STUDIES IN ORGANOPHOSPHORUS CHEMISTRY

by

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THESIS PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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FOR MY MOTHER

DECLARATION

I declare that this thesis is my own composition, that the work of which it is a record has been carried out by myself, and that it has not been submitted in any previous application fo a higher degree.

This thesis describes results of research carried out in the Department of Chemistry, University of Edinburgh, under th supervision of Professor J. I. G. Cadogan since 1 October 1971, the date of my admission as a research student.

8/11/74.

Acknowledgements

I wish to thank Professor J. I. G. Cadogan for suggesting the topics of research which have resulted in the realisation of this thesis; I also wish to express my gratitude for his invaluable advice and constant encouragement during the last three years.

I am indebted to members of the academic staff of the Department of Chemistry at Edinburgh University for helpful discussions and to the technical staff for all of the services which are so efficiently provided but without which, this research would have been made immeasurably more difficult.

Finally, I wish to thank Professor J. I. G. Cadogan for providing laboratory facilities and the University of Edinburgh for financial support.

LECTURE COURSES

The following courses and lectures have been attended during the period from October 1971 to October 1974:

(1) Attendance for three years at Laboratory 5 research group seminars — 3 units

(2) Attendance at a Chemical Society Summer School on Mass Spectrometry in Sheffield, 1972. — 2 units

(3) Attendance at a series of five lectures by Professor P. L. Pauson on 'Organometallic Reagents in Organic Synthesis'. — 1 unit

(4) Attendance at a series of five lectures by Dr. R. M. Lynden-Bell on 'High Resolution N. M. R.' — 1 unit

(5) Attendance at the Chemical Society Autumn Meeting at Nottingham in 1972. — 1 unit

ABSTRACT

The reactions of tervalent phosphorus reagents with aryl 2-nitrophenyl ethers in boiling cumene give pentacoordinate phosphorus derivatives of the benz-1, 3, 2-oxazaphospholine ring system . These reactions have been used to synthesise a series of heterocyclic phosphoranes with various substituents at phosphorus and in the exocyclic N-aryl ring.

The variable-temperature behaviour of the p. m. r. spectra of these derivatives have been investigated to probe the effect of such substituents on the permutational isomerisations of the phosphorus ligands.

The hydrolysis reactions of these derivatives have been studied and are found to be strongly catalysed by acids. In particular, 2, 2-dimethoxy-2-phenyl-3-p-tolyl-2, 2-dihydrobenz-1, 3, 2--oxazaphospholine hydrolyses in neutral solution to give mainly dimethyl phenylphosphonate and 2-p-toluidinophenol; but, in acidic solutions, rapid cleavage of an endocyclic phosphorus-heteroatom bond occurs to generate an acyclic phosphorus ester and methanol. This primary hydrolysis product recyclises more slowly to give the cyclic phosphonamidate 2-oxo-2-phenyl-3-p-tolylbenz-1, 3, 2-oxazaphospholine and methanol. The subsequent behaviour of this latter species has been partially elucidated by observations in the ^{31}P n. m. r. probe. In contrast, hydrolysis of the N-mesityl analogue 3-mesityl-2, 2-dimethoxy-2-phenyl-2, 2-dihydrobenz-1, 3, 2-oxazaphospholine gave no dimethyl phenylphosphonate but the cyclic phosphonamidate 3-mesityl-2-oxo-2-phenylbenz-1, 3, 2-oxazaphospholine was isolated in good yield under acidic conditions.

Hydrolysis of 3-aryl-2-methoxy-2, 2-diphenyl-2, 2-dihydrobenz--1, 3, 2-oxazaphospholine gives an acyclic tetracoordinate phosphorus derivative and methanol in high yield. The assignment of the product as a phosphinamide rather than a phosphinate is discussed.

Hydrolysis of 3-mesityl-2, 2, 2-trimethoxy-2, 2-dihydrobenz--1, 3, 2-oxazaphospholine gives the cyclic phosphoramidate monoester

2-hydroxy-3-mesityl-2-oxobenz-1, 3, 2-oxazaphospholine in high yield. Intermediates have been observed and /or isolated and their structures are discussed.

The reaction of 3-mesityl-2, 2-dimethoxy-2-phenyl-2, 2-dihydrobenz-1, 3, 2-oxazaphospholine with diols has been investigated briefly.

The rates of reductive cyclisation of o-nitrobenzalaniline by a series of tervalent phosphorus reagents to give 2-phenylindazole have been studied. Acyclic P(III) compounds reacted more rapidly than their five-membered cyclic analogues, thus indicating nucleophilic attack by the P(III) reagent in the rate-determining step of the reaction.

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SECTION II -- EXPERIMENTAL

SECTION I

INTRODUCTION

I

INTRODUCTION

Foreword

Investigation of the products which are obtained when aryl 2-nitrophenyl ethers are boiled with an excess of tervalent phosphorus reagents has revealed a novel and efficient preparation of a series of heterocyclic pentacoordinate phosphorus compounds. In the second and third sections of this thesis the extension of this preparation and the hydrolysis of the derived phosphoranes will be discussed; some mention will also be made of their dynamic stereochemistry.

The first, introductory, section is devoted to providing a wide theoretical background for the subsequent sections. The structure, stability and dynamic stereochemistry of phosphoranes is discussed, the extension of these ideas to the reactions of tervalent and pentavalent tetracoordinate phosphorus compounds is briefly outlined and is followed by a general account of alternative syntheses and the general reactions of phosphoranes. Finally, a brief survey is made of the previous work done in this laboratory which has led us to the present research.

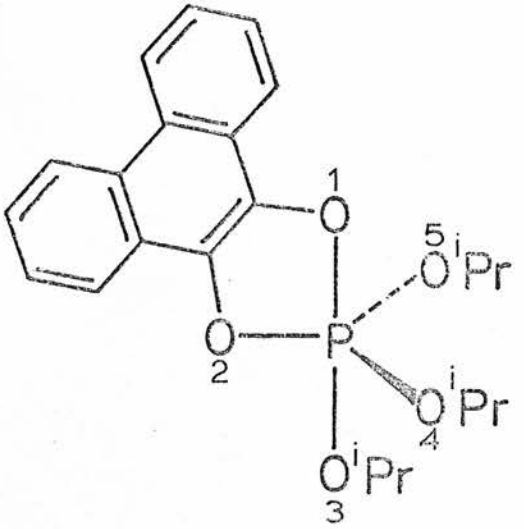
The following abbreviations have been used in the text:

BPR - Berry pseudorotation
TR - Turnstile rotation
TBP - Trigonal-bipyramid
PI - Permutational isomerisation

1. The Skeletal Geometry of Phosphoranes

Pentacoordinate phosphorus compounds (phosphoranes) have a strong tendency to adopt the skeletal geometry of a trigonal bipyramid (TBP). Earlier studies by electron diffraction on phosphorus pentafluoride[1] and phosphorus pentachloride,[2] by chlorine nuclear quadrupole resonance on dichlorotrifluorophosphorane,[3] and by X-ray crystallography on pentaphenylphosphorane,[4] are being continually supported by an increasing number of structure determinations.[5] Deviations[6] from ideal geometry are frequent, but only one example of a square-pyramid has so far been reported.[7]

The apical bonds are generally longer than the equatorial bonds;[1] this is probably related to the relative σ-character. Ramirez et al.[5a] obtained the molecular structure of 2,2,2-triisopropoxy-4,5-(2',2"-biphenyleno)-2,2-dihydro-1,3,2-dioxaphospholine (1) which shows features which seem to be general amongst oxyphosphoranes.



(1)

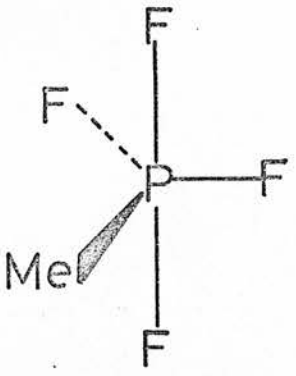
The five- (or four-) membered ring occupies an apical-equatorial distribution (the terms apical and equatorial are used here to indicate those positions which are otherwise termed axial and equatorial by some

authors). CNDO/2 calculations indicate[8] that whereas diequatorial placement of the ring results in large overall strain, the apical-equatorial placement is comparatively strain-free. Diapical placement of small rings is, of course, impossible. There is considerable intramolecular crowding. In particular, the apical ring oxygen in (1) was found to be only 2.63Å from the carbon attached to the equatorial oxygen — O_4. Cruikshank[9] predicted that a P—O single bond length should be 1.76Å. Although the P—O_1 bond length is 1.75Å, the P—O_3 bond length is only 1.64Å, the equatorial exocyclic bond length is 1.59Å and the endocyclic P—O_2 bond length is 1.63Å. It has been suggested[10] that these short lengths are the consequence of considerable pd-π bonding, which is greatest in the equatorial bonds. This result is in accord with theoretical calculations as will be discussed below. It was also observed[10] that the endocyclic bonds were longer than the equivalent exocyclic bonds; this would be unexpected from steric considerations but is understandable within the pd-π argument. The exocyclic oxygen atoms are free to exert considerable lone-pair back donation to phosphorus, whereas the endocyclic oxygens would be expected to delocalise much of such electron density into the ring and phenanthrenyl system.

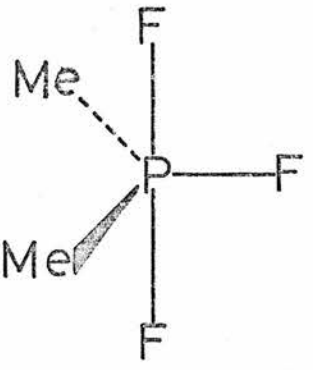
2. Bonding Theories

Early attitudes to the bonding in pentacoordinate TBP molecules were centred around the simple sp^3d hybridisation model.[11] However, Rundle[12] used a model which neglected d-orbitals in the basis set, viewed the equatorial bonds as normal and constructed the apical bonds

from 3-centre orbitals comprising the phosphorus $3p_z$ and ligand 1s orbitals. He successfully predicted that the apical bonds should be longer and hence that more electronegative ligands would occupy these positions. The electron diffraction studies of Bartell and Hansen[1] on methyltetrafluorophosphorane (2) and dimethyltrifluorophosphorane (3) confirmed this result.



(2)



(3)

Gillespie *et al.*[8] pointed out the shortcomings of earlier calculations[13] employing the Hückel MO approximation, as regards the choice of optimum P-3d exponents. These latter workers[8] employed a CNDO/2 calculation in which d-orbitals were included in the universal basis set, so that the extent of d-orbital participation could arise naturally. The calculation correctly predicted the energetic preference for methyl groups and the oxygen anion to occupy equatorial sites. The latter prediction is finding considerable application in the understanding of reactions of P(V) tetracoordinate molecules which invoke TBP intermediates and permutational isomerisation (PI; *v. infra*).

These calculations also indicated that the lower energy phosphorane isomers were those with the greatest electron density on phosphorus

and that this stabilisation could be accounted for by extensive back donation of electron density from the ligands into the phosphorus d-orbitals, especially from the equatorial positions. Removal of d-orbitals from the basis set resulted in the incorrect[14] prediction[15] that the most stable isomer of dichlorotrifluorophosphorane should contain an apical chlorine atom.

A further prediction was that an overall stabilisation of the TBP will result when all of the equatorial or both of the apical sites are occupied by the same type of substituent.

Semi-empirical calculations by Hoffmann et al.[16] on phosphorane confirmed the widely accepted belief that more electronegative substituents have an apical preference, whilst less electronegative substituents have an equatorial preference. They also showed that π-donors prefer equatorial sites whilst π-acceptors prefer apical sites, and in the case of an equatorial substituent with a single donor orbital this orbital will preferentially occupy the equatorial plane.

The overall picture is a predominantly sp framework with extensive pd-π back-bonding, especially from equatorial ligands.

3. The General Stability of Phosphoranes

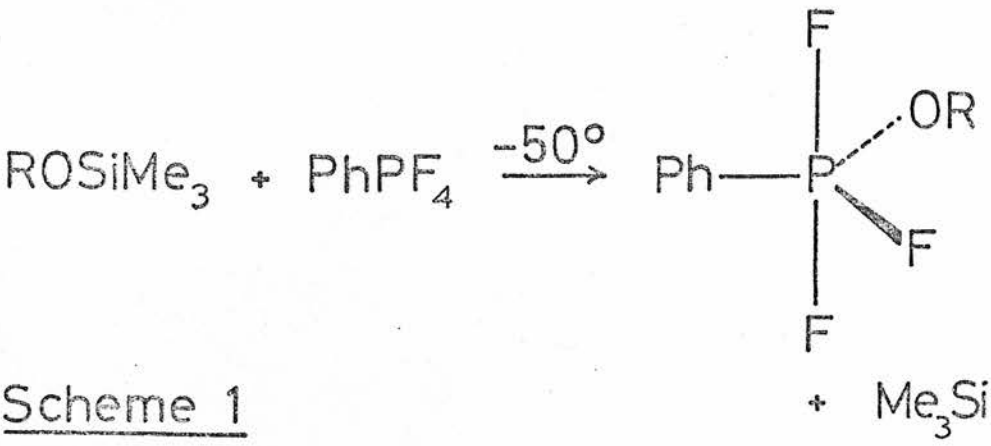
Ligand site-preferences have already been outlined above. Several other factors are of primary importance to the stability of a given phosphorane.

Electronegative ligands stabilise phosphoranes. Thus, phosphorus pentafluoride is comparatively stable, but pentaethoxyphosphorane has only recently been prepared and is unstable at room temperature.

Furthermore, phosphorane (PH_5) has never been isolated, although Cowley et al.[18] have managed to prepare tris(trifluoromethyl)dihydrophosphorane in which the inherent instability of the PH_5 structure is reduced by the presence of three electronegative ligands. Ramirez[19] has frequently emphasised that the stability of organophosphoranes is enhanced by increasing the number of alkoxy groups. Thus, Denney et al.[20] prepared 2,2,2-triethoxy-2,2-dihydro-1,3,2-dioxaphospholane and the 2,2,2-tri-n-butyl analogue; the former could be distilled under reduced pressure but the latter decomposed readily at room temperature.

The stability increase accompanying the substitution of more electronegative ligands may not be entirely due to electronegativity effects. As has been mentioned, the phosphorane structure is highly crowded and thus is easily destabilised by bulky groups. More electronegative atoms (e.g. F>O>N>C) often carry fewer substituents.

The effect of bulk on stability is exemplified by the series of alkoxy substituted fluorophosphoranes prepared[21] by the action of alkoxytrimethylsilanes on phenyltetrafluorophosphorane (scheme 1).

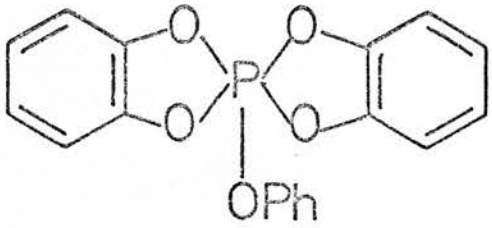


Scheme 1

When R was a tertiary alkyl group the phosphorane decomposed below -50° whereas, when R was a primary alkyl group, decomposition occurred at between $+60^{\circ}$ and $+120^{\circ}$.

The incorporation of small rings into the structure stabilises the phosphorane. Four- and five-membered rings are highly effective, but six-membered rings are less efficient. This stabilisation may be explained in at least two complementary ways. Cyclisation decreases intramolecular crowding relative to the acyclic case,[22] by effectively "tying back" the ligands into nearly planar rings.

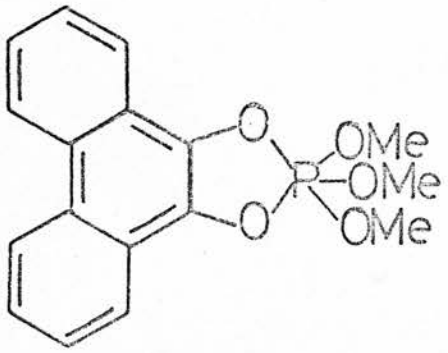
Thus pentaphenoxyphosphorane reacted readily with 2 molar equivalents of catechol in methylene chloride at 25° to give the spirocyclic phosphorane (4).[23] In the presence of less catechol, the monocyclic



(4)

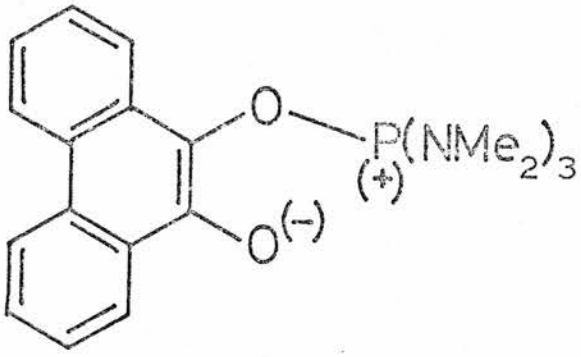
phosphorane was isolable, but there is a considerable driving-force towards the spirocyclic derivative.

^{31}P N.m.r. studies have shown that whereas (5) has the pentacoordinate form ($\delta^{31}P = +49$ ppm),[24] (6) exists as a zwitterion



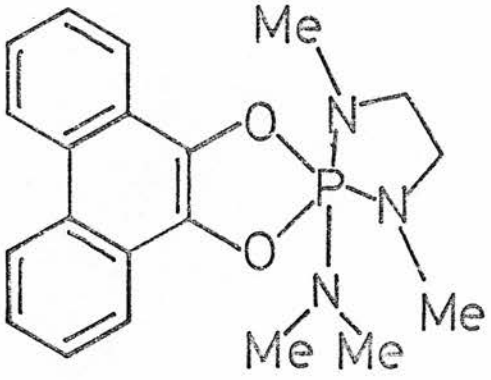
(5)

($\delta^{31}P = -38.5$ ppm).[25] This may be explained by additional electronic stabilisation of the phosphonium form by three amino groups, relative to the stabilisation which could be afforded to a similar form of (5) by



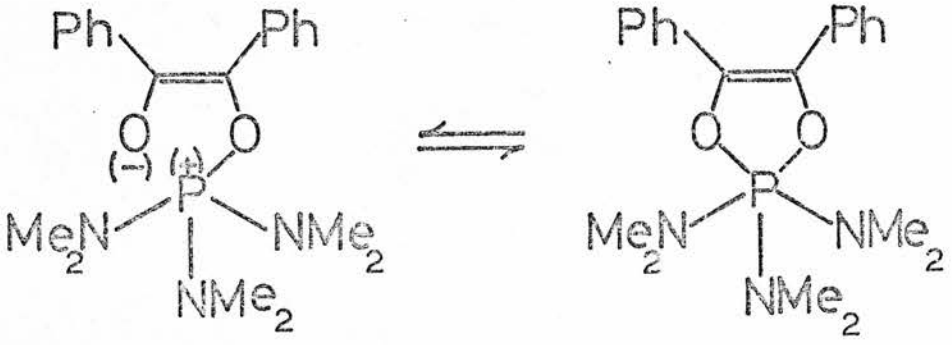
(6)

three methoxy groups. However, steric effects are the major consideration as the cyclic analogue of (6), (7), is once more pentacoordinate at phosphorus ($\delta^{31}P = +29.8$ ppm).[25]



(7)

Both ring-opened and ring-closed forms of a similar phosphorane have been isolated.[26] When benzil was reacted with hexamethylphosphorustriamide in hexane at 5°, a yellow crystalline solid (8a) separated out rapidly. Redissolution of this solid in hexane was difficult, but re-evaporation gave colourless prisms (8b). The ^{31}P n.m.r. chemical shift of (8) depended strongly on the nature and dilution of



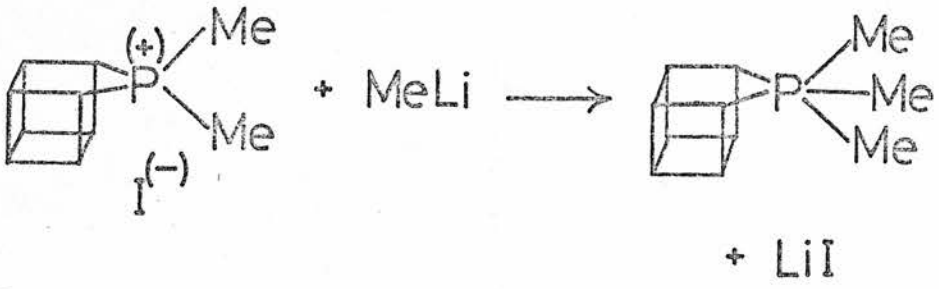
(8a) (8b)

the solvent, indicating that there was a rapid equilibration of the two forms.

A further example of the steric preference for small-ring systems over acyclic systems is the observation[27] that when 2,2,2-trimethoxy--4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene was heated with benzyl alcohol at +100° exchange of exocyclic groups occurred but the ring was completely preserved. An intrinsically lower reactivity of cyclic systems is also evident,[27] as no reaction was observed at +40° in this system, whilst pentaethoxyphosphorane exchanged rapidly with isopropanol at room temperature.[28]

It is well recognised[29,30] that there is a thermodynamic advantage in converting cyclic P(III) or(tetrahedral) P(V) compounds into TBP P(V) intermediates, so long as the ring consists of four or five atoms and can occupy an apical-equatorial distribution. It thus seems reasonable to suppose that isolable TBP cyclic phosphoranes should be more stable than their acyclic analogues in respect of reaction to give lower-coordination products.

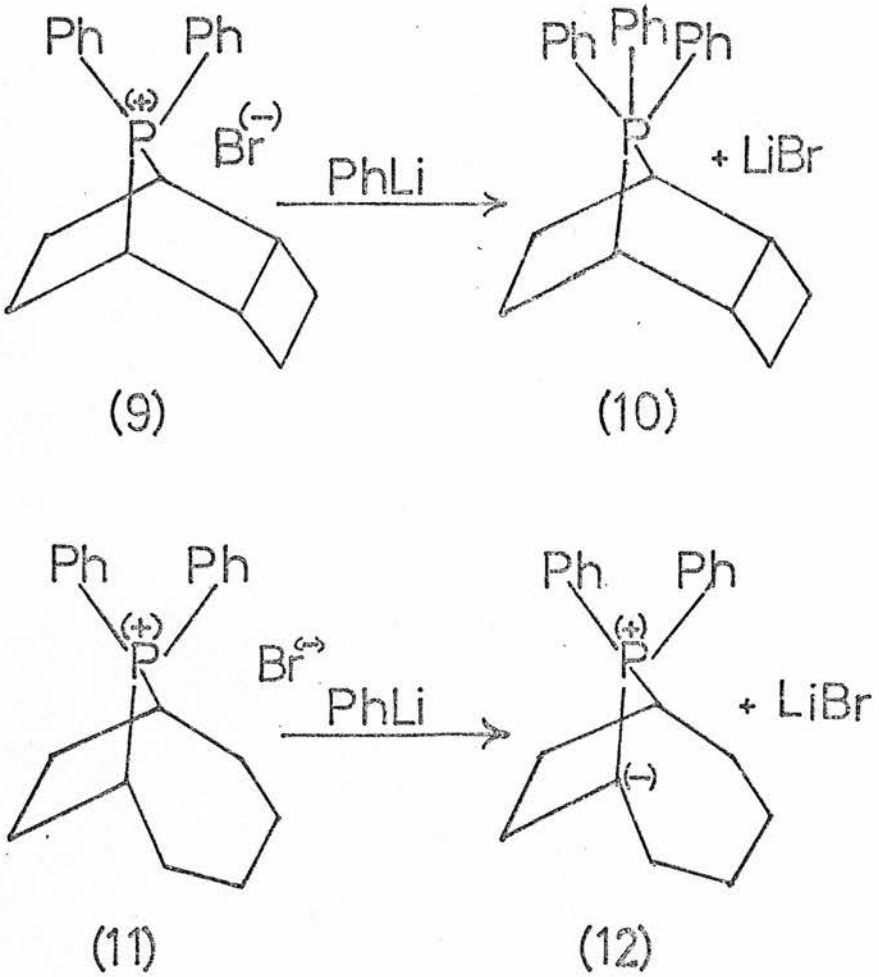
Katz et al.[31] utilised this factor in their synthesis of trimethylhomocubylphosphorane (scheme 2). This was the first example of a stable pentaalkyl phosphorane. The analogous reaction between methyl lithium



Scheme 2

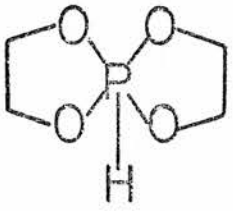
and tetramethylphosphonium iodide[32] produced only trimethylmethylene-phosphorane.

Katz[33] has investigated this phenomenon in some detail and has located the cross-over point at which the incipient ring strain is no longer capable of preventing ylide formation in preference to the penta-coordinate phosphorane. Thus (9) in scheme 3 reacts with phenyl lithium to give the phosphorane (10), but (11) forms the phosphonium ylide (12) instead. The additional ring-strain provided by one extra bond in (10) is sufficient to discourage ylide formation.



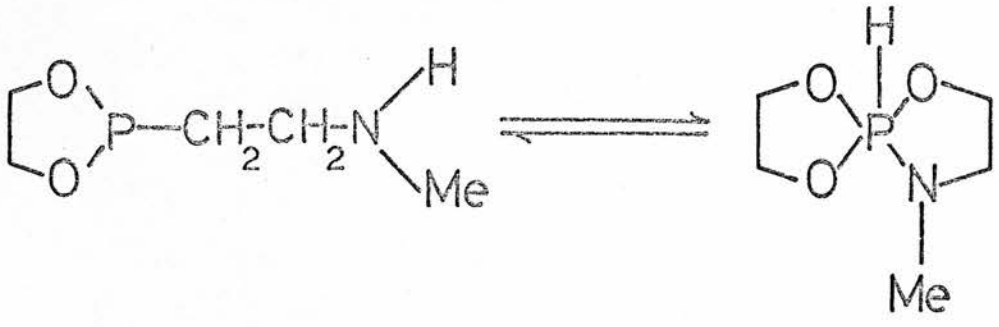
Scheme 3

Burgada et al.[34] have extensively studied the reactions of five-membered cyclic phosphoramidites with diols. The product, from the reaction of 1,2-ethanediol with 2-dimethylamino-1,3,2-dioxaphospholane, exists entirely as the spirocyclic phosphorane (13).



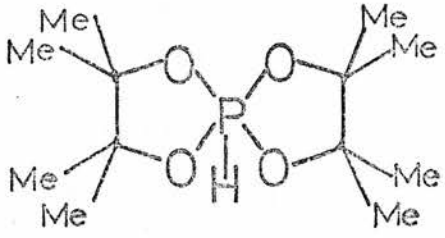
(13)

An equilibrium between P(III) tricoordinate and P(V) pentacoordinate forms has, however, been observed[35] for a similar product (14). The ^{31}P n.m.r. spectrum showed a strong singlet at -135 ppm (14a) and a doublet (J_{PH} 800Hz) at +44 ppm (14b).



(14a);- 85% (14b);- 15%

The stability of the pentacoordinate form relative to the cyclic phosphite is exemplified by the observation[36] that (15) is still undissociated at +150°.



(15)

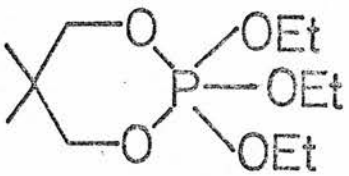
The stabilising influence of a five-membered ring is clearly exemplified by the lack of phosphate products in the reaction mixture obtained from heating 2,2,2-trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2--dioxaphospholene with benzyl alcohol at 100°.[27] In contrast, pentaethoxyphosphorane reacted with benzyl alcohol at -20° to give mainly phosphates.[20]

A further cause of cyclic phosphorane stability has been suggested by Brennan,[37] who observed that whereas the adduct of ozone and triethyl phosphite decomposes above -95°,[38] the adduct (17) formed between the caged phosphite (16) and ozone is stable at ca. 0° (scheme 4); Brennan suggested that entropy factors were responsible.

(16) (17)

Scheme 4

Similar stabilisation is not so marked when a six-membered ring is present. Some stabilisation is apparent, in that (18) reacts only very

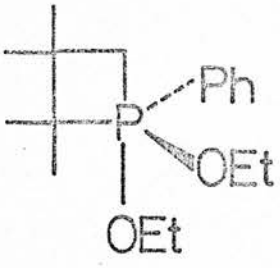


(18)

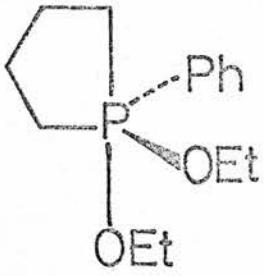
slowly with butanol at room temperature.[39]

The six-membered ring is puckered, thus there is less release of steric strain relative to the acyclic form; furthermore, there is no significant difference in ring strain between the pentacoordinate and tetra- or tricoordinate systems.

A comparative study of the effect of small rings in stabilising pentacoordinate structures against ionisation to the phosphonium form was made by Denney et al.[41] The phosphorane (19), containing a phosphetane ring, exhibited a sharp ethoxy methylene quintet in toluene at



(19)



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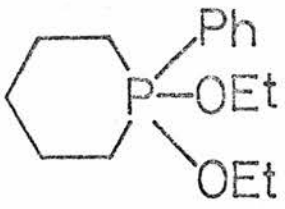
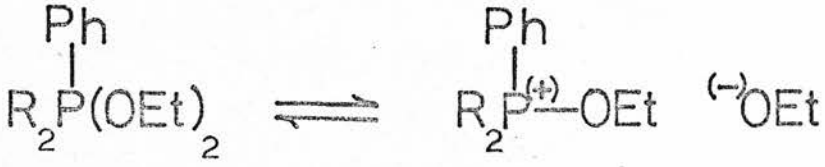


(21)

+100°. The ethoxy methylene region of the room temperature p.m.r. spectrum in chlorobenzene of the phospholane derivative (20) exhibited a sharp quintet which broadened at +100°. In contrast, the same region of the p.m.r. spectrum of the phosphorinane derivative (21) contained a broad "mound" at +30° which sharpened into a broad quartet at +100°. In methylene chloride these changes occurred at lower temperatures. The observed loss of phosphorus coupling with changes in temperature and solvent is explicable if an ionisation process occurs (scheme 5).[41]

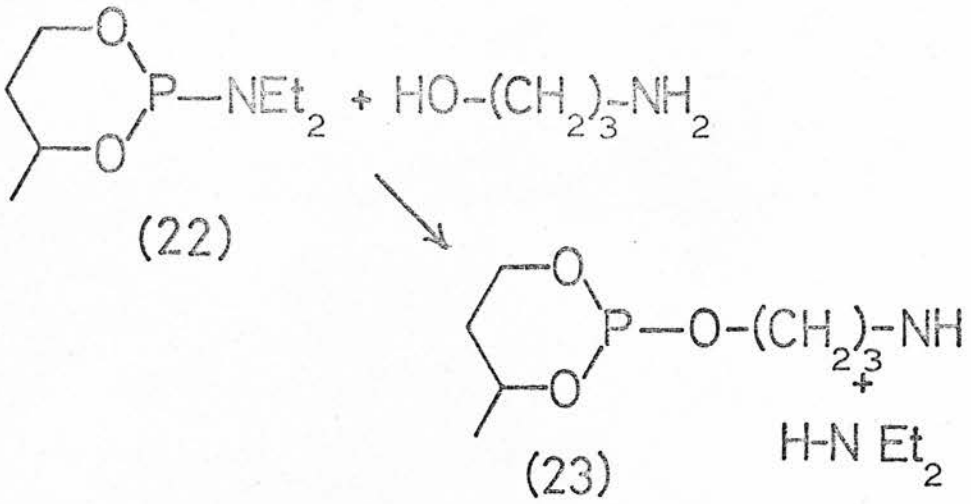


Scheme 5

The tendency to ionise decreases with decreasing ring size due to the increase of ring strain in the incipient cyclic phosphonium ion.

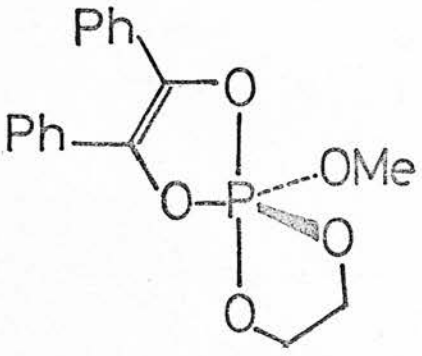
In a similar way, the product (23) obtained[42] from the trans-

sterification of the cyclic phosphoramidite (22) with 1,3-propanolamine xists entirely as the phosphite (cf. compound (14) above).

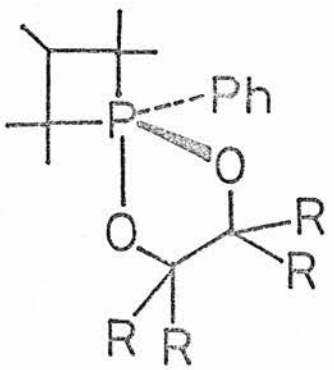


(22) (23)

Four- and five-membered spirocyclic phosphoranes are especially table. The pentaalkoxyphosphorane (24) was recovered unchanged from oiling diglyme,[43] and the dialkoxyphosphorane (25) was recrystallisable rom water.[44] Acyclic pentaalkoxyphosphoranes are often thermally un-table,[17] and even monocyclic alkoxyphosphoranes are highly reactive owards water (v. infra).



(24)



(25) R=CF_3

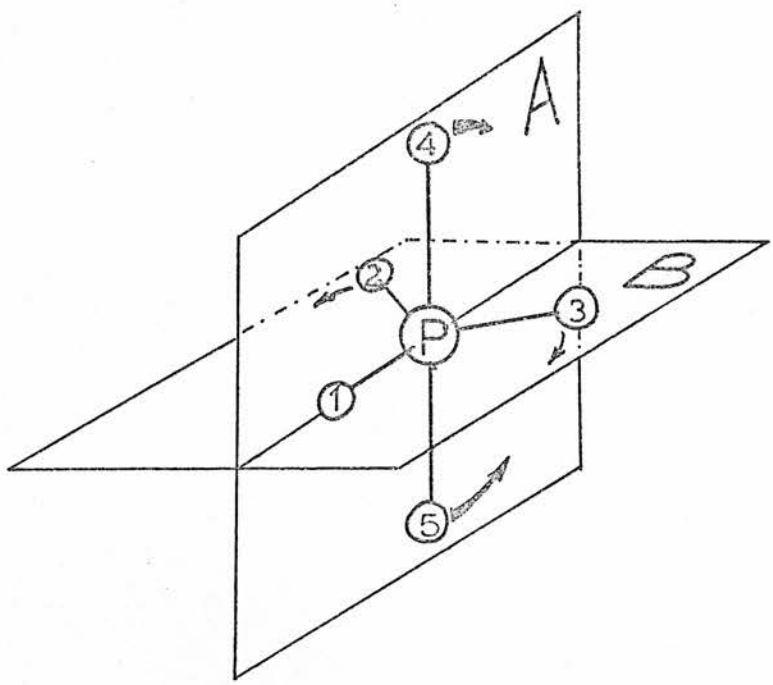
4. Permutational Isomerisation of Phosphoranes

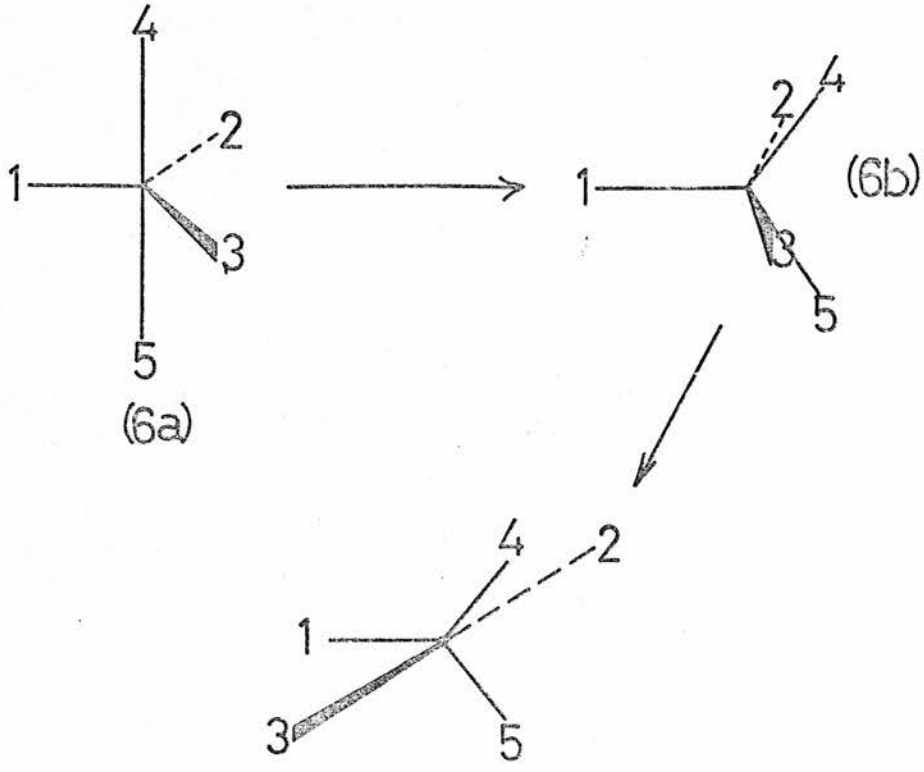
(a) General phenomena and mechanisms

The i.r. and electron diffraction data for phosphorus pentafluoride indicate that the molecule is a TBP in which the equatorial and apical bond lengths differ. Furthermore, in studies by Downs and Johnson[46] on phosphorus pentachloride (also a TBP),[47] only three atoms were isotopically substituted within five seconds, the remaining pair requiring 100 minutes to become 90% exchanged. This indicates that the electronic environment of apical and equatorial atoms also differed. In contrast, the ^{19}F n.m.r. spectrum of phosphorus pentafluoride consists of just one resonance[48] over a wide temperature range.

It was realised that this apparent contradiction could be resolved if a process exists by which the five pentafluoride fluorines could interchange at a rate between 10^2 and $10^8 s^{-1}$, thus appearing equivalent on the n.m.r. but not on the i.r. time-scale. A mechanism was proposed by Berry,[49] which he named pseudorotation. Berry pseudorotation (BPR) exchanges both pairs of apical and equatorial ligands in a concerted bond-bending process, whilst the fifth (pivot) ligand remains static. This process is detailed in scheme 6. The apical and equatorial bonds move in two orthogonal planes, A and B respectively, which intersect in the pivot bond (1—P) and are defined by the apical and equatorial ligands of the starting TBP (6a). As the ligands move there is a simultaneous shortening of apical and lengthening of equatorial bonds to reach the transition state (6b) which has idealised C_{4v} symmetry; continuation of the process generates the new TBP (6c).

The result of BPR on the skeletal orientation is an apparent 90°





Scheme 6

rotation about the pivot, hence the term pseudorotation.

A sequence of five BPR employing each ligand in turn as the pivot will generate the enantiomer of the original TBP.

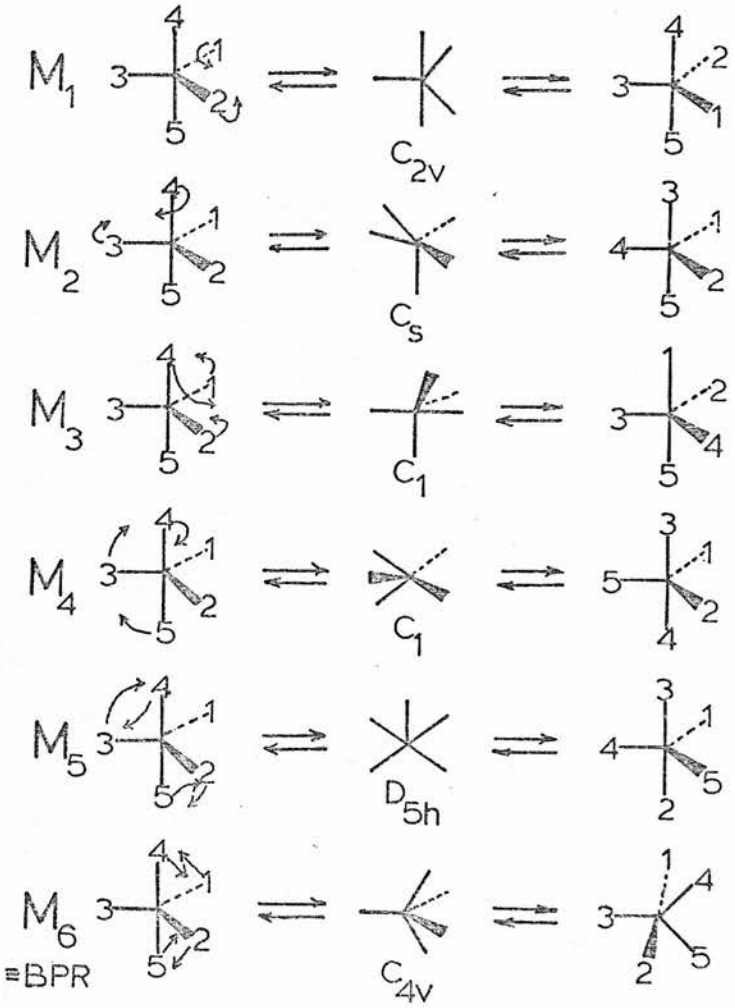
Muetterties[50] symbolised all conceivable modes and the symmetries of their transition states (scheme 7).

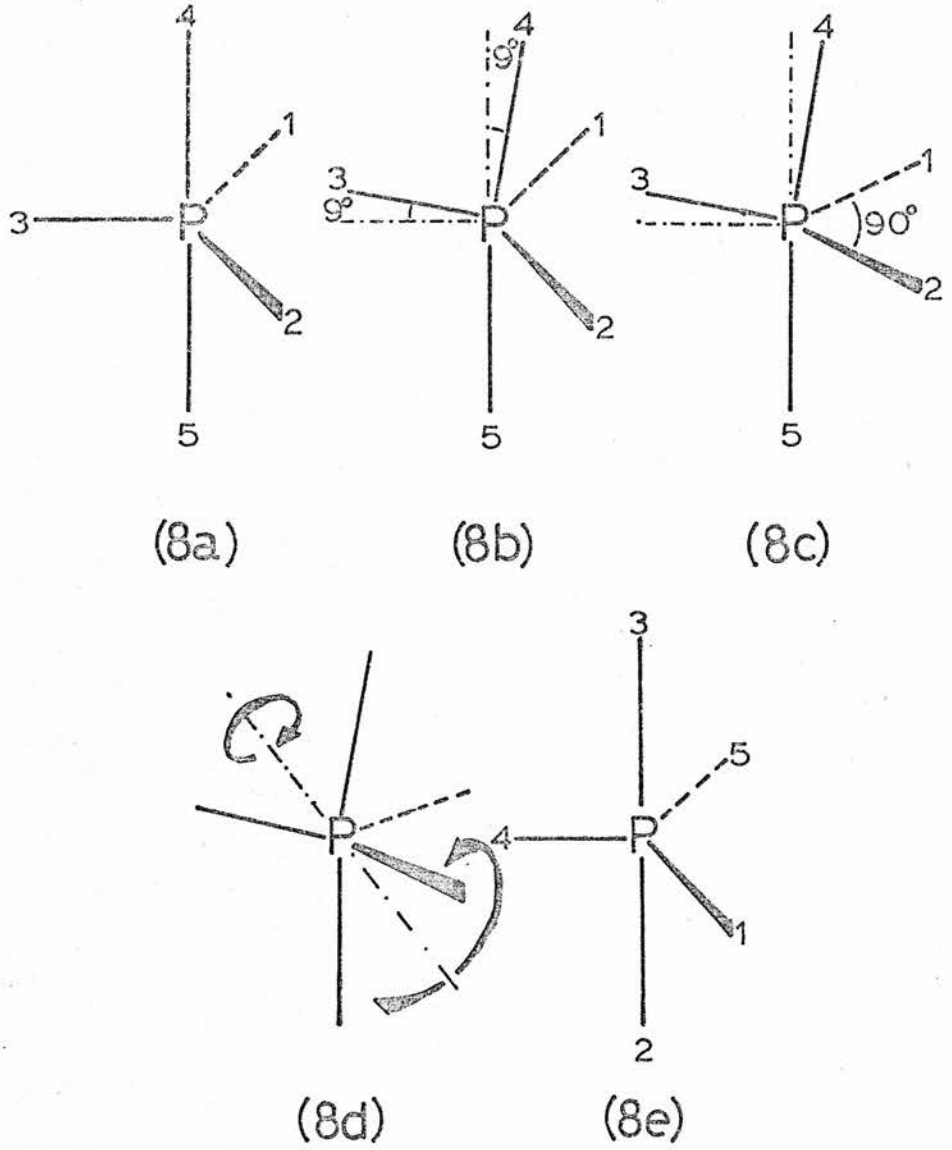
M_5 Involves a highly-crowded transition state and is therefore unlikely. Only M_6 (BPR) involves the simultaneous interchange of both pairs of apical and equatorial ligands. Whitesides and Mitchell,[51] having compared the variable temperature ^{31}P n.m.r. spectra of dimethylaminotetrafluorophosphorane with simulated spectra for the M_6 mode and modes involving the interchange of only one pair of apical and equatorial ligands, concluded that for this molecule, only an M_6 (BPR) mode was compatible. Few comparable studies have been made on other molecules: however, many qualitative observations of the variable-temperature n.m.r. behaviour of phosphoranes and studies invoking TBP intermediates support this view.

A second, physically possible process which was not considered by Muetterties,[50] but which is consistent with the Whitesides-Mitchell experiment,[51] was suggested by Ugi et al.[52] in 1970. This process involves a net internal rotation of a pair of apical and equatorial ligands relative to the remaining trio. The action is analogous to the motion of a turnstile, hence the name "turnstile rotation" (TR).

Turnstile rotation may be visualised as a combination of three independent motions, as detailed below in scheme 8. In reality, these motions begin simultaneously and occur synchronously. In diagram 8b the ligand pair (3 and 4) tilts through 9° away from the apical ligand (5) about an axis through P perpendicular to the plane 3P4. In diagram

Scheme 7





Scheme 8

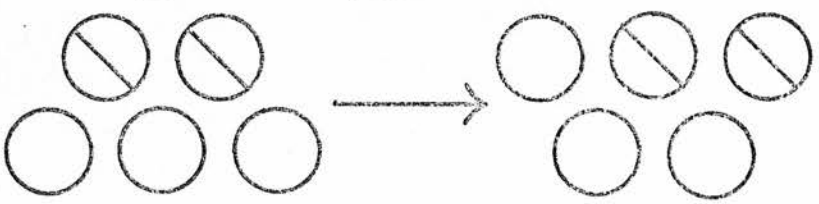
8c, the equatorial ligands (1 and 2) undergo a relative bending motion to reduce the diequatorial (1P2) angle from 120° to 90°. In diagram 8d, the pair (3,4) rotates through 30° relative to the opposite rotation of the trio (1,2,5) to reach the transition state known as the 30° TR barrier. The rotation then continues for a further 30° with the syn-

chronous reversal of the bending modes (diagrams 8b and 8c) to generate the new TBP (diagram 8e).

Once again, a sequence of five TR are required to generate the enantiomer of the initial TBP. However there are four possible TR for every BPR, making the former mechanism statistically more likely.[52]

Turnstile rotation has an additional flexibility which is not possessed by Berry pseudorotation. If the new TBP generated by the reverse bending mode after 60^{o} internal rotation is of high energy, it may become energetically favourable to continue the rotation for a further 60^{o} before the unbending motion occurs. Thus an unfavourable TBP can be by-passed. This process is known as a double turnstile rotation $(TR)^{2}$. Again, if this second TBP is also unfavourable, a 120^{o} rotation may occur before the generation of a new TBP by reverse bending; this constitutes the $(TR)^{3}$ process.

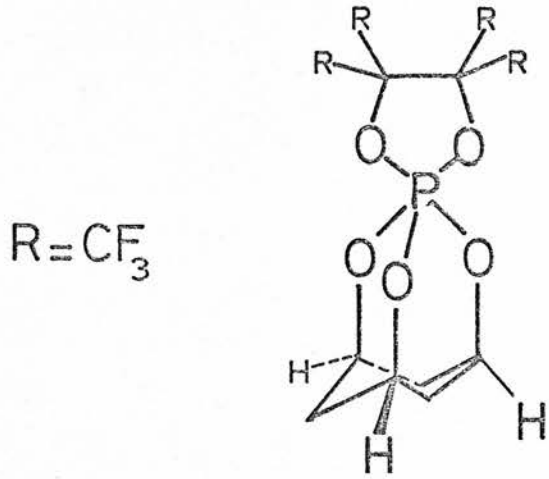
A second refinement has also been suggested.[52] A profile for the TR process, generated by CNDO/2 calculations on phosphorus pentafluoride,[8] revealed that a favourable pathway exists in the 0^{o} TR situation (scheme 8, diagram 8c above) by which the pair ligand (4) nearest to the trio ligands (1 and 2) can cross over to become a trio ligand. The apical ligand (5) becomes part of a new pair. Thus further internal rotation can occur without the generation of a new intermediate TBP from the 0^{o} TR situation. This process is known as a TR switch (scheme 9).



Scheme 9

Hoffmann et al.[53] compared the theoretical energetics of TR and BPR pathways for phosphorus pentafluoride and phosphorane, concluding that for these ideal systems the C_{4v} (BPR) barrier was more favourable than the C_s (TR) barrier. However, both mechanisms refer to ideal systems and in the presence of additional constraints the true transition state may be different. In non-ideal cases the true PI pathway may be considerably distorted.[53]

Ramirez et al. contend[52] that whilst either mechanism is acceptable for acyclic systems, only the TR process (in which the ring acts as a pair) is realistic when one or more small rings are present. These workers have extensively studied[54] the variable-temperature n.m.r. of the caged pentaoxyphosphorane (26). The ^{13}C n.m.r. spectrum at room

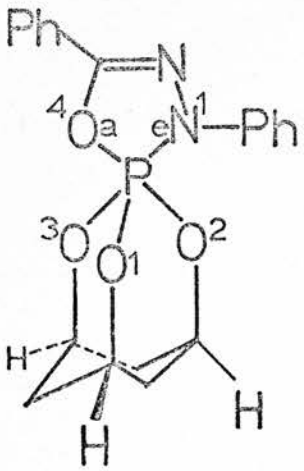


(26)

temperature shows a single resonance for all three methine carbons and another single resonance for the three methylene carbons. Similarly, the methine and methylene protons are individually equivalent in the p.m.r. spectrum even at -100°. The ^{19}F n.m.r. spectrum was examined to -160° without loss of equivalence between the twelve fluorine nuclei, although broadening at this temperature[55] confirmed that a PI process was in operation with a free-energy barrier of less than 5kcal mol^{-1}.

Calculations[52] have shown that the optimum geometry for phosphorus pentafluoride at the 30° TR barrier has a pair FPF angle of 95°; furthermore, the 9° tilt of the pair produces an F_aPF_a angle of 171°. In the caged polycyclic tetraoxyphosphorane (27), the molecular structure derived by X-ray crystallography[54] was revealed as being a highly-strained TBP with angles as shown. A regular TBP should have angles of 90° for the first four, and an angle of 180° for the last of this list.

$O_4PN_1 = 83.8°$
$O_3PO_1 = 106.3°$
$O_3PO_2 = 98.4°$
$O_1PO_2 = 97.1°$
$O_4PO_2 = 169.8°$

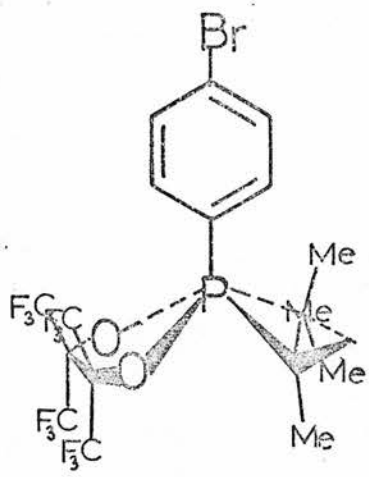


(27)

The deviations are clearly in the direction of the 30° TR barrier and it was suggested[54] that this favourable distortion was the origin of the extraordinarily facile PI observed for (26), thus lending support to the TR concept.

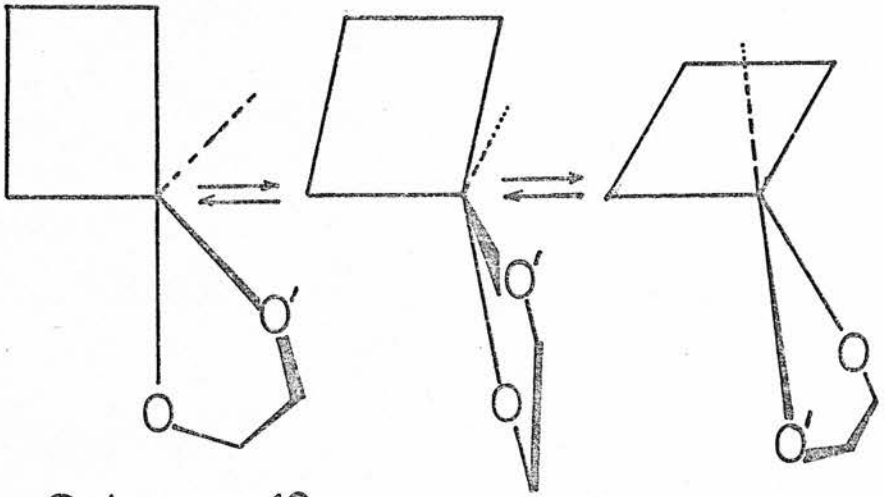
Trippett[7] recently reported the first known example of a penta-coordinate phosphorus compound with square-pyramidal geometry. The spirocyclic adduct (28) obtained by the reaction of hexafluoroacetone with a 1-p-bromophenylphosphetane was found, by X-ray crystallography, to contain both rings in basal positions with an apical p-bromophenyl group.

Although this molecule possesses the transition state geometry of the BPR process, the observation[56] that the complete equivalence of all



(28)

twelve fluorine atoms does not occur until ca. +160° does not invalidate the BPR concept as this structure represents the transition state between TBP structures having both rings apical-equatorial. The process which provides equivalence of all fluorines requires a PI route via a TBP with a diequatorial phosphetane ring (scheme 10). The transition state for this process has an apical-basal phosphetane ring. Indeed

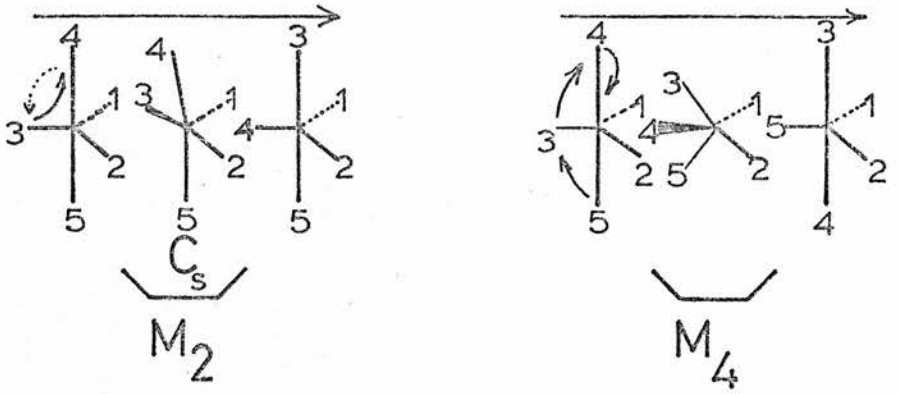


Scheme 10

the observation[56] that there is a facile PI process giving equivalence to two pairs of CF_3 groups may be a direct consequence of the favourable C_{4v} approximated ground-state. The direct observation of this geometry

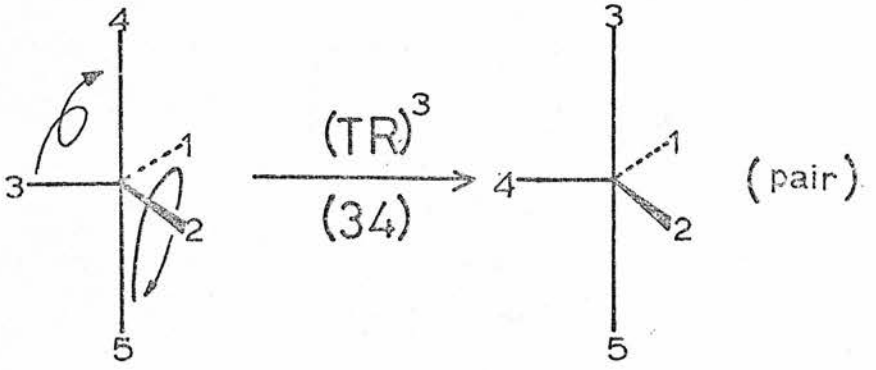
negates the view[52] that TR is the only process applicable to cyclic systems.

A recent report by Cowley et al.[57] on the complete line-shape analysis of the p.m.r. spectra of trifluorodihydrophosphorane (F_3PH_2) and trifluoromethyltetrahydrophosphorane should be mentioned as a cautionary note. These workers discovered that the PI of these molecules in the slow exchange region were only satisfied by Musher's[58] M_2 or M_4 modes which in Muetterties' symbolism[50] are those in scheme 11.



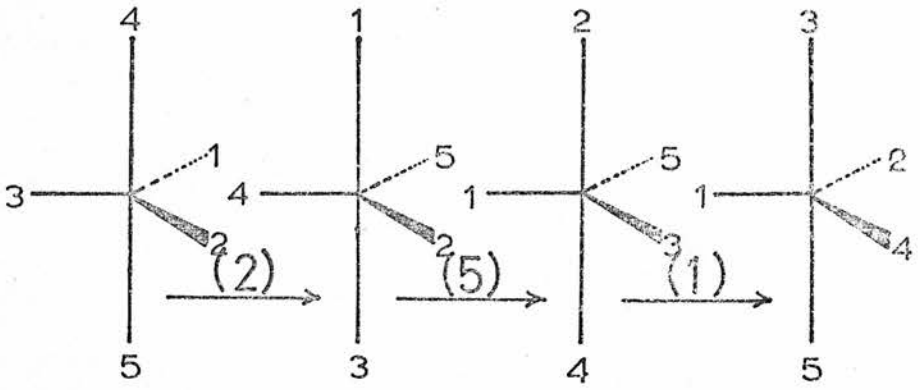
Scheme 11

The result of the M_2 mode is equivalent to either a $(TR)^3$ (scheme 12)



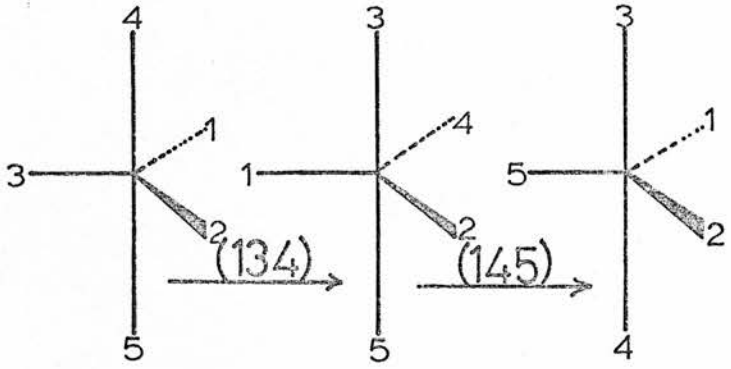
Scheme 12

or a sequence of three BPR (scheme 13). The result of the M_4 mode is



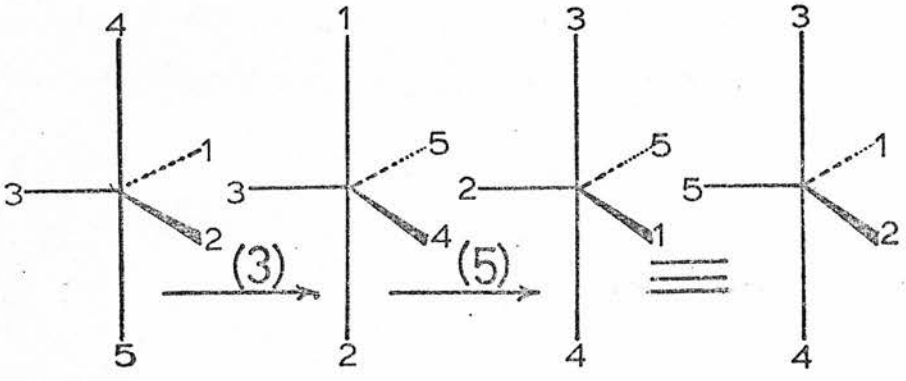
Scheme 13 (pivot)

equivalent to two $(TR)^2$ (scheme 14),



Scheme 14 (trio)

or two BPR processes (scheme 15).



Scheme 15 (pivot)

Both of these multiple routes would be statistically less likely

than a single process. Thus, if in certain cases the M_2 or M_4 modes are allowed, some mechanistic schemes may require re-examination.

(b) Examples of PI

The ease with which isomeric forms of a given phosphorane can interconvert depends upon the energy of the transition states in the process. Little is known about these barriers in the majority of cases. However, calculations[53] on PF_5 and PH_5 have indicated that (in BPR terms) lower energy transition states will be found when the least electronegative and better π-donor groups occupy the apical positions of the square-pyramid. Similarly, more bulky groups will occupy apical rather than basal sites.

In the absence of information about the transition state, the stabilities of the individual TBP in a PI itinerary are important. These intermediate TBP may be true intermediates or, as suggested by Mislow,[59] merely transition states.

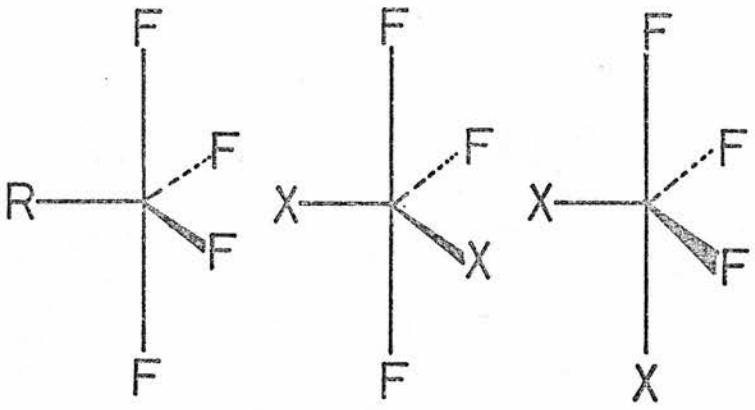
Thus, the rules outlined in section 3 above, for the stability of phosphoranes, also obtain for ease of PI.

Electronic site preferences (electronegativity and back-bonding) are known as stereoelectronic effects, whilst ring and bulk effects are known as steric preferences. Energies associated with these effects are referred to as stereoelectronic, or steric, strains.

(i) Electronic effects.

Phosphoranes which contain four identical ligands are capable of facile interchange of these ligands between apical and equatorial sites without placing the fifth ligand in an unfavourable, apical position. Thus, Schmutzler et al.[60] observed just one type of fluorine atom in the

^{19}F n.m.r. spectra of tetrafluorophosphoranes (29) at temperatures down to -120°.[61]



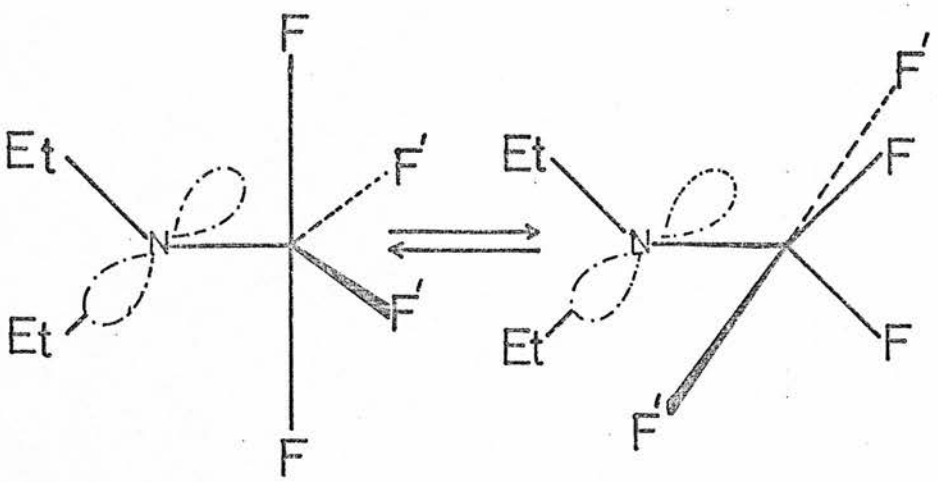
(29) (30) (31)

In contrast, trifluorophosphoranes (30) can only interchange fluorine environments by PI via high energy TBPs such as (31), in which an electronegative group and a more electropositive group are unfavourably exchanged. Thus, below +25°, the ^{19}F n.m.r. spectrum of (30) (where X = Cl,CF_3) indicates two distinct fluorine environments[52] as would be expected for (30) undergoing a PI which was slow on the n.m.r. time-scale.

In the system R_3PF_2, both fluorines can occupy the preferred apical positions without PI, and the spectrum thus showed no temperature dependence.[60]

In contrast, it was observed[61] that, whereas (29) (where R = Et_2N) showed fluorine equivalence at +25°, the ^{19}F n.m.r. signal broadened on cooling and separated into two sharp doublets at -85°. A similar result was obtained for (29) (where R = SMe,SEt,SPh).[62] The increased barrier to PI compared with other RPF_4 molecules (q.v.) is believed[62] to be the result of restricted rotation about the P—N or P—S bonds due to pd-π back bonding from the ligand to phosphorus. The nitrogen or sulphur

atom has only one donor orbital which will preferentially lie in the equatorial plane.[53] Thus (in the BPR formulation with the heteroatom as the pivot), the BPR causes rotation of the TBP through 90°, converting the originally equatorial plane into an apical plane. The heteroatom p-orbital orientation thus becomes unfavourable and exerts a drag upon the "rotation" about the pivot bond (scheme 16). In this way, a ligand may exert a barrier to PI without altering its skeletal position.



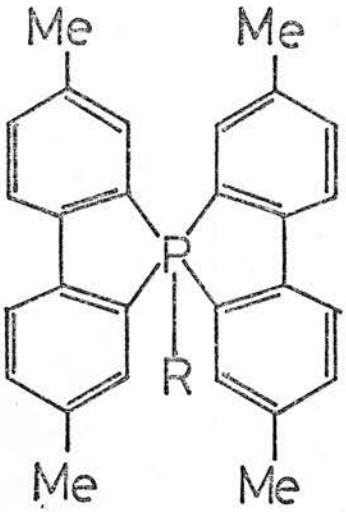
Scheme 16

(ii) Steric effects

In the absence of electronic differences between ligands, steric effects predominate and act in two ways. PI may be restricted by ligand interactions during the TBP interconversion, and a TBP carrying a bulky substituent in the apical position will be destabilised relative to the TBP in which this ligand occupies an equatorial position. This latter effect is the consequence of apical ligands being separated by 90° from three ligands, whilst the equatorial ligands are separated by 90° from only two ligands.[22] The longer 120° interactions are negligible.[22]

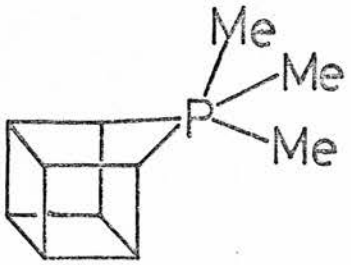
Thus, the relatively unhindered phosphorus pentafluoride shows fluorine equivalence to at least -197°,[63] but a series of substituted

bis-biphenylene phosphoranes (32) show methyl-averaged and -unaveraged spectra at room temperature depending upon the bulk of the ligand R.[64] When R = Ph, the methyl groups give rise to one sharp singlet, whereas when R = 1-naphthyl, two sharp methyl singlets appear.



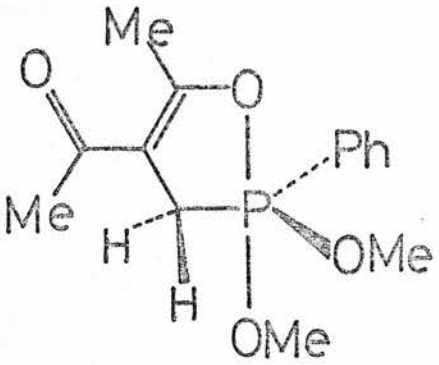
(32)

The lowest barrier so far measured for phosphoranes carrying five identical atoms was ΔG^{*} = ca. 5kcal mol^{-1} for trimethylhomocubylphosphorane (33) in which the methyl resonance broadened below -128°.[65]

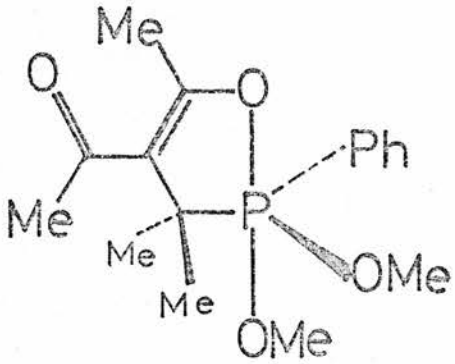


(33)

Gorenstein[66] measured the free-energy barrier to PI in (34) and (35), and found an increase from ca. 10kcal mol^{-1} to ca. 16 kcal mol^{-1} with the introduction of the gem-dimethyl group. Models showed no great increase of steric interaction and it was surmised[66] that solvent steric interactions might be important.



(34)

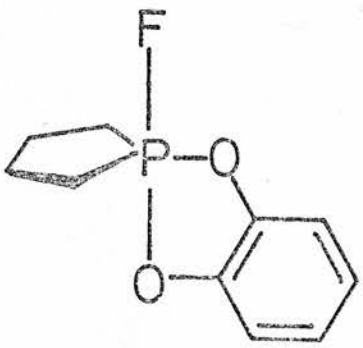


(35)

(iii) Ring-strain effects

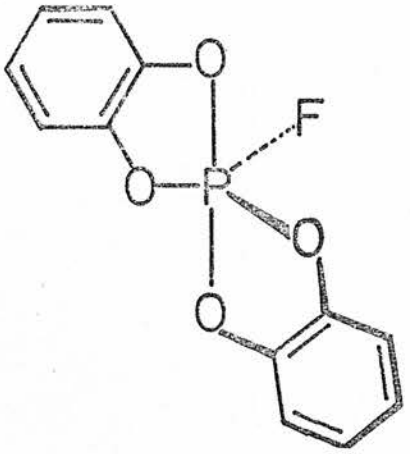
The introduction of four- and five-membered rings into a phosphorane has a highly restricting influence on the available PI processes. Small rings preferentially occupy an apical-equatorial distribution[8] and high temperatures, or strong counterbalancing forces, are required to force such rings into a diequatorial distribution. Small and medium rings are incapable of occupying diapical sites.

If a strongly electronegative group is present in the molecule, the energy required to place this ligand in an equatorial site may outweigh the steric strain in placing the ring in a diequatorial position. At room temperature, the ^{19}F n.m.r. chemical shift (δ_F = 21.65 ppm) and low coupling constant (J_{PF} = 829.2 Hz) indicate[67] that the spirocyclic phosphorane (36) has the stereochemistry shown.



(36)

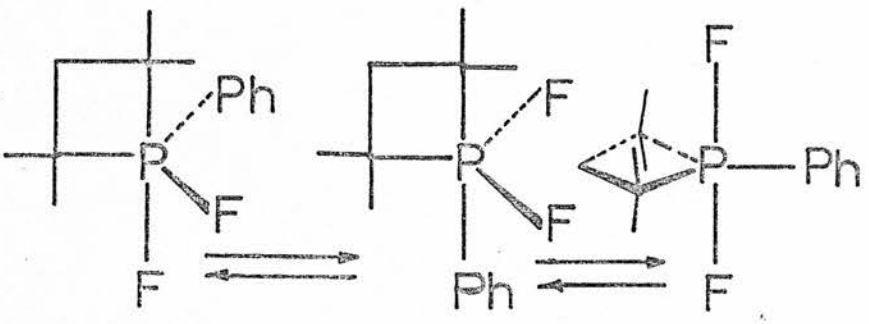
However, when the ring termini are also fairly electronegative, diequatorial ring-placement is additionally destabilised. The spirocyclic phosphorane (37) has an equatorial fluorine atom[67] (δ_F = 70.4 ppm; J_{P-F} = 1018 Hz). This was the first known example of the most



(37)

electronegative atom occupying an equatorial site in the ground state TBP.

At room temperature, the p.m.r. spectrum of (38) in scheme 17 shows four equivalent methyl groups and the ^{31}P n.m.r. spectrum contains



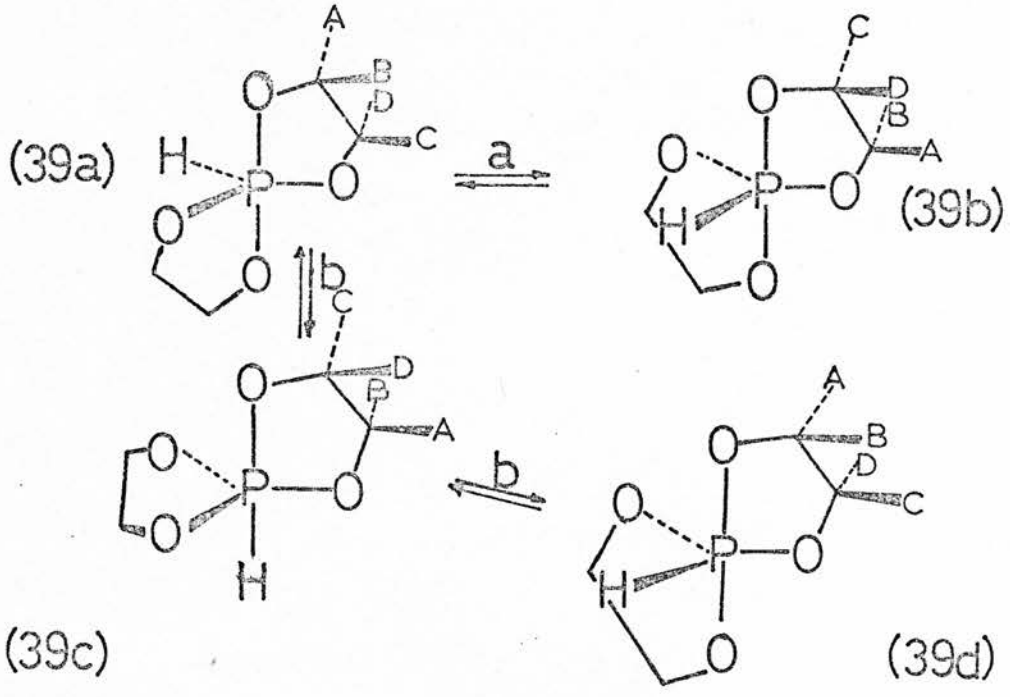
(38a) (38b) (38c)

Scheme 17

one broad absorption (40 ppm width). The ^{19}F n.m.r. spectrum shows one broad absorption at +50 ppm (relative to CCl_3F). At ca. -100°, the ^{19}F, ^{31}P and ^{1}H n.m.r. spectra are uniquely satisfied if there is a

mixture of two isomers (38a) and (38c), in a ratio of 2.4:1, with (38a) undergoing a rapid PI process in which the ring remains in apical-equatorial distributions and the phenyl group remains amongst the equatorial sites, thus making cis pairs of phosphetane methyl substituents equivalent. At room temperature the interconversion of (38a) and (38c) is fast and must proceed via (38b).[68] It is interesting that (38b) should be less stable than (38c).

Houalla and Wolf[69] observed the variable-temperature n.m.r. behaviour of the spirocyclic phosphorane (39) in scheme 18. Process (a) occurs rapidly at -70° producing the result: A ≡ D and B ≡ C. In order



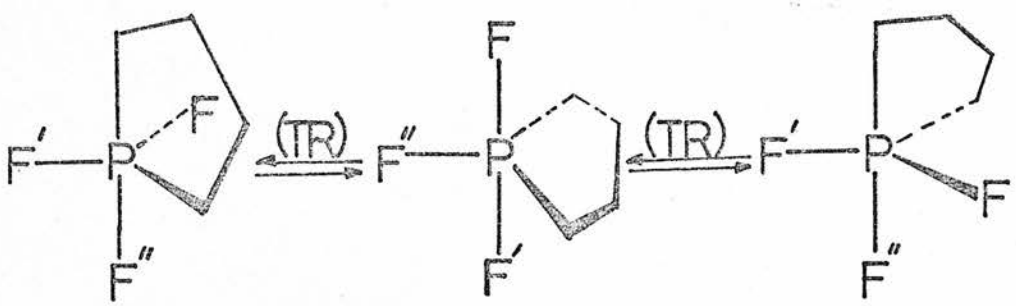
Scheme 18

A=B=C=D;=Me

to make A and B, as well as C and D, equivalent, process (b) is required which proceeds via the high-energy isomer (39c). This process became fast above +37° (ΔG^{*} = 15.6 kcal mol^{-1}). Within the TR concept,[8] interconversion of (39b) and (39d) might proceed in one step via a $(TR)^2$

mechanism, effectively by-passing (39c).

Six-membered rings have little preference between apical-equatorial and diequatorial placement. Thus, the five-membered cyclic phosphorane (40) undergoes rapid PI between all possible isomers of (40): e.g. (40a), (40b) and (40c) in scheme 19 at room temperature. The apical-equatorial

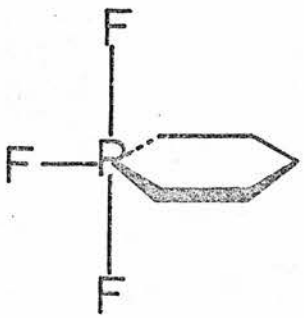


(40a) (40b) (40c)

Scheme 19

ring preference counterbalances the diapical fluorine electronegativity preference. Only at -70° does the structure "freeze" into form (40b).[60]

In contrast,[60] the six-membered ring analogue (41) is frozen into a single form at room temperature, F—P coupling constants indicating

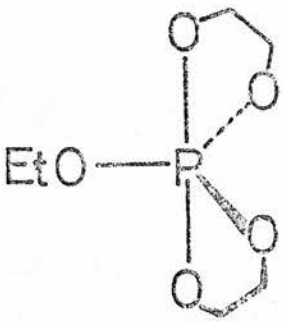


(41)

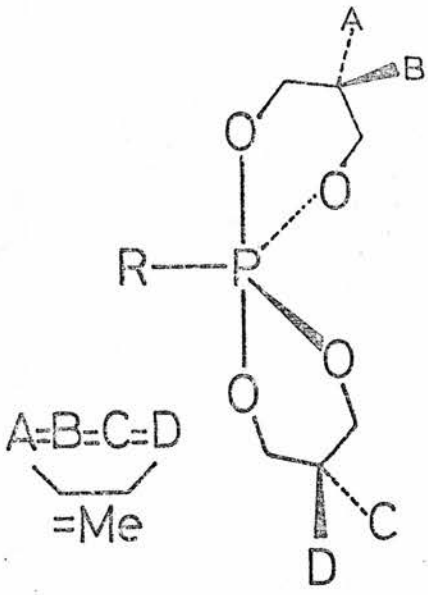
diapical fluorine atoms. Diequatorial ring strain is therefore comparatively small.

Denney et al.[20] observed the p.m.r. spectrum of the spirocyclic

phosphoranes (42) and (43) at various temperatures. The multiplet due to the ring methylene groups of (42) became a simple doublet at +172°,



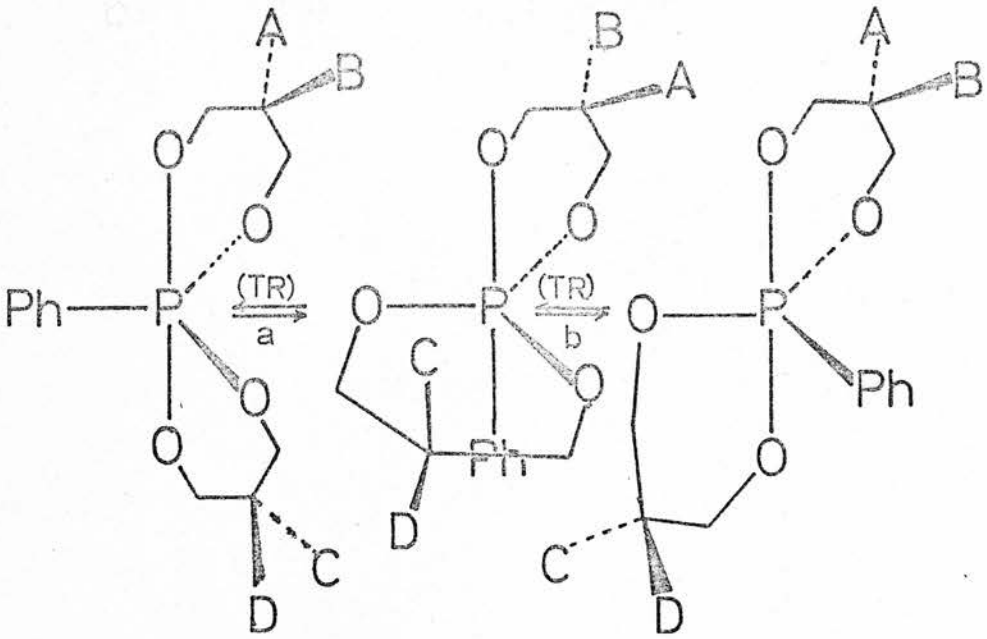
(42)



(43)a: R=EtO

b: R=Ph

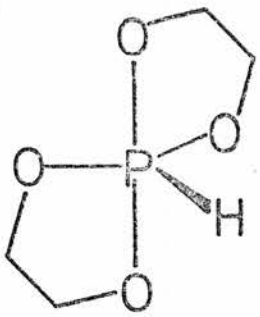
indicating that all methylene protons were equivalent. This requires a sequence of PI processes via a TBP with a diequatorial five-membered ring ($\triangle G^* \sim +22$ kcal mol^{-1}).[75] In contrast, (43a) showed one singlet due to the complete equivalence of all ring methyl groups even at -65°. The ring methyl singlet of (43b) split into two singlets at -65°, giving $\triangle G^* = 12$ kcal mol^{-1} for the process in scheme 20, which places the phenyl group unfavourably apical. The sequence of (a + b) makes A ≡ B; a further sequence with the second ring diequatorial is required to complete the equivalence. Thus diequatorial placement of a five-membered ring requires a considerable expenditure of energy, whilst the diequatorial six-membered ring is readily achieved.



Scheme 20

It is unfortunate that the coalescence temperature at which the PI of tetraethoxyphenylphosphorane becomes slow has not yet been reported. This information would permit an estimation of the effect of six-membered rings on the PI barrier. It has been reported[40] that the ethoxy groups of tetraethoxyphenylphosphorane remain equivalent at -60°.

An interesting comparison can be made between the tendency of a proton and an ethoxy group to occupy an apical position by comparing the coalescence temperatures of (42) and (39) (q.v.). The analogue of (39), which contains four methyl groups in both rings, had a free energy of activation for diequatorial ring-placement which was 2.8 kcal mol^{-1} higher than for (39).[69] Thus from $\Delta G^* = 15.6$ kcal mol^{-1} for (39),[69] one obtains a calculated energy barrier of ca. 12.8 kcal mol^{-1} for (44). The high-energy processes for (42) and (44) differ only in the apical placement of the exocyclic group. Thus a proton is 9.2 kcal mol^{-1} more



(44)

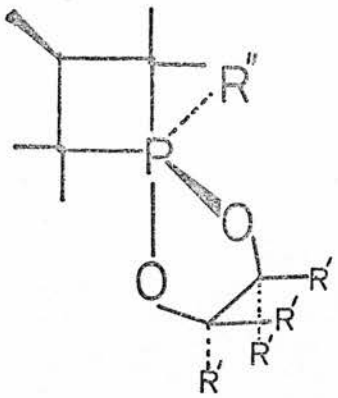
apicophilic (v. infra)[8] than an ethoxy group. Clearly, this is not an electronegativity effect. It may be a combination of the low steric bulk of a proton and the back-bonding ability of the alkoxyl oxygen. A similar observation was made by Trippett et al.[71] (v. infra).

(c) The apicophilicity scale

The three factors which have been discussed above — electronegativity, π-donor ability and steric effects of a given ligand — combine to produce the apicophilicity[8] or apicophobicity[8] of that ligand. A highly apicophilic ligand is one which has a great tendency to occupy the apical sites of a TBP. An apicophilic ligand would typically possess high electronegativity, poor π-donor ability and low bulk. The combination of these three preferences is known as the "modified" polarity rule,[22] in contrast to the "generalised" polarity rule,[22] which did not consider the effect of pd-π back bonding.

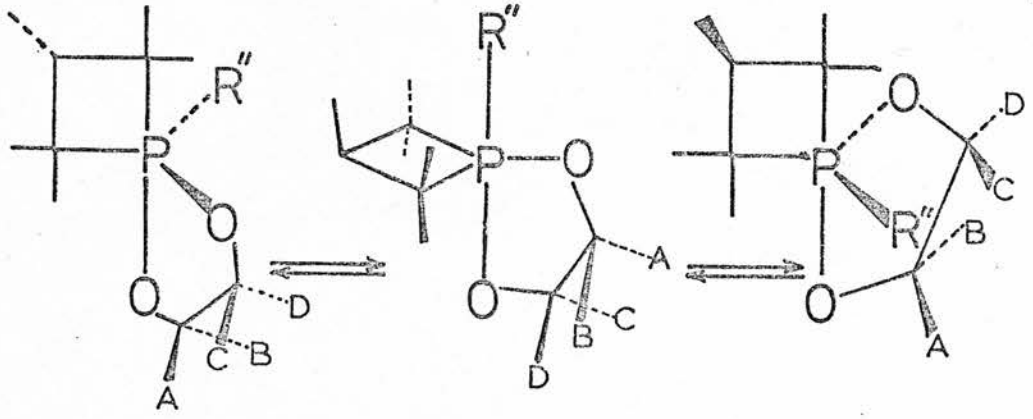
Trippett et al. studied the variable temperature ^{19}F n.m.r. spectrum of (45).[56,71]. The free-energy barrier as obtained from the coalescence of the gem-trifluoromethyl groups (scheme 21) A,B and C,D is composed of the energy required to place the phosphetane ring diequatorially and the energy required to move R" from an equatorial to an apical position. (A,C and B,D pairs are already equivalent due to

$R' = CF_3$



(45)

a low-energy process.). Thus, comparison of the difference in the free-energy barrier for a series of (45), against the nature of R", will yield



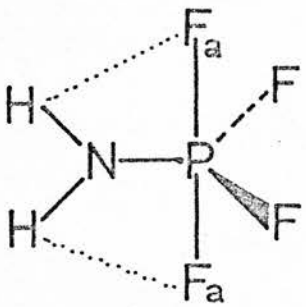
Scheme 21

an order of relative apicophilicities. The order obtained [71] was: $H > OCH(CF_3)_2 \sim PhO > NMe_2 > Me > Pr^i > CH{=}CMe_2 > Ph$. Comparison of this sequence with the relative electronegativities: $OCH(CF_3)_2 > OPh > Ph > NMe_2 > CH{=}CMe_2 > Pr^i > Me > H$, indicates that the electronegativity scale is not being followed. In particular, it was found [71] that the dimethylamino group should be very much more apicophilic than the comparably-sized isopropyl group, and that the apicophilicity difference between phenoxy and phenyl was much larger than that between ethoxy and phenyl, assessed from previous work.[40,70] Both the phenyl group and

the dimethylamino group have reduced apicophilicities due to their π-donor abilities.

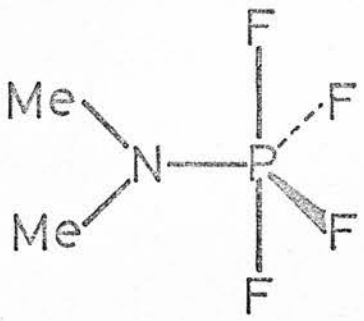
In a separate study, Trippett et al.[73] also found a low apicophilicity for the thioethoxy group (EtS) and suggested that, whilst preferential occupation of equatorial sites was due in part to pd-π effects, PI was additionally hindered by restricted rotation about the P—S bond. This has already been mentioned in section 4(b)(i) above, with reference to work by Schmutzler.[62] A controversy exists as to whether these two pd-π factors are separable, a view which is held by Muetterties et al.[74] but opposed by Trippett.[75]

An additional, unconventional constraint on PI was observed by Cowley and Schweiger[76] when these authors were investigating the geometry of aminotetrafluorophosphorane (46). The $^{15}N—^{1}H$ coupling constant suggested that the nitrogen atom was sp^2 hybridised. Furthermore,



(46)

it was observed that the amino protons were symmetrically arranged with respect to the fluorine atoms. This suggests the structure shown in diagram (46). The amino group atoms, the apical fluorines and the phosphorus atom are all coplanar. This arrangement is as expected[53] for efficient pd-π overlap from nitrogen to phosphorus. Dimethylaminotetrafluorophosphorane (47) has a free-energy barrier to PI of ca. 9 kcal mol^{-1};[51] in contrast, the same barrier for (46) is greater than



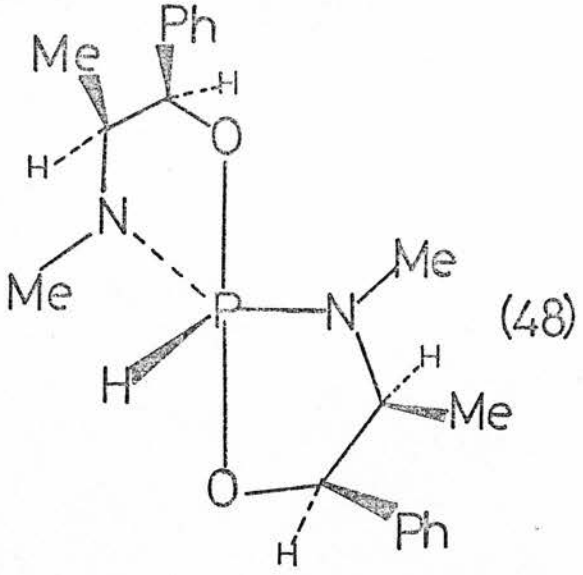
(47)

15 kcal mol^{-1}. It was concluded that the coplanar arrangement of amino protons and apical fluorines allowed maximum H.....F hydrogen bonding. In BPR terms the bending of the P—F_a bond away from the amino group (pivot) would clearly be resisted by this intramolecular bonding.

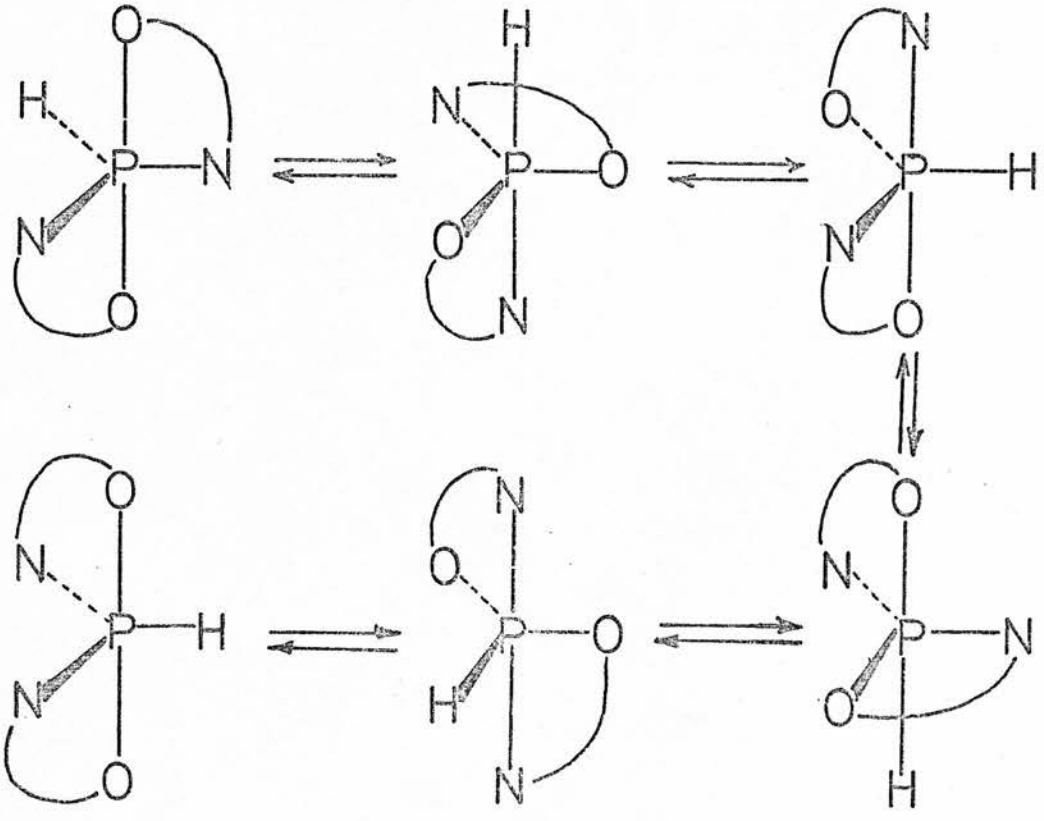
In contrast to Trippett's apicophilicity conclusions,[71] Cavell et al.,[77] studying a series of bis- and tris-trifluoromethylphosphorane derivatives, obtained the following order of apicophilicities: F, Cl> CF_3> $OSiMe_3$, OMe, SMe, NMe_2, H, Me. The chlorine and trifluoromethyl groups are in an inverse order to that which would be expected from both electronegativity and π-bonding considerations. The total order is, however, in complete agreement with the inductive scale.[77]

(d) Methods for studying PI

The major tool in the study of PI processes is n.m.r. spectroscopy, where variable-temperature studies reveal both the nature and the free-energy barriers of the processes. Recently, polarimetry has provided[73] thermodynamic parameters for the PI in scheme 22 by following the rate of racemisation of an optically pure sample of (48). Scheme 22 details the process which is involved, in terms of the TR formalism. Values of $\Delta G^* = 23.8$ kcal mol^{-1} and $\Delta S^* = -3$ eu were obtained. The former value reflects, once more, the energetic unfavourability of placing a



(48)



Scheme 22

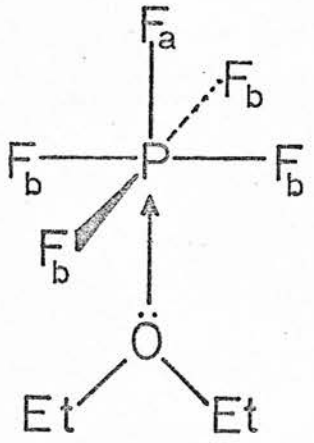
five-membered ring diequatorially and the latter value is consistent with an intramolecular PI process.

(e) Irregular processes

The PI processes discussed above involve deformations without bond-breaking or alteration of the coordination number at phosphorus. These processes are known as regular processes.

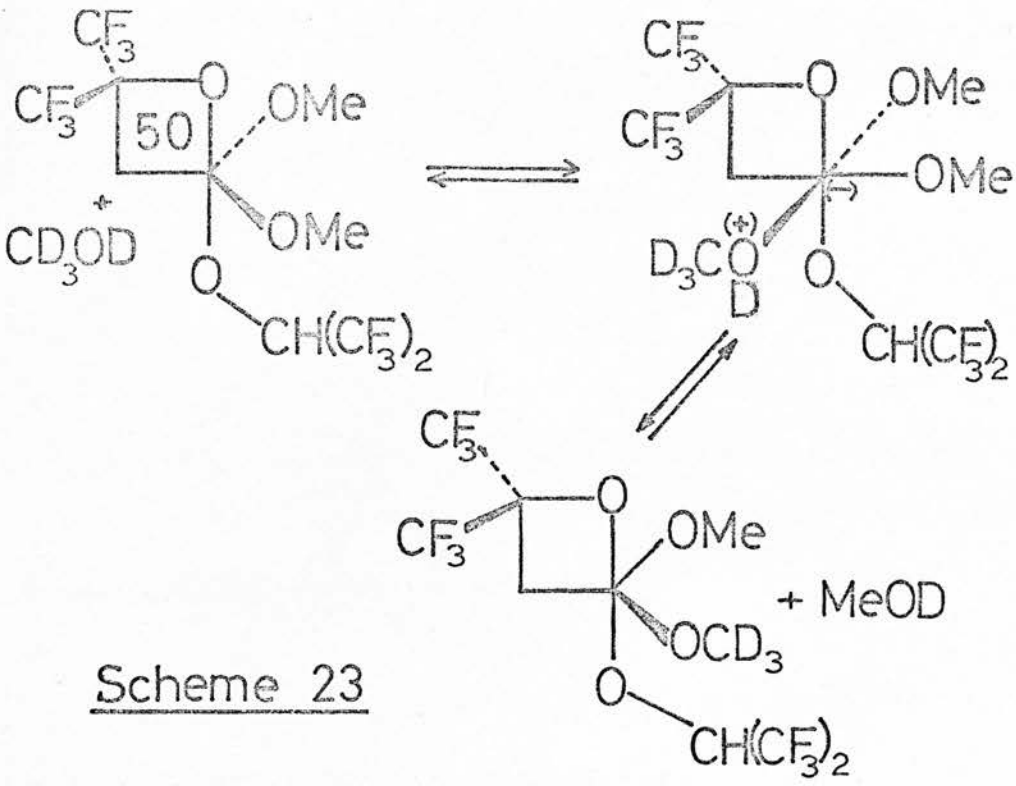
Irregular processes exist and occur in two ways: (i) via a hexa-coordinate transition state or intermediate, usually by base-catalysed reaction; and (ii) via a tetracoordinate intermediate which may be by acid-catalysed or simply thermal,[22] reaction.

Gibson et al.[79] observed that the ^{19}F n.m.r. spectrum of phosphorus pentafluoride consisted of a pair of doublets and a pair of quintets when the solution contained excess diethyl ether. This was interpreted as being evidence for the octahedral complex (49). The ligands lose their apical and equatorial distinction in species such as (49), thus a PI process could result.



(49)

Ramirez et al.[80] have observed the facile, base-catalysed substitution of a methoxy group of (50) by deuterated methanol. Similar alkoxy group exchange could cause PI (scheme 23). This example is particularly

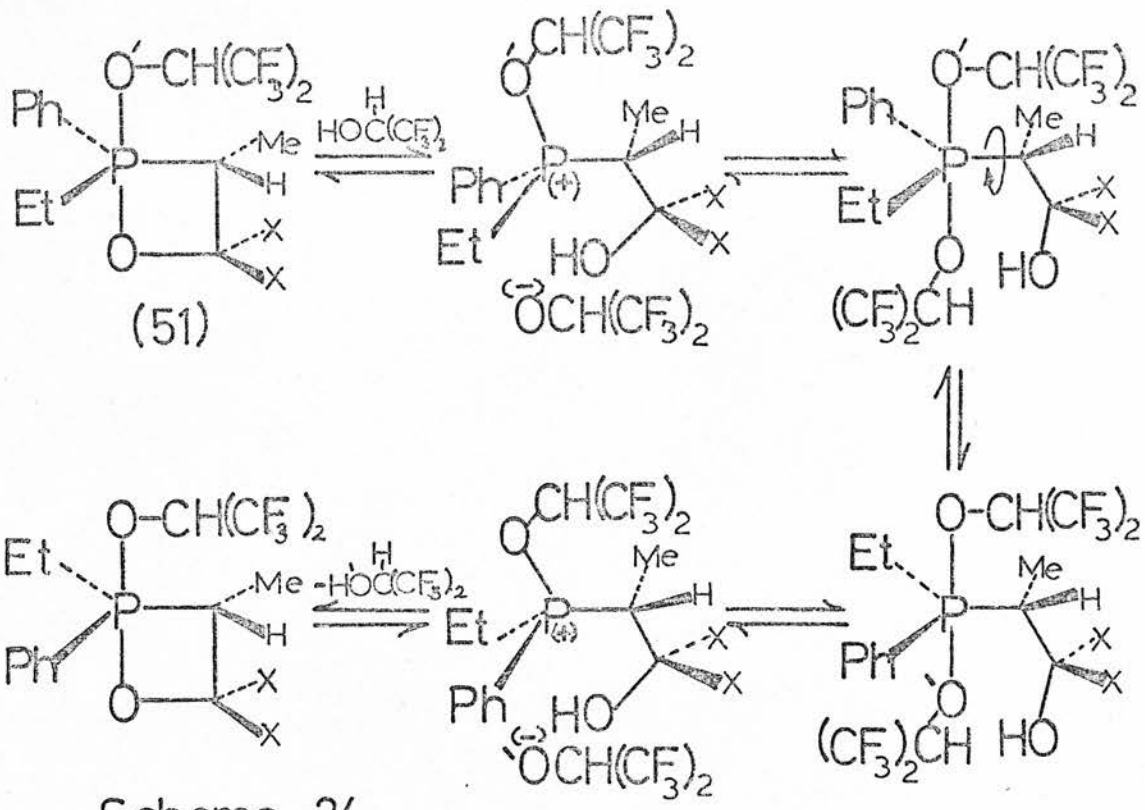


Scheme 23

significant as the rate of exchange by the irregular process exceeded that of the regular process placing the hexafluoroisopropoxy group equatorially.

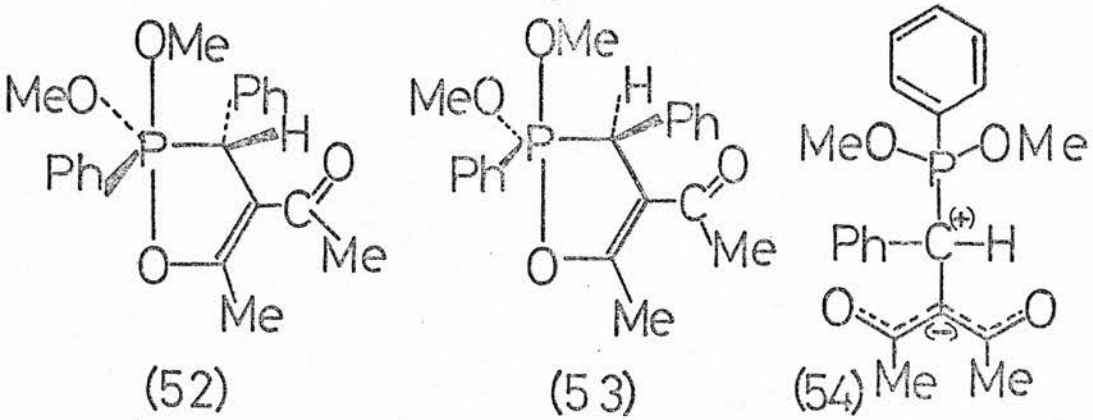
Acid-catalysis leads to the isomerisation of (51) in scheme 24.[81]

Thermal isomerisation has been observed[82] for the oxyphosphorane isomers (52) and (53). Below -20° each isomer was "frozen". Above 0°, positional exchange of the methoxy groups was noticed, but there was no isomerisation between (52) and (53). Above 50°, isomerisation was observed due to a regular process via a TBP with an apical phenyl group. Above 70°, the ring and acetyl methyl group resonances broadened and



Scheme 24

then coalesced at +125°, sharpening to a singlet at +151°. These changes were reversible and indicated a rapid equilibrium between (52), (53) and the acyclic dipolar species (54).



Many other irregular processes exist, but the distinction between such processes and a regular process can usually be made by varying the conditions. For example, a solvent-change should not greatly affect a regular process but will strongly affect an irregular, ionisation

process.[41] Furthermore, a bond-breaking process should involve loss of coupling to phosphorus.

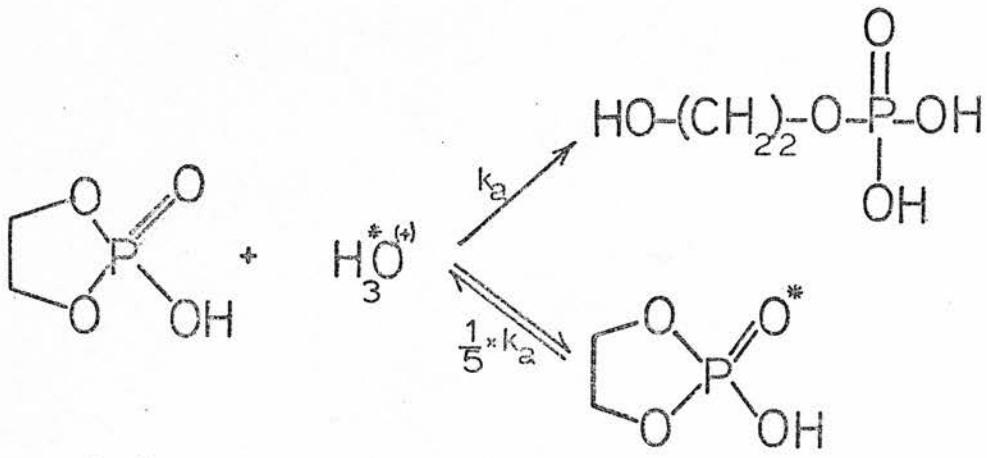
5. Oxyphosphoranes as Reactive Intermediates

(a) General background

Many of the reactions of P(III) and tetracoordinate P(V) compounds with nucleophiles are believed to proceed through the intermediacy of TBP structures. The point of attack depends upon the strength of the nucleophile, the power of the leaving group, the balance between stereoelectronic and steric effects in the intermediate and, to a lesser extent, upon the steric interaction between the nucleophile and the substrate. The product distribution and stereospecificity depend upon the relative rates of available PI processes and the rate of breakdown of the intermediate. Some doubt can still be supported (e.g.[59]) as to the point of departure of the leaving group. Apical departure is the generally-held notion and is favoured by the observation that apical bonds are weaker and longer[83] than the comparable equatorial bonds.[10,72] In principle, the nucleophile could attack either the faces or the edges of the tetrahedral substrate. Edge attack, which introduces the nucleophile into an equatorial position of the intermediate, has been considered by Westheimer *et al.*[84] and by Cram *et al.*,[85] amongst others. CNDO/2 computations on the interaction of fluoride ion with phosphorus oxyfluoride (POF_3)[81] clearly favoured face attack. This was attributed[81] to the diminished ligand interaction encountered by the nucleophile, before a reasonable bonding distance could be achieved, compared with edge attack. Most experimental observations can best be rationalised on the apical entry-departure scheme; consequently, this is the most widely-held view.

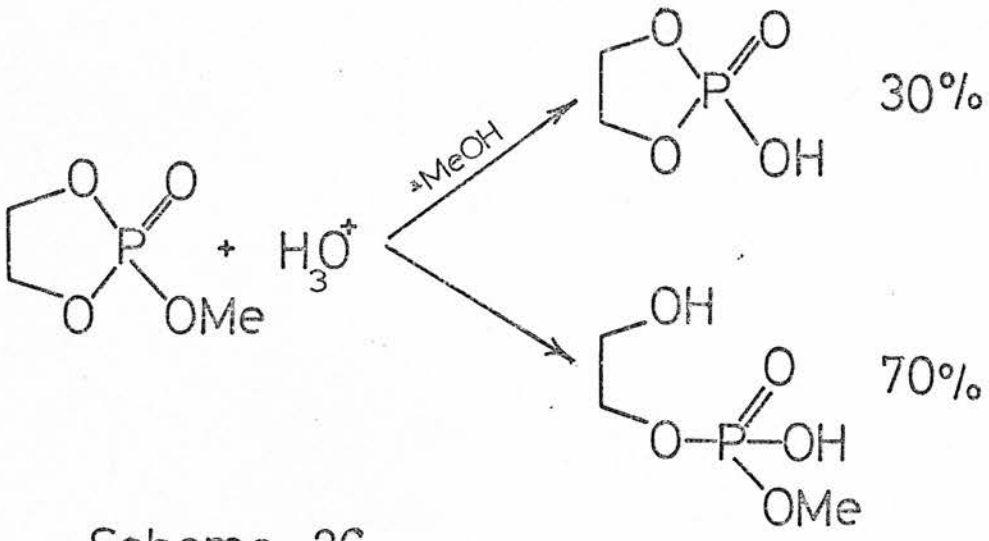
Nevertheless, several authors including Trippett et al.[86] and Ezzel et al.[87] have presented experimental justification for equatorial departure and Mislow[59] has made cautionary notes. The former[86] experimental evidence has a more reasonable explanation in terms of apical entry and departure, in view of revised opinions as to the apicophilicity of the oxygen anion (v. infra).

Phosphorus TBP intermediates were first suggested by McEwan et al.[88] to explain the stereospecific inversion observed in the basic hydrolysis of optically active methylethylphenylbenzylphosphonium iodide, which gave optically active methylethylphenylphosphine oxide. Westheimer et al.,[84] having observed that the acidic hydrolysis of the P—O bond in ethylene phosphate was 10^8 times more rapid than the comparable hydrolysis of dimethyl phosphate, attributed this acceleration to the release of ring strain in forming acyclic products from the strained phosphate. However, it was also observed[84] that this hydrolysis was accompanied by a rapid exchange of oxygen atoms between the substrate and labelled water (scheme 25). Furthermore, the similarly-accelerated acidic hydrolysis of methyl ethylene phosphate was accompanied by ca. 30% of exocyclic



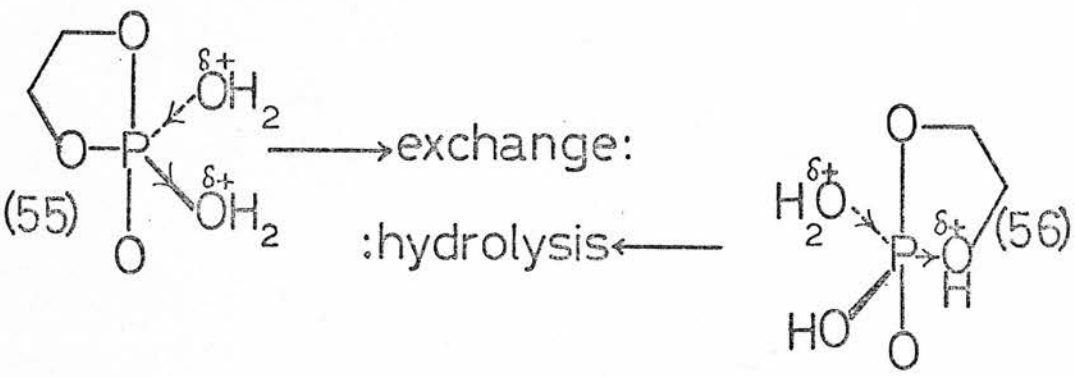
Scheme 25

cleavage of methanol[29] (scheme 26). The exchange and exocyclic cleavage processes occurred to similar extents and were therefore considered to represent analogous processes. Westheimer et al.[84] unified



Scheme 26

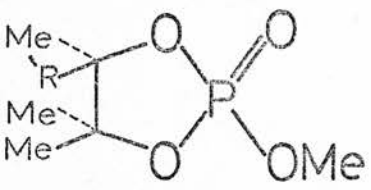
these results by suggesting an edge attack and equatorial departure scheme, in which all these processes occurred via similar TBP transition states (55) and (56). The accelerated rates were therefore due to



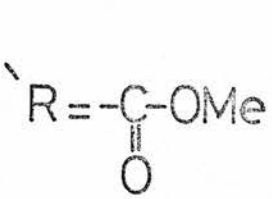
the ring strain released by placing the ring in an apical-equatorial distribution, rather than to strain released in endocyclic cleavage.

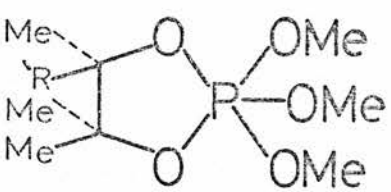
Ramirez et al.[89] observed that the hydrolysis of both the cyclic triester (57) and the pentaoxyphosphorane (58) were extremely rapid and proceeded with predominant ring-retention. A cyclic oxyphosphorane

intermediate (59) was suggested for the latter hydrolysis and, by



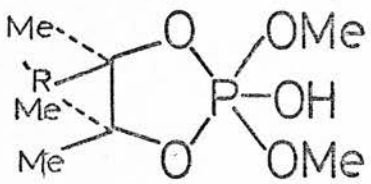
(57)





(58)

analogy, a similar pentacoordinate intermediate seemed reasonable for the former.

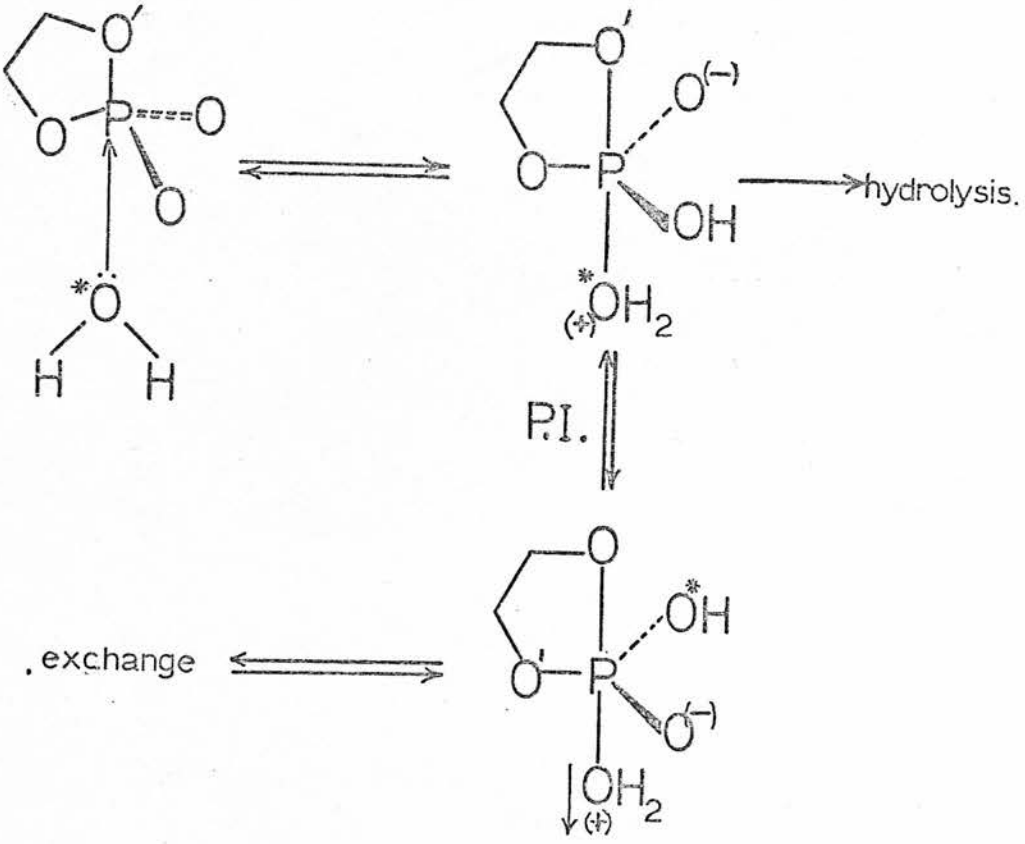


(59)

Westheimer[29] subsequently agreed that a common TBP intermediate, formed from face attack by water, could explain his observations if PI processes were invoked to rearrange this intermediate to allow apical departure of the relevant ligand (scheme 27: see page 48).

(b) Nucleophilic attack on cyclic tetracoordinate phosphorus species

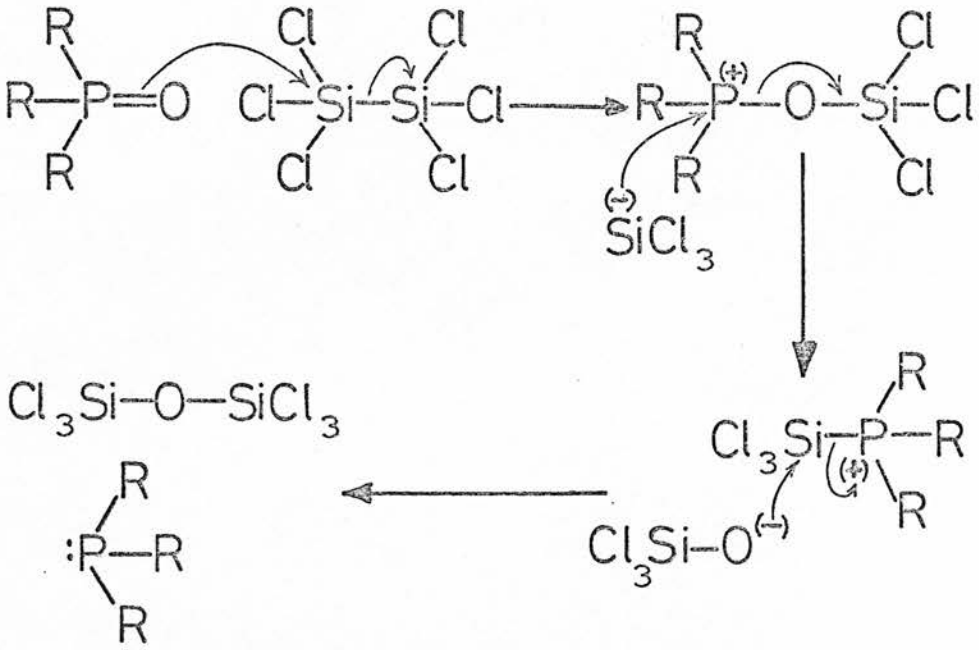
A nucleophile may attack any of the four faces of an acyclic, tetrahedral phosphorus compound. However, when the substrate contains a small (four- or five-membered) ring incorporating the phosphorus atom, attack is usually restricted to the two faces opposite the ring termini so that the TBP intermediate is generated with an apical-equatorial ring distribution. This distribution results in a relatively strain-free situation,[8] whereas a diequatorial ring is considerably strained.[8] Kinetic studies on the isomerisation of oxyphosphoranes have indicated free-energy



Scheme 27

differences between these orientations of as much as 20 kcal mol^{-1}.[66,69,78]

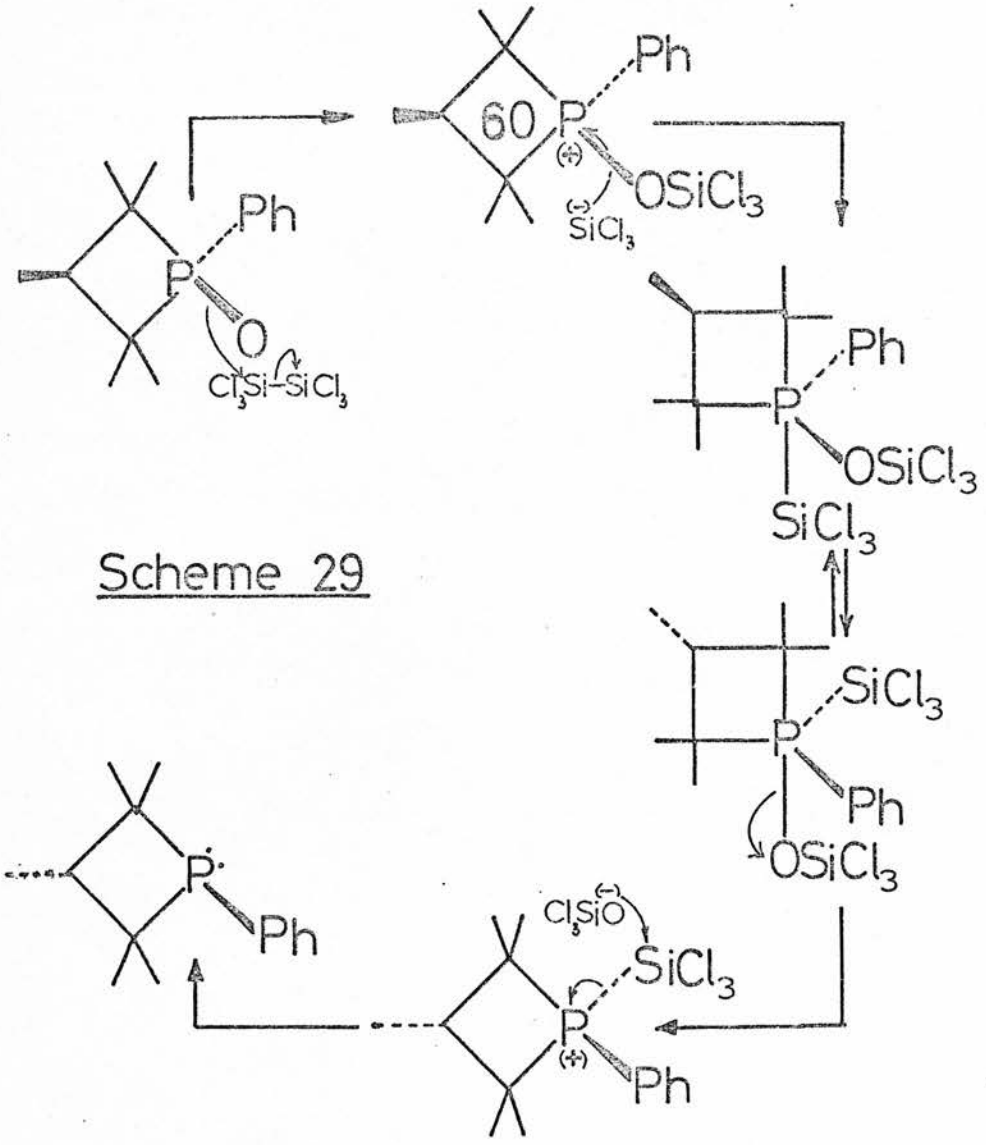
Thus, acyclic phosphine oxides are reduced by trichlorosilane with triethylamine to give phosphines with inversion of configuration at phosphorus;[90] analogous cyclic phosphetane oxides are reduced with retention.[91] Similarly, Mislow et al.[92] observed inversion when acyclic phosphine oxides were reduced by hexachlorodisilane, but the analogous phosphetane oxides were reduced with retention.[93] The reduction proceeds by the steps in scheme 28.[59] Clearly, the reaction should proceed with configurational inversion at phosphorus. However, a concerted reaction



Scheme 28

on the phosphetanium adduct (60) in scheme 29 would require a transition state with a high-energy, diequatorial ring.[56] Instead, the reaction must proceed as shown (scheme 29). The single PI process is required to allow the trichlorosiloxy group (Cl_3SiO^-) to depart from an apical position.

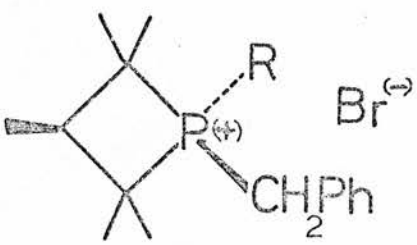
A similar situation is found in the basic hydrolysis of (acyclic) phosphonium and phosphetanium salts. McEwan et al.[88] observed complete inversion at phosphorus in the hydrolysis of acyclic salts; whereas,



Scheme 29

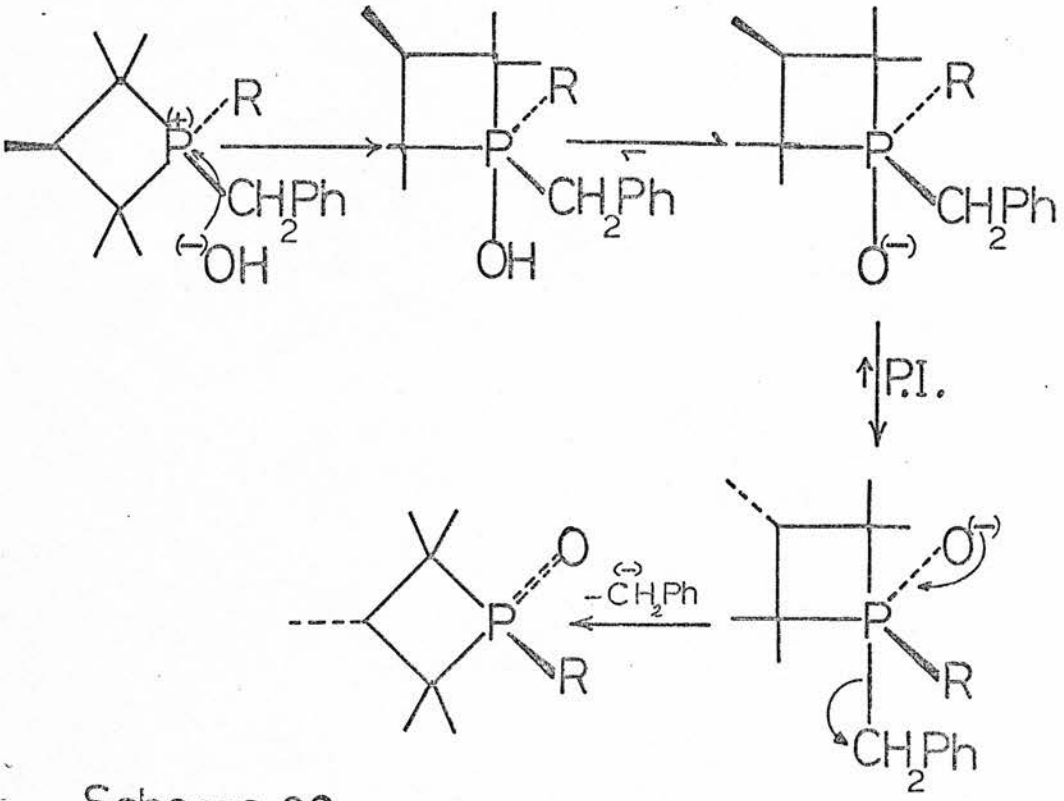
Trippett et al.[86] observed retention in the hydrolysis of the benzylphosphetanium bromide (61). Trippett[86] argued that the PI process

R= Ph



(61)

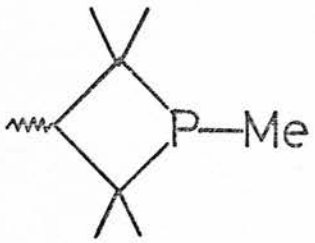
required to transfer the benzyl group to an apical site should be unfavourable, owing to the apicophilicity of the hydroxy group; in consequence, equatorial departure of the benzyl anion was considered to be the more likely course. It has since been realised[94] that the hydroxy group will be predominantly ionised under the reaction conditions. In accordance with the predictably[53] more favourable back bonding from equatorial sites, a very facile PI process should occur to place the anionic oxygen equatorially.[94,95] Thus, the benzyl group becomes an apical ligand and can depart from this site (scheme 30).



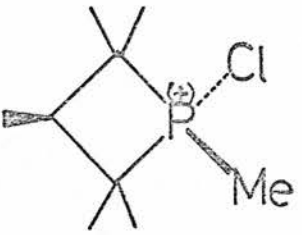
Scheme 30

Further examples of the apicophobicity of the anionic oxygen atom may be found in work by Cremer et al.[96] These authors also emphasised the fineness of the product balance due to the relative rates of PI processes and loss of the leaving group.

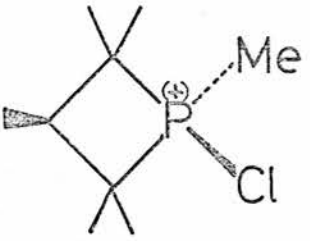
If both nucleophile and leaving group are highly electronegative, the stereoelectronic gain in placing these groups in a diapical distribution may overcome the strain involved in a diequatorial ring-placement. Thus, treatment of either the cis- or the trans-isomers of the phosphetane (62) with chlorine gave[97] the same product mixture, which exhibited an exchange broadened p.m.r. spectrum at room temperature. On cooling to -20°, the spectrum sharpened into a pattern which was discernible as a mixture of the cis- and trans-isomers of the phosphetanium ions (63).



(62)

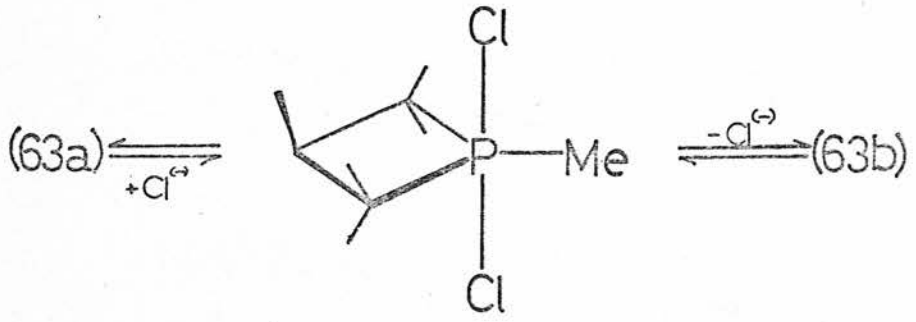


(63a)



(63b)

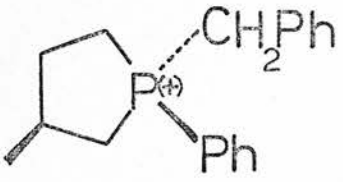
The room temperature broadening was due to a slow exchange between isomers (63a) and (63b) by reversible attack of chloride ion. The results were rationalised[97] on a scheme originally proposed by Quin et al.,[98] as in scheme 31.



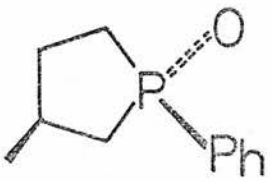
Scheme 31

The apical-equatorial ring preference decreases with larger rings. Thus, although the phospholanium salt (64) undergoes basic hydrolysis to

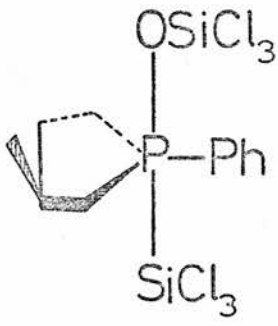
give the phospholane oxide (65), with retention of configuration at phosphorus,[99] the same oxide (65) is reduced with inversion.[99] In the first case, the benzyl group is of relatively low apicophilicity, allowing the ring to occupy an apical-equatorial distribution. In the latter



(64)



(65)



(66)

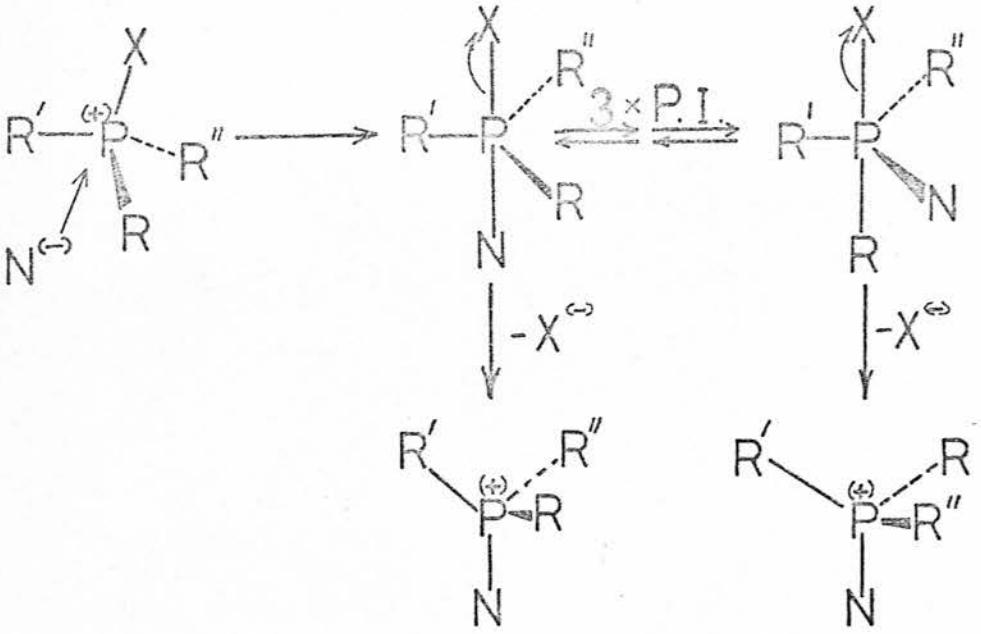
case, both the trichlorosilyl and trichlorosiloxy groups are of high electronegativity; thus, the ring is forced into a diequatorial distribution and the intermediate (66) is of the geometry shown. Configurational inversion results.

(c) Consequences of PI processes in the intermediate on the products and rate of reaction

The rate and nature of PI processes available to a TBP intermediate can profoundly affect the course of a reaction.

If the initially formed intermediate has an apical leaving group, the product distribution and stereochemistry will depend upon the rate of departure of that group, relative to the rate of competitive PI processes. Such a process can either place an alternative leaving group in an apical position or, through a series of three individual steps, can allow the same leaving group to depart from the "opposite" apex. In the latter case, the product will be a mixture of the two possible isomers,

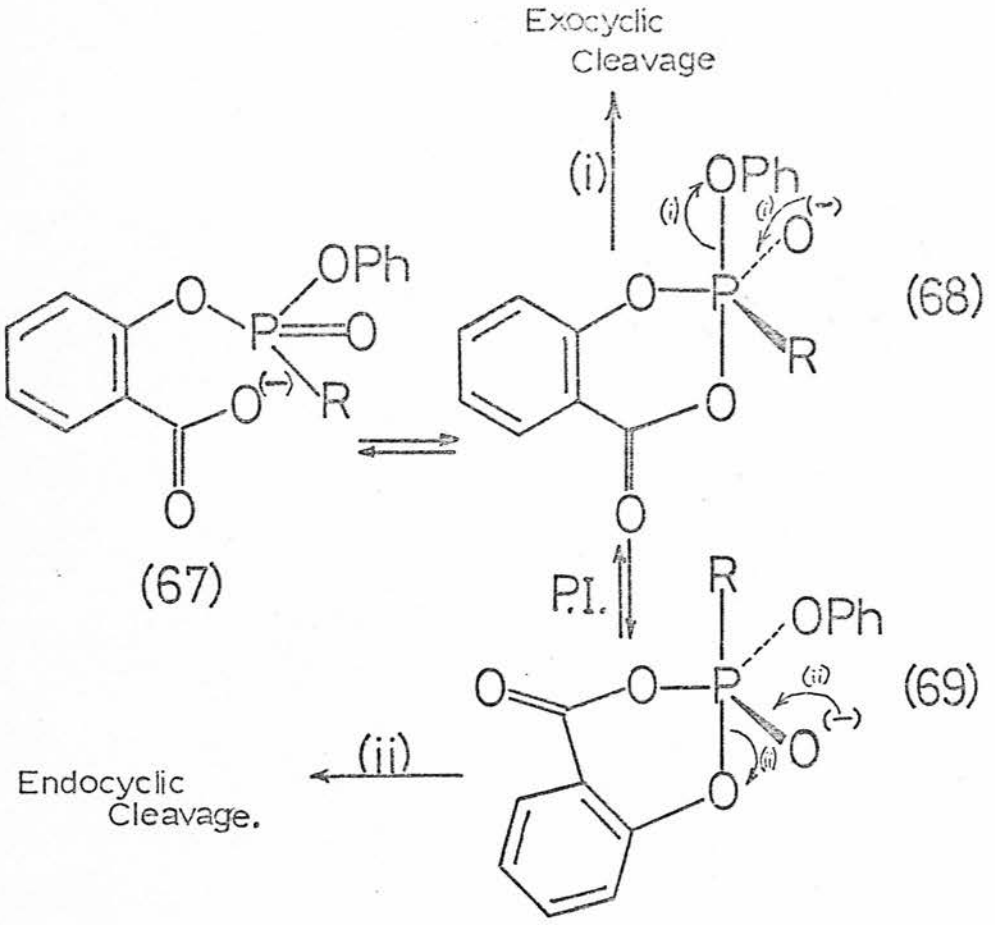
the ratio depending upon the rate of the PI process (scheme 32).



Scheme 32

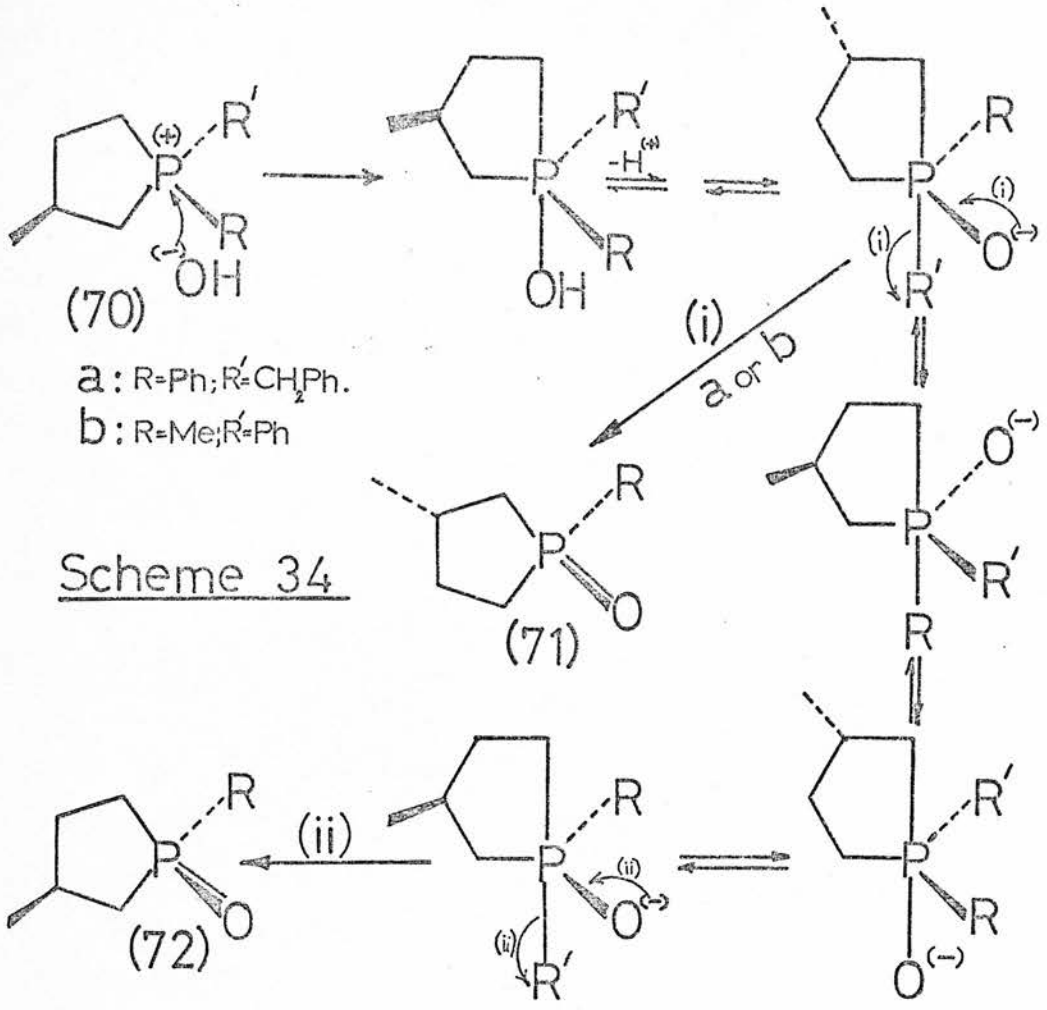
An impressive example of product control by the rate of PI processes has been observed by Kirby et al.[100,101] These workers have attributed the accelerated rate of basic hydrolysis of o-carboxyphenoxy esters (67), relative to that of the p-carboxy analogues, to intramolecular nucleophilic attack by the o-carboxy group at phosphorus, thus generating the cyclic oxyphosphorane intermediate (68) in scheme 33. The o-carboxyphenoxy group is more labile than phenoxide; thus the intermediate (68a) underwent almost exclusive endocyclic cleavage,[100] following the facile PI process which interchanges the endocyclic ligands between apical and equatorial positions and only requires interchange of the exocyclic phenoxy ligands. In contrast, (67b) hydrolysed with 95% exocyclic cleavage.[101] The PI process, in this case, would involve the exchange of an oxygen anion for a phenoxy ligand in the apical position. This high-energy process is therefore non-competitive with the loss of

phenoxide (scheme 33).



Scheme 33

Marsi et al.[102] observed stereochemical control in the hydrolysis of phospholanium salts. The benzylphospholanium salt (70a) hydrolysed in basic solution, with inversion of configuration, to give only (71a), whereas the phenylphospholanium salt (70b) gave a 50:50 mixture of the cis- and trans-isomers of the product (71b) and (72b), as in scheme 34. Benzyl anion is a relatively good leaving group in comparison with phenyl; thus, the benzyl anion was lost after the single PI process required to place it in an apical position. In contrast, the rate of loss of the phenyl anion was much slower than the full cycle of PI processes (of

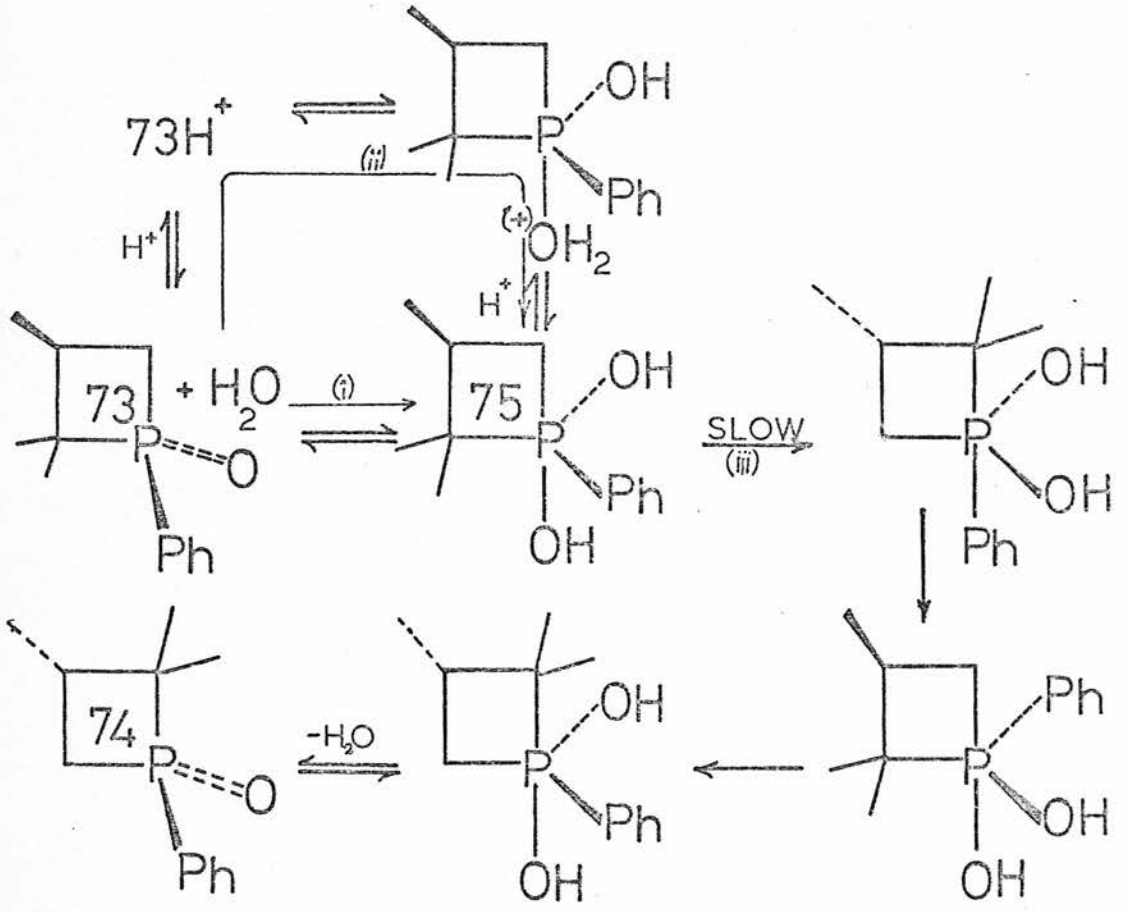


Scheme 34

which three out of the six are shown in the scheme); hence the observed lack of stereospecificity.

PI processes may also become the rate-determining step of a reaction. Thus, both Gorenstein[103] and Westheimer et al.[104] have reported cases in which maxima appear in the pH-rate profiles of acid-catalysed reactions. Although other acid-catalysed, hydrolytic reactions also show low-pH maxima (due to a reduction in the activity of water),[103] the former rate maxima occurred between pH 0.5 and 2.0 when the activity coefficient (f_{H_2O}) should still be ca. 1.[105] Gorenstein[103] observed the rate of epimerisation of the phosphetane oxide (73) to (74) as in scheme 35. In neutral solution, the intermediate (75) can only be produced by route (i);

in acidic solution, path (ii) is also available. Thus, the rate of epimerisation increases as the pH falls. However, the PI process (step (iii)) is slow, due to the apical placement of the phenyl group; it is also invariant with pH. Thus, a point is reached when the rate of steps (i) + (ii) exceeds that of step (iii) and a pH-rate maximum is found.



Scheme 35

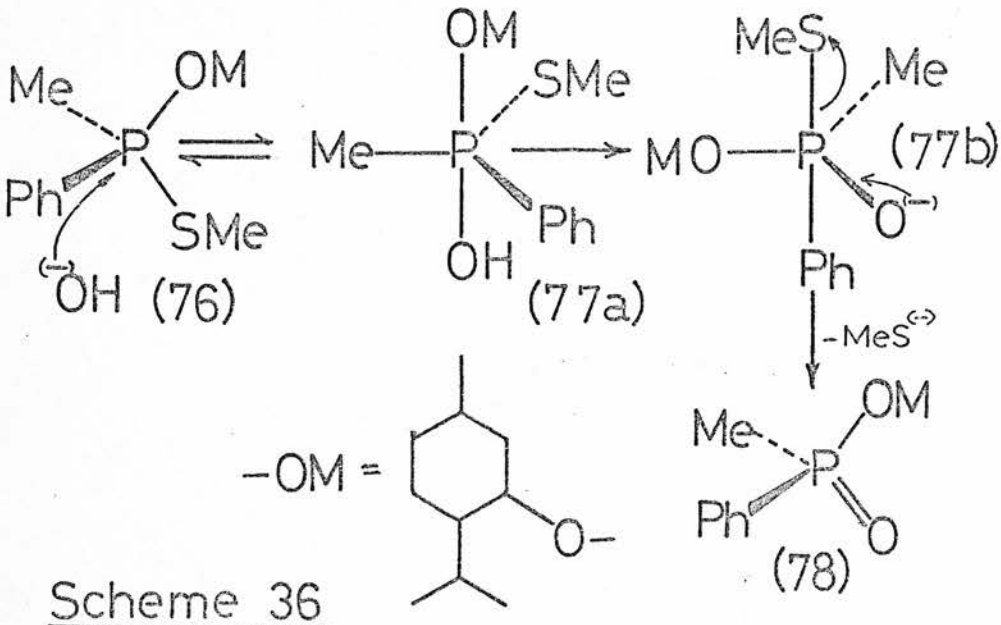
An effective example of PI product-control is to be found in the unification of the work of Westheimer et al. and Aksnes et al. on the hydrolysis of cyclic phosphate and phosphonate esters under acidic and basic conditions in a review by Hudson et al.[30]

(d) Nucleophilic attack on acyclic tetracoordinate phosphorus species

A brief mention is now made of the situations encountered in acyclic

systems. Ring constraints are absent; therefore, attack opposite the leaving group, with an SN2-type transition state, might be expected. This has been observed by McEwan *et al.*[88] and by Hudson *et al.*,[106] but is by no means the general case.

In phosphonium systems, attack usually occurs at the tetrahedral face opposite the most electronegative ligand. Thus, Trippett *et al.*[107] observed that basic hydrolysis of the phosphonium salt (76) gave the phosphinate (78) with retention of configuration at phosphorus, thereby implying attack opposite the more electronegative menthoxy group to give the intermediate (77a), which underwent a single PI process to the isomer (77b), with subsequent apical loss of the better leaving group (thiomethoxide ion) as in scheme 36. De Bruin *et al.*[108] studied a similar system

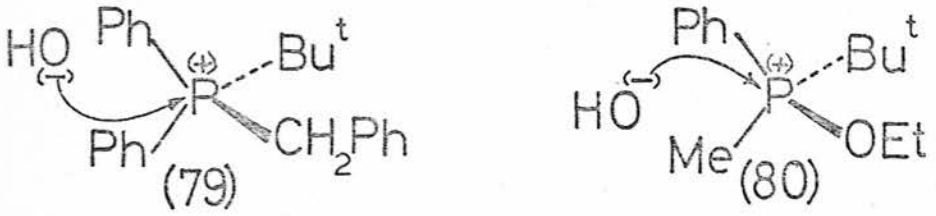


Scheme 36

in detail and reported that, as would be expected from scheme 36, loss of alkoxide ion proceeded with inversion. This study[108] also furnished good evidence for the apical entry and departure scheme.

In the absence of a strongly electronegative group, the point of attack may be determined by steric interactions between the substrate and

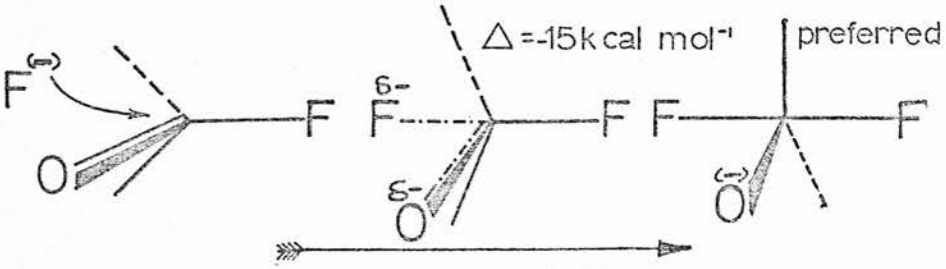
the incoming nucleophile. Trippett et al.[109] observed hydrolytic loss of benzyl anion from the phosphonium salt (79) with predominant retention of configuration; in contrast, Mislow et al.[110] observed that the alkoxyphosphonium salt (80) was hydrolysed with inversion (scheme 37).



Scheme 37

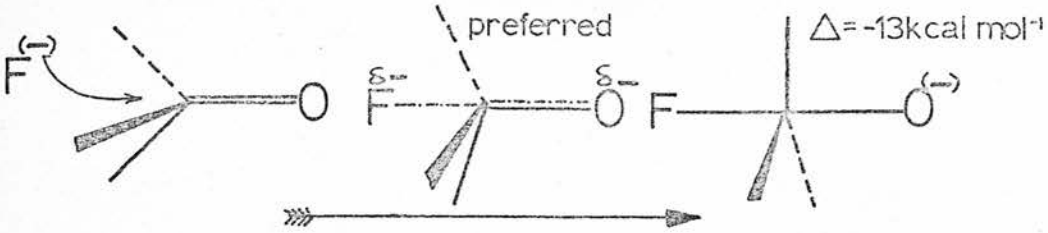
In the first case, all ligands are of similar electronegativity; thus, attack occurs at the least sterically-hindered face. In the second case, the electronegative group directs the attack.

An additional factor may become important in molecules containing a phosphoryl group. CNDO/2 calculations[81] on the attack of fluoride ion at phosphorus oxyfluoride indicated that attack opposite the most electronegative group is thermodynamically advantageous (scheme 38),



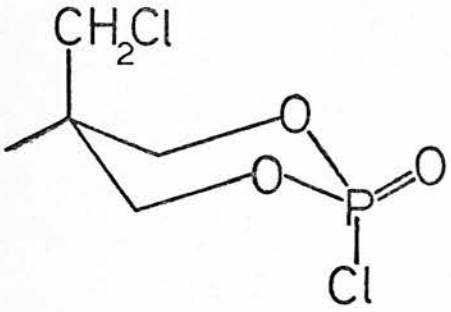
Scheme 38

whereas attack opposite the phosphoryl group reduces the electrostatic interaction between the nucleophile and the developing charge on the phosphoryl oxygen. Hence, the latter is kinetically preferred (scheme 39).

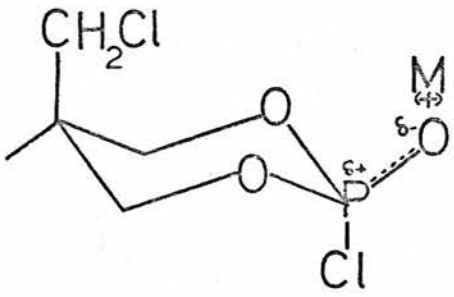


Scheme 39

Wadsworth[111] has presented evidence for nucleophilic attack opposite the phosphoryl group in the dioxaphosphorinane oxide (81), by observing a degree of configurational retention at phosphorus. The addition of salts increased the degree of inversion. Metal ions form a complex (82) with the phosphoryl oxygen which "blankets" the



(81)

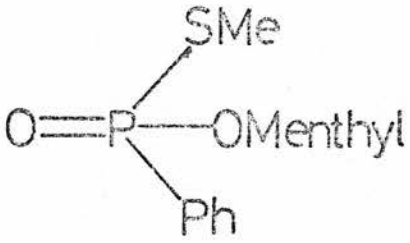


(82)

developing electrostatic charge, thus reducing the repulsion towards the approaching nucleophile. The explanation is, in fact, more complicated as the degree of inversion also increases with the basicity of the nucleophile. This was suggested[111] to imply that as the reactants become stronger, there is an increased preference towards a direct SN2 process. The metal ion withdraws electronic charge from the phosphorus atom, thereby enhancing its electrophilicity and causing increased inversion.

In contrast to the results of Trippett et al.[107] on phosphonium salts, Mislow et al.[112] observed that thiomethoxide was displaced by

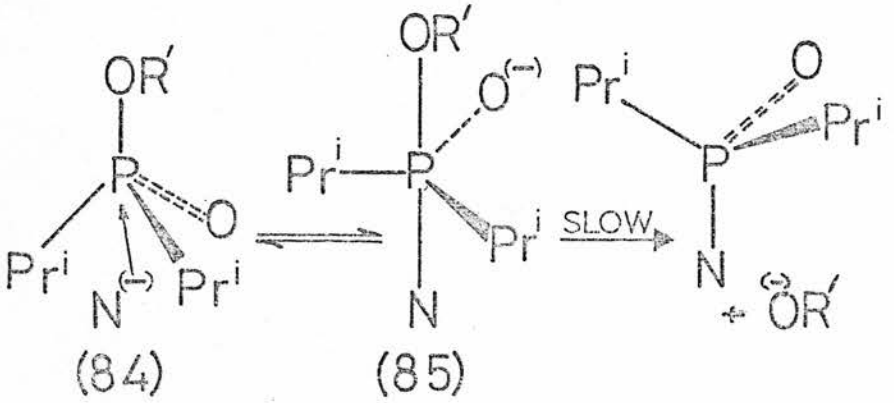
attack of methoxide at the neutral analogue (83) with configurational inversion. De Bruin et al.[113] studied this system in detail with the



(83)

surprising conclusion that nucleophilic attack opposite the less electronegative thiomethoxy group was preferred by a factor of five.

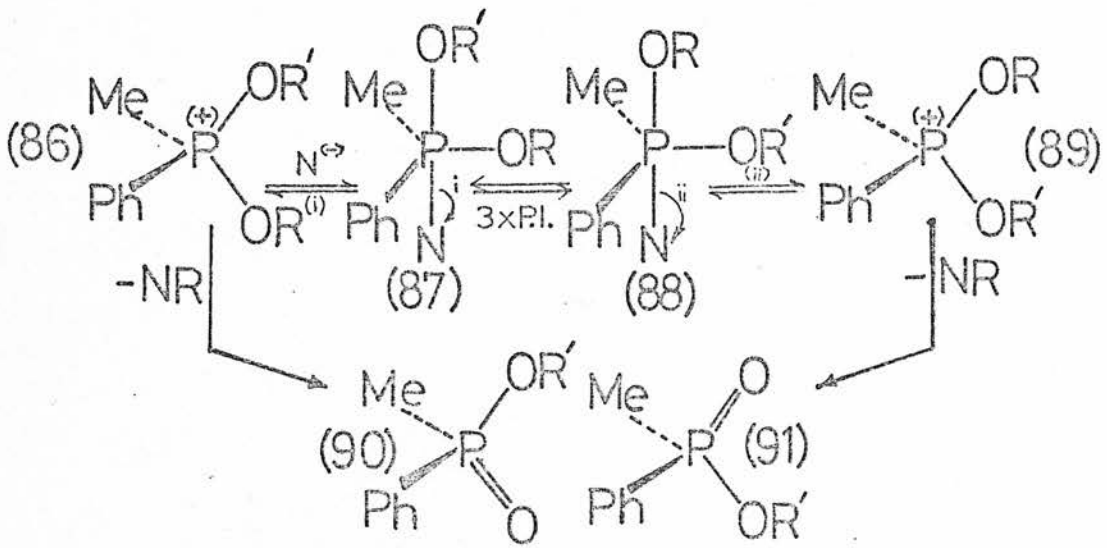
Haake et al.[114] examined the hydrolysis of a series of phosphinate esters ($R_2P(O)OR'$). The rate of reaction depended strongly upon the acidity of the leaving group OR', indicating a rate-determining decomposition of the TBP intermediate. The reaction exhibited a first-order dependency on both substrate and hydroxide ion concentrations, suggesting a pre-equilibrium formation of this intermediate. When R was isopropyl, an induction period preceded the establishment of good second-order kinetics. The formation (scheme 40) of the intermediate (85) from the



Scheme 40

substrate (84) is accompanied by a release of steric strain between the alkyl groups; consequently, a more crowded substrate will generate a relatively more stable intermediate and the equilibrium concentration of the intermediate will be greater than in a less crowded system. In contrast, the steric bulk of the substituents will hinder nucleophilic attack. Both factors combine to retard establishment of the pre-equilibrium; hence the induction period.

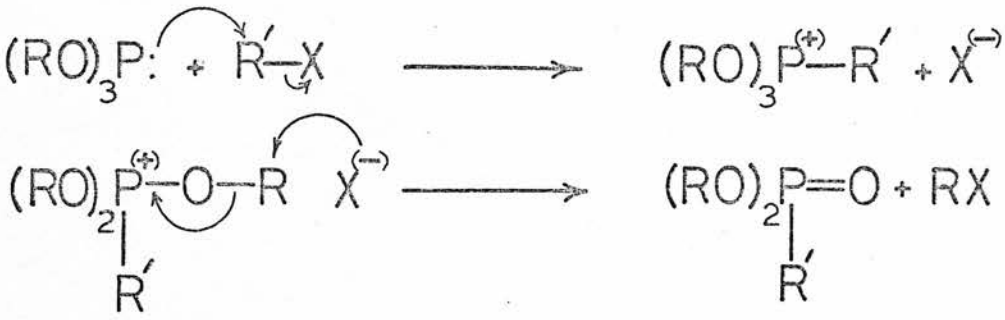
The observation of PI-derived phenomena may suggest, but does not necessarily prove, that a TBP structure is an obligatory component of a reaction scheme. De Bruin et al.[115] have studied the dealkylation of the chiral alkoxyphosphonium salt (86). Different nucleophiles gave varying degrees of epimerisation at phosphorus. In a qualitative way, "harder"[116] nucleophiles increased the degree of epimerisation, whilst "softer"[116] nucleophiles caused less, or no epimerisation. Dealkylation occurs by nucleophilic attack at the alkoxy carbon with subsequent C—O cleavage. The epimerisation was rationalised[115] (scheme 41) by the suggestion that "hard" nucleophiles preferentially attacked the "hard" phosphonium centre rather than the "soft" alkyl carbon, thus generating



Scheme 41

the TBP intermediate (87). This intermediate has a long enough lifetime to isomerise to (88), by a sequence of three PI processes; however, the nucleophile is of insufficient strength to expel the alkoxy group. Instead, the intermediates dissociate to either of the epimeric phosphonium species (86) or (89). The nucleophile re-attacks at the alkoxy carbon to generate the epimeric products (90) and (91).

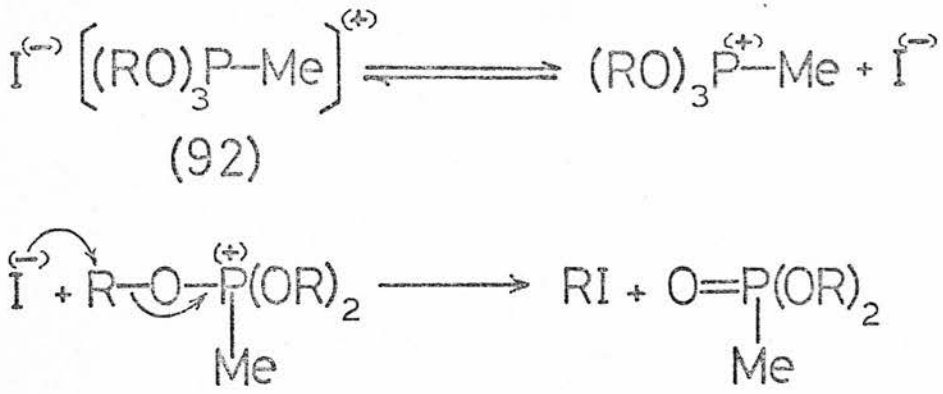
Similarly, the Arbuzov reaction[117] is believed to proceed via formation of a phosphonium salt which is dealkylated with C—O cleavage to give a neutral phosphoryl derivative (scheme 42). There is ample



Scheme 42

experimental evidence for this scheme. Thus, acyclic phosphites react more rapidly with alkyl iodides than do their five-membered, cyclic analogues,[118,119] suggesting a tetrahedral rather than a TBP type of intermediate.[30] A crystalline Arbuzov intermediate has been isolated[120] from the reaction of trineopentyl phosphite with methyl iodide. This adduct (92) had a negative ^{31}P n.m.r. chemical shift, which is more consistent with a phosphonium structure than with a pentacoordinate structure;[121] furthermore, a solution of this salt decomposed with first-order kinetics to the expected Arbuzov products within a few hours. All of these observations are consistent with scheme 43.

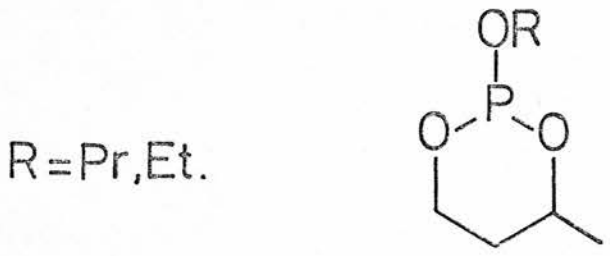
This mechanism (schemes 42 and 43) indicates that the reaction should occur with configurational retention at phosphorus. Nevertheless,



(92)

Scheme 43 $R = -CH_2C(CH_3)_3$

Bodkin and Simpson[122] observed very low stereospecificity in the reactions of geometrical isomers of 2-alkoxy-4-methyl-1,3,2-dioxaphosphorinanes (93). These workers[122] suggested that a pentacoordinate



(93)

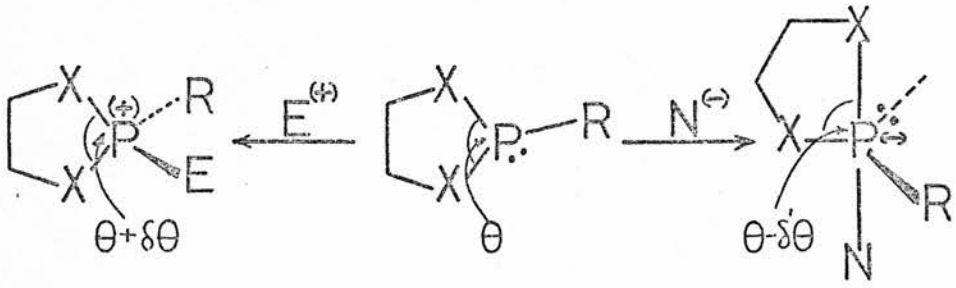
intermediate was first formed (reversibly) from the phosphite and alkyl halide. This intermediate had a sufficient lifetime to allow PI cycles to occur. Subsequent decomposition gave a quasi-phosphonium and halide ions; reaction then proceeded through the normal mechanism.[117]

(e) The small-ring effect

Reactions of cyclic (four- or five-membered) tetracoordinate phosphorus compounds, which involve the intermediacy of TBP structures, often exhibit accelerated rates relative to their acyclic analogues. Such effects were first investigated by Westheimer et al.[29] in the hydrolysis

of phosphorus esters. Hudson et al.[30] have reviewed the available evidence and have extended the theory to provide a mechanistic probe for the reactions of tervalent phosphorus compounds.

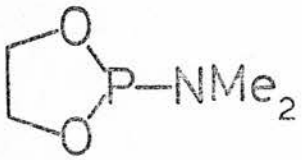
The natural angle at tervalent phosphorus is ca. 100°.[124] When a cyclic (four- or five-membered) P(III) compound reacts as a nucleophile, rehybridisation increases this angle towards 109° and consequently the ring strain is enhanced. When the same species acts as an electrophile, a ten-electron intermediate is formed. If this latter species has TBP geometry and the ring is able to occupy an apical-equatorial distribution, then the angle at phosphorus will decrease towards 90° and ring strain is released (scheme 44).



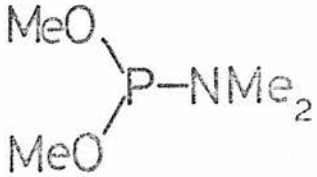
Scheme 44

Thus, four- or five-membered cyclic tervalent phosphorus species should exhibit decelerated or accelerated rates of reaction, depending upon whether they react as nucleophiles or electrophiles.

This hypothesis[30] was tested on the Arbuzov reaction of the phosphoramidites (94) and (95).[125] Quaternisation of the phosphorus atom

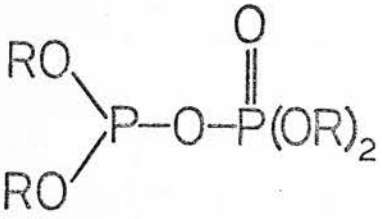


(94)

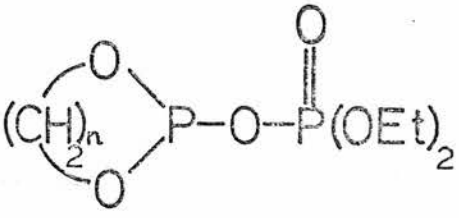


(95)

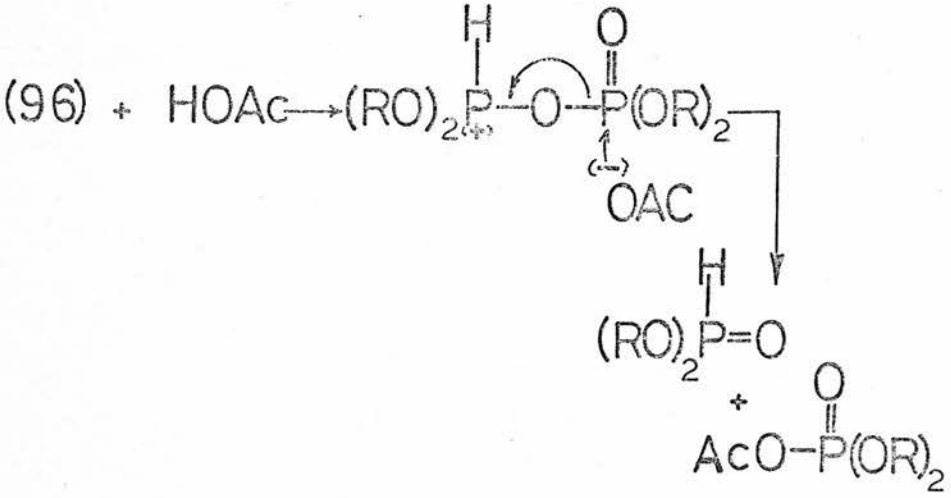
was indicated by a shift of the ^{31}P n.m.r. resonance from -137 ppm to -27.8 ppm. A threefold rate reduction was observed for the cyclic compound (94). Michalski et al.[126] have shown that the phosphorus phosphoric anhydride ester (96) reacted with acetic acid at 80°, whereas the cyclic esters (97) and (98) failed to react when heated at 120° for three hours. Consequently, the mechanism in scheme 45 was proposed.[126]



(96)

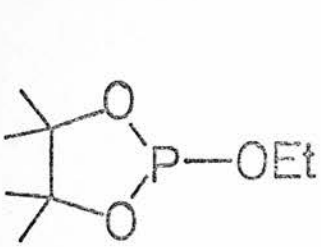


n=2 (97)
n=3 (98)

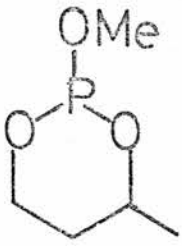


Scheme 45

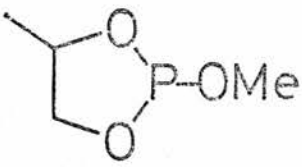
The unreactivity of the six-membered species is unexpected since ring strain effects should be comparatively lacking. In support of this statement, Aksnes et al.[119] observed that the five-membered cyclic phosphite (99) reacted 2.5 times more slowly than the six-membered cyclic phosphite (100) with methyl iodide. Similarly, Denney et al.[127] compared the reactivities of the phosphites (100) and (101) with that of trimethyl



(99)

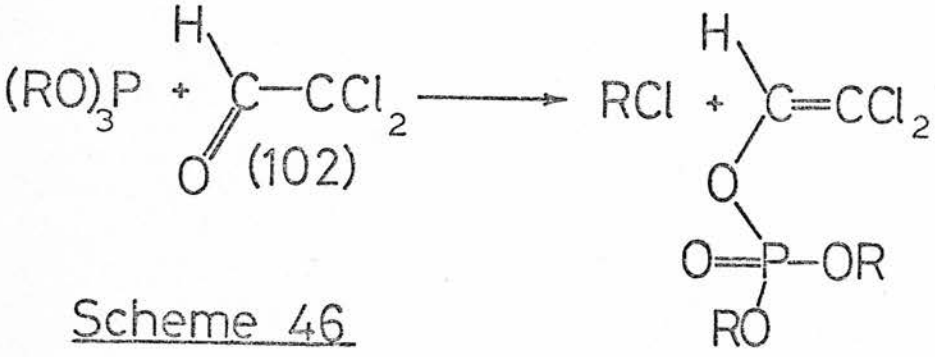


(100)



(101)

phosphite in the Perkow reaction (scheme 46). The six-membered and



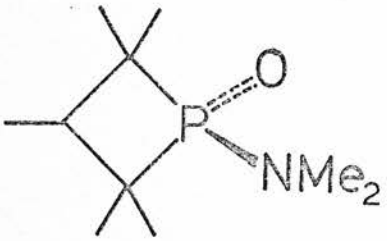
Scheme 46

acyclic phosphites were similar, but the five-membered phosphite was of considerably reduced reactivity. The Perkow reaction is believed to involve rate-determining nucleophilic attack by P(III) on the carbonyl carbon of the substrate (102).

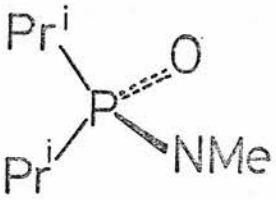
Hudson et al.[30] have also shown that it is possible to assess bond-formation in the intermediate by observing the magnitude of the rate decelerations.

When P(III) acts as an electrophile, the analysis is more complicated. Rate enhancements will only be observed if the ring occupies an apical-equatorial distribution in the intermediate. If the stereoelectronic strain involved in placing the exocyclic group in an equatorial position is great, the ring may be forced into a diequatorial distribution and, consequently, small rings should give a rate decrease once again.

Haake et al.[128,129] observed that the rate of the acid-catalysed hydrolysis of the cyclic phosphinamide (103) was only 1.5×10^{-3} times that of the acyclic phosphinamide (104). The amide function is labilised by N-protonation in acidic solutions and rapid hydrolysis occurs by an A2 mechanism.[130] Haake suggested[128] that greater lability

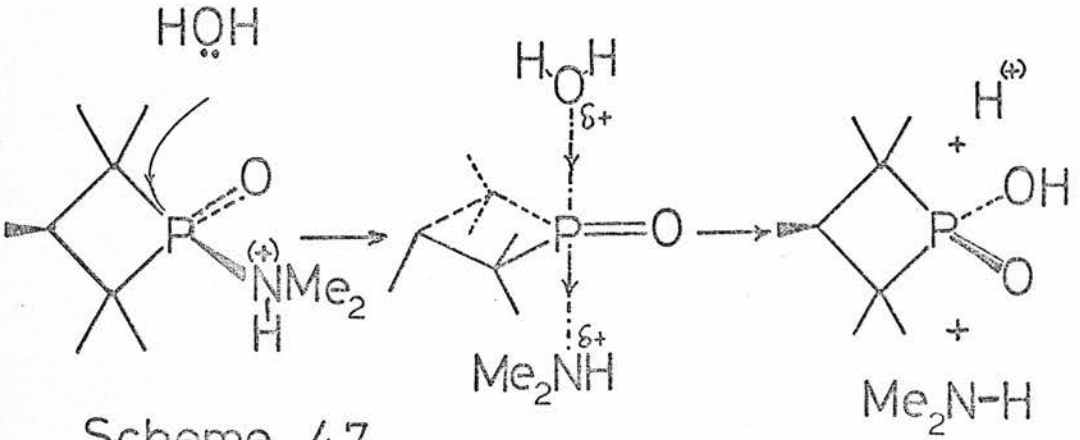


(103)



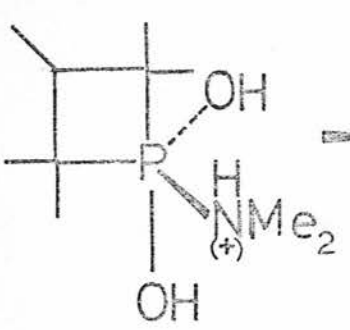
(104)

of the leaving group favours a direct displacement (SN2) mechanism; thus, the alkyl groups are forced into a diequatorial distribution in the transition state and the presence of a small ring will raise the activation energy of the reaction (scheme 47). Trippett et al.[131] disagreed

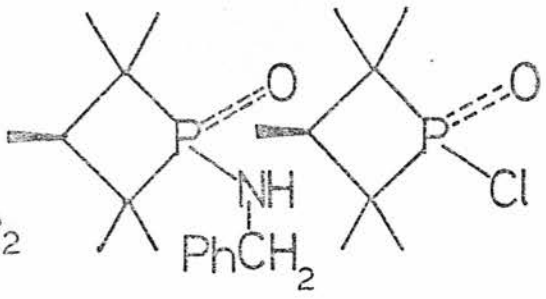


Scheme 47

and suggested that attack on the cyclic system occurred, as usual, at a tetrahedral face opposite a ring ligand; thus generating an intermediate with an apical-equatorial ring distribution (105). In contrast, the acyclic system was free to undergo direct displacement. The additional barrier towards hydrolysis in the cyclic case was then due to the



(105)

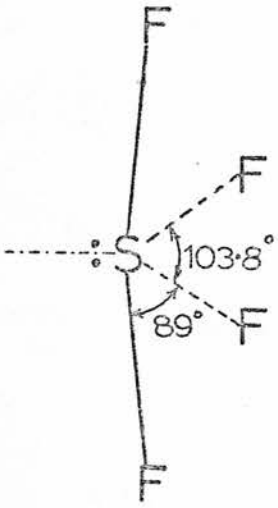


(106)

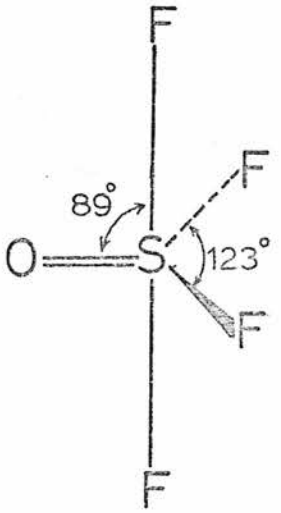
(107)

stereoelectronic strain caused by placing the highly-electronegative, protonated amide function in an equatorial position. The mechanism in scheme 47 indicates that the hydrolysis should proceed with inversion. However, Trippett et al.[132] have reported that the cyclic phosphinamide (106) reacts with HCl to give the chlorophosphetane oxide (107) with retention. This reaction is, clearly, of a similar type to the above hydrolysis.

There may be an additional incentive for diequatorial ring-placement in the tetracoordinate TBP system. Electron diffraction studies[133] have shown that the diequatorial angle in sulphur tetrafluoride (108) is only 103.8°. The sulphur system is comparable with the phosphorus system, as witnessed by the structure[133] of SOF_4 (109), which is a nearly regular



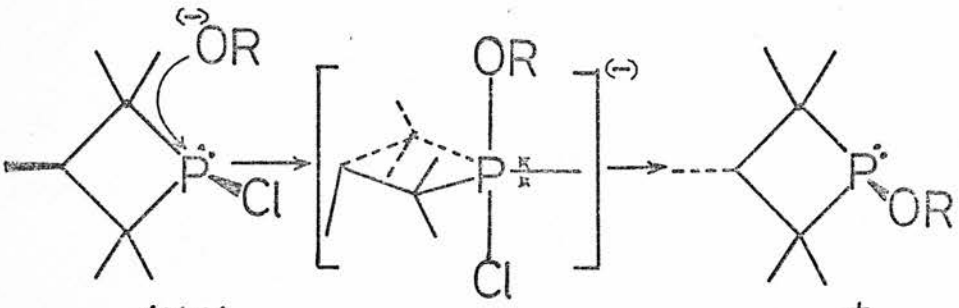
(108)



(109)

TBP. If the same angle-diminution exists amongst the phosphorus analogues, the diequatorial ring strain would be greatly decreased relative to that in the pentacoordinate structures.

This has been suggested [30] to account for the inversion of configuration observed [134] when the chlorophosphetane (110) was treated with alkoxide ion (scheme 48).

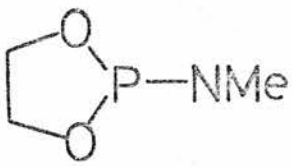


(110)

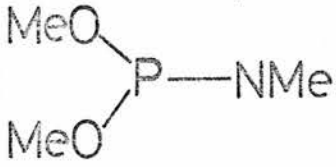
Scheme 48

Despite these reservations, large rate enhancements have been observed [30] when P(III) species act as electrophiles. Thus, Hudson *et al.* [125] have found that the cyclic phosphoramidite (111) reacted ca. 340 times as fast as the acyclic analogue (112), with phenyl isocyanate. Accordingly, the mechanism in scheme 49 was proposed, with the transition state (113).

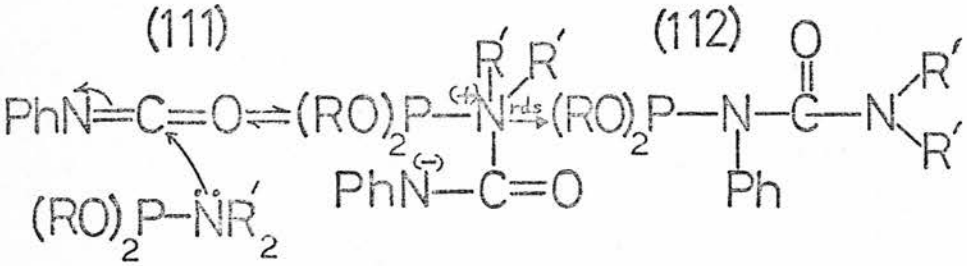
The origin of the small-ring effect is not fully understood. The bond angle in methyl ethylene phosphate is 99.1° [135] in contrast to the preferred tetrahedral angle of 109.5°. Calculations [136] indicated that an energy release of 3-6 kcal mol^{-1} could be expected in passing from the ground state to a TBP intermediate having an apical-equatorial ring (preferred angle of 90°). In contrast, an increase in ring strain of 5-7 kcal mol^{-1} should result from the formation of a similar intermediate having a diequatorial ring. [136] The rate of hydrolysis of methyl ethylene

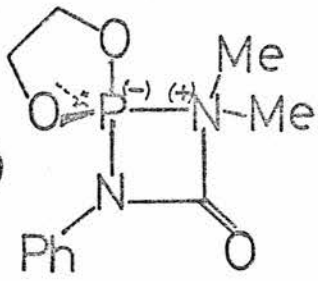


(111)



(112)



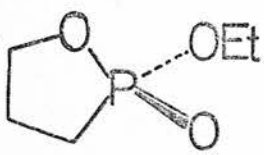


(113)

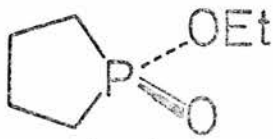
Scheme 49

phosphate is greater than that of trimethyl phosphate by a factor of ca.10^6,[137] which represents a difference in activation energy of 8.5 kcal mol^{-1}.[29] Thus some, but not all, of the acceleration is attributable to ring strain release.[29]

Aksnes et al.[138] observed that the activation enthalpy for basic hydrolysis of ethyl propylphostonate (114) was only 2.4 kcal mol^{-1} less than that for the phosphinate analogue (115), accounting for a rate factor



(114)



(115)

of only 50 out of the observed factor of 50 x 10^5. However, the activation entropy of (114) was 18.4 eu more positive than that of (115), accounting for a rate factor of 10^4. This entropy difference also accounted for the major part of the rate enhancement for (114) over the six-membered ring and acyclic analogues.[138]

It has been reported[125] that Songstad has attributed the decelerated rate of reaction of cyclic phosphites, compared with acyclic phosphites, towards isoselenocyanate, entirely to entropy effects.

The nature of the entropy effect is still a matter for conjecture. It has been suggested[139] that it may be associated with the loosening of the "pseudorotational" motion of the ring, i.e. to the effects of ring angle on the movement of the methylene groups.[125]

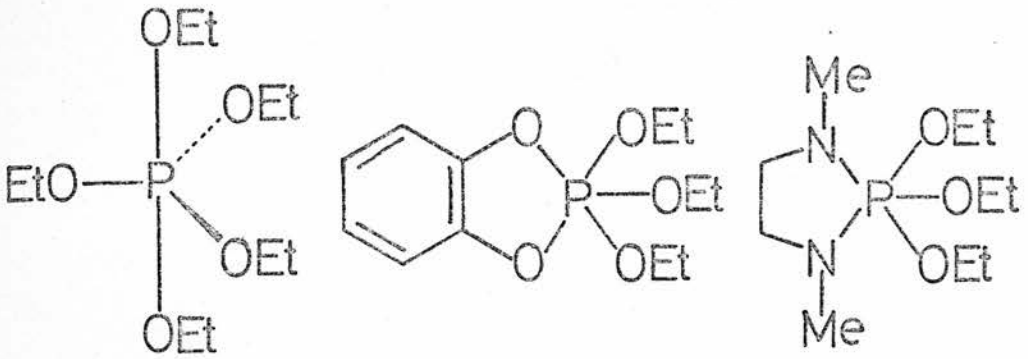
6. The Preparation and Reactions of Phosphoranes

(a) Synthesis

Few pentacoordinate phosphorus compounds were known before 1950. In the last twenty-five years, however, a vast number have been synthesised and many hundreds of stable phosphoranes have now been isolated.

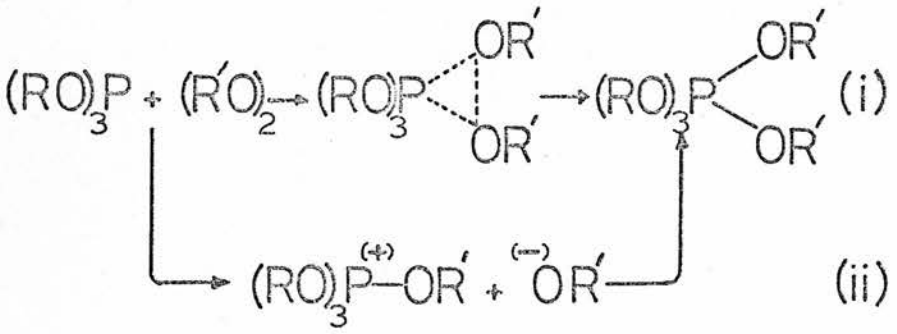
Methods for the preparation of phosphoranes have been extensively reviewed by Hellwinkel[140] and only the strictly organic phosphoranes are considered here. In most cases, preparations involving the use of tervalent phosphorus compounds are applicable to phosphites, phosphonites, phosphinites and phosphines; however the stability of the product decreases with a reduction in the number of P–O bonds.[19]

Denney *et al.* have pioneered the reaction of diethyl and dimethyl peroxides, as well as thioperoxides and disulphides, with acyclic[39,17] and cyclic tervalent phosphorus reagents to produce alkoxy phosphoranes such as (116),[17] (117)[141] and (118).[70] This process has been discussed[141] and two mechanisms are likely (scheme 50). Mechanism (i) is favoured by the reactivity order, acyclic P(III) < six-membered cyclic



(116) (117) (118)

P(III) < five-membered cyclic P(III), which is opposite to that which would be expected [30] for mechanism (ii).

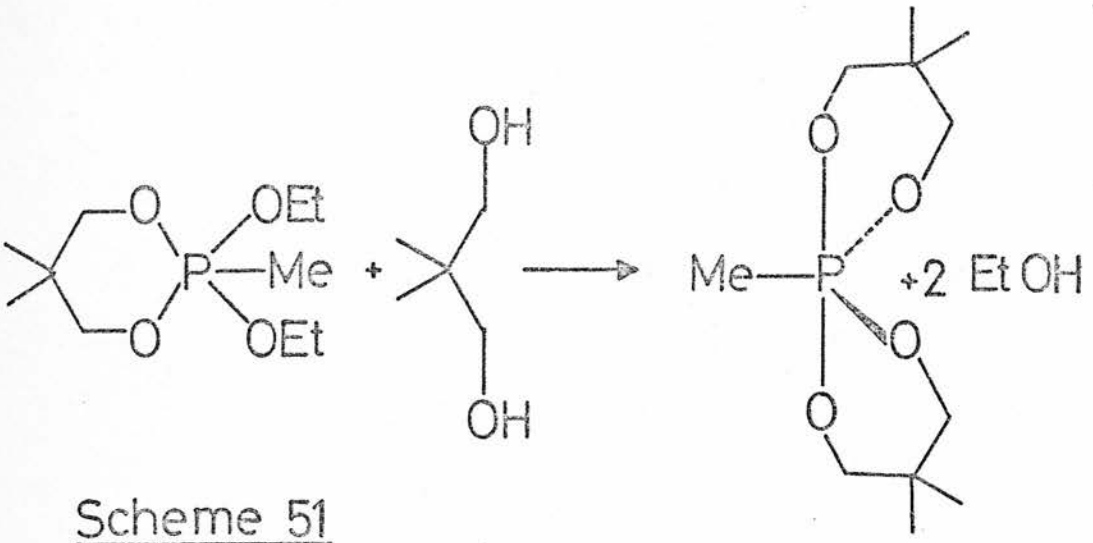


Scheme 50

Denney et al. have extended this preparative route to the formation of spirocyclic phosphoranes by the reaction of cyclic alkoxyphosphoranes with diols (scheme 51).[20]

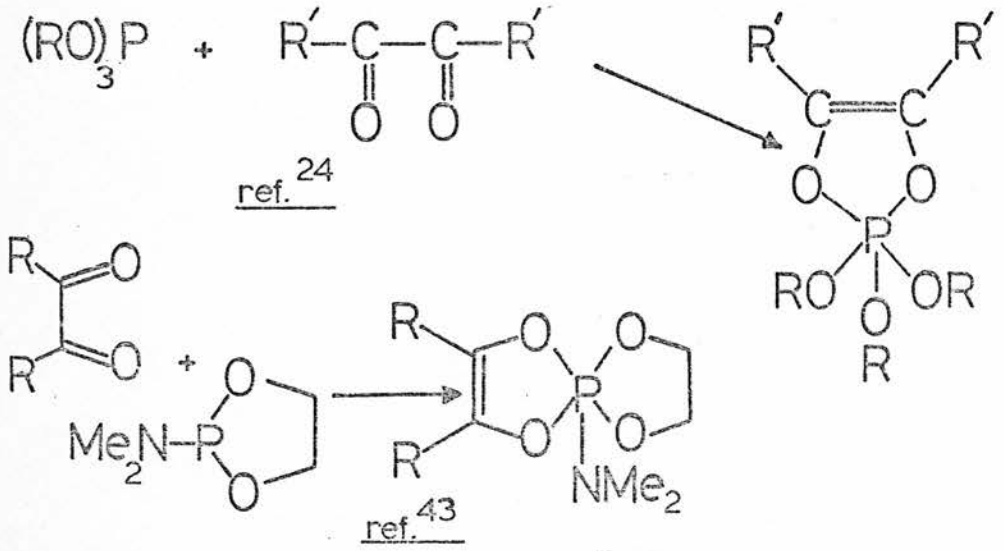
Pentaphenoxyphosphorane has been prepared by Ramirez et al.[23] by the addition of five molar equivalents of phenol to a cold solution of phosphorus pentachloride containing five molar equivalents of 2,4,6-trimethylpyridine (to remove the HCl formed in the reaction).

The most extensively used reaction for obtaining cyclic oxyphosphoranes is principally due to Ramirez and his co-workers. Tervalent phosphorus reagents react with 1,3-unsaturated systems to give unsaturated



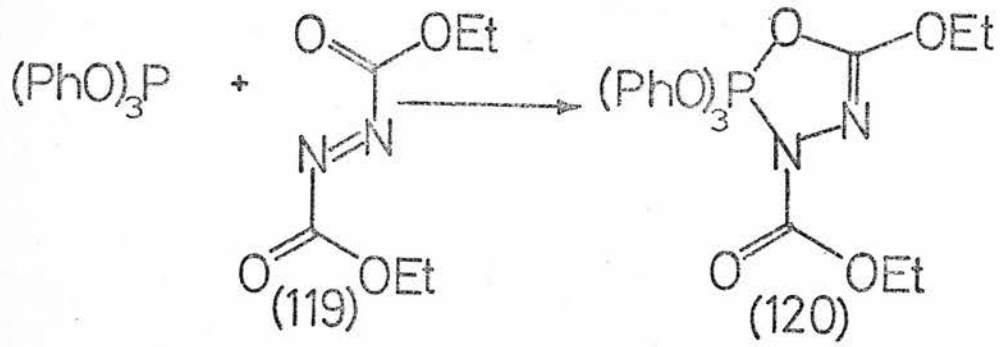
Scheme 51

five-membered ring phosphoranes and spirocyclic phosphoranes. The reaction is usually performed at room temperature and is exothermic. The reactions in scheme 52 are representative.

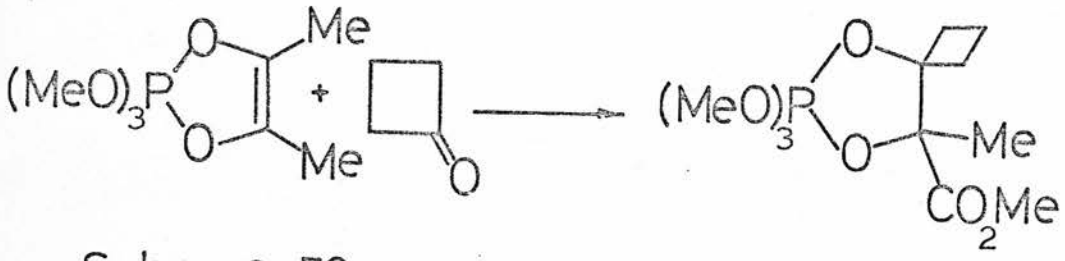


Scheme 52

Ginsburg et al.[142] reacted triphenyl phosphite with the azo-compound (119) to obtain the phosphorane (120).

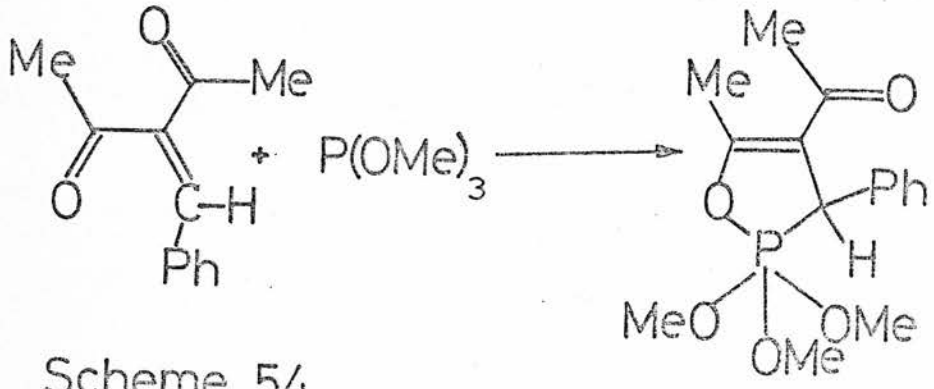


This approach has been extended, by further reaction of the unsaturated-ring adducts with monocarbonyl compounds, to give saturated, cyclic phosphoranes (scheme 53).[143]



Scheme 53

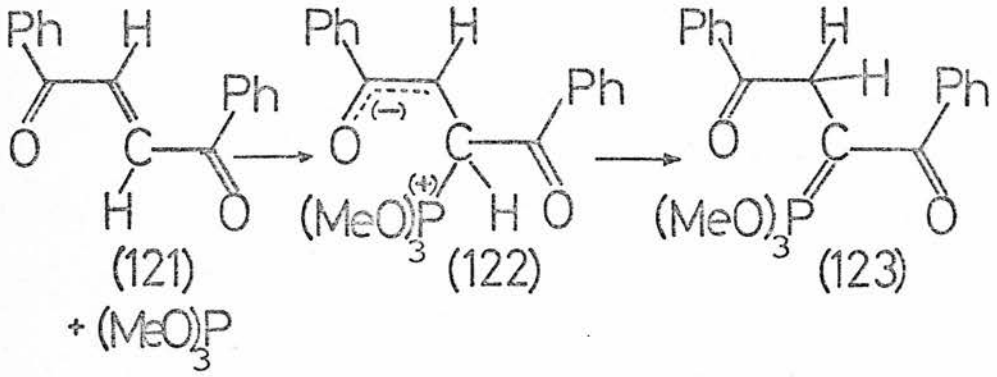
The 1,2-oxaphospholene system is accessible through the reaction of tervalent phosphorus reagents with 1,3-unsaturated ketones[144] (scheme 54).



Scheme 54

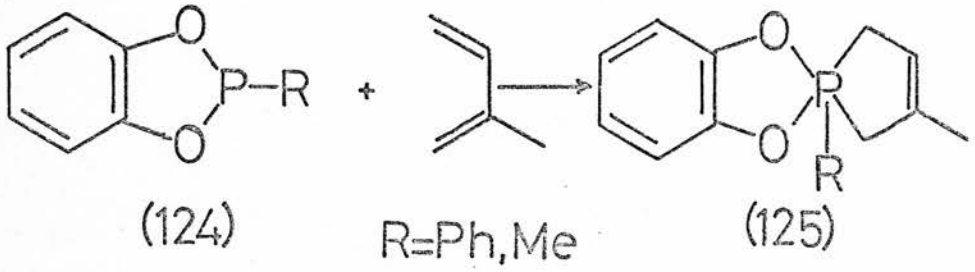
The product is, however, dependent on the ketone used.[144] Thus, treatment of trans-dibenzoylethylene (121) with trimethyl phosphite yielded the alkoxyalkylidene phosphorane (123). Both reactions proceed via the

dipolar intermediate (122),[144] which can either cyclise to the alkoxyphosphorane or, as in this case, undergo a rapid proton-transfer to give the observed product (123) as in scheme 55.

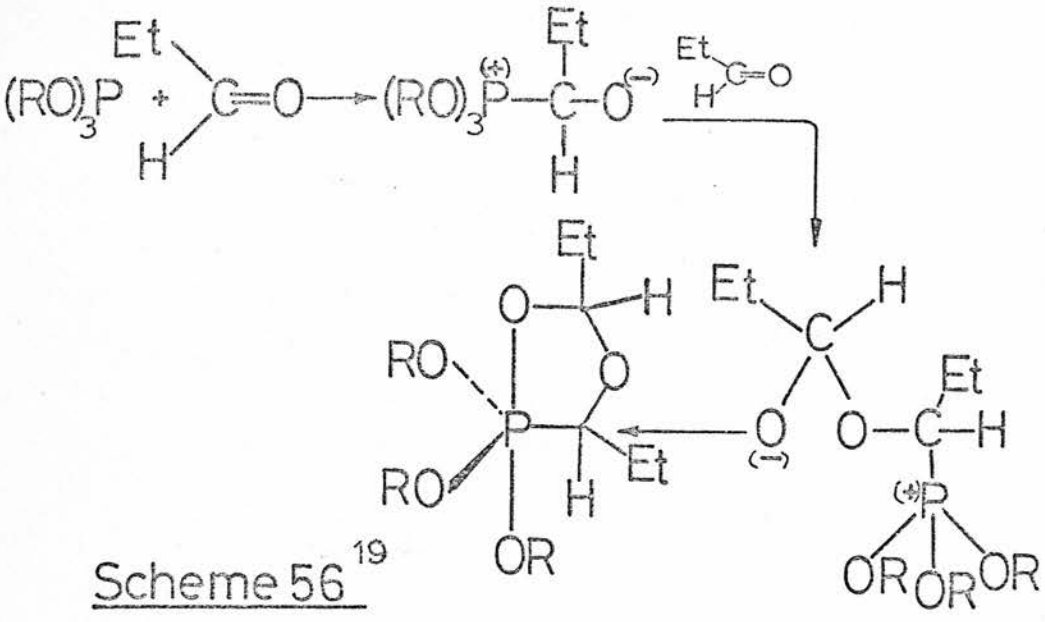


Scheme 55

Wieber et al.[145] reacted the cyclic phosphonite (124) with 2-methylbuta-1,3-diene at room temperature. After three days, in the absence of solvent, the adduct (125) was obtained in ca. 90% yield. A similar reaction was employed by Razumova et al.[146]

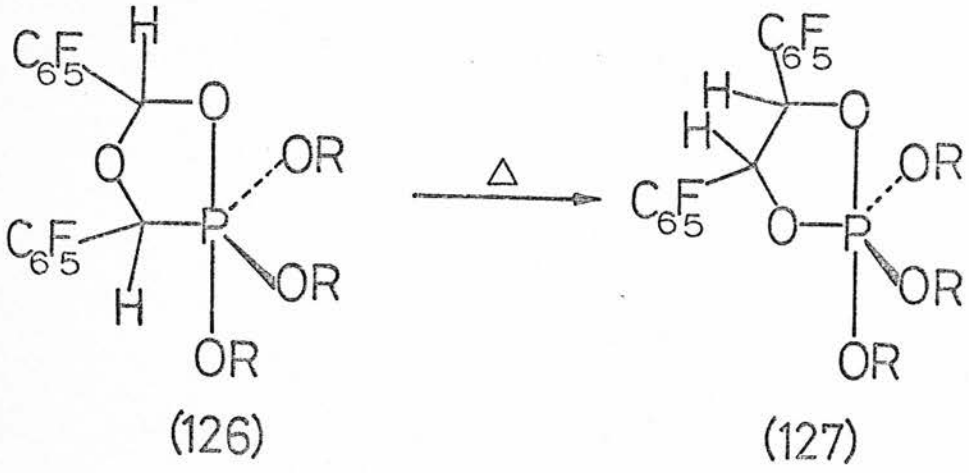


Tervalent phosphorus compounds react with two molar equivalents of monocarbonyl compounds to give phosphoranes derived from either the 1,3,2-dioxaphospholane or 1,4,2-dioxaphospholane systems, depending upon the nature of the carbonyl and the temperature. Non-activated carbonyls are, in general, attacked at the carbonyl carbon as in scheme 56.[147] Pentafluorobenzaldehyde reacts with trialkyl phosphites, at low temperature, via initial attack by phosphorus on the carbonyl carbon to give



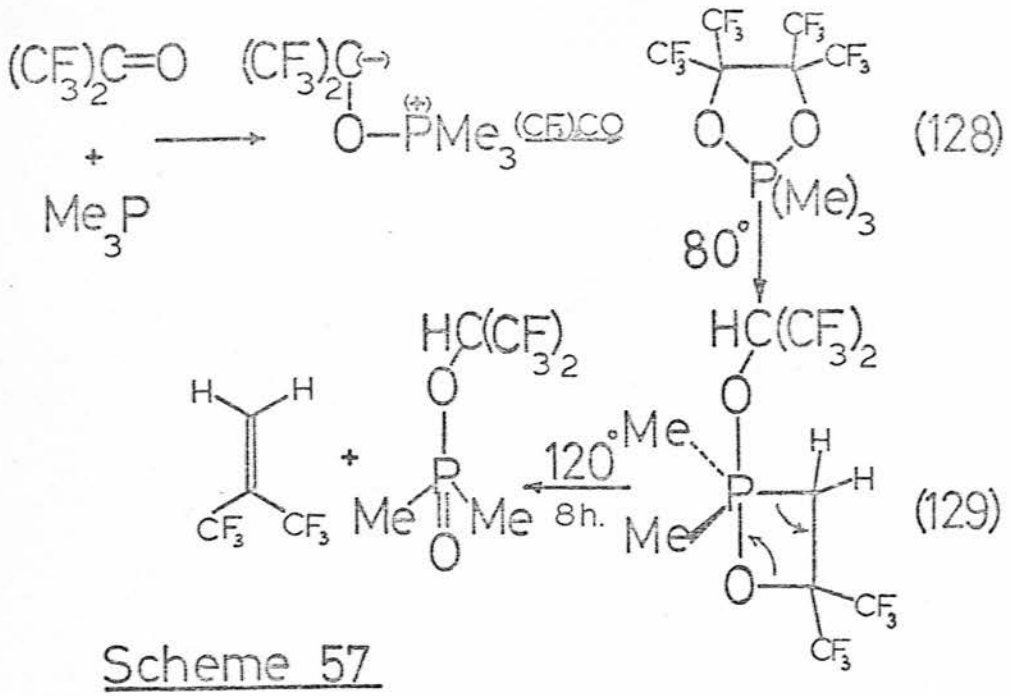
Scheme 56[19]

the 1,4,2-dioxaphospholane derivative (126).[148] However, rearrangement occurs on warming to give the 1,3,2-dioxaphospholane (127).[82] In the



(126) (127)

presence of strongly electron-withdrawing groups, the carbonyl oxygen is attacked, even at low temperatures (-70°), to give the 1,3,2-dioxaphospholane derivative. Thus, hexafluoroacetone reacts with trimethylphosphine to give the dialkoxyphosphorane (128).[149] This phosphorane undergoes a useful rearrangement,[149] when heated in benzene at 80°, to give the 1,2-oxaphosphetane derivative (129). The latter phosphorane



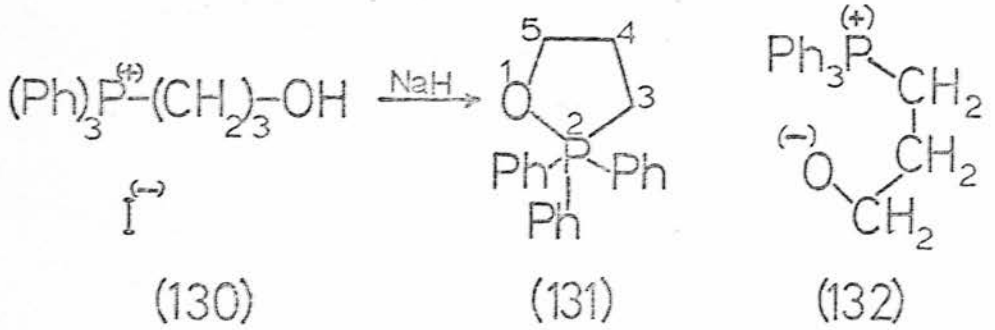
(128)

(129)

Scheme 57

decomposes on thermolysis, to give bis(trifluoromethyl)methyl dimethylphosphinate and 1,1-bis(trifluoromethyl)ethylene, as would be expected for a Wittig-type adduct (scheme 57).[149]

Several workers[150,151] have obtained phosphoranes by treatment of phosphonium salts, carrying 3- or 4-hydroxylated chains, with base. Thus, Hands et al.[151] treated 3-hydroxypropyltriphenylphosphonium iodide (130) with sodium hydride, to obtain the cyclic phosphorane (131), as in scheme 58. The alternative, betaine structure (132) was excluded by the p.m.r. spectrum, which indicated that the methylene protons in the

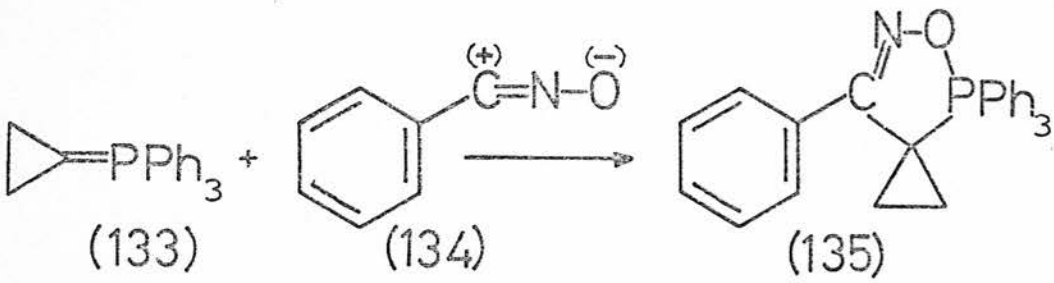


(130) (131) (132)

Scheme 58

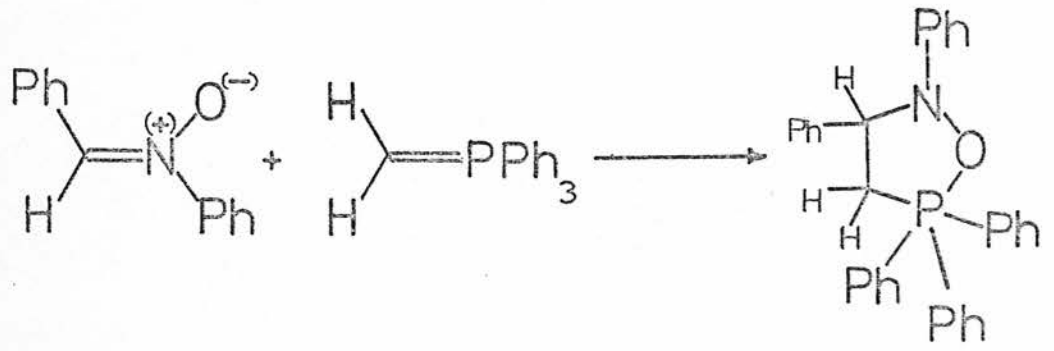
5-position were coupled to phosphorus (J_{PH} 11Hz).

1,3-Dipolar compounds can add across the double-bond of phosphine alkylenes to give cyclic phosphoranes. Thus, Bestmann et al.[152] reacted cyclopropylidenetriphenylphosphorane (133) with phenylcyanate (134), to give the adduct (135) which had a ^{31}P chemical shift of +34.1 ppm (scheme 59). Similarly, Huisgen[153] mixed C,N-diphenylnitrone (136)



Scheme 59

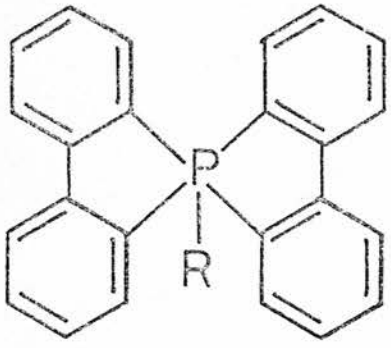
with one equivalent of methylenetriphenylphosphorane (137) in diethyl ether at 20°, to obtain the adduct (138) in 93% yield (scheme 60).



Scheme 60

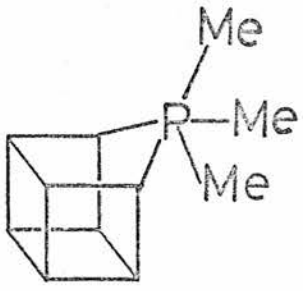
Pentaphenylphosphorane was prepared first, by Wittig et al.[32] in 1948, through the reaction of phenyl lithium with tetraphenylphosphonium

iodide. This preparation has since been extended, especially into the preparation of spirocyclic alkyl and aryl phosphoranes, e.g. (139).[154] An especially interesting derivative, trimethylhomocubylphosphorane (140), was the first stable pentaalkylphosphorane[31] to be isolated.



R=H, alkyl, aryl.

(139)



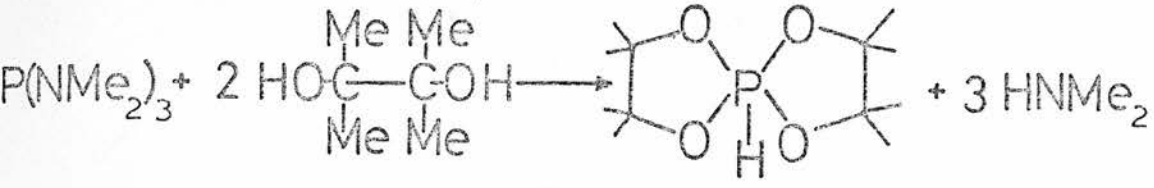
(140)

Pentaaryl, monocyclic and spirocyclic phosphoranes may also be prepared by Wittig's method,[155] through the reaction of an aryl lithium with phosphine tosylimines such as triphenylphosphine-p-tolylsulphonylimine.

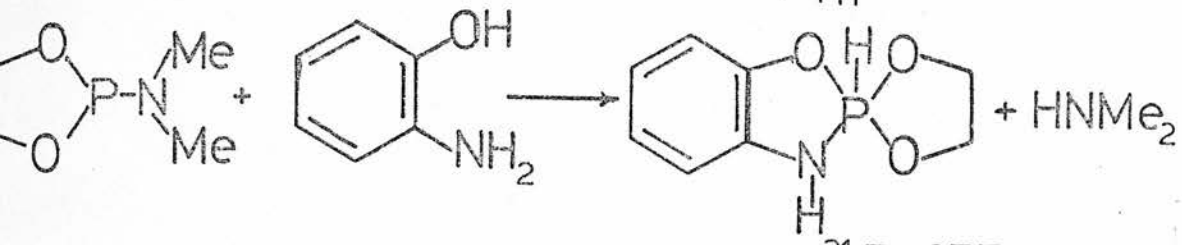
Burgada et al.[156,157] and Brazier et al.[35] have synthesised a wide range of spirocyclic phosphoranes containing a P—H bond, through the reaction of amino-substituted P(III) compounds with diols and aminoalcohols. Several examples are shown in scheme 61.

This preparation has been extended by Burgada et al. by condensation of the P—H bond of the product with aldehydes,[158] ketimines[159] and carboxylic acids[160] (scheme 62).

The reaction with carboxylic acids lends further versatility via the action of alcohols and amines on the product[160] (scheme 63).

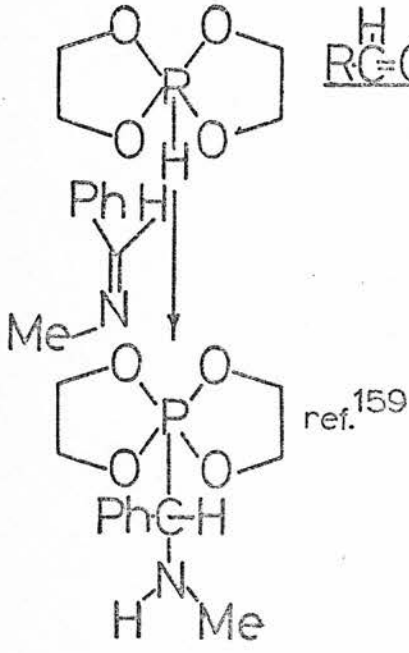


ref.[157] { $\delta^{31}P$: +40ppm. ; J_{PH} = 800Hz.



ref.[35] { $\delta^{31}P$: +37·7ppm ; J_{PH} = 825 Hz.

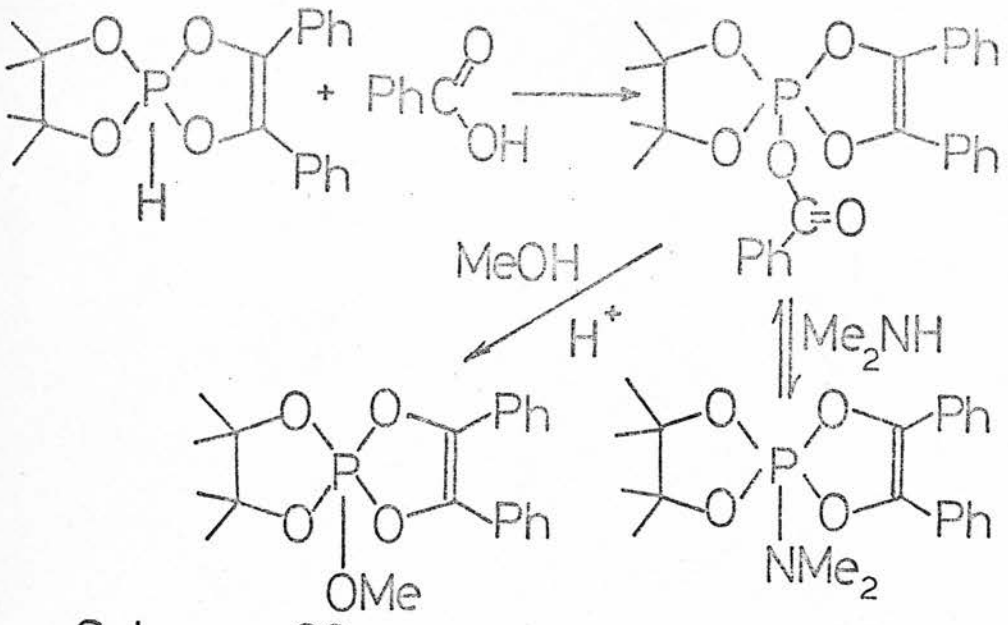
Scheme 61



ref.[158]

ref.[159]

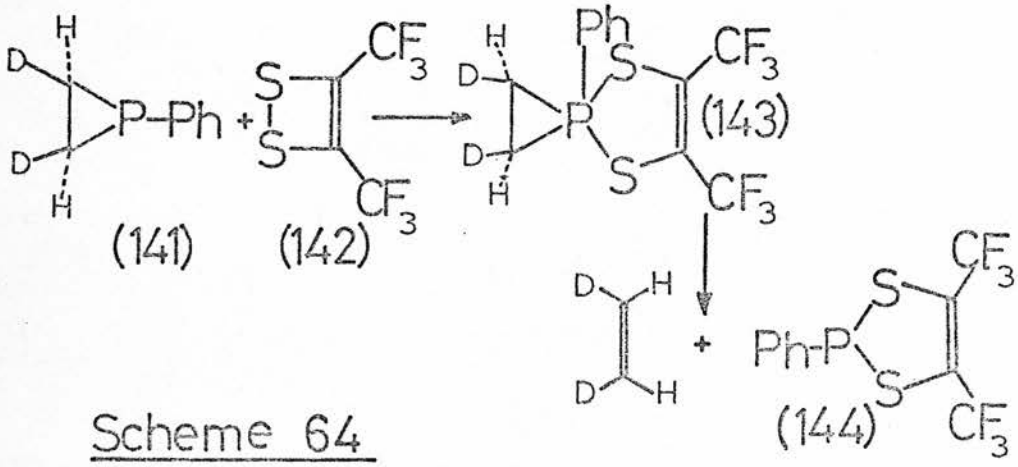
Scheme 62



Scheme 63

The preparation of four-, five- and six-membered ring compounds presents no problem; however, there are few examples of stable phosphoranes incorporated into three-membered rings.

Denney et al.[161] attempted the preparation of the spirocyclic phosphorane (143), by the reaction of the phenylphosphirane (141) with the dithietene (142) at -78° in methylene chloride. The phosphorane was not

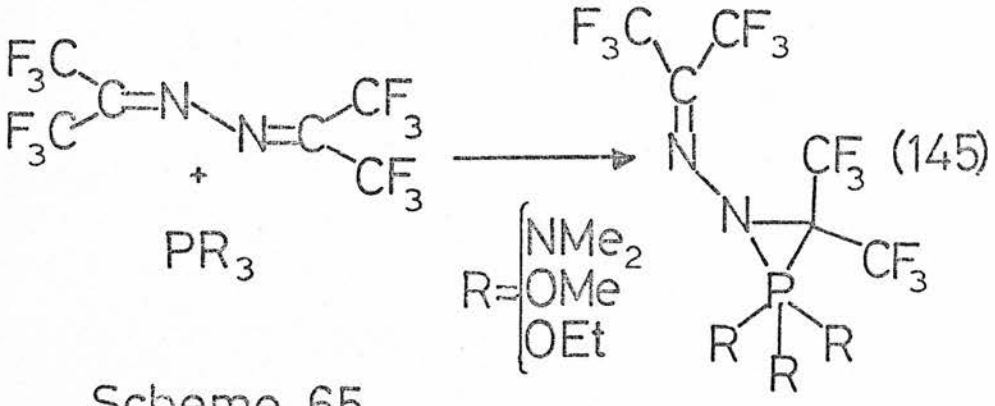


Scheme 64

isolated, but a 75% yield of the thiophosphonite (144) and 73% of ethylene were obtained. When pure cis-dideuterated phosphirane was used, only

cis-dideuterioethylene was obtained (scheme 64). Denney[161] suggested that the phosphorane (143) is formed and decomposes in concerted fashion.

The isolation of 1,2 λ^5-azaphosphoridine derivatives has been achieved by Fehn et al.;[162] the products (145) have "considerable thermal stability" (scheme 65).

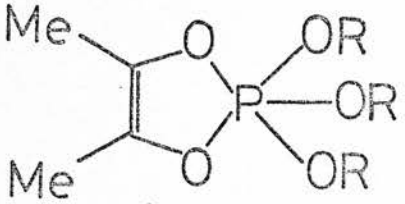


Scheme 65

(b) Thermal decomposition

Two general categories of thermal decomposition are apparent. The phosphorane may eliminate a tervalent phosphorus species, or a pentavalent phosphoryl species. In many cases, both types of product are observed.

Kukhtin et al.[163] successfully distilled the 2,2,2-trialkoxy-4,5--dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (146a) in vacuo; however, the propoxy and butoxy analogues (146b,c) decomposed to the appropriate



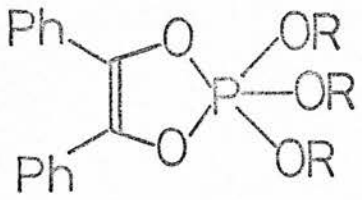
(146)a; R = Et.
b; Pr.
c; Bu.

146b,c ⟶ $(RO)_3P$
R=Pr.(50%)
Bu(72%)

Scheme 66

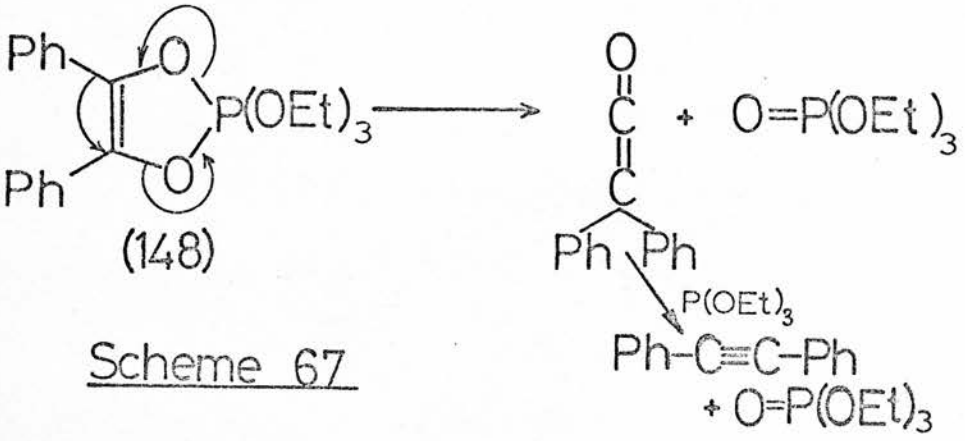
phosphites (scheme 66).

Trialkyl phosphites react with benzil to give isolable 1:1 adducts (147).[164] Mukaiyama et al.[165] heated equimolar quantities of benzil and triethyl phosphite at 215° for 15 minutes and obtained triethyl phosphate (81%), diphenylketene (11%) and diphenylketene dimer. When two molar



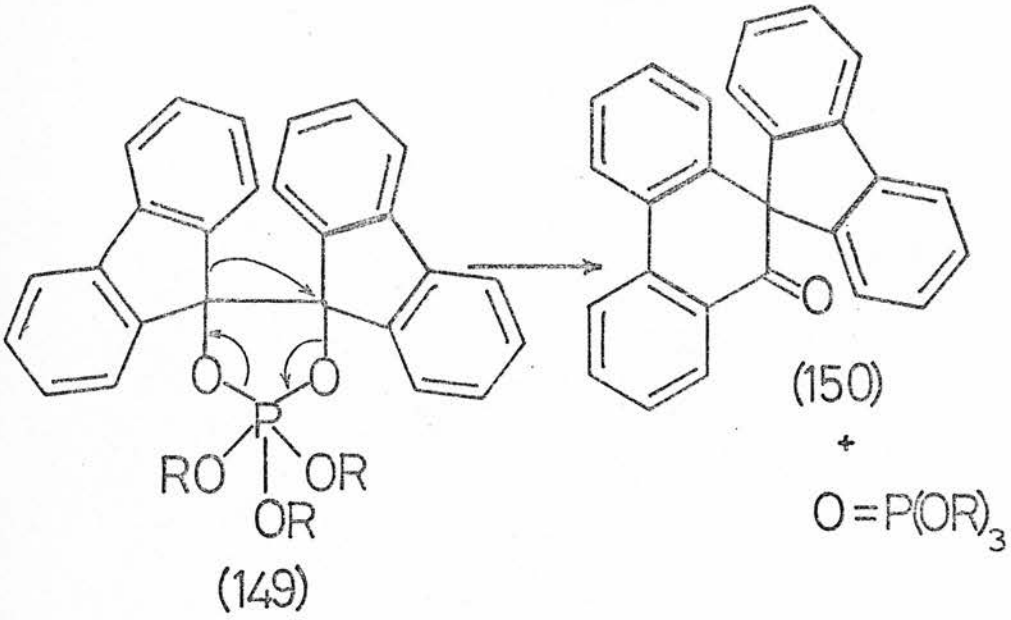
(147)

equivalents of phosphite were used, with a 2.5-hour reaction time, the products were diphenylacetylene (60%), triethyl phosphate (88%) and diphenylketene dimer (24%). These results were explained as a concerted fragmentation of the 1:1 adduct (148) to diphenylketene and triethyl phosphate. In the presence of excess phosphite, deoxygenation of the ketene yielded diphenylacetylene (scheme 67).



Scheme 67

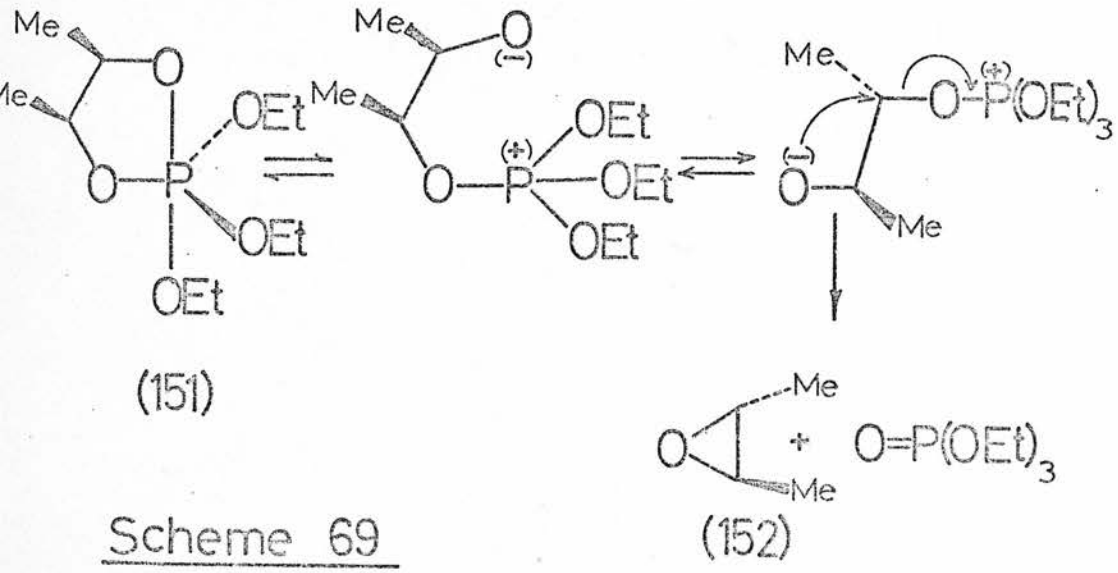
A similar rearrangement was suggested by Ramirez et al.[166] to account for the production of (150), when the dioxaphospholane (149) was heated in diglyme at 161° (scheme 68). The alternative product, fluorenone, was also isolated. Ramirez has considered the thermolysis of dioxaphospholanes in methanolic solution, in some detail.[19] In each



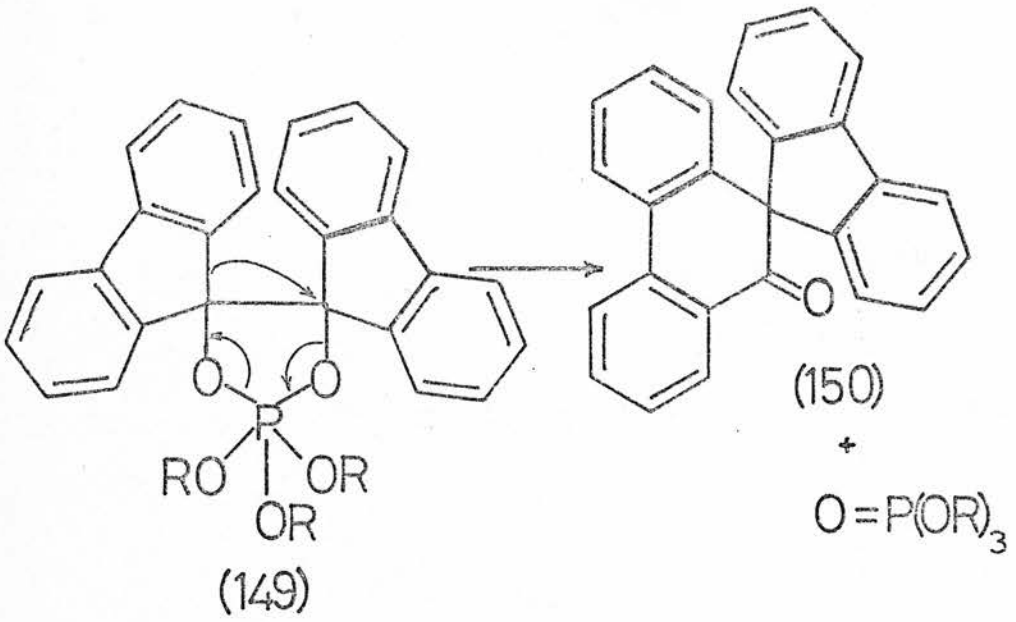
Scheme 68

case, an endocyclic O—P bond is cleaved to form a zwitterion. The fate of this species depends upon the nature of the substituents at the "ring" carbon atoms; but, in each case, the phosphorus atom is ejected as a simple phosphate with the "exocyclic" ligands intact.

Similar reactions have been studied by Denney et al.[141] The phosphorane (151) decomposed stereospecifically to the epoxide (152),



Scheme 69



Scheme 68

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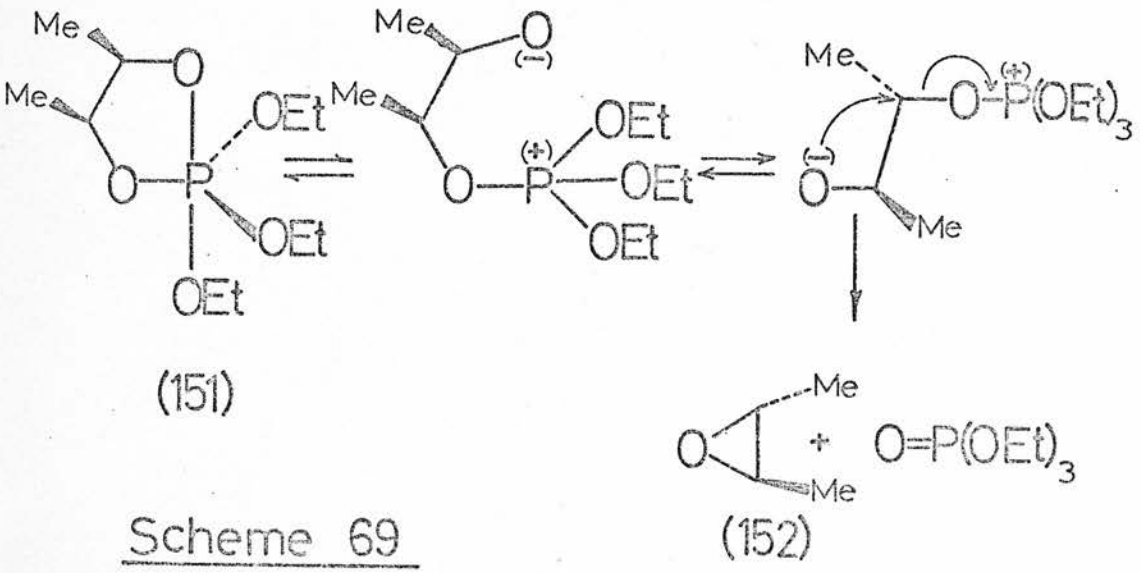
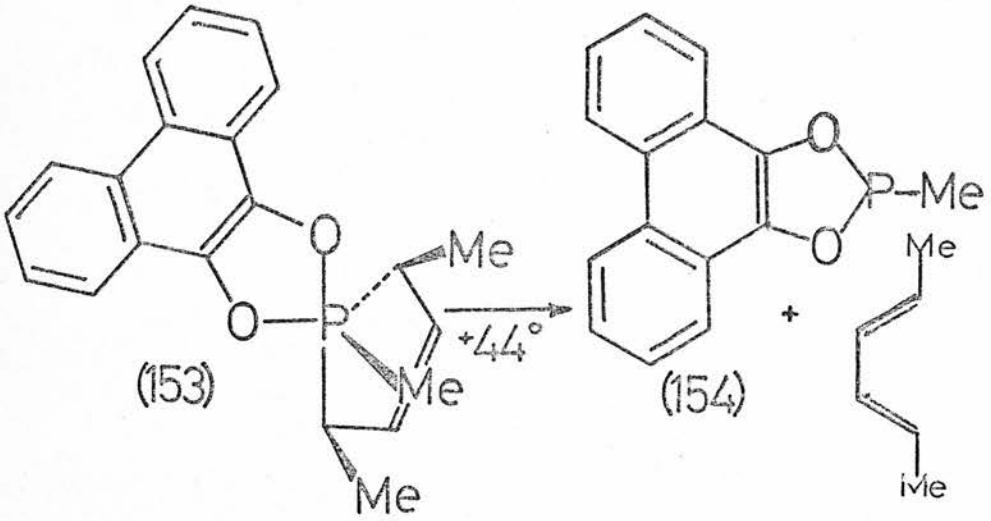


Scheme 69

when pyrolysed at 117° for 42 hours, suggesting the heterolytic mechanism in scheme 69.

In sharp contrast to these reactions, the spirocyclic phosphorane (153) fragmented, by a concerted homolytic process, to give the phosphonite (154) and 100% of trans-trans-hexa-2,4-diene as in scheme 70.[167]

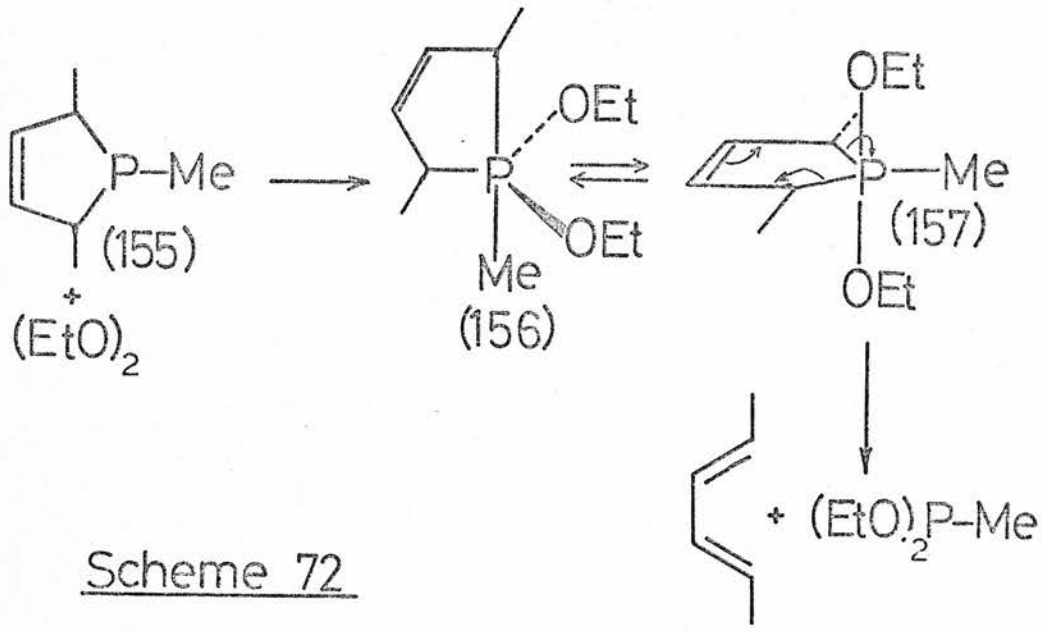


Scheme 70

It was also observed[167] that reaction of the cyclic phosphine (155) with diethyl peroxide, at room temperature, gave no isolable phosphorane. The 99% stereospecific diene was obtained once more. Hoffmann recently examined the theoretical stereochemistry for the concerted fragmentation of TBP phosphoranes. It was found[53] that diapical and diequatorial

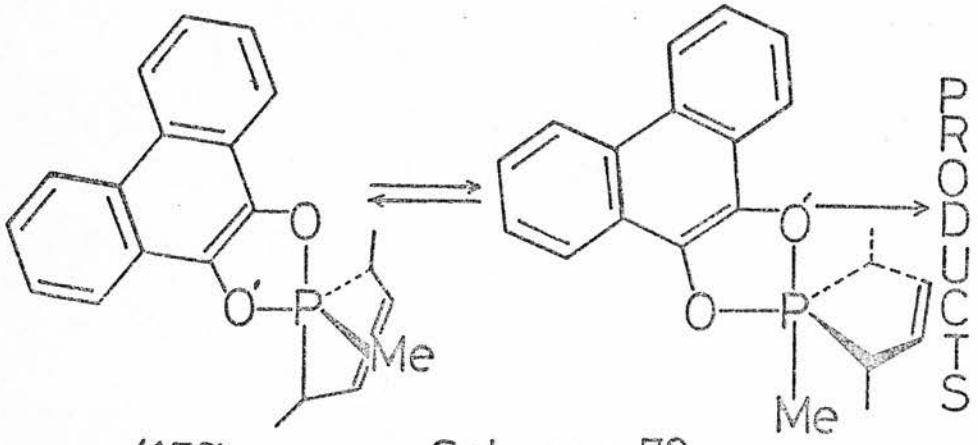
Scheme 71

fragmentations were allowed, whereas the short path, apical-equatorial fragmentation was forbidden (scheme 71). Hall et al.[167] suggested that the diene is produced from (155) via the phosphorane (156), which must rearrange by a single PI process to its isomer (157) before the allowed,[53]



Scheme 72

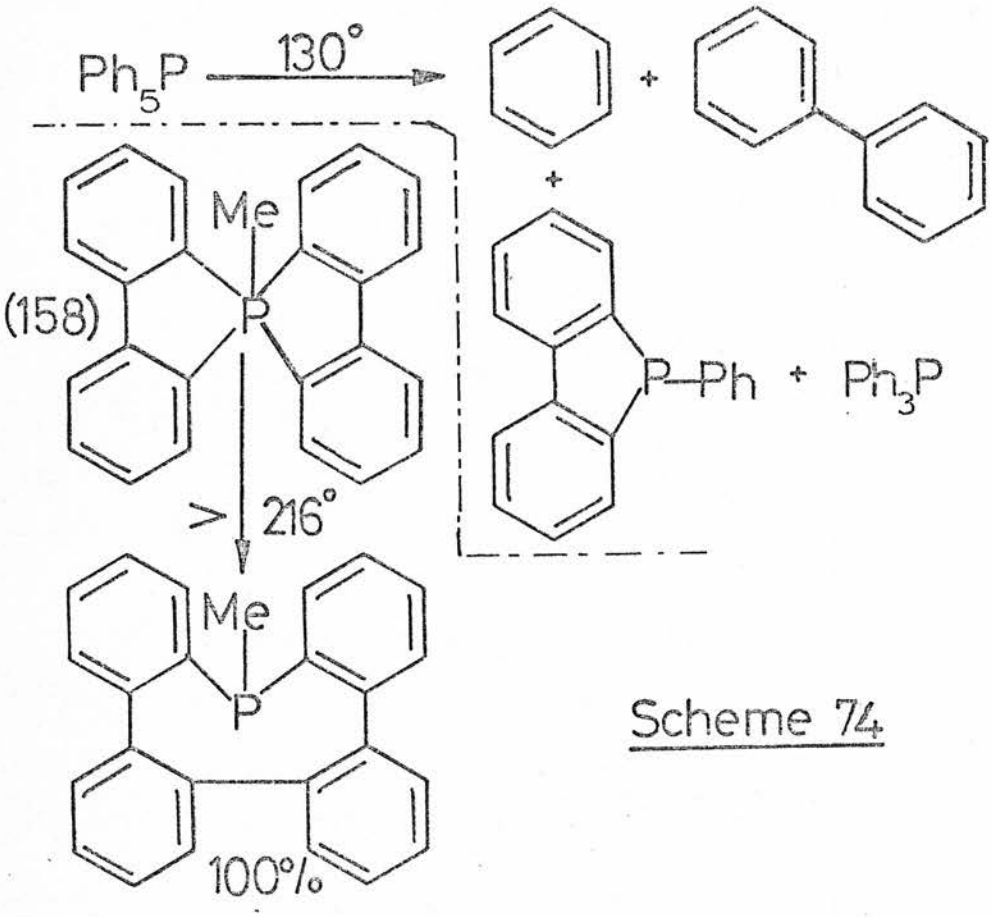
concerted fragmentation can occur (scheme 72). The energy input required to place the ring in a diequatorial distribution is partially offset by the energy released in placing the two electronegative ethoxy groups in apical positions. In contrast, fragmentation of the spirocyclic phosphorane (153) involves a PI process (scheme 73) with no such compensatory



(153) Scheme 73

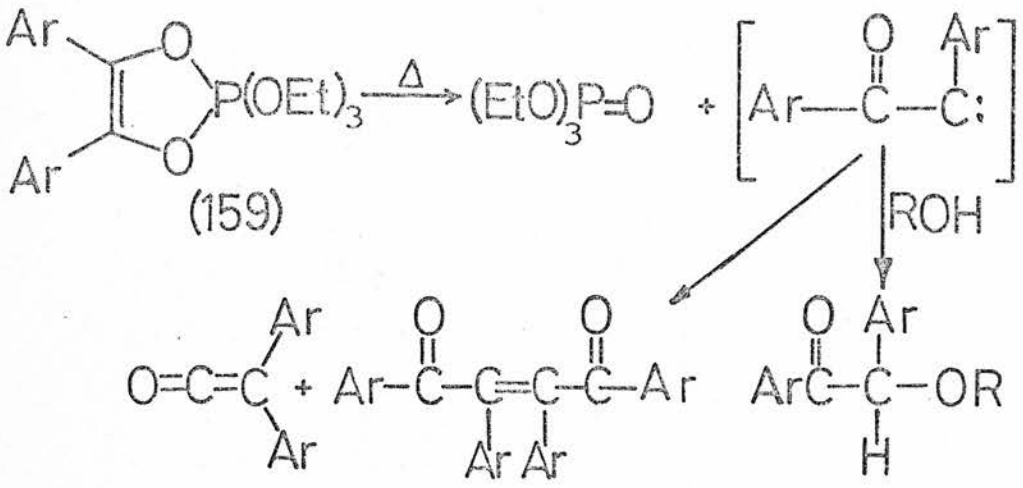
effect, since the electronegative ligands are constrained into an apical-equatorial distribution by the five-membered dioxaphospholine ring. Thus, the latter phosphorane is more stable towards thermal decomposition.

Homolytic decompositions are also implicated in the fragmentation of pentaphenylphosphorane[168] and the spirocyclic phosphorane (158) as in scheme 74.[169]



Scheme 74

Finally, a carbenoid species has been suggested,[170] to explain the products formed when the dioxaphospholene derivative (159) was thermolysed in the presence of a metal-ion catalyst (scheme 75).



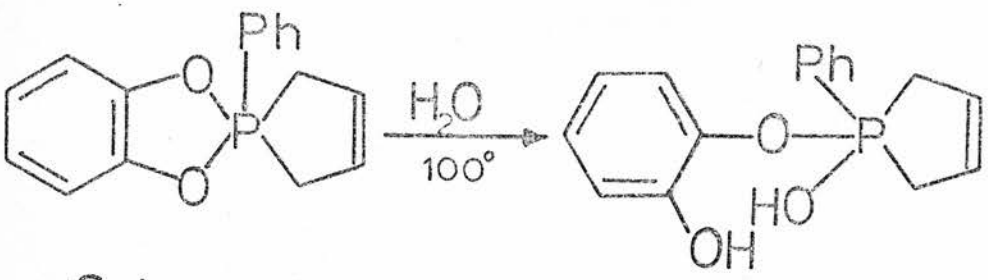
Scheme 75

(c) The hydrolysis of oxyphosphoranes

Many cyclic and acyclic oxyphosphoranes are very sensitive towards hydrolysis; the reactions are often exothermic. The hydrolytic behaviour of cyclic oxyphosphoranes has been studied extensively by Ramirez and his co-workers. Although much is known of the products, little evidence exists as to the mechanism of their formation.

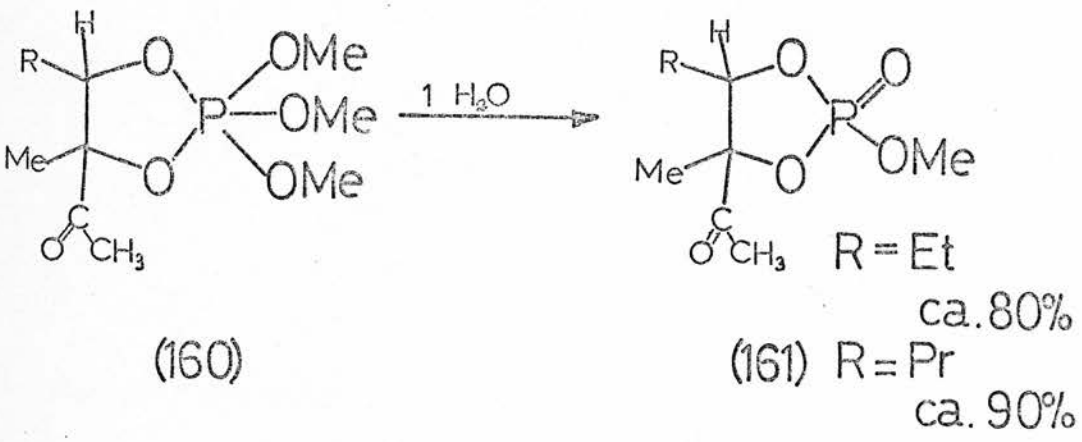
Three types of hydrolytic decomposition are commonly encountered. Firstly, the molecule may eliminate a phosphoryl species by cleavage of both endocyclic bonds; the "exocyclic" ligands remain attached to phosphorus. Secondly, the initial product may be formed by cleavage of one endocyclic and one exocyclic bond to give an acyclic phosphorus ester. Thirdly, only exocyclic cleavage may occur until the cyclic monohydroxylic ester is reached. The third of these categories is the predominant type.

The only isolable phosphorus-containing products are usually tetracoordinate species; however, Russian workers[171] have reported the isolation of a pentacoordinate hydroxylic product (scheme 76). Some representative hydrolyses will now be considered.



Scheme 76

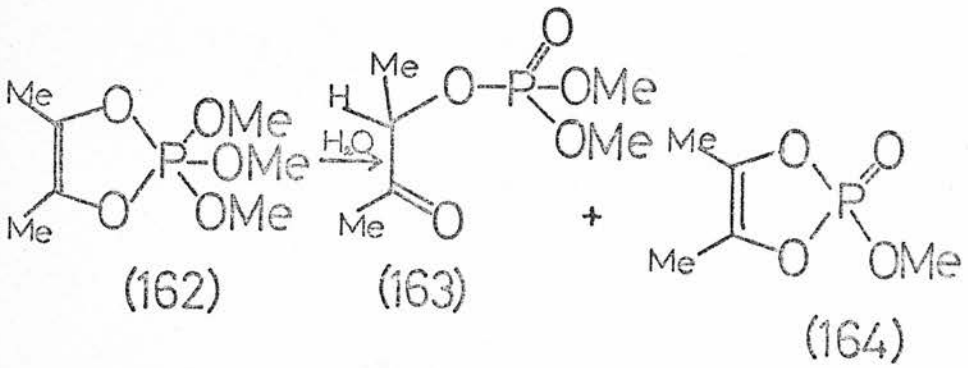
When the cyclic oxyphosphorane (160) was treated with a molar equivalent of water in benzene at 20°,[172] a large yield of the cyclic phosphate triester (161) was obtained. In contrast,[173] the dioxaphospholene derivative (162) gave 70% of the acyclic triester (163) and only



(160)

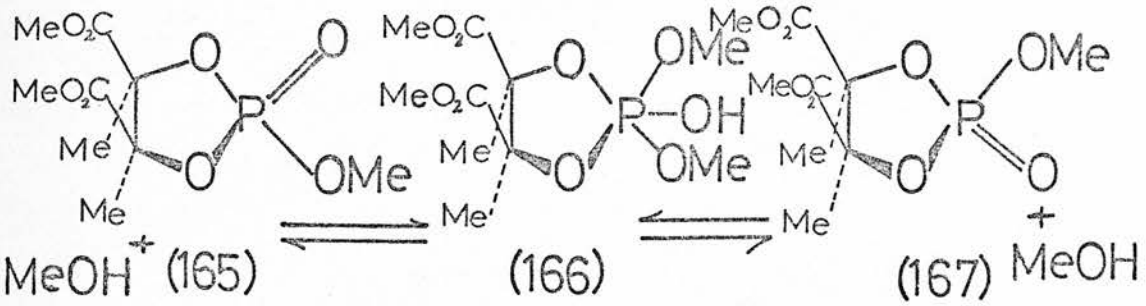
(161)

30% of the cyclic triester (164). When the same hydrolysis was allowed to proceed at 80° the major product was trimethyl phosphate.[173]



(162) (163) (164)

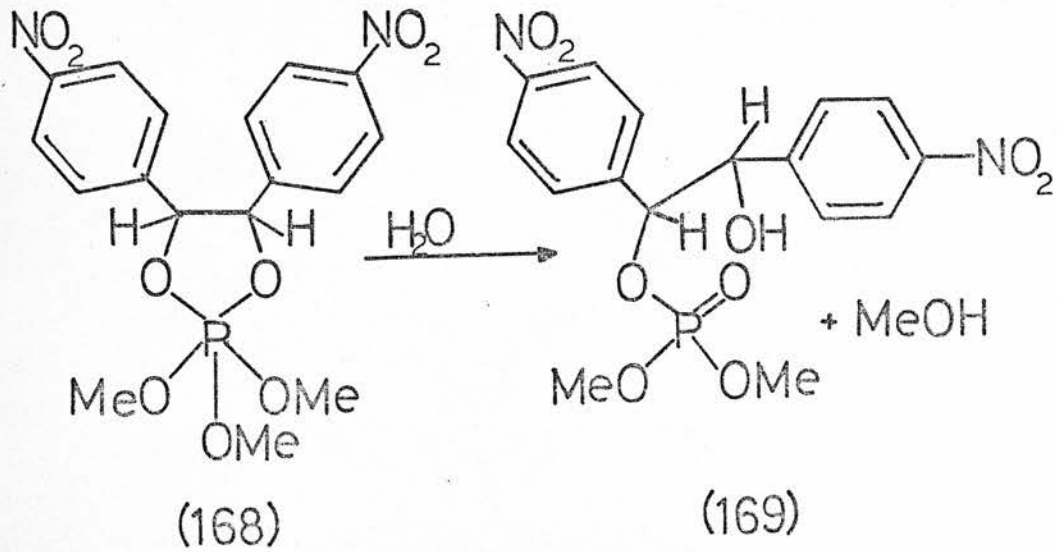
It had been shown previously by the same workers[174] that a solution of the cyclic triester (165) underwent configurational inversion at phosphorus upon ageing. It was suggested[174] that this could be due to the methanol-catalysed, reversible formation of the oxyphosphoranyl intermediate (166), as in scheme 77. This intermediate could collapse to either the original triester (165) or to the isomeric (167). An approximately equimolar mixture of the two isomers was eventually obtained.



Scheme 77

The cyclic triester (164), above, reacted rapidly with methanol to give the acyclic triester (163), above.[173] Thus the initial hydrolysis may have yielded the cyclic triester entirely, which could be subsequently attacked by methanol formed in the reaction.

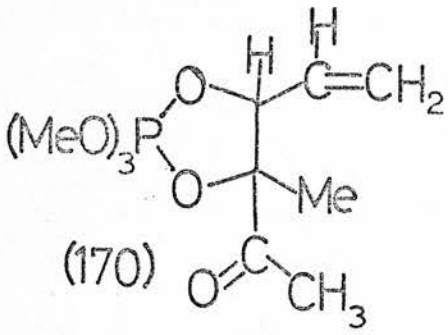
It has been reported[175] that the pentaoxyphosphorane (168) hydro-



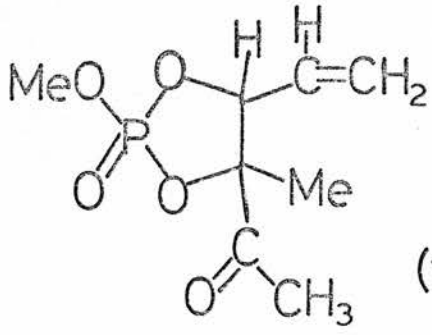
lysed exclusively to the acyclic triester (169); there was no evidence of a cyclic triester intermediate. Thus, direct endocyclic cleavage by attack of water on phosphorus may have occurred in this case.

There is a considerable tendency towards ring-retention in the attack of hydroxylic reagents on cyclic oxyphosphoranes and their cyclic phosphate derivatives.[19] It has been suggested[173] that this may be due to the increased steric strain which would be encountered in the transition state leading to ring-opening. Phosphorane derivatives of the dioxaphospholane ring-system should be more crowded than the corresponding dioxaphospholenes; hence ring preservation is less usual in the former class.[19]

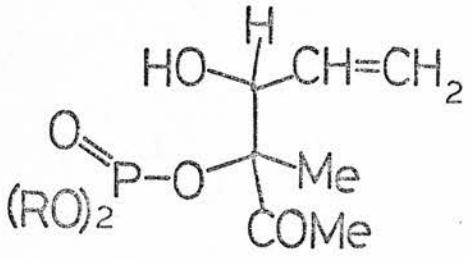
The hydrolysis of the cyclic oxyphosphorane (170) was studied in detail.[176]



(170)

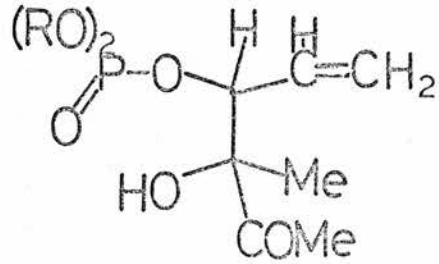


(171)



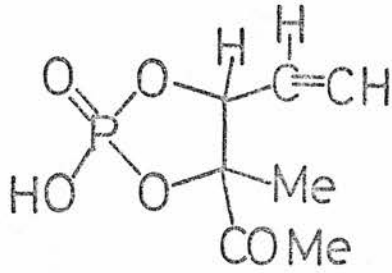
(172):R=Me

(175):R=H



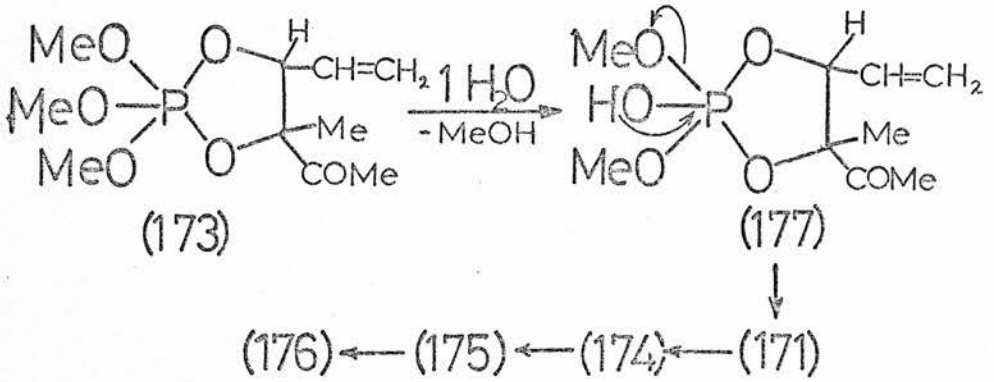
R=Me:(173)

R=H :(176)



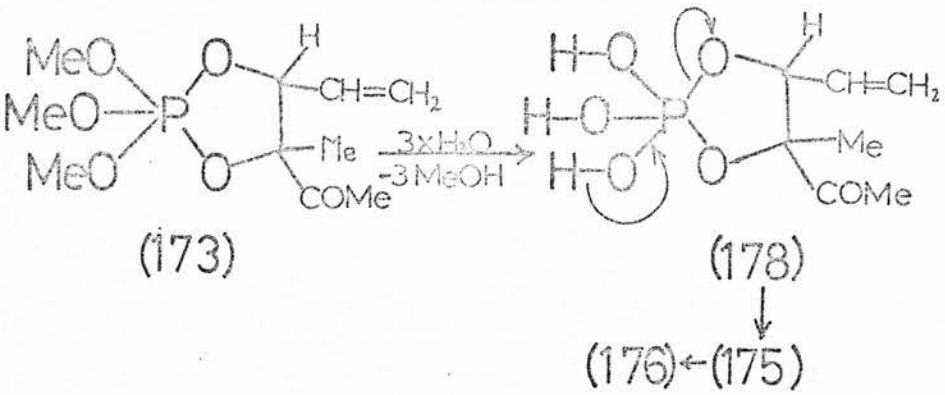
(174)

In the presence of 1 mol equivalent of water, the sole initial product was the cyclic triester (171). This triester (171) reacted rapidly with methanol to give, initially, the kinetically preferred ∝-triester (172) which rearranged, as it was formed, to the thermodynamically more stable ß-triester (173). Further hydrolysis of the cyclic triester (171) gave, initially, the cyclic diester (174), which in turn hydrolysed via the acyclic ∝-monoester (175) to the thermodynamically favoured ß-monoester (176). Hydrolysis of the cyclic oxyphosphorane (170) in the presence of excess water gave a mixture of the acyclic mono- and triesters but no acyclic diester. Two mechanisms were proposed for this last hydrolysis.[176] The oxyphosphorane (170) could undergo a substitutive displacement of methanol by water to give the cyclic pentacoordinate intermediate (177). Subsequent collapse of this intermediate would generate the final products via the formation and decomposition of the cyclic tri- and diesters (171) and (174) as in scheme 78. Alternatively, all three methoxy groups may



Scheme 78

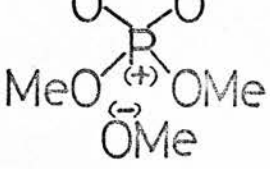
be rapidly displaced by water to give the oxyphosphorane intermediate (178), which can collapse immediately to the acyclic monoesters (scheme 79). The latter scheme was favoured[176] due to the absence of any



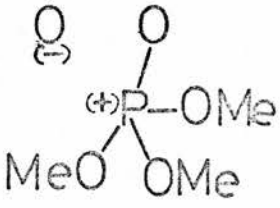
Scheme 79

acyclic diesters. However, the formation of ca. 25% of the acyclic 3-triester (173)[176] suggests that at least a part of the reaction must have proceeded via the cyclic phosphate esters.

Initial attack by water on an oxyphosphorane may proceed either by direct substitution at pentacoordinate phosphorus via an octahedral intermediate[27] or transition state; or, by attack at the phosphonium centre of an ion pair such as (179), or a zwitterion such as (180). These species being present in small, equilibrium concentrations with the phosphorane. The formation of (179) should be disfavoured by the small-ring effect (q.v.) and the zwitterion should lead directly to acyclic prod-



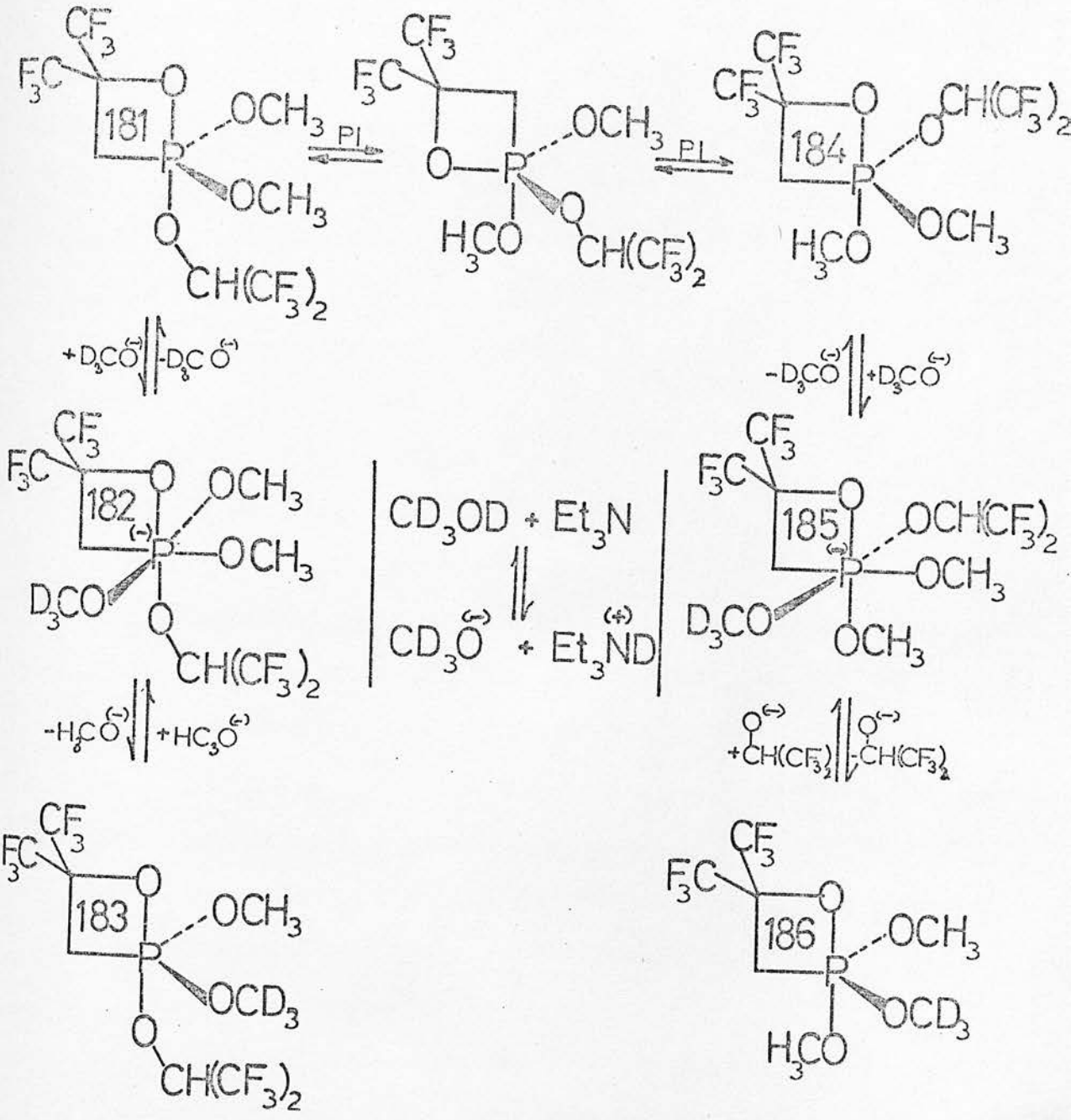
(179)



(180)

ucts,[27] which in many cases are formed only as secondary products.

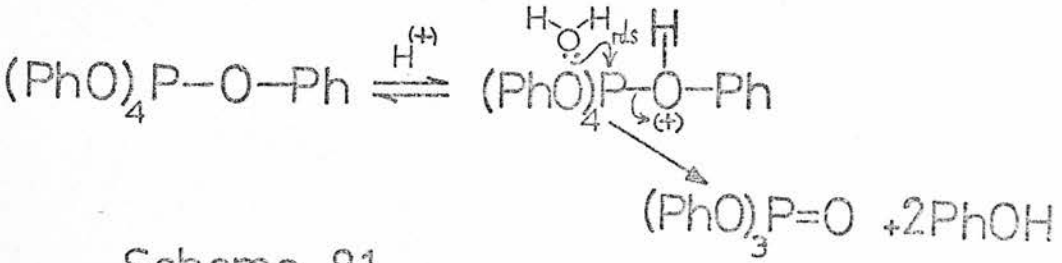
Convincing evidence for the direct substitution mechanism has been presented by Ramirez et al.[80] When a solution of the 1,2-oxaphosphetane



Scheme 80

derivative (181) was treated with CD_3OD in an n.m.r. tube at 25°, methanol was produced rapidly, in preference to the more acidic hexafluoroisopropanol. After several minutes, the methanol resonance declined and hexafluoroisopropanol was produced, together with the 1,2-oxaphosphetane derivative (186). These observations are rationalised in scheme 80. It was suggested[80] that an octahedral transition state or intermediate is involved, which can only lose an alkoxy group from an equatorial site. The highly-apicophilic hexafluoroisopropoxy ligand preferentially occupies an apical position in the substrate (181) and the PI process required to place this group in an equatorial position is slower than the irregular methanol-exchange. Hence, the kinetically favoured products are methanol and the CD_3O substituted 1,2-oxaphosphetane derivative (183), formed via the octahedral species (182). However, methanol can attack the small concentration of the substrate isomer (184) to give the thermodynamically favoured, trimethoxy-substituted 1,2-oxaphosphetane derivative (186) and hexafluoroisopropanol, via (185).

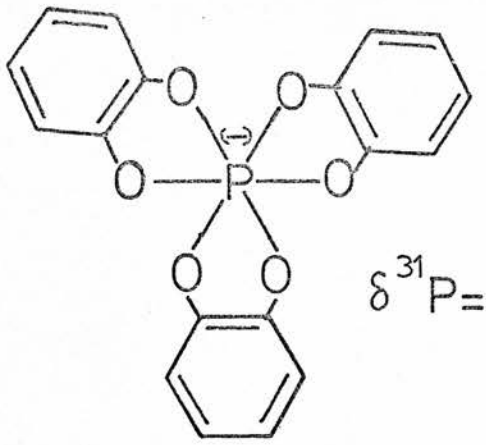
Westheimer et al.[177] have recently studied the kinetics of the hydrolysis of a series of pentaaryloxyphosphoranes, in detail. Reaction occurred in neutral solution but was greatly accelerated in the presence of both acid and base. The hydrolytic behaviour in basic and neutral solution was consistent with the intermediacy of an octahedral species. The acid-catalysed process was less clearly assignable, but indicated pre-equilibrium protonation, followed by rate-determining attack by water



Scheme 81

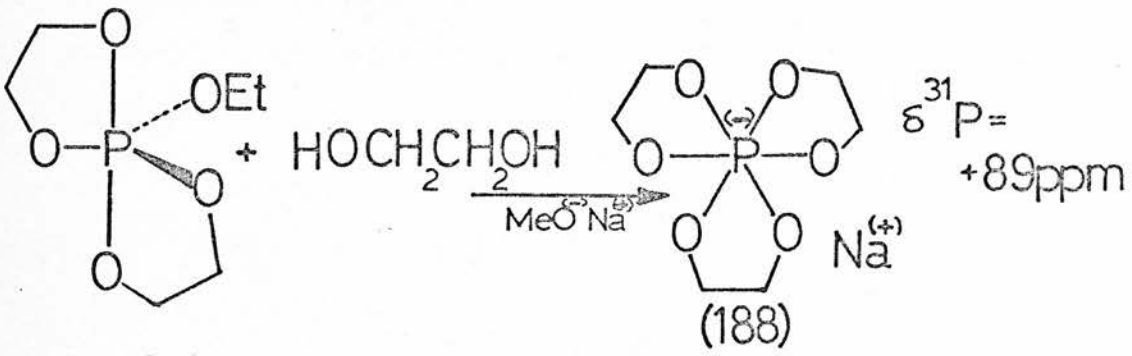
via a crowded transition state. Scheme 81 is, at least, consistent with these results.

Stable octahedral phosphorus species are well known. For example, Hellwinkel et al.[178] have isolated (187) and Denney et al.[179] have obtained (188) by the reaction in scheme 82. Octahedral species are



(187)

$\delta^{31}P = +82$ ppm



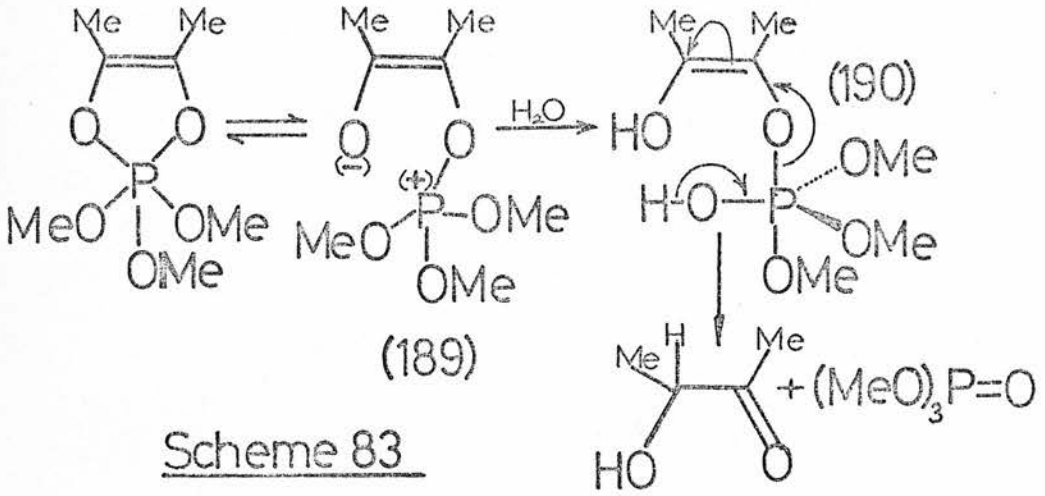
(188)

Scheme 82

characterised by large positive ^{31}P chemical shifts.

It seems likely that both pre-ionisation and direct substitution mechanisms occur in the hydrolysis of cyclic oxyphosphoranes. The alcohol-exchange reaction[80] described above failed to occur in either neutral or acidic solution, but occurred readily in the presence of base, suggesting that basic hydrolysis may well occur via an octahedral species. In contrast, the high temperature hydrolysis[173] which produced mainly trimethyl phosphate may be best explained by a pre-ionisation

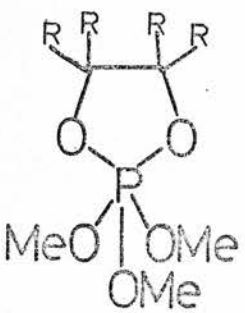
mechanism. Ring cleavage gives the zwitterion (189), which is attacked rapidly by water at the phosphonium centre, generating the intermediate oxyphosphorane (190). Ring constraints are absent, hence the more labile group (acetoin) is displaced (scheme 83). Denney et al. have



Scheme 83

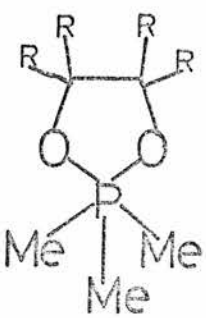
shown[41] that the extent of ionisation in phosphoranes increases with temperature; this may explain the temperature-dependent mechanism of hydrolysis above.

The pre-ionisation mechanism is supported by several other experimental observations. Ramirez et al.[52] have reported that, whereas the pentaoxyphosphorane (191) shows an invariant ^{31}P chemical shift in solutions containing various concentrations of hexafluoroisopropanol and is remarkably stable towards hydrolysis, the dioxyphosphorane (192) has a strongly solvent-dependent chemical shift and is instantly destroyed by



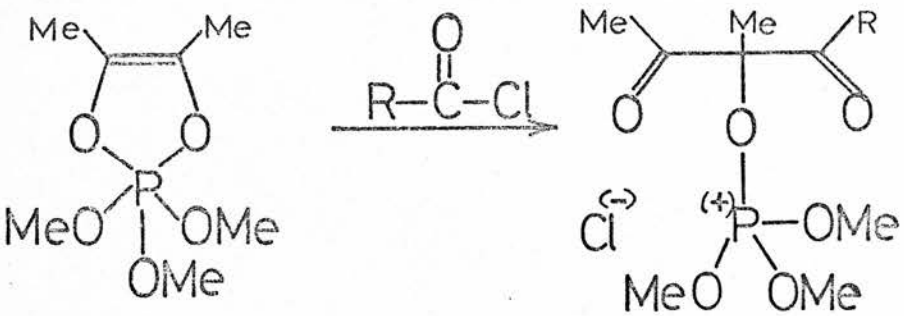
(191)

R = CF_3



(192)

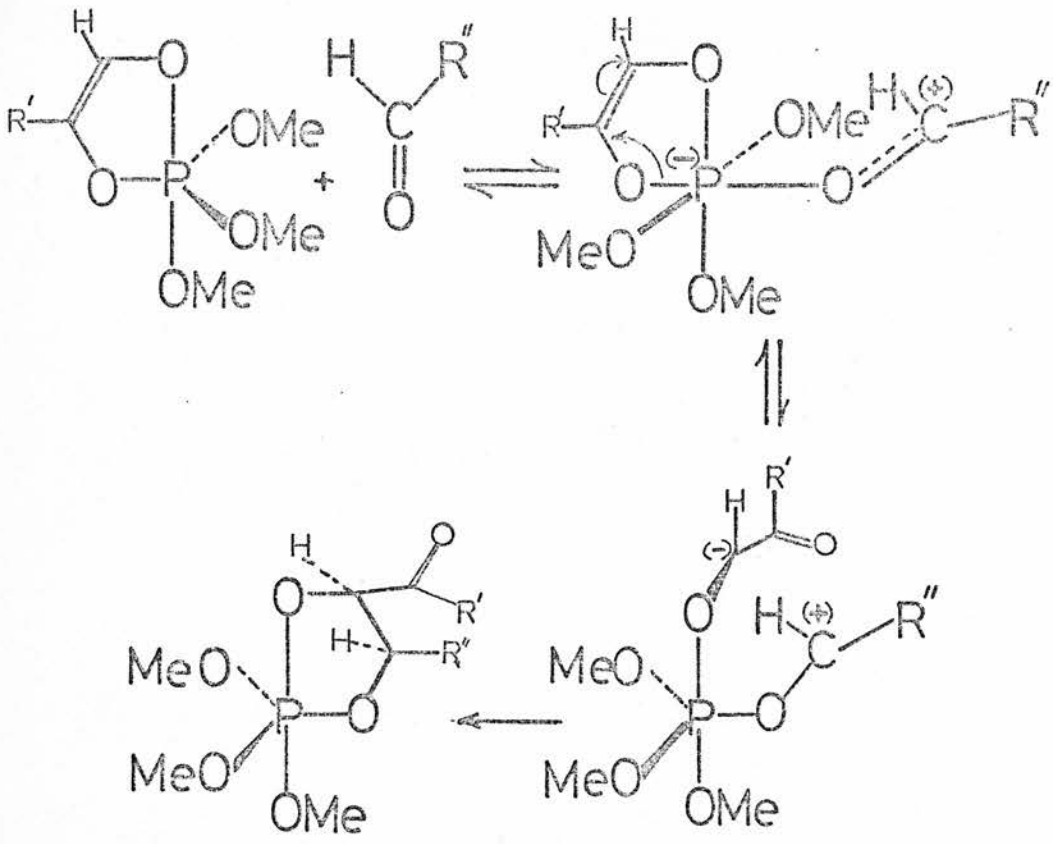
water. Solvent-dependence is indicative of an equilibrium between ionic and non-ionic forms of a molecule; the inference is that the ionised form is highly prone to attack by water. When the pentaoxyphosphorane (193) was treated with incompletely dry acyl chlorides, trimethyl phosphate was a major byproduct.[180] The acylation reaction is believed to proceed via the intermediate phosphonium species (194) and the analogy to the reaction in scheme 83 is obvious.



(193) (194)

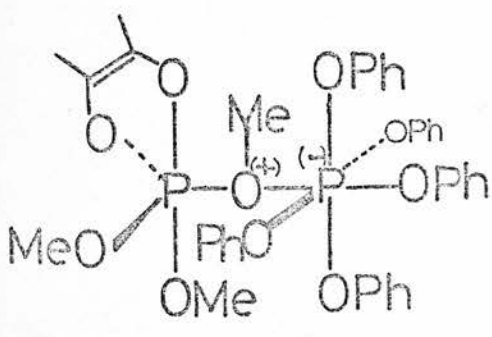
(d) Octahedral species in other reactions

Apart from hydrolysis and alcohol exchange, several other reactions may involve octahedral species. Oxyphosphorane derivatives of the dioxaphospholene system react with a wide range of carbonyl compounds. These condensations are stereospecific and follow a rigid pattern. Ramirez has discussed these reactions in detail.[19] The observed products suggest[19] the mechanism in scheme 84. A proton is shown at the quasi-apical position of the dioxaphospholene ring and the carbonyl has been drawn as an aldehyde. These features are not obligatory, but it is the steric interactions between these groups which determine the nature and stereochemistry of the products.

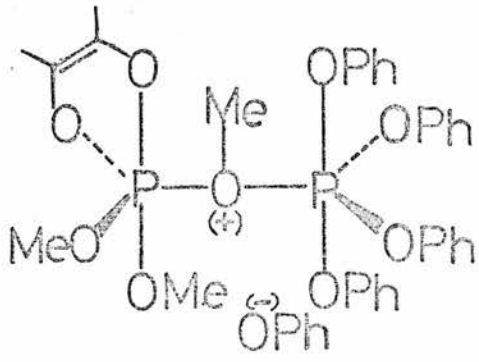


Scheme 84

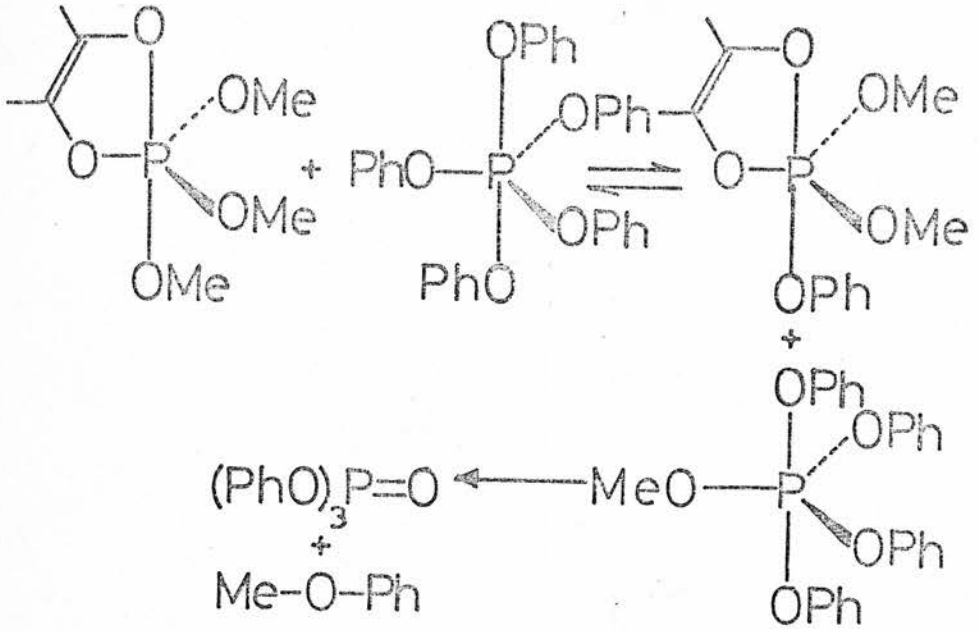
An interesting example of irregular ligand-exchange has recently been observed.[15] When a relatively stable five-membered cyclic oxyphosphorane and a less stable acyclic oxyphosphorane interacted in benzene solution at 25°, ligand-exchange occurred (scheme 85: see overleaf). Two possible intermediates (195) and (196) have been proposed. The former involves an octahedral centre.



(195)



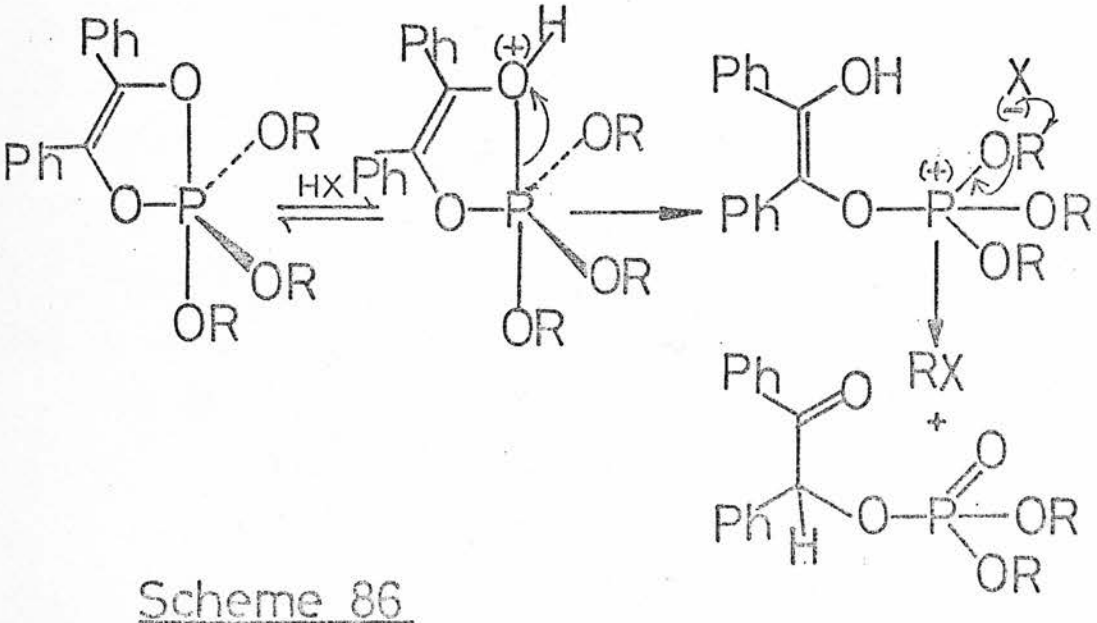
(196)



Scheme 85

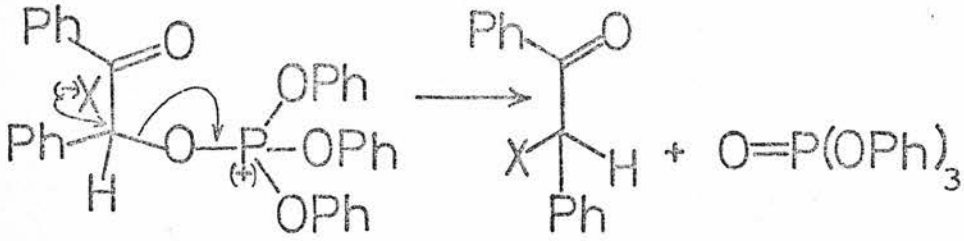
(e) Other reactions involving tetrahedral species

Pentacoordinate derivatives of the 1,3,2-dioxaphospholene system react readily with hydrogen halides as in scheme 86. Attack by halide



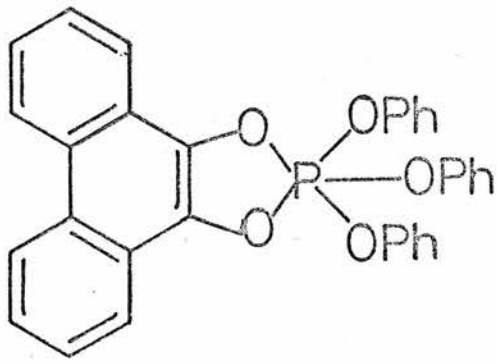
Scheme 86

ion on an "exocyclic" carbon of the phosphonium intermediate is preferred but, if this is unfavourable, as in scheme 87,[164] attack may occur at the



Scheme 87

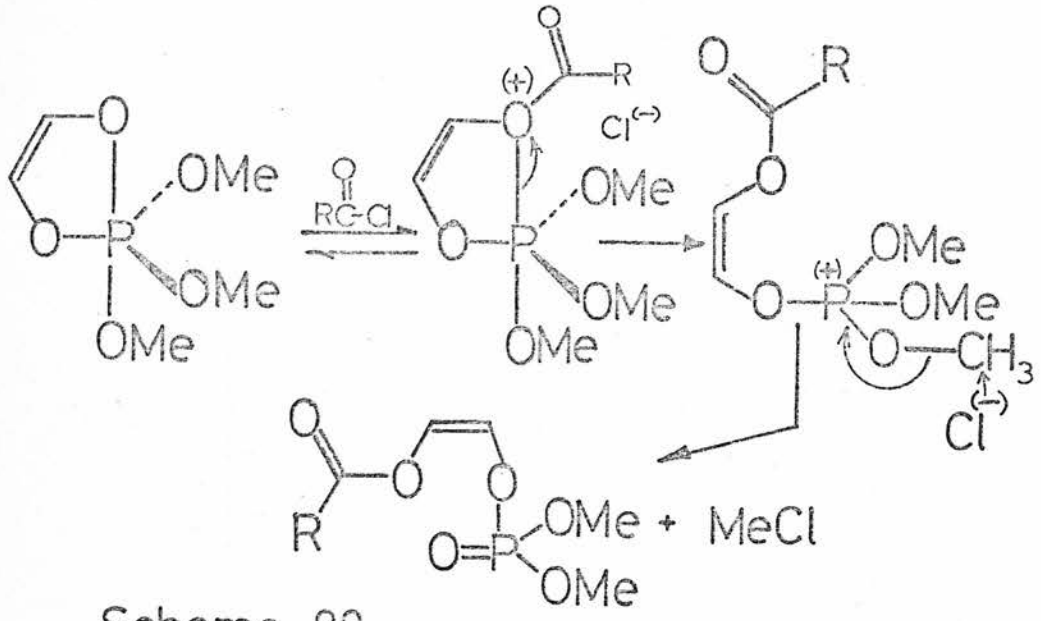
"endocyclic" carbon. Blocking both positions as in (197)[164] renders the phosphorane inert to attack by hydrogen halides.



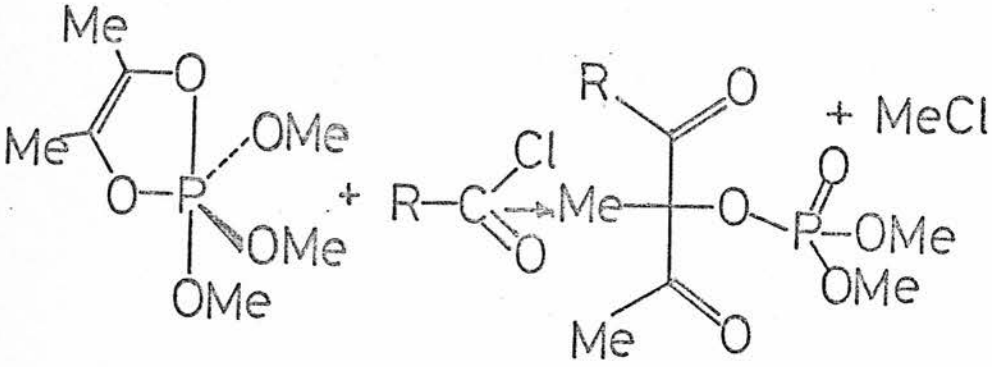
(197)

Similar reactions can occur with acyl halides;[181] the acyl group attacks the endocyclic apical-oxygen in place of the proton (scheme 88). However, this is sterically prevented when the dioxaphospholene ring carbons carry substituents other than protons. In the latter, more normal case endocyclic C-acylation[180] (scheme 89) or exocyclic O-acylation[19] occurs instead. The latter reaction gives the ester of the acylating agent and an enediolcyclophosphate. The balance between these two alternatives is strongly affected by the solvent and the halogen atom.[19]

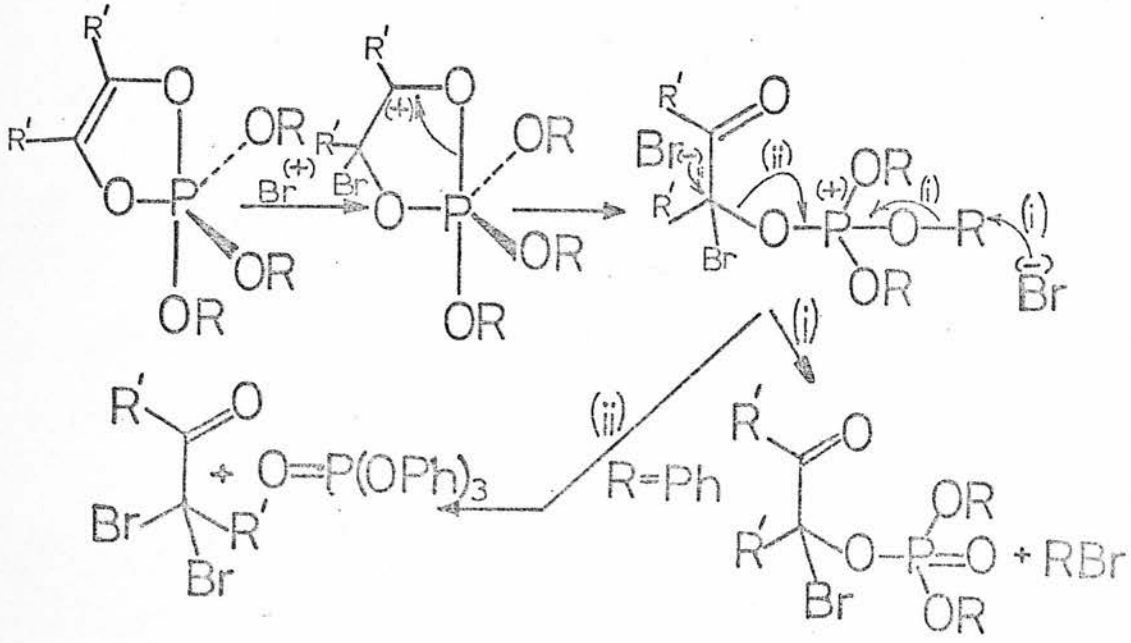
1,3,2-Dioxaphospholene derivatives also react readily with halogens,[164] as in scheme 90. The halonium ion adds to the endocyclic quasi-apical carbon adjacent to the more basic endocyclic apical-oxygen. A phosphonium



Scheme 88



Scheme 89



Scheme 90

halide is formed, once again, by rupture of the endocyclic, apical P—O bond. Subsequent attack by halide ion occurs preferentially at an "exocyclic" alkoxy group (path (i)); if this is prevented, "endocyclic" attack occurs (path(ii)).

The dioxaphospholene derivatives also react with ozone[182] and with molecular oxygen,[182] although slowly.

The reactions of analogous dioxaphospholanes are less extensive due to the lack of an endocyclic double-bond.[19]

Acyclic oxyphosphoranes are highly reactive and, with the exception of transesterification by diols,[23,20] reactions usually result in tetra-coordinate phosphorus species. Potentially useful reactions include facile alkylation of mildly acidic species such as phenols.[28]

7. The Reductive Cyclisation of Aromatic Nitro-compounds

The reductive cyclisation of aromatic nitro-compounds was reported first in 1962,[183] when 2-nitrobiphenyl was boiled with triethyl phosphite to give carbazole in 82.5% yield. Since that time, Cadogan and his co-workers have made a detailed study of the reaction.

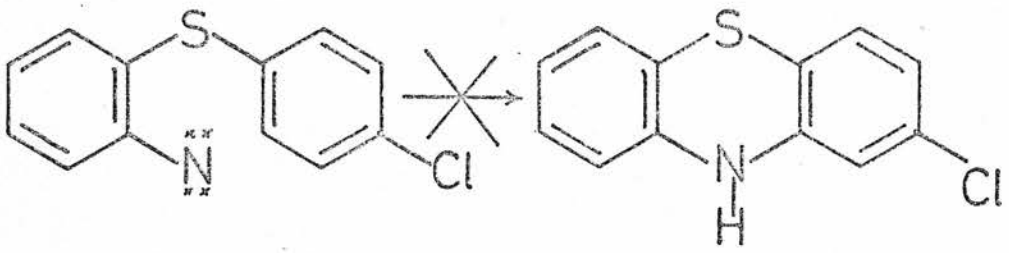
The reactions may, in principle, proceed through the intermediacy of nitrenes, or of a nitrene precursor such as (198). In some cases,[184]

$$(RO)_3\overset{(+)}{P}—O—\overset{(-)}{N}—Ar \qquad (198)$$

there is good evidence for nitrenes, although in others[185] the latter mode cannot be excluded.

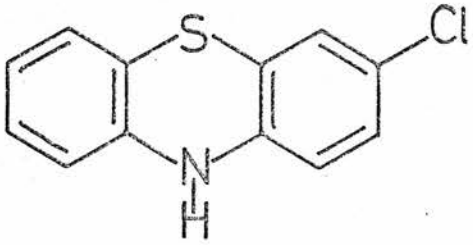
The deoxygenation of aryl 2-nitroaryl sulphides has provided considerable interest. It was found that 2-nitrophenyl phenyl sulphide gave phenothiazine in 60% yield.[186] Closer examination[187] of the products

from the reaction of substituted phenyl 2-nitrophenyl sulphides with triethyl phosphite revealed that, instead of the product expected from a direct insertion by the nitrene into the C—H bond ortho to the



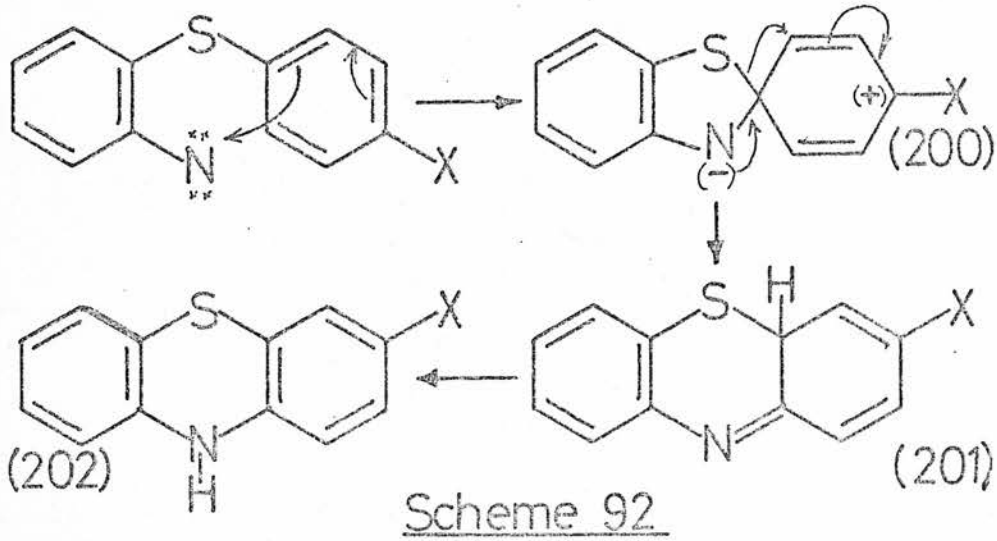
Scheme 91

sulphide link (scheme 91), the isomeric phenothiazine (199) was formed.



(199)

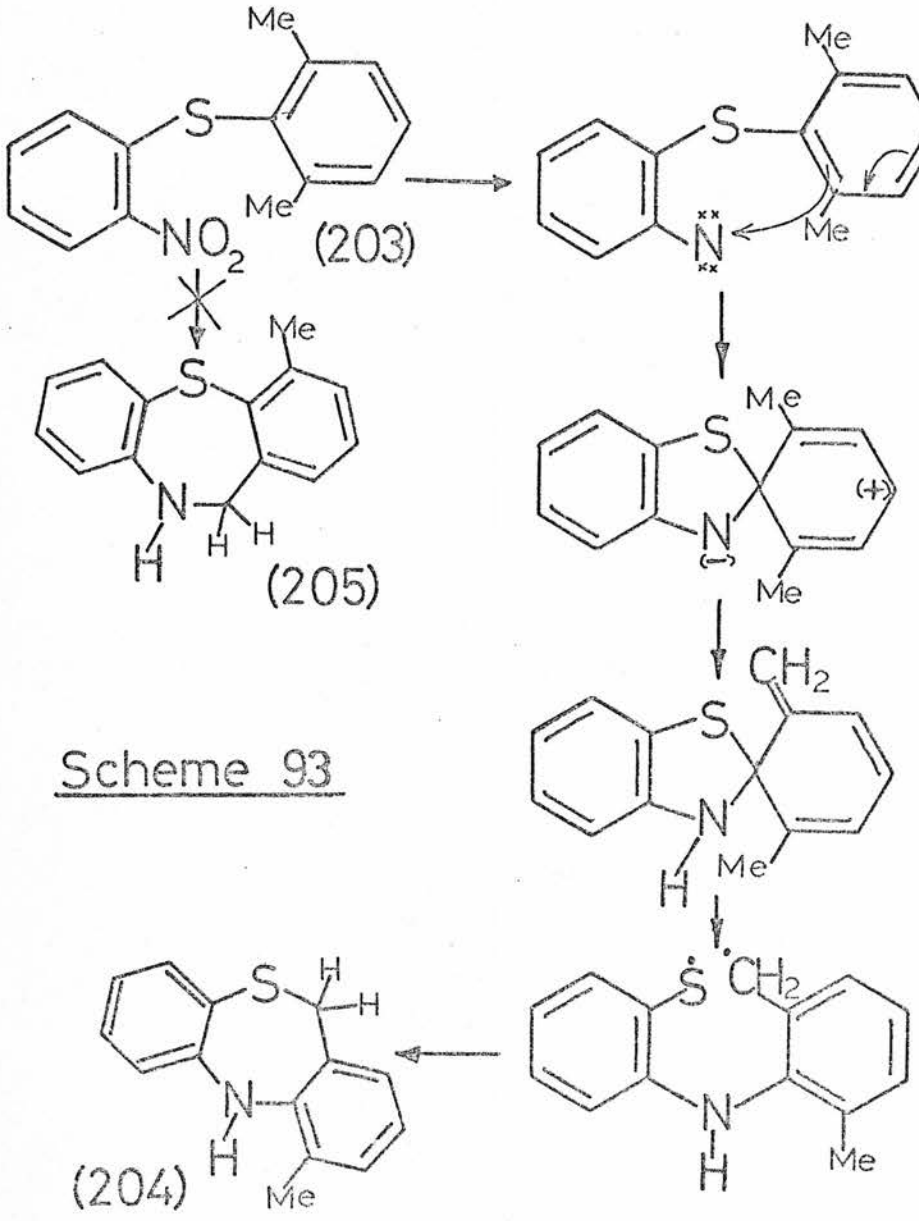
It was suggested that the reaction must proceed, instead, via a five-membered, spirocyclic intermediate (200), formed by nitrene attack at the electron-rich 1'-position (scheme 92), which then rearranged by a



Scheme 92

1,3-sigmatropic shift to the intermediate (201). The product (202) was formed subsequently, by a stabilising prototropic shift from one of the (originally) 2'-positions.

The effect of preventing this final prototropic shift was thm investigated by blocking the ortho-positions with groups other than hydrogen. Once again, the direct insertion products were not obtained. Thus 2,2-dimethylphenyl 2-nitrophenyl sulphide (203) gave the thiazepine (204) rather than the isomer (205).[185] The result was rationalised by the steps in scheme 93.[185]



Scheme 93

Thermolysis of the corresponding azides[185] has produced similar results. In contrast, attempts to cyclise aryl 2-azido aryl ethers had failed.[188]

Lim[189] set out to investigate whether the "blocked-ortho effect" would result in the successful cyclisation of these compounds. When 2,6-dimethylphenyl 2-nitrophenyl ether was boiled with excess triethyl phosphite in cumene, the expected oxazepine was obtained, but only in 5% yield. However, a previously unidentified product was also isolated, in 70% yield.

Investigation of the synthesis and chemistry of analogues of the latter compound has been the major aim of this research.

S E C T I O N I I

EXPERIMENTAL

SYMBOLS AND ABBREVIATIONS

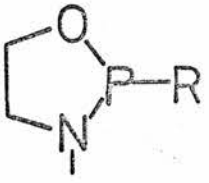
b. p.	boiling point
m. p.	melting point
t. l. c.	thin-layer chromatography
R. f.	ratio of distance moved by component to that moved by solvent
g. l. c.	gas liquid chromatography
R. t.	retention time
n. m. r.	nuclear magnetic resonance
s; d; t	singlet; doublet; triplet
J	coupling constant
i. r.	infrared
(s); (m); (w)	strong; medium; weak
M^+	mass of molecular ion
m/e	mass to charge ratio
m^*	metastable peak
$t_{\frac{1}{2}}$	half-life time
h; min; s	hours; minutes; seconds
ppm	parts per million
mMol	millimoles

II

EXPERIMENTAL

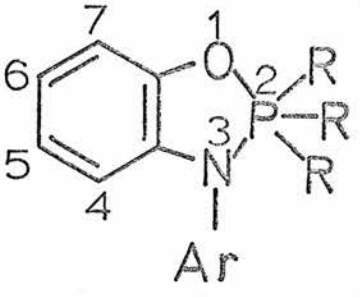
1. General Nomenclature

The names of the cyclic phosphoranes and their cyclic derivatives have been derived from a scheme outlined by Ramirez.[19] The basic unit is taken as the tervalent 1,3,2-oxazaphosphorus species (1).



(1)

Pentacoordinate phosphorus structures are then indicated by the prefix 2,2-dihydro. Thus, the generalised phosphorane (2) is named as

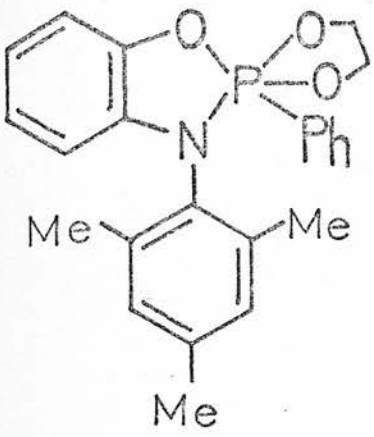


(2)

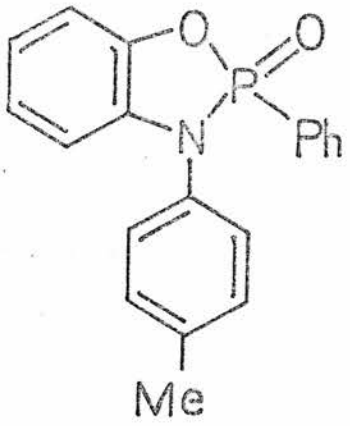
2,2,2-triR-3-Ar-2,2-dihydrobenz-1,3,2-oxazaphospholine. One exception to standard nomenclature has been retained to emphasise derivation from this basic structure: this is the derivative (3), which is named below as spiro-2,2-ethylenedioxy-3-mesityl-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine.

A typical cyclic tetracoordinate derivative is shown in

diagram (4) and is named as 2-oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxaza-phospholine.



(3)



(4)

2. General Experimental Techniques and Instrumentation

(a) Techniques

Due to the water-lability of the phosphoranes and their primary hydrolysis products all materials, apart from general chemicals, aryl 2-nitrophenyl ethers and compounds of generally known air and water stability, were handled in a dry-box flushed with nitrogen. Recrystallisations were performed under dry nitrogen fed to the top of a reflux condenser connected to the flask.

Similarly, all products were encapsulated in the dry-box and stored in dessicators over phosphorus pentoxide.

Reactions involving these materials were generally performed in an atmosphere of dry nitrogen.

(b) Instrumentation

Melting points were obtained on a Kofler hot-stage microscope apparatus.

Infrared spectra were recorded on a Perkin-Elmer 157G Grating

spectrophotometer. Solids were examined as nujol mulls and liquids as thin films. Solution spectra were obtained using matched cells (path length 0.1 mm) with sodium chloride windows. Polystyrene w_{max} 1603 cm^{-1} was used as reference for calibration purposes.

Proton magnetic resonance spectra were recorded on a Varian Anaspect EM-360 n.m.r. spectrometer, operating at 60 MHz with a probe temperature of 33°, or on a Varian HA-100 instrument, operating at 100 MHz with a probe temperature of 28°. Chemical shifts were recorded as τ values in ppm using tetramethylsilane (T.M.S.) as reference.

^{31}P Magnetic resonance spectra were obtained on a Varian HA-100 spectrometer or on an XL-100 instrument. All chemical shifts are quoted with respect to 85% phosphoric acid; upfield resonances are positive, downfield resonances are negative.

Mass spectra and exact mass measurements were recorded on an AEI MS 902 mass spectrometer. G.l.c./mass spectrometry was performed on a system employing a Pye 104 g.l.c. instrument linked to a V.G. Micromass 12 spectrometer.

Microanalyses were carried out on a Perkin-Elmer Elemental Analyser 240.

3. Preparation of Materials

(a) (i) Light petroleum (b.p. 40-60° and b.p. 60-80°) and benzene were redistilled and dried over sodium wire. Methylene chloride was purified and stored over molecular-sieve as detailed in Vogel.[190] Cyclohexane and diethyl ether were dried over sodium wire. Dioxan was purified and stored over molecular-sieve as detailed in Vogel.[191] Chloroform was dried over molecular-sieve. Ethanol and methanol were super-dried as

detailed in Vogel,[192] then stored over molecular-sieve. Triethylamine was stored over sodium hydroxide. Extra-dry triethylamine was prepared by standing over sodium hydroxide for 24 h, then redistilling from a 2% mixture of naphthyl isocyanate on to molecular-sieve. Phosphorus trichloride, phenylphonous dichloride and diphenylphosphinous chloride were redistilled before use.

Thin-layer chromatography was performed on 0.3 mm layers of alumina (Merck, aluminium oxide G type E). Components in the developed chromatogram were detected by their fluorescence in ultraviolet light, or by their reaction with iodine.

Except where stated, starting materials were commercially available samples and were not further purified.

(ii) Trimethyl phosphite was allowed to stand over sodium wire for 24 h, redistilled from fresh sodium in an atmosphere of dry nitrogen, b.p. 107-108° (lit.[193] 111-112°), and stored over molecular-sieve.

(iii) Dimethyl phenylphosphonite. Methanol (16g; 0.5 mol) and triethylamine (51g; 0.5 mol) in ether (250 ml) were stirred under dry nitrogen in a salt-ice bath, whilst phenylphosphonous dichloride (35.6g; 0.2 mol) in ether (75 ml) was added dropwise over 4 h. The mixture was stirred at room temperature for a further 2 h, then filtered to remove the insoluble triethylamine hydrochloride. The filtrate was evaporated and distilled *in vacuo* under dry nitrogen. Dimethyl phenylphosphonite was obtained as a colourless oil (16.6g; 49%), b.p. 96-101°/12 mm (lit.[194] 101-102°/15 mm). The purity was confirmed by p.m.r. spectroscopy ($CDCl_3$): (τ) 2.3-2.9 (complex band; 5H; aromatic protons); 6.46 (d, J_{P-O-Me} 10 Hz; 6H; 2xP-O-Me).

I.r. ($CHCl_3$): 1000-1050 cm^{-1} (intense, broad absorption; (P)-O-C stretch); 1435 cm^{-1} (s) (sharp absorption; P-Ph).

(iv) Methyl diphenylphosphinite was prepared by the method of Quin and Anderson.[195] Methanol (8g; 0.25 mol) and diphenylphosphinous chloride (44.2g; 0.2 mol) reacted, in the presence of triethylamine (26g; 0.26 mol) with ether (200 ml) as solvent under an atmosphere of dry nitrogen, to give methyl diphenylphosphinite (30.5g; 82%), b.p. 95-96.5°/0.1 mm (lit.[194] 151-152°/10 mm). The purity was confirmed by p.m.r. ($CDCl_3$): (τ) 2.4-2.8 (complex band; 10H; aromatic protons); 6.36 (d, J_{P-O-Me} 13 Hz; 3H; P-O-Me).

I.r. ($CHCl_3$): 885 cm^{-1} (s), 1180 cm^{-1} (s) (P-O-Me); 1000 cm^{-1} (w), 1440 cm^{-1} (s) (sharp absorptions; P-Ph).

(v) 1,2-Ethanediol was dried over anhydrous sodium sulphate (24 h), decanted and redistilled on to molecular-sieve.

(vi) 2-Phenyl-1,3,2-dioxaphospholane was prepared by the method described by Mukaiyama, Fujisawa, Tamura and Yokata.[196] Thus, 1,2-ethanediol (6.2g; 0.1 mol) reacted with phenylphosphonous dichloride (18.0g; 0.1 mol), in the presence of triethylamine (20.2g; 0.2 mol) with benzene (100 ml) as solvent under an atmosphere of dry nitrogen, to give 2-phenyl-1,3,2-dioxaphospholane (6.5g; 36%), b.p. 89-90°/2.0 mm (lit.[196] 79-80°/0.8 mm). The product was used immediately as it polymerises readily even in the absence of impurities or light.[196]

(vii) Diphenylphosphinic chloride was prepared by passing a slow stream of oxygen through diphenylphosphinous chloride heated at 130°. The reaction was followed by i.r. spectroscopy; the appearance of the phosphoryl absorption at 1240 cm^{-1} was observed in particular. No further change was noticed after 6 h. Diphenylphosphinic chloride was obtained as a colourless oil b.p. 145-150°/0.2 mm (lit.[194] b.p. 215-218°/13 mm), by distillation under dry nitrogen.

(viii) Dimethyl phenylphosphonate. Ether-washed lead tetraacetate (13.7g; 0.03 mol) was added slowly to a stirred solution of dimethyl phenylphosphonite (4.5g; 0.027 mol) in methylene chloride. An instantaneous reaction was indicated by the deposition of a thick, white precipitate; the slurry was allowed to stir for 15 min. The mixture was filtered and the filtrate was washed with water (2 x 40 ml). The methylene chloride layer was dried over anhydrous magnesium sulphate, filtered and evaporated. The p.m.r. spectrum of the crude product indicated a quantitative conversion to dimethyl phenylphosphonate b.p. 76°/0.1 mm (lit.[194] 247°/760 mm).

(ix) Benzenephosphonic acid. Phenylphosphonyl dichloride (0.5g; 2.5 mMol) was added dropwise to vigorously-stirred, cold water (1 ml; 50 mMol) to give, on cooling, a white, crystalline solid. This solid was recrystallised from boiling water, filtered and dried at 100° for 15 h. The white crystals obtained were identified as benzenephosphonic acid (0.14g; 35%); m.p. 163-165° (lit. m.p.[197] 161-162°); the infrared spectrum was correct.[198] The recrystallisation filtrate was evaporated and shown to be pure benzenephosphonic acid (0.26g); m.p. 161-164°.

(x) Methyl 4-hydroxy-3,5-dimethylbenzoate was prepared by the method of Cavill and Vincent.[199] Thus, 4-hydroxy-3,5-dimethylbenzoic acid (25g; 0.15 mol) in methanol (140g) was boiled under reflux in the presence of concentrated sulphuric acid (1.5g) under dry nitrogen for 12 h, giving, after treatment, methyl 4-hydroxy-3,5-dimethylbenzoate (23.1g; 85%); m.p. ~160° as a brown powder which was not purified further. The mass spectrum was characteristic[200] of a methyl benzoate: correct M^+ at m/e 180 (66%); major fragments, 149 (100%; M^+-MeO; m* @ 123.3 for direct fragmentation from M^+); 121 (10%; m* @ 98.3 for fragmentation from 149; 149-CO).

I.r. spectrum (nujol): 1685 cm^{-1} (s) (broad absorption; C=O stretch); 3325 cm^{-1} (s) (broad absorption; OH stretch).

P.m.r. spectrum ($CDCl_3$): (τ) 2.31 (s; 2H; aromatic protons); 6.14 (s; 3H; OMe); 7.74 (s; 6H; 2 x Me); 4.54 (s; 1H; phenolic proton).

(xi) 1,3-Propanediol was dried over anhydrous magnesium sulphate for 24 h, then distilled under reduced pressure in an atmosphere of dry nitrogen. The pure diol was stored over molecular-sieve.

(xii) Phenyl diphenylphosphinate. A solution of phenol (0.47g; 5 mMol) in ether (20 ml) was stirred under dry nitrogen, whilst a solution of diphenylphosphinic chloride (2.4g; 10 mMol) and triethylamine (1.02g; 10 mMol) in ether (10 ml) was added. The reaction was monitored by g.l.c. (5% SE30 at 160°) for the disappearance of phenol. A white precipitate was deposited. The mixture was stirred overnight, then filtered. The filtrate was washed with 1N sodium hydroxide aqueous solution (2 x 5 ml), then with water (3 x 10 ml) and dried over magnesium sulphate. The solution was filtered and evaporated to give a white solid, which was recrystallised from dry ethanol (3 ml) and identified as phenyl diphenylphosphinate (0.66g; 45%); m.p. 133-135° (lit. m.p.[201] 136°).

The mass spectrum showed the correct molecular ion at m/e 294 (65%); with major fragments at 293 (68%; M^+-H; m* @ 292 for direct fragmentation from M^+); 201 (100%; $(Ph_2PO)^+$).

I.r. spectrum ($CHCl_3$): 925 cm^{-1} (s) ((P)-O-C stretch); 1115 cm^{-1} (w), 1132 cm^{-1} (s) (sharp absorptions; POC deformation region); 1195 cm^{-1} (s) (P=O stretch); 1440 cm^{-1} (s) (sharp absorption; P-Ph).

$\delta^{31}P$ ($CDCl_3$): -30.4 ppm.

(b) Aryl 2-nitrophenyl ethers

These compounds were prepared by the method of Wright and Jorgensen,[202] with the modification that an atmosphere of dry nitrogen was used which gave a cleaner reaction. The following is a typical example.

A mixture of methyl 4-hydroxy-3,5-dimethylbenzoate (32.5g; 0.18 mol), o-chloronitrobenzene (23.7g; 0.15 mol), potassium hydroxide pellets (8.4g; 0.15 mol) and dimethyl sulphoxide (200 ml) was stirred at 90° for 24 h. Temperatures in excess of 90° produced a less clean product and consequently a lower yield.

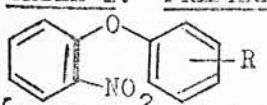
The resulting dark-coloured solution was poured into 2N hydrochloric acid (300 ml) containing ice chips (100g) and stirred vigorously. The oil crystallised, was filtered and sucked as dry as possible, then recrystallised from methanol to give pale-yellow needles of 4-carbomethoxy--2,6-dimethylphenyl 2-nitrophenyl ether (15.9g; 43%); m.p. 133-135°.

The mass spectrum gave the correct molecular ion at m/e 301 (41%); major fragments, 270 (22%; M^+-OMe); 179 (100%, $M^+-C_6H_4NO_2$; m* © 106.4 for direct fragmentation from M^+).

I.r. spectrum (nujol): 1350 cm^{-1} (s); 1520 cm^{-1} (s) (Aryl-NO_2); 1710 cm^{-1} (s) (C=O stretch).

P.m.r. spectrum ($CDCl_3$): (τ) 2.04 (d), 2.61 (t), 2.90 (t), 3.50 (d) (4H; aromatic protons); 2.16 (s; 2H; aromatic protons); 6.09 (s; 3H; CO_2Me); 7.82 (s; 6H, 2 x Me).

TABLE 1: PREPARATION OF ARYL 2-NITROPHENYL ETHERS



R	Yield (%)	m.p. (°C)	Analysis (%)* C	H	N
2,4,6-Trimethyl	50	74.5-76 (lit. m.p.[189] 74-75°)			
4-Methyl	43	46-48 (lit. m.p.[201] 49°)			
2,4-Dimethyl‡	58	60-61	69.3	5.5	5.6
			69.1	5.4	5.8
4-Carbomethoxy-2,6--dimethyl‡	43	133-135	63.9	5.1	4.6
			63.8	5.0	4.7
2,4,6-Tri-t-butyl	No ether was formed; phenol recovered in 60% yield.				

(Notes: * Upper figures are found values; lower are expected.
‡ New compounds.

4. Preparation of 2,2-Dihydrobenz-1,3,2-Oxazaphospholine Derivatives

(a) General method

These materials were produced by reaction of aryl 2-nitroaryl ethers with excess of tervalent phosphorus reagent. The general method was as follows.

A mixture of the nitro-compound (0.01 mol), cumene (80 ml) and the tervalent phosphorus species (0.04 mol) was boiled under reflux under an atmosphere of dry nitrogen for 48 h. Lower boiling fractions (cumene and phosphorus light esters) were removed by distillation under dry nitrogen at water-pump pressure. The residue was a brown, viscous oil which was then worked up by distillation and/or crystallisation.

All products were handled in a nitrogen dry-box and stored over phosphorus pentoxide. Recrystallisations were performed under dry nitrogen on a heated oil-bath.

(b) Phosphoranes derived from 2,4,6-trimethylphenyl 2-nitrophenyl ether

(i) 3-Mesityl-2,2,2-trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine

Reaction of the nitro-compound (2.57g; 0.01 mol) and trimethyl phosphite (4.96g; 0.04 mol) in cumene (80 ml) followed by removal of lower boiling fractions gave a black, viscous oil. This residue was dissolved in ether and transferred under nitrogen to a small-scale distillation flask from which it was distilled *in vacuo*.

The product was collected as a highly-viscous, yellow oil b.p. 109-111°/0.05 mm (2.63g), which solidified on cooling. Dissolution in a minimum quantity of boiling light petroleum (b.p. 40-60°) under dry nitrogen, followed by cooling, gave white needles identified as 3-mesityl-2,2,2-trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine (1.42g; 41%); m.p. 75-77° (sealed tube on Callenkamp, Kofler m.p. unreliable).

A sample of analytical purity was obtained by sublimation (93°/0.1 mm) and yielded the following data. (Found: C, 62.1; H, 6.7; N, 4.2. $C_{18}H_{24}NO_4P$ requires C, 61.9; H, 6.9; N, 4.0%).

The mass spectrum showed the correct molecular ion at m/e 349 (100%; found 349.143132, required 349.144286); major fragments, 318 (28%; M^+-OMe; m* @ 289.8 for direct fragmentation from M^+); 303 (22%; M^+-OMe, Me); 209 (29%; M^+-$OP(OMe)_3$; m* @ 125.2 for direct fragmentation from M^+); 208 (53%; found 208.111716, $C_{15}H_{14}N$ requires 208.112619; 209-H).

I.r. spectrum ($CHCl_3$): 953 cm^{-1} (s), 975 cm^{-1} (s), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1073 cm^{-1} (intense, broad absorption; P-O-Me); 1180 cm^{-1} (w) (sharp absorption; P-O-Me); 1268 cm^{-1} (s) (sharp absorption; CO/CN stretch).

P.m.r. spectrum ($CDCl_3$): (τ) 3.0-3.6 (complex band; 5H; aromatic protons); 4.05-4.20 (complex doublet; 1H; aromatic proton); 6.47 (d, J_{P-O-Me} 13.0 Hz; 9H; 3 x P-O-Me); 7.70 (s; 3H; p-Me); 8.02 (s; 6H; 2 x o-Me). The doublet at 6.47τ collapsed to a singlet when it was irradiated at 40,478,411 Hz (corrected frequency), confirming phosphorus spin-spin coupling.

$\delta^{31}P$ ($CDCl_3$): +57.2 ppm (85% H_3PO_4 external capillary).

(ii) 3-Mesityl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz--1,3,2-oxazaphospholine

Reaction of the nitro-compound (5.14g; 0.02 mol) and dimethyl phenylphosphonite (13.64g; 0.08 mol) in cumene (160 ml), followed by removal of lower boiling fractions, gave a pale-brown oil which crystallised on standing. The reaction was remarkably clean. The solid residue was distilled *in vacuo* and, following the removal of residual phosphonate ester, a highly-viscous, yellow oil was collected in a single fraction (b.p. 176-197°/0.25 mm). This oil solidified rapidly and was ground to

a dry, white powder. The product was identified as 2-mesityl-2,2--dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine (7.19g; 86%). A p.m.r. spectrum confirmed that the material was pure.

An alternative method of isolation was also used. The solid reaction residue was recrystallised twice from cyclohexane (25 ml, distilled from calcium hydride on to molecular-sieve) to give a dry, white, crystalline powder. Triethylamine hydrochloride, occasionally present as a minor impurity, was eliminated by dissolving the powder in a minimum of ether and filtering through a plug of dried celite. Removal of solvent left a dry, white powder (3.1g; 37%); m.p. 162-163.5° (best value obtained; the m.p. varies between 140° and 160° due to hydrolysis).

A sample was sublimed (155-160°/0.25 mm) and yielded the following data. (Found: C, 70.1; H, 6.4; N, 3.7. $C_{23}H_{26}NO_3P$ requires C, 69.9; H, 6.6; N, 3.5%).

The mass spectrum showed the correct parent ion at m/e 395 (85%; found 395.165326, required 395.165021); major fragments, 364 (21%; M^+-OMe); 349 (71%; M^+-OMe, Me); 209 (34%; M^+-PhP(O)$(OMe)_2$; m* @ 110.6 for direct fragmentation from M^+); 208 (100%).

I.r. spectrum ($CHCl_3$): 950 cm^{-1} (s), 973 cm^{-1} (s), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1080 cm^{-1} (s) (broad absorption; P-O-Me); 1175 cm^{-1} (w) (sharp absorption; P-O-Me); 1260 cm^{-1} (s) (sharp absorption; CO/CN stretch); 1440 cm^{-1} (w) (sharp absorption; P-Ph).

P.m.r. spectrum ($CDCl_3$): (τ) 2.1-2.9 (complex band; 5H; P-Ph protons); 2.9-3.6 (complex band; 5H; aromatic protons); 3.96-4.12 (complex doublet; 1H; aromatic proton); 6.60 (broad doublet, J_{P-O-Me} 12.0 Hz; 6H; P-O-Me); 7.70 (s; 3H; p-Me of mesityl ring); 7.89 (s; 6H; 2 x o-Me of mesityl ring).

$\delta^{31}P$ ($CDCl_3$): +46.7 ppm.

(iii) 3-Mesityl-2-methoxy-2,2-diphenyl-2,2-dihydrobenz--1,3,2-oxazaphospholine

Reaction of the nitro-compound (2.57g; 0.01 mol) and methyl diphenylphosphinite (8.64; 0.04 mol) in cumene (80 ml) gave, after removal of lower boiling fractions, a viscous, black oil. This oil was distilled to give, after removal of residual phosphate esters, a viscous, yellow oil (b.p. ca. 200°/0.1 mm) which solidified on cooling. Thorough washing of the product with light petroleum (b.p. 40-60°) left a white powder, identified as 3-mesityl-2-methoxy-2,2-diphenyl-2,2-dihydrobenz-1,3,2--oxazaphospholine (2.8g; 64%).

In an alternative isolation procedure, the product was precipitated from the crude reaction residue by addition of ether (20 ml), filtered and recrystallised from ether (90 ml). White crystals (2.2g; 50%), m.p. 196-198°, were obtained and recrystallised from cyclohexane (ca. 5 ml; recrystallisation efficiency 89%).

The following data were obtained. (Found: C, 76.1; H, 6.4; N, 3.1. $C_{28}H_{28}NO_2P$ requires C, 76.2; H, 6.4; N, 3.2%).

The mass spectrum showed the correct molecular ion at m/e 441 (100%; found 441.184907, required 441.185756); major fragments, 410 (23%; M^+-OMe); 233 (31%; M^+-208, m* @ 123.1 for direct fragmentation from M^+); 209 (47%; M^+-$OPPh_2$(OMe); m* @ 99.0 for direct fragmentation from M^+); 208 (100%, 209-H).

I.r. spectrum ($CHCl_3$): 940 cm^{-1} (s), 970 cm^{-1} (m), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1055 cm^{-1} (s) (broad absorption; P-O-Me); 1180 cm^{-1} (w) (sharp absorption; P-O-Me); 1000 cm^{-1} (w), 1436 cm^{-1} (s) (sharp absorptions; P-Ph); 1255 cm^{-1} (s) (CO/CN stretch).

P.m.r. spectrum ($CDCl_3$): (τ) 1.9-2.2 and 2.4-2.8 (complex bands; 10H; 2 x P-Ph); 3.05-3.60 (complex band; 5H; aromatic protons); 3.95-4.10

(complex doublet; 1H; aromatic proton); 7.51 (d, J_{P-O-Me} 11.0 Hz; 3H; P-O-Me); 7.73 (s; 3H; p-Me of mesityl ring); 8.01 (s; 6H; 2 x o-Me of mesityl ring).

$\delta^{31}P$ ($CHCl_3$): +44.2 ppm (external 85% H_3PO_4 capillary).

(iv) Spiro-2,2-ethylenedioxy-3-mesityl-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

A mixture of the nitro-compound (2.57g; 0.01 mol) and 2-phenyl-1,3,2-dioxaphospholane (6.6g; 0.04 mol) in cumene (80 ml) under dry nitrogen was examined by t.l.c. (benzene solvent), after refluxing for 16 h. Only one spot developed (strong, R.f. 0.66), correlating exactly with an authentic sample of the expected phosphorane prepared previously by an alternative route (see §II.10a). No nitro-compound remained (R.f. 0.84) and the undeveloped residue was relatively weak. The pale-brown solution contained a "sandy" deposit which was filtered out (0.46g; insoluble in acetone and chloroform; this material is probably polymer derived from the dioxaphospholane[196]). Low boiling fractions were removed from the filtrate as usual, leaving a pale-brown, viscous oil. A white precipitate, deposited on the addition of ether, was filtered off and washed well with ether, yielding a sticky, white powder (5.88g). The filtrate was evaporated to a pale-yellow solid (4.0g). Both fractions were examined by p.m.r. Good integral-correlation was obtained for a mixture of the expected phosphorane (2.47g; 42%); methylene chloride (19%, used as a solvent during product isolation) and 2-oxo-2-phenyl-1,3,2-dioxaphospholane (39%; all weight percentages). The filtrate fraction contained a small, unidentified component incorporating the mesityl function, in addition to the above components. However, it was assessed that the phosphorane contributed 0.92g to this mixture. This gives a total yield of 89%. Attempts to recrystallise the crude

product directly were unsuccessful, owing to the insolubility of the cyclic phosphonate oil; all fractions were combined and distilled. Having discarded a lower boiling fraction, a pale-yellow, viscous oil was collected (180-200°/0.25 mm) which crystallised on cooling. This fraction was recrystallised twice from ether to give colourless plates, m.p. 189.5-191° (authentic: m.p. 188.5-190°). Mass, i.r. and p.m.r. spectra were all identical with those recorded for the spirophosphorane described in §II.10a below, and identified there as spiro-2,2-ethylenedioxy-3-mesityl-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine.

(c) Phosphoranes derived from p-tolyl 2-nitrophenyl ether

(i) 2,2,2-Trimethoxy-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

Reaction of the nitro-compound (4.6g; 0.02 mol) and trimethyl phosphite (9.9g; 0.08 mol) in cumene (160 ml), followed by the removal of lower boiling fractions, gave a black oil which partially crystallised on cooling.

After removal of residual trimethyl phosphate by distillation, products were collected in two further fractions. The first fraction (152°/0.2 mm; 3.17g), which was a viscous, yellow oil, solidified on cooling; the p.m.r. spectrum indicated a mixture of two components. The major component (78 molar %) had resonance absorptions as expected for the required phosphorane. The minor component showed two sharp p.m.r. singlets of equal intensities at 6.2τ (OMe) and at 7.8τ (Me); the infrared spectrum ($CHCl_3$) showed a weak, sharp absorption at 3425 cm^{-1} (N-H stretch) and a strong absorption at 1600 cm^{-1}. Neither of these absorptions is observed in the infrared of the pure phosphorane, but both are characteristic of a diarylamine. On the basis of this information the minor

component was postulated to be N-(2-methoxyphenyl)-p-toluidine (22 molar percentage). The second distillation fraction, a yellow oil (1.2g) had p.m.r. resonance absorptions assignable to these compounds, but contained several other components whose identity could not be determined. Thus, the yield of phosphorane could be calculated as being in excess of 40%.

The first fraction was recrystallised four times from light petroleum (b.p. 60-80°); the filtrates were yellow and, in their p.m.r. spectra, resonances assigned to the substituted diphenylamine increased in intensity relative to those assigned to the phosphorane. The product crystallised as colourless needles, m.p. 108-111°, and was identified as 2,2,2-trimethoxy-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine.

The mass spectrum showed the correct molecular ion at m/e 321 (100%; found 321.112904, $C_{16}H_{20}NO_4P$ requires 321.112987); major fragments, 290 (24%; M^+-MeO; m* @ 261 for direct fragmentation from M^+); 275 (24%; M^+-MeO, Me); 194 (21%; large m* @ 117.3 for direct fragmentation from M^+); 180 (28%; M^+-$OP(OMe)_3$, H; m* @ 101 for direct fragmentation from M^+).

I.r. spectrum ($CHCl_3$): 930 cm^{-1} (m), 975 cm^{-1} (s), 1023 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1075 cm^{-1} (intense, broad absorption; P-O-Me); 1270 cm^{-1} (s) (sharp absorption; CO/CN).

P.m.r. spectrum ($CDCl_3$): (τ) 2.7-3.7 (complex band; 7H; aromatic protons); 3.88-4.06 (complex doublet; 1H; aromatic proton); 6.50 (d, J_{P-O-Me} 13 Hz; 9H; 3 x P-O-Me); 7.60 (s; 3H; tolyl Me).

$\delta^{31}P(CDCl_3)$: +55.9 ppm.

(ii.1) 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

Reaction of the nitro-compound (2.29g; 0.01 mol) and dimethyl phenylphosphonite (6.8g; 0.04 mol) in cumene (80 ml) followed by removal of lower boiling fractions gave a dark-brown, viscous oil. After removal

of residual phosphorus esters, the product was distilled as a highly-viscous, orange oil (b.p. 173-175°/0.15 mm) which solidified and was ground to a white powder. P.m.r. indicated pure 2,2-dimethoxy-2-phenyl--3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine (2.28g; 77%). Recrystallisation from ether (50 ml) gave colourless needles (54% efficiency), m.p. 153-153.5°, which yielded the following data. (Found C, 68.4; H, 6.0; N, 3.9. $C_{21}H_{22}NO_3P$ requires C, 68.7; H, 6.0; N, 3.8%).

The mass spectrum showed the correct molecular ion at m/e 367 (100%; found 367.132773, required 367.133723); major fragments, 336 (15%; M^+-OMe); 321 (M^+-OMe,Me); a large m* at 306-307 could arise from fragmentation of either M^+ to 336 or of 336 to 321; 194 (24%; m* @ 102.6 for direct fragmentation from M^+).

I.r. spectrum ($CHCl_3$): 925 cm^{-1} (m), 970 cm^{-1} (s), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1080 cm^{-1} (s) (P-O-Me); 1260 cm^{-1} (s) (sharp absorption CO/CN); 1435 cm^{-1} (w) (sharp absorption; P-Ph).

P.m.r. spectrum ($CDCl_3$): (τ) 2.2-2.8 (complex band; 5H; P-Ph); 2.83 (s; 4H; tolyl ring aromatic protons); 3.18-3.55 (complex band; 3H; aromatic protons); 3.72-3.90 (complex doublet; 1H; aromatic proton); 6.63 (d, J_{P-O-Me} 12 Hz; 6H; 2 x P-O-Me); 7.63 (s; 3H; tolyl Me).

$\delta^{31}P$ ($CDCl_3$): +44.74 ppm; undecoupled spectrum showed a multiplet which was interpretable as a heptet of doublets; heptet J=12.5 Hz, doublet J= 4-5 Hz.

(ii.2) The isolation of 2-p-toluidinophenol

In a separate preparation of this phosphorane, the product distilled as a viscous, yellow oil in a continuous fraction (b.p. 185-195°/0.1 mm). The p.m.r. spectrum indicated that there were three major components. The greatest component was later identified as 2-oxo-2-phenyl-3-p-tolylbenz-

-1,3,2-oxazaphospholine, the lesser component was the phosphorane and the least component was dimethyl phenylphosphonate. 2-Oxo-2-phenyl--3-p-tolylbenz-1,3,2-oxazaphospholine was also the only significant component of the distillation residue, suggesting that it may be formed by thermolysis of the phosphorane.

The distilled oil was chromatographed on alumina. Elution with 10% methanol in ethyl acetate gave a dark-green oil (0.76g). No other significant fractions were obtained, and no trace of the phosphorane or the cyclic phosphonamidate was detectable when the column residue was extracted into an aqueous methanol solution.

Attempts to purify the green-oil fraction by crystallisation from light petroleum (b.p. 40-60°) produced tar, but a small yield (0.13g) of a white, fibrous material was obtained. Sublimation of this product (52°/0.025 mm) gave colourless needles identified as 2-p-toluidinophenol, m.p. 56-58°. The following data were obtained. (Found: C, 78.4; H, 6.7; N, 7.2. $C_{13}H_{13}NO$ requires C, 78.4; H, 6.6; N, 7.0%).

The mass spectrum showed the correct molecular ion at m/e 199 (100%; found 199.099581, required 199.099708); major fragments, 184 (M^+ - Me); 183 (M^+ - Me,H); 108 (M^+ - tolyl radical); all < 10%.

I.r. spectrum ($CHCl_3$): 3600 cm^{-1} (w) (sharp absorption; unbonded OH); 3425 cm^{-1} (m) (very broad absorption; bonded OH and NH); 1610 cm^{-1} (s) (sharp absorption; aromatic ring band); 1310 cm^{-1} (m) (sharp absorption; C-N stretch); 1290 cm^{-1} (m) (sharp absorption; C-O stretch); 1210-1235 cm^{-1} (m) (broad absorption).

P.m.r. spectrum ($CDCl_3$): the solution was pale green and gave a poorly-resolved spectrum, due to the production of radical centres in the molecule (a characteristic of these 2-aminophenols). When the solution was shaken with a 1% dithionite solution in D_2O, a well-resolved spectrum was obtained: (τ) 2.6-3.6 (complex band; 8H; aromatic protons); 7.75

(s; 3H; tolyl Me). In the absence of D_2O there were two broad absorptions at 4.2 and 4.8 (1H each; OH and NH).

Subsequent experiments have shown that this compound is most easily isolated by sublimation of the crude product from chromatography. Failure to observe either the phosphorane or 2-oxo-2-phenyl-3-p-tolylbenz--1,3,2-oxazaphospholine is attributed to their tendency to hydrolyse rapidly to 2-p-toluidinophenol.

(ii.3) The isolation of 2-oxo-2-phenyl-3-p-tolylbenz--1,3,2-oxazaphospholine

In a further attempt to produce the phosphorane, the product was distilled as a yellow oil (175-180°/0.1 mm) and recrystallised from ether under dry nitrogen as usual. A second recrystallisation gave fine, white needles, m.p. 148-150°, which were identified as 2-oxo-2-phenyl-3--p-tolylbenz-1,3,2-oxazaphospholine.

No further product could be isolated; the yield was 15% based on starting nitro-compound. The following data were obtained. (Found: C, 70.8; H, 5.0; N, 4.4. $C_{19}H_{16}NO_2P$ requires C, 71.0; H, 5.0; N, 4.4%). The mass spectrum showed the correct molecular ion at m/e 321 (100%; found 321.092809, required 321.091861); major fragment, 320 (9%; m* @ 319 for direct fragmentation from M^+). No other fragments of greater than 5% relative abundancy were recorded.

I.r. spectrum ($CHCl_3$): 920 cm^{-1}, 980 cm^{-1}, 1020 cm^{-1} (all medium, sharp absorptions; (P)-O-C stretch region); 1130 cm^{-1} (s) (sharp absorption; POC deformation region); 1260 cm^{-1} (s) (broad absorption; P=O); 1443 cm^{-1} (s) (sharp absorption; P-Ph).

P.m.r. spectrum ($CDCl_3$): (τ) 2.1-3.3 (complex band; 13H; aromatic protons); 7.72 (s; 3H; tolyl Me).

$\delta^{31}P$ ($CDCl_3$): -29.4 ppm.

2-Oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine was also obtained when 2,2-dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2--oxazaphospholine was recrystallised from dry cyclohexane. Thus, the phosphorane (0.94g; 2.6 mMol), m.p. 151-153°, was recrystallised from cyclohexane (30 ml) to give the 2-oxo-2-phenylbenz-1,3,2-oxazaphospholine (0.75g; 90%), m.p. 148-149°. Nevertheless, the phosphorane has been successfully recrystallised from cyclohexane with 78% efficiency. It is believed that the presence of traces of acidic hydrolysis product in the phosphorane sample cause this decomposition.

(iii) 2-Methoxy-2,2-diphenyl-3-p-tolyl-2,2--dihydrobenz-1,3,2-oxazaphospholine

Reaction of the nitro-compound (2.29g; 0.01 mol) and methyl diphenylphosphinite (8.64g; 0.04 mol) in cumene (80 ml) gave, after removal of lower boiling fractions, a brown, viscous oil which crystallised on standing. This residue was stirred under dry nitrogen with cold ether (70 ml), then filtered. A brown, crystalline powder was obtained which yielded a white, crystalline material (2.64g), m.p. 188-191°, after washing with ether. The filtration residue was evaporated and treated with cold ether to yield a further 0.48g of pale-brown crystals with the same infrared spectrum and melting point. The combined product was recrystallised from cyclohexane (35 ml) to give lustrous, white plates m.p. 188-189°, identified as 2-methoxy-2,2-diphenyl-3-p-tolyl-2,2--dihydrobenz-1,3,2-oxazaphospholine (recrystallisation efficiency 94%; yield of product after one recrystallisation, 3.12g; 76%).

The following data were obtained. (Found: C, 75.5; H, 5.9; N, 3.3. $C_{26}H_{24}NO_2P$ requires C, 75.5; H, 5.9; N, 3.4%).

The mass spectrum showed the correct molecular ion at m/e 413 (100%; found 413.152983, required 413.154458); major fragments, 399 (17%;

hydrolysis products of phosphorane); 382 (19%; $M^+ - OMe$); 201 (31%; $(OPPh_2)^+$); 180 (12%; $M^+ - OP(OMe)Ph_2$, H). There were no significant m*.

I.r. spectrum ($CHCl_3$): 925 cm^{-1} (s), 960 cm^{-1} (s), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1050 cm^{-1}(s) (broad absorption); 1000 cm^{-1} (w), 1440 cm^{-1} (s) (sharp absorptions; P-Ph).

P.m.r. spectrum ($CDCl_3$): (τ) 1.9-2.3, 2.5-2.7 (complex bands; 10H; 2 x P-Ph); 2.76 (s; 4H; tolyl ring protons); 2.3-3.6 (complex band; 3H; aromatic protons); 3.82-3.97 (complex doublet; 1H; aromatic proton); 7.56 (d, J_{P-O-Me} 10 Hz; 3H; P-O-Me); 7.64 (s; 3H; tolyl Me). The doublet at 7.56 collapsed to a singlet when irradiated at 40,478,904 Hz confirming phosphorus spin-spin coupling.

$\delta^{31}P$ ($CDCl_3$): +39.9 ppm.

(d) Phosphoranes derived from miscellaneous aryl 2-nitrophenyl ethers

(i) 2,2-Dimethoxy-2-phenyl-3-(2',6'-xylyl)-2,2--dihydrobenz-1,3,2-oxazaphospholine

2,6-Dimethylphenyl 2-nitrophenyl ether (2.43g; 0.01 mol) reacted with dimethyl phenylphosphonite (6.8g; 0.04 mol) in cumene (80 ml) to give, after the removal of lower boiling fractions, a pale-brown solid.

Following the removal of residual dimethyl phenylphosphonate, the product distilled as a viscous, colourless oil (b.p. 170-172°/0.2 mm), which crystallised rapidly on cooling and was identified as 2,2-dimethoxy--2-phenyl-3-(2',6'-xylyl)-2,2-dihydrobenz-1,3,2-oxazaphospholine (3.17g; 83%. The purity was confirmed by p.m.r.). The product was sublimed (100°/0.2 mm) to give white crystals, m.p. 108-110°, from which the following data were obtained. (Found: C, 69.3; H, 6.2; N, 3.6. $C_{22}H_{24}NO_3P$ requires C, 69.3; H, 6.3; N, 3.7%).

The mass spectrum gave the correct molecular ion at m/e 381 (97%;

found 381.148179, required 381.149372); major fragments, 350 (17%; $M^+ - OMe$); 335 (49%; $M^+ - OMe$, Me); 195 (31%; $M^+ - OP(OMe)_2Ph$; m* @ 99.8 for direct fragmentation from M^+); 194 (100%; $M^+ - OP(OMe)_2Ph$, H).

I.r. spectrum ($CHCl_3$): 960 cm^{-1} (s), 970 cm^{-1} (s), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1075 cm^{-1}(s) (broad absorption; P-O-Me); 1175 cm^{-1} (m) (sharp absorption; P-O-Me); 1260 cm^{-1} (s) (sharp absorption; C-O/C-N stretch); 1435 cm^{-1} (m) (sharp absorption; P-Ph).

P.m.r. spectrum ($CDCl_3$): (τ) 2.2-2.8 (complex band; 5H; P-Ph); 2.93 (s; 3H; xylyl ring protons); 3.1-3.6 (complex band; 3H; aromatic protons); 4.02-4.16 (complex doublet; 1H; aromatic proton); 6.62 (broad doublet, J_{P-O-Me} 12.5 Hz; 6H; 2 x P-O-Me); 7.86 (s; 6H; 2 x xylyl Me).

$\delta^{31}P$ ($CDCl_3$): +47.1 ppm.

(ii) 3-(4'-Carbomethoxy-2',6'-dimethylphenyl)-2,2,2--trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine

Reaction of 4-carbomethoxy-2,6-dimethylphenyl 2-nitrophenyl ether (3.01g; 0.01 mol) with trimethyl phosphite (4.96g; 0.04 mol) in cumene (80 ml) gave, after removal of lower boiling fractions, a pale-brown solid.

Recrystallisation from light petroleum (b.p. 40-60°) gave a pale-brown powder identified as 3-(4'-carbomethoxy-2',6'-dimethylphenyl)-2,2,2--trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine (2.9g; 74%). The p.m.r. spectrum of this sample indicated some impurities which were later identified as hydrolysis products of the phosphorane. However, these components were assessed to contribute less than 10%. Sublimation (124°/0.25 mm) gave colourless crystals m.p. 64-66° (this m.p. is not considered to be reliable, due to the rapidity with which the phosphorane hydrolyses).

The following data were obtained. (Found: C, 57.8; H, 3.6; N, 6.1.

$C_{19}H_{24}NO_6P$ requires C, 58.0; H, 3.6; N, 6.2%).

The mass spectrum gave the correct molecular ion at 393 (100%; found 393.132696, required 393.134114); major fragments, 362 (40%; $M^+ - OMe$); 347 (60%; $M^+ - Me, OMe$); 253 (24%; $M^+ - OP(OMe)_3$; m* @ 162.9 for direct fragmentation from M^+); 252 (92%; found 252.101225, $C_{16}H_{14}NO_2$ requires 252.102447; 253 - H).

I.r. spectrum ($CHCl_3$): 940 cm^{-1} (w), 970 cm^{-1} (s), 1020 cm^{-1} (s); (sharp absorptions; (P)-O-C stretch region); 1075 cm^{-1} (s) (broad absorption; P-O-Me); 1715 cm^{-1} (s) (broad absorption; ester C=O stretch).

P.m.r. spectrum ($CDCl_3$): (τ) 2.19 (s; 2H; carbomethoxyaryl aromatic protons); 3.0-3.6 (complex band; 3H; aromatic protons); 4.06-4.26 (complex doublet; 1H; aromatic proton); 6.10 (s; 3H; MeCO); 6.44 (d, J_{P-O-Me} 13 Hz; 9H; 3 x P-O-Me); 7.83 (s; 6H; 2 x Me).

$\delta^{31}P$ ($CDCl_3$): +58.1 ppm.

5. P.m.r. Variable-temperature Studies on 2,2-Dihydrobenz-1,3,2-Oxazaphospholine Derivatives

(a) General procedure

The phosphorane (ca. 40 mg) was dissolved in an appropriate solvent (0.3 ml; dry methylene chloride for low temperatures, diphenyl ether for elevated temperatures), in 5 mm n.m.r. tubes. The sample temperature was adjusted in the probe in 5° or 10° intervals using a Varian temperature-control unit. The temperature was allowed to stabilise for five minutes before spectra were recorded on a Varian HA-100 instrument, using a 250 Hz sweep-width. Where separation of a single peak (or doublet) into several peaks (or doublets) was observed, the coalescence temperature (T_c) refers to that temperature at which the separate peaks (or doublets)

merged to become just indistinguishable. The exact temperature was then found by calibration against the chemical shift of a methanol sample in a separate tube. Coalescence temperatures could not be located to better than $\pm 1^{\circ}$. Other temperatures are corrected by ΔT, where $\Delta T = T_c^{\text{instrument}} - T_c^{\text{tube}}$; experience has indicated that such a correction is valid over the $0-100^{\circ}$ temperature range to an accuracy of $\pm 3^{\circ}$.

ΔG^* values for the three-site exchange processes in subsections (b) and (c) below would require complete line-shape analyses. ΔG^* for the two-site exchange processes observed in subsections (d), (e) and (f) were calculated by a combination of a simplified Gutowsky-Holm equation for the situation at the coalescence temperature: $2\pi\tau\Delta\nu = \sqrt{2}$ (Pople, Schneider and Bernstein; high resolution n.m.r., p. 223 (McGraw-Hill 1959)), where τ is half of the lifetime of either site and $\Delta\nu$ is the frequency separation of the site-occupant resonances at slow-exchange, and the Eyring equation

$$\sigma k' = \frac{kT}{h} e^{-\Delta G^*/RT}$$

(W.J. Moore, Physical Chemistry (Longmans 1963), p. 297), where σ is the transmission coefficient, k' is the rate constant for the exchange process and T is the absolute temperature, other symbols being conventional. Thus:

$$k' = \frac{1}{2\tau} = \frac{\pi\Delta\nu}{\sqrt{2}}$$

and hence:

$$\Delta G^* = RT \ln \left(\frac{\sigma kT\sqrt{2}}{\pi\Delta\nu h}\right)$$

All chemical shifts are quoted in ppm from the resonance position of the solvent, upfield signals being positive.

N.B.: It was observed that individual groups exhibited different temperature-dependent shifts even in the absence of exchange; hence it is not always obvious that the slow-exchange resonances are truly averaged in the fast-exchange situation.

(b) 3-Mesityl-2,2,2-trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine

The solvent was methylene chloride. At $+28^{\circ}$ the three methoxy groups attached to phosphorus resonated as a single, sharp doublet (+1.76 ppm; J_{P-O-Me} 13.0 Hz). As the temperature was lowered this signal broadened, although the doublet splitting remained constant, until at ca. -65° a broad "mound" remained. Further cooling to ca. -72° produced a new peak structure, which was clearly identifiable at ca. -80° as two broad doublets: + 1.65 ppm (50% resolved; J_{P-O-Me} 14.5 Hz; 6H; 2 x equatorial OMe); + 2.19 ppm (barely resolved; J_{P-O-Me} 10 Hz; 3H; apical OMe). T_c, at which this low-temperature structure coalesced into the normal-temperature structure, was measured as -71°. Irradiation of the sample at 40,478,240±10 Hz when the temperature was -55°, T_c and -80°, caused sharpening of the methoxyl resonances and collapse of doublets (where resolved), thus confirming that coupling to phosphorus persisted.

A scan of the entire spectrum at -80° indicated that no other resonances showed temperature variations over the observed range. In particular the o-Me singlet of the mesityl ring remained sharp.

(c) 3-(4'-Carbomethoxy-2',6'-dimethylphenyl)-2,2,2-trimethoxy--2,2-dihydrobenz-1,3,2-oxazaphospholine

The solvent was methylene chloride. Analogous behaviour was observed to that exhibited by the phosphorane in subsection (b) above, except that the accurate coalescence temperature was measured as $T_c = -75^{\circ}$.

Accurate location of the coalescence was aided by irradiating the sample at 40,478,180 Hz so as to decouple the methoxyl doublets causing intensity enhancement and simplifying the line shape.

Below T_c, the separation of the apical and equatorial methoxyl doublets was ca. 57 Hz.

(d) 3-Mesityl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

The solvent was methylene chloride. The spectra obtained at various temperatures are recorded in Figure II.1 (p. 133).

At $+45^{\circ}$ the two methoxy groups attached to phosphorus resonated as a sharp doublet (+ 1.90 ppm; J_{P-O-Me} 12.3 Hz). As the temperature was reduced, this signal broadened to a low hump at ca. -4° which resolved into two broad resonances at ca. -10° (+ 1.5 ppm and + 2.4 ppm). Further cooling to ca. -60° caused the sharpening of these resonances into two sharp doublets: + 1.12 ppm (d, J_{P-O-Me} 14.0 Hz; 3H; equatorial OMe) and 2.47 ppm (d, J_{P-O-Me} 10.8 Hz; 3H; apical OMe). The temperature at which these resonances coalesced into a single broad resonance was accurately measured as $T_c = -5^{\circ}$. Thus, with $\Delta\nu = 94$ Hz and $\sigma = 0.5$: $\Delta G^{*} = 52 \pm 0.5 kJ\ mol^{-1}$ for the exchange of equatorial and apical methoxyls.

The o-methyls of the mesityl ring resonated as a sharp singlet at $+45^{\circ}$ (+ 3.2 ppm); as the sample was cooled the singlet broadened, until at below -30° it split into two singlets, clearly resolved at ca. -60°: + 3.16 ppm (3H) and + 3.33 ppm (3H). The p-Me singlet remained sharp throughout this temperature range.

The coalescence temperature for this latter process was measured accurately as $T_c' = -32^{\circ}$. Assuming this to be also due to a two-site exchange process, $\Delta G^{*} = 50 \pm 0.5 kJ\ mol^{-1}$ ($\Delta\nu = 16$ Hz; $\sigma = 0.5$). As

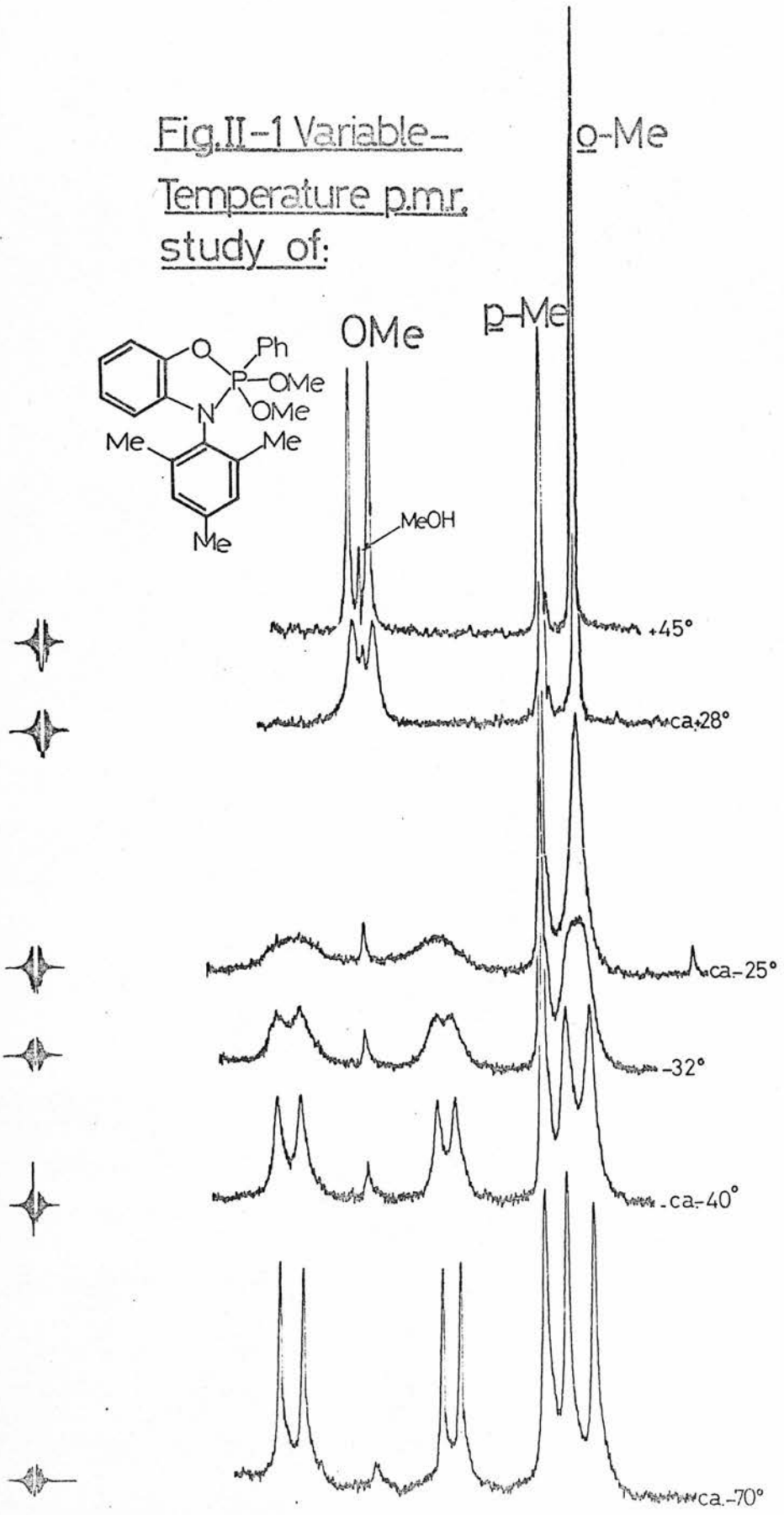


Fig.II-1 Variable-Temperature p.m.r. study of:

can be seen from the figure, the resolution of these singlets closely paralleled the resolution of the methoxyl singlets into doublets.

No other changes were observed in the spectrum over this temperature range.

(e) 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz--1,3,2-oxazaphospholine

The same pattern of behaviour as was observed for the methoxy groups in subsection (c) above was observed for this compound, except that the methoxyl doublet + 1.94 ppm (J_{P-O-Me} 12.8 Hz; 6H) was sharp at +28° and the T_c for the separation of the single doublet into two resonances was accurately measured as $T_c = -50°$; hence, with $\Delta\nu$ = 104 Hz and σ = 0.5, $\Delta G^* = 43 \pm 0.5 kJ\ mol^{-1}$ for the exchange of methoxy groups.

At ca. -80° the methoxyl resonances had resolved into two sharp doublets: + 1.53 ppm (J_{P-O-Me} 14.5 Hz; 3H; equatorial OMe) and + 2.55 ppm (J_{P-O-Me} 11.0 Hz; 3H; apical OMe).

The aromatic region was poorly resolved at -80°; however, the intensity of the singlet due to the tolyl ring protons was observed to have decreased considerably and other resonances not present at +28° were observed in this region. A definite pattern could not be discerned.

The solvent was methylene chloride.

(f) Spiro-2,2-ethylenedioxy-3-mesityl-2-phenyl-2,2--dihydrobenz-1,3,2-oxazaphospholine

The spectrum at +28° is detailed in §II.10a below. The features significant to this temperature study were a complex multiplet due to the ethylenedioxy ring protons and three singlets due to the mesityl protons at: (τ) 7.70; 7.88 and 8.14 in $CDCl_3$.

Low temperature

The solvent was $CDCl_3$. The spectrum was observed to -60°. Apart from a general loss of resolution which caused the disappearance of fine structure in the ethylenedioxy ring multiplet and left a very broad doublet, no other changes were observed. A similar loss of fine structure was observed for the aromatic region. The mesityl methyl resonances remained essentially unchanged.

In methylene chloride, the temperature was reduced to ca. -90°. Once more, extensive loss of resolution was observed; the ethylenedioxy ring multiplet became a broad, structureless absorption. Any temperature dependency could not be distinguished from simple viscosity broadening.

High temperature

The solvent was diphenyl ether. No change was observed up to ca. $+140^{\circ}$. At $+150^{\circ}$ the two upfield mesityl methyl resonances started to coalesce; at the same time the two ethylenedioxy multiplet bands lost their fine structure and started to coalesce. The mesityl methyl resonances coalesced at $+175^{\circ}$ (accurate temperature). At this temperature the ethylenedioxy resonance consisted of two just-resolvable "mounds"; this structure was still resolvable at ca. $+182^{\circ}$, but at ca. $+192^{\circ}$ the ethylenedioxy resonance was a single symmetrical "mound" whilst the mesityl methyl resonance had sharpened into a singlet of ca. 50% of the height which would be expected for fast exchange of two methyl groups. This process was reversible.

Assuming a two-site exchange process for the mesityl methyl groups, and using $T_c = +175^{\circ}$, $\sigma = 0.5$ and $\Delta\nu = 13.5$ Hz, then $\Delta G^{*} = 96 \pm 0.5$ kJ mol.$^{-1}$

(g) 3-Mesityl-2-methoxy-2,2-diphenyl-2,2-
-dihydrobenz-1,3,2-oxazaphospholine

The methoxyl doublet remained sharp with J_{P-O-Me} 11.0 Hz between +28° and +200°. No significant frequency shift or change in J was observed. The solvent was diphenyl ether.

(h) 2-Methoxy-2,2-diphenyl-3-p-tolyl-2,2-
-dihydrobenz-1,3,2-oxazaphospholine

The methoxyl doublet remained sharp with J_{P-O-Me} 11.0 Hz between +28° and +200°. No significant frequency shift or change in J was observed. The solvent was diphenyl ether.

6. The Hydrolysis of 2,2-Dihydrobenz-1,3,2-
-Oxazaphospholine Derivatives

(a) 3-Mesityl-2,2,2-trimethoxy-2,2-dihydrobenz-
-1,3,2-oxazaphospholine

(i) The isolation of 2-(2',4',6'-trimethylanilino)phenol

The ultimate hydrolysis product of 3-mesityl-2,2,2-trimethoxy-2,2-
-dihydrobenz-1,3,2-oxazaphospholine is 2-(2',4',6'-trimethylanilino)phenol. Thus, to obtain a sample of this material, 2,4,6-trimethylphenyl 2-nitrophenyl ether (4.7g; 0.018 mol) and trimethyl phosphite (9.9g; 0.08 mol) in cumene (160 ml) were boiled under reflux in an atmosphere of dry nitrogen for 48 h to give, after the removal of lower boiling fractions, a dark-brown, viscous oil. This oil was dissolved in a mixture of ethanol (250 ml) and 2N aqueous hydrochloric acid (12.5 ml), then stirred under reflux in an atmosphere of nitrogen for 24 h. After cooling, the

solution was neutralised with bench sodium hydroxide solution; the ethanol was evaporated and the residue was dissolved in ether (150 ml). The ether layer was washed with water (4 x 50 ml), dried over anhydrous magnesium sulphate, then evaporated to give a brown, viscous oil. This residue was chromatographed on alumina.

Elution with 1% methanol in ethyl acetate gave a dark-green, viscous oil with a single peak when analysed by g.l.c. (5% SE30 @ 200°). This peak was confirmed subsequently to be due to the anilinophenol (1.25g; 30%). The oil was sublimed (90°/0.2 mm) with 66% efficiency to give colourless crystals identified as 2-(2',4',6'-trimethylanilino)phenol, m.p. 93-95°. Resublimation of this product gave an analytically pure material, m.p. 102-103°. The following data were obtained. (Found: C, 79.1; H, 7.6; N, 6.2. $C_{15}H_{17}NO$ requires C, 79.3; H, 7.5; N, 6.2%).

The mass spectrum gave the correct molecular ion at m/e 227 (100%).

I.r. spectrum ($CHCl_3$): 3600 cm^{-1} (s) (sharp absorption; unbonded OH); 3420 cm^{-1} (m) (sharp absorption; unbonded NH); 3100-3500 cm^{-1} (m) (broad absorption; bonded OH/NH); 1265 cm^{-1} (s) (sharp absorption; CO/CN stretch).

The $CDCl_3$ solution of this material turned green rapidly and a poorly-resolved spectrum was obtained with a broad resonance at 4.9 τ (2H; OH + NH protons), which disappeared when the solution was shaken with aqueous sodium dithionite. A well-resolved spectrum was then obtained: (τ) 3.08 (s; 2H; mesityl ring protons); 3.1-3.4 (complex multiplet; 3H; aromatic protons); 3.68-3.80 (complex multiplet; 1H; aromatic proton); 7.71 (s; 3H; mesityl p-Me); 7.86 (s; 6H; 2 x mesityl o-Me).

(ii) Hydrolysis of the phosphorane in 5% aqueous dioxan

The phosphorane (0.61g; 1.76 mMol), dissolved in 5% aqueous dioxan,

was stirred at 30°. The disappearance of the phosphorane was followed by g.l.c. (5% SE30 at 183°); after 90 min no peaks were detectable. In particular, there were no peaks for 2-(2',4',6'-trimethylanilino)phenol or trimethyl phosphate. During the reaction the pH fell from 6 to 1. The solution was evaporated to a white powder identified as 2-hydroxy-3--mesityl-2-oxobenz-1,3,2-oxazaphospholine (0.50g; 99%); the p.m.r. spectrum showed no impurities. Recrystallisation from benzene gave a white, crystalline powder (0.38g; 75%), which decomposed at its melting point (ca. 223°; lit.[189] ca. 210°). The following data were obtained. (Found: C, 62.5; H, 5.9; N, 4.9. $C_{15}H_{16}NO_3P$ requires C, 62.3; H, 5.6; N, 4.8%).

The mass spectrum gave the correct molecular ion at m/e 289 (100%; found 289.086828, required 289.086775); major fragments, 271 (35%; $M^+ - H_2O$; m* @ 254 for direct fragmentation from M^+); 224 (12%; M^+ - (HO)PO,H); 208 (17 %; M^+-$HOPO_2$,H); 119 (27%; mesityl radical cation).

I.r. spectrum ($CHCl_3$): ca. 2600 cm^{-1} (w), 2320 cm^{-1} (w), ca. 1900 cm^{-1} (w) (very broad absorptions; P-O-H[203]); 1275 cm^{-1} (s) (sharp absorption; P=O); 1025 cm^{-1} (intense, broad absorption; P-O-C).

P.m.r. spectrum ($CDCl_3$): (τ) -1.0 (variable position, exchanges with D_2O; s; 1H; P-O-H); 2.65 (s; 2H; mesityl ring protons); 2.8-3.2 (complex band; 3H; aromatic protons); 3.72-3.88 (complex band; 1H; aromatic proton); 7.65 (s; 3H; mesityl Me); 7.84 (s; 6H; 2 x mesityl o-Me).

$\delta^{31}P$ ($CDCl_3$): -15.9 ppm.

(iii) Hydrolysis of the phosphorane with 1 mol equivalent of water

The phosphorane (0.46g; 0.13 mMol) was dissolved in dry methylene chloride (2 ml), and analysed by g.l.c. (2% NPGS @ 182°). Only one peak appeared (R.t. 3.8 min). Water (23.6 ml; 0.13 mMol) was added through

a suba-seal and the solution was maintained at room temperature for 12 h. After 90 min the g.l.c. trace was clear. Evaporation of solvent left a grey powder. The p.m.r. spectrum ($CDCl_3$) of this residue had the following features: (τ) the aromatic region was very similar to that of 2-hydroxy-3-mesityl-2-oxobenz-1,3,2-oxazaphospholine; a symmetrical doublet appeared at 6.12 (J 12 Hz) and three singlets at 7.68, 7.74 and 7.82; a very small resonance also appeared at 2.4 and was observed to drift rapidly downfield (P-O-H); integrations suggested that the product was a mixture of 2-hydroxy- and 2-methoxy-3-mesityl-2-oxobenz-1,3,2--oxazaphospholine in molar ratio 1:2.3. A sample was sublimed (75°/0.01 mm) to give a pale-cream powder. The p.m.r. spectrum was very similar, but integration suggested a ratio of 1:4. The mass spectrum showed a molecular ion at 303 (100%) and major fragments, 271 (50%; M^+ - MeOH; large m* @ 242.3 for direct fragmentation from M^+); 224 (25%; M^+ - (MeO) PO, H); 208 (30%; M^+ - $(MeO)PO_2$, H).

No significant peaks appeared at 289 or 227, but a 0.3% peak appeared at 335, the mass expected for the acyclic phosphate or phosphoramidate diester. No m* appeared for fragmentation of 335 to 303.

Thus, the predominant product of hydrolysis by one mol equivalent of water is 3-mesityl-2-methoxy-2-oxobenz-1,3,2-oxazaphospholine with the following n.m.r. assignments: (τ) 2.8-3.2 (complex band; 3H; aromatic protons); 3.70-3.84 (complex band; 1H; aromatic proton); 6.12 (d, J_{P-O-Me} 12 Hz; 3H; P-O-Me); 7.68 (s; 3H; Me); 7.74 (s; 3H; Me); 7.82 (s; 3H; Me).

(iv) Hydrolysis of the phosphorane in 50:50 (v/v) $CDCl_3$: CD_3COCD_3 observed by p.m.r. and g.l.c./mass spectrometry

The phosphorane (50 mg) was dissolved in $CDCl_3/CD_3COCD_3$ (50:50 v/v; 0.5 ml) in an n.m.r. tube; one drop of D_2O was added and the solution

was observed in the EM-360 probe (33°). Simultaneously, the reaction was followed by g.l.c. (5% SE30 at 182°; direct injection on to the column packing). As the reaction proceeded, four new resonances were observed: (τ) 4.66 (s; CH_3OH); 6.36 (d; J 11 Hz); 7.65 (s); 7.76 (s) (component A). After 17 min, the doublet integration was twice the methanol integration, and comparison of the methoxyl and methyl region integrations suggested that a compound with the following characteristics was being produced: (τ) 6.36 (d, J_{P-O-Me} 11 Hz; 6H; 2 x P-O-Me); 7.65 (s; 6H; mesityl o-Me); 7.76 (s; 3H; mesityl p-Me). At the same time, g.l.c. showed that as the phosphorane peak (R.t. 10 min) declined, a new peak (R.t. 15 min) increased until at t = 30 min this latter peak exceeded the phosphorane peak and the product resonances exceeded the phosphorane resonances in p.m.r. intensity. At this time a mass spectrum was taken of the g.l.c. component (R.t. 15 min) which showed the following peaks: m/e 303 (100%, M^+); 271 (42%); 224 (18%); 208 (48%). No peak appeared at 335, nor m* for a 335 fragmentation to 303.

A second product doublet @ 6.14τ (J 12 Hz) (component B), faintly visible throughout the hydrolysis, increased rapidly after t = 30 min. The phosphorane disappeared at t = 35 min and both doublets had disappeared by t = 37 min leaving a spectrum identified as that of methanol and 2-hydroxy-3-mesityl-2-oxobenz-1,3,2-oxazaphospholine. The g.l.c. trace was clear; hence, negligible 2-(2',4',6'-trimethylanilino)phenol was formed.

(v) Hydrolysis of the phosphorane in $CDCl_3$ observed by p.m.r. spectroscopy

The phosphorane (50 mg) was dissolved in $CDCl_3$ (0.5 ml) in an n.m.r. tube; one drop of D_2O was added, and the solution was observed in the EM-360 probe (33°). The same hydrolysis components were observed as in

subsection (iv) above; however, component A increased rapidly until t = 10 min and declined thereafter until, at t = 30 min, both A and the phosphorane disappeared. Component B increased rapidly from t = 0 accompanied by singlets of equal intensity at 7.68τ, 7.74τ and 7.82τ. These singlets and the doublet at 6.14τ were identified as belonging to 3--mesityl-2-methoxy-2-oxobenz-1,3,2-oxazaphospholine in subsection (iii) above. Integrations are compatible with a mixture composed predominantly of this cyclic phosphoramidate and methanol at t = 30 min.

Thereafter, the cyclic phosphoramidate hydrolysed smoothly to 2-hydroxy-3-mesityl-2-oxobenz-1,3,2-oxazaphospholine after 120 min. No unidentified resonances appeared.

Linear first-order plots were obtained for the disappearance of the cyclic phosphoramidate doublet (k^1 = 0.035 min, $t_{\frac{1}{2}}$ = 20 min), and the appearance of methanol (k^1 = 0.029 min^{-1}, $t_{\frac{1}{2}}$ = 24 min). The discrepancy between these values is attributed to the partitioning of methanol into the aqueous layer, which is outside the probe.

(b) 3-Mesityl-2,2-dimethoxy-2-phenyl-2,2--dihydrobenz-1,3,2-oxazaphospholine

(i) The isolation of 3-mesityl-2-oxo-2-phenylbenz--1,3,2-oxazaphospholine

Aqueous toluene-4-sulphonic acid (0.5 ml) was added to a solution of the phosphorane (1.39g; 3.5 mMol) dissolved in dioxan (19 ml) to give a 2.5% aqueous solution containing toluene-4-sulphonic acid (0.06g; 0.32 mMol). The solution was stirred for 5 min at 35°; then, anhydrous magnesium sulphate (7g) was added to remove the water. The solution was filtered, evaporated and redissolved in chloroform (50 ml), shaken with 1% aqueous sodium bicarbonate solution (2 x 20 ml) and washed with water

(3 x 20 ml). The chloroform layer was dried over anhydrous magnesium sulphate, then filtered and evaporated to a pale-blue powder. Recrystallisation from cyclohexane (20 ml) gave white crystals, m.p. 137.5-139°, identified as 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine (1.0g; 81% yield). The p.m.r. spectrum of the recrystallisation filtrate-residue (0.12g) indicated the same material with less than 4% contamination by 2-(2',4',6'-trimethylanilino)phenol. Thus, the true yield of 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine is ca. 91%.

The following data were obtained. (Found: C, 72.1; H, 5.8; N, 4.0. $C_{21}H_{20}NO_2P$ requires C, 72.2; H, 5.8; N, 4.0%).

The mass spectrum showed the correct molecular ion at m/e 349 (100%; found 349.121743, required 349.123123); major fragment, 208 (20%; $M^+ - PhPO_2$, H).

I.r. spectrum ($CHCl_3$): 953 cm^{-1} (s), 980 cm^{-1} (s), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1275 cm^{-1} (s) (sharp absorption; P=O); 1440 cm^{-1} (m) (sharp absorption; P-Ph).

P.m.r. spectrum ($CDCl_3$): (τ) 2.1-2.9 (complex band; 5H; P-Ph); 3.0-3.3 (complex band (incorporating two broad singlets ca. 1H each, at 3.02 and 3.24); 5H; aromatic protons); 3.70-3.86 (complex band; 1H; aromatic proton); 7.63 (s; 3H; mesityl Me); 7.75 (s; 3H; mesityl Me); 8.56 (s; 3H; mesityl o-Me).

$\delta^{31}P$ ($CDCl_3$): -28.6 ppm; undecoupled spectrum, broad triplet J_{P-H} 13.4 Hz (P-o-H(phenyl) coupling).

(ii) Hydrolysis of the phosphorane in 5% aqueous dioxan (neutral)

Water (0.5 ml) was added to a solution of the phosphorane (0.49g; 1.24 mMol) in dioxan (9.5 ml) stirred at 30°; the reaction was monitored by g.l.c. on 5% SE30 (212°, direct injection on to column packing). No reaction was detectable over 335 min, then at 395 min the reaction was

observed to have occurred and reached completion. The only product was identified as 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine. At 335 min the pH was 6-7 and at 395 min it had fallen to pH 4 (universal indicator papers). The product was freeze-dried to constant weight to give a white powder. A sample was examined by p.m.r. which suggested a 96% yield of the above cyclic phosphonamidate. However, a fine suspension remained undissolved and failed to extract into water. Dissolution of the product in a minimum of benzene, followed by filtration, left a white precipitate (5 mg) with m.p. $> 288^{\circ}$ (c.f. $PhP(O)(OH)_2$; m.p. 161°); the i.r. spectrum (nujol) showed broad absorptions at 2350 cm^{-1} and 1640 cm^{-1} suggestive of POH. Attempts to recrystallise the main product failed to produce pure cyclic phosphonamidate.

(iii) Hydrolysis of the phosphorane in 50:50 (v/v) $CDCl_3$: CD_3COCD_3 observed by p.m.r. spectroscopy

The phosphorane (ca. 30 mg) was dissolved in a 50:50 (v/v) solution of $CDCl_3$: CD_3COCD_3 containing one drop of T.M.S. as reference (0.5 ml) in an n.m.r. tube. One drop of D_2O was added and the p.m.r. spectrum was recorded at intervals on an EM-360 spectrometer. The tube was maintained at 23° between scans.

A rapid hydrolysis was observed, giving after 50 min 3-mesityl-2--oxo-2-phenylbenz-1,3,2-oxazaphospholine and methanol as the sole detectable products. G.l.c. on 5% SE30 confirmed this observation and discounted the production of 2-(2',4',6'-trimethylanilino)phenol or dimethyl phenylphosphonate. During the hydrolysis, three other resonances were detectable: (τ) 6.38 (d, J 11 Hz); 7.56 (s); the third resonance (ca. 7.8-7.9) was obscured by the CHD_2COCD_3 multiplet. The ratio of the former resonances remained 1:1 throughout. Assuming that the doublet resonance was due to one methoxy group, the product ratio

after 30 min was 19% of phosphorane; 33% of the final cyclic phosphonamidate and 48% of the unknown.

No phosphorane remained at t = 45 min and the unknown disappeared rapidly thereafter (t = 55 min).

(iv) Hydrolysis of the phosphorane in $CDCl_3$ observed by p.m.r. spectroscopy

In $CDCl_3$ an identical pattern emerged, although hydrolysis proceeded more slowly. The unknown resonances were observed at: (τ) 6.34 (d, J 11 Hz); 7.54 (s); 7.82 (s). The former pair of resonances were in ratio 1:1. It was not possible to obtain a reliable ratio for the latter singlet due to the closeness of other resonances.

A sample of 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine was dissolved in $CDCl_3$ in the presence of one drop of dry methanol. No change in the spectrum was observed after 5 min and after 15 h. The addition of D_2O to this solution also produced no effect. This effectively discounts the production of the unknown by reaction of methanol with the cyclic phosphonamidate.

N.B.(1): Apart from undissolved D_2O, the solutions in subsections (iii) and (iv) above showed no detectable precipitates throughout.

N.B.(2): The phosphorane was also hydrolysed in 3% aqueous dioxan by boiling under reflux for 30 min. The product mixture, analysed by g.l.c. (5% SE30/210°), showed only 2-(2',4',6'-trimethylanilino)phenol and 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine, in 15:85 peak ratio. No increase in the small impurity peak for dimethyl phenylphosphonate was detectable.

(c) 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-
- 1,3,2-oxazaphospholine

(i) Hydrolysis of the phosphorane in 5% aqueous dioxan

The phosphorane (0.66g; 1.8 mMol) dissolved in 5% aqueous dioxan (10 ml) was stirred at 30°. The reaction was monitored by g.l.c. (5% SE30/212°; direct injection on to column packing). After 5 h no phosphorane remained; the g.l.c. trace indicated only two major products, identified as dimethyl phenylphosphonate and 2-p-toluidinophenol. A third, minor product was identifiable as 2-oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine. The pH before and after the reaction was 6-7 (universal indicator papers). Evaporation of the solution left a pale-purple oil, which was dissolved in ether and extracted with water (12 x 10 ml). The ether layer was dried over anhydrous magnesium sulphate, filtered and evaporated to constant weight, giving a highly-viscous, green oil identified by i.r. and p.m.r. as 2-p-toluidinophenol (0.35g). The p.m.r. spectrum indicated 95% purity; thus, the yield of 2-p-toluidinophenol was ca. 95%.

The aqueous layer was extracted with chloroform (4 x 20 ml), dried over anhydrous magnesium sulphate, filtered and evaporated to give a blood-red oil; this colour persisted despite filtration through a plug of activated alumina. The oil was identified by p.m.r., i.r. and mass spectrometry as dimethyl phenylphosphonate (0.26g; 77%).

The residual aqueous layer was evaporated to give a small yield of white powder which, when redissolved in water and titrated with standard sodium hydroxide (methyl-red indicator), was found to contain 0.1 mMol of H^+. The most probable source is benzenephosphonic acid (6% yield — see subsection (ii) below).

(ii) Benzenephosphonic acid in the presence of methanol (control experiment)

Benzenephosphonic acid (0.043g; 0.27 mMol) and methanol (0.02g; 0.63 mMol) dissolved in dioxan (1.5 ml) were stirred at 30° for 5 h. Analysis by g.l.c. under identical conditions to those used in subsection (i) above failed to detect any dimethyl phenylphosphonate. The solvent was removed, leaving a white powder, m.p. 160-163° ($PhPO(OH)_2$; lit. m.p.[197] 161°). Titration of authentic benzenephosphonic acid with aqueous sodium hydroxide demonstrated that the acid is essentially monobasic with methyl-red as indicator. Titration of the experimental product thus showed that benzenephosphonic acid was recovered in 98% yield.

Hence, no dimethyl phenylphosphonate is produced by this route.

(iii) Hydrolysis of the phosphorane in 20% aqueous dioxan at 60°

The phosphorane (0.97g; 2.6 mMol) dissolved in 20% aqueous dioxan, was heated at 60° under a reflux condenser; the reaction was monitored by g.l.c. (1% SE30 at 180°; direct injection on to column packing). After 2 h no phosphorane remained and heating was stopped. The only detectable products were 2-p-toluidinophenol and a minor component of dimethyl phenylphosphonate. The pH of the solution had dropped from pH6-7 to pH3. Evaporation of the solvent left a pale-purple, highly-viscous oil. Chloroform was added, giving a purple solution containing a precipitate. The precipitate was filtered and dissolved in boiling ethanol (10 ml); benzene (40 ml) was added and the solution was extracted with water (4 x 20 ml) until the aqueous layer was no longer acidic. Evaporation of water gave a white powder identified by i.r. as benzenephosphonic acid (0.31g; 74%: after drying for 15 h at 100°/7 mm); m.p. 160-162° (lit. m.p.[197] 160°).

The chloroform filtrate, on evaporation, gave a viscous, purple oil

identified by i.r. as 2-p-toluidinophenol. The p.m.r. spectrum indicated ca. 10% (molar) of dimethyl phenylphosphonate; the yield of the phenol was 99% (assessed by p.m.r.).

(iv) The reaction of 2-oxo-2-phenyl-3-p-tolylbenz--1,3,2-oxazaphospholine with methanol

2-Oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine (0.16g; 4.9 mMol), dissolved in dry methanol (15 ml), was stirred under dry nitrogen at 60°. The reaction was monitored by g.l.c. (5% SE30 at 211°, gas flow rate 150 ml min^{-1}; direct injection on to column packing). After 35 min reaction was indicated by the appearance of a peak (R.t. 15.5 min) of equal intensity to that due to the cyclic phosphonamidate (R.t. 11.5 min). After 90 min the peak ratio was ca. 1:4 but heating for a further 3 h produced no additional change. Solvent was evaporated at 35° under reduced pressure, giving a colourless solid (0.18g; 3% in excess of the theoretical 100% incorporation of 1 mol of methanol). The following spectral data were recorded.

P.m.r. spectrum ($CDCl_3$): (τ) 2.0-3.5 (complex band; 12-13H; aromatic protons); 3.8 (broad resonance; 1H; N-H); 4.13 (d, J 10 Hz; 3H; P-O-Me); 7.63 (s; 3H; tolyl Me). No trace of methanol was observed. Comparison of the resonance at 7.63 with the doublet at 4.13 suggested that up to 10% of 2-oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine could be present. No dimethyl phenylphosphonate was produced.

The mass spectrum showed the correct molecular ion at m/e 353 (50%); major fragments, 321 (100%; M^+ - MeOH: m* @ 292 for direct fragmentation from M^+); 199 (100%; M^+ - OPPh, CH_2O).

I.r. spectrum ($CHCl_3$): 815 cm^{-1} (s) (P-O-(C) stretch); 940 cm^{-1} (s) (P=O); 1210-1260 cm^{-1} (broad absorption; P-O-C (aryl) deformation); 1605 cm^{-1} (s) (aromatic C=C); 3350 cm^{-1} (w) (broad absorption; bonded

N-H); 3415 cm^{-1} (m) (fairly sharp absorption; unbonded N-H).

The i.r. spectrum showed great similarity to that obtained for 2-p-toluidinophenyl diphenylphosphinate (see subsection (e)(iii) below, p. 158).

G.l.c. analysis of the i.r. solution (5% SE30 at 211°) now indicated that the product and the cyclic phosphonamidate were in 9:1 ratio. This suggested that the removal of methanol from the reaction mixture at 35° increased the product yield.

The product was identified as methyl 2-p-toluidinophenyl phenylphosphonate.

N.B.: Further attempts to repeat this reaction were unsuccessful; the cyclic phosphonamidate was recovered together with a small yield of product.

(v) Hydrolysis of the phosphorane in 50:50 (v/v) $CDCl_3$: CD_3COCD_3 observed by p.m.r. spectroscopy

The phosphorane (40 mg) was dissolved in a 50:50 solution of $CDCl_3$ and CD_3COCD_3, containing one drop of T.M.S. as reference (0.5 ml), in an n.m.r. tube. One drop of D_2O was added and the p.m.r. spectrum was recorded, at intervals, on an EM-360 spectrometer. The tube was maintained at 23° between scans.

During the hydrolysis, four components (apart from the phosphorane and methanol) were observed. These were identified as:

A: 2-p-toluidinophenol: (τ) 7.74 (s).

B: Unknown, containing: 6.3 (d, J 11 Hz); 7.80 (s) ratio of d:s ca. 1:1.

C: 2-oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine: 7.70 (s).

D: Dimethyl phenylphosphonate: 6.26 (d).

At t = 1 h. 10 min, the major resonance was due to the phosphorane; A and B were visible. At t = 23 h, no phosphorane remained; A, B and C were all present in ratio ca. 2:3:1. Dimethyl phenylphosphonate, now present to ca. 25% yield, did not vary significantly hereafter.

B was observed to decrease gradually, whilst A and C increased, until at t = 28 h, B had disappeared. At t = 46 h, 2-p-toluidinophenol and dimethyl phenylphosphonate remained. This result was confirmed by g.l.c. A doublet, yield ca. 13% based upon the aromatic integration (assuming that this doublet is due to a one-methoxyl resonance) also remained at: (τ) 6.35 (d; J 11 Hz); no corresponding p-tolyl methyl resonance was observed.

The solution remained clear throughout; however, a small aqueous layer was present and the methanol integration reached only 60% of its expected maximum, presumably due to solvent partitioning.

The p.m.r. resonances for methyl 2-p-toluidinophenyl phenylphosphonate in 50:50 $CDCl_3/CD_3COCD_3$ are recorded here for comparison with the unknown B: (τ) 1.9-3.5 (complex band); 6.16 (d, J_{P-O-Me} 11 Hz); 7.72 (s). In addition, the aromatic region of B incorporated a prominent singlet at 3.03τ whilst methyl 2-p-toluidinophenyl phenylphosphonate had a similar singlet at 3.00τ. Superposition of spectra strongly suggested that B and the latter phosphonate are not the same.

(vi) Hydrolysis of the phosphorane in 50:50 (v/v) $CDCl_3$:CD_3COCD_3 (acid conditions) observed by p.m.r. spectroscopy

The phosphorane (40 mg) was dissolved in a 50:50 solution of $CDCl_3$ and CD_3COCD_3 containing one drop of T.M.S. as reference (0.5 ml), in an n.m.r. tube. One drop of 2N aqueous hydrochloric acid was added and the reaction was observed in the EM-360 probe (33°). Spectra were recorded at intervals.

At t = 1 min, no phosphorane remained. Apart from a small singlet at 7.70τ (corresponding to C in subsection (v) above), the rest of the spectrum showed only methanol and those signals assigned to the unknown B (subsection (v) above). Over the next 24 min the singlet and doublet due to B decreased rapidly, whilst the singlet at 7.70τ increased. The singlet at 7.80τ persisted after the disappearance of the accompanying doublet at 6.3τ (t = 24 min), suggesting that another component resonates at this frequency as well as B. At t = 24 min a singlet at 7.74τ (ascribed to 2-p-toluidinophenol) was observed to be increasing. At t = 55 min the other resonances in the tolyl methyl region were greatly decreased and the latter singlet was predominant. At t = 2 h.35 min the only significant resonance in the tolyl methyl region was due to 2-p-toluidinophenol; superposition of the spectrum on that of pure 2-p-toluidinophenol confirmed that this was the predominant final product.

From t = 24 min, a doublet at 6.4τ (J 12 Hz) was observed to increase and at t = 2 h.35 min this signal integrated to 45% yield (assuming it is due to one methoxy group). At the same time the methanol yield was 54%, both based on the aromatic integration. No resonance other than that due to 2-p-toluidinophenol, in the tolyl methyl region, was of significant size, suggesting that the doublet at 6.4τ must be an independent species, probably methyl hydrogen phenylphosphonate.

(vii) Hydrolysis of the phosphorane in $CDCl_3$ (acid conditions), observed by p.m.r. spectroscopy

The phosphorane (40 mg), dissolved in $CDCl_3$ in an n.m.r. tube, was treated with one drop of 2N aqueous hydrochloric acid. The solution was observed in the EM-360 cavity after 30 s and found to contain no phosphorane and only one significant set of resonances apart from methanol. The spectral data are as follows: (τ) 2.0-3.5 (complex band; ca. 13H;

aromatic protons); 6.25 (d, J 11 Hz; 3H; P-O-Me); 7.77 (s; ca. 3H; tolyl Me). The slight uncertainty in the integrations is due to the presence of a small singlet at 7.63 attributed to 2-oxo-2-phenyl-3-p--tolylbenz-1,3,2-oxazaphospholine. Superposition of the spectrum on that of the material assigned as methyl 2-p-toluidinophenyl phenylphosphonate indicated that the two materials were not the same. On this basis, the initial hydrolysis product, above, is postulated to be methyl N-o--hydroxyphenyl-P-phenyl-N-p-tolylphosphonamidate.

(d) 3-Mesityl-2-methoxy-2,2-diphenyl-2,2-dihydrobenz-1,3,2--oxazaphospholine

(i) The acidic hydrolysis of the phosphorane in 5% aqueous dioxan

The phosphorane (0.75g; 17 mMol), dissolved in 5% aqueous dioxan (20 ml), containing toluene-4-sulphonic acid (0.32 mMol), was stirred at 35° for one hour. A white precipitate was deposited rapidly and the solution became pale-purple. T.l.c. (benzene) indicated that no phosphorane (R.f. 0.63) remained after 30 min.

The precipitate was filtered and washed with dioxan; the filtrate was evaporated, redissolved in chloroform (25 ml) and washed with water (2 x 10 ml), then dried over anhydrous magnesium sulphate. Solvent removal left a pale-brown powder which was washed till white with dry ether. Both solid fractions were combined and identified as a material with molecular formula $C_{27}H_{26}NO_2P$ (0.69g; 96%).

Due to the insolubility of this material it was difficult to recrystallise; dissolution in hot chloroform was possible but reprecipitation only occurred in small yield and good analytical figures were not obtained. (Found: C, 73.1; H, 5.8; N, 3.1. $C_{27}H_{26}NO_2P$ requires C, 75.9; H, 6.1; N, 3.3%). The source of these discrepancies is

attributed to the tendency of the material to trap solvents which cannot be removed even when the material is heated at 110°/7 mm for several days. The yield, given above, was assessed from the p.m.r. spectrum which showed a resonance identified as dioxan. Further evidence (see subsection (e)(ii) below, p. 156) discounts an erroneous molecular formula.

The following data were obtained: m.p. ca. 155° (variable; decomposition suspected).

The mass spectrum gave the correct molecular ion at m/e 427 (100%; found 427.168075, $C_{27}H_{26}NO_2P$ requires 427.170107); major fragments, 209 (16%; $M^+ - OP(OH)Ph_2$; large m* @ 102.3 for direct fragmentation from M^+); 208 (56%; 209-H); 201 (27%; $(OPPh_2)^+$); 194 (14%).

I.r. spectrum ($CHCl_3$): 980 cm^{-1} (s); 1120 cm^{-1} (s); 1150 cm^{-1} (s) (broad absorption; P=O); 1435 cm^{-1} (s) (sharp absorption; P-Ph); 3400 cm^{-1} (very weak, broad absorption).

P.m.r. spectrum ($CDCl_3$): (τ) -0.9 (s; 1H; phenolic OH); 2.2-3.0 (complex band; 10H; 2 x P-Ph); 3.0-3.5 (complex band; 6H; aromatic protons); 7.67 (s; 6H; 2 x mesityl Me); 7.85 (s; 3H; mesityl p-Me). The low field singlet exchanges with D_2O.

$\delta^{31}P$ ($CDCl_3$): -32.9 ppm.

This material was identified as N-(2-hydroxyphenyl)-N-mesityl-P,P--diphenylphosphinamide.

The ethereal filtrate was evaporated to give a pale-brown powder (23 mg) and analysed by p.m.r. spectroscopy. The p.m.r. spectrum suggested a mixture of the phosphinamide and its isomer 2-(2',4',6'--trimethylanilino)phenyl diphenylphosphinate, in ca. 50:50 ratio. A small amount of methyl diphenylphosphinate also appeared. The maximum isolated yield of 2-(2',4',6'-trimethylanilino)phenyl diphenylphosphinate was 1.5%.

(ii) The low temperature behaviour of N-(2-hydroxyphenyl)-N-mesityl-P,P-diphenylphosphinamide observed by p.m.r. spectroscopy

The compound, dissolved in methylene chloride in an n.m.r. tube, was cooled in the HA-100 probe. The p.m.r. spectrum was observed at several temperatures and the results are recorded in Figure II.2 (p. 154).

As the sample was cooled, a general decrease of resolution was observed; however, between -85° and -90°, the singlet assigned to the mesityl o-Me protons was observed to broaden more rapidly than that due to the p-Me protons, suggesting that the former were undergoing an exchange process, which was becoming slow on the p.m.r. time-scale. The aromatic region showed a severe loss of resolution at -90°; however, the change in the P-Ph proton-resonance region was more extensive than that in the rest of the aromatic region.

At -90° some precipitation of material was observed. It was conjectured that the effect observed in the mesityl methyl region could be due to the presence of some 2-(2',4',6'-trimethylanilino)phenyl diphenylphosphinate. The o-Me and p-Me mesityl resonances of this compound coincide with the p-Me and o-Me resonances (respectively) of the phosphinamide. There are indications that the phosphinamide may rearrange thermally to the diphenylphosphinate and hence some of the latter could have been formed during recrystallisation prior to this experiment. The phosphinamide, being the less soluble isomer, could precipitate at low temperatures giving an apparent enhancement of the p-Me resonance with respect to the o-Me resonance. However, the ratio of the o-Me resonance integration to that of the p-Me at $+28^{\circ}$ was 1.8:0.95 which allowed a maximum contamination by the diphenylphosphinate of ca. 3%. As no overall loss in intensity was noticed at low temperature, such a contamination would be insufficient to explain the observed

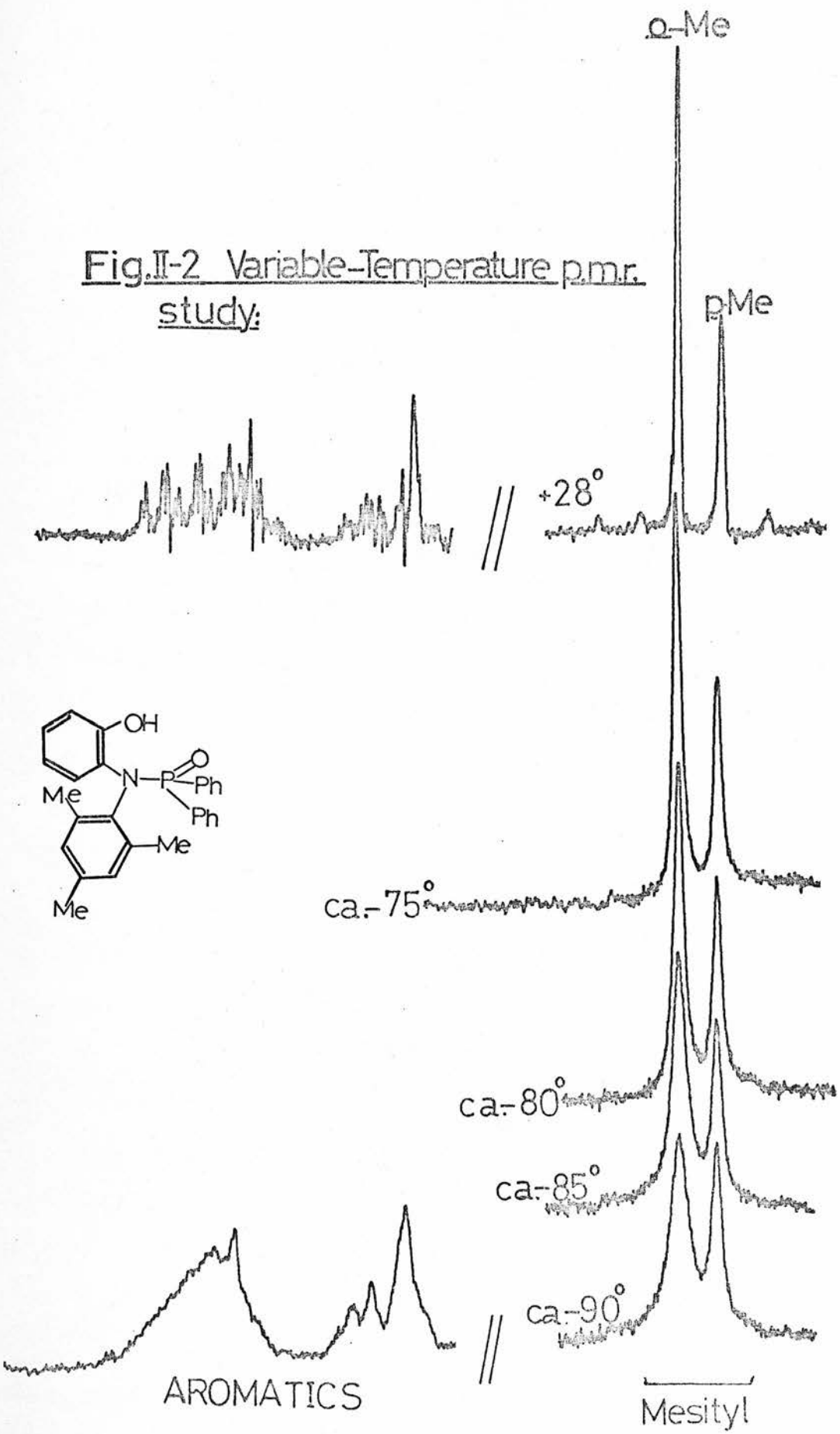


Fig.II-2 Variable-Temperature p.m.r. study:

phenomenon.

(iii) The reaction of 2-(2',4',6'-trimethylanilino)phenol with diphenylphosphinic chloride

A mixture of 2-(2',4',6'-trimethylanilino)phenol (0.39g; 1.7 mMol) diphenylphosphinic chloride (0.82g; 3.5 mMol) and triethylamine (0.35g; 3.5 mMol) in dry ether (30 ml) was stirred for 30 min at room temperature under an atmosphere of dry nitrogen. A white precipitate was deposited and g.l.c. analysis (5% SE30 at 210°) indicated that all of the anilinophenol had reacted. Excess diphenylphosphinic chloride was destroyed by stirring for 15 min with water (10 ml). The resulting diphenylphosphinic acid was removed by shaking the ethereal layer with aqueous 1% sodium bicarbonate solution (4 x 20 ml). Finally, the ethereal layer was washed with water (3 x 10 ml), dried over anhydrous magnesium sulphate and evaporated to give a colourless, transparent solid. Recrystallisation from light petroleum (b.p. 60-80°) gave a white powder m.p. ca. 210°, identified as 2-(2',4',6'-trimethylanilino)phenyl diphenylphosphinate (0.30g; 41%). (Found: C, 75.5; H, 6.0; N, 3.1. $C_{27}H_{26}NO_2P$ requires C, 75.9; H, 6.1; N, 3.3%).

The mass spectrum gave the correct molecular ion at m/e 427 (100%; found 427.169731, required 427.170107); major fragments, 209 (24%; $M^+ - OP(O)Ph_2$; m* @ 102.3 for direct fragmentation from M^+); 208 (68%; 209-H); 201 (28%; $(Ph_2PO)^+$).

I.r. spectrum ($CHCl_3$): 860 cm^{-1} (s) (P-O-(C) stretch); 925 cm^{-1} (intense, broad absorption; (P)-O-C stretch); 1100 cm^{-1} (s), 1110 cm^{-1} (s), 1130 cm^{-1} (s) (sharp absorptions; POC deformation region); 1170 cm^{-1} (intense absorption; P=O); 1600 cm^{-1} (s) (aromatic C=C); 3315 cm^{-1} (m) (broad absorption; bonded N-H); 3420 cm^{-1} (m) (fairly sharp absorption; unbonded N-H).

P.m.r. spectrum ($CDCl_3$): (τ) 1.9-2.8 (complex band; 10H; 2 x P-Ph); 2.9-4.1 (complex band, including a singlet (2H) at 3.12; 6H; aromatic protons); 6.3 (broad; 1H; exchanges with D_2O; N-H); 7.70 (s; 3H; mesityl p-Me); 7.83 (s; 6H; 2 x mesityl o-Me).

$\delta^{31}P$ ($CDCl_3$): -32.5 ppm.

(iv) The base-catalysed rearrangement of N-(2-hydroxyphenyl)--N-mesityl-P,P-diphenylphosphinamide

A slurry of N-(2-hydroxyphenyl)-N-mesityl-P,P-diphenylphosphinamide (60 mg) was dissolved in $CDCl_3$; the ^{31}P magnetic resonance spectrum showed one peak at -32.9 ppm. Triethylamine (1 drop) was added and the solution was maintained at 35° for 1.75 h. The spectrum was rescanned, and two closely-spaced singlets of similar intensity were observed at -32.9 ppm and -32.4 ppm. After a further 8 h the solution was evaporated to give a white powder. I.r. and p.m.r. spectroscopy confirmed that the product was 2-(2',4',6'-trimethylanilino)phenyl diphenylphosphinate.

(e) 2-Methoxy-2,2-diphenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

(i) Neutral hydrolysis of the phosphorane in 3.5% aqueous dioxan

The phosphorane (0.68g; 1.64 mMol), dissolved in 3.5% aqueous dioxan (14.5 ml), was stirred at 35° for 40 h. The solution was monitored by t.l.c. and no reaction was observed.

(ii) Acidic hydrolysis of the phosphorane in 5% aqueous dioxan

The phosphorane (0.64g; 1.56 mMol), dissolved in 5% aqueous dioxan (20 ml) containing toluene-4-sulphonic acid (0.32 mMol), was stirred at 35° for one hour. The solution became dark-purple immediately and a

white, gelatinous precipitate formed. T.l.c. (in benzene) indicated that no phosphorane (R.f. 0.78) remained after 12 min.

The precipitate was filtered and washed with dioxan; the filtrate was evaporated, redissolved in chloroform and washed with water (2 x 10 ml), finally drying over anhydrous magnesium sulphate. This solution was filtered and evaporated to a pale-brown powder which was washed with dry ether until white. Both solid fractions were combined, dried and identified as N-(2-hydroxyphenyl)-P,P-diphenyl-N-p-tolylphosphinamide (0.56g; 90%). The melting point was variable and suggested a rearrangement process occurring above 140° to give a lower melting point material, probably 2-p-toluidinophenyl diphenylphosphinate (see subsection (iii) below).

The following data were obtained. (Found: C, 75.2; H, 5.5; N, 3.5. $C_{25}H_{22}NO_2P$ requires C, 75.2; H, 5.6; N, 3.5%).

The mass spectrum gave the correct molecular ion at m/e 399 (100%; found 399.137845, required 399.138808); major fragments, 201 (38%; $(Ph_2PO)^+$; m* @ 101.3 for direct fragmentation from M^+); 183 (9%).

I.r. spectrum ($CHCl_3$): 1000 cm^{-1} (m); 1125 cm^{-1} (m); 1440 cm^{-1} (s) (sharp absorption; P-Ph). No obvious P=O absorption.

P.m.r. spectrum ($CDCl_3$): (τ) 0.24 (s; 1H; exchanges with D_2O; phenolic OH); 2.0-2.8 (complex band; 10H; 2 x P-Ph); 2.8-3.6 (complex band; 8H; aromatic protons); 7.88 (s; 3H; tolyl Me).

$\delta^{31}P$ ($CDCl_3$): -30.8 ppm.

The ethereal filtrate was evaporated to give a brown powder (47 mg). The p.m.r. spectrum of this residue indicated that it was a ca. 50:50 mixture of the above phosphinamide and its isomer 2-p-toluidinophenyl diphenylphosphinate (yield ca. 4%); a small amount of methyl diphenylphosphinate was also detected.

When the phosphinamide was dissolved in boiling dioxan,

recrystallisation failed to occur; solvent removal gave a white powder which was identified by p.m.r. and i.r. spectroscopy as pure 2-p--toluidinophenyl diphenylphosphinate.

(iii) The base catalysed rearrangement of N-(2-hydroxyphenyl)--P,P-diphenyl-N-p-tolylphosphinamide

The phosphinamide (0.2g; 0.5 mMol) and extra-dry triethylamine (0.08 ml; 0.5 mMol) in dry chloroform (25 ml) were maintained at room temperature. The solution composition was monitored by t.l.c. (ether) and the phosphinamide (R.f. 0.6) was observed to isomerise quantitatively to 2-p-toluidinophenyl diphenylphosphinate (R.f. 0.2) with $t_{\frac{1}{2}}$ ca. 40 min. The solvent was removed after 7.5 h to give a white powder, which was recrystallised from a 40:60 mixture of light petroleum (b.p. 60-80°) and cyclohexane to give white crystals m.p. 117-118° (0.17g; 85%). The following data were obtained. (Found: C, 75.2; H, 5.5; N, 3.4. $C_{25}H_{22}NO_2P$ requires C, 75.2; H, 5.6; N, 3.5%).

The mass spectrum gave the correct molecular ion at m/e 399 (100%; found 399.137845 required 399.138808); major fragments, 308 (32%; M^+ - tolyl); 307 (27%; 308-H; m* @ 306 for framentation from 308 to 307); 201 (82%; $(Ph_2PO)^+$).

I.r. spectrum ($CHCl_3$): 875 cm^{-1} (m) (P-O-(C) stretch); 925 cm^{-1} (s) (broad absorption; (P)-O-C stretch); 1100 cm^{-1} (s), 1110 cm^{-1} (m), 1130 cm^{-1} (s) (sharp absorptions; POC deformation region); 1180 cm^{-1} (s) (broad absorption; P=O); 1605 cm^{-1} (s) (aromatic C=C); 3340 cm^{-1} (m) (broad absorption; bonded N-H); 3425 cm^{-1} (m) (fairly sharp absorption; unbonded NH).

P.m.r. spectrum ($CDCl_3$): (τ) 2.0-3.5 (complex band; ca. 18H; aromatic protons); 7.72 (s; 3H; tolyl Me). No detectable N-H proton in -5 to +10τ region; however, the aromatic region integration before

and after the addition of D_2O suggested that such a resonance may occur in that region.

$\delta^{31}P$ ($CDCl_3$): -33.2 ppm.

(iv) Ferric chloride test

(1) A solution of the phosphinamide in ethanol gave a faint green colouration with aqueous ferric chloride.

(2) A solution of the diphenylphosphinate in ethanol gave a temporary yellow precipitate, but the solution remained yellow.

Thus the test suggests that the isomers are correctly assigned.

(v) Observation of 2-p-toluidinophenyl diphenylphosphinate in acidic, aqueous dioxan

The diphenylphosphinate (9 mg) was dissolved in a 5% aqueous solution of dioxan (0.4 ml) containing toluene-4-sulphonic acid (0.32 mMol/20 ml solution) at 35°. The reaction was monitored by t.l.c. (ether) over 24 h and no N-(2-hydroxyphenyl)-P,P-diphenyl-N-p-tolylphosphinamide was detected.

(vi) Hydrolysis of the phosphorane in 50:50 (v/v) $CDCl_3$: CD_3COCD_3 observed by p.m.r. spectroscopy

The phosphorane (30 mg) was dissolved in a 50:50 solution of $CDCl_3$ and CD_3COCD_3 containing one drop of T.M.S. as reference (0.8 ml) in an n.m.r. tube. One drop of D_2O was added and the p.m.r. spectrum was recorded at intervals, on an EM-360 spectrometer. The solution was maintained at 23° between scans. The aromatic region was employed as an integration standard.

The reaction was observed over 19 h after which no phosphorane remained and the products were identified as methanol (6.65%), methyl

diphenylphosphinate (6.26; d, J 11 Hz; ca. 10%), 2-p-toluidinophenol (7.73τ; s; ca. 10%) and N-(2-hydroxyphenyl)-P,P-diphenyl-N-p-tolylphosphinamide (7.86τ; s; ca. 90%). No intermediates or 2-p-toluidinophenyl diphenylphosphinate were observed. At the close of the reaction the solution was purple and a white precipitate of the phosphinamide was present, hence the true yield of methyl diphenylphosphinate is probably less than estimated above.

(vii) Hydrolysis of the phosphorane in 50:50 (v/v) $CDCl_3$:CD_3COCD_3 in the presence of excess 2,6-lutidine observed by p.m.r. spectroscopy

The phosphorane (30 mg) was dissolved in a 50:50 solution of $CDCl_3$ and CD_3COCD_3 containing one drop of T.M.S. as reference (0.8 ml) in an n.m.r. tube. 2,6-Lutidine (57 ml; 10 molar equivalents) and one drop of D_2O were added; the p.m.r. spectrum was recorded at intervals, on an EM-360 spectrometer. The solution was maintained at 23° between scans.

The yield of methyl diphenylphosphinate and 2-p-toluidinophenol was not noticeably altered from that obtained in subsection (vi) above. The rate of reaction was slightly decreased. Thus, after 19 h a small amount of the phosphorane was still observed. The major product after 19 h was once again the phosphinamide; however, this was observed to rearrange slowly to 2-p-toluidinophenyl diphenylphosphinate, so that after 57 h this was the major product and no phosphinamide remained.

(viii) Attempted methylation of 2-p-toluidinophenyl diphenylphosphinate and N-(2-hydroxyphenyl)-P,P-diphenyl-N-p-tolylphosphinamide

Solutions of both compounds in ether, containing a little super-dried methanol to solubilise, were treated with excess ethereal

diazomethane prepared by the method detailed in Vogel.[204] Neither solution showed visible reaction, although the phosphinamide solution showed a very slow evolution of nitrogen. After 48 h the solvent was evaporated using a stream of dry nitrogen. The residue from both solutions was a dark-red oil containing a few colourless crystals. T.l.c. of both solutions (ether) indicated a complex mixture of at least four components. The p.m.r. spectra ($CDCl_3$) were identical and consisted of the following resonances: (τ) 2.0-3.5 (complex band; integration 12 cm); 6.23 (s; integration 0.7 cm); 6.42 (s; integration 0.4 cm); 7.76 (s; integration 0.7 cm). Comparison of this spectrum with 2-p-toluidinophenyl diphenylphosphinate and the material obtained in §II.4(c)(i) above (p. 121) postulated as N-(2-methoxyphenyl)-p-toluidine suggested that all of these components could be present. In particular the singlets at 6.23τ and 6.42τ could be interpreted as a singlet due to the methoxy group of N-(2-methoxyphenyl)-p-toluidine (at 6.23) superimposed upon the methyl diphenylphosphinate methoxyl doublet. The p-tolyl methyl resonances of all components would coincide at 7.76τ.

(f) Spiro-2,2-ethylenedioxy-3-mesityl-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

The phosphorane (30 mg) dissolved in $CDCl_3$ was treated with 2 drops of D_2O and maintained at 23°. The solution was scanned at intervals on the EM-360 p.m.r. spectrometer. No change was observed in the spectrum over 216 h.

7. Hydrolysis Studied by ^{31}P n.m.r. Spectroscopy.

(a) Introduction

The hydrolysis of 3-mesityl- and 3-p-tolyl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholines was studied in 5% aqueous dioxan at 35° by ^{31}P n.m.r. spectroscopy in the XL-100 spectrometer probe with proton noise-decoupling. 10 mm Diameter tubes were used. Line widths are narrow, hence peak heights were representative of peak areas.

The major problem encountered was the non-availability of a suitable buffer system, so that the pH tended to fall during the reactions.

Positive identification of products was made by the addition of the pure material to the reaction solution after the final scan.

Due to the nuclear Overhauser effect, the relative peak heights of a mixture of components are not representative of their relative concentrations; however, individual peak heights were found to be linearly related to the component concentration. Thus, separate solutions of known concentration of each component, containing the same concentration of a calibrant, were scanned before each experiment; the same concentration of the calibrant was then used in the reaction solution and the intensity ratio of a component to the calibrant was interpretable as a true concentration. In the event, individual readings showed a spread of ±5% and in several instances this was found to be larger. Resonances due to unknown components could not be calibrated, therefore graphs are plotted using peak ratios and concentrations are noted where reliable. The use of an external capillary of calibrant was found to be unreliable, a 40% difference in ratio being found for the same solution run before and after the reaction.

Various techniques were tried; the best of these is detailed below.

7. Hydrolysis Studied by ^{31}P n.m.r. Spectroscopy.

(a) Introduction

The hydrolysis of 3-mesityl- and 3-p-tolyl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholines was studied in 5% aqueous dioxan at 35° by ^{31}P n.m.r. spectroscopy in the XL-100 spectrometer probe with proton noise-decoupling. 10 mm Diameter tubes were used. Line widths are narrow, hence peak heights were representative of peak areas.

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Various techniques were tried; the best of these is detailed below.

(b) General method

A stock solution was prepared containing the calibrant, dry triethyl phosphate (2.26g; 0.012 mol) and the n.m.r. lock — deuterobenzene (10 ml) — made up to 25 ml with dioxan. Solutions of standards and the phosphorane were prepared by dissolving the material (1.17 mMol) in the stock solution (2.5 ml) and diluting to 5 ml with dioxan. A range of concentrations for calibration were similarly made by diluting a solution of standard (3 ml) and stock (1 ml) to 5 ml with dioxan. Each solution was scanned five times and the peak ratios were averaged.

Reaction mixtures were prepared by mixing the stock phosphorane solution (1.5 ml) with a 20% aqueous dioxan solution (0.5 ml) containing the required weight of toluene-4-sulphonic acid (when used), thus obtaining 5% aqueous dioxan solutions of the phosphorane (0.35 mMol; i.e. 0.18M).

The solution was scanned at intervals, using 142 transients of which the first 15 were not recorded, allowing "steady-state" to be attained.

The parameters for a typical experiment are recorded:

HOURS = 0.02; SPC WDT (HZ) = 5000; TRU SPC WDT = 5120; ACQ TIME (S) = 0.8; PUISE WD (US) = 10; DATA LENGTH = 8192; SEN ENH (S) = 0.20; FT LENGTH = 8192. PLOT: START (HZ) = 5000; FINISH (HZ) = -120; REF PT (HZ) = 2500.

(c) 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

(i) Hydrolysis in neutral solution

When the calibrant was placed in a capillary in the solution, no reaction was observed over 95 min. When the calibrant was dissolved in the solution, a slow hydrolysis was observed. The major product was dimethyl phenylphosphonate (73%, standard deviation 7%), resonating at

-21.3 ppm. Two minor resonances also appeared at -20.0 ppm and -18.1 ppm. A barely discernible resonance appeared intermittently at -28.6 ppm identified positively as 2-oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine. When the solution was rescanned, 1.5 h after the disappearance of the phosphorane, the resonance at -20.0 ppm had vanished. The pH remained at ca. 6 (universal indicator papers).

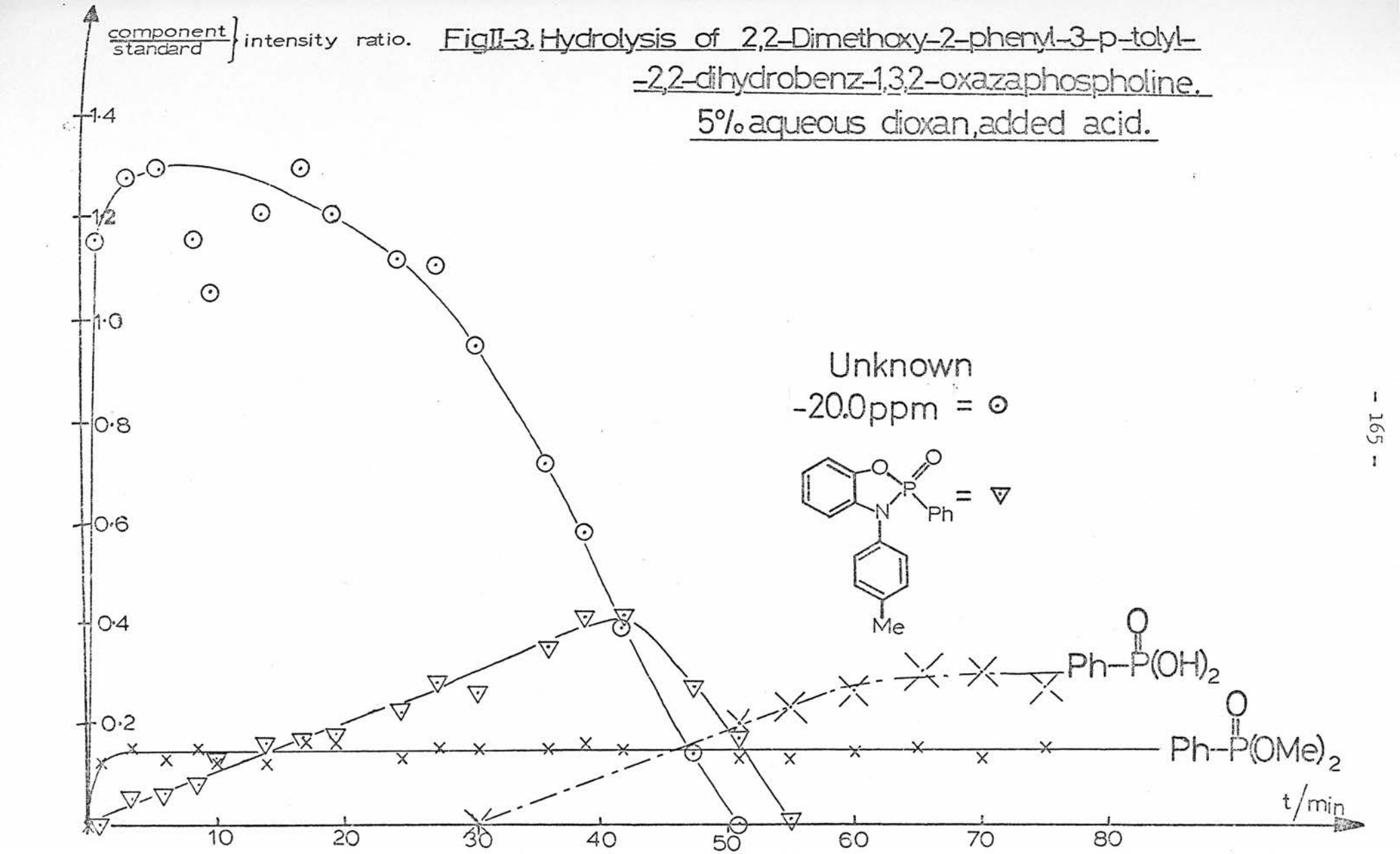
The disappearance of the phosphorane followed linear first-order behaviour within experimental error ($t_{\frac{1}{2}}$ = 13 min); the appearance of dimethyl phenylphosphonate was too erratic for meaningful interpretation.

(ii) Hydrolysis in the presence of added acid

In subsection (i) above, it was stated that no hydrolysis occurred in neutral solution when the calibrant was used externally. To that solution was added one small crystal of toluene-4-sulphonic acid, later assessed as being ca. 2.3 mg which would give a solution 6.0 mM in acid. The pH at the end of the experiment (i.e. at t = 75 min) was 3 (universal indicator papers). This method of adding acid is not reliable as it may give rise to a solution of inhomogeneous acid content; however, the results are of interest as supporting evidence. The course of hydrolysis is plotted in Figure II.3 (p. 165)

The phosphorane vanished in less than 1 min, giving three initial products at: -28.5 ppm, identified as 2-oxo-2-phenyl-3-p-tolylbenz--1,3,2-oxazaphospholine (ca. 2%); -21.3 ppm, identified as dimethyl phenylphosphonate (11% ±2%); and -20.0 ppm (unknown; assessed by difference as ca. 90%). The dimethyl phenylphosphonate concentration remained constant thereafter.

The resonance at -20.0 ppm decayed until it vanished at t = 55 min; the cyclic phosphonamidate (-28.5 ppm) increased, reaching a maximum at t = 42 min and decaying until it vanished at t = 60 min. A new resonance


component / standard } intensity ratio.
Fig II-3. Hydrolysis of 2,2-Dimethoxy-2-phenyl-3-p-tolyl--2,2-dihydrobenz-1,3,2-oxazaphospholine. 5% aqueous dioxan, added acid.
1·4
1·2
1·0
0·8
0·6
0·4
0·2
Unknown
-20.0ppm = ⊙
Ph
= ▽
Me
Ph–P(OH)2
Ph–P(OMe)2
t/min
10
20
30
40
50
60
70
80

appeared at -18.3 ppm at t = 30.5 min and at -16.9 ppm at t = 36 min, but neither became significant and the former disappeared at t = 65 min. A broad resonance appeared at -15.9 ppm (positively identified as benzenephosphonic acid).

At t = 75 min the only resonances present were due to dimethyl phenylphosphonate (-16.9 ppm) and benzenephosphonic acid, the last being the major resonance.

(iii) Hydrolysis in the presence of 10^{-4}M toluene-4--sulphonic acid solution

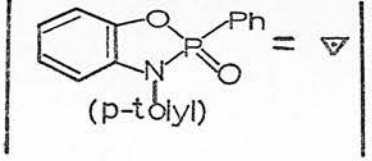
The course of this hydrolysis is plotted in Figure II.4 (p. 167). Once again, resonances appeared at -21.4 ppm (dimethyl phenylphosphonate), -19.9 ppm, -18.2 ppm, and -28.5 ppm (2-oxo-2-phenyl-3-p-tolylbenz-1,3,2--oxazaphospholine), this last only being observed intermittently and at low concentration.

The phosphorane hydrolysed over ca. 200 min. The appearance of dimethyl phenylphosphonate (final yield 78 ±5%) followed first-order kinetics ($t_{\frac{1}{2}}$ ca. 60 min); the phosphorane intensities were erratic.

The -19.9 ppm resonance appeared at t = 6 min; the resonance at -18.2 appeared at t = 28 min.

(iv) Hydrolysis in the presence of 0.016M toluene-4--sulphonic acid solution

The course of this hydrolysis is plotted in Figure II.5 (p. 168). The phosphorane vanished in less than 1 min. As before, resonances appeared at -28.6 ppm (2-oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine), -21.3 ppm (dimethyl phenylphosphonate; yield ca. 3% at t = 1 min, maintained thereafter), -19.9 ppm, -18.2 ppm and -16.8 ppm. All of these resonances were visible at t = 1 min. At t = 4 min, a resonance



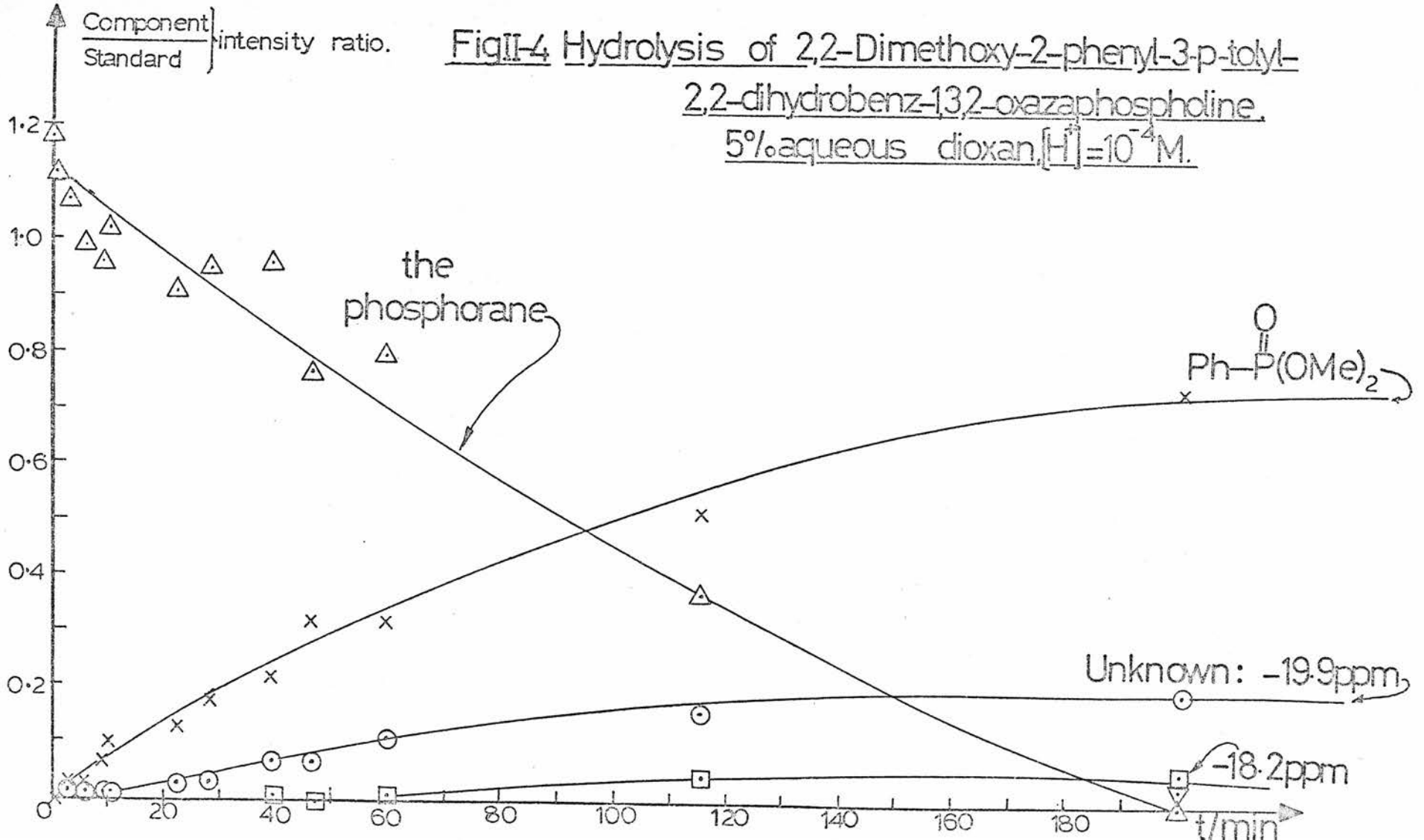
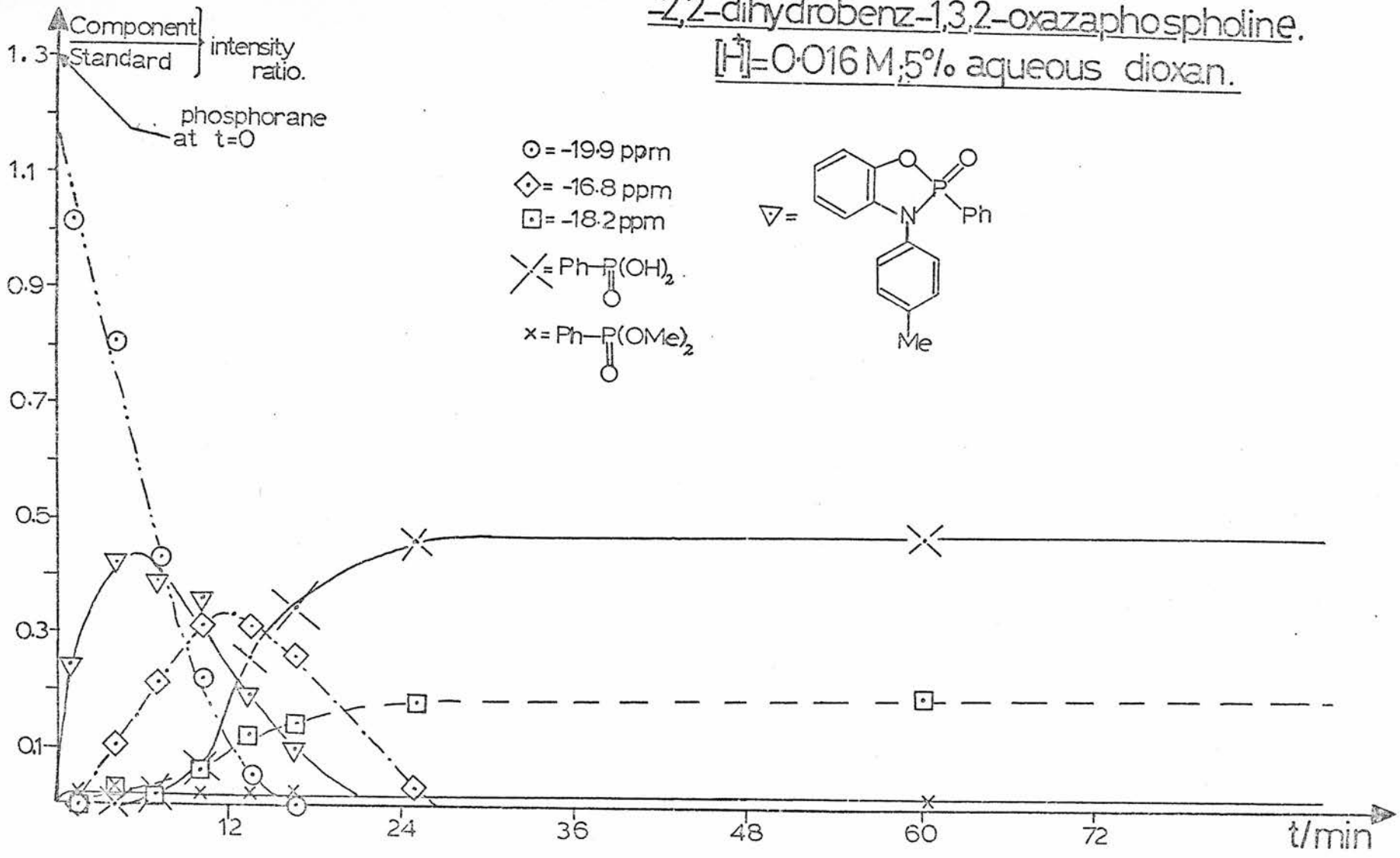


Fig II-4 Hydrolysis of 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine. 5% aqueous dioxan, $[H^+] = 10^{-4}$ M.

Fig II-5 Hydrolysis of 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine. [H⁺]=0·016 M; 5% aqueous dioxan.



appeared at -15.8 ppm (benzenephosphonic acid) which moved to lower field as it increased (at t = 104 min, δ = -16.1 ppm). Resonances which do not alter position with increased concentration also showed similar shifts with time and acidity increase; hence, this was taken as an indication of a fall in pH during the reaction. All product resonances, except that at ca. 20 ppm and triethyl phosphate, were observed to move downfield; the latter pair moved upfield.

2-Oxo-2-phenyl-3-p-tolylbenz-1,3,2-oxazaphospholine reached a maximum concentration of 33 ±2% at t = 5 min.

N.B.: The times at which components were observed to have disappeared are marked as zero points on the graph.

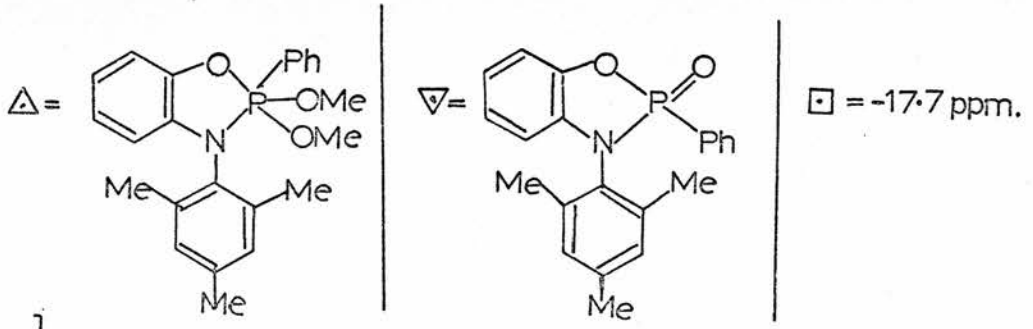
(d) 3-Mesityl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

(i) Hydrolysis starting from neutral solution

The course of this hydrolysis is plotted in Figure II.6 (p. 170). Three major product resonances were observed at -27.8 ppm (3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine which reached a maximum yield of 74 ±10% at t = 40 min), -17.7 ppm (broad resonance) which appeared at t = 34 min, and -15.5 ppm (broad resonance, attributed to benzenephosphonic acid) which appeared initially at a time between t = 120 min and t = 300 min.

Two minor resonances appeared intermittently at -43.2 ppm and ca. -21.8 ppm.

The phosphorane vanished at ca. t = 41 min. No dimethyl phenylphosphonate was observed.



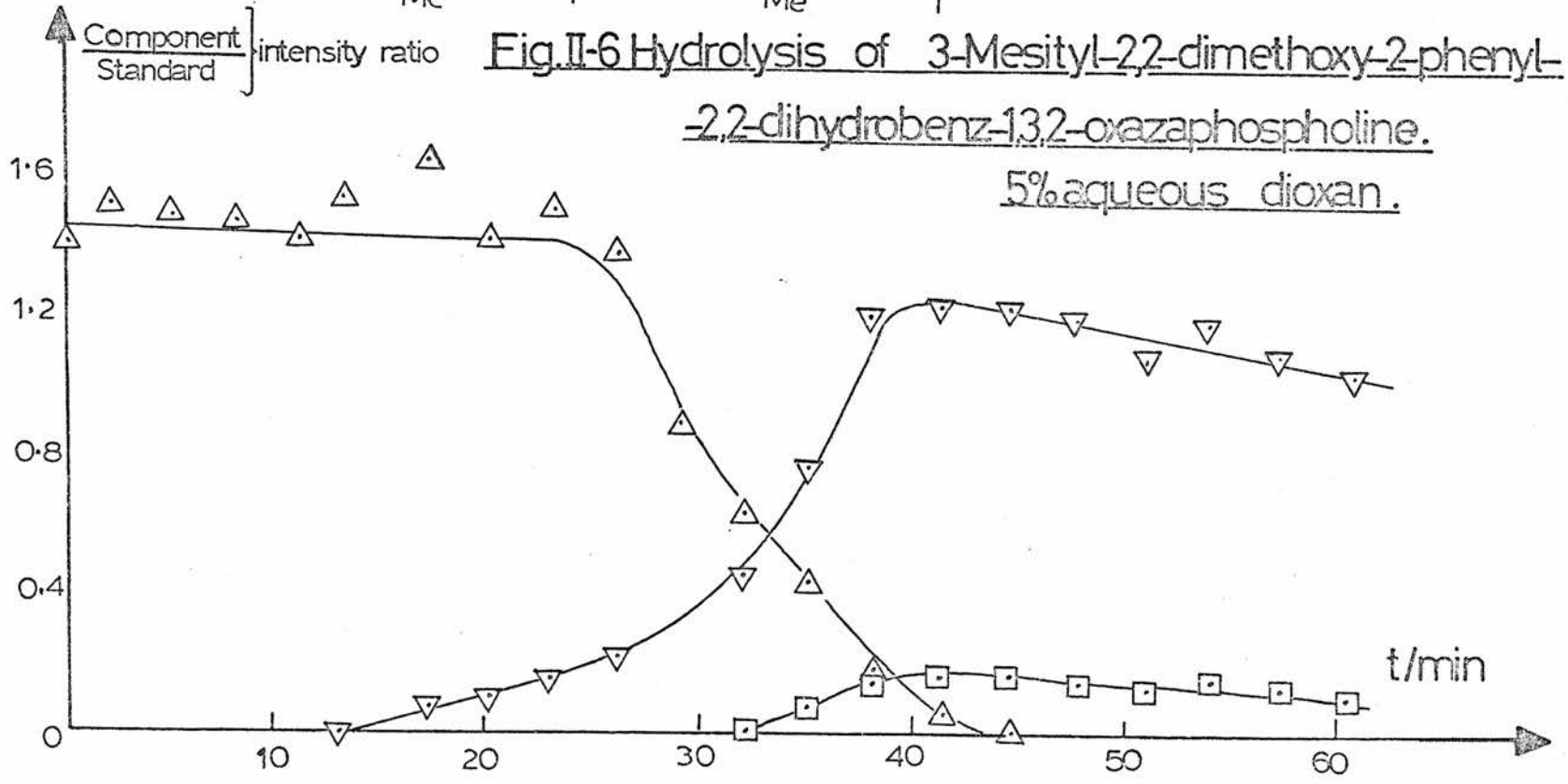


Fig.II-6 Hydrolysis of 3-Mesityl-2,2-dimethoxy-2-phenyl--2,2-dihydrobenz-1,3,2-oxazaphospholine.
5% aqueous dioxan.

(ii) Hydrolysis in the presence of 0.016M toluene-4--sulphonic acid solution

The phosphorane vanished in less than 1 min to give products resonating at -27.8 ppm (identified as 3-mesityl-2-oxo-2-phenylbenz-1,3,2--oxazaphospholine) and at -19.0 ppm. The calibration for the cyclic phosphonamidate was unreliable, as it suggested a yield of 100%, whilst the intensity ratio of the two products was 84:16 respectively. Both product resonances decreased with time, that at -19.0 ppm being the less stable. Thus, at t = 91 min the cyclic phosphonamidate was not noticeably decreased, whilst the -19.0 ppm resonance had decreased by 5%. A scan taken at t = 19.5 h showed a 72% decrease for the cyclic phosphonamidate and a ca. 95% decrease for the -19.0 ppm resonance.

At t = 90 min, resonances appeared at -18.3 ppm and -16.1 ppm; the latter was positively identified as benzenephosphonic acid. At t = 19.5 h, both of these resonances had increased and were in a ratio of ca. 1:3 respectively. Benzenephosphonic acid was the major product at this time.

No dimethyl phenylphosphonate was produced in the reaction.

(e) Summary

Whilst the calibration produces reliable qualitative and time-dependent information, the absolute values obtained for yields are not considered to be reliable except as a general guide. The assessed accuracies have been given.

The reason for this failure is not understood; however, it has been noticed that temperature variations affect resonance intensities to a different extent across the scan. There is also the possibility that standards, run necessarily in the absence of water, may show higher intensities when water is added.

8. The Hydrolysis of Phosphoranes in ^{18}O Enriched Water

(a) General approach

The phosphoranes were hydrolysed in aqueous dioxan solution. The water contained 5.25% ^{18}O and 0.232% ^{17}O. Mass spectra of methanol and 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine were obtained and the ratios of the $(M + 2)^+$ to M^+ intensities were calculated. These ratios are referred to as P_{M+2}/P_M.

The following theoretical analyses were employed.

(i) 3-Mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine

According to Beynon,[205] for a molecule $C_wH_xN_yO_z$ in which the carbon consists of ^{13}C and ^{12}C in the ratio c:(100-c), hydrogen of ^{2}H and ^{1}H in the ratio h:(100-h), nitrogen of ^{15}N and ^{14}N in the ratio n:(100-n), and the oxygen of ^{18}O, ^{17}O and ^{16}O in the ratios $o_2:o_1:(100-o_1-o_2)$, the ratio of the probability of obtaining an atomic combination of mass $(M + 2)$ to the probability of obtaining an atomic combination of mass M may be calculated. This ratio, P_{M+2}/P_M was calculated for the cyclic phosphonamidate in the case that the phosphoryl oxygen was derived solely from added water. Thus, 50% of the oxygen in the product would be derived from the natural environment and 50% from the enriched environment. Essentially, the product oxygen is derived from an average environment in which $o_1 = \frac{(0.0391 + 0.232)}{2}$ and $o_2 = \frac{(0.2005 + 5.25)}{2}$. Calculation gave 0.0857 for P_{M+2}/P_M. Tables[206] give the ratio for the case where all oxygen is at natural abundance, as $P_{M+2}/P_M = 0.0303$.

(ii) Methanol

Using the same calculation for methanol, in which the above values of o_1 and o_2 were again employed, gave the result that for 50% of the

product methanol to have oxygen derived from added water P_{M+2}/P_M = 0.0282, whilst natural methanol should have P_{M+2}/P_M = 0.00202.[205]

(iii) General experimental techniques

Mass spectra of the hydrolysis products were obtained by g.l.c./mass spectrometry. The peak for 3-mesityl-2-oxo-2-phenylbenz-1,3,2--oxazaphospholine was obtained using a 5% SE30 column at 212°. The peak for methanol was obtained using a Porapak Q column at 210° on which the retention times for water, methanol and dioxan were respectively 2.7 min, 3.5 min and 19 min with a gas flow rate of 10 ml/15 s. The mass spectrometer output was fed directly to a computer giving a print-out of peak masses and their relative intensities.

(b) 3-Mesityl-2,2-dimethoxy-2-phenyl-2,2--dihydrobenz-1,3,2-oxazaphospholine

(i) Observation of 3-mesityl-2-oxo-2-phenylbenz--1,3,2-oxazaphospholine

Unenriched water: 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine (0.18g; 0.5 mMol), dissolved in dry dioxan (2.5 ml), was analysed by g.l.c./mass spectrometry (5% SE30 at 202°). The intensity ratio of $(M+2)^+$ to M^+ was 0.032 averaged over four spectra (standard deviation 0.003).

Enriched water: The phosphorane (0.19g; 0.5 mMol) was dissolved in dry dioxan (2.38 ml) in a 5 ml flask under nitrogen. Enriched water (125 ml; 5%) was added by syringe through a suba-seal. The solution was heated at 35° and monitored by g.l.c. No reaction was observed at t = 1.5 h, but at t = 2.25 h hydrolysis had occurred to completion and the only detectable product was the cyclic phosphonamidate. The

solution was frozen until just before analysis. The cyclic phosphonamidate showed a P_{M+2}/P_M ratio of 0.085 (standard deviation over three spectra 0.001).

(ii) Observation of methanol produced during the hydrolysis

The same solution was analysed with respect to methanol. The theoretical threshold for computer detection was 0.2 units which should have been ample for the detection of methanol $(M+2)^+$ peaks, with M^+ peaks often integrating to several thousands of units. However, the threshold was apparently not being attained; in most cases methanol ^{13}C fragments were not detected and no m/e 34 was observed at all. In one case, however, where a peak was detected at 33, the P_{33}/P_{32} ratio was 0.015 (the intensity of 32 having been corrected for the ^{13}C fragment of 31). The theoretical ratio is 0.01184 which suggested that 33 also included an ^{18}O fragment for 31. Calculation showed that P_{31}/P_{33} (calc.) would be 0.002; the theoretical ratio for natural methoxyl is 0.002.[205]

The uncertainty of the true threshold disallowed the calculation of upper limits for P_{M+2}/P_M.

(c) Observation of methanol obtained from the acidic hydrolysis of phosphoranes

The same g.l.c. mass spectrometry technique was employed except that the mass spectra were obtained directly from the mass spectrometer recorder.

Solutions of the phosphoranes (0.14g) in dioxan (1.5 ml) were treated with a solution of toluene-4-sulphonic acid in enriched water (0.08 ml) to give 5% aqueous solutions, 0.016M in acid and 0.2M in

phosphorane. The natural water of crystallisation of toluene-4-sulphonic acid monohydrate created a negligible enrichment error. The solutions were warmed at 35° for 30 min to ensure completion of the reaction (see §II.7 above), then frozen till required.

The solutions were injected on to a Porapak Q column at 210° and the methanol mass spectrum was obtained at 30 eV ion-current. A natural methanol spectrum was obtained consecutively and in the same way. A background spectrum was scanned.

P_{M+2}/P_M ratios were calculated using P_M values corrected for the M-1 ^{13}C peak and the background m/e 32.

(i) Natural methanol

$P_{M+2}/P_M = 0.003 \pm 0.0007$.

(ii) Methanol obtained from the hydrolysis of 3-mesityl-2,2--dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

$P_{M+2}/P_M = 0.004$ and 0.004 ± 0.0007.

(iii) Methanol obtained from the hydrolysis of 2,2-dimethoxy-2--phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine

$P_{M+2}/P_M = 0.004$ and 0.003 ± 0.0007.

These ratios are upper limits as it was not possible to correct accurately for the base-line ripple under the M + 2 peak. The ratios are, however, accurate to the tolerances stated.

(d) Observation of 3-mesityl-2-oxo-2-phenylbenz-1,3,2--oxazaphospholine in enriched water

The cyclic phosphonamidate (0.16g; 0.0047 mol) dissolved in dry

dioxan (5 ml) was treated with enriched water (0.12g; 4%) and left at room temperature for 30 h. The solution acidity dropped to pH2 (universal indicator paper). The solvent was removed (40° at 0.2 mm) to give a pale-pink powder. The p.m.r. spectrum of this powder indicated an 8:1 mixture of the cyclic phosphonamidate and 2-(2',4',6'--trimethylanilino)phenol. The mass spectrum was obtained on the MS-9 spectrometer and P_{M+2}/P_M calculated as 0.07 over 10 scans (standard deviation 0.006).

9. The Effect of Solvent-Change on the ^{31}P n.m.r. Chemical Shifts of Phosphoranes

(a) General method

None of the species mentioned below showed concentration-dependent chemical shifts. Solvent-dependent shifts were observed using deuterochloroform solutions containing various percentages (v/v) of 1,1,1,3,3,3--hexafluoropropan-2-ol (referred to hereafter as h.f.p.), dried over molecular-sieve.

A stock solution of the phosphorane (260 mg in 1 ml of a $CDCl_3$ solution) was prepared. Individual solutions were created by adding appropriate volumes of h.f.p. and $CDCl_3$ to 0.2 ml of the stock to give 0.5 ml solutions containing 52 mg of phosphorane.

The solutions were scanned immediately in the XL-100 probe at 35°.

(b) 3-Mesityl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz--1,3,2-oxazaphospholine

Solutions containing 0, 10, 23, 46 and 50% of h.f.p. were used. In

each case several new resonances were observed of which one was identified as 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine; there were also two resonances at+47.6 ppm and+50.9 ppm attributed to the products of ligand exchange with h.f.p. The present phosphorane was clearly identifiable and the decrease in δ is plotted against h.f.p. % concentration in Figure II.7 (page 178).

3-Mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine also showed a decrease in δ which is plotted on the same graph.

Other solvent systems gave the following chemical shifts (in these cases no other resonances were observed).

$CDCl_3$: +46.7 ppm. $CDCl_3$ + 0.5 mol equivalents of h.f.p.: +46.3 ppm. Dioxan: +47.8 ppm. 5% Aqueous dioxan: +47.6 ppm

(c) 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2--dihydrobenz-1,3,2-oxazaphospholine

In this case, results were less readily interpretable as the phosphorane was extremely labile; however, the following reliable chemical shifts were obtained: $CDCl_3$: +44.8 ppm. $CDCl_3$ + 0.5 mol equivalent of h.f.p.: +44.3 ppm. Dioxan: +45.8 ppm. 5% Aqueous dioxan: +45.5 ppm.

These values suggest that the solvent dependency is slightly greater than for the mesityl analogue, but to no great extent.

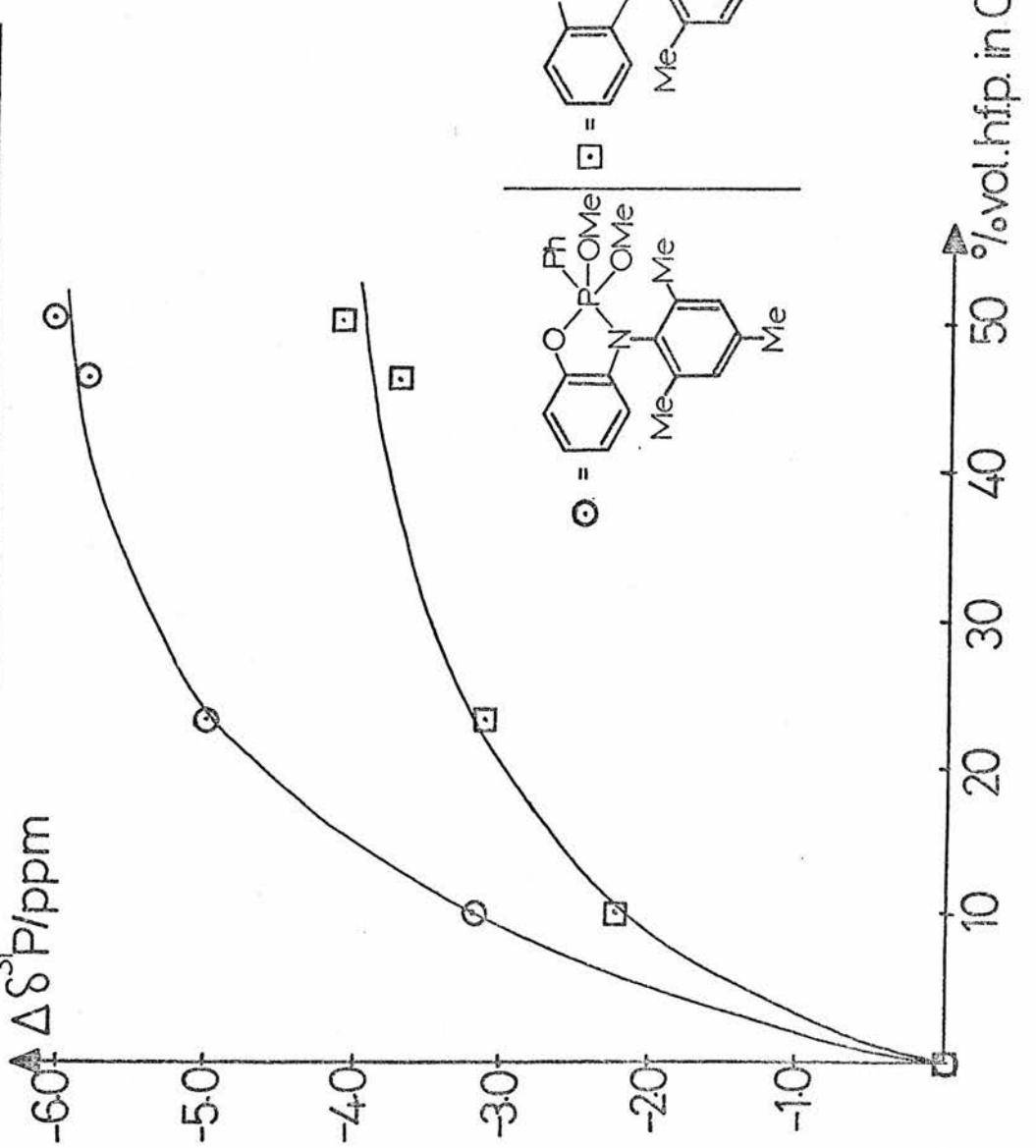
10. The Reaction of 3-Mesityl-2,2-Dimethoxy-2-Phenyl--2,2-Dihydrobenz-1,3,2-Oxazaphospholine with Diols

(a) Reaction with 1,2-ethanediol

(i) The phosphorane (0.54g; 1.2 mMol) and dry 1,2-ethanediol (0.7g;

Fig.II-7

Solvent Dependence of ^{31}P n.m.r.Shifts.



12 mMol) were dissolved in dry dioxan (20 ml) under dry nitrogen and left at room temperature for 42 h. Solvent removal and examination by p.m.r. indicated a 1:1.5 molar ratio of product and starting material.

The material was redissolved in dioxan (20 ml) and 1,2--ethanediol was added (5 ml); the solution was left at room temperature for a further 70 h. The solvent and 1,2-ethanediol were evaporated, leaving a dry, white powder. The p.m.r. spectrum indicated a mixture of 80% product, 10% of the original phosphorane and 10% of 3-mesityl-2--oxo-2-phenylbenz-1,3,2-oxazaphospholine (present to the same extent as before the reaction). A sample of the product was obtained as a white, crystalline powder (m.p. 188.5-190°) by sublimation (180° at 0.2 mm) and identified as spiro-2,2-ethylenedioxy-3-mesityl-2-phenyl-2,2-dihydrobenz--1,3,2-oxazaphospholine. (Found: C, 70.0; H, 6.2; N, 3.4. $C_{23}H_{24}NO_3P$ requires C,70.2; H, 6.2; N, 3.6%).

The mass spectrum showed the correct molecular ion at m/e 393 (100%; found 393.148603, required 393.149372); major fragments, 349 (62%; $M^+ - OCH_2CH_2$); 209 (24%; $M^+ - PhP(O)OCH_2CH_2O$); 208 (81%; 209-H).

I.r. ($CHCl_3$): 950 cm^{-1} (s), 975 cm^{-1} (s), 1020 cm^{-1} (s) (sharp absorptions; (P)-O-C stretch region); 1080 cm^{-1} (intense absorption; P-O-CH_2); 1260 cm^{-1} (s) (sharp absorption; CO/CN stretch); 1440 cm^{-1} (sharp absorption; P-Ph).

P.m.r. spectrum ($CDCl_3$): (τ) 1.96-2.26 and 2.54-2.80 (complex bands; 5H; P-Ph); 3.0-3.5 (complex band; 5H; aromatic protons); 4.0-4.16 (complex doublet; 1H; aromatic proton); 5.7-6.5 (complex band; 4H; ethylenedioxy protons); 7.70 (s; 3H; mesityl Me); 7.88 (s; 3H; mesityl Me); 8.14 (s; 3H; mesityl Me).

The ethylenedioxy multiplet consisted of two multiplets centred on 5.97τ and 6.28τ. The lower field multiplet was a symmetrical octet with the general appearance of a pair of overlapping quintets;

irradiation at 40,479,210 Hz produced a broad quintet. The higher field multiplet had the appearance of a quintet which collapsed to a broad triplet on irradiation at 40,479,210 Hz.

$\delta^{31}P$ ($CDCl_3$): +33.3 ppm.

(ii) When 3-mesityl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2--oxazaphospholine (ca. 40 mg), dissolved in $CDCl_3$ (0.5 ml), was treated with 1,2-ethanediol (1 drop) in an n.m.r. tube at 23°, the formation of the spirophosphorane was evident in less than 2 h. After 4 h, comparison of the mesityl methyl p.m.r. resonances suggested a conversion of ca.40%; after 23 h, conversion was 95% complete. Removal of solvent left a white powder with the correct molecular ion at m/e 393 in the mass spectrum.

(b) Reaction with 1,3-propanediol

The phosphorane (1.03g; 2.6 mMol) and 1,3-propanediol (1.98g; 26 mMol) in dry dioxan (20 ml) were boiled in an atmosphere of dry nitrogen under a 3" reflux column containing glass helices. The head of the column was attached to a water-cooled condenser and a receiver cooled in ice. The temperature of the reaction flask was regulated so that vapour was reaching the top of this column. Any methanol formed should have distilled.

After 5 h, solvent and excess diol were evaporated (130° at 0.1 mm) to give a white powder which was examined by p.m.r. spectroscopy. The only resonances observed were those of the starting phosphorane.

The small volume of distillate collected during the reaction-time was also observed by p.m.r. and found to contain only dioxan. No methanol was present.

The phosphorane was recovered in 82% yield.

11. Miscellaneous

The isolation of 2-oxo-2-phenyl-3-(2',6'-xylyl)benz-1,3,2-oxazaphospholine.

The phosphorane, 2,2-dimethoxy-2-phenyl-3-(2',6'-xylyl)-2,2-dihydro-benz-1,3,2-oxazaphospholine (0.43g; 1.1 mMol) was treated with water (0.2 ml) at room temperature for 16 h. The solvent was removed at the oil pump on a warm water-bath to leave a pale-brown, transparent solid. Several attempts to obtain a pure product by recrystallisation failed; a blue powder with a wide melting range was recovered each time. However, the mass spectrum gave a molecular ion at m/e 335 (found 335.106298, $C_{20}H_{18}NO_2P$ requires 335.107510). The i.r. spectrum ($CHCl_3$) differed only slightly from that of 3-mesityl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholine (II-6-(b)(i)). Thus, the hydrolysis product is identified as 2-oxo-2-phenyl-3-(2',6'-xylyl)benz-1,3,2-oxazaphospholine.

P.m.r. spectrum ($CDCl_3$): (τ) 2.0 - 3.3 (complex band; 13H; aromatic protons); 3.7 - 4.0 (complex band; 1H; aromatic proton); 7.56 (s; 3H; Me); 8.50 (s; 3H; Me).

SECTION III

DISCUSSION

III

DISCUSSION

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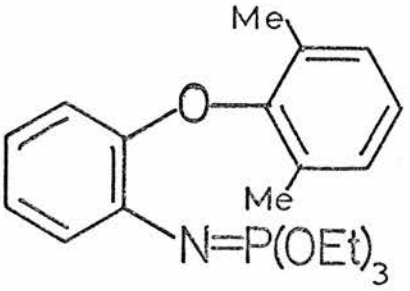
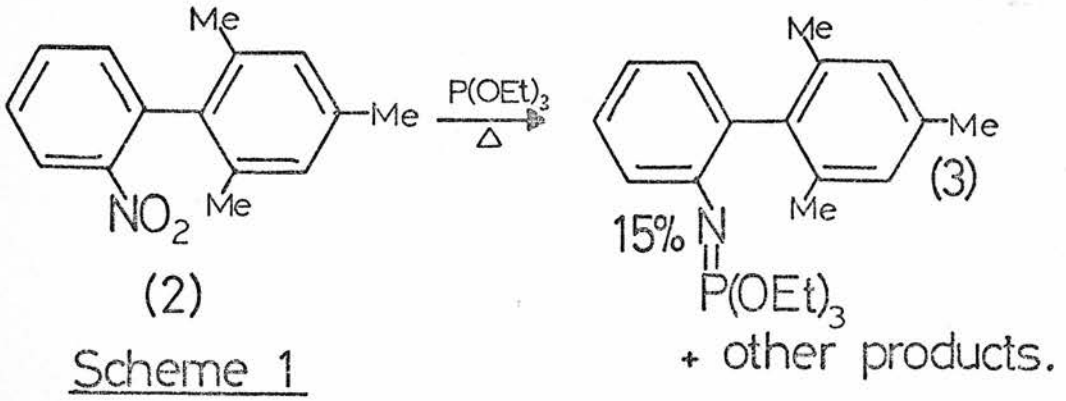
1. Prologue and Programme of Research

In 1971 Lim[189] reported the isolation of a high yield (70%) of a colourless solid from the reaction of 2,6-dimethylphenyl 2-nitrophenyl ether with triethyl phosphite in boiling cumene. This, hitherto unreported, material was initially assigned as triethyl N-o-(2,6-dimethylphenoxy)phenylphosphorimidate (1) in the light of existing results on a similar reaction. Thus, Cadogan et al.[184] had reported the isolation



(1)

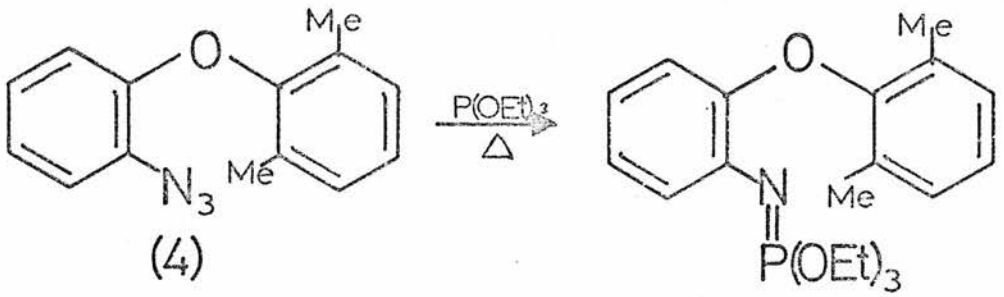
of triethyl N-(2',4',6'-trimethylbiphenyl-2-yl)phosphorimidate from the thermal deoxygenation of 2,4,6-trimethyl-2-nitrobiphenyl by triethyl phosphite as in scheme 1.



(2)

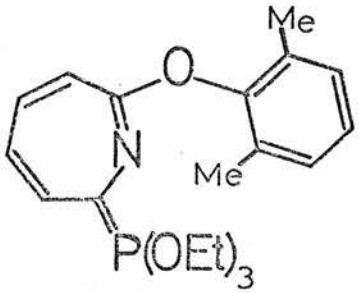
Scheme 1

This assignment (1) was subsequently discredited by Armour and Cadogan,[207] by the synthesis of an authentic sample of the phosphorimidate (1) by an unambiguous, known method,[208] viz, reaction of the azide (4) with triethyl phosphite (scheme 2).



Scheme 2

A further assignment was then made.[189] The i.r. spectrum revealed a strong absorption band at 1260 cm^{-1} and the p.m.r. spectrum showed a one-proton multiplet at 4.2τ significantly upfield of the main aromatic band. The i.r. absorption was assigned to a P=C stretch and the p.m.r. multiplet to a non-aromatic proton. Accordingly, ring-expansion of the nitrophenyl ring was suggested, the product being 7-triethoxyphosphoranylidene 2-(2,6-dimethylphenoxy)azepine (5). A CCl_4 solution of this



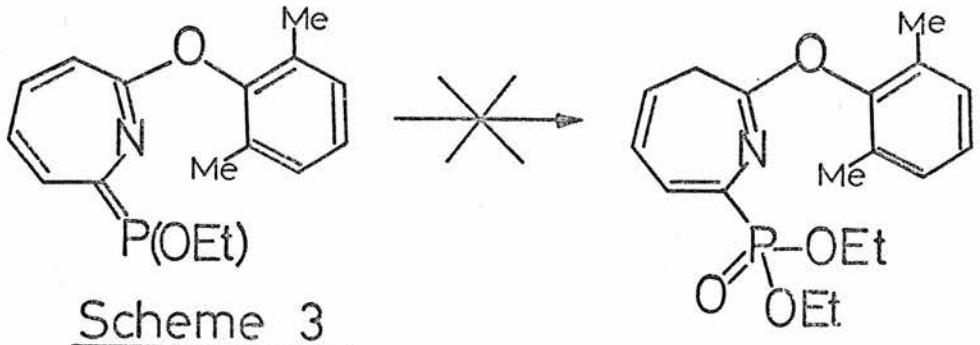
(5)

compound hydrolysed rapidly in the presence of D_2O with the elimination of all three ethoxy groups. The i.r. spectrum of the product revealed absorptions typical[203] of P-OH (2400 cm^{-1}) and P=O (1200 cm^{-1}) functions. The mass-spectral parent ion was also in agreement with the tentatively

assigned structure (6), 2-(2,6-dimethylphenoxy)azepin-7-ylidene phosphenic acid. It was noted, however, that such a product was most

(6)

unexpected in view of earlier results[209,210] which would suggest the hydrolysis pathway in scheme 3. Furthermore, hydrolysis of methylene-



Scheme 3

phosphoranes usually results in the cleavage of the P=C bond.[211]

The original object of the present work was the investigation of this unusual hydrolysis. However, it was soon apparent that both the starting material and its hydrolysis product were incorrectly assigned.

The present investigation has elucidated the correct structure of the product from the deoxygenation reaction. The synthesis and chemistry of further, analogous derivatives have been investigated.

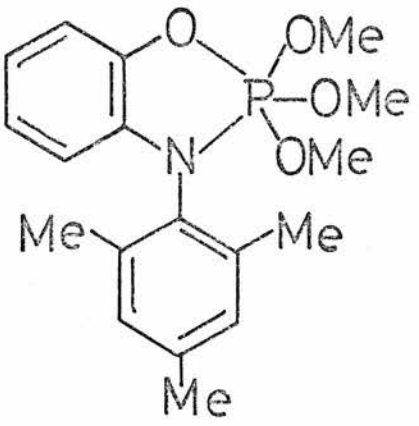
2. Reactions of Aryl 2-Nitrophenyl Ethers with Tervalent Phosphorus Reagents

In the previous investigation[189] of this reaction, the products were isolated by elution chromatography through an alumina column. This procedure was found to give, frequently, low and unreliable yields. In this investigation, the products were obtained in consistently good yields by distillation of the crude reaction residue after solvent removal. The highly-viscous oils obtained were recrystallised to give colourless, crystalline solids. In several instances, the major product was crystallised directly from the reaction residue. Although attention was paid to by-products, these were usually obtained in very low yields.

(a) Reaction of 2,4,6-trimethylphenyl 2-nitrophenyl ether with trimethyl phosphite

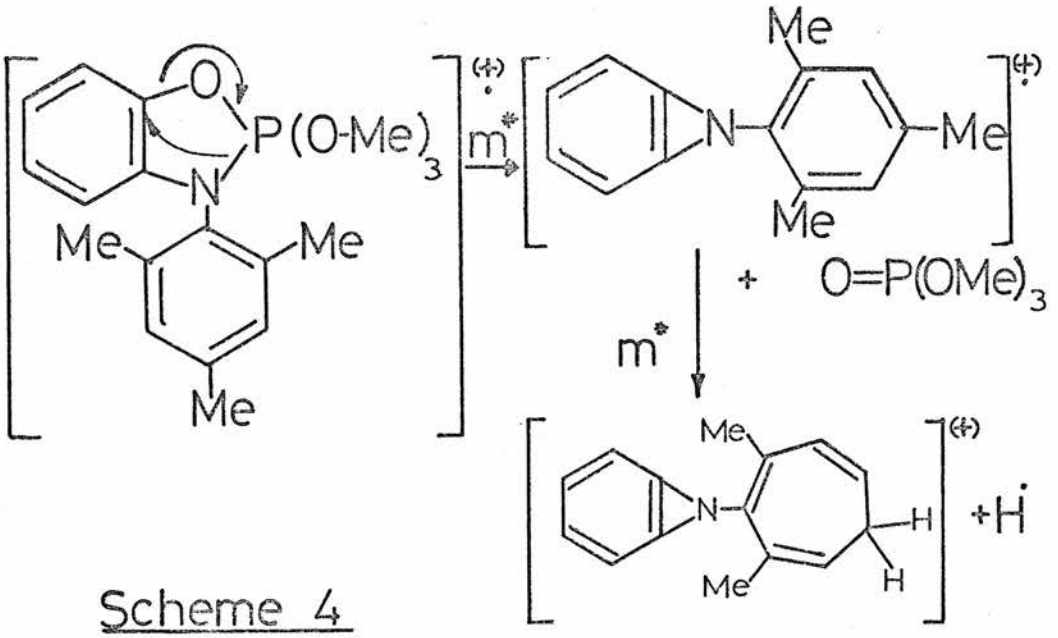
The product was obtained in 41% yield as white needles. The i.r. mass-spectral parent ion and p.m.r. spectrum confirmed that this was an analogous derivative to that obtained by Lim[189] from the reaction of the same ether with triethyl phosphite.

The mass spectrum contained a peak at m/e 208 (53%) which was inconsistent with the phosphoranylidene azepine structure. This was a key observation. Credit is due to Tait[212] for the realisation that the fragment was consistent with a new formulation of this material as 3-mesityl-2,2,2-trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine (7). A strong metastable peak was observed for the direct fragmentation of the parent ion to a peak at m/e 209 (29%), consistent with the elimination of trimethyl phosphate. A further metastable peak was just



(7)

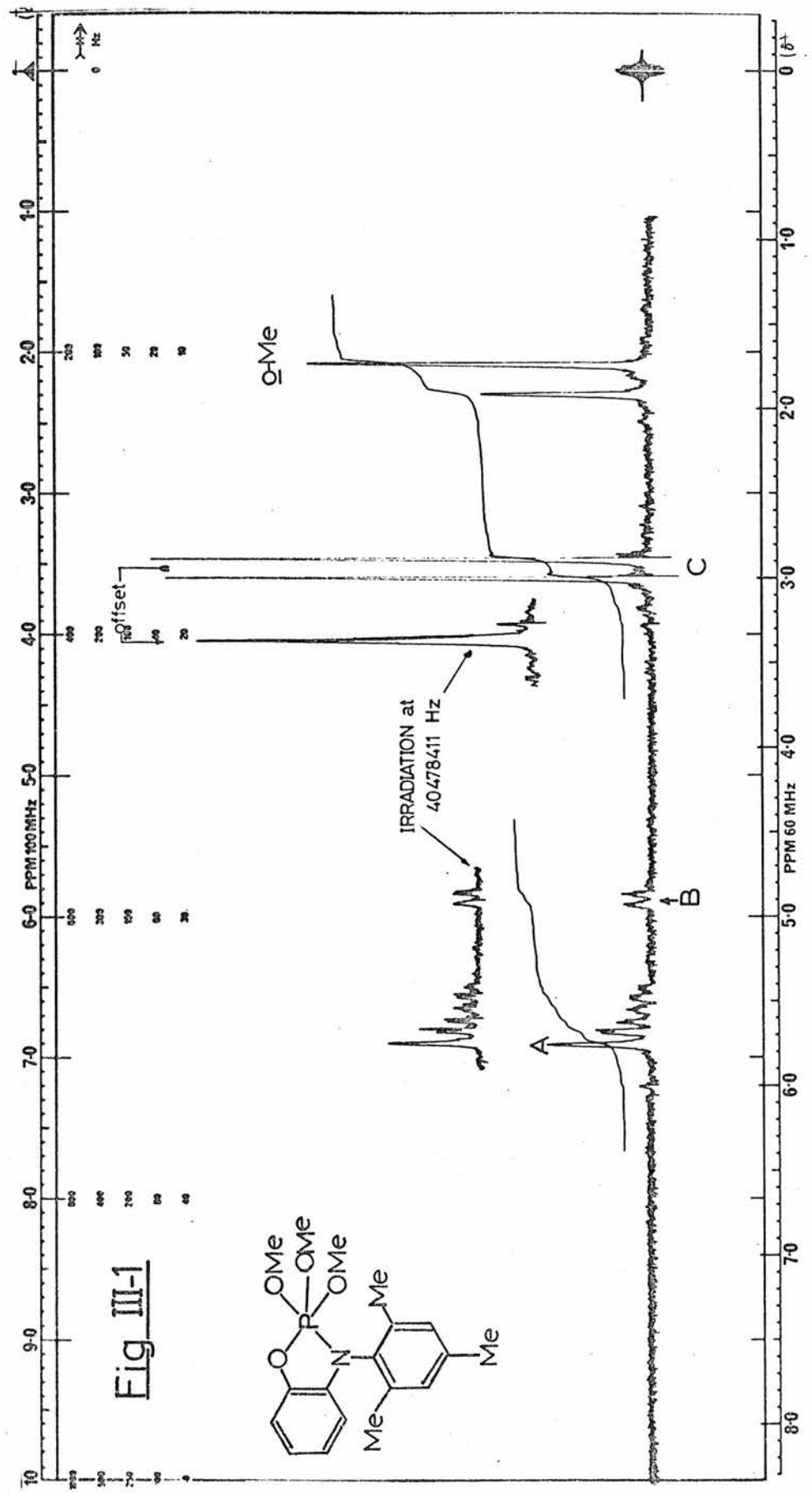
discernible at m/e ca. 207, which suggested that the m/e 209 fragment collapses to the peak at m/e 208. An exact mass determination on the



Scheme 4

latter peak confirmed that this was due to a species of formula $C_{15}H_{14}N$. A fragmentation pattern can be drawn (scheme 4). The second step is well documented.[200] The prent ion also fragments directly (m*) by the loss of a methoxy group (m/e 318; 28%). A strong fragment appeared at m/e 303, which is due to the loss of both a methoxy and a methyl group; no metastable peak was detected to suggest that this might be the result of a concerted fragmentation.

The p.m.r. spectrum (Figure III.1) shows a pattern which has become familiar as being a characteristic of this class of compound. The


PPM 100 MHz
PPM 60 MHz
IRRADIATION at
40478411 Hz
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OMe
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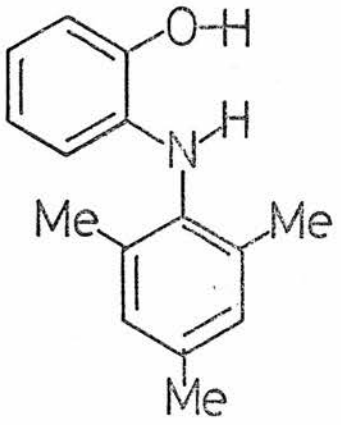
Me
O
P
N

Fig III-1

aromatic region includes a low-field, two-proton singlet (A) which is assigned to the meta protons of the mesityl function. The one-proton, complex doublet (B), widely separated from the other aromatic resonances, will be discussed in detail below. The phosphorane methoxy functions resonate as one doublet, (C); this is characteristic of groups undergoing fast positional exchange by an intramolecular, regular process. Phosphorus spin-tickling caused the collapse of this resonance to a singlet, thus confirming phosphorus to hydrogen spin-spin coupling. The mesityl o-methyl groups resonate as one six-proton singlet as expected, since the molecule has a plane of symmetry through the heterocyclic ring atoms.

The large positive chemical shift of the phosphorus nucleus ($\delta^{31}P$ = +57.2 ppm) strongly suggests a pentacoordinate environment for this atom.[121] The originally proposed[189] phosphoranylidene azepine would be expected[121] to exhibit a low or negative shift.

Complete hydrolysis of the phosphorane gave a white, crystalline solid identified as 2-(2',4',6'-trimethylanilino)phenol (8). This product was assigned on the basis of mass-spectral and i.r. evidence.

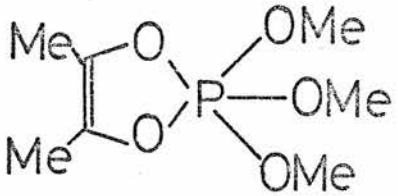


(8)

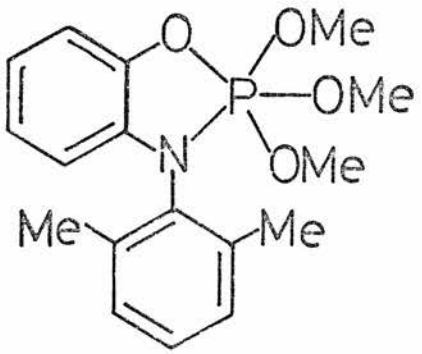
The i.r. spectrum revealed sharp absorptions at 3600 cm^{-1} and 3420 cm^{-1}, assignable as unbonded O-H and N-H stretch bands respectively. A broad absorption at 3100-3500 cm^{-1} was attributed to the corresponding bonded

absorptions. Of particular interest was the observation of a strong absorption at 1265 cm^{-1}; this absorption was also present in the parent phosphorane and had been assigned[189] to a P=C stretch. Clearly, this cannot be the case and this band has been reassigned as a CO or CN stretch. The p.m.r. spectrum was also compatible with structure (8). The phenolic and amino protons resonated as a broad two-proton signal at ca. 4.9τ, which disappeared when the solution was shaken with D_2O. The material (8) gradually turned green on exposure to air and light and is probably the cause of the blue colouration noticed by Lim,[189] when the primary hydrolysis product of the phosphorane was allowed to hydrolyse further.

The i.r. spectrum (Figure III.2) of the phosphorane (4) has been described in detail in section II. The strongest band, at 1073 cm^{-1}, is assigned to the P-O-Me stretch in accordance with a similar band at 1075 cm^{-1} observed by Ramirez et al.[24] in the i.r. spectrum of the 1,3,2-dioxaphospholene derivative (9).

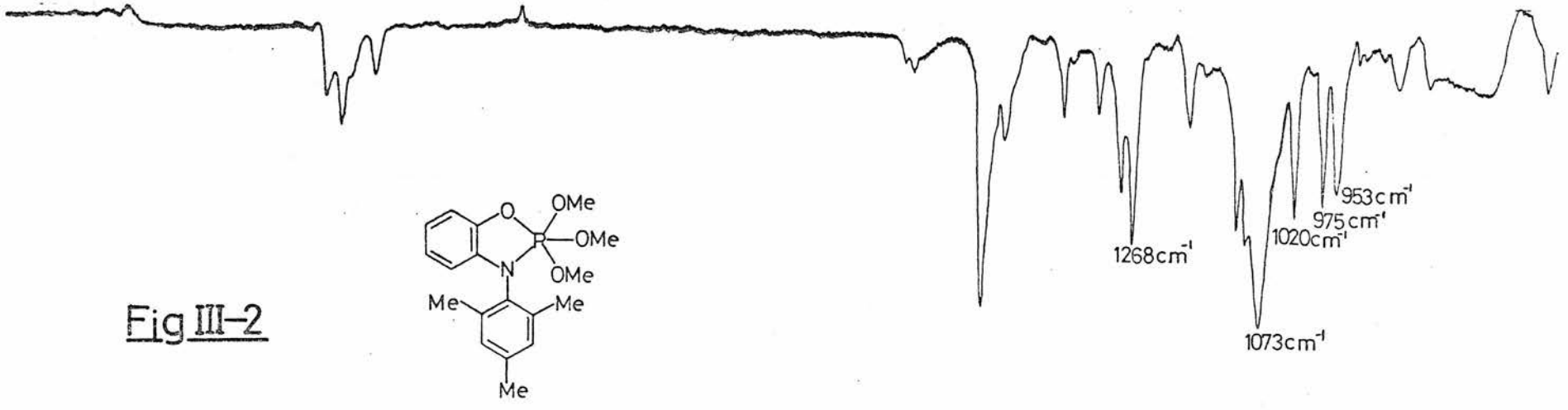


(9)



(10)

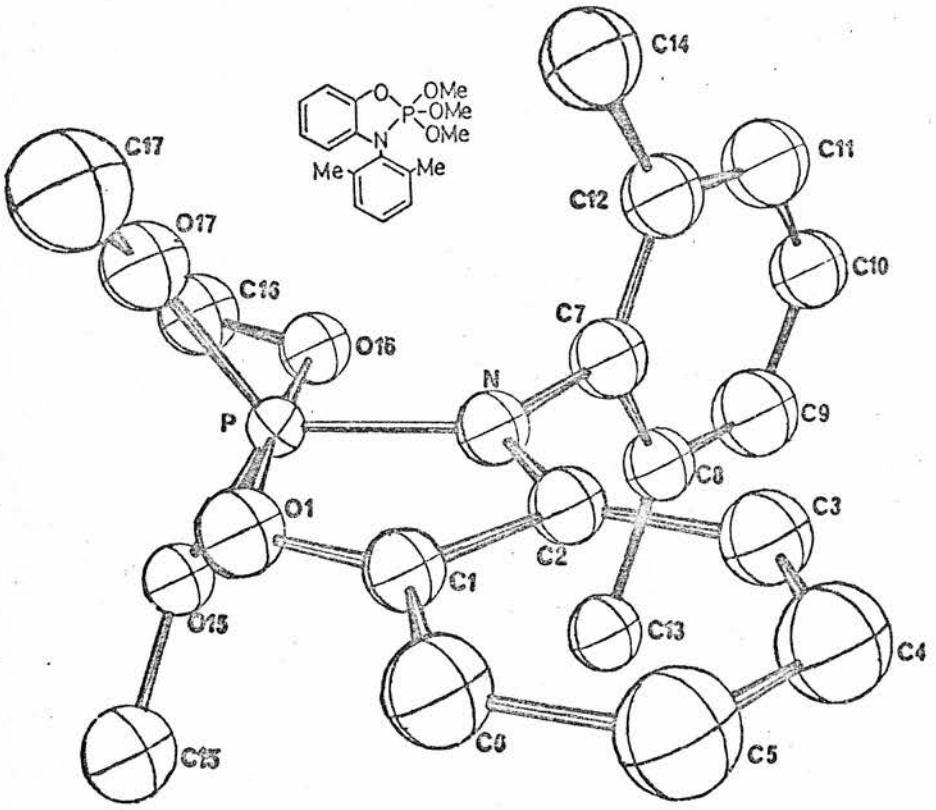
An X-ray crystallographic analysis by Gould et al.[213] on the product (10), isolated from the reaction of 2,6-dimethylphenyl 2-nitrophenyl ether with trimethyl phosphite,[212] has confirmed the new structural assignment. The stereoprojection is shown in Figure III.3 and the more


1268cm⁻¹
1073cm⁻¹
1020cm⁻¹
975cm⁻¹
953cm⁻¹

O
OMe
P
OMe
N
OMe
Me
Me
Me

Fig III-2

Fig III-3


C14
OMe
OMe
OMe
O
P
N
Me
Me
C17
C11
O17
C12
C10
C16
C7
O16
N
P
C9
C8
O1
C3
C2
C1
O15
C13
C4
C6
C5
C15

important parameters are listed in Table I.

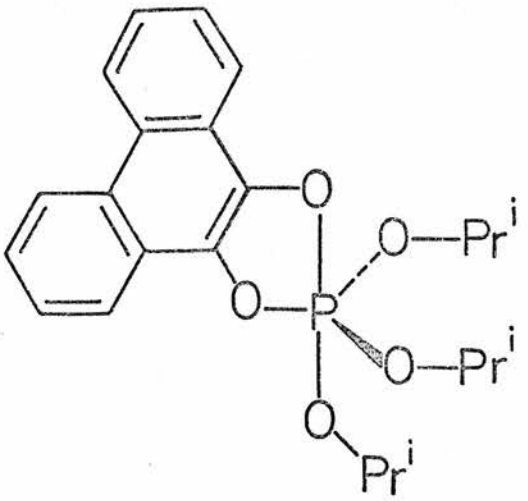
TABLE I: MOLECULAR STRUCTURE OF 2,2,2-TRIMETHOXY-3-(2',6'-XYLYL)--2,2-DIHYDROBENZ-1,3,2-OXAZAPHOSPHOLINE (10)

Bond Angles (°) about Phosphorus		Bond Angles (°) about Nitrogen		Bond Lengths (Å) to Phosphorus	
O(1)-P-O(16)	176.0	C(2)-N-P	117	P-O(1)	1.74
O(1)-P-O(15)	91.9	C(2)-N-C(7)	117	P-N	1.68
O(1)-P-O(17)	90.4	C(7)-N-P	126	P-O(16)	1.61
O(1)-P-N	86.7		360	P-O(15)	1.60
N-P-O(15)	123.9	Heterocyclic Bond Lengths (Å)		P-O(17)	1.57
N-P-O(17)	124.3			Methoxy Bond Lengths (Å)	
O(15)-P-O(17)	111.8				
O(16)-P-O(15)	90.3	N-C(7)	1.46	O(15)-C(15)	1.42
O(16)-P-O(17)	91.8	N-C(2)	1.40	O(16)-C(16)	1.43
O(16)-P-N	89.3	O(1)-C(1)	1.30	O(17)-C(17)	1.50

The phosphorus atom lies at the centre of a slightly distorted TBP. The heterocyclic ring occupies an apical-equatorial distribution, with the oxygen atom at an apical site in accordance with the relative apicophilicities[8] of the phenoxy and amino ligands (bulk and electronic differences). The plane of the xylyl ring is orthogonal to the nearly planar heterocyclic ring. The sum of the bond angles about nitrogen is 360°, indicating that this atom is planar and suggesting sp^2 hybridisation. This planarity aids the back donation of electrons from the nitrogen lone pair orbital to phosphorus. In this example, back donation will be particularly favourable as the five-membered ring holds the amino group in the apical plane, causing the $\underline{N}$-p_z lone-pair orbital to lie in the equatorial plane, an orientation which has been predicted[53] to be ideal for maximum pd-π overlap. Indeed, the P-N bond length is only 1.68 Å, whereas a single P-N bond should be ca. 1.8 Å.[214]

Considerable pd-π character is apparent in the shortening of other bonds to phosphorus; Cruikshank[9] predicted a P-O single-bond length of 1.76 Å. The apical, endocyclic bond is longer than the apical, exocyclic

bond; nevertheless, both are shortened. The shortest P-O bond is found in the equatorial plane. These results are in agreement with theory[53] and with the conclusions reached by Hamilton et al.,[5a,10] who obtained the molecular structure of the phenanthrenyl-1,3,2-dioxaphospholine derivative (11). Thus, less back bonding is to be expected from



(11)

apical than from equatorial sites[53] and endocyclic ligands will delocalise less electron density on to phosphorus, due to the possibility of delocalisation into the benzoxazaphospholine system. Consequently, the endocyclic C-N bond is shorter than the theoretical single-bond length.[214]

As the plane of the 2',6'-xylyl ring is orthogonal to the plane of the amino ligand, delocalisation of electron density from nitrogen into this system is prevented.

The equatorial, exocyclic O-P-O bond angle is seriously compressed (8° from the preferred 120°); the C(7)-N-P bond angle is similarly expanded. No such distortion was observed by Hamilton et al.[5a,10] in the phenanthrenyl-1,3,2-dioxaphospholine derivative (11) above. This distortion may be due to steric interaction between the equatorial methoxy ligands and the methyl groups attached to the 2,6-dimethylphenyl ring. The exocyclic apical-equatorial O-P-O bond angles are all very

close to the ideal (90°); therefore, a similar steric interaction does not seriously affect the apical methoxy ligand.

(b) Other pentacoordinate benz-1,3,2-oxazaphospholine derivatives

The spectroscopic characteristics of the other pentacoordinate derivatives, which have been synthesised by the deoxygenation of aryl 2-nitrophenyl ethers, do not differ fundamentally from those described above for 3-mesityl-2,2,2-trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine. Significant trends will be discussed en masse in separate sections, below.

(i) ^{31}P N.m.r. chemical shifts and experimental yields

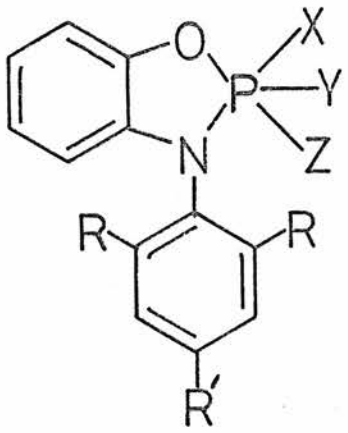


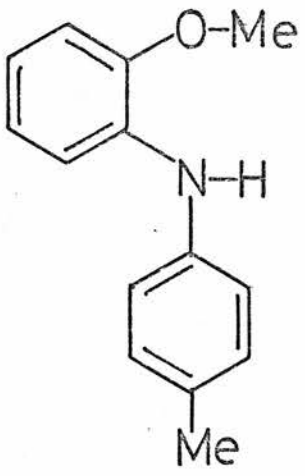
TABLE II ($CDCl_3$)

Compound	R	R'	X	Y	Z	Yield (%)	$\delta^{31}P$ (ppm)
I	Me	Me	OMe	OMe	OMe	41	+57.2
II	Me	Me	OMe	OMe	Ph	86	+46.7
III	Me	Me	OMe	Ph	Ph	64	+44.2
IV	Me	Me	$-OCH_2-CH_2-O-$		Ph	ca. 89	+33.3
V	H	Me	OMe	OMe	OMe	> 40	+55.9
VI	H	Me	OMe	OMe	Ph	77	+44.7
VII	H	Me	OMe	Ph	Ph	76	+39.9
VIII	Me	H	OMe	OMe	Ph	83	+47.1
IX	Me	(CO_2Me)	OMe	OMe	OMe	ca. 74	+58.1

Experimental yields

The experimental yields in Table II are not strictly comparable as

mechanistic guides. They reflect rather the ease with which the products could be isolated. In most cases the only significant by-products were due to hydrolysis of the phosphorane. One exception was the reaction of trimethyl phosphite with p-tolyl 2-nitrophenyl ether. The product was obtained by distillation at 152° under reduced pressure (0.2 mm). Despite the constancy of the distillation temperature, the product was a mixture of the phosphorane and an unknown in a molar ratio of 0.8:0.2. The unknown was not isolated, but was tentatively identified as N-(2-methoxyphenyl)-p-toluidine (12) in ca. 10% total yield. The



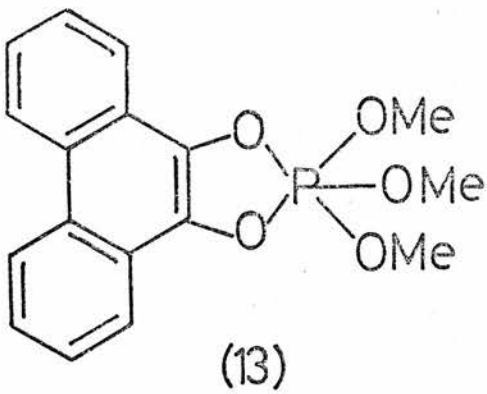
(12)

assignment was made on the basis of spectroscopic observations on the mixture. The i.r. spectrum exhibited a weak, sharp absorption at 3425 cm^{-1} (N-H) and a strong absorption at 1600 cm^{-1}; both were absent in the pure phosphorane, but present in diphenylamine. A singlet at 6.2τ in the p.m.r. spectrum was attributed to a methoxy function rather than to an N-methyl function;[215] it was also of the expected intensity. There was no ^{31}P n.m.r. resonance of comparable intensity to the phosphorane resonance, ruling out a phosphorus-containing structure. This reaction has not been investigated further.

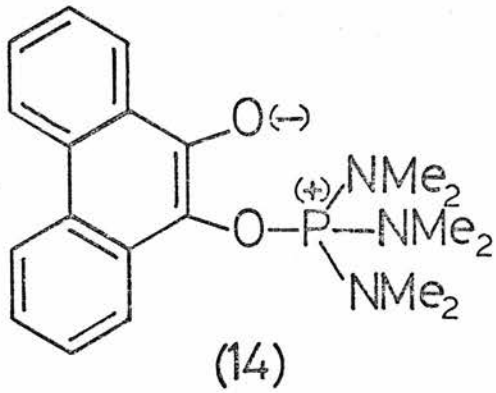
^{31}P N.m.r. chemical shifts

All chemical shifts were in the region of +30 to +60 ppm. Such

values strongly support a pentacoordinate, rather than a zwitterionic structure. Thus, Ramirez et al.[216] reported a ^{31}P n.m.r. chemical shift of +44.7 ppm for the pentaoxyphosphorane (13), but a negative shift of -38.5 ppm for the triamino-substituted derivative (14), which was accordingly assigned the dipolar structure shown. The chemical shift decreases with the substitution of methoxy functions by phenyl



(13)

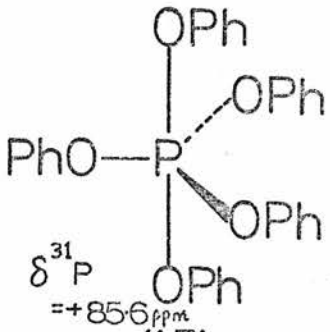


(14)

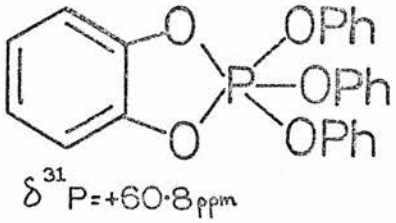
groups. It is of interest that the decrease from I to II is 10.5 ppm whilst substitution of the second methoxy function (III) causes a further decrease of only 2.5 ppm. It may be significant that the chemical shifts of the equivalent tervalent phosphorus compounds show a similar pattern; however, the effect is of far greater magnitude. Thus, $\delta^{31}P$ (ppm):[121] $P(OMe)_3$ = -140 ppm, $Ph\text{-}P(OMe)_2$ = -159 ppm, $Ph_2P\text{-}OMe$ = -116 ppm. Ramirez et al.[24] observed that the percentage increase in chemical shift from tervalent phosphorus to pentavalent phosphoryl was similar for several pairs of compounds and that this increase (ca. 100%) continued with the introduction of a further oxygen ligand to generate the pentacoordinate structure.[147,217]

The introduction of a second five-membered ring into the phosphorane (cf. IV and II, Table II) caused a 13 ppm decrease in the chemical shift. This is a general phenomenon. Thus, pentaphenoxyphosphorane (15), the monocyclic analogue (16) and the spirocyclic analogue (17) exhibited chemical shift reductions of ca. 25 ppm with the successive introduction

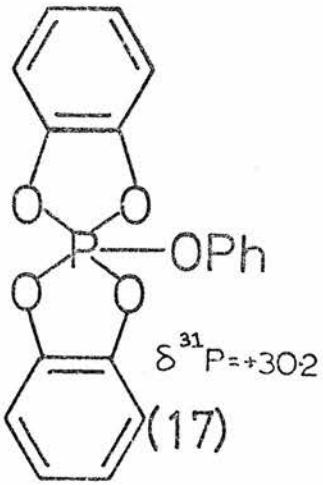
of five-membered rings.[23,218]



(15)



(16)



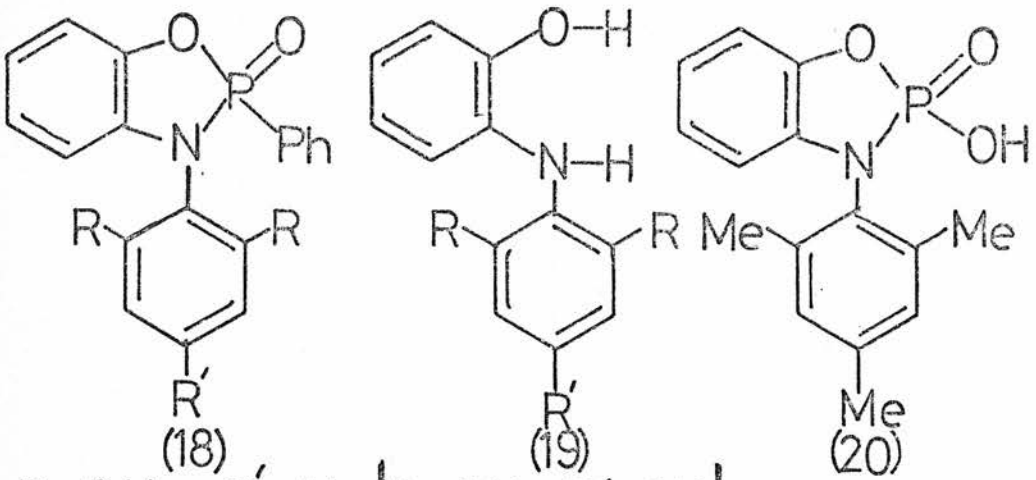
(17)

In contrast, phosphoranes containing a six-membered ring show, if anything, a small increase in chemical shift compared with their acyclic analogues.[43,20] This may be a further manifestation of the reduction in steric crowding, accompanying the incorporation of ligands into five-membered rings.

The introduction of an electron-withdrawing group into the acyclic N-aryl ring (IX in Table II) produced a small increase in the chemical shift.

(ii) I.r. spectra

All of the phosphoranes studied showed similar i.r. spectra with appropriate modifications for the replacement of alkoxy functions by phenyl groups. A group of three strong, sharp absorptions appeared at ca. 950, 970 and 1020 cm^{-1} and seem to be a characteristic of the heterocyclic ring-system as they were also observed in the spectra of the 3-aryl-2-oxo-2-phenylbenz-1,3,2-oxazaphospholines (18) but not in the anilinophenols (19). However, these absorptions were not observed in the spectrum of the cyclic phosphoramidate monoester (20).

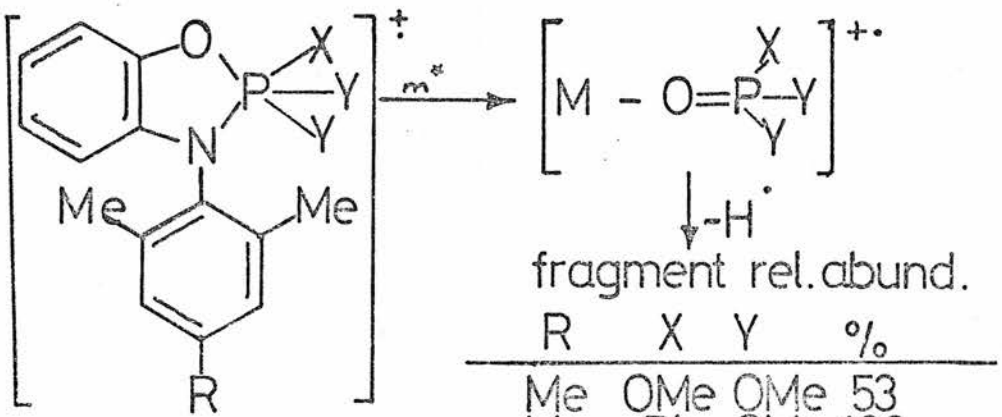


(18) (19) (20)

R=CH$_3$ R′=H | R=CH$_3$ R′=CH$_3$
R=H R′=CH$_3$ | R=H R′=CH$_3$
R=CH$_3$ R′=CH$_3$ |

(iii) Mass spectra

All of the phosphoranes in which the N-aryl substituent carried o--methyl groups showed direct (m*) fragmentations with loss of the appropriate neutral phosphoryl fragment as in scheme 5. An extremely favourable fragmentation by loss of a proton followed. In most cases



fragment rel.abund.

R	X	Y	%
Me	OMe	OMe	53
Me	Ph	OMe	100
Me	OMe	Ph	100
H	Ph	OMe	100
CO$_2$Me	OMe	OMe	92
Me	OCH	CHO	81

Scheme 5

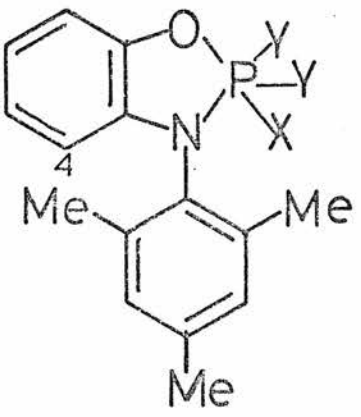
a metastable peak appeared in the region expected for this latter process. The abundancies of the second fragment are recorded in scheme 5.

In contrast, phosphoranes carrying an N-p-tolyl function fragmented directly (m*) with loss of both the phosphoryl fragment and the proton. The corresponding ion at m/e 180 was normally of relatively low abundance (ca. 30%); the predominant fragment was the molecular ion (100%). There is no obvious reason for this change in pattern.

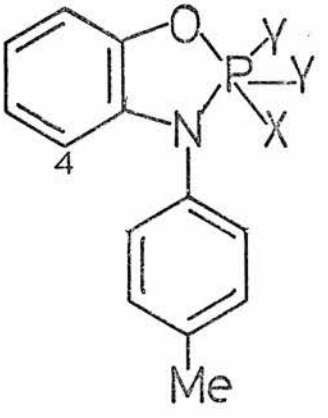
(iv) P.m.r. spectra — the assignment of the one-proton multiplet at ca. 4τ

The p.m.r. spectra of all phosphoranes were in agreement with their assigned structures. In each case, a one-proton, complex doublet appeared at ca. 4τ, clearly separated from the main aromatic band, whose protons resonated at lower field. This upfield resonance has been assigned to the 4-position proton of the two systems (21) and (22) from evidence presented below.

In each case the 4-position proton moved upfield by ca. 0.2τ with the introduction of two o-methyl groups into the exocyclic N-aryl system in place of protons. The relevant chemical shifts are listed in Table III.



(21)

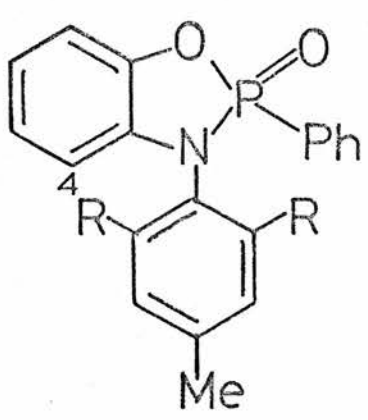


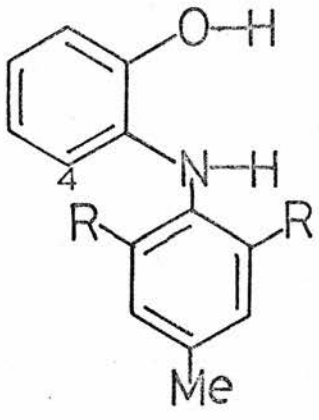
(22)

TABLE III: τ VALUES OF THE 4-H PROTON IN PHOSPHORANES (21) AND (22)

Compound	X	Y	4-H (τ) / ppm
21a	MeO	MeO	4.12
22a	MeO	MeO	3.93
21b	Ph	MeO	4.06
22b	Ph	MeO	3.84
21c	MeO	Ph	4.05
22c	MeO	Ph	3.80

This comprison is reinforced by the observation that both 3-mesityl--2-oxo-2-phenylbenz-1,3,2-oxazaphospholine (23) and 2-(2',4',6'-trimethylanilino)phenol (24), exhibited a one-proton multiplet, upfield of the main aromatic band; in contrast, the N-p-tolyl analogues (25) and (26) did not. These results are tabulated below (Table IV).





(23) . . . . R=Me . . . . (24)

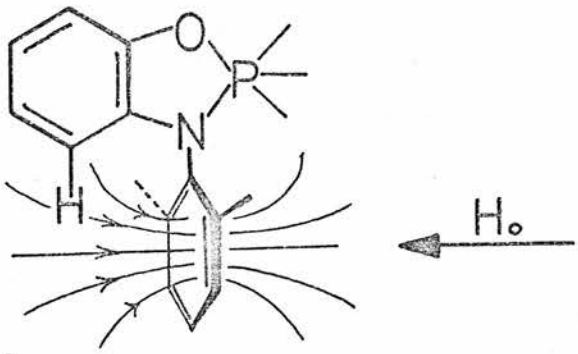
(25) . . . . R=H . . . . . (26)

TABLE IV: τ VALUES OF THE 4-H PROTON OF (23), (24), (25) AND (26)

Compound	4-H (τ) /ppm
23	3.70-3.86
25	< 3.3
24	3.68-3.80
26	< 3.6

Models indicate that rotation of the N-aryl system about the exocyclic C-N bond should be severely restricted, due to steric interaction between the o-methyl groups of the N-mesityl function and the 4-position proton. X-Ray data and variable-temperature p.m.r. studies

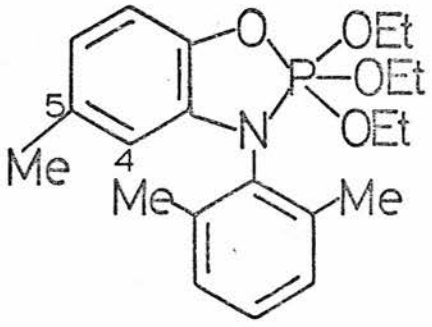
support this view. It is therefore suggested that the mesityl ring is able to oscillate through only a small angle about the C-N bond; hence, the 4-position proton is shielded by the aromatic ring current (scheme 6). When the o-methyl groups are replaced by protons, the steric



Scheme 6

hindrance is decreased but the ring is still unable to rotate freely. Hence, the 4-position proton resonates at lower field but is still significantly shielded with respect to the other aromatic protons.

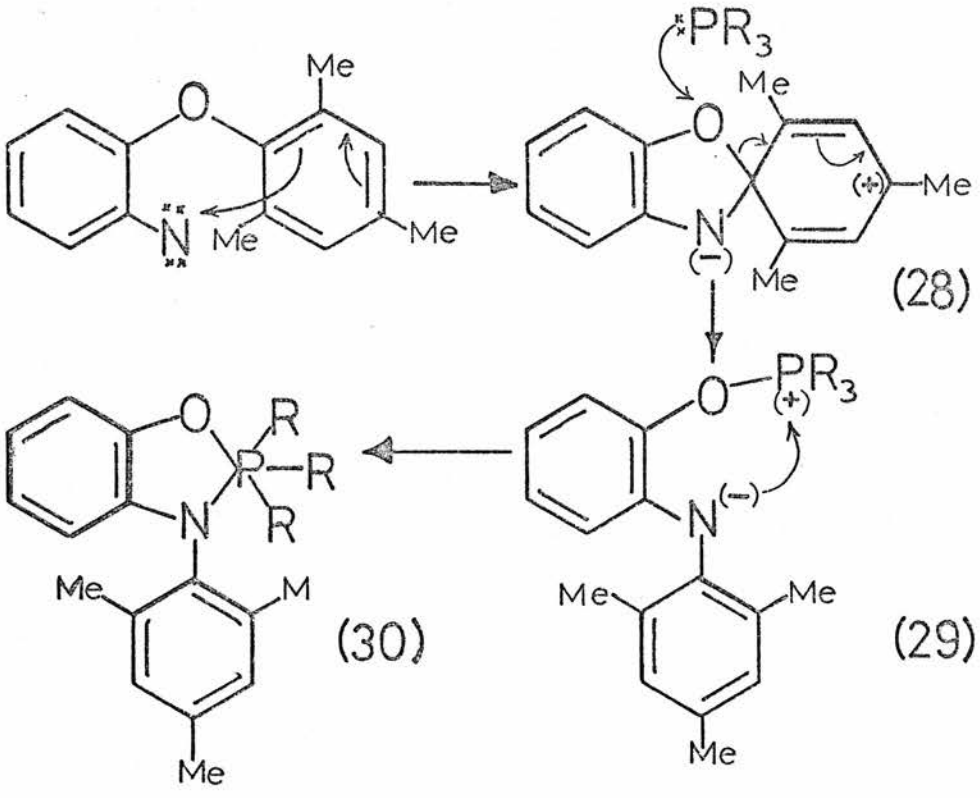
In conclusion, Tait[212] synthesised the 5-methyl derivative (27) and found that the 4-position proton resonated as a broad singlet instead of as a doublet, thus giving strong support to the positional assignment of this proton.



(27)

(c) Proposed mechanisms for the formation of the phosphoranes

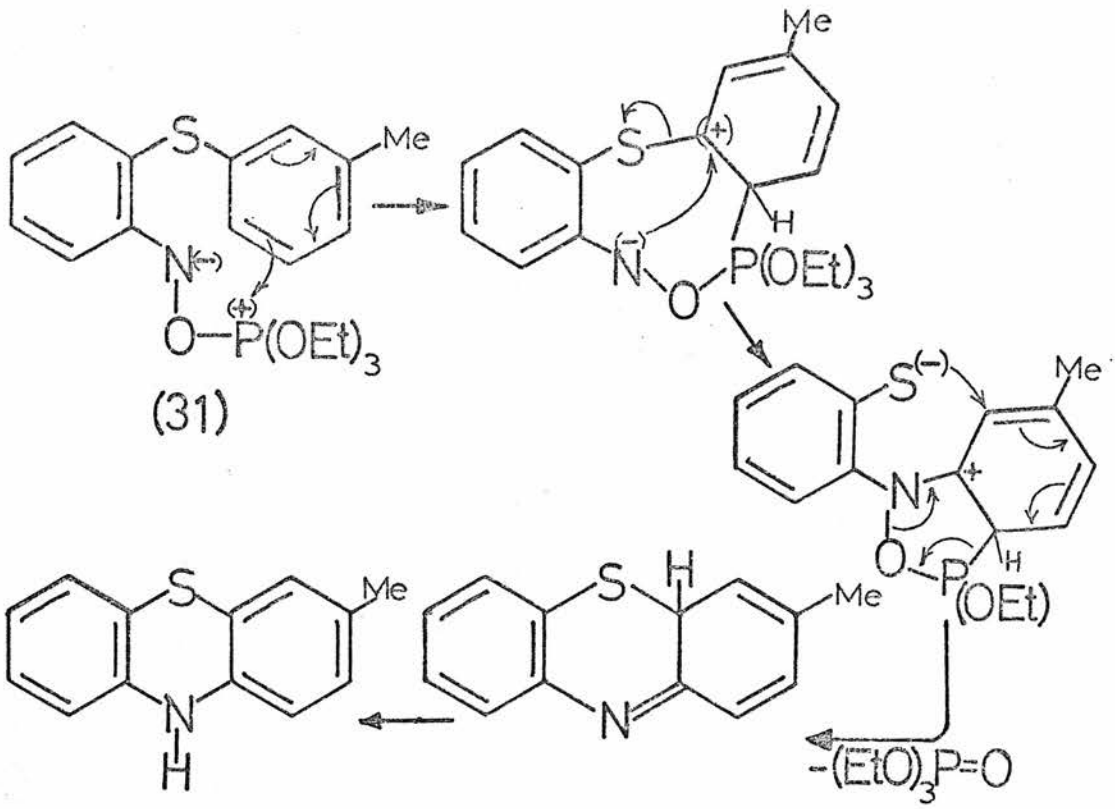
Previous investigations[185,219] of the reductive cyclisation of aromatic nitro-compounds have suggested the intermediacy of a spirodienyl species. The following mechanism has been proposed[220] as being consistent with previous and present results (scheme 7). Deoxygenation



Scheme 7

of the nitro group generates a nitrene, which attacks the electron-rich 1'-position of the mesityl ring to give the spirodienyl intermediate (28). Nucleophilic attack by the tervalent phosphorus reagent on the bridgehead oxygen then produces the zwitterion (29), stabilising the system by rearomatisation. Finally, the ring closes to give the observed product (30).

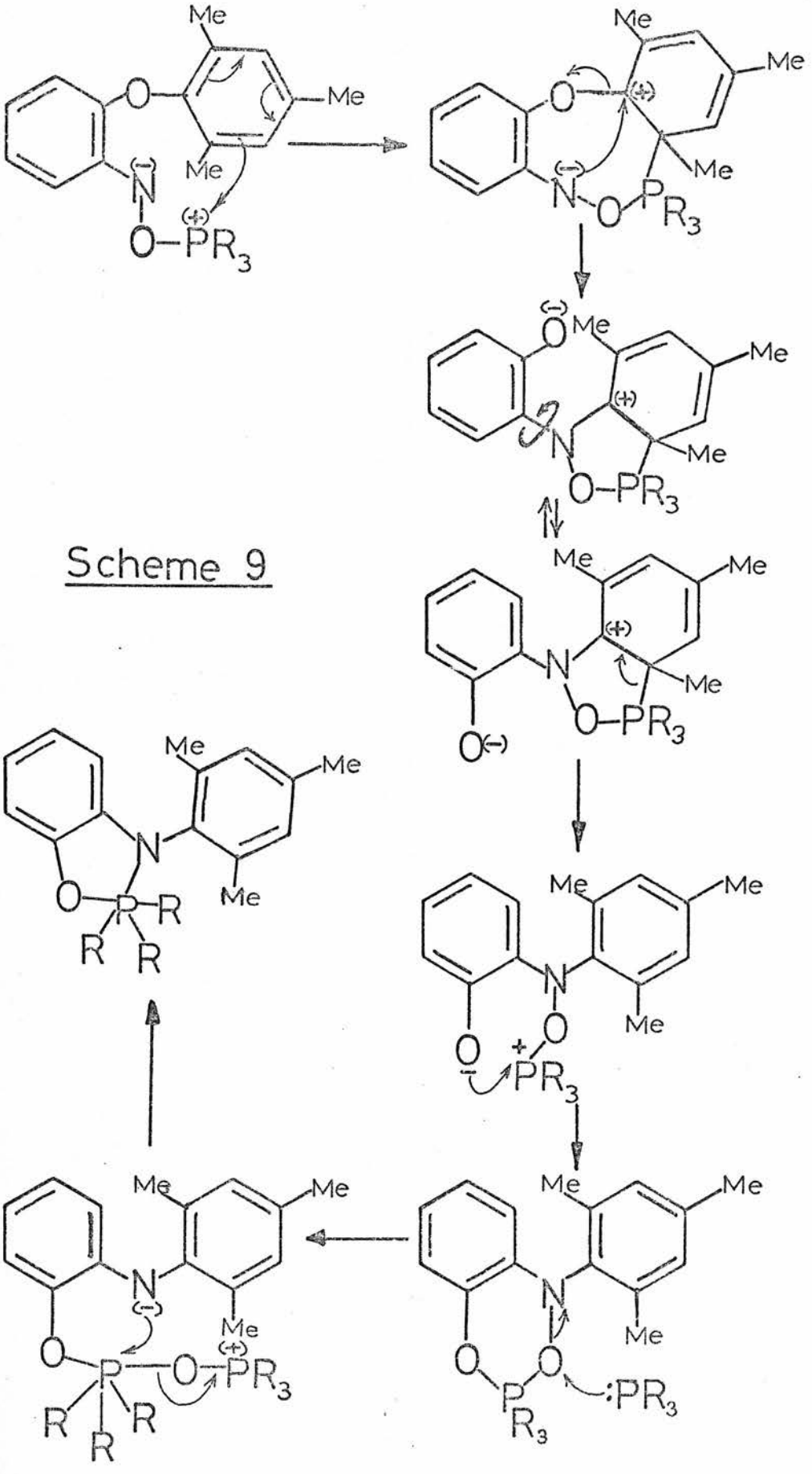
Recent investigations in this laboratory[221] have indicated that, whilst cyclisation of aryl 2-azidophenyl sulphides may well proceed via



Scheme 8

nitrenes and a spirodienyl intermediate, deoxygenation of the corresponding aryl 2-nitrophenyl sulphides may involve the nitrene precursor (31) and the steps in scheme 8, instead.

Accordingly, an alternative scheme is also proposed for phosphorane formation in the P(III) deoxygenation of aryl 2-nitrophenyl ethers (scheme 9).

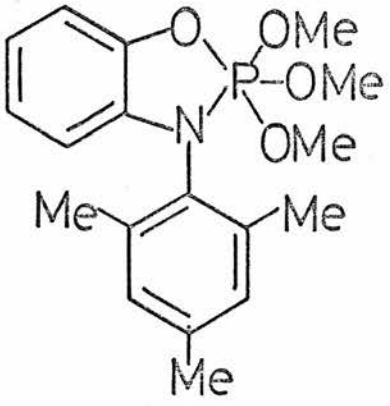


Scheme 9

3. Variable-Temperature P.m.r. Studies on Phosphoranes

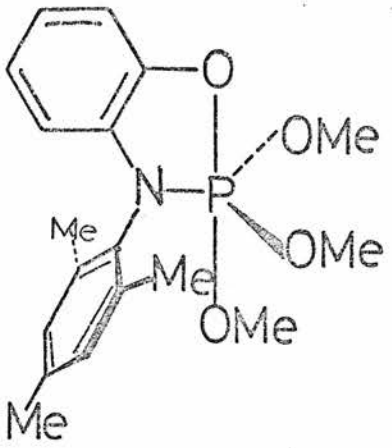
In common with the majority of pentacoordinate phosphorus compounds, most of the pentaccordinate derivatives of the benz-1,3,2-oxazaphospholine system exhibit a rapid, intramolecular ligand exchange at normal temperatures. In all of the low-temperature examples discussed below, the methoxy group exhibited phosphorus-hydrogen spin-coupling above and below the coalescence temperature. The observed phenomenon is therefore a bond-deformation process and, in view of the considerable number of precedents, it is almost certainly a regular process.

At +28°, 3-mesityl-2,2,2-trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine (32) exhibited a single, sharp doublet (J_{P-O-Me} 13.0 Hz) due to



(32)

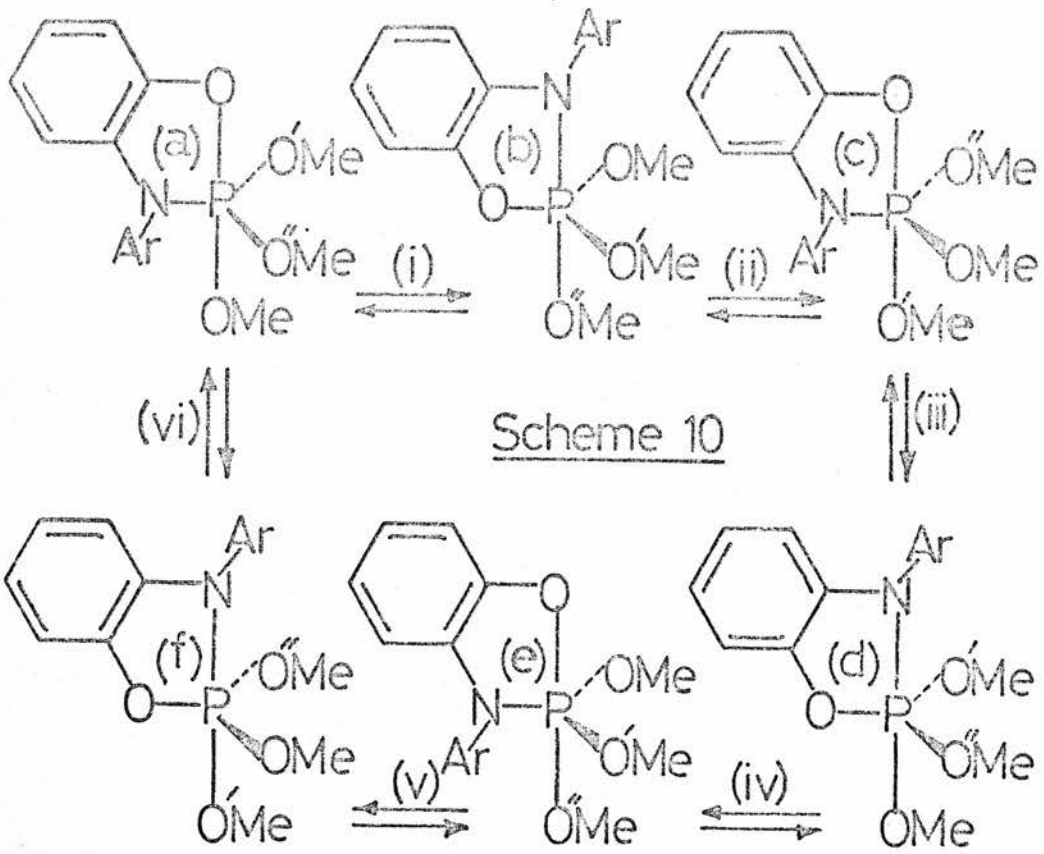
rapid exchange of all three methoxy groups. At temperatures below -80°, this resonance split into two broad doublets; the lower-field doublet had twice the intensity of the higher-field doublet and a coupling constant (J_{P-O-Me}) of 14.5 Hz. The higher-field doublet exhibited the reduced coupling constant of 10 Hz. Since the apical ligands are further from, and hence interact less strongly with, the phosphorus atom, the higher-field doublet with the small coupling constant must be due to a single, apical methoxy group. Hence, the stable geometry at low temperature is that in diagram 33, with the heterocyclic ring occupying the apical-equatorial plane as expected. The equatorial methoxyls



(33)

remain equivalent as do the o-methyl groups of the mesityl function, indicating a plane of symmetry through the heterocyclic ring, on the n.m.r. time-scale at least.

As the temperature was increased, the doublets coalesced ($T_c = -71^{\circ}$), indicating that the ligand-exchange process was becoming fast on the p.m.r. time-scale. The permutational isomerisation process (PI) involved may be a Berry pseudorotation (BPR)[49] or a Turnstile rotation (TR).[52] These processes are indistinguishable by the available evidence, but, for clarity, the TR formalism will be employed. The series of PI processes required to produce magnetic equivalence between the three methoxy ligands is outlined in scheme 10. Only steps (i), (ii), (iii) and (iv) are required, but it is reasonable to assume that the process will be circular if possible. The high-energy points of this process should theoretically correspond to isomers (b), (d) and (f). These isomers are relatively disfavoured in three ways. The endocyclic oxygen has a greater apicophilicity than nitrogen, due to its higher electronegativity. Furthermore, the apicophobicity of the amino ligand is enhanced due to the equatorial preference of π-donor groups. It has already been mentioned that the geometry and orientation of this ligand is ideal for maximum back donation to phosphorus. The third

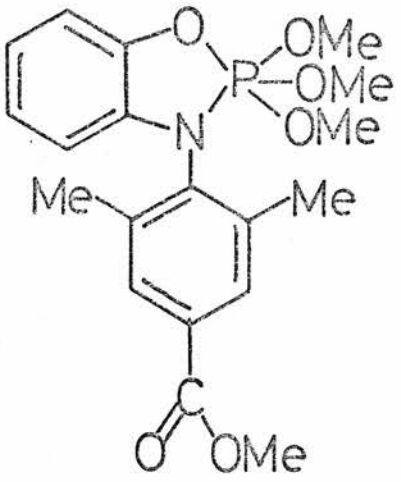


Scheme 10

cause of a low apicophilicity is the bulk of the equatorial ligand. This point will be discussed later.

The relative contributions of these three effects are difficult to assess. An electron-withdrawing group in one of the aryl functions, ortho or para to the amino group, should increase the delocalisation of the nitrogen lone-pair into these functions, hence reducing the phosphorus pd-π back bonding. This, in turn, should decrease the apicophobicity of the amino ligand. If pd-π back bonding is an important contributor to the PI barrier, the coalescence temperature will fall.

This line of investigation has not been pursued so far. However, the effect of substituting a carbomethoxy group for the p-methyl group in the N-mesityl function has been tried. Thus, 3-(4'-carbomethoxy--2',6'-dimethylphenyl)-2,2,2-trimethoxy-2,2-dihydrobenz-1,3,2-oxazaphospholine (34) showed a P-methoxyl coalescence temperature of -75°. Due

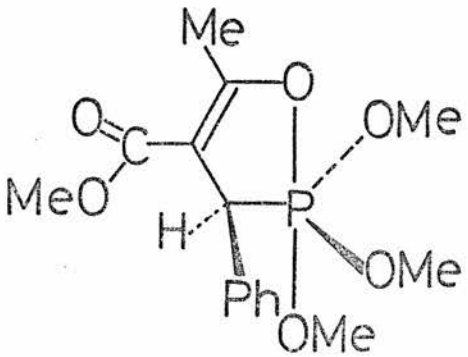


(34)

to the difficulty of accurately locating the coalescence temperature, a detailed comparison cannot be made between this temperature and that obtained for the N-mesityl analogue (32), which had $T_c = -71^{\circ}$. However it is obvious that any effect must be small.

It was subsequently realised that this result was to be expected if the N-mesityl function is sterically prevented from describing more than a small oscillation about the C-N bond. Efficient withdrawal of electrons from the nitrogen p_z-orbital requires that the mesityl ring should be coplanar with the heterocyclic amino function. This is not possible.

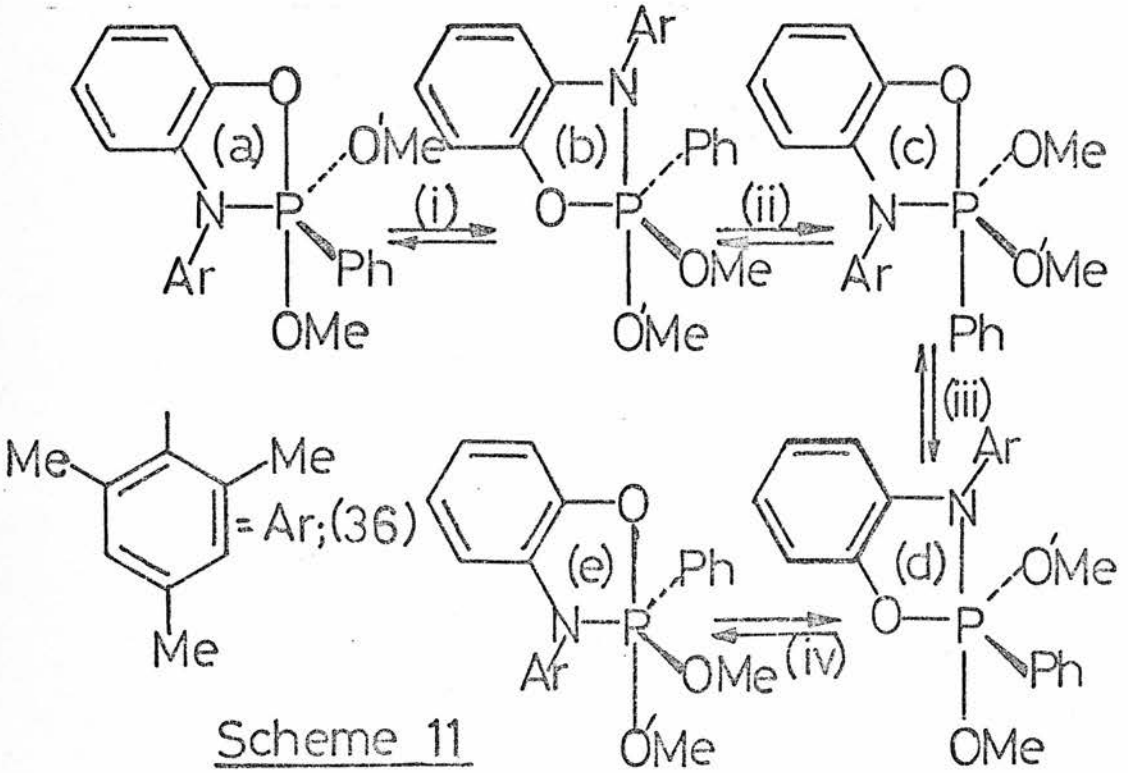
Ramirez et al.,[82] previously reported a coalescence temperature of ca. -40° for the methoxy ligands of the tetraoxyphosphorane (35).



(35)

In this case the process is of higher energy, presumably due to the lower electronegativity of the carbon atom compared with nitrogen.

The substitution of less electronegative groups in the TBP should increase the barrier to PI due to the unfavourability of exchanging electropositive for electronegative groups in the apical sites. To test this idea, in this system, 3-mesityl-2,2-dimethoxy-2-phenyl-2,2--dihydrobenz-1,3,2-oxazaphospholine (36) was synthesised and the spectra are reproduced for various temperatures in Figure III.4 (p. 210). At $+45^{\circ}$, there was a single sharp doublet (J_{P-O-Me} 12.3 Hz) due to the magnetically-equivalent methoxy ligands. At $+28^{\circ}$, there was evidence for slow exchange between these groups and, at -60°, two sharp, three-proton doublets were observed, symmetrically placed about the original resonance position. The upfield doublet (J_{P-O-Me} 10.8 Hz) is assigned to the apical methoxy ligand and the downfield doublet (J_{P-O-Me} 14.0 Hz) to the equatorial methoxyl. The most stable form is therefore the TBP

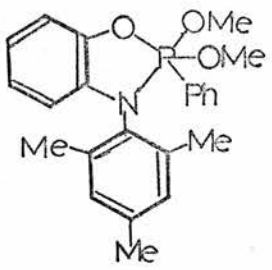


Scheme 11

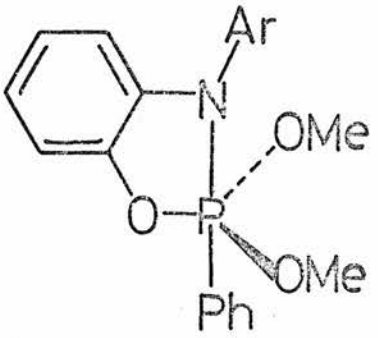
(36a) — or (36e) — as expected (scheme 11).

Equivalence of the methoxy ligands is achieved (scheme 11) in a similar way to that which was described in scheme 10 for the trimethoxy

Fig III–4. Variable-Temperature p.m.r. study of:

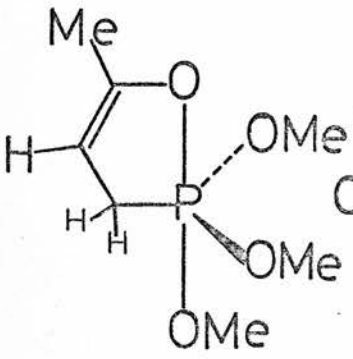


analogue. However, in the present case, the high-energy TBP may be that with either the phenyl group (36c) or the amino group (36b or d) apical. The full sequence (i), (ii), (iii) and(iv) is required. Diagrammatically, it is possible to produce equivalence of the methoxy groups by a series of only two such processes; but this involves an intermediate TBP with both phenyl and amino functions apical (37). This is doubly unfavourable and hence unlikely. It is uncertain which

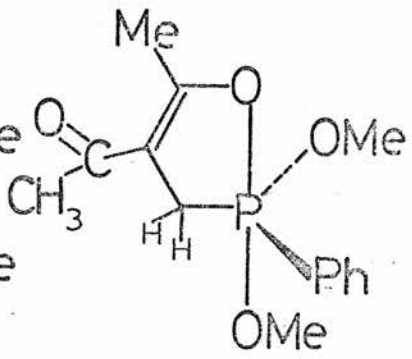


(37)

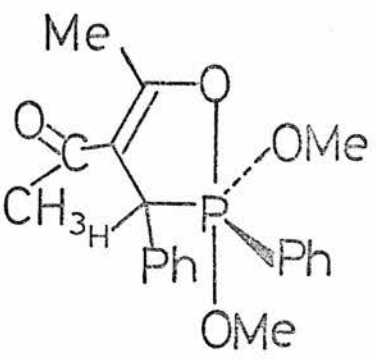
of the two intermediate isomers (36b/d) and (36c) should be the least favourable. Gorenstein[66] observed that the free-energy barriers for the tetraoxyphosphorane (38) and the trioxyphosphorane (39) were almost identical. He thus concluded that the process required to place the



(38)



(39)

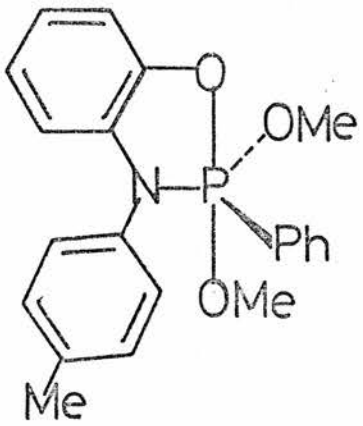


(40)

phenyl group apical in (39) was not particularly unfavourable. In contrast, he observed[66] that substitution of one of the ring-methylene protons of (39) with a phenyl group as in (40) caused an increase in the

free-energy barrier of ca. 5 kcal mol^{-1} or 50%. He concluded that steric bulk was considerably more important than electronegativity considerations.

2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine (41) was synthesised to probe the effect of the mesityl o-methyl



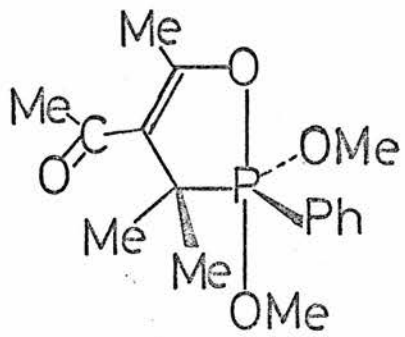
(41)

groups on the energy of the PI process. The overall behaviour was identical to that observed for the N-mesityl analogue (36), but, in contrast, the methoxyl resonance was a sharp doublet at +28° and the coalescence temperature was -50° ($\triangle G^*$ = 43.0 kJ mol^{-1}; 10.3 kcal mol^{-1}).

The N-mesityl analogue (36) had a coalescence temperature of -5° ($\triangle G^*$ = 52 kJ mol^{-1}; 12.5 kcal mol^{-1}), a difference in $\triangle G^*$ of 17%. This energy difference is probably due to the difference in steric interactions between the exocyclic ligands and the N-aryl function during the interconversion of the isomeric TBP. A second, but highly speculative, reason lies in the possibility of freer rotation of the N-aryl group about the C-N bond, when o-methyl substituents are lacking. Interaction between the nitrogen p_z-orbitals and the exocyclic aryl system (possible if the amino and N-aryl functions were coplanar) would result in decreased availability of electrons for back bonding to phosphorus. Thus, the apicophobicity of the amino function would fall. The dimethyl phenylphosphonite derivatives are eminently suited to probe

this and other effects due to their relatively high coalescence temperatures.

An additional spectral change was observed in the p.m.r. spectrum of 3-mesityl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine (36), when the temperature was reduced (Figure III.4, above). The o-methyl resonance of the mesityl ring broadened and split into two three-proton singlets at ca. -60°. The coalescence temperature for this process was -32° (whereas the P-methoxy coalescence temperature was -5°). It was originally concluded that this was evidence for rapid rotation of the mesityl group about the C-N bond which was decelerated on the n.m.r. time-scale by steric interaction with the phosphorus exocyclic ligands when fast exchange of the latter groups was inhibited. However, it has been pointed out by Gorenstein et al.,[222] who observed a similar difference in temperatures for the coalescence of the gem-dimethyl groups and P-methoxy ligands in (42), that the coalescence

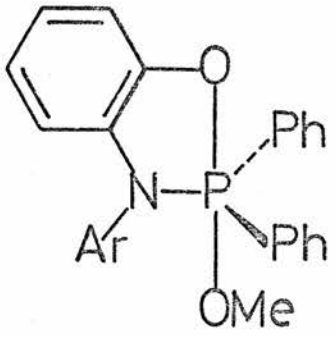


(42)

temperature of a given process depends on the frequency separation of the exchanging groups. Thus, the free-energy barrier for the equivalence of the mesityl o-methyl groups was calculated and found to be 50 kJ mol^{-1}. This is 1 kJ mol^{-1} outside the assessed experimental error of ± 0.5 kJ mol^{-1}, but it is believed that this is probably an indication of a larger experimental error, rather than of a process separate from P-methoxyl exchange. Accordingly, it is believed that the mesityl ring

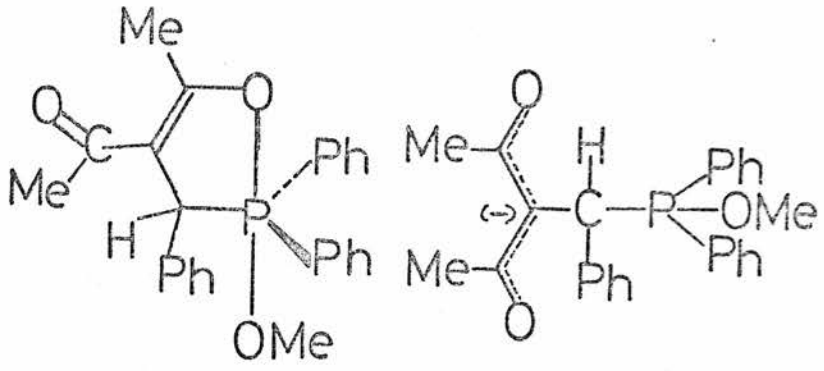
cannot rotate fully and that the apparent equivalence of the o-methyl groups is due to the rapid positional exchange of the exocyclic phosphorus ligands, which also averages the o-methyl environment. The upfield singlet is assigned to the group syn to the shielding phenyl ligand.

This study was pursued to its logical conclusion with the synthesis of 3-mesityl-2-methoxy-2,2-diphenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine (43). The methoxy ligand resonated as a sharp doublet (J_{P-O-Me} 11.0 Hz) between +28° and +200° without observable change. The temperature invariance and low coupling constant suggest a frozen structure, with the



Ar=mesityl;(43)
Ar=p-tolyl ;(44)

methoxy ligand apical, as in the diagram above (43). The p-tolyl analogue (44) exhibited identical behaviour, despite the reduction in steric effects. If the methoxy group was to move into an equatorial position, both a phenyl group and the amino function would have to be placed unfavourably apical. It is probable that there is no contribution from this high-energy form at all, even at +200°. A similar observation has been made by Ramirez et al.[217] for the dioxyphosphorane (45). In this case, however, the endocyclic P-O bond was broken reversibly at +127°, to give the open dipolar species (46). This process would presumably cause a change in the chemical shift and J_{P-O-Me} of the methoxy ligand. As this was not observed in our investigations, such a process probably did not occur. Evidently, the 2,2-dihydrobenz-1,3,2--oxazaphospholine system is considerably more stable than the



(45) (46)

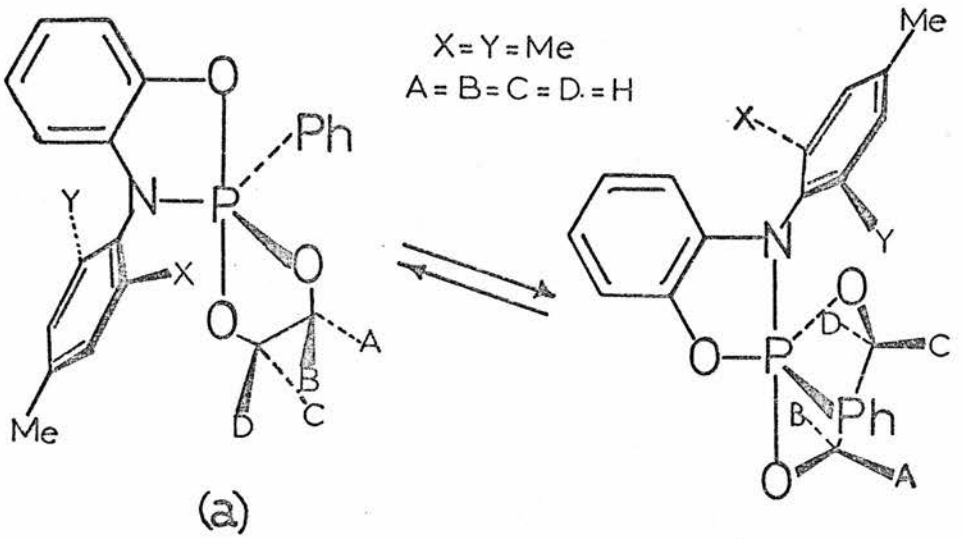
2,2-dihydro-1,2-oxaphospholene system.

The relative importance of electronic and steric effects in determining the height of the barrier to PI is uncertain. Several authors[71,77] have emphasised the electronic contributions; however, Gorenstein's work[66] certainly suggests a predominantly steric effect. Thus, the difference in coalescence temperature between the N-mesityl trimethoxy- and the N-mesityl dimethoxy-substituted phosphoranes - (32) and (36), above - may be largely the consequence of increased steric interactions due to the P-phenyl ligand in (36).

Spiro-2,2-ethylenedioxy-3-mesityl-2-phenyl-2,2-dihydrobenz-1,3,2--oxazaphospholine (47) was observed in the p.m.r. probe at high and low temperatures. The ethylenedioxy ring protons resonate as a complex

(47)

multiplet at +28°. The N-mesityl o-methyls resonate as two separate three-proton singlets, indicating different environments for these groups. The ethylenedioxy splitting pattern is complex and phosphorus spin-tickling provided no elucidation of the structure. However, the pattern has certain symmetrical aspects which suggest that some interchange of the apical and equatorial ring-termini may be occurring. This idea was strengthened by the observation that the pattern broadened into a single, broad doublet at ca. -60° ($CDCl_3$). Some viscosity-broadening was apparent in the rest of the spectrum, but this was not as extensive. It is tentatively proposed that a rapid interchange of the ring termini between apical and equatorial positions occurs above -60° as in scheme 12; below this temperature, the process is inhibited,

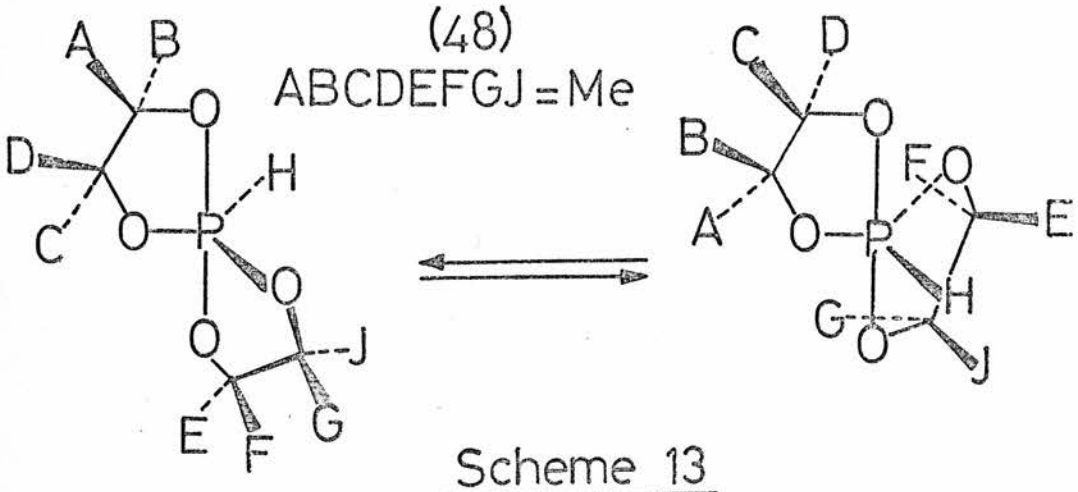


Scheme 12

chiefly due to steric interaction between the P-phenyl ligand and the N-mesityl group. This process should supply partial equivalence within the pairs of ethylenedioxy protons A,C and B,D, since these groups are in respectively similar positions in isomers (a) and (b). Total equivalence of these pairs is not possible as an apical amino group in

(b) is dissimilar to an apical ring oxygen in (a). Note that this same process maintains the N-mesityl o-methyl protons in different environments, the methyl group Y remaining syn to the phenyl group in both (a) and (b). Hence, two separate resonances are observed for these groups at both low and normal temperatures.

Similar low-energy processes have been observed by Denney et al.[20] and Houalla et al.[36] In these cases, however, complete equivalence of pairs of substituents in both rings was possible, the ring termini being symmetrical about their C-C bonds. Houalla et al.[36] reported that the spectrum of the spirocyclic phosphorane (48) was invariant down to -70° and suggested the process in scheme 13. Steric and stereoelectronic barriers should be considerably lower for the exchange in scheme 13 than for that in scheme 12; hence, lack of evidence for a low-temperature slow exchange in the latter case is as expected.

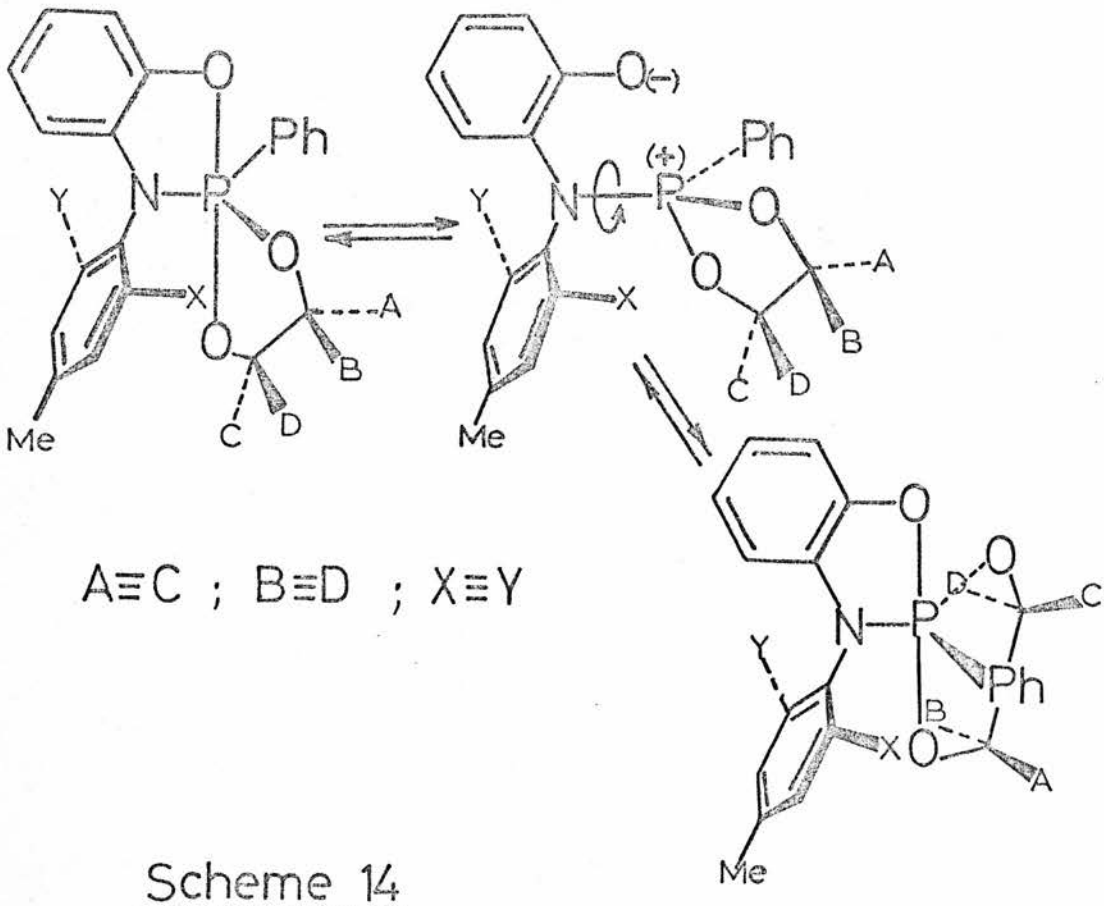


Scheme 13

At +150°, the mesityl o-methyl singlets of (47) started to coalesce and the ethylenedioxy multiplet broadened. Coalescence of the o-methyl singlets occurred at +175° (ΔG^{*} = 96 kJ mol^{-1}; 23 kcal mol^{-1}) and the ethylenedioxy resonance coalesced to a symmetrical "mound" at +192°. These effects were reversible.

Three possible explanations must be considered. The steric

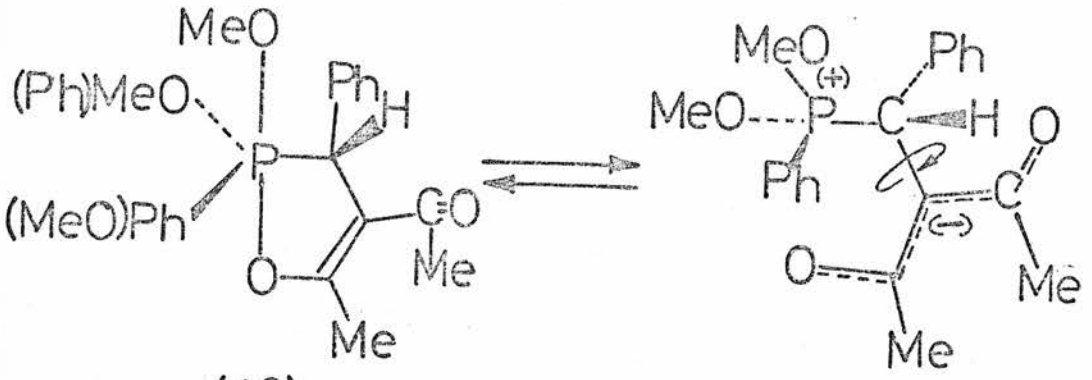
inhibition towards rotation of the N-mesityl ring could be overcome at high temperature, thus giving equivalence to the o-methyl groups. However, this fails to explain the accompanying change in the ethylenedioxy resonance. One of the spirocyclic rings could undergo reversible cleavage as observed by Gorenstein et al.[222] and Ramirez et al.[217] on other systems. This is exemplified in scheme 14. This process would



Scheme 14

interchange the position of the P-phenyl group with respect to the mesityl o-methyl groups and would also make cis pairs of ethylenedioxy protons equivalent (compare the low-temperature process in scheme 12, above, which only partially interchanged the environments of these protons).

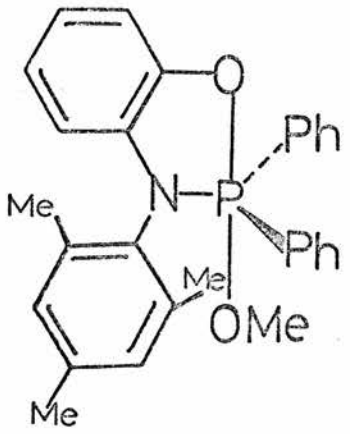
When Ramirez et al.[217] observed this type of effect (scheme 15) in the high-temperature spectrum of the trioxyphosphorane (49), the coalescence temperature was ca. +125° in the absence of a solvent. In



(49)

Scheme 15

contrast, we have observed no ring-opening of the aminodioxyphosphorane (50) even at +200° in chlorobenzene. It seems unlikely that thermal



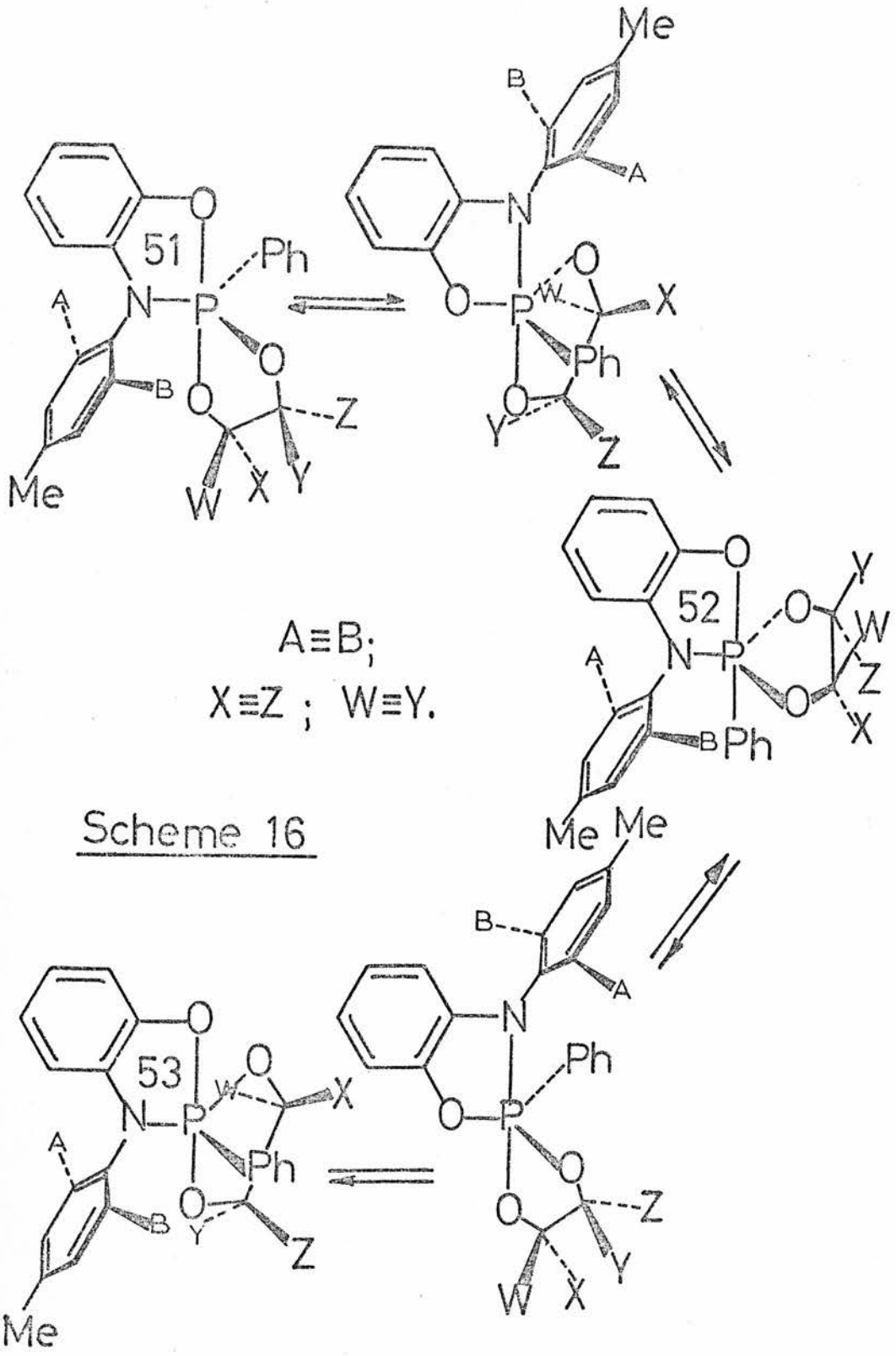
(50)

ring-opening should be so much easier in the spirocyclic oxyphosphorane (47) than in (50) — especially since the zwitterionic form of (47) in scheme 14 should be disfavoured by the small-ring effect.

A preferable explanation invokes a high-temperature, regular PI process in which the enantiomers (51) and (53) interchange via the TBP (52), in which the ethylenedioxy ring is placed diequatorially (scheme 16).

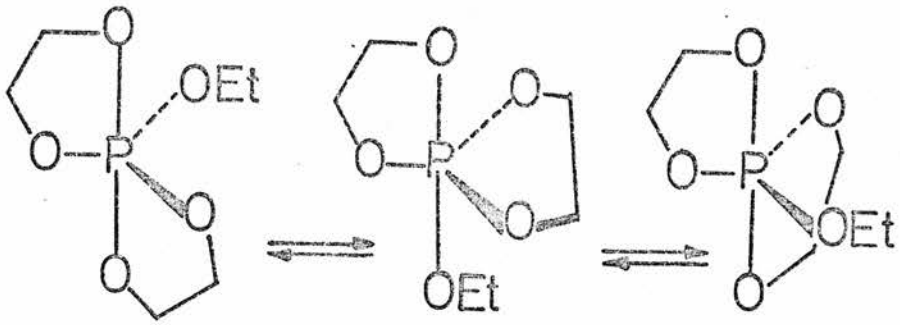
Clearly, this scheme allows the equivalence of both the o-methyl substituents (A and B) and the cis ethylenedioxy protons (W,Y) and (X,Z).

The free-energy barrier of 23 kcal mol^{-1} is, however, rather low for a process which places the ethylenedioxy ring in a diequatorial



Scheme 16

distribution. Denney et al.[20] observed a coalescence temperature of 172° for the process in scheme 17 which approximates to a free-energy



Scheme 17

barrier of ca. 22 kcal mol^{-1}.[75] In this case, the energy required to place the ethylenedioxy ring diequatorially is not increased by also having to place a less electronegative (e.g. phenyl) ligand in an apical position.

4. Hydrolysis of Benz-1,3,2-Oxazaphospholine Derivatives

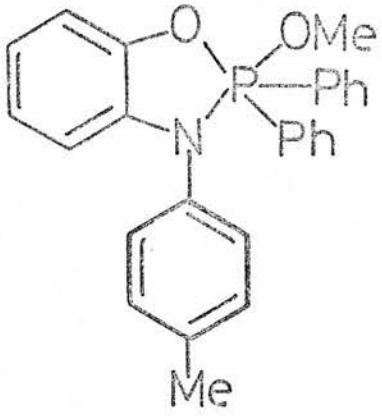
(a) 3-Aryl-2-methoxy-2,2-diphenyl-2,2-dihydrobenz--1,3,2-oxazaphospholine derivatives

(i) General

When 2-methoxy-2,2-diphenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2--oxazaphospholine (54) was dissolved in a 5% aqueous dioxan solution, 0.016 M in toluene-4-sulphonic acid at 35°, a white, sparingly soluble powder was deposited rapidly. The hydrolysis of the phosphorane was complete in less than 30 min.

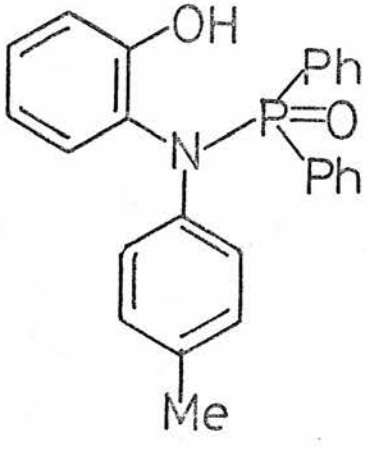
Examination of the products showed that a material with the empirical formula $C_{25}H_{27}NO_2P$ had been formed in 94% yield, together with less than 4% of an isomeric product and a very small quantity of methyl diphenylphosphinate. Conclusive structural assignments for the former

products have proved to be somewhat elusive; however, in balance, the available evidence has led to the following conclusion. The

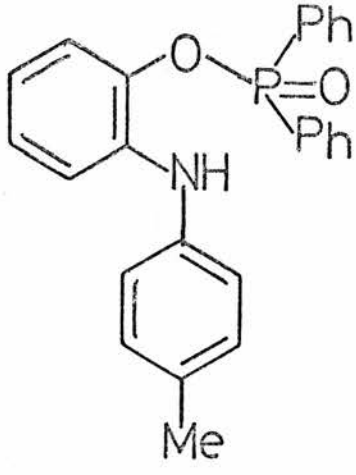


(54)

major hydrolysis product is N-(2-hydroxyphenyl)-P,P-diphenyl-N-p-tolylphosphinamide (55); whilst the isomeric, minor hydrolysis product is 2-p-toluidinophenyl diphenylphosphinate (56). The evidence for these assignments will be considered in the following pages.



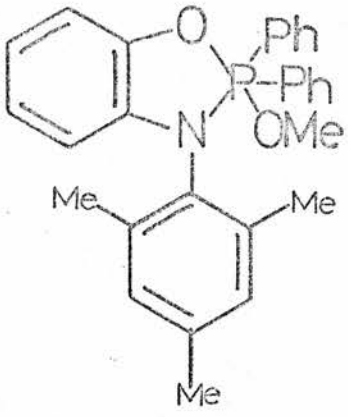
(55)



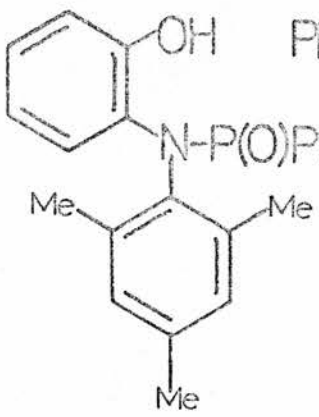
(56)

When the analogous N-mesityl phosphorane (57) was submitted to the same hydrolysis conditions, a similar and even less soluble, white powder was obtained in 96% yield at approximately the same rate. Once again, small yields of an isomeric material (<1.5%) and methyl diphenylphosphinate were obtained.

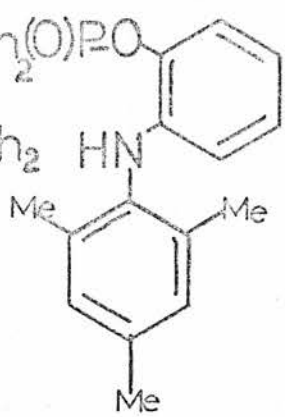
In contrast, no hydrolysis was detectable when the N-p-tolylphosphorane (54) was heated at 35° in neutral, 3.5% aqueous dioxan for 40 h.



(57)



(58)



(59)

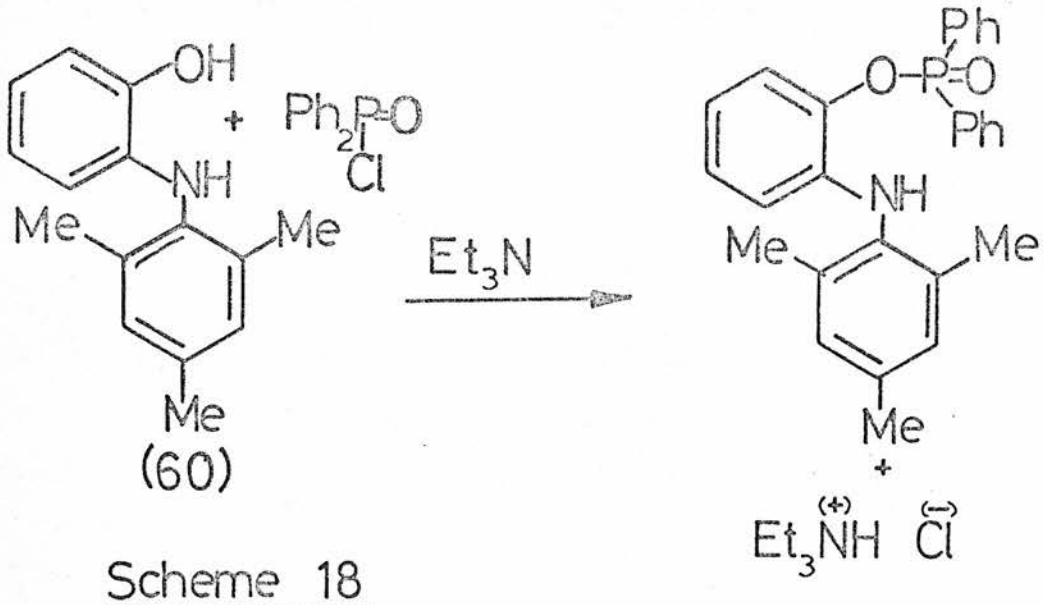
Comparisons of the i. r. and p. m. r. spectra of the major and minor isomers of both hydrolyses leave no doubt that both phosphoranes hydrolyse with predominant cleavage of the same phosphorus-hetero-atom bond, which, under the present structural assignment, is the P-O bond. Thus, the minor products exhibit a characteristic i. r. band in the 3400 cm^{-1} region consisting of a moderately sharp absorption at ca. 3420 cm^{-1} and a broader absorption at lower frequency (see Figure III-6). Furthermore, the major products exhibit sharp, one-proton resonances at ca. 0τ in their p. m. r. spectra and exocyclic N-aryl para methyl resonances upfield of those in the spectra of the corresponding minor products. Accordingly, the major and minor hydrolysis products of (57) are (58) and (59) respectively.

It may be important that the major hydrolysis products (henceforth referred to as the phosphinamides), were thermally unstable with respect to their minor-product isomers (henceforth referred to as the phosphinates). Thus, when the N-p-tolyl-substituted phosphinamide (55) was dissolved in boiling dioxan over several minutes, the N-p-tolyl-substituted phosphinate (56) was obtained in quantitative yield. Furthermore, neither the N-p-tolyl-substituted phosphinamide (55) nor the N-mesityl-substituted phosphinamide (58) exhibited consistent melting points, whereas the phosphinates (56) and (59) melted sharply at lower temperatures.

(ii) Evidence for the assignment of the major and minor, isomeric hydrolysis products.

(ii. 1) Alternative synthesis of the minor isomer

It was believed that treatment of 2-(2', 4', 6'-trimethylanilino)-phenol (60) with diphenylphosphinic chloride should result in O- rather than N-phosphorylation as in Scheme 18. A derivative was isolated in 41% yield and was identified as the minor hydrolysis



Scheme 18

product as would be expected from Scheme 18. This derivative was readily soluble in ether and chloroform, whereas the phosphinamide (58) is relatively insoluble in most cold solvents. No trace of the phosphinamide could be detected in the crude product mixture, nor were there any identifiable side-products.

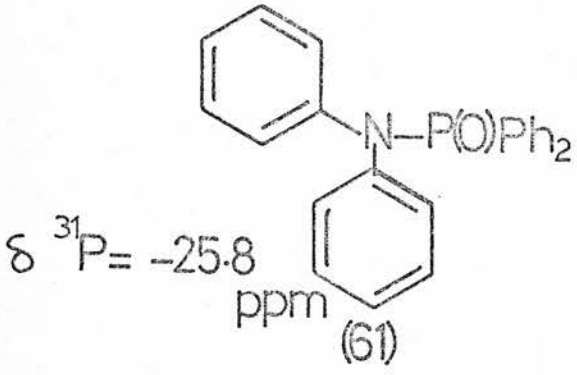
In the forthcoming descriptions, unless otherwise mentioned, the data which is presented for the N-mesityl derivatives is paralleled by similar data for the N-p-tolyl derivatives.

(ii. 2) P.m.r. spectra

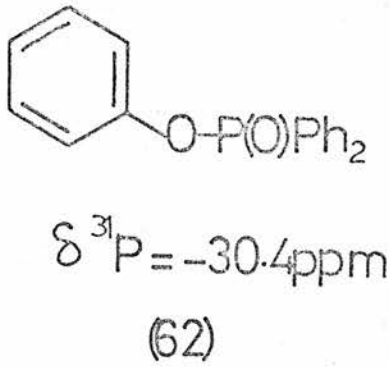
The phosphinate isomer (59) exhibited a broad one-proton resonance at ca. 6.3τ, whereas the phosphinamide isomer (58) exhibited a sharp, one-proton singlet at -0.9τ. These signals are suggestive of arylamino and phenolic protons, respectively.[215]

(ii.3) ^{31}P N.m.r. spectra

The chemical shifts of the two isomeric hydrolysis products were disappointingly uninformative. The phosphinate isomer (59) resonated at -32.5 ppm, whilst the phosphinamide (58) resonated at -32.9 ppm. Comparison with the closest analogues available (61)



(61)

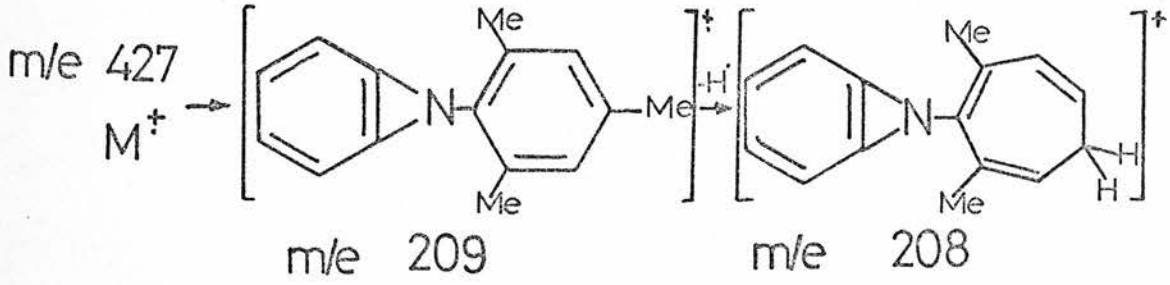


(62)

and (62) (the latter was synthesised by the author), would seem to be valueless.

(ii.4) Mass spectra

These were almost identical for the N-mesityl phosphinate and phosphinamide isomers, which may be a consequence of the tendency of the latter to rearrange thermally to the former. The observed fragmentation is summarised in Scheme 19. There was also a major fragment at m/e 201 (27%), assignable to $(Ph_2PO)^+$.



Scheme 19

The mass spectra of the N-p-tolyl isomers were different, however. The phosphinamide (55) gave a single, significant peak at m/e 201 (38%; $(Ph_2PO)^+$) due to direct fragmentation of the molecular ion. The phosphinate isomer (56) also gave this fragment (82%), but, in addition, a peak appeared at m/e 308 (32%) which fragmented directly, by loss of a proton, to m/e 307 (27%). These latter fragments

correspond to the sequential loss of the p-tolyl group, followed by a proton. Either isomer could have fragmented in this way.

(ii.5) I.r. spectra

The major hydrolysis products - the phosphinamides (55) and (58) - gave little information in their i.r. spectra. The spectrum for (58) is reproduced in Figure III-5. There were no obvious N-H or O-H absorptions. In contrast, the spectra of the phosphinates (56) and (59) provided some valuable indications. The i.r. spectrum of the N-mesityl phosphinate is reproduced in Figure III-6, together with the i.r. spectra of diphenylamine and phenyl diphenylphosphinate with which there were strong similarities. Thus, a moderately sharp absorption at 3420 cm^{-1} parallels the unbonded N-H absorption of diphenylamine at 3430 cm^{-1} and the C=C stretch at 1600 cm^{-1} is strong in both diphenylamine and the N-mesityl phosphinate (59), but not in the corresponding phosphinamide (58). Both the N-mesityl phosphinate (59) and phenyl diphenylphosphinate exhibit intense absorptions at 925 cm^{-1} ((P)-O-C stretch) and strong, sharp absorptions at ca. 1115 cm^{-1} and 1130 cm^{-1} (P-O-C deformations).

(ii.6) Ferric chloride test.

The N-p-tolyl phosphinate and phosphinamide isomers (56) and (55) were dissolved in methanol and each solution was treated with a drop of aqueous ferric chloride solution. Due to solubility problems, concentrations were low and colour changes were indistinct. However, a faint-green coloration was observed for the phosphinamide (55) and a temporary, yellow precipitate for the phosphinate (56) suggesting, once again, that the former is phenolic[223] and the latter is a non-phenolic amine.[223]

(ii.7) Summary

The evidence is generally inconclusive. However, i.r. and p.m.r. spectroscopic evidence, with support from the ferric chloride test suggest the assignments proposed which, for clarity, are reproduced in Scheme 20.

Fig.Ⅲ-5 I.r. spectrum

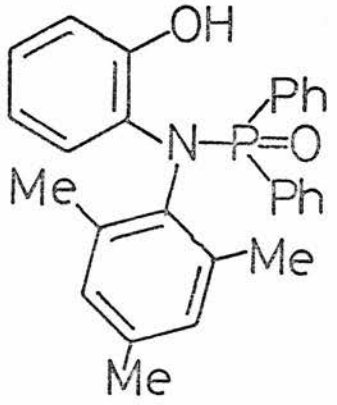
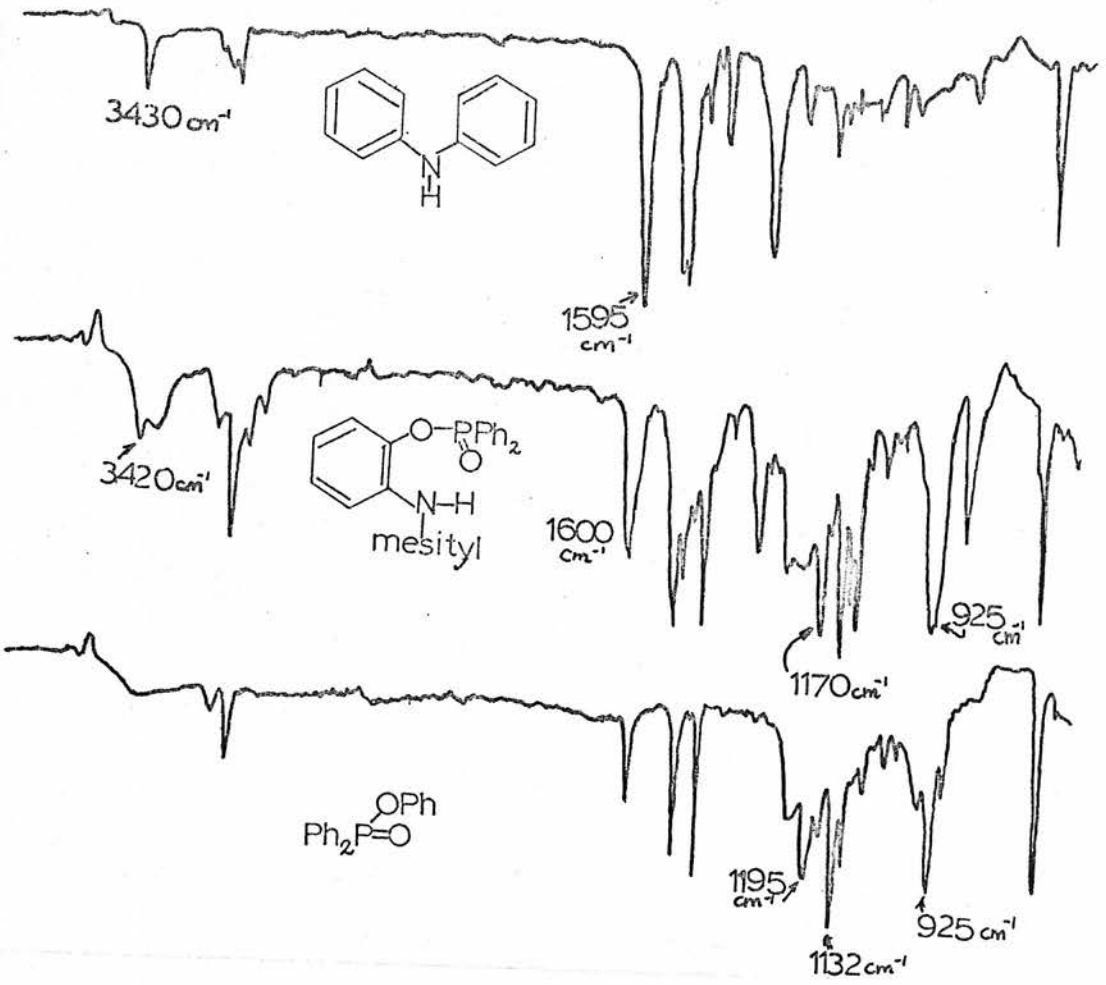
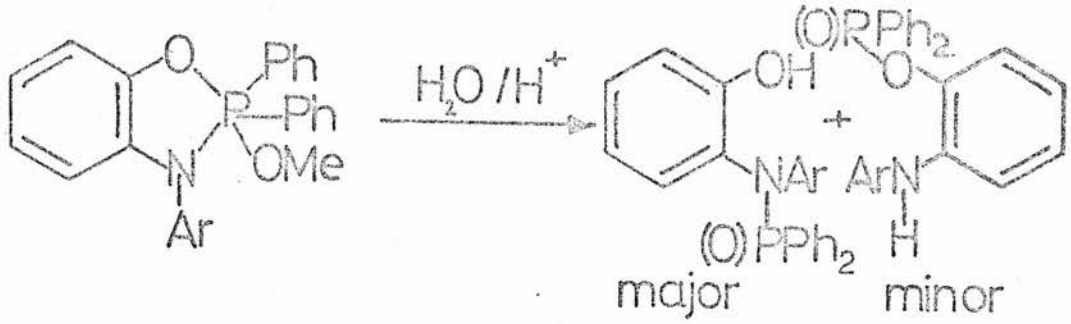


Fig III-6 I.r. spectra



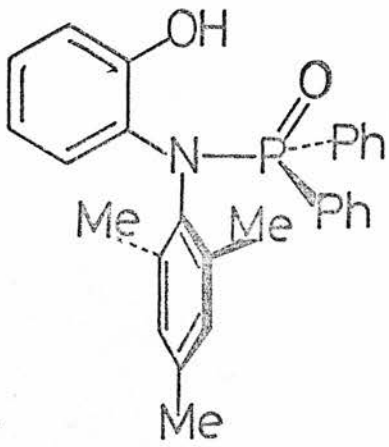


Scheme 20

Chemical evidence for the assignment is lacking, an attempted methylation of the N-p-tolyl phosphinate and phosphinamide isomers with diazomethane gave the same complex mixtures of products. Similarly, as will become apparent, no conclusion can be drawn from the formation of only one product by phosphorylation of the related anilinophenol, (ii. 1) above.

(iii) Low temperature p. m. r. spectrum of N-(2-hydroxyphenyl)-N-mesityl-P,P-diphenylphosphinamide.

A solution of the major hydrolysis product, the N-mesityl phosphinamide (58) in methylene chloride was cooled in the p. m. r. probe. The resulting spectral changes are reproduced in



(58)

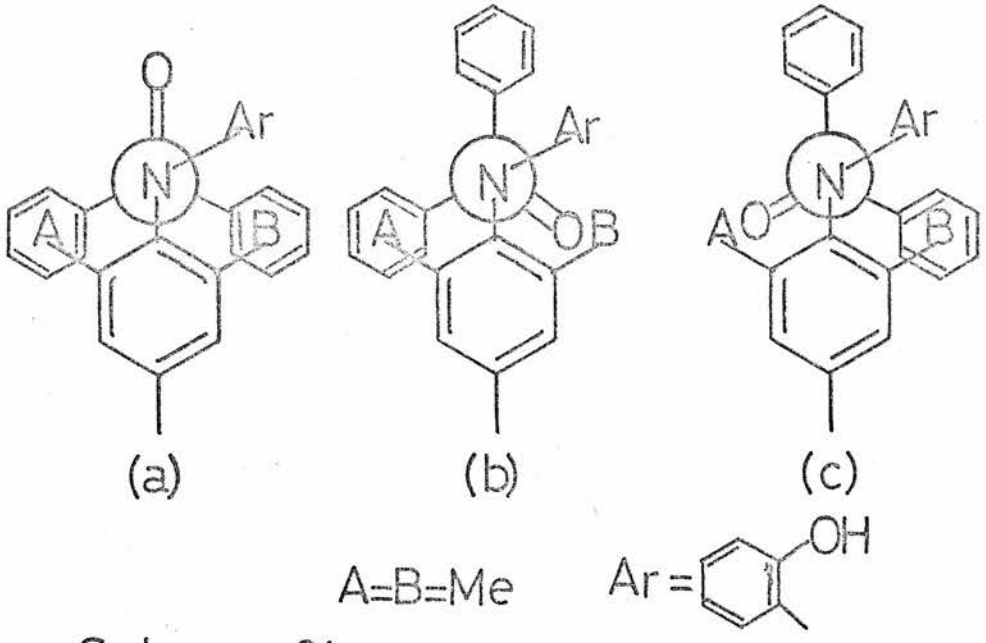
Figure III-7. At -85° to -90° there was evidence of non-equivalence between the N-mesityl o-methyl groups. Such non-equivalence is hard to explain for either of the isomeric hydrolysis products of the N-mesityl parent phosphorane. However it could arise through

Fig. III-7

Variable-Temperature p.m.r. study on:

restricted rotation about the P-N bond of (58).

If it is assumed that the more stable forms of (58) have the "staggered" conformation as in Scheme 21 and that (b) and (c)



Scheme 21

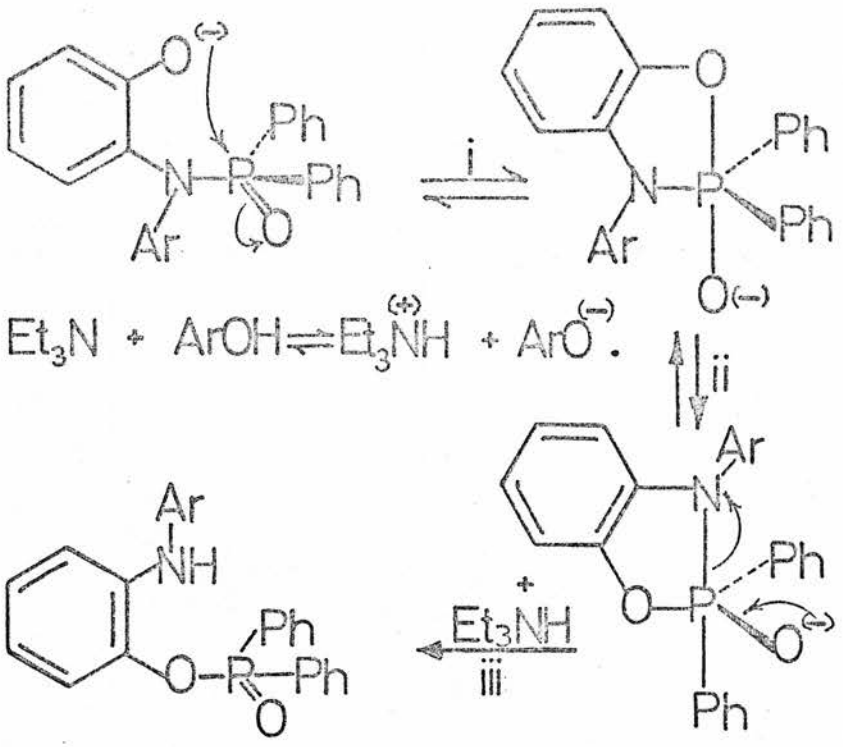
are the more highly-populated conformers, then when the rotation becomes slow, there should be two distinct environments for the mesityl o-methyl groups due to the shielding effect of the P-phenyl group acting on only one of the o-methyl groups. The nitrogen atom has been drawn in pyramidal form; however, rapid inversion at nitrogen should not upset this argument.

(iv) The base-catalysed rearrangement of N-(2-hydroxyphenyl)-P,P-diphenyl-N-p-tolylphosphinamide

The N-p-tolyl phosphinamide (55) rearranged quantitatively to the phosphinate isomer (56) when a solution of the former was warmed at 35° in the presence of 1 mol equivalent of triethylamine. The half-life of the reaction was ca. 40 min. A similar, complete rearrangement was observed in the case of the N-mesityl analogue of (55) by ^{31}P n.m.r. spectroscopy.

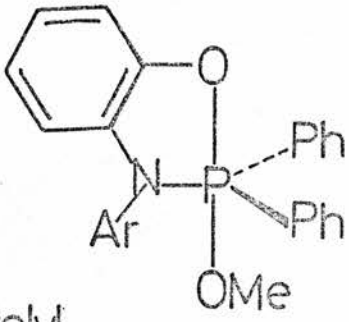
These observations mean that whichever isomer was formed first during the phosphorylation of the anilinophenol (§4.(a)(ii.1) above), only the phosphinate isomer should ultimately be obtained, as was the case.

This rearrangement may be rationalised in the following way (Scheme 22). Intramolecular attack by phenoxide can occur at faces opposite the phenyl or phosphoryl groups but not opposite the amino



Scheme 22

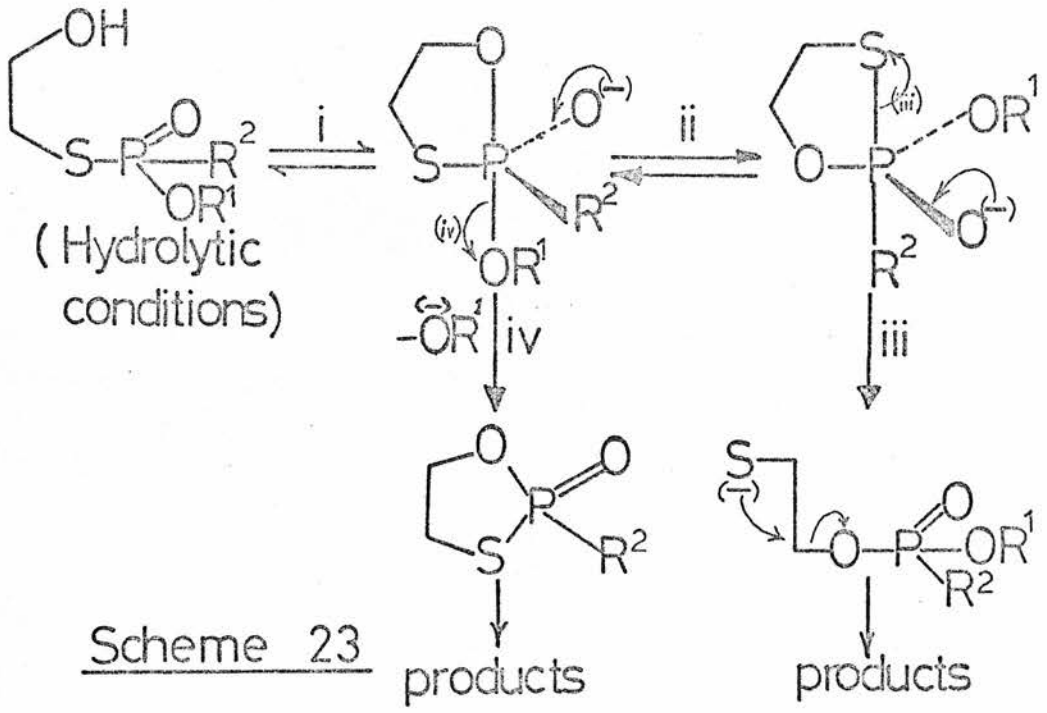
ligand as this would result in diapical placement of the five-membered ring. Attack opposite the phosphoryl group may be kinetically preferred as, in this way, electrostatic interaction is minimised.[81] Step (ii) involves a PI process similar to that which has been shown to be absent in the parent phosphorane (61) although the steric inhibition will be the same in this case. There is ample evidence, however,



(61)

Ar=p-tolyl
or mesityl.

that in contrast to the apicophilic methoxy ligand, the oxygen anion is highly apicophobic since favourable pd-π charge delocalisation is possible from the equatorial positions.[53] This equatorial preference has been exhibited in the work of De Bruin et al.,[224] Kirby et al.[100] and Cremer et al.,[96] amongst many others. Furthermore, there is evidence that the apicophilicity of the phenyl group is superior to that of the oxygen anion. Thus Gay and Hamer[225] presented evidence for the following reaction scheme (Scheme 23). When R^2 was an alkoxy group, reaction occurred



Scheme 23

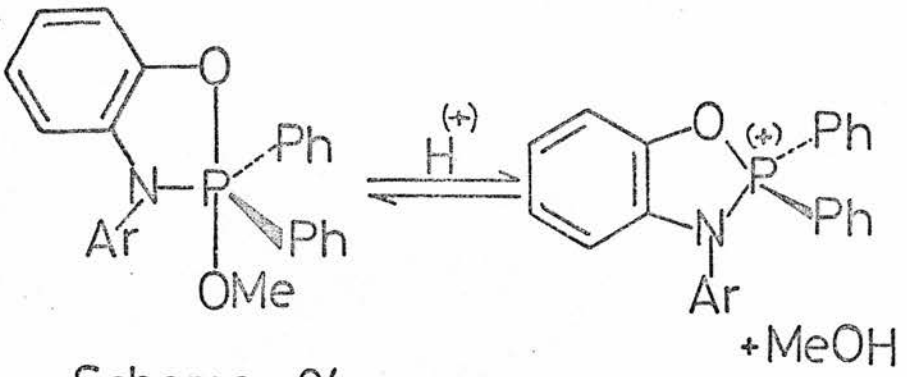
exclusively via step (iii) due to the favourability of the PI process (step (ii)) and the departure of the better leaving group. When R^2 was a phenyl group, step (ii) became less favourable owing to the necessity of placing this group in an apical position. Thus, 28% of the reaction proceeded via step (iii) whilst 72% proceeded via step (iv). When R^2 was an oxygen anion, reaction proceeded exclusively via step (iv).

In Scheme 22, step (iii) is probably aided and made irreversible by the bulk of the arylamino group.

(v) Rationalisation of the hydrolysis

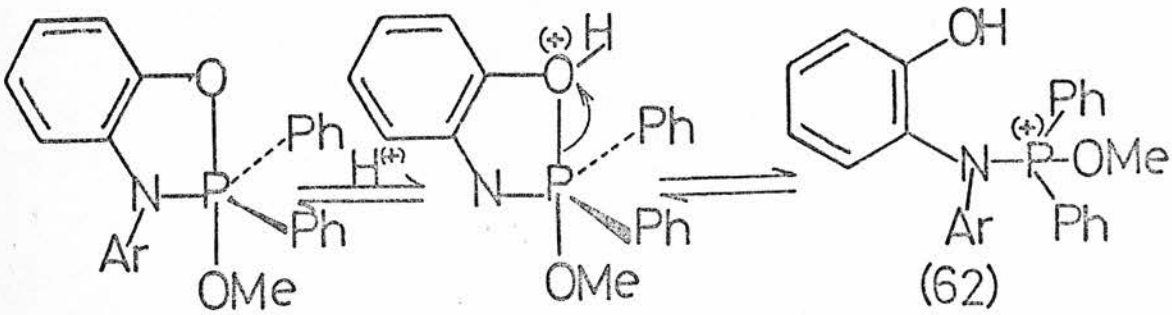
A control experiment has shown that the minor hydrolysis product, the phosphinate (56), does not rearrange to the major product, the phosphinamide (55), under the conditions of hydrolysis, (acidic, aqueous dioxan at 35°).

In theory, hydrolysis of the phosphorane to the phosphinamide- (55) or (58) - may occur by attack of water on either a preionised, phosphonium species, or on the neutral phosphorane via an octahedral species.



Scheme 24

Preionisation may occur either by exocyclic cleavage (Scheme 24), or by endocyclic cleavage (Scheme 25). The former

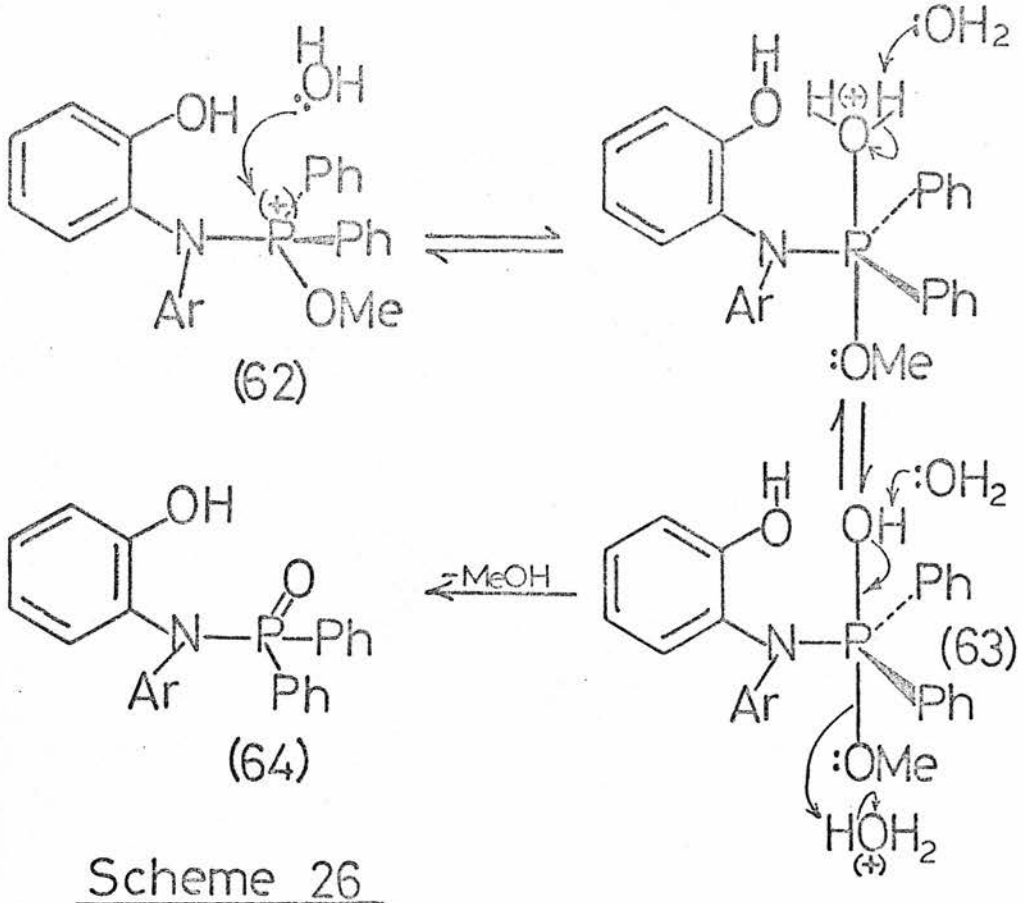


Scheme 25

process is less likely due to the small-ring strain effect. The latter process is therefore the probable mode.

Attack by water (hard solvent) occurs on the phosphonium

centre (hard acid) of (62) in Scheme 26, rather than at the methoxy carbon (soft acid) - HASAB theory.[116] Entry should occur at the tetrahedral face opposite the more electronegative (i. e. methoxy)



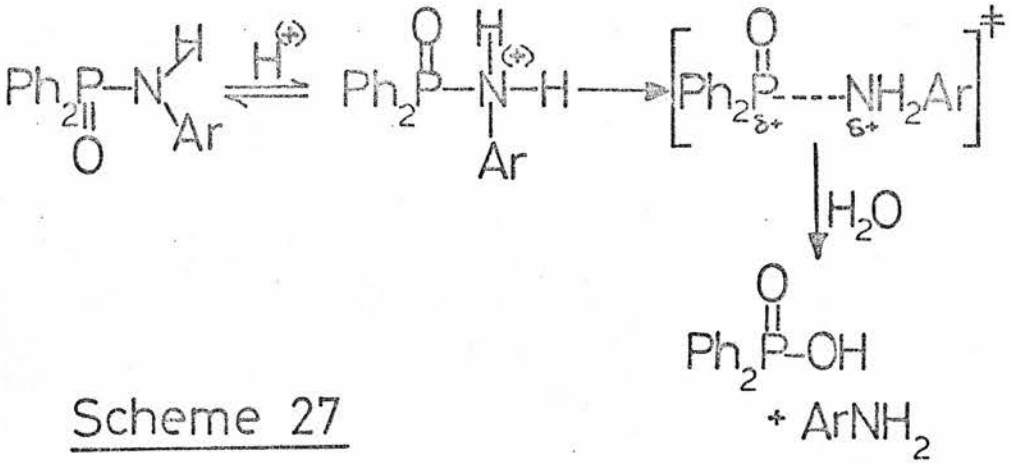
Scheme 26

group, to generate the intermediate (63). PI of this species (63) to allow departure of the amino function is disfavoured as it would require equatorial placement of both apicophilic (hydroxy and methoxy) groups as well as apical placement of phenyl and the bulky amino ligand. Hence P-O cleavage predominates, methanol is eliminated and the observed phosphinamide (64) is formed (Scheme 26).

Attack via an octahedral species is unlikely, considering the products and acid-catalysed nature of the hydrolysis. Ramirez et al.[80] have presented evidence for such a scheme and observed that cleavage was exclusively equatorial. The rate-determining factor in the present hydrolysis would be the rate of the PI process required to place either the methoxy, or the phenoxy group in an

equatorial position. O-Protonation should retard rather than enhance this step.

It is surprising that further hydrolysis of the phosphinamide does not occur. Haake et al.[226] recently presented evidence that the hydrolysis of a series of N-aryl-P,P-diphenylphosphinamides in 10% aqueous dioxan, 0.5M in hypochlorous acid at 25°, proceeds readily by the A1 mechanism in Scheme 27. In particular, when



Scheme 27

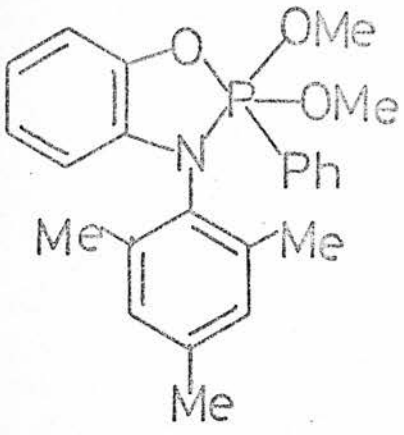
Ar was p-methoxyphenyl, the hydrolytic half-life was ca. 15 min ($10^5 k = 161\ s^{-1}$). However, in our investigation, the acid concentration was only 3% of that above and contained only 50% of the above, water concentration. The lability of the amido group depends strongly upon N-protonation.

The fact that the N-P bond of the initial phosphorane does not cleave in preference to the O-P bond is more readily explainable. The nitrogen lone pair, necessary to allow protonation, is heavily committed to pd-π back donation to phosphorus and delocalisation into the benzoxazaphospholine system (c.f. Haake et al.[123])

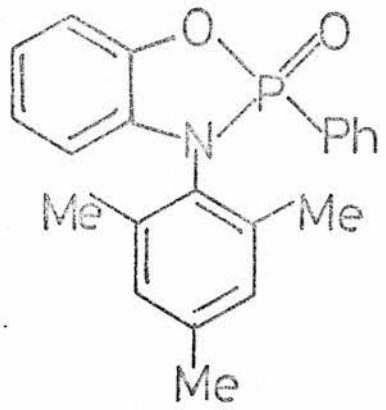
(b) 3-Aryl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine derivatives

(i) 3-Mesityl-2,2-dimethoxy-2-phenyl-2,2-dihydrobenz-1,3,2-oxazaphospholine.

Hydrolysis of the phosphorane (65) in acidic, 2.5% aqueous dioxan at 35° gave after five minutes, ca. 91% of a white, crystalline



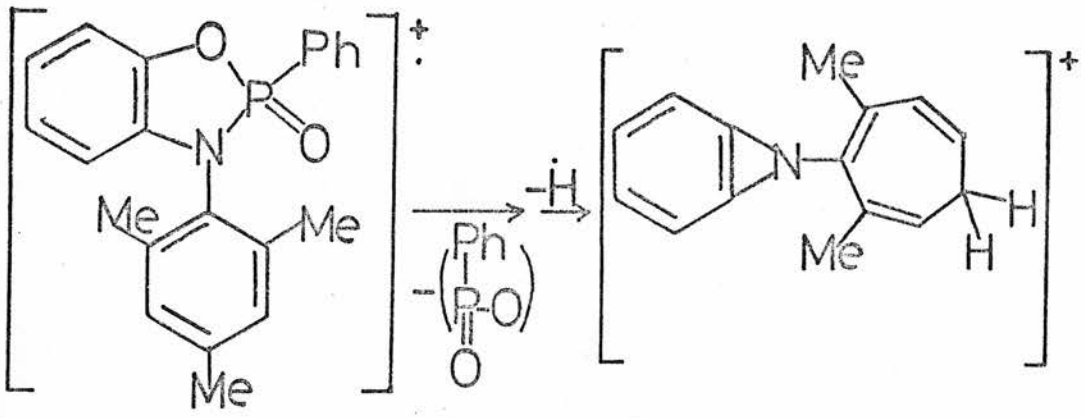
(65)



(66)

powder which was assigned the structure (66), 3-mesityl-2-oxo-2--phenylbenz-1, 3, 2-oxazaphospholine.

All analytical and spectral data were in agreement with this formulation. The mass spectrum exhibited the correct molecular ion at m/e 349 (100%) and the only major fragment was that due to the - by now familiar- pattern (Scheme 28).

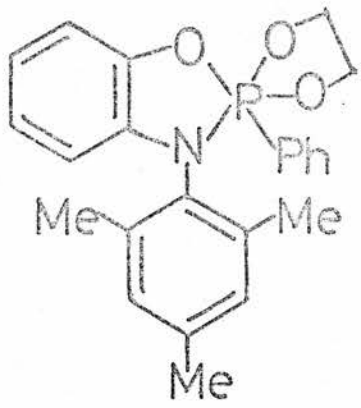


m/e 349 m/e 208

Scheme 28

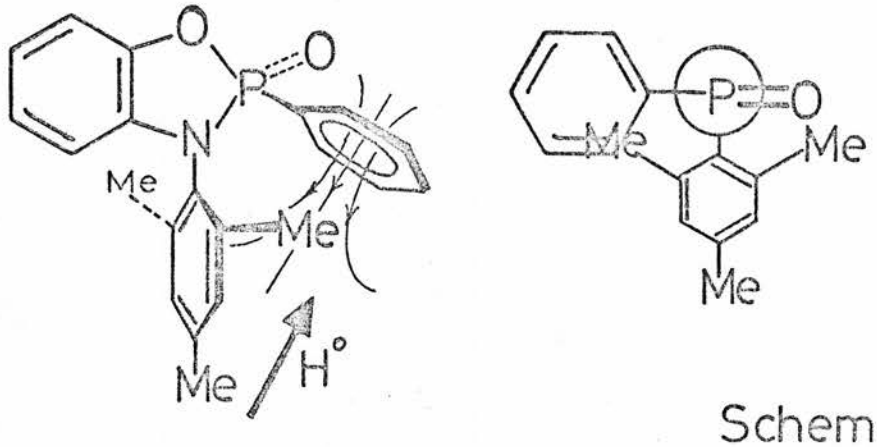
The ^{31}P n.m.r. spectrum showed a broad triplet at -28.6 ppm, the 13.4 Hz coupling constant is assigned to the o-protons of the P-phenyl ring.

The p.m.r. spectrum, in common with that of the spirocyclic phosphorane (67), showed two separate, three-proton singlets (in this



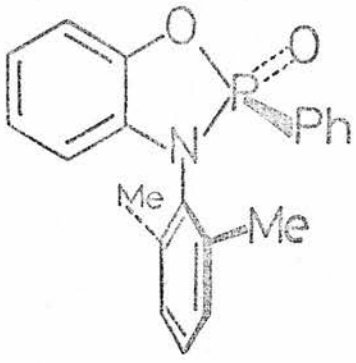
(67)

case separated by ca. 0.9 ppm), due to the o-methyl groups of the N-mesityl function. Furthermore, whereas the meta protons of the N-mesityl function of other phosphoranes resonated as a broad singlet, the meta protons of this cyclic phosphonamidate (66) resonated as two, one-proton singlets, (separated by 0.22 ppm). Rotation of the mesityl ring about the C-N bond is sterically prevented; thus, the methyl group syn to the P-phenyl ring is shielded (Scheme 29).



Scheme 29

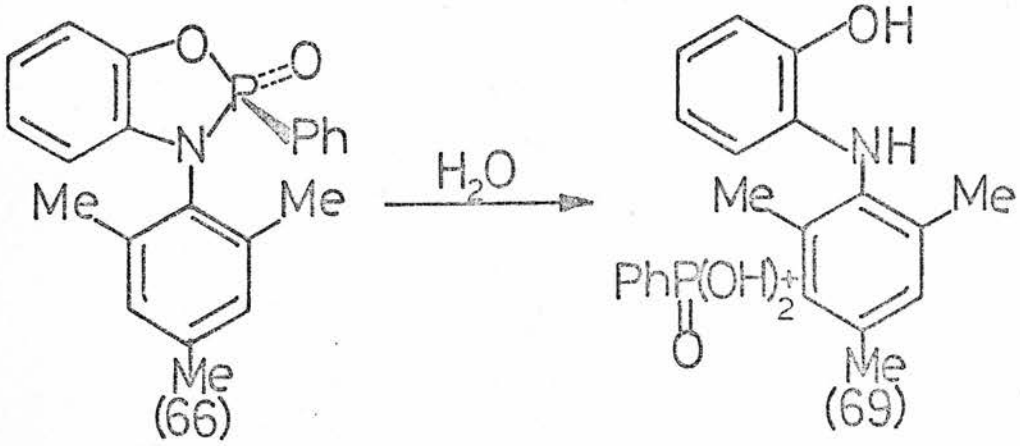
This hypothesis was tested by the synthesis and hydrolysis of 2, 2-dimethoxy-2-phenyl-3-(2', 6'-xylyl)-2, 2-dihydrobenz-1, 3, 2--oxazaphospholine to give the N-(2', 6'-xylyl) analogue (68) of the cyclic phosphonamidate (66). The former compound (68), exhibited two, three-proton singlets separated by 1.06 ppm due to o-methyl groups of the exocyclic N-aryl ring.



(68)

No hydrolysis of the phosphorane (65) in 5% aqueous dioxan at 35° was observable over 1.5 h; however, rapid reaction occurred in the presence of trace amounts of acid. Thus, observation of a 5% aqueous dioxan, neutral solution of the phosphorane in the ^{31}P n.m.r. probe at 35° gave the curves which are reproduced in Figure III-8. Each curve is plotted as an intensity ratio against time for reasons explained in section II.

Hydrolysis was initially very slow, but detectable by the appearance of a resonance due to the cyclic phosphonamidate (66), above. However, after 25 min the hydrolysis accelerated suddenly with the production of the cyclic phosphonamidate as the major product (ca. 74% max) and a minor, so-far unidentified, product resonating at -17.7 ppm. Both products slowly hydrolysed further and a signal at -15.5 ppm, probably due to benzenephosphonic acid appeared. The cyclic phosphonamidate (66) has not been studied in detail, but it is known to hydrolyse under mild conditions to



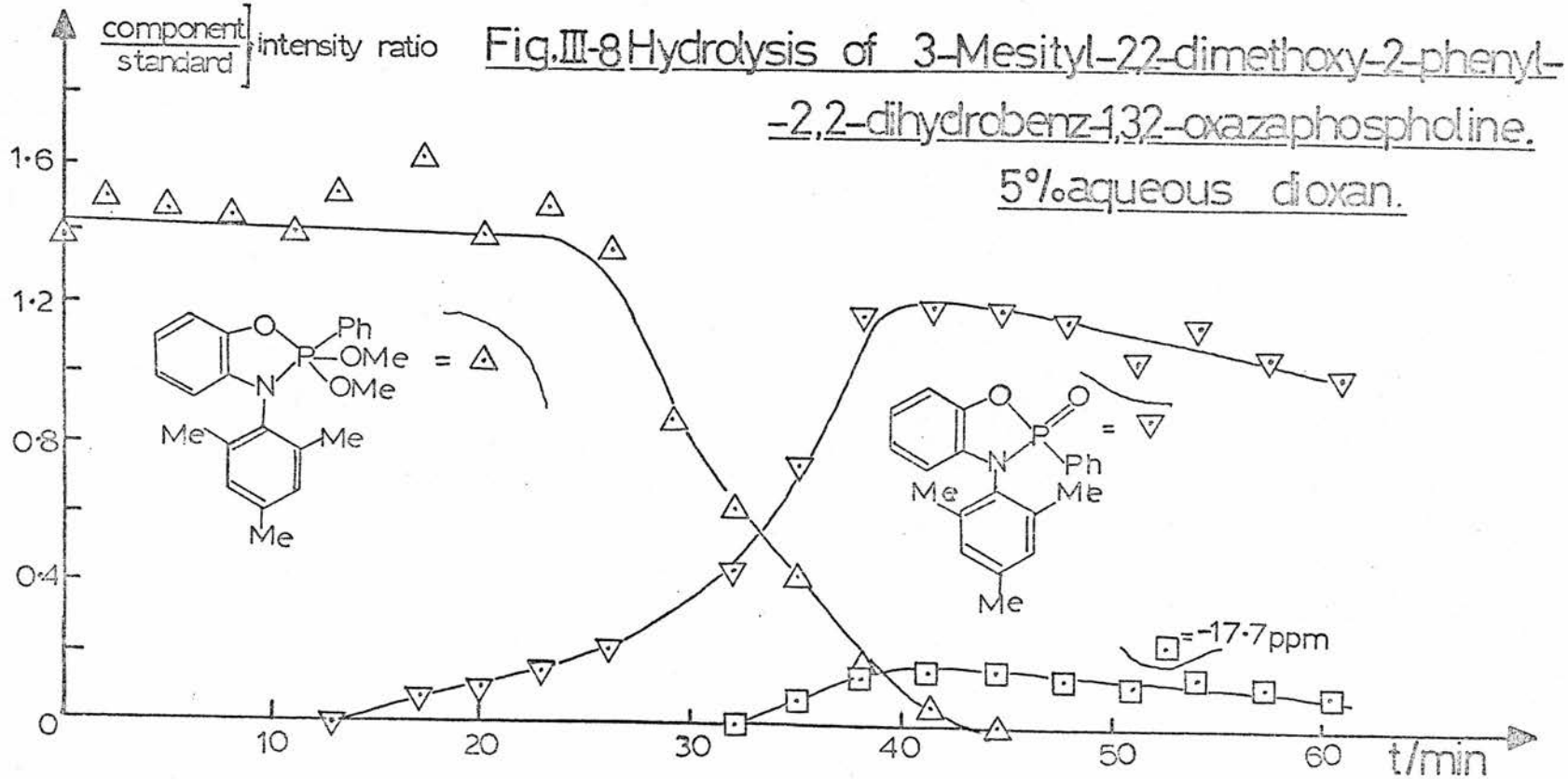
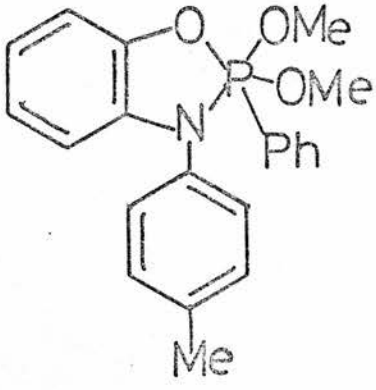


Fig.III-8 Hydrolysis of 3-Mesityl-2,2-dimethoxy-2-phenyl--2,2-dihydrobenz-1,3,2-oxazaphospholine. 5% aqueous dioxan.

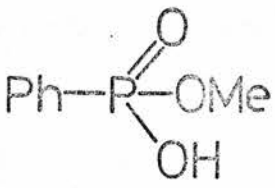
2-(2',4',6'-trimethylanilino)phenol (69). No intermediate acyclic ester has been detected so far, but any such species would be acidic and could catalyse the hydrolysis.

To test this theory of acid-catalysis the phosphorane was hydrolysed in the ^{31}P n.m.r. probe under similar conditions but in the presence of 0.016 M toluene-4-sulphonic acid. The phosphorane disappeared in less than 1 min to be replaced immediately by product resonances at -27.8 ppm due to the cyclic phosphonamidate (66) as above and a resonance at -19.0 ppm which is, as yet, unidentified. Calibration for the cyclic phosphonamidate (66) was unreliable, but the peak-height ratio was 84:16 respectively. Due to the differing intensifications of resonances by the nuclear Overhauser effect, which depend upon the relative proximities of decoupled protons, this cannot be taken as more than a rough guide of yield. Both products were observed to react further over the following 19.5 h, after which time, only ca. 5% of the original concentration of the unknown remained but ca. 72% of the cyclic phosphonamidate (66) was left. The products of these further decompositions were observed as relatively broad resonances at -18.3 ppm and -16.1 ppm in a peak-area ratio of ca. 1:3 respectively. The major product (-16.1 ppm) was identified as benzenephosphonic acid by the addition of a sample of the pure material. The identity of the resonance at -18.3 ppm is unknown; however, some speculation can be made as to its possible structure. As will be discussed in the following section, hydrolysis of the N-p-tolyl analogue (70) of the phosphorane in question, gave as a final hydrolysis product a



(70)

compound with an identical chemical shift. This, and further evidence (to be discussed), suggests that these resonances are due to the same material, which is therefore most probably methyl hydrogen benzenephosphonate (71). Obviously, identical resonance positions of products from hydrolysis of two different substrates could be fortuitous, and might occur in this case within the phosphinate ester

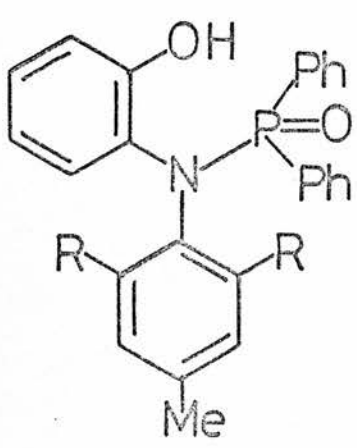


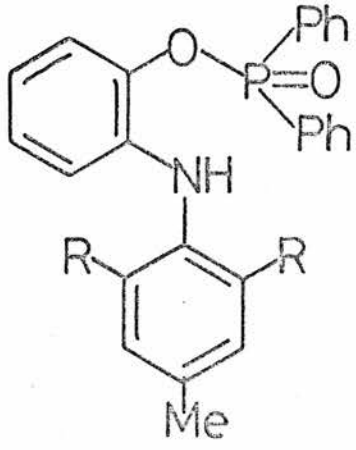
(71)

(72).....R = H.....(74)

(73).....R = Me...(75)

pairs (72), (73) and (74),(75) since the differing features within these pairs are remote from the phosphorus nucleus. However, comparison of the chemical shifts of the four compounds (76), (77), (78) and (79) indicate that a detectable difference should be expected.





R=H ; (76); $\delta^{31}P$ = -30·8ppm | R=H ; (78); $\delta^{31}P$ = -33·2ppm

R=Me; (77); $\delta^{31}P$ = -32·9ppm | R=Me; (79); $\delta^{31}P$ = -32·5ppm

($CDCl_3$)

The identity of the unknown at -17.7 ppm in the "initially neutral" hydrolysis was most probably methyl benzenephosphonate as well. The resonance was relatively broad and pH-dependent shift-changes of this magnitude (0.6 ppm), have been recorded (p. 169). This resonance appeared after 34 min when the cyclic phosphonamidate (66) concentration was high but the phosphorane concentration was low. This suggests that this component (-17.7 ppm) was formed from the cyclic phosphonamidate (66).

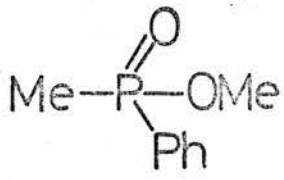
In contrast, the minor, primary product of the acid-catalysed hydrolysis (resonating at -19.0 ppm), must have been formed directly from the phosphorane. It appeared immediately, but disappeared more rapidly than the cyclic phosphonamidate (66).

In conclusion, the cyclic phosphonamidate (66) was formed directly from the phosphorane by an acid-catalysed process. In the presence of acid, a secondary hydrolysis product was formed, also from the phosphorane.

No dimethyl phenylphosphonate was observed in either reaction. There was no evidence that the minor hydrolysis product of the acid-catalysed process (resonating at -19.0 ppm), decomposed to the cyclic phosphonamidate (66), nor was there firm evidence for any intermediate between the phosphorane and the cyclic phosphonamidate (66). However, the intermittant appearances of resonances at -43.2 ppm and at -21.8 ppm in the "initially neutral" hydrolysis were recorded.

In agreement with these observations, when the hydrolysis of the phosphorane (65) was observed in $CDCl_3$ or a 50:50 (v/v) mixture of $CDCl_3$:CD_3COCD_3 with one drop of D_2O at 23°, hydrolysis was observed to give eventually, only two detectable products, which were the same cyclic phosphonamidate (66) and methanol. No other products containing either methoxy functions or the mesityl ring were observed. Nevertheless, three unknown resonances were observed during the course of the hydrolysis, which increased and decreased together, suggesting that they belonged to the same molecule. In $CDCl_3$ these resonances were as follows: a doublet

(J 11 Hz) at 6.34τ and two singlets at 7.54τ and 7.82τ. The doublet and the former singlet were in intensity ratio 1:1 and, whereas the latter singlet was of the same peak-height as the former singlet, accurate integration was impossible due to the presence of other resonances in the same region. Assuming that the doublet was due to a 3-proton species; the product ratio after 30 min (in $CDCl_3$:CD_3COCD_3), consisted of 19% of the phosphorane, 33% of the cyclic phosphonamidate and 48% of the unknown. The apparent intensity equivalence of the upfield singlets of the unknown suggested that they might not be due to mesityl methyl groups and might therefore be due to a phosphorus-split, methyl resonance in a substance such as methyl methylphenylphosphinate (80). The latter is in fact excluded by the observed τ values; furthermore, the absence of

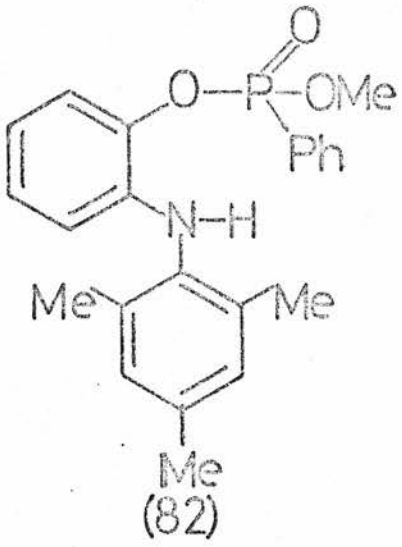


(80)

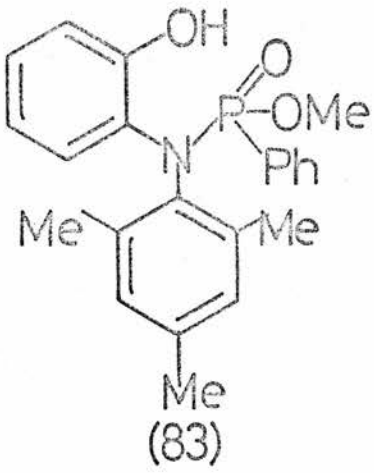
(81)

2-(2',4',6'-trimethylanilino)phenol (81) or any other mesityl-containing species (apart from the cyclic phosphonamidate (66)) in the final product mixture, suggests that these resonances must be due to an intermediate or intermediates in the formation of the cyclic phosphonamidate. It seems probable that they all correspond to a single compound. It is suggested that this intermediate is one of the two acyclic esters (82) or (83).

The consideration of possible mechanisms is postponed until the hydrolysis observations on the p-tolyl analogue (84) have been discussed.

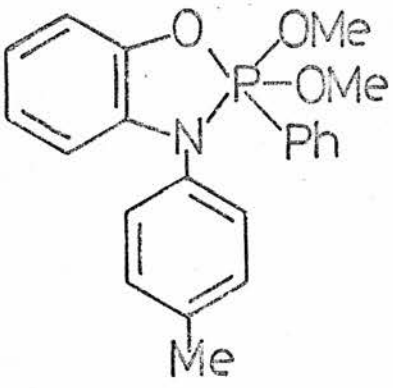


(82)

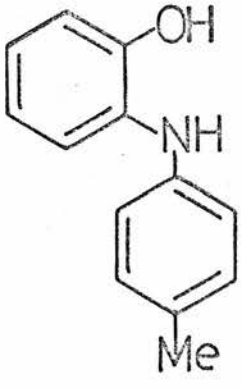


(83)

(ii) 2, 2-Dimethoxy-2-phenyl-3-p-tolyl-2, 2-dihydrobenz--1, 3, 2-oxazaphospholine



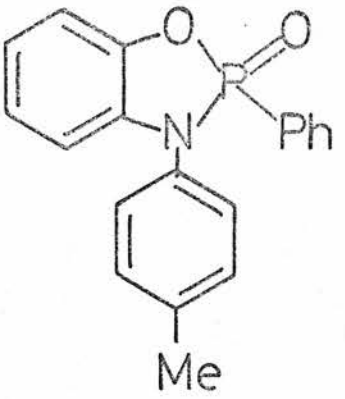
(84)



(85)

(ii. 1) The hydrolysis

When this phosphorane was hydrolysed in neutral, 5% aqueous dioxan at 30°, the phosphorane had disappeared after ca. 5 h. The products were identified as 2-p-toluidinophenol ((85); ca. 95%) and dimethyl phenylphosphonate (77%). Some acidic, water-soluble material was also isolated but not identified. Titration indicated a 6% yield of a monobasic species. Although some 2-oxo-2-phenyl-3-p-tolybenz-1, 3, 2-oxazaphospholine (86) was detected by g.l.c., none could be isolated.

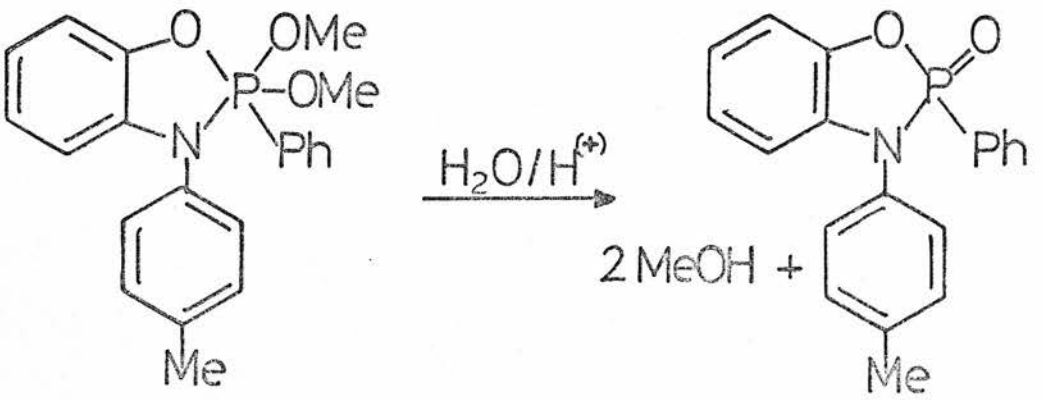


(86)

A control experiment, in which a solution of benzenephosphonic acid and 2 mol equivalents of methanol dissolved in dioxan were heated at 30° for 5 h, showed that dimethyl phenylphosphonate was not derived from this source. Similarly, dimethyl phenylphosphonate was not formed when the cyclic phosphonamidate (86) was heated with methanol at 60°. Further experiments have shown that dimethyl phenylphosphonate is formed directly by hydrolysis of the phosphorane.

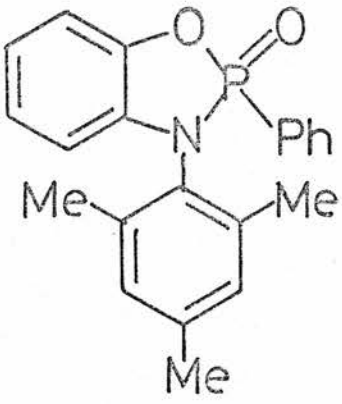
In contrast, when the phosphorane was heated at 60° in 20% aqueous dioxan, no phosphorane remained after 2 h. The major products were benzenephosphonic acid (74%) and 2-p-toluidinophenol (85) above,(99%); less than 10% of dimethyl phenylphosphonate was detected by p.m.r. spectroscopy.

2-Oxo-2-phenyl-3-p-tolylbenz-1, 3, 2-oxazaphospholine (86), has been isolated twice. In both cases when the parent phosphorane (84) was recrystallised from dry cyclohexane. It is suggested that traces of water may have been present and that acidic impurities catalysed the process in Scheme 30.

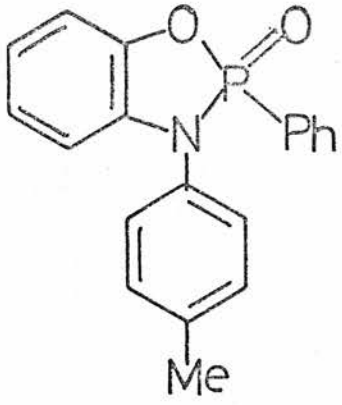


Scheme 30

The spectral and analytical data were compatible with this structure. It has become apparent that, unlike the N-mesityl analogue (66), the N-p-tolyl cyclic phosphonamidate (86) is very susceptible to hydrolysis. Due to the small-ring effect, the slow

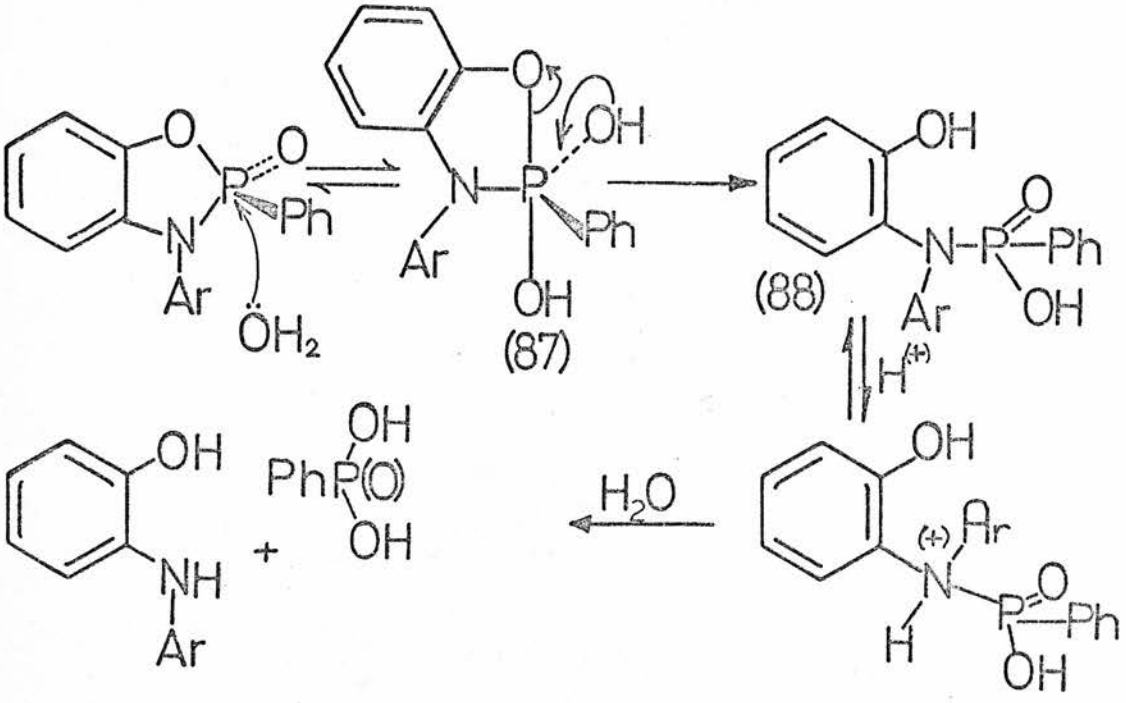


(66)



(86)

hydrolysis of the N-mesityl compound (66) is the more anomalous. The difference may be rationalised as in Scheme 31, by assuming that water attacks the phosphorus atom opposite the more electronegative ring ligand (oxygen), to give the intermediate (87). The

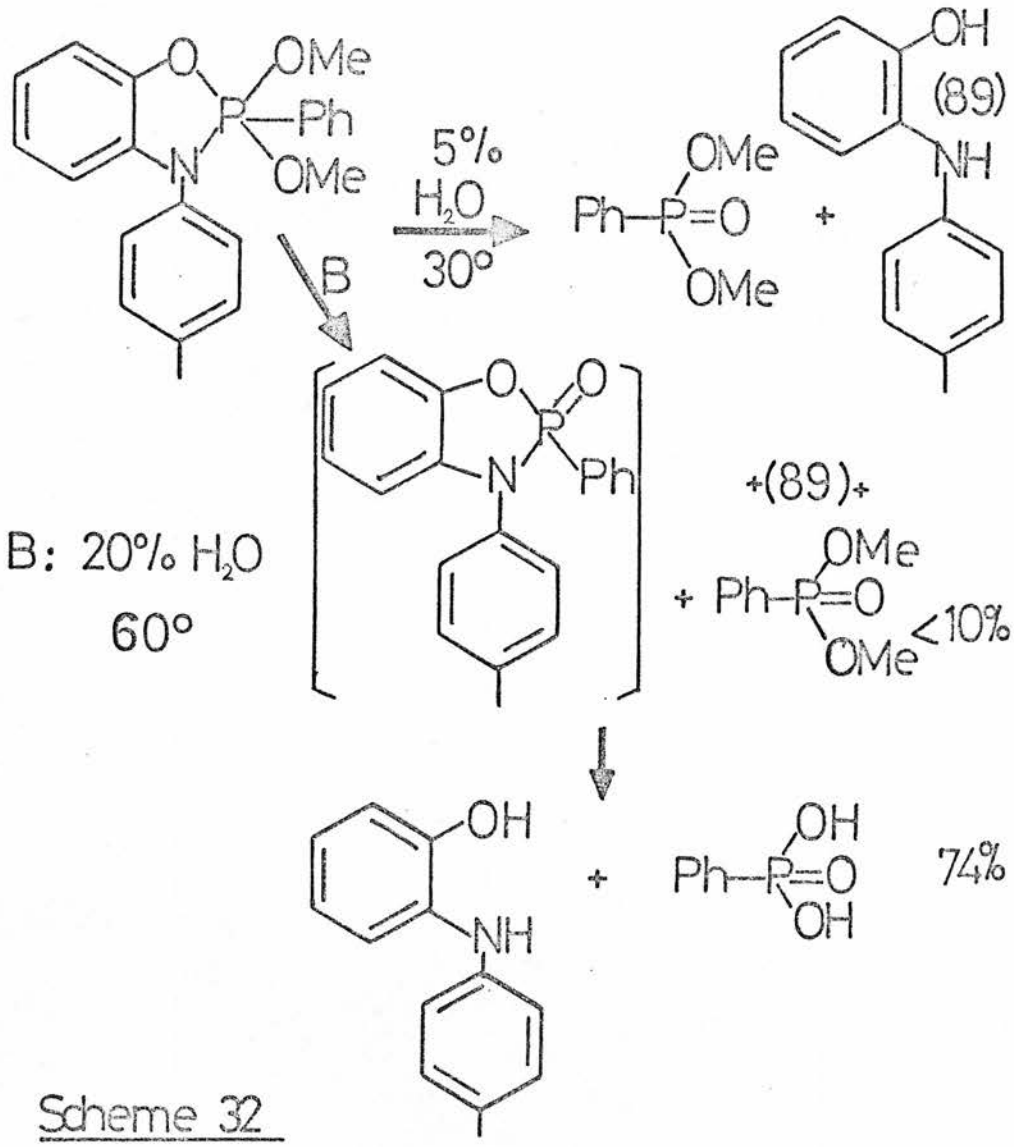


Scheme 31

ring cleaves at the apical P-O bond. The phosphonamidate (88), so formed, will be acidic, protonation[226] and consequent labilisation of the amide group will occur, resulting in hydrolytic cleavage of the P-N bond[226] to give the products observed in the hydrolysis at 60°.

It is suggested that the relatively slow hydrolysis of the N-mesityl cyclic phosphonamidate is due to the additional steric hindrance encountered by water in approaching the tetrahedral face adjacent to the N-aryl substituent, due to the presence of o-methyl groups.

The results of both hydrolytic reactions are shown in Scheme 32.



Scheme 32

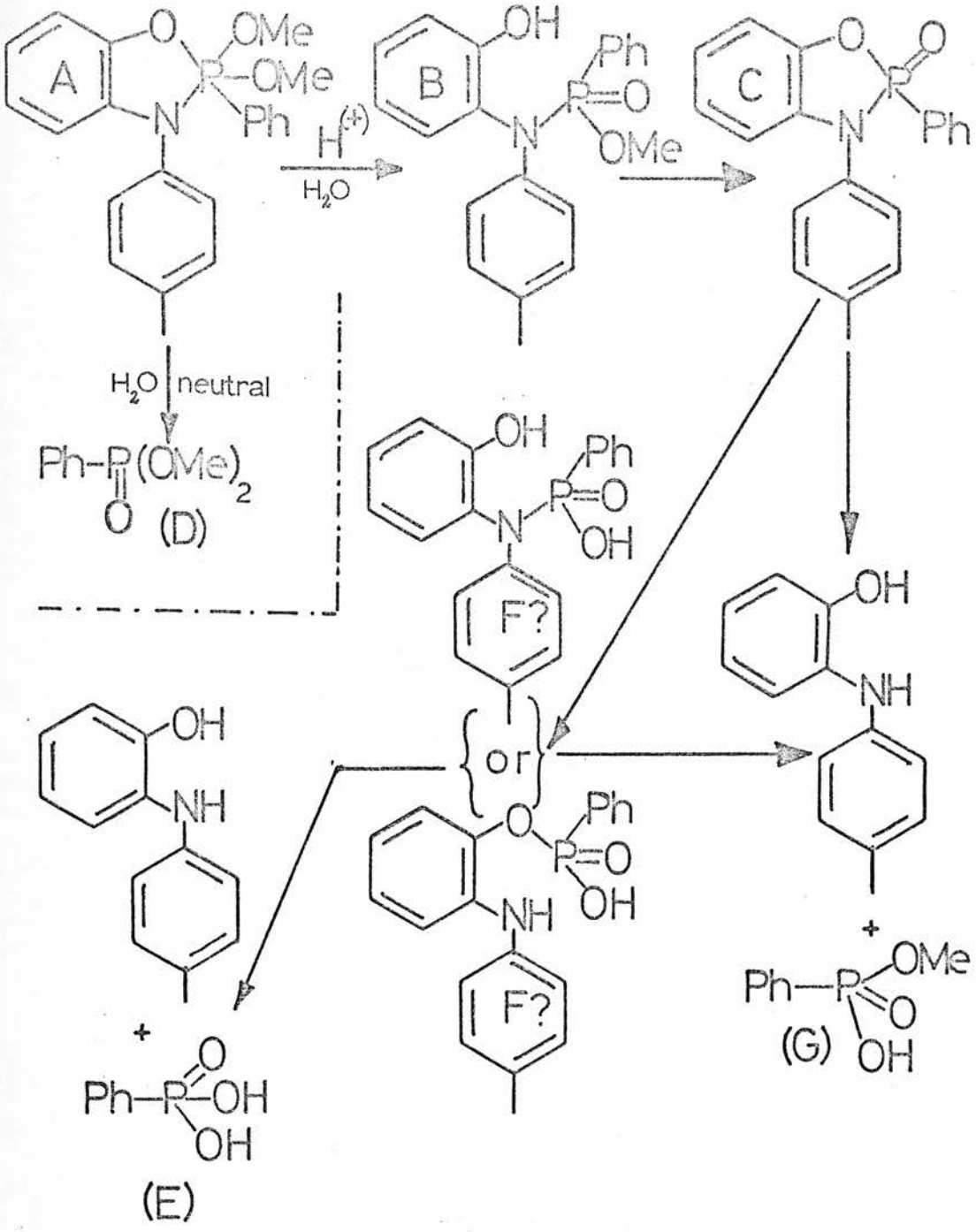
The hydrolysis of this phosphorane in 5% aqueous dioxan was observed in the ^{31}P n.m.r. probe at 35°. In the absence of

the n. m. r. calibrant-$(EtO)_3P=O$- no hydrolysis was observed over 95 min. However, in the presence of ca. 1 mol equivalent of calibrant, a slow hydrolysis was observed with a half-life of ca. 13 min. The solution remained essentially neutral throughout. The major product was dimethyl phenylphosphonate (ca. 73%); two minor products appeared at -20.0 ppm and at -18.1 ppm. The -20.0 ppm resonance disappeared 90 min after the disappearance of the phosphorane resonance.

A barely discernible resonance appeared intermittantly at -28.6 ppm identified as the cyclic phosphonamidate (86).

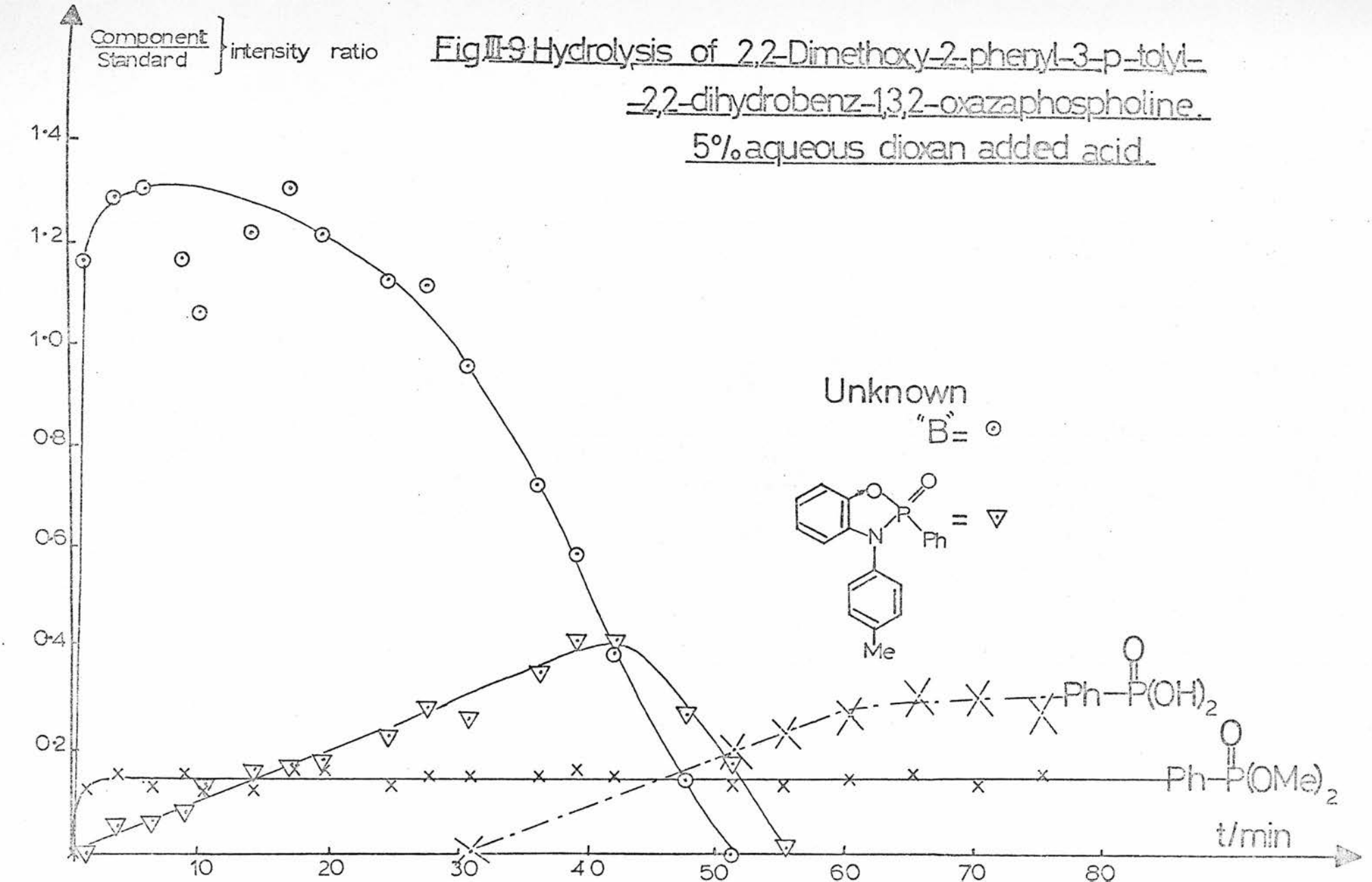
The hydrolysis was then observed in acidic solution. The evidence obtained has suggested the sequence of events and products in Scheme 33. The justification for this scheme will be developed in the following pages. Attention is drawn to the letters in Scheme 33, by which the materials will be named in this discussion.

(SCHEME 33 OVER.)



Scheme 33

When a minimum amount of solid toluene-4-sulphonic acid was added to a neutral, aqueous dioxan solution of the phosphorane, the phosphorane resonance was replaced immediately by a major resonance at -20.0 ppm (assessed as ca. 90% yield; named hereafter as B) and dimethyl phenylphosphonate (ca. 11%; D). The course of the hydrolysis, thereafter, is plotted in Figure III-9. Clearly,


Component / Standard } intensity ratio
Fig III-9 Hydrolysis of 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine.
5% aqueous dioxan added acid.
1·4
1·2
1·0
0·8
0·6
0·4
0·2
Unknown
"B" = ⊙
Ph
= ▽
Me
Ph–P(OH)2
Ph–P(OMe)2
t/min
10
20
30
40
50
60
70
80

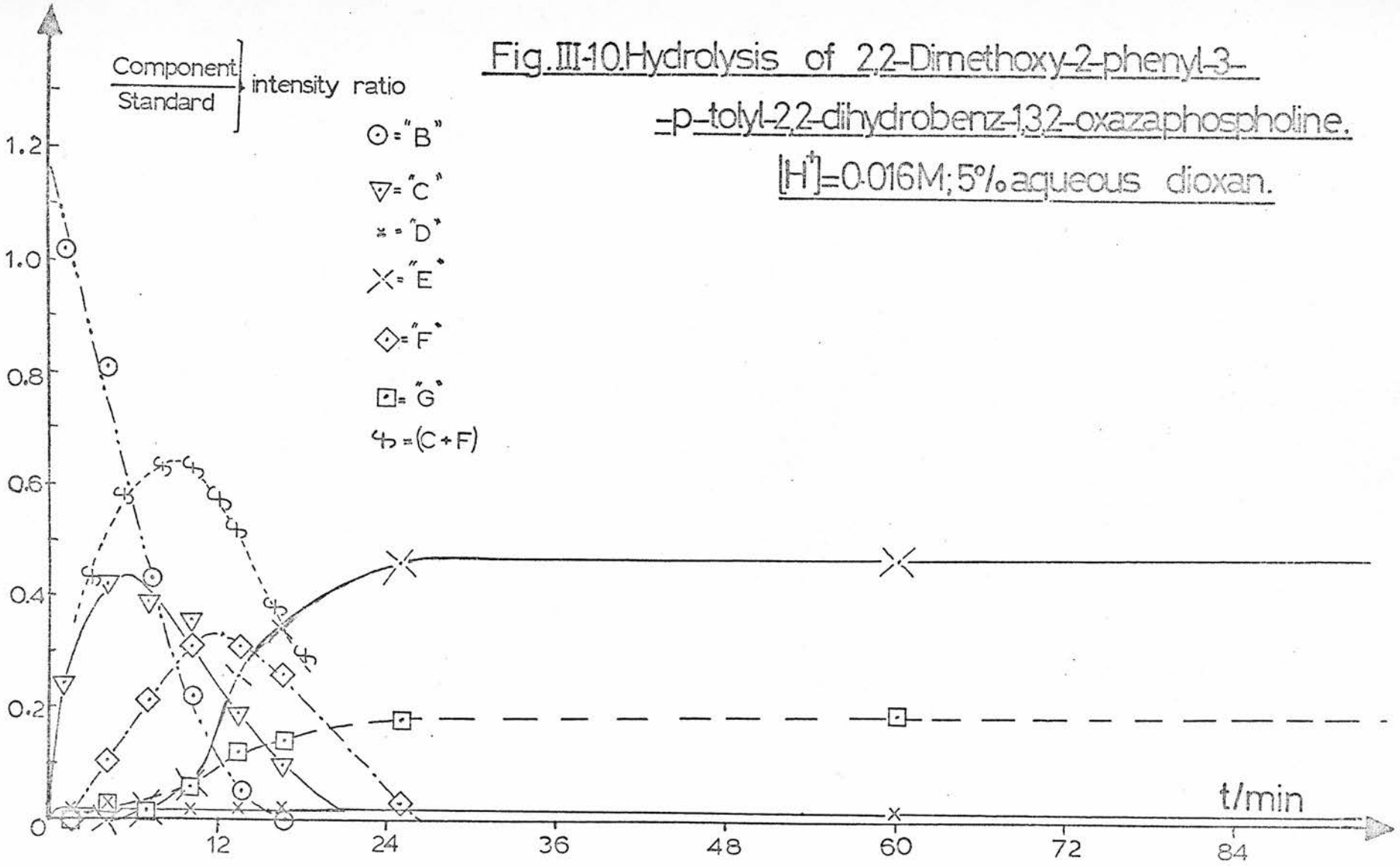
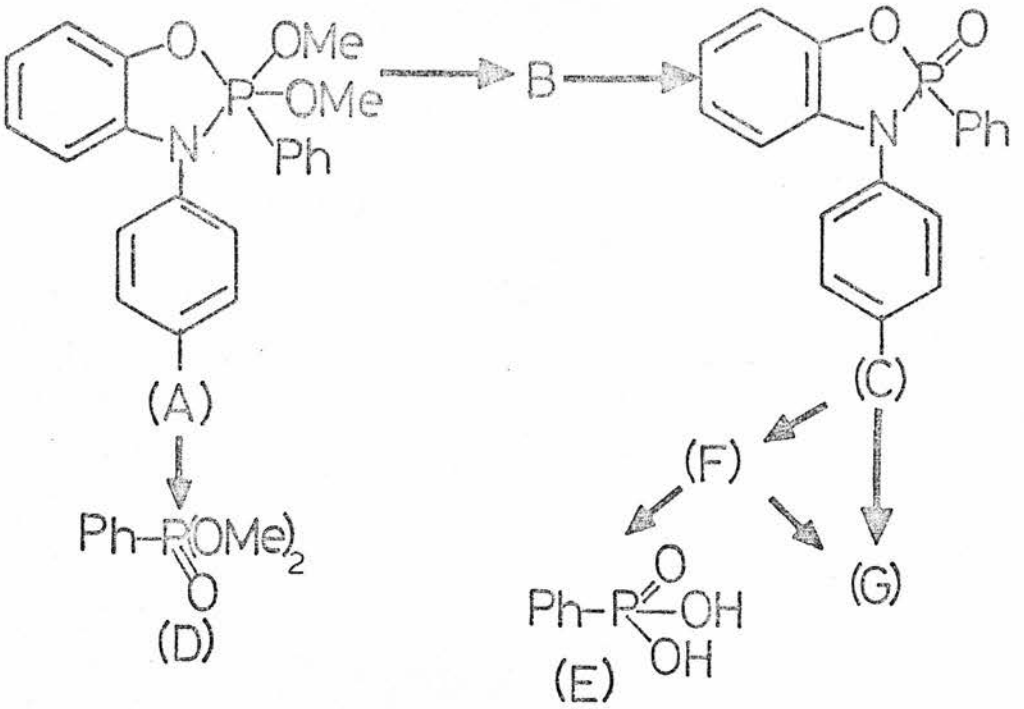


Fig. III-10. Hydrolysis of 2,2-Dimethoxy-2-phenyl-3-p-tolyl-2,2-dihydrobenz-1,3,2-oxazaphospholine. $[H^+]$=0.016M; 5% aqueous dioxan.

dimethyl phenylphosphonate (B) can only have been formed from the phosphorane, since the concentration remained steady after the disappearance of the phosphorane. In contrast, the unknown (B) decayed to the cyclic phosphonamidate (86 or C), which decomposed, in turn, to benzenephosphonic acid (E). The unconventional shape of the curve due to B is unexplained.

When the same hydrolysis was observed in the presence of a 0.016M concentration of toluene-4-sulphonic acid, the curves in Figure III-10 were obtained. General trends are the same; the phosphorane disappeared in less than 1 min to be replaced by the unknown intermediate (B), and a very small (<3%) yield of dimethyl phenylphosphonate (D). The subsequent behaviour was complex and in caution it is noted that these reactions were performed under unbuffered conditions. However, the position of maximum slope in the curve representing the production of a third component (F; -16.8 ppm) corresponds approximately with the maximum in the curve representing the cyclic phosphonamidate (C; -28.6 ppm). Furthermore, the point of maximum slope in the curve representing the production of benzenephosphonic acid (E; -15.8 ppm) corresponds with the maximum in the curve representing F rather than that representing **C**. The curve representing the production of the other major final product (G; -18.2 ppm) has a point of maximum slope which corresponds, most closely, to the curve representing the variation of the combined concentrations of the cyclic phosphonamidate (C) and the unknown (F). These observations suggest the sequence of products in Scheme 34.

The hydrolysis was also observed in the presence of less acid (10^{-4}M), the results were somewhat erratic. However, the following facts were of interest. Dimethyl phenylphosphonate was the major product but its rate of production was slower than in neutral solution, the yield was still high (ca. 80%). The minor products were once again B, G and an intermittant resonance due to the cyclic phosphonamidate (C). The hydrolysis was not followed



Scheme 34

to completion, which explains the non-appearance of benzene-phosphonic acid (E).

The above results all suggest, that the cyclic phosphonamidate (C) is not formed directly from the phosphorane but is produced via an intermediate. This intermediate (B) is formed by an acid-catalysed process. Dimethyl phenylphosphonate is, in contrast, only formed from the phosphorane and by a reaction which is probably not catalysed by acid. Thus, no more dimethyl phenylphosphonate can be formed after the disappearance of the phosphorane, consequently the yield was decreased in the presence of acid.

(ii. 2) Hydrolysis observed by pmr. spectroscopy

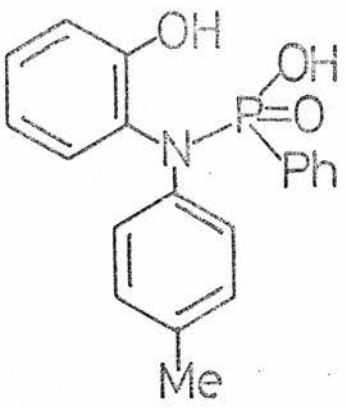
The results of these experiments are recorded in section II-6 (c). In $CDCl_3$:CD_3COCD_3 (50:50 v/v) with one drop of D_2O, the phosphorane hydrolysed to give dimethyl phenylphosphonate (ca. 25%), 2-p-toluidinophenol and an unknown whose spectrum

consisted of a doublet at 6.35τ (J=11Hz) without any accompanying tolyl p-methyl resonances. Assuming that this doublet was due to a single methoxy group, the yield was assessed as 13%. A second unknown whose spectrum consisted of a doublet at 6.30τ (J11Hz) and a singlet at 7.80τ (ratio 1:1), was also observed during the hydrolysis. As these latter signals declined, the resonance due to 2-p-toluidinophenol and a singlet at 7.70τ assigned to the cyclic phosphonamidate (C) increased. The latter resonance finally disappeared as well. These results are compatible with Scheme 34 if the second unknown is the intermediate (B) and the first unknown is the minor final product (G).

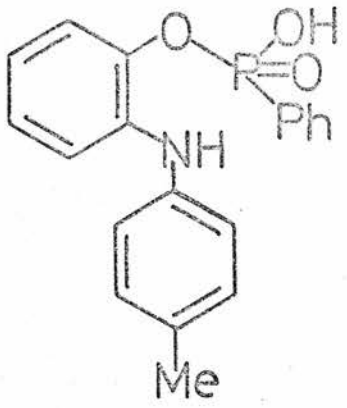
To test this correlation, a solution of the phosphorane in $CDCl_3$:CD_3COCD_3 (50:50 v/v) was treated with one drop of 2N aqueous HCl and observed by pmr spectroscopy. The phosphorane resonances were replaced immediately by resonances due to methanol and the signals assigned to the intermediate (B) in the previous paragraph. As these latter resonances declined, resonances attributable to the cyclic phosphonamidate (C) appeared and increased over the subsequent 24 min. After this time, resonances due to 2-p-toluidinophenol increased rapidly and the cyclic phosphonamidate (C) resonances declined.

It was observed that the singlet at 7.70τ-assigned to the intermediate (B)-persisted after t=24 min (at which time the corresponding doublet at 6.30τ disappeared). It is suggested that this chemical shift position is occupied by both the p- tolyl methyl resonance of B and the resonance of the same group in the unknown, described as F in Scheme 34, above. As no methoxyl doublet accompanies this latter resonance, a demethoxylated ester is indicated which is most probably either (90) or (91).

From t=24 min to t=2 h.35 min, a doublet at 6.4τ (J 12Hz), was observed to increase. At the latter time, the only resonance in the methyl region was assignable to 2-p-toluidinophenol. Assuming that this doublet was due to the resonance of one methoxyl, the yield of this component was ca. 45%. Comparison of this result

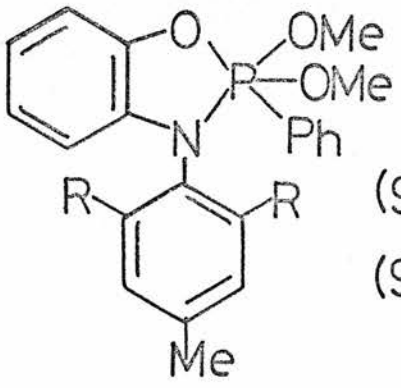


(90)



(91)

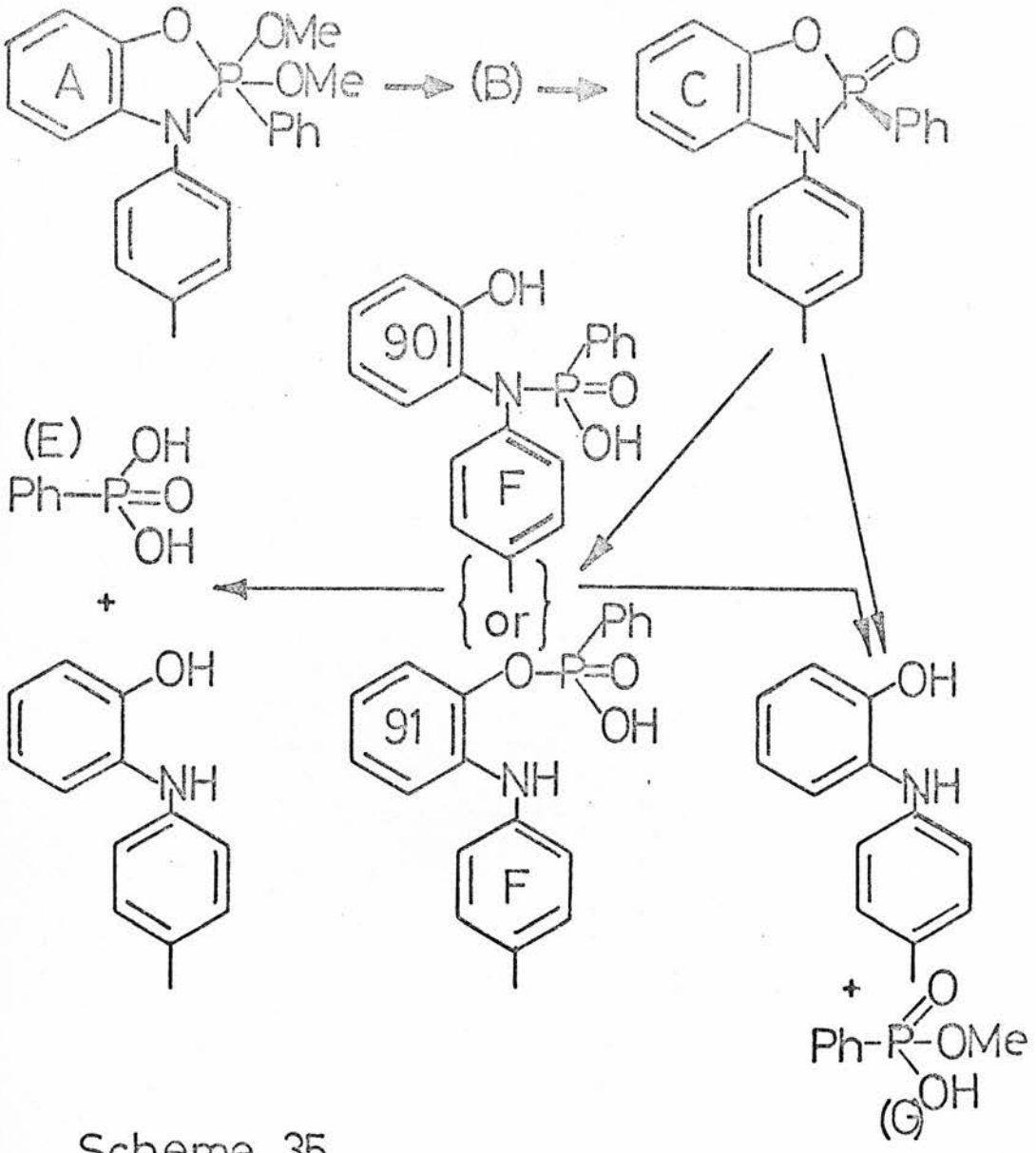
with the observation, above, of a ^{31}P n.m.r. resonance at -18.3 ppm (G) which was the final hydrolysis product from both of the phosphoranes (92) and (93), suggests that this component is methyl hydrogen



(92): R = Me

(93): R = H

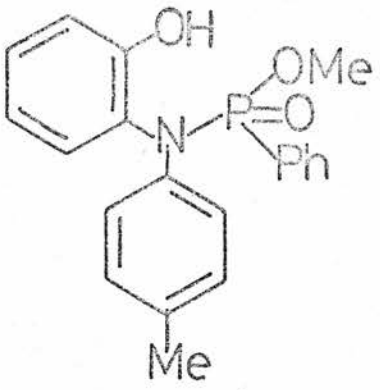
benzenephosphonate. Hence, an updated version of Scheme 34 is now possible (Scheme 35).



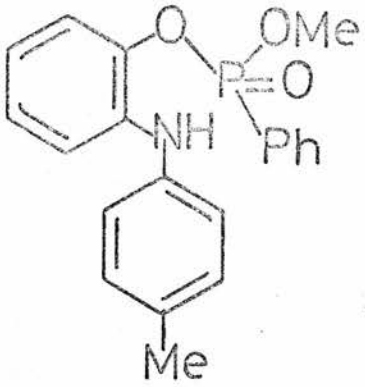
Scheme 35

(ii. 3) The identity of the intermediate (B)

The ^{31}P n. m. r. chemical shift of -20. 9 ppm suggests a tetracoordinate phosphorus species. A solution of the parent phosphorane in $CDCl_3$ was treated with one drop of 2N HCl as above. The phosphorane p. m. r. resonances were replaced immediately (less than 30 s), by a resonance due to methanol and a species containing 13 aromatic protons, a three-proton doublet at 6. 25τ (J_{P-O-Me} 11Hz) and a three-proton singlet at 7. 77τ. These signals strongly suggest one of the structures (94) or (95).

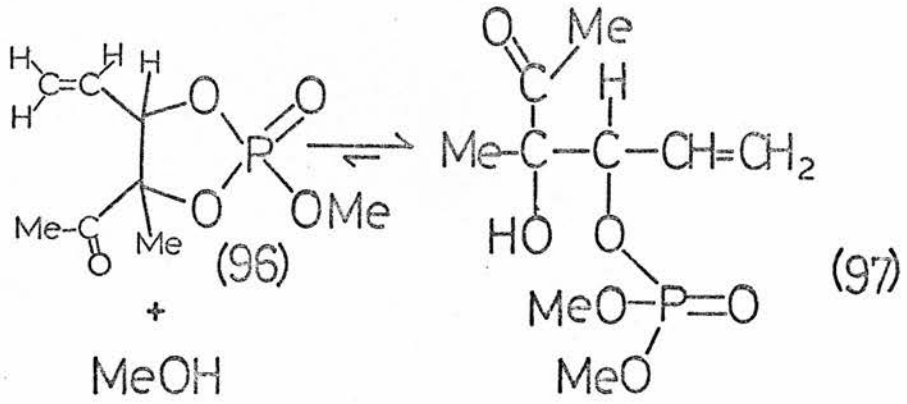


(94)



(95)

Ramirez et al.[176] have shown that the cyclic triester (96) reacts readily with methanol to give the acyclic triester (97). It



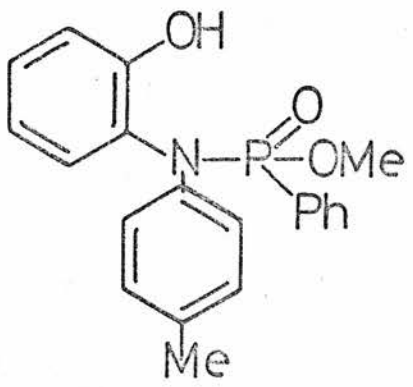
was considered therefore that a possible route to one of the isomers (94) or (95) might lie in a similar reaction between the cyclic phosphonamidate (86) and methanol .

When the latter materials were heated together at 60°, g.l.c. indicated the formation of a product in ca. 50% yield within 35 min; however, no change in the ratio of the cyclic phosphonamidate to this product was observed after 90 min when the ratio was 1:4 respectively. Evaporation gave a material in >90% yield. The p.m.r. spectrum of this product was compatible with either of the expected acyclic esters. The mass spectrum showed the correct parent ion at m/e 353 (50%) and a direct fragmentation pattern to the cyclic phosphonamidate, m/e 321 (100%). An anomalous feature was the appearance of a peak at m/e 199 (100%) apparently due to the loss of formaldehyde and a (PhPO) fragment. The sample had been kept

for several days and hydrolysis may have occurred to 2-p-toluidinophenol, which has a parent ion with this mass to charge ratio.

The i. r. spectrum showed great similarity to that assigned above to 2-p-toluidinophenyl diphenylphosphinate, with an additional strong peak at 1045 cm^{-1} assigned to the P-O-Me stretch. On this evidence, the product was assigned the structure of the O-P isomer (95) above, methyl 2-p-toluidinophenyl phenylphosphonate. All attempts to repeat this preparation have resulted in only very small yields of this product and neither analytical, nor ^{31}P n. m. r. data have been obtained so far.

Comparison of the p. m. r. spectrum of (95) with that of the hydrolysis intermediate (B) revealed significant differences. In $CDCl_3$: CD_3COCD_3 (50:50 v/v) the methoxyl doublet of the intermediate (B) resonated at 6. 3τ (J_{P-O-Me} 11Hz) whereas that of (95) resonated at 6. 16τ (J_{P-O-Me} 11Hz). The p-tolyl methyl resonance of the intermediate appeared at 7. 80τ, whilst that of (95) appeared at 7. 72τ. Furthermore, the aromatic region of the intermediate contained a prominent singlet at 3. 03τ whilst a similar singlet in (95) resonated at 3. 00τ. Superposition of the spectra also suggested that the two compounds were not the same. On this basis, the intermediate (B) is tentatively assigned the structure (94), methyl N-(2-hydroxyphenyl)- N-p-tolyl-P-phenylphosphonamidate.



(94)

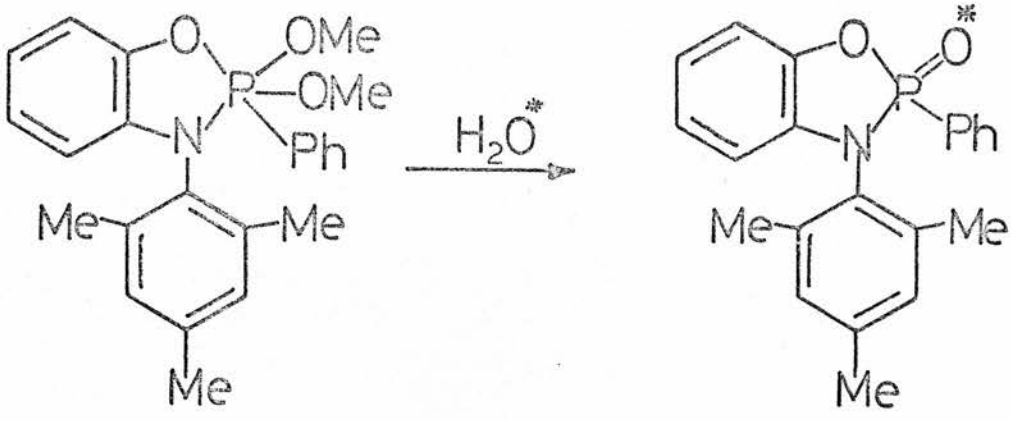
(iii) Further mechanistic guides

Several further observations have been made which bear on

the mechanism of hydrolysis of the above pair of aminotrioxyphosphoranes.

(iii.1) H_2O^{18} Studies

When the N-mesityl phosphorane (98) was hydrolysed under "neutral" conditions it was found that one atom of oxygen from the enriched water was incorporated into the cyclic phosphonamidate (99) as in Scheme 36. However, a separate experiment showed that

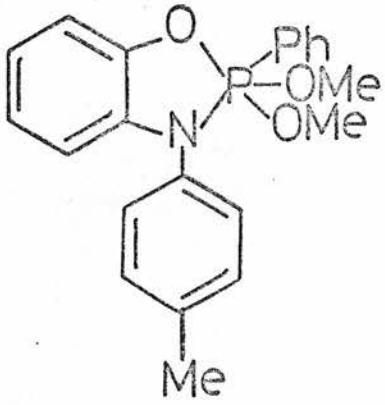


(98) Scheme 36 (99)

[N.B. (99b): O* is natural]

under the same conditions the cyclic phosphonamidate (99b) completely exchanged one oxygen atom with enriched water. Thus, the previous result was inconclusive.

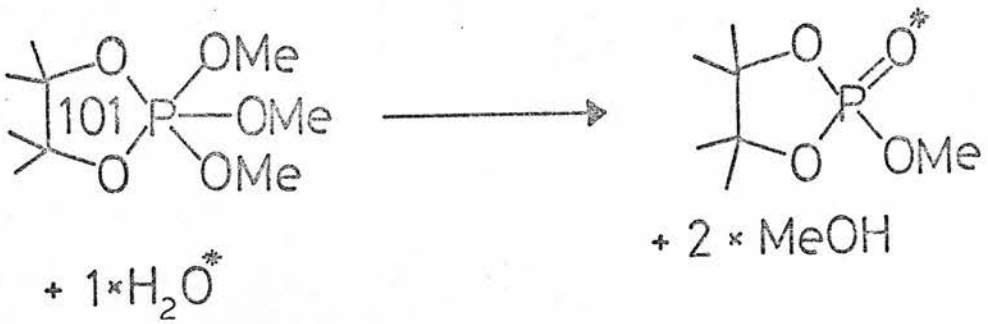
Accordingly, the methanol obtained from the hydrolysis of both the N-mesityl and N-p-tolyl phosphoranes (98) and (100) in 5%



(100)

aqueous dioxan, 0.016 M in toluene-4-sulphonic acid was examined by mass spectrometry. In neither case was incorporation of any oxygen from the water into product methanol detected. Thus, under acidic conditions methanol is only released by P-O cleavage.

A similar result was obtained by Ramirez et al.[89] who treated the pentaoxyphosphorane (101) with 1 mol equivalent of enriched water at 20° in benzene. The result is indicated in Scheme 37.

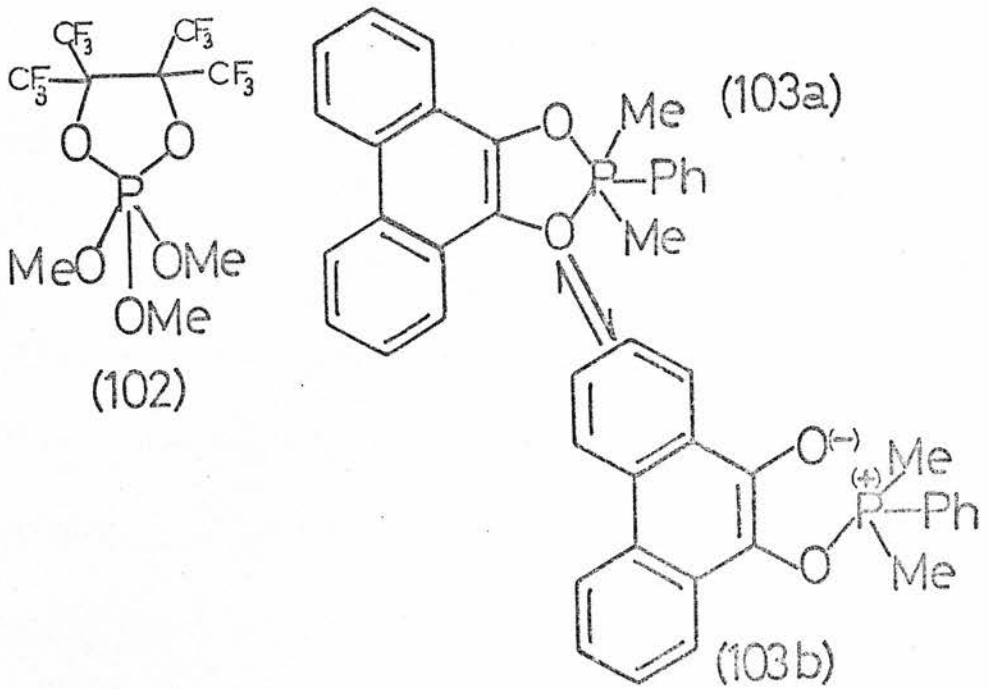


Scheme 37

(iii. 2) Solvent dependence of ^{31}P chemical shifts.

Hexafluoroisopropanol (h.f.p.) is a relatively acidic solvent and would consequently be expected to encourage the ionisation of a phosphorane to a greater extent than would be possible in chloroform alone.

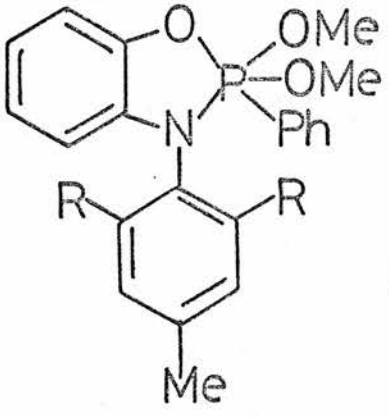
Ramirez et al.[52] observed a negligible (1.3 ppm) downfield shift for the pentaoxyphosphorane (102) when the solvent was changed from deuterochloroform to h.f.p. In contrast, the dioxyphosphorane



(103) exhibited a very large shift (+1.5 ppm to -85.3 ppm) with the same solvent change. These results were rationalised[52] by the suggestion that whereas (102) was stabilised into the pentacoordinate form by five electronegative ligands, (103) was destabilised towards the zwitterionic form (103b) due to the presence of three less electronegative substituents. Thus, an equilibrium exists between (103a) and (103b) in solution; the relative concentrations and hence the averaged shift depend upon the solvent.

A correlation was drawn between the considerable stability of (102) towards water, the instantaneous hydrolysis of (103) and the relative solvent dependence of the chemical shifts. Accordingly, it was suggested[52] that the rapid hydrolysis was due to attack by water on the zwitterionic form (103b).

When solutions of the N-mesityl and N-p-tolyl phosphoranes (104) and (105) in $CDCl_3$ were treated with 0.5 molar equivalents of h.f.p., a shift of 0.4 ppm downfield was noted for (104) and 0.5 ppm



R = Me ; (104)

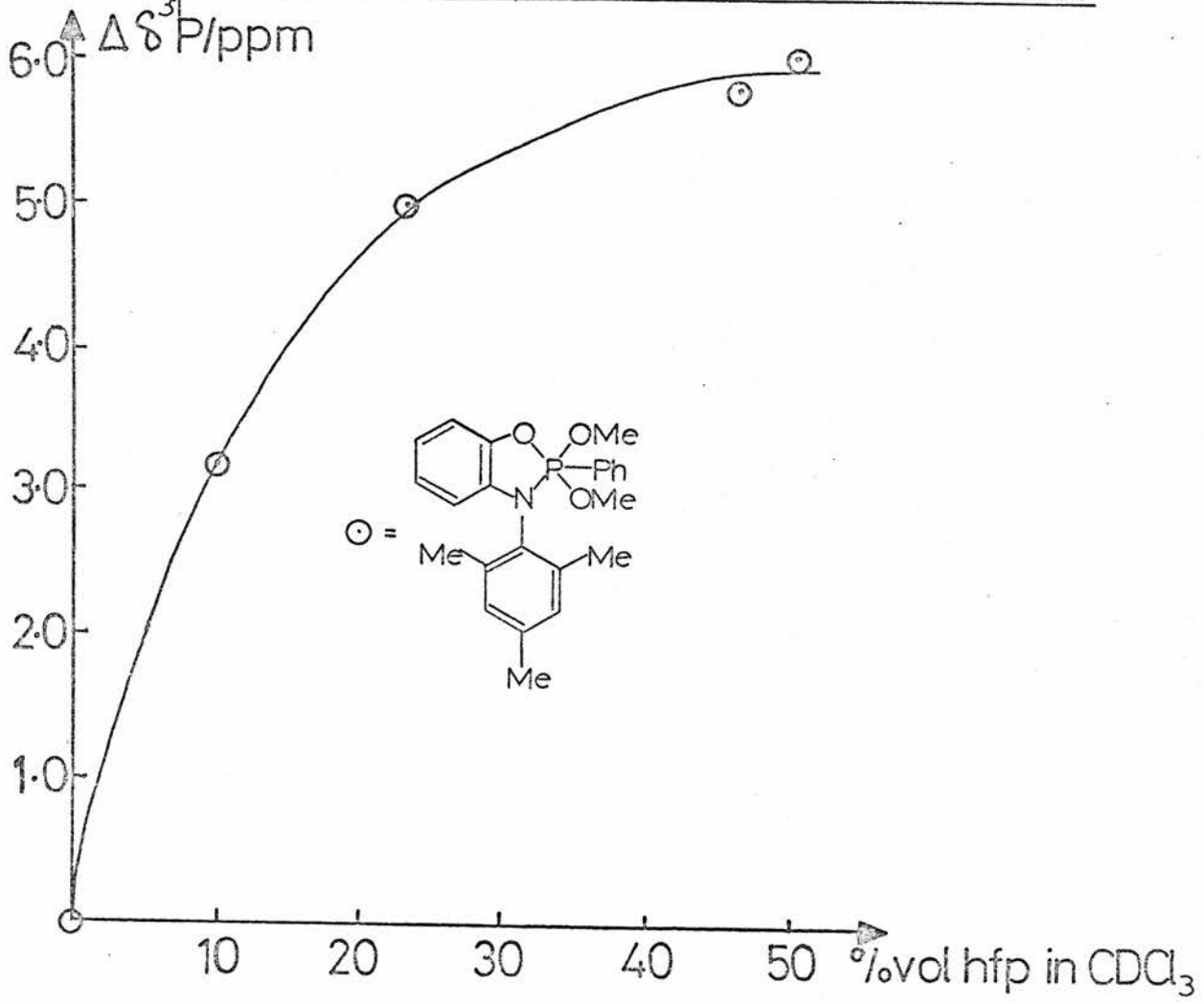
R = H ; (105)

for (105). Studies in more concentrated h.f.p. were hampered by the tendency of both phosphoranes to react, both with h.f.p. to give resonances upfield of the parent phosphoranes - presumably the mono- and di-exchanged phosphoranes - and, under the acidic conditions, with any traces of moisture.

The N-p-tolyl phosphorane (105) was considerably more reactive than was the N-mesityl analogue (104); hence further results could not be obtained for (105). The N-mesityl phosphorane (104) exhibited the dependence in Figure III-11. In h.f.p. :$CDCl_3$ (50:50 v/v), the downfield shift was 6 ppm. Considering the non-

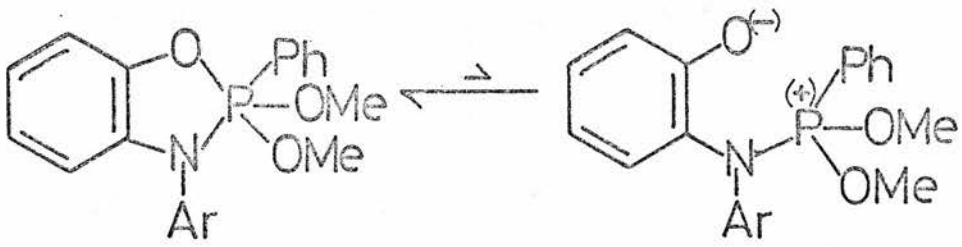
Fig.III-11

Solvent Dependence of ^{31}P n.m.r. Shifts.



linearity of the curve and the shift value for (104), given above, it seems probable that the N-p-tolyl phosphorane (104) has a slightly greater ionisation tendency.

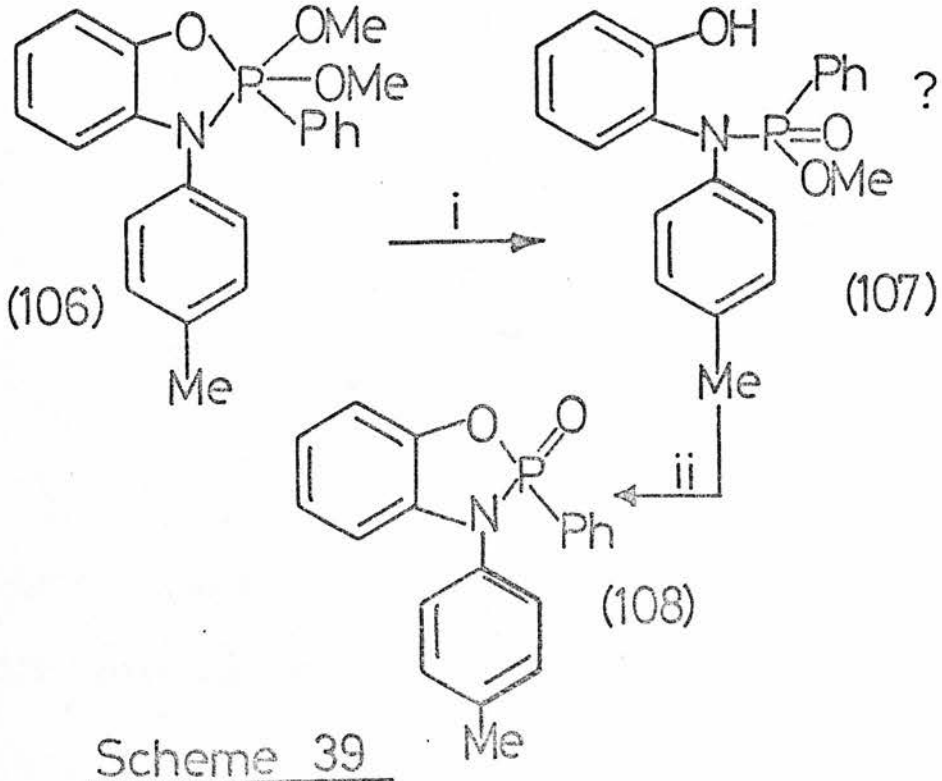
Both (104) and (105) are clearly more prone to ionisation than (102) but much less so than (103). The probable mode of ionisation is shown in Scheme 38.



Scheme 38

(iv) Proposed mechanism for hydrolysis

Attention is first focussed upon the possible mechanisms by which 2, 2-dimethoxy-2-phenyl-3-p-tolyl-2, 2-dihydrobenz-1, 3, 2--oxazaphospholine (106) hydrolyses to 2-oxo-2-phenyl-3-p-tolylbenz--1, 3, 2-oxazaphospholine (108). The experimental evidence underlying the proposed steps in Scheme 39 has been discussed above.



Scheme 39

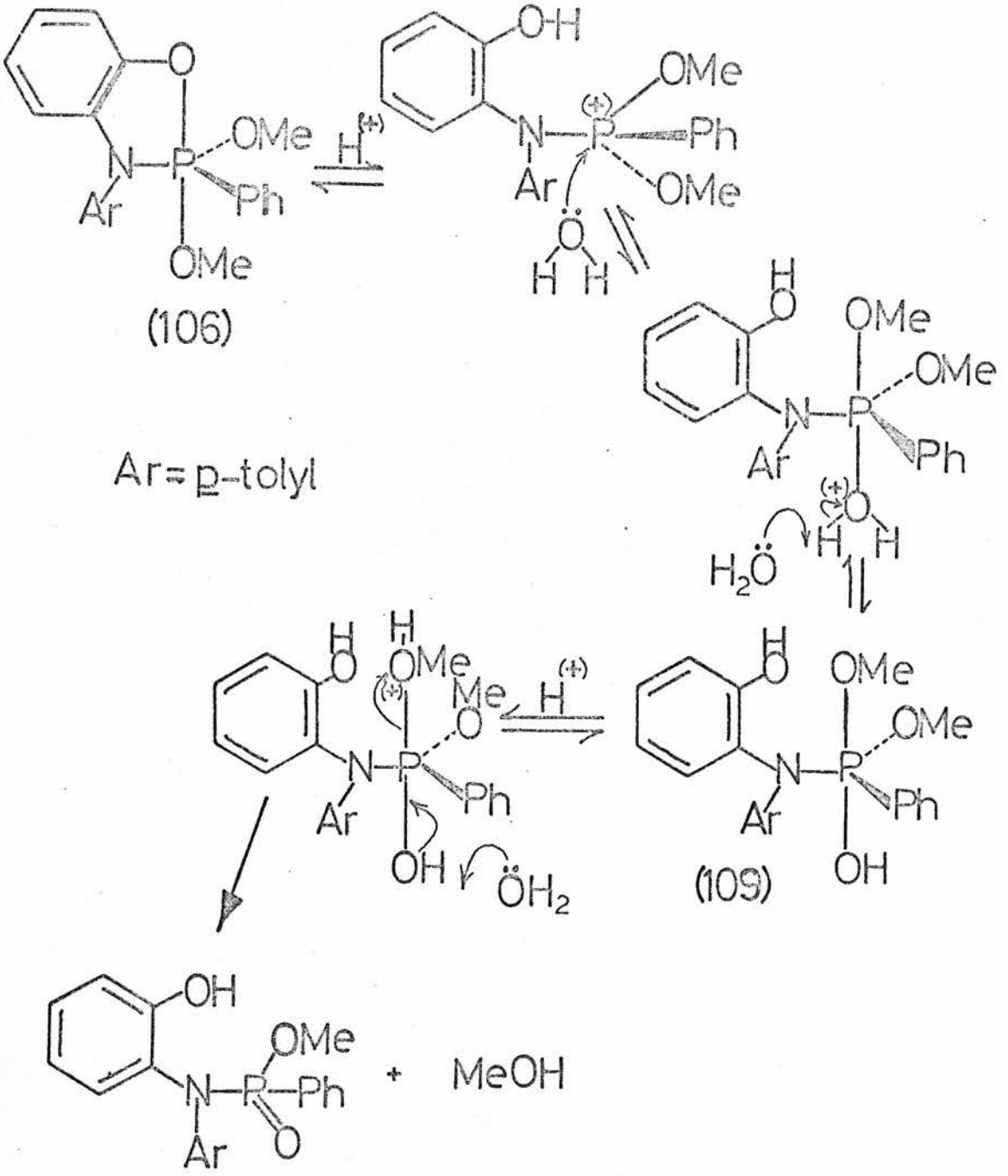
The identity of the intermediate species (107) - previously referred to as intermediate (B) - is not positively established. The two stage mechanism from (106) to (108) is, however, strongly supported. The separate steps (i) and (ii) are discussed independently.

The solvent-dependence of the ^{31}P chemical shift of (106) supports the theory that in acidic solution, hydrolysis of (106) to the acyclic phosphonamidate (107) may occur by attack of water on the zwitterionic form of the phosphorane (Scheme 38, above). Scheme 40 outlines the mechanism proposed for step (i).

Water attacks the protonated zwitterionic form of (106) at the phosphonium centre to generate the intermediate TBP structure (109). Subsequent decomposition of this intermediate by apical loss of methanol, must proceed more rapidly than the regular permutational isomerisation of (109) which would place the amino ligand in an apical site, allow N-protonation and hence, P-N cleavage to give dimethyl phenylphosphonate and 2-p-toluidinophenol. These products are observed, but in very low yield under acidic conditions.

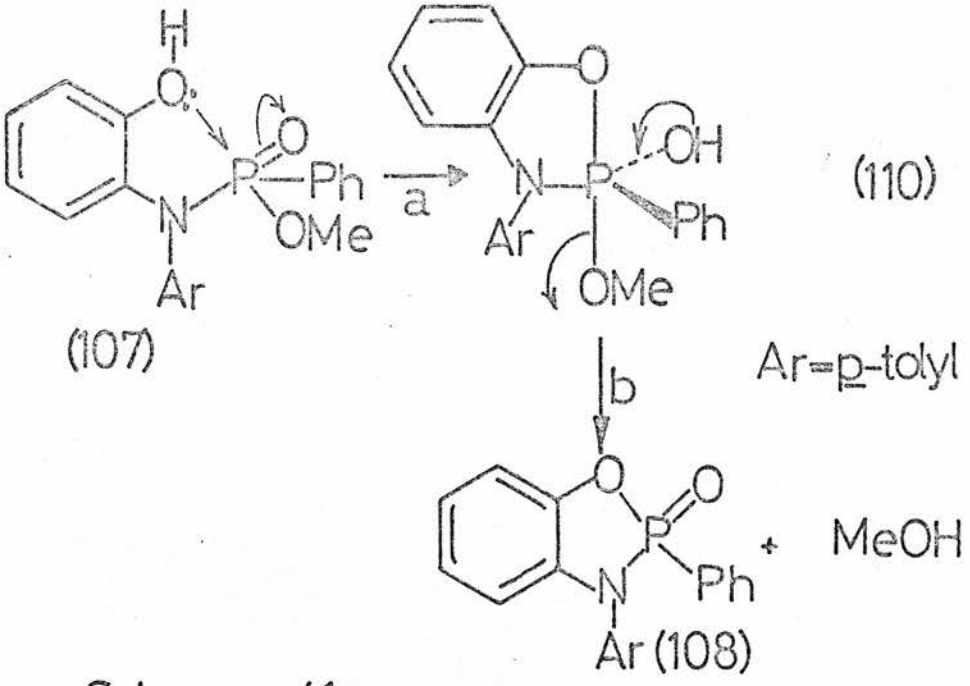
It is to be expected that the hydroxy ligand will be undissociated and, in contrast with the oxygen anion, the hydroxy ligand is apicophilic. Furthermore, the amino group will be apicophobic due to steric factors. Hence PI of intermediate (109) should be resisted.

(SCHEME 40 OVER)



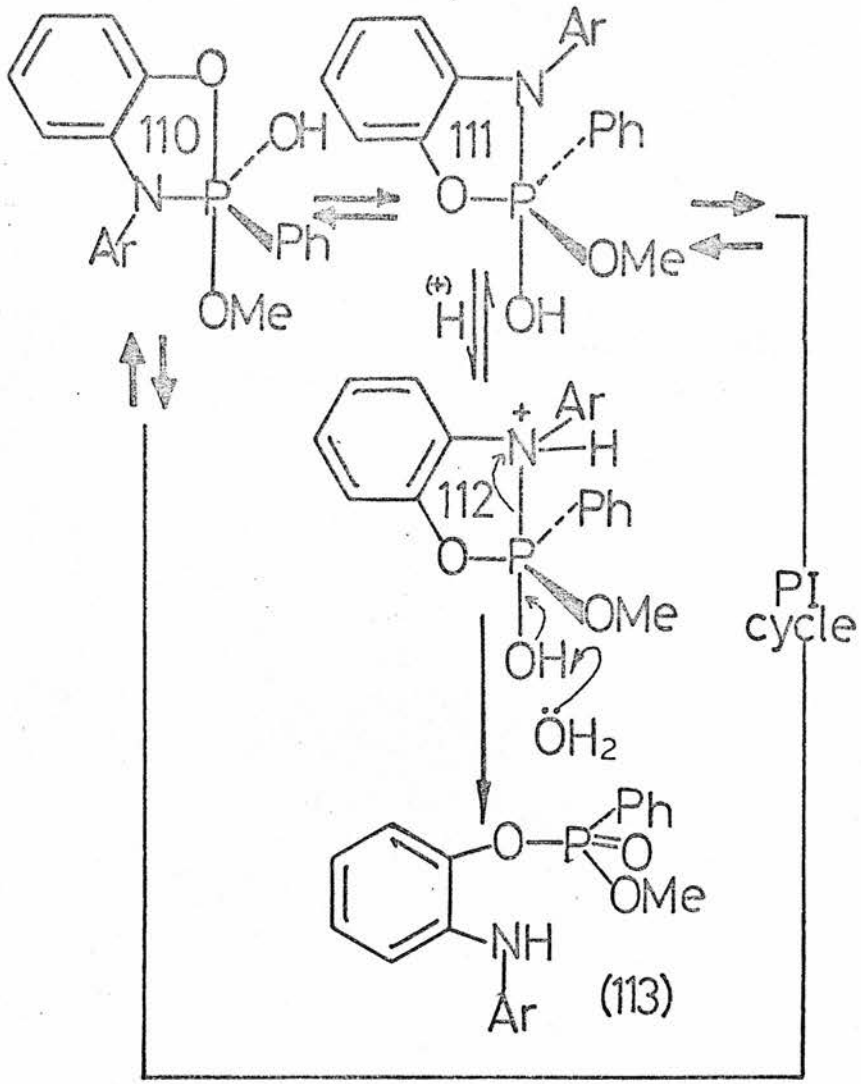
Scheme 40

The second stage of the reaction-depicted in Scheme 41- results in the formation of the cyclic phosphonamidate (108) from



Scheme 41

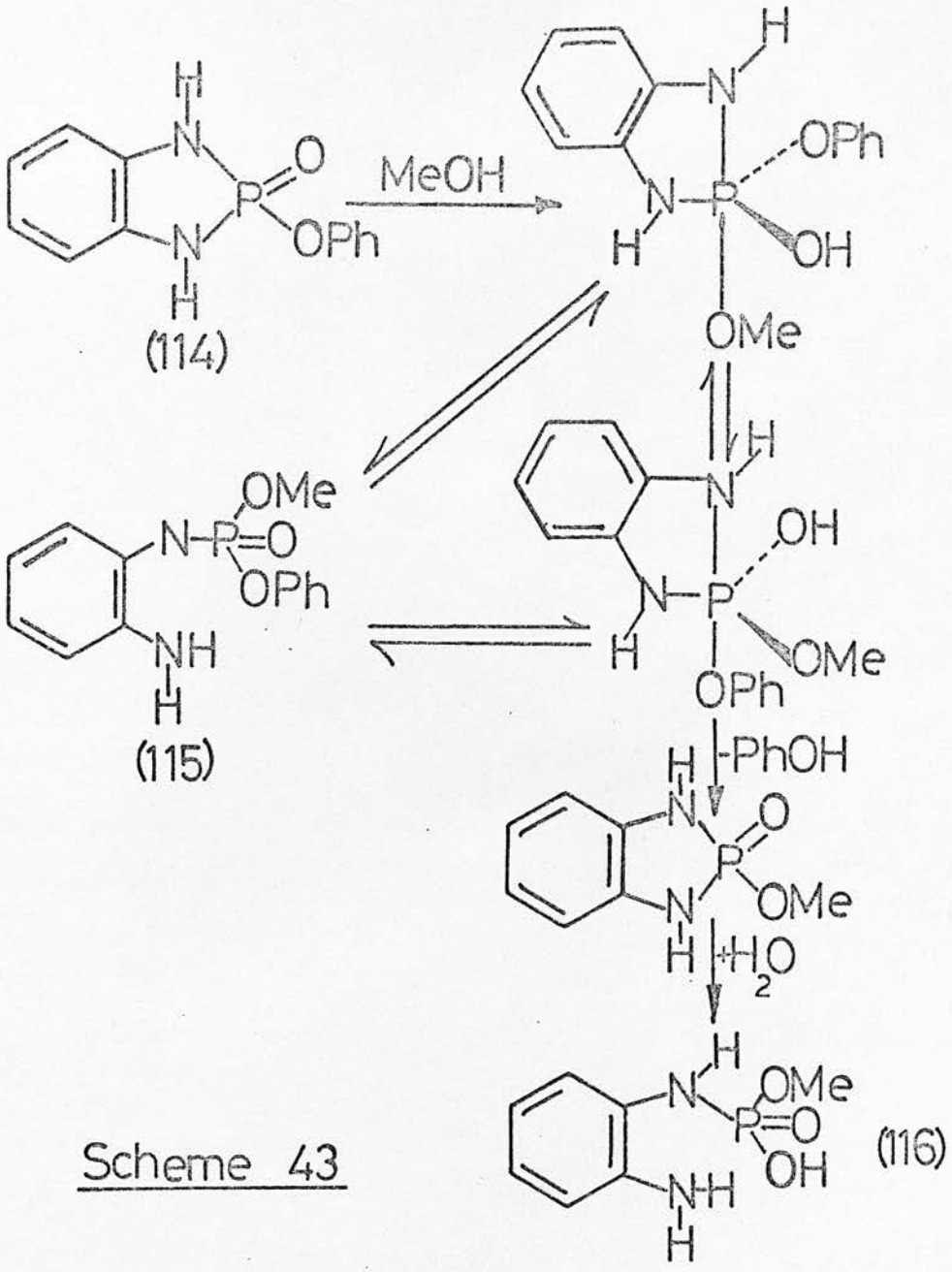
the acyclic phosphonamidate (107). The phenoxy group attacks phosphorus at the tetrahedral face opposite the most electronegative, exocyclic ligand (methoxyl) generating the TBP intermediate (110) which then loses methanol by apical P-O cleavage. It is surprising, in this case, that methanol elimination seems to be the exclusive mode of decomposition of (110). Considering the facile PI process observed for the parent phosphorane (106), it might be expected that such a process could occur to generate an isomeric intermediate (111) as in Scheme 42. N-Protonation, followed by P-N cleavage would produce the acyclic phosphonate (113). Such a product has not been observed. However, these studies have not reached such a level of sophistication as to allow this product to be excluded. The intermediate isomer (111) should be a high-energy component of the PI cycle (Scheme 42), hence a low concentration is expected which may make the reaction in Scheme 42 non-competitive with that in Scheme 41.



Scheme 42

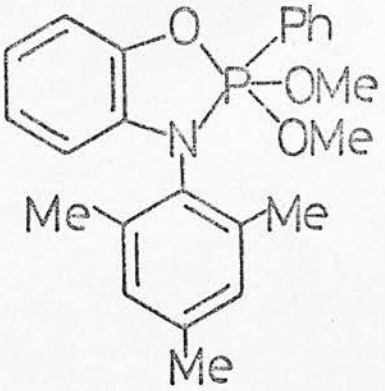
A similar cyclisation reaction has been suggested by Koizumi et al.[227] When the cyclic phosphorodiamidate (114) was boiled with methanol for 2 h, aqueous work up of the reaction mixture gave the products (115) and (116) in 17% and 48% yields, respectively. However, prolonged heating gave only (116).

These results were rationalised[227] as in Scheme 43.



Scheme 43

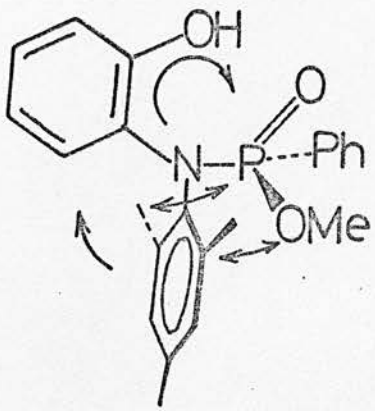
The ^{31}P n.m.r. studies on the hydrolysis of the analogous N-mesityl phosphorane (117) gave no evidence for the existence of an acyclic intermediate between the phosphorane and the cyclic phosphonamidate. The only initial product, other than the cyclic phosphonamidate, was unidentified but the rate of decomposition of this minor component was too slow to allow it to be an important



(117)

intermediate, if at all. However, p.m.r. spectroscopy provided evidence for an intermediate. It is suggested that the N-mesityl phosphorane (117) hydrolyses by an identical route to that proposed for the N-p-tolyl analogue (106), above. However, the acyclic intermediate recyclises as quickly as it is formed and was therefore not observed in the ^{31}P n.m.r. studies.

The recyclisation may be accelerated by the greater steric repulsion between the N-mesityl o-methyl substituents and the groups attached to phosphorus (Scheme 44). A greater preference

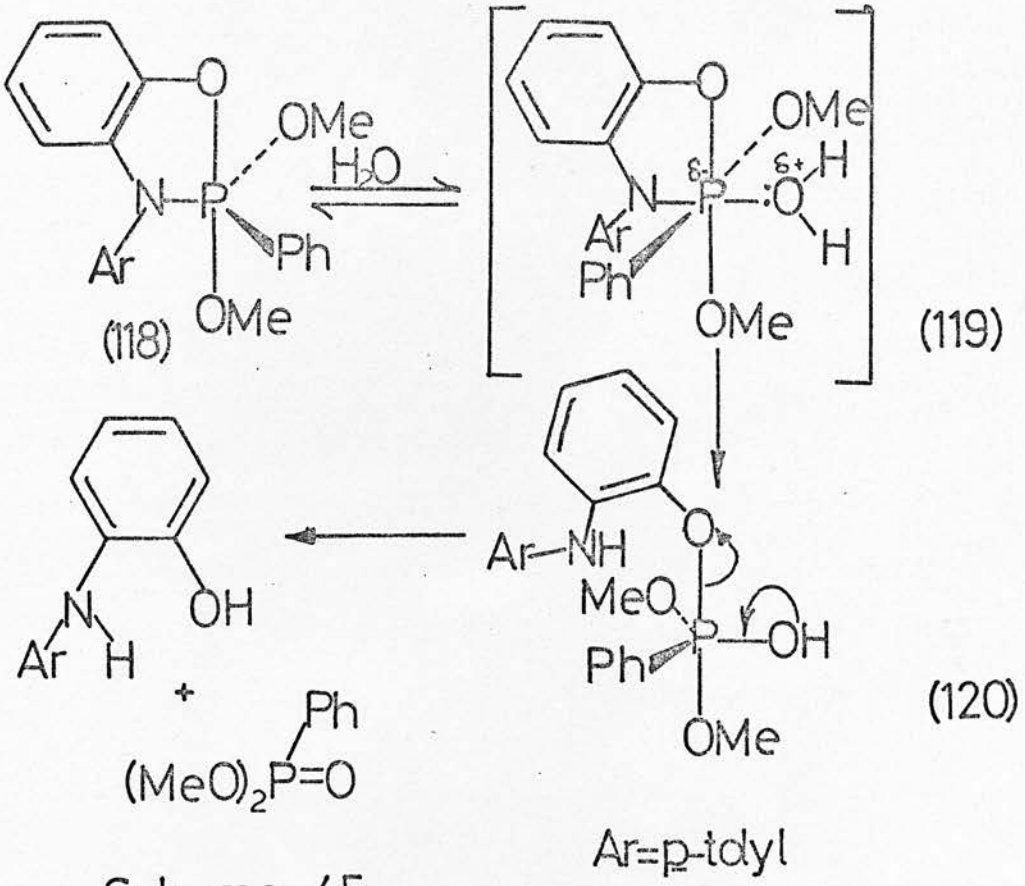


Scheme 44

for the pentacoordinate form of the N-mesityl phosphorane is also suggested by the slightly smaller solvent-dependence of the ^{31}P n.m.r. chemical shift compared with that of the N-p-tolyl analogue.

The direct formation of dimethyl phenylphosphonate from the

N-p-tolyl phosphorane (118) by a reaction which showed no detectable acid catalysis, suggests a complete change in mechanism from the acid-catalysed process. It is suggested that this reaction may proceed by direct attack of water on the pentacoordinate form of the phosphorane, to expel the arylamino ligand via an octahedral species (119), as in Scheme 45. The pentacoordinate intermediate (120) can



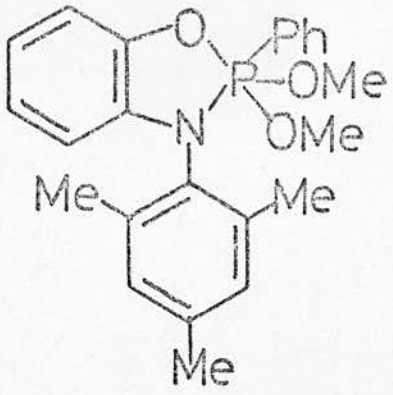
Scheme 45

then lose either a methoxyl or the aryloxy group directly from an apical position.

Loss of the aryloxy group is preferred as delocalisation can aid the development of negative charge at the apical oxygen. Hence, the products are 2-p-toluidinophenol and dimethyl phenylphosphonate.

Initial attack by water opposite an equatorial methoxy group of the phosphorane is resisted by steric interaction between the incoming molecule and the bulky N-aryl group.

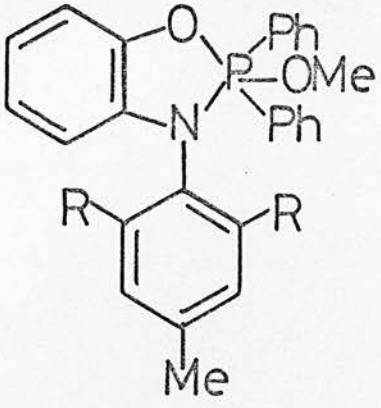
Hydrolysis of the N-mesityl analogue (121) does not occur in this way as increased steric compression will occur between the



(121)

equatorial phosphorus ligands and the N-mesityl group before an equivalent P-O bond distance is reached by water. Hence, no dimethyl phenylphosphonate has been detected during the hydrolysis of (121).

This latter explanation is, however, in conflict with the observation that both the N-mesityl and N-p-tolyl phosphoranes (122) and (123) gave small yields of methyl diphenylphosphinate on hydrolysis.



R=Me ; (122)
R=H ; (123)

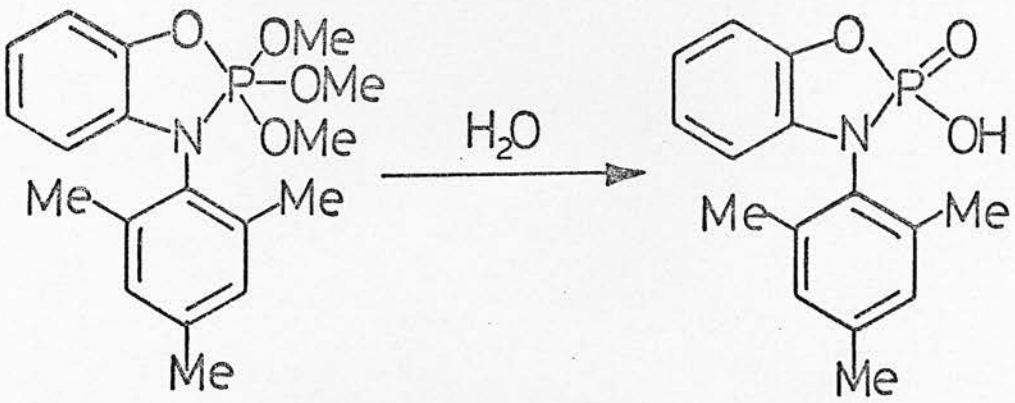
Ramirez et al.[80] have shown that the alcohol exchange reactions of a series of phosphoranes is base-catalysed and proceeds via an octahedral species. It therefore seems logical that if methyl diphenylphosphinate and dimethyl phenylphosphonate were formed by such a process, addition of base to the hydrolysis medium should enhance the yields of these simple esters.

When the phosphorane (123) in $CDCl_3$:CD_3COCD_3 (50:50 v/v)

was treated with one drop of water, the production of ca. 10% of methyl diphenylphosphinate was observed by p. m. r. spectroscopy. The addition of 10 mol equivalents of 2, 6-lutidine to a similar solution caused no significant alteration in this yield, or to the rate of the hydrolysis.

(c) 3-Mesityl-2, 2, 2-trimethoxy-2, 2-dihydrobenz-1, 3, 2--oxazaphospholine

When this phosphorane (124) was warmed at 30° in 5% aqueous dioxan, hydrolysis was complete in 90 min. The pH fell from ca. 6 to 1 during the reaction and a 99% yield of a white powder, assigned the structure (125) 2-hydroxy-3-mesityl-2-oxobenz-1, 3, 2-oxazaphospholine, was obtained. The assignment was based on a correct



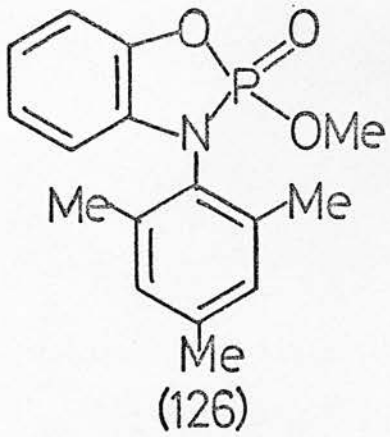
(124) (125)

analysis, exact mass measurement and compatible mass, i. r., p. m. r. and ^{31}P n. m. r. spectra. In particular, the p. m. r. spectrum exhibited a sharp, one-proton singlet at -1. 0τ which vanished after the addition of water and was assigned to the P-OH proton; furthermore, there was no methoxy resonance. The i. r. spectrum exhibited a series of weak, broad absorptions at 2600, 2320 and 1900 cm^{-1} assignable to P-O-H absorptions[203] and a strong absorption at 1275 cm^{-1} which was assigned to the phosphoryl stretch. The ^{31}P n. m. r. resonance appeared at -15. 9 ppm which is compatible[121] with tetracoordinate phosphorus.

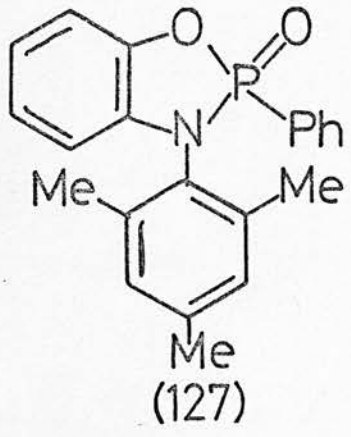
When the phosphorane (124), dissolved in methylene chloride,

was treated with 1 mol equivalent of water at room temperature, a mixture of two products was isolated and examined by p. m. r. spectroscopy. The phosphoramidate monoester, 2-hydroxy-3--mesityl-2-oxobenz-1, 3, 2-oxazaphospholine (125) was clearly identifiable. In addition, another set of signals of 2. 3 times the intensity of the first was observed. Attempts to purify the product by sublimation were not successful. However, the second, major product was observed to have increased in concentration relative to the monoester (125).

The major product was identified as 3-mesityl-2-methoxy--2-oxobenz-1, 3, 2-oxazaphospholine (126) on the basis of compatible p. m. r. and mass spectra. The p. m. r. spectrum exhibited a three-proton doublet at 6. 12τ ($J_{P\text{-}O\text{-}Me}$ 12 Hz) and a trio of three-proton



(126)

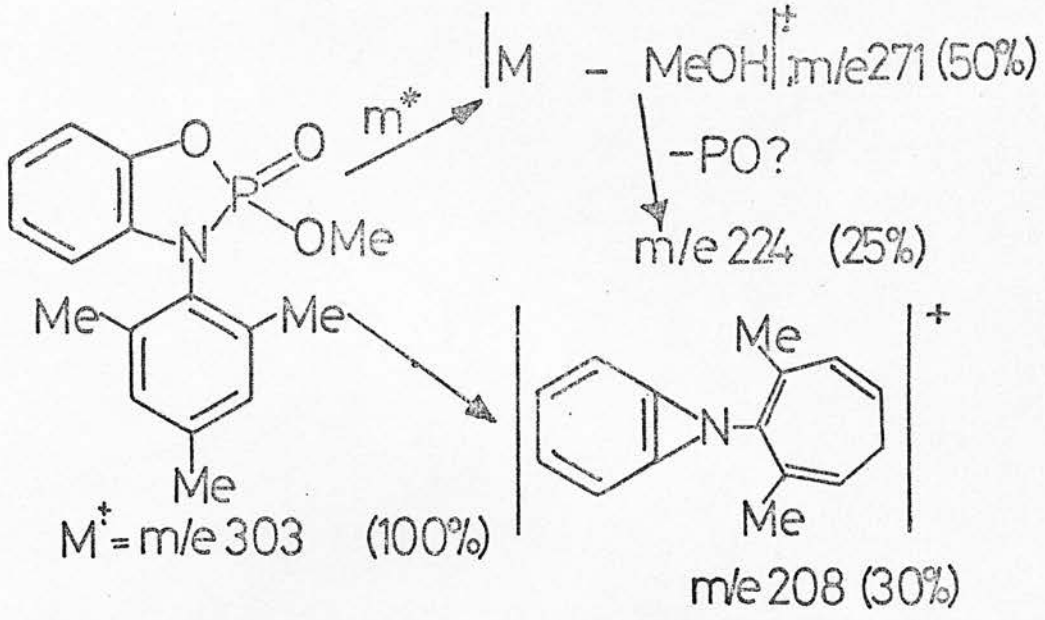


(127)

singlets at 7. 68, 7. 74 and 7. 82τ in addition to an aromatic region similar to that of the cyclic monoester secondary product (125). The observation of the non-equivalent N-mesityl methyl groups was crucial, as it suggests a cyclic rather than an acyclic ester in analogy to the cyclic phosphonamidate (127).

The mass spectrum exhibited the correct molecular ion and the fragmentations outlined in Scheme 46.

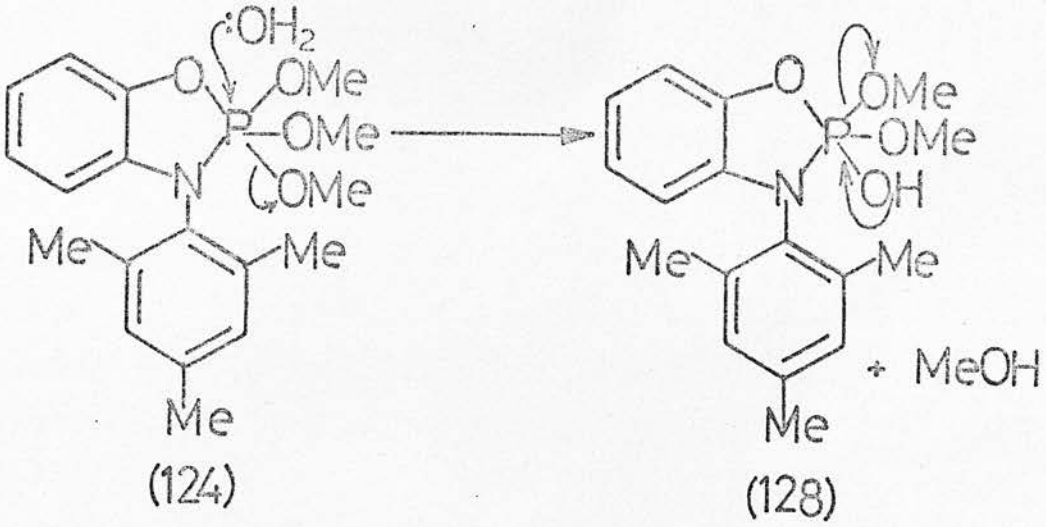
The hydrolysis products are compatible with the simple pathway exhibited in Scheme 47 which has been suggested by Ramirez[180] for the similar pentaoxyphosphorane (129).



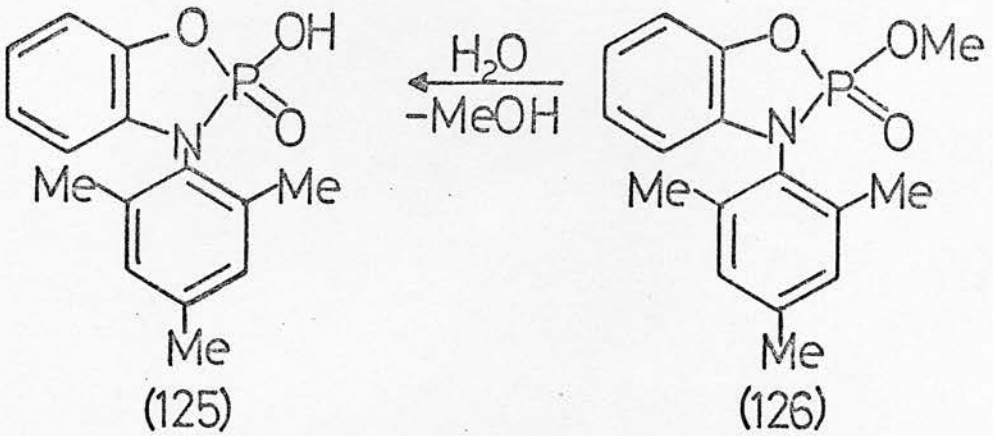
Scheme 46

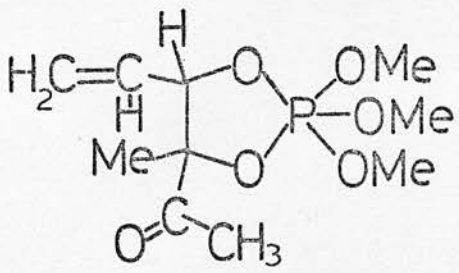
When a solution of the phosphorane in $CDCl_3$ was hydrolysed by excess D_2O and observed by p.m.r. spectroscopy, signals due to the cyclic diester (126) appeared from t=0 and increased until at 30 min, methanol and this component were the only significant materials present. Thereafter, the cyclic phosphoramidate diester (126) hydrolysed smoothly with a half-life of ca. 20 min to the cyclic phosphoramidate monoester (125). This was as expected. However, an unknown component containing a doublet (J_{P-O-Me} 11 Hz) at 6.36τ and singlets at 7.65 and 7.76τ was observed to increase rapidly in concentration over the first 10 min but to decline thereafter and to disappear with the phosphorane resonances at t=30 min.

When the same system was examined in $CDCl_3$:CD_3COCD_3 (50:50 v/v), this same unknown intermediate was observed as the predominant product over the first 30 min. The cyclic phosphoramidate diester (126) only became clearly visible after 30 min and



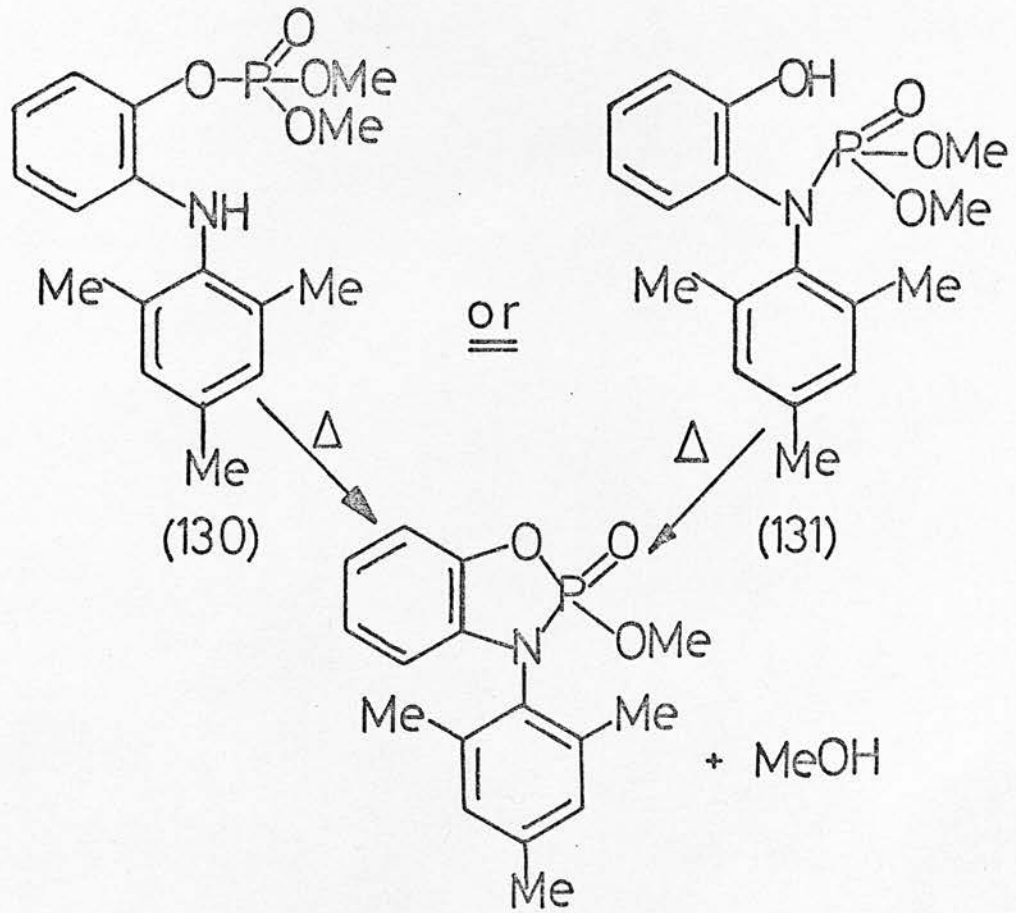
Scheme 47





(129)

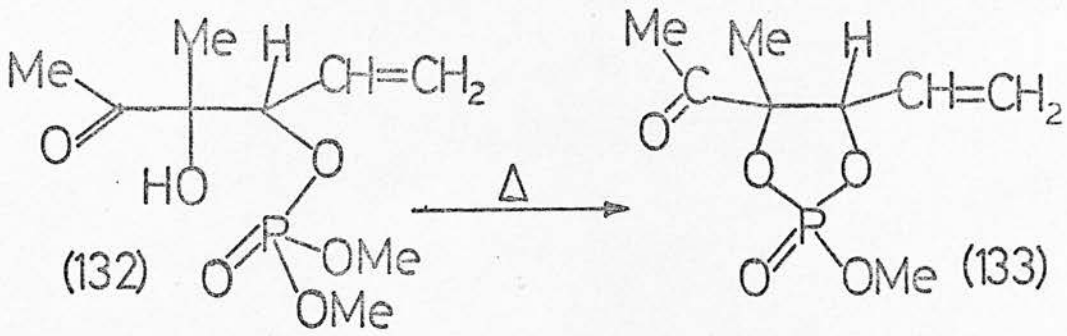
only the cyclic monoester (125) remained after 37 min. In this case, the unknown resonances could be clearly identified as a six-proton doublet and six-proton and three-proton singlets at 7.65 and 7.76τ, respectively. The reaction was followed by g.l.c. and a peak was observed to increase and decrease with the rise and fall of the p.m.r. resonances of the unknown. A mass spectrum was obtained for this component and was practically identical to that obtained from the cyclic diester (126), 3-mesityl-2-methoxy-2-oxobenz--1, 3, 2-oxazaphospholine. As the p.m.r. spectrum of the unknown had suggested an acyclic ester such as (130) or (131), a peak at m/e 335 was expected. No such peak was found, nor was there a metastable fragment to indicate that the acyclic ester - (130) or (131) - had recyclised. It seems probable, however, that the unknown is



Scheme 48

indeed one of the esters (130) or (131) and that thermolysis in the mass spectrometer caused recyclisation to the cyclic phosphoramidate (126) as in Scheme 48. Ramirez et al[176] have shown that

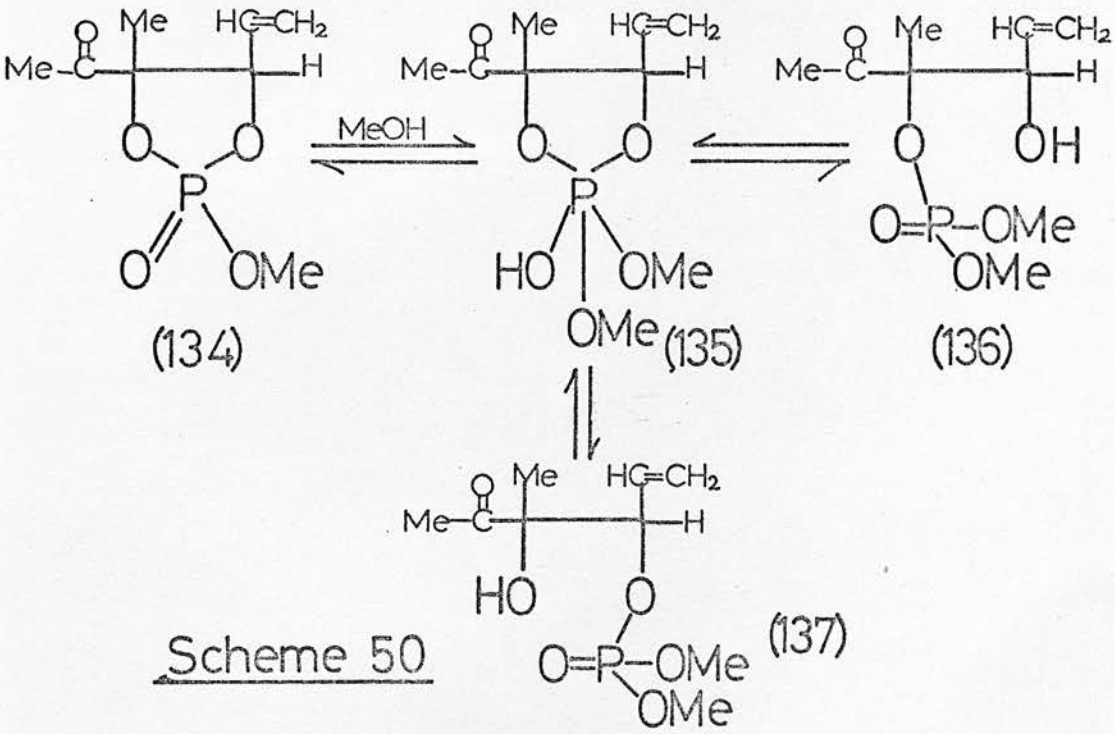
when the acyclic triester (132) is heated in vacuo, one mole equivalent of methanol is lost and the cyclic triester (133) is formed (Scheme 49).



(132) (133) + MeOH

Scheme 49

The origin of the unknown intermediate (130) or (131) in Scheme 48 is uncertain. Ramirez et al.[176] have shown that the cyclic triester (134) reacts rapidly with methanol to give the acyclic

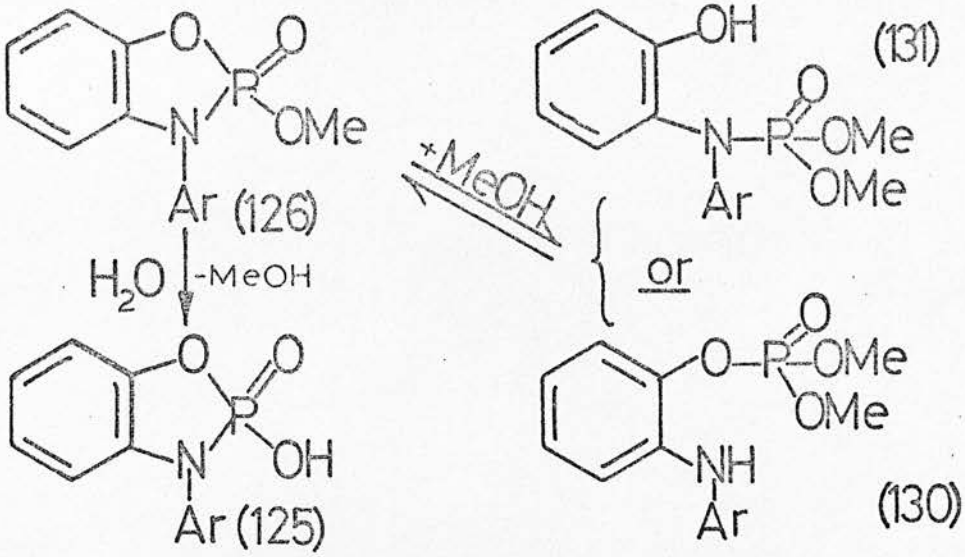


(134) (135) (136) (137)

Scheme 50

triester (136) which rearranges, presumably via the common intermediate (135), to the thermodynamically more stable product (137) as in Scheme 50. It is possible that an analogous situation obtains in our system.

Thus, hydrolysis of the phosphorane (124) would give, initially, the cyclic phosphoramidate (126). Methanol formed in the reaction could

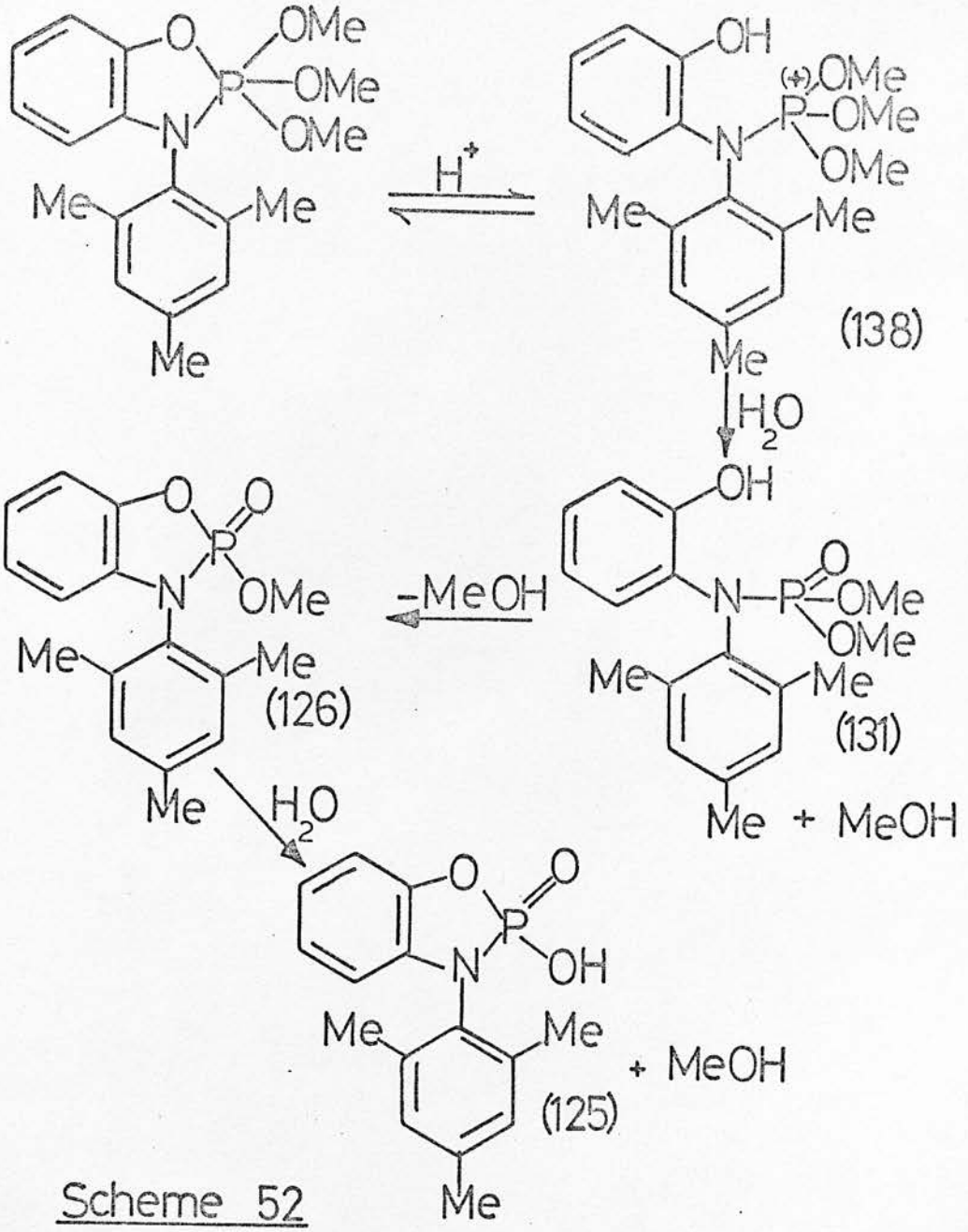


Scheme 51

Ar=mesityl

reattack the latter compound to give an equilibrium concentration of the acyclic ester-either (130) or (131)-with (126). Hydrolysis of the cyclic ester (126) would gradually form the cyclic phosphoramidate monoester (125), hence the ultimate disappearance of (126) and the unknown-(130) or (131)-as in Scheme 51.

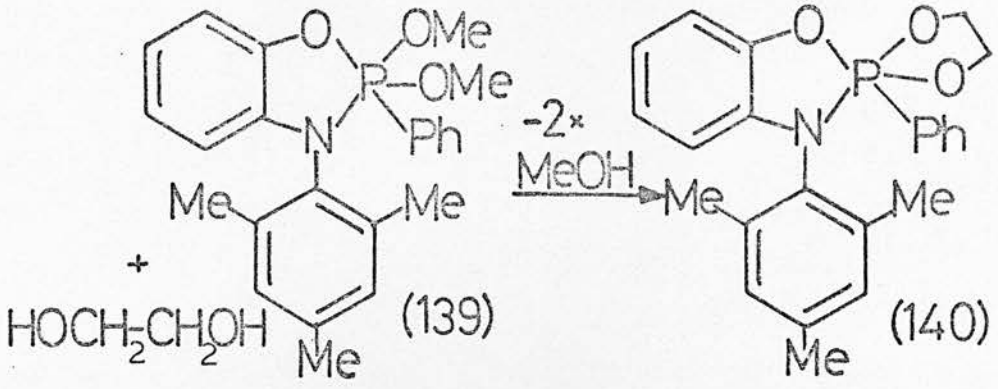
An alternative explanation - Scheme 52 - of the hydrolysis observations is made in analogy with the previously suggested mechanisms for the other phosphoranes above. Attack by water occurs on the protonated zwitterion (138) to generate, initially, the acyclic phosphoramidate diester (131), which recyclises to the cyclic diester (126). Subsequent hydrolysis gives the final product (125). This latter scheme has the advantage of not requiring methanol to compete overwhelmingly with water - which is present in large excess - for attack at the cyclic phosphoramidate (126).


OMe
OMe
OMe
O
P
N
Me
Me
Me
H+
OH
(+)OMe
P–OMe
OMe
(138)
H2O
O
P
OMe
–MeOH
N–P=O
OMe
(126)
(131)
+ MeOH
H2O
OH
+ MeOH
(125)

Scheme 52

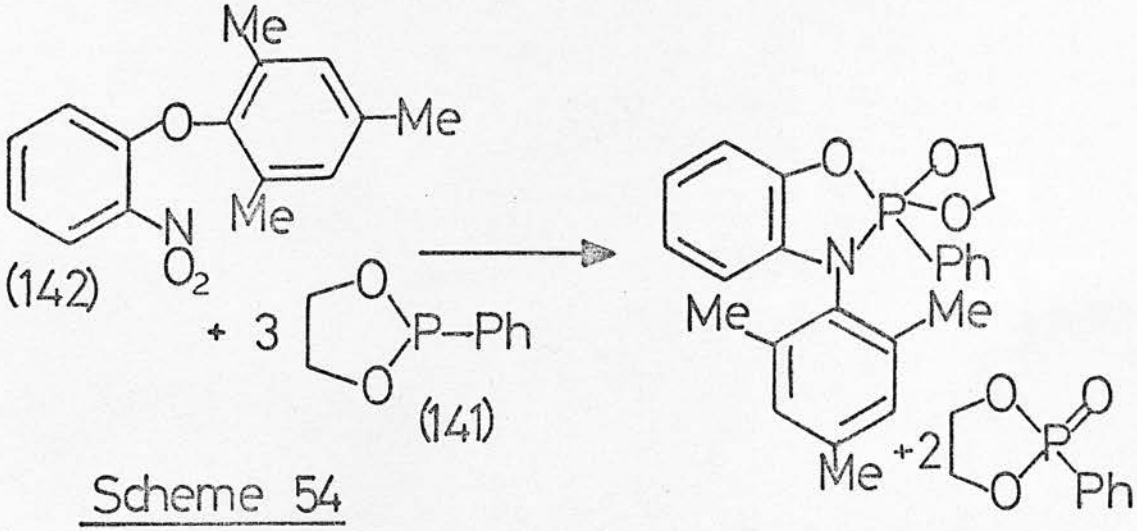
5. The Reactions of Diols with 3-Mesityl-2, 2-Dimethoxy-2--Phenyl-2, 2-Dihydrobenz-1, 3, 2-Oxazaphospholine

The phosphorane (139) reacted with 1, 2-ethanediol at room temperature, to give the spirocyclic phosphorane (140), spiro-2, 2--ethylenedioxy-3-mesityl-2-phenyl-2, 2-dihydrobenz-1, 3, 2-oxaza-phospholine (Scheme 53). The assignment of this structure was



Scheme 53

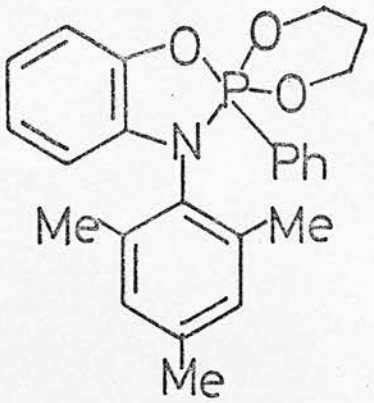
based on correct analytical data, compatible mass, i. r. and ^{31}P n. m. r. data. The same product (140) was also obtained in good yield from the reaction of 2-phenyl-1, 3, 2-dioxaphospholane (141) with the nitro-compound (142) in boiling cumene (Scheme 54).



Scheme 54

Transesterifications by diols are well known and are considered to be due to the favourability of forming spirocyclic phosphoranes containing two five-membered rings which reduce the intramolecular crowding at phosphorus.

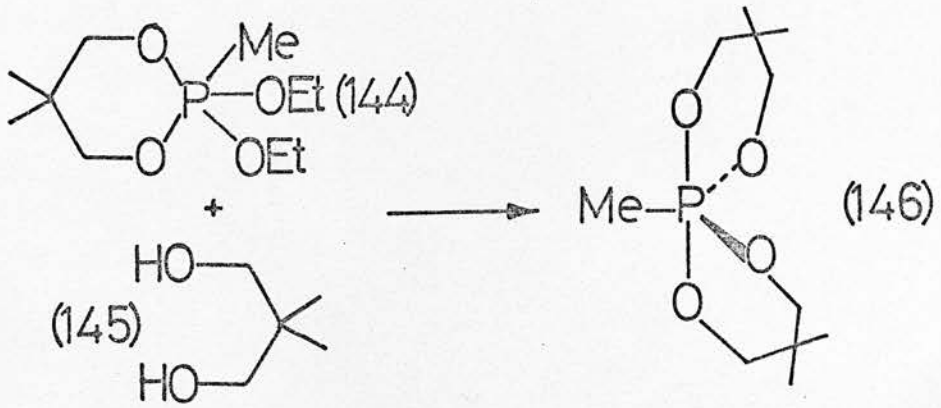
In contrast, no reaction was detectable when the same phosphorane was boiled under reflux in dioxan with a ten-fold excess of 1, 3-propanediol for five hours. The expected phosphorane (143)



(143)

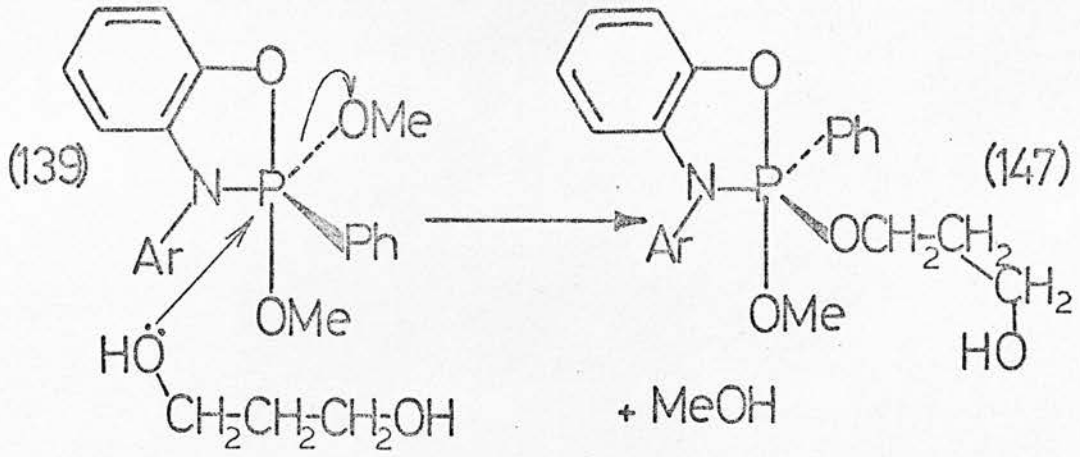
would be a less favourable structure than the five-membered spirocyclic analogue (140) as six-membered rings are puckered and therefore do not substantially reduce the intramolecular crowding.

However, Denney et al.[20] reacted the cyclic phosphorane (144) with neopentyl glycol (145) and obtained the spirocyclic phosphorane



Scheme 55

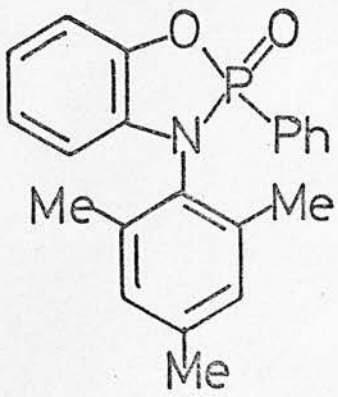
(146) as in Scheme 55. The benz-1, 3, 2-oxazaphospholine derivative (139) should be initially more crowded than the tetraoxyphosphorane (144); thus, initial attack by the diol on (139) would be less facile. Nevertheless, it is surprising that no product was detected at all from



Scheme 56 Ar = Mesityl

the reaction of (139) with 1, 3-propanediol. The first stage of the reaction (Scheme 56) should be almost as facile as with 1, 2-ethanediol. In addition, reattack by methanol on (147) should be disfavoured since the reaction was carried out in such a way as to boil-off any methanol formed.

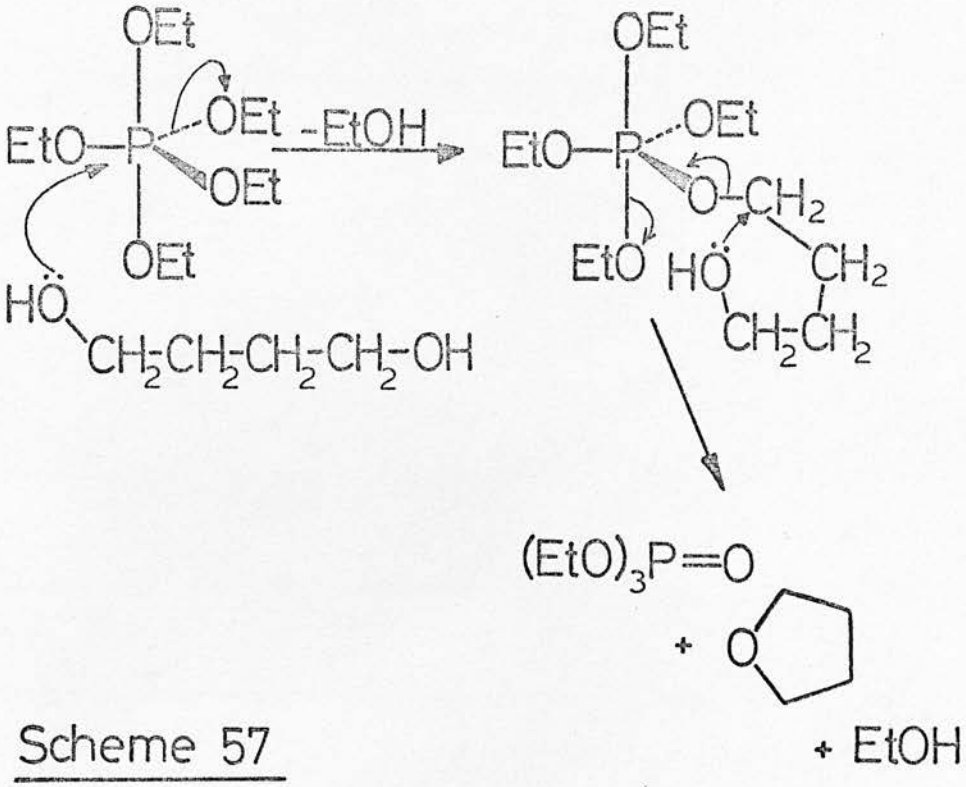
Excess 1, 3-propanediol was removed from the reaction mixture by prolonged heating at 130° (0.1 mm), to give the starting phosphorane (139) in only 85% yield. P.m.r. spectroscopy of this crude product showed that the product was of higher purity than before the reaction as it lacked the small amount of 3-mesityl-2-oxo--2-phenylbenz-1, 3, 2-oxazaphospholine (148) initially present as an



(148)

impurity. Whilst codistillation of the phosphorane may have caused the 15% yield reduction, it is also possible that, in view of the observed

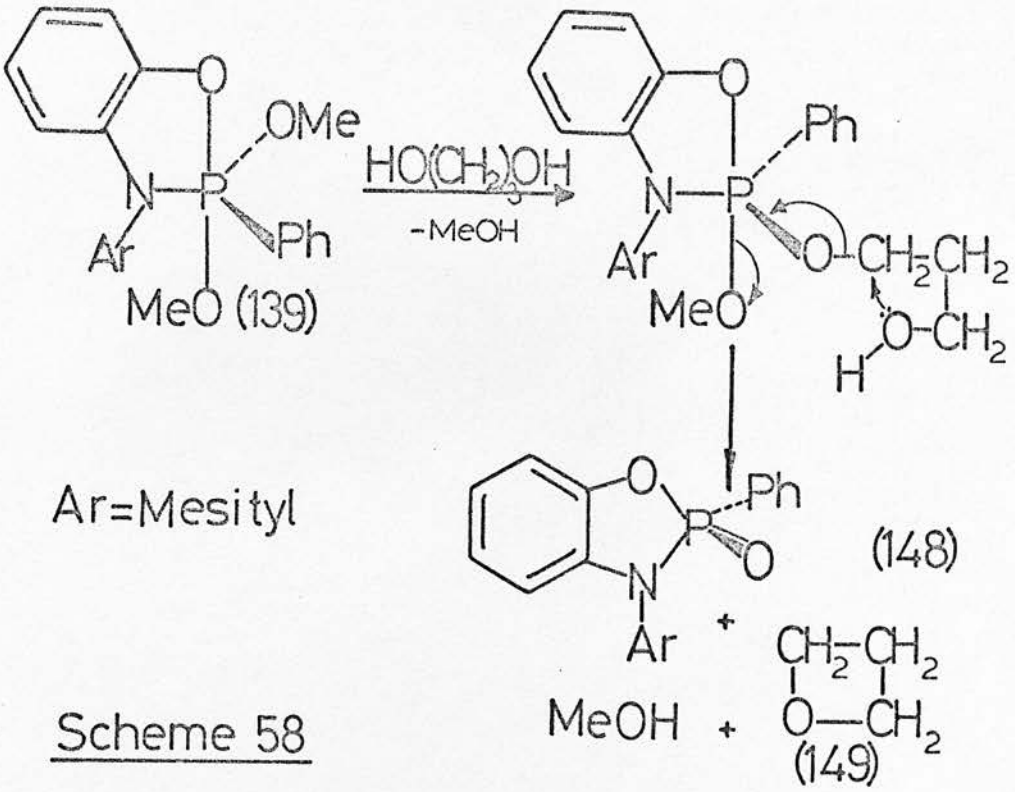
higher volatility of the cyclic phosphonamidate (148), more of the latter material was formed in the reaction but was lost during the work-up. If this is so, a possible explanation of the failure to observe any of the monocyclic oxyphosphorane (147) can be suggested. Denney et al.[20] observed that when pentaethoxyphosphorane was



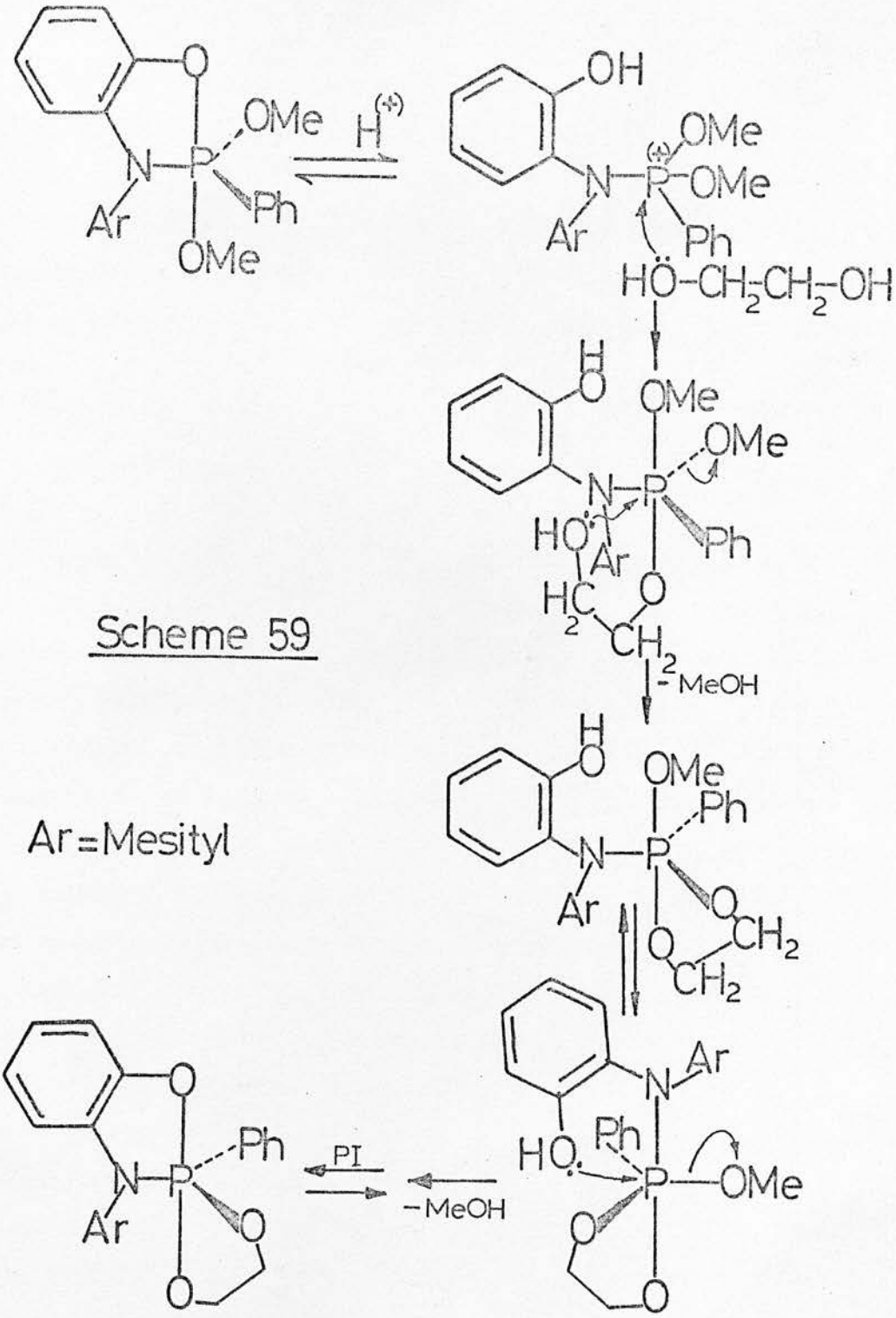
Scheme 57

treated with 1,4-butanediol at 0°, an exothermic reaction was observed; tetrahydrofuran was isolated in 87% yield. The mechanism in Scheme 57 can explain this result. It is possible that under the prolonged heating in our reaction, a similar process occurred to give oxetane (149) and the cyclic phosphonamidate (148) as outlined in Scheme 58.

An alternative and equally speculative explanation for the lack of products from this reaction is that, in common with the hydrolyses, the exchange reaction is also highly sensitive to acid-catalysis and a mechanism as in Scheme 59 operates. Thus, the absence of catalytic impurities in the 1,3-propanediol reaction would result in no reaction at all.


OMe
Ph
Ar
MeO (139)
HO(CH2)3OH
-MeOH
Ph
Ar
MeO
O-CH2CH2
H
O-CH2
Ar=Mesityl
Ph
(148)
Ar
+
CH2-CH2
MeOH + O—CH2
(149)

Scheme 58



Scheme 59

Ar=Mesityl

6. Summary and Conclusion

Deoxygenation of aryl 2-nitrophenyl ethers with tervalent phosphorus reagents provides a very efficient preparative route to the benz-1, 3, 2-oxazaphospholine ring-system.

Variable temperature n. m. r. studies on the pentacoordinate derivatives have provided some interesting results; however, an investigation of substituent effects from the endocyclic benzene ring upon the free-energy barriers to regular permutational isomerisations at phosphorus has not yet been pursued and could be worthwhile.

The investigation of the hydrolysis of these pentacoordinate benz-1, 3, 2-oxazaphospholine derivatives has provided a preliminary insight into possible mechanisms. However, much further work is required. A crucial factor has been the assignment of the major and minor isomers obtained by acidic hydrolysis of 3-aryl-2--methoxy-2, 2-diphenyl-2, 2-dihydrobenz-1, 3, 2-oxazaphospholine derivatives (§ III-4(a)). The evidence available at present tends to support the assignments which have been made and thus indicates initial P-O cleavage of the heterocyclic ring. However, this latter conclusion is very important and further confirmatory evidence is imperative. Other points of potential interest will be the positive identification of the intermediates observed during the hydrolysis of the aminotrioxyphosphoranes and aminotetraoxyphosphoranes (§§ III-4(b) and III-4(c)). The ring-opening and recyclisation process which these observations suggested was totally unexpected.

Practically, it is clear that a suitable buffering medium must be obtained for use in observing reactions within the ^{31}P n. m. r. probe. Ample data is available for the preparation of such solutions in 10% aqueous dioxan; however, it may not be possible to maintain a high enough concentration of the phosphorane under these conditions.

The investigations which have been described and discussed in the foregoing pages have embraced the synthesis, the regular isomerisations and the hydrolysis of a class of heterocyclic compounds which are potentially, of great interest.

APPENDICES

APPENDIX I

This appendix contains a copy of the publication by J. I. G. Cadogan, D. S. B. Grace, P. K. K. Lim, and B. S. Tait (Chem. Comm., 1972, 520), which is partially based on work described in this thesis.

Formation of Phosphoranes and Related Compounds in Trialkyl Phosphite Deoxygenations of 2,6-Dimethylaryl 2-Nitrophenyl Ethers and 2,6-Dimethylaryl-2-nitrophenylmethane

By J. I. G. Cadogan,* D. S. B. Grace, P. K. K. Lim, and B. S. Tait
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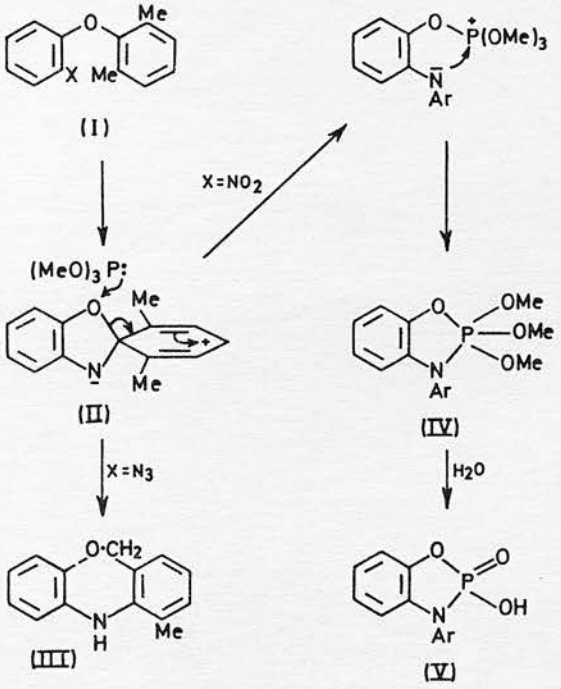
Formation of Phosphoranes and Related Compounds in Trialkyl Phosphite Deoxygenations of 2,6-Dimethylaryl 2-Nitrophenyl Ethers and 2,6-Dimethylaryl-2-nitrophenylmethane

By J. I. G. CADOGAN,* D. S. B. GRACE, P. K. K. LIM, and B. S. TAIT
(*Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh* EH9 3JJ)

Summary Trialkyl phosphite deoxygenation of 2,6-dimethylphenyl 2-nitrophenyl ether gives the aminotextroxyphosphorane (IV) and that of 2-nitrophenyl-2,4,6-trimethylphenylmethane gives diethyl *o*-(2,4,6-trimethylphenylamino)benzylphosphonate, which novel products support the intermediacy of a spirodiene in these reactions.

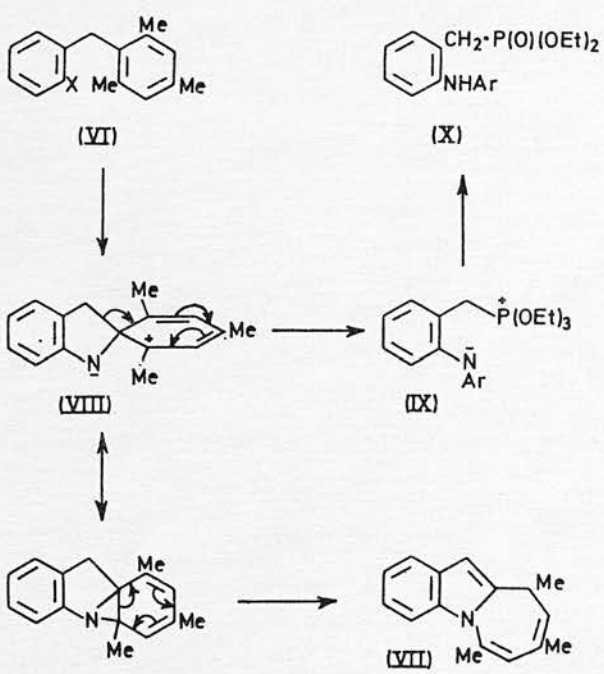
WE have reported previously[1,2] many examples of rearrangements occurring during the deoxygenation of nitro-compounds by triethyl phosphite. The course of these reactions can be interpreted in terms of a spirodienyl intermediate, *e.g.* (II), although direct evidence is lacking. We now report two new examples of the reaction which not only lead to new types of product hitherto undetected in the reaction series, but also provide strong support for the intermediacy of a spirodienyl intermediate.



SCHEME 1.

Thus, while the ether (I; X = N_3) gives the dibenzooxazepine (III) (11%),[2] deoxygenation of the corresponding nitro-compound (I; X = NO_2) by excess of trimethyl phosphite gives the crystalline aminotetroxyphosphorane (IV) (50%). Reactions with triethyl phosphite or the 2,4,6-trimethylphenyl homologue proceed similarly and the structural assignment is supported by mass and ^{31}P and ^{1}H n.m.r. spectroscopy, and by progressive hydrolysis to the acid (V) and to 2′,6′-dimethylphenyl-2-hydroxyphenylamine. The isolation of this phosphorane system points to reaction as in Scheme 1 wherein the intermediate spirodiene (II) reverts to aromaticity *via* nucleophilic attack by tervalent phosphorus on the bridgehead oxygen. An alternative involves collapse of (II) to a quinoneimine and hence (IV) by reaction with phosphite.

Similarly, whereas (VI; X = N_3) gives various isomeric azepinoindoles [*e.g.* (VII)],[3] a result which we confirm, the corresponding 2-nitro-derivative (VI; X = NO_2) in the presence of triethyl phosphite gives, additionally, the phosphonate (X) (7%). This points to reaction *via* the spirodiene (VIII) in Scheme 2, analogous to Scheme 1, although it has still to be resolved whether (X) arises from (IX) *via* direct elimination of ethylene or *via* a rapidly decomposed phosphorane, analogous to (IV).



SCHEME 2.

Thus in both cases (I and VI; X = NO_2) the trialkyl phosphite has dual roles as a deoxygenating reagent and as a nucleophile towards the intermediate in the reaction, thereby acting as its own mechanistic probe.

(*Received, 18th February* 1972; *Com.* 256.)

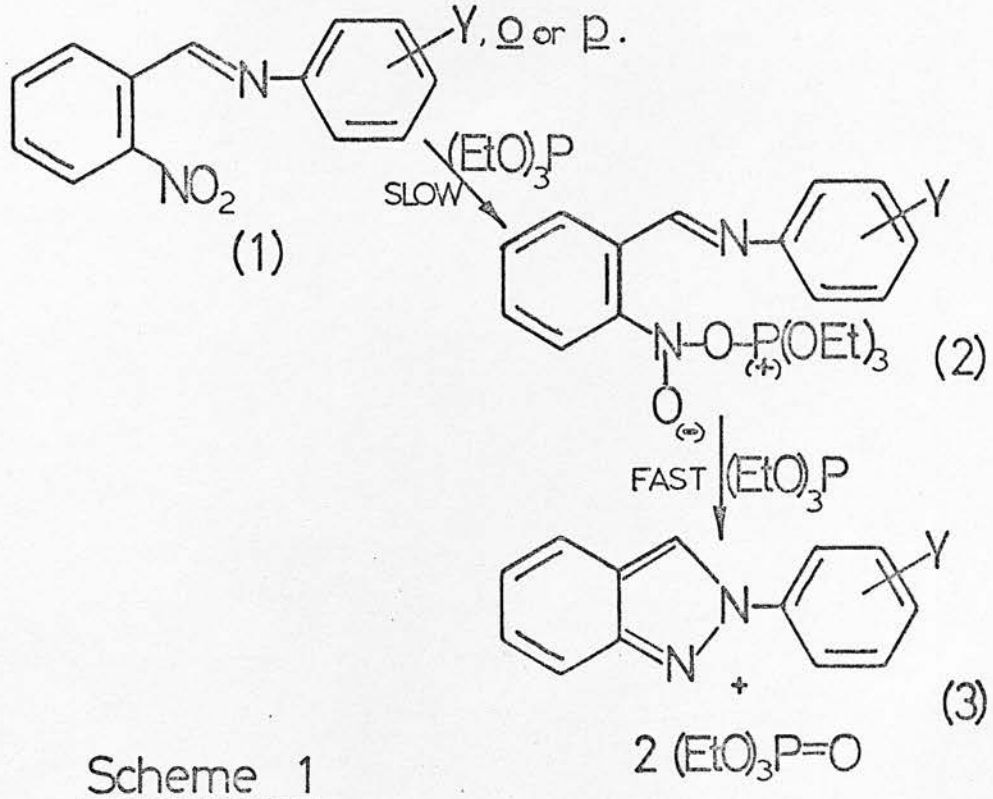
[1] J. I. G. Cadogan and S. Kulik, *J. Chem. Soc.* (*C*), 1971, 2621.
[2] J. I. G. Cadogan and P. K. K. Lim, *Chem. Comm.*, 1971, 1431.
[3] G. R. Cliff and G. Jones, *J. Chem. Soc.* (*C*), 1971, 3418.

APPENDIX II A NOTE ON THE SMALL-RING EFFECT AND ITS RELEVANCE TO THE MECHANISM OF DEOXYGENATION OF NITRO-COMPOUNDS BY TERVALENT PHOSPHORUS REAGENTS.

1. Introduction

Cadogan et al.[228] have shown that the rate of phosphite deoxygenation of a series of substituted o-nitrobenzalanilines (1), to give the corresponding 2-phenylindazoles (3), is accelerated by the presence of electron-withdrawing substituents in the ring remote from the nitro group.

The results supported the rate-determining formation of a zwitterionic intermediate (2), from nucleophilic attack by phosphite on one of the oxygen atoms of the nitro-group as in Scheme 1.



Scheme 1

The use of the small-ring effect[30] in differentiating between rate-determining nucleophilic and electrophilic attack by tervalent phosphorus reagents, has been outlined in Section I (pp. 64-72).

The investigation described in this note was intended to supply supporting evidence for the previous investigation[228] by employing the latter concept.[30]

2. Experimental

(a) Preparation of materials

(i) o-Nitrobenzalaniline was prepared by a standard method[229] and was supplied by Armour[228]. The material was obtained as bright-yellow crystals, m. p.[228] 64-65° (lit. m. p.[229] 64-66°).

(ii) 2-Phenylindazole was prepared by a standard method[229] and was supplied by Armour[228]. The material was obtained as pale-yellow crystals, m. p.[228] 82° (lit. m. p.[229] 81-82°).

(iii) Triethyl and trimethyl phosphites were dried over sodium wire (24 h) and redistilled in an atmosphere of dry nitrogen.

(iv) 2-Chloro-1, 3, 2-dioxaphospholane was prepared via a method supplied by Hudson[230]. Thus, phosphorus trichloride (55 ml) in dry methylene chloride (125 ml) under dry nitrogen, was treated with 1, 2-ethanediol (38. 7 ml) added dropwise at such a rate that the stirred mixture refluxed gently. When HCl evolution ceased, the solvent was removed and the residual oil was distilled under nitrogen to give 2-chloro-1, 3, 2-dioxaphospholane as a colourless oil (36 g; 45%), b. p. 43-44°/10 mm (lit. b. p.[231] 45. 5-47. 0°/15 mm).

(v) 2-Diethylamino-1, 3, 2-dioxaphospholane was prepared via a method supplied by Hudson.[230] Thus, 2-chloro-1, 3, 2-dioxaphospholane (36. 5 g; 0. 3 mol) in benzene (100 ml) under an atmosphere of dry nitrogen was treated with diethylamine (42 g; 0. 6 mol), dropwise, over 20 min. The mixture was stirred for 2 h, filtered, evaporated and distilled to give the product as a colourless oil (17. 5 g; 27%), b. p. 65-66. 5°/2 mm (lit. b. p.[230] 50°/2 mm). P. m. r. and ^{31}P n. m. r. spectra of the product were scanned just prior to use.

P. m. r. spectrum ($CDCl_3$): (τ) 5. 8-6. 3 (complex multiplet; 4H; methylene ring protons); 7. 0 (quartet of doublets, $J_{\underline{P}\text{-}N(C\underline{H}_2CH_3)_2}$ 9. 0 Hz, $J_{C\underline{H}_2\text{-}C\underline{H}_3}$ 7. 3 Hz; 4H; $-P(NEt_2)$ methylene protons); 8. 95 (t, $J_{C\underline{H}_2\text{-}C\underline{H}_3}$ ca. 7 Hz; 6H; $-P(NEt_2)$ methyl protons). No

other resonances were observed.

$\delta^{31}P$ ($CHCl_3$): -143.6 ppm (ext. 85% H_3PO_4 capillary); lit.[230] -144 ppm.

(vi) 2-Ethoxy-1, 3, 2-dioxaphospholane was prepared by adding dry ethanol (9.2 g; 0.2 mol) in light petroleum (b.p. 40-60°; 20 ml), dropwise, to a stirred solution of 2-chloro-1, 3, 2-dioxaphospholane (25.2 g; 0.2 mol) and dry triethylamine (30.3 g, 0.3 mol) in light petroleum (b.p. 40-60°; 60 ml). An atmosphere of dry nitrogen was employed and the solution was cooled on a salt-ice bath. The mixture was stirred vigorously for 2.25 h, filtered, evaporated and distilled to give the product as a colourless oil (16.7 g; 61%), b.p. 47.5 - 48.5°/10 mm (lit. b.p.[194] 50.5-51°/15 mm). P.m.r. and ^{31}P n.m.r. spectra of the product were scanned prior to use.

P.m.r. spectrum ($CDCl_3$): (τ) 5.7-6.4 (complex multiplet incorporating a complex band and a quartet of doublets, the latter centred on 6.19, $J_{P\text{-}O\text{-}C\underline{H}_2\text{-}C\underline{H}_3}$ 8.5 Hz, $J_{C\underline{H}_2\text{-}C\underline{H}_3}$ 6.5 Hz; 6H; methylene ring protons and P-OEt methylene protons); 8.82 (t; $J_{C\underline{H}_2\text{-}C\underline{H}_3}$ 7.0 Hz; 3H; P-OEt methyl protons). No other resonances were observed.

$\delta^{31}P$ ($CHCl_3$): -134.1 ppm (ext. 85% H_3PO_4 capillary); lit.[121] -131 to -134 ppm.

(vii) Hexamethylphosphorus triamide was a commercial sample (b.p. 55-58°/15 mm) and was not redistilled.

(b) Experimental technique and results

Approximately 0.001 mol of the substrate, 0.02 mol of the tervalent phosphorus reagent and 0.001mol of trans-stilbene, or, in the case of 2-ethoxy-1, 3, 2-dioxaphospholane, of anthracene, were placed in the reaction vessel which had been flushed with nitrogen. A positive pressure of nitrogen was maintained throughout the reaction. The vessel was suspended in a constant-temperature bath at 91.5° ± 0.3° and the contents were allowed to equilibrate.

Samples (10 μl) were withdrawn through a suba-seal cap using a leak-proof microlitre syringe and stored in sealed capillary tubes at CO_2-acetone temperature. Samples were melted before analysis, dissolved in 10-30 μl of dry methylene chloride, or, in the case of hexamethylphosphorus triamide, of dry benzene and injected onto a 5% SE30 column in a Pye 104 gas liquid chromatograph. The column temperature was 160-180° depending upon the reagents. The peaks of the chromatogram were integrated by a Kent Chromalog-2 integrator. The ratios of the substrate and of the product to the standard were used to calculate the pseudo first-order rate constants. These ratios were plotted against time and a suitable t=O value was selected. Good first-order plots were then obtained for the appearance of 2-phenylindazole (Figs. 1, 2, 3, 4 series b). The same experiments also gave good first-order plots for the consumption of o-nitrobenzalaniline. Only two deviations were found (Figs. 3a and 4a) and the plots for these cases suggest an experimental fault rather than a difference in mechanism. The linear plot obtained in Fig. 3b is reproduced on Fig. 3a.

The curves shown are the result of least mean square calculations and the rate data are recorded in Table I.

The only reliable data obtained for deoxygenation by 2-ethoxy-1, 3, 2-dioxaphospholane were those obtained from the appearance of product. The decelerated rate of this process could theoretically be due to the production of 2-phenylindazole becoming a side-reaction. However, comparison of the ratios for the substrate at t=O and 2-phenylindazole at $t=\infty$ with a calibration graph indicated that the conversion of o-nitrobenzalaniline into 2-phenylindazole remained very high. Thus, the rate constant for the appearance of 2-phenylindazole is considered to be an accurate value for the rate of deoxygenation of o-nitrobenzalaniline.

TABLE I. Pseudo first-order rate date for the reaction of o-nitrobenzalaniline with excess of tervalent phosphorus reagent at $91.5^{\circ} \pm 0.3^{\circ}$

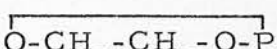
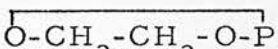
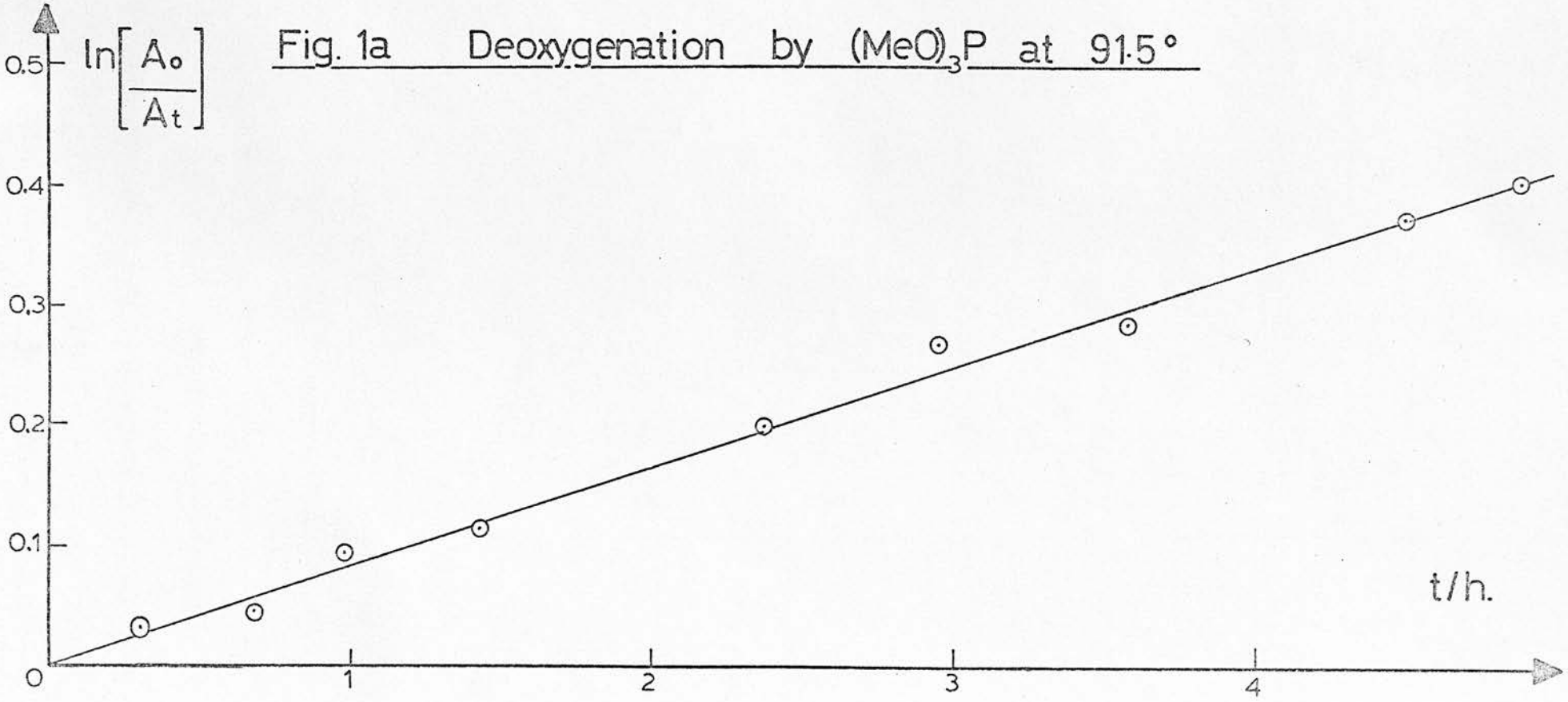
P (III) reagent	o-Nitrobenzalaniline consumption			2-Phenylindazole production		
	$k'(s^{-1})$	$t_{1/2}$ (min)	Fig.	$k'(s^{-1})$	$t_{1/2}$ (min)	Fig.
$(MeO)_3P$	2.29×10^{-5}	505	1a	2.65×10^{-5}	630	1b
$(EtO)_3P$	3.42×10^{-5}	337	2a	3.43×10^{-5}	338	2b
	3.06×10^{-5}	378	3a	2.92×10^{-5}	396	3b
	Erratic Results		4a	0.52×10^{-5}	2244	4b
$(Me_2N)_3P$	Reaction complete in less than 20 min.					

Fig. 1a Deoxygenation by $(MeO)_3P$ at 91.5°



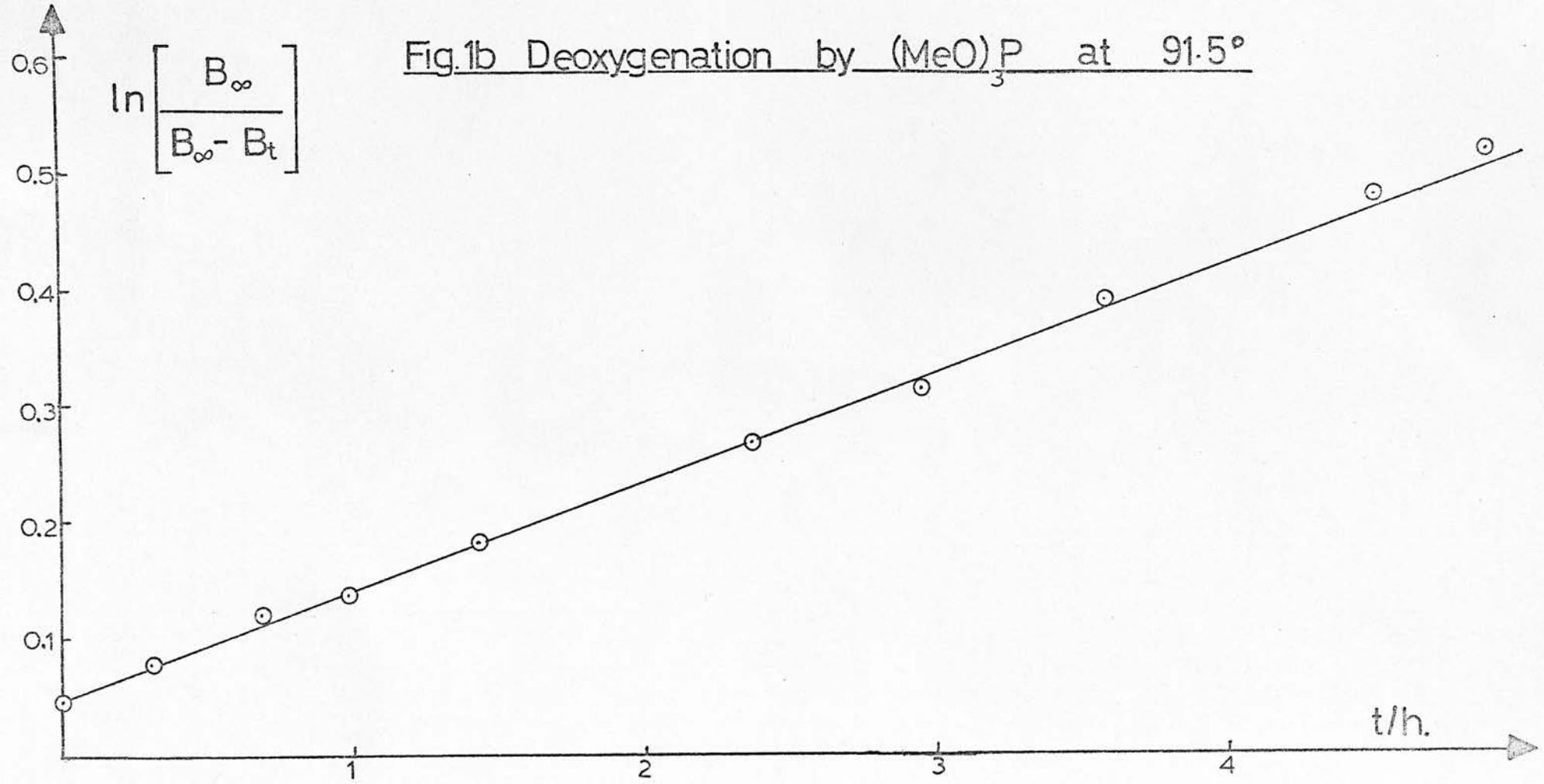


Fig.1b Deoxygenation by (MeO)3P at 91.5°
ln [B∞ / (B∞ - Bt)]
0.6
0.5
0.4
0.3
0.2
0.1
1
2
3
4
t/h.

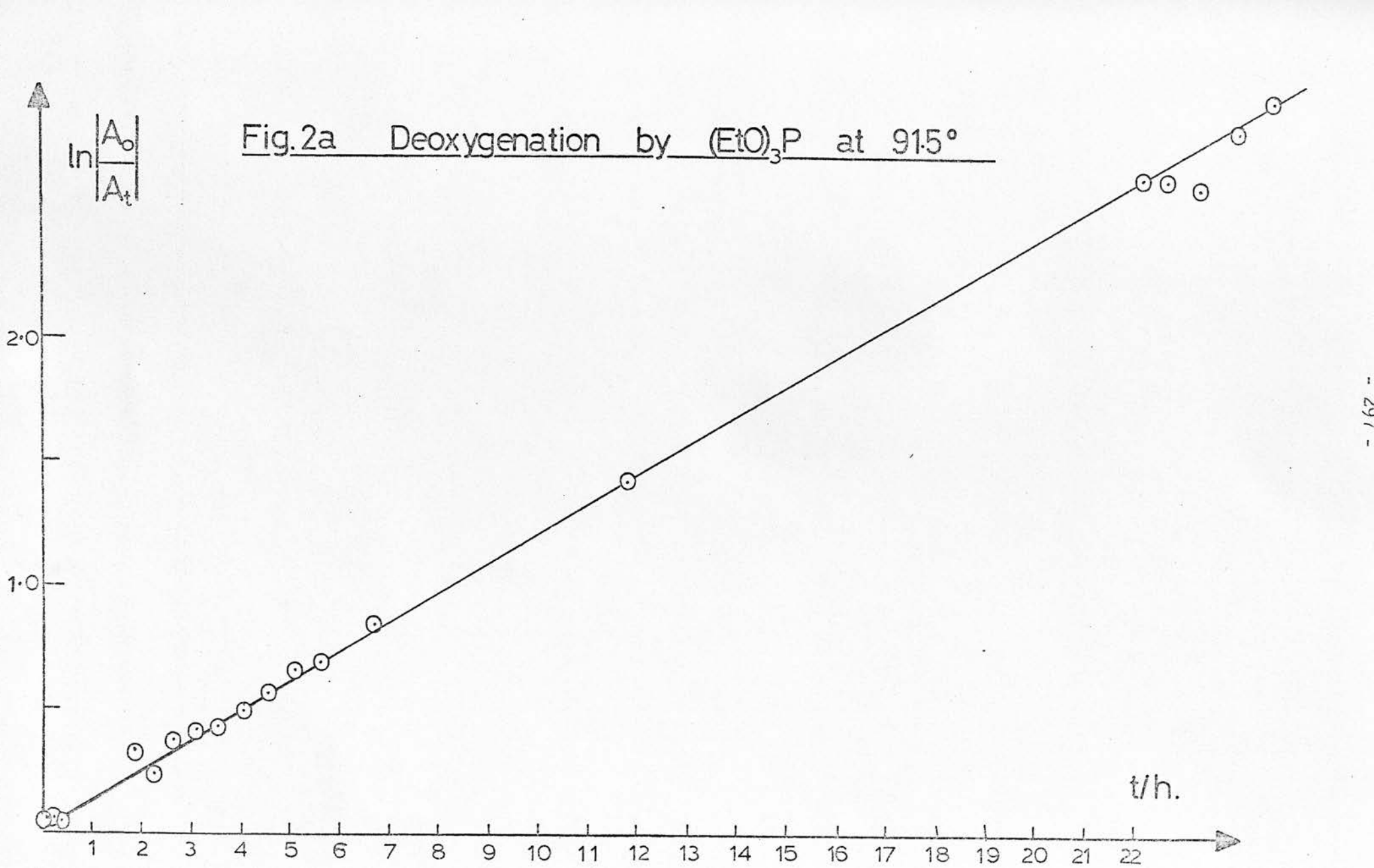


Fig. 2a Deoxygenation by $(EtO)_3P$ at 91·5°

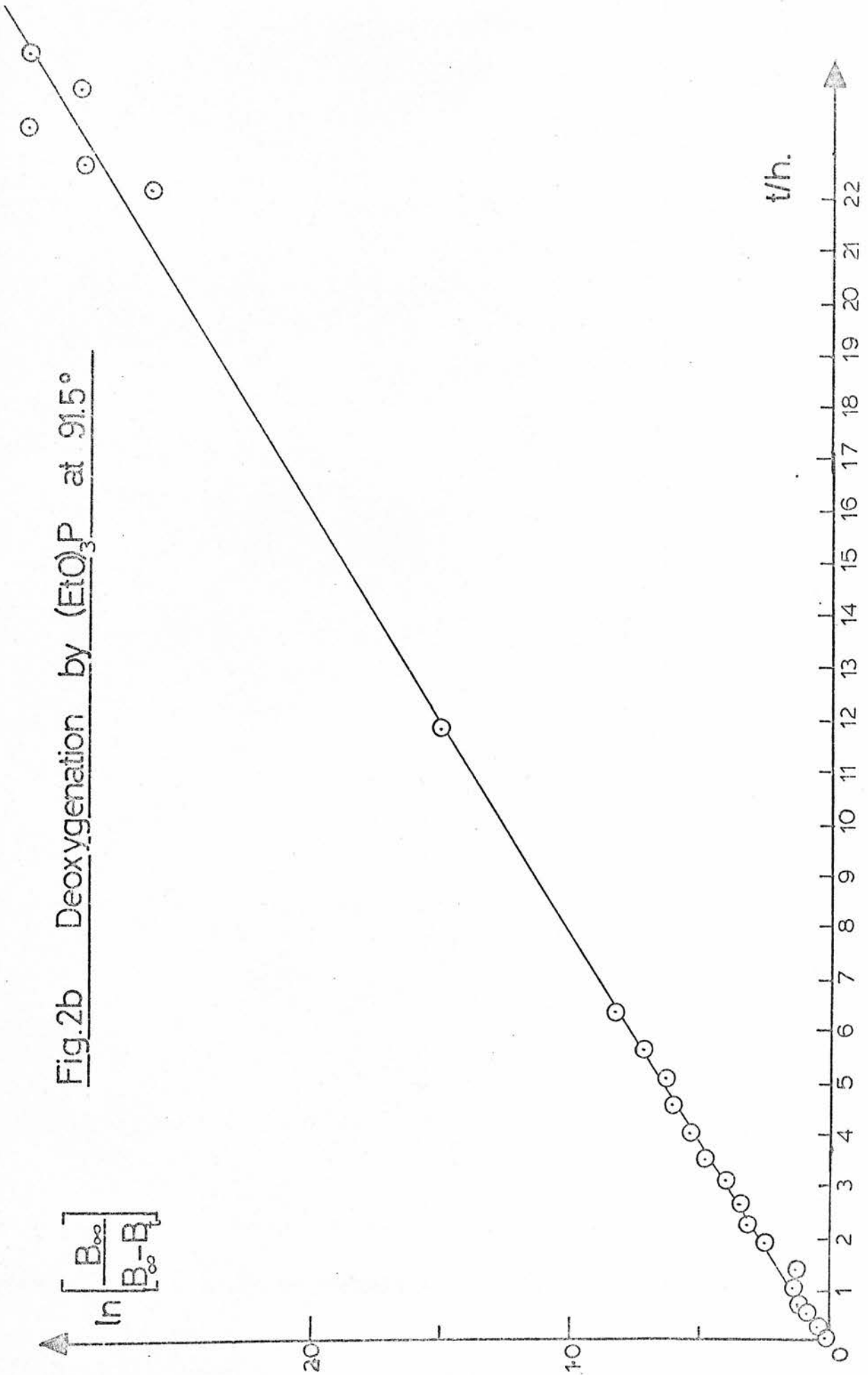
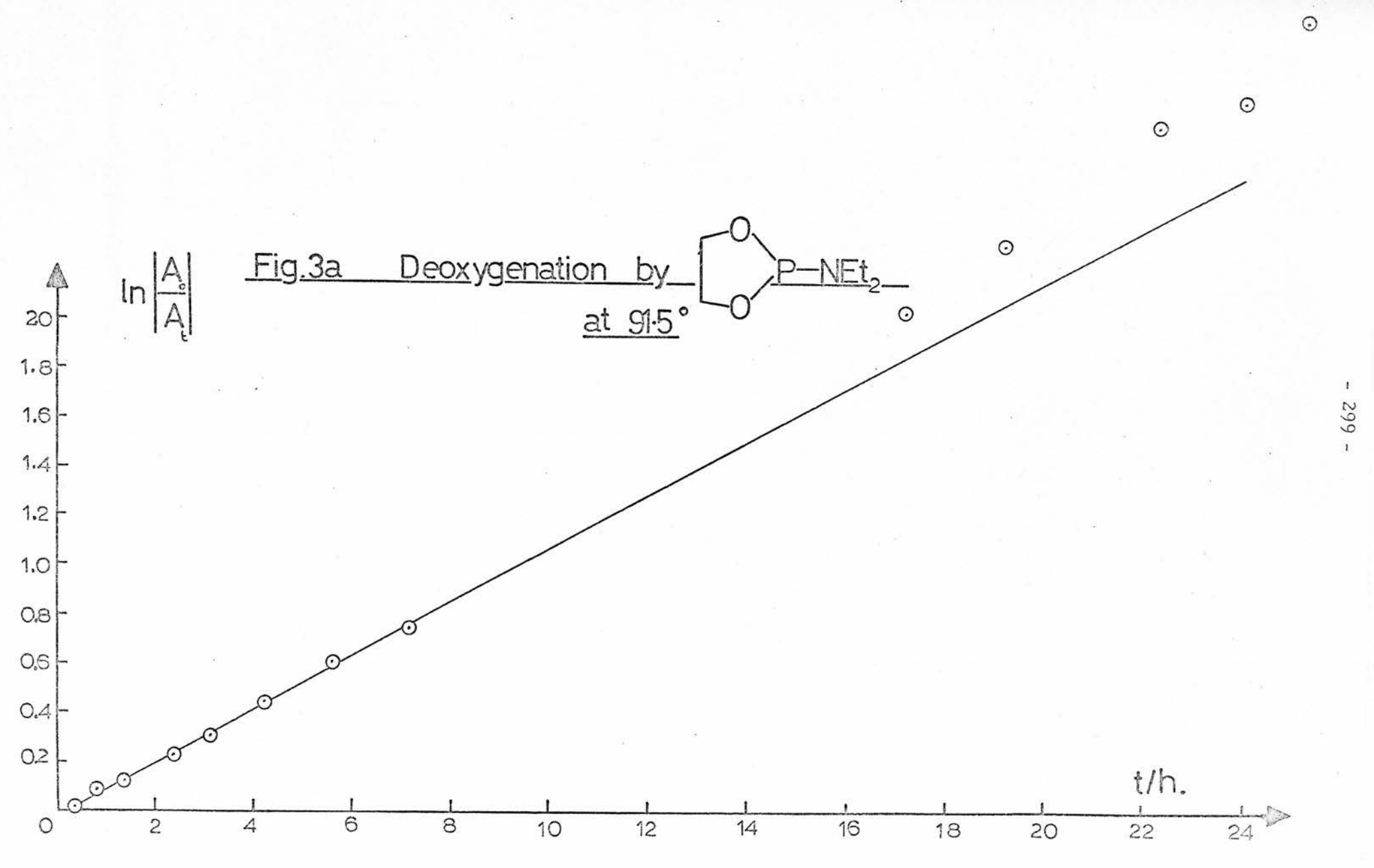


Fig.2b Deoxygenation by $(EtO)_3P$ at 91.5°
$\ln\left[\frac{B_\infty}{B_\infty - B_t}\right]$
20
10
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
t/h.


ln |A_o / A_t|
Fig.3a Deoxygenation by
O
O
P—NEt2
at 91·5°
20
1·8
1·6
1·4
1·2
1·0
0·8
0·6
0·4
0·2
0
2
4
6
8
10
12
14
16
18
20
22
24
t/h.

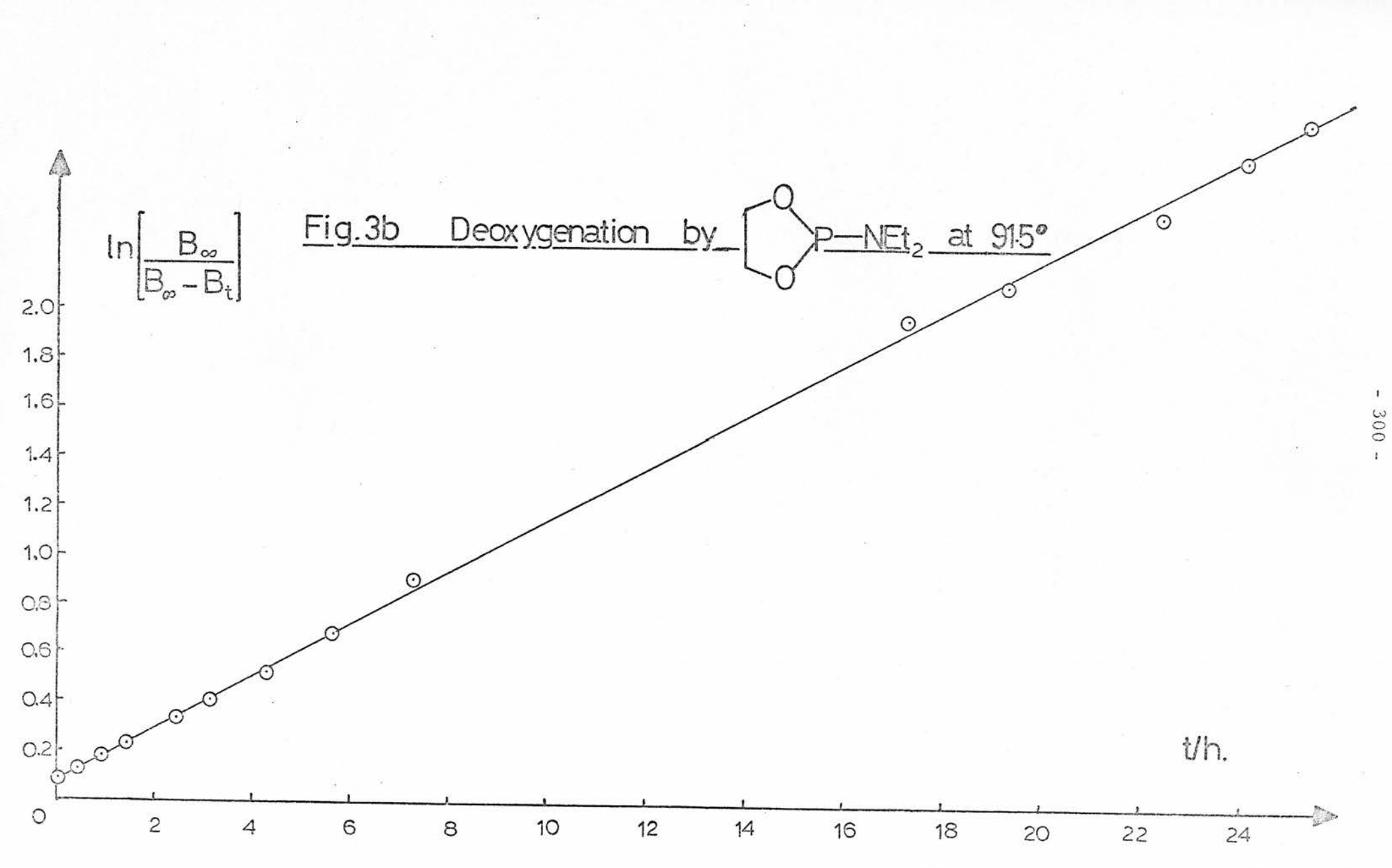
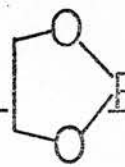


Fig.3b Deoxygenation by P—NEt2 at 91.5°
ln[B∞/(B∞ − Bt)]
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
2
4
6
8
10
12
14
16
18
20
22
24
t/h.

Fig.4a Deoxygenation by  P–OEt at 91.5°

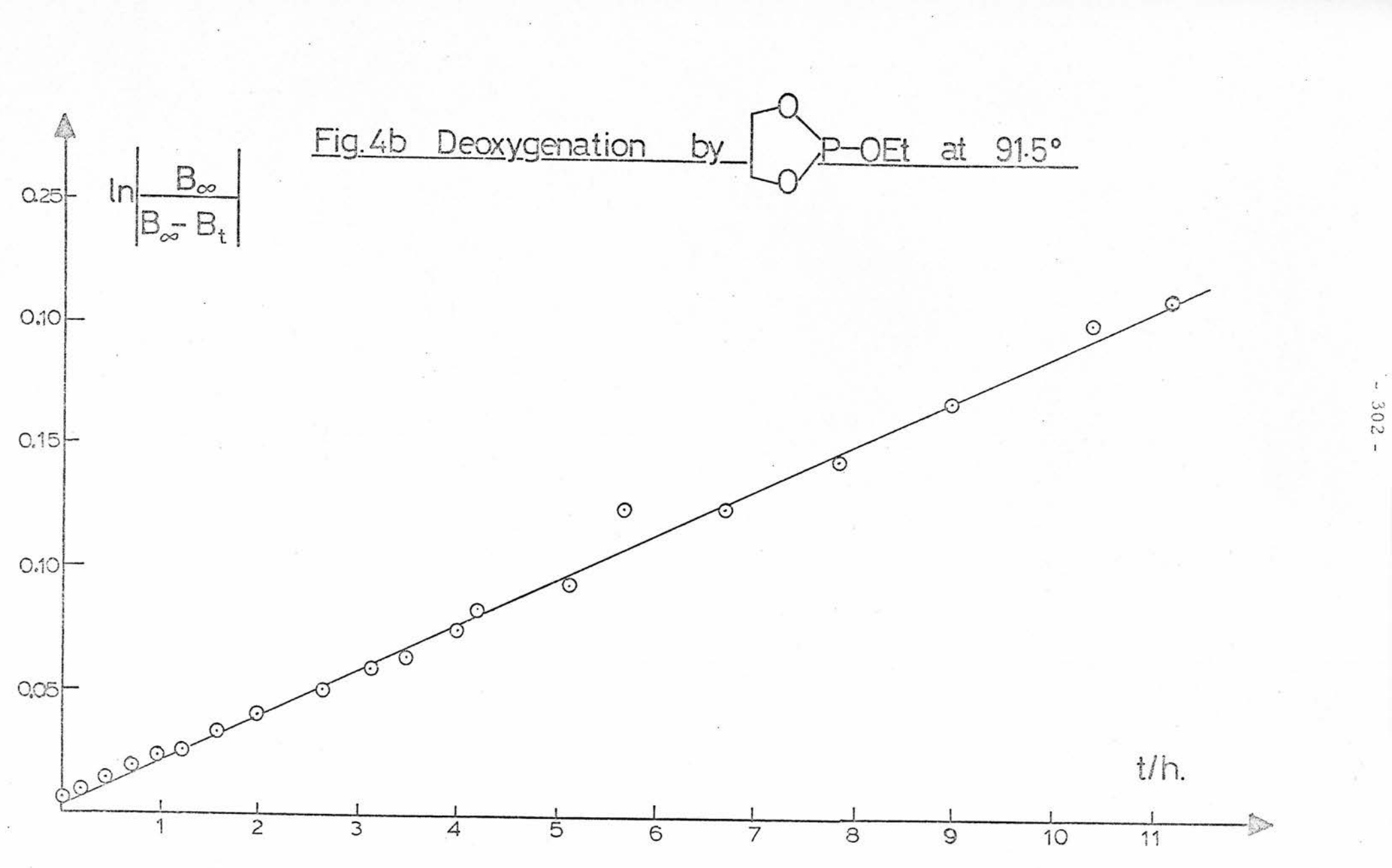
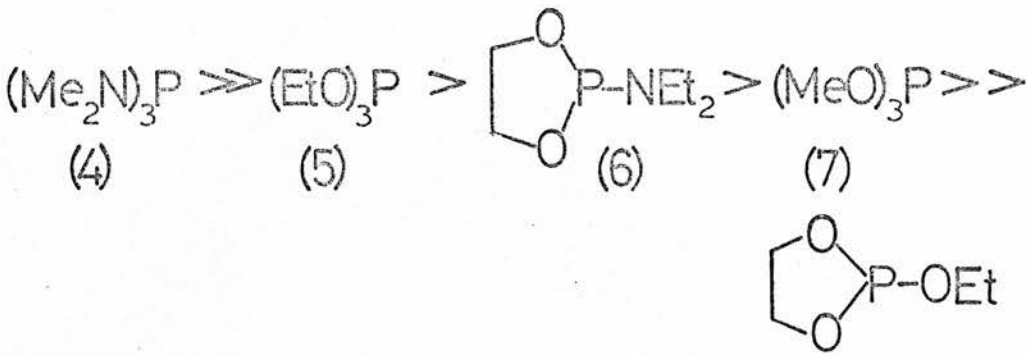


Fig.4b Deoxygenation by P–OEt at 91.5°
ln |B∞ / (B∞ − Bt)|
0.25
0.10
0.15
0.10
0.05
t/h.
1
2
3
4
5
6
7
8
9
10
11

3. Discussion

According to Hudson,[30] incorporation of the phosphorus atom of tervalent phosphorus reagents into small (four- or five-membered) rings should result in rate deceleration or rate enhancement relative to the acyclic analogues, depending upon whether phosphorus behaves as a nucleophile or as an electrophile.

The present investigation provides the reactivity order in Scheme 2, for the deoxygenation of o-nitrobenzalaniline by a series of tervalent phosphorus reagents.



Scheme 2

Triethyl phosphite reacted ca. 7 times as fast as the cyclic analogue 2-ethoxy-1, 3, 2-dioxaphospholane (8). In contrast, 2-diethylamino-1, 3, 2-dioxaphospholane (6) exhibited a similar reactivity to that of triethyl phosphite. However, hexamethylphosphorus triamide (4) was more than 50 times as reactive as triethyl phosphite, hence the reactivity of the cyclic phosphoramidite (6) is a combination of deactivation by the small-ring effect and activation by the favourable electronic influence of the amido function.

In conclusion, this investigation supports a rate-determining nucleophilic attack by tervalent phosphorus on the nitro group of o-nitrobenzalaniline as suggested by Cadogan et al.,[228] the magnitude of the rate deceleration caused by the five-membered ring is comparable to results obtained by other workers.[30]

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