 1·5 | 4·0 |
|---|---|---|---|---|
| | (IX) | (LXI) | (XXI) | (XX) |

Previous studies have shown that five-membered cyclic esters of phosphonic and phosphoric acids are hydrolysed $10^5 - 10^9$ times as rapidly as the corresponding six-membered cyclic esters and open-chain analogues[20,69]. Similarly in phosphonium salts, the four- and five-membered ring systems undergo reaction much more rapidly than the six-membered ring systems[70]. Haake et al[7,26,28], however, observed that incorporation of phosphorus into four and five-membered ring systems in the phosphinate series produced little effect on the rate of alkaline hydrolysis. Haake proposed that in view of the combination of possible steric and ring size effects which would predict a very slow rate of hydrolysis of (IX) if displacement were proceeding in SN2 fashion, the slightly faster hydrolysis of ethylpentamethyltrimethylenephosphinate (IX) compared with ethyldiethylphophinate (LXI) indicated that displacement must be possible by a pathway with a geometry in which entering and leaving groups may be other than co-linear with phosphorus. The result therefore supports the presence of a pentacoordinate intermediate in the reaction.
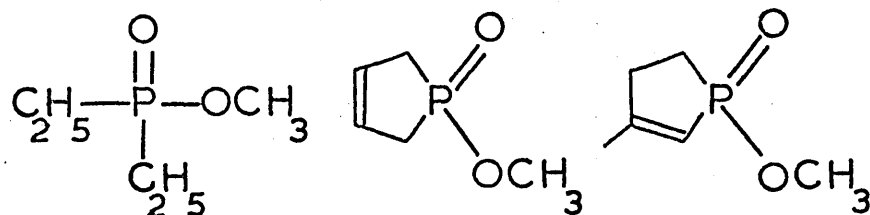


| Relative Rate | 1·0 | 42·0 | 1·2 |
|---|---|---|---|
| | (LXII) | (LXIII) | (LXIV) |

The rate effects obtained for the series of five-membered ring phosphinic acid esters were interpreted[26,28] on the basis of a deceleration in the alkaline hydrolysis of the 2-phospholenes ( XXI ) and ( LXIV) compared with the

corresponding 3-pholene (LXIII), due to conjugation of the double bond with phosphorus.

Large rate effects were observed by Haake et al[28-30] on the variation of the ester group in phosphinates. The rate ratios for groups (R') in diethylphosphinates $[(C_2H_5)_2PO_2R']$ were found to be methyl (157) > ethyl (21) > isopropyl (1), and for diphenylphosphinates $[(C_6H_5)_2PO_2R']$, methyl (320) > ethyl (26) > isopropyl (1). Treatment of the data by equation 13 gave $\rho^* = 8$ and $\delta = 1.5$ for diethylphosphinates and $\rho^* = 11$ and $\delta = 0.6$ for diphenylphosphinates. In contrast, the ratios for the alkaline hydrolysis of acetates $(CH_3CO_2R)$ are methyl (6) > ethyl (4) > isopropyl (1), furthermore[71], $\rho^* = 1.34$ and $\delta = 0.7$. Haake[28] proposed that the origin of the large O-alkyl substituent effects was related to the mechanism of hydrolysis of phosphinate esters, and the contrast with carboxylates is due to the difference in mechanism.



ground state              transition state

(LXV)                     (LXVI)                   (LXVII)
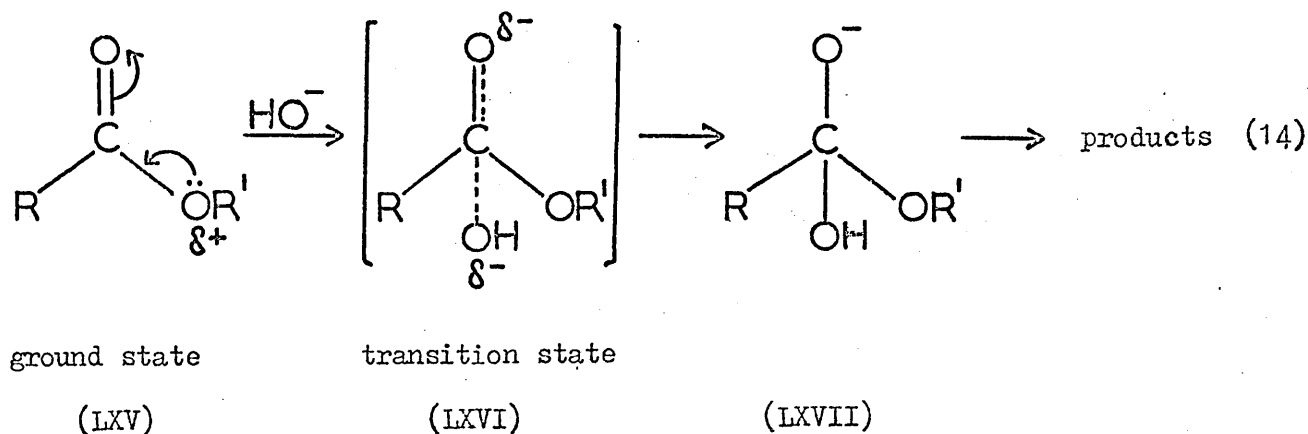
In benzoates, oxygen-18 studies have demonstrated that the rate-determining step is the formation of the tetrahedral intermediates[72]. Therefore, O-alkyl substituents have their primary effect in the ground state; because of the π-interaction of the oxygen atom with the carbonyl group, the alkyl oxygen will be partially positive and withdraw electrons from the alkyl group. The interaction thus resembles that for acyl substituents.

$$HO^- + \text{(XXVII structure, } R_2P(=O)OCH_3) \xrightarrow[k_{-1}]{K_1} \text{(pentacoordinate intermediate)} \xrightarrow{K_2} R_2PO_2^- + CH_3OH \tag{8}$$
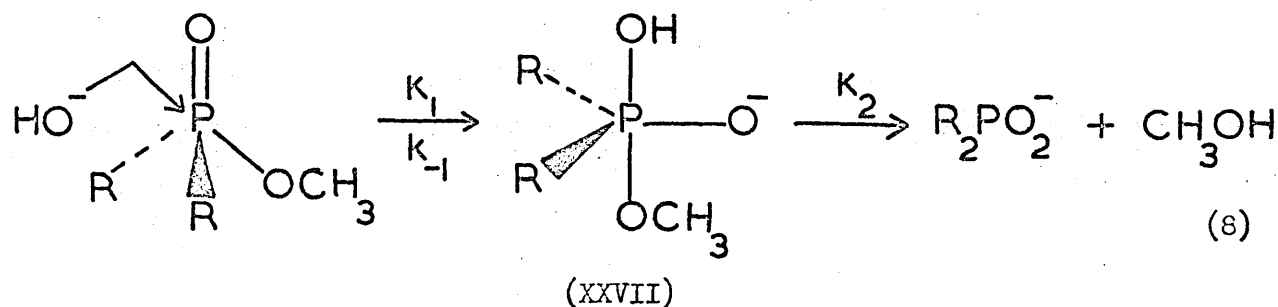
(XXVII)

In phosphinates the substituent effects are quite different. The $\rho^*$ values are too large to be explained by rate-determining attack of hydroxide ion to form a pentacoordinate intermediate (XXVII), and require the breakdown of the intermediate to be rate-determining. The charge on the alkyl oxygen will then change (equation 15) from partially positive in the ground state, to the partial negative charge of the developing alkoxide ion in the transition state. The large $\rho^*$ values can then be interpreted on the basis of interactions of the substituent with a partially positive and partially negative alkyl oxygen.

$$\underset{\text{ground state}}{R_2P(O)(OR')^{\delta+}} \xrightarrow{HO^-} \text{(XXVII)} \longrightarrow \underset{\text{transition state}}{\left[ \begin{array}{c} ^{\delta-}OR \\ R_2P\text{-----}O^{\delta-} \\ OH \end{array} \right]} \longrightarrow \text{products} \tag{15}$$
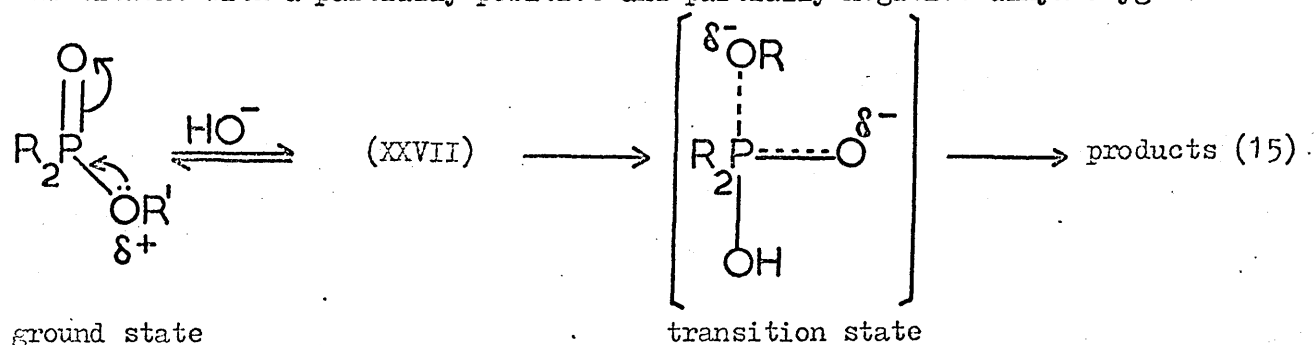
The transition state (and the pentacoordinate intermediate) are oxyanions which will have high solvation requirements. Steric hindrance to solvation of the negative oxygen atom will be considerably greater in pentacoordinate intermediates from phosphinate esters than in the tetracoordinate intermediates from carboxylates, due to greater steric crowding inherent in placing five rather than four groups around a central atom. This steric hindrance to solvation of the transition state may also contribute to the large $\rho^*$ value observed for phosphinate esters.

The hypothesis of rate-determining breakdown of the intermediate is further supported by examination of the relative barriers expected for loss of $^-$OH and $^-$OR. The relative heights of the barriers for decomposition of (XXVII)

to ester $(k_{-1})$ or products $(k_2)$, should depend on the relative basicity of the

two leaving groups. Since alkoxide ions are more basic than hydroxide ions

$k_2 < k_{-1}$; i.e. rate-determining conversion of intermediate to products. When

the leaving group is less nucleophilic than the entering group $k_2 > k_{-1}$ and

the reaction constants will be a measure of electronic effects for intermediate

formation only, and should therefore be reduced. Thus in the alkaline hydrolysis

of arylphosphinates $(C_6H_5)_2PO_2C_6H_4X$ where the phenoxide ion is a better

leaving group than hydroxide ion[64], $\rho$ is reduced to 2·2.

The occurrence of $\pi$-bonding involving the overlap of a phosphorus d-orbital

with a p-orbital of an adjacent atom has been firmly established for a number

of tetracovalent phosphacyl compounds.[73] Such $p\pi - d\pi$ bonding has been

demonstrated in instances in which nonbonding electrons of electronegative

atoms, primarily oxygen, nitrogen, sulphur and chlorine, are donated to the

empty phosphorus d-orbital. The possibility of a comparable interaction

involving the donor properties of a $\pi$-bonded system has stimulated discussion

in recent literature. For organic compounds, some of the strongest evidence

for conjugation has been obtained from electronic absorption spectra, and this

approach has been widely utilised in studies of organophosphorus compounds.

In an extensive study Jaffé, Freedman and Doak[74] examined the ultraviolet

absorption spectra of triphenylphosphine oxide and a number of arylphosphonous,

arylphosphonic, and diarylphosphinic acids containing bromo, chloro, and nitro

substituents, and found evidence of only very weak $p\pi - d\pi$ bond formation.

Small bathochromic shifts of $< 10$ m$\mu$ relative to the parent arene and a 1·5 – 5

fold increase in the intensity of absorption were observed, and any fine

structure found in the spectrum of the parent compound was usually unaltered

by the presence of the phosphacyl group. Furthermore, the consecutive addition

of phenyl radicals to the phosphorus atom in the series changed the molar

absorption coefficient in a ratio more or less equal to the number of phenyl

rings introduced, leading to the conclusion that each ring linked to the

phosphacyl group is only slightly affected as far as its $\pi$-electron system is concerned, thus indicating no or very weak conjugation.

Griffin and Hseih[75,76] studied the ultraviolet absorption spectra of a wide range of para-substituted triarylphosphine oxides and observed substantial shifts of the wavelength of the primary band relative to that of the parent substituted benzene. The magnitude of these shifts were roughly comparable with the displacements observed in the corresponding substituted benzoic acids, and it was concluded that the $\pi$-orbital of the aromatic nucleus could interact with an empty d-orbital of the phosphorus atom. Thus in tetracovalent phosphorus compounds, the phosphacyl group can be regarded as a potential electron-withdrawing group which can interact with an electron-donating group in the para-position of the benzene ring. The $p\pi$ — $d\pi$ interaction is weaker than $p\pi$ — $p\pi$ interactions, but becomes more important with increase in electron-donating power of the substituent.

Griffin and Hseih[75,76] further reasoned that the strength of the $p\pi$ — $d\pi$ interaction should also be dependent on the magnitude of the positive charge on phosphorus. Accordingly, the absorption spectra of a series of para-substituted phenylphosphonium salts revealed larger shifts than were observed for the corresponding phosphine oxides.

Similar results to the above were obtained independently by Schiemenz and Roehlk[77] who examined the ultraviolet spectra of a series of phosphorus-substituted anilines $\left[ p\text{-}XC_6H_4NH_2; \; X = P(C_6H_5)_2, \; P(O)(C_6H_5)_2, \; P(S)(C_6H_5)_2, \; \overset{+}{P}CH_3(C_6H_5)_2 \; \text{and} \; \overset{+}{P}(C_6H_5)_3 \right]$, and compared these spectra with those of para-toluidine and para-phenylenediamine. Consideration of the spectra revealed fairly strong bathochromic shifts of the main absorption band relative to that of aniline. The magnitude of the effect decreased with increasing electron density at the phosphorus atom, in the order $\overset{+}{P}(C_6H_5)_3 > \overset{+}{P}CH_3(C_6H_5)_2 > P(S)(C_6H_5)_2 \approx P(O)(C_6H_5)_2 \approx P(C_6H_5)_2$. The phosphorus atom acted as a strong insulator between the rings i.e. no through conjugation or interaction between different

aryl groups was observed.

The general conclusions of this study were further supported by examination

of para-anisyl[78] and para-nitrophenyl[79] systems.

$$CH_2=CH-\overset{\displaystyle OR}{\underset{\displaystyle OR}{P}}=O$$
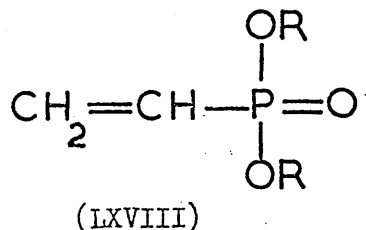
(LXVIII)

The possibility of conjugation in vinylphosphorus compounds has been

investigated by a number of workers. Esters of vinylphosphonic acids (LXVIII)

were prepared as early as 1945[80], and the addition of nucleophilic reagents to

the double bond were investigated by Pudovic[81], who found that under the

catalytic action of alkoxide ion the addition scheme is as follows:

$$BH + {}^{-}OR \rightleftharpoons \overset{..}{B} + ROH$$

$$CH_2=CHP(O)(OR)_2 + \overset{..}{B} \longrightarrow \overset{\frown}{BC_2H_3P(O)}(OR)_2$$

$$\overset{\frown}{BC_2H_3P(O)}(OR)_2 + ROH \rightleftharpoons BC_2H_4P(O)(OR)_2 + {}^{-}OR$$

where       $B = NH_3$     $CH_2(COOC_2H_5)_2$     $HP(O)(OC_2H_5)_2$

                $RNH_2$     $CH_2(COOC_2H_5)CN$     $HP(S)(OC_2H_5)_2$

                $R_2NH$     $CH_3COCH_2COOC_2H_5$     $RPH(O)(OR)$

                $H_2S$     $RSH$    $C_6H_5CH_2CN$     etc.
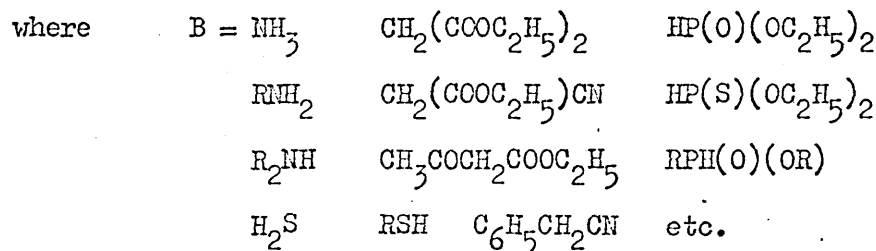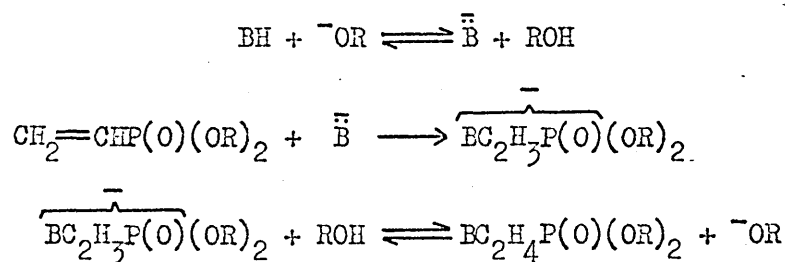
Scheme III

The reactivity of the double bond in vinylphosphorus compounds has also

been investigated by Kabachnik with a number of co-workers. In addition to

vinylphosphonic acid derivatives a number of alkylalkylvinylphosphinates

(LXIX)[82], alkylhydrogenvinylphosphinates (LXX)[82], and tertiary vinylphosphine

oxides (LXXI)[83] were prepared and studied.

$$CH_2=CH-\overset{\underset{\textstyle OR}{\textstyle |}}{\overset{\textstyle R}{\overset{\textstyle |}{P}}}=O \qquad\qquad CH_2=CH-\overset{\underset{\textstyle OR}{\textstyle |}}{\overset{\textstyle H}{\overset{\textstyle |}{P}}}=O$$

$$\text{(LXIX)} \qquad\qquad\qquad \text{(LXX)}$$

$$CH_2=CH-\overset{\underset{\textstyle R}{\textstyle |}}{\overset{\textstyle R}{\overset{\textstyle |}{P}}}=O$$

$$\text{(LXXI)}$$
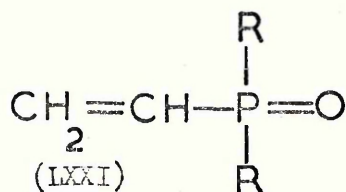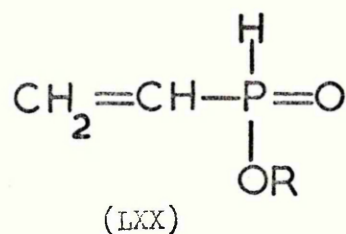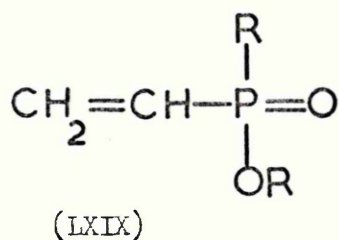
A property of the vinylphosphorus compounds was found to be rapid nucleophilic
(Michael) additions to the double bond, indicating the electron density of the
vinyl group to be depleted by the phosphacyl group, much in the manner of an
$\alpha,\beta$-unsaturated carboxylic ester. Thus piperidine addition to vinylphosphonates
and similar systems yields $\beta$-piperidinoethyl organophosphorus compounds
(equation 16). Addition of electrophilic agents such as chlorine and bromine
was found to be difficult[80,84].

$$\underset{\text{(piperidine)}}{\bigcirc\!\!-\!NH} + CH_2=CH-\overset{\textstyle O}{\overset{\textstyle \|}{P}}(OC_4H_9)_2 \longrightarrow \bigcirc\!\!-\!N-CHCH_2\overset{\textstyle O}{\overset{\textstyle \|}{P}}(OC_4H_9)_2 \qquad (16)$$
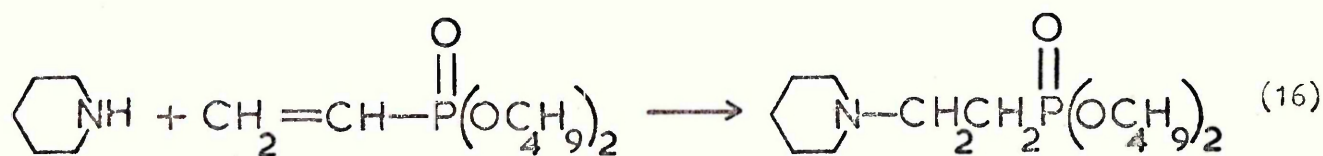
The rate of addition of the nucleophilic agents varies with the nature of the
groups linked to phosphorus, and increases with increasing electrophilic
character of the substituent. Thus addition of piperidine to (LXX; $R = C_4H_9$)
takes place with a violent exothermic reaction, whereas addition to (LXXI;
$R = C_4H_9$) requires prolonged heating.

$$CH_2=CH-P\!\!\underset{\textstyle R}{\overset{\textstyle R}{\big<}} \qquad\qquad CH_2=CH-P\!\!\underset{\textstyle OR}{\overset{\textstyle OR}{\big<}}$$
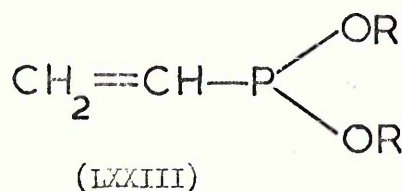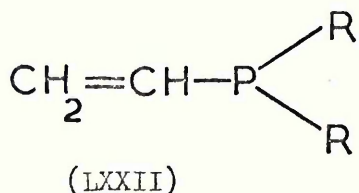
$$\text{(LXXII)} \qquad\qquad\qquad \text{(LXXIII)}$$

Vinyl compounds of trivalent phosphorus (LXXII) and (LXXIII) were also
found to add piperidine in the $\beta$-position[85]. In this case $\beta$-orientation must
also be due to the conjugative participation of d-orbitals of the phosphorus
atom, just as has been observed in vinylsilanes.

Analysis of spectroscopic data for vinylphosphorus compounds[86], however, indicates the absence of conjugation in these molecules. The absorption maximum in the ultraviolet region, as compared with that of 1-hexene, was found to be either unchanged or slightly shifted to shorter wavelength. Molar absorption coefficients are also little affected. Similar results were obtained from infrared and Raman spectra, and from molar refraction studies.

Kabachnik[86] suggested that the apparent contradiction of chemical and spectroscopic evidence may be due to the magnitude of the effect anticipated. Optical methods reveal the presence or absence of strong interactions corresponding in energy to quanta of electronic or vibrational excitations. Chemical evidence, however, is sensitive to weaker interactions, the energy of which though lower, is high enough to affect markedly the reaction constant or the equilibrium. The apparent contradiction thus arises due to the fact that the conjugation is too weak to be observed spectroscopically, but is strong enough to be detected by more sensitive chemical means.

The possibility that the weak interactions in question should be readily revealed radiospectroscopically (since the quantum energy of radio frequencies is considerably lower than that of the optical range), was investigated by Mastrukova and Melentyeva in collaboration with Voevodsky and Solodovnikov. Hein et al had shown previously that triarylphosphine oxides[87] and trialkyl-phosphine oxides[88] form with potassium in tetrahydrofuran, the so-called "phosphyls" of the metal-ketal type (LXXIV).

$$R_3P{=}O \; + \; K \; \longrightarrow \; R_3\overset{\bullet}{P}{-\!-}OK$$
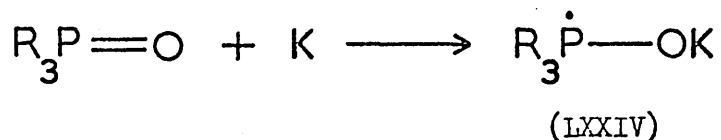
(LXXIV)

The E.P.R. spectrum of potassium triphenylphosphine oxide (LXXIV; R = $C_6H_5$) reveals the spin of the unpaired electron to be delocalised in all three rings, and the molecule is thus presented as a single conjugated system. The spectra

of potassium dimethylphenylphosphine oxide and potassium methyldiphenylphosphine oxide similarly indicate delocalisation of the spin of the unpaired electron in the phenyl rings. It was thus concluded[86] that phosphorus participates in conjugation and is not a barrier disconnecting conjugated regional systems. The conjugation must, however, be classified as a weak interaction.



(LXXV)          (LXXVII)          (LXXVI)
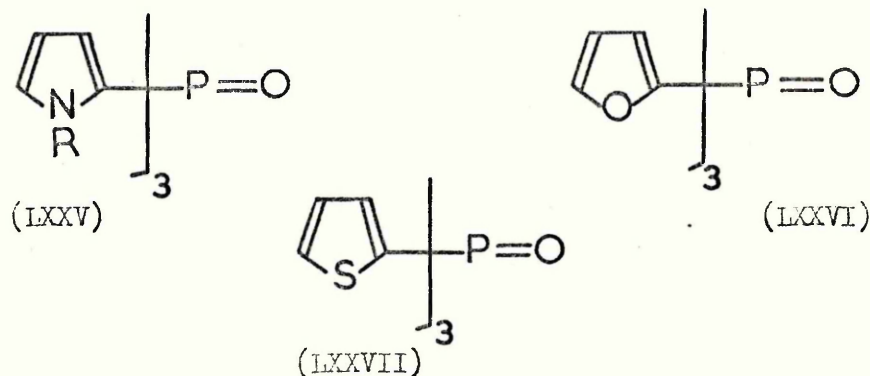
U.V. evidence for a $p\pi$ — $d\pi$ conjugative interaction in heteroaryl-phosphine oxides was obtained by Griffin et al[89]. The appearance of absorption bands at $237 \cdot 5$ m$\mu$ for tri-(2-pyrrolyl)phosphine oxide (LXXV; R = H) and 243 m$\mu$ for tri-2-(1-methylpyrrolyl)phosphine oxide (LXXV; R = $CH_3$) represented bathochromic shifts relative to the parent heteroarenes of $26 \cdot 5$ m$\mu$ and 35 m$\mu$ respectively. The hypsochromic shifts for (LXXV; R = H and R = $CH_3$) relative to the 2-carbonyl substituted pyrroles indicated that the degree of conjugation in (LXXV; R = H and R = $CH_3$) is much weaker.

Similar conclusions were obtained from the spectrum of tri-(2-furyl)-phosphine oxide (LXXVI). The intense absorption at 238 m$\mu$ represented a 33 m$\mu$ bathochromic shift of the primary absorption band of the parent heterocycle. In this instance, however, the bathochromic shift relative to the parent arene is almost as large as that produced by a carboxyl group.

The conjugative interaction in the case of tri-(2-thienyl)phosphine oxide (LXXVII) is less apparent. The bathochromic shift (7 m$\mu$) relative to thiophen is only slightly greater than that produced by a typical inductive substituent (2-bromothiophen, $\Delta\lambda = 4 \cdot 5$ m$\mu$), and much less than shifts produced by carbonyl substituents ($\Delta\lambda = 37 \cdot 5 - 47 \cdot 5$ m$\mu$).
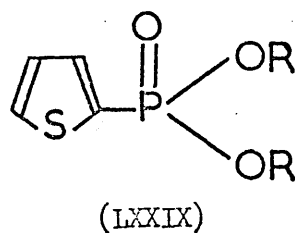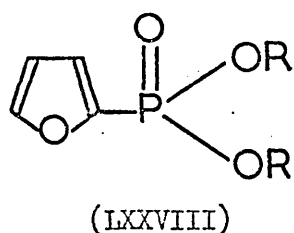
(LXXVIII)　　　　　　　　(LXXIX)

A detailed analysis[90] has been made of the $^1$H n.m.r. spectra of the above phosphine oxides (LXXV), (LXXVI) and (LXXVII) and of the related dimethyl-(2-furyl)phosphonate (LXXVIII; R = CH$_3$) and dimethyl-(2-thienyl)phosphonate (LXXIX; R = CH$_3$), and the chemical shift data has been used to indicate the presence of $p_\pi$——$d_\pi$bonding in these heteroarylphosphorus compounds. Substantial deshielding of H(5) in (LXXVI) – (LXXIX) was interpreted as a reflection of $p_\pi$——$d_\pi$interactions, represented by the contribution of canonical form (C) (Scheme IV) to the resonance hybrid. Deshielding of H(3) in (LXXVI) – (LXXIX) relative to the parent heteroarene was also observed, possibly indicating the contribution of form (B); whilst the chemical shift of H(4) was found to be quite insensitive to the presence of substituents at C(2).



(A)　　　　　　　　(B)　　　　　　　　(C)

Scheme IV

(F)　　　　　　　　(E)　　　　　　　　(D)
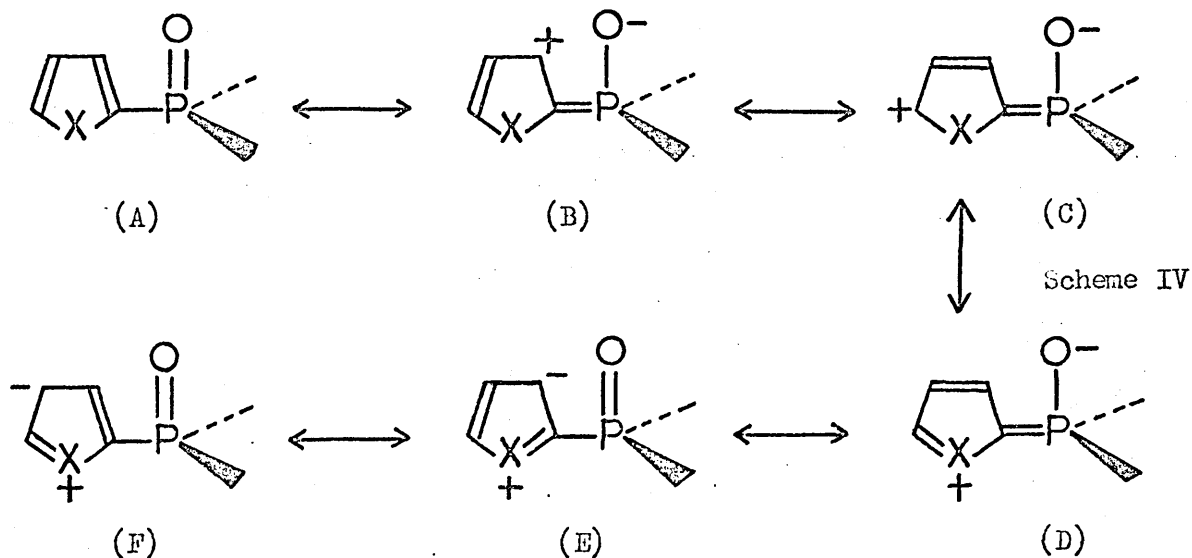
The increase in solvent polarity results in greater decreases in chemical shift at H(5) than for any other ring proton. On the basis of the concept of a $p_\pi$——$d_\pi$interaction, the canonical form (C) possessing the greatest degree of charge separation, would be expected to be increasingly stabilised compared with the other charge separated structures, (B), (D), (E) and (F).

In contrast to the behaviour of the phosphonylated furans and thiophens, the chemical shifts of H(3) and H(5) of the phosphonylated pyrroles (LXXV; R = H and R = CH$_3$) are almost the same as those observed for the parent arene. The results thus indicate p$_\pi$— d$_\pi$ bonding to be a more important determinant of $^1$H parameters for the 2-furyl and 2-thienyl compounds than for their 2-pyrrolyl analogues, an observation contrary to that based on ultraviolet spectroscopy[89]. Consequently, it would appear that the contribution of structures (B) – (D) (Scheme IV) to the ground and excited states of these molecules are, as would be expected, substantially different.

On the basis of this data it is of interest to consider the results of Allen et al[91,92], who reported the effect of possible p$_\pi$— d$_\pi$ bonding to be of little consequence in the determination of the rates of alkaline of 2-thienyl- and 2-furylphosphonium salts. In this case the inductive effect of the substituents, due to the electronegative heteroatom, was shown to predominate. It was of interest therefore, in view of the differences in mechanism which exist for nucleophilic displacement reactions at phosphonium and phosphacyl centres, to investigate the effects of possible p$_\pi$— d$_\pi$ conjugation and σ-inductive electron-withdrawal by heteroaryl substituents on the chemistry of some heteroarylphosphacyl compounds.

Phosphonium salt chemistry has also indicated a significant difference in the nature of pyrrolyl compounds compared with their furyl and thienyl analogues. Thus pyrrolylphosphacyl compounds have been included in the study in order to extend this interesting comparison to other organophosphorus derivatives.

3.2 The Synthesis of Heteroarylphosphonate Esters.

A number of phosphonates bearing heterocyclic substituents at phosphorus have been prepared, and much of the earlier work concerning the synthesis and properties of these compounds has been covered in a review by Redmore[93].

Griffin et al[94] reported the synthesis of dimethyl-(2-furyl)phosphonate

(LXXVIII; R = CH$_3$) and dimethyl-(2-thienyl)phosphonate (LXXIX; R = CH$_3$) by the photolysis of the heteroaryl iodides in the presence of trimethylphosphite. In view of the good yields obtained for a number of substituted phenylphosphonates by this method, it was suggested that the poor yields of (LXXVIII; R = CH$_3$) and (LXXIX; R = CH$_3$) were probably due to the purity of the heteroaryl iodides and possibly photolytic instability of the heteroarylphosphonate products. Other aryl iodides which failed to give the required products by this method included 2-iodoquinoline for which a non-characterisable product was obtained, and ortho- and meta-iodonitrobenzenes in which the intervention of a nitrene was suspected.

The preparation of arylphosphonates by the reaction of aromatic iodo or bromo compounds with excess trialkylphosphite in the presence of copper at elevated temperatures, was reported by Tavs et al[95]. Phosphonates obtained by this procedure included the diethyl esters of phenyl-, p-tolyl-, p-chlorophenyl- and 2-naphthylphosphonic acids. A free radical mechanism was suggested for the reaction.

An alternative to this approach involves the preparation of a number of vinylphosphonates and arylphosphonates by the reaction between trialkylphosphite and organic halide, at elevated temperatures, in the presence of nickel chloride as a catalyst[96,97]. Compounds obtained by this method included the diethyl esters of a series of substituted phenylphosphonic acids, diethyl-(2-naphthyl)phosphonate, and diethyl-(2-thienyl)phosphonate (LXXIX; R = C$_2$H$_5$) which was obtained in 88% yield. The reaction between phosphonate ester and alkyl halide in the presence of nickel chloride to give the corresponding phosphinate was also reported[97]. Thus the addition of diethylphenylphosphonate to a suspension of nickel chloride in 2-bromothiophen at 160°, gave ethylphenyl-(2-thienyl)phosphinate (LXXX; R = C$_2$H$_5$) which was later hydrolysed to phenyl-(2-thienyl)phosphinic acid (LXXX; R = H).

(LXXX)
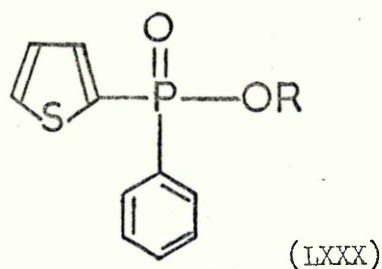
A similar method to the above for the preparation of vinyl-, and substituted phenylphosphonates has been reported by Martin[98]. In this case the compounds were prepared by the reaction at elevated temperatures of trialkylphosphite and organic halide over palladium chloride or palladium acetate.

A further available route to phosphonate esters bearing 2-thienyl substituents at phosphorus is made available by the Friedel-Craft reaction of phosphorus trichloride and thiophen in the presence of stannic chloride to give 2-thienylphosphonous dichloride (LXXXI) in 50% yield[99]. This procedure is a modification of that described by Sachs[100] in 1892. The phosphonous dichloride can be converted by standard transformations into a series of derivatives[99,100] (Scheme V).
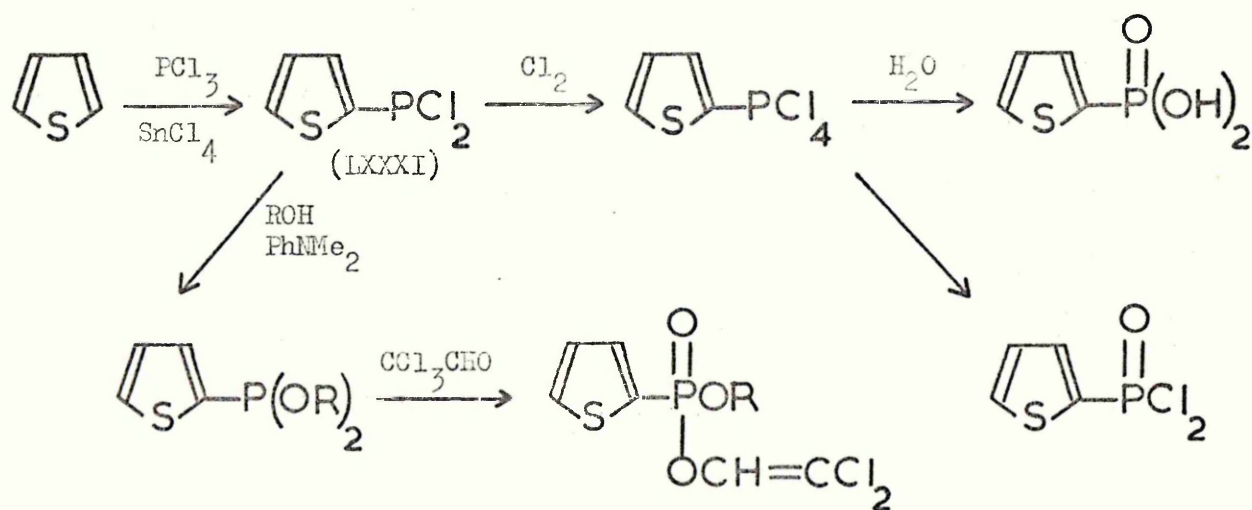


Scheme V

In principle, the reaction of phosphoryl chloride or dialkylphosphoro-chloridates with one equivalent of Grignard or lithium reagent, should yield a phosphonic acid dihalide or diester. In practice this is not readily achieved;

the product phosphonic acid derivative competes with the starting halide for

reaction with the organometallic reagent, so that a complex product mixture

results.

In 1951, Burger and Dawson[101] found that the addition of diethylphosphoro-

chloridate to arylmagnesium halide caused a reaction which could not be halted

before the triarylphosphine oxide stage was reached. The yields based on the

amount of aryl halide used were between 33% and 75%. Phenylmagnesium bromide

and diethylphosphorochloridate furnished triphenylphosphine oxide, and the

corresponding phosphine oxides were similarly obtained from the reactions of

p-chlorophenyl-, p-tolyl-, p-biphenyl-, 2-thienyl-, and 2-naphthylmagnesium

bromides. Addition of diethylphosphorochloridate to arylmagnesium halide

protected sterically by an ortho substituent, however, was found to give

dialkylarylphosphonate. In this manner o-chlorophenyl-, o-tolyl-, o-biphenyl-,

and naphthalene-1-phosphonates were obtained from the corresponding Grignard

reagents. It was also found that sterically hindered or unhindered aryl-

magnesium halides or aryl-lithium compound could be converted to esters of

phosphonic acids by "reverse addition", i.e. the addition of Grignard reagent

or aryl-lithium derivative to the dialkylphosphorochloridate; diethylphenyl-

phosphonate and diethyl-p-tolylphosphonate were prepared by this method.

$$
\text{(a)} \quad \text{ArMgX} + (\text{RO})_2\text{POCl} \longrightarrow \overset{\overset{\text{OMgXCl}}{|}}{\text{ArP}}(\text{OR})_2
$$
(LXXXII)

$$
\text{(b)} \quad \text{LXXXII} + \text{ArMgX} \longrightarrow \overset{\overset{\text{OMgX}}{|}}{\text{Ar}_2\text{P}}(\text{OR})\text{Cl} + \text{ROMgX}
$$
(LXXXIII)

$$
\text{(c)} \quad \text{LXXXIII} + \text{ArMgX} \longrightarrow \text{Ar}_3\text{P}(\text{Cl})\text{OMgX} \overset{\text{H}_2\text{O}}{\longrightarrow} \text{Ar}_3\text{PO} + \text{MgXCl}
$$
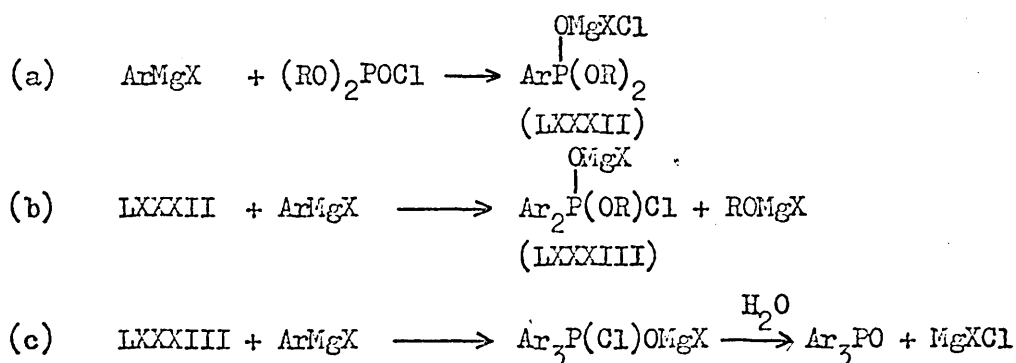
Scheme VI

Further to their study, Burger and Dawson[102] suggested possible complex

formation and stepwise displacement in the interaction of arylmagnesium halide

with dialkylphosphorochloridate. The mechanism (Scheme VI) was based on the observation of Swain and Boyles[103] that the reduction of diisopropyl ketone with n-propylmagnesium halide could be greatly inhibited by complexing the ketone with magnesium bromide and allowing the complex to react with the Grignard reagent.



(LXXXIV)                                             (LXXV)
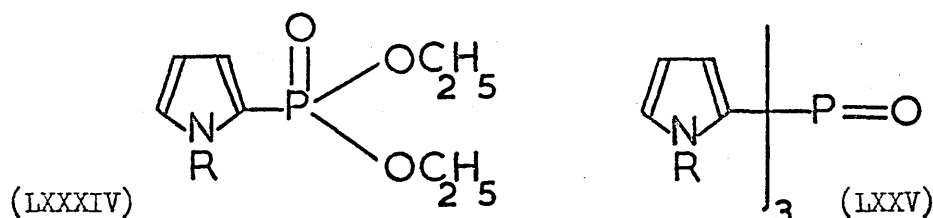
Griffin et al[104] reported the synthesis of diethyl-(2-pyrrolyl)phosphonate (LXXXIV; R = H) by the reverse addition of pyrrolylmagnesium bromide to diethylphosphorochloridate. The 1-methyl analogue (LXXXIV; R = CH$_3$) was similarly prepared by the addition of 2-(1-methylpyrrolyl)-lithium to diethyl-phosphorochloridate; in this case, however, brief reaction times were necessary to prevent the formation of tri-2-(1-methylpyrrolyl)phosphine oxide (LXXV; R = CH$_3$). The attempted acidic hydrolysis of (LXXXIV; R = H), both at reflux and room temperatures, led to the formation of resinous material. Basic hydrolysis, however, led to quantitative dephosphonation of (LXXIV; R = H), yielding pyrrole (70%) and 2-ethylpyrrole (28%). This result is unusual since previous cases of carbon-phosphorus bond cleavage under basic conditions had been shown to involve compounds possessing an electron-withdrawing group in close proximity to the phosphonyl group, notably dialkylacylphosphonates[105], 2-chloroalkyl-[106], and p-nitrobenzylphosphonic acids[107]. The mechanism preferred by Griffin[104] (Scheme VII) involved the formation of the anion (LXXXV). Protonation of (LXXXV) at the 2-position would yield the pyrrolenine (LXXXVI), which could either undergo proton abstraction to regenerate (LXXXV) or collapse with carbon-phosphorus bond cleavage, to give the aromatic anion (LXXXVII), and the ion (LXXXVIII).
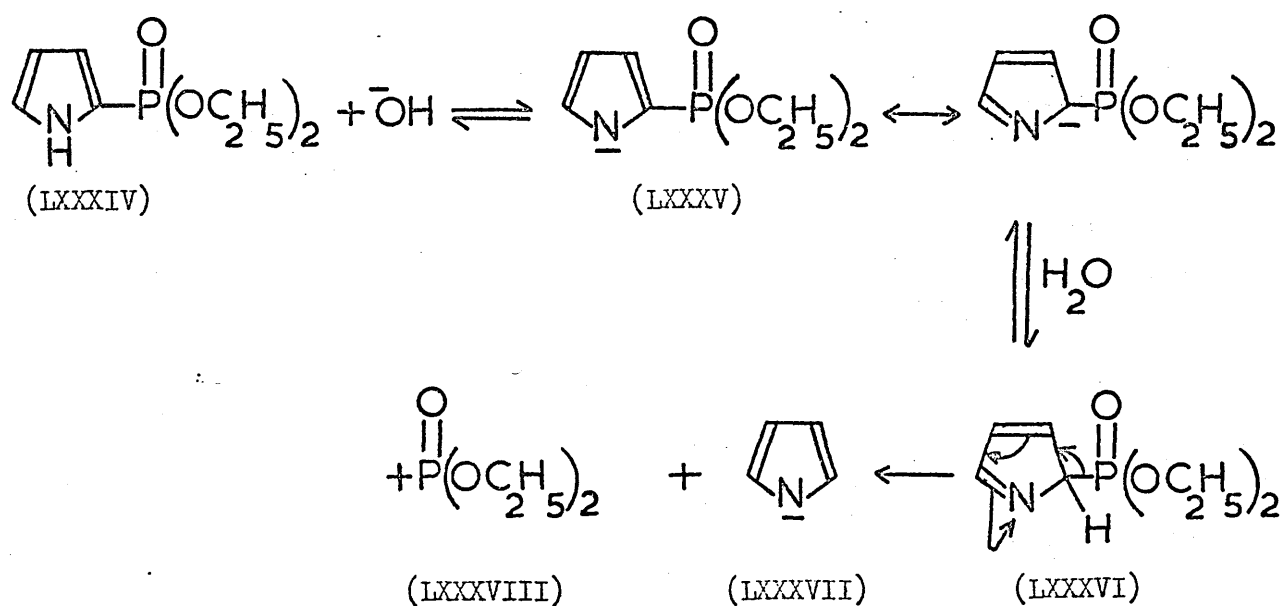
**Scheme VII**

Formation of 2-ethylpyrrole was explained by an alternative mode of collapse

of (LXXXV) (Scheme VIII). Attack of the negative charge at the 2-position of

(LXXXV) on an O-ethyl group would lead to the pyrrolenine (IXC), which could

undergo scission to form (XC) and (XCI). Protonation of (XC) and hydration of

(XCI) would lead to 2-ethylpyrrole and monoethylphosphate.
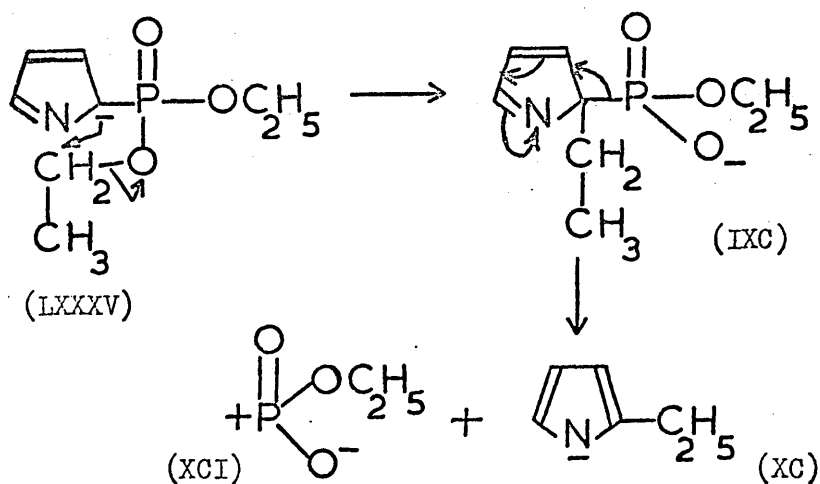


**Scheme VIII**

A similar process to the above had previously been demonstrated by Szmuszkovicz[108],

who showed that alkaline hydrolysis of diethyl-$\gamma$-(3-indolyl)-$\gamma$-ketopropyl-

phosphonate (XCII) leads to the formation of a monobasic acid, ethyl-$\gamma$-

[3-(1-ethylindolyl)]-$\gamma$-ketopropylphosphonate (XCIII), as the major product.

Conversion of (XCII) to its N-anion by base, followed by the alkylation of the

anion by the dialkylphosphonate, was postulated as the course of the reaction.
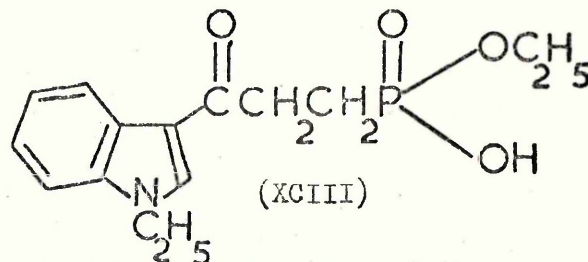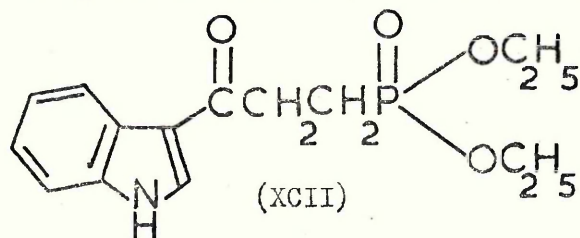


The role proposed for hydroxide ion, solely for the generation of the

anion (LXXXV) in the dephosphonation process of (LXXXIV; R = H), received

support from the behaviour of diethyl-2-(1-methylpyrrolyl)phosphonate (LXXXIV;

R = $CH_3$) with base. Treatment of (LXXXIV; R = $CH_3$) with refluxing 10% aqueous

sodium hydroxide gave the monoester (XCIV), the normal product of the basic

treatment of dialkylarylphosphonates[109].
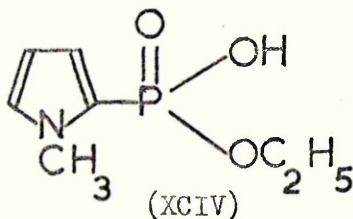


In the present study, diethyl-2-(1-methylpyrrolyl)phosphonate (LXXXIV;

R = $CH_3$) was prepared by the reverse addition of 2-(1-methylpyrrolyl)-lithium

to diethylphosphorochloridate at ice-bath temperature, according to the

procedure described by Griffin et al[104]. In this method, the 2-(1-methyl-

pyrrolyl)-lithium was generated[110] by the addition of n-butyl-lithium[111] to

1-methylpyrrole in ether, and the resulting mixture heated under reflux. Gjós

and Gronowitz[112], however, reported that higher yields of 2-(1-methylpyrrolyl)-

lithium are obtained when the above addition takes place in the presence of

tetramethylethylenediamine. A comparison of the two methods, in the present

study, confirmed this result. Furthermore, no metal exchange was observed to

take place in the reaction between n-butyl-lithium and 1-methylpyrrole in a

light-petroleum solvent.

Analysis of the phosphonate product by g.l.c. indicated a mixture

containing 90% of the required ester (LXXXIV; R = $CH_3$). A similar result was

obtained from analysis of the integrated peak intensities of the n.m.r.
spectrum, in which an excess of $P-O-C_2H_5$ protons were indicated. Final
purification of the product was effected by repeated distillation through a
spinning-band column. The identity of the impurities was not investigated
further. Griffin et al[104], however, reported the isolation of triethylphosphate
from this reaction, and thus it is possible that cleavage of the ether solvent
by the aryl-lithium reagent takes place, the subsequent reaction of the cleavage
products with diethylphosphorochloridate may then give rise to impurities.


(XCV)
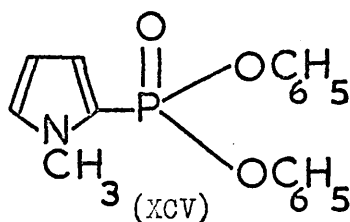
Diphenyl-2-(1-methylpyrrolyl)phosphonate (XCV) was similarly prepared by
the reverse addition of 2-(1-methylpyrrolyl)-lithium to diphenylphosphoro-
chloridate in ether. Removal of the solvent in the latter stages of the
preparation produced a brown oil which slowly solidified on standing. Attempted
recrystallisation from n-hexane produced a yellow oil, but decantation and
seeding of the hexane with triphenylphosphate gave white crystals, which after
further recrystallisation melted sharply at $73^\circ$.


(LXXVIII)
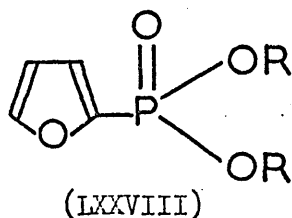
The production of 2-furyl-lithium by the reaction of n-butyl-lithium and
furan in ether was reported by Levine et al[113]. The reverse addition of
2-furyl-lithium, obtained by this method, to diphenylphosphorochloridate in
the attempted preparation of diphenyl-(2-furyl)phosphonate (LXXVIII; $R = C_6H_5$)
led to the formation of a viscous oil. Recrystallisation from a range of
solvents and attempted separation of the complex reaction mixture by column
chromatography failed to produce a characterisable product, whilst attempted

distillation of the oil led to extensive decomposition and the formation of phenol. The equivalent reaction using 2-furyl-lithium produced by the reaction of phenyl-lithium and furan in ether, gave similar results. Separation of the mixture produced from this reaction into a number of components, however, was achieved by thin-layer chromatography, using a 10% ethyl acetate-hexane elution solvent. The most intense band obtained as a result of the separation was extracted and recrystallised from n-hexane, to give white crystals melting sharply at 49°. The compound was subsequently identified as triphenylphosphate (literature[114], m.p. 49°). The extraction of a second band produced a yellow oil which could not be induced to crystallise. Examination and comparison of the n.m.r. spectrum of this compound with that of authentic material, however, indicated the product to be tri-(2-furyl)phosphine oxide (LXXVI).

The isolation of triphenylphosphate and tri-(2-furyl)phosphine oxide from the reaction mixture thus possibly indicates reaction between the phosphonate product (LXXVIII; R = $C_6H_5$) and organometallic reagent with the expulsion of phenate anion to form phosphine oxide. Reaction between diphenylphosphoro-chloridate and the phenate anion, thus produced, must then take place to give the triphenylphosphate. Evidence in favour of such a proposal is presented in a paper by Griffin et al[89], in which tri-(2-furyl)phosphine oxide is prepared by the reaction between diethylphosphorochloridate and 2-furyl-lithium.

Preliminary experiments by Shepard et al[115] indicated the preparation of 2-furylmagnesium bromide to take place with difficulty. It was reported[115] that an ethereal solution of 2-bromofuran did not react with magnesium nor with magnesium activated by heating with iodine. Some reaction was observed with a magnesium-copper alloy[116] previously heated with iodine, but it was noted that a considerable excess of magnesium remained undissolved when the reaction had subsided. Gilman et al[117], however, reported the ready formation of 2-furylmagnesium iodide from the relatively unstable 2-iodofuran (XCVI).
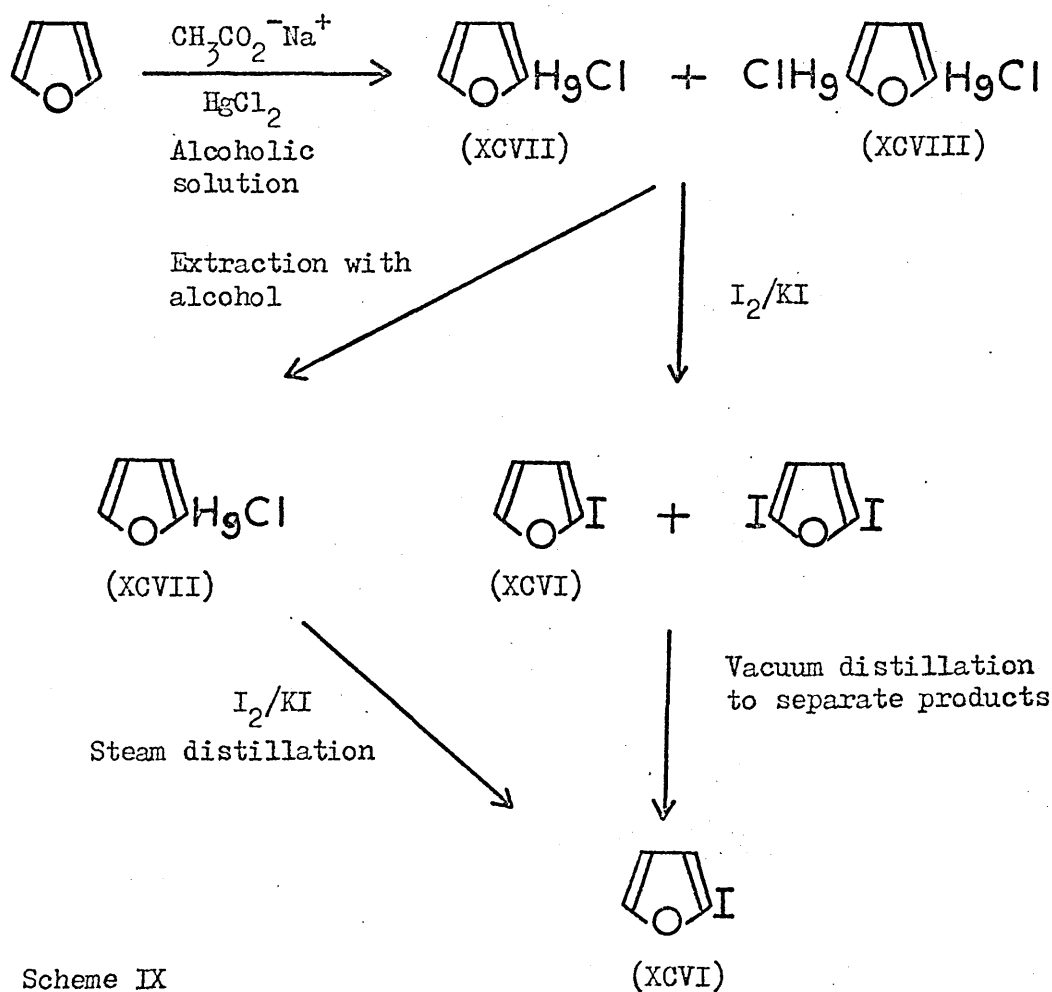
Scheme IX

The method described by Gilman and Wright[118] (Scheme IX) for the preparation of 2-iodofuran (XCVI), involved the reaction of furan with mercuric chloride-sodium acetate in 95% ethanol. The cooled, tightly stoppered flask was then set aside to allow precipitation of the mixture of 2-chloromercurifuran (XCVII) and 2,5-dichloromercurifuran (XCVIII). The reaction of iodine-potassium iodide solution with the mixture of (XCVII) and (XCVIII), followed by steam distillation, led to a mixture of iodofurans from which 2-iodofuran was separated by vacuum distillation from calcium chloride, with much decomposition. In the present study, improved yields of 2-iodofuran were obtained when 2-chloromercurifuran (XCVII) was extracted from the mixture of mercuricals with hot ethanol in which (XCVIII) is insoluble. Treatment of the purified 2-chloromercurifuran with iodine-potassium iodide followed by steam distillation

then gave a reasonably pure sample of 2-iodofuran (XCVI) without the need for fractional distillation. The 2-iodofuran (XCVI) thus prepared, was immediately diluted with ether, since it is relatively more stable in solution. After drying, the ether solution was used for the preparation of the corresponding Grignard reagent.

The reverse addition of 2-furylmagnesium iodide to diphenylphosphoro-chloridate followed by treatment under the usual reaction conditions and work up, resulted in a brown oil which slowly solidified on standing. Recrystallisation from n-hexane produced white needles melting at $50^{o}$.

The reaction of 2-furylmagnesium iodide and diethylphosphorochloridate under a variety of conditions and reaction times resulted in the formation of a complex reaction mixture. Vacuum distillation of the crude mixture took place with notable resinification in the distillation flask, and poor yields of the required phosphonate ester (LXXVIII; $R = C_2H_5$) were isolated. Analysis of each fraction thus obtained, indicated the presence of a number of components; in some cases as many as six components were observed. Products with improved purity were, however, obtained from the analogous reaction employing 2-furyl-lithium as the organometallic reagent. Redistillation of the products obtained from this reaction yielded fractions containing >90% of the required diethyl-(2-furyl)phosphonate (LXXVIII; $R = C_2H_5$), together with a number of components, as indicated by g.l.c. and analysis of the integrated peak intensities obtained from the n.m.r. spectrum. Microanalytically pure diethyl-(2-furyl)phosphonate was, however, only obtained following preparative g.l.c. separation of these samples.
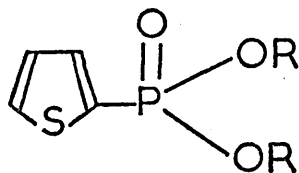


(LXXIX)

In contrast, the reverse addition of 2-thienylmagnesium bromide to an ethereal solution of diethylphosphorochloridate at reflux temperature, followed

by treatment under the usual reaction conditions and work up, produced an oil
which distilled at a steady temperature to give diethyl-(2-thienyl)phosphonate
(LXXIX; R = $C_2H_5$) in good yield. G.l.c. analysis of the product indicated the
absence of impurities, and a satisfactory microanalysis was obtained without
the need for further purification.

Diphenyl-(2-thienyl)phosphonate (LXXIX; R = $C_6H_5$) was similarly prepared
in high yield by the analogous reaction with diphenylphosphorochloridate;
removal of the solvent gave a solid product which was recrystallised from
n-hexane to give crystals, melting at $75^\circ$.

Investigation of the reaction of 2-thienyl-lithium and the corresponding
phosphorohalidate obtained diphenyl- and diethyl-(2-thienyl)phosphonates, with
fewer of the troublesome side products received from the analogous reactions
of 2-furyl- and 2-(1-methylpyrrolyl)-lithium reagents. Thus samples of
(LXXIX; R = $C_6H_5$ or $C_2H_5$) of sufficient purity, as indicated by g.l.c. and
n.m.r. were obtained by either recrystallisation or redistillation of the
product. Reductions in yields compared with the reactions of 2-thienylmagnesium
bromide were, however, observed indicating the latter procedure to be more
efficient.



(IC)
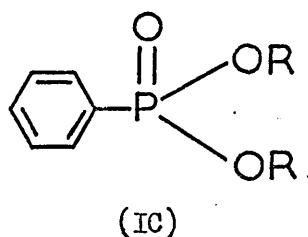
Diethylphenylphosphonate (IC; R = $C_2H_5$) was obtained by the reaction of
phenylphosphonic dichloride with absolute ethanol in benzene solvent in the
presence of pyridine, according to the general method described by Kosolapoff[119].
Filtration of the solution in the latter stages of the procedure, followed by
removal of the solvent yielded the product which was purified by vacuum
distillation. The purity of the compound was checked by g.l.c. and found to
be > 99% pure.

Diphenylphenylphosphonate (IC; R = C$_6$H$_5$) was similarly prepared by the reaction of phenylphosphonic dichloride and phenol. Removal of the benzene solvent gave a white solid which was recrystallised from n-hexane, to give crystals melting at 73.5$^\circ$.

3.3 Studies of the Rate of Alkaline Hydrolysis of Diethylheteroarylphosphonate Esters.
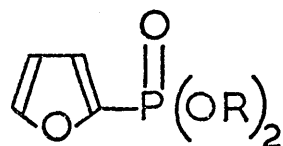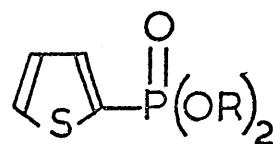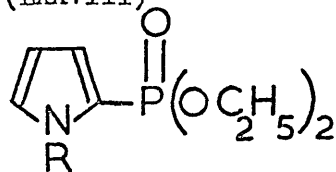


(LXXVIII)    (LXXIX)
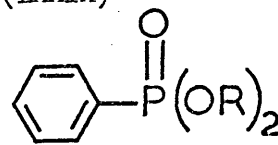
(LXXXIV)    (IC)

The kinetics of alkaline hydrolysis of the diethyl esters of 2-furyl-, 2-thienyl-, 2-(1-methylpyrrolyl)-, and phenylphosphonic acids (LXXVIII, LXXIX and IC; R = C$_2$H$_5$) and (LXXXIV; R = CH$_3$) in 50% aqueous dioxan have been studied by a titrimetric procedure. The esters undergo hydrolysis on treatment with one mole of sodium hydroxide to give the half-esters, and a second-order rate-law is observed. The rate data is presented in Table 3.1..

# Table 3.1.

## Second-Order Rate Constants for the Alkaline Hydrolysis of Phosphonate Esters $RP(O)(OC_2H_5)_2$ in Aqueous Dioxan (50% v/v; 0.1 M in KCl).

| R | Ester (M) | NaOH (M) | Temperature (°C) | $k_{obs}$ (l mol$^{-1}$sec$^{-1}$) |
|---|---|---|---|---|
| 2-Furyl | 0.05 | 0.05 | 59.7 | $4.53 \times 10^{-3}$ |
|  | 0.05 | 0.05 | 49.9 | $2.44 \times 10^{-3}$ |
| Phenyl | 0.05 | 0.05 | 59.7 | $9.74 \times 10^{-4}$ |
|  | 0.05 | 0.05 | 50.0 | $4.89 \times 10^{-4}$ |
| 2-Thienyl | 0.05 | 0.05 | 59.7 | $8.88 \times 10^{-4}$ |
|  | 0.05 | 0.05 | 50.0 | $4.90 \times 10^{-4}$ |
| 2-(1-Methylpyrrolyl) | 0.05 | 0.05 | 69.8 | $8.45 \times 10^{-5}$ |
|  | 0.05 | 0.05 | 59.8 | $3.81 \times 10^{-5}$ |

The rate data reveals several features of interest. Over the temperature range studied the rates of hydrolysis of the diethylphosphonate esters are in the order 2-furyl > phenyl ≈ 2-thienyl > 2-(1-methylpyrrolyl), the relative rates being 120 : 25 : 1. The results contrast sharply with previous data obtained for the alkaline hydrolysis of heteroarylphosphonium salts[91,92] for which the overall rates of hydrolysis were observed to decrease in the order 2-furyl > 2-thienyl > 2-(1-methylpyrrolyl) > phenyl, the relative rates being of the order $10^{11} : 10^8 : 5 : 1$. The variation of the substituent effects must therefore be considered in the context of differing structural environments and also the differences in reaction mechanism.

As discussed in section 1.1 of this thesis, in the alkaline hydrolysis of phosphonium salts although the inductive effect of substituents on the adjacent phosphorus atom is important in the pre-equilibrium stages of the reaction, a major contribution to the relative rates of alkaline hydrolysis is made by the relative stabilities of the departing carbanions in the rate-determining step

of the reaction.  It has also been shown[91,92] that the effects of $p\pi$ — $d\pi$

bonding between the $\pi$-electron system of the heterocyclic ring and the

phosphorus 3d orbitals appear to be of little consequence in influencing the

rate of reaction.

Nucleophilic displacements at phosphacyl centres have also been shown to

be sensitive to electronic effects of substituents, and in cases where

conjugative groups are linked to phosphorus large rate effects have been

observed[2,3].  A possible explanation for the relative rates of alkaline

hydrolysis of the above phosphonate esters is thus that in addition to their

ability to act as $\sigma$-electron acceptors, the heteroaryl substituents are

potential $\pi$-electron donors.  A $p\pi$ — $d\pi$ interaction between the $p\pi$ orbitals

of the heteroaryl ring and the 3d orbitals of phosphorus may therefore take

place, and this interaction serves to level out the rates of alkaline hydrolysis.

The u.v. absorption and n.m.r. spectroscopic observations obtained by Griffin

et al[89,90] for phosphorus compounds containing 2-furyl, 2-thienyl and

2-(1-methylpyrrolyl) substituents would appear to support such an interaction.

In addition to the effects which such an interaction would have on the

relative rates of alkaline hydrolysis of the above diethylphosphonate esters,

work by Aksnes et al[55] has shown that electron-withdrawing substituents, which

make the phosphorus atom more positive, also have the effect of increasing the

strength of the bond between phosphorus and the leaving group.  Since the

hydrolysis reaction involves bond-breaking as well as bond-formation in the

transition state, this effect which increases with increasing electronegativity

of the substituents would also serve to make more equal the rates of alkaline

hydrolysis of the above phosphonates.

The activation parameters for the above alkaline hydrolysis reactions

have been calculated and are given in Table 3.2..

## Table 3.2.

### Activation Parameters for the Alkaline Hydrolysis of Phosphonate Esters $RP(O)(OC_2H_5)_2$ .
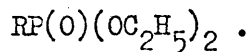
| R | $E_A$ (kJ mol$^{-1}$) | $\Delta S$ (JK$^{-1}$mol$^{-1}$) | $\log_{10}$ PZ |
|---|---|---|---|
| 2-Furyl | 56.4 | -121.0 | 6.5 |
| 2-Thienyl | 54.8 | -139.5 | 5.6 |
| Phenyl | 63.6 | -112.2 | 7.0 |
| 2-(1-Methylpyrrolyl) | 75.5 | -103.6 | 7.4 |

Examination of the data in Table 3.2. reveals a slight correlation between the activation parameters and the relative rates of reaction. Thus a decrease in the energy of activation for the hydrolysis of the 2-furyl-, and 2-thienyl-phosphonates appears to be compensated by increases in the activation entropy for the reactions of the phenyl and 2-(1-methylpyrrolyl) analogues. Aksnes et al[55] observed that increases in the rate of alkaline hydrolysis of the diethyl esters of chloromethyl-, and dichloromethylphosphonic acids, compared with diethylmethylphosphonate were accompanied by a small but significant decrease in the activation energy for the reaction. In contrast, mesomeric substituents such as alkoxy or dialkylamino groups were found to produce an increase in the activation energy[57,120]. On the basis of these results, the decrease in activation energy observed for the reactions of the 2-furyl-, and 2-thienyl-phosphonates compared with the phenyl analogue, possibly indicates some inductive electron-withdrawal from the phosphorus atom by the heteroaryl substituents assisting the approach of the nucleophile and bond-formation. In contrast the increase in activation energy for the alkaline hydrolysis reaction of diethyl-2-(1-methylpyrrolyl)phosphonate compared with the phenyl analogue, may indicate decreased electron-withdrawal by the 2-(1-methylpyrrolyl) substituent compared with phenyl, and possibly electron-donation by the

$\pi$-system of the 1-methylpyrrolyl group. Evidence that such electronic interactions are possible is provided by phosphonium salt hydrolysis and $pK_a$ data for the corresponding carboxylic acids. Thus while furan- and thiophencarboxylic acids are considerably stronger than unsubstituted benzoic acid, pyrrolecarboxylic acid is weaker[121].

$$\text{furyl}-\overset{O}{\overset{\|}{C}}-OC_2H_5 \qquad \text{thienyl}-\overset{O}{\overset{\|}{C}}-OC_2H_5 \qquad \text{phenyl}-\overset{O}{\overset{\|}{C}}-OC_2H_5$$
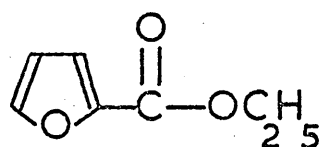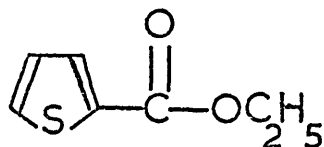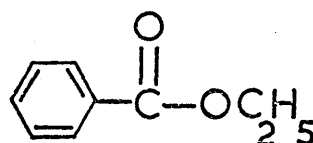
$$(C) \qquad\qquad (CI) \qquad\qquad (CII)$$

It is of interest to compare the relative rates of alkaline hydrolysis of the above diethylheteroarylphosphonate esters with the corresponding data for the alkaline hydrolysis of the ethyl heteroarylcarboxylate esters (C), (CI) and (CII). Oae and Price[122] have reported that the rates of alkaline hydrolysis of the above carboxylates in 70% aqueous dioxan decrease in the order ethyl 2-furoate $>$ ethyl 2-thenoate $>$ ethyl benzoate, the relative rates being 4·65 : 1·03 : 1. These results differ slightly from the work published by Imoto et al[123], who found the above rates of reaction in 85% ethanol, to decrease in the order ethyl 2-furoate $>$ ethyl benzoate $>$ ethyl 2-thenoate, the relative rates being 4·35 : 1·08 : 1. In either case, however, the results compare favourably with the alkaline hydrolysis data for the corresponding phosphonate esters, in which the diethyl ester of 2-furylphosphonic acid was found to hydrolyse some five times faster than the corresponding esters of 2-thienyl- and phenylphosphonic acids. The results thus possibly indicate that the rate of alkaline hydrolysis of phosphonate esters is about as dependent on the electronic effect of substituents as in the analogous reaction of carboxylates.

The rate data, together with the activation parameters published by Oae and Price[122] for the alkaline hydrolysis of the above heteroarylcarboxylate esters is presented in Table 3.3..

## Table 3.3.

### Rate Constants and Activation Parameters for the Alkaline Hydrolysis of Ethyl Esters of Aromatic and Heterocyclic Carboxylic Acids in 70% Aqueous Dioxan.

| Ester | $k_{obs}$ (25°) (1 mol$^{-1}$sec$^{-1}$) | $E_A$ (kJ mol$^{-1}$) | $\Delta S$ (JK$^{-1}$mol$^{-1}$) | $\log_{10}$ PZ |
|---|---|---|---|---|
| Ethyl benzoate | $3 \cdot 42 \times 10^{-3}$ | $58 \cdot 6$ | $- 95 \cdot 5$ | $7 \cdot 8$ |
| Ethyl 2-thenoate | $3 \cdot 51 \times 10^{-3}$ | $61 \cdot 5$ | $- 85 \cdot 6$ | $8 \cdot 3$ |
| Ethyl 2-furoate | $15 \cdot 9 \times 10^{-3}$ | $57 \cdot 5$ | $- 86 \cdot 3$ | $8 \cdot 3$ |

Comparison of the data in Tables 3.1. and 3.3. shows that the corresponding phosphonyl and carbonyl esters have almost identical activation energies, but the activation entropies are more positive for the esters of the carboxylic acids. Aksnes et al[55] obtained a similar comparison between the activation parameters for the alkaline hydrolysis of the ethyl esters of methyl-, chloromethyl-, and dichloromethylphosphonic acids, and the corresponding data for ethyl acetate and its chloro-substituted analogues. It was suggested by Aksnes[55] that the reason for the difference in activation entropies is most likely the greater restriction laid upon the transition state for the alkaline hydrolysis of phosphonate esters. From isotopic exchange studies[18] with [18]O enriched water, it is known that esters of carboxylic acids freely exchange oxygen under alkaline conditions, indicating that an intermediate is formed with fully developed $\sigma$-bonds. The absence of such evidence for the hydrolysis of phosphonate esters possibly indicates a concerted mechanism with a trigonal-bipyramidal sp$^3$d-hybridised transition state. The data in Table 3.2. and 3.3. also reveal the entropy of activation for the alkaline hydrolysis of the ethyl esters of furan- and thiophencarboxylic acids to be more positive than for the phenyl compound, whereas in the hydrolysis of phosphonate esters the reverse is true. It may therefore be possible that there is some stabilisation of the

intermediate by the 2-furyl and 2-thienyl groups in the carboxylate ester

hydrolysis which is not possible in the analogous stage of the phosphonate

ester hydrolysis.

The similarity in the relative rates of reaction of the above phosphonate

and carboxylate ester is unusual in view of results reported by other workers.

For example the relative rate constants for the alkaline hydrolysis of various

phosphonate esters[55] $RP(O)(OC_2H_5)_2$ , are $C_2H_5$, 0·13; $CH_3$,1; $ClCH_2$, 15·6;

$Cl_2CH$, 108; whereas the relative rate constants for the corresponding carboxylic

acid esters are estimated[55] as $C_2H_5$, 0·9; $CH_3$, 1; $ClCH_2$, 258; $Cl_2CH$, 5000.

Similarly ethylchloromethylphosphonochloridate undergoes solvolysis 1·2 times

faster than ethylmethylphosphonochloridate[11], whereas Branch and Nixon[124]

showed a rate difference of 24 : 1 for the solvolysis of chloroacetyl chloride

compared with acetyl chloride.

The above data for methylcarboxylic acid esters and halides and their

chloro-substituted analogues indicate bond-formation to be the dominant factor

in determining the rates of the nucleophilic reaction. In contrast, bond-

breaking influences are more important in the corresponding reactions of

phosphonic acid esters and halides. Thus it is possible that the similarity

in the rates of reaction of the heteroarylcarboxylic and phosphonic acid esters

may be a summation of two effects. Griffin et al[89,90] have established $p\pi$ — $p\pi$

interactions in heteroarylcarbonyl compounds to be significantly larger than

$p\pi$ — $d\pi$ interactions in phosphacyl compounds. The rate of nucleophilic attack

in (C) and (CI) may therefore be reduced compared with (CII) as a result of

$p\pi$ — $p\pi$ interactions between the heteroaryl group and the carbonyl centre.

Once the intermediate in the reaction is formed, however, rapid cleavage of

the leaving group may take place. Alternatively, nucleophilic attack at the

phosphonyl centres of (LXXVIII and LXXIX; R = $C_2H_5$) may be less affected by

$p\pi$ — $d\pi$ interactions. The inductive effect of the heteroaryl group may,

however, increase the strength of the bond from phosphorus to the leaving

group in the transition state of the hydrolysis of (LXXVIII and LXXIX; $R = C_2H_5$) thus resulting in the similarity of the relative rates of alkaline hydrolysis.

3.4 Studies of the Infrared and [31]P n.m.r. Spectra of Heteroarylphosphonate Esters.

In order to investigate further the electronic effect of the heterocyclic substituent on the adjacent phosphorus atom in the heteroarylphosphonate esters (LXXVIII, LXXIX and IC; $R = C_2H_5$) and (LXXXIV; $R = CH_3$), the variation of a number of spectroscopic parameters with substituents has been studied.
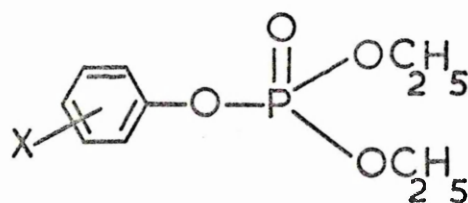


(XLIV)

In their investigation of the effect of structure on the reactivity of some diethyl substituted phenylphosphates (XLIV), Fukuto and Metcalf[44] observed increases in the infrared stretching frequency of the P-O-aromatic bond with increasing electron-withdrawing ability of the substituent on the phenyl ring. This data was later correlated with the lability of the bond as measured by the alkaline hydrolysis of the phosphate esters, and a linear relationship between the frequency of vibration and the rate of alkaline hydrolysis was effectively obtained.
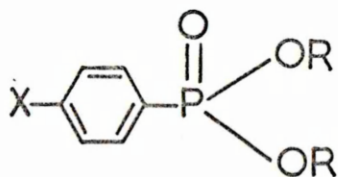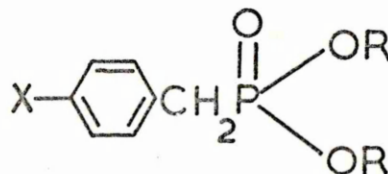


(CIII)          (CIV)

Cheng-Yeh Yuan et al[125] similarly observed a variation in the stretching vibration of the P-O-alkyl bond with the polar nature of the substituent in a series of para-substituted phenyl-, and benzylphosphonates (CIII; $R = C_2H_5$, $C_4H_9$, $C_8H_{17}$) and (CIV; $R = C_2H_5$, $C_4H_9$, $C_8H_{17}$). The same workers also noted increases in the frequency of the phosphonyl (P=O) stretching vibration with

increasing 'electronegativity' of the substituents on the phenyl ring. A linear
correlation between $\nu$ P=0 and the polar nature of the substituents as measured
by the Hammett $\sigma$ constant was obtained, and a quantitative relationship was
explained by the conjugation effects of the benzene ring with the phosphonyl
group.

Bell et al[126] also reported a linear correlation between the wavelength
of the phosphonyl absorption in phosphoryl halides and the sum of the Pauling
electronegativity constants of the halogens. Furthermore, it was found that
other more complex groups e.g. alkoxy and hydroxy, influenced the stretching
absorption in a constant and additive manner. The band shifts are determined
primarily by the electrical effect of the substituent group on the bond force
constant arising from changes in the bond order, since the mass of the group
appears to have little effect on the position of the stretching absorption.

$$\lambda(\mu) = \frac{39 \cdot 96 - \sum X}{3 \cdot 995} \tag{17}$$

From the observed linear relationship Bell et al[126] derived equation 17
to determine a numerical value for the effect of the substituent on the
phosphoryl bond, the 'phosphoryl absorption shift constant' (X), which is
comparable in magnitude to Pauling electronegativity constant. Exploratory
studies of other bond vibrations in pentavalent organophosphorus molecules,
indicated a dependence of the P-F, P-Cl and P-O-C stretching vibrations on the
phosphoryl absorption shift constant of the substituent groups. The shift
constant values, however, had considerably less influence on these bonds than
on the phosphoryl linkage.

Work by Davis[127] established a linear relationship between the phosphoryl
absorption shift constant (X) derived from equation 17 and the Taft polar
substituent constant[68] ($\sigma^{*}$) for a number of organic groups.

The infrared spectra of each of the diethylheteroarylphosphonate esters

(LXXVIII, LXXIX and IC; R = $C_2H_5$) and (LXXXIV; R = $CH_3$) have been obtained and the phosphonyl stretching frequencies examined critically. The spectra revealed the position of the P-O-$C_2H_5$ band to remain constant for each of the phosphonate esters. Some small shift of the phosphonyl stretching frequency was, however, observed and the frequencies of this band are listed in order of increasing wavenumber in Table 3.4..

<div align="center">

Table 3.4.

Frequencies ($cm^{-1}$) of the Phosphonyl Infrared Stretching Vibration of Diethyl-heteroarylphosphonate Esters $RP(O)(OC_2H_5)_2$ .

</div>

| R | $\nu$ P=O |
|---|---|
| 2-(1-Methylpyrrolyl) | 1250 |
| Phenyl | 1252 |
| 2-Thienyl | 1255 |
| 2-Furyl | 1261 |

The observed shifts in the frequency of the phosphonyl stretching vibrations presented in Table 3.4. are small; for comparison the phosphonyl stretching frequencies of the diethyl esters of methyl-, chloromethyl-, and dichloromethyl-phosphonic acids are 1243 $cm^{-1}$, 1271 $cm^{-1}$ and 1281 $cm^{-1}$ respectively[55]. Examination of the data in Table 3.4., however, provides further evidence for the electron-withdrawing character of the 2-furyl and 2-thienyl substituents and maintains the order of 'electronegativity' of the heterocyclic groups to be 2-furyl $>$ 2-thienyl $>$ phenyl $>$ 2-(1-methylpyrrolyl), in keeping with the order indicated by the $pK_a$'s of the corresponding carboxylic acids.

The results in Table 3.4. are therefore of some interest. Deady et al[128] examined the infrared spectra of cyanoderivatives of furan, thiophen and pyrrole, and measured the electronic effect of the heterocyclic substituent by the effect on the intensity of the $C \equiv N$ stretching vibration. In each case the heterocycle was found to act as an electron-donor and increase the intensity of the

stretching vibration compared with that of benzonitrile. The effect was found to decrease in the order 2-pyrrolyl $>$ 2-thienyl $>$ 2-furyl and substituent $(\sigma^+)$ values of -1·33, -0·44 and -0·13 respectively, were determined for the heteroaryl substituents.



(CV)
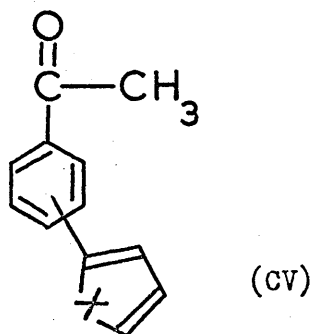
In an investigation of the effect of heteroaryl substituents on the infrared stretching frequency of the carbonyl bond in heteroaryl substituted acetophenones (CV), Marino et al[129] similarly found the 2-furyl and 2-thienyl substituents in the para- position of the phenyl ring to be electron-donating and decrease the frequency of the stretching vibration compared with the unsubstituted acetophenone. Substituent values $(\sigma^+ p)$ of -0·45 for the 2-furyl substituent and -0·38 for the 2-thienyl substituent were determined, to reflect the electron-donating effect. In the meta- position of the phenyl ring, however, the heteroaryl substituents were found to increase the stretching frequency of the carbonyl bond as a result of inductive electron-withdrawal.

The infrared stretching frequencies of the carbonyl bond in heteroaryl-carboxylic acids[122] are also of some interest, since they also reflect an electron-donating effect by the heterocyclic substituent resulting in a decrease in the frequency of the stretching vibration. The data[122] is listed in Table 3.5..

| Acid | $\nu c{=}0^{*}$ |
|------|------|
| 2-Thiophencarboxylic acid | 1680 |
| 2-Furoic acid | 1685 |
| Benzoic acid | 1690 |

* The stretching vibrations are characteristic of the associated form of the acid.

The data in Table 3.5. thus shows the heterocyclic substituents to be electron-donating as indicated by their effect on the frequency of the carbonyl infrared stretching vibration. The electron-withdrawing effect which the 2-furyl and 2-thienyl substituents appear to exert on the phosphonyl bond, however, must therefore reflect a decrease in the extent of this electron-donation. Thus on the basis of the infrared data presented, the reduction in $p\pi$ — $d\pi$ conjugation between the heteroaryl substituent and the phosphonyl group, compared with the $p\pi$ — $p\pi$ conjugation between the substituent and the carbonyl or nitrile group, results in an apparent overall electron-withdrawing effect by the heterocycle, due to the inductive effect of the electronegative heteroatom.

The electron-donation by the heteroaryl substituent to the carbonyl bond as indicated by the frequency of the infrared stretching vibration in heteroarylcarboxylic acids[122], compared with the electron-withdrawing effect indicated by the p$K_a$'s of these acids[121], requires some comment. It would appear that the infrared data must reflect both the inductive and mesomeric effects in the molecule, whereas the p$K_a$ of the acid is determined predominantly by the inductive effect of the substituent.

The possibility that ^{31}P chemical shifts offer a direct way to measure the electron-donating ability of substituent groups attached to phosphorus has

been examined by a number of workers. Letcher and Van Wazer[130] investigated the problem by a comparison of the $^{31}$P chemical shifts of a number of phosphonate anions $(RPO_3^{2-})$ and triphenyl- and trialkylphosphonium ions $(\overset{+}{R}PR^1_3)$. Since both the phosphonate anions and phosphonium cations fall into the class of $MPZ_3$ compounds, where Z is fixed and M represents a series of substituent groups, the difference $(\Delta\delta)$ between the chemical shift of a pair of anions of the type $RPO_3^{2-}$ and an equivalent pair of cations of the type $\overset{+}{R}PR^1_3$ should bear a fixed proportion to each other. Thus from the electronegativity difference between oxygen and carbon, quantum mechanical reasoning requires that the value of $\Delta\delta$ for a given pair of phosphonate anions $(RPO_3^{2-})$, should be twice as large as that for an equivalent pair of quaternary triphenylphosphonium cations $(\overset{+}{R}P(C_6H_5)_3)$. No such relationship was obtained, possibly as a result of minor variations in the $\pi$-character of the P—O bonds of the phosphonate anions, with variations in the nature of the organic group R. Van Wazer et al did, however, note a regular correlation between $\Delta\delta$ and Taft[68] $(\sigma^*)$ substituent values for the phosphonate anions, while $\Delta\delta$ for the phosphonium cations correlated simply with the Pauling electronegativities of the substituent groups.

Freedman et al[131,132] investigated the effect of various substituent groups on $^{31}$P n.m.r. chemical shifts of a series of meta-, and para-substituted phenylphosphonic acids and related esters, and obtained a correlation between the chemical shift and the corresponding Hammett $\sigma_p$ or $\sigma_m$ substituent constants[133], and also with the Taft[68] $\sigma_I$ or $\sigma_R$ components of the Hammett sigma constants. In the case of ortho-substituted phosphonic acids, a similar correlation was observed between the $^{31}$P chemical shifts and substituent constants derived by Taft[134] from the esterification and hydrolysis of ortho-substituted benzoate esters. In each case the correlation was opposite to that expected on the basis of the electron-withdrawing ability of the substituents. Thus the more electron-donating substituents decrease the shielding of the

phosphorus nucleus, as required by quantum mechanical theory[130].

In view of the results obtained by Letcher and Van Wazer[130], in which a correlation between the ^{31}P chemical shifts of $RPO_3^{2-}$ and $RP(C_6H_5)_3^+$ was not observed, Freedman[131] suggested that the relationship between the ^{31}P chemical shift of the substituted phenylphosphonic acids and esters with the polarity of the substituent may be due to the attenuation of the phenyl group, which serves to prevent large changes in the $\pi$-character of the P—O bond. Substituted phenylphosphonates thus prove valid for estimating the electron-donating ability of the substituent on the phenyl group.

The ^{31}P chemical shift data for the diethylheteroarylphosphonate esters (LXXVIII, LXXIX and IC; $R = C_2H_5$) and (LXXXIV; $R = CH_3$) is presented in Tab⁷(LXXVIII, LXXIX and IC; $R = C_2H_5$) and (LXXXIV; $R = CH_3$) is presented in Table 3.6..

<u>Table 3.6.</u>

[31]P Chemical Shift Data for Diethylheteroarylphosphonates in Chloroform

| Compound | $\delta$ /p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| Diethylphenylphosphonate | −16·7 |
| Diethyl-(2-thienyl)phosphonate | −10·9 |
| Diethyl-2-(1-methylpyrrolyl)phosphonate | − 9·45 |
| Diethyl-(2-furyl)phosphonate | − 3·9 |

Examination of the data in Table 3.6. reveals a trend to a greater shielding of the phosphorus nucleus on passing from phenyl, to 2-thienyl to 2-(1-methylpyrrolyl), to 2-furyl substituent, indicating the electron-withdrawing ability of the heteroaryl rings to increase in that order. The data thus contrasts with results obtained from the study of the phosphonyl infrared stretching vibrations and the rates of alkaline hydrolysis in estimating the relative electronic effect of the 2-(1-methylpyrrolyl) substituent. Similar seemingly anomalous ^{31}P chemical shift data was also obtained for the tri-heteroaryl- and heteroarylmethylphosphonium salts, for which the electron-

withdrawing ability of the substituents was indicated as 2-(1-methylpyrrolyl) $>$ 2-furyl $>$ 2-thienyl $>$ phenyl and 2-(1-methylpyrrolyl)methyl $>$ 2-furylmethyl $>$ 2-thenyl $>$ benzyl, respectively (Chapter 1, section 3). A possible steric effect by the 1-methyl group of the 2-(1-methylpyrrolyl) substituent was suggested to explain these results and $^{31}$P chemical shift data of phosphonium salts containing the o-tolyl substituent was given to illustrate the apparent increase in shielding of the phosphorus in the presence of a possible steric effect by an ortho-methyl group. Thus a similar effect by the 1-methyl group in diethyl-2-(1-methylpyrrolyl)phosphonate is possible. Evidence in support of this proposal is provided in the work by Freedman et al[131] by the absence of a definite correlation between the $^{31}$P chemical shifts of ortho-mono-substituted phenylphosphonic acids and Hammett $\sigma$ constants or Taft $\sigma_I$ or $\sigma_R$ constants, and the need to introduce substituent constants derived from the reactions of ortho-substituted benzoate esters. In this respect the $^{31}$P chemical shift of diethyl-(o-tolyl)phosphonate would be useful to assess the effect of the ortho-methyl group in this situation.

The results in Tables 3.5. and 3.6. indicate an overall increased electron-withdrawing ability of the 2-furyl and 2-thienyl substituents compared with the phenyl substituent when attached to the phosphonyl group. In the case of the 2-furyl substituent this increased 'electronegativity' is reflected to a limited extent in the greater rate of alkaline hydrolysis of the 2-furyl-phosphonate ester (LXXVIII; R = $C_2H_5$) compared with the phenyl analogue (IC; R = $C_2H_5$) which, however, undergoes alkaline hydrolysis at rates comparable with the 2-thienylphosphonate ester (LXXIX; R = $C_2H_5$). Thus a possible levelling of the electronic effects of substituents in the mechanism of the hydrolysis reaction is indicated.

Similar relative rates of reaction have been observed for the alkaline hydrolysis of the corresponding carboxylate esters[122,123], though it has been suggested by previous workers[2,3] that differences exist in the mechanisms of

the two reactions.  Thus, mesomeric contributions by the $\pi$-system of the substituent and the rate of bond-formation with the nucleophile are important in the reaction of carbonyl compounds, whereas there is a greater effect by the leaving group in the alkaline hydrolysis of phosphonyl derivatives.  In view of these considerations, in order to assess the importance of the leaving group in the alkaline hydrolysis of heteroarylphosphonate esters, it was of interest to investigate the chemistry of the corresponding diphenylheteroaryl-phosphonates (LXXVIII, LXXIX and IC; $R = C_6H_5$) and (XCV).

3.4 Studies of the Chemistry of Diphenylheteroarylphosphonate Esters.

The increased lability of the P-O-aromatic bond compared with the P-O-alkyl bond was noted by Hudson and Keay[48] who observed the exclusive release of p-nitrophenol from ethyl-p-nitrophenylmethylphosphonate.  Fukuto and Metcalf[44] suggested that a further indication of the lability of this bond may be obtained from the frequency of the infrared stretching vibration. Absorption bands resulting from stretching motions in the P-O-C linkages are usually the most intense bands in the spectrum[135].  The vibrations are complex, consisting of simultaneous stretching of the P-O and C-C bonds, both in and out of phase, and there has been some disagreement as to the correct vibrational assignments.  In general, however, it is convenient in considering a given P-O-aromatic linkage, to view the higher frequency vibration ($1180$-$1260$ cm$^{-1}$) as "mostly C-O stretching", and to view the lower frequency vibration ($900$-$980$ cm$^{-1}$) as "mostly P-O stretching".

In the spectra of the diphenylheteroarylphosphonate esters under consideration, no trend between the nature of the heteroaryl substituent and the frequency of the stretching vibration of the P-O-aromatic bond was indicated in either of the above regions.  The probable explanation for the absence of such a trend in both the diethyl-, and diphenylheteroarylphosphonate esters is that the largest single effect on the frequency of the P-O-C vibration in organophosphorus esters results from the nature of the carbon atom in the

linkage, and thus substituents at phosphorus will have little effect on the frequency of vibration. As in the case of the diethylphosphonate esters, a variation in the frequency of the phosphonyl (P=O) stretching vibration was observed and the frequencies of this band are listed in Table 3.7..

<u>Table 3.7.</u>

<u>Frequencies $(cm^{-1})$ of the Phosphonyl Infrared Stretching Vibration in Diphenylheteroarylphosphonate Esters</u> $RP(O)(OC_6H_5)_2$ .

| R | $\nu$ P=O |
|---|---|
| 2-(1-Methylpyrrolyl) | 1265 |
| Phenyl | 1265 |
| 2-Thienyl | 1268 |
| 2-Furyl | 1285 |

The results in Table 3.7. thus confirm the earlier indication of increased electron-withdrawal from the phosphonyl group by the 2-furyl and 2-thienyl substituents compared with phenyl and 2-(1-methylpyrrolyl) groups. In addition, the overall increase in the frequency of the phosphonyl vibration compared with the diethylheteroarylphosphonate esters suggests increased electron-withdrawal by the phenyl ester groups. The electron-withdrawing ability of the substituents at phosphorus decreases in the order, 2-furyl $>$ 2-thienyl $>$ phenyl $\approx$ 2-(1-methylpyrrolyl), and thus there is a slight difference from the order suggested by the infrared data for the diethylphosphonate analogues.

The series of diphenylphosphonate esters (LXXVIII, LXXIX and IC; R = $C_6H_5$) and (XCV), have also been investigated by [31]P n.m.r. spectroscopy and the chemical shifts are recorded in Table 3.8..

## Table 3.8.

$^{31}$P Chemical Shift Data for Diphenylheteroarylphosphonates in Chloroform.

| Compound | $\delta$ $^{31}$P/p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| Diphenylphenylphosphonate | $-10 \cdot 25$ |
| Diphenyl-(2-thienyl)phosphonate | $- 4 \cdot 1$ |
| Diphenyl-2-(1-methylpyrrolyl)phosphonate | $- 2 \cdot 5$ |
| Diphenyl-(2-furyl)phosphonate | $+ 3 \cdot 0$ |

The data in Table 3.8. reveals several features of interest. The order of electronegativity indicated by the $^{31}$P chemical shifts of the diethylheteroarylphosphonate esters is maintained as, 2-furyl $>$ 2-(1-methylpyrrolyl) $>$ 2-thienyl $>$ phenyl, and thus the irregularity in the $^{31}$P chemical shifts of the 2-(1-methylpyrrolyl) compounds remains. There is also a general increase in the shielding of the phosphorus nuclei of the diphenylphosphonate esters compared with the corresponding diethylphosphonate analogues, indicating an increase in the electron-withdrawal from phosphorus by the phenyl ester groups compared with the ethyl ester groups.

## Table 3.9.

$^{31}$P Chemical Shift Difference ($\Delta\delta$) between Diphenyl and Diethyl Esters of Heteroarylphosphonic Acids.

| Acid | $\Delta\delta$/p.p.m. |
|---|---|
| Phenylphosphonic | $6 \cdot 45$ |
| 2-Thienylphosphonic | $6 \cdot 8$ |
| 2-(1-Methylpyrrolyl)phosphonic | $6 \cdot 95$ |
| 2-Furylphosphonic | $6 \cdot 9$ |

Comparison of the data in Tables 3.6. and 3.8. reveals that the difference in $^{31}$P chemical shift ($\Delta\delta$) between the diphenyl and diethyl esters of each phosphonic acid is reasonably constant, (Table 3.9.). Therefore the indication

is that the substituent groups have characteristic additive effects on the chemical shift of the phosphorus, and any interaction between the $\pi$-orbitals of the heterocyclic rings and phosphorus appears to be only slightly affected by the nature of the ester groups. In this respect, it is of interest that $\Delta\delta$ is larger for the heteroaryl substituents than for the phenyl analogue, for which the lack of conjugation with the phosphorus atom has been noted[2].

The kinetics of alkaline hydrolysis of the diphenylheteroarylphosphonate esters (LXXVIII, LXXIX and IC; R = $C_6H_5$) and (XCV) have been studied and the initial second-order rate constants are presented in Table 3.10..

Table 3.10.

Second-Order Rate Constants for the Alkaline Hydrolysis of Diphenylheteroaryl-phosphonate Esters $RP(O)(OC_6H_5)_2$ in Aqueous Dioxan (50% v/v; 0·1M in KCl).

| R | Ester (M) | NaOH (M) | Temperature (°C) | $k_{obs}$ (1 mol$^{-1}$ sec$^{-1}$) |
|---|---|---|---|---|
| 2-Furyl | 0·01 | 0·01 | 39·8 | 10·50 x 10$^{-2}$ |
| | 0·01 | 0·01 | 29·7 | 7·28 x 10$^{-2}$ |
| Phenyl | 0·01 | 0·01 | 39·8 | 11·06 x 10$^{-2}$ |
| | 0·01 | 0·01 | 29·7 | 6·61 x 10$^{-2}$ |
| 2-Thienyl | 0·01 | 0·01 | 39·8 | 6·42 x 10$^{-2}$ |
| | 0·01 | 0·01 | 29·7 | 4·11 x 10$^{-2}$ |
| 2-(1-Methylpyrrolyl) | 0·01 | 0·01 | 39·8 | 4·71 x 10$^{-3}$ |
| | 0·01 | 0·01 | 29·7 | 2·27 x 10$^{-3}$ |

The results in Table 3.10. reveal the alkaline hydrolysis reaction to proceed more quickly for the diphenylheteroarylphosphonates than for the corresponding diethyl esters. Such rate increases would be expected on the basis of the increased electron-withdrawal from the phosphorus atom in the diphenyl esters as indicated by the above spectroscopic studies. The increased

electron-withdrawal would serve to increase the positive nature of the phosphorus atom and assist the approach of the nucleophile. In addition an increased rate of alkaline hydrolysis of the diphenyl esters would be expected on the basis of the greater stability of the phenate anion as the leaving group.

The following order for the rate of the alkaline hydrolysis reaction is obtained, 2-furyl $\approx$ phenyl $>$ 2-thienyl $>$ 2-(1-methylpyrrolyl), the relative rates being 25 : 16 : 1. There is thus a slight difference from the order observed for the diethylphosphonate esters and a reduction in the relative orders of reactivity.

The activation parameters for the above reactions have been calculated and are given in Table 3.11..

Table 3.11.

Activation Parameters for the Alkaline Hydrolysis of Diphenylheteroaryl-phosphonate Esters $RP(O)(OC_6H_5)_2$ .

| R | $E_A$ (kJ mol$^{-1}$) | $\Delta S$ (J K$^{-1}$ mol$^{-1}$) | $\log_{10}$ PZ |
|---|---|---|---|
| 2-Furyl | 28·6 | −172·4 | 3·8 |
| 2-Thienyl | 34·8 | −156·3 | 4·6 |
| Phenyl | 39·9 | −135·6 | 5·7 |
| 2-(1-Methylpyrrolyl) | 55·6 | −112·1 | 6·95 |

Examination of the data in Table 3.11. reveals a similar trend in the activation parameters to that observed for the alkaline hydrolysis of the diethylphosphonate esters. Decreases in the activation energy for the reactions of the 2-furyl- and 2-thienylphosphonates are compensated by increases in the activation entropy for the reactions of the phenyl- and 2-(1-methylpyrrolyl)-phosphonates. It would be expected, however, that there is a fundamental difference in the mechanisms of the two reactions[28]. Since alkoxide ions are more basic than hydroxide ions, it would be expected that loss of the departing anion in the alkaline hydrolysis of diethylphosphonates is an important factor

in determining the relative reactivities. In the reaction of the diphenyl-phosphonates, however, the leaving group is less nucleophilic than the entering group and thus the reaction constant will be more a measure of the electronic effects for bond-formation. On this basis the results indicate the positive charge on the phosphorus atom in the phosphonate esters to decrease in the order, 2-furyl $\approx$ phenyl $>$ 2-thienyl $>$ 2-(1-methylpyrrolyl), and thus the results indicate a degree of $\pi$-electron donation by the heterocyclic substituent which compensates for $\sigma$-electron-withdrawal due to the inductive effect of the heteroatom.

In the alkaline hydrolysis of the diethylphosphonate esters, it was suggested that the reduction in the activation energies for the reaction of the 2-furyl and 2-thienyl compounds may possibly indicate increased electron-withdrawal from the phosphorus by the 2-furyl and 2-thienyl substituents compared with the phenyl and 2-(1-methylpyrrolyl) analogues. This interaction would assist the approach of the nucleophile and bond-formation. A similar argument may be applied to the reaction of the diphenylphosphonate esters and evidence to support this proposal is provided by infrared and $^{31}$P n.m.r. spectroscopic data. The reduction in the relative rates of reaction would then be attributed to the greater lability of the P-O-phenyl bond which serves to level out the electronic contributions of the heteroaryl substituents.

3.5 Studies of the Chemistry of Heteroarylmethylphosphonate Esters.

In view of the difficulty in determining the relative importance of the $\sigma$-, and $\pi$-interactions between the heterocyclic substituent and phosphorus, a study of the chemistry of a series of heteroarylmethylphosphonates has been made. In these esters, $\pi$-interactions between the ring and phosphorus are not possible, and thus the effect of inductive electron-withdrawal by the hetero-cyclic ring may be more easily recognised.

The Arbuzov and Michaelis-Becker reactions are among the most widely used procedures for forming carbon-phosphorus bonds[136] and have been successfully

applied in the synthesis of heteroarylphosphorus derivatives. Nucleophilic

displacements on heterocyclic halides have been well studied for alkoxides,

amines etc. and a general order of reactivity has been recognised for these

nucleophiles. Thus at one extreme 2-halo-2,4,6-triazines have a high

susceptibility to displacement of halide whereas 2-halopyridines are relatively

unreactive[137]. For the case of displacement by trialkylphosphites (Arbuzov)

or dialkylmetal phosphonates (Michaelis-Becker) a similar order of reactivity

appears to exist although no kinetic measurements have been reported. A review

by Redmore[93] summarises the use of these reactions to prepare a number of

heteroarylphosphorus derivatives.

$$\underset{\text{H}_3\text{C}}{\phantom{a}}\text{CH}_2\text{P(OC}_2\text{H}_5)_2 \quad (\text{CVI})$$
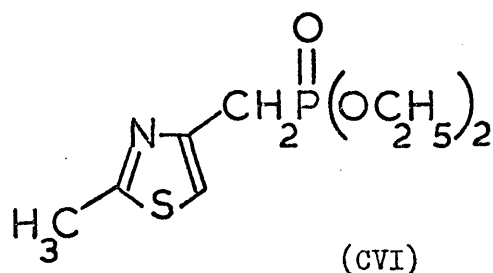
In addition to phosphorus compounds in which the phosphorus atom is linked

directly to the heterocyclic nucleus, a number of workers have applied these

procedures to prepare compounds in which the phosphorus atom is isolated from

the ring by one or more methylene groups. Thus Arbuzov and Lugovkin[138]

reported the synthesis of diethyl-4-(2-methylthiazolyl)methylphosphonate (CVI)

by the dropwise addition of 4-chloromethyl-2-methylthiazole to triethylphosphite

preheated to 150-5°.

$$\text{CH}_2\text{P(OR)}_2 \qquad \text{CH}_2\text{P(OR)}_2$$

(CVII)          (CVIII)

$$\langle \rangle N(CH_2)_n \overset{O}{\underset{\|}{P}}(OC_2H_5)_2$$

(CIX)
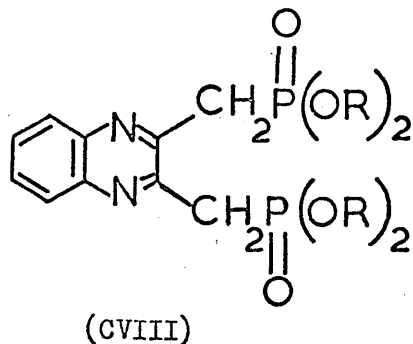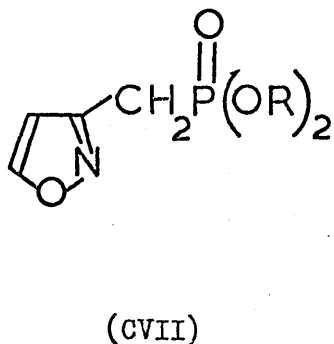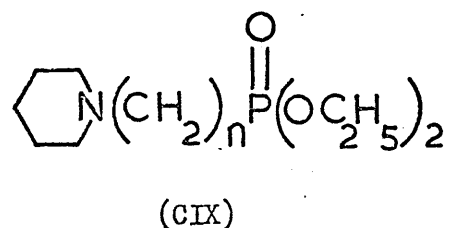
Extension of the work gave esters of phosphonic acids containing isoxazole (CVII) and quinoxaline (CVIII) groups[139] by the reaction of trialkylphosphite or sodium dialkylphosphonate with the halomethyl derivatives. A number of diethylpiperidinophosphonates (CIX; n = 2 or 3) were similarly prepared[140].

$$\langle \rangle CH_2 \overset{O}{\underset{\|}{P}} \underset{OR}{\overset{OR}{<}}$$

(CX)
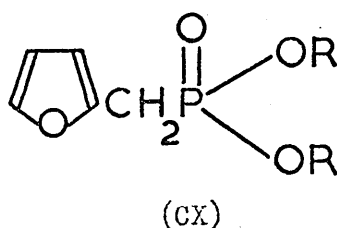
In a publication concerned with the synthesis of diethylphosphonate esters of heterocyclic systems containing oxygen, Arbuzov and Lugovkin[141] reported the formation of diethyl-(2-furylmethyl)phosphonate (CX; R = $C_2H_5$) by the reaction of sodium diethylphosphonate and 2-bromomethylfuran. Kellog et al[142] similarly reported the synthesis of dimethyl-(2-furylmethyl)phosphonate (CX; R = $CH_3$) by the reaction of trimethylphosphite and 2-chloromethylfuran.

In the present study, 2-bromomethylfuran prepared as described by Zanetti[143], was added dropwise to a suspension of sodium diethylphosphonate in ether, and the resulting mixture heated under reflux. Filtration of the reaction mixture to remove sodium bromide followed by removal of the ether solvent gave the required diethyl-(2-furylmethyl)phosphonate (CX; R = $C_2H_5$), which was purified by distillation. Examination of the integrated peak intensities of the n.m.r. spectrum of (CX; R = $C_2H_5$) and g.l.c. analysis, indicated the product to be free of contaminants. A microanalytically pure sample of (CX; R = $C_2H_5$) was only obtained, however, after repeated distillation through a spinning-band column.

(CXI)          (CXII)
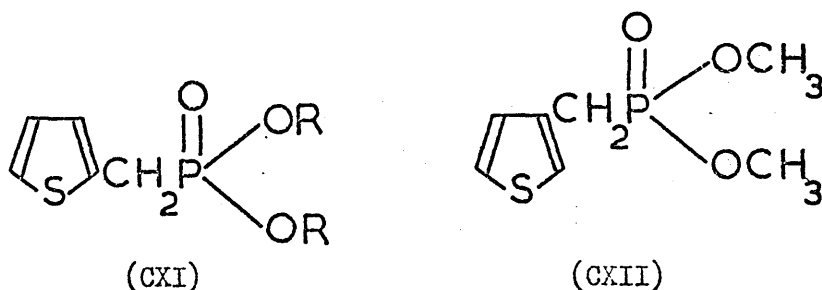
Kellog et al[142] reported the synthesis of dimethyl and diethyl esters of

2-thenylphosphonic acid (CXI; R = $CH_3$ or $C_2H_5$) by the reaction between

trialkylphosphite and 2-thenyl chloride; dimethyl-(3-thenyl)phosphonate (CXII)

was prepared by the same general procedure. In the present study, the reaction

between sodium diethylphosphonate and 2-thenyl chloride was preferred. Thus

the addition of 2-thenyl chloride, prepared by the procedure of Blick and

Leonard[144], to a suspension of sodium diethylphosphonate in ether, under the

usual reaction conditions, gave diethyl-(2-thenyl)phosphonate (CXI; R = $C_2H_5$)

in good yield. Examination of the product by n.m.r. and g.l.c. indicated the

compound to be free of contaminants, and a satisfactory microanalysis was

obtained.

Diethylbenzylphosphonate (CXIII) was similarly prepared using the above

general procedure by the reaction of sodium diethylphosphonate with benzyl

chloride[145].



(CXIII)
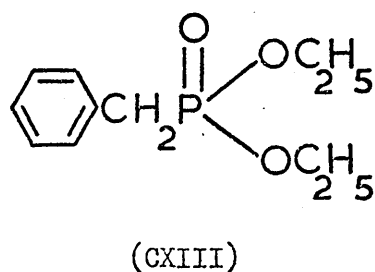
The reaction between phosphite and amine or alcohol derivatives to form

the corresponding phosphonic acid esters has also been reported. Thus

Laughlin[146] prepared diphenyl-n-alkylphosphonates containing large alkyl groups,

by heating triphenylphosphite with the appropriate alcohol at 220-250° in the

presence of a suitable halide catalyst e.g. sodium iodide. Evidence was given

to suggest that the reaction proceeds through an alkyldiphenylphosphite intermediate, which then rearranges to the isomeric phosphonate. In the present study, the attempted preparation of diphenyl-(2-furylmethyl)phosphonate (CX; R = $C_6H_5$) by the reaction of triphenylphosphite and 2-furylmethyl alcohol led to the formation of resinous non-characterisable material. It is also of interest that the attempted reaction of sodium diphenylphosphonate and heteroarylmethyl halide achieved similar results.



$$(CH_3)_2N-\langle\bigcirc\rangle-CH_2\overset{\overset{O}{\|}}{P}\overset{OC_2H_5}{\underset{OC_2H_5}{\big\langle}}$$

(CXIV)

$$(CH_3)_2N-\langle\bigcirc\rangle-CH_2N(C_2H_5)_2$$

(CXV)
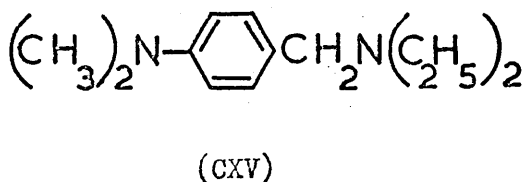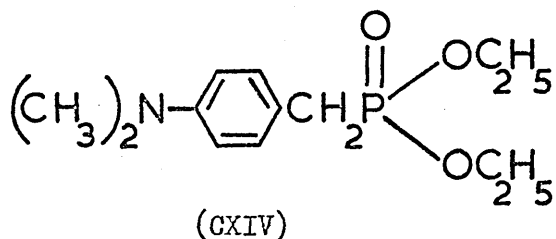
Ivanov[147] reported the preparation of diethyl-p-dimethylaminobenzyl- phosphonate (CXIV) by the reaction of diethyl-p-dimethylaminobenzylamine (CXV) and triethylphosphite in the presence of acetic acid. Heating the methiodide of (CXV) with triethylphosphite gives the same phosphonate product (CXIV).

$$R\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{+}{N}(C_2H_5)_2CH_3\overset{-}{I}$$

(CXVI)

$$R\overset{\overset{O}{\|}}{C}CH_2CH_2\overset{\overset{O}{\|}}{P}\overset{OC_2H_5}{\underset{OC_2H_5}{\big\langle}}$$

(CXVII)
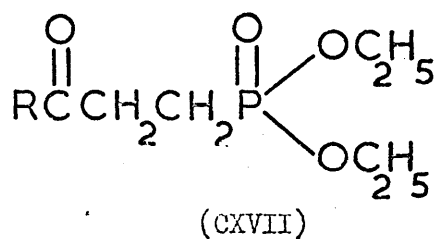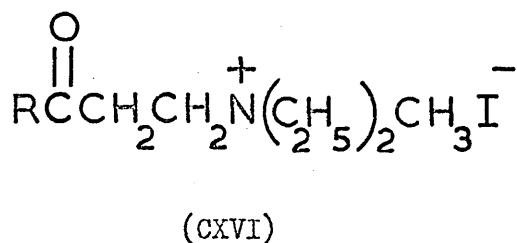
Myers et al[148] reported the synthesis of 3-ketophosphonic acid esters by the reaction of triethylphosphite and a Mannich base methiodide. Thus triethylphosphite reacts smoothly on heating with 3-ketobutyldiethylmethyl-ammonium iodide (CXVI; R = $CH_3$) to eliminate the nitrogen function and produce diethyl-3-ketobutylphosphonate (CXVII; R = $CH_3$) from which the free acid is obtained on hydrolysis with hydrochloric acid. The methyl iodide derivative of 1-diethylamino-3-phenylpropan-3-one (CXVI; R = $C_6H_5$) reacts similarly to give the corresponding phosphonate ester (CXVII; R = $C_6H_5$). The reaction between triethylphosphite and the hydrochloride of the Mannich base also gives

the phosphonate ester but in slightly lower yield, and the product is somewhat

cleaner when the methiodide is used. In contrast to the quaternary salts, no

reaction was observed between triethylphosphite and the free base. A low yield

of the required phosphonate is given, however, from the reaction of free base

and diethylphosphite in the presence of catalytic amounts of sodium diethyl-

phosphonate.



(CXVIII)                    (CXIX)
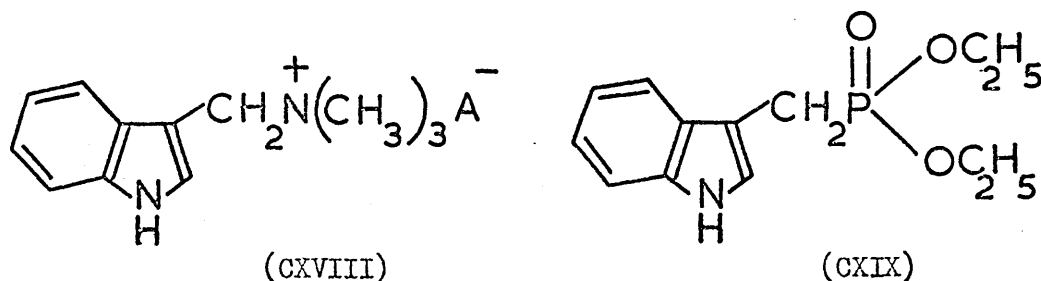
Myers et al[149] extended the investigation to the heterocyclic Mannich base

gramine (3-dimethylaminomethylindole) and its quaternary derivatives. Thus

gramine methiodide (CXVIII; A = I) and gramine methosulphate (CXVIII; A = $CH_3SO_4$),

were found to react when heated with triethylphosphite, to give diethyl-3-

indolylmethylphosphonate (CXIX) in approximately 75% yield. Reactions between

gramine methiodide or gramine methosulphate with diethylhydrogenphosphite

under conditions similar to those used with triethylphosphite, produced only

high boiling resins from which no diethyl-3-indolylmethylphosphonate could be

isolated. Similar results were obtained in a reaction between the free base

and triethylphosphite. The reaction between sodium diethylphosphonate and

gramine methiodide (CXVIII; A = I) in alcoholic solution gives the required

phosphonate in 20% yield, while the analogous reaction with gramine methosulphate

(CXVIII; A = $CH_3SO_4$) gives (CXIX) in 75% yield. Attempts to hydrolyse the

ester (CXIX) in acid medium were unsuccessful and resulted in extensive

decomposition of the molecule. Hydrolysis by aqueous sodium hydroxide produced

the half ester.

(CXX): pyrrole ring with N-CH$_3$, 2-position CH$_2$N$^+$(CH$_3$)$_3$ I$^-$

(CXXI): pyrrole ring with N-CH$_3$, 2-position CH$_2$P(=O)(OC$_2$H$_5$)(OC$_2$H$_5$)

(CXX)    (CXXI)
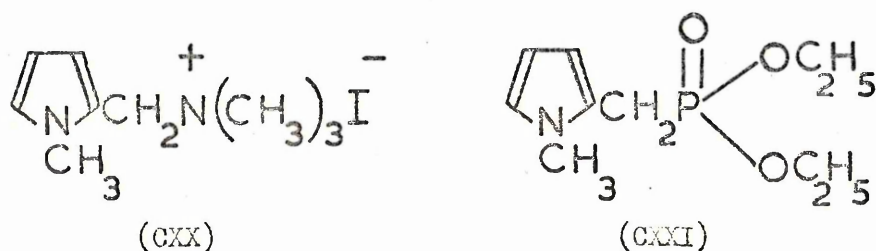
It was of interest to investigate the applicability of the above routes to the preparation of the corresponding 1-methylpyrrolylmethylphosphonate (CXXI). Thus 2-(dimethylaminomethyl)-1-methylpyrrole was prepared from the reaction between dimethylammonium chloride, formaldehyde and 1-methylpyrrole according to the procedure reported by Treibs et al[150]. Treatment of the amine with methyl iodide in ether gave the quaternary salt (CXX). However, the reaction of trimethyl-(1-methylpyrrol-2-yl)methylammonium iodide (CXX) with an excess of triethylphosphite under a variety of conditions resulted in only trace amounts of impure diethyl-(1-methylpyrrol-2-yl)methylphosphonate (CXXI) as indicated by n.m.r., together with unreacted triethylphosphite. Large amounts of resinous material were also obtained from the reaction, indicating some polymerisation of the 2-(1-methylpyrrolyl)methyl system, possibly via the carbonium ion (CXXII).

(CXXII): pyrrole ring with N-CH$_3$, 2-position $^+$CH$_2$

(CXXIII): heterocyclic ring with X, 2-position CH$_2$C(=O)-OH

(CXXII)    (CXXIII)
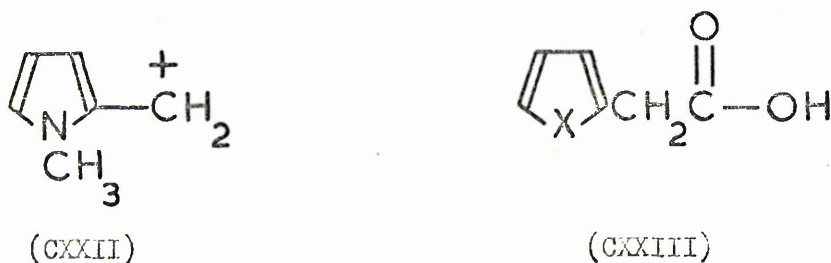
Evidence for the lack of conjugation between the heterocyclic ring and the carbonyl group, in heteroarylmethylcarbonyl compounds, has been obtained by a number of workers. Sugimoto et al[151] have shown $\lambda$ max in the u.v. spectra of 2-thienylacetic acid (CXXIII; X = S) and thiophen itself to occur at 235 m$\mu$, whereas $\lambda$ max for 2-thiophencarboxylic acid in which the carbonyl group is attached directly to the heterocyclic ring, occurs at 270 m$\mu$. Similarly, Smith et al[152] observed the rate of the acid catalysed esterification of

2-furylacetic acid (CXXIII; X = 0) to take place several hundred times faster

and with a large reduction in activation energy, compared with the analogous

reaction of 2-furoic acid. It was suggested that the difference in the

relative reactivities was due to conjugation effects in the reaction of

2-furoic acid which were absent for 2-furylacetic acid.

In view of the absence of conjugation in heteroarylmethylcarbonyl compounds,

it seems reasonable to assume that $\pi$-interactions between the ring system and

phosphorus in the analogous heteroarylmethylphosphonyl compounds are not

possible and thus the effect of electron-withdrawal by the heterocyclic ring

may therefore be more easily recognised.
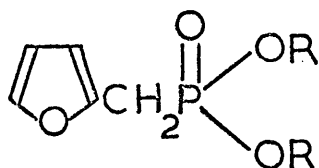


(CX)
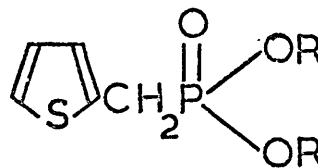
(CXI)
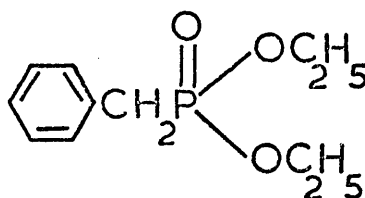
(CXIII)

Examination of the infrared spectra of the diethylheteroarylmethyl-

phosphonates (CX, CXI; R = $C_2H_5$) and (CXIII), did not reveal any significant

differences in the position of the various stretching vibrations. The frequency

of the phosphonyl band ($\nu$P=0) remained constant at 1250 cm$^{-1}$, and the

frequency of the P-O-$C_2H_5$ band remained constant at 1030 cm$^{-1}$. Some variation

in the $^{31}$P n.m.r. chemical shifts was, however, observed and the data is

presented in Table 3.12..

# Table 3.12.

$^{31}$P Chemical Shift Data for Diethylheteroarylmethylphosphonates in Chloroform.

| Compound | $\delta^{31}$P/p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| Diethylbenzylphosphonate | −22·75 |
| Diethyl-(2-thenyl)phosphonate | −21·00 |
| Diethyl-(2-furylmethyl)phosphonate | −19·75 |

The data in Table 3.12. reveals a trend to a greater shielding of the phosphorus nucleus on passing from benzyl-, to 2-thenyl-, to 2-furylmethyl-phosphonate, indicating the electron-withdrawing ability of the substituents to increase in that order. As the heterocyclic nucleus in heteroarylmethyl-phosphonates is isolated from phosphorus by a methylene group and $\pi$-interactions between the ring system and phosphorus are not possible, the results in Table 3.12. thus reflect electron-withdrawal solely by the inductive effect of the heterocyclic ring. The same general order of electronegativity of the heterocyclic substituents is, however, obtained from $^{31}$P chemical shift data of the diethyl- and diphenylheteroarylphosphonates in which the phosphorus is linked directly to the heterocyclic system. It is of interest, however, that the $^{31}$P chemical shifts of the heteroarylphosphonates (Table 3.6.) are appreciably more positive than those of the heteroarylmethylphosphonates (Table 3.12.). Since $p\pi$ — $d\pi$ bonding between the ring system and phosphorus would be expected to make the chemical shift more negative, the above data thus possibly indicates that the effects of any $p\pi$ — $d\pi$ bonding which may be present is of little consequence in influencing the $^{31}$P chemical shift of heteroarylphosphonates.

A further indication of the electron-withdrawing ability of the heteroaryl-methyl substituents has been obtained from a study of the polarographic reduction of the corresponding heteroarylmethylcarboxylic acids (CXXIII; X = O, S or NH). Thus Nakaya[153] et al observed that the half-wave potentials

of the acids were positive and in the order 2-pyrrolylmethyl$>$ benzyl$>$
2-furylmethyl$>$ 2-thenyl. From the results, Hammett substituent values (which
give some indication of the electron-attracting nature of the substituent) of
0·6, 1·5, 2·27 and 2·55 were derived for the 2-pyrrolylmethyl, benzyl,
2-furylmethyl and 2-thenyl substituents respectively. These were compared
with the value ($\sigma$= 0) for unsubstituted acetic acid. A linear correlation
between the half-wave potential and the $pK_a$ of each acid was also obtained.

Allen et al[154] have previously investigated the $^{31}$P chemical shifts of
triphenylheteroarylmethylphosphonium salts and also observed the shielding of
the phosphorus to decrease in the order, 2-furylmethyl$>$ 2-thenyl$>$ benzyl.
Further confirmation of this order of electron-withdrawing ability of the
substituents was established from the relative stabilities of the heteroaryl-
methyl and benzyl carbanions and the rates of alkaline hydrolysis of the
triphenylheteroarylmethylphosphonium salts, which were shown to decrease in
the order, 2-furylmethyl$>$ 2-thenyl$>$ benzyl.

The kinetics of alkaline hydrolysis of the diethylheteroarylmethyl- and
benzylphosphonate esters (CX, CXI; R = $C_2H_5$) and (CXIII) in 50% aqueous dioxan,
to give the monoester, have been studied and the second-order rate constants
are presented in Table 3.13..

Table 3.13.

Second-Order Rate Constants for the Alkaline Hydrolysis of Diethylheteroaryl-methylphosphonate Esters $RP(O)(OC_2H_5)_2$ in Aqueous Dioxan (50% v/v: 0·1M in KCl).

| R | Ester (M) | NaOH (M) | Temperature (°C) | $k_{obs}$ (1 mol$^{-1}$ sec$^{-1}$) |
|---|---|---|---|---|
| Benzyl | 0·05 | 0·05 | 60 | $10·83 \times 10^{-5}$ |
|  | 0·05 | 0·05 | 50 | $5·34 \times 10^{-5}$ |
| 2-Thenyl | 0·05 | 0·05 | 60 | $3·71 \times 10^{-4}$ |
|  | 0·05 | 0·05 | 50 | $1·80 \times 10^{-4}$ |
| 2-Furylmethyl | 0·05 | 0·05 | 60 | $6·78 \times 10^{-4}$ |
|  | 0·05 | 0·05 | 50 | $3·27 \times 10^{-4}$ |

The results in Table 3.13. reveal several features of interest. Over the temperature range studied, the rates of alkaline hydrolysis of the heteroaryl-methyl- and benzylphosphonates are in the order 2-furylmethyl $>$ 2-thenyl $>$ benzyl, the relative rates being 6 : 3 : 1. The results are thus in contrast with those obtained for the diethylheteroarylphosphonates (LXXVIII, LXXIX and IC; $R = C_2H_5$) for which the rates of alkaline hydrolysis decrease in the order, 2-furyl (5) $>$ phenyl $\approx$ 2-thienyl (1), and the diphenylheteroarylphosphonate esters (LXXVIII, LXXIX and IC; $R = C_6H_5$) the relative reactivity of which decreases in the order 2-furyl $\approx$ phenyl (1·5) $>$ 2-thienyl (1). Assuming that there are no $\pi$-interactions between the phenyl ring and phosphorus[74] in the phenylphosphonates (IC; $R = C_2H_5$ or $C_6H_5$) and since the rates of alkaline hydrolysis of the heteroarylmethylphosphonates reflect solely the inductive effect of the heterocyclic ring, the results in Table 3.13. strongly indicate a $\pi$-mesomeric effect between the $p\pi$ orbitals of the heterocyclic substituent and the 3d orbitals of phosphorus in the alkaline hydrolysis reactions of diethyl- and diphenylheteroarylphosphonate esters (LXXVIII, LXXIX; $R = C_2H_5$ or $C_6H_5$). In addition from the rate data in Tables 3.2., 3.10. and 3.13., the

effect appears to be stronger for a 2-thienyl substituent than for a 2-furyl substituent.

Since the rates of alkaline hydrolysis of the diethyl esters of the 2-furyl- and 2-thienylphosphonic acids are some 2 - 7 times faster than for the corresponding diethylheteroarylmethylphosphonates, this would suggest that the extent of $p\pi$— $d\pi$ conjugation is relatively small, for a large effect would result in a more significant decrease in the rate of reaction of the heteroarylphosphonate esters. In comparison the second-order rate constants for the alkaline hydrolysis of triethylphosphate under the same conditions are $9 \cdot 97 \times 10^{-5}$ $1 \text{ mol}^{-1}\text{sec}^{-1}$ and $4 \cdot 28 \times 10^{-5}$ $1 \text{ mol}^{-1}\text{sec}^{-1}$ at $59 \cdot 7^{\circ}\text{C}$ and $50^{\circ}\text{C}$ respectively, indicating the deactivating $p\pi$— $d\pi$ conjugation to be more significant in this molecule than for the diethyl esters of 2-furyl- and 2-thienylphosphonic acids. In addition, the greater energy of activation for the alkaline hydrolysis of triethylphosphate ($77 \cdot 9 \text{ kJ mol}^{-1}$) compared with the corresponding data for diethyl-(2-furyl)phosphonate ($56 \cdot 4 \text{ kJ mol}^{-1}$) and diethyl-(2-thienyl)phosphonate ($54 \cdot 8 \text{ kJ mol}^{-1}$) is further evidence of the increased conjugation. There is, however, some similarity in the rate constants and activation energies for the alkaline hydrolysis of triethylphosphate and diethyl-2-(1-methylpyrrolyl)phosphonate ($75 \cdot 5 \text{ kJ mol}^{-1}$).

The activation parameters for the reactions of the heteroarylmethyl- and benzylphosphonate esters have been calculated and are presented in Table 3.14..

Table 3.14.

Activation Parameters for the Alkaline Hydrolysis of Diethylheteroarylmethyl-phosphonate Esters $RP(O)(OC_2H_5)_2$ .

| R | $E_A$ (kJ mol$^{-1}$) | $\Delta S$ (J K$^{-1}$mol$^{-1}$) | $\log_{10}$ PZ |
|---|---|---|---|
| Benzyl | $63 \cdot 3$ | $-131 \cdot 3$ | $5 \cdot 96$ |
| 2-Thenyl | $64 \cdot 7$ | $-117 \cdot 0$ | $6 \cdot 72$ |
| 2-Furylmethyl | $65 \cdot 7$ | $-109 \cdot 2$ | $7 \cdot 12$ |

Examination of the data in Table 3.14. reveals the energies of activation for the reactions to remain reasonably constant and the entropies of activation and $\log_{10}$ PZ values to be dominant in determining the relative rates of reaction. There is a very slight increase in activation energy with increasing rate of reaction. A similar effect has been observed by Hudson and Moss[11] in the solvolysis of methyl- and chloromethylphosphonochloridates. In this case it was suggested that the data indicated bond-making and bond-breaking influences to be of comparable importance and the increase in activation energy was then due to the increase in the P—Cl and P=O bond energies. The accompanying decrease in electrostatic energy (being a free energy) produces the increase in the rate of reaction at the particular temperature of measurement. The data in Table 3.14. is in contrast with the corresponding data for the heteronuclear phosphonate esters (Tables 3.2. and 3.11.) where a wider variation of activation energies and entropies is observed, this may be further evidence of opposing inductive and mesomeric effects in the alkaline hydrolysis reactions of these compounds.

It is of interest that whilst the rate data for the kinetics of alkaline hydrolysis of the above phosphonate esters show a degree of $p\pi - d\pi$ interaction between the heterocyclic ring and phosphorus, very little evidence of such an interaction is indicated from the spectroscopic results obtained in this study. Griffin et al[89], however, have previously deduced from u.v. studies that some conjugation exists in phosphine oxides containing 2-furyl, 2-thienyl, 2-pyrrolyl and 2-(1-methylpyrrolyl) substituents. In addition, the [1]H n.m.r. spectra of these compounds together with the spectra of dimethyl-(2-furyl)-phosphonate and dimethyl-(2-thienyl)phosphonate has also provided further evidence[90] for a conjugation effect between the heterocyclic ring and the adjacent phosphorus atom. The [31]P n.m.r. data of the diphenyl- and diethyl-heteroarylphosphonate esters, however, together with the phosphonyl infrared stretching vibration data has indicated that the $\sigma$-electron-withdrawal by the

heteroaryl substituent is predominant and suggest electron-donation by the π-system of the heterocycle to be of little importance. The apparent contradiction between the ^{31}P and infrared spectroscopic data and the chemical evidence (i.e. the rate data) may possibly be explained by the fact that the conjugation is too weak to be observed by these spectroscopic techniques, but is strong enough to be detected by the more sensitive chemical means[86].

Alternatively the reduction in the reactivity of phosphorus compounds towards nucleophiles obtained on the replacement of alkyl groups by alkoxy groups has been attributed by Dostrovsky and Halmann[9], and by Heath[12] to an electromeric effect. Similarly, it is possible that such an effect might provide a suitable explanation for the apparent discrepancy between the rate and spectroscopic data obtained for the above phosphonate esters.

## 3.6 Studies of the Chemistry of Pyridylmethylphosphonate Esters.

It has thus been established that the 2-furyl and 2-thienyl substituents are more electron-withdrawing than phenyl. This ability to accept electron-density by the inductive effect is reflected in the rate data for the alkaline hydrolysis of the diethyl esters of the 2-furylmethyl-, 2-thenyl-, and benzylphosphonic acids. Since the kinetics of alkaline hydrolysis of hetero-arylmethylphosphonates provides a convenient method of investigating the nature of the inductive electronic effects of heterocycles, it was of interest to study the chemistry of a series of pyridylmethylphosphonates. Thus in addition to enabling a comparison of the substituent effects of the six-membered "π-deficient" heteroaromatic ring systems[155] with those of the "π-excessive" heterocycles[155] to be made, the relative electronic effects at the 2-,3-, and 4-positions of the pyridyl ring have also been investigated.

Diethylmethylphosphonate and diethylchloromethylphosphonate have also been prepared and their spectroscopic properties and kinetics of alkaline hydrolysis have been investigated, in order that further comparisons of the electronic effects of the above heterocycles with those of other substituents

could be made.



(CXXIV)



(CXXV)



(CXXVI)



(CXXVII)
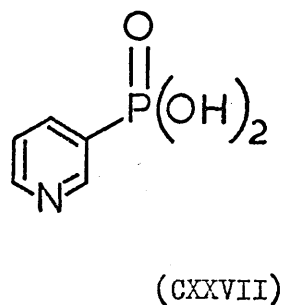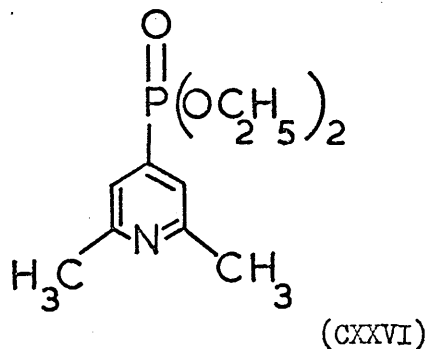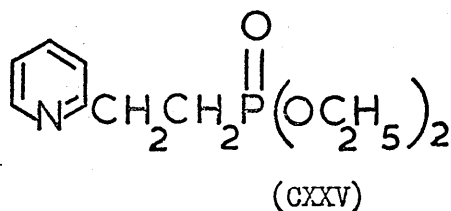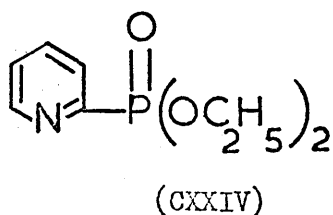
All reported syntheses of phosphonic acid esters containing the pyridine nucleus in which the phosphorus atom is either linked directly to the heterocycle or isolated by one or more methylene groups have involved nucleophilic displacement by phosphorus. Initial attempts by Arbuzov and Lugovkin[140] to prepare diethyl-(2-pyridyl)phosphonate (CXXIV) by the reaction of either 2-bromo-, or 2-iodopyridine with sodium diethylphosphonate were unsuccessful despite long reflux periods. In addition, these same workers[140] reported 2-vinylpyridine to be the principal product from the reaction between 1-bromo-2-(2-pyridyl)ethane and sodium diethylphosphonate, and only a small yield of diethyl-2-(2-pyridyl)ethylphosphonate (CXXV) was obtained. Redmore[156], however, reported the synthesis of (CXXIV) together with a series of substituted 2-pyridylphosphonates from the reaction between the respective N-methoxy-pyridinium salt and an alkali metal derivative of diethylphosphonate. In cases where the 2-position is blocked, introduction of the diethylphosphonyl group occurs in the 4-position; thus diethyl-2,6-dimethylpyridine-4-phosphonate (CXXVI) is formed in the reaction between lithium diethylphosphonate and 2,6-dimethylpyridinium methosulphate. Cadogan[157] reported the formation of diethyl-(2-pyridyl)phosphonate when 2-nitropyridine-N-oxide is heated with triethylphosphite, whilst it is of interest that the corresponding reaction

with 4-nitropyridine-N-oxide fails to give the required phosphonate ester.

3-Pyridylphosphonic acid (CXXVII) has been obtained by Burger et al[158] on the treatment of 3-pyridyldiazonium fluoroborate with phosphorus trichloride in the presence of cuprous bromide.
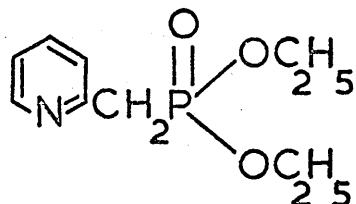


(CXXVIII)
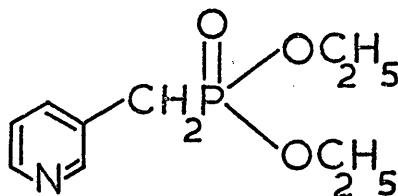
(CXXIX)
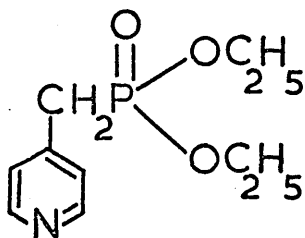
(CXXX)

The synthesis of diethyl esters of 2-, 3-, and 4-pyridylmethylphosphonic acids (CXXVIII), (CXXIX) and (CXXX) respectively by the Michaelis–Becker reaction involving the condensation of the chloromethylpyridine with sodium diethylphosphonate has been reported by Michalski et al[159-161]. These compounds containing the methylene group, activated by the adjacent pyridyl and phosphonyl groups are of particular interest in view of their possible use for the synthesis of pyridine derivatives. Thus the metallic derivatives of such compounds are formed readily, and can be converted by the Wittig reaction with aldehydes and ketones into alkenylpyridines[159-162].

In the present study, the chloromethylpyridines were obtained by the reaction between thionyl chloride and the corresponding pyridylcarbinol according to the general procedure described by Mosher and Tessieri[163]. After the period of reflux, the chloromethylpyridine hydrochloride was precipitated by the addition of benzene, filtered and recrystallised from ethanol. The hydrochloride was then neutralised by dissolution in aqueous sodium carbonate solution. The chloromethylpyridine thus formed was extracted with benzene and

the solution dried before addition to a refluxing solution of sodium diethyl-phosphonate in benzene. Filtration of the reaction mixture to remove sodium chloride, followed by removal of the solvent gave the required phosphonates (CXXVIII), (CXXIX) and (CXXX), which were purified by vacuum distillation. The yields for the reactions are reduced, presumably due to the self-quaternisation of the chloromethylpyridine. Thus, Mosher and Tessieri[163] reported that it is possible to recover only 30% of the chloromethylpyridine following the neutralisation of the hydrochloride in basic medium. Examination of the peak intensities in the n.m.r. spectra of (CXXVIII), (CXXIX) and (CXXX) together with g.l.c. analysis indicated the products to be free of contaminants.

$$ClCH_2\overset{\overset{\displaystyle O}{\|}}{P}\!\!\underset{OC_2H_5}{\overset{OC_2H_5}{<}}$$

(CXXXI)

$$CH_3\overset{\overset{\displaystyle O}{\|}}{P}\!\!\underset{OC_2H_5}{\overset{OC_2H_5}{<}}$$
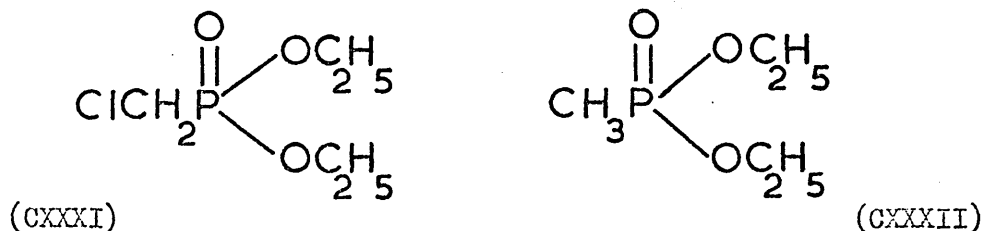
(CXXXII)

Diethylchloromethylphosphonate (CXXXI) was obtained by the reaction of chloromethylphosphonic dichloride with absolute ethanol in benzene solution in the presence of pyridine, according to the general method described by Kosolapoff[119]. The purity of the product was checked by microanalysis, examination of the n.m.r. spectrum and g.l.c. analysis.

Diethylmethylphosphonate (CXXII) was obtained by the Arbuzov reaction of methyl iodide and triethylphosphite[164]. The purity of the compound was similarly checked by the examination of the integrated peak intensities in the n.m.r. spectrum, microanalysis and g.l.c. analysis.

The contrasting chemistry of pyridine and the 5-membered ring heterocycles of furan, thiophen and pyrrole, is commonly understood in terms of the "$\pi$-deficient" nature of the pyridine ring[155] compared with the "$\pi$-excessive" character of the 5-membered ring systems[155]. Thus the many differences in chemical reactivity which are observed between pyridine and furan, thiophen

and pyrrole (e.g. the relative rates of electrophilic and nucleophilic substitution) are explained on the basis of electron-availability at the ring carbon atoms. In addition, the relative abilities of the furyl, thienyl and pyrrolyl substituents compared with pyridyl to stabilise an electron-deficient transition state are responsible for the large differences which are observed in side chain reactivity. Thus 2-furyl- and 2-thienylethyl acetates[165] undergo pyrolysis more quickly than phenylethyl acetate, which in turn is pyrolysed more quickly than 2-,3-, or 4-pyridylethyl acetates[166]. In addition the pinacol-pinacolone rearrangement of the mixed pinacols (CXXXIII; X = O or S) both proceed with exclusive migration of the heterocycle[167], whereas the reaction of the mixed pinacols bearing 2-, and 3-pyridyl substituents (CXXXIV) proceed with the preferential migration of the phenyl group[168].



(CXXXIII)     (CXXXIV)
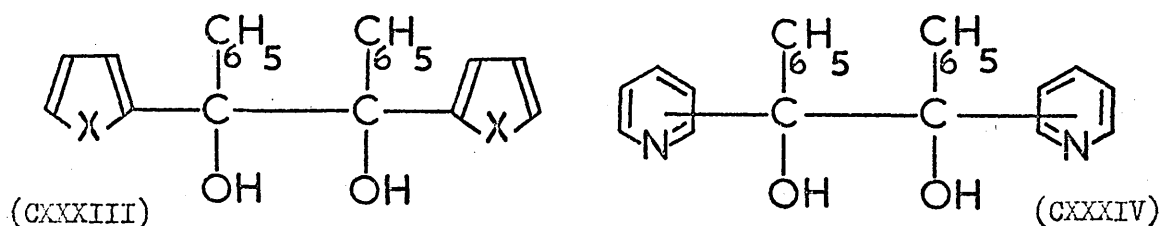
A further useful illustration of the differences in the nature of pyridine and the 5-membered heterocycles is obtained from $^{13}C$ n.m.r. spectroscopy. The chemical shifts of the ring carbon atoms (in p.p.m. relative to carbon disulphide) are given below[169].
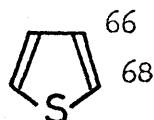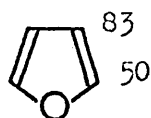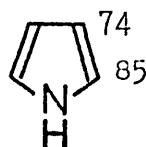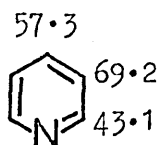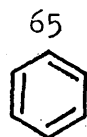
The $^{13}C$ n.m.r. chemical shift data reveals that whilst the electron-density at the 3-position of pyridine is comparable with that of the ring carbon atoms of benzene and the 5-membered ring systems (and slightly greater than the 2-position of furan) the electron-density at the 2-, and 4-positions is reduced. Thus the atoms most affected by the more electronegative ring nitrogen atom in pyridine are at the 2-,6-, and 4-positions.

This information, however, is in slight contrast with the relative electronegativities of the pyridine ring carbon atoms as indicated by the $pK_a$ data of the corresponding pyridylacetic acids[170]. Thus the acid strength is seen to decrease in the order 2-pyridyl-> 3-pyridyl-> 4-pyridylacetic acid, (Table 3.15.).

<div align="center">

Table 3.15.

Ionisation Constants of Pyridylacetic Acids in Water.

</div>

| Acid | $pK_a$ |
|------|------|
| 2-Pyridylacetic acid | 5·58 |
| 3-Pyridylacetic acid | 5·64 |
| 4-Pyridylacetic acid | 5·74 |

In view of this data it is of interest to consider the $^{31}P$ chemical shifts of the diethyl esters of the analogous pyridylmethylphosphonic acids. On the basis of the small differences observed in $pK_a$ data of the pyridylacetic acids, it would be expected that any trend which is observable in the $^{31}P$ chemical shifts of the phosphonates would be correspondingly small. The $^{31}P$ n.m.r. data together with the $^{31}P$ chemical shifts of the diethyl esters of methyl-, and chloromethylphosphonic acids are presented in Table 3.16..

## Table 3.16.

### $^{31}$P Chemical Shift Data for Diethylphosphonate Esters in Chloroform.

| Compound | $\delta\,^{31}$P/p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| Diethyl-(2-pyridylmethyl)phosphonate | -21·75 |
| Diethyl-(3-pyridylmethyl)phosphonate | -21·75 |
| Diethyl-(4-pyridylmethyl)phosphonate | -21·00 |
| Diethylmethylphosphonate | -26·00 |
| Diethylchloromethylphosphonate | +16·75 |

The data in Table 3.16. reveals that there is very little difference in the $^{31}$P chemical shift of the 2-,3-, and 4-pyridylmethylphosphonates. The results do, however, indicate the 4-pyridylmethyl group to be slightly more electronegative than the 2-, and 3-pyridylmethyl substituents, which on the basis of these results have the same effect on the shielding of the phosphorus. Comparison of the data in Tables 3.16. and 3.12. also reveals that the 2-,3-, and 4-pyridylmethyl groups have a similar effect on the $^{31}$P chemical shift to the benzyl, 2-thenyl and 2-furylmethyl groups. Indeed the electron-withdrawing inductive effect of the 2-furylmethyl substituent is apparently greater than for each of the pyridylmethyl groups, which have comparable electronegativities to 2-thenyl, but are slightly more electron-withdrawing than benzyl. The $^{31}$P chemical shifts of the above compounds are more positive than for diethyl-methylphosphonate and thus indicate electron-withdrawal by each of the heteroarylmethyl and benzyl groups compared with methyl; a much greater effect, however, is noticeable for the chloromethyl substituent.

The frequencies of phosphonyl infrared stretching vibrations of the above phosphonate esters also reflect a similar trend of electron-withdrawing ability. Thus the stretching frequency of the phosphonyl bond occurs at 1250 $cm^{-1}$ for each of the heteroarylmethylphosphonates compared with 1243 $cm^{-1}$ for diethyl-methylphosphonate and 1271 $cm^{-1}$ for diethylchloromethylphosphonate. The $^{31}$P

n.m.r. and infrared data thus indicate that the 2-furyl, 2-thienyl, phenyl and pyridyl groups are all inductively electron-withdrawing; the effect, however, is small in comparison with electron-withdrawing properties of the chloro-substituent.
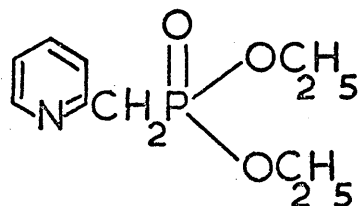


(CXXVIII)
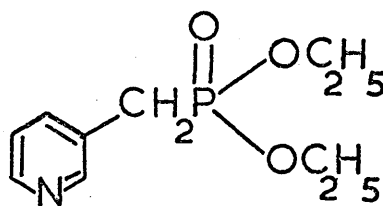


(CXXIX)
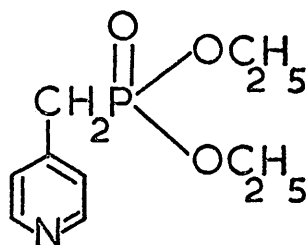


(CXXX)

The kinetics of alkaline hydrolysis of the diethyl esters of 2-,3-, and 4-pyridylmethylphosphonic acids (CXXVIII), (CXXIX) and (CXXX), in 50% aqueous dioxan have been studied, and the second-order rate constants are presented in Table 3.17..

Table 3.17.

Second-Order Rate Constants for the Alkaline Hydrolysis of Pyridylmethyl-phosphonate Esters $RP(O)(OC_2H_5)_2$ in Aqueous Dioxan (50% v/v; 0·1M in KCl).

| R | Ester (M) | NaOH (M) | Temperature (°C) | $k_{obs}$ (1 mol$^{-1}$ sec$^{-1}$) |
|---|---|---|---|---|
| 2-Pyridylmethyl | 0·05 | 0·05 | 59·8 | $4·38 \times 10^{-4}$ |
| | 0·05 | 0·05 | 49·8 | $2·20 \times 10^{-4}$ |
| 3-Pyridylmethyl | 0·05 | 0·05 | 59·8 | $6·15 \times 10^{-4}$ |
| | 0·05 | 0·05 | 49·9 | $2·81 \times 10^{-4}$ |
| 4-Pyridylmethyl | 0·05 | 0·05 | 60·0 | $8·31 \times 10^{-4}$ |
| | 0·05 | 0·05 | 50·0 | $3·71 \times 10^{-4}$ |

The activation parameters for the above reactions have been calculated and are given in Table 3.18..

Table 3.18.

Activation Parameters for the Alkaline Hydrolysis of Pyridylmethylphosphonate Esters $RP(O)(OC_2H_5)_2$ .

| R | $E_A$ (kJ mol$^{-1}$) | $\Delta S$ (J K$^{-1}$ mol$^{-1}$) | $\log_{10}$ PZ |
|---|---|---|---|
| 2-Pyridylmethyl | 61·6 | −124·7 | 6·3 |
| 3-Pyridylmethyl | 70·74 | − 94·5 | 7·9 |
| 4-Pyridylmethyl | 72·1 | − 88·1 | 8·2 |

The rate data in Table 3.17. thus reveals the rates of alkaline hydrolysis of the pyridylmethylphosphonates (CXXVIII), (CXXIX) and (CXXX) to decrease in the order 4-pyridylmethyl $>$ 3-pyridylmethyl $>$ 2-pyridylmethyl, the relative rates being 1·8 : 1·4 : 1. In each case the increase in rate is accompanied by an increase in the activation energy for the reaction (Table 3.18.), the activation entropies and $\log_{10}$ PZ terms are therefore dominant in determining the relative rates of reaction. There is some correlation between the rates of alkaline hydrolysis of the pyridylmethylphosphonates and the corresponding $^{31}$P chemical shift data (Table 3.16.), which indicates the 4-pyridylmethyl substituent to be more electron-withdrawing than the 2-pyridylmethyl and 3-pyridylmethyl substituents, when attached to phosphorus. There is some disagreement, however, between the relative order of electron-withdrawing ability of the 2-,3-, and 4-pyridylmethyl substituents indicated by these results, and the order which would possibly be predicted on the basis of $^{13}$C n.m.r. chemical shifts of the pyridine ring carbon atoms[169], and also by the $pK_a$'s of the corresponding pyridylacetic acids[170]. It is thus of interest to consider the observations of other workers on related systems.
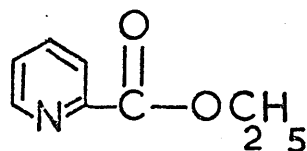
(CXXXV)
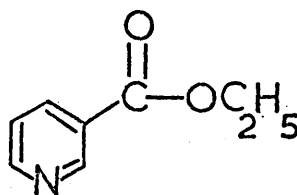


(CXXXVI)
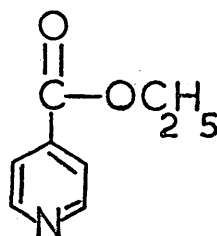


(CXXXVII)

The rates of alkaline hydrolysis of the ethyl esters of pyridylcarboxylic acids (CXXXV), (CXXXVI) and (CXXXVII) have been studied by Falkner and Harrison[171] and by Agren and Van der Veen[172]. In both cases the relative order of reactivity was shown to be ethyl 4-pyridylcarboxylate > ethyl 2-pyridylcarboxylate > ethyl 3-pyridylcarboxylate, the relative rates being 5 : 2 : 1; in each case the increase in rate of alkaline hydrolysis was accompanied by a decrease in activation energy. Falkner[171] suggested that whilst the increased rate of alkaline hydrolysis of ethyl 4-pyridylcarboxylate compared with ethyl 3-pyridylcarboxylate is in agreement with evidence that the ring nitrogen atom withdraws electrons more effectively from the 4-, than from the 3-position, the lower rate of hydrolysis of ethyl 2-pyridylcarboxylate compared with the 4-isomer may be due to the operation of a steric effect. For comparison, the rate of alkaline hydrolysis of the 3-pyridylcarboxylate ester proceeds 93 times faster than that of ethyl benzoate, reflecting the greater electronegativity of all positions of the pyridyl ring compared with phenyl.
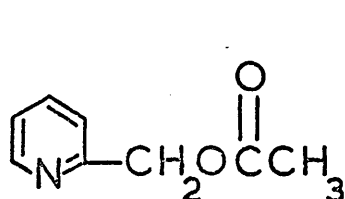
(CXXXVIII)
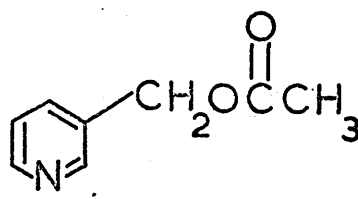


(CXXXIX)
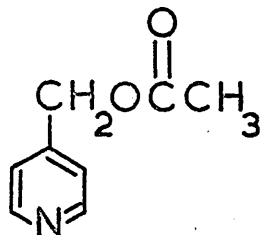


(CXL)

Simonetta and Favini[173] have reported the rates of alkaline hydrolysis of the pyridylmethyl acetates (CXXXVIII), (CXXXIX) and (CXL) to be in the order 4-pyridylmethyl $>$ 3-pyridylmethyl $>$ 2-pyridylmethyl. The mechanism of the hydrolysis reaction was shown to involve acyl-oxygen fission and the reaction is therefore promoted by electron-withdrawing groups in the alkyl function[174]. Thus in the alkaline hydrolysis of a series of phenyl substituted benzyl acetates[175], the order of reactivity $m\text{-}O_2NC_6H_4CH_2OAc >$ $m\text{-}MeOC_6H_4CH_2OAc >$ $C_6H_5CH_2OAc >$ $p\text{-}MeOC_6H_4CH_2OAc$, was observed. The electron-withdrawing ability of the pyridylmethyl groups indicated in the above reactions is therefore in agreement with the data obtained for the alkaline hydrolysis of the analogous pyridylmethylphosphonates (CXXVIII), (CXXIX) and (CXX).
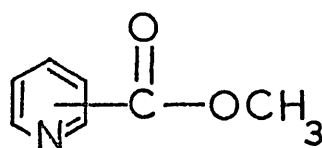


(CXLI)
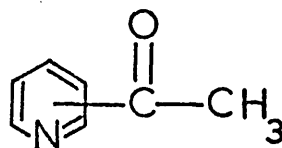


(CXLII)
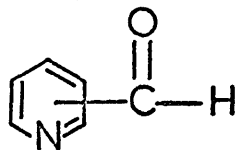


(CXLIII)

Further evidence regarding the relative electronic effects of pyridyl substituents has been obtained by Katritzky[176], from studies of the infrared spectra of a series of pyridylcarbonyl compounds (CXXXV) - (CXXXVII) and (CXLI) - (CXLIII). This data is reproduced in Table 3.19..

## Table 3.19.

Frequencies $(cm^{-1})$ of the Carbonyl Infrared Stretching Vibration of some Pyridylcarbonyl Compounds.

| Compound | 2-Pyridyl | 3-Pyridyl | 4-Pyridyl | Phenyl |
|---|---|---|---|---|
| Ethyl carboxylate | 1723 | 1724 | 1730 | 1716 |
| Methyl carboxylate | 1730 | 1730 | 1735 | 1724 |
| Methyl ketone | 1695 | 1690 | 1700 | 1680 |
| Aldehyde | 1717 | 1712 | 1721 | 1705 |

On the basis of the above data, it would appear that the 4-position of the pyridyl ring exerts a greater electron-withdrawing effect than the 2-, and 3-positions, and this would explain the increased rate of alkaline hydrolysis of the 4-pyridylmethylphosphonate compared with the 3-isomer. The explanation of the relative rates of alkaline hydrolysis of the 2-, and 3-pyridylmethyl-phosphonates is, however, more complex. The infrared[176] and $^{13}$C n.m.r. data[169] together with the rates of alkaline hydrolysis of the pyridylcarboxylates (CXXXV) and (CXXXVI)[171,172], would suggest that the 2-position is marginally more electron-withdrawing than the 3-position from centres directly attached to the pyridine ring. The situation appears to be reversed, however, for nucleophilic reactions involving 2-pyridylmethyl and 3-pyridylmethyl groups as substituents[173]. It is possible therefore, that $\pi$-bonding may occur between pyridine and substituents attached at the 3-position. In addition there may be a steric effect in reactions involving 2-pyridylmethyl substituents; the reduction in the frequency factor $(log_{10} PZ)$ for the alkaline of diethyl-(2-pyridylmethyl)phosphonate compared with $log_{10} PZ$ for the reactions

of the 3-, and 4-isomers (Table 3.18.) would appear to support this proposal.

The data in Tables 3.13. and 3.17. reveal that the rates of alkaline hydrolysis of the pyridylmethylphosphonates are comparable with those of the 2-furylmethyl-, and 2-thenylphosphonates. Thus diethyl-(4-pyridylmethyl)-phosphonate (CXXX) undergoes hydrolysis 1·1 times faster than diethyl-(2-furyl-methyl)phosphonate (CX; $R = C_2H_5$), whilst diethyl-(2-pyridylmethyl)phosphonate (CXXXVIII) undergoes alkaline hydrolysis 1·2 times faster than diethyl-(2-thenyl)phosphonate (CXI; $R = C_2H_5$). It would appear therefore, that in the absence of $p\pi$—$d\pi$ overlap between the heterocyclic ring and the reaction site, the $\sigma$-inductive effect exerted by the electronegative heteroatoms in pyridine, furan and thiophen, are roughly equal. The differences which are obtained for other side chain reactivities e.g. the pyrolysis of arylethyl acetates[165,166], are therefore due to mesomeric electron transfer by the furyl and thienyl substituents which is absent in the case of pyridyl substituents.

### 3.7 The Alkaline Hydrolysis of Chloromethyl- and Methylphosphonate Esters.

The kinetics of alkaline hydrolysis of the diethyl esters of chloromethyl- and methylphosphonic acids (CXXXI) and (CXXXII) have been studied and the second-order rate constants are presented in Table 3.20..

### Table 3.20.

Second-Order Rate Constants for the Alkaline Hydrolysis of Phosphonate Esters $RP(O)(OC_2H_5)_2$ in Aqueous Dioxan (50% v/v; 0·1M in KCl).

| R | Ester (M) | NaOH (M) | Temperature (°C) | $k_{obs}$ (1 mol$^{-1}$sec$^{-1}$) |
|---|---|---|---|---|
| Chloromethyl | 0·02 | 0·02 | 60 | $2·13 \times 10^{-2}$ |
| | 0·02 | 0·02 | 49·8 | $1·21 \times 10^{-2}$ |
| Methyl | 0·05 | 0·05 | 60 | $12·64 \times 10^{-4}$ |
| | 0·05 | 0·05 | 50 | $6·44 \times 10^{-4}$ |

The activation parameters for the above reactions have been calculated and are given in Table 3.21..

## Table 3.21.

Activation Parameters for the Alkaline Hydrolysis of Phosphonate Esters

$RP(O)(OC_2H_5)_2$ .

| R | $E_A$ (kJ mol$^{-1}$) | $\Delta S$ (J K$^{-1}$ mol$^{-1}$) | $\log_{10}$ PZ |
|---|---|---|---|
| Chloromethyl | 49·5 | −128·5 | 6·1 |
| Methyl | 60·32 | −119·9 | 6·6 |

The rate data in Table 3.20. thus reveals that diethylchloromethyl-phosphonate (CXXXI) undergoes alkaline hydrolysis some 17 times faster than diethylmethylphosphonate (CXXXII). This result is thus in agreement with the work of Aksnes[55] who observed (CXXXI) to be hydrolysed 15·6 times faster than (CXXXII), and with Hudson[11] who observed the relative rates of alkaline hydrolysis to be 12 : 1. The increased rate of reaction of the chloromethyl-phosphonate is accompanied by a small decrease in activation energy (Table 3.21.) which is partially compensated by decreases in activation entropy and $\log_{10}$ PZ.

Comparison of the data in Table 3.20. with data in Tables 3.13. and 3.17., however, reveals that diethylmethylphosphonate undergoes alkaline hydrolysis more quickly than the benzyl-, 2-thenyl-, and 2-furylmethyl-, or each of the pyridylmethylphosphonates. A similar result has been obtained by Chabrier et al[177] who reported relative rates of 13 : 1 for the alkaline hydrolysis of diethylmethylphosphonate and diethylbenzylphosphonate respectively, compared with the ratio of 12 : 1 obtained in this study.

[31]P n.m.r. and infrared spectroscopic data have indicated electron-withdrawal by the $\sigma$-inductive effect of the substituents to increase the positive nature of the phosphorus atom in heteroarylmethylphosphonates compared with diethylmethylphosphonate and on this basis the relative rates of alkaline

hydrolysis cannot be explained in terms of simple electron-withdrawal from the phosphorus atom. Furthermore, examination of the data in Tables 3.14., 3.18. and 3.21. does not indicate the possibility of a steric interaction in the hydrolysis reactions of the heteroarylmethylphosphonates in view of the similarity in $\log_{10}$ PZ values. The effect of the leaving group on the relative rates of alkaline hydrolysis of phosphonate esters has, however, been indicated earlier, and it has been suggested[55] that electronegative substituents which withdraw electrons from the phosphorus atom also have the effect of increasing $p\pi$—$d\pi$ overlap between the leaving group and phosphorus. Thus the relative rates of alkaline hydrolysis of the diethylmethyl and diethylchloromethyl-phosphonates are 1 : 15·6 whereas the relative rates for the corresponding carboxylic esters (in which there is no comparable effect due to the leaving group) are 1 : 258. It is thus possible that in the case of the heteroaryl-methylphosphonates where electron-withdrawal from the phosphorus atom is reduced compared with the chloromethyl analogue, the effect of strengthening the bond to the leaving group will be sufficient to reduce the rate of alkaline hydrolysis relative to diethylmethylphosphonate where it is expected that the methyl substituent is electron-donating.

Haake et al[28] have provided evidence for the intervention of a penta-coordinate intermediate in the alkaline hydrolysis of phosphinate esters. The extension of this concept to the alkaline hydrolysis of phosphonate esters could possibly explain the above results.



(CXLIV)                                                            (18)
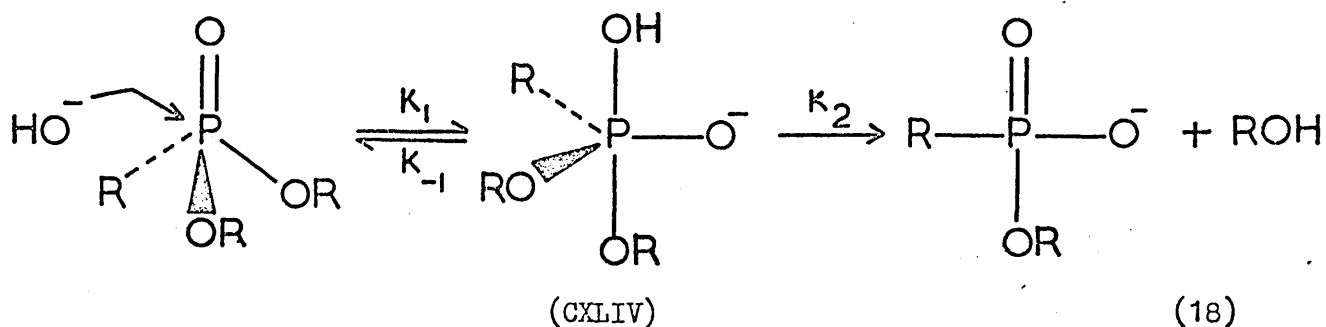
Thus in the alkaline hydrolysis of diethylchloromethylphosphonate the electron-withdrawing effect of the chloromethyl substituent increases $k_1$ such that the amount of (CXLIV) present at equilibrium is much greater than for diethyl-methylphosphonate. In the case of the heteroarylmethylphosphonate esters, however, although the electron-withdrawing effect of the heteroarylmethyl substituent increases $k_1$ compared with that for diethylmethylphosphonate, the difference in the amount of (CXLIV) present at equilibrium is insufficient to overcome the decreases in $k_2$ resulting from the strengthening of the bond to the leaving group. As a result the overall rate of alkaline hydrolysis of the heteroarylmethylphosphonate is reduced.

Comparison of the data in Tables 3.1. and 3.20. also reveals that diethyl-methylphosphonate undergoes alkaline hydrolysis in 50% aqueous dioxan 1·3 times faster than diethylphenylphosphonate (IC; $R = C_2H_5$). This data thus contrasts with the results of Hudson[48] who found the rates of alkaline hydrolysis of diethylphenylphosphonate and diethylmethylphosphonate in water, to be in the ratio of 1·8 : 1. Reference to the studies of other workers has indicated similar findings. Thus, Chabrier et al[177] have found the alkaline hydrolysis of dimethylmethylphosphonate to proceed 1·2 times faster than for dimethyl-phenylphosphonate (IC; $R = CH_3$), whereas Christol et al[178] have reported the increased rate of alkaline hydrolysis of (IC; $R = CH_3$) compared with dimethyl-methylphosphonate, the ratio being 1·8 : 1. Extension of the survey to the reactivity data of other organophosphorus derivatives, however, reveals that the methyl ester of dimethylphosphinic acid undergoes alkaline hydrolysis 12·5 times faster than methyldiphenylphosphinate[26,28]. In addition[10] ethylmethyl-phosphonyl chloride (CXLV; $R = CH_3$) undergoes solvolysis in 5% aqueous acetone 1·4 times faster than ethylphenylphosphonyl chloride (CXLV; $R = C_6H_5$) under the same conditions.

$$
\begin{array}{c}
O \\
\parallel \\
R-\!\!-P-\!\!-Cl \\
\mid \\
OC_2H_5
\end{array}
$$

(CXLV)
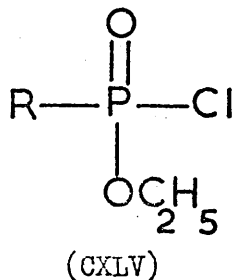
Hudson[48] has explained his results in terms of the inductive effect of the phenyl substituent, which aids the approach of the nucleophile. Indeed $^{31}P$ n.m.r. and infrared spectroscopic data obtained in the present study support the suggestion of increased electron-withdrawal from the phosphorus atom in the corresponding phosphonate esters by the phenyl substituent compared with the methyl substituent. However, as in the case of the heteroarylmethylphosphonates, it could be suggested that the relative rates of alkaline hydrolysis of (IC; $R = C_2H_5$) and (CXXXII) are determined by the effect of the substituent on the bond to the leaving group.

3.8 Studies of the Chemistry of Substituted Phenylphosphonates. The Investigation of a Structive-Reactivity Correlation in the Alkaline Hydrolysis of Phosphonate Esters.

The rate data for the alkaline hydrolysis of the above heteroaryl-phosphonates and heteroarylmethylphosphonates has shown that the rate of nucleophilic attack at the phosphonyl group is influenced by both, inductive effects through the $\sigma$-bonds linking the substituents to phosphorus, and also to mesomeric effects involving $p\pi$ orbitals of the substituent and $d\pi$ orbitals of phosphorus. Furthermore the importance of the leaving group is also indicated. In particular the results for the heteroarylphosphonates are significant since they offer direct evidence for both $\sigma$-electron-withdrawal and also $\pi$-electron-donation by an aromatic substituent linked to the phosphonyl group, and also the consequence of these effects upon the rate of nucleophilic attack at phosphorus. The rate data thus confirms directly the earlier spectroscopic evidence for these electronic effects which has been obtained by

other workers. Thus bathochromic shifts of the primary band in the u.v.

absorption spectra of a series of triheteroaryl-[89] and p-substituted triphenyl-

phosphine oxides[75,76] relative to the parent arene, together with $^1$H n.m.r.

data[90], support the proposal of $\pi$-mesomeric effects in phosphacyl compounds

containing aromatic substituents linked to phosphorus.
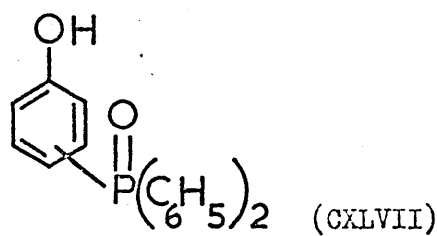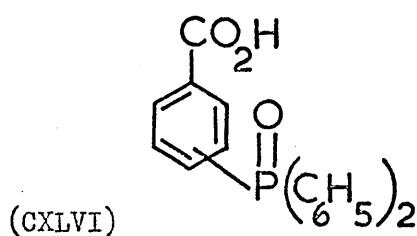


(CXLVI)          (CXLVII)

A quantitative measure of the resonance electron-withdrawing effect of

the diphenylphosphinyl group was obtained by Monagle et al[179] by the study of

the dissociation constants of benzoic acids (CXLVI) and phenols (CXLVII)

containing the diphenylphosphinyl group as a substituent. It was shown that

for each series the para-isomer is more acidic than the meta- isomer,

consequently for both benzoic acids (CXLVI) and phenols (CXLVII), $\sigma_p$ obtained

from the study is greater than $\sigma_m$; the difference $\sigma_p - \sigma_m$ being greater in the

case of the phenols (CXLVII) where resonance effects are expected to be more

significant. The values of $\sigma_m$, which reflect inductive effects only, are

approximately equal for the benzoic acid and phenol. The relationship of the

$\sigma$ values thus corroborates the spectral evidence indicating the presence of a

resonance effect, involving $p\pi - d\pi$ interactions with phosphorus.

The value of $\sigma_p$ obtained by Monagle et al[179] for the diphenylphosphinyl

group in the acid (CXLVI), where there is no direct resonance, is in good

agreement with the $\sigma_p$ value obtained by Griffin et al[180] following the analysis

of the $^{13}$C n.m.r. spectrum of triphenylphosphine oxide. The substituent values

($\sigma_p$ and $\sigma_p^+$) for other phosphorus substituents were also determined by Griffin

in this study.

In order to further study the interaction of the phosphonyl group with

substituents and in particular the effect of such interactions upon the rate

of nucleophilic displacement reactions of phosphorus, and also to obtain

further information regarding the transition state, it was of interest to

investigate the possibility of a structure-reactivity (Hammett) correlation

for the alkaline hydrolysis of substituted arylphosphonate esters.

Methods for the preparation of substituted phenylphosphonic acids and the

corresponding acid esters are well established and much of the earlier work

concerning the synthesis and physical properties of these compounds has been

covered in reviews by Kosolapoff[119] and later by Freedman and Doak[105]. The

earlier methods include the Friedel-Crafts reaction[181] between the substituted

benzene derivative and phosphorus trichloride in the presence of aluminium

chloride, to give a halophosphine complex which is subsequently treated with

chlorine gas and then alcohol under reduced pressure at low temperatures to

produce the ester. Other procedures include the reaction between aryldiazonium

salts[182,183] and phosphorus trichloride, in the presence of copper salts,

followed by the hydrolysis to produce the acid which can be esterified, and

also the reaction between organometallic intermediate and the corresponding

halophosphate ester. More recent methods for obtaining substituted phenyl-

phosphonate esters include the photolytic modification of the Arbuzov reaction

developed by Griffin et al[94], and also the nickel[97] or palladium salt[98]

catalysed Arbuzov reaction.
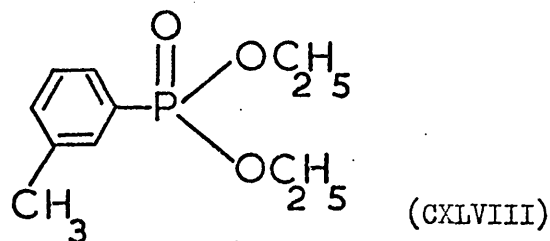


(CXLVIII)

In the present study diethyl-(m-tolyl)phosphonate (CXLVIII) was prepared

by the photolysis of m-iodotoluene in the presence of triethylphosphite,

according to the general procedure described by Griffin et al[94]. The mixture

was degassed by flushing with dry nitrogen and irradiated with a medium

pressure quartz mercury discharge lamp. The excess triethylphosphite was then removed and the product purified by repeated distillation. The final purity of the product was checked by g.l.c. analysis and analysis of the integrated peak intensities in the n.m.r. spectrum of the compound. Attempts to prepare diethyl-(p-methoxyphenyl)phosphonate (CIL) and diethyl-(m-formylphenyl)-phosphonate (CL) by this procedure resulted in poor yields of the products, such that alternative methods of preparation were investigated. In addition, the attempted photochemical synthesis of diethyl-(p-aminophenyl)phosphonate and diethyl-(m-chlorophenyl)phosphonate (CLI) were similarly unsuccessful and in each case the starting materials were recovered.



(CIL)                    (CL)
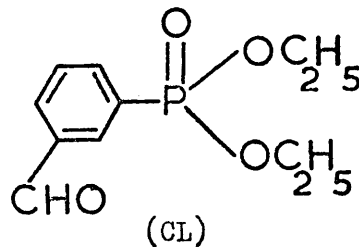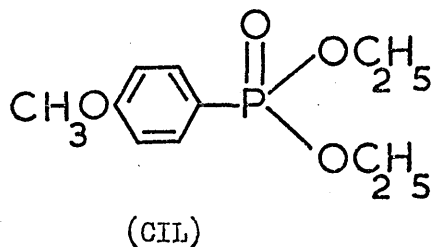
The synthesis of diethyl-(p-methoxyphenyl)phosphonate (CIL) was carried out according to the general procedure described by Tavs[97]. Thus triethyl-phosphite was added dropwise under nitrogen, to a suspension of nickel chloride in p-bromoanisole maintained at $160^\circ$. Following the removal of the nickel salt in the latter stages of the procedure, the residual oil was distilled to give the phosphonate ester (CIL) in good yield. The g.l.c. and n.m.r. analyses of the compound indicated a purity of $>99\%$.



(CLI)  Cl                    (CLII)
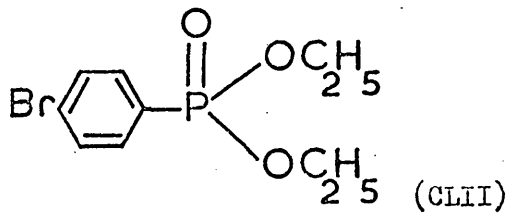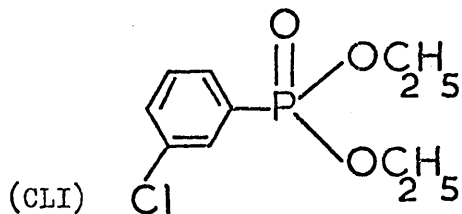
Diethyl-(m-chlorophenyl)phosphonate (CLI) was obtained by the reverse addition[101] of m-chlorophenylmagnesium bromide to diethylphosphorochloridate in ether, at reflux temperatures. Diethyl-(p-bromophenyl)phosphonate (CLII)

was similarly prepared from p-bromophenylmagnesium bromide. In each case a high purity of the product was indicated by g.l.c. and n.m.r. analysis.

The Hammett equation has been applied successfully to a number of reactions involving organophosphorus compounds. Initially, Jaffe, Freedman and Doak[184] reported the application of the relationship to the dissociation constants of a number of substituted phenylphosphonic acids. More recently the equation has been extended by Quin and Dysart[185] to the dissociation constants of arylphosphinic acids, and in modified form[186] by Kabachnik to a variety of phosphoric acid derivatives and their mono-, and dithio- analogues[187]. In addition, Freedman et al have investigated substituent effects in $^{31}$P n.m.r. and have obtained linear correlations between the $^{31}$P chemical shifts of a number of substituted phenylphosphonic acid derivatives[131,132] and the corresponding $\sigma_m$ or $\sigma_p$ constants.

The $^{31}$P chemical shifts of the substituted phenylphosphonate esters (CXLVIII) - (CLII) prepared in this study have been obtained and are presented in Table 3.22..

### Table 3.22.

$^{31}$P Chemical Shift Data for Substituted Phenylphosphonates in Chloroform.

| Compound | $\delta\ ^{31}$P/p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| Diethyl-(m-chlorophenyl)phosphonate | −14·1 |
| Diethyl-(m-formylphenyl)phosphonate* | −14·2 |
| Diethyl-(p-bromophenyl)phosphonate | −15·5 |
| Diethylphenylphosphonate | −16·75 |
| Diethyl-(m-tolyl)phosphonate | −17·0 |
| Diethyl-(p-methoxyphenyl)phosphonate | −17·3 |

* G.l.c. analysis of this compound indicated a purity of ≃90%

The values in p.p.m. for the chemical shifts of the substituted phenyl-phosphonates are plotted in Figure 3.1. versus the corresponding Hammett $\sigma_m$ or $\sigma_p$ substituent constants[133]. In agreement with the results obtained by
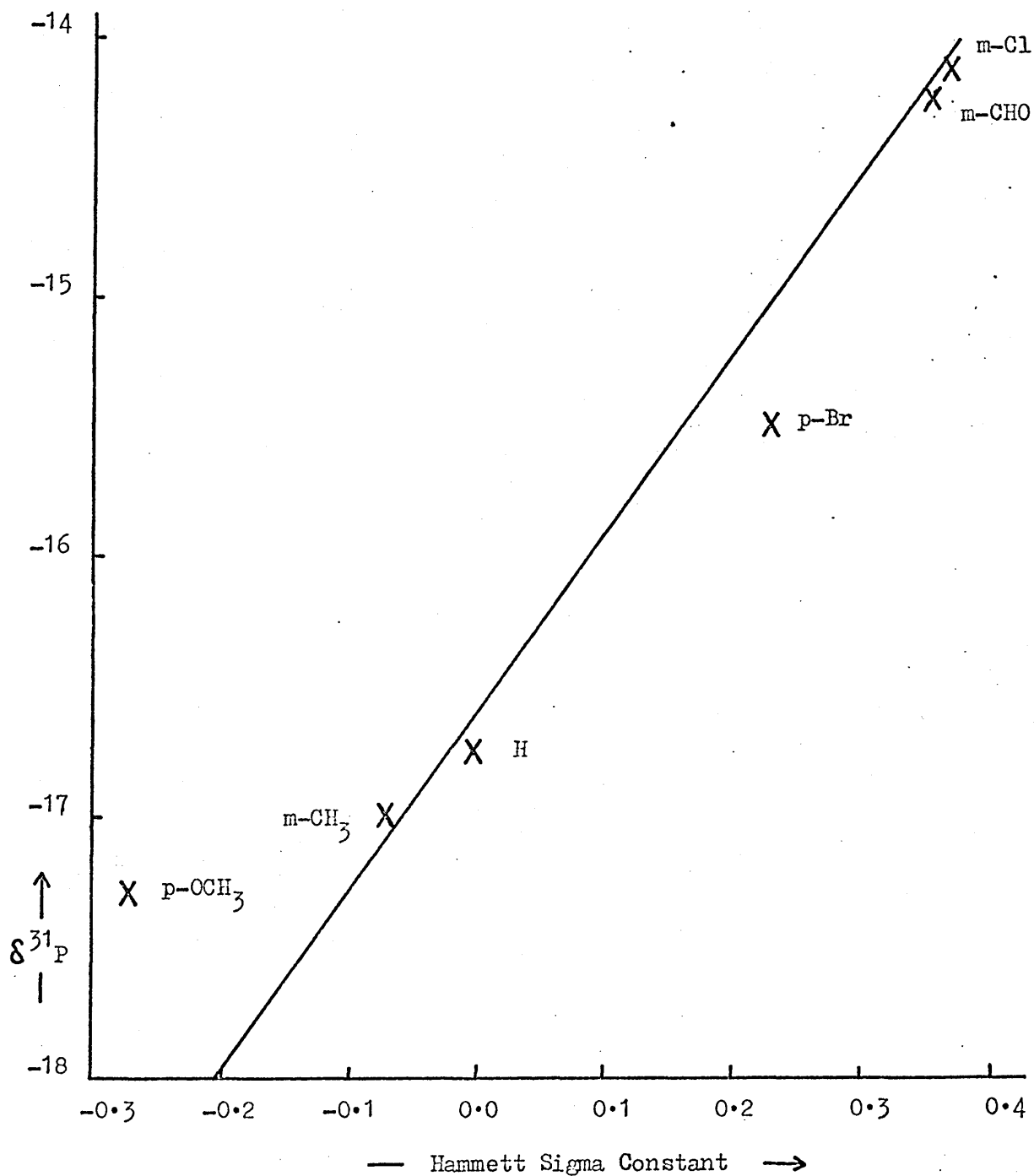
Figure 3.1.

$^{31}P$ Chemical Shift (p.p.m. relative to 85% $H_3PO_4$) of Substituted Diethylphenyl-phosphonates in Chloroform vs $\sigma_m$ or $\sigma_p$ the Hammett Substituent Constant.

Freedman et al[131,132], the data in Table 3.22. indicates the $^{31}$P chemical shift to be affected in a direction opposite to that expected on the basis of the electron-withdrawing ability of the substituent, as predicted by quantum mechanical theory[130]. In addition a linear relationship between the $^{31}$P chemical shifts and the Hammett substituent constants[133] is indicated (correlation coefficient = 0·96). The largest deviation from the correlation (Figure 3.1.) is obtained for the p-methoxyphenylphosphonate (CIL). The $^{31}$P chemical shift is more positive than is predicted by the $\sigma_p$ constant and therefore the result possibly indicates the $\sigma$-inductive electron-withdrawing effect of the p-methoxy group to be more important in comparison with the mesomeric electron-donation, in the determination of $^{31}$P chemical shift. Evidence in favour of this proposal is provided by the improved correlation coefficient of 0·98 which is obtained when the $\sigma^o$ constant for the substituents, which reflects solely the inductive effect of the substituent, is plotted against the $^{31}$P chemical shift (Figure 3.2.). A similar situation has been indicated previously for the $^{31}$P n.m.r. spectra of heteroarylphosphonates. Thus the $^{31}$P chemical shifts of the heteroarylphosphonate esters have indicated the electron-withdrawing ability of the heteroaryl substituents to decrease in the order, 2-furyl $>$ 2-(1-methylpyrrolyl) $>$ 2-thienyl $>$ phenyl, whilst the kinetics of alkaline hydrolysis of these compounds have suggested a levelling of the electron-withdrawing effects as a result of $p\pi - d\pi$ mesomeric interactions.

It is of interest to compare the slopes of the correlations between $^{31}$P chemical shifts of the substituted phenylphosphonates and Hammett substituent constants which have been obtained in the present study, with the corresponding data of Freedman et al[132]. Slopes of 5·33 and 6·32 respectively, were obtained for the plots of $^{31}$P chemical shift against $\sigma$ and $\sigma^o$ in the present study, compared with slopes observed by Freedman[132] of 5·79 and 4·58 for the meta- and para-substituted compounds respectively in acetone solution, and slopes of 6·20 and 5·13 for the meta- and para-substituted phosphonates in ethanol
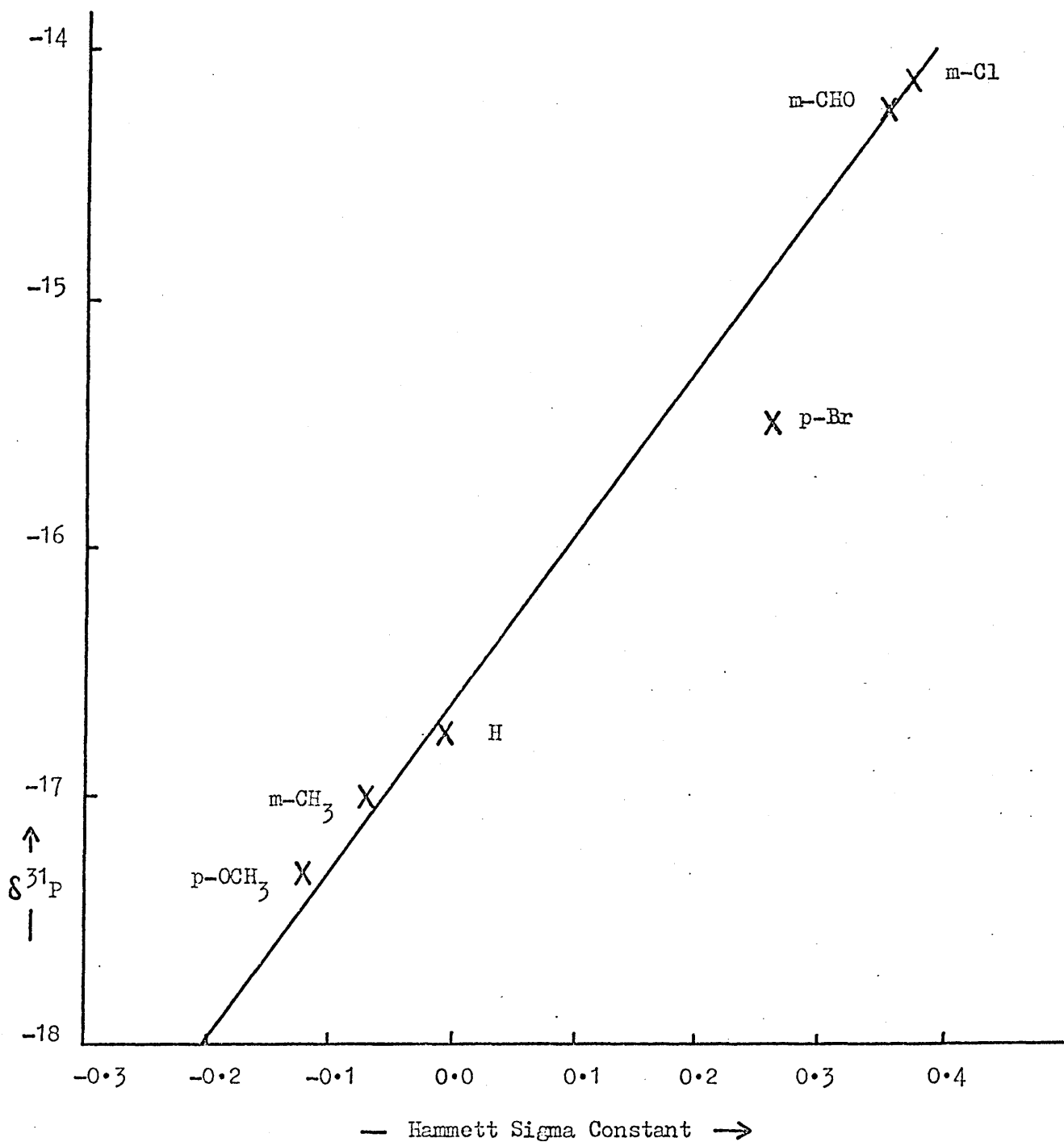
Figure 3.2.

$^{31}P$ Chemical Shift (p.p.m. relative to 85% $H_3PO_4$) of Substituted Diethylphenyl-phosphonates in Chloroform vs $\sigma^o$ the Hammett Substituent Constant.

solution. There is thus a close agreement between the results of the present study and the corresponding data obtained by Freedman et al[132].
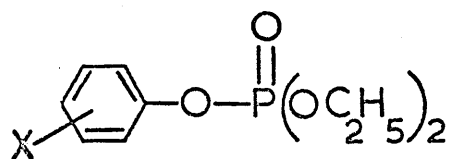


(XLIV)
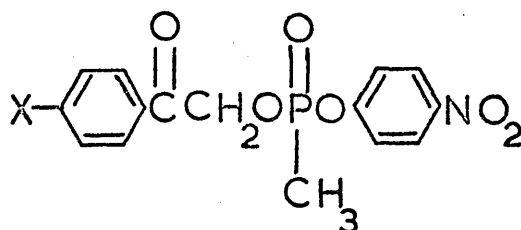


(XLVI)
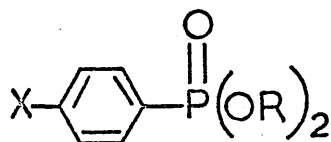


(CIII)
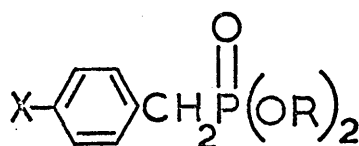


(CIV)

The extension of the Hammett equation[51] to nucleophilic displacement at phosphorus (specifically $^-OH$) has been demonstrated by a number of workers. Fukuto and Metcalf[44] obtained a linear correlation (slope = 1·3) between log k (hydrolysis) and the corresponding Hammett substituent value for a series of substituted phenyl diethylphosphates (XLIV). Arrangement of the data into a conventional Hammett plot by Lieske et al[54] gave a reaction constant $(\rho)$ of 1·9. A correlation was similarly obtained by Lieske[54] for the alkaline hydrolysis of a number of para-substituted phenacyl-p-nitrophenylmethyl-phosphonates (XLVI) with a resultant reaction constant $(\rho)$ of 1·43. Chinese workers[125] have also studied the effect of substituents on the lability of the P-O-alkyl bond of dialkyl p-substituted phenyl- and benzylphosphonates (CIII and CIV; R = $C_2H_5$, $C_4H_9$, $C_8H_{17}$) as measured by the rates of alkaline hydrolysis. It was reported that a quantitative relationship exists between the corresponding $\sigma_p$ substituent constants and the rate constant for the reaction, and from their data a $\rho$ value of 2·1 can be calculated. It was also proposed that the investigation had shown the alkaline hydrolysis of phosphonate esters to proceed via attack by the nucleophile at phosphorus.

The kinetics of alkaline hydrolysis of the substituted phenylphosphonate esters (CXLVIII), (CIL), (CLI) and (CLII) in 0·05 molar solution in 50% aqueous dioxan have been studied and the second-order rate constants are presented in Table 3.23..

## Table 3.23.

Second-Order Rate Constants for the Alkaline Hydrolysis of Substituted Phenyl-phosphonate Esters in Aqueous Dioxan (50% v/v: 0·1M in KCl) at 59·7°C.

| Compound | $k_{obs}$ (1 mol$^{-1}$ sec$^{-1}$) |
|---|---|
| Diethyl-(m-chlorophenyl)phosphonate | $37 \cdot 17 \times 10^{-4}$ |
| Diethyl-(p-bromophenyl)phosphonate | $25 \cdot 33 \times 10^{-4}$ |
| Diethylphenylphosphonate | $9 \cdot 74 \times 10^{-4}$ |
| Diethyl-(m-tolyl)phosphonate | $5 \cdot 50 \times 10^{-4}$ |
| Diethyl-(p-methoxyphenyl)phosphonate | $2 \cdot 56 \times 10^{-4}$ |

The log $(k/k_o)$ values have been plotted versus the appropriate $\sigma_m$ or $\sigma_p$ constant[133] for the substituent. A correlation coefficient (r) of 0·99 is obtained and a reaction constant ($\rho$) of 1·88 is determined from the slope of the graph. The Hammett plot is shown in Figure 3.3..

The data in Table 3.23. reveals that the rate of the hydrolysis reaction is increased by electron-withdrawing substituents and decreased by electron-donating substituents, and this is reflected in a positive reaction constant. Furthermore, of particular importance, is the fit of the p-methoxy compound with the correlation obtained in this study, indicating resonance type interactions in the hydrolysis reaction since the inductive effect alone would increase the rate of alkaline hydrolysis of (CIL) compared with unsubstituted diethylphenylphosphonate (IC; R = $C_2H_5$).

The reaction constant ($\rho$) is interpreted as a measure of the susceptibility of the reaction to substituent effects[188], and it is thus of interest to compare
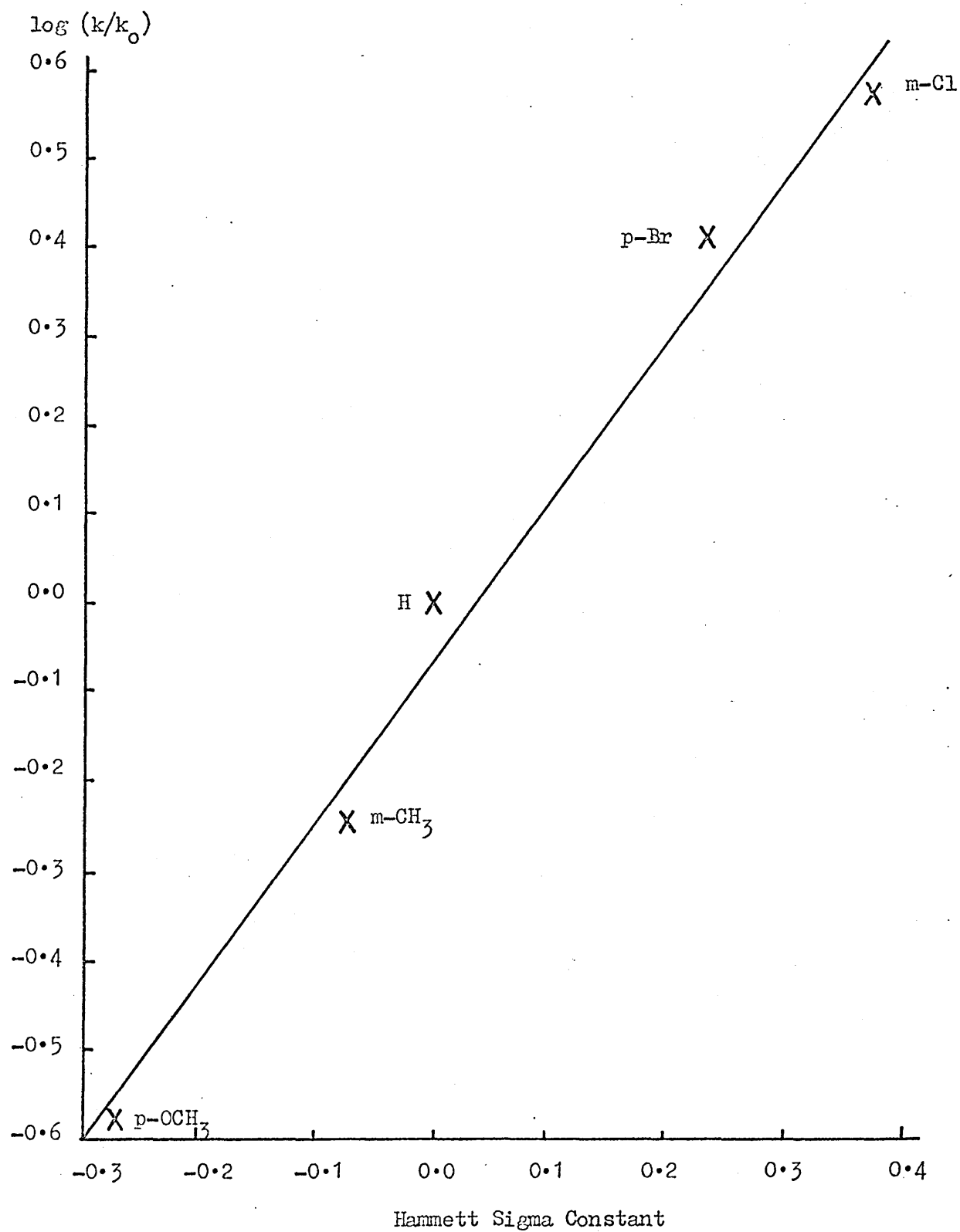
Figure 3.3.

Log $(k/k_o)$ for the Alkaline Hydrolysis of Substituted Diethylphenylphosphonates vs $\sigma_m$ or $\sigma_p$ the Hammett Substituent Constant.

the reaction constant obtained in this study with the corresponding constant for the alkaline hydrolysis of ethyl benzoates. The value of $\rho$ for the latter reaction is solvent dependent and values of 1·82 to 2·85 for the alkaline hydrolysis of meta- and para-substituted ethyl benzoate esters have been listed by Jaffé[133]. The reaction constant obtained in the above study of phosphonate ester hydrolysis falls within this range and therefore it would appear that substituent effects on the rate of alkaline hydrolysis of diethylphenyl-phosphonate esters are comparable with effects obtained for the alkaline hydrolysis of the corresponding ethyl benzoates. This result has been suggested previously by the similarity in the relative rates of alkaline hydrolysis of the diethylheteroarylphosphonate esters and the relative rates of alkaline hydrolysis of ethyl heteroarylcarboxylates[122,123].

The data, however, does not give unambiguous evidence regarding the extent of the interaction between the substituted aryl group and the phosphonyl group. It could be argued that a comparison of the $\rho$ constants for the alkaline hydrolysis of diethylphenylphosphonate esters and ethyl benzoates[133] indicates similar interactions between the substituted aryl moiety and the phosphonyl group to those involved between the substituted aryl moiety and the carbonyl group. It has been indicated[11] previously, however, that whereas bond-making and bond-breaking processes are of comparable importance in the determination of rates of alkaline hydrolysis of phosphonate esters, the rate constant for the alkaline hydrolysis of carboxylate esters reflects predominantly the effect of substituent on bond-formation. The similarity in the reaction constants for the alkaline hydrolysis of diethylphenylphosphonates and ethyl benzoates therefore reflects solely a similarity of substituent effects on the overall reaction constant in each case.

The size of the reaction constant is also an indication of the extent of charge development during the reaction at the atom of the reacting side chain adjacent to the ring. Thus the reaction constant for the alkaline hydrolysis

of ethyl benzoates[133] in which the carbon adjacent to the ring is involved in both bond-making and bond-breaking processes is much larger than for benzyl acetate hydrolysis[133] ($\rho = 0.47$) in which the reaction site is isolated from the phenyl ring by a methylene group. The reaction constant obtained in this study ($\rho = 1.88$) is thus further proof of nucleophilic attack by hydroxide ion at the phosphorus atom during the alkaline hydrolysis of phosphonate esters.

## 3.9 Studies of the Chemistry of Heteroarylphosphinates and Phosphine Oxides.

In conclusion, the above study of heteroarylphosphonates has been extended to the closely related phosphinic acid derivatives. There has been much recent interest in the chemistry of diarylphosphinic acids and the related esters. Haake et al have established that electronic effects are important in nucleophilic displacement reactions at phosphinyl phosphorus and in the alkaline hydrolysis of (IL) and (L), a linear correlation has been reported between the rates of hydrolysis and the corresponding Hammett $\sigma$ constants for the substituents X[64]. Further work by Haake[30] on compounds of type (LIII; R = CH$_3$) and by Cooke[67] on compounds of types (LIV; R = CH$_3$) and (LV; R$^1$ = CH$_3$) has shown negligible differences in the rates of the alkaline hydrolysis reactions of these cyclic phosphinates compared with those of the acyclic analogues (L), indicating $\pi$-interactions between the phenyl rings and phosphinyl phosphorus to be independent of bond angle.



(IL)



(L)
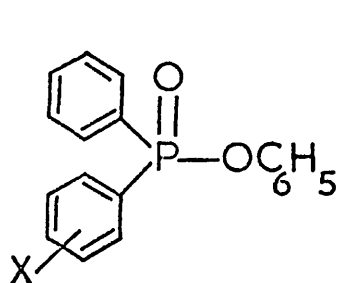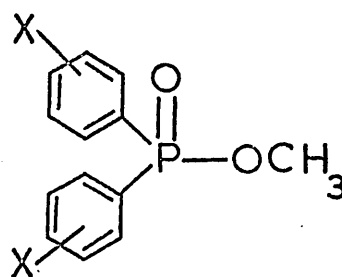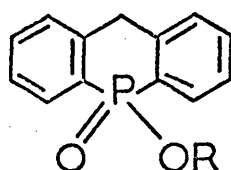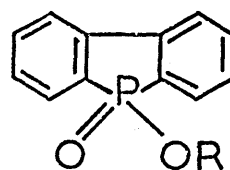


(LIII)



(LIV)
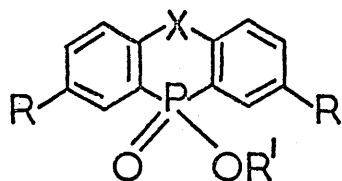
(LV)

Kabachnik[86,189] has shown that the Hammett equation is applicable to substituent effects on the strengths of organophosphorus acids of the general type (CLIII), and a linear relationship has been obtained in various media for oxyacids and thioacids of phosphorus with various substituents A and B.
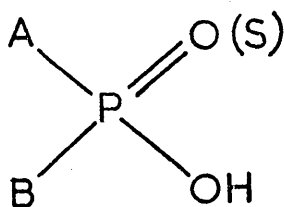
(CLIII)

However, it was noted[86,189] that significant deviations from a linear correlation are obtained when two aryl groups are simultaneously attached to phosphorus, as in diarylphosphinic acids. It was suggested that a possible explanation for the deviations is the disturbance of conjugation between the $\pi$-electrons of the aromatic systems and the phosphinyl bond, possibly as a consequence of steric hindrance due to the overlap of the Van der Waal spheres of the ortho-hydrogens. The phenyl rings are turned around the P—C axis and are thus displaced from a position favourable to conjugation.

In view of these findings, it was of interest to investigate the chemistry of heteroarylphosphinate esters. Previous evidence obtained in this study has indicated $p\pi - d\pi$ interactions to be more important in heteroarylphosphonates than in the corresponding phenylphosphonates. It was thus considered that the possible effects of a reduction in conjugation between the substituent and phosphorus in phosphinate esters will be more significant in 2-furyl- and 2-thienylphosphinates, and on this basis the effect would be more easily recognised.

Methods of preparing phosphinic acids are presented in a recent review by Kosolapoff[190], and include the alkaline hydrolysis of tertiary phosphine oxides. Reactions involving C—P bond cleavage have been reported by a number of workers[191-193], and in cases of mixed phosphine oxides the group which is preferentially cleaved is the one most capable of forming the most stable carbanion. Thus Freedman et al[194] have shown that fusion of the phospholane oxides (CLIV) and (CLV) with sodium hydroxide yields 1-hydroxy-2,5-dicyclohexyl-phospholane-1-oxide (CLVI) and 1,4-diphenylbutylphenylphosphinic acid (CLVII) respectively.



(CLIV)



(CLV)



(CLVI)



(CLVII)
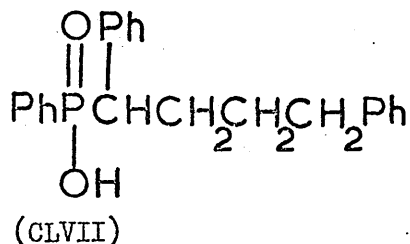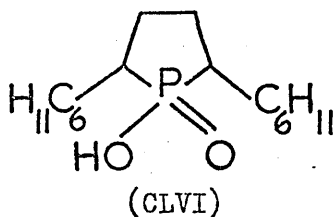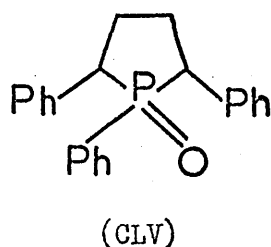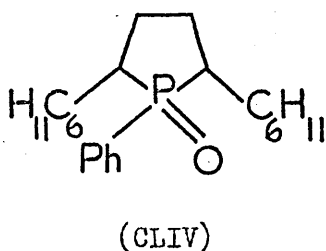
Carbon-phosphorus bonds in heteroarylphosphorus systems appear to be more susceptible to cleavage upon treatment with base than C—P bonds in aliphatic or aromatic derivatives. Thus triphenylphosphine oxide is able to withstand vigorous base treatment without bond cleavage, although certain aminophenyl-phosphonic acids undergo C—P bond cleavage with nucleophiles[105]. In addition, boiling aqueous alkali is sufficient for removal of a phenylethynyl[195] or hydroxymethyl[196] group from tertiary phosphine oxides, whilst a trifluoromethyl group is removed when tertiary phosphine oxides containing two or three such groups react with water or amine at room temperature[197].

Griffin et al[192], however, have reported that tri-(2-thienyl)phosphine

oxide (LXXVII) undergoes significant bond cleavage upon heating with aqueous

sodium hydroxide to give a mixture of di-(2-thienyl)phosphinic acid and

thiophen together with sodium metaphosphate. It was suggested that the greater

degree of cleavage in (LXXVII) compared with triphenylphosphine oxide is a

reflection of the greater stability of the 2-thienyl carbanion in comparison

with the phenyl carbanion. The formation of tertiary phosphine oxides thus

serves as a further possible method for investigating the relative reactivity

of heteroarylphosphorus compounds.
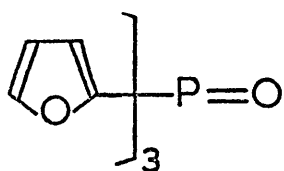


(LXXVI)
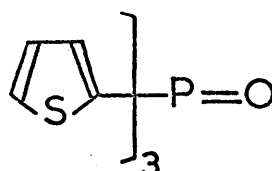


(LXXVII)
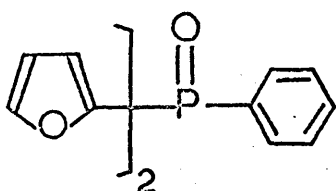


(CLVIII)
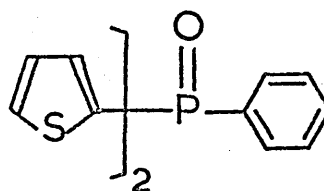


(CLIX)
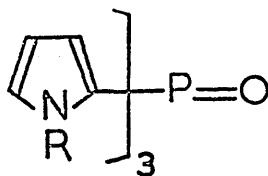


(LXXV)

Tri-(2-furyl)phosphine oxide (LXXVI) and tri-(2-thienyl)phosphine oxide

(LXXVII) were prepared according to the general procedure described by Griffin

et al[89]. Thus phosphorus oxychloride in ether, was added dropwise to the

corresponding heteroaryl-lithium reagent contained in ether and maintained at

ice-bath temperature. Following the addition, the mixture was heated under

reflux, cooled and hydrolysed. After separation and drying of the organic phase,

removal of the solvent gave the corresponding phosphine oxides in yields of 15 – 20%. Di-(2-furyl)phenylphosphine oxide (CLVIII) and phenyldi-(2-thienyl)-phosphine oxide (CLIX) were similarly prepared from the reaction between 2-furyl-lithium or 2-thienyl-lithium and phenylphosphonic dichloride.

Considerably higher yields of the corresponding phosphine oxides were obtained by the synthesis of the heteroarylphosphine and the subsequent oxidation of the phosphine in acetone, using hydrogen peroxide. Tri-(2-furyl)-phosphine oxide (LXXVI), tri-(2-thienyl)phosphine oxide (LXXVII) and tri-2-(1-methylpyrrolyl)phosphine oxide (LXXV; R = CH$_3$) were prepared using this procedure.

The alkaline hydrolysis of the phosphine oxides (LXXV; R = CH$_3$) – (LXXVII), (CLVIII) and (CLIX) gave contrasting results. Thus an equimolar mixture of tri-(2-furyl)phosphine oxide (LXXVI) and sodium hydroxide in 50% aqueous dioxan was heated under reflux for 72 hours to give di-(2-furyl)phosphinic acid (CLX) in 72% yield, together with an 8% recovery of unreacted (LXXVI). Tri-(2-thienyl)phosphine oxide (LXXVII) and sodium hydroxide were similarly heated under reflux for 120 hours to yield di-(2-thienyl)phosphinic acid (CLXI) in 37% yield together with a 60% recovery of unreacted phosphine oxide. In contrast, however, the reaction of tri-2-(1-methylpyrrolyl)phosphine oxide with aqueous sodium hydroxide gave no significant C—P bond cleavage and a quantitative recovery of unreacted phosphine oxide (LXXV; R = CH$_3$) was obtained. Haake et al[31] have recently reported an increased activity of hydroxide ion in dimethyl sulphoxide. Attempts to obtain di-2-(1-methylpyrrolyl)phosphinic acid (CLXII) by the reaction of excess sodium hydroxide and tri-2-(1-methyl-pyrrolyl)phosphine oxide (LXXV; R = CH$_3$) with 70% dimethyl sulphoxide / water as solvent, however, similarly resulted in near quantitative recovery of starting material. The result thus confirms the observations of Griffin et al[104] who have previously reported the absence of 1-methylpyrrole in the reaction mixture following the attempted hydrolysis of (LXXV; R = CH$_3$). The

order of reactivity indicated by the hydrolysis of the triheteroarylphosphine oxides was confirmed by the alkaline hydrolysis of the mixed phosphine oxides (CLVIII) and (CLIX). Thus, (2-furyl)phenylphosphinic acid (CLXIII) was obtained in 70% yield from the reaction between sodium hydroxide and di-(2-furyl)phenylphosphine oxide (CLVIII) in 50% aqueous dioxan, following a reflux period of 72 hours. The corresponding reaction of phenyldi-(2-thienyl)-phosphine oxide, however, resulted in negligible cleavage of the 2-thienyl group from phosphorus and recovery of unreacted phosphine oxide (CLIX) in 80% yield.
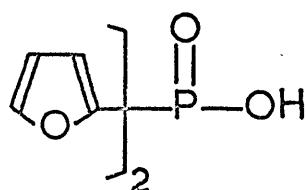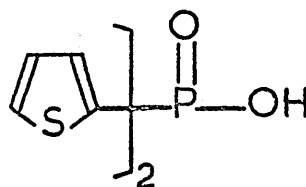


(CLX)  (CLXI)
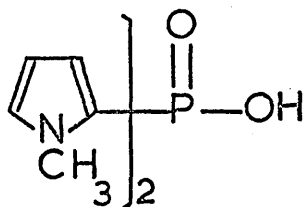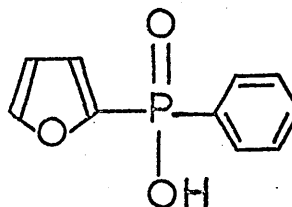
(CLXII)  (CLXIII)

The above results thus indicate the reactivity of the triheteroaryl-phosphine oxides to decrease in the order 2-furyl > 2-thienyl > 2-(1-methyl-pyrrolyl). In addition, the 2-furyl carbanion is seen to be more stable than the phenyl carbanion. Phosphonium salt hydrolysis[91,92] has shown the electron-withdrawing ability of the heteroaryl groups to decrease in the order 2-furyl > 2-thienyl > 2-(1-methylpyrrolyl) whilst the relative stabilities of the heteroaryl carbanions decrease in the order 2-thienyl > 2-furyl > 2-(1-methyl-pyrrolyl). It would appear therefore that the relative reactivities of the phosphine oxides are determined primarily by the electron-withdrawing effects of the substituents which aids the approach of the nucleophile. The reaction,

therefore, closely resembles the analogous alkaline hydrolysis of phosphonium salts, in that the relative reactivity is dependent on both the electron-withdrawing abilities of the substituents and also the relative stabilities of the departing carbanions.

In view of the apparent composite nature of the rate constant for the alkaline hydrolysis of phosphine oxides, and since the above results do not provide quantitative information regarding the relative rates of reaction, it is not possible to determine the effects of possible $p_\pi - d_\pi$ bonding between the substituents and the phosphinyl group. It could be argued that the apparent greater ease of hydrolysis of tri-(2-thienyl)phosphine oxide compared with triphenylphosphine oxide (in contrast with the alkaline hydrolysis of the phenyl- and 2-thienylphosphonates, which are hydrolysed at approximately the same rate) possibly indicates that the effects of $p_\pi - d_\pi$ bonding appear to be of little consequence in influencing the rate of reaction. This approach, however, would neglect the difference in the stability of the 2-thienyl and phenyl carbanions.

The lack of P—C bond cleavage in the alkaline hydrolysis of tri-2-(1-methylpyrrolyl)phosphine oxide, has prompted further investigations into possible routes for obtaining di-2-(1-methylpyrrolyl)phosphinic acid (CLXII). Kosolapoff[198] has reported the preparation of diphenyl- and di-(p-chlorophenyl)-phosphinic acids by the reaction of equimolar amounts of the corresponding Grignard reagent and phosphorus oxychloride. Thus 2-(1-methylpyrrolyl)-lithium was added dropwise to an equimolar quantity of phosphorus oxychloride contained in ether and maintained at ice-bath temperature. After the addition was complete, the mixture was heated under reflux for a short period and then left overnight. Hydrolysis of the reaction mixture with ice cold water, followed by trituration of the insoluble material with sodium hydroxide and acidification with dilute hydrochloric acid, however, yielded a brown tarry material which could not be induced to crystallise.

$$\left[\underset{\underset{CH_3}{|}}{\text{pyrrolyl}}\right]_2 -\overset{\overset{O}{\|}}{P}-N(C_2H_5)_2$$
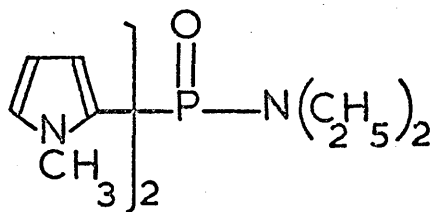
(CLXIV)

The facile hydrolysis of diphenylphosphinamidates to the corresponding phosphinic acid under mildly acid conditions has been reported by Haake et al[33]. N,N-diethyldi-2-(1-methylpyrrolyl)phosphinamidate (CLXIV) was thus prepared by the addition of N,N-diethylamidodichlorophosphate to a gently refluxing ether solution of 2-(1-methylpyrrolyl)-lithium. Following a further period of reflux, the reaction mixture was cooled and hydrolysed. Separation of the organic layer followed by drying, and removal of the solvent have an oil which was purified by distillation. The solid distillate was then further purified by recrystallisation from n-hexane.

Attempted cleavage of (CLXIV) with refluxing aqueous hydrochloric acid, however, led to the formation of a resinous material, thus reflecting the sensitivity of pyrrole derivatives to protic acids. The hydrolysis of the phosphinamidate (CLXIV) under alkaline conditions in dimethyl sulphoxide gave negligible amounts of the required phosphinic acid, and recovery of starting material. Rate constants for the alkaline hydrolysis of diphenylphosphinamidates have been obtained by Haake[33] who similarly reports the stability of the P—N bond to base. Nevertheless this data reveals the increased susceptibility of diphenylphosphinamidates towards nucleophilic displacement compared with the 2-(1-methylpyrrolyl)phosphinamidate (CLXIV). It is thus indicated that the apparent decrease in electron-withdrawing ability of the 2-(1-methylpyrrolyl) substituent compared with phenyl, contributes to the inherent stability of the phosphinamidate (CLXIV) towards alkaline hydrolysis.

The anomalous chemistry of the 2-(1-methylpyrrolyl) derivatives in

comparison with the 2-furyl and 2-thienyl analogues which has been revealed in the phosphonium salt chemistry, has thus been extended throughout the investigation to phosphonates and phosphine oxides, and is further indicated for phosphinamidates. The evidence contained in this study would therefore appear to support the suggestion of other workers regarding the relative distribution of electron-density in furan, thiophen and pyrrole. Thus it has been proposed[121] that in furan and thiophen the $\sigma$-inductive effect of the heteroatom is more important than the $\pi$-moment and thus the electron-density is directed towards the heteroatom, whereas in pyrrole, the $\pi$-moment predominates and the direction of electron-density is towards the ring. This situation may possibly explain the apparent difference in the electron-withdrawing ability of the 2-(1-methylpyrrolyl) substituent compared with the 2-furyl and 2-thienyl substituents which has been indicated throughout this work.



(CLXV)　　　　　　(CLXVI)
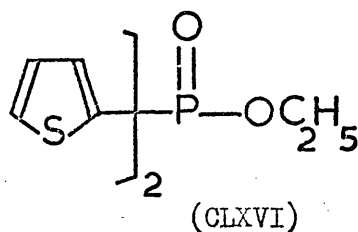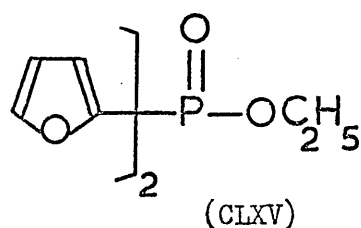
The ethyl esters of di-(2-furyl)phosphinic acid and di-(2-thienyl)-phosphinic acid (CLXV) and (CLXVI) respectively, were obtained from the reaction between the corresponding phosphinic acid and diazoethane. Thus an ether solution of diazoethane, prepared by the action of aqueous potassium hydroxide on N-ethyl-N[1]-nitro-N-nitrosoguanidine according to the method described by Stanley[199], was added slowly to a solution of the phosphinic acid in ethanol, maintained at ice-bath temperature. Removal of the solvent in the latter stages of the procedure gave the phosphinate ester (CLXV) or (CLXVI), which in each case was recrystallised from hexane. The purity of the compounds were checked by microanalysis, and analysis of the integrated peak intensities in the n.m.r. spectrum.

Diphenylphosphinyl chloride was prepared by the oxidation of diphenyl-chlorophosphine in carbon tetrachloride using gaseous oxygen, according to the method described by Smirnov and Khardin[200]. After the reaction was complete, the solvent was removed and the product distilled. The phosphinyl chloride in benzene solution with pyridine was then esterified by the addition of ethanol to give ethyldiphenylphosphinate (CLXVII). The final product was distilled under vacuum and the purity checked by g.l.c. and n.m.r. analysis.

$$\left[ \underset{}{\phantom{x}}\text{Ph} \right]_2 \overset{\overset{\displaystyle O}{\|}}{P} - OC_2H_5$$
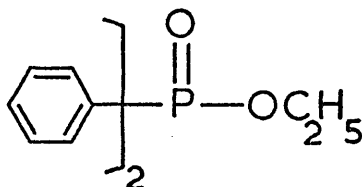
(CLXVII)

The $^{31}P$ chemical shifts of the phosphinate esters (CLXV), (CLXVI) and (CLXVII), have been obtained and are recorded in Table 3.24..

### Table 3.24.

$^{31}P$ Chemical Shift Data for Heteroarylphosphinates in Chloroform.

| Compound | $\delta^{31}P$/p.p.m. (rel. to 85% $H_3PO_4$) |
|---|---|
| Ethyldi-(2-furyl)phosphinate | $-4\cdot25$ |
| Ethyldi-(2-thienyl)phosphinate | $-16\cdot0$ |
| Ethyldiphenylphosphinate | $-27\cdot2$ |

The data in Table 3.24. reveals a trend to a greater shielding of the phosphorus nucleus on passing from phenyl- to 2-thienyl- to 2-furylphosphinate, indicating the electron-withdrawing ability of the substituents to increase in that order. It is of interest that the $^{31}P$ chemical shifts of the diethyl-heteroarylphosphonates (Table 3.6.) are more positive than their ethylphosphinate analogues, indicating the ethoxy group to be more electron-withdrawing than either the phenyl or heteroaryl groups, whereas kinetic data from the rates of alkaline hydrolysis has shown appreciable $p\pi - d\pi$ bonding between the ethoxy group and phosphorus. In the discussion of the $^{31}P$ n.m.r. spectra of the

heteroaryl- and substituted phenylphosphonate esters, it has been indicated that the chemical shift is determined primarily by the inductive effect of substituents and that $\pi$-bonding appears to be of minor importance. The above results would appear to give further support to this proposal.

On the basis of this argument it would be expected that the data presented in Table 3.24. would give little information regarding the changes in $p\pi - d\pi$ bonding which result when a second heteroaryl group is attached to phosphorus. In addition, the $^{31}P$ chemical shifts would indicate a decrease in the positive nature of the phosphorus in the phosphinate esters compared with the corresponding phosphonate ester, and would therefore predict a decrease in the rates of nucleophilic displacement. The kinetics of alkaline hydrolysis of the phosphinate esters (CLXV), (CLXVI) and (CLXVII) in 50% aqueous dioxan have been studied, and the second-order rate constants are presented in Table 3.25..

<u>Table 3.25.</u>

<u>Second-Order Rate Constants for the Alkaline Hydrolysis of Heteroarylphosphinate Esters</u> $R_2P(O)OC_2H_5$ <u>in Aqueous Dioxan (50% v/v; 0·1M in KCl).</u>

| R | Ester (M) | NaOH (M) | Temperature ($^{\circ}$C) | $k_{obs}$ (1 mol$^{-1}$sec$^{-1}$) |
|---|---|---|---|---|
| 2-Furyl | 0·01 | 0·01 | 30·5 | $2\cdot76 \times 10^{-2}$ |
| | 0·01 | 0·01 | 40·0 | $4\cdot89 \times 10^{-2}$ |
| 2-Thienyl | 0·01 | 0·01 | 30·3 | $1\cdot02 \times 10^{-3}$ |
| | 0·01 | 0·01 | 40·0 | $2\cdot19 \times 10^{-3}$ |
| Phenyl | 0·01 | 0·01 | 30·5 | $2\cdot57 \times 10^{-4}$ |
| | 0·01 | 0·01 | 40·0 | $5\cdot98 \times 10^{-4}$ |

The activation parameters for the above reactions have been calculated and are given in Table 3.26..

## Table 3.26.

### Activation Parameters for the Alkaline Hydrolysis of Heteroarylphosphinate Esters $R_2P(O)OC_2H_5$

| R | $E_A$ (kJ mol$^{-1}$) | $\Delta S$ (J K$^{-1}$mol$^{-1}$) | $\log_{10}$ PZ |
|---|---|---|---|
| 2-Furyl | 47·7 | −118·2 | 6·6 |
| 2-Thienyl | 62·0 | − 98·1 | 7·7 |
| Phenyl | 70·5 | − 81·7 | 8·5 |

The rate data in Table 3.25. reveals several features of interest. Over the temperature range studied, the rates of alkaline hydrolysis of the phosphinate esters are in the order 2-furyl $>$ 2-thienyl $>$ phenyl, the relative rates being 90 : 4 : 1. The rate increases are accompanied by a decrease in activation energy for the reaction (Table 3.26.) which is partially compensated by decreases in the entropy of activation and $\log_{10}$ PZ. The rate differences for the alkaline hydrolysis of the phosphinate esters are therefore much larger than the rate differences obtained for the corresponding phosphonate esters. In addition, comparison of the rate data in Tables 3.25. and 3.1. reveals that the phosphinate esters are hydrolysed more rapidly than their phosphonate analogues. Thus ethyldi-(2-furyl)phosphinate (CLXV) undergoes alkaline hydrolysis 35 times faster than diethyl-(2-furyl)phosphonate (LXXVIII; R = $C_2H_5$) whereas the di-(2-thienyl) and diphenylphosphinates (CLXVI) and (CLXVII) respectively undergo alkaline hydrolysis 9·3 and 2·8 times more rapidly than their corresponding phosphonate analogues (LXXIX; R = $C_2H_5$) and (IC; R = $C_2H_5$).

The results of this study would therefore appear to support the suggestion by Kabachnik[86,189] that a disturbance in $\pi$-bonding is obtained when two aryl groups are attached to phosphorus, possibly as a result of steric interactions. In addition to the work by Kabachnik[86,189], Haake et al[28] have confirmed the

importance of steric effects in nucleophilic displacement reactions at phosphinyl phosphorus. Thus the rates of alkaline hydrolysis of methyldialkyl-phosphinates $(R_2PO_2CH_3)$ indicate a distortion of the rate order predicted by the Taft substituent constants $(\overset{**}{\sigma})$ as a result of steric effects, which are reflected in the steric reaction constant $(\overset{**}{\rho})$ derived from the Taft equation (equation 13)[68]. Furthermore the alkaline hydrolysis of methyldiisopropyl-phosphinate (XXXVIII; X = $OCH_3$) indicates an induction period to precede second-order kinetics, as a result of $^-$OH-isopropyl interactions in the transition state. Similarly Trippett[27] has also reported a sharp decrease in nucleophilic reactivity on passing from diisopropylphosphinyl compounds to di-t-butylphosphinyl derivatives, compared with the comparatively small effect observed in the phosphonate series. Thus on the basis of these results it would appear that a reduction in conjugation is possible when two aryl or heteroaryl groups are attached to phosphorus.

The failure by Haake et al[30] and by Cooke[67] to observe these effects is possibly due to the reduction in $p_\pi$—$d_\pi$ conjugation between the phenyl group and phosphorus when compared with 2-furyl and 2-thienyl substituents. On the basis of this argument it would seem that phosphorus compounds containing 2-furyl and 2-thienyl groups provide a better model for assessing changes in conjugation between a substituent and phosphorus than their phenyl analogues.

# EXPERIMENTAL

G.l.c. analyses were carried out using a Pye series 104 chromatograph
with a 5 ft column of Apiezon L on Celite, and a flame ionisation detector.

Infrared Spectra were recorded as liquid films or as potassium bromide
discs using a Grubb Parsons 'Spectromaster' double beam spectrometer. The
calibration of the instrument was accurate to $\pm 1$ cm$^{-1}$.

Spinning-band distillations were carried out using a Nester-Faust
spinning-band column equipped with an 18" stainless steel band and a partial
take off head.

Refractive Indices were determined using a Bellingham and Stanley Ltd.
Abbé 60 refractometer.

## Preparation of Heteroaryl- and Phenylphosphonate Esters.

Diethyl-(2-thienyl)phosphonate (LXXIX; R = $C_2H_5$) - 2-Thienylmagnesium bromide (0·1 mol) [prepared from 2-bromothiophen (16·3 g, 0·1 mol) and magnesium (2·43 g, 0·1 mol)] in ether (80 cm$^3$) was added dropwise, with constant stirring under nitrogen, to a gently refluxing solution of diethylphosphorochloridate (17·3 g, 0·1 mol) in ether (50 cm$^3$). The resulting solution was heated under reflux for 2 h, cooled in ice, and hydrolysed by the addition of dilute hydrochloric acid. The organic phase was separated and the aqueous phase extracted with ether. The combined organic layers were dried ($Na_2SO_4$) and the solvent evaporated. The residue was distilled to give the ester, (17·6 g, 80%), b.p. 118° at 1·5 mmHg (lit.,[97] b.p. 103–104° at 0·1 mmHg) (Found: C, 43·3; H, 6·1. Calc. for $C_8H_{13}O_3PS$: C, 43·6; H, 5·9%); $\tau$ (CDCl$_3$) 2·2 – 2·6 (2H, m), 3·02 (1H,m), 5·7 – 6·27 (4H, m), and 8·53 (6H, t); $\delta^{31}P$ (CHCl$_3$) – 10·9 p.p.m..

The ester (LXXIX; R = $C_2H_5$) was also prepared by the addition of 2-thienyl-lithium (0·1 mol) to diethylphosphorochloridate (0·1 mol) in ether solution; however, the yield in this case was only 6 g (27%) after distillation through a spinning-band column. Hence the above procedure is to be preferred.

Diphenyl-(2-thienyl)phosphonate (LXXIX; R = $C_6H_5$) - 2-Thienylmagnesium bromide (0·1 mol) [prepared from 2-bromothiophen (16·3 g, 0·1 mol) and magnesium (2·43 g, 0·1 mol)] in ether (80 cm$^3$) was added dropwise, with stirring under nitrogen, to a refluxing solution of diphenylphosphorochloridate (17·9 g, 0·07 mol) in ether (50 cm$^3$). The resulting solution was heated under reflux for 3 h, cooled in ice, and hydrolysed by the addition of dilute hydrochloric acid. The organic layer was separated, and the aqueous phase was extracted with ether. The combined organic layers were dried ($Na_2SO_4$), and the solvent evaporated. The residue which solidified on standing was recrystallised from n-hexane to give a white solid (15·83 g, 75·4%), m.p. 75° (Found: C, 60·8; H, 4·3. $C_{16}H_{13}O_3PS$ requires C, 60·75; H, 4·1%); $\tau$ (CDCl$_3$) 2·15 – 2·45 (2H, m), and 2·55 – 3·0 (11H, m); $\delta^{31}P$ (CHCl$_3$) – 4·1 p.p.m..

The ester (LXXIX; $R = C_6H_5$) was also prepared by the reverse addition of 2-thienyl-lithium to diphenylphosphorochloridate in ether; however, the yield in this case was only 8% after recrystallisation. Hence the above procedure is to be preferred.

Diethyl-2-(1-methylpyrrolyl)phosphonate (LXXXIV; $R = CH_3$) - a solution of 1-methylpyrrole (12·2 g, 0·15 mol) in ether (100 cm³) was added dropwise, with stirring under nitrogen to n-butyl-lithium (0·15 mol) in light petroleum (b.p. 40-60°) (80 cm³). When the addition was complete, a solution of tetramethylethylenediamine (17·4 g, 0·15 mol) in ether (50 cm³) was added and the resulting mixture was heated under reflux for 20 h. After the period of reflux, the lithium reagent slurry was transferred under nitrogen to a dropping funnel and added over a period of 2 h, to a solution of diethylphosphorochloridate (22·5 g, 0·13 mol) in ether (100 cm³). The reaction mixture was maintained at ice-bath temperature during the addition. After the addition was complete, the reaction mixture was heated under reflux for 1·5 h, before being cooled in ice and hydrolysed by the addition of ammonium chloride solution (10% w/v; 100 cm³). The organic layer was separated, and the aqueous phase extracted with ether. The combined organic layers were dried $(Na_2SO_4)$ and the solvent evaporated to give a brown oil. Distillation gave the crude ester, (9·0 g, 32%), b.p. 109-120° at 0·3 mmHg (lit.,[104] b.p. 122·5 -126° at 3·0 mmHg). Further purification was effected by distillation through a spinning-band column until the product had >99% purity by g.l.c. analysis. (Found: C, 49·4; H, 7·35; N, 6·45. Calc. for $C_9H_{16}NO_3P$: C, 49·75; H, 7·35; N, 6·45%); $\tau$ (CDCl$_3$) 3·2 (2H, m), 3·9 (1H, m), 5·7 - 6·2 (4H, m), 6·22 (3H, s), and 8·7 (6H, t); $\delta^{31}P$ (CHCl$_3$) - 9·45 p.p.m..

Diphenyl-2-(1-methylpyrrolyl)phosphonate (XCV) - was prepared by the reverse addition of 2-(1-methylpyrrolyl)-lithium (0·1 mol) to diphenylphosphorochloridate (26·8 g, 0·1 mol) in ether, according to the general procedure described above. The residue which slowly solidified on standing, was

recrystallised from n-hexane to give a white solid (3·4 g, 11%), m.p. 73°.

(Found: C, 66·1; H, 5·35. $C_{17}H_{16}NO_3P$ requires C, 65·2; H, 5·1%); $\tau$ (CDCl$_3$) 2·6 - 3·2 (12H, m), 3·7 - 3·9 (1H, m), and 6·12 (3H, s); $\delta^{31}$P (CHCl$_3$) - 2·5 p.p.m..

Diethyl-(2-furyl)phosphonate (LXXVIII; R = $C_2H_5$) - 2-furyl-lithium (0·2 mol) [prepared from furan (13·6 g, 0·2 mol) and n-butyl-lithium (0·2 mol)] in ether (175 cm$^3$) was added dropwise with constant stirring under nitrogen, to a solution of diethylphosphorochloridate (34·5 g, 0·2 mol) in ether (100 cm$^3$) cooled to -40°. The resulting mixture was allowed to warm to room temperature, stirred for 12 h, and then heated under reflux for 2 h. After the period of reflux, the resulting solution was cooled in ice and hydrolysed by the addition of ammonium chloride solution (10% w/v; 100 cm$^3$). The organic layer was separated, and the aqueous phase extracted with ether. The combined organic layers were dried ($Na_2SO_4$) and concentrated to give a brown oil which was distilled to give the crude ester, b.p. 105-109° at 0·2 mmHg. Further purification was effected by preparative g.l.c. (10 ft. column of Apiezon L on Celite, at 190°, nitrogen flow rate 50 cm$^3$ min$^{-1}$) (Found: C, 46·9; H, 6·75. $C_8H_{13}O_4P$ requires C, 47·05; H, 6·35%); $\tau$ (CDCl$_3$) 2·55 (1H, m), 3·05 (1H, m), 3·73 (1H, m) 5·75 - 6·22 (4H, m), and 8·72 (6H, t); $\delta^{31}$P (CHCl$_3$) - 3·9 p.p.m..

In subsequent preparations of (LXXVIII; R = $C_2H_5$) purification was effected by distillation through a spinning-band column, until the product had >99% purity by g.l.c. analysis.

2-Iodofuran (XCVI) - a mixture of 2-chloromercurifuran (XCVII) and 2,5-dichloromercurifuran (XCVIII) was prepared according to the general procedure described by Gilman and Wright[118]. The mixture was separated by extraction with boiling ethanol; hot filtration left mainly 2,5-dichloromercurifuran as the residue whilst the cooled alcoholic filtrate yielded 2-chloromercurifuran, which was recrystallised several times from ethanol to give white crystals m.p. 151°

(lit.,[118] m.p. 151°).

The 2-chloromercurifuran (89 g, 0·29 mol) was then suspended in water
(900 cm³) and stirred vigorously throughout the slow addition of iodine
(76·2 g, 0·6 mol) in water (430 cm³). The slight excess of iodine remaining
at the end of the reaction was reduced with sodium thiosulphate solution
(10% w/v). The mixture was then steam distilled to yield 2-iodofuran (36 g,
64%). The product was immediately diluted with ether, since it is relatively
more stable in solution. After drying, the ether solution was used for the
preparation of the corresponding Grignard reagent.

<u>Diphenyl-(2-furyl)phosphonate</u> (LXXVIII; R = $C_6H_5$) - 2-furylmagnesium iodide
(0·09 mol) [prepared from 2-iodofuran ( 18 g, 0·09 mol) and magnesium (2·43 g,
0·1 mol)] in ether (80 cm³), was added dropwise, with stirring under nitrogen,
to a gently refluxing solution of diphenylphosphorochloridate (18·8 g, 0·07 mol)
in ether (100 cm³). The resulting solution was heated under reflux for 1 h,
cooled in ice, and hydrolysed by the addition of dilute hydrochloric acid.
The organic layer was separated, and the aqueous phase extracted with ether.
The combined organic layers were dried ($Na_2SO_4$) and the solvent evaporated.
The residue which solidified on standing was recrystallised from n-hexane, to
yield white crystals (5·8 g, 27·6%), m.p. 50° (Found: C, 64·05; H, 4·45.
$C_{16}H_{13}O_4P$ requires C, 64·0; H, 4·35%); $\tau$ ($CDCl_3$) 2·25 - 2·4 (1H, m), 2·5 - 3·0
(11H, m), and 3·45 - 3·65 (1H, m); $\delta^{31}P$ ($CHCl_3$) + 3·0 p.p.m..

The attempted preparation of diethyl-(2-furyl)phosphonate (LXXVIII;
R = $C_2H_5$) by the reaction of 2-furylmagnesium iodide (0·09 mol) and diethyl-
phosphorochloridate (0·09 mol) in ether, according to the general procedure
described above, resulted in a complex product mixture, from which pure ester
(LXXVIII; R = $C_2H_5$) was not isolated.

<u>Diethylphenylphosphonate</u> (IC; R = $C_2H_5$) - was prepared by the reaction of
phenylphosphonic dichloride (48·7 g, 0·25 mol) with absolute ethanol (34·5 g,
0·75 mol) in dry benzene (200 cm³), in the presence of pyridine (39·5 g, 0·5 mol)

according to the general procedure described by Kosolapoff[119] and had b.p. $114^{\circ}$ at 0·2 mmHg (lit.,[119] b.p. 117–118$^{\circ}$ at 1·5 mmHg) (53·5 g, 75%); $\tau$ (CDCl$_3$) 1·95 – 2·7 (5H, m) 5·65 – 6·14 (4H, m), and 8·68 (6H, t); $\delta^{31}$P (CDCl$_3$) –16·75 p.p.m..

Diphenylphenylphosphonate (IC; R = C$_6$H$_5$) – was similarly prepared by the addition of phenylphosphonic dichloride (25·4 g, 0·13 mol) in benzene (75 cm$^3$) to a refluxing solution of phenol (26·3 g, 0·28 mol)and pyridine (20·5 g, 0·26 mol) in benzene (200 cm$^3$), according to the general procedure described by Kosolapoff[119]. The residue, which solidified on standing, was recrystallised from n–hexane to give crystals (24·7 g, 61·4%), m.p. 73·5$^{\circ}$ (lit.,[119] m.p. 73–74$^{\circ}$); $\tau$ (CDCl$_3$) 2·05 – 3·38 (15H, m); $\delta^{31}$P (CHCl$_3$) –10·38 p.p.m..

The reaction between 2–furyl–lithium and diphenylphosphorochloridate – the attempted preparation of diphenyl-(2-furyl)phosphonate (LXXVIII; R = C$_6$H$_5$) by the reverse addition of 2–furyl–lithium (0·1 mol) [prepared from phenyl–lithium (0·1 mol) and furan (6·8 g, 0·1 mol)] in ether (100 cm$^3$) to diphenylphosphoro-chloridate (26·9 g, 0·1 mol) in ether solution according to the general procedure described for the preparation of (LXXVIII; R = C$_2$H$_5$) resulted in the formation of a brown viscous oil.

A small quantity (400 mg) of the product in ethyl acetate was separated by t.l.c. [ethyl acetate – n–hexane (10 : 90) as eluant] to give four components. The more intense bands were extracted with hot chloroform to yield the following products. Band 2. The compound from Band 2 was recrystallised from n–hexane to give a white solid (125 mg, 31%), m.p. 49$^{\circ}$, which was subsequently identified as triphenylphosphate (lit.,[114] m.p. 49$^{\circ}$): $\tau$ (CDCl$_3$) 2·87 (15H, s); (m/e 326, M$^+$). Band 3. Evaporation of the solvent gave a yellow oil (65 mg, 16%) which could not be induced to crystallise. Examination and comparison of the n.m.r. spectrum of this compound with that of authentic material, however, indicated the product to be tri-(2-furyl)phosphine oxide: $\tau$ (CDCl$_3$) 2·1 – 2·2 (3H, m), 2·5 – 2·9 (3H, m), and 3·25 – 3·45 (3H, m).

The Preparation of Benzyl- and Heteroarylmethylphosphonate Esters.

Diethylbenzylphosphonate (CXIII) — benzyl chloride (12·65 g, 0·1 mol) in ether (50 cm$^3$) was added dropwise, with constant stirring under nitrogen, to a suspension of sodium diethylphosphonate (0·15 mol) [prepared from diethyl-phosphonate (20·7 g, 0·15 mol) and metallic sodium (3·45 g, 0·15 mol)] in ether (100 cm$^3$). The resulting mixture was stirred for 12 h, and then heated under reflux for a further 4 h. The reaction mixture was then cooled, and filtered to remove the sodium chloride which had precipitated during the reaction. The ether was evaporated from the filtrate, and the residue distilled to give the ester, (15·1 g, 66·2%), b.p. 124–126° at 0·2 mmHg (lit.,[145] b.p. 155° at 14 mmHg) (Found: C, 58·1; H, 7·4. Calc. for $C_{11}H_{17}O_3P$: C, 57·9; H, 7·45%); $\tau(CDCl_3)$ 2·71 (5H, s), 5·77 – 6·25 (4H, m), and 6·88 (2H, d, $^2J_{PCH}$ 21 Hz), and 8·77 (6H, t); $\delta^{31}P$ (CHCl$_3$) −22·75 p.p.m..

Diethyl-(2-furylmethyl)phosphonate (CX; R = $C_2H_5$) — was similarly prepared, by the dropwise addition of 2-furfuryl bromide[143] (0·14 mol) in ether to a suspension of sodium diethylphosphonate (0·14 mol) [prepared from diethyl-phosphonate (19·32 g, 0·14 mol) and metallic sodium (3·22 g, 0·14 mol)] in ether, according to the general procedure described above. Removal of the ether solvent from the filtrate, followed by distillation of the residue gave the ester (15·5 g, 51%), b.p. 104–108° at 0·7 mmHg (lit.,[141] 117–120° at 2 mmHg). The product was further purified by distillation through a spinning-band column. (Found: C, 49·45; H, 6·65. Calc. for $C_9H_{15}O_4P$: C, 49·55; H, 6·90%); $\tau$ (CDCl$_3$) 2·64 (1H, m), 3·70 (2H, m), 5·7 – 6·2 (4H, m), 6·78 (2H, d, $^2J_{PCH}$ 21 Hz), and 8·73 (6H, t); $\delta^{31}P$ (CHCl$_3$) −19·75 p.p.m..

Diethyl-(2-thenyl)phosphonate (CXI; R = $C_2H_5$) — was similarly prepared, by the dropwise addition of 2-thenyl chloride[144] (11·5 g, 0·087 mol) in ether (100 cm$^3$) to a suspension of sodium diethylphosphonate (0·087 mol) [prepared from diethylphosphonate (12 g, 0·087 mol) and metallic sodium (2 g, 0·087 mol)] in ether, according to the general procedure described above. Removal of the

ether solvent from the filtrate, followed by distillation of the residue gave the ester (9·8 g, 48%), b.p. 138–140° at 2·2 mmHg (lit.,[142] b.p. 112° at 0·1 mmHg). The product was further purified by distillation through a spinning-band column. (Found: C, 46·3; H, 6·6. Calc. for $C_9H_{15}O_3PS$: C, 46·15; H, 6·4%); $\tau$ ($CDCl_3$) 2·7 – 3·18 (3H, m), 5·68 – 6·18 (4H, m), 6·65 (2H, d, $^2J_{PCH}$ 21 Hz), and 8·7 (6H, t); $\delta^{31}P$ ($CHCl_3$) –21 p.p.m..

Diethyl-(2-pyridylmethyl)phosphonate (CXXVIII) – 2-pyridylmethyl chloride[163] [prepared by neutralisation of the hydrochloride (62 g, 0·38 mol)] in benzene was added dropwise, with constant stirring under nitrogen, to a refluxing solution of sodium diethylphosphonate (0·38 mol) [prepared from diethyl-phosphonate (55·2 g, 0·4 mol) and metallic sodium (8·74 g, 0·38 mol)] in benzene (150 cm³). The resulting solution was heated under reflux for a further 1·5 h, cooled in ice and filtered. The filtrate was washed with water (3 × 20 cm³), dried ($Na_2SO_4$) and concentrated. The residue was distilled to give the ester (22·5 g, 26%), b.p. 119° at 0·2 mmHg (lit.,[162] b.p. 112° at 0·2 mmHg). Further purification of the product was effected by distillation through a spinning-band column. (Found: C, 52·4, H, 7·0; N, 6·1. Calc. for $C_{10}H_{16}NO_3P$: C, 52·0; H, 6·95; N, 6·4%); $\tau$ ($CDCl_3$) 1·33 – 1·58 (1H, m), 2·17 – 3·03 (3H, m), 5·74 – 6·23 (4H, m), 6·65 (2H, d, $^2J_{PCH}$ 22·5 Hz), and 8·8 (6H, t); $\delta^{31}P$ ($CHCl_3$) –21·75 p.p.m..

Diethyl-(3-pyridylmethyl)phosphonate (CXXIX) – was similarly prepared by the dropwise addition of 3-pyridylmethyl chloride[163] [prepared by neutralisation of the hydrochloride (30·5 g, 0·19 mol)] in benzene, to a refluxing solution of sodium diethylphosphonate (0·37 mol) [prepared from diethylphosphonate (51 g, 0·37 mol) and metallic sodium (8·5 g, 0·37 mol)] in benzene (150 cm³), according to the general procedure described above. Concentration of the filtrate, followed by distillation of the residue, gave the ester (6·3 g, 15%), b.p. 100° at 0·02 mmHg (lit.,[161] 97–101° at 0·02 mmHg); $\tau$ ($CDCl_3$) 1·3 – 1·55 (2H, m), 2·1 – 2·4 (1H, m), 2·53 – 2·84 (1H, m), 5·68 – 6·17 (4H, m),

6·83 (2H, d, $^2J_{PCH}$ 21 Hz), and 8·75 (6H, t); $\delta\,^{31}P$ (CHCl$_3$) −21·75 p.p.m.; (m/e 229, M$^+$).

<u>Diethyl-(4-pyridylmethyl)phosphonate</u> (CXXX) — was similarly prepared by the dropwise addition of 4-pyridylmethyl chloride[163] [prepared by neutralisation of the hydrochloride (36·2 g, 0·22 mol)] in benzene (200 cm$^3$), to a refluxing solution of sodium diethylphosphonate (0·22 mol) [prepared from diethyl-phosphonate (33·12 g, 0·24 mol) and metallic sodium (5·06 g, 0·22 mol)] in benzene, according to the general procedure described above. Concentration of the filtrate, followed by distillation of the residue, gave the ester (5·5 g, 11%), b.p. 127° at 0·3 mmHg (lit.,[160] b.p. 89° at 0·05 mmHg); $\tau$ (CDCl$_3$) 1·3 − 1·5 (2H, m), 2·62 − 2·83 (2H, m), 5·72 − 6·2 (4H, m), 6·86 (2H, d, $^2J_{PCH}$ 22·5 Hz), and 8·75 (6H, t); $\delta\,^{31}P$ (CHCl$_3$) −21·0 p.p.m.; $n_D^{25}$ 1·4962 (lit.,[160] $n_D^{25}$ 1·4955); (m/e 229, M$^+$).

<u>Diethylchloromethylphosphonate</u> (CXXXI) — was prepared by the reaction of chloromethylphosphonic dichloride (42 g, 0·25 mol) with absolute ethanol (34·5 g, 0·75 mol) in dry benzene (200 cm$^3$), in the presence of pyridine (39·5 g, 0·5 mol) according to the general procedure described by Kosolapoff[119] and had b.p. 86-87° at 1 mmHg (lit.,[119] b.p. 60° at 0·07 mmHg) (33·9 g, 72·7 %). The product was further purified by distillation through a spinning-band column. (Found: C, 32·4; H, 6·6. Calc. for $C_5H_{12}ClO_3P$: C, 32·15; H, 6·45%); $\tau$(CDCl$_3$) 5·54 − 6·03 (4H, m), 6·39 (2H, d, $^2J_{PCH}$ 12·5 Hz), and 8·64 (6H, t); $\delta\,^{31}P$ (CHCl$_3$) +16·75 p.p.m..

<u>Diethylmethylphosphonate</u> (CXXXII) — triethylphosphite (110·0 g, 0·66 mol) and methyl iodide (100·0 g, 0·71 mol) were heated under reflux for 2 h under anhydrous conditions. Iodoethane (96 g, 0·62 mol) was then distilled from the reaction mixture, and the residue distilled to give the ester (95·0 g, 95%), b.p. 59-60° at 1·0 mmHg (lit.,[164] b.p. 64-65° at 2·0 mmHg) (Found: C, 39·45; H, 8·6. Calc. for $C_5H_{13}O_3P$: C, 39·45; H, 8·55%); $\tau$ (CDCl$_3$) 5·65 − 6·15 (4H, m), and 8·39 − 8·79 (9H, m); $\delta\,^{31}P$ (CHCl$_3$) −26·0 p.p.m..

The Attempted Preparation of Diethyl-2-(1-methylpyrrol-2-yl)methylphosphonate
(CXXI) - a stirred suspension of trimethyl-(1-methylpyrrol-2-yl)methylammonium
iodide[150] (22·1 g, 0·08 mol) in triethylphosphite (68 g, 0·41 mol) was heated,
under nitrogen, in an oil bath. At a bath temperature of $170^{\circ}$ a clean white
precipitate was formed in the reaction mixture and the mixture was heated under
reflux at this temperature for a further 1 h. At no time, however, did the
mixture become completely homogeneous. After cooling, the solid was removed
by filtration. The filtrate was distilled at reduced pressure to give
triethylphosphite (55 g, 80% recovery), together with a second higher boiling
fraction, b.p. $116^{\circ}$ at 0·2 mmHg (0·4 g). The n.m.r. of the product indicated
a mixture, possibly the impure phosphonate ester (CXXI).

Preparation of Substituted Phenylphosphonate Esters.

Diethyl-(m-tolyl)phosphonate (CXLVIII) - a solution of m-iodotoluene (17·5 g,
0·08 mol) in triethylphosphite (66·4 g, 0·4 mol) contained in a 200 $cm^3$ silica
reaction vessel, was degassed by flushing with dry nitrogen and irradiated at
room temperature with a medium-pressure quartz mercury discharge lamp for 24 h.
Excess triethylphosphite was then removed under vacuum and the residue distilled
to give the ester (8 g, 43·9%). Further purification of the compound was
effected by distillation through a spinning-band column until the product had
>99% purity by g.l.c. analysis, b.p. $108^{\circ}$ at 0·4 mmHg (lit.,[94] $104-105^{\circ}$ at
0·4 mmHg); $\tau$ ($CDCl_3$) 2·1 - 2·67 (4H, m), 5·6 - 6·1 (4H, m), 7·57 (3H, s), and
8·66 (6H, t); $\delta^{31}P$ ($CHCl_3$) $-17·0$ p.p.m.; (m/e 228, $M^+$).

Diethyl-(m-formylphenyl)phosphonate (CL) - was prepared similarly by the
irradiation of a solution of m-iodobenzaldehyde (18·6 g, 0·08 mol) in triethyl-
phosphite (66·4 g, 0·4 mol) for 45 h. Distillation of the residue gave the
ester (9·9 g, 51%), b.p. $128-136^{\circ}$ at 0·25 mmHg. Further purification of the
compound was effected by distillation through a spinning-band column. G.l.c.
analysis, and examination of the peak intensities in the n.m.r. spectrum,
however, indicated the product to be approximately 90% pure. Further

distillation did not improve the purity, and the compound (CL) was not used in the study of the kinetics of alkaline hydrolysis. $\tau$ (CDCl$_3$) - 4·2 (s, C$\underline{H}$O), 1·4 - 2·75 (m, Ar$\underline{H}$), 5·55 - 6·05 (m, O-C$\underline{H}_2$), and 8·65 (t, O-CH$_2$C$\underline{H}_3$); $\delta$ $^{31}$P (CHCl$_3$) -14·2 p.p.m..

Diethyl-(p-methoxyphenyl)phosphonate (CIL) - was prepared according to the general procedure described by Tavs[97]. Triethylphosphite (66·4 g, 0·4 mol) was added dropwise with constant stirring, under nitrogen, to a suspension of anhydrous nickel chloride (2·2 g) in p-bromoanisole (62·3 g, 0·33 mol) maintained at 160° using an oil bath. Whilst the triethylphosphite was being added, ethyl bromide began to distil from the reaction mixture, and the rate of addition was controlled in order that the ethyl bromide distilled at a steady rate; during the reaction, 22 g of ethyl bromide was collected in a cooled receiver. When the addition was complete, the reaction mixture was heated for a further 1 h. On cooling, the deep green semi-crystalline mass was treated with water (100 cm$^3$) and the resulting emulsion extracted with ether (3 x 50 cm$^3$). The combined ether extracts were dried (Na$_2$SO$_4$) and the solvent evaporated. The residue was distilled to give the ester (47 g, 58·4%), b.p. 129-130° at 0·35 mmHg (lit.,[97] b.p. 113-114° at 0·1 mmHg). Further purification of the compound was effected by distillation through a spinning-band column, until the product had >99% purity by g.l.c. analysis; $\tau$ (CDCl$_3$) 2·0 - 2·45 (2H, m), 2·85 - 3·15 (2H, m), 5·67 - 6·2 (4H, m), 6·17 (3H, s), and 8·7 (6H, t); $\delta$ $^{31}$P (CHCl$_3$) -17·3 p.p.m.; (m/e 244, M$^+$).

Diethyl-(p-bromophenyl)phosphonate (CLII) - p-bromophenylmagnesium bromide (0·1 mol) [prepared from p-dibromobenzene (23·6 g, 0·1 mol) and magnesium (2·43 g, 0·1 mol)] in ether (75 cm$^3$) was added dropwise, with constant stirring under nitrogen, to a solution of diethylphosphorochloridate (17·3 g, 0·1 mol) in ether (100 cm$^3$) maintained at ice-bath temperature. The resulting solution was heated under reflux for 2 h, cooled and hydrolysed by the addition of dilute hydrochloric acid. The organic layer was separated and the aqueous

phase extracted with ether. The combined organic layers were dried ($Na_2SO_4$), and the solvent evaporated. The residue was distilled to give the ester (8·3 g, 24%), b.p. 117–120° at 0·4 mmHg (lit.,[119] b.p. 126–128° at 0·5 mmHg). The compound was purified further by spinning-band fractionation, until the product had >99% purity by g.l.c.; $\tau$ (CDCl$_3$) 2·0 – 2·5 (4H, m), 5·65 – 6·15 (4H, m), and 8·7 (6H, t); $\delta$ $^{31}$P (CHCl$_3$) –15·5 p.p.m..

Diethyl-(m-chlorophenyl)phosphonate (CLI) – was similarly prepared by the reverse addition of m-chlorophenylmagnesium bromide (0·15 mol) [prepared from m-bromochlorobenzene (28·73 g, 0·15 mol) and magnesium (3·65 g, 0·15 mol)] in ether (100 cm$^3$), to diethylphosphorochloridate (25·9 g, 0·15 mol) in ether (100 cm$^3$). The residue was distilled to give the ester (16·8 g, 45%), b.p. 108–110° at 0·3 mmHg (lit.,[201] b.p. 100–101° at 0·3 mmHg). Further purification was effected by spinning-band fractionation until the product had >99% purity by g.l.c. analysis; $\tau$ (CDCl$_3$) 1·9 – 2·7 (4H, m), 5·55 – 6·05 (4H, m), and 8·65 (6H, t); $\delta$ $^{31}$P (CHCl$_3$) –14·1 p.p.m..

The Attempted Preparation of Diethyl-(p-methoxyphenyl)phosphonate (CIL) – by the irradiation at room temperature for 21 h, of p-iodoanisole (18·72 g, 0·08 mol) and triethylphosphite (66·4 g, 0·4 mol), using a medium-pressure quartz mercury discharge lamp, resulted in the formation of crude ester (5 g, 25·6%), b.p. 130–156° at 0·4 mmHg. G.l.c. analysis, and examination of the integrated peak intensities in the n.m.r. spectrum indicated the product to be 66% pure. Spinning-band distillation increased the purity of the ester to a maximum of 77%. This product was not used in the study of the kinetics of alkaline hydrolysis.

The Attempted Preparation of Diethyl-(p-aminophenyl)phosphonate – by the irradiation of p-iodoaniline (17·5 g, 0·08 mol) and triethylphosphite (66·4 g, 0·4 mol) under the same conditions, resulted in negligible reaction and the recovery of iodoaniline (15·8 g, 90% recovery), m.p. 66° (ex n-hexane).

The Attempted Preparation of Diethyl-(m-chlorophenyl)phosphonate (CLI) – by the irradiation of m-bromochlorobenzene (15·3 g, 0·08 mol) and triethylphosphite (66·4 g, 0·4 mol) under the same conditions, similarly resulted in negligible reaction and the recovery of m-bromochlorobenzene (6·2 g, 40% recovery), b.p. 196°.

Hydrolysis of Diethylphosphonate Esters.

The following general procedure was used: the phosphonate ester was heated under reflux in aqueous sodium hydroxide solution (10% w/v) until a homogeneous reaction mixture was formed. The solution was then cooled and acidified with concentrated hydrochloric acid, whereupon an oil separated from the mixture. The oil was extracted with chloroform, and the combined extracts dried ($Na_2SO_4$). Evaporation of the solvent gave the monoester, which was recrystallised. In cases where the monoester could not be induced to crystallise, the product was isolated as the dicyclohexylamine salt.

Hydrolysis of Diphenylphosphonate Esters.

The phosphonate ester was heated under reflux in aqueous sodium hydroxide solution (10% w/v) until a homogeneous reaction mixture was formed. The solution was then cooled and acidified with concentrated hydrochloric acid. The monoester, together with phenol formed during the hydrolysis reaction were then extracted with chloroform. The chloroform solution was then extracted several times with aqueous sodium bicarbonate (10% w/v). Acidification of the aqueous solution yielded the monoester which was filtered and recrystallised.

Preparation of Dicyclohexylamine Salts.

To the monoester dissolved in 4-5 volumes of benzene was added dicyclohexylamine (0-20% excess) in 4-5 molumes of benzene. On standing, the salt crystallised from the solution and was collected. If the salt did not crystallise, the benzene was evaporated and the solid residue recrystallised. The yields in most cases were quantitative.

Analytical Data for Monophosphonate Esters.

Ethylhydrogen-(2-thienyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 159° (ex n-hexane). Found: C, 58·2; H, 8·7; N, 3·85. $C_{18}H_{32}NO_3PS$ requires C, 57·9; H, 8·6; N, 3·75%.

Ethylhydrogen-2-(1-methylpyrrolyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 150° (ex n-hexane). Found: C, 61·8; H, 9·5; N, 7·4. $C_{19}H_{35}N_2O_3P$ requires C, 61·6; H, 9·45; N, 7·55%.

Ethylhydrogen-(2-furyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 132° (ex n-hexane). Found: C, 60·65; H, 8·9; N, 3·8. $C_{18}H_{32}NO_4P$ requires C, 60·5; H, 8·95; N, 3·9%.

Ethylhydrogenphenylphosphonate - isolated as the dicyclohexylamine salt, m.p. 141° (ex n-hexane) (lit.,[109] m.p. 140·7-141·8°). Found: C, 65·25; H, 9·4; N, 3·65. Calc. for $C_{20}H_{34}NO_3P$: C, 65·4; H, 9·25; N, 3·8%.

Ethylhydrogenbenzylphosphonate - m.p. 64° (ex n-hexane) (lit.,[109] 63-64°). Found: C, 53·8; H, 6·3. Calc. for $C_9H_{13}O_3P$: C, 54·0; H, 6·5%.

Ethylhydrogen-(2-furylmethyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 133° (ex n-hexane). Found: C, 61·7; H, 9·4; N, 3·9. $C_9H_{34}NO_4P$ requires C, 61·45; H, 9·15; N, 3·8%.

Ethylhydrogen-(2-thenyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 132° (ex n-hexane). Found: C, 59·2; H, 8·85; N, 3·55. $C_{19}H_{34}NO_3PS$ requires C, 58·9; H, 8·8; N, 3·6%.

Ethylhydrogenchloromethylphosphonate - isolated as the dicyclohexylamine salt, m.p. 156° (ex n-hexane). Found: C, 53·2; H, 9·2; N, 4·1. $C_{15}H_{31}NClO_3P$ requires C, 53·1; H, 9·15; N, 4·1%.

Ethylhydrogenmethylphosphonate - isolated as the dicyclohexylamine salt, m.p. 137° (ex n-hexane). Found: C, 59·2; H, 10·55; N, 4·5. $C_{15}H_{32}NO_3P$ requires C, 59·0; H, 10·5 ; N, 4·6%.

Ethylhydrogen-(m-tolyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 130° (ex n-hexane). Found: C, 66·25; H, 9·3; N, 3·65. $C_{21}H_{36}NO_3P$

requires C, 66·15; H, 9·45; N, 3·70%.

Ethylhydrogen-(p-methoxyphenyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 126–128° (ex n-hexane). Found: C, 63·35; H, 9·05; N, 3·4. $C_{21}H_{36}NO_4P$ requires C, 63·5; H, 9·05; N, 3·55%.

Ethylhydrogen-(p-bromophenyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 164° (ex n-hexane). Found: C, 54·15; H, 7·65; N, 3·15. $C_{20}H_{33}NBrO_3P$ requires C, 53·8 ; H, 7·4; N, 3·15%.

Ethylhydrogen-(m-chlorophenyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 145° (ex n-hexane). Found: C, 59·6; H, 8·3; N, 3·4. $C_{20}H_{33}NClO_3P$ requires C, 59·8; H, 8·2; N, 3·5%.

Phenylhydrogen-(2-thienyl)phosphonate - isolated as the dicyclohexylamine salt, m.p. 151–152° (ex n-hexane). Found: C, 63·0; H, 7·5; N, 3·3. $C_{22}H_{32}NO_3PS$ requires C, 62·7; H, 7·6; N, 3·3%.

Phenylhydrogen-2-(1-methylpyrrolyl)phosphonate - m.p. 93° (ex n-hexane). Found: C, 55·95; H, 5·1; N, 5·9. $C_{11}H_{12}NO_3P$ requires C, 55·7; H, 5·1; N, 5·9%.

Phenylhydrogen-(2-furyl)phosphonate - the lack of sufficient phosphonate ester (LXXVIII; R = $C_6H_5$)prevented the isolation of an alkaline hydrolysis product for this compound.

Phenylhydrogenphenylphosphonate - m.p. 78–79° (ex n-hexane). Found: C, 61·75; H, 4·75. $C_{12}H_{11}O_3P$ requires C, 61·55; H, 4·7%.

The Kinetics of Alkaline Hydrolysis.

The hydrolyses were carried out in aqueous 50% (v/v) dioxan, 0·1M in KCl, at equal initial concentrations of phosphonate ester and sodium hydroxide, and were followed by a conventional back-titration procedure, in which the decrease in sodium hydroxide was determined. The solutions were in a thermostatted bath controlled to ± 0·1°C. The data were evaluated by the method of integration using the least squares programme on a I.M.E. 120 electronic desk calculator, and in all cases a plot of $^1/[OH^-]$ versus time was linear, confirming a second-order rate law.

The Hammett reaction constants and linear correlation coefficients were similarly calculated using the least squares programme on a I.M.E. 120 electronic desk calculator.

Preparation of Phosphine Oxides.

Tri-(2-furyl)phosphine – phosphorus trichloride (13·8 g, 0·1 mol) in benzene (75 cm$^3$) was added dropwise with stirring under nitrogen, to a solution of 2-furyl-lithium (0·5 mol) [prepared from n-butyl-lithium (0·5 mol) and furan (38 g, > 0·5 mol)] in ether (200 cm$^3$) . The resulting solution was heated under reflux for 1 h, before being cooled in ice and hydrolysed by the addition of ammonium chloride solution (10% w/v; 150 cm$^3$). The organic layer was separated, dried ($Na_2SO_4$) and evaporated; the residue solidified to give yellow crystals of crude tri-(2-furyl)phosphine (18 g, 79%). The phosphine, in acetone (100 cm$^3$) with hydrogen peroxide (100 vol; 25 cm$^3$) gave tri-2-furylphosphine oxide (LXXVI), (12 g, 62%), m.p. 114° (ex n-hexane-ethanol) (lit.,[89] m.p. 113·5-114°); $\tau$ (CDCl$_3$) 2·18 – 2·3 (3H, m), 2·68 – 2·9 (3H, m), and 3·33 – 3·5 (3H, m).

The phosphine oxide (LXXVI) was also prepared according to the general procedure described by Griffin et al[89]. Thus phosphoryl chloride (23 g, 0·15 mol) in ether (100 cm$^3$) was added dropwise with stirring under nitrogen, to a solution of 2-furyl-lithium (0·6 mol) in ether (200 cm$^3$), cooled to -20°. After the addition was complete the mixture was allowed to warm to room temperature and then heated under reflux for 3 h. The reaction mixture was then cooled in ice and hydrolysed by the addition of sodium carbonate solution (10% w/v; 150 cm$^3$). The organic layer was then separated, and the aqueous phase extracted with further portions of ether. The combined organic layers were then washed with water, dried ($Na_2SO_4$) and the solvent evaporated to give the phosphine oxide (LXXVI) (7·26 g, 20%).

Tri-2-(thienyl)phosphine – was similarly prepared by the general procedure described above. Thus phosphorus trichloride (13·8 g, 0·1 mol) in benzene

($75 \text{ cm}^3$) was added dropwise with constant stirring under nitrogen, to a solution of 2-thienyl-lithium (0·5 mol) [prepared from n-butyl-lithium (0·5 mol) and thiophen (46 g, >0·5 mol)] in ether ($200 \text{ cm}^3$). Evaporation of the solvent in the final stages of the procedure yielded crude tri-(2-thienyl)phosphine ($15 \cdot 6$ g, $56\%$). The phosphine, in acetone ($100 \text{ cm}^3$) with hydrogen peroxide (100 vol; $20 \text{ cm}^3$) gave tri-(2-thienyl)phosphine oxide (LXXVII), ($13 \cdot 0$ g, $79\%$), m.p. $130^\circ$ (ex n-hexane-ethanol) (lit.,[89] m.p. $129$–$130^\circ$); $\tau$ ($\text{CDCl}_3$) $2 \cdot 0$ – $2 \cdot 55$ (6H, m), and $2 \cdot 6$ – $2 \cdot 9$ (3H, m).

The phosphine oxide (LXXVII) was also prepared according to the general procedure described by Griffin et al[89]. Phosphoryl chloride (23 g, $0 \cdot 15$ mol) in ether ($100 \text{ cm}^3$) was added dropwise with stirring under nitrogen, to a solution of 2-thienyl-lithium ($0 \cdot 6$ mol) in ether ($200 \text{ cm}^3$), cooled to $-20^\circ$. Evaporation of the solvent in the final stages of the procedure yielded the phosphine oxide (LXXVII), ($6 \cdot 7$ g, $15\%$).

Tri-2-(1-methylpyrrolyl)phosphine – was prepared as described in Chapter 1 of this thesis. The phosphine (5 g, $0 \cdot 0185$ mol) in acetone ($50 \text{ cm}^3$) with hydrogen peroxide (100 vol; $100 \text{ cm}^3$) gave tri-2-(1-methylpyrrolyl)phosphine oxide (LXXV; R = $\text{CH}_3$), ($3 \cdot 9$ g, $74\%$), m.p. $138^\circ$ (ex n-hexane) (lit.,[89] m.p. $136$–$137 \cdot 5^\circ$); $\tau$ ($\text{CDCl}_3$) $2 \cdot 95$ – $3 \cdot 15$ (3H, m), $3 \cdot 73$ – $4 \cdot 05$ (6H, m), and $6 \cdot 14$ (9H, s).

Di-(2-furyl)phenylphosphine Oxide (CLVIII) – phenylphosphonic dichloride ($19 \cdot 5$ g, $0 \cdot 1$ mol) in ether ($100 \text{ cm}^3$) was added dropwise, with constant stirring under nitrogen to a chilled solution of 2-furyl-lithium ($0 \cdot 4$ mol) in ether ($200 \text{ cm}^3$). The resulting solution was heated under reflux for 3 h, cooled, and hydrolysed by the addition of sodium carbonate solution ($10\%$ w/v; $200 \text{ cm}^3$). The organic layer was separated, and the aqueous phase extracted with ether. The combined organic layers were dried ($\text{Na}_2\text{SO}_4$), and the solvent evaporated to give a yellow oil, which solidified on standing. The solid was recrystallised to give the phosphine oxide (CLVIII), (4 g, $16\%$), m.p. $126^\circ$ (ex benzene-n-hexane) (Found: C, $65 \cdot 0$; H, $4 \cdot 5$. $\text{C}_{14}\text{H}_{11}\text{O}_3\text{P}$ requires C, $65 \cdot 1$; H, $4 \cdot 25\%$);

$\tau$ (CDCl$_3$) 1·8 – 2·75 (7H, m), 2·83 – 3·0 (2H, m), and 3·34 – 3·6 (2H, m).

Phenyldi-(2-thienyl)phosphine Oxide (CLIX) – was similarly prepared by the addition of phenylphosphonic dichloride (39 g, 0·2 mol) in ether (100 cm$^3$) to a chilled solution of 2-thienyl-lithium (0·6 mol) in ether (250 cm$^3$). Evaporation of the solvent in the final stages of the procedure yielded a yellow crystalline residue. The compound was recrystallised to give the phosphine oxide (CLIX), (4 g, 7%), m.p. 131$^\circ$ (ex benzene-n-hexane) (Found: C, 58·2; H, 3·95. C$_{14}$H$_{11}$LPS$_2$ requires C, 57·95; H, 3·8%); $\tau$ (CDCl$_3$) 1·85 – 2·92 (11H, m).

The preparation of N,N-Diethyldi-2-(1-methylpyrrolyl)phosphinamidate (CLXIV) – N,N-diethylamidodichlorophosphate (26·0 g, 0·14 mol) in ether (100 cm$^3$) was added during a period of 1 h, to a gently refluxing solution of 2-(1-methyl-pyrrolyl)-lithium (0·44 mol) [prepared from n-butyl-lithium (0·44 mol) and 1-methylpyrrole (36·0 g, 0·44 mol)] in ether (300 cm$^3$). The resulting mixture was heated under reflux for a further 4 h, cooled in ice, and hydrolysed by the addition of ammonium chloride solution (10% w/v; 200 cm$^3$). The organic layer was separated, and the aqueous phase extracted with ether. The combined organic layers were dried (MgSO$_4$) and the solvent evaporated. The brown residue was distilled to give the phosphinamidate (CLXIV), (11 g, 28%), b.p. 140–160$^\circ$ at 0·35 mmHg. The distillate which solidified on standing was then recrystallised to give a white solid, m.p. 94$^\circ$ (Found: C, 60·05; H, 8·0; N, 14·9. C$_{14}$H$_{22}$N$_3$OP requires C, 60·2; H, 7·95; N, 15·05%); $\tau$ (CDCl$_3$) 3·0 – 3·2 (2H, m), 3·6 – 3·95 (4H, m), 6·12 (6H, s), 6·45 – 7·12 (4H, m), 8·95 (6H, t); $\delta^{31}$P (CHCl$_3$) –11·75 p.p.m..

The Alkaline Hydrolysis of Phosphine Oxides.

Tri-(2-furyl)phosphine Oxide (LXXVI) – a mixture of tri-(2-furyl)phosphine oxide (5 g, 0·02 mol) and sodium hydroxide (0·81 g, 0·02 mol) in aqueous dioxan (50% v/v; 60 cm$^3$) was heated under reflux for 72 h. The mixture was then cooled, and extracted with chloroform. The chloroform layer was dried (MgSO$_4$)

and evaporated to give unchanged phosphine oxide (LXXVI), (0·4 g, 8% recovery).
The aqueous phase was acidified with concentrated hydrochloric acid to give a
white solid. The compound was recrystallised to give di-(2-furyl)phosphinic
acid (CLX), (2·8 g, 71%), m.p. 149° (ex n-hexane-ethanol) (Found: C, 48·7;
H, 3·5. $C_8H_7O_4P$ requires C, 48·5; H, 3·55%); $\tau$ $(CD_3)_2CO$ 2·0 – 2·15 (2H, m),
2·7 – 2·85 (2H, m), 3·3 – 3·45 (2H, m), and 4·55 (1H, s); the signal at 4·55 $\tau$
disappeared on the addition of $D_2O$.

Tri-(2-thienyl)phosphine Oxide (LXXVII) – a mixture of tri-(2-thienyl)phosphine
oxide (4·2 g, 0·014 mol) and sodium hydroxide (0·57 g, 0·014 mol) in aqueous
dioxan (50% v/v; 50 cm$^3$) was heated under reflux for 120 h. The solution was
cooled and extracted with chloroform. The organic layer was dried $(MgSO_4)$
and the solvent evaporated to give unchanged phosphine oxide (LXXVII), (2·5 g,
60% recovery). The aqueous phase was acidified with concentrated hydrochloric
acid to yield a white solid, which was filtered and recrystallised to give
colourless crystals of di-(2-thienyl)phosphinic acid (CLXI), (1·2 g, 37%),
m.p. 193° (lit.,[192] m.p. 193°); $\tau$ $(CDCl_3)$ – 1·75 (1H, s) 2·0 – 2·55 (4H, m),
and 2·6 – 2·9 (2H, m); the signal at –1·75$\tau$ disappeared on the addition of $D_2O$.

Di-(2-furyl)phenylphosphine Oxide (CLVIII) – similarly a mixture of
di-(2-furyl)phenylphosphine oxide (1 g, 0·004 mol) and sodium hydroxide
(0·16 g, 0·004 mol) in aqueous dioxan (50% v/v; 20 cm$^3$) was heated under reflux
for 72 h. The solution was then cooled and extracted with chloroform. The
organic layer was dried $(MgSO_4)$ and the solvent evaporated to give unchanged
phosphine oxide (CLVIII), (0·1 g, 10% recovery). The aqueous phase was
acidified with concentrated hydrochloric acid to give (2-furyl)phenylphosphinic
acid (CLXIII) (0·55 g, 70%). The product was dissolved in ethanol and isolated
as the dicyclohexylamine salt, m.p. 179° (ex n-hexane) (Found: C, 67·85;
H, 8·25; N, 3·55. $C_{22}H_{32}NPO_3$ requires C, 67·85; H, 8·25; N, 3·6%); $\tau$ $(CDCl_3)$
1·9 – 2·75 (6H, m), 3·05 – 3·25 (1H, m), 3·55 – 3·75 (1H, m), and 6·6 – 9·4
(24H, m).

The Attempted Alkaline Hydrolysis of Tri-2-(1-methylpyrrolyl)phosphine Oxide

(LXXV; R = CH$_3$) – a mixture of tri-2-(1-methylpyrrolyl)phosphine oxide (1·3 g, 0·0045 mol) and sodium hydroxide (0·36 g, 0·009 mol) in aqueous dioxan (50% v/v; 20 cm$^3$) was heated under reflux for 168 h. The solution was then cooled and extracted with chloroform. The organic layer was dried (MgSO$_4$) and the solvent evaporated to give unchanged phosphine oxide (LXXV; R = CH$_3$) (1·15 g, 88% recovery). The aqueous phase was acidified with concentrated hydrochloric acid, without precipitation of di-2-(1-methylpyrrolyl)phosphinic acid (CLXII).

Similarly the attempted alkaline hydrolysis of (LXXV; R = CH$_3$) (2 g, 0·007 mol) with sodium hydroxide (0·56 g, 0·014 mol) in aqueous dimethyl sulphoxide (70% v/v; 20 cm$^3$) occurred without formation of the phosphinic acid (CLXII), and resulted in the recovery of unchanged phosphine oxide (1·76 g, 88% recovery), following a reflux period of 72 h.

The Attempted Alkaline Hydrolysis of Phenyldi-(2-thienyl)phosphine Oxide

(CLIX) – a mixture of phenyldi-(2-thienyl)phosphine oxide (1 g, 0·0035 mol) and sodium hydroxide (0·14 g, 0·0035 mol) in aqueous dioxan (50% v/v; 20 cm$^3$) was heated under reflux for 72 h. The solution was then cooled, and extracted with chloroform. The organic layer was dried (MgSO$_4$) and the solvent evaporated to give unchanged phosphine oxide (CLIX) (0·8 g, 80% recovery). The aqueous phase was acidified with concentrated hydrochloric acid without precipitation of phosphinic acid. The acidified solution was extracted with chloroform and the extract dried (MgSO$_4$). Evaporation of the solvent did not yield phenyldi-(2-thienyl)phosphinic acid.

The Attempted Alkaline Hydrolysis of N,N-Diethyldi-2-(1-methylpyrrolyl)-phosphinamidate (CLXIV) – a mixture of N,N-diethyldi-2-(1-methylpyrrolyl)-phosphinamidate (1 g, 0·0036 mol) and sodium hydroxide (0·3 g, 0·0075 mol) in aqueous dioxan (50% v/v; 10 cm$^3$) was heated under reflux for 17 h. The solution was then cooled and extracted with chloroform. The organic layer was dried

($MgSO_4$) and the solvent evaporated to give the phosphinamidate (0·5 g, 50%

recovery, after recrystallisation from n-hexane). The aqueous phase was

acidified with hydrochloric acid, without precipitation of di-2-(1-methyl-

pyrrolyl)phosphinic acid (CLXII).

Similarly the attempted alkaline hydrolysis of (CLXIV) (1 g, 0·0036 mol)

with sodium hydroxide (0·3 g, 0·0075 mol) in aqueous dimethyl sulphoxide

(80% v/v; 12 cm$^3$) occurred without formation of the phosphinic acid (CLXII),

and resulted in the recovery of unchanged phosphinamidate (0·4 g, 40% recovery)

following a reflux period of 48 h.

The Acid Hydrolysis of N,N-Diethyldi-2-(1-methylpyrrolyl)phosphinamidate (CLXIV)

– to a solution of N,N-diethyldi-2-(1-methylpyrrolyl)phosphinamidate (1 g,

0·0036 mol) in dioxan (10 cm$^3$) was added dilute hydrochloric acid (2M, 10 cm$^3$),

and the resulting mixture was heated under reflux for 1 h during which time a

dark brown resin separated. The nature of the product was not investigated

further.

The Attempted Preparation of Di-2-(1-methylpyrrolyl)phosphinic Acid (CLXII)

– a solution of 2-(1-methylpyrrolyl)-lithium (0·2 mol) [prepared from n-butyl-

lithium (0·2 mol) and 1-methylpyrrole (45 g,> 0·2 mol)] in ether (600 cm$^3$)

was added dropwise with stirring under nitrogen, to a solution of phosphoryl

chloride (30·7 g, 0·2 mol) in ether (250 cm$^3$), maintained at ice-bath temperature.

The resulting solution was heated under reflux for 1·5 h, cooled and left

overnight. The mixture was then hydrolysed by the addition of ice-cold water,

and the insoluble material triturated with dilute sodium hydroxide. The

solution was filtered and acidified with dilute hydrochloric acid to yield a

brown oil which was extracted with chloroform. The extract was dried ($MgSO_4$)

and the solvent evaporated to give a brown residue which could not be induced

to crystallise.

Preparation of Phosphinate Esters.

Ethyldi-(2-furyl)phosphinate (CLXV) – diazoethane (0·02 mol) [prepared[199] from N-ethyl-N[1]-nitro-N-nitrosoguanidine (3·2 g, 0·02 mol) and potassium hydroxide (4·6 g, 0·08 mol)] in ether (50 cm$^3$) was added slowly to a chilled solution of di-(2-furyl)phosphinic acid (2 g, 0·01 mol) in absolute ethanol (30 cm$^3$). After the addition was complete, the mixture was allowed to stand for 1 h, before excess diazoethane was removed by the passage of nitrogen through the solution. The mixture was then dried (Na$_2$SO$_4$), and the solvent evaporated to give a yellow oil which solidified on standing. The solid was recrystallised to give the ester (1·3 g, 57%), m.p. 76$^\circ$ (ex n-hexane) (Found: C, 53·15; H, 5·0. C$_{10}$H$_{11}$O$_4$P requires C, 53·1; H, 4·9%); $\tau$ (CDCl$_3$) 2·2 – 2·35 (2H, m), 2·65 – 2·82 (2H, m), 3·38 – 3·55 (2H, m), 5·55 – 6·08 (2H, m), and 8·62 (3H, t); $\delta^{31}$P (CHCl$_3$) –4·25 p.p.m..

Ethyldi-(2-thienyl)phosphinate (CLXVI) – was similarly prepared by the addition of diazoethane (0·02 mol) [prepared[199] from N-ethyl-N[1]-nitro-N-nitrosoguanidine (3·2 g, 0·02 mol) and potassium hydroxide (4·6 g, 0·08 mol)] in ether (50 cm$^3$) to a chilled solution of di-(2-thienyl)phosphinic acid (2 g, 0·009 mol) in absolute ethanol (30 cm$^3$). Evaporation of the solvent in the latter stages of the procedure gave a colourless oil which solidified on standing. The solid was recrystallised to give the ester (1·4 g, 62%), m.p. 61$^\circ$ (ex n-hexane) (Found: C, 46·55; H, 4·2. C$_{10}$H$_{11}$O$_2$PS requires C, 46·5; H, 4·25%); $\tau$ (CDCl$_3$) 2·15 – 2·5 (4H, m), 2·65 – 3·0 (2H, m), 5·58 – 6·08 (2H, m), and 8·63 (3H, t); $\delta^{31}$P (CHCl$_3$) –16·0 p.p.m..

Ethyldiphenylphosphinate (CLXVII) – diphenylphosphinyl chloride (7·5 g, 0·032 mol) [prepared by the oxidation of diphenylchlorophosphine[200]] in benzene (25 cm$^3$) was added dropwise with constant stirring under nitrogen, to a refluxing solution of absolute ethanol (4·6 g, 0·01 mol) and pyridine (5·6 g, 0·07 mol) in benzene (25 cm$^3$). The resulting solution was heated under reflux for 12 h, cooled and filtered to remove the pyridinium hydrochloride

precipitated during the reaction. The benzene was evaporated from the filtrate, and the residue distilled to give the ester (5 g, 64%), b.p. 170-172$^{\circ}$ at 1·5 mmHg (lit.,[119] b.p. 173-175$^{\circ}$ at 1·5 mmHg); $\tau$ (CDCl$_3$) 1·8 - 2·8 (10H, m), 5·66 - 6·15 (2H, m), and 8·67 (3H, t); $\delta^{31}$P (CHCl$_3$) -27·2 p.p.m.. G.l.c. analysis indicated the product to be $>$99% pure.

The Alkaline Hydrolysis of Phosphinate Esters.

The same general procedure was used as for the diethylphosphonate esters. Thus, the phosphinate was heated under reflux in sodium hydroxide solution (10% w/v) until a homogeneous reaction mixture was formed. The solution was then cooled, and acidified with hydrochloric acid. The mixture was then extracted with chloroform, and the combined extracts dried (Na$_2$SO$_4$). Evaporation of the solvent gave the acid which was recrystallised.

Di-(2-furyl)phosphinic Acid – m.p. 149$^{\circ}$ (ex n-hexane-ethanol).

Di-(2-thienyl)phosphinic Acid – m.p. 193$^{\circ}$ (ex n-hexane-ethanol) (lit.,[192] m.p. 193$^{\circ}$).

Diphenylphosphinic Acid – m.p. 195$^{\circ}$ (ex n-hexane-ethanol) (lit.,[192] 195-196$^{\circ}$).

The Kinetics of Alkaline Hydrolysis.

The hydrolyses were carried out in aqueous dioxan (50% v/v; 0·1M in KCl) at equal initial concentrations of phosphinate ester and sodium hydroxide, and were followed by a conventional back-titration procedure in which the decrease in sodium hydroxide was determined. The solutions were in a thermostatted bath controlled to $\pm$1$^{\circ}$. The data were evaluated by the method of integration using the least squares programme of a I.M.E. 120 electronic desk calculator, and in all cases a plot of 1/[OH$^-$] versus time was linear, confirming a second-order rate law.

Purification of Dioxan.

The dioxan solvent used in the kinetics of alkaline hydrolysis of the phosphonate and phosphinate esters, was purified according to the general procedure described by Vogel[202].

## REFERENCES

1. E.M. Kosower, "An Introduction to Physical Organic Chemistry," Wiley, New York, N.Y., 1968; A.J. Parker, Adv. Phys. Org. Chem., 1967, 5, 173; S.L. Johnson, 1967, 5, 237; T.C. Bruice and S.J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W.A. Benjamin, New York, N.Y., 1966.

2. R.F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N.Y., 1965.

3. A.J. Kirby and S. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967.

4. J.R. Cox Jr., and O.B. Ramsay, Chem. Rev., 1964, 64, 317.

5. A.J. Kirby and A.G. Varvoglis, J. Amer. Chem. Soc., 1967, 89, 415.

6. P. Haake and D.A. Tyssee, Tet. Lett., 1970, 3513; D.A. Tyssee, L.P. Bausher, and P. Haake, J. Amer. Chem. Soc., 1973, 95, 8066.

7. P. Haake, R.D. Cook, T. Koizumi, P.S. Ossip, W. Schwarz, and D.A. Tyssee, J. Amer. Chem. Soc., 1970, 92, 3828; P. Haake and P.S. Ossip, J. Amer. Chem. Soc., 1971, 93, 6924.

8. L. Keay, J. Org. Chem., 1963, 28, 329.

9. I. Dostrovsky and M. Halmann, J. Chem. Soc., 1953, 516.

10. R.F. Hudson and L. Keay, J. Chem. Soc., 1960, 1859.

11. R.F. Hudson and G.E. Moss, J. Chem. Soc., 1964, 1040.

12. D.F. Heath, J. Chem. Soc., 1956, 3804.

13. R.F. Hudson and L. Keay, J. Chem. Soc., 1956, 2463.

14. R.F. Hudson, Ann. Chim., 1963, 53, 47.

15. J.A.A. Ketelaar, H.R. Gersmann, and K. Koopmans, Rec. Trav. Chim., 1952, 71, 1253.

16. R.F. Hudson and L. Keay, J. Chem. Soc., 1956, 3269.

17. E. Blumenthal and J.B.M. Herbert, Trans. Faraday Soc., 1945, 41, 611.

18. M.L. Bender, J. Amer. Chem. Soc., 1951, 73, 1626.

19. E.L. Muetterties and R.A. Schunn, Quart. Rev. Chem. Soc., 1966, 20, 245.

20. P.C. Haake and F.H. Westheimer, J. Amer. Chem. Soc., 1961, 83, 1102.

21. F. Covitz and F.H. Westheimer, J. Amer. Chem. Soc., 1963, 85, 1773.

22. E.A. Dennis and F.H. Westheimer, J. Amer. Chem. Soc., 1966, 88, 3432.

23. R.S. Berry, J. Chem. Phys., 1960, 32, 933.

24. E.A. Dennis and F.H. Westheimer, J. Amer. Chem. Soc., 1966, 88, 3431.

25. R. Schmutzler, Angew. Chem. Intern. Ed. Engl., 1965, 4, 496.

26. P. Haake, R.D. Cook, W. Schwarz, and D.R. McCoy, Tet. Lett., 1968, 5251.

27. W. Hawes and S. Trippett, Chem. Comm., 1968, 577.

28. R.D. Cook, C.E. Diebert, W. Schwarz, P.C. Turley, and P. Haake, J. Amer. Chem. Soc., 1973, 95, 8088.

29. R.D. Cook, P.C. Turley, C.E. Diebert, A.H. Fierman, and P. Haake, J. Amer. Chem. Soc., 1972, 94, 9260.

30. P. Haake, C.E. Diebert, and R.S. Marmor, Tet. Lett., 1968, 5247.

31. P. Haake and G.W. Allen, Tet. Lett., 1970, 3113.

32. R.J. Gillespie, J. Chem. Soc., 1963, 4672; Inorg. Chem., 1966, 5, 1634.

33. T. Koizumi and P. Haake, J. Amer. Chem. Soc., 1973, 95, 8073.

34. J.R. Corfield, N.J. De'ath, and S. Trippett, Chem. Comm., 1970, 1502.

35. S.E. Cremer and B.C. Trivedi, J. Amer. Chem. Soc., 1969, 91, 7200.

36. W. Hawes and S. Trippett, J. Chem. Soc. (C), 1969, 1455.

37. S.E. Cremer, Chem. Comm. 1970, 616; Mazhar-ul-Haque J. Chem. Soc. (B), 1970, 934, 938.

38. R.D. O'Brien, "Toxic Phosphorus Esters," Academic Press, New York, 1960.

39. J.A. Cohen and R.A. Oosterbaan, "Handbuch der Experimentellen Pharmakologie: Cholinesterases and Anticholinesterase Agents," (sub-editor: G.B. Koelle), Springer-Verlag, Berlin, 1963, p. 356.

40. I.B. Wilson, J. Biol. Chem., 1952, 199, 113.

41. A.F. Childs, D.R. Davies, A.L. Green and P. Rutland, Brit. J. Pharmacol. Chemother., 1955, 10, 462.

42. H.S. Jansz, D. Brons and M.G.P.J. Warringa, Biochim. et Biophys. Acta, 1959, 34, 573.

43. B.J. Jandorf, H.O. Michel, N.K. Schaffer, R. Egan and W.H. Summerson, Discussions Faraday Soc., 1955, 20, 134.

44. T.R. Fukuto and R.L. Metcalf, J. Agr. Food Chem., 1956, 4, 930.

45. W.N. Aldridge and A.N. Davison, Biochem. J., 1952, 51, 62.

46. T.R. Fukuto and R.L. Metcalf, J. Amer. Chem. Soc., 1959, 81, 372.

47. T.R. Fukuto, R.L. Metcalf and M.Y. Winton, J. Econ. Entomol., 1959, 52, 1121.

48. R.F. Hudson and L. Keay, J. Chem. Soc., 1956, 2463.

49. E.D. Hughes, Trans. Faraday Soc., 1941, 37, 603.

50. W. Gerrard, W.J. Green, and R.A. Nutkins, J. Chem. Soc., 1952, 4076.

51. L.P. Hammett, "Physical Organic Chemistry", Chapter VII, p. 208. McGraw-Hill, New York, 1940.

52. C.N. Lieske, E.G. Miller Jr., J.J. Zeger, and G.M. Steinberg, J. Amer. Chem. Soc., 1966, 88, 188.

53. C.N. Lieske, J.W. Hovanec, G.M. Steinberg, and P. Blumbergs, Chem. Comm., 1968, 13.

54. C.N. Lieske, J.W. Hovanec, G.M. Steinberg, J.N. Pikulin, W.J. Lennox, A.B. Ash, and P. Blumbergs, J. Agr. Food Chem., 1969, 17, 255.

55. G. Aksnes and J. Songstad, Acta Chem. Scand., 1965, 19, 893.

56. L. Ginjaar and S. Vel, Rec. Trav. Chim., 1958, 77, 955.

57. L. Larsson, Svensk. Kem. Tidskr., 1958, 10, 70.

58. H. Böhme, Ber. deut. chem. Ges., 1941, 74, 248; H. Böhme and W. Schurhoff, Ber. deut. chem. Ges., 1951, 84, 28.

59. A.H. Fainberg and S. Winstein, J. Amer. Chem. Soc., 1956, 78, 2770.

60. R.F. Hudson and L. Keay, J. Chem. Soc., 1960, 1865.

61. A.L. Green, G.L. Sainsbury, B. Saville, and M. Stansfield, J. Chem. Soc., 1958, 1583.

62. H.K. Hall Jr., J. Org. Chem., 1956, 21, 248.

63. R.F. Hudson and D.C. Harper, J. Chem. Soc., 1958, 1356.

64. P. Haake, D.R. McCoy, W. Okamura, S.R. Alpha, S.Y. Wong, D.A. Tyssee,

J.P. McNeal, and R.D. Cook, Tet. Lett., 1968, 5243.

65. H. Van Bekkum, P.E. Verkade, and B.M. Wepster, Rec. Trav. Chim., 1959, 78, 815, and references therein.

66. Mazhar-ul-Haque and C.A. Caughlan, Chem. Comm., 1966, 921; T-T. Liang and K-C. Chi, Hua Hsueh Hsueh Pao, 1965, 31, 155.

67. R.D. Cook and H.K. Norrish, Tet. Lett., 1973, 521.

68. R.W. Taft Jr., J. Amer. Chem. Soc., 1952, 74, 3120; in "Steric Effects in Organic Chemistry," M.S. Newman, Ed., Wiley, New York, N.Y., 1956, Chap. 13.

69. J. Kumamoto, J.R. Cox Jr., and F.H. Westheimer, J. Amer. Chem. Soc., 1956, 78, 4858; A.B. Eberhard and F.H. Westheimer, J. Amer. Chem. Soc., 1965, 87, 253.

70. G. Aksnes and K. Bergesen, Acta Chem. Scand., 1965, 19, 931; 1966, 20, 2508; S.E. Cremer, B.C. Trivedi, and F.H. Weitl, J. Org. Chem., 1971, 36, 3226.

71. C.K. Hancock, B.J. Yager, C.P. Falls, and J.O. Schreck, J. Amer. Chem. Soc., 1963, 85, 1297.

72. S.A. Shain and J.F. Kirsch, J. Amer. Chem. Soc., 1968, 90, 5848.

73. R.F. Hudson, "Advances in Inorganic Chemistry and Radiochemistry" vol. 5, H.J. Emelens and A.G. Sharpe, Ed., Academic Press Inc., New York, N.Y., 1963, p. 347; J.R. Van Wazer, "Phosphorus and its Compounds," vol. 1, Interscience Publishers, Inc., New York, N.Y., 1958.

74. H.H. Jaffé and L.C. Freedman, J. Amer. Chem. Soc., 1952, 74, 1069, 2930; H.H. Jaffé, J. Chem. Phys., 1954, 22, 1430; L.D. Freedman and G.O. Doak, J. Amer. Chem. Soc., 1955, 77, 6221; L.D. Freedman, J. Amer. Chem. Soc., 1955, 77, 6223; H.H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley and Sons, Inc., New York, N.Y., 1962, pp. 497-501.

75. H.H. Hseih, Ph.D. Thesis, University of Pittsburgh, 1964.

76. C.E. Griffin and H.H. Hseih, unpublished results.

77. G.P. Schiemenz and K. Röhlk, Chem. Ber., 1971, 104, 1722.

78. G.P. Schiemenz, _Justus Liebigs Ann. Chem._, 1971, _30_, 752.

79. G.P. Schiemenz and H.U. Siebeneick, _Phosphorus_, 1972, _1_, 179.

80. M.I. Kabachnik, _Izv. Akad. Nauk SSSR, Otd. Khim. Nauk_, 1947, 233.

81. A.N. Pudovik, _Uspekhi Khimii_, 1954, _23_, 575.

82. M.I. Kabachnik, E.N. Zvetkov, and Chang Chung-Yu, _Dokl. Akad. Nauk SSSR_, 1960, _131_, 1334.

83. M.I. Kabachnik, Chang Chung-Yu, and E.N. Zvetkov, _Dokl. Akad. Nauk SSSR_, 1960, _135_, 603.

84. M.I. Kabachnik and T. Ya. Medved, _Izv. Akad. Nauk SSSR, Otd. Khim. Nauk_, 1959, 2142; M.I. Kabachnik, T.Ya. Medved, _Izv. Akad. Nauk SSSR, Otd. Khim. Nauk_, 1961, 270.

85. M.I. Kabachnik, E.N. Zvetkov, and Chang Chung-Yu, _Tet. Lett._, 1962, 5; Chang Chung-Yu, Thesis of Dissertation INEOS Akad. Nauk SSSR, Moskva, 1961.

86. M.I. Kabachnik, _Tetrahedron_, 1964, _20_, 655.

87. Fr. Hein, H. Plust, and H. Pohlemann, _Z. anorg. allg. Chem._, 1953, _272_, 25.

88. Fr. Hein, and H. Hecker, _Chem. Ber._, 1960, _93_, 1339.

89. C.E. Griffin and R.A. Polsky, _J. Org. Chem._, 1961, _26_, 4772; C.E. Griffin, R.P. Peller, K.R. Martin, and J.A. Peters, _J. Org. Chem._, 1965, _30_, 97.

90. R.H. Kemp, W.A. Thomas, M. Gordon, and C.E. Griffin, _J. Chem. Soc. (B)_, 1969, 527.

91. D.W. Allen, _J. Chem. Soc. (B)_, 1970, 1490.

92. D.W. Allen, B.G. Hutley, and M.T.J. Mellor, _J. Chem. Soc. Perkin II_, 1972, 63.

93. D. Redmore, _Chem. Rev._, 1971, 71, 315.

94. R. Obrycki and C.E. Griffin, _J. Org. Chem._, 1968, _33_, 632.

95. P. Tavs and F. Korte, _Tetrahedron_, 1967, _23_, 4677.

96. P. Tavs and H. Weitkamp, _Tetrahedron_, 1970, _26_, 5529.

97. P. Tavs, _Chem. Ber._, 1970, 103, 2428.

98. D.J. Martin, _Chem. Abstr._ 1972, _76_, 34399 w.

99. M. Bentov, L. David, and E.D. Bergmann, _J. Chem. Soc._, 1964, 4750.

100. H. Sachs, Chem. Ber., 1892, 25, 1514.

101. A. Burger and N.D. Dawson, J. Org. Chem., 1951, 16, 1250.

102. A. Burger and N.D. Dawson, J. Org. Chem., 1953, 18, 207.

103. C.G. Swain and H.B. Boyles, J. Amer. Chem. Soc., 1951, 73, 870.

104. C.E. Griffin, R.P. Peller, and J.A. Peters, J. Org. Chem., 1965, 30, 91.

105. L.D. Freedman and G.O. Doak, Chem. Rev., 1957, 57, 479.

106. J.A. Maynard and J.M. Swan, Australian J. Chem., 1963, 16, 596.

107. A. Meisters and J.M. Swan, Australian J. Chem., 1963, 16, 725.

108. J. Szmuszkovicz, J. Amer. Chem. Soc., 1958, 80, 3782.

109. R. Rabinowitz, J. Amer. Chem. Soc., 1960, 82, 4564.

110. D.A. Shirley, B. Gross, and P.A. Roussel, J. Org. Chem., 1955, 20, 225.

111. H. Gilman, J.A. Beel, C.G. Brannen, N.W. Bullock, G.E. Dunn and L.S. Miller,
     J. Amer. Chem. Soc., 1949, 71, 1499.

112. N. Gjøs and S. Gronowitz, Acta Chem. Scand., 1971, 25, 2596.

113. R. Levine and V. Ramanathan, J. Org. Chem., 1962, 27, 1216.

114. Hoeflak, Rec. Trav. Chim., 1916, 36, 24.

115. A.F. Shepard, N.R. Winslow, and J.R. Johnson, J. Amer. Chem. Soc., 1930,
     52, 2083.

116. H. Gilman, J.M. Peterson, and F. Schulze, Rec. Trav. Chim., 1928, 47, 19.

117. H. Gilman, H.E. Mallory, and G.F. Wright, J. Amer. Chem. Soc., 1932, 54, 733.

118. H. Gilman and G.F. Wright, J. Amer. Chem. Soc., 1933, 55, 3302.

119. G.M. Kosolapoff, "Organophosphorus Compounds," Wiley, New York, 1950.

120. G. Aksnes, Acta Chem. Scand., 1960, 14, 1515.

121. G. Marino, J. Heterocyclic Chem., 1972, 9, 817.

122. S. Oae and C.C. Price, J. Amer. Chem. Soc., 1957, 79, 2547.

123. E. Imoto, Y. Otsuji, T. Hirai, and H. Inoue, J. Chem. Soc. Japan, 1956,
     77, 804, 809.

124. G.E.K. Branch and A.C. Nixon, J. Amer. Chem. Soc., 1936, 58, 2499.

125. Cheng-Yeh Yuan, Wein Chen Yeh, Ming-Chuan Ko, and Li-Ying Chou,

Hua Hsueh Hsueh Pao (Acta Chimica Sinica), 1964, 30, 458.

126. J.V. Bell, J. Heisler, H. Tannenbaum, and J. Goldenson, J. Amer. Chem. Soc., 1954, 76, 5185.

127. M.A. Davis, J. Org. Chem., 1967, 32, 1161.

128. L.W. Deady, R.A. Shanks, and R.D. Topsom, Tet. Lett., 1973, 1881.

129. F. Fringuelli, G. Marino, and A. Taticchi, J. Chem. Soc. Perkin II, 1972, 158.

130. J.R. Van Wazer and J.H. Letcher, "$^{31}$P Nuclear Magnetic Resonance," "Topics in Phosphorus Chemistry Series," eds. M. Grayson and E.J. Griffith, Interscience, New York, 1967, vol. 5, p. 179.

131. C.C. Mitsch, L.D. Freedman, and C.G. Moreland, J. Magnetic Resonance, 1970, 3, 446.

132. C.C. Mitsch, L.D. Freedman, and C.G. Moreland, J. Magnetic Resonance, 1971, 5, 140.

133. H.H. Jaffe, Chem. Rev., 1953, 53, 191.

134. R.W. Taft Jr., J. Amer. Chem. Soc., 1952, 74, 2729.

135. R.A. Nyquist and W.J. Potts Jr., "Anal. Chem. Phosphorus Compounds," ed. M. Halmann, Interscience, New York, 1972, 189.

136. R.G. Harvey and E.R. De Sombre, Top. Phosphorus Chem., 1964, 1, 57.

137. R.G. Shepherd and J.L. Fedrick, Adv. Heterocyclic Chem., 1965, 4, 262.

138. B.A. Arbuzov and B.P. Lugovkin, Zhur. Obshchei Khim. (J. Gen. Chem.), 1951, 21, 1869; Chem. Abstr., 1952, 46, 6122 e.

139. B.A. Arbuzov and V.M. Zoroastrova, Bull. Acad. Sci. U.S.S.R. Div. Chem. Sci., 1954, 697 (English Translation); Chem. Abstr. 1956, 50, 2547 c.

140. B.A. Arbuzov and B. P. Lugovkin, J. Gen. Chem. U.S.S.R., 1952, 22, 1247 (English Translation); Chem. Abstr. 1954, 48, 2682 e.

141. B.A. Arbuzov and B.P. Lugovkin, J. Gen. Chem. U.S.S.R., 1952, 22, 1241 (English Translation); Chem. Abstr., 1954, 48, 2682 e.

142. R.M. Kellog, M.B. Groen, and H. Wynberg, J. Org. Chem., 1967, 32, 3093.

143. J.E. Zanetti, J. Amer. Chem. Soc., 1927, 49, 1065.

144. F.F. Blicke and F. Leonard, J. Amer. Chem. Soc., 1946, 68, 1934.

145. B.C. Saunders, G.J. Stacey, F. Wild, and I.G.E. Wilding, J. Chem. Soc., 1948, 699.

146. R.G. Laughlin, J. Org. Chem., 1962, 27, 3644.

147. B.E. Ivanov and S.S. Krokhina, Izv. Akad. Nauk SSSR, Ser. Khim., 1970, 11, 2629; Chem. Abstr. 1971, 75, 6034 j.

148. T.C. Myers, R.G. Harvey, and E.V. Jensen, J. Amer. Chem. Soc., 1955, 77, 3101.

149. T.C. Myers and A.F. Torralba, J. Org. Chem., 1957, 22, 972.

150. A. Treibs and A. Deitl, Ann., 1958, 619.

151. Y. Sugimoto, S. Nishimura, and E. Imoto, Chem. Abstr., 1961, 55, 12029 h.

152. H.A. Smith, J.B. Conley, and W.H. King, J. Amer. Chem. Soc., 1951, 73, 4633.

153. J. Nakaya, H. Kinoshita, and S. Ono, Nippon Kagaku Zasshi, 1957, 78, 935; Chem. Abstr., 1959, 53, 21276 e.

154. D.W. Allen and B.G. Hutley, J. Chem. Soc. Perkin II, 1972, 67.

155. A. Albert, "Heterocyclic Chemistry" Athlone Press, London, 1968.

156. D. Redmore, J. Org. Chem., 1970, 35, 4114.

157. J.I.G. Cadogan, D.J. Sears, and D.M. Smith, J. Chem. Soc. (C), 1969, 1314.

158. R.D. Bennett, A. Burger, and W.A. Volk, J. Org. Chem., 1958, 23, 1940.

159. E. Maruszewska-Wieczorkowska, J. Michalski, and A. Skowronska, Roczniki Chem., 1956, 30, 1197.

160. E. Maruszewska-Wieczorkowska, and J. Michalski, Roczniki Chem., 1964, 38, 625.

161. R. Bodalski, A. Malkiewicz and J. Michalski, Bull. Acad. Polon. Sci., Ser. Sci. Chim., 1965, 13, 139; Chem. Abstr., 1965, 63, 8310 e.

162. P. Bednarek, R. Bodalski, J. Michalski, and S. Musierowicz, Bull. Acad. Polon. Sci. Ser. Sci. Chim., 1963, 11, 507.

163. H.S. Mosher and J.E. Tessieri, J. Amer. Chem. Soc., 1951, 73, 4925.

164. A.H. Ford-Moore and J.H. Williams, J. Chem. Soc., 1947, 1465.

165. R. Taylor, J. Chem. Soc. (B), 1968, 1397.

166. R. Taylor, J. Chem. Soc., 1962, 4881.

167. M.R. Kegelman and E.V. Brown, J. Amer. Chem. Soc., 1953, 75, 5961.

168. M.R. Kegelman and E.V. Brown, J. Amer. Chem. Soc., 1953, 75, 4649.

169. M.H. Palmer, "The Structure and Reactions of Heterocyclic Compounds,"
     E. Arnold Ltd., London, 1967.

170. F.R. Stermitz and W.H. Huang, J. Amer. Chem. Soc., 1971, 93, 3427.

171. P.R. Falkner and D. Harrison, J. Chem. Soc., 1960, 1171.

172. A. Agren and G.T. van der Veen, Svensk Farm. Tidskr., 1963, 67, 437.

173. M. Simonetta and G. Favini, Gazz. Chim. Ital., 1954, 84, 566; Chem. Abstr.,
     1955, 49, 13992 d.

174. C.K. Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and
     Sons Ltd., London, 1953.

175. M. Simonetta and G. Favini, Gazz. Chim. Ital., 1955, 85, 1025;
     Chem. Abstr., 1956, 49, 3044 c.

176. A.R. Katritzky, A.M. Munro, J.A.T. Beard, D.P. Dearnaley, and N.J. Earl,
     J. Chem. Soc., 1958, 2182.

177. Nguyen Thanh Thuong and P. Chabrier, C.R. Acad. Sci. Paris, 1970, 86.

178. H. Christol and C. Marty, J. Organometallic Chem., 1968, 12, 471.

179. J.J. Monagle, J.V. Mengenhauser, and D.A. Jones, J. Org. Chem., 1967,
     32, 2477.

180. H.L. Retcofsky and C.E. Griffin, Tet. Lett., 1966, 1975.

181. G.M. Kosolapoff and W.F. Huber, J. Amer. Chem. Soc., 1947, 69, 2020.

182. G.O. Doak and L.D. Freedman, J. Amer. Chem. Soc., 1951, 73, 5658.

183. L.D. Freedman and G.O. Doak, J. Amer. Chem. Soc., 1953, 75, 4905.

184. H.H. Jaffe, L.D. Freedman and G.O. Doak, J. Amer. Chem. Soc., 1953, 75, 2209.

185. L.D. Quin and M.R. Dysart, J. Org. Chem., 1962, 27, 1012.

186. M.I. Kabachnik, Dokl. Akad. Nauk SSSR, 1956, 110, 393; T.A. Mastrukova,
     A.E. Shipov, T.A. Melent'yeva, and M.I. Kabachnik, Zh. Obshch. Khim.,
     1959, 29, 2178.

187. M.I. Kabachnik, T.A. Mastrukova, A.E. Shipov, and T.A. Melent'yeva,

Tetrahedron, 1960, 9, 10.

188. C.D. Johnson, "The Hammett Equation," Cambridge University Press, 1973.

189. M.I. Kabachnik, T.A. Mastrukova, and T.A. Melent'yeva, Tetrahedron, 1962, 17, 239, and references therein.

190. G.M. Kosolapoff and L. Maier, "Organic Phosphorus Compounds," Volume 6, Wiley, New York, 1973.

191. L. Horner, H. Hoffmann, and H.G. Wippel, Chem. Ber., 1958, 91, 64.

192. K.R. Martin and C.E. Griffin, J. Heterocyclic Chem., 1966, 3, 92.

193. L.P. Zhuravleva, M.I. Z'ola, M.G. Suleimanova, and A.V. Kirsanov, Zh. Obshch. Khim., 1968, 38, 342; Chem. Abstr., 1968, 69, 27484 x.

194. B.R. Ezzell and L.D. Freedman, J. Org. Chem., 1970, 35, 241.

195. G.K. Fedorova, Ya.P. Shaturskii, L.S. Moskalevskaya, Yu.S. Grushin, and A.V. Kirsanov, Zh. Obshch. Khim., 1967, 37, 2686; Chem. Abstr., 1968, 69, 67490 c.

196. A. Hoffmann, J. Amer. Chem. Soc., 1930, 52, 2995.

197. M.A.A. Beg and H.C. Clark, Can. J. Chem., 1961, 39, 564.

198. G.M. Kosolapoff, J. Amer. Chem. Soc., 1949, 71, 369.

199. C.W. Stanley, J. Agr. Food Chem., 1966, 14, 321,

200. A.N. Smirnov and A.P. Khardin, Zh. Obshch. Khim., 1969, 39, 2138; Chem. Abstr., 1970, 72, 21747 a.

201. J.M. Denham and R.K. Ingham, J. Org. Chem., 1958, 23, 1298.

202. A.I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1948.

## Post-graduate Courses of Study

The following post-graduate lectures were attended.

1. At the University of Sheffield.

(a) Structure determination by mass spectrometry (6 lectures)

(b) Principles of nuclear magnetic resonance and chemical applications (6 lectures)

(c) Kinetics of Enzymic Action (6 lectures)

2. The Chemical Society Summer School in Mass Spectrometry, University of Sheffield, March 1972.