Some Rearrangements of Unsaturated Phosphonate Esters:
Triethyl Phosphite/Iodine as a Reagent for Dehydration and Condensation
by Dianne Cooper.
A thesis
Presented for the degree of Doctor of Philosophy in the Faculty of Science of the University of Leicester.
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STATEMENT

The accompanying thesis, submitted for the degree of Doctor of Philosophy, is based upon work conducted by the author in the Department of Chemistry of the University of Leicester and the Central Research Laboratory, Ciba-Geigy (U.K. Ltd.), mainly during the period between October 1976 and October 1979.

All the work recorded in this thesis is original, unless otherwise acknowledged in the text or by references. No part of the work has been submitted for another degree in this or any other university.

Dianne Cooper.

December 1980
Some Rearrangements of Unsaturated Phosphonate Esters: Triethyl Phosphite/Iodine as a Reagent for Dehydration and Condensation by Dianne Cooper

A review is presented of the Claisen, Cope and Carroll rearrangements, with consideration of the mechanisms operative in and the synthetic applications of these reactions.

The Claisen orthoester rearrangement of several systems derived from $\beta,\gamma$-unsaturated $\alpha$-hydroxyphosphonates is described. The presence of the phosphoryl substituent appears to deactivate the Claisen system. A corresponding acetoacetic ester derivative failed to undergo a Carroll rearrangement.

The $[2,3]$ sigmatropic rearrangement of allylic sulphenates derived from $\beta,\gamma$-unsaturated $\alpha$-hydroxyphosphonates is described. The rearrangement of Claisen systems generated by the addition of allylic alcohols to diethyl (3-methyl-buta-1,2-dienyl) phosphonate is reported. Where the participating alcohol is allyl alcohol the two possible ketonic products of Claisen rearrangement are formed at room temperature.

The ready rearrangement observed in this case is explained in terms of the reaction proceeding via the first-formed allylic anion intermediates rather than via the neutral adducts.

An example of a Cope rearrangement involving the participation of an allenic phosphonate ester is described. The product of this rearrangement, a mixture of isomeric dienes, was converted into the corresponding Diels Alder adduct upon reaction with N-phenyl maleimide.

The synthesis of a vinylallenic phosphonate with the potential to undergo an intramolecular ene reaction was achieved. Although the product of the ene reaction, a 1,3,5-hexatriene, was not isolated, species resulting from the cyclisation and aromatisation of this product were characterised. A modification to this system produced a vinylallenic phosphonate amenable to function as the diene fragment in a Diels Alder cycloaddition reaction. The formation of an adduct with N-phenyl maleimide is described.

A short review of the use of PPh$_2$CCl$_4$ as a reagent for dehydration and condensation is presented as an introduction to Part 2.

The reaction between simple phosphites and elemental iodine is investigated and the use of the intermediate species formed as reagents for dehydration and condensation is described.
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Traditionally, the Claisen rearrangement has involved the thermal sigmatropic reorganisation of vinyl and aryl allylic ethers by a concerted, intramolecular process (Equation 1). This definition has now been expanded to include the rearrangement of any system fulfilling the basic requirement of six connected atoms with terminal unsaturated linkages, the all-carbon case being known as the Cope rearrangement (Equation 2).

The reaction, named after its discoverer (Claisen, 1912) was first observed when ethyl O-allylacetocetate (1) was subjected to distillation at atmospheric pressure in the presence of ammonium chloride.¹

Although the rearrangement is formally an equilibrium, the disparity in energies of the starting material and the product in aliphatic systems is such that the forward reaction goes virtually to completion. The driving force here is the energy gained in formation of the carbonyl double bond.
For allyl phenyl ethers, where the vinyl component is an integral part of an aromatic ring the product of rearrangement is an orthodienone. If the phenyl ether is unsubstituted in the ortho position (2) a rapid enolisation follows, restoring the aromaticity of the system to give an ortho allyl phenol (ortho rearrangement). That the ortho rearrangement proceeds with an inversion of the structure of the allyl group, i.e. that the \( \gamma \) carbon atom of the ether side chain becomes directly attached to the ring, has been confirmed by the labelling of the \( \alpha \) and \( \gamma \) positions of the allyl group.\(^2\)

Where the ortho positions are substituted and enolisation is impossible a second cyclic reorganisation, a Cope rearrangement, gives a paradienone and hence a para allyl phenol on enolisation (para rearrangement). An overall retention of structure of the allyl group is seen here as a result of two inversions.

In general, the rearrangements of both aliphatic and aromatic systems are thermally induced, unresponsive to free radical initiators,
and are relatively insensitive to acid-base catalysis, structural changes and solvent effects. Kinetic studies indicate the reorganisation to be unimolecular, with activation enthalpy, entropy and volume in harmony with a concerted, cyclic process having a highly ordered transition state.\textsuperscript{3,17}

The orbital symmetry theory of concerted reactions places the Claisen rearrangement in the category of sigmatropic migrations, these involving bond migration through a cyclic transition state in which an atom or group is simultaneously joined to both termini of a $\pi$ electron system.

\[
\begin{array}{c}
\sigma \\
1 \quad 2 \quad 3 \\
0 \quad 1' \quad 2' \quad 3'
\end{array}
\xrightleftharpoons{}
\begin{array}{c}
\sigma \\
1 \quad 2 \quad 3 \\
1' \quad 2' \quad 3'
\end{array}
\xrightleftharpoons{}
\begin{array}{c}
\sigma \\
1 \quad 2 \quad 3 \\
0 \quad 1' \quad 2' \quad 3'
\end{array}
\]

This change is described as a sigmatropic reaction of order (3,3), both termini of the $\sigma$ bond having moved to the third carbon atom along the $\pi$ system according to the numbering shown.

The six membered transition state involved may also be considered as two interacting allyl systems. For thermal rearrangement, the symmetry allowed process involves either suprafacial-suprafacial or antarafacial-antarafacial interaction of the allyl systems, the latter being less likely to be found as it requires twisting for overlap of orbitals. The two possible geometries for the suprafacial-suprafacial transition state, the four centred or chairlike arrangement, and the six centred or boatlike arrangement are both relatively strain free.
For molecules which can readily adopt either arrangement the chairlike geometry is strongly favoured. Moreover, of the two alternative chairlike arrangements the one which minimises 1,3 pseudo diaxial interaction is preferred. This has been demonstrated by examination of the reaction kinetics and product stereochemistry in the aliphatic Claisen rearrangement of the four isomeric crotlyl propenyl ethers.\(^4,5\) The trans, trans isomer \((4)\) gave in excess of 97% of the corresponding threo aldehyde via a chairlike transition state. This has a free energy of activation advantage of approximately three kcal. mol\(^{-1}\) over the boatlike conformation, which leads to the erythro aldehyde (Scheme 1). In addition, the trans, trans isomer is found to rearrange nine times faster than the cis, cis isomer, the two cis, trans isomers being intermediate in reaction rate. This may be attributed to the favourable equatorial disposition of the two methyl substituents in the transition state for the rearrangement of the trans, trans isomer.

![Scheme 1](image-url)
The stereoselectivity of the Claisen rearrangement has also been demonstrated by asymmetric induction in optically active molecules. The (+) isomer of the vinyl ether of cyclopenten-3-ol (5) gives upon rearrangement at 180-185°C in a sealed tube, an 81% yield of (-) cyclopentene-3-acetaldehyde (6).

\[
\begin{align*}
\text{(5)} & \quad \rightarrow \quad \begin{array}{c}
\text{[insert diagram here]}
\end{array} \quad \text{(6)}
\end{align*}
\]

Conversion of the R-(+) vinyl ether into the R-(−) aldehyde demonstrates that the new C-C bond formed in the rearrangement is cis to the C-O bond being broken, this being consistent with the accepted cyclic mechanism.

The general high degree of stereoselectivity and retention of optical purity exhibited by these reactions recommend their use for synthetic purposes. Of particular interest is the use of the aliphatic Claisen rearrangement in the area of natural product synthesis, where transformation with the maintainence of stereochemistry is essential. At the same time, rearrangement of suitably designed precursors has been utilised as a common method of synthesis of unsaturated aldehydes, ketones, amides, esters and carboxylic acids (Table 1).

Difficulty in the preparation of allyl vinyl ethers in good yield discouraged early widespread use of the Claisen rearrangement. Progress in this field was initiated by the transvinyletherification reaction of alkyl vinyl ethers with alcohols as described by Watanabe and Conlon.\(^7\)
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Here, treatment of an allyl or propargyl alcohol with a vinyl ether derivative in the presence of the Lewis acid mercuric acetate, gives the corresponding allyl or propargyl vinyl ether; isolated after neutralisation of the equilibrated mixture, or by slow distillation from the equilibrated mixture. In this way the cyclohexenyl ethers (7a) and (7b) may be prepared in 35-40% yield by vinylation of the corresponding cyclohexenols with ethyl vinyl ether. Upon heating to 190-195°C the vinyl ethers rearrange cleanly to unsaturated aldehydes (8a) and (8b).^8

\[ (7a) \text{ R} = \text{H} \quad (7b) \text{ R} = \text{Me} \]
\[ (8a) \text{ R} = \text{H} \quad (8b) \text{ R} = \text{Me} \]

Application of this method to the rearrangement of vinyl ethers of suitably constituted polycyclic allylic alcohols provides a stereospecific method for the introduction of an angular substituent into polycyclic systems.^8

\[ \Delta 190-195^\circ \text{C} \]
\[ 2\text{hrs.} \]

\[ 75-80\% \]
Modifications to the transvinyletherification reaction use dry hydrogen chloride,\(^9\) phosphoric acid,\(^{10,11}\) p-toluene sulphonie acid\(^{12}\) or oxalic acid\(^{13}\) as the catalytic agent, rearrangement in these cases occurring in situ.

The stereoselectivity of the reactions may be increased by the introduction of substituents into the allyl vinyl ether skeleton. This effect has been demonstrated by Faulkner and Petersen in a study of the rearrangement of allyl vinyl ethers derived from 2-methyl-1-penten-3-ol.\(^{13}\) Treatment of the allylic alcohol with an excess of ethyl vinyl ether containing mercuric acetate gave the allyl vinyl ether (9), which on heating to 110°\(^{\circ}\)C in a sealed tube was quantitatively converted into the unsaturated aldehyde (10) as a mixture of isomers, 90% trans and 10% cis.

The preferential formation of the trans isomer may be explained in terms of the reaction proceeding via the chairlike transition state in which 1,3 diaxial interaction is minimised, more readily.
The transition state leading to the formation of cis product becomes even less energetically favourable upon introduction of a substituent R into the system at the 3 position, there being a related increase in the diaxial interaction with the ethyl substituent in the 1 position. As a consequence of this, a greater proportion of the allyl vinyl ether will rearrange via the transition state leading to the trans isomer than does so in the absence of the substituent R. That the process becomes more stereoselective in this case has been illustrated by the reaction of a mixture of 2-methyl-1-penten-3-ol with two equivalents of isopropenyl methyl ether in the presence of a catalytic amount of oxalic acid. Upon heating in a sealed tube to 110°C this mixture gave a 76% yield of the unsaturated ketone (11), containing less than 1% cis isomer.

\[
\text{Me} \quad \text{Et} \quad \Delta \quad 24 \text{ hrs.} \quad \text{Me} \quad \text{Et} \\
\text{OH} \quad \text{Me} \quad \text{O} \quad \text{Me} \\
\text{OMe} \quad \text{Me} \quad \text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Me} \quad \text{Et} \quad \text{Me} \quad \text{O} \\
(11) \quad > 99\% \text{ trans}
\]

Similarly, a high degree of stereoselectivity is observed in the rearrangement of ethers resulting from the treatment of an allylic alcohol with 3-methoxyisoprene. Reduction of the resulting ketone with sodium borohydride in methanol generates an allylic alcohol amenable to a further addition of 3-methoxyisoprene, and a consequent elongation of the carbon chain by four units.
This two step process, known as the methoxyisoprene Claisen rearrangement lends itself readily to the production of successive head to tail isoprene units with trans double bonds, a feature of many natural products. The synthetic sequence has been exemplified by a total synthesis of all trans squalene.\textsuperscript{14}

A Claisen rearranged product having an unsaturated linkage $\alpha,\beta$ to the carbonyl group may also be obtained by the use of an olefinic ketal as the transvinylating reagent. The ketal is prepared by treatment of the corresponding $\alpha,\beta$ unsaturated ketone with orthoformate and excess alcohol, and on combination with an allylic alcohol an in situ rearrangement is catalysed by a trace of 2,4 dinitrophenol.

In the same manner as for the methoxyisoprene rearrangement, reduction of the carbonyl function of this product (12) enables elongation of the carbon chain. This route has been utilised in the synthesis of
the juvenile hormone precursor (13). \(^{(15)}\) (R=Et, R'=CO\_2Me, R''=Me)

\[
\text{CH}_2\text{R} - \text{H} - \text{CH} - \text{R} - \text{R'} - \text{H}
\]

(13)

Synthetically, this method is preferable to the methoxyisoprene rearrangement, ketals being more readily accessible than the corresponding dienol ethers. Also, lower temperature, shorter heating period and weaker acidity of the reaction mixture give a relatively cleaner product, affording better yields on purification.

The preparation of \(\gamma,\delta\)-unsaturated esters may be effected by the Claisen orthoester rearrangement. This involves heating an allylic alcohol with an excess of triethyl orthoacetate in the presence of a weak acid, eg. propionic acid. The first formed orthoester (15), loses ethanol to give the ketene acetal (16), which rearranges to the olefinic ester (17)\(^{(18)}\).

\[
\text{MeC(OEt)}_3 + \text{HO} \xrightarrow{\text{H}^+} \text{R}_1 \text{R}_2 \xrightarrow{\text{-EtOH}} \text{Me} \text{R}_1 \text{R}_2 \xrightarrow{\text{EtOH}} \text{R}_1 \text{R}_2 \xrightarrow{\text{EtO}} \text{R}_1 \text{R}_2
\]

(14) (15) (16)

(17)

In this way, alcohol (14) (R\(_1\) = Me, R\(_2\) = CH\(_2\)CH\(_2\)C(Me)=CH\(_2\) ) upon
heating with 7 equivalents of triethyl orthoacetate and 0.06 equivalents of propionic acid at 138°C, under conditions for the distillative removal of ethanol, gave diene ester (18) in 92% yield, and in excess of 98% trans isomer. Conversion into the essentially pure trans aldehyde (19) may be achieved in 80% yield by reduction of the ester with excess lithium aluminium hydride in ether at 0°C, followed by oxidation with 4 equivalents of filtered Collins solution.

Application of this method to the synthesis of all trans squalene is comparable in efficiency with the methoxyisoprene method, approximately 98% stereoselectivity being achieved for each double bond. Although the orthoester process involves more steps these are easy to perform and the reagents required are commercially available.

The methods considered for the preparation of allyl vinyl ether derivatives may also be applied to formation of the corresponding propargyl vinyl ethers from propargyl alcohols. The rearrangement products here will be homoallenyl carbonyl compounds.

Generally, more severe reaction conditions are required, this being a reflection of the difficulty in accommodating the linear, rigid, propargyl group in the transition state for rearrangement.
A temperature of 250°C is needed to obtain a 20-30% yield of rearranged product (21) in the case of propargyl vinyl ether (20) where $R_1=R_2=R_3=R_4=H$.\(^\text{16}\)

Increased substitution has been found to lead to an easier rearrangement at lower temperature, indicating that steric hindrance in the transition state is not an important factor. Where substituent $R_1=R_2=R_3=R_4=\text{Me}$ in compound (20) a 76% yield of the allenic aldehyde may be isolated after a period of fifteen minutes at 140°C.

\[
\begin{align*}
\text{Me} & \quad \text{CHO} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

The observed substituent effect suggests that a mechanism involving a series of one electron shifts is more likely for this process than the standard two electron shift representation.

As the homoallyl carbonyl compounds produced are easily isomerised by base, this sequence of reactions can be employed for the preparation of conjugated dienic carbonyl systems. The synthesis of Ec-ionone described by Saucy and Marbet is a good example of this.\(^\text{12}\)
In systems where alternative rearrangement pathways are available, e.g., compound (22) in which either an allyl group or a propargyl group may participate, rearrangement will occur exclusively through the allyl system to produce the skeletal structure: \( \text{CH}_2=\text{CH}-\text{O}-\text{CH} \quad \text{C} \equiv \text{CH} \quad \) 

\[ \text{(22)} \]

The Meerwein-Eschenmoser method for transvinyletherification employs a mixture of 1-dimethylamino-1-methoxyethene and/or the corresponding acetal of \( N,N \)-dimethylacetamide as the vinylating agent. The rearrangement product, a \( \gamma,\delta \)-unsaturated amide, is formed in situ in refluxing solvent, no acid catalyst being required.\(^{18,19}\)

\[ \text{OH} + \text{CH} = \text{C} + \text{OMe} + \text{NMe}_2 \quad \text{Δ} \quad \text{xylene} \]

A related reaction involving the rearrangement of an allenyl vinyl ether derivative has been reported by Picini and Pouliquen.\(^{20}\) Here, boron trifluoride catalysed addition of (1-methylallenyl) carbinol to ynamines results in the isolation of moderate yields of the corresponding unsaturated amides. The participation of allylic amines necessitates
temperatures in excess of 280°C for rearrangement.

\[
\text{Me} \\
\text{H}_2\text{C} = \equiv \text{C}-\text{CH}_2\text{OH} + \text{R-} \equiv \text{C}-\text{C-NEt}_2 \xrightarrow{\text{BF}_3} \left[ \text{R-} \equiv \text{CH} = \text{C} - \bigcirc \text{Et}_2 \right] \\
\text{Me}
\]

This general scheme has also been used in the preparation of conjugated dienic amides, rearrangement of a propargyl vinyl ether derivative giving an allenyl amide which is amenable to base catalysed isomerisation.21

Claisen rearrangements involving the enolate anions of allyl esters may be used in the preparation of \(\gamma,\delta\)-unsaturated carboxylic acids. These reactions require no pre-equilibration of allylic alcohol with excess reagent, and the mild conditions necessary permit the rearrangement of acid sensitive and thermally labile esters.

\[
\text{R}_1 \equiv \text{C}-\text{CH} = \equiv \text{H} \\
\text{R}_2 \equiv \text{C} - \bigcirc \text{R}_3 \\
\text{R}_1 \equiv \text{Me} \\
\text{R}_2 = \text{R}_3 = \text{Me} \quad 80\%
\]

\[
\text{R}_1 \equiv \text{R}_2 \equiv \text{R}_3 \equiv \text{Me} \\
\text{R}_1 \equiv \text{R}_2 \equiv \text{R}_3 \equiv \text{Me} \\
\text{R}_1 \equiv \text{R}_2 \equiv \text{R}_3 \equiv \text{Me}
\]

\[
\text{R}_1 \equiv \text{R}_2 \equiv \text{R}_3 \equiv \text{Me} \\
\text{R}_1 \equiv \text{R}_2 \equiv \text{R}_3 \equiv \text{Me}
\]

\[
\text{Method A} \\
1) \text{NaH, 110°C, 24 hours} \\
2) \text{H}_2\text{O}^+
\]

\[
\text{Method B} \\
1) 1.05 \text{ molar LiIICA}/\text{THF/-78°C} \\
2) \text{Me}_3\text{SiCl} \\
3) 55°C
\]
Generation of the enolate anion may be effected by sodium hydride, Method A, rearrangement occurring on heating the reaction mixture at 110°C for 24 hours. Alternatively, use of lithium N-isopropylcyclohexylamide, Method B, gives the corresponding lithium enolate which rearranges on warming to room temperature, or slightly above. For the allylic esters of primary acids, i.e. \( R^2 \cdot R^3 = H \), the rearrangement of the lithium enolate is sufficiently slow to allow undesired side reactions, and trimethylsilyl chloride is used to trap the enolate anion prior to rearrangement at 55°C. Conversion into the corresponding \( \gamma,\delta \)-unsaturated carboxylic acid is then achieved simply by acidification of the reaction mixture.

A reaction that appears to have much in common with the Claisen rearrangement is the thermal rearrangement-decarboxylation of the acetoacetic esters of allylic alcohols, discovered by Carroll in 1940. In the original experiments \( \gamma,\delta \)-unsaturated ketones, e.g. (24), were produced by the action of heat on a mixture of a \( \beta,\gamma \)-unsaturated alcohol and ethyl acetoacetate, in the presence of a catalytic amount of alkali. At this time a mechanism analogous to a Michael addition was proposed for the reaction. Subsequently, the true nature of the transformation was recognised by Kimel and Cope, who isolated and rearranged pure samples of allylic acetoacetates. They called attention to the similarity to the Claisen rearrangement and proposed the cyclic mechanism shown in Scheme 2, involving electron reorganisation via a chelated enol form.
Reaction involving intermediacy of the alternative, but less likely enol form (25), would result in a mechanism bearing an even closer resemblance to that of the Claisen rearrangement.

An indication that enol (25) might be a feasible intermediate is the observation that allylic cyanoacetates, in which only an enol corresponding to (25) is possible, undergo the same thermal rearrangement.26
An alternative method of preparation of the acetoacetic esters involves the reaction of diketene with $\beta,\gamma$-unsaturated alcohols in the presence of 0.01 mole equivalents of sodium alkoxide. Preparation of resolved, chiral, allyl acetoacetates in this manner has been used to demonstrate that the rearrangement-decarboxylation proceeds with the same high degree of stereoselectivity as is exhibited by the Claisen rearrangement. Thus, on heating at 200-220°C for a period of twelve hours, optically active cyclohexen-3-yl acetoacetate is converted into 2-cyclohexen-1-yl acetone with retention of optical activity, in accord with a concerted mechanism for the rearrangement.

\[
\begin{align*}
\text{(-)} & \quad \xrightarrow{\text{200-220°C}} \quad \text{12 hrs.} \\
\text{(+)}
\end{align*}
\]

The stereochemical parallel between the acetoacetate and the Claisen rearrangement has been found to extend to reaction occurring with geometrical specificity. Rearrangement of acetoacetate (26) with loss of carbon dioxide gives the corresponding $\gamma,\delta$-unsaturated ketone in which the two largest substituents attached to the double bond are trans oriented. This preference for the alkene with larger groups trans is also a characteristic of the Claisen rearrangement, where it is taken as being evidence for reaction via a chairlike conformation for the six-membered transition state, with the larger substituents equatorial.
Synthetic applications of this reaction in which the stereo-specificity exhibited is taken advantage of include a total synthesis of \( \psi \)-ionone from acetone.\textsuperscript{28}
The isomerisation of 1,5-dienes in a (3,3) sigmatropic process is known as the Cope rearrangement. The reaction is normally reversible and gives an equilibrium mixture of starting material and product which is rich in the thermodynamically more stable isomer. 4-Methyl-1,5-hexadiene and 1,5-heptadiene, for example, equilibrate in the gas phase at 220-300°C to give a mixture consisting of approximately 85% of the more highly substituted diene, as a mixture of cis and trans isomers.29,30

Where the diene is symmetrical about the (3,4) bond the product is identical to the starting material and consequently under normal conditions the rearrangement cannot be detected. Systems which undergo this 'degenerate Cope rearrangement' are said to have fluxional structures and include the fused cyclopropane derivative (27) in the cisoid form, and a series of related structures (28) in which a bridging group maintains the cisoid form.
The Cope rearrangement has its greatest synthetic utility where one of the isomeric components is strongly favoured at equilibrium. The driving force responsible for shifting the equilibrium in a given direction may be an increase in conjugative interaction, the relief of ring strain, or, in more complex cyclic systems, subtle differences in conformational stabilities.

In the original studies carried out by Cope and co-workers the systems were constructed to provide a driving force of double bond conjugation with cyano, carboxy, or phenyl groups.\textsuperscript{31-34}

\[
\text{Me} \quad \text{CO}_2\text{Et} \quad 4\text{hrs.} \quad 150-160^\circ\text{C} \quad \begin{array}{c}
\longrightarrow \\
\end{array} \quad \text{Me} \quad \text{CO}_2\text{Et}
\]

Rearrangements in such systems occur readily in the range 150-200\(^\circ\)C in good yield, where the starting materials are heated alone for short periods of time. The vinyl double bond of the vinylallyl malonic acid derivative may be part of a ring as in the indene derivative (29),\textsuperscript{32} but rearrangement fails to occur where the vinyl group is part of a benzene or naphthalene nucleus.\textsuperscript{33,34}

\[
\begin{array}{c}
\text{NC} \\
\text{CO}_2\text{Et} \\
\end{array} \quad (29) \quad \begin{array}{c}
\longrightarrow \\
\end{array} \quad \begin{array}{c}
\text{NC} \\
\text{CO}_2\text{Et} \\
\end{array} \quad 63\%
\]

The same principle has also been applied by Conia and co-workers to systems in which the activating system is ketonic. 3-Isopropenyl-3-methyl-5-hexen-2-one (30) rearranges upon heating to a mixture of
three isomeric dienic ketones. Further heating of this mixture of equilibrated isomers results in quantitative and stereospecific conversion to the cyclopentene (31).  

![Chemical structure of isomeric dienic ketones and their conversion to cyclopentene](image)

Other examples of Cope rearrangements in hexadiene systems in which the activating group is carbonyl are to be found in allylated cyclohexadienes, eg. (32), which represent the intermediates in the reversible ortho-para migrations of the para Claisen rearrangement. Such transformations, having the additional driving force of aromatisation, occur with ease.

![Chemical structure of Cope rearrangement](image)

Mechanistic studies of the rearrangement of meso and d,1,3,4 dimethyl-1,5-hexadienes show that, as for the Claisen rearrangement, the transition state of the Cope rearrangement prefers a chairlike to a boatlike conformation. The meso isomer rearranges almost exclusively, (99.7%), to cis, trans-2,4-octadiene, at 225°C, this stereochemistry
being consistent only with a chairlike conformation for the transition state. Cis, cis or trans, trans product would be derived from the boatlike conformation.

![Diagram](image)

A difference in free energy of activation of about 6 kcaI mol\(^{-1}\) favours the chairlike geometry and of the two chairlike arrangements available the one in which 1,3 diaxial interactions are minimised is preferred by approximately 2 kcaI mol\(^{-1}\). Consequently, d,1-3,4-dimethyl-1,5-hexadiene rearranges to trans,trans-2,4-octadiene via a transition state having diequatorial methyl groups, rather than to the cis, cis isomer via the transition state having diaxial methyl groups.

![Diagram](image)

Although the chairlike transition state is preferred, in sterically constrained molecules where a boatlike conformation represents the only accessible pathway to product, this may be achieved without an excessive expenditure of energy. Notable examples include the Cope rearrangement of cis-1,2-divinylcyclopropane\(^{38}\) and cis-1,2-divinylcyclobutane,\(^{39}\) both involving a boatlike transition state, but occurring extremely readily on account of the relief of strain in the small rings.
Cope rearrangements in 1,5-hexenynes and 1,5-hexadiynes appear to proceed readily, as do those in systems incorporating allenyl functions as the unsaturated linkages.

Since the diynes give rise to cyclised products predominantly, the intermediacy of the expected Cope product is conjectural in these systems. Upon heating to a temperature of 340°C in a flow system, the enyne (33) gives three different products. With longer contact times, or an increase in temperature to 385°C the amount of allenyl product decreases, and the amount of cyclised product increases, supporting the theory that the allenyl Cope product is the precursor of the cyclic ones.

1,5-Hexadiyne (34) is transformed in 85% yield to the cyclised product 3,4-dimethylenecyclobutene in a flow reactor at 350°C, none of the normal Cope product, bis(allene) being detected.
Cyclobutene formation here, may be interpreted as occurring via a rate determining Cope reaction followed by a very rapid electrocyclic ring closure.

Thermal rearrangements in systems containing either cyclic (35) or open chain (36) allenyl functions lead to the expected Cope products.

Although the open chain allenyl compounds may easily adopt the favoured chairlike conformation for rearrangement (37), it is by no means clear that the cyclic allenes are able to achieve this, and a non-concerted mechanism may be operative here.
There exists a fairly wide range of preparative procedures for the formation of suitable precursors for Cope rearrangement. The systems originally studied by Cope and co-workers were prepared by alkylation of alkylidene malonic acid derivatives with allylic halides. Alkylidene ketones may be substituted for the malonic acid derivative, as exemplified by Conia, and propargyl halides may replace the allyl halides.

Hydrocarbons with 1,5-unsaturated linkages may also be prepared by coupling the appropriate allyl or propargyl halide over magnesium.
An irreversible Cope rearrangement occurs where the 1,5-diene has a 3-hydroxy substituent; the primary product in this case, an enol, rapidly tautomerising to the corresponding ketone. This process has been named the 'oxy-Cope rearrangement'.

The utility of the rearrangement as a preparative method for 5,6-unsaturated carbonyl compounds is complicated by a competing cleavage reaction leading to the formation of β-hydroxy alkenes. A study involving the thermolysis of ten different methyl substituted 3-hydroxy-1,5-dienes suggests that both the rearrangement and the cleavage products are formed by concerted, electrocyclic processes.

In no instance is there evidence of crossover products resulting from the radical coupling of the like fragments. Also, in all cases, increase in reaction temperature results in an increase in the production of cleavage product at the expense of rearranged product, this reflecting the higher activation energy required by the less symmetrical transition state for β-hydroxy alkene cleavage. The simple 1,5-hexadien-3-ol (38) gives a 57% yield of rearranged product when distilled through a helices packed column at 380°C. Methylation at C₂, C₃, or C₄ of the hexadiene system has little effect upon the product.
distribution, whereas the presence of methyl groups at C₁, C₅ and C₆ enhances cleavage due to steric and electronic factors (Table 2).

Substitution at C₅ will stabilise the formation of a transient positive charge, a factor which favours the transition state required by cleavage. The introduction of cis methyl substituents at C₁ or C₆ causes steric hindrance to rearrangement. In the case of the C₆ substituent, the cleavage reaction is also disadvantaged, but to a lesser extent due to the smaller steric requirements of a proton.

The effects of methyl substitution on the thermolysis of 3-hydroxy-1,5-hexadienes

<table>
<thead>
<tr>
<th>Position of methyl groups</th>
<th>% rearrangement</th>
<th>% cleavage</th>
</tr>
</thead>
<tbody>
<tr>
<td>H O</td>
<td>57</td>
<td>43</td>
</tr>
<tr>
<td>0</td>
<td>29</td>
<td>70</td>
</tr>
<tr>
<td>1</td>
<td>64</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>66</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>33</td>
<td>67</td>
</tr>
<tr>
<td>4,6</td>
<td>55</td>
<td>45</td>
</tr>
</tbody>
</table>

Table 2

Oxy-Cope rearrangement may also be achieved in systems where triple bonds have replaced either of the double bonds of the allyl vinyl alcohol precursor. 5-Hexen-1-yn-3-ol, thermolysed in a flow system at 370°C gives a 35% yield of the Cope product (39), in addition to two cyclic products, (40) and (41). The cyclopentene derivatives appear to arise from initially formed allenol.
Under the same reaction conditions, 1-hexen-5-yn-3-ol gives a 12% yield of 4,5-hexadienal (42), via an acetylenic oxy-Cope rearrangement. The major product here is 3-cyclopentenecarboxaldehyde (43). A competing cleavage reaction favoured at higher temperatures results in the formation of acrolein and allene or propyne.
Evidence suggests that the hydroxy alkene cleavage which often predominates in these reactions, together with undesired cyclisation processes, may be minimised by the use of esters in the place of the hydroxy compounds. The diacetate (44) is reported to rearrange to the corresponding dienol ester in 70% yield at 240°C.\(^4^8\)

\[
\begin{align*}
\text{AcO} & \quad 240^\circ C \\
\text{AcO} & \quad \text{AcO}
\end{align*}
\]

(44)

This may be contrasted with the result reported for the glycol (45) which gives 1-formylcyclopentene in only 40% yield when heated under reduced pressure in the same temperature range.\(^4^9\)

\[
\begin{align*}
\text{HO} & \quad 240^\circ - 260^\circ C \\
\text{HO} & \quad \text{HO} \\
\text{HO} & \quad \text{CHO}
\end{align*}
\]

(45)

Trimethylsilyl derivatives of alcohols have also been used in the same way with success in minimising cleavage.\(^5^0\)

Work of Evans and Golod\(^5^1\) suggests that generation of the enolate anion of a 3-hydroxy-1,5-diene causes Cope rearrangement to occur at a rate \(10^{10}\) to \(10^{17}\) times faster than the rearrangement of the analogous allyl vinyl system. A study of the rearrangement of the anions derived from the bicyclic dienols (46a) and (46b) shows that the nature of the metal counter-ion has a significant effect upon the rate of reaction (Table 3).
Although alkoxides (46a), M= Li, MgBr showed no evidence of rearrangement in refluxing THF over a period of 24 hours, the corresponding sodium alkoxide rearranged to the enolate (47a) with a half-life of 1-2 hours under these conditions. The potassium alkoxide underwent rearrangement within several minutes and upon quenching of the enolate mixture with water, the methoxy ketone (48a) was obtained in greater than 98% yield. Maximal rate acceleration is found to occur with the ion pair dissociation achieved upon addition of ionophores to the reaction mixture.
A question arises as to the mechanism operative in these enolate anion rearrangements. Gas phase pyrolysis of the parent dienol (49) gives a 45% yield of the Cope product, the authors favouring the intermediacy of a diradical rather than a concerted rearrangement, even though structurally the reacting molecule could achieve a six centred transition state geometry.

![Chemical Structure](image)

In the case of enolate anions, observations suggest a concerted mechanism, but do not rigorously exclude the possibility of intervening diradicals or carbanions. Under conditions in which diene (46a), M= K rearranges within minutes, diene (50) shows no rearrangement even after heating in refluxing THF for 24 hours.

![Chemical Structure](image)

Precursors for the oxy-Cope rearrangement require a hydroxy substituent at the 3 position of a 1,5-hexadiene system. Such structures are commonly prepared by the action of allyl or propargyl Grignard reagents on the appropriate α,β-unsaturated carbonyl compounds. Alternatively, vinyl Grignard reagents may be used with β,γ-unsaturated carbonyl compounds.
Base-catalysed addition of a dialkyl hydrogen phosphite to the
>\text{C}=\text{O}
 of an \(\alpha,\beta\)-unsaturated aldehyde results in formation of the

\text{corresponding \(\beta,\gamma\)}-unsaturated \(\alpha\)-hydroxyphosphonate.\(^{53}\)

\[
\begin{align*}
\text{RONa} + (\text{RO})_2\text{P} & \longrightarrow (\text{RO})_2\text{P}-\text{CH}-\text{CH}=\text{CHR} \\
1,2\text{ addition (51)}
\end{align*}
\]

In unsaturated ketones the reactivity of the carbonyl group is
lowered somewhat by the decrease in the polarisation due to the attached
alkyl group. Consequently, the nature of the addition product with
dialkyl hydrogen phosphites is determined by the relative electrophilic
character of the carbonyl and alkene linkages. Generally there is found
to be a strong preference for Michael addition of the phosphite to the
carbon-carbon double bond.\(^{54}\)

\[
\begin{align*}
0 & \quad 0 \\
(\text{RO})_2\text{PH} + R''\text{C}-\text{CH}=\text{CHR} & \longrightarrow \left[ \begin{array}{c}
\text{RONa} \\
\text{OH} \\
R''-\text{C}=\text{CH}-\text{CH}(\text{R'})\text{P(OR)}_2
\end{array} \right] \\
1,4\text{ addition (52)}
\end{align*}
\]

Reaction of 3-buten-2-one with dimethyl hydrogen phosphite in the
presence of sodium methoxide was found to give product, 95\% of which
resulted from a 1,4 addition of phosphite [(52); \(R=R'''=\text{CH}_3\), \(R''=\text{H}\)]. The
remaining 5\%, from 1,2 phosphite addition [(51); \(R=R'''=\text{CH}_3\), \(R''=\text{H}\)]
separated from the isolated reaction product as a white crystalline
solid. The formation of the 1,2 addition product as an oil, in 17\% yield,
has previously been reported,\(^{54}\) with the use of boron trifluoride etherate
as a catalyst. Here, co-ordination of the acidic catalyst to the carbonyl
oxygen enhances the activity of this grouping towards nucleophilic attack. The same effect is noted in the presence of catalytic AlCl$_3$ or HCl.

$$\text{C}=\text{O} \quad \text{[A}=\text{H}^+, \text{BF}_3.0(C_2H_5)_2, \text{AlCl}_3]$$

The improvement in the efficiency of the addition to $\text{C}=\text{O}$ in the presence of an acidic catalyst is, however, insufficient to render this method a viable general means of conversion of $\alpha,\beta$-unsaturated ketones into the corresponding $\alpha$-hydroxyphosphonates.

Interest in $\beta,\gamma$-unsaturated $\alpha$-hydroxyphosphonates was founded on the idea that these compounds might function as the allylic alcohol component of the allyl vinyl ether system required for the Claisen rearrangement.

Initial studies involved the use of diethyl (1-hydroxy-allyl) phosphonate (53) prepared by the base catalysed addition of diethyl hydrogen phosphite to acrolein.

$$\begin{align*}
\text{EtOH} + \text{(EtO)$_2$PCl} & \quad \text{or} \quad \text{HCl} + \text{(EtO)$_3$P} \\
\text{EtONa} & \\
\text{(EtO)$_2$P-H} + \text{H-C=CH$_2$} & \rightarrow \text{(EtO)$_2$P-CH-CH$_2$=CH$_2$}
\end{align*}$$

(53)

Later, an improved method of preparation of this compound was employed, involving addition of acrolein to equimolar amounts of triethyl phosphite and dry HCl, at low temperature. The triethyl phosphite-hydrogen chloride mixture may also be formed by reaction of diethyl chlorophosphite with ethanol.
Transvinyletherification of allylic alcohol (53) was attempted by treatment with ethyl vinyl ether in the presence of mercuric acetate, as described by Watanabe and Conlon. 7

\[
\begin{align*}
\text{(EtO)}_2\text{P} & \quad \text{Ethyl vinyl ether} \\
\text{OH} & \quad \text{Mercuric acetate} \\
\end{align*}
\]

This reaction relies upon a large excess of ethyl vinyl ether to displace the equilibrium to the right hand side. However, no evidence of incorporation of the vinyl grouping was observed, with either mercuric acetate or 2,4-dinitrophenol as the catalyst. The stability of the α-hydroxyphosphonate under the conditions of reaction may be ascribed to hydrogen-bond formation between the phosphoryl and hydroxyl groups. Intermolecular hydrogen-bonding leading to dimeric species (54) is believed to predominate here, the stability of the intramolecular hydrogen-bond being lower as it involves formation of the energetically less favourable five-membered ring (55). 56, 57

\[
\begin{align*}
\text{(54)} & \\
\text{(55)} & \\
\end{align*}
\]

Acid catalysed reaction of α-hydroxyphosphonate (53) with triethyl orthoacetate proved to be a more successful means of generation of a system amenable to Claisen rearrangement. Here, use of triethyl orthoacetate (b.p. 142°C) as the vinylating agent enables a higher reaction temperature to be employed than is possible with ethyl vinyl
ether (b.p. 33°C), this being conducive both to the formation of the intermediates involved, and to the subsequent rearrangement.

\[
\begin{align*}
\text{(53)} & \quad \xrightarrow{\Delta} \quad \text{(56)} \\
\text{(57)} & \quad \xrightarrow{\Delta} \quad \text{-(EtOH)}
\end{align*}
\]

A mixture of α-hydroxyphosphonate (53), triethyl orthoacetate (7 mole equivalents), and a catalytic amount of propionic acid was heated under conditions for the distillative removal of ethanol. The exclusion of two mole equivalents of ethanol was found to occur readily upon heating the reaction mixture to just below the boiling point of the orthoester, this suggesting successful formation of the ketene-acetal (56). After a period of 3 hours at the same temperature followed by the removal of excess orthoester, crude reaction product showed evidence of the desired product of rearrangement γ,δ-unsaturated ester (57), together with unrearranged ketene-acetal. Completion of the rearrangement was effected by further heating of the crude reaction product at a higher temperature, the process being monitored by n.m.r. spectroscopy. Disappearance of a signal at 5.37 in the 
H n.m.r. spectrum, ascribed to the methylene protons (a) of ketene-acetal (56) was accompanied by the simultaneous loss of a signal at +20.16 p.p.m. in the 
31P n.m.r. spectrum.
This is in accord with the conversion of (56) into the \( \gamma,\delta \)-unsaturated ester (57), as a consequence of which the (a) protons experience a downfield shift becoming coincident with the signal due to the methylene protons (b) of the phosphonate ester grouping.

An increase in the reaction temperature, enhancing in situ rearrangement, was achieved by reducing the excess of triethyl orthoacetate used. Thus, reaction with completion of the rearrangement process occurred on heating a mixture of \( \alpha \)-hydroxyphosphonate (53) and triethyl orthoacetate in a 1:1.4 molar ratio at a temperature of 175°C for 3 hours.

The participation of higher molecular weight orthoesters leads to the attainment of higher reaction temperatures, this facilitating the rearrangement process. Conversion of \( \alpha \)-hydroxyphosphonate (53) into the corresponding \( \gamma,\delta \)-unsaturated ester (58) was effected on heating with triethyl orthopropionate [(59); 4 mol. eq.] for a period of 2.5 hours at 175°C.
A feature of this reaction which may arise as a direct consequence of the higher reaction temperature attained, was cleavage of the phosphorus ester grouping, this leading to the appearance of diethyl hydrogen phosphite as a by-product.

The α-hydroxyphosphonates [(51); R=Me, Et, R'=Ph] produced by the base-catalysed addition of dialkyl hydrogen phosphites to cinnamaldehyde were found to react with orthoesters in an analogous manner.

\[ \begin{align*}
\text{O} & \quad \text{(RO)}_2P
\begin{array}{c}
\text{\begin{array}{c}
\text{Ph} \\
\text{\small OH}
\end{array}}
\end{array}
\end{align*} + \text{MeC(OEt)}_3 \rightarrow \begin{align*}
\text{O} & \quad \text{(RO)}_2P
\begin{array}{c}
\text{\begin{array}{c}
\text{Ph} \\
\text{\small OH}
\end{array}}
\end{array}
\end{align*}
\]

(51) \ R=\text{Me, Et}

Less severe reaction conditions seem to be required here for the rearrangement process. A mixture of α-hydroxyphosphonate [(51); R=Me, R'=Ph] and triethyl orthoacetate (1:7 molar ratio) gave the product of Claisen rearrangement, γ,δ-unsaturated ester [(60); R=Me, R'=Ph], on heating to a temperature of 130°C for a period of 4 hours. The use of a higher reaction temperature in this case gave crude reaction product showing a multiplicity of peaks in the region of the $^{31}\text{P}$ n.m.r. spectrum associated with the desired compound. This effect is attributed to the occurrence of exchange between the ester groupings of the phosphonate and the orthoester under these conditions, leading to the
formation of a mixture of products. The use of reagents having identical ester substituents eliminated the problem. Thus, α-hydroxyphosphonate [(51); R=Et] gave γ,δ-unsaturated ester [(60); R=Et] in 68% isolated yield on heating with two mole equivalents of triethyl orthoacetate at a temperature of 145°C for a period of 4 hours.

Combination of the corresponding methyl esters proved to be less efficient, large amounts of unreacted α-hydroxyphosphonate being recovered. The difficulty experienced in the vinyl etherification-rearrangement process here is attributed to the restriction on the reaction temperature imposed by the boiling point of trimethyl orthoacetate (b.p. 108°C).

It was discovered that in this system the initial product of the Claisen rearrangement may undergo a prototropic shift to bring the phenyl group into conjugation with the double bond.

\[
\begin{align*}
\begin{array}{c}
\text{(MeO)}_2P \ \text{Ph} \\
\text{O} \ \ H \\
\text{OEt}
\end{array}
\end{align*}
\rightarrow
\begin{align*}
\begin{array}{c}
\text{(MeO)}_2P \ 	ext{H(a)} \\
\text{O} \ 	ext{H} \text{Ph}
\end{array}
\end{align*}
\]

Isomerised product (61) appeared as a minor component of the crude reaction product, but became the major component on attempted purification by column chromatography with alumina absorbent. This process is accompanied by a shift in the $^{31}$P n.m.r. signal for this compound from +20.97 to +29.2 p.p.m., the isomerised product also giving rise to a characteristic doublet of doublets in the $^1$H n.m.r. spectrum due
to the methylene protons (a).

It is evident from the results obtained that the electron withdrawing effect of the phosphoryl substituent leads to a deactivation of the Claisen system, rearrangement proceeding at an elevated temperature to that required by the corresponding unsubstituted system. This need to resort to high reaction temperatures results in there being a greater risk of loss of potential product in polymer formation. In a reaction closely related to that already considered an attempt was made to produce a Claisen system by reaction of diethyl phosphonoacetaldehyde diethyl acetal\textsuperscript{58} (62) with an allylic alcohol.

\[
\begin{align*}
\text{R} & \quad \text{H}^+ \\
\text{OH} & \quad -\text{EtOH} \\
& \quad \text{EtO} \quad \text{P} (\text{OEt})_2 \\
\text{EtO} & \quad \text{P} (\text{OEt})_2 \\
& \quad \text{OEt} \quad \text{O} \\
(62)
\end{align*}
\]

Upon heating a mixture of the diethyl acetal and crotyl alcohol at 130°C with the distillative removal of ethanol, spectral data suggested the successful formation of the Claisen precursor, allyl vinyl ether (63). In addition, the appearance of characteristic features of an aldehyde, absorption in the I.R. spectrum at 1725 cm\textsuperscript{-1} together with a signal at \( \delta \) 9.6 p.p.m. in the \( ^1\)H n.m.r. spectrum, implied that some degree of rearrangement was also being achieved. However, suitable conditions for completion of the rearrangement process could not be found. Prolonged periods of heating and higher reaction temperatures led only to the formation of a complex mixture of reaction products.
Following the success of the Claisen orthoester rearrangement utilising an unsaturated α-hydroxyphosphonate as the allylic alcohol component, it seemed reasonable to believe that the thermal rearrangement-decarboxylation of the corresponding acetoacetic ester derivatives might be achieved. Scheme (3) illustrates the envisaged reaction sequence, with mechanism following that proposed by Kimel and Cope and the allylic acetoacetic ester being produced from diketene in accord with their method.

Scheme 3

In practice, reaction of dimethyl (1-hydroxyallyl) phosphonate with diketene in the presence of catalytic sodium methoxide commenced only upon strong heating, this being in contrast with the systems of Kimel and Cope which required temperatures in the region of 25-30°C. Reaction product, isolated by distillation after heating at 110°C for 5 hours, consisted of the allyl acetoacetic ester [(64); R=Me] as a keto-enol mixture (50% keto; 10% enol), together with unreacted α-hydroxyphosphonate (40%). There was no evidence of the presence of the
expected product of rearrangement-decarboxylation [(65); R=Me].
Prolonged heating of a sample of the distillate in an effort to induce rearrangement resulted only in polymer formation.

At this time a report appeared in the Russian literature on the reaction of diethyl (1-hydroxy-alkyl) phosphonates with acetoacetic ester and with diketene. The preparation of allylic acetoacetic ester [(64); R=Et] was described, this being achieved by treatment of the corresponding α-hydroxyphosphonate with diketene in the presence of a catalytic amount of triethylamine. Use of triethylamine as the base here enabled reaction to be achieved at 50°C in the course of 1-2 hours, the product being isolated in 73% yield as a mixture of the tautomeric forms. The report also stated that the reaction product was shown to contain no trace of the unsaturated ketone [(65); R=Et].

In an attempt to effect the rearrangement with simultaneous or subsequent decarboxylation of the allylic acetoacetate [(64); R=Me] the technique of flash vacuum thermolysis was employed. Here, the sample is subjected to a high temperature for an extremely short period of time, under conditions which minimise the risk of polymer formation. At furnace temperatures of up to 700°C only unchanged material was recovered following the process. This was remedied by increasing the temperature to 800°C where a great change was found to occur, including some polymerisation. A g.l.c. analysis of the soluble portion of the resulting material indicated there to be a minimum of eight different compounds present. I.R. and 1H n.m.r. spectra showed that these included unchanged allylic acetoacetate. From this, it would appear that although under these conditions the desired transformation may be occurring, it is by no means the only energetically favourable pathway open to the system.
A reaction bearing a close relationship to the Claisen rearrangement is the (2,3) sigmatropic rearrangement of allylic sulphenates,\(^{60a,b,61}\) phosphites,\(^{62a,b}\) phosphinites\(^{63a,b,64}\) and of allyl benzyl ether anions\(^{65}\) (Wittig rearrangement).

\[
\text{O} \xrightarrow{X} \text{O} \xrightarrow{X}
\]

\(X = P, S, C\) \hspace{1cm} (66)

Here, a concerted pericyclic rearrangement involving a five-membered transition state and six electrons (66), may be achieved in a system derived from an allyl vinyl ether by the replacement of the double bond of the vinyl ether linkage with a heteroatom bearing a lone pair of electrons eg. P, S or by a carbanion.

Mislow and co-workers\(^{60a,b}\) have suggested that the reversible (2,3) sigmatropic rearrangement of an achiral allylic sulphenate intermediate is instrumental in bringing about the thermal racemisation of optically active sulphoxides.
(+)-Allyl p-tolyl sulfoxide (67) was found to racemise in benzene or p-xylene at conveniently measured rates in a temperature range of 50-70°C, kinetic evidence being consistent with a concerted cyclic rearrangement mechanism for the process.

The independent synthesis and rearrangement of labelled allylic sulphenates has confirmed the intermediacy of (68) and also supports the concerted nature of the transformation. Reaction of p-toluene-sulphenyl chloride with lithium crotyl alcoholate at 0°C in ether or glyme yields α-methylallyl p-tolyl sulfoxide (69) only, there being no evidence for the presence of crotyl p-tolyl sulfoxide (70), a conceivable product of a non-concerted rearrangement.

\[
\text{MeC}_6\text{H}_4\text{SCL} + \text{MeC}_6\text{H}_4\text{CH}-\text{CH}_2\text{OLi} \rightarrow \begin{array}{c}
\text{MeC}_6\text{H}_4\text{S}\text{O} \\
\text{MeC}_6\text{H}_4\text{S}^\text{me}
\end{array}
\]

The absence of the first formed allylic sulphenate indicates that the driving force of >S=O formation results in the equilibrium lying on the side of the sulfoxide even under the mild conditions employed (work-up temperature not exceeding 25°C).

Although the products and the stereochemistry observed in the Wittig rearrangement of some allyl benzyl ethers are in accord with the operation of a highly ordered cyclic mechanism, it has been suggested
that the dissociation-recombination process responsible for the Wittig rearrangement of alkyl and aryl benzyl ethers\textsuperscript{66} may compete favourably here.

Kinetic studies and labelling experiments have shown that this is not the case for the rearrangement of allylic phosphites\textsuperscript{62a,b} and phosphinites\textsuperscript{63a,b}. For example, $\alpha$-methylallyl diphenylphosphinite (71) and crotyl diphenylphosphinite (72) rearrange on heating in benzene at 100°C (sealed tube under argon)\textsuperscript{63b} to crotyldiphenylphosphine oxide and $\alpha$-methylallyldiphenylphosphine oxide respectively, with greater than 99% specificity.

\[
\begin{align*}
\text{Ph}_2\text{P} & \quad \text{O} \quad \text{H} \quad \text{Me} \\
\text{Ph}_2\text{P} & \quad \text{O} \quad \text{H} \quad \text{Me} \\
(71) & \quad \rightarrow \\
\text{Me} & \quad \text{Me} \\
\text{Ph}_2\text{P} & \quad \text{O} \quad \text{Me} \\
(72) & \quad \rightarrow \\
\end{align*}
\]

It is of interest to note that the allylic phosphite-phosphonate and phosphinite-phosphine oxide rearrangements proceed considerably less readily than the corresponding sulphenate-sulphoxide rearrangement, a temperature of 100°C being the minimum at which the transformation has been achieved\textsuperscript{63b}. As a consequence of this (R)-allylmethylphenylphosphine oxide (73) was found to suffer no loss of optical purity when heated at 200°C in $\pi$-xylene for 12 hours, whereas allyl $\pi$-tolyl sulphoxide
is readily racemised at temperatures around 50°C.

The allylic sulphenate system required for (2,3) sigmatropic rearrangement may be conveniently synthesised by the reaction of an allylic alcohol with an aryl sulphenyl chloride, in the presence of a suitable base. p-Chlorophenylsulphenyl chloride, with triethylamine base, was chosen for a series of reactions involving the participation of a dialkyl (1-hydroxyallyl) phosphonate [(51); R=Me, Et, Pr; R*=H,Ph] as the allylic component. In each case studied, the resulting allylic sulphenate (74) was found to undergo rearrangement at room temperature or below to the corresponding β,γ-unsaturated sulfoxide (75).
In general the crude reaction products were viscous oils having low thermal stability and proving unsuited to adsorption chromatography. As a consequence, only in the case of the di-isopropyl ester was the resulting sulphoxide fully purified and characterised, this being achieved due to the fortuitously high crystalline nature of the compound.

Comparison of the spectroscopic data recorded for this particular derivative [(75); R=Pr\(^i\), R'=H] with those of the crude reaction products obtained during the series of experiments, showed in each case a predominance of allylic sulphoxide in the product mixture. This indicates that the formation and rearrangement of the allylic sulphenate intermediate is occurring efficiently. Attempts to induce the formation of crystalline products with reactions involving 2,4-dinitrophenyl-sulphenyl chloride were unsuccessful.

The initial product of (2,3) sigmatropic rearrangement shows no tendency to undergo an isomerisation to bring the carbon-carbon double bond into conjugation with the sulphoxide grouping. Such a transformation would result in the positioning of a methylene group adjacent to the phosphorus atom, this giving rise to easily distinguished features in the \(^1\)H, \(^{13}\)C, and \(^{31}\)P n.m.r. spectra. The preference for \(\alpha,\beta\)-unsaturation with respect to the phosphoryl grouping and \(\beta,\gamma\)-unsaturation with respect to the sulphoxide grouping is in agreement with the positions of the base-catalysed equilibria found in alkenyl sulphoxides\(^{70}\) and phosphonates\(^{71}\).

In contrast to the allylic sulphenates, literature precedent suggests that the corresponding phosphites derived from dialkyl (1-hydroxy-allyl) phosphonates will not readily undergo \((2,3)\) sigmatropic transformation. This was verified by the preparation and the attempted
rearrangement of diethyl (1-diethoxyphosphinyl-prop-2-enyl) phosphite (76).

Synthesis of phosphite (76) from diethyl (1-hydroxyallyl) phosphonate and diethyl chlorophosphite in the presence of triethylamine, was followed by heating at temperatures of up to 180°C. Under these conditions there was no evidence to suggest that rearrangement to the diphosphonate (77) was being achieved; the phosphite merely becoming contaminated by oxidised product.

The reluctance of this type of system to undergo rearrangement is thought to be a consequence of the relatively high bond strength of the P-O linkage in the phosphite (E_{P-O} ≈ 91 Kcal mol^{-1})\textsuperscript{72}, this conferring a special stability on the molecule. Systems in which a sulphur atom replaces the phosphite oxygen eg. crotyl diphenylthiophosphinite (78), rearrange\textsuperscript{64} under conditions comparable with those required to effect the sulphenate-sulphoxide rearrangement. (E_{P-S} ≈ 55 Kcal mol^{-1})\textsuperscript{72}

(\textsuperscript{78})

(\textsuperscript{79})
Solutions of phosphites possessing an ester radical with a $\beta,y$-acetylenic linkage undergo a 2,3 sigmatropic rearrangement to the corresponding 1,2-alkadienyl phosphonates upon standing at room temperature. The process is usually highly exothermic and in the absence of a solvent or adequate cooling may become uncontrollably violent.

Studies involving the phosphorus esters of substituted 2-propyn-1-ols have shown that the ease of rearrangement parallels the ability of the phosphite carrying carbon atom to stabilise positive charge. This has led to the suggestion of a concerted but non-synchronous mechanism for the reaction, involving the five-membered transition state (80). In all cases where the propargyl grouping contains substituents on the one or three carbon atoms, the rearrangement is seen to be accompanied by inversion.
The ease of the rearrangement is probably the result of the very favourable planar transition state between the acetylenic and allenic structures, through which the molecule passes with only small changes in the bond angles. Allyl phosphites, for which no similar planar transition state can be constructed, are stable under comparable conditions. The driving force of the reaction is provided by the energy gain associated with formation of the strong $\geq P=O$ bond.

Where $R_1$ and/or $R_2 = H$, allene (81) may undergo a second transformation, acetylenic phosphonate (82) being formed as a result of a prototropic rearrangement.

\[ \text{RO}(\text{RO})_2P \高素质 R_1 \quad \text{R}_1 \text{and/or} \quad \text{R}_2=H \quad \text{R} \quad \text{H} \quad \text{RO}(\text{RO})_2P - C \equiv C \quad \text{R}_1 \quad \text{R}_2 \quad \text{R} \quad \text{H} \]

The allenic isomer is formed exclusively in the rearrangement of dialkyl (1,1-dimethyl-2-propynyl) phosphites.

\[ \text{RO} > P - O \quad \text{RO} \quad \text{H} \quad \text{C} \equiv \text{C} \quad \text{C} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \]

The stability of the dialkyl (3-methyl-buta-1,2-dienyl) phosphonates (83) may be explained by the inductive effect of the two methyl substituents hindering prototropic isomerisation and also by the hyperconjugative effect of these groups with the double bond.

The insensitivity of these particular phosphorus esters to prototropic rearrangement makes them suitable to act as a model system for a study of the mode of addition of nucleophilic reagents to allenic...
phosphonates. The basic character of nucleophilic species often promotes the interconversion of allenic and acetylenic isomers where this is energetically favourable and it is not always obvious whether the products of nucleophilic addition are derived from the allene, the acetylene, or both.

High selectivity for central attack is demonstrated in nucleophilic additions to substituted allenes, in general this being the carbon atom with the greatest electrophilic character. Also, the reactivity of the allene is greatly enhanced by electron-withdrawing substituents, in the absence of these there being little or no addition of nucleophilic reagents. The allyl anion formed here as a result of central attack by the nucleophile does not represent a resonance stabilised allylic anion. The 2p orbital of the terminal carbon atom, which carries the negative charge, is orthogonal to the bonding orbitals and electron delocalisation is at a minimum here.

A rotation of 90° about the carbon-carbon sigma bond is necessary to give a planar intermediate with allylic resonance stabilisation. Evidence as to the nature of the intermediate involved can in principle be obtained from studies involving optically active allenes, racemic product being expected from the planar allylic intermediate.
Where the allene is unsymmetrically substituted the reactivities of the two double bonds are likely to be different and the attacking reagent may therefore be expected to show some selectivity between them.

Base catalysed addition of ethanol to diethyl (3-methyl-buta-1,2-dienyl) phosphonate [(83), R=Et], can in theory give rise to two different products, (84a) and (84b), each derived from the allylic intermediate formed on initial attack by ethoxide anion on the central carbon atom.

The first report of this reaction by Pudovik et al. in 1964 favoured structure (84a) for the addition product, this based upon evidence from the $^1$H n.m.r. spectrum. Following further investigation the same group revised their decision, the results of ozonolysis, oxidation and hydrolysis of the addition product favouring structure (84b).

```
(83)

(84a)

(84b)
```

The reactions shown in the diagram are:
- **Oxidation with KMnO₄** to CH₃COOH
- **Ozonolysis** with acetone peroxide
- **Hydrolysis** to (EtO)₂P⁻CH₂⁻C⁻CH(Me)₂

```
(93)
```
From a thermodynamic point of view, the formation of diethyl (2-ethoxy-3-methyl but-2-enyl) phosphonate (84b) is favoured because the conjugative effect of two methyl groups attached to a double bond is greater than the effect due to the interaction of the phosphoryl grouping with the double bond.\textsuperscript{79}

The addition of an allylic alcohol to allene (83) in a manner analogous to that of ethanol would generate a system having the necessary requirement for a subsequent Claisen rearrangement, the remaining double bond of the allene functioning as the vinyl component. In common with the addition of ethanol the addition of the allylic alcohol might be seen to occur across either of the two double bonds of the allene, the intermediates formed giving rise to two distinct ketonic products in the event of Claisen rearrangement occurring. The envisaged reaction sequence is illustrated in Scheme (4).

\begin{align*}
\text{(83)} & \xrightarrow{\text{HO}} \text{(84a)} \xrightarrow{\text{HO}} \text{(84b)} \\
\text{(85)} & \xrightarrow{\text{HO}} \text{(86)}
\end{align*}
Reaction of this type has been observed upon addition of the sodium derivative of allyl alcohol to the related compound, 3-methylbuta-1,2-dienyl phenyl sulphoxide. Enol ether (87) may be isolated from the reaction mixture after a period of 1 hour at 20°C in THF.

Distillation of (87) from zinc carbonate induces Claisen rearrangement and elimination of benzene sulphenic acid to produce dienone (88).

This is a general reaction for the addition of primary and secondary allylic alcohols to allenyl phenyl sulfoxides. In the above case changing the solvent to benzene results in addition across the other double bond, adduct (89) rearranging to phenyl sulphonyl ketone (90) on distillation from zinc carbonate.
Diethyl (3-methyl-buta-1,2-dienyl) phosphonate was prepared from 2-methyl-3-buten-2-ol and diethyl chlorophosphite in the presence of pyridine. The first formed acetylenic phosphite undergoes an in situ rearrangement in solution in ether to give the desired allene [(83); R=Et].

The sodium salt of allyl alcohol was generated by the action of sodium hydride on a solution of the alcohol in THF at 0°C. To this was added one mole equivalent of the allenic phosphonate in the same solvent, the resulting mixture being stirred at room temperature for a period of two hours. Addition of one mole equivalent of HCl followed by isolation, gave a crude reaction product consisting of four major phosphorus containing components, all having chemical shifts in the +21 to +23 p.p.m.
region of the $^{31}$P n.m.r. spectrum. Complete reaction of the starting material was shown to have occurred by the disappearance of the allene stretch (1955 cm$^{-1}$) from the I.R. spectrum, strong new absorptions having appeared at 1710 and 1610 cm$^{-1}$.

Vacuum distillation was found to result in little change in composition from that of the crude reaction product. Separation of the four major phosphorus containing components was achieved by use of preparative g.l.c., the compounds being characterised by their $^1$H n.m.r., I.R. and mass spectra. The data recorded for the isolated components were found to be consistent with their presence in the original reaction product, this indicating that no further chemical change occurs under the conditions of chromatography.

The two major reaction products were found to be those expected from addition of allyl alcohol to the allenic phosphonate, followed by Claisen rearrangement.

$$
\begin{align*}
\text{(85)} & \quad \text{(86)} \\
\text{(Eto)}_2 & \text{P} - \text{CH}_2 - \text{C} - \text{CMe}_2 \\
\text{EtO} & \text{P} - \text{CH} - \text{C} - \text{CHMe}_2
\end{align*}
$$

There appears to be a preference of approximately two to one for addition of the allylic alcohol across the double bond bearing the phosphonate ester substituent, ketones (85) and (86) representing 37% and 19% respectively of the total reaction product. Preferential addition of the alcohol across the double bond carrying the phosphoryl grouping might be anticipated, nucleophilic addition being promoted by the presence of electron-withdrawing substituents.

-57-
The least abundant of the four components isolated, 7% of the total product, was found to be a derivative of (85), ester exchange having resulted in the replacement of one of the ethoxy substituents by an allyloxy group.

\[
\begin{align*}
\text{(EtO)}_2 & \text{O} \\
\text{(CH}_2=\text{CHCH}_2\text{O)} & \text{P} - \text{CH}_2 - \text{C} - \text{CMe}_2 \\
\text{O} & \\
\end{align*}
\]

Exchange of this type appears to occur very readily and led to the abandonment of a reaction in which allyl alcohol was used as the solvent, the allyloxy anion being generated in this case by the addition of an equivalent of sodium metal.

At first sight the fact that the rearrangement proceeds readily at room temperature seems surprising. If however, it is accepted that rearrangement occurs of the allyl anion intermediate rather than of the neutral species derived from the addition, an analogy may be drawn between this system and the enolate anion Cope system of Evans and Golob\textsuperscript{51} (page 30). Here, oxy-Cope rearrangements in which the oxygen atom bears a negative charge are found to proceed at rates \(10^{10}\) to \(10^{17}\) times faster than the corresponding allyl vinyl systems, this being equivalent to a decrease in the activation energy of up to 23 kcaL mol\textsuperscript{-1}.

Rearrangement of an allyl anion intermediate involves a Claisen system in which the carbon atom substituent at the 2 position of the vinyl fragment bears a formal negative charge. It seems reasonable to believe that the ease of the rearrangement may be attributed to this negative charge, the effect being the same as that in the enolate anion system.
Thus, addition of the allyloxy anion to the central carbon atom of allene (83) produces the allylic anions (91) and (92), which undergo a Claisen rearrangement followed by protonation of the resulting enolate anions, to yield ketones (85) and (86).

The fourth component isolated by preparative g.l.c. from the crude reaction product and representing 16.4% of the total, was found to have a molecular weight of 250 and showed a very strong absorption in the I.R. spectrum at 1610 cm$^{-1}$. The data are consistent with this being the product of addition of one mole of ethanol to the allenic phosphonate, the intense absorption in the I.R. spectrum being coincident with that reported in the literature for the adduct.$^{78}$ The presence of ethanol in the reaction mixture most probably arises from the displacement of ethoxy substituents from the phosphonate ester; evidence that ester
exchange does occur being provided by the isolation of product containing mixed ester groupings.

There still remains some uncertainty as to the exact structure of the adduct between the allenic phosphonate and ethanol.

\[
\begin{align*}
\text{(84a)} & \quad \text{(84b)} \\
(\text{EtO})_2\text{P} & \quad (\text{EtO})_2\text{P}-\text{CH}_2\text{Me} \\
\text{CH(Me)}_2 & \quad \text{CH(Me)}_2 \\
\text{H} & \quad \text{OEt} \\
\text{OEt} & \quad \text{EtO} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

The \(^1\)H n.m.r. spectrum is inconsistent with structure (84b) despite it being the product of addition across the double bond activated to nucleophilic attack, and also being the thermodynamically favoured product. In common with the initial report by Pudovik et al.\textsuperscript{77} the \(^1\)H n.m.r. data are thought to favour structure (84a), there being no signal in the region of the spectrum associated with methyl groups attached to a double bond (δ 1.6 p.p.m.) and no distinctive doublet corresponding to a methylene group adjacent to phosphorus.

In an effort to discover whether the addition-rearrangement sequence is of general application the reaction was repeated with the tertiary allylic alcohol, 2-methyl-3-buten-2-ol. Here, generation of the allyloxy anion with sodium hydride as described for the reaction with allyl alcohol, gave rise to a crude reaction product having several phosphorus containing components including some unreacted starting material, and the major of these components having a \(^{31}\)P chemical shift of +22.9 p.p.m. Distillation of the crude reaction product resulted in the concentration of this component and one other of chemical shift +20.37 p.p.m., the I.R. spectrum of the distillate showing strong absorptions at 1710 and 1610 cm\(^{-1}\).
Separation of this two component mixture by preparative g.l.c. enabled the identification of the constituents. The major component was found to arise from addition of ethanol to the allenic phosphate and the minor to be the ketone (93), this resulting either from hydrolysis of the enol ether (84a and/or b) or from the addition of one mole of water to the starting material.

Under these reaction conditions no evidence was found for products derived from addition of the allylic alcohol to the allene. This may be a consequence of the failure to generate the anion of the tertiary alcohol, difficulty arising here due to steric hindrance by the methyl substituents.

In order to encourage anion formation, a second reaction involved heating the mixture of tertiary allylic alcohol and sodium hydride in refluxing THF, for a period of twenty minutes prior to the addition of allenic phosphonate. This resulted in the formation of a new major...
reaction product of $^{31}$P chemical shift +27.2 p.p.m.. Again there was found to be a significant amount of unreacted starting material and no evidence for product of Claisen rearrangement, there being no $>\text{C}=\text{O}$ stretch in the I.R. spectrum. However, the presence in the $^1$H n.m.r. spectrum of a doublet ($J=21\text{Hz}$) centred at $\delta 2.8$ (characteristic of $-\text{CH}_2-$ adjacent to phosphorus), together with a strong absorption at 1610 cm$^{-1}$ in the I.R. spectrum, did suggest that addition of the allylic alcohol might have occurred to give enol ether (94).

During separation of unreacted starting material by distillation a chemical change was found to have occurred in the reaction product, this being consistent with the Claisen rearrangement of (94). Fraction three of the distillate (b.p. 132-144$^\circ\text{C}$ 0.05mm.) contained in addition to a small amount of the component having a $^{31}$P chemical shift of +27.2 p.p.m., and ascribed to (94), a new compound showing $>\text{C}=\text{O}$ absorption in the I.R. spectrum and a doublet ($J=21\text{Hz}$) centred at $\delta 3.1$ in the $^1$H n.m.r. spectrum. That the new compound formed was the product of Claisen rearrangement, ketone (95), was confirmed following its isolation by preparative g.l.c.. The rearrangement process commencing upon distillation appears to go to completion under chromatographic conditions, fraction three consisting of ketone (95) only, by g.l.c..

Despite successful identification of the product of Claisen rearrangement here, this does not indicate an efficient reaction process,
fraction three of the distillate representing only a 5% yield of desired product. The presence of unreacted starting material and the large residue of high boiling material obtained on distillation, suggest that neither the addition, nor the rearrangement processes are occurring readily in this case.

Inefficiency in formation of the addition product may again be attributed to difficulty in generation of the allyloxy anion, or alternatively, to lack of reactivity of this species once formed. Certainly, the anion of the tertiary alcohol seems to be more selective in its action than that of the primary alcohol, addition being seen to occur across the activated double bond of the allene only. In contrast to the system derived from the primary allylic alcohol, the resulting enol ether (94) requires a high temperature to effect Claisen rearrangement.

The reluctance of this system to rearrange is not thought to be a consequence of the presence of the additional methyl substituents. More probably, the necessity for a high temperature arises due to the fact that the system undergoing rearrangement is a neutral species rather than the negatively charged allyl anion intermediate. Unreacted tertiary alcohol may function as the proton source required for the formation of a neutral addition product from the first formed intermediate. Application of heat then becomes necessary for the subsequent Claisen rearrangement, there being as a consequence the simultaneous loss of potential product in polymer formation.

Similar behaviour was observed in the reaction of the secondary alcohol 3-buten-2-ol with diethyl (3-methyl-buta-1,2-dienyl) phosphonate, under the same conditions. Enol ether (96), resulting from addition of the allylic alcohol across the activated double bond of the allene, predominated at room temperature. In this case a small amount of the Claisen rearranged product (97) was also present, this presumably being
derived from the corresponding allyl anion intermediate. Again, rearrangement of the neutral addition product was induced under conditions of distillation.

\[
\begin{align*}
\text{(96)} & \quad \rightarrow \quad \text{(97)}
\end{align*}
\]

In order to take advantage of the lower energy barrier to rearrangement of the allylic anion system it is necessary for this intermediate to be formed in an aprotic environment. This may only be achieved by the efficient generation of the allyloxy anion, no unreacted alcohol remaining to act as a proton source. In an effort to improve on the efficiency of anion production the tertiary alcohol 2-methyl-3-buten-2-ol was reacted with potassium hydride, this having a greater reactivity than the corresponding sodium reagent. Addition of the allenic phosphonate to this reaction mixture led to the formation of several different phosphorus containing components, none predominating, and there being no evidence of the presence of either addition or rearranged product. Similar behaviour was found on attempted generation of the tertiary allyloxy anion with metallic potassium.

That the reaction between the tertiary allylic alcohol and the allene does not parallel that of the primary allylic alcohol, was also found by Cookson and Goplan in their studies on 3-methyl-buta-1,2-dienyl phenyl sulphoxide.\(^8\) The tertiary alcohols 2-methyl but-3-en-2-ol and linalo-ol are reported to give no reaction with the allyl phenyl sulphone, as either their sodium or potassium salts.

-64-
Thus, it would appear at this stage that for a facile rearrangement process the Claisen system must be generated with the incorporation of an allylic anion, and that this may be most easily achieved by use of a primary allylic alcohol.

A similar reaction should be possible with other allenic compounds. The base catalysed addition of alcohols to 1-cyanoallenes was first reported in 1959 by Kurtz et al.\textsuperscript{81}

![Chemical structure](image)

At this time it was found that the adduct with allyl alcohol gave Claisen rearranged product almost quantitatively at temperatures above 200°C. It might be of interest to investigate whether this rearrangement would occur at a more moderate temperature with addition of one equivalent of allyloxy anion rather than addition via a base catalysed process.

![Chemical structure](image)
There are several examples in the literature of Cope rearrangements in which either one or both of the unsaturated linkages of the 1,5-hexadiene system are provided by allenic double bonds (see page 25). Taking advantage of the ready rearrangement of a β,γ-acetylenic phosphite to the corresponding allenic phosphonate, a suitably designed phosphite could give rise to an allene incorporating the necessary structure for a subsequent Cope rearrangement. Phosphite (100) in reaction Scheme 5 exemplifies such a system; the methyl substituent here inhibiting the further rearrangement of allene (101) to the isomeric acetylenic phosphonate.

Scheme (5)

Allene (101) was prepared as formulated in Scheme (5). Reaction of 5-hexen-2-one with sodium acetylide in liquid ammonia gave the corresponding acetylenic alcohol (99) in 58% yield. This was converted into phosphite (100) on treatment with diethyl chlorophosphite in the presence of pyridine. Under the conditions of the reaction, in
ethereal solution at room temperature, rearrangement of the phosphite occurred. The resulting allenic phosphonate (101) was isolated in yields of up to 72% on distillation of the crude reaction mixture.

In an attempt to effect a Cope rearrangement of compound (101) a neat sample was heated at 140°C for a period of 3 hours. After this time the allene stretch in the I.R. spectrum had disappeared and the absorption at +15.7 p.p.m. in the 31P n.m.r. spectrum due to the allenic phosphonate had been replaced by new absorptions at +16.94 and +18.1 p.p.m. The physical data recorded of the product isolated were in accord with this being the expected product of Cope rearrangement, diene (102).

![Diagram of chemical structures]

This compound exists as an unequal mixture of two isomers (102a) and (102b), these differing in configuration about the double bond bearing the phosphoryl substituent. There are as a consequence two similar but distinct absorptions seen in the 31P n.m.r. spectrum of the diene, the relative intensities of the peaks suggesting an isomer ratio of approximately 1:0.26.

-67-
The optimum conditions for the Cope rearrangement were found by heating a neat sample of (101) at a temperature in the region of 140-150°C with monitoring of either the disappearance of the allene stretch in the I.R. spectrum, or the $^{31}$P n.m.r. absorption due to the allene. Completion of the rearrangement process required a period of about 2 hours. Prolonged heating, or heating at higher temperatures resulted in the formation of dimeric species, these presumably arising from a Diels Alder addition in which one molecule functions as the diene and the other as the dienophile.

It is not easy to predict whether the formation of isomer (102a) or (102b) will be favoured as a result of the Cope rearrangement. However, having obtained an unequal mixture of these two isomers, assignment of a structure to both the major and minor components should be possible with reference to the difference in Diels Alder reactivity predicted for the two isomers. With the diene in the $\pi$-cis conformation required for the Diels Alder addition the position of the phosphoryl substituent in isomer (102a) will be such that there will be steric hindrance to approach of the incoming dienophile. This is not the case for isomer (102b) which would consequently be expected to exhibit a greater reactivity in cycloaddition reactions.

An investigation carried out with various dienophiles indicated that this diene shows in general a low aptitude for participation as the 4π component in (4+2) cycloaddition reactions. A suppression of reactivity might be anticipated here in view of the presence of the electron withdrawing phosphoryl substituent on the diene.

No reaction was observed on heating equimolar amounts of diene (102) and dimethyl acetylene dicarboxylate at 100°C in the absence of solvent.
With maleic anhydride in solution in benzene at 70°C, very little change was noted in the $^{31}$P n.m.r. spectrum over a period of 45 hours. Stronger heating of this mixture in the absence of solvent (150°C; 6 hours) resulted in there being a large reduction in the amount of starting material present, the minor isomer disappearing completely. Among the several new phosphorus containing components seen, mass spectral data indicated the presence of the expected addition product (103).

Cycloaddition occurring under milder reaction conditions and with the elimination of side reactions was achieved using the more reactive dienophile, N-phenyl maleimide.
A neat mixture of equimolar amounts of diene (102) and N-phenyl maleimide was heated at 96°C. After a period of 1 hour the absorption in the $^{31}$P n.m.r. spectrum associated with the minor isomer had disappeared completely, there being two new absorptions appearing, at +25.2 and +26.8 p.p.m.. Over a further period of six hours at the same temperature there was a steady growth in the signal due to the new component at +26.8 p.p.m. with a corresponding decay of the signal associated with the major isomer of the diene.

The results indicate that as predicted there is a significant difference in the Diels Alder reactivity of the isomeric dienes. It is quite possible that the major component of the diene, shown to be the more hindered isomer (102a), undergoes no cycloaddition whatsoever with dienophiles less reactive than N-phenyl maleimide.

Purification of the Diels Alder adduct (104) by column chromatography resulted in isolation of only one of the two isomeric species, this being the major component (104a). A conceivable explanation of the failure to recover the minor component lies in the possibility of isomerisation occurring on the chromatography column. A conformational change in the cyclohexene ring structure drawn for molecule (104a) results in the most bulky substituents, the phosphoryl grouping and the five membered ring, occupying equatorial or pseudo equatorial positions. For isomer (104b) one of these two substituents must always occupy an axial or pseudo axial position. On this basis, isomer (104a) might be expected to be the thermodynamically favoured product, providing a driving force for isomerisation to occur.

However, it did not prove possible to effect the isomerisation by treatment of the crude reaction product mixture with base, this somewhat discrediting the theory.
The ene reaction, first recognised by Alder in 1943, usually involves the thermal reaction of an alkene containing an allylic hydrogen (the ene), with an electron deficient double bond (the enophile), to form a 1:1 adduct.

\[
\begin{align*}
\text{Z=CR}_2:0 & \quad \text{X=Y=} \quad >C=C< \quad 0=0 \\
& >C=0 \quad -N=0 \\
& >C=S \quad -N=N-
\end{align*}
\]

The reactivity of the components of the ene reaction often parallels their reactivity in the Diels Alder reaction to which it bears some similarity. Like the Diels Alder cycloaddition the reaction goes best with electron deficient enophiles and electron rich ene components, though simple alkenes possessing an allylic hydrogen atom may participate. Alder discovered that propene reacts with maleic anhydride in benzene at elevated temperature and pressure to give allyl succinic anhydride (105) as the only product. Similar behaviour is observed with 2-pentene, isobutylene, cyclopentene and cyclohexene.

The reaction involves the allylic shift of one double bond, with transfer of the allylic hydrogen from the ene to the enophile and bonding between the unsaturated termini. Formally, not only does this
bear some relationship to the Diels Alder reaction but may also be regarded as an intermolecular variant of the symmetry allowed 1,5-hydrogen shift; although the transition state geometries of all three reactions are different.

The mechanism of the ene reaction has been the subject of much discussion, both concerted pericyclic \(^{84,85}\) and stepwise \(^{86}\) pathways having been suggested. Evidence supporting the concerted nature of the reaction in one case is the formation of optically active products upon reaction of optically active alkenes with maleic anhydride. This is an example of asymmetric induction.

\[ R = \text{Ph} \]
\[ R = (\text{CH}_3)_2\text{CH(CH}_2)_3 - \]

Determination of absolute configuration of the product (106) suggests that the orientation of the addition is controlled by simple steric factors, the bulky group \(R\) being directed away from the enophile.

Generally, experimental evidence favours the predominance of the concerted pathway with stepwise addition occurring only where the transition state for a concerted ene reaction becomes difficult for steric reasons.

Alkenes with strained double bonds show particular readiness to enter into ene reactions, the driving force in this case being the migration of the double bond from a more to a less strained situation.
The naturally occurring sesquiterpene caryophyllene for example, containing a strained trans double bond reacts smoothly with maleic anhydride in refluxing benzene$^{88}$.

![Chemical structures](image)

Intramolecular ene reactions are also found to proceed readily, these benefiting from favourable entropies of reaction. Three different modes of thermally induced intramolecular reaction may be distinguished, as categorised by Oppolzer and Snieckus$^{89}$. In each case the enophile is linked by an appropriate bridge to the olefinic terminal (Type 1), the central atom (Type 2), or the allylic terminal (Type 3) of the ene unit.

![Reaction structures](image)
Of these, Type 1 reactions are the most common, the majority being concerned with the thermolysis of 1,6-dienes. Huntsman\textsuperscript{90a,b,c} showed that 1,6-dienes, eg. (107) undergo cyclisation to the corresponding vinyl cyclopentanes.

\begin{equation}
\text{Me} \quad \text{Me} \\
\text{CH}_2 \quad \text{H} \quad \xrightarrow{500^\circ\text{C}} \quad \text{Me} \quad \text{C}_3 \\
\text{(107)} \quad \text{(108)}
\end{equation}

This demonstrates the effective participation of non-activated double bonds in the intramolecular ene process, in contrast to the necessity for activated enophiles in the bimolecular counterpart. The greater ease of the intramolecular process may be attributed to entropic advantage, the measured entropy of activation being in the region of 12-27 cal.k\textsuperscript{-1}.mol\textsuperscript{-1} less negative than that found in intermolecular cases\textsuperscript{91,92}.

The regioselectivity observed here typifies that found in the intramolecular ene transformation of many 1,6-diene systems, with predominant C-C bond formation occurring between the closest olefinic termini to yield five-membered rings.
In addition, stereochemical selectivity is exhibited in these rearrangements, cyclisation of (107) yielding a 4:1 mixture of the C(3)-epimers^93 and also ring closure of (109) giving compounds (110) and (111) in a ratio of 14:1^90.

In recent years examples of intramolecular ene reactions involving the participation of an allenic enophile have been discovered. Sulphoxide (112) cyclises almost quantitatively to the cyclopentene derivative (113) on heating to 200°C^94. Striking enhancement of this reaction may be achieved by Lewis acid catalysis.
In a second example the rearrangement of a vinylallene intermediate has been utilised in synthesis of the physiologically important 1-hydroxyvitamin D system. Allene (114) undergoes thermolysis in refluxing isooctane to give 3-deoxy-1-hydroxy vitamin D$_3$ (115), in 52% yield.

Continuing the investigation of the thermal rearrangements open to substituted allenic phosphonate esters a system with potential to undergo an intramolecular ene reaction was designed and prepared. As in previous cases the allenic phosphonate was produced by rearrangement of the corresponding β,γ-acetylenic phosphite. Scheme (6) outlines the overall reaction sequence.
Acetylenic alcohol (116) was prepared in 47% yield by the action of sodium acetylide on 4-methyl-3-penten-2-one, as described by Gymerman, Heilbron and Jones96. This method involves the use of an excess of sodium acetylide, the reagent being prepared from sodamide instead of sodium, in liquid ammonia. In this way the acetylide appears to be produced in a considerably more reactive condition.

It was anticipated that reaction of the acetylenic alcohol with diethyl chlorophosphite in the presence of pyridine would give the desired vinylallene system (118), following an in situ rearrangement of the intermediate β,γ-acetylenic phosphite (117). In practice, the major phosphorus-containing component of the crude reaction product appeared to be diethyl hydrogen phosphite, this characterised by the
position of the signal in the $^{31}$P n.m.r. spectrum and also by the presence of an absorption at $\delta 12.6$ in the $^1$H n.m.r. spectrum, ascribed to the low field half of the P-H doublet ($J_{P-H} = 700$Hz). The formation of this compound may be the consequence of an elimination of the phosphoryl moiety from the intermediate phosphite. It is possible that this process may compete readily with the rearrangement to the allene, on account of the stability of the tertiary allylic carbonium ion formed on cleavage of the C-O bond.

Despite the predominance of diethyl hydrogen phosphite, the presence of a weak allene stretch in the I.R. spectrum of the crude reaction product suggested that rearrangement had occurred to some extent, to yield the desired allene (118). Separation of diethyl hydrogen phosphite was achieved by vacuum distillation, the amount recovered representing 58% of that theoretically possible based upon the starting material, diethyl chlorophosphite. The higher boiling fractions of the distillate (b.p. 120-124°C, 0.5mm.) were shown by $^{31}$P n.m.r. spectroscopy to consist of a mixture of four different phosphorus containing components [$^{31}$P (CH$_2$Cl)$_2$] +16.1, +19.9, +30.4 and +31.4 p.p.m.]. Two of these components [+30.4 and +31.4 p.p.m.] had not been apparent in the original reaction product.

A sample of the distillate was heated for a period of 1 hour at 75°C, this resulting in the loss of the allene stretch from the I.R. spectrum and also the disappearance of the signal at +16.1 p.p.m. from the $^{31}$P n.m.r. spectrum. Heating the sample for a further 1 hour at 110°C,
caused the disappearance of a second phosphorus containing component (+19.9 p.p.m.), this coinciding with the appearance of another species (+19.3 p.p.m.).

It seems that this is a complex system involving several components which may be produced successively by the action of heat. A sequence of this type, derived from the vinylallene (118) may be formulated and is outlined in Scheme (7).

In this reaction sequence an intramolecular ene rearrangement of the vinylallene is followed by the thermal cyclisation of the resulting 1,3,5-hexatriene (119). The electrocyclic ring closure of acyclic hexatrienes via a disrotatory pathway is well established, the equilibrium lying almost completely in favour of the cyclic form. The 2,4,6-octatriene (122) for example, is converted into the cis-dimethylcyclohexadiene (123) at 132°C\(^9\). There is no evidence for the presence of the
thermodynamically more stable trans-isomer here.

A possible further transformation of the 1,3-cyclohexadiene system (120) upon heating, is the elimination of one molecule of hydrogen to give the aromatic phosphonate (121). The necessity for a high reaction temperature might be anticipated here, as the aromatisation of this type of system is usually carried out with the aid of an oxidising agent.

The high boiling fractions of the reaction product from the allene preparation were examined by g.l.c.. It was hoped that the application of this technique on a preparative scale would enable the separation and identification of one or more of the components of the mixture. The optimum conditions to achieve separation proved to involve an operating temperature of 200°C, both fractions of distillate showing the same three major components at this temperature. A preparative separation was carried out with the understanding that under these conditions it would only be feasible to isolate those reaction products having a high degree of thermal stability.

The component having the shortest retention time proved to be the major component of the mixture (50% estimated yield by g.l.c.) and gave spectral data consistent with the structure of the 1,3-cyclohexadienyl phosphonate (120). The chemical shift of this compound in the $^{31}$P n.m.r. spectrum (+30.4 p.p.m.) showed that its formation had commenced upon
distillation of the crude reaction product. In the same way, comparison of $^{31}$P n.m.r. chemical shifts indicated that the second component to be isolated by preparative g.l.c. had also been first observed at the distillation stage. This compound, present as a g.l.c. estimated 7% of the mixture gave a similar $^{31}$P n.m.r. chemical shift (+31.4 p.p.m.) to that of the 1,3-cyclohexadienyl phosphonate, but differed in that its $^1H$ n.m.r. spectrum showed the presence of three olefinic protons, two of these in the same chemical environment and all three being uncoupled. This, taken in conjunction with an observed reduction in intensity of the signal due to vinyl methyl protons led to the assignment of the structure (124) to this component.

As illustrated, this species may be derived from 1,3-cyclohexadiene (120) via a [1,5]non-concerted migration of a hydrogen atom. Its appearance as a minor rather than a major component of the mixture may be associated with the presence of the energetically disfavoured exocyclic double bond. The third and final component to be isolated by preparative g.l.c. constituted approximately 31% of the mixture and its presence in trace amounts in all fractions collected indicated that it was being formed on the column. The position of the signal due to this compound in the $^{31}$P n.m.r. spectrum (+19.3 p.p.m.) showed that it had previously appeared only upon strong heating of the distillate. Further spectral data recorded in this case were in keeping with the component being the aromatic phosphonate (121), formed on elimination of a hydrogen molecule from the 1,3-cyclohexadiene (120). Characteristic signals seen
in the $^1$H n.m.r. spectrum were a six proton singlet (δ 2.35 p.p.m.) due to the methyl hydrogens and three aromatic protons, two of these being chemically equivalent and showing spin-spin coupling to phosphorus.

The characterisation of those components of the system having a high thermal stability provides indirect evidence for the intermediacy of the vinylallene (118) and of 1,3,5-hexatriene (119). Although under the chosen reaction conditions it proved impossible to isolate these species, the circumstances under which they will exist may be formulated by reference to the appearance and disappearance of signals showing intermediacy in the $^{31}$P n.m.r. spectrum. In this case absorptions at +16.1 p.p.m. and +19.9 p.p.m. were both present in the original reaction mixture which was subjected to a maximum temperature of refluxing THF, but disappeared upon heating to higher temperatures. Of the two +16.1 was predominant at first but vanished on heating at 75°C, its disappearance coinciding with a loss of the allene stretch from the I.R. spectrum and an increase in intensity of the signal at +19.9 p.p.m.. This observation is consistent with the vinylallene having undergone partial ene rearrangement in refluxing THF, with completion of the process at 75°C, to give the 1,3,5-hexatriene (119) of $^{31}$P n.m.r. chemical shift +19.9 p.p.m.. The appearance of the signal due to the 1,3-cyclohexadiene (120) at 75°C indicates that cyclisation has also commenced at this temperature, the process being complete at 110°C, as shown by the disappearance of the signal at +19.9 p.p.m. from the $^{31}$P n.m.r. spectrum.

Other circumstantial evidence for the intermediacy of the hexatriene and cyclohexadiene systems is the presence of a complex absorption centred at 255nm in the U.V. spectrum of the mixture after heating at 75°C.

The progressive reaction leading to the formation of aromatic phosphonate (121) which occurs on the g.l.c. column, may also be brought about by the direct action of heat on the product mixture.
The most efficient conversion achieved involved heating a nitrobenzene solution of the distilled reaction product in the presence of a catalytic amount of palladium on charcoal to encourage loss of hydrogen. The formation of the aromatic phosphonate was monitored by $^{31}$P n.m.r. spectroscopy and a conversion of approximately 80% of the material present into this species occurred over a period of 10 hours at 200°C.

A modification to the system designed for intramolecular ene reaction,\(^{(118)}\), was carried out with the aim of producing a vinylallenic phosphonate with the potential to function as the diene fragment in a Diels Alder reaction. The ene reaction may be avoided in this system simply by the replacement of the allylic carbon atom of the ene unit with a hydrogen atom.

In the first instance, the allenic methyl substituent was also replaced by hydrogen; this in an effort to discourage the cleavage of the intermediate phosphite experienced previously in the course of preparation of the allenic phosphonate \((118)\). The substitution of the methyl substituent by a hydrogen atom reduces the stability of the carbonium ion formed upon cleavage of the phosphite.

Synthesis of the resulting model system for the Diels Alder addition,\(^{(127)}\), was effected by reaction of diethyl chlorophosphite with the acetylenic alcohol \((125)\), product formation proceeding via the corresponding \(\beta,\gamma\)-acetylenic phosphite \((126)\).
The spectral data of the crude reaction product here, indicated the successful formation of allenic phosphonate (127); this accompanied by some diethyl hydrogen phosphite. However, upon distillation a change was found to occur in the chemical composition of the product, much of the allene being converted into a component giving a signal in the $^{31}$P n.m.r. spectrum at +23 p.p.m., a position 10 p.p.m. downfield of that shown by the allene. In addition, the appearance of a weak absorption at 2225 cm$^{-1}$ in the I.R. spectrum of the distillate suggested the presence of an acetylenic grouping.

It is well established that allenic systems of this type readily isomerise, this occurring via the process of prototropic rearrangement. For example, treatment of diethyl (buta-1,2-dienyl) phosphonate
(128) with a catalytic amount of base (EtONa), yields an equilibrium mixture consisting of one allene and two acetylenic isomers.

\[
\begin{align*}
\text{Me} & \equiv \text{C} \equiv \text{C} & \text{H} \quad \text{Me} - \text{C} \equiv \text{C} - \text{P(OEt)}_2 \\
\text{H} & \quad \text{H} & \quad \text{Me} - \text{CH}_2 - \text{C} \equiv \text{C} - \text{P(OEt)}_2 \\
\text{H} & \quad \text{H} & \quad \text{Me} - \text{C} \equiv \text{C} - \text{CH}_2 - \text{P(OEt)}_2 \\
\end{align*}
\]

\( ^{31}\text{P} \text{ n.m.r.} + 13 \text{ p.p.m.} \)

\( \text{Me} \equiv \text{C} \equiv \text{C} - \text{P(OEt)}_2 \)

\( ^{31}\text{P} \text{ - 9 p.p.m.} \)

The equilibrium concentrations of the species involved have been explained in terms of the relative stabilities of the carbanions intermediate in the prototropic rearrangement.97a

Of the two acetylenic isomers corresponding to the allenic phosphonate (127) only one was found to be present in the distillate, this being the species in which the acetylenic group is in conjugation with the double bond (131). The methylene group adjacent to the phosphorus atom in this isomer gives rise to a characteristic doublet in the \( ^1\text{H} \text{n.m.r. spectrum (J}_{\text{P-H}} = 22 \text{ Hz).} \)
The stated absence of the second acetylenic isomer (132) is based upon the lack of a signal to high field of the reference in the $^{31}\text{P}$ n.m.r. spectrum of the distillate. Literature values of the $^{31}\text{P}$ chemical shifts of alk-1-ynyl phosphonates lead to the prediction of a chemical shift of between -5 and -10 p.p.m. for this compound. A further reduction in the amount of the allene isomer present in the distillate was found to occur on heating to 104°C, an equilibrium composition of approximately 10% allene (127) and 90% acetylene (131) being achieved after a period of 1 hour at this temperature.

A closer study of the rearrangement process showed the allenic isomer to be thermally stable below a temperature of 80°C; though in the presence of base prototropic rearrangement occurred readily at room temperature, an extremely exothermic reaction being noted in the absence of solvent.

For the purpose of the proposed Diels Alder addition reaction, crude product from the allene preparation was used, thus avoiding the problem of isomerisation found to occur upon purification. Addition of pyridine to a mixture of equimolar amounts of hex-4-en-1-yn-3-ol (125) and diethyl chlorophosphite in THF at 0°C, gave a first formed species producing a signal at +137.7 p.p.m. in the $^{31}\text{P}$ n.m.r. spectrum, and attributed to $\beta$,γ-acetylenic phosphite (126). Over a period of 3½ hours at room temperature this signal diminished in intensity, there being a corresponding increase in the intensity of absorptions at +6.4 and +12.7 p.p.m.. These observations may be interpreted in terms of the cleavage or rearrangement of phosphite (126) to yield diethyl hydrogen phosphite and vinylallenic phosphonate (127) respectively. The by-product of the reaction, pyridine hydrochloride was removed by filtration and one equivalent of N-phenyl maleimide was then added to the filtrate. A reactive dienophile was chosen here to encourage the formation of an adduct under mild reaction conditions.
After two days at room temperature the $^{31}$P n.m.r. spectrum of the reaction mixture showed there to be two phosphorus containing components of chemical shift +23.1 and +6.4 p.p.m.. The presence of diethyl hydrogen phosphite, assumed to be responsible for the absorption at +6.4 p.p.m., was confirmed by the $^1$H n.m.r. spectrum of the reaction product.

Conversion of the vinylallenic phosphonate (127) into the Diels Alder adduct (133) was expected to be accompanied by only a small change if any in $^{31}$P n.m.r. chemical shift, both the precursor and the addition product being vinyl phosphonates. The replacement of the signal at +12.7 p.p.m. by one at +23.4 p.p.m. is more in accord with a change in the environment of the phosphorus atom from that of a vinyl phosphonate to that of an allyl phosphonate. Such a transformation may be accounted for by the first formed adduct undergoing a subsequent rearrangement to bring the exocyclic double bond into the six-membered ring. This being the case, the possibility then arises of the existence of several different isomeric cyclohexadiene derivatives in which the phosphonate ester substituent is in an allylic position.

The complexity of the $^1$H n.m.r. spectrum of the crude reaction product was such that no definitive evidence could be drawn from it for the presence of the adduct as a single isomer of a substituted cyclohexadiene. However, a doublet of strong intensity at 0.9 did
imply the predominance of a species in which the methyl substituent at $C_2$ was still attached to a saturated carbon atom. This, together with two olefinic protons of a corresponding intensity suggested the presence of the rearranged adduct as isomer (134).
Subsequently, the methyl substituted vinyl allenic phosphonate (136),
derived from 3-methylhex-4-en-1-yn-3-ol, was synthesised for use in
an analogous Diels Alder reaction. As predicted, formation of compound
(136) was accompanied by a predominant cleavage of the intermediate
phosphite leading to poor yields of the desired product.

Equimolar amounts of vinylallenic phosphonate (136) and N-phenyl
maleimide were heated in refluxing THF for a period of 1½ hours, there
being one major phosphorus containing component of the reaction
mixture after this time \[ ^{31}P \text{ (THF) } +23.1 \text{ p.p.m.} \]. The major features
of the \(^1H\) n.m.r. spectrum of the crude reaction product suggested
structure (138) for the adduct, this being of the same form as that
found in the previous case.

\[ \text{(136)} \]
\[ \text{(137)} \]
\[ \text{(138)} \]

The dominating features of the \(^1H\) n.m.r. spectrum included a
three proton doublet (50.9), a three proton singlet (51.9) and a one
proton doublet (56.05). These were found to be unchanged when an attempt
was made to purify the product by passage down a silica column. There was on this occasion no evidence to suggest the presence of the corresponding aromatic phosphonate following the process of chromatography.

An example of Diels Alder addition involving a related vinylallenic phosphonate (139) has recently appeared in the Russian literature. It is reported that this compound combines with the dienophiles acrolein, acrylonitrile, methyl acrylate and maleic anhydride to give the corresponding adducts (140a, b) in yields of between 57-77%.

\[
(RO)_2P(O)\text{CH}CH_2 + R_2CH=CH_2 \rightarrow (RO)_2P(\text{O})\text{CHR}CHCHCH_2\text{CHR}CH=CH_2
\]

\[
(RO)_2P(\text{O})\text{CHR}CHCHCH_2\text{CHR}CH=CH_2 \rightarrow (RO)_2P(\text{O})\text{CHR}CHCHCH_2\text{CHR}CH=CH_2
\]

\[
(RO)_2P(\text{O})\text{CHR}CHCHCH_2\text{CHR}CH=CH_2 \rightarrow (RO)_2P(\text{O})\text{CHR}CHCHCH_2\text{CHR}CH=CH_2
\]
GENERAL EXPERIMENTAL DETAILS

All operations involving air or moisture sensitive compounds were carried out under an atmosphere of dry, oxygen-free nitrogen.

Koch-Light 'Celite' was used as a filtering aid and was heated to dryness prior to use.

The short-path still distillations referred to involved use of the Leybold-Heraeus laboratory still KDL1.

Small scale distillations were carried out using a Kugelröhr apparatus, and the boiling points quoted are for the oven temperature at which distillation occurred.

Preparative high performance liquid chromatography was carried out on my behalf by the separations unit of the Central Research Laboratory, Ciba-Geigy (U.K. Ltd.).

Hydrocarbon solvents were dried over sodium wire. THF and diethyl ether were dried over sodium wire and distilled from lithium aluminium hydride prior to use. Ethyl acetate was stirred with anhydrous potassium carbonate and fused calcium chloride, followed by distillation. Ethanol and methanol were refluxed over and distilled from their magnesium alkoxides. Pyridine and triethylamine were refluxed with and distilled from potassium hydroxide. The dried reagents were stored over potassium hydroxide.

INSTRUMENTATION

Routine $^1$H n.m.r. spectra were recorded using a Varian T-60, 60 MHz. spectrometer or a Varian EM390, 90 MHz. spectrometer, with tetramethylsilane as an internal standard. 100 MHz. $^1$H n.m.r. spectra were recorded on a Jeol NM-PS-100 spectrometer.

Fourier-transform $^{31}$P n.m.r. spectra were recorded on a Jeol JNM-FX-60 spectrometer with aqueous tetrahydroxyphosphonium perchlorate
as an external standard. Chemical shifts are quoted as being negative to high field of this standard and are accurate to $\pm 0.2$ p.p.m. ($\pm 4.8$ Hz.).

$^{13}$C n.m.r. spectra were recorded on the same instrument with tetramethylsilane as a standard.

Mass spectra were recorded using a V.G. Micromass 16B instrument; in each case the molecular ion is given first, followed by fragments of high abundance in order of decreasing mass.

Infra-red spectra were recorded on a Perkin Elmer 237 or a 257 spectrometer as thin films or nujol mulls in the case of solid samples.

U.V. spectra were recorded on a Unicam SP800 spectrometer.

Melting points were obtained using a Kofler heating stage and are uncorrected.

Gas chromatography was carried out using a Pye Unicam 104 chromatograph or 105 preparative chromatograph, using nitrogen as the carrier gas and flame ionisation detectors.
EXPERIMENTAL

Preparation of dimethyl (1-hydroxy-1-methylallyl) phosphonate [(51); R=R''=Me, R*=H]

Addition of dimethyl hydrogen phosphite to 3-buten-2-one, using the method described by Kitaev and Pudovik\(^5^3\) for the addition of dialkyl hydrogen phosphites to \(\alpha,\beta\)-unsaturated aldehydes, gave a mixture of dimethyl (1-hydroxy-1-methylallyl) phosphonate and dimethyl (3-oxo-butyl) phosphonate. The addition products were isolated by vacuum distillation as a colourless oil (3.8g., 50%). b.p. 100-110°C, 7mm. Upon standing, a crystalline solid separated from the distillate, isolation of which gave dimethyl (1-hydroxy-1-methylallyl) phosphonate (0.2g., 5%) m.p. 84-86°C (from ethyl acetate/light petroleum)

(Found: C, 40.13; H, 7.51; P, 17.74% \(C_6H_{12}O_4P\) requires C, 40.1; H, 7.27; P, 17.2%)  
\(^{31}\text{P} n.m.r. (CDCl}_3\) +29.1p.p.m.  
\(^1\text{H} n.m.r. (CDCl}_3\) 6 1.4(d.,3H, J=16Hz); 3.8(d.,6H, J=10Hz); 4.5(Broad s.,1H); 5.2(m.,2H); and 5.7(m.,1H)  
\(\gamma\) max 3350-3380, 1640, 1245 and 1060 cm\(^{-1}\)  
mass spec. m/e 180, 137, 110 and 71

Preparation of diethyl (1-hydroxyallyl) phosphonate (53)

This compound was initially prepared from diethyl hydrogen phosphite and acrolein by the method of Pudovik and Kitaev\(^5^3\) in yields of upto 39%. Later preparations employed the low temperature addition of acrolein to equimolar amounts of diethyl chlorophosphite and ethanol, as described by Gazizov et al.\(^5^5\) Diethyl (1-hydroxyallyl) phosphonate was obtained as a colourless oil, b.p. 124-128°C, 0.25mm.
Preparation of dialkyl (1-hydroxy-3-phenyl-prop-2-enyl) phosphonates

[(31); R=Me, Et, R'=Ph]

These compounds were prepared from the corresponding dialkyl hydrogen phosphite and cinnamaldehyde as described by Pudovik and Kitaev;\(^{53}\) in yields of up to 62%. Products were isolated as white crystalline solids; dimethyl (1-hydroxy-3-phenyl-prop-2-enyl) phosphonate m.p. 100-102\(^\circ\)C, (lit\(^{55}\) 101\(^\circ\)C) and diethyl (1-hydroxy-3-phenyl-prop-2-enyl) phosphonate m.p. 104-105\(^\circ\)C, (lit\(^{53}\) 103-104\(^\circ\)C)

Preparation of diethyl (4-ethoxycarbonyl-but-1-enyl) phosphonate (37)

a) Using a 1:7 molar ratio of \(\alpha\)-hydroxyphosphonate to orthoester

A mixture of diethyl (1-hydroxyallyl) phosphonate (3g., 0.015 mol.), triethyl orthoacetate (17.5g., 7 mol. eq.) and propionic acid (0.06g., 0.06 mol. eq.) was heated under conditions for the distillative removal of ethanol, at an oil bath temperature of 140\(^\circ\)C for a period of 3 hours. Removal of the excess of orthoester under reduced pressure gave a yellow oil (4.1g.) consisting of one major and two minor phosphorus containing components.

\[^{31}P\text{ n.m.r. (CDCl}_3\text{)}\] +17.95, +20.16 and +21.58 p.p.m.

Further heating of the crude reaction product for 1\(\frac{1}{2}\) hours at 140\(^\circ\)C resulted in the disappearance of the signal at +20.16 p.p.m. due to one of the minor components. This was accompanied by the loss of a signal at \(\delta\) 3.7 in the \(^1\)H n.m.r. spectrum.

b) Using a 1:1.4 molar ratio of \(\alpha\)-hydroxyphosphonate to orthoester

A mixture of diethyl (1-hydroxyallyl) phosphonate (19.4g., 0.1 mol.), triethyl orthoacetate (22.7g., 1.4 mol. eq.) and propionic acid (0.44g.,

\(^{31}P\text{ n.m.r. (CDCl}_3\text{)}\] +21.7 p.p.m.
0.06 mol. eq.) was heated under conditions for the distillative removal of ethanol (constant reflux head). After a period of 3 hours at 175°C (oil-bath temperature), the excess of orthoester was removed under reduced pressure giving a residual oil (25.27g.) possessing one major phosphorus containing component [\(^{31}P\) (CDCl\(_3\)) +17.95 p.p.m.].

G.l.c. also indicated there to be one major component, this representing 54% of the total product. Isolation by short path still distillation gave diethyl (4-ethoxycarbonyl-but-1-enyl) phosphonate (14.4 g., 55%, 88% g.l.c. estimated purity) b.p. 81°C, 0.01 mm. Further purification was achieved by preparative high performance liquid chromatography.

\[
\text{(Found: C, 48.34; H, 8.14; P, 12.51\% C}_{11}H_{21}O_{5}P \text{ requires C, 50.01; H, 8.00; P, 11.72\%)}
\]

\(^{31}P\) n.m.r. (CDCl\(_3\)) +17.95 p.p.m.

\(^1H\) n.m.r. (CDCl\(_3\)) \(\delta 1.3(\text{m.}, 9H); 2.5(\text{broad s.}, 4H); 4.05(\text{quintet}, 6H, J=7Hz); 5.6(\text{t.}, 1H, J=17Hz)\) and 6.8(m., 1H)

\(\gamma\) max. 2980, 2940, 2910, 1735, 1635, 1250 and 1040 cm\(^{-1}\)

mass spec. \(m/e 264, 191, 163, 135, 117, 99.\)

\(^{13}C\) n.m.r. (CDCl\(_3\) /\(^1H\) decoupled)
\[
\begin{align*}
\delta 14.28; 16.43(\text{d.}, 2C, J_{P-C}=5.8Hz); 29.15(\text{d.}, 1C, J_{P-C}= 21.5Hz); 32.33; 60.51; 61.61(\text{d.}, 2C, J_{P-C}=5.8Hz); 118.31(\text{d.}, 1C, J_{P-C}=187.5Hz); 150.6(\text{d.}, 1C, J_{P-C}=5.8Hz) \text{ and } 171.9
\end{align*}
\]

Interpretation of this spectrum was aided by comparison with the \(^{13}C\) n.m.r. spectrum of dimethyl vinyl phosphonate.\(^{100}\)

-95-
Dimethyl vinyl phosphonate

\[ {^{13}C \text{n.m.r. (CDCl}_3/^1H \text{ decoupled)}} \]

\[ \delta \text{ 52.35(d., 2C, } J_{P-C}=5.9 \text{Hz); 124.5(d., 1C, } J_{P-C}=183.59 \text{Hz) and 136.2(s., 2C).} \]

Preparation of triethyl orthopropionate (59)

This compound was prepared from propionitrile via the corresponding imino ester hydrochloride, using the method described by Meerwein.\textsuperscript{101}

Purification by distillation gave triethyl orthopropionate (20.6 g., 54\%) b.p. 125-127°C, (lit.;\textsuperscript{101} 126-128°C).

Preparation of diethyl (4-ethoxycarbonyl-4-methyl-but-1-enyl) phosphonate (58)

A mixture of diethyl (1-hydroxyallyl) phosphonate (4.4 g., 0.023 mol), triethyl orthopropionate (16g., 4 mol. eq.) and propionic acid (3 drops)
was heated under conditions for the distillative removal of ethanol.
After a period of 2½ hours at 175°C (oil bath temperature) the excess of orthoester was removed under reduced pressure, giving a residual oil possessing two major phosphorus containing components [\(^{31}\text{P} (\text{CDCl}_3) +17.74\) and +7.2 p.p.m.]. The chemical shift of +7.2 p.p.m. suggests the presence of diethyl hydrogen phosphite, this being supported by the observation of a signal in the \(^1\text{H} \text{n.m.r.}\) spectrum at δ 12.6 ascribed to the low field half of the P-H doublet (\(J_{\text{P-H}}=700\text{Hz}\)). Separation of reaction products by distillation gave diethyl (4-ethoxycarbonyl-4-methyl-but-1-enyl) phosphonate as a yellow oil (3.05 g., 48%) b.p. 130-135°C, 0.3 mm. An analytically pure sample of this compound could not be isolated.

\[\begin{align*}
31\text{P n.m.r. (CDCl}_3) & \quad +17.74 \text{ p.p.m.} \\
1\text{H n.m.r. (CDCl}_3) & \quad \delta 1.3 (\text{m.}, 12\text{H}); 2.5 (\text{m. poorly resolved}, 3\text{H}); \\
 & \quad 4.05 (\text{quartet}, 6\text{H}, J=7\text{Hz}); 5.6 (\text{t.}, 1\text{H}, J=17\text{Hz}); \\
 & \quad \text{and } 6.8 (\text{m.}, 1\text{H}) \\
\gamma \text{ max} & \quad 2980, 2940, 2910, 1735, 1635, 1250 \text{ and } 1040 \text{ cm}^{-1} \\
\text{mass spec.} & \quad m/e 278, 205, 177 \text{ and } 149
\end{align*}\]

Preparation of diethyl (4-ethoxycarbonyl-3-phenyl-but-1-enyl) phosphonate [(60); \(R=\text{Et}\)]

A mixture of diethyl (1-hydroxycinnamyl) phosphonate (11.9 g., 0.04 mol.), triethyl orthoacetate (14.3 g., 2 mol. eq.) and propionic acid (0.17 g., 0.06 mol.eq.) was heated under conditions for the distillative removal of ethanol at a temperature of 145°C (oil bath) for a period of 4 hours. Removal of the excess of orthoester gave a residual oil (13.84 g.) possessing one major phosphorus containing component [\(^{31}\text{P} (\text{CDCl}_3) +18.15\) p.p.m.]. Isolation by short path still distillation gave diethyl (4-ethoxycarbonyl-3-phenyl-but-1-enyl) phosphonate as a yellow oil.

-97-
(9.2 g., 68%, 90% g.l.c. estimated purity) b.p. 95°C, 0.01 mm. Further purification was achieved by preparative high performance liquid chromatography.

(Found C, 59.86; H, 7.45; P, 9.24% \( \text{C}_{17} \text{H}_{25} \text{O}_3 \text{P} \) requires C, 60.0; H, 7.4; P, 9.10%) 

\(^{31}\text{P n.m.r. (CDCl}_3)\) +18.15 p.p.m.

\(^1\text{H n.m.r. (CDCl}_3)\)

δ 1.3(m., 9H); 2.8(d., 2H, \( J=8 \text{Hz} \)); 4.05(m., 7H); 5.6(t., 1H, \( J=17 \text{Hz} \)); 6.8(m., 1H) and 7.25(broad s., 5H)

\( \gamma \) max 

2980, 2920, 2900, 1735, 1625, 1600, 1250, 1035, 960, and 690 cm\(^{-1}\)

mass spec. 

m/e 340, 295, 267, 176, 161, 132 and 131

Preparation of dimethyl (4-ethoxycarbonyl-3-phenyl-but-1-enyl) phosphonate ([60]; \( R=\text{Me} \))

A mixture of dimethyl (1-hydroxycinnamyl) phosphonate (3 g., 0.012 mol.), triethyl orthoacetate (13.6 g., 7 mol. eq.) and propionic acid (4 drops) was heated under conditions for the distillative removal of ethanol, at 130°C for a period of 4 hours. Removal of the excess of orthoacetate gave a residual oil possessing one major phosphorus containing component \([^{31}\text{P (CDCl}_3) \) +20.97 p.p.m.\]. Chromatography of a sample of the crude reaction product on UGI alumina with ether-chloroform gave the isomeric product, dimethyl (4-ethoxycarbonyl-3-phenyl-but-2-enyl) phosphonate (61) (0.66 g., 56%).

\(^{31}\text{P n.m.r. (CDCl}_3)\) +29.2 p.p.m.

\(^1\text{H n.m.r. (CDCl}_3)\)

δ 1.2(t., 3H, \( J=7 \text{Hz} \)); 2.8(d. of d., 2H, \( J=8 \text{Hz}, J=22 \text{Hz} \)); 3.6(s., 2H); 3.75(d., 6H, \( J=11 \text{Hz} \)); 4.1(quartet, 2H, \( J=7 \text{Hz} \)); 5.9 (quartet, 1H, \( J=8 \text{Hz} \)) and 7.3(broad s., 5H)
Reaction on a 0.1 molar scale followed by isolation of the major component of the product by short path still distillation gave dimethyl (4-ethoxycarbonyl-3-phenyl-but-l-enyl) phosphonate as a pale yellow oil (17.7g., 57%) b.p. 92°C, 0.09mm.

**Preparation and the attempted rearrangement of the acetoacetic ester of diethyl (1-hydroxyallyl) phosphonate (64)**

A mixture of diethyl (1-hydroxyallyl) phosphonate (3.9g., 0.023mol.), diketene (2.17g., 0.026mol.) and a catalytic amount of a saturated solution of sodium methoxide in methanol was heated at 110°C for a period of 5 hours with toluene (10 cm³) solvent. Following the removal of volatiles the residue was distilled (Kugel distillation) to give a colourless oil (3.7g.) b.p. 110°C, 0.03mm. The distillate was shown by ³¹P and ¹H n.m.r. spectra to consist of a mixture of unreacted α-hydroxyphosphonate (40%) and the acetoacetic ester derivative as a mixture of its tautomeric forms (50% keto; 10% enol).

**Characteristic data for the acetoacetic ester:**

\[
\gamma_{\text{max}} \quad 2980, 1735, 1625, 1250, 1035, 820, 760 \\
\text{and } 700 \, \text{cm}^{-1}
\]

**mass spec.**

m/e 312, 267, 239, 192, 157, 134, 105 and 92
Preparation of p-chlorophenylsulphenyl chloride

This compound was prepared from p-chlorothiophenol and chlorine on a 0.083 molar scale using the method described by Sparke and co-workers. Distillation of the crude reaction product under reduced pressure gave p-chlorophenylsulphenyl chloride (14.15g., 96%) as a red fuming liquid. b.p. 70-74°C, 3mm. (lit. 86-90°C, 5mm)

Preparation of di-isopropyl (1-hydroxyallyl) phosphonate [(51); R=Pr\textsuperscript{i}, R'=H]

This compound was prepared in yields of up to 54% using the base catalysed addition of di-isopropyl hydrogen phosphite to acrolein described by Pudovik and Kitaev.

\[ ^{31}\text{P n.m.r. (CDCl}_3\text{)} \quad +20.16 \text{ p.p.m.} \]

Preparation of (3-di-isopropylphosphinyl-prop-2-enyl) p-chlorophenyl sulfoxide [(75); R=Pr\textsuperscript{i}, R'=H]

To a solution of di-isopropyl (1-hydroxyallyl) phosphonate (7.8g., 0.035 mol.) and triethylamine (3.89g., 0.039 mol.) in ether (400 cm\textsuperscript{3}), was added dropwise with cooling (ice-bath) and stirring, a solution of p-chlorophenylsulphenyl chloride (6.26g., 0.035 mol.) in the same solvent. Upon completion of the addition the ice-bath was removed and the reaction mixture stirred for a further 2 hours. Separation of amine hydrochloride by filtration (celite aided), followed by removal of solvent from the filtrate, gave an orange-brown oil which crystallised upon cooling. Repeated recrystallisation of the residue gave (3-di-isopropylphosphinyl-prop-2-enyl) p-chlorophenyl sulfoxide (2g., 16%) m.p. 75-77°C (from petroleum ether 60-80°C)

(Found C, 49.39; H, 6.11; P, 7.92; S, 8.53 % \(\text{C}_{15}\text{H}_{22}\text{O}_4\text{ClPS} \text{ requires C, 49.36; H, 6.08; P, 8.49; S, 8.78 %} \) )

-100-
\(^{31}\)P n.m.r. (CDCl\(_3\)) +12.5 p.p.m.

\(^{1}\)H n.m.r. (CDCl\(_3\))
\(\delta\) 1.3 (doublet of doublets, 12H, \(J=12\) Hz; 2H, \(J=6\) Hz; 6.2-7.05 (m, 1H) and 7.6 (s, 4H).

\(\gamma_{\text{max}}\)
2950, 1640, 1245, 1050, 1010 and 82 cm\(^{-1}\)

mass spec.
m/e (for \(^{35}\)Cl) 364, 316, 306, 280, 222, 205, 181, 163, 159, 121 (100%) and 125.

\(^{13}\)C n.m.r. (CDCl\(_3\)/\(^{1}\)H decoupled) \(\delta\) 23.9 (d, 4C, \(J_{P-C}=6\) Hz); 50.5 (d, 1C, \(J_{P-C}=138\) Hz); 70.77 (d, 2C, \(J_{P-C}=88\) Hz); 128.05 (d, 1C, \(J_{P-C}=186.7\) Hz); 125.64; 129.53; 136.75; 136.35; 137.6 and 141.7.

Following a comparison of this spectrum with the \(^{13}\)C n.m.r. spectrum of dimethyl vinyl phosphonate (see page 96), the doublet centred at \(\delta\) 128.05 (\(J_{P-C}=186.7\) Hz) is assigned to the vinyl carbon atom adjacent to the dialkylphosphinyl group.

The absence of a signal in the \(^{13}\)C n.m.r at around +32.5 p.p.m. (d, \(J_{P-C}=138\) Hz), characteristic of the allylic -CH\(_2\)- of a dialkylallyl phosphonate, shows there to be no contribution here from the isomer which is \(\alpha,\beta\)-unsaturated with respect to the sulfoxide grouping.

\(^{31}\)P n.m.r. (CDCl\(_3\))

(3-dimethoxyphosphinylprop-2-enyl) \(P\)-chlorophenyl sulfoxide +17.1 p.p.m.

(3-diethoxyphosphinylprop-2-enyl) \(P\)-chlorophenyl sulfoxide +14.9 p.p.m.

(3-dimethoxyphosphinyl-1-phenyl-prop-2-enyl) \(P\)-chlorophenyl sulfoxide +20.37 p.p.m.
Preparation and attempted rearrangement of diethyl (1-diethoxyphosphinyl-prop-2-enyl) phosphite (76)

To a mixture of diethyl (1-hydroxyallyl) phosphonate (6g., 0.031 mol.) and diethyl chlorophosphite (4.8g., 0.031 mol.) in ether (200 cm$^3$), was added dropwise with cooling (ice-bath) and stirring, a solution of triethylamine (3.13g., 0.031 mol.) in the same solvent (50 cm$^3$). Upon completion of the addition, the reaction mixture was allowed to attain room temperature and stirred at this temperature for 1 hour. Separation of amine hydrochloride by filtration (celite aided), followed by removal of solvent from the filtrate, gave a colourless oil (9.53g.). The $^{31}$P n.m.r. spectrum of the crude product showed the characteristic two sets of doublets predicted for the desired product, diethyl (1-diethoxyphosphinyl-prop-2-enyl) phosphite [$^{31}$P (CH$_2$Cl$_2$/CDCl$_3$) +140.4 p.p.m. (d., J=17Hz) and +18.7 p.p.m. (d., J=17Hz)]. Distillation of the crude reaction product (maximum oil-bath temperature 180°C) gave a mixture of diethyl (1-diethoxyphosphinyl-prop-2-enyl) phosphite [(2.05g., 21%) b.p. 130-136°C, 0.1 mm.] and diethyl (1-diethoxyphosphinyl-prop-2-enyl) phosphate [(4.1g., 40%) b.p. 136-150°C, 0.1 mm.]. Neither the fractions nor the residue showed evidence of the presence of the product of (2,3) sigmatropic rearrangement, diethyl (3-diethoxyphosphinyl-prop-1-enyl) phosphonate (77).

Diethyl (1-diethoxyphosphinyl-prop-2-enyl) phosphate

$^{31}$P n.m.r. (CDCl$_3$/CH$_2$Cl$_2$) +16.5 p.p.m. (d., J=29Hz) and

-1.2 p.p.m. (d., J=29Hz)

$^1$H n.m.r. (CDCl$_3$)

δ 1.3 (m., 12H, J=7Hz); 4.0 (septet, 8H, J=7Hz); 4.75 (doublet of doublets, 1H, J=13Hz, J=7Hz); 5.4 (m., 2H) and 6.0 (m., 1H)

-102-
$\gamma_{\text{max}}$ 2990, 1640, 1230, 1030 and 960 cm$^{-1}$

mass spec. m/e 330, 274, 263, 218, 193, 176, 164, 138, 137, 121, 111, 109, 99 and 81.
Preparation of diethyl (3-methyl-buta-1,2-dienyl) phosphonate
[(83); R=Et]

To a mixture of 2-methyl-3-butyn-2-ol (8.4g., 0.1 mol.) and diethyl chlorophosphite (15.65g., 0.1 mol.) in ether (200 cm$^3$), was added dropwise with cooling (ice-bath) and stirring a solution of pyridine (7.9g., 0.1 mol.) in the same solvent (50 cm$^3$). Upon completion of the addition the reaction mixture was allowed to attain room temperature and stirred at this temperature for a further hour. Pyridine hydrochloride was then separated by filtration (celite aided). Removal of solvent followed by vacuum distillation gave diethyl (3-methyl-buta-1,2-dienyl) phosphonate as a colourless oil (12.95g., 63%) b.p. 85°C, 0.5 mm (lit. 95°C, 0.8 mm)

$^{31}$P n.m.r. (CDCl$_3$/CH$_2$Cl$_2$) +15.93 p.p.m.

$^1$H n.m.r. (CDCl$_3$)

δ 1.3 (t., 6H, J=7 Hz); 1.75 (doublet of doublets, 6H, J=7 Hz, J=3 Hz); 4.1 (quintet, 4H, J=7 Hz) and 5.1 (m., 1H)

Addition of allyl alcohol to diethyl (3-methyl-buta-1,2-dienyl) phosphonate

To a mixture of sodium hydride (2.88g., 0.06 mol. -50% dispersion in oil) in THF (40 cm$^3$) at 0°C was added dropwise a solution of allyl alcohol (3.48g., 0.06 mol.) in the same solvent (10 cm$^3$). The reaction mixture was allowed to warm up to 20°C for a period of 15 minutes, after which it was cooled to 0°C and a solution of diethyl (3-methyl-buta-1,2-dienyl) phosphonate (12.24g., 0.06 mol.) in THF (10 cm$^3$) was added dropwise. Upon completion of the addition the reaction mixture was allowed to warm up to room temperature and was stirred for 2 hours, after which time 60 cm$^3$ of 1M HCl were added. The aqueous and THF layers were
separated, the aqueous portion being extracted with ether and the
organic solutions combined. The mixed THF and ether solution was then
washed with water, dried (MgSO₄), and the solvent removed, to give an
orange oil (11.8g.). The ³¹P n.m.r. spectrum of the crude reaction product
showed there to be four major phosphorus containing components, and the
I.R. spectrum contained new strong absorptions at 1710 and 1610 cm⁻¹.

³¹P n.m.r. (CDCl₃/CH₂Cl₂) +21.17, +22.99, +22.18 and +21.58 p.p.m.
- listed in descending order of peak intensity.

Separation and characterisation was achieved by use of preparative g.l.c.
( Column 10% OV17; operating temperature 186°C; 40 µl injections were
collected as eight separate fractions.)

Fraction 3 Retention time 6.8 minutes. Concentrating diethyl (2-ethoxy-
3-methyl but-1-enyl) phosphonate (84a) in 16.4% yield (g.l.c. estimated).
Physical data favouring this structure over that of diethyl (2-ethoxy-3-
methyl but-2-enyl) phosphonate (84b).

³¹P n.m.r. (CDCl₃) +23.19 p.p.m.
¹H n.m.r.  δ 1.1(d., 6H, J=6.5Hz); 1.3(t., 6H, J=7Hz);
3.35(quintet, 1H, J=6.5Hz); 3.75(quartet, 2H, J=7Hz); 4.1(quintet, 4H, J=7Hz) and 4.3
(d., 1H, J=8Hz)

γ max 2980; 2940; 1610; 1470; 1445; 1350; 1310;
1250; 1030 and 950 cm⁻¹

mass spec. m/e 250, 235, 220, 178, 164, 150, 123 and 105

Fraction 4 Retention time 7.8 minutes. Concentrating diethyl (1-allyl-
2-methyl-2-oxo butyl) phosphonate (86) in 19.2% yield (g.l.c. estimated).

³¹P n.m.r. (CDCl₃) +21.98 p.p.m.
¹H n.m.r. (CDCl₃) δ 1.05(d., 3H, J=3Hz); 1.15(d., 3H, J=3Hz);
1.3(t., 6H, J=7Hz); 2.25-3.2(m., 4H);
4.1 (quintet, 4H, J=7Hz); 4.95 (m., 1H); 5.1 (m., 1H) and 5.65 (m., 1H)

The chiral centre at the 1 position of this molecule gives rise to the magnetic non-equivalence of the two methyl groups which appear as doublets at δ 1.05 and 1.15.

\[ \gamma_{\text{max}} \] 2990, 2940, 1705, 1640, 1250 and 1030 cm\(^{-1}\)

mass spec. m/e 262, 219, 191, 179, 163, 109 and 81

Fraction 6 Retention time 12.2 minutes. Concentrating diethyl (3-allyl-3-methyl-2-oxo butyl) phosphonate (85) in 37% yield (g.l.c. estimated)

\[ \text{\(^3\)P n.m.r. (CDCl}_3\)} \] +21.37 p.p.m.

\[ \text{\(\text{^1}H\ n.m.r. (CDCl}_3\)} \] δ 1.15 (s., 6H); 1.3 (t., 6H, J=7Hz); 2.2 (d., 2H, J=7Hz); 3.1 (d., 2H, J=21Hz); 4.1 (quintet, 4H, J=7Hz); 4.95 (m., 1H); 5.1 (s., 1H) and 5.65 (m., 1H)

\[ \gamma_{\text{max}} \] 3000, 2940, 1710, 1640, 1470, 1395, 1370, 1250 and 1020 cm\(^{-1}\)

mass spec. m/e 262, 179, 151, 137, 125, 109, 97 and 81

Fraction 8 Retention time 16.4 minutes. Concentrating allyl, ethyl (3-allyl-3-methyl-2-oxo butyl) phosphonate in 7% yield (g.l.c. estimated)

\[ \text{\(^3\)P n.m.r. (CDCl}_3\)} \] +21.78 p.p.m.

\[ \text{\(\text{^1}H\ n.m.r. (CDCl}_3\)} \] δ 1.15 (s., 6H); 1.3 (t., 3H, J=7Hz); 2.2 (d., 2H, J=7Hz); 3.1 (d., 2H, J=21Hz); 4.1 (quintet, 2H, J=7Hz); 4.95 (m., 2H); 5.1 (s., 2H) and 5.65 (m., 2H)

\[ \gamma_{\text{max}} \] 3000, 2940, 1710, 1640, 1470, 1395, 1370, 1250 and 1020 cm\(^{-1}\)

mass spec. m/e 274, 233, 191, 163, 149
Reaction of 2-methyl-3-buten-2-ol with diethyl (3-methyl-buta-1,2-dienyl) phosphonate (a). This was carried out by the same method as described for the reaction with allyl alcohol, on a 0.04 molar scale. The crude reaction product, an orange coloured oil, consisted of several phosphorus containing components, there being one major \([^{31}\text{P} \text{ (CDCl}_3/\text{CH}_2\text{Cl}_2) +22.9 \text{ p.p.m}.]\]. Analytical g.l.c. indicated there to be two major reaction products. (Column 10% OV 17; operating temperature 195°C)

<table>
<thead>
<tr>
<th>Retention Time (Mins.)</th>
<th>Estimated Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.2</td>
<td>26</td>
</tr>
<tr>
<td>6.8</td>
<td>67</td>
</tr>
</tbody>
</table>

Isolation of these two components was achieved by distillation of the crude reaction product, the distillate (b.p. 100°C, 0.25 mm) showing strong absorptions in the I.R. spectrum at 1710 and 1610 cm\(^{-1}\). Separation of the two components was then effected by preparative g.l.c. (conditions as above).

**Fraction 2** Retention time 5.2 minutes. Diethyl (3-methyl-2-oxo butyl) phosphonate (93)

\[^{31}\text{P} \text{ n.m.r. (CDCl}_3/\text{CH}_2\text{Cl}_2) +20.37 \text{ p.p.m.}\]

\[^{1}\text{H} \text{ n.m.r. (CDCl}_3\] 5 1.1(d., 6H, J=7Hz); 1.3(t., 3H, J=7Hz);
2.9(m., 1H); 3.1(d., 2H, J=23Hz) and
4.1(quintet, 4H, J=7Hz)

\(\gamma_{\text{max}} \) 1710 cm\(^{-1}\) (lit., 1710 cm\(^{-1}\))

**Fraction 4** Retention time 6.8 minutes. This compound was found to have identical physical data (n.m.r., I.R. and mass spectra) to a component isolated in the corresponding reaction with allyl alcohol, and postulated as being diethyl (2-ethoxy-3-methyl but-1-enyl) phosphonate (84a).
The reaction was carried out as previously except that the mixture of tertiary alcohol and sodium hydride having been allowed to attain room temperature was then heated in refluxing THF for a period of 20 minutes. Following this the reaction mixture was cooled to 0°C and the allenic phosphonate added as before. The crude reaction product (6.2g) was in this case found to contain a significant amount of unreacted starting materials. In addition there was one new major phosphorus containing component present [\(^{31}\)P (CH\(_2\)Cl\(_2\)) +27.2 p.p.m.], this coinciding with the appearance of a doublet at \(\delta 2.8\) p.p.m. (J=21Hz) in the \(^1\)H n.m.r. spectrum and a strong absorption in the I.R. spectrum at 1610 cm\(^{-1}\).

A further chemical change occurred upon distillation of the crude reaction product. Fraction three of the distillate (0.6g., b.p. 132-144°C, 0.05 mm) consisted predominantly of a new compound [\(^{31}\)P (CH\(_2\)Cl\(_2\)) +21.17 p.p.m.], which was not present in the original product.

Isolation by preparative g.l.c. gave diethyl (2-oxo-3,3,6-trimethyl hept-5-enyl) phosphonate (95). (Column 10% OV 17; operating temperature 200°C) Retention time 21.4 minutes.

\(^1\)H n.m.r. (CDCl\(_3\))

\(\delta 1.1\text{ (s., 6H); 1.3\ (t., 6H, J=7Hz); 1.65\ (d., 6H, J=7Hz); 2.2\ (d., 2H, J=7Hz); 3.1\ (d., 2H, J=21Hz); 4.1\ (quintet, 4H, J=7Hz) and 5.0\ (m., 1H)}\)

\(\gamma\) max

2980, 2930, 1710, 1470, 1445, 1390, 1370, 1250, 1035 and 965 cm\(^{-1}\)

Mass spec. m/e 290, 275, 248, 222, 179, 151 and 137
Reaction of 3-buten-2-ol with diethyl (3-methyl-buta-1,2-dienyl) phosphonate

The procedure outlined in method (b) for the corresponding reaction with the tertiary alcohol was employed. As with the tertiary alcohol the predominant species present in the reaction product came from the addition of the allylic alcohol to the activated double bond of the allene \[^{31}\text{P} (\text{CH}_2\text{Cl}_2) +26.8 \text{ p.p.m.} \]. There was however also evidence of the presence of rearranged product, \[^{31}\text{P} (\text{CH}_2\text{Cl}_2) +21.17 \text{ p.p.m.} \], the amount of this increasing upon distillation. Isolation of the rearranged product was not achieved.

Preparation of 3-methylhept-6-en-1-yn-3-ol (99)

This compound was prepared from sodium acetylide and hex-5-en-2-one on a 0.5 molar scale by an adaptation of the method described in Organic Synthesis \(^{102}\) for the preparation of 1-ethynyl-cyclohexanol. This includes the generation of sodium acetylide from a sodium in liquid ammonia solution saturated with acetylene gas, as recommended by Vaughn, Hennion, Vogt and Nieuwland.\(^{103}\) Distillation of the crude reaction product under reduced pressure gave 3-methylhept-6-en-1-yn-3-ol as a colourless liquid (35.8g.; 58%) b.p. 64-66°C, 16mm.

\[ {^1\text{H n.m.r. (CDCl}_3) \delta 1.5(s., 3\text{H}); 1.8(m., 2\text{H}); 2.35(m., 2\text{H}); 2.5(s., 1\text{H}); 2.8(broad s., 1\text{H}, \text{D}_2\text{O exchangeable}); 5.05(t., 2\text{H}, J=14\text{Hz}) \text{ and } 5.9(m., 1\text{H}) } \]

\[ \gamma_{\text{max}} 3400, 3320, 3100, 3000, 2960, 2870, 2130, 1645, 1510, 1375, 1120 \text{ and } 920 \text{ cm}^{-1} \]
Preparation of diethyl chlorophosphite

In a dissociative reaction between triethyl phosphite and phosphorus trichloride based upon that described by Saunders et al., the preparation of this compound was achieved in yields of up to 91%.

\[ ^{31}P \text{n.m.r. (CH}_2\text{Cl}_2 \] \(+166.5 \text{ p.p.m.} \]

Preparation of diethyl (3-methyl hepta-1,2,6-trienyl) phosphonate (101)

To a mixture of 2-ethynylhex-5-en-2-ol (22.3 g., 0.18 mol.) and diethyl chlorophosphite (28.1 g., 0.18 mol.) in dry ether (250 cm³), was added dropwise with cooling (ice-bath) and stirring a solution of pyridine (14.2 g., 0.18 mol.) in the same solvent (50 cm³). Upon completion of the addition, the ice-bath was removed and the reaction mixture stirred for a further two hours. Pyridine hydrochloride was then separated by filtration (celite aided). Removal of solvent followed by distillation of the crude reaction product gave diethyl (3-methyl hepta-1,2,6-trienyl) phosphonate as a colourless oil (31.9 g., 72%) b.p. 110-112°C, 0.6 mm.

\[ ^{31}P \text{n.m.r. (CDCl}_3/\text{CH}_2\text{Cl}_2 \] \(+15.7 \text{ p.p.m.} \]

\[ ^{1}H \text{n.m.r. (CDCl}_3 \] \(\delta 1.3(t., \text{ 6H, J}=7\text{Hz}); 1.8(\text{doublet of doublets, 3H, J}=7\text{Hz}, \text{ J}=3\text{Hz}); 2.2(\text{m., 4H}); 5.15(\text{m., 2H}) \text{ and } 5.9(\text{m., 1H}). \]

Y max

3000, 2930, 1960, 1645, 1450, 1375, 1250, 1045, 965 and 825 cm⁻¹

mass spec.

m/e 244, 215, 214, 188, 187, 151, 146, 125, 107, 106 and 91.

Rearrangement of diethyl (3-methyl hepta-1,2,6-trienyl) phosphonate

A sample of this compound (20 g., 0.08 mol.) was heated at a temperature of 150°C for a period of two hours in the absence of solvent. After this time the allene stretch in the I.R. spectrum had disappeared. Distillation under reduced pressure gave diethyl (2-isopropenylpenta-1,4-
dienyl) phosphonate (102) as a colourless oil (17.7g, 89%) b.p.
110-112°C, 0.6 mm.

\[^{31}\text{P} \text{n.m.r. (CDCl}_3/\text{CH}_2\text{Cl}_2)\] +18.1 and +16.9 p.p.m.

(ratio of 0.26:1 by peak intensity.)

\[^{1}\text{H} \text{n.m.r. (CDCl}_3\)] 6 1.3(t., 6H, J=7Hz); 1.9(s., 3H); 2.9(d.,
2H, J=6Hz); 4.1(quintet, 4H, J=7Hz) and
4.9-6.1(m., 6H)

\(\gamma_{\text{max.}}\)
3000, 2950, 2930, 1650, 1620, 1600, 1450,
1395, 1250, 1045 and 965 cm\(^{-1}\)

mass spec. m/e 244, 215, 214, 188, 187, 173, 107,
106, 105 and 91.

Formation of a Diels Alder adduct of diethyl (2-isopropenylpenta-1,4-
dienyl)phosphonate with N-phenyl maleimide (104)

A mixture of diethyl (2-isopropenylpenta-1,4-dienyl) phosphonate
(8g., 0.032mol.) and N-phenyl maleimide (5.67g., 0.032mol.) was heated
at 96°C, the reaction being monitored by \(^{31}\text{P} \text{n.m.r.} \) spectroscopy. A
total of 7 hours at this temperature was required for the disappearance
of the two signals in the \(^{31}\text{P} \text{ spectrum due to diene, these being replaced}
by new signals \(\left[^{31}\text{P (CH}_2\text{Cl}_2\right] +25.2 \text{ and } +26.8 \text{ p.p.m.}\). A 2 grams
sample of the crude reaction product, a viscous yellow oil, was
purified by column chromatography (silica/ether and ethyl acetate). A
single isomer of the Diels Alder adduct, 3-allyl-2-(diethoxyphosphinyl)-
4-methyl-8-phenyl-8-azabicyclo[4.3.0]non-3-en-7,9-dione was obtained as
a pale yellow oil (1.3g., 66%) \(\left[^{31}\text{P n.m.r. (CH}_2\text{Cl}_2\right] +26.8 \text{ p.p.m.}\). High
vacuum distillation carried out prior to analysis gave a colourless
glass. Oven temperature 250°C, 0.005mm.
(Found H, 6.59; N, 3.15; P, 7.03\% C\textsubscript{22}H\textsubscript{28}O\textsubscript{5}NP requires C, 63.3; H, 6.76; N, 3.36; P, 7.42\%). A satisfactory analysis for carbon content could not be obtained (60.47\%). The low results may possibly be attributed to incomplete combustion of the sample, the presence of residual ash being noted by the analyst.

\textsuperscript{1}H n.m.r. (CDCl\textsubscript{3})

\begin{align*}
\delta & \quad 1.3 (\text{doublet of triplets, } 6\text{H, } J=7\text{Hz, } J=3\text{Hz}); \\
& \quad 1.75 (d., 3\text{H, } J=5\text{Hz}); \\
& \quad 2.2-3.6 (\text{complex overlapping multiplets, } 7\text{H}); \\
& \quad 4.1 (\text{doublet of quintets, } 4\text{H, } J=7\text{Hz, } J=3\text{Hz}); \\
& \quad 4.9 (d., 1\text{H, } J=11\text{Hz} \text{ and d., 1H, } J=15\text{Hz}); \\
& \quad 5.4 (m., 1\text{H}) \text{ and } 7.25 (m., 5\text{H}).
\end{align*}

\begin{align*}
\gamma_{\text{max}} & \quad 2980, 2940, 1715 \text{ (broad), } 1600, 1500, 1385, \\
& \quad 1245, 1040 \text{ and } 960 \text{ cm}^{-1}
\end{align*}

mass spec.

\begin{align*}
&m/e 417, 376, 280, 279, 252, 251, 213, 186 \text{ (metastable) and } 132 \text{ (100\%).}
\end{align*}
Preparation of 3,5-dimethylhex-4-en-1-yn-3-ol (116)

This compound was prepared from 4-methyl-3-penten-2-one and sodium acetylide on a 0.5 molar scale using the method described by Cymerman, Heilbron and Jones. Distillation of the crude reaction product under reduced pressure gave 3,5-dimethylhex-4-en-1-yn-3-ol as a colourless liquid (29.1 g., 47%). b.p. 44-48°C, 2 mm. (lit., 67-67.5°C, 22 mm.)

\[ \text{H n.m.r. (CDCl}_3 \] 8 1.6(d., 3H, J=1Hz); 1.75(d., 3H, J=1Hz);
1.95(s., 3H); 2.15(s., 1H, D_2O exchangeable);
2.5(s., 1H) and 5.3(broad s., 1H).

Preparation and rearrangement of diethyl (3,5-dimethylhexa-1,2,4-trienyl) phosphonate (118)

To a mixture of 3,5-dimethylhex-4-en-1-yn-3-ol (12.4 g, 0.1 mol.) and diethyl chlorophosphite (15.6 g, 0.1 mol.) in THF (200 cm³) was added dropwise with cooling (ice-bath) and stirring, a solution of pyridine (7.9 g, 0.1 mol.) in the same solvent (50 cm³). Upon completion of the addition the reaction mixture was stirred at room temperature for 2 hours and at 66°C for a further ½ hour. Upon cooling, pyridine hydrochloride was separated by filtration (celite aided) and the solvent removed from the filtrate to give an orange oil (23.9 g). This was shown by \(^{31}\text{P n.m.r.} \) spectroscopy to consist of three phosphorus containing components \( \left[ ^{31}\text{P (CH}_2\text{Cl})_2 \right] +7.2 \) (major), +16.1 and +19.9 p.p.m.]

Distillation of a 10 g portion of the crude reaction product gave diethyl hydrogen phosphite (3.3 g; 58% based on diethyl chlorophosphite). b.p. 60°C, 0.5 mm. Two higher boiling fractions of distillate (b.p. 120-124°C, 0.5 mm) were found to be of similar composition and consisted of a mixture of four different phosphorus containing components \( \left[ ^{31}\text{P (CH}_2\text{Cl})_2 \right] +16.1, \)
+19.9, +30.4 and +31.4 p.p.m.]. The combined fractions (2.05g) represent
a 20% yield based upon the desired product, diethyl (3,5-dimethylhexa-
1,2,4-trienyl) phosphonate. They each showed an allene stretch (1955 cm\(^{-1}\))
in the I.R. spectrum, together with several overlapping absorptions around
1600 cm\(^{-1}\) and maxima were observed in the U.V. spectrum (EtOH) at 245
and 272 nm. G.l.c. analysis showed the fractions to consist of three
major components under the chromatographic conditions (column 10% OV17;
operating temperature 200\(^{\circ}\)C). Preparative g.l.c. conducted with the same
operating conditions enabled the separation of these three components.

**Fraction 4** Retention time 11 minutes. Concentrating diethyl (3,5-
dimethylcyclohexa-2,4-dienyl) phosphonate (120) in 50% yield (g.l.c.
estimated).

\[ ^{31}\text{P n.m.r. (CH}_2\text{Cl}_2 \] +30.4 p.p.m.

\[ ^{1}\text{H n.m.r. (CDCl}_3 \] 6 1.3(t., 6H, J=7Hz); 1.75(m., 6H);
2.1-3.1(m., 3H); 4.1(quintet, 4H, J=7Hz);
5.3(d., 1H, J=9Hz) and 5.55(s., 1H).

**Fraction 6** Retention time 12.4 minutes. Concentrating diethyl
(3-methyl-5-methylene-cyclohex-3-enyl) phosphonate (124) in 7% yield
(g.l.c. estimated)

\[ ^{31}\text{P n.m.r. (CH}_2\text{Cl}_2 \] +31.4 p.p.m.

\[ ^{1}\text{H n.m.r. (CDCl}_3 \] 6 1.3(t., 6H, J=7Hz); 1.75(s., 3H); 1.85-
2.8(m., 5H); 4.1(quintet, 4H, J=7Hz);
4.8(s., 2H) and 5.95(s., 1H).

**Fraction 8** Retention time 16.4 minutes. Concentrating diethyl
(3,5-dimethylphenyl) phosphonate (121) in 31% yield (g.l.c. estimated).

\[ ^{31}\text{P n.m.r. (CH}_2\text{Cl}_2 \] +19.3 p.p.m.

\[ ^{1}\text{H n.m.r. (CDCl}_3 \] 6 1.3(t., 6H, J=7Hz); 2.35(s., 6H); 4.1
(quintet, 4H, J=7Hz); 7.1(s., 1H) and
7.4(d., 2H, J=14Hz).

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The mass spectra of all three components separated by g.l.c. show a marked similarity. In each case the molecular ion corresponding to the aromatic phosphonate (m/e 242) predominates. It is assumed that the process of aromatisation seen to occur on chromatographic treatment also occurs in the mass spectrometer, during or prior to ionisation.

mass spec. m/e 242, 214, 186, 171 and 105.

A neat sample of the product mixture present in the high boiling fractions of distillate was heated at 200°C for a period of \( \frac{1}{2} \) hour. The \(^{31}\)P n.m.r. spectrum (CH\(_2\)Cl\(_2\)) of the sample then showed a major absorption at +19.3 p.p.m., this characteristic of diethyl (3,5-dimethyl-phenyl) phosphonate. As a result of the treatment the sample had become a black viscous oil and broad, unresolved signals in the \(^{31}\)P n.m.r. spectrum around +30 p.p.m. suggested decomposition to have occurred. A sample of the same distillate as a solution in nitrobenzene was heated at 200°C in the presence of a catalytic amount of palladium on charcoal. Monitoring the reaction by \(^{31}\)P n.m.r. spectroscopy showed the appearance and increase in intensity of the signal due to the aromatic phosphonate \([^{31}\text{P (nitrobenzene)} +18.7 \text{ p.p.m.}].\) There was no spectral evidence to suggest that this was accompanied by the decomposition previously seen. After a period of 10 hours approximately 80% of the material was present as the aromatic phosphonate.

Preparation of hex-4-en-1-yn-3-ol (125)

This compound was prepared from crotonaldehyde and sodium acetylide using the method of Heilbron, Jones and Weedon\(^9\) on one tenth of the scale described in the literature. Hex-4-en-1-yn-3-ol was obtained as a colourless oil (37.5g., 32%) b.p. 48-50°C, 0.3mm. (lit\(^9\) 74-75°C, 30mm)
$^1$H n.m.r. (CDCl$_3$)  δ 1.7(d., 3H, J=4.5Hz); 2.35(broad s.,
1H, D$_2$O exchangeable); 2.45(d., 1H, J=2Hz);
4.8(broad d., 1H, J=6Hz) and 5.45-6.15
(m., 2H).

Preparation of diethyl (hexa-1,2,4-trienyl) phosphonate (127)

To a mixture of hex-4-en-1-yn-3-ol (9.6g., 0.1 mol) and diethyl
chlorophosphite$^{82}$ (15.6g., 0.1 mol) in ether (400 cm$^3$) was added
dropwise with cooling (ice-bath) and stirring, a solution of pyridine
(7.9g., 0.1 mol) in the same solvent. Upon completion of the addition
the ice-bath was removed and the reaction mixture stirred for a further
2 hours. Separation of pyridine hydrochloride by filtration (celite
aided), followed by the removal of solvent from the filtrate, gave a
yellow oil (21.4g.) which became dark brown in colour on standing at
room temperature. This crude reaction product gave spectral data consistent
with those predicted for diethyl (hexa-1,2,4-trienyl) phosphonate (127),
there being some diethyl hydrogen phosphite also present.

$^{31}$P n.m.r. (CH$_2$Cl$_2$)  +13.7 p.p.m.

$^1$H n.m.r. (CDCl$_3$)  δ 1.3(t., 6H, J=7Hz); 1.8(broad s., 3H);
4.1(quintet, 4H, J=7Hz) and 5.0-6.4(m., 4H).

γ max.
2980, 1945, 1645, 1600, 1250, 1020 and 965 cm$^{-1}$

Distillation of the crude product gave a main fraction (8.0g.; 38% b.p. 97-105°C, 0.2mm.) comprising of diethyl (hexa-1,2,4-trienyl)
phosphonate [(127) 25%] and diethyl (hex-4-en-2-ynyl) phosphonate
[(131) 75%]. The percentages stated here are based upon measured
integrals in the $^1$H n.m.r. spectrum; these values being supported by
the relative heights of the signals recorded in the $^{31}$P n.m.r. spectrum
for the two components. The proportion of the acetylenic phosphonate
increased to 90% on heating a sample of the distillate at $104^\circ$C for 1 hour; the relative amounts being estimated as before. Sustained heating at this temperature produced no further change in the chemical composition of the distillate.

**Diethyl (hex-4-en-2-ynyl) phosphonate (131)**

$^{31}$P n.m.r. ($\text{CH}_2\text{Cl}_2$) +21.3 p.p.m.

$^1$H n.m.r. ($\text{CDCl}_3$) $\delta$ 1.35(t., 6H, $J=7$Hz); 1.75(d., 3H, $J=6$Hz); 2.8(doublet of doublets, 2H, $J=22$Hz, $J=2$Hz); 4.2(quintet, 4H, $J=7$Hz); 5.2(broad doublet, 1H, $J=15$Hz) and 6.0(m., 1H).

$\gamma_{\text{max.}}$ 2985, 2930, 2910, 2225 (weak), 1445, 1395, 1260, 1165, 1040 and 960 cm$^{-1}$.

Mass spec. m/e 216, 188, 187, 160, 159, 151, 125, 121 and 109 (100%).

**Formation of a Diels Alder adduct of diethyl (hexa-1,2,4-trienyl) phosphonate (127) with N-phenyl maleimide**

Diethyl (hexa-1,2,4-trienyl) phosphonate was prepared in the manner described previously on a 0.01 molar scale using THF as the solvent instead of ether. Following completion of the addition of base at $0^\circ$C the $^{31}$P n.m.r. spectrum of the reaction mixture showed one major absorption [+137.7 p.p.m. (THF)]. This absorption was found to diminish in intensity when the reaction mixture was permitted to warm up to room temperature, there being a corresponding increase in intensity of signals at +12.7 and +6.4 p.p.m.. After $3\frac{1}{2}$ hours stirring at room temperature pyridine hydrochloride was separated by filtration (celite aided) and to the filtrate was added N-phenyl maleimide (1.73g., 0.01 mol). Following a period of two days standing at room temperature the resulting solution was found to consist of two phosphorus containing components [+23.1 and +6.4 p.p.m. (THF)]. The $^1$H n.m.r. spectrum indicated the
presence of diethyl hydrogen phosphite (25% estimation based upon measurement of the integral of the low field half of the P-H doublet) and of some unreacted N-phenyl maleimide (25%). Due to the complexity of this spectrum a detailed interpretation was not possible, although there was some evidence to suggest the presence of the rearranged adduct
5-diethoxyphosphinylmethylene-2-methyl-8-phenyl-8-azabicyclo[4.3.0]non-3,5-dien-7,9-dione (134)

$^1$H n.m.r. (CDCl$_3$)  5 0.9(d., 3H, J=6Hz); 1.3(t., 6H, J=7Hz); 4.1(quintet, 4H, J=7Hz) and 6.25(broad singlet, 2H)

No change was observed in the $^{31}$P n.m.r. spectrum when a sample of the crude reaction product was heated in refluxing THF for a period of 5 hours. A significant change had however occurred to the corresponding $^1$H n.m.r. spectrum, this including the increase in intensity of an absorption at 51.8.

Two grams of the crude reaction product were freed from unreacted N-phenyl maleimide and the by-product diethyl hydrogen phosphite by column chromatography (alumina/petrol and ethyl acetate). Recrystallisation of the material recovered gave 6-diethoxyphosphinylmethylene-3-methyl-N-phenyl phthalimide (135) (0.45g., 23%) as a white solid (from petrol/ethyl acetate) m.p. 136-137°C (Found C, 61.1; H, 5.76; N, 3.45 and P, 7.99% requires C, 62.05; H, 5.72; N, 3.61 and P, 7.99%)

$^{31}$P n.m.r. (CDCl$_3$/CH$_2$Cl$_2$) +22.9 p.p.m.

$^1$H n.m.r. (CDCl$_3$)  5 1.3(t., 6H, J=7Hz); 2.75(d., 3H, J=2Hz); 3.8(d., 2H, J=21Hz); 4.1(quintet, 4H, J=7Hz) and 7.45(m., 7H)

mass spec.  m/e 387 (100%), 359, 342, 331, 314, 313, 264, 250, 223 and 124.
Preparation of 3-methylhex-4-en-l-yn-3-ol

This compound was prepared from 3-penten-2-one and sodium acetylide on a 0.5 molar scale, using the method described by Gymerman, Heilbron and Jones.\(^9\) 2-methylhex-4-en-l-yn-3-ol was obtained as a colourless liquid (8.9g., 16%). b.p. 36°C, 0.4 mm. (lit\(^9\) 59°C, 23 mm.)

\(^1\)H n.m.r. (CDCl\(_3\))
- \(\delta\) 1.45(s., 3H); 1.7(d., 3H, J=6Hz);
- 2.1(s., 1H, D\(_2\)O exchangeable); 2.35(s., 1H);
- 5.5(d., 1H, J=15Hz) and 5.9(doublet of quartets, 1H, J=15Hz, J=6Hz)

Preparation of diethyl (3-methylhexa-l,2,4-trienyl) phosphonate (136)

This compound was prepared from 3-methylhex-4-en-l-yn-3-ol and diethyl chlorophosphite on a 0.05 molar scale, using the same method as that described for diethyl (3,5-dimethylhexa-1,2,4-trienyl) phosphonate (118). The crude reaction product, an orange oil (11.1g) was shown by \(^{31}\)P n.m.r. spectroscopy to consist of two phosphorus containing components [\(^{31}\)P (CH\(_2\)Cl\(_2\)) +7.2 (major) and +14.1 p.p.m.]. Distillation under reduced pressure gave diethyl hydrogen phosphite (4.25g., 60% based upon diethyl chlorophosphite), b.p. 60°C, 0.4 mm. and diethyl (3-methylhexa-l,2,4-trienyl) phosphonate (2.5g., 22%) b.p. 110°C, 0.4 mm.

\(^{31}\)P n.m.r. (CH\(_2\)Cl\(_2\)) +14.1 p.p.m.
\(^1\)H n.m.r. (CDCl\(_3\))
- \(\delta\) 1.35(t., 6H, J=7Hz); 2.8(m., 6H);
- 4.1(quintet, 4H, J=7Hz) and 5.2-6.2(m., 3H).

\(\gamma\) max. 2980, 2930, 1945, 1390, 1250, 1040 and 960 cm\(^{-1}\)
Formation of a Diels Alder adduct of diethyl (3-methylhexa-1,2,4-trienyl) phosphonate (136) with N-phenyl maleimide

A mixture of diethyl (3-methylhexa-1,2,4-trienyl) phosphonate (1g., 0.004 mol.) and N-phenyl maleimide (0.75 g., 0.004 mol.) in THF (10 cm³) was heated at 66°C for a period of 1½ hours, after which there was found to be one major phosphorus containing component [\(^{31}\text{P}(\text{THF}) +23.1 \text{ p.p.m.}]\). The \(^{31}\text{P}\) n.m.r. spectrum and the major features of the \(^{1}\text{H}\) n.m.r. spectrum were unchanged when the crude reaction product was purified by column chromatography (silica/petrol and ethyl acetate). The major features of the \(^{1}\text{H}\) n.m.r. spectrum of the recovered material, a yellow oil (0.8 g., 46%), suggested the presence of the rearranged adduct as 5(diethoxyphosphinylmethylene)-2,4-dimethyl-6-phenyl-8-azabicyclo[4.3.0]non-3,5-dien-7,9-dione (138)

\[\text{\(^{1}\text{H}\) n.m.r. (CDCl\textsubscript{3})} \]

\begin{align*}
&\text{5} 0.9(d., 3H, J=6\text{Hz}); 1.3(t., 6H, J=7\text{Hz}); \\
&1.9(s., 3H); 4.1(\text{quintet, 4H, J=7Hz}); 6.07 \\
&(d., 1H, J=7Hz) \text{ and } 7.4(m., 5H) - \text{assignment of the remaining signals could not be made with confidence.}
\end{align*}

mass spec. \[m/e 403, 401, 278, 265, 264 \text{ and } 213.\]
Trivalent phosphorus exhibits nucleophilic character due to the lone pair of electrons on the phosphorus atom. This behaviour is shown in reactions both at electron deficient centres eg. \( >\text{C}=\text{O} \) and electron rich centres eg. halogen, oxygen. The nucleophilicity of phosphorus towards halogen atoms may be explained in terms of two major contributing factors, these being the favourable energy of formation of the phosphorus-halogen bond and the polarisability of the phosphorus atom, which effects a reduction in the total energy of the system upon interaction with a centre of high electron density.

In circumstances where the phosphorus nucleophile has a choice of centre of attack then the course of the reaction will be determined both by the strength of the new bond formed and by leaving group ability. The nucleophilic substitution reaction between phosphines and alkyl halides results in the formation of phosphonium salts.

\[
\text{R}_3\text{P} + \text{R}^1\text{CH}_2\text{X} \rightarrow \text{R}_3\text{P}^+\text{CH}_2\text{R}^1 + \text{X}^\ominus \quad \text{X}=\text{Cl}, \text{Br}, \text{I}
\]

Here, attack at the carbon centre results in the displacement of a halide ion, a far better leaving group than the alkyl anion which attack at halogen would produce.

Where the tervalent phosphorus compound possesses an alkoxy substituent, the phosphite equivalent of the phosphonium salt undergoes a subsequent rearrangement to the corresponding phosphonate. The reaction of trialkyl phosphites with alkyl halides to give dialkyl phosphonates is known as the Michaelis-Arbusov reaction.

\[
\begin{align*}
(R\text{O})_3\text{P} + \text{R}^1\text{X} & \rightarrow (RO)_3\text{P}^+\text{R}^1\text{X}^\ominus \\
(R\text{O})_2\text{P} & \rightarrow (RO)_2\text{P}^+\text{R}^1 + RX
\end{align*}
\]

\( R, R^1 = \text{Alkyl} \quad \text{X}=\text{Cl}, \text{Br}, \text{I} \)

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Phosphinites \([\text{ROP} \text{R}_2]\) and phosphonites \([(\text{RO})_2 \text{PR}]\) undergo an identical reaction to form phosphine oxides and phosphinates respectively. The rate of the reaction increases on the substitution of alkoxy groups with alkyl substituents, there being as a result an increase in the nucleophilic character of the phosphorus atom. The driving force for these reactions is formation of the extremely strong phosphorus-oxygen double bond.

Triaryl phosphites react with alkyl halides to give a salt which decomposes only upon heating to more than \(200^\circ\text{C}\).

\[
\text{(ArO)}_3\text{P} + \text{RX} \rightarrow \text{(ArO)}_3\text{P}^\ominus \text{RX}^\ominus \quad \text{X} = \text{Cl, Br, I}
\]

Formation of \(\text{P}=\text{O}\) in this case would necessitate nucleophilic attack on the aromatic nucleus, this being an extremely slow process unless the ring is especially activated.

The reaction of trialkyl (or mixed alkyl/aryl) phosphites with halogen molecules proceeds in a manner analogous to the Arbusov reaction.

\[
\text{(RO)}_3\text{P} + \text{X} - \text{X} \rightarrow [(\text{RO})_3\text{PX}_2 \rightleftharpoons (\text{RO})_3\text{P}^\ominus \text{X}^\ominus] \rightarrow (\text{RO})_2\text{P(O)}\text{X} + \text{RX}
\]

The first step of the reaction is generally formulated as being nucleophilic attack by phosphorus on the halogen to give a phosphonium ion. Alternatively, reaction may proceed via a molecular or free radical pathway to give a pentacovalent intermediate. Whether the first formed adduct is exclusively of one structure, or an equilibrium mixture of the two is dependent upon the nature of the halide ion, and upon the substituents on phosphorus.
The final products of this reaction are derived from the halotralkoxy phosphonium salt via an SN₂ displacement by the halide ion. This is in accord with mechanistic studies carried out using optically active phosphite\textsuperscript{104a,b}. Thus, tri-2-octyl phosphite upon reaction with chlorine or bromine, gives 2-halo-octane, with inversion of configuration.

\[ (\text{C}_6\text{H}_13)_3\text{PO} + X_2 \rightarrow (\text{C}_8\text{H}_{17}O)_2\text{P}X + (\text{C}_6\text{H}_{13})_3\text{PO} \]

The reaction of phosphites with chlorine provides a useful method for the synthesis of phosphoryl chlorides. The corresponding bromides and iodides are formed in solution but in general have been found to decompose upon attempted isolation. Evidence for the quantitative production of these species in solution has been obtained by their conversion in almost theoretical yield to stable, crystalline amino-phosphonates, upon treatment with an appropriate amine\textsuperscript{105} eg. aniline.

\[ (\text{EtO})_2\text{P} + 2\text{PhNH}_2 \rightarrow (\text{EtO})_2\text{P} - \text{NHPh} + \text{PhNH}_2\cdot\text{HI} \]

As in their reaction with alkyl halides, triaryl phosphites give addition products which are not amenable to Arbusov type rearrangement. Where further triaryl phosphite is available, the first formed adduct may undergo disproportionation to a diaryloxyhalophosphine and a tetra-aryloxyhalorphosphate\textsuperscript{121, 122}.

\[ (\text{ArO})_3\text{P} + X_2 \rightarrow (\text{ArO})_3\text{PX}_2 \rightarrow (\text{ArO})_3\text{PX} \]

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The reaction of triphenyl phosphine and carbon tetrachloride to give dichlorotriphenylphosphorane \((\text{141})\) and dichloromethylene-phosphorane \((\text{142})\) was discovered in 1962 by Rabinowitz and Marcus\(^{106}\).

\[
\text{PPh}_3 + \text{CCl}_4 \rightarrow \text{Ph}_3\text{PCl}_2 + \text{Ph}_3\text{P} = \text{CCl}_2 \\
\text{(141)} \quad \text{(142)}
\]

Since this time the two component system has proved to be of great synthetic utility as a reagent for chlorination, dehydration and P-N linkage. Of the various tertiary phosphine/tetrahalomethane systems investigated \(\text{PPh}_3/\text{CCl}_4\) has been the most utilised, being the most conveniently handled and easily prepared. A review of its preparative applications has been presented by Appel\(^{107}\).

Mechanistic studies of this type of reaction have discounted the participation of free radical or carbene intermediates, and it is believed that the ionic mechanism depicted in Scheme (8) best describes the process occurring.

Interaction is initiated by the polarising action of the permanent dipole phosphine on the tetrahalomethane, to give the dipolar associate
The amount of charge transfer here depends upon the substituents carried by the phosphorus atom, the limiting case being represented by the halophosphonium trihalomethanide (144). Appreciably more stable than (144), the trihalomethyl phosphonium halide (146) is produced by rearrangement, presumably via the pentavalent phosphorane (145). Further reaction with tertiary phosphine results in the dehalogenation of (146) to yield dihalomethylene phosphorane (142) and dihalophosphorane (141).

\[
R_3P + [R_3P-CX_3]^{+}X^- \rightarrow R_3PX_2 + R_3P = CX_2
\]

\(X = Cl\) \(R = Ph\)

(146) \hspace{1cm} (141) \hspace{1cm} (142)

In the presence of a proton active substrate the \(PPh_3/CCl_4\) system may undergo reaction via one of two mechanistic pathways, the same end product being obtained in each case.

The major route, "Path A", involves an initial interaction of substrate and dipolar associate (143) with the elimination of chloroform.

\[
\delta^+ \quad \delta^-
\]

\[
Ph_3P \quad Cl \quad CCl_3 \quad \rightarrow \quad [Ph_3P \text{- substrate}]^{+}Cl^- + CHCl_3
\]

\(\text{substrate\H}\)

Path A

This pathway competes with the naturally occurring subsequent reactions of dipolar associate (143) according to Scheme (8).

Dichlorotriphenyl phosphorane (141), a product of Scheme (8), may undergo reaction with substrate to afford the same intermediate as in "Path A", and HCl. This constitutes the first stage of the alternative mechanistic route, "Path B".

-125-
\[
\text{Ph}_3\text{PCl}_2 + \text{substrate} - H \rightarrow [\text{Ph}_3\text{P} - \text{substrate}]^+ \text{Cl}^- + \text{HCl}
\]

**Path B**

The dichloromethylene phosphorane (142) acts as an HCl acceptor to give a salt (147). This salt is able to react with a further amount of phosphine to generate more of reactive intermediate (141) amenable to interaction with substrate, together with ylid (148).

\[
\text{HCl} + \text{Ph}_3\text{P} = \text{CCl}_2 \rightarrow [\text{Ph}_3\text{P} - \text{CHCl}_2]^+ \text{Cl}^- \quad (142)
\]

\[
\text{Ph}_3\text{PCl}_2 + \text{Ph}_3\text{P} = \text{CHCl} \quad (141) \quad (148)
\]

Trapping of liberated HCl by ylid (148) leads to formation of the stable chloromethyltriphenylphosphonium chloride (149).

\[
\text{HCl} + \text{Ph}_3\text{P} = \text{CHCl} \rightarrow [\text{Ph}_3\text{P} - \text{CH}_2\text{Cl}]^+ \text{Cl}^- \quad (148) \quad (149)
\]

The overall reaction via "Path B" may be represented by:

\[
3\text{Ph}_3\text{P} + \text{CCl}_4 + 2\text{H} - \text{substrate} \rightarrow 2[\text{Ph}_3\text{P} - \text{substrate}]^+ \text{Cl}^- + [\text{Ph}_3\text{P} - \text{CH}_2\text{Cl}]^+ \text{Cl}^- \quad (126)
\]
The complexity of this system in no way detracts from its utility as a reagent for synthesis, as both paths A and B lead to desired product and the total yield is generally good. In practice, triphenyl phosphine and carbon tetrachloride are used in a 1:1 molar ratio, the two components being mixed only in the presence of substrate. The rate of reaction is greatly influenced by the chosen reaction medium, an acceleration being observed in polar solvents on account of the more efficient solvation of the ionic intermediates involved.

The ability of $\text{PPh}_3\text{Cl}_4$ to act as a dehydrating agent was discovered in its reaction with carboxamides. In the presence of a tertiary nitrogen base, e.g., triethylamine or pyridine, the elements of water are removed to give the corresponding nitrile in 80-90% yield. Thiocarboxamides react analogously. Approximately 50% of the product is formed by dehydration via the dichlorophosphorane, "Path B".

\[
\begin{align*}
\text{Ph}_3\text{P} + \text{CCl}_4 + \text{RC}(X)\text{NH}_2 & \rightarrow [\text{Ph}_3\text{P}-\text{X}-\text{C}=\text{NH}]^\oplus \text{Cl}^\ominus + \text{CHCl}_3 \\
\text{X} = 0, S & \\
\text{R} - \text{C} = \text{N} + \text{Ph}_3\text{P} = \text{X} &
\end{align*}
\]

"PATH A"

\[
\begin{align*}
\text{Ph}_3\text{PCl}_2 + \text{RC}(X)\text{NH}_2 & \rightarrow [\text{Ph}_3\text{P}-\text{X}-\text{C}=\text{NH}]^\oplus \text{Cl}^\ominus + \text{HCl} \\
\text{Ph}_3\text{P}=\text{CCl}_2 + \text{HCl} & \rightarrow [\text{Ph}_3\text{P}-\text{CHCl}_2]^\oplus \text{Cl}^\ominus + \text{PPh}_3 [\text{Ph}_3\text{P}-\text{CH}_2\text{Cl}]^\oplus \text{Cl}^\ominus \\
R & + \text{HCl} \\
[\text{Ph}_3\text{P}-\text{X}-\text{C}=\text{NH}]^\oplus \text{Cl}^\ominus & \rightarrow \text{Ph}_3\text{P}=\text{X} + \text{R} - \text{C} = \text{N} \\
\text{Overall:} & \\
3\text{Ph}_3\text{P} + \text{CCl}_4 + 2\text{R} - \text{C}(X)-\text{NH}_2 + 2\text{Et}_3\text{N} & \rightarrow 2\text{R} - \text{C} = \text{N} + 2\text{Ph}_3\text{P} = \text{X} \\
& + [\text{Ph}_3\text{P}-\text{CH}_2\text{Cl}]^\oplus \text{Cl}^\ominus
\end{align*}
\]
The nitrile synthesis may be applied equally well to aliphatic and aromatic compounds and is also applicable to the production of nitriles which are not accessible by the use of the usual strongly acidic dehydrating agents.

Similarly, nitriles are produced by the dehydration of aldoximes. Mechanistic studies, using deuterated acetaldoxime have shown that the hydrogen atom of the chloroform comes solely from the hydroxyl group of the aldoxime\(^{109}\).

\[
\begin{align*}
\text{Ph}_3\text{P} + \text{CCl}_4 + \text{DON} = \text{CHR} & \rightarrow [\text{Ph}_3\text{P}-\text{O}=\text{CHR}] \text{Cl}^+ + \text{DCCl}_3 \\
[\text{Ph}_3\text{P}-\text{O}=\text{CHR}] \text{Cl}^+ + \text{Et}_3\text{N} & \rightarrow \text{RC} \equiv \text{N} + \text{Ph}_3\text{P}=\text{O}
\end{align*}
\]

The intramolecular removal of water in this manner has also given rise to general synthetic methods for the production of isocyanides, carbodiimides, aziridines and C-ethoxycarbonyl-C-imidoylketene imines\(^{110a-d}\). The achievement of high yields of product under mild conditions is a characteristic of these reactions.

On treatment with \(\text{PPPh}_3/\text{CCl}_4\), alcohols and carboxylic acids are converted into the corresponding alkyl\(^{107}\) and acyl chlorides\(^{111}\).

\[
\begin{align*}
\text{Ph}_3\text{P} + \text{CCl}_4 + \text{R-OH} & \rightarrow [\text{Ph}_3\text{P}-\text{OR}] \text{Cl}^+ + \text{CHCl}_3 \\
\text{Ph}_3\text{P}=\text{O} + \text{RCl} & \rightarrow \text{C(O)alkyl, C(O) aryl} \\
\text{R} & = \text{alkyl, aryl}
\end{align*}
\]

Formation of the acid chlorides of some phosphoric esters and phosphinic acids has also been achieved by this process\(^{112}\).
Addition of an alcohol or amine to the three component system RCOOH/PPh$_3$/CCl$_4$ leads to the formation of the corresponding ester or amide. High yields of ester are only achieved when the alcohol is added as the last component following a prereaction of the carboxylic acid with PPh$_3$/CCl$_4$. The strength of the carboxylic acid used also has some bearing upon the efficiency of ester formation, as the acylphosphonium salt assumed as an intermediate may undergo attack by the alcohol either at the phosphorus atom or at the carbonyl carbon atom. The more electrophilic the carbonyl carbon, i.e., the stronger the carboxylic acid, the more ester formation is favoured.

In the case of amide synthesis, PPh$_3$/CCl$_4$ is heated in refluxing THF for thirty minutes, cooled to 5°C, and the carboxylic acid added. The mixture is then allowed to stand for ten minutes prior to addition of two equivalents of amine, thus allowing time for formation of the triphenylacyloxyphosphonium chloride. In this manner yields of amide of between 83-97% have been achieved.
Of particular synthetic interest is the application of this method to the formation of peptides from N-protected amino-acids and amino-acid esters. Upon addition of CCl₄ to a mixture of the carboxylic acid component, the amine component and triphenyl phosphine in acetonitrile, good yields of peptide free from racemisation have been obtained. Alternatively, the amine component may be used in the form of the hydrochloride salt in the presence of an extra equivalent of base.

Mechanistic studies have shown that there is a dependence of reaction rate upon the strength of base added, and also that reaction via the dichlorophosphorane plays a significant role in the condensation.

Where the condensing reagent is used in stoichiometric amounts there is no evidence of competing reactions with side-chain groupings.
For example, the hydroxyl groups of serine, threonine and tyrosine are not converted to chloro and the amide grouping of glutamine is not dehydrated to the nitrile. Also, perhaps surprisingly in this case, there is no evidence of P-N linkage with the amine component. Ammonia, primary and secondary amines react with the \( \text{Ph}_3\text{P}/\text{CCl}_4 \) system to give aminophosphonium chlorides.

Although condensation without racemisation has been achieved for the hexapeptide, Z-Leu-Ala-Phen-Gly-Pro-OBz\( \text{l} \), it is found that in some cases a degree of racemisation will occur. A notable example of this arises in the preparation of N-benzoyl-L-leucylglycine ethyl ester (the Young test), where under the standard conditions the peptide is formed as a completely racemic mixture. It has been discovered however that much of this racemisation may be suppressed by the addition of an equivalent of 1-hydroxybenzotriazole to the reaction mixture.

Peptide formation then proceeds via the 1-hydroxybenzotriazole ester.

\[
\text{[Ph}_3\text{P-O-CO-R]} + \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \rightarrow \begin{array}{c}
\text{N} \\
\text{N}
\end{array} + \text{Ph}_3\text{P}=\text{O} + \text{HCl}
\]

In this manner, coupling of N-benzoyl leucine and glycine ethyl ester has been achieved to give an 89% yield of peptide, of which 80.3% is the L-enantiomer. i.e. an enantiomeric excess of 60.6%. 

-131-
There are few well established methods of synthesis of carbon-phosphorus bonds utilising readily available and thus inexpensive starting materials. The development of new procedures for the formation of the C-P bond is desirable due to the increasing application of organophosphorus compounds in a number of diverse fields, e.g. as herbicides, antibiotics, oil additives and agents in water treatment. To this end an investigation was undertaken, based upon the generation of reactive carbon centres and their capture intramolecularly by tervalent phosphorus to create the desired new bond. Precursors for this process require a double bond which may be activated, by electrophilic attack, to concomitant nucleophilic attack by a tervalent phosphorus atom situated at a suitable position in the molecule. Ring closure might then be followed by an Arbusov type reaction to give a stable end product.

Reaction of this type has been achieved in similar systems involving carbonium ion capture by phosphoryl oxygen.\(^{118}\)

\[
\text{Scheme 9}
\]

Treatment of the homoallylic phosphate \((150)\) with 1.1 mole equivalents of iodine in acetonitrile affords an 87% yield of cyclic phosphate \((151)\) over a period of two days at 25°C. This is illustrated in Scheme 9.

An attempt was made to extend this process to a system having a suitably placed tervalent phosphorus atom as the nucleophilic species in the molecule. Scheme 10 outlines the envisaged reaction sequence.
for o-allylphenyl diphenyl phosphite (152), upon addition of one mole equivalent of iodine in acetonitrile at room temperature.

\[
\begin{align*}
\text{Ph} & \quad \begin{array}{c}
\text{P}(	ext{OPh})_2 \\
\text{(152)}
\end{array} \\
\text{Ph} & \quad \begin{array}{c}
\text{P}(	ext{OPh})_2 \\
\text{(153)}
\end{array}
\end{align*}
\]

Scheme 10

Following the formation of phosphonium intermediate (153), addition of methanol should enable ester exchange and production of stable cyclic phosphonate (154) via an Arbusov elimination of methyl iodide.

In practice no visible reaction was observed between iodine and the phosphite precursor (152). Decolourisation of the iodine solution occurred only upon addition of methanol, the product consisting of several phosphorus containing species showing \(^{31}\text{P}\) n.m.r. chemical shifts in the region of the spectrum around -50 p.p.m.. Aqueous work-up of the reaction mixture gave one major phosphorus containing component of chemical shift -10.68 p.p.m. and ascribed to a species of the type \((\text{RO})_2\text{P}(\text{O})(\text{OH})\). \(R=\text{o-allylphenyl, phenyl, methyl}\).

The analogous reaction between o-allylphenyl diethyl phosphite and iodine in acetonitrile gave a major product before work-up, of chemical shift -48.6 p.p.m..

This region of the spectrum is generally associated with penta-co-ordinate phosphorus species and prompted the speculation that the presence of the surprisingly long lived Arbusov intermediates of the type \((\text{RO})_3\text{P}^2\) was being observed.
No evidence was seen for products arising from an initial electrophilic attack on the allylic double bond. The apparent lack of reactivity of the double bond under these conditions relative to that of the trivalent phosphorus, makes the envisaged reaction sequence seem improbable.

To investigate the significance of the absorptions seen in the -50 p.p.m. region of the $^{31}$P n.m.r. spectrum, the reaction between iodine and a simple phosphite, triethyl phosphite was studied.

When a solution of triethyl phosphite (in $\text{CH}_2\text{Cl}_2$, $\text{CH}_3\text{CN}$ or ether) was treated at $0^\circ\text{C}$ with one mole equivalent of iodine, the iodine colouration was discharged immediately and the $^{31}$P n.m.r. spectrum showed one absorption only at -42.5 p.p.m. (ether, to high field $\text{H}_3\text{PO}_4$). Experiments with different ratios of phosphite to iodine showed that this was due to a 1:1 complex. Over a period of several days at room temperature the absorption at -42.5 p.p.m. was slowly replaced by a major absorption at -13.0 p.p.m. and minor absorptions at -13.9 and -1.0 p.p.m.

Previous accounts of the reaction between simple phosphites and iodine have described rapid reactions occurring at low temperatures to give dialkyl iodophosphonates as the initial reaction products.\textsuperscript{119, 120} Peshchenko and Kostina\textsuperscript{119} have reported that ethyl iodide and a polymer of unestablished structure are formed on combination of equimolar quantities of triethyl phosphite and iodine at -5$^\circ$C. The yield of ethyl iodide isolated was 80% calculated for the equations:

$$\text{(EtO)}_3\text{P} + \text{I}_2 \rightarrow \text{[(EtO)}_3\text{PI}_2\text{]} \rightarrow \text{(EtO)}_2\text{P(O)}\text{I} + \text{EtI}$$

$$\text{EtI} + \frac{1}{n} \text{[(EtO-P(O)-O]}_n$$
Less than one mole equivalent of iodine was found to be utilised in the corresponding reaction of triphenyl phosphite with iodine; this was indicated by a retention of the iodine colouration by the reaction mixture. $^{31}$P n.m.r. spectroscopy indicated first formed species of chemical shifts +38.7, −49.8 and +174.4 p.p.m. (CH$_2$Cl$_2$), upon addition of one mole equivalent of triphenyl phosphite to a solution of iodine in dichloromethane at 0°C. The absorption due to the major phosphorus containing component at 0°C (+38.7 p.p.m.) was found to diminish and eventually to disappear when the reaction mixture was allowed to stand at room temperature. After a period of $\frac{3}{2}$ days at room temperature the major component of the mixture was that having an absorption in the $^{31}$P n.m.r. spectrum at −49 p.p.m..

Earlier studies of the reaction between triphenyl phosphite and iodine have shown the stability of triphenoxydi-iodophosphorane (155) both in solution and by isolation and characterisation of the compound. Scheme (11) illustrates the course of reaction as described by Rydon and Tonge and the $^{31}$P n.m.r. data obtained have been interpreted in terms of this sequence with chemical shifts assigned accordingly.

$$
(\text{PhO})_3\text{P} + \text{I}_2 \rightleftharpoons (\text{PhO})_4\text{PI} + (\text{PhO})_2\text{PI} \\
+ 38.7 \text{ ppm} \quad + 174.4 \text{ ppm} \\
\downarrow + \text{I}_2 \\
2(\text{PhO})_3\text{PI}_2 \quad - 49 \text{ ppm} \\
(155)
$$

**Scheme (11)**
The observation of absorption in the -50 p.p.m. region of the $^{31}\text{P}$ n.m.r. spectrum of triaryl phosphate/halogen adducts, known to be reluctant to undergo $\geq \text{P}=\text{O}$ formation by Arbusov rearrangement, suggests that the species seen at 0°C for the triethyl phosphate/iodine system [chemical shift -42.5 p.p.m. (ether)], is also due to an intermediate formed prior to Arbusov rearrangement. This species may be formulated as triethoxydi-iodophosphorane (156), which undergoes a slow decomposition to polymer (157) via the product of Arbusov rearrangement, diethyl iodophosphonate.

$$\text{(EtO)}_3\text{P} + \text{I}_2 \longrightarrow [(\text{EtO})_3\text{PI}_2] \longrightarrow (\text{EtO})_2\text{P(O)I} + \text{EtI}$$

(156)

$$\text{(EtO)}_2\text{P(O)I} \longrightarrow \text{EtI} + \frac{1}{n}[(\text{EtO})\text{P}(O)-\text{O}]_n$$

(157)

The apparent stability of the triethoxydi-iodophosphorane suggests that it might be amenable to use as a dehydrating or condensing agent in the presence of tertiary amine, in a manner analogous to $\text{Ph}_3\text{PCl}_2$ or $\text{PPh}_3\text{CCl}_4$.

$$\text{(EtO)}_3\text{PI}_2 + \begin{bmatrix} \text{XH} + \text{YOH} \\ \text{or} \\ \text{H}_2\text{O} \end{bmatrix} \longrightarrow 2\text{R}_3\text{N} \frac{\text{2R}_3\text{N}}{(\text{EtO})_3\text{P=O} + \text{X-Y} + 2\text{R}_3\text{N} \cdot \text{HI}}$$

The ability of the triethyl phosphate/iodine system to remove the elements of water was tested in an attempted preparation of benzonitrile, by the dehydration of benzamide and of $\alpha$-benzaldoxime.
The general preparative procedure for both the dehydration and the condensation reactions involved the addition of a solution of iodine in CH$_3$CN or CH$_2$Cl$_2$, to a solution of equivalent amounts of the reactant(s) and phosphite, plus two equivalents of triethylamine in the same solvent. The resulting mixture was stirred at room temperature for a period of two hours before work-up, this being aided by the water solubility of the by-products.

In this manner, benzamide gave benzonitrile (64%), and benzaldoxime gave benzonitrile (61% isolated, 81% estimated by g.l.c.). The proposed reaction pathway, illustrated in Scheme (12) for the case of benzaldoxime, parallels that of Ph$_2$PCl$_2$ in this reaction.

\[
\begin{align*}
&C_6H_5-CH=N-OH + \left[ (\text{EtO})_3P - I \right] \overset{\text{Et}_3N}{\longrightarrow} C_6H_5-CH=N-O-P(\text{OEt})_3 \\
&\text{(EtO)$_3$P$_2$} \\
&\text{CN} + (\text{EtO})_3P = O
\end{align*}
\]

Scheme (12)

An alternative breakdown of phosphonium ion intermediate (158) is possible, this involving an initial Arbusov rearrangement and resulting in the formation of the triethylammonium salt of diethyl phosphite as a by-product.
Monitoring the dehydration of α-benzaldoxime by $^{31}$P n.m.r. spectroscopy showed the conversion of triethyl phosphite to new phosphorus containing components of the reaction mixture having chemical shifts of -1.2 & -13.13 p.p.m. ($\text{CH}_2\text{Cl}_2$). An authentic sample of triethyl phosphate was shown to have a chemical shift of -1.2 p.p.m. in the same solvent, and its presence in the crude reaction product was confirmed by analytical g.l.c. A quantitative analysis by g.l.c. indicated there to be less than a mole equivalence of triethyl phosphate to benzonitrile.

At this point a closer study was made of the reactive intermediate observed immediately upon mixing triethyl phosphite and iodine at 0°C; this previously postulated as being triethoxydi-iodophosphorane (156). The $^1$H n.m.r. spectrum of equimolar amounts of triethyl phosphite and iodine in deuterated solvent at 0°C, was found to be consistent with the presence of equimolar amounts of diethyl iodophosphonate and ethyl iodide. The molar proportion of ethyl iodide was found to increase slowly upon standing at room temperature in accord with the decomposition of the iodophosphonate to polymer (157) and ethyl iodide.

$$\text{(EtO)}_3\text{P} + \text{I}_2 \longrightarrow \text{(EtO)}_2\text{P(O)} + \text{EtI} \longrightarrow 1/\text{n[(EtO)}_\text{PO}_2\text{]} + \text{EtI}$$

(157)

This definitive experiment negates any circumstantial evidence for the stability of the triethoxydi-iodophosphorane intermediate in solution at 0°C. It does not however, exclude the possibility of the participation of this species as a reactive intermediate in the dehydration process as described. Upon addition of iodine as the last component of the reacting system, formation of a triethyl phosphite...
iodine adduct having a phosphonium salt or pentacovalent structure, will occur. Decay of this intermediate will proceed via a nucleophilic attack on the phosphonium ion. In addition to the second step of the Arbusov rearrangement, ie. attack by the iodide counterion to give diethyl iodophosphonate, there is the possibility of the competing reaction pathway leading to dehydration of the substrate as shown in Scheme (12). This is initiated by nucleophilic attack on the phosphonium ion by benzaldoxime in the presence of triethylamine. The major pathway leading to the breakdown of phosphonium salt will be determined in any particular system by the nucleophilicity of the substrate relative to that of the iodide ion.

Dehydration of the substrate may also be achieved via diethyl iodophosphonate as illustrated in Scheme (13).

\[
\begin{align*}
(\text{EtO})_2\text{P(O)}\text{I} + \text{CH=N-OH} & \quad \xrightarrow{+\text{Et}_3\text{N}} \quad \text{CH=N-O-P(OEt)_2} \\
-\text{Et}_3\text{N.HI} & \quad \text{(EtO)}_2\text{P(O)}\text{O}^{-} \quad + \quad \text{CN}
\end{align*}
\]

Scheme (13)

Confirmation of this mode of reaction was obtained by carrying out the dehydration under conditions where a pre-reaction of triethyl phosphite and iodine to give the iodophosphonate preceded the addition of the substrate and triethylamine. In this way only one phosphorus containing product was anticipated, this being the triethylammonium salt of diethyl phosphate as dictated by Scheme (13).
In practice, the $^{31}$P n.m.r. spectrum of the crude reaction product was found to show the same two absorptions, of chemical shifts -1.2 and -13.3 p.p.m., as seen under the previous reaction conditions. The relative intensities of these two absorptions had however changed; the intensity of the peak at -1.2 p.p.m. previously ascribed to triethyl phosphate, decreasing from 71% of the whole to 57%. This observation may be explained in terms of there being two species present in the system having a chemical shift of -1.2 p.p.m.. One of these is triethyl phosphate, obtained via reaction Scheme (12) and seen only where iodine is added as the last component of the reaction mixture. The other is the phosphorus containing product of the dehydration by diethyl iodophosphonate, this being according to Scheme (13) the triethylammonium salt of diethyl phosphate. In the absence of reported data, an estimated chemical shift for this species would lie in the desired region, based upon values of 0 p.p.m. and -1.3 p.p.m. quoted in the literature for the parent acid (EtO)$_2$P(O)OH.\textsuperscript{123} The reaction of diethyl iodophosphonate with one mole of water in the presence of two moles of triethylamine would be expected to produce this triethylammonium salt.

\begin{equation}
(\text{EtO})_2\text{P(O)}\text{I} + \text{H}_2\text{O} \xrightarrow{2\text{Et}_3\text{N}} (\text{EtO})_2\text{P(O)}\text{O}^\ominus\text{Et}_3\text{NH} + \text{Et}_3\text{NH}_\text{I}.
\end{equation}

In practice, the above equation was found not to be valid for this system, in excess of one mole equivalent of triethylamine hydroiodide being isolated from the crude reaction mixture. The $^{31}$P n.m.r. spectrum of the products indicated the presence of one phosphorus containing component only, this having a chemical shift of -13.3 p.p.m.. These observations, supported by $^1$H n.m.r. and mass spectral data.
suggest further reaction of the diethyl phosphate formed with a second mole of diethyl iodophosphonate to give tetraethyl pyrophosphate.

\[(\text{EtO})_2\text{P(O)}\text{I} + \text{H}_2\text{O} \xrightarrow{+\text{Et}_3\text{N}} (\text{EtO})_2\text{P-OH}^\circ\]

\[-\text{Et}_3\text{N.HI}\]

This process, occurring as a side reaction in the dehydration of benzaldoxime, explains the presence of the absorption at -13.3 p.p.m. in the $^{31}\text{P}$ n.m.r. spectrum of this system. The rate of formation of tetraethyl pyrophosphate will be directly dependent upon the prevailing concentration of diethyl iodophosphonate. If all the diethyl phosphate produced was converted into the pyrophosphate by subsequent reaction with iodophosphonate, then this process, wasteful of dehydrating agent, would limit the efficiency of the conversion of benzaldoxime into benzonitrile to 50%. This not being the case, it must be assumed that the concentration of iodophosphonate is insufficient to effect this conversion, the remaining diethyl phosphate appearing as its triethylammonium salt at -1.2 p.p.m. in the $^{31}\text{P}$ n.m.r. spectrum.

For the dehydration of benzaldoxime where iodine is added as the last component of the reaction mixture an overall representation of the mechanistic paths followed may be obtained by the combination of Schemes (12) and (13).
\[
(EtO)_3P = O + \text{Ar} = \text{N}
\]

\[
+ Et_3N
\text{Et}_3N \cdot HI
\]

\[
(EtO)_3P - O - N = CH \rightarrow \text{Ar} = \text{N}
\]

Scheme 12

\[
+ C_6H_5CH=N-OH
+ Et_3N
- Et_3N \cdot HI
\]

\[
(EtO)_3P + I_2 \rightarrow [(EtO)_3PI_2 \equiv (EtO)_3P - I \cdot I^{-}]
\]

Scheme 13

\[
+ C_6H_5CH=N-OH
+ Et_3N
- Et_3N \cdot HI - EtI
\]

\[
(EtO)_3P - O - N=C\text{H} = \text{O}
\]

\[
\rightarrow \text{Ar} = \text{N} + (EtO)_2P(O)(OH)
\]

\[
+ Et_3N
\]

\[
Et_3NH(EtO)_2P - O^2\text{O} \cdot \text{O}
\]

\[
+ Et_3N
+ (EtO)_2P(O)I
- Et_3N \cdot HI
\]

\[
(EtO)_2P - O - P(OEt)_2
\]

-142-
As noted previously, the relative contributions to the yield of dehydration product arising from initial attack on the triethoxyiodophosphonium ion by the substrate (Scheme 12) and by the iodide counter-ion (Scheme 13), will depend upon the relative nucleophilicities of these species. An analysis of these relative contributions was attempted for the dehydration of benzaldoxime. Estimation by analytical g.l.c. of the molar proportions of benzonitrile : triethyl phosphate produced, gives some indication of the proportion of product derived from the direct attack of substrate on the triethoxyiodophosphonium ion.

In calculation of the molar ratio of benzonitrile to triethyl phosphate in this manner, it was found necessary to make a correction for the presence of a species having the same retention time as triethyl phosphate, this arising from a partial decomposition of the tetraethyl pyrophosphate on the column. The amount of this component relative to benzonitrile was calculated from the g.l.c. trace of products resulting from dehydration via diethyl iodophosphonate only, no triethyl phosphate being produced in this case. Subtraction of this amount from the peak due to both triethyl phosphate and the unknown species, in the trace of the dehydration products where both mechanistic pathways are operative, enabled the molar ratio of triethyl phosphate to benzonitrile to be estimated. An error arises in the correction made here due to the fact that the amount of tetraethyl pyrophosphate present will be greater where dehydration takes place via the iodophosphonate only than where a dual mechanism exists, this being shown by $^{31}$P n.m.r. spectroscopy. The increase in amount is explained by the direct dependence of tetraethyl pyrophosphate production upon the prevailing concentration of iodophosphonate. This error does however lead to over-
correction resulting in an underestimation, rather than an over-
estimation of the triethyl phosphate present.

This method of calculation, accepting the error in correction,
gives a molar ratio of benzonitrile to triethyl phosphate of 1 : 0.55,
(i.e. a 55\% molar equivalence) for the dehydration of benzaldoxime to
benzonitrile. Whilst the limits of accuracy of a quantitative treatment
of the analytical g.l.c. data are realised, the results obtained seem
consistent in this case with approximately one half of the dehydration
process leading to the formation of triethyl phosphate, via direct
attack of the substrate on the triethoxyiodosphonium ion.

This mode of reaction becomes the exclusive route to product
where the dehydrating agent is derived from triaryl phosphite and
iodine. Analytical g.l.c. showed almost complete conversion of benzal-
aldoxime to benzonitrile on the substitution of triphenyl phosphite for
triethyl phosphite in the general preparative procedure.

\[
(\text{PhO})_3\text{PI}_2 + \text{H} + \text{Et}_3\text{N} \rightarrow (\text{PhO})_3\text{PO}^+ - \text{O}^- + \text{Et}_3\text{N} \cdot \text{HI} + \text{Et}_3\text{N} \cdot \text{HI} + \text{Et}_3\text{N} \cdot \text{HI} + \text{Et}_3\text{N} \cdot \text{HI} + \text{Et}_3\text{N} \cdot \text{HI} + \text{Et}_3\text{N} \cdot \text{HI}
\]

The \textsuperscript{31}P n.m.r. spectrum of the crude reaction product indicated
the presence of one major phosphorus containing species of chemical
shift -17.5 p.p.m. (CDCl\textsubscript{3}/CH\textsubscript{2}Cl\textsubscript{2}), this being the correct region of
the spectrum for the compound triphenyl phosphite to show absorption.

\[[\text{(PhO)}_3\text{P} = 0 -18.1 \text{ p.p.m. (CDCl}_2)]\] A more detailed study of this reaction
was not made.
In addition to intramolecular reaction, the dual mechanism operative in the triethyl phosphite/iodine system may be used to effect an intermolecular removal of the elements of water. The ability of the system to act as a condensing agent was demonstrated by the production of N-benzyl benzamide (89% crude; 63% pure), from a combination of benzoic acid and benzylamine with the elimination of water.

\[
\text{O} \quad \begin{array}{c}
\text{C} - \text{O} - \text{P(OEt)}_3 \\
\text{I}^\ominus
\end{array}
\]

(160)

\[
\begin{array}{c}
\text{O} \\
\text{C} - \text{O} - \text{P(OEt)}_2
\end{array}
\]

(161)
The first formed intermediates, phosphonium salt (160) and mixed anhydride (161), will in both cases yield amide on nucleophilic attack at the carbonyl carbon atom by the amine. In the absence of an amine the mixed anhydride is the stable end product, this being formed directly from diethyl iodophosphonate and benzoic acid or by an Arbusov rearrangement of the intermediate phosphonium salt (160).

$$\begin{align*}
\text{Phosphonium salt} & \quad \text{Mixed anhydride} \\
\text{C-O-P(OEt)}_3 & \quad \text{C-O-P(OEt)}_2 + \text{EtI}
\end{align*}$$

(160)

The formation of a phosphonium salt or mixed anhydride here serves to activate the adjacent carbonyl grouping towards nucleophilic attack. This enables the formation of the amide bond with high efficiency under mild reaction conditions, a characteristic which has led to the use of several organophosphorus mixed anhydride type intermediates as coupling reagents for the synthesis of peptides from N-protected amino acids. One of the more recently reported agents of this type is derived from the reaction of a carboxylic acid component with diethyl bromophosphonate, the latter being formed by the reaction of triethyl phosphite with bromine at -25 to -30°C. In this manner, amides and peptides have been synthesised in high yield, racemisation of the latter being minimised by careful control of the reaction conditions.

It is of paramount importance in peptide synthesis that coupling is achieved with minimal racemisation, an efficient coupling agent being one which gives a good yield of product of high optical activity. The coupling of N-benzoyl-L-leucine and glycine ethyl ester (the Young Test) has proved to be a valuable reaction for the assessment of the efficiency of peptide coupling reagents. In each case so far examined this model reaction has yielded crude product of a high degree of chemical purity.
and the degree of racemisation can therefore be estimated directly from the optical rotation. As a model reaction it is also a stringent test of suitability of the reagent, due to the high susceptibility of benzoyl-L-leucine to racemisation on coupling. The main cause of this racemisation has been found to be due to intermediate azlactone formation in the presence of tertiary amine or an excess of glycine ethyl ester, as illustrated for the p-nitrophenyl ester of N-benzoyl-L-leucine.

This effect is also accentuated where the amine component of the reaction mixture is used as its hydrochloride salt, the chloride ion promoting azlactone formation in the same manner.

The ability of a coupling reagent to give product of high optical activity in the Young test is thus an indication of its suitability as a reagent for general peptide synthesis.

The efficiency of the triethyl phosphite/iodine adduct as a coupling reagent was found to parallel that of triphenylphosphine/carbon tetrachloride, a good yield of optically inactive peptide being produced by the standard reaction.
In the presence of one mole equivalent of 1-hydroxybenzotriazole\textsuperscript{127, 117} reaction via the triazole ester gave an 83\% yield of N-benzoyl-leucyl-glycine ethyl ester having a 39\% excess of the L enantiomer. (ie. 60.5\% reaction with retention of configuration). This preliminary finding suggests that the triethyl phosphite /iodine system may be worthy of general application to peptide synthesis. It may prove possible to increase the degree of retention of configuration on coupling by a modification of the reaction conditions.
GENERAL EXPERIMENTAL DETAILS

These were as described in Part 1. In addition, the solvents dichloromethane and acetonitrile were refluxed over and distilled from calcium hydride and phosphorus pentoxide respectively, prior to use.

Optical rotation measurements were made using a Perkin Elmer 141 automatic polarimeter.
EXPERIMENTAL

Preparation of o-allylphenyl diphenyl phosphite (152)

To a mixture of diphenyl chlorophosphite (5g, 0.02 mol.) and o-allylphenol (2.65g, 0.02 mol.) in ether (100 cm³) at 0°C was added, with stirring and cooling (ice-bath) a solution of triethylamine (2g, 0.02 mol.) in the same solvent (50 cm³). Following the addition the reaction mixture was stirred at room temperature for a period of two hours. Triethylamine hydrochloride was separated by filtration (celite aided) and solvent removed from the filtrate to give a colourless oil (7.2 g).

\[ ^{31}P \text{ n.m.r. (CDCl}_3\text{)} +128.4 \text{ p.p.m.} \]

Preparation of γ-allylphenyl diethyl phosphite

Preparation was carried out in the same manner and on the same scale as for the o-allylphenyl diphenyl phosphite, to give a colourless oil.

\[ ^{31}P \text{ n.m.r. (CDCl}_3\text{)} +133.9 \text{ p.p.m.} \]

These compounds were subsequently used for reaction without further purification. Attempted distillation in both cases led to a mixture of products resulting from ester exchange.

Reaction of γ-allylphenyl diphenyl phosphite with iodine

To a solution of γ-allylphenyl diphenyl phosphite (1.5g, 0.0063 mol) in acetonitrile (5 cm³) was added a solution of iodine (1.19g, 0.0046 mol) in the same solvent (18 cm³) at room temperature. After a period of 44 hours one mole equivalent of methanol (0.14g, 109 µl) was added to the reaction mixture. Following a further 18 hours at room temperature

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during which time much of the iodine colouration was discharged, the solvent was removed. The $^{31}$P n.m.r. spectrum of the crude reaction products showed major phosphorus containing components of chemical shift $-45.5$, $-49.0$ and $-51.2$ p.p.m. (CDCl$_3$).

Treatment of the crude reaction product with a 10% sodium thiosulphate solution gave one major phosphorus containing compound, of chemical shift $-10.6$ p.p.m. (CDCl$_3$).

Reaction of o-allylphenyl diethyl phosphite with iodine

Treatment of a solution of o-allylphenyl diethyl phosphite (0.17g, 0.00075 mol.) in acetonitrile, with a solution of iodine (0.19g, 0.00077 mol.) in the same solvent at room temperature, gave with the discharge of iodine colouration one major phosphorus containing species [$^{31}$P n.m.r. $-48.6$ p.p.m. (CH$_3$CN/CDCl$_3$)].

Reaction of triethyl phosphite with iodine

To a solution of triethyl phosphite (1.66g, 0.01 mol.) in ether (20 cm$^3$) at 0°C, was added dropwise with cooling (ice-bath) and stirring a solution of iodine (2.53g, 0.01 mol.) in the same solvent (100 cm$^3$). The iodine colouration was discharged immediately upon addition. The $^{31}$P n.m.r. spectrum of the reaction mixture, recorded as soon as possible after completion of the addition showed one absorption only at $-42.5$ p.p.m. (ether). Reaction in CH$_2$Cl$_2$ and CH$_3$CN gave analogous species of chemical shift $-41.5$ and $-41.9$ p.p.m. respectively.

The addition of a second mole equivalent of iodine to the reaction mixture indicated no further incorporation, the iodine colouration remaining and the $^{31}$P n.m.r. spectrum being unchanged. The absorption
at -42.5 p.p.m. diminished over a period of six days at room temperature, giving rise to a major absorption at -13.0 p.p.m. and minor absorptions at -13.9 and -1.0 p.p.m..

$^1$H n.m.r. spectrum of a solution containing equimolar amounts of triethyl phosphite and iodine

To a solution of iodine (0.213g, 8.39 x 10$^{-4}$ mol.) in deuterated dichloromethane (3 cm$^3$), contained in a 10 mm n.m.r tube at 0°C, was added a solution of triethyl phosphite (0.136g, 8.39 x 10$^{-4}$ mol.) in the same solvent (1 cm$^3$). The $^31$P n.m.r. spectrum of the mixture showed a single absorption at -41.5 p.p.m.. The $^1$H n.m.r. spectrum of the solution was found to be consistent with the presence of equimolar quantities of iodoethane and diethyl iodophosphonate.

100 MHz $^1$H n.m.r. (CD$_2$Cl$_2$) δ 1.4(t., 6H, J=7Hz); 4.1(septet, 4H, J=7Hz); 1.85(t., 3H, J=7.5Hz) and δ 3.15(quartet, 2H, J=7.5Hz).

$^1$H n.m.r. (authentic sample of EtI) 1.85(t., 3H) and 3.13 (quartet, 2H).

The relative amount of iodoethane present in the reaction mixture was found to increase with time. Upon standing for 21 hours at room temperature the ratio of EtI:(EtO)$_2$P(O)I increased from 1:1 to 1.37:1 (calculated by $^1$H n.m.r. integration).

Reaction of triphenyl phosphite with iodine

To a solution of iodine (2.53g, 0.01 mol.) in dichloromethane at 0°C, was added a solution of triphenyl phosphite (3.1g, 0.01 mol.) in the same solvent. Complete decolourisation of the iodine solution was not achieved. The $^31$P n.m.r. spectrum of the resulting mixture showed a major absorption at +38.5 p.p.m. and minor absorptions at
-49.8 and +174.4 p.p.m. No unreacted triphenyl phosphite remained. Upon standing at room temperature the signal at +38.5 p.p.m. disappeared and after 3½ days the reaction mixture consisted of one major phosphorus containing component (-49 p.p.m.) with a minor component (+174.4 p.p.m.) and a broad absorption (+12.3 p.p.m.) interpreted as being due to polymeric material.

**General preparative procedure for dehydration and condensation reactions utilising (EtO)\(_2\)P/I\(_2\)**

A solution of iodine in acetonitrile or dichloromethane, was added dropwise with cooling (ice-bath) and stirring, to a solution of equivalent amounts of the reactant(s) and triethyl phosphite, plus 2 equivalents of triethylamine in the same solvent. Upon completion of the addition the ice-bath was removed and the reaction mixture stirred for a further two hours prior to work-up.

**Preparation of benzonitrile by dehydration.**

(a). From α-benzaldoxime

α-Benzaldoxime was prepared by combination of benzaldehyde and hydroxylamine hydrochloride as described in Vogel.\(^{128}\) Yield 19.3g (81%), colourless oil, b.p. 114ºC, 2.5 mm. (lit.\(^{128}\), 122-124ºC, 12 mm.).

The dehydration on a 0.029 molar scale was carried out as described above, dichloromethane being used as the solvent. Upon completion of the reaction, removal of solvent was followed by the precipitation of triethylamine hydroiodide with ether; the solid being separated by filtration. The filtrate was washed thoroughly with water, dried (MgSO\(_4\)) and solvent removed, to give a crude yield of benzonitrile of 81% (estimated by g.l.c.). Isolation of pure benzonitrile was achieved in 61% yield by column chromatography [alumina/60-80ºC petroleum ether (85%) and diethyl ether (15%)].
Calibration shows benzonitrile to have approximately 2.2 times the response of benzaldoxime in the detector. Compensation of relative areas accordingly gives an 81% conversion of α-benzaldoxime to benzonitrile.

(b). From benzamide

Dehydration of benzamide in the same manner as for benzaldoxime gave an estimated g.l.c. yield of benzonitrile of 64%. The poor solubility of benzamide is believed to limit the efficiency of this process.

(c). From benzaldoxime with diethyl iodosphonate as the dehydrating agent

To a solution of iodine (4.19g, 0.017 mol.) in dichloromethane (70 cm$^3$) at 0°C, was added dropwise with cooling (ice-bath) and stirring, a solution of triethyl phosphite (2.74g, 0.017 mol.) in the same solvent (30 cm$^3$). Completion of the addition coincided with decolourisation of the iodine solution. This was followed immediately by the dropwise addition of a mixture of benzaldoxime (2g, 0.017 mol.) and triethylamine (3.34g, 0.034 mol.) in dichloromethane (30 cm$^3$). The ice-bath was removed and the combined solutions allowed to stir for two hours at room temperature. Triethylamine hydroiodide was removed by precipitation and filtration as previously described. Removal of solvent gave a g.l.c. estimated yield of benzonitrile of 75%.

Analytical g.l.c. (Column 10% E 30; operating temperature 142°C)
<table>
<thead>
<tr>
<th></th>
<th>Benzonitrile</th>
<th>Benzaldoxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention time (mins)</td>
<td>3.8</td>
<td>9.6</td>
</tr>
<tr>
<td>Relative areas</td>
<td>0.0138</td>
<td>0.0021</td>
</tr>
</tbody>
</table>

Relative response Benzonitrile: Benzaldoxime 2.2 : 1

**Reaction of diethyl iodophosphonate with water in the presence of tertiary amine**

To a solution of iodine (4.19g, 0.017 mol.) in dichloromethane (70 cm³) at 0°C, was added dropwise with cooling (ice-bath) and stirring, a solution of triethyl phosphite (2.74g, 0.017 mol.) in the same solvent (30 cm³). To the resulting colourless solution was added dropwise a mixture of triethylamine (3.34g, 0.034 mol.) and water (297 μl, 0.0165 mol.). The reaction mixture was allowed to stir at room temperature for two hours. Concentration of the solution gave crude reaction product having one phosphorus containing component of ³¹P n.m.r. chemical shift -13.1 p.p.m.. Triethylammonium hydroiodide (5.1g, 67% yield based upon triethylamine starting material) was isolated from the crude reaction product following its precipitation with ether. Removal of solvent from the filtrate gave a colourless oil (2.75g), having physical data consistent with the structure of tetraethyl pyrophosphate.

\[
^1H \text{ n.m.r. (CDCl}_3) \quad \delta 1.35(t., 6H, J=7Hz) \text{ and } 4.1(\text{quintet, } 4H, J=7Hz).
\]

\[
\gamma_{\text{max.}} \quad 2980, 1370, 1285, 1165, 1030, 980 \text{ and } 940 \text{ cm}^{-1}
\]

Mass spec. 
\[
m/e 290, 263, 236, 207, 179 \text{ and } 161
\]

Analytical g.l.c. (Column 10% E 30; operating temperature 142°C)
Three peaks seen under these conditions, of retention time (mins) 6.2, 12 and 26.6 (the latter being very broad).
Dehydration of $\alpha$-benzaldoxime. Analysis of crude reaction products
by $^{31}$P n.m.r. spectroscopy and analytical g.l.c.

Crude reaction products studied prior to work-up.

(1). Dehydration by the general procedure

<table>
<thead>
<tr>
<th>Chemical shift (p.p.m.)</th>
<th>Peak height (units)</th>
<th>% of total phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.2</td>
<td>55</td>
<td>71</td>
</tr>
<tr>
<td>-13.3</td>
<td>22</td>
<td>29</td>
</tr>
</tbody>
</table>

(2). Dehydration via diethyl iodophosphonate

<table>
<thead>
<tr>
<th>Chemical shift (p.p.m.)</th>
<th>Peak height (units)</th>
<th>% of total phosphorus</th>
</tr>
</thead>
<tbody>
<tr>
<td>-1.2</td>
<td>81</td>
<td>57</td>
</tr>
<tr>
<td>-13.3</td>
<td>61.5</td>
<td>43</td>
</tr>
</tbody>
</table>

(1). Dehydration by the general procedure

Analytical g.l.c. (Column 10% E 30; operating temperature 142°C)

Three peaks were observed on the g.l.c. trace, these being due to benzonitrile, triethyl phosphate and $\alpha$-benzaldoxime. A test solution of equimolar proportions of these three components shows unequal response in the detector. Response for benzonitrile is 2.25 times that for triethyl phosphate and 2.2 times that for $\alpha$-benzaldoxime.

<table>
<thead>
<tr>
<th>Component</th>
<th>Retention time (mins)</th>
<th>Peak areas (absolute)</th>
<th>Peak areas (corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$-Benzaldoxime</td>
<td>9.6</td>
<td>0.0011</td>
<td>0.00239</td>
</tr>
<tr>
<td>Benzonitrile</td>
<td>3.8</td>
<td>0.01</td>
<td>0.0038</td>
</tr>
<tr>
<td>Triethyl phosphate + unknown species</td>
<td>6.2</td>
<td>0.0085</td>
<td></td>
</tr>
</tbody>
</table>

Molar ratio of benzonitrile : triethyl phosphate + unknown species

= 1 : 0.85

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(2) Dehydration via diethyl iodophosphonate

Analytical g.l.c. (Column 10% E 30; Operating temperature 142°C).

Three peaks were observed on the g.l.c. trace, these being due to benzonitrile, the decomposition product of tetraethyl pyrophosphate and benzaldoxime. The response for the decomposition product is taken as being the same as that for triethyl phosphate.

<table>
<thead>
<tr>
<th>Retention time (mins)</th>
<th>Peak areas (absolute)</th>
<th>Peak areas (corrected)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzaldoxime</td>
<td>9.6</td>
<td>0.0021</td>
</tr>
<tr>
<td>Benzonitrile</td>
<td>3.8</td>
<td>0.0138</td>
</tr>
<tr>
<td>Decomposition product of tetraethyl pyrophosphate</td>
<td>6.2</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

Molar ratio of benzonitrile to unknown species = 1 : 0.304
Thus molar ratio of benzonitrile to triethyl phosphate = 1 : 0.546
ie. there is a 54.6% molar equivalence of triethyl phosphate to benzonitrile for the general procedure leading to the dehydration of α-benzaldoxime.

Dehydration of α-benzaldoxime by (PhO)₂I₂

To a solution of α-benzaldoxime (2g, 0.016 mol.), triphenyl phosphite (4.96g, 0.016 mol.) and triethylamine (3.34g, 0.033 mol.) in dichloromethane at 0°C, was added dropwise with cooling (ice-bath) and stirring, a solution of iodine (4.19g, 0.016 mol.) in the same solvent. The discharge of the iodine colouration was noted initially, but as addition proceeded the colour accumulated resulting in a dark brown solution. The reaction mixture was allowed to stand at room temperature for a period of 40 hours, the brown colouration persisting. Following concentration of the reaction mixture, the ³¹P n.m.r. spectrum showed one major phosphorus containing compound of chemical shift -17.5 p.p.m.
(CDCl$_3$/CH$_2$Cl$_2$) c.f. Ph$_3$P = $-18.1$ p.p.m. (CH$_2$Cl$_2$). A minor absorption at $+128.4$ p.p.m. due to unreacted phosphite was noted.

Triethylamine hydroiodide was removed as before. G.l.c. analysis of the crude reaction product showed only benzonitrile and a small amount of $\alpha$-benzaldoxime. It was estimated that greater than 90% of the starting material had been consumed.

Analytical g.l.c. (Column 10% E 30; operating temperature $184^{\circ}$C)

<table>
<thead>
<tr>
<th></th>
<th>Benzonitrile</th>
<th>Benzaldoxime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retention time (mins)</td>
<td>1</td>
<td>1.8</td>
</tr>
<tr>
<td>$\gamma_{\text{max}}$</td>
<td>$2225$ cm$^{-1}$ ($\text{C} \equiv \text{N}$), $1200$ cm$^{-1}$ ($\text{&gt;P} = 0$).</td>
<td></td>
</tr>
</tbody>
</table>

Preparation of $N$-benzyl benzamide from benzoic acid and benzylamine

The preparation was carried out as described in the general procedure on a 0.04 molar scale and with dichloromethane as the solvent. Stirring of the reaction mixture for two hours was followed by removal of solvent and precipitation of triethylammonium iodide by addition of ether. The salt was then separated by filtration (celite aided) and the filtrate washed thoroughly with water. Removal of solvent gave an oil which crystallised on cooling. The resulting solid was washed with water, and dried overnight at $40^\circ$C, to give $N$-benzyl benzamide (7.45g, 89%).

Recrystallisation from ethanol/water gave a 63% yield of pure product, m.p. 104-105°C (lit.$^{129}$ 105-106°C)

Preparation of diethyl phosphoric benzoic mixed anhydride

To a mixture of benzoic acid (6.1g, 0.05 mol.), triethyl phosphate (8.3g, 0.05 mol.) and triethylamine (5.05g, 0.05 mol.), in dichloromethane (100 cm$^3$) was added dropwise with cooling (ice-bath) and stirring, a solution of iodine (12.6g, 0.05 mol.) in the same solvent (350 cm$^3$). The resulting mixture was stirred at room temperature for a period of
2 hours. The removal of solvent and separation of triethylammonium iodide was carried out as previously described. Removal of solvent from the filtrate gave a yellow oil consisting of one major phosphorus containing component. [\(^{31}\)P n.m.r. -13.3 p.p.m. (\(\text{CDCl}_3\))] Distillation gave a colourless oil, diethyl phosphoric benzoic mixed anhydride. (8.8g, 68%) b.p. 140-150°C, 0.6 mm. (lit.\(^{130}\) 110-111°C, 0.01 mm.)

The \(^1\)H n.m.r. spectrum of the distillate indicated contamination of the mixed anhydride with unreacted benzoic acid. Correction to account for this impurity (calculated by \(^1\)H n.m.r. integration) gave a yield of desired product of 43%.

\(^1\)H n.m.r. (\(\text{CDCl}_3\)) \(\delta\) 1.25(t., 6H, J=7Hz); 4.15(quintet, 4H, J=7Hz) and 7.4(m., 5H).

\(\gamma\) max. 1790, 1600, 1450, 1275 and 1035 cm\(^{-1}\)

Mass spec. \(m/e\) M\(^+\) 258, 227, 220, 198, 180, 162 and 106

Preparation of N-benzoyl-L-leucine\(^{116}\)

To a solution of L-leucine (13.1g, 0.1 mol.) in sodium hydroxide solution (50 cm\(^3\), 2M) with cooling (ice-bath) and stirring, was added dropwise simultaneously, benzoyl chloride (11.6 cm\(^3\)) and sodium hydroxide solution (60 cm\(^3\), 2M). The solution was kept strongly alkaline at all times. Upon completion of the addition the reaction mixture was stirred for fifteen minutes; this followed by extraction by ether. The aqueous layer was made acid to Congo red, and the oily product extracted with ether. Removal of solvent gave a colourless oil which was taken up in chloroform/60-80°C petroleum ether. After several days white crystals of N-benzoyl-L-leucine (14.6g, 62%) were deposited from solution. m.p. 105-106°C (lit.\(^{116}\) 106°C) Specific rotation (ethanolic solution) \([\alpha]_D^{20}\) -7.3° (c=2.6) lit.\(^{116}\) \([\alpha]_D^{23}\) -6.9° (c=2.6)
Preparation of N-benzoyl-leucyl-glycine ethyl ester

Preparation from benzoyl-L-leucine and glycine ethyl ester hydrochloride was carried out on a 0.025 molar scale in acetonitrile, as described in the general procedure. Use of the amine component as the hydrochloride salt necessitates the addition of an extra mole of triethylamine to complex with the hydrogen chloride liberated. Stirring of the reactants for a period of two hours at room temperature was followed by the removal of solvent and separation of the triethylammonium salts as previously described. The ethereal solution of reaction products was washed thoroughly with water, dried (MgSO₄) and solvent removed to give crude peptide which was optically inactive. Purification by recrystallisation gave N-benzoyl-D,L-leucyl-glycine ethyl ester (3.8g, 48%) m.p. 145-146°C (lit. 146°C) from ethyl acetate/60-80°C petroleum ether.

Preparation of N-benzoyl-leucyl-glycine ethyl ester in the presence of 1-hydroxybenzotriazole

Commercial 1-hydroxybenzotriazole hydrate was heated to 110°C for a period of 8 hours in vacuo, in the presence of phosphorus pentoxide, to remove the elements of water. Repetition of the peptide synthesis, with addition of the 1-hydroxybenzotriazole (3.44g, 0.025 mol.) to the reactants, gave peptide having a 39% enantiomeric excess of the L-isomer (ie 30.5% D, and 69.5% L, enantiomers).
\[ \alpha_D^{20} (\text{EtOH}) = -13.29\degree c=3.1 \] (lit. 116, 117 \[ \alpha_D^{20} (\text{EtOH}) = -34\degree c=3.1 \])

Prior to optical rotation measurement the crude reaction product was purified by column chromatography. (silica/diethyl ether and ethyl acetate). This gave an 83% yield of chemically pure peptide. This method of purification is necessary, as recrystallisation leads to a concentration of the D,L-peptide.
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