Tervalent Phosphorus Compounds in Organic Synthesis

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1 Introduction

The ease with which tervalent phosphorus can expand its valence shell to accommodate ten electrons, the high nucleophilic reactivity of certain tervalent phosphorus compounds, and the strong bonds which phosphorus forms with carbon, nitrogen, oxygen, and sulphur are factors which contribute to the high reactivity of materials such as trialkyl phosphites or triarylphosphines towards a wide variety of organic compounds. As a result, tervalent phosphorus compounds have become one of the most versatile classes of reagents available in general organic synthesis, with reactions ranging from the simple removal of hydroperoxides from ethers, or decomposition of ozonides, through the synthesis of alkenes or complex nitrogen heterocycles, to intervention in the chemistry of penicillins, or as synthetic precursors of vitamin B_{12}.

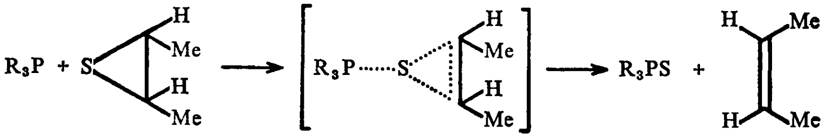
This review, which is not intended to be comprehensive because much of the earlier relevant work has been summarized, is directed mainly towards the use of these readily available organic reagents in general organic synthesis rather than towards the more specialist aspects of the phosphorus chemistry involved.

On perusal of the literature, three main types of reaction emerge: (*a*) desulphurization, (*b*) deoxygenation, and (*c*) reaction with halogen-containing materials, all of which have major applications in organic chemistry. In addition there are those cases, not considered here *in extenso*, where a tervalent precursor is used to produce a quinquevalent phosphorus reagent of general synthetic value; examples of this are the Wittig and Horner reagents, the related phosphinimines, Ramirez' oxyphosphoranes, and triphenyl phosphite ozonide, all of which have an extensive literature of their own.

2 Desulphurization Reactions

In accord with the soft character of the reactants, tervalent phosphorus has a high affinity for free and bound sulphur, which has led to many useful synthetic reactions. The size and high polarizability of tervalent phosphorus enable it to utilize the empty orbital of sulphur more effectively than is the case for oxygen or nitrogen, and indeed elemental sulphur adds readily to phosphines and phosphites in air to give the sulphide rather than the oxide[1] *via* a Menshutkin-type reaction involving successive nucleophilic displacements of phosphorus on sulphur.[2]

A. Alkenes from Episulphides.—That episulphides can be converted into the corresponding alkenes by reaction with trisubstituted phosphines or phosphites has been known since 1958.[3,4] Unlike the corresponding deoxygenation of epoxides,[5] which proceeds non-stereospecifically, initially *via* nucleophilic attack on carbon,[6] this reaction occurs with complete stereospecificity *via* a smooth displacement on sulphur (Scheme 1). The reaction has some synthetic value, for example in the formation of thermochromic alkenes, which can only be produced with difficulty by other routes.[7]



Scheme 1

B. Vinylogous Amides and β-Diketones from Thioimidates and Related Compounds.—This method, developed by Eschenmoser *et al.*[8] as a key step in the synthesis of corrins, involves the reaction of the thioimidate with a mixture of base and a tervalent phosphorus compound [*e.g.* Bu_3P, $(EtO)_3P$]; alkylative coupling to give an episulphide followed by desulphurization leads to the product (Scheme 2).[8b,c] As well as being valuable in corrin building (Scheme 3),[8c] the reaction, when modified, is generally useful, as shown by its extension to the synthesis of enolizable β-diketones (Scheme 4).[8b,c]

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[1] F. W. Hoffman and T. R. Moore, *J. Amer. Chem. Soc.*, 1958, **80**, 1150; W. Strecker and R. Spiraler, *Ber.*, 1926, **59**, 1772.

[2] P. D. Bartlett and G. Meguerian, *J. Amer. Chem. Soc.*, 1956, **78**, 3710; P. D. Bartlett, E. F. Cox, and R. E. Davis, *ibid.*, 1961, **83**, 103.

[3] R. D. Schuetz and R. L. Jacobs, *J. Org. Chem.*, 1958, **23**, 1799; A. Schönberg and M. M. Sidky, *J. Amer. Chem. Soc.*, 1959, **81**, 2259.

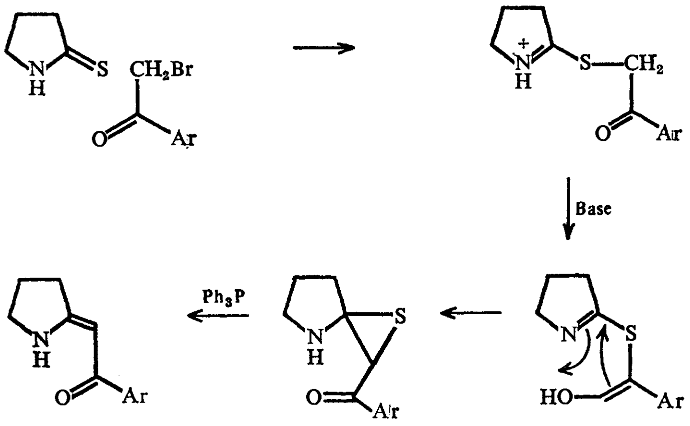
[4] R. E. Davis, *J. Org. Chem.*, 1958, **23**, 1767.

[5] (*a*) C. B. Scott, *J. Org. Chem.*, 1957, **22**, 1118; (*b*) G. Wittig and W. Haag, *Chem. Ber.*, 1955, **88**, 1654.

[6] M. J. Boskin and D. B. Denney, *Chem. and Ind.*, 1959, 330.

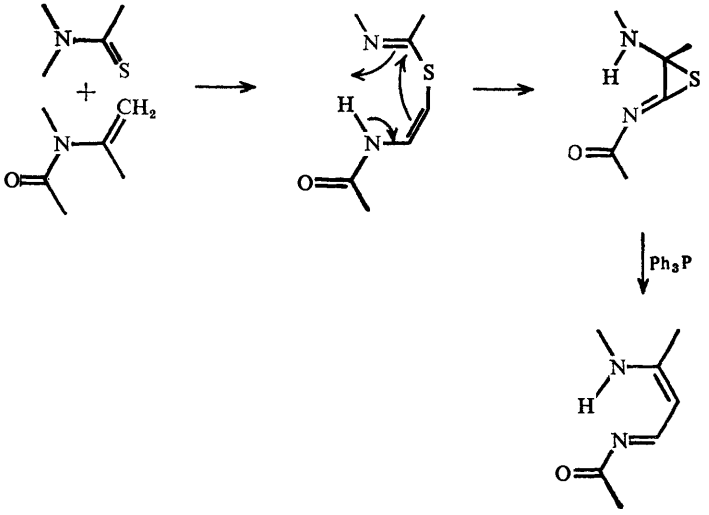
[7] M. M. Sidky, M. R. Mahran, and L. S. Poulos, *J. prakt. Chem.*, 1970, **312**, 51.

[8] (*a*) Y. Yamada, D. Miljkovik, P. Wehrli, B. Golding, P. Löliger, R. Keese, K. Müller, and A. Eschenmoser, *Angew. Chem. Internat. Edn.*, 1969, **8**, 343; (*b*) M. Roth, P. Dubs, E. Gotschi, and A. Eschenmoser, *Helv. Chim. Acta*, 1971, **54**, 710; (*c*) A. Eschenmoser, *Quart. Rev.*, 1970, **24**, 366.



Ar = *p*-BrC$_6$H$_4$

Scheme 2



Scheme 3

C. **Alkenes from Thionocarbonates.**—That E. J. Corey and R. A. E. Winter's[9] synthesis of alkenes from thionocarbonates is now widely used is not surprising:

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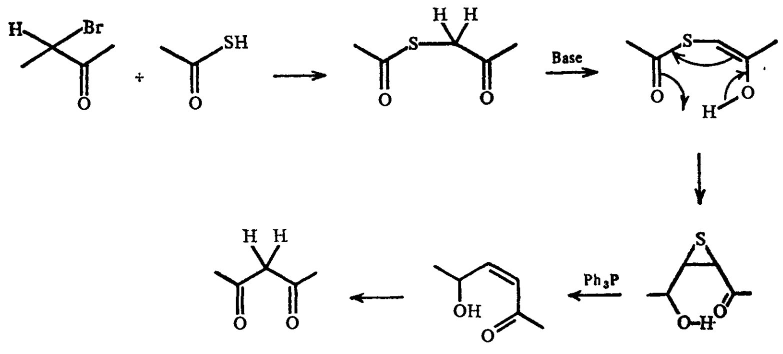
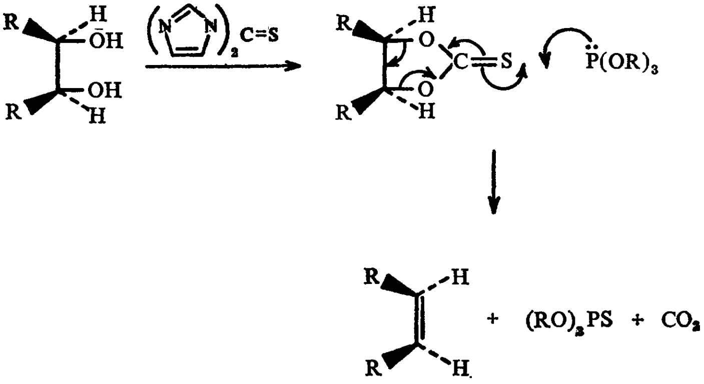
[9] E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, 1963, **85**, 2677; E. J. Corey, *Pure Appl. Chem.*, 1967, **14**, 19.



Scheme 4

in essence it allows a diol to be converted *via cis*-elimination into an alkene with retention of stereochemistry. Thus, the reaction of the diol with thiophosgene or, better, thiocarbonyldi-imidazole leads to a cyclic thionocarbonate which undergoes stereospecifically *cis*-elimination on reaction with tervalent phosphorus reagents [*e.g.* $(RO)_3P$, R_3P, $(R_2N)_3P$] (Scheme 5). The observed stereospecificity



Scheme 5

points to the absence of dipolar intermediates and to reaction *via* a carbene or, more likely, *via* a concerted loss of CO_2 and $R_3P{=}S$. Examples demonstrating the versatility of this reaction (Scheme 6) include the synthesis of unsaturated sugars and related compounds[10] and of unstable alkenes hitherto difficult to obtain such as cyclobutene,[11] *cis*-cinnamic acid,[12] both enantiomers of *trans*-

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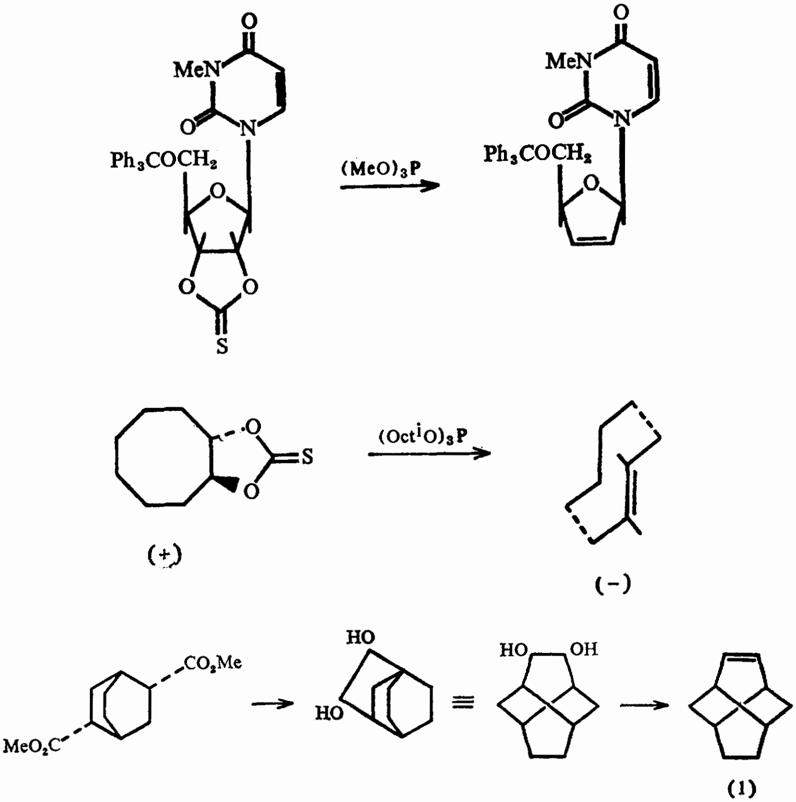
[10] W. V. Ruyle, T. Y. Shen, and A. A. Patchett, *J. Org. Chem.*, 1965, **30**, 4353; T. L. Nagabhushah, *Canad.J. Chem.*, 1970, **48**, 383; D. Horton and C. G. Tindall, jun., *J. Org. Chem.* 1970, **35**, 3558.

[11] W. Hartman, H.-M. Fischler, and H.-G. Heine, *Tetrahedron Letters*, 1972, 853.

[12] C. Sandris, *Tetrahedron*, 1968, **24**, 3589.



Scheme 6

cyclo-octene[13] (with high optical purity), *trans*-cycloheptene (trapped by 2,5-diphenyl-3,4-isobenzofuran),[14a] and (+)-twistene (1).[14b]

Similar elimination reactions occur with the corresponding 1,2-trithiocarbonates[14a] but reactions with the related 1,3-trithiocarbonates[14c] proceed without complete elimination of sulphur. In this case the reaction stops at the ylide stage. Nevertheless this has its synthetic possibilities because on reaction with certain aldehydes, keten thioacetals are formed, which in turn can be hydrolysed to substituted acetic acids (Scheme 7). The reaction does not proceed with ketones. The parent keten thioacetals also have other synthetic uses.[15]

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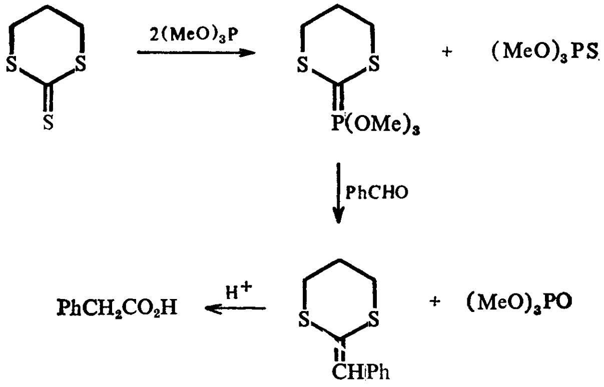
[13] E. J. Corey and K. I. Shulman, *Tetrahedron Letters*, 1968, 3655.

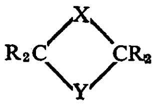
[14] (*a*) E. J. Corey, F. A. Corey, and R. A. E. Winter, *J. Amer. Chem. Soc.*, 1965, **87**, 934; (*b*) M. Tichy and J. Sicher, *Tetrahedron Letters*, 1969, 4609; (*c*) E. J. Corey and G. Märkl, *ibid.*, 1967, 3201.

[15] E. J. Corey and D. Seebach, *Angew. Chem. Internat. Edn.*, 1965, **4**, 1075, 1077.

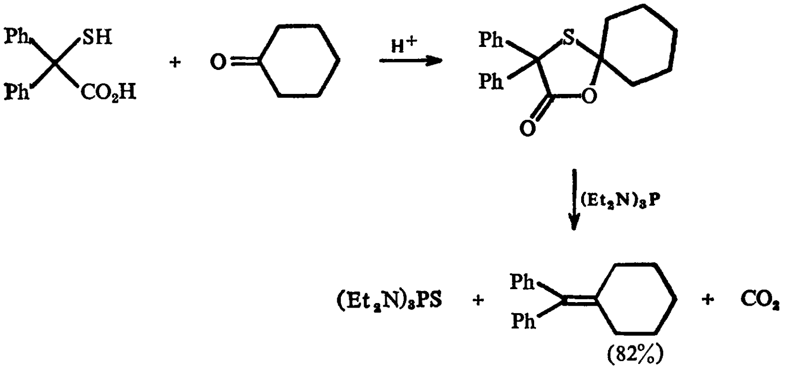


Scheme 7

D. Alkenes from 1,3-Oxathiolan-5-ones and Azosulphides.—These reactions are examples of D. H. R. Barton's alkene synthesis by two-fold extrusion processes,[16] the principle being elimination of X and Y from the species



In the first, 1,3-oxathiolan-5-ones, readily prepared from thiobenzilic acid and benzaldehyde or various ketones, on treatment with $(Et_2N)_3P$ at high temperature give alkenes in high yield (Scheme 8) even when highly sterically hindered



Scheme 8

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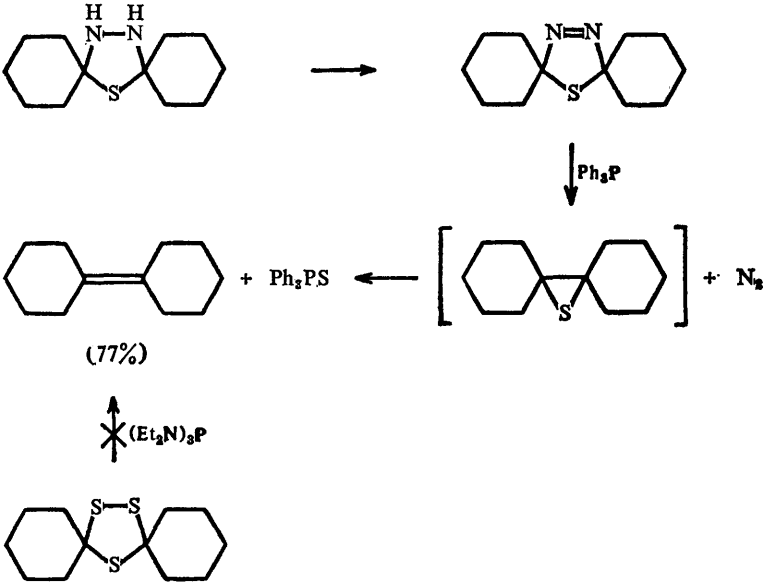
[16] D. H. R. Barton and B. J. Willis, *Chem. Comm.*, 1970, 1225; *J.C.S. Perkin I*, 1972, 305; D. H. R. Barton, E. H. Smith, and B. J. Willis, *Chem. Comm.*, 1970, 1266.

alkenes are required. The reaction is limited, however, by the need for incorporating phenyl or other conjugated residues to facilitate loss of carbon dioxide.

In the second related synthesis triphenylphosphine is used to extract sulphur with elimination of nitrogen from azosulphides formed from ketones by their reaction with H_2S and hydrazine, followed by oxidation (Scheme 9). The corresponding trithia-system (Scheme 9) is very much more stable and resists attack even by the strongly nucleophilic $(Et_2N)_3P$.



Scheme 9

In neither case has a mechanism been established, but intermediate formation of the corresponding episulphide is a strong possibility.

E. Hydrocarbons by Desulphurization of Thiols and Sulphides.—Alkanethiols readily undergo quantitative desulphurization to the corresponding alkanes[17a] by reaction under radical conditions (light or AIBN) with trialkyl phosphites or trialkylphosphines (Scheme 10).[17b] The corresponding reaction with toluene-α-

$$R^1SH \rightarrow R^1S\cdot$$
$$R^1S\cdot + R^2{}_3P \rightarrow R^2{}_3\dot{P}SR^1 \rightarrow R^2{}_3P{=}S + R^1\cdot$$
$$R^1\cdot + R^1SH \rightarrow R^1H + R^1S\cdot \textit{ et seq.}$$

Scheme 10

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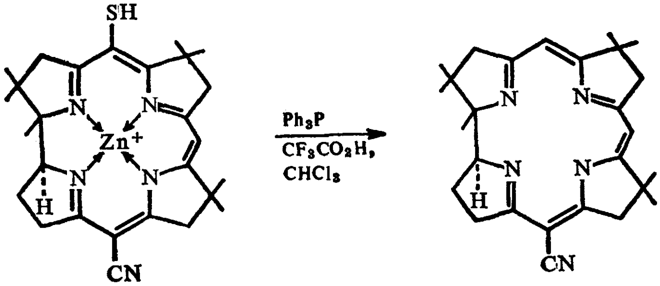
[17] (*a*) F. W. Hoffmann, R. J. Ess, R. C. Simmons, and R. S. Hanzel, *J. Amer. Chem. Soc.* 1956, **78**, 6414; (*b*) C. Walling and R. Rabinowitz, *ibid.*, 1957, **79**, 5326.

thiol and $(Et_2N)_3P$ is reported to give $(Et_2N)_2PSCH_2Ph$.[18] The key step in the desulphurization is the reaction of a thiyl radical with tervalent phosphorus to give an intermediate thiophosphoranyl radical which subsequently decomposes *via* fission of the weaker PS—R bond to give a chain-carrying alkyl radical.[19] This simple method of reducing thiols to hydrocarbons has not been widely used, although it has been used by Eschenmoser to desulphurize a 5-mercapto-corrin-zinc complex cleanly (Scheme 11).[20] The possibility of using this step to produce an alternative method of desulphurization of sulphides has been investigated by Corey and Block.[21] Thus photolysis of dibenzyl sulphide in the presence of trimethyl phosphite gives bibenzyl (59%), presumably *via* benzylthio-radicals which are in turn desulphurized by the phosphite to give benzyl radicals (Scheme 12). Similarly diallyl sulphide gives biallyl. Treatment of those dialkyl sulphides which give shorter-lived alkyl radicals, however, leads to mixtures of products.



Scheme 11

$$PhCH_2{-}S{-}CH_2Ph \xrightarrow{h\nu} PhCH_2S\cdot + \cdot CH_2Ph$$

$$PhCH_2S\cdot + (RO)_3P \rightarrow (RO)_3\dot{P}SCH_2Ph$$

$$\downarrow$$

$$PhCH_2CH_2Ph \longleftarrow Ph\dot{C}H_2 + (RO)_3PS$$

Scheme 12

Dialkyl and diaryl monosulphides, in general, are unreactive towards tervalent phosphorus compounds under ionic conditions, but 3-substituted thietans, which are strained, are exceptional.[22] Thus 3-chlorothietan on treatment with triphenylphosphine in boiling xylene gives allyl chloride; possible routes are shown in Scheme 13.

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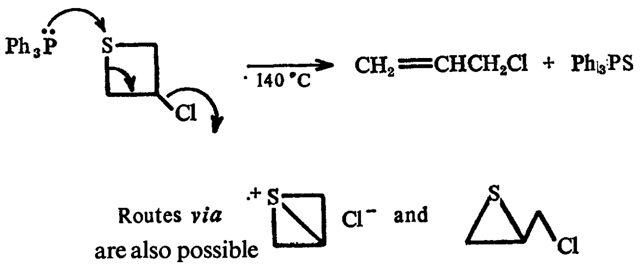
[18] C. Steube and H. P. Lankelma, *J. Amer. Chem. Soc.*, 1956, **78**, 976.

[19] C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, 1959, **81**, 1243; C. Walling, O. H. Basedow, and E. S. Savas, *ibid.*, 1960, **82**, 2181.

[20] A. Fischli and A. Eschenmoser, *Angew. Chem. Internat. Edn.*, 1967, **6**, 866.

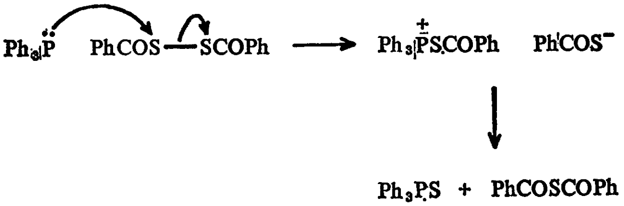
[21] E. J. Corey and E. Block, *J. Org. Chem.*, 1969, **34**, 1233.

[22] D. C. Dittmer and S. M. Kotin, *J. Org. Chem.*, 1967, **32**, 2009.



Scheme 13

F. Sulphides from Disulphides.—The ease and course of desulphurization of disulphides depend on the nature of the tervalent phosphorus compound. It has long been known[23] that triphenylphosphine reacts with acyl, thioacyl, and vinylogous acyl disulphides, *via* nucleophilic displacement on sulphur, to give the corresponding monosulphide (Scheme 14), whereas diethyl and dipheny disulphide fail to react. Dialkenyl sulphides such as dimethylbut-2-enyl disulphide react, on the other hand, by way of an S_{Ni}' allylic rearrangement (Scheme 15),[24a] and this has been put to elegant use in a synthesis of squalene from farnesyl chloride.[24b] The conversion of the metabolite sporidesmin into the corresponding epithiodioxopiperazine by triphenylphosphine is an example of the higher reactivity of acyl disulphides towards this reagent (Scheme 16).[25] That this reaction proceeds *via* epimerization supports reaction as in Scheme 14.



Scheme 14

Trialkyl phosphites react even with simple sulphides such as diethyl disulphide at high temperature in a manner that is analogous to the Arbusov reaction in that the quasiphosphonium salt, formed by nucleophilic displacement on sulphur, undergoes dealkylation at the more electrophilic *O*-alkyl group, rather than at *S*-alkyl (Scheme 17),[26] to give a dialkyl *S*-ethyl phosphorothiolate, say. Thus

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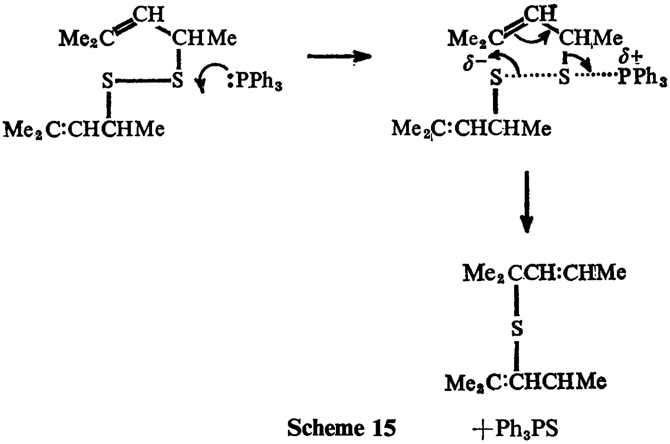
[23] A. Schonberg and M. Barakat, *J. Chem. Soc.*, 1949, 892; F. Challenger and D. Wilson, *ibid*, 1950, 26; A. J. Parker and N. Kharasch, *Chem. Rev.*, 1959, **59**, 621.

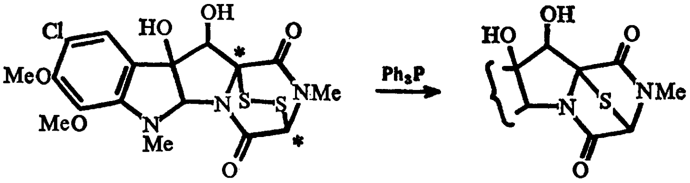
[24] (*a*) M. B. Evans, G. M. C. Higgins, C. G. Moore, M. Porter, B. Saville, J. F. Smith, B. R. Trego, and A. A. Watson, *Chem. and Ind.*, 1960, 897; (*b*) G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Comm.*, 1969, 99.

[25] S. Safe and A. Taylor, *J. Chem. Soc.* (*C*), 1971, 1189.

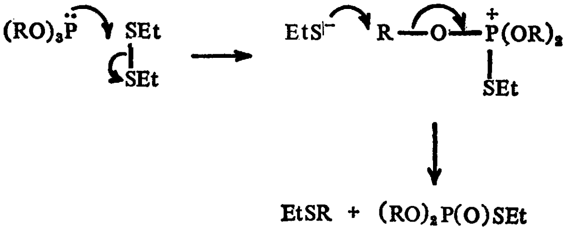
[26] A. C. Poshkus and J. E. Herweh, *J. Amer. Chem. Soc.*, 1957, **79**, 4245; H. I. Jacobson, R. G. Harvey, and E. V. Jensen, *ibid.*, 1955, **77**, 6064.



Scheme 15



Scheme 16



Scheme 17

in the case of triethyl phosphite and diethyl disulphide the product is diethyl sulphide in which one of the ethyl groups originates in the phosphite.

An interesting variant of this reaction has recently been employed in the penicillin series.[27] It had been previously established that penicillin sulphoxides rapidly undergo a thermal six-electron electrocyclic rearrangement to the isomeric open-chain sulphenic acid. D. H. R. Barton and his colleagues found that this reacted with isobutanethiol to give the corresponding 4-isobutyl dithioaceti-

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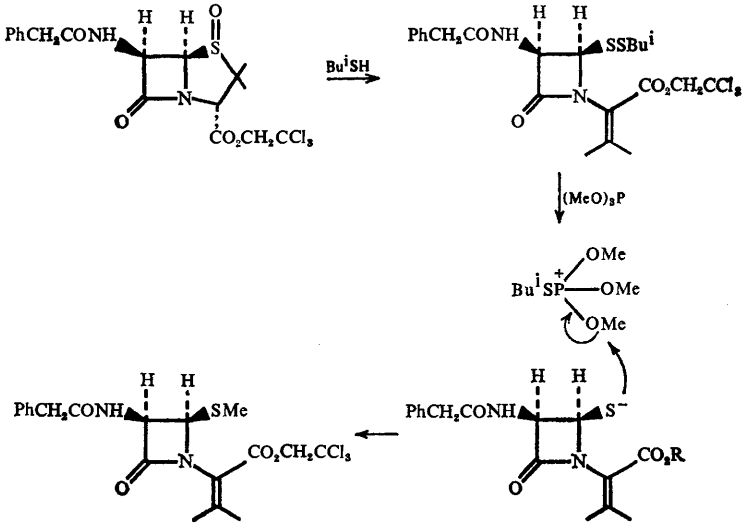
[27] D. H. R. Barton, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt, B. F. Looker, and W. G. E. Underwood, *Chem. Comm.*, 1971, 1137.

dinone which, on treatment with trimethyl phosphite, gave the corresponding monothioazetidinone in good yield (Scheme 18).



Scheme 18

Under radical conditions the reaction between dialkyl disulphides and triethyl phosphite takes yet a different course, resembling that between thiols and the phosphite (Scheme 10). Di-isobutyl disulphide and triethyl phosphite under these conditions give the monosulphide and triethyl phosphorothionate in excellent yields.[20] This has been adapted to provide a route to thioesters by performing the reaction under a pressure of carbon monoxide (Scheme 19).[20]

$$R^1S\cdot + (R^2O)_3P \rightarrow (R^2O)_3\dot{P}SR^1 \rightarrow (R^2O)_3PS + R^1\cdot$$
$$R^1\cdot + CO \rightarrow R^1CO\cdot$$
$$R^1CO\cdot + R^1S\cdot SR^1 \rightarrow R^1CO\cdot SR^1 + R^1S\cdot \textit{ et seq.}$$

Scheme 19

For most desulphurizations of disulphides, however, $(Me_2N)_3P$ or $(Et_2N)_3P$ appear to be the best reagents, leading to high yields of dialkyl sulphides under mild conditions.[28a] The course of the reaction differs slightly from that described in Schemes 17 and 18, in that *S*-dealkylation rather than *N*-dealkylation of the quasiphosphonium salt to give the corresponding phosphorothionate is preferred (Scheme 20). Examples of desulphurizations by this reagent include the con-

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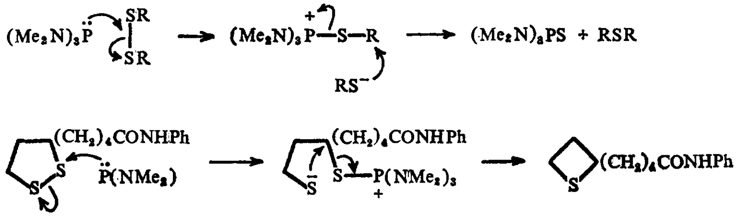
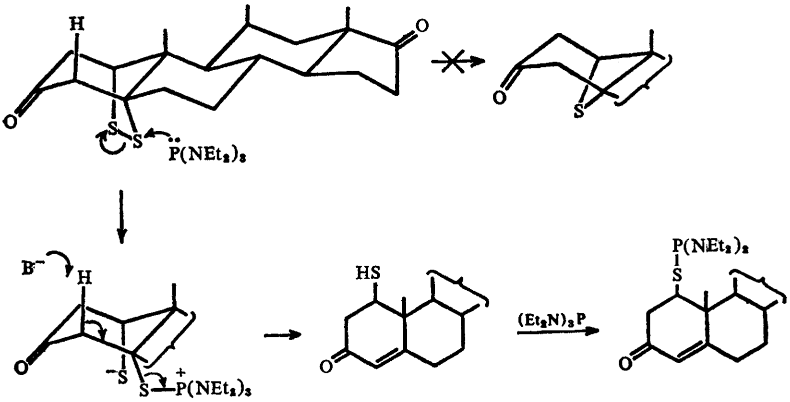
[28] (*a*) D. N. Harpp and J. G. Gleason, *J. Amer. Chem. Soc.*, 1971, **93**, 2437; (*b*) D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, 1970, **35**, 3259.



Scheme 20

version of protected cystine into L-lanthionine and of the amide of the vitamin α-lipoic acid into the corresponding thietan (Scheme 20).[28a] The latter involves intramolecular dealkylation of the type which is impossible in the steroidal disulphide shown in Scheme 21, which instead reacts to give the steroidal phosphorothiodiamidite shown,[28b] *via* thiol formation and subsequent reaction with $(Et_2N)_3P$ as previously described.[19]



Scheme 21

G. Carbodi-imides from Thioureas and Disulphides from Thiols.—Conversion of thioureas into carbodi-imides[29] can be regarded as a variation of the disulphide to sulphide reaction, but it depends first on an alleged, but nonetheless intriguing, triphenylphosphine-catalysed *oxidation* of thiols to disulphides effected by diethyl azodicarboxylate.[30] The mechanism of this reaction is obscure and more work is required, although a charge-transfer complex between phosphine and

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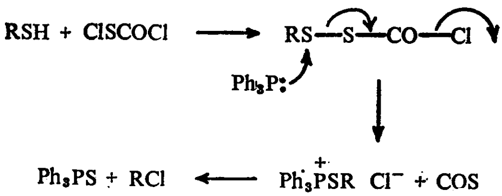
[29] O. Mitsunobu, K. Kato, and F. Kakese, *Tetrahedron Letters*, 1969, 2473.
[30] K. Kato and O. Mitsunobu, *J. Org. Chem.*, 1970, **35**, 4227.

azo-compound is probably involved (Scheme 22). Extension of this reaction to desulphurization of thioureas *via* the thiol tautomer, again by an obscure route, has also been reported.[30]

$$\begin{tikzcd} \mathrm{EtO_2CN{=}NCO_2Et} \arrow[r, "\mathrm{Ph_3P}"] & \text{[charge-transfer complex]} \arrow[d, "\mathrm{RSH}"] \\ & \mathrm{RSSR} + \mathrm{(EtO_2CNH)_2} + \mathrm{Ph_3P} \end{tikzcd}$$

Scheme 22

H. Alkyl Halides from Thiols.—This[31] is also a variant of the disulphide desulphurization and involves conversion of the thiol into an alkyl chlorocarbonyl disulphide by reaction with chlorocarbonylsulphenyl chloride followed by reaction with triphenylphosphine (Scheme 23).



Scheme 23

I. Sulphinates from Thiolsulphonates.—That alkyl but not aryl esters of aliphatic and aromatic thiolsulphonic acids react readily with trialkyl phosphites to give alkyl sulphinates was reported in 1960;[32] isomeric alkyl sulphones, arising from the bidentate nature of the sulphinic anion, were also sometimes formed (Scheme 24).[33] The reaction was recently extended to include reactions of $(Et_2N)_3P$ with acyclic and alicyclic esters (Scheme 24).[34]

J. Amines from Sulphenamides.—The classic Gabriel synthesis fails when applied to branched primary alkylamines as a result of difficulty in forming the required *N*-alkyl-phthalimide. This can be overcome in some cases by synthesis of the latter using the reaction of the more easily formed sulphenamide with $(Me_2N)_3P$ (Scheme 25).[35]

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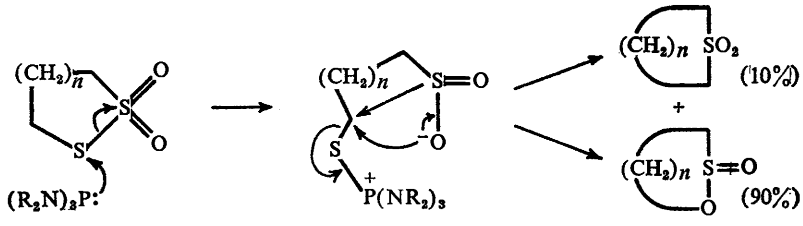
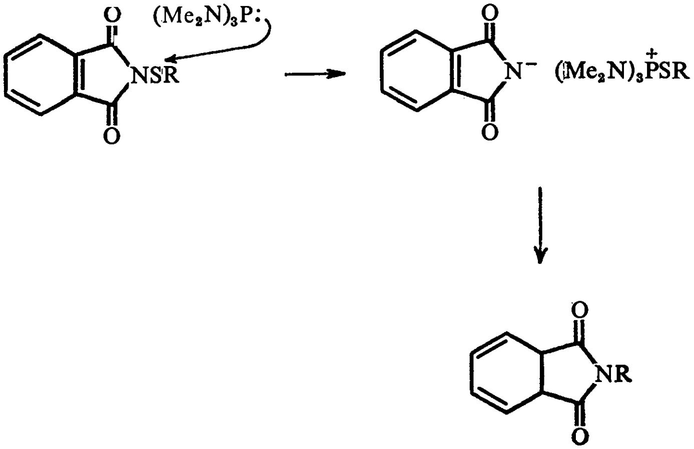
[31] D. L. J. Clive and C. V. Denyer, *J.C.S. Chem. Comm.*, 1972, 773.
[32] J. Michalski, T. Modro, and J. Wieczorkowski, *J. Chem. Soc.*, 1960, 1665.
[33] D. N. Harpp, J. G. Gleason, and D. K. Ash, *J. Org. Chem.*, 1971, **36**, 322.
[34] D. N. Harpp and J. G. Gleason, *Tetrahedron Letters*, 1969, 1447.
[35] D. N. Harpp and B. A. Orwig, *Tetrahedron Letters*, 1970, 2691.

$$(EtO)_3P + R^1SO_2SR^2 \longrightarrow (EtO)_3\overset{+}{P}SR^2\ R^1SO_2^- \longrightarrow \begin{array}{c}(EtO)_2P(O)SR^2\\ +\\ R^1SOOEt + R^1SO_2Et\end{array}$$



Scheme 24



Scheme 25

K. Sulphides from Sulphoxides and Sulphenates.—Simple sulphoxides are deoxygenated to sulphides by a variety of tervalent phosphorus reagents.[36] Phosphorus trichloride appears to be particularly useful in the case of aromatic sulphoxides.[36c] Penicillin sulphoxides are also deoxygenated, but the nature of the rearranged products indicates that the reaction involves deoxygenation of the first-formed tautomeric sulphenic acid (see above) to the corresponding thiol, which then condenses with the amido side-chain to give the observed thiazoline derivative (Scheme 26).[37] On the other hand, alkyl sulphenates are desulphurized

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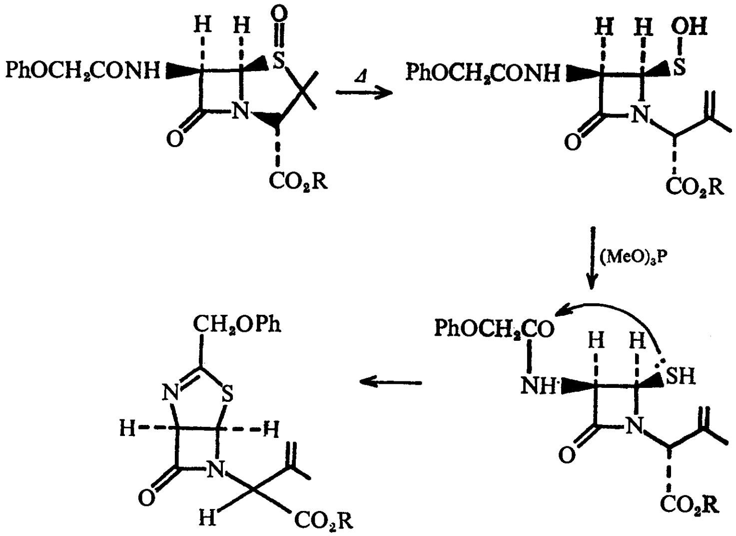
[36] (*a*) E. H. Amonoo-Neizer, S. K Ray, R. A. Shaw, and B. C. Smith, *J. Chem. Soc.*, 1965, 4296; (*b*) S. Oae, A. Nakanishi, and S. Kozuka, *Tetrahedron*, 1972, **28**, 549; (*c*) I. Granoth, A. Kalir, and Z. Pelah, *J. Chem. Soc.* (*C*), 1969, 2424.

[37] R. D. G. Cooper and F. L. Jose, *J. Amer. Chem. Soc.*, 1970, **92**, 2575.



Scheme 26

to ethers.[38] There appears to be a measure of reagent specificity, however; tributylphosphine, but not triethyl phosphite or triphenylphosphine, is successful in reducing $\mathrm{Bu^tSOR}$.[38] Trimethyl phosphite can be used with the more reactive allyl sulphenates,[39] but in this case deoxygenation rather than desulphurization occurs together with other reactions.

L. Preparation of Amides and Applications in Peptide Synthesis.—The reaction of triphenylphosphine with sulphenamide has been used to effect condensation of amino- and carboxy-groups in peptide synthesis (Scheme 27).[40] The reaction

$$\begin{array}{c}\mathrm{Ph_3P + R^1SNR^2_2 + R^3CO_2H \rightarrow \underbrace{Ph_3\overset{+}{P}SR^1 + R^3CO_2^-} + R^2_2NH} \\ \downarrow \\ \mathrm{R^2_2NCOR^3 + Ph_3PO \xleftarrow{R^2_2NH} Ph_3\overset{+}{P}OCOR^3 + R^1S^-}\end{array}$$

Scheme 27

was found to be more satisfactory when copper(II) carboxylate was used[40,41] to precipitate copper(II) mercaptide, thus eliminating an unwanted side-reaction of

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[38] D. H. R. Barton, G. Page, and D. A. Widdowson, *Chem. Comm.*, 1970, 1466.

[39] D. A. Evans and G. C. Andrews, *J. Amer. Chem. Soc.*, 1972, **94**, 3672.

[40] T. Mukaiyama, M. Ueki, H. Maruyama, and R. Matsueda, *J. Amer. Chem. Soc.*, 1968, **90**, 4490.

[41] M. Ueki, H. Maruyama, and T. Mukaiyama, *Bull Chem. Soc. Japan*, 1971, **44**, 1108.

the mercaptide with the starting sulphenamide [$R^1S^- + R^1SNR_2^2 \rightarrow R^1SSR^1 + R_2^2N^-$]. An extension of the reaction enabled the free amino-compound to be used with a disulphide (Scheme 28).[42a] The unwanted by-product in this case

$$\begin{tikzcd}
 & 2Ph_3P + 2R^1SSR^1 \rightarrow 2[Ph_3\overset{+}{P}SR^1\ {}^-SR^1] \arrow[d, "\begin{array}{l}2R^2CO_2H +\\ CuCl_2 + 2Base\end{array}"] \\
2R^3NHCOR^2 + Cu(SR^1)_2 + 2B{,}HCl & 2[Ph_3\overset{+}{P}OCOR^2\ R^1S^-] \arrow[l, "2R^3NH_2"']
\end{tikzcd}$$

Scheme 28

was the thiol ester R^2COSR^1, which was eliminated by the use of a soft metal halide such as AgCl or $HgCl_2$. In the application of this reaction to peptide synthesis, however, some racemisation occurred, *e.g.* in the reaction of *N*-benzoyl-L-leucine with ethylglycine. This was almost eliminated by the use of di-*p*-anisylmercury or anisylmercuric bromide. Racemisation was also avoided by the use of 2,2′-dipyridyl disulphide[42a,b] because, in this case, the released mercaptide exists in the thione form, hence no metal ion is required for its removal. Alternatively, the use of the mercuric salt of the water-soluble phosphine $Ph_2PC_6H_4SO_3H$-*p* eliminates racemisation in certain cases.[42c] The use of a water-soluble disulphide [$2I^-\ (Me_3NC_6H_4S)_2^{2+}$] has also been recommended.[43] The disulphide method has been adapted to a solid-phase peptide synthesis.[42d]

Triphenyl phosphite has been used in the synthesis of peptides[44a] and steroidal amides.[44b] In the presence of imidazole as a catalyst, good yields of unracemized material can be obtained using benzoxycarbonyl or t-butyloxycarbonyl protecting groups. Amides may also be prepared by activation of the acid component using mercuric chloride, pyridine, and mono-, di-, or tri-alkyl phosphites.[45]

M. Applications in Phosphorylation.—The reaction of triphenylphosphine with 2,2′-dipyridyl disulphide has also been utilized to phosphorylate alcohols and amines, pyrophosphates being formed as by-products (Scheme 29).[44c]

3 Deoxygenation Reactions

A. Reaction with Nitro- and Nitroso-compounds: Synthesis of Heterocycles.—Since the first report of the reaction in 1962,[46] use of the reductive cyclization of

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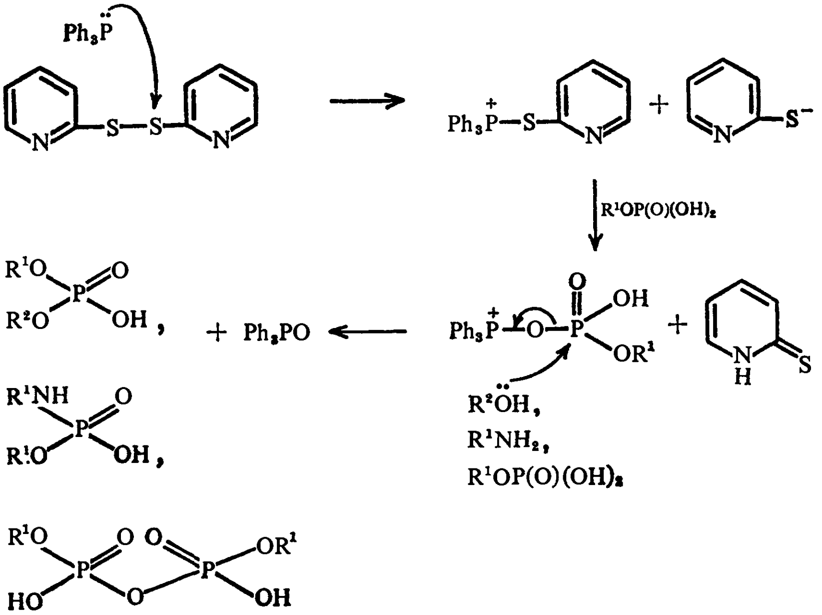
[42] (*a*) R. Matsueda, H. Maruyama, M. Ueki, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, 1971, **44**, 1373; (*b*) T. Mukaiyama, R. Matsueda, and M. Suzuki, *Tetrahedron Letters*, 1970, 1901; (*c*) T. Mukaiyama, K. Goto, R. Matsueda, and M. Ueki, *ibid.*, 1970, 5293; (*d*) T. Mukaiyama, R. Matsueda, and H. Maruyama, *Bull. Chem. Soc. Japan*, 1970, **43**, 1271.

[43] Yu. V. Mitin and G. P. Vlasov, *Doklady Akad. Nauk. S.S.S.R.*, 1968, **179**, 353.

[44] (*a*) Yu. V. Mitin and O. V. Glinskya, *Tetrahedron Letters*, 1969, 5267; *J. Gen. Chem.* (*U.S.S.R.*), 1971, **41**, 1152; (*b*) J. E. Herz and R. E. Mantecon, *Org. Prep. Proced. Int.*, 1972, **4**, 123; (*c*) T. Mukaiyama and M. Hashimoto, *Bull. Chem. Soc. Japan*, 1971, **44**, 196, 2284.

[45] N. Yamazaki and F. Higashi, *Bull. Chem. Soc. Japan*, 1973, **46**, 1236, 1239.

[46] J. I. G. Cadogan and M. Cameron-Wood, *Proc. Chem. Soc.*, 1962, 361.



Scheme 29

aromatic nitro-compounds by trialkyl phosphite and related compounds as a general route to five-, six-, and seven-membered nitrogen heterocycles has increased.[47]

In general the nitro-compound is allowed to boil under reflux, under nitrogen in a solvent, *e.g.* t-butylbenzene, with two equivalents or more of the phosphorus compound, usually triethyl phosphite. There is strong evidence in some cases[48a] that the reaction proceeds *via* a nitrene, although in others a nitrene precursor cannot be excluded.[*][48b,c]

$$(RO)_3P + ArNO_2 \rightarrow (RO)_3\overset{+}{P}\text{—O—N}(O^-)Ar \rightarrow (RO)_3PO + ArNO$$

$$(RO)_3P + ArNO \rightarrow (RO)_3\overset{+}{P}\text{—O—}\overset{-}{N}Ar \rightarrow (RO)_3PO + ArN\colon$$

$$\text{Overall: } 2(RO)_3P + ArNO_2 \rightarrow 2(RO)_3PO + ArN\colon$$

---

[*] For simplicity most mechanisms in the following section are discussed in terms of nitrenes, although this does not imply that the existence of a nitrene precursor has been established in all cases.

[47] (*a*) J. I. G. Cadogan, *Quart. Rev.*, 1968, **22**, 222; (*b*) *Synthesis*, 1969, 11; (*c*) *Accounts Chem. Res.*, 1972, **5**, 303.

[48] (*a*) J. I. G. Cadogan, and M. J. Todd, *J. Chem. Soc.* (*C*), 1969, 2808; (*b*) J. I. G. Cadogan and S. Kulik, *ibid.*, 1971, 2621; (*c*) P. K. Brooke, R. B. Herbert, and F. G. Holliman, *Tetrahedron Letters*, 1973, 761; (*d*) M. A. Armour, J. I. G. Cadogan, and D. S. B. Grace, unpublished results.

The intermediacy of the corresponding nitroso-compound is likely but can only be inferred because it reacts at least 10^6 times faster than the nitro-precursor under similar conditions.[49] In accord with this the rate of deoxygenation increases with increasing nucleophilicity of the phosphorus reagent:[48a,d]

$$\mathrm{Ph_3P < (Pr^iO)_3P \approx (EtO)_3P < (MeO)_3P < (EtO)_2PNEt_2 < EtOP(NEt_2)_2} \\ \mathrm{< (EtO)_2PMe \approx Ph_2POEt \approx (Et_2N)_3P < (Me_2N)_3P,}$$

although triethyl phosphite is the most widely used reagent on grounds of availability and ease of handling and work-up.

(i) *Formation of five-membered nitrogen-containing heterocycles.* Carbazoles,[46,50,51] carbolines,[50,52] indoles,[50,54] indazoles,[50,53,55] triazoles,[50,53,56] imidazoles,[57,58,62b] anthranils,[57,59] furoxans,[60] tetrazapentalenes,[50,61] and many related polycyclic derivatives[50,62,63] are produced in good to excellent yields (40–95%) if the nitrene or its precursor is generated from nitro-compounds having a suitable *ortho*-side-chain (Scheme 30). Given an option of forming a six- or a five-membered ring the nitrene always reacts to give the latter,[50] a steric preference which has been used diagnostically in structure determination. Benz-1,3-oxazoles have also been produced by this route from *o*-nitrophenyl benzoates, almost certainly, in this case, *via* the nitrene precursor $\mathrm{Ar\overset{-}{N}—O—\overset{+}{P}(OEt_3)}$.[64]

(ii) *Six-membered nitrogen-containing heterocycles. Formation of phenothiazines, dihydrophenazines, quinolines, and related compounds.* Despite the obvious ease with which the phosphite– nitro-group reaction proceeds to give five-membered nitrogen-containing heterocyclic compounds, it is not difficult to be persuaded on intuitive grounds that cyclization of 2-nitrophenyl phenyl sulphide to give the six-membered phenothiazine should also be easily achieved, as is the case (60% yield).[65] Closer examination of substituent effects, however, revealed that the reaction does *not* proceed *via* direct nitrene insertion into the C—H bond *ortho* to the sulphide link[66] but rather by the formation of a five-membered

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[49] P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 1963, 42.

[50] J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 1965, 4831.

[51] I. Puskas and E. K. Fields, *J. Org. Chem.*, 1968, **33**, 4237.

[52] T. Kametani, T. Yamanaka, and K. Ogasawara, *Chem. Comm.*, 1968, 996.

[53] J. I. G. Cadogan and R. J. G. Searle, *Chem. and Ind.*, 1963, 1434.

[54] R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604; *J. Amer. Chem. Soc.*, 1966, **88**, 3781; R. J. Sundberg and T. Yamazaki, *J. Org. Chem.*, 1967, **32**, 290.

[55] J. I. G. Cadogan and R. K. Mackie, *Org. Synthesis*, 1968, **48**, 113.

[56] B. M. Lynch, and Y. Y. Hung, *J. Heterocyclic Chem.*, 1965, **2**, 218.

[57] J. I. G. Cadogan, R. Marshall, D. M. Smith, and M. J. Todd, *J. Chem. Soc.* (*C*), 1970, 2441.

[58] H. Suschitzky and M. E. Sutton, *J. Chem. Soc.* (*C*), 1968, 3058.

[59] A. J. Boulton and A. Ur-Rahman, *Tetrahedron*, 1966, Suppl. 7, 49.

[60] A. J. Boulton, I. J. Fletcher, and A. R. Katritzky, *Chem. Comm.*, 1968, 62.

[61] J. C. Kauer and R. A. Carboni, *J. Amer. Chem. Soc.*, 1967, **89**, 2633.

[62] (*a*) K. E. Chippendale, B. Iddon, and H. Suschitzky, *J.C.S. Perkin I*, 1972, 2023; 1973, 125, 129; (*b*) R. Garner, G. V. Garner, and H. Suschitzky, *J. Chem. Soc.* (*C*), 1970, 825.

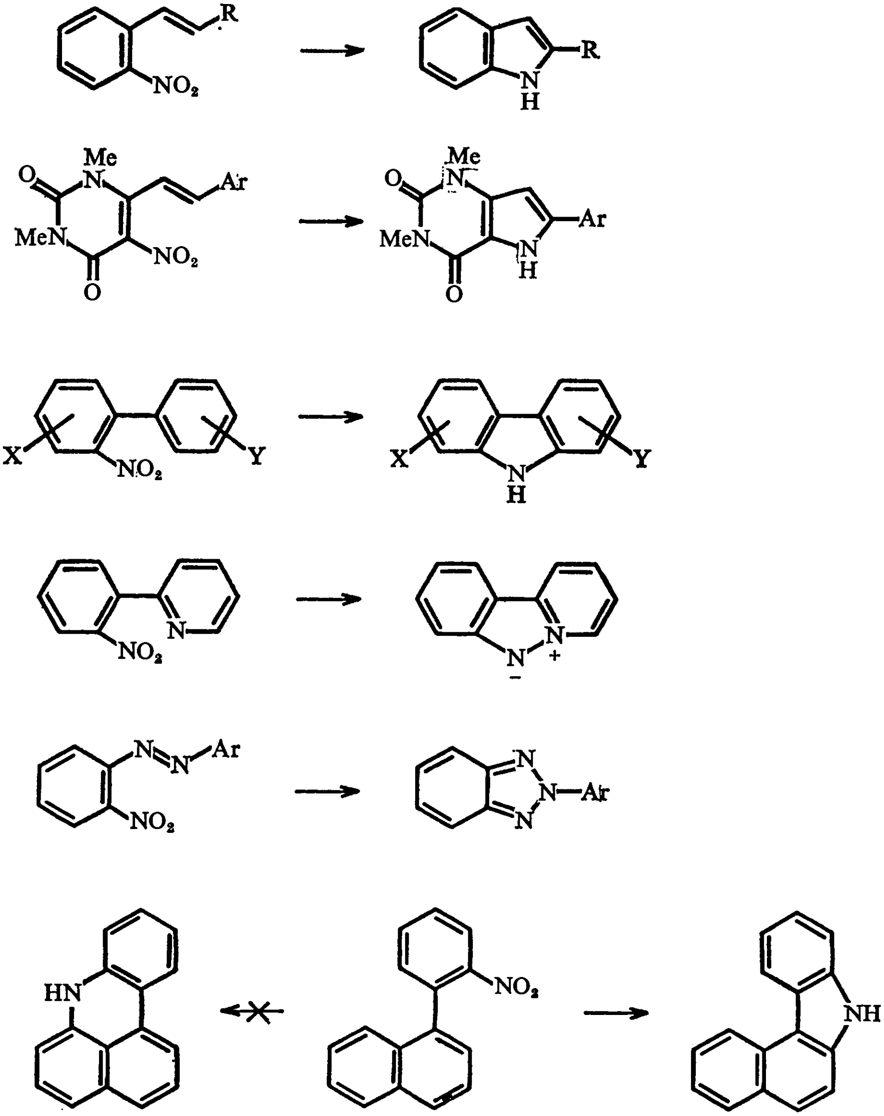
[63] D. G. Saunders, *Chem. Comm.*, 1969, 680.

[64] L. Leyshon and D. G. Saunders, *Chem. Comm.*, 1971, 1608.

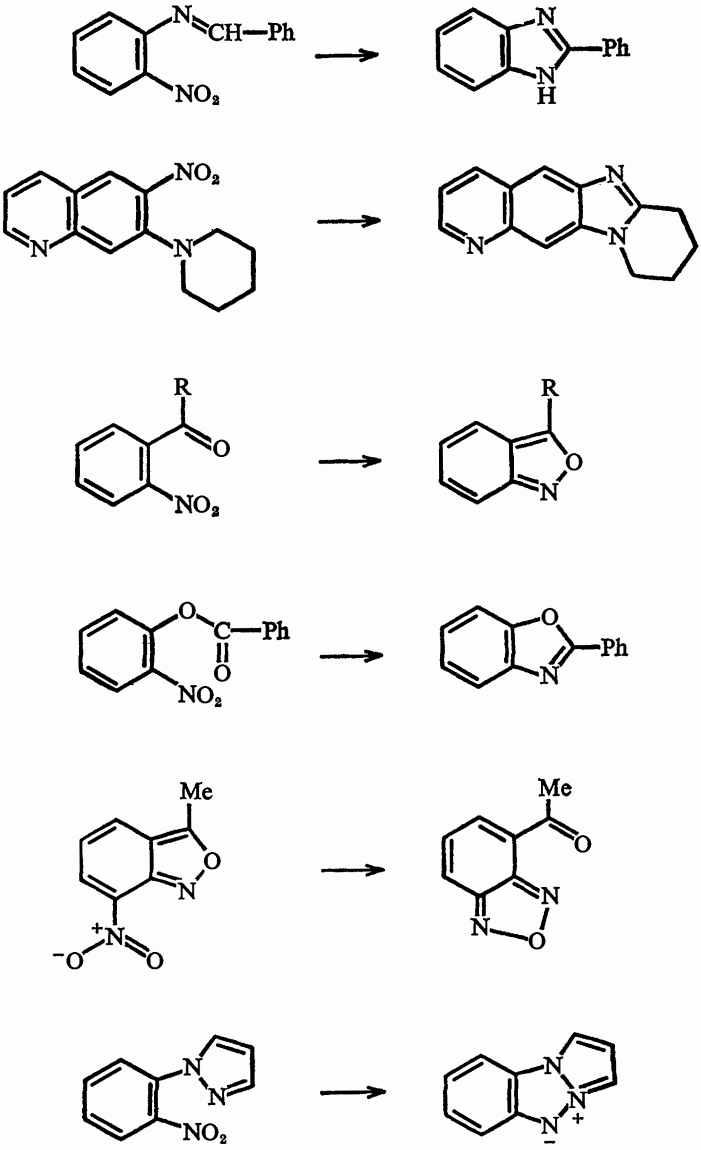
[65] J. I. G. Cadogan, R. K. Mackie, and M. J. Todd, *Chem. Comm.*, 1966, 491.

[66] J. I. G. Cadogan, S. Kulik, and M. J. Todd, *Chem. Comm.*, 1968, 736; J. I. G. Cadogan, S. Kulik, C. Thomson, and M. J. Todd, *J. Chem. Soc.* (*C*), 1970, 2437.

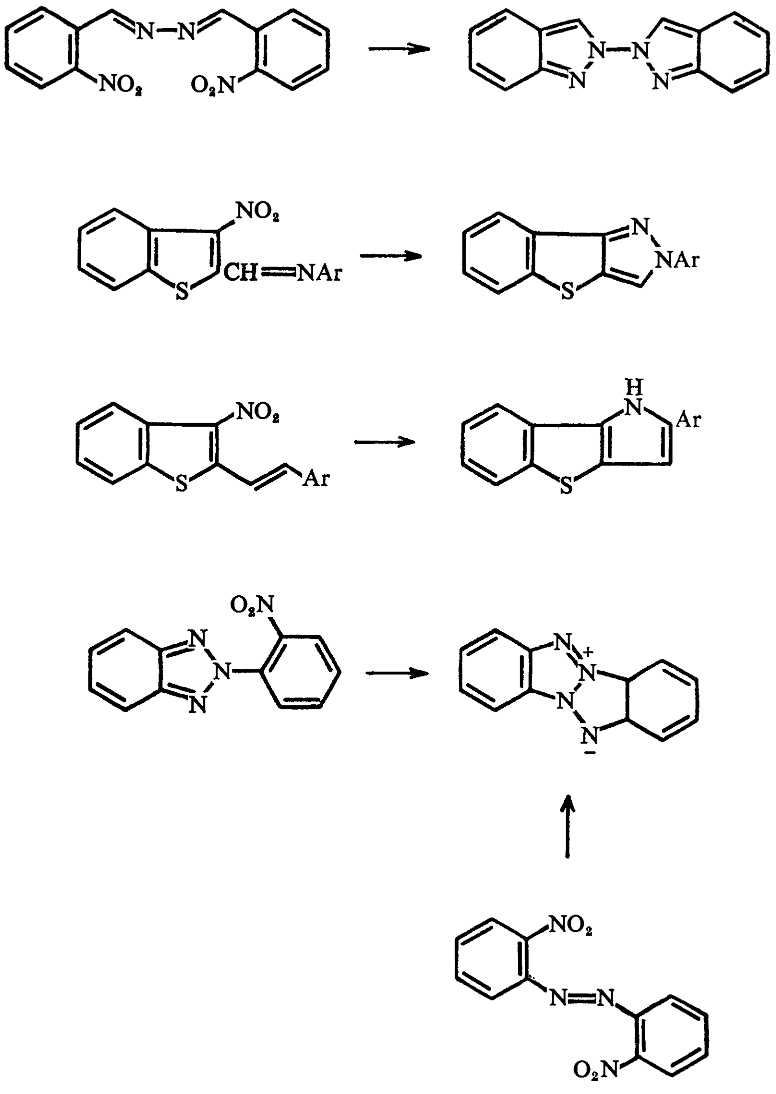
nitrogen-containing intermediate, thus conforming with pattern, which, after 1,2-sigmatropic shift of sulphur, followed by prototropy, leads to the 'rearranged product (Scheme 31). This stabilizing prototropic shift is impossible, however,



Scheme 30

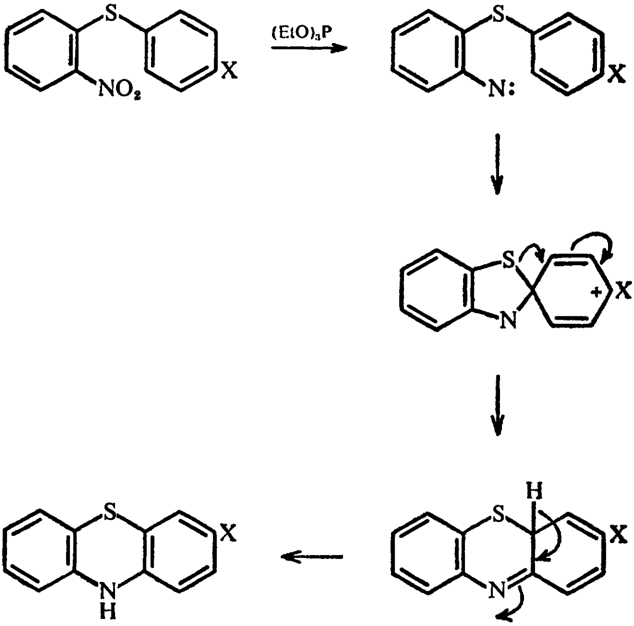


Scheme 30 continued



Scheme 30 continued

when both *ortho*-positions in the starting sulphide are blocked and under these conditions a series of intriguing molecular rearrangements arise. These include the formation of 5,11-dihydro-4-methyldibenzo[*b*,*e*][1,4]thiazepine from 2,6-dimethylphenyl 2-nitrophenyl sulphide, rather than the expected isomeric 10,11-dihydro-[*b*, *f*][1,4] product which might have been expected *via* direct



Scheme 31

nitrene insertion (Scheme 32).[48b] Also of interest are the monodemethoxylation and transmethoxylation reactions evident in the deoxygenation of 2,6-dimethoxyphenyl 2-nitrophenyl sulphide (Scheme 33).[48b] Perhaps most interesting of all is the isolation of 1,4a-diethoxycarbonyl-4a*H*-phenothiazine, which corresponds to the non-aromatic intermediate postulated in the above rearrangements, from 2,6-diethoxycarbonylphenyl 2-nitrophenyl sulphide (Scheme 34).[48b]

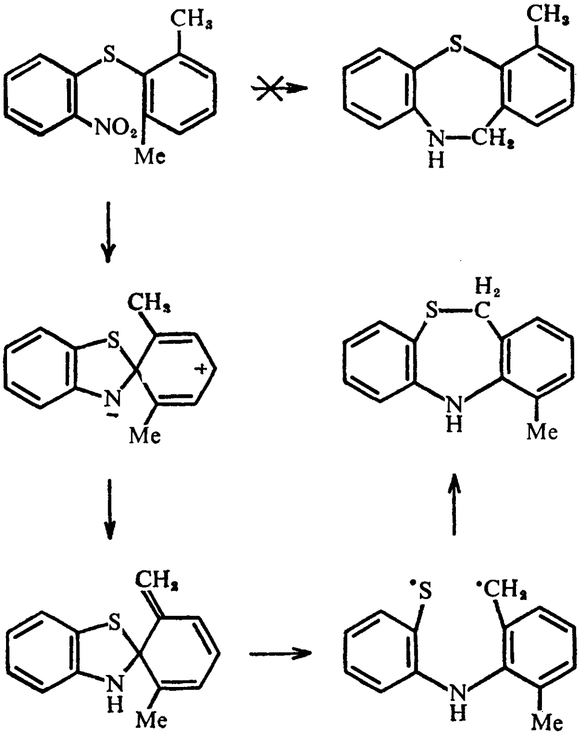
Formation of dihydrophenazines does not appear to occur *via* the phosphite–nitro-group reaction unless the vulnerable bridgehead N—H group is protected. Thus the N—H protected *N*-acetyl-2-nitro-2′-methylthiodiphenylamine reacted as would be expected on the basis of earlier work on related sulphur-bridged compounds (Scheme 31):[67] rearrangement of the spirodienyl intermediate gave both possible hydroaromatic species, one of which undergoes demethylthiolation while the other tautomerizes to give 1-thiomethyl-5-acetyl-5,10-dihydrophenazine (Scheme 35).

In contrast to the corresponding S- and N-bridged compounds, 2-nitrophenyl phenyl ethers give very low, if not negligible, yields of phenoxazines,[68] the major products being novel five-membered heterocycles containing N, O, and P as described below.[69]

[67] Y. Maki, T. Hosokami, and M. Suzuki, *Tetrahedron Letters*, 1971, 3509.

[68] J. I. G. Cadogan and P. K. K. Lim, *Chem. Comm.*, 1971, 1431.

[69] J. I. G. Cadogan, D. S. B. Grace, P. K. K. Lim, and B. S. Tait, *J.C.S. Chem. Comm.*, 1972, 520.



Scheme 32

The reductive cyclization reaction using triethyl phosphite has been used to convert 4-(2-nitrophenyl)pyridine into a benzo[*c*]naphthyridine,[70] formed in equal quantity with a carboline derivative (Scheme 36), the former indicating interaction with the adjacent ester carbonyl group. Similar cyclizations involving neighbouring carbonyl groups lead to oxazolo[5,4-*b*]quinolines,[71] quinolines,[72] isoindoloquinazolines,[73a] and 9,9-dihydropyrazoloquinolinyl phosphonates.[73b]

(iii) *Formation of five-membered* PNO *Heterocycles: the 1,3,2-benzoxazaphospholanes*. By-products found in the reductive cyclization of 2-nitroaryl aryl sulphides to phenothiazines (Scheme 31) included *N*-aryl-*N*-2-(*o*-thioethylphenyl)phosphoramidates,[48b] presumably arising by the route outlined in Scheme 37, wherein the key intermediate spirodienyl species, as well as rearranging to the phenothiazine,

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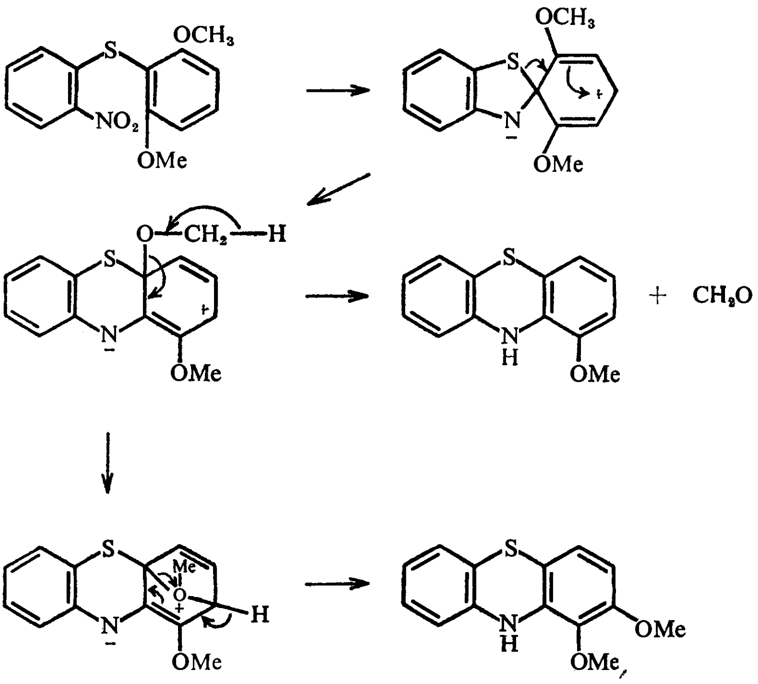
[70] T. Kametani, T. Yamanaka, and K. Ogasawara, *J. Chem. Soc.* (*C*), 1969, 138.

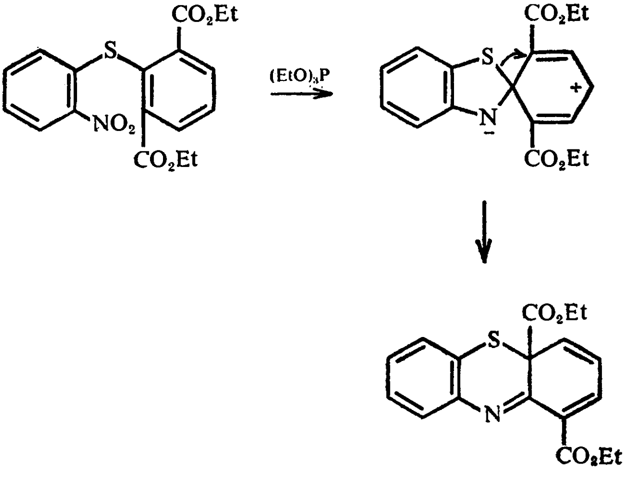
[71] T. Kametani, T. Yamanaka, and K. Ogasawara, *Chem. Comm.*, 1968, 786.

[72] T. Kametani, K. Nyu, T. Yamanaka, H. Yagi, and K. Ogasawara, *Chem. and Pharm. Bull.* (*Japan*), 1969, **17**, 2093.

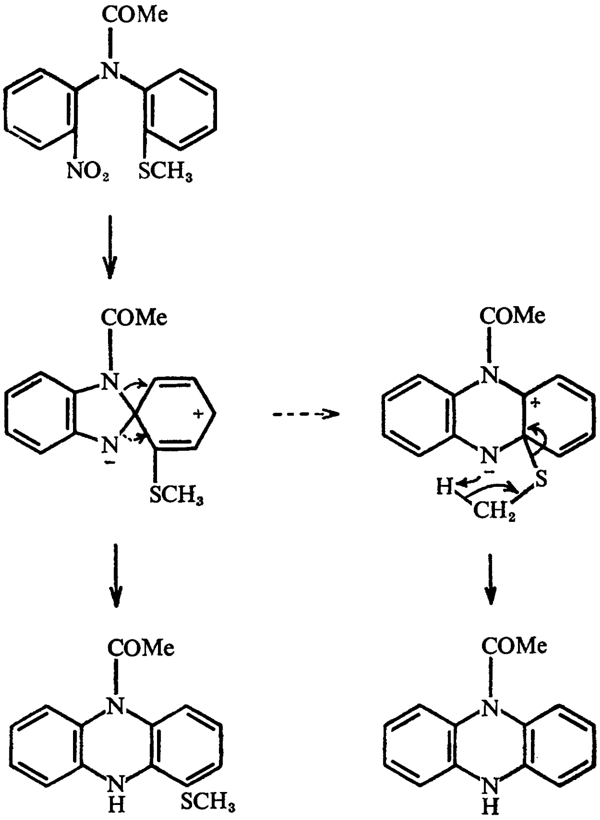
[73] (*a*) T. Kametani, K. Nyu, T. Yamanaka, and S. Takano, *J. Heterocyclic Chem.*, 1971, **8**, 1071; (*b*) T. Nishiwaki, G. Fukuhara, and T. Takahashi, *J.C.S. Perkin I*, 1973, 1606.



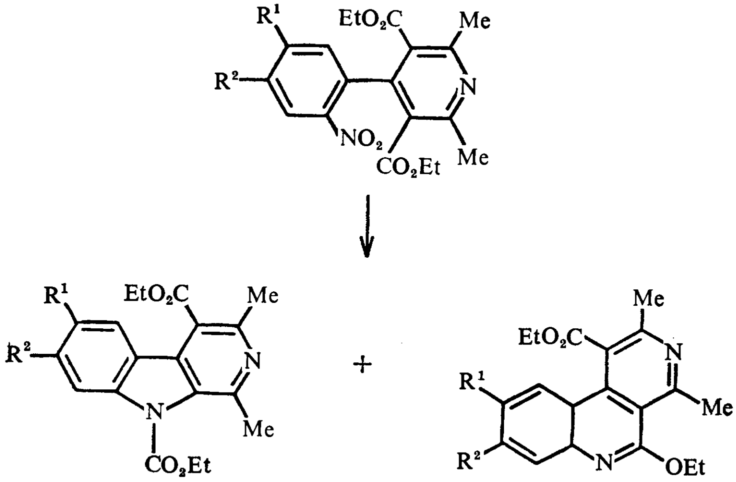
Scheme 33



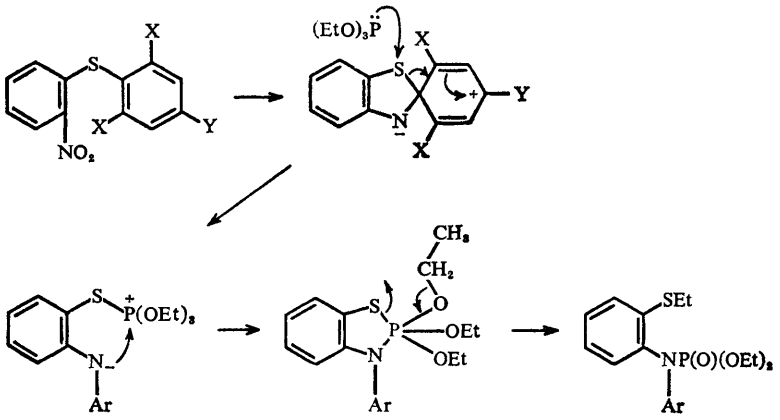
Scheme 34



Scheme 35



Scheme 36



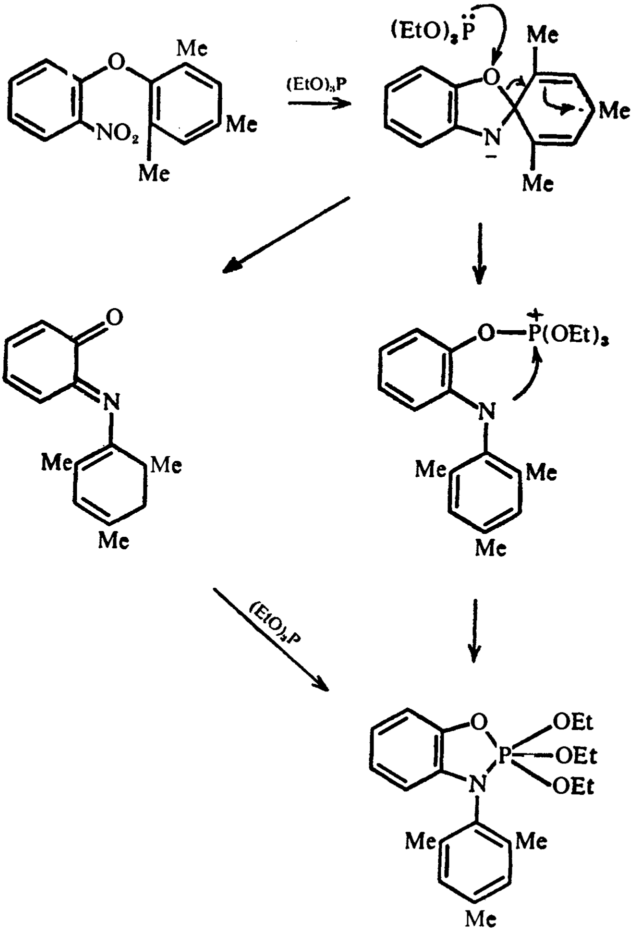
X = Y = Me or X = MeO, Y = H ; Ar = 2,6-X_2-4-Y-C_6H_2

Scheme 37

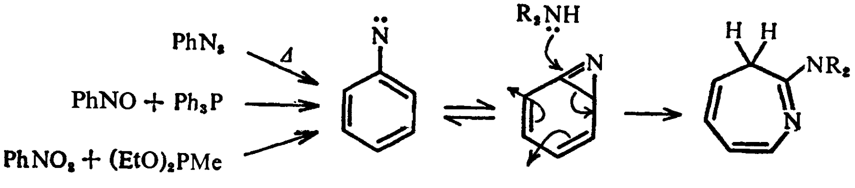
also reacts with excess triethyl phosphite. In these cases the postulated intermediate five-membered PNS heterocycle was not detected, but in the corresponding reactions using 2-nitroaryl aryl ethers excellent yields (up to 95%) of the corresponding oxygen derivatives were obtained (Scheme 38).[69,74] The difference in stability between the S and O five-membered derivatives lies in the great nucleophilicity of the sulphur atom. The new heterocycles so formed are of interest because the phosphorus atom is fully five-co-ordinate and has trigonal-bipyramidal geometry.

(iv) *Formation of seven-membered nitrogen heterocycles:* 3H-*azepines*. Ring expansion of aryl azides by thermolysis in the presence of amines to give 3*H*-azepines is well known,[75] and is generally considered to proceed *via* the aryl-nitrene–7-azabicyclo[4,1,0]hepta-2,4,6-triene equilibrium[75–77] (Scheme 39). In accord with this and the postulate[49] that nitrenes are formed in the deoxygenation of nitroso-arenes with tervalent phosphorus compounds, the reaction of nitrosobenzene with triphenylphosphine in diethylamine gives 2-diethylamino-3*H*-azepine in 60% yield; yields with other amines are variable[78] (Scheme 39). Higher yields are obtained by the reaction of the parent nitrobenzene with diethyl methylphosphonite [$(EtO)_2PMe$] in diethylamine,[48a,79] a reaction which is fairly general.[80,81] The only other nucleophile besides amines which has so

[74] J. I. G. Cadogan, D. S. B. Grace, and B. S. Tait, unpublished observations.
[75] W. Lwowski, 'Nitrenes,' Interscience, New York, 1970.
[76] R. Huisgen, D. Vossius, and M. Appl, *Angew. Chem.*, 1955, 67, 756.
[77] W. von E. Doering and R. A. Odum, *Tetrahedron*, 1966, **22**, 81.
[78] M. Brenner and R. A. Odum, *J. Amer. Chem. Soc.*, 1966, **88**, 2074.
[79] J. I. G. Cadogan and M. J. Todd, *Chem. Comm.*, 1967, 178.
[80] J. I. G. Cadogan and H. McWilliam, unpublished observations.
[81] F. R. Atherton and R. W. Lambert, *J.C.S. Perkin I*, 1973, 1079.

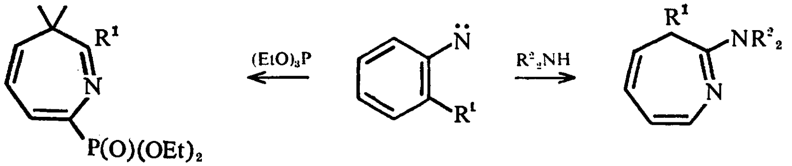


Scheme 38



Scheme 39

far been found to lead to significant ring expansion in these reactions is the tervalent phosphorus reagent itself,[82] and in these cases we have the intriguing observation that the position of substitution is different (Scheme 40). The mechanism is clearly not yet fully understood, and the possible intermediacy of 1*H*-azepines cannot be excluded.[83]



Scheme 40

B. Reactions with Peroxides, Hydroperoxides, Peresters, and Ozonides.—Diacyl peroxides, such as benzoyl, acetyl, or malonyl peroxides, are rapidly and quantitatively deoxygenated *via* nucleophilic displacement on peroxidic oxygen to the corresponding anhydrides in the presence of triphenylphosphine[84,85] or triethyl phosphite.[86] The reaction is so fast and reliable that it can be used as a monitor to study rates of decomposition of diacyl peroxides.[86b] Peroxydicarbonates[87] and peresters, such as t-butyl perbenzoates,[88] are similarly reduced to the corresponding phosphine oxide and dialkylcarbonic anhydride or ester, respectively. Alkyl hydroperoxides are also very rapidly reduced to the corresponding alcohols,[89] again *via* an ionic mechanism, and this provides a very simple method for deperoxidization of contaminated ethers, and a one-step synthesis of steroidal tertiary α-ketols.[90] In the latter the first step is autoxidation of the ketone by oxygen, followed by deoxygenation of the hydroperoxide (Scheme 41).

The powerful reducing effect of phosphites on hydroperoxide has led to an investigation of their use as antioxidants for the oxidation of cumene. In these

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[82] J. I. G. Cadogan, D. J. Sears, D. M. Smith, and M. J. Todd, *J. Chem. Soc.* (*C*), 1969, 2813; J. I. G. Cadogan and R. K. Mackie, *ibid.*, 1969, 2819; R. J. Sundberg, B. P. Das, and R. H. Smith, *J. Amer. Chem. Soc.*, 1969, **91**, 658.

[83] R. J. Sundberg, S. R. Suter, and M. Brenner, *J. Amer. Chem. Soc.*, 1972, **94**, 513.

[84] F. Challenger and V. K. Wilson, *J. Chem. Soc.*, 1927, 209.

[85] M. A. Greenbaum, D. B. Denney, and A. K. Hoffmann, *J. Amer. Chem. Soc.*, 1956, **78**, 2563; D. B. Denney and M. A. Greenbaum, *ibid.*, 1957, **79**, 979; W. Adam and J. W. Kiehl, *J. C. S. Chem. Comm.*, 1972, 797.

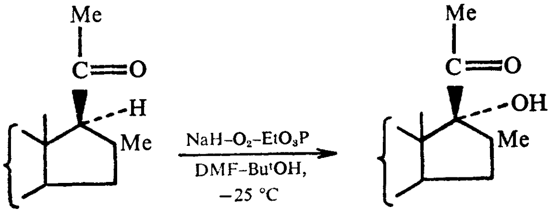
[86] (*a*) P. Bunyan, A. J. Burn, and J. I. G. Cadogan, *J. Chem. Soc.*, 1963, 1527; (*b*) D. L. Brydon and J. I. G. Cadogan, *J. Chem. Soc.*, (*C*), 1968, 819.

[87] W. Adam and A. Rios, *J. Org. Chem.*, 1971, **36**, 407.

[88] D. B. Denney, W. F. Goodyear, and B. Goldstein, *J. Amer. Chem. Soc.*, 1961, **83**, 1726.

[89] (*a*) C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, 1959, **81**, 1243; (*b*) L. Horner and W. Jurgeleit, *Annalen*, 1955, **591**, 138; (*c*) D. B. Denney, W. F. Goodyear, and B. Goldstein, *J. Amer. Chem. Soc.*, 1960, **82**, 1393.

[90] J. N. Gardner, F. E. Carlon, and O. Gnoj, *J. Org. Chem.*, 1968, **33**, 3294.



Scheme 41

cases the mechanism is complicated by the intervention of free-radical processes in addition to ionic steps.[91]

In contrast to the foregoing ionic reactions, triphenylphosphine and trialkyl phosphites react with di-t-butyl peroxide or di-α-cumyl peroxide *via* homolytic processes involving alkoxyl radicals,[92] although it should be noted that the simpler diethyl peroxide reacts with cyclic phosphites to give the corresponding cyclic phosphoranes.[93] In yet another differing case ascaridole is readily deoxygenated to give *p*-cymene.[94]

The former reaction of alkoxyl radicals with phosphites has been developed to provide a route to steroidal phosphates, using the photolysis of steroidal nitrites (RONO) in tri-isopropyl phosphite (Scheme 42),[95] from which it appears

$$\mathrm{R^1ONO} \rightarrow \mathrm{R^1O}\cdot \xrightarrow{(\mathrm{Pr^iO})_3\mathrm{P}} \mathrm{R^1O\dot{P}(OPr^i)_3}$$
$$\downarrow$$
$$\mathrm{R^1OP(O)(OPr^i{}_2)} + \mathrm{Pr^i}\cdot$$

Scheme 42

that β-scission from the intermediate phosphoranyl radical, in these cases, proceeds largely with retention of the massive steroidal fragment.

Many examples of the very valuable reduction of ozonides by tervalent phosphorus compounds have been reported, *e.g.* Scheme 43,[89b,96,97] the reaction

[91] K. J. Humphris and G. Scott, *J.C.S. Perkin II*, 1973, 826, 831.

[92] C. Walling, O. H. Basedow, and E. S. Savas, *J. Amer. Chem. Soc.*, 1960, **82**, 2181; P. J. Krusic, W. Mahler, and J. K. Kochi, *ibid.*, 1972, **94**, 6033; A. G. Davies, D. Griller, and B. P. Roberts, *J.C.S. Perkin II*, 1972, 993.

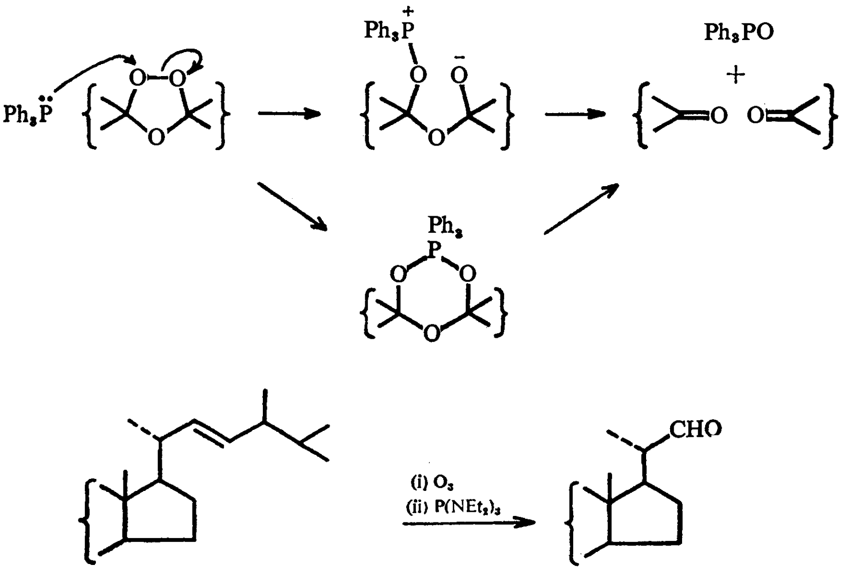
[93] D. B. Denney, D. Z. Denney, C. D. Hall, and K. L. Marsi, *J. Amer. Chem. Soc.*, 1972, **94**, 245.

[94] T. Kametani and K. Ogasawara, *Chem. and Ind.*, 1968, 1772.

[95] D. H. R. Barton, J. T. Bentley, R. H. Hesse, F. Mutterer, and M. M. Pechet, *Chem. Comm.*, 1971, 912.

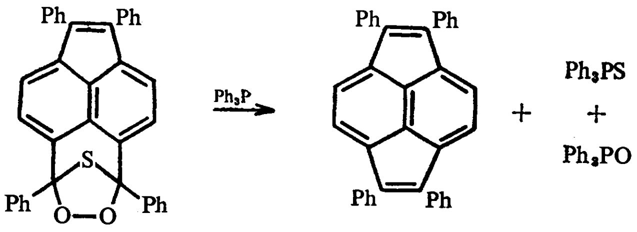
[96] J. Carles and S. Fliszár, *Canad. J. Chem.*, 1970, **48**, 1309; 1972, **50**, 2552.

[97] J. J. Pappas, W. P. Keaveney, M. Berger, and R. V. Rush, *J. Org. Chem.*, 1968, **33**, 787; A. Furlenmeier, A. Furst, A. Langemann, G. Waldvogel, P. Hocks, U. Kerb, and R. Wiechert, *Helv. Chim. Acta*, 1967, **50**, 2387; W. S. Knowles and Q. E. Thompson, *J. Org. Chem.*, 1960, **25**, 1031.



Scheme 43

probably proceeding *via* nucleophilic attack on oxygen to give a phosphorane[96] rather than a dipolar intermediate. Related reactions with thio-ozonides, on the other hand, proceed *via* attack on sulphur and subsequent formation of a carbon–carbon bond (Scheme 44).[98]



Scheme 44

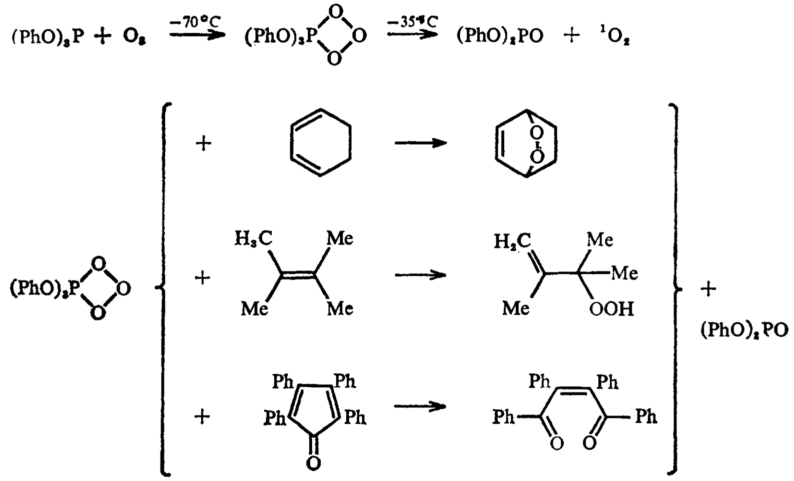
C. Reactions with Ozone: the Reagent (PhO)$_3$PO$_3$.—Triarylphosphines[99] and trialkyl and triaryl phosphites[100] all react readily with ozone to give excellent

[98] J. M. Hoffmann, jun., and R. H. Schlessinger, *Tetrahedron Letters*, 1970, 797.

[99] L. Horner, H. Schaefer, and W. Ludwig, *Chem. Ber.*, 1958, **91**, 75.

[100] Q. E. Thompson, *J. Amer. Chem. Soc.*, 1961, **83**, 845.

yields of the corresponding P=O compounds. In the case of triphenyl phosphite a 1:1 adduct $(PhO)_3PO_3$ can be isolated which is stable at —70 °C but which decomposes cleanly to triphenyl phosphate and oxygen at —35 °C (Scheme 45).



Scheme 45

The principle of conservation of spin suggests that the oxygen so evolved should have singlet multiplicity, and this proved to be so in many, but not all, cases.[101] Triphenyl phosphite ozonide is therefore a reagent of considerable value, and although a detailed discussion of this *quinque*valent reagent is strictly outside the scope of this Review, a brief outline of some of its reactions[102] is given in Scheme 45.

D. Reduction of Epoxides to Alkenes.—Both triethyl phosphite[5a] and triphenylphosphine[5b] smoothly reduce epoxides to the corresponding alkene. In contrast to the related desulphurization of thiirans[4] the reaction is not stereospecific. Boskin and Denney[6] showed that tributylphosphine converted *trans*-2,3-epoxybutane into a mixture of *cis*- (72%) and *trans*- (28%) but-2-ene, whereas the *cis*-epoxide gave a ratio of 19:81 *cis*- to *trans*-isomer. This suggests that there is a reaction, in the former case say, *via* nucleophilic attack on carbon to given an *erythro*-betaine, of the type familiar from the Wittig reaction; rotation and bond formation and cleavage, as in Scheme 46, then account for the formation of *cis*-but-2-ene. The *trans*-isomer is accounted for on the basis of the dissociation of the betaine into aldehyde and ylide, which can then recombine to give both

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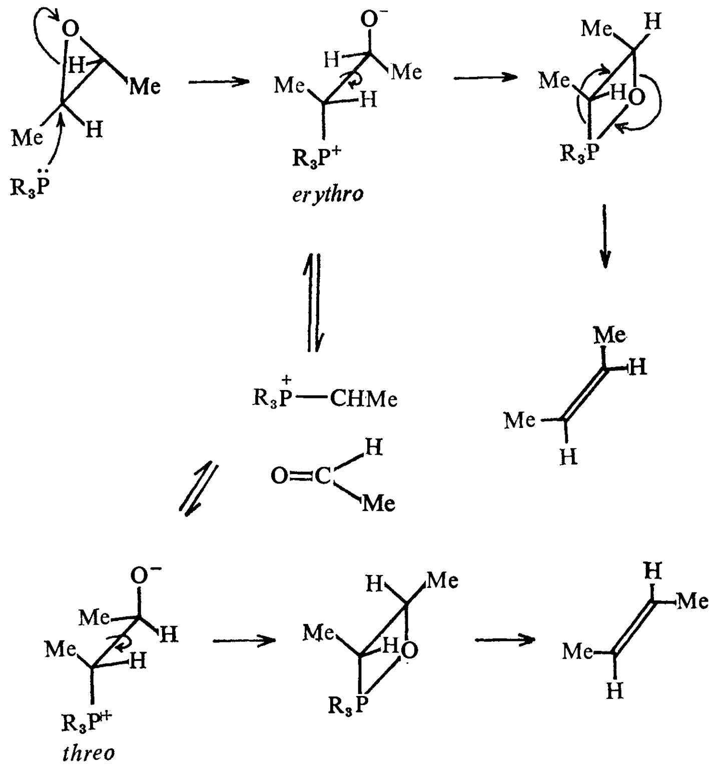
[101] R. W. Murray and M. L. Kaplan, *J. Amer. Chem. Soc.*, 1968, **90**, 537; P. B. Bartlett, and G. D. Mendenhall, *ibid.*, 1970, **92**, 210; L. M. Stevenston and D. E. McClure, *ibid.*, 1973, **95**, 3074; S. D. Razumovskii and G. D. Mendenhall, *Canad. J. Chem.*, 1973, **51**, 1257.

[102] R. W. Murray, J. W. P. Ling, and M. L. Kaplan, *Ann. New York Acad. Sci.*, 1970, **171**, 121

threo- and *erythro*-betaines, the former giving rise to the *cis*-olefin on elimination. The method, although useful, is therefore limited by the lack of stereospecificity.



Scheme 46

E. Deoxygenation of Amine *N*-Oxides, Nitrile Oxides, Isocyanates, Azoxy-compounds, and Nitrites.—Tervalent phosphorus compounds deoxygenate amine *N*-oxides to the corresponding amines. They are particularly useful in the heterocyclic series because, in general, deoxygenation proceeds smoothly without affecting other substituents in the ring.[103] Phosphorus trihalides are very reactive

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[103] A. R. Katritzky and J. M. Lagowski, 'Chemistry of the Heterocyclic *N*-Oxides,' Academic Press, New York, 1971.

in this respect[104] and, in general, substitution of halogen atoms by organic groups tends to reduce the activity of the reagent. The ease of reduction of pyridine *N*-oxide decreases in the order $PCl_3 > PhPCl_2 > Ph_2PCl \gg (PhO)_3P > (EtO)_3P \gg Ph_3P > Bu_3P > Et_2PPh$,[105] while electron-releasing groups in the pyridine ring increase the reaction rate towards a given phosphorus reagent.[106] This suggests that nucleophilic attack by the N—O⁻ function on the tervalent phosphorus atom is occurring, but the situation is reversed in the case of deoxygenation of furoxans to furazans.[107] Most deoxygenations proceed smoothly[103] but in the case of the reaction of 2-nitropyridine *N*-oxide with triethyl phosphite, nucleophilic displacement of the nitro-group also occurs, to give diethyl 2-pyridylphosphonate,[108] thus paralleling the corresponding reaction with *o*-dinitrobenzene.

As might be expected, nitrile oxides (RCNO), isocyanates (RNCO), and azoxy-compounds [ArNN(O)Ar] are all reduced by phosphites or phosphines to the corresponding cyanides,[109] isocyanides,[110] and azo-compounds.[50,110,111] Alkyl nitrites are also reduced but the major reaction is conversion into the corresponding alcohol, there being no evidence for the intermediacy of the hoped-for alkoxynitrene.[112]

4 Reactions with Carbonyl Compounds

Only some of the many reactions of tervalent phosphorus compounds with carbonyl compounds are useful in general organic synthesis as opposed to the production of organophosphorus compounds. Some involve the formation of a quinquecovalent phosphorus reagent which is then used in a subsequent process. Of these the most important are undoubtedly the oxyphosphoranes.

A. Conversion of Aromatic Aldehydes, Ketones, and Anhydrides into Arylated Olefin Oxides and Olefins.—Aromatic aldehydes may be converted into the corresponding stilbene oxides under relatively mild conditions using $(Me_2N)_3P$.[113] Similarly, but under more forcing conditions (180 °C), benzaldehyde reacts with the anion of diphenylphosphine oxide to give a good yield (85%) of *cis*- and *trans*-stilbene oxides.[114] There is no direct evidence of carbene intervention in these reactions and it is more likely that wholly ionic routes are followed. In

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[104] E. Ochiai, *J. Org. Chem.*, 1953, **18**, 534.

[105] F. Ramirez and A. M. Aguair, Amer. Chem. Soc. Abstracts of 134th Meeting 1958, p. 42N.

[106] T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 1964, 2319.

[107] C. B. Grundmann, *Chem. Ber.*, 1964, **97**, 575.

[108] J. I. G. Cadogan, D. J. Sears, and D. M. Smith, *J. Chem. Soc. (C)*, 1969, 1314.

[109] C. Grundmann and H.-D. Frommeld, *J. Org. Chem.*, 1965, **30**, 2077.

[110] T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, 1962, **27**, 3651.

[111] L. Horner and H. Hoffman, *Angew. Chem.*, 1956, **68**, 473; W. Luttke and V. Schabacker, *Annalen*, 1965, **687**, 236.

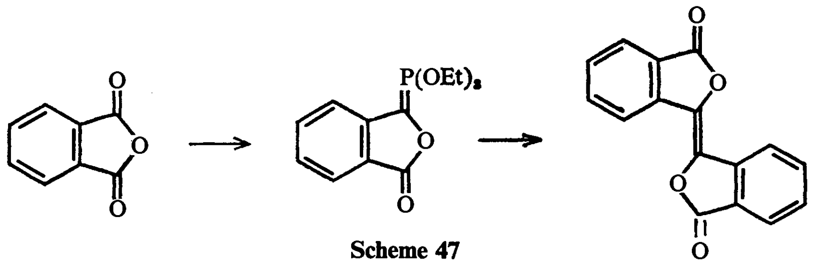
[112] J. H. Boyer and J. D. Woodyard, *J. Org. Chem.*, 1968, **33**, 3329.

[113] V. Mark, *J. Amer. Chem. Soc.*, 1963, **85**, 1884; *Org. Synth.*, 1966, **46**, 42; F. Ramirez, S. B. Bhatia, and C. P. Smith, *Tetrahedron*, 1967, **23**, 2067; F. Ramirez, A. S. Gulati, and C. P. Smith, *J. Org. Chem.*, 1968, **33**, 13.

[114] W. M. Horspool, S. T. McNeilly, J. A. Miller, and I. M. Young, *J.C.S. Perkin I*, 1972, 1113.

other cases, notably furfural,[115] benzophenone,[116] and acyl-ferrocenes,[114,117] olefins are formed directly, but usually in low yields.

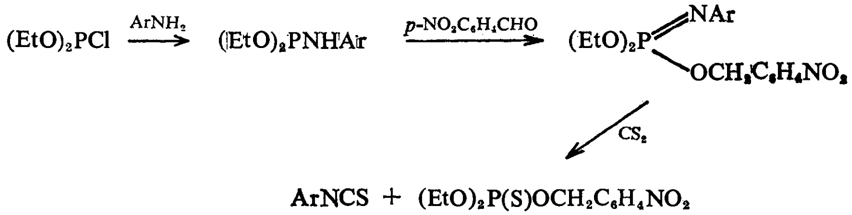
In a most interesting related reaction, phthalic anhydride is readily converted into 3,3′-biphthalidylidene (70%),[118a] again probably *via* a non-carbene route[118b] (Scheme 47).



Scheme 47

B. Formation of Enamines.—In contrast to the foregoing reactions of aromatic ketones, certain aliphatic ketones, *e.g.* cyclohexanone, react with $(Me_2N)_3P$ to give enamines.[119] Acetone, butan-2-one, and propanal give normal aldol condensates.

C. Formation of Aryl Isothiocyanates.—The aryl group of the isothiocyanate ultimately produced in this reaction originates in the phosphorus reagent, a diethyl *N*-arylamidite.[120] This, on reaction with *p*-nitrobenzaldehyde, gives a phosphorimidate and hence the aryl isothiocyanate by subsequent reaction with carbon disulphide (Scheme 48).



$$(EtO)_2PCl \xrightarrow{ArNH_2} (EtO)_2PNHAr \xrightarrow{p\text{-}NO_2C_6H_4CHO} (EtO)_2P{\overset{\displaystyle \nearrow NAr}{\underset{\displaystyle \searrow OCH_2C_6H_4NO_2}{}}} \xrightarrow{CS_2} ArNCS + (EtO)_2P(S)OCH_2C_6H_4NO_2$$

Scheme 48

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[115] B. A. Arbusov and V. M. Zoroastrova, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk,* 1960, 1030 (*Chem. Abs.,* 1960, **54,** 24627).

[116] A. C. Poshkus and J. E. Herweh, *J. Org. Chem.,* 1964, **29,** 2567; I. A. Degen, D. G. Saunders, and B. P. Woodford, *Chem. and Ind.,* 1969, 267.

[117] P. L. Pauson and W. E. Watts, *J. Chem. Soc.,* 1963, 2990.

[118] (*a*) F. Ramirez, H. Yamanaka, and O. H. Basedow, *J. Amer. Chem. Soc.,* 1961, **83,** 173; (*b*) C. W. Bird and D. Y. Wong, *Chem. Comm.,* 1969, 932.

[119] R. Burgada and J. Roussel, *Bull. Soc. chim. France,* 1970, 192.

[120] A. N. Pudovik, E. S. Batyeva, and V. D. Nesterenko, *Izvest. Akad. Nauk. S.S.S.R., Ser khim,* 1972, 501 (*Chem. Abs.,* 1972, **77,** 88604).

D. Formation of Oxophosphoranes.—α-Diketones condense with trialkyl phosphites and other tervalent reagents to give cyclic oxyphosphoranes.[121] In certain cases simple monocarbonyl compounds in 2:1 ratio also give oxyphosphoranes. Extensive work on this reaction by Ramirez' school has shown that these compounds are very versatile reagents in organic synthesis.[121,122] These quinquecovalent compounds of phosphorus, strictly, are outside the scope of this review but a few examples of their reactions are given in Scheme 49.[121–124] Not all oxyphosphoranes can be isolated and in some cases their intermediacy has been assumed, as in the reaction of triethyl phosphite with benzil in the presence of copper sulphate, for example. This reaction is believed to proceed *via* a carbenoid species (Scheme 50) on the basis of the formation of oxazole derivatives when the reaction is carried out in the presence of phenyl isocyanate and dicyclohexylcarbodi-imide.[125] In the absence of copper sulphate, diphenylketen dimer and diphenylacetylene are produced,[126] the latter presumably *via* deoxygenation of diphenylketen to a carbene intermediate which then rearranges to the alkyne (Scheme 51).[127] Closely related to this is the postulated[128] formation of cyanophenylcarbene by photolysis of the oxyphosphorane formed from triethyl phosphite and benzoyl cyanide.[129] The carbene was trapped as a cyclopropane.

5 Reactions with Halogens and Halogen-containing Compounds

A. With Halogens and Hydrogen Halides: Formation of Alkyl Halides.—The reaction of trialkyl phosphites with halogens to give the corresponding phosphorohalidate and an alkyl halide has been known for many years.[130] A recent modification has been used for the preparation of alkyl iodides.[131] The preparation of optically active alkyl halides by reaction of phosphites, phosphonites, phosphinites, and dialkyl phosphonates has been studied extensively by Hudson *et al.*[132] (Scheme 52). The reaction of phosphines with halogens gives rise to 1:1 adducts

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[121] (*a*) F. Ramirez, *Accounts Chem. Res.*, 1968, **1**, 168; (*b*) *Bull. Soc. chim. France*, 1966, 2443; (*c*) *Pure Appl. Chem.*, 1964, **9**, 337; (*d*) F. Ramirez, G. V. Loewengart, E. A. Tsolis, and K. Tasaka, *J. Amer. Chem. Soc.*, 1972, **94**, 3531.

[122] (*a*) F. Ramirez, H. J. Kugler, and C. P. Smith, *Tetrahedron*, 1968, **24**, 3153; (*b*) F. Ramirez, A. V. Patwardhan, N. B. Desai, N. Ramanathan, and C. V. Greco, *J. Amer. Chem. Soc.*, 1963, **85**, 3056; (*c*) F. Ramirez, S. B. Bhatia, C. D. Telefus, and C. P. Smith, *Tetrahedron*, 1969, **25**, 771; (*d*) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, 1967, **89**, 3030.

[123] F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Amer. Chem. Soc.*, 1962, **84**, 1317.

[124] T. Mori, T. Nakahara, and H. Nozaki, *Canad. J. Chem.*, 1969, **47**, 3651.

[125] T. Mukaiyama and T. Kumamoto, *Bull. Chem. Soc. Japan*, 1966, **39**, 879.

[126] T. Mukaiyama, H. Nambu, and T. Kumamoto, *J. Org. Chem.*, 1964, **29**, 2243.

[127] T. Mukaiyama, H. Nambu, and M. Okamato, *J. Org. Chem.*, 1962, **27**, 3651.

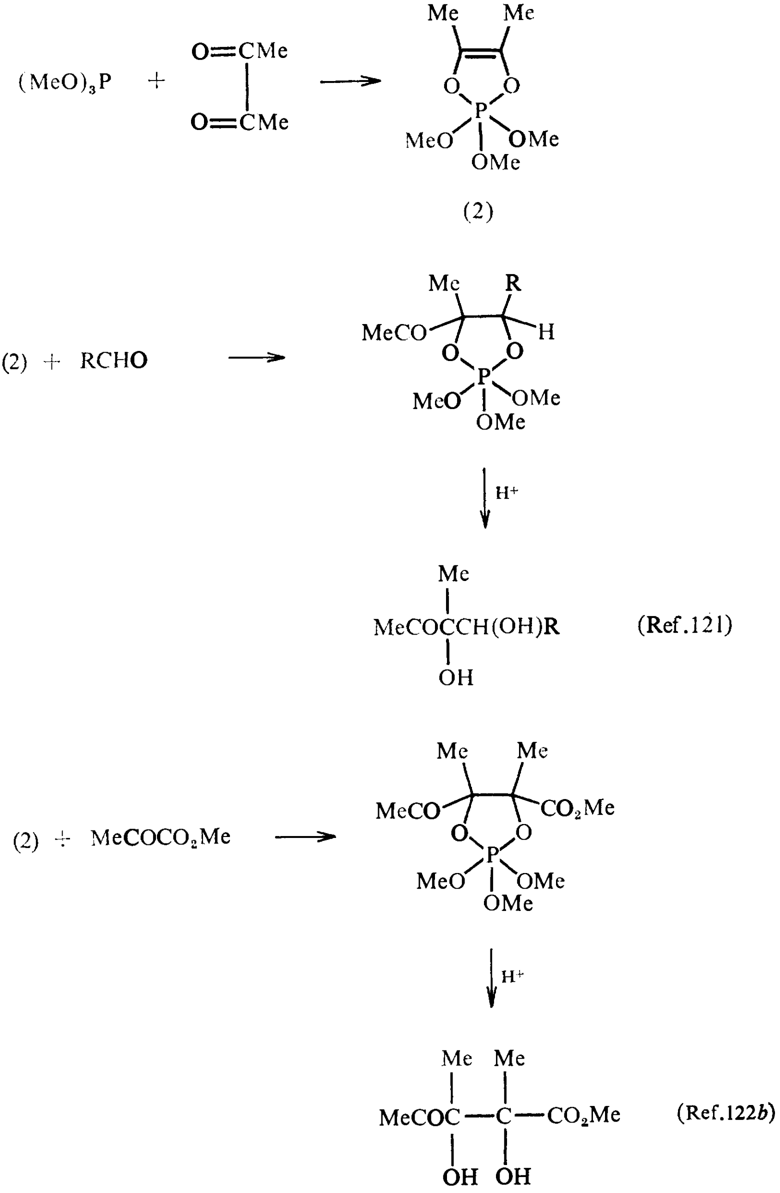
[128] P. Petrellis and G. W. Griffin, *Chem. Comm.*, 1968, 1099.

[129] T. Mukaiyama, I. Kuwajima, and K. Ohno, *Bull. Chem. Soc. Japan*, 1965, **38**, 1954.

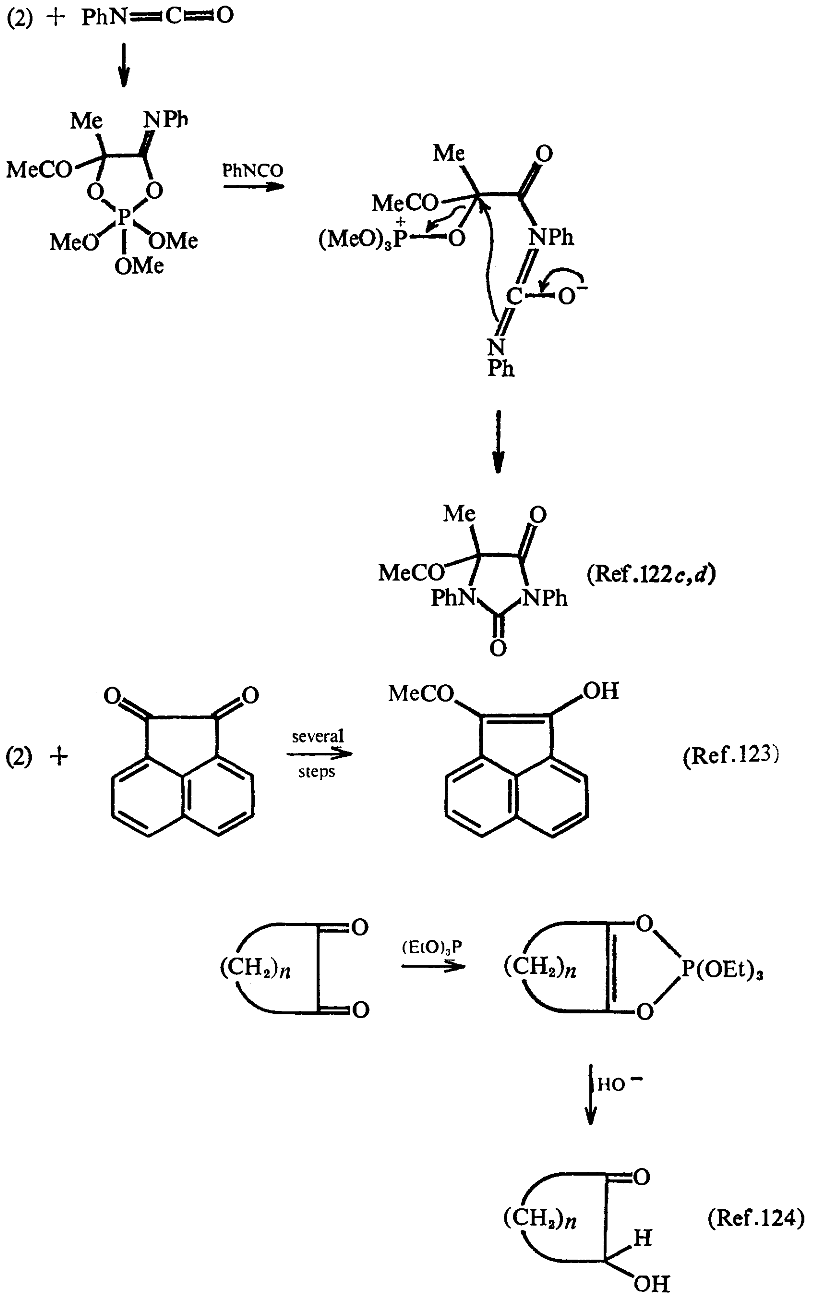
[130] H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 1945, 380.

[131] E. J. Corey and J. E. Anderson, *J. Org. Chem.*, 1967, **32**, 4160.

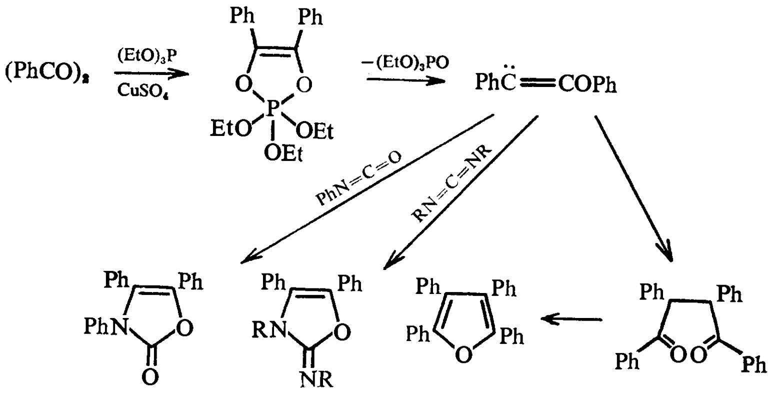
[132] H. R. Hudson, *Synthesis*, 1969, 112; H. R. Hudson, A. R. Qureshi, and (Mrs) D. Ragoonanan, *J.C.S. Perkin I*, 1972, 159.


(MeO)₃P
O=CMe
O=CMe
(2)
(2) + RCHO
H⁺
MeCOCCH(OH)R
(Ref.121)
(2) + MeCOCO₂Me
H⁺
MeCOC—C—CO₂Me
(Ref.122b)

Scheme 49



Scheme 49 continued



Scheme 50

$$\mathrm{Ph\ddot{C}{=}COPh} \rightarrow \mathrm{Ph_2C{=}C{=}O} \xrightarrow{\mathrm{(EtO)_3P}} \mathrm{Ph_2C{=}C:} \rightarrow \mathrm{PhC{\equiv}CPh}$$

[As from Scheme 50]

Scheme 51

$$\mathrm{Ph_2POR} \xrightarrow{\mathrm{HX}} \mathrm{Ph_2\overset{+}{P}H{\cdot}OR\ X^-} \rightarrow \mathrm{Ph_2P(O)H + RX}$$

Scheme 52

which are useful in the conversion of alcohols into alkyl halides.[133] The reaction is nearly always S_N2, converting, for example, optically active *endo*-norbornol into *exo*-norbornyl bromide with no significant racemisation.[134a] When, however, a similar experiment is carried out with the *exo*-alcohol a mixture is formed (Scheme 53).[134b]

Phosphine dihalides also convert amino-alcohols into aziridines[135] and acids into acyl halides.[136] Ph_3PBr_2 in dimethylformamide reacts with cholest-5-ene-3β,4β-diol to give a mixture of an unsaturated bromide and an unsaturated aldehyde, possibly by way of $Me_2\overset{+}{N}{=}CHBr$[137] in a Vilsmeier reaction (Scheme 54). Ethers are cleaved by Ph_3PBr_2, giving good yields of alkyl bromides except

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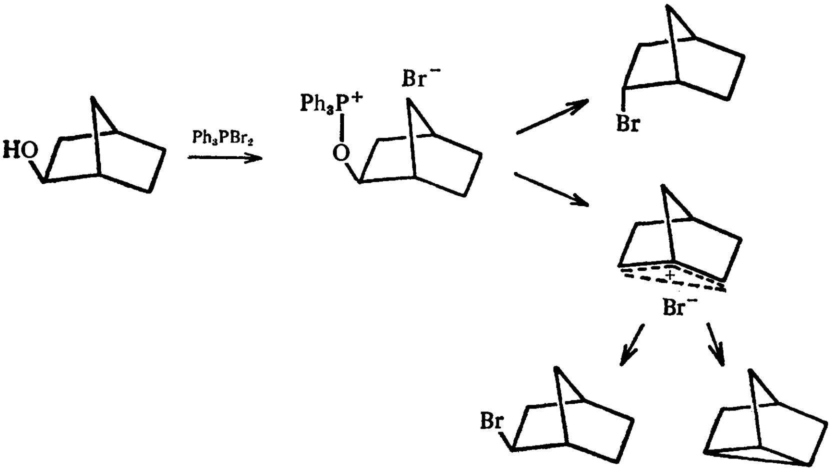
[133] L. Horner, H. Oediger, and H. Hoffmann, *Annalen*, 1959, **626**, 26; G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, 1964, **84**, 964; G. A. Wiley, B. M. Rein, and R. L. Hershkowitz, *Tetrahedron Letters*, 1964, 2509.

[134] (*a*) J. P. Schaefer and D. S. Weinberg, *J. Org. Chem.*, 1965, **30**, 2635; (*b*) *ibid.*, p. 2639.

[135] I. Okada, K. Ichimura, and R. Sudo, *Bull. Chem. Soc. Japan*, 1970, **43**, 1185.

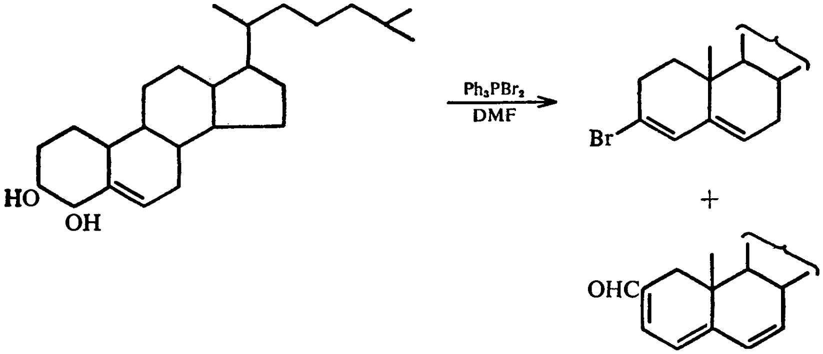
[136] H.-J. Bestmann and L. Mott, *Annalen*, 1966, **693**, 132.

[137] R. Stevenson, T. Dahl, and N. S. Bhacca, *J. Org. Chem.*, 1971, **36**, 3243.



Scheme 53

in the case of t-butyl ethers, in which case isobutene is formed.[138] Benzoins are oxidized to benzils,[139a] oximes give ketenimines,[139b] and phenols give aryl bromides.[140]



Scheme 54

The Rydon reagent, triphenyl phosphite dihalide, and the related alkyltriphenoxyphosphonium halides [$(PhO)_3PR^+$ Hal$^-$] are also useful in the

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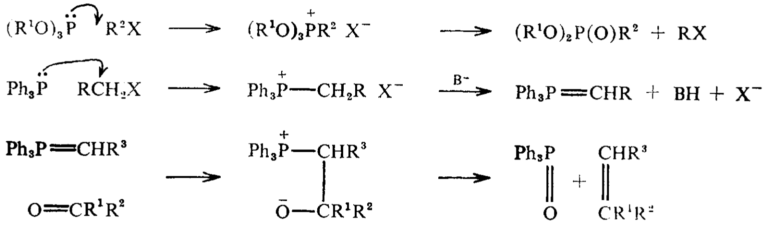
[138] A. G. Anderson and F. J. Freenor, *J. Amer. Chem. Soc.*, 1964, **86**, 5037; *J. Org. Chem.*, 1972, **37**, 626.

[139] (*a*) T.-L. Ho, *Synthesis*, 1972, 697; (*b*) M. Masaki, K. Fukui, and M. Ohta, *J. Org. Chem.*, 1967, **32**, 3564.

[140] J. P. Schaefer and J. Higgins, *J. Org. Chem.*, 1967, **32**, 1607.

preparation of alkyl halides[141] from alcohols. Recent applications include the iodination of hydroxy-groups in nucleosides[142] and carbohydrates.[143]

B. Reactions with Alkyl Halides: Formation of Ylides.—The Michaelis–Arbusov reaction[144] of trialkyl phosphites with alkyl halides, which has been reviewed,[145] is the most widely used method of forming P—C bonds. It involves nucleophilic attack by phosphorus to give a quasiphosphonium salt which undergoes dealkylation as shown in Scheme 55. In the case of reaction with triaryl- or trialkyl-phosphines, the resulting quaternary phosphonium salt is relatively stable towards dealkylation. Providing there is an available α-proton, however, these salts react readily with base to give phosphorus ylides, the reactivity of which towards carbonyl compounds is the basis of the Wittig olefin synthesis, which has proved to be so remarkably valuable in recent years (Scheme 55). An enormous number of applications of this reaction have been recorded and reviewed.[146]



Scheme 55

C. Reactions with Polyhalogenomethanes.—Trialkyl phosphites react with carbon tetrachloride in an Arbusov-type reaction to give dialkyl trichloromethylphosphonates[147] by an ionic route[148] involving the interchangeable ion pair $[(R^1O)_3PCl^+\ CCl_3^- \rightleftharpoons (R^1O)_3PCCl_3^+\ Cl^-]$. In the presence of an alcohol R^2OH, a mixture of phosphates, alkyl chlorides, R^1Cl and R^2Cl, and chloroform results (Scheme 56).[149] It was soon realised that modification of this reaction by the

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[141] H. N. Rydon, *Chem. Soc. Special Publ.*, 1957, **8**, 61; D. K. Black, S. R. Landor, A. N. Patel, and P. F. Whiter, *J. Chem. Soc.* (*C*), 1967, 2260; J. O. H. Verheyden and J. G. Moffatt, *J. Amer. Chem. Soc.*, 1966, **88**, 5684.

[142] G. A. R. Johnston, *Austral. J. Chem.*, 1968, **21**, 513; J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 1970, **35**, 2319, 2868.

[143] N. K. Kochetkov and A. I. Usov, *Methods Carbohydrate Chem.*, 1972, **6**, 205.

[144] A. Michaelis and R. Kaehne, *Ber.*, 1898, **31**, 1048; A. E. Arbusov, *J. Russ. Phys. Chem. Soc.*, 1906, **38**, 687.

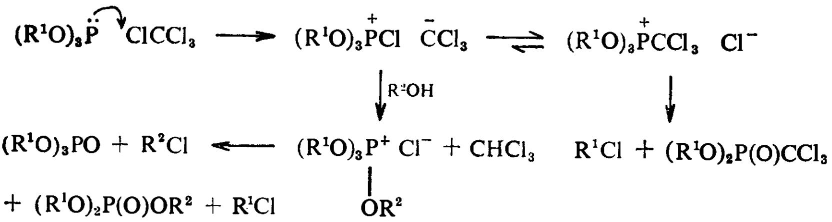
[145] H.-G. Henning and G. Hilgetag, *Z. Chem.*, 1967, **7**, 169.

[146] A. W. Johnson, 'Ylides,' Academic Press, New York, 1966.

[147] G. Kamai and L. Egorava, *Zhur. obshchei Khim.*, 1946, **16**, 1521 (*Chem. Abs.*, 1947, **41**, 5439).

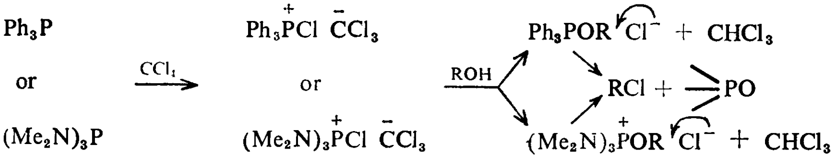
[148] R. E. Atkinson, J. I. G. Cadogan, and J. T. Sharp, *J. Chem. Soc.* (*B*), 1969, 138.

[149] P. C. Crofts and I. M. Downie, *J. Chem. Soc.*, 1963, 2559.



Scheme 56

use of triphenylphosphine[150] or $(Me_2N)_3P$[151] should lead to the conversion of an alcohol into the corresponding alkyl halide, and this has been achieved (Scheme 57). Considerable interest in this reaction has been shown recently, Mainly because the conditions are so mild that sensitive alcohols, such as carbohydrates,[152] may be converted into chlorides, particularly since protective groups commonly



Scheme 57

used with carbohydrates (acetal, ether, ester) are stable to the reagent. Triphenylphosphine has been the most widely used reagent but the use of $(Me_2N)_3P$ sometimes simplifies the isolation of the alkyl halide because the resulting phosphine oxide is water-soluble.[151] Trioctylphosphine has been reported as being more reactive than triphenylphosphine in this reaction.[153] As expected from Scheme 57 the reaction proceeds with inversion of configuration[154] although there is considerable racemisation in the analogous reaction with carbon tetrabromide.[155] The method has been used successfully for conversion of hydroxy-carboxylic esters into the corresponding chlorides.[156]

Many extensions of the reaction have been reported: primary and secondary

[150] A. J. Burn and J. I. G. Cadogan, *J. Chem. Soc.*, 1963, 5788.

[151] I. M. Downie, J. B. Lee, and M. F. S. Matough, *Chem. Comm.*, 1968, 1350.

[152] J. B. Lee and T. J. Nolan, *Canad. J. Chem.*, 1966, **44**, 1331; *Tetrahedron*, 1967, **23**, 2789; C. R. Haylock, L. D. Melton, K. N. Slessor, and A. S. Tracey, *Carbohydrate Res.*, 1971, **16**, 375.

[153] J. Hooz and S. S. H. Gilani, *Canad. J. Chem.*, 1968, **46**, 86.

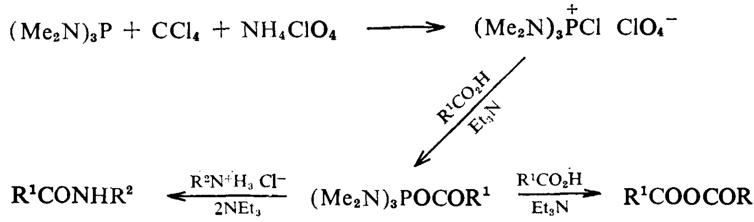
[154] R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 1970, **35**, 1627; R. Appel, R. Kleinstück, K. D. Ziehn, and F. Kudl, *Chem. Ber.*, 1970, **103**, 3631.

[155] R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 1971, **36**, 403.

[156] J. B. Lee and I. M. Downie, *Tetrahedron*, 1967, **23**, 359.

alcohols sometimes give nitriles on treatment with triphenylphosphine, carbon tetrachloride, and sodium cyanide in DMSO,[157] presumably by competitive attack by the cyanide ion on the intermediate quasiphosphonium species $[Ph_3POR]^+$. On the other hand the reaction of $KCN–PhCH_2CH_2OH–Ph_3P–CCl_4$–DMSO gave only the phenethyl chloride.[155] However, Castro and Selve[158a] have shown that at low temperatures in tetrahydrofuran the alkoxyphosphonium chloride is stable and that nucleophiles, *e.g.* N_3^-, SCN^-, PhS^-, CN^-, and I^-, can compete favourably with chloride ions in the decomposition of the salt. As a result of the greater reactivity of primary alcohols in these reactions, methyl α-D-glucopyranose reacts preferentially at C-6 and functionalization of this position is facilitated.[158b] Weaker nucleophiles cannot compete satisfactorily with chloride ions. However, if the chloride is converted into the perchlorate prior to reaction with primary amines, good yields of monoalkylated amines are formed.[158c] It has been suggested that this reaction could be extended to introduce a primary amino-group into carbohydrates, *via* the nitrile.[157] The reaction has also been used to convert toluene-α-thiol into benzyl chloride.[159]

Acids are readily converted into acyl halides[160] and, by a modification of the reaction, amides (including peptides), nitriles, and anhydrides can be prepared (Scheme 58).[161] Amines yield aminophosphonium salts[162] while nitriles,[163] isocyanides,[164] and carbodi-imides[165] are formed from amides, formamides, and ureas, respectively. In some instances the reactivity of the trichloromethyl anion has been exploited. This has been described as an ametallic carbanion by



Scheme 58

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[157] D. Brett, I. M. Downie, and J. B. Lee, *J. Org. Chem.*, 1967, **32**, 855.

[158] (*a*) B. Castro and C. Selve, *Bull. Soc. chim. France*, 1971, 2296; (*b*) B. Castro, Y. Chapleur, B. Gross, and C. Selve, *Tetrahedron Letters*, 1972, 5001; (*c*) B. Castro and C. Selve, *Bull. Soc. chim. France*, 1971, 4368.

[159] R. G. Weiss and E. I. Snyder, *Chem. Comm.*, 1968, 1358.

[160] J. B. Lee, *J. Amer. Chem. Soc.*, 1966, **88**, 3440.

[161] B. Castro and J. R. Dormoy, *Tetrahedron Letters*, 1972, 4747; E. Barstow and V. J. Hruby, *J. Org. Chem.*, 1971, **36**, 1305; S. Yamada and Y. Takeuchi, *Tetrahedron Letters*, 1971, 3595; T. Wieland and A. Seeliger, *Chem. Ber.*, 1971, **104**, 3992; R. Appel, R. Kleinstück, and K. D. Ziehn, *ibid.*, p. 1030.

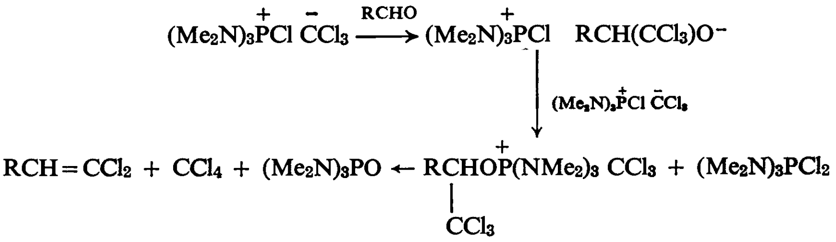
[162] R. Appel, R. Kleinstück, K. D. Ziehn, and F. Kudl, *Chem. Ber.*, 1970, **103**, 3631.

[163] E. Yamoto and S. Sugasawa, *Tetrahedron Letters*, 1970, 4383.

[164] R. Appel, R. Kleinstück, and K. D. Ziehn, *Angew. Chem. Internat. Edn.*, 1971, **10**, 132.

[165] R. Appel, R. Kleinstück, and K. D. Ziehn, *Chem. Ber.*, 1971, **104**, 1335.

Castro *et al.*[166] (Scheme 59). The same group of workers have prepared secondary alcohols,[167] vinyl esters,[168] glycidic esters,[169] and α-keto-esters.[169] Other uses of carbon tetrachloride-phosphine systems include the conversion of aldehydes into acetylenes,[170] conversion of epoxides into *vic*-dihalides,[171] and the conversion of enolizable ketones into vinyl halides.[172]



$$\begin{array}{c}
(\mathrm{Me_2N})_3\overset{+}{\mathrm{P}}\mathrm{Cl}\ \overset{-}{\mathrm{C}}\mathrm{Cl_3} \xrightarrow{\mathrm{RCHO}} (\mathrm{Me_2N})_3\overset{+}{\mathrm{P}}\mathrm{Cl}\quad \mathrm{RCH(CCl_3)O^-}\\
\downarrow (\mathrm{Me_2N})_3\overset{+}{\mathrm{P}}\mathrm{Cl}\ \overset{-}{\mathrm{C}}\mathrm{Cl_3}\\
\mathrm{RCH{=}CCl_2} + \mathrm{CCl_4} + (\mathrm{Me_2N})_3\mathrm{PO} \leftarrow \underset{\mathrm{CCl_3}}{\mathrm{RCH}}\mathrm{O}\overset{+}{\mathrm{P}}(\mathrm{NMe_2})_3\ \mathrm{CCl_3} + (\mathrm{Me_2N})_3\mathrm{PCl_2}
\end{array}$$

Scheme 59

D. Reactions with *vic*-Dihalides.—The most useful application is debromination but its success depends on the nature of the dihalide. Thus, 1,2-dibromoethane with triethyl phosphite gives the normal Arbusov product.[173] However, when electron-withdrawing groups are attached to both carbon atoms, debromination occurs.[174,175] This also occurs in certain circumstances when only one electron-withdrawing group is present. For example, diethyl 1-cyano-2-chloroethylphosphonate is formed from 2,3-dichloropropionitrile[176] but 2,3-dibromopropionitrile gives over 80% of acrylonitrile.[175] Similar debrominations may be accomplished using tertiary phosphines.[174,177,178] Low yields of cyclohexene are reported[177] from *trans*-1,2-dibromocyclohexane but up to 40% can be obtained by use of tributylphosphine. For dihalides of the type $R^1CHXCHXR^2$ it is found that both *meso*- and *erthyro*-isomers as well as (±)- and *threo*-forms yield *trans*-olefins,[177,178] except in the case of (±)-stilbene dibromide when a mixture of *trans*- and *cis*-products is formed. In this case Borowitz *et al.*[177] claim

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[166] B. Castro, J. Villieras, R. Burgada, and G. Lavielle, Colloques Internationaux du C.N.R.S. No. 182, 'Chemie Organique du Phosphore', 1969, p. 235.

[167] B. Castro, R. Burgada, G. Lavielle, and J. Villieras, *Bull. Soc. chim. France*, 1969, 2770.

[168] J. Villieras, G. Lavielle, and J. C. Combret, *Compt. rend.*, 1971, **272**, *C*, 691.

[169] J. Villieras, P. Coutrot, and J. C. Combret, *Compt. rend.*, 1970, **270**, *C*, 1250; J. Villieras, G. Lavielle, and J. C. Combret, *Bull. Soc. chim. France*, 1971, 898.

[170] E. J. Corey and P. L. Fuchs, *Tetrahedron Letters*, 1972, 3769.

[171] N. S. Isaacs and D. Kirkpatrick, *Tetrahedron Letters*, 1972, 3869.

[172] N. S. Isaacs and D. Kirkpatrick, *J.C.S. Chem. Comm.*, 1972, 443.

[173] G. M. Kosolapoff, *J. Amer. Chem. Soc.*, 1944, **66**, 109.

[174] K. C. Pande and G. Trampe, *J. Org. Chem.*, 1970, **35**, 1169.

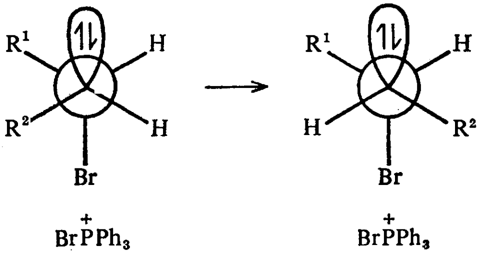
[175] J. P. Schroeder, L. B. Tew, and V. M. Peters, *J. Org. Chem.*, 1970, **35**, 3181.

[176] V. S. Abramov and N. A. Il'ina, *Zhur. obshchei Khim.*, 1956, **26**, 2014 (*Chem. Abs.*, 1957, **51**, 1822).

[177] I. J. Borowitz, D. Weiss, and R. K. Crouch, *J. Org. Chem.*, 1971, **36**, 2377.

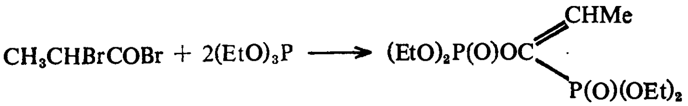
[178] C. J. Devlin and B. J. Walker, *J.C.S. Perkin I*, 1972, 1249.

that addition of isopropyl alcohol increases the fraction of *cis*-compound formed owing to the removal of Ph_3PBr_2, which catalyses the *cis–trans* isomerization. The fact that pure *cis*-compound is not formed in the presence of the alcohol is assumed to be due to HBr. However, Devlin and Walker[178] claim that *cis–trans* isomerization is 'not extensive' and that the preponderance of *trans*-isomer formed is due to inversion and rotation of the ion pair shown in Scheme 60.



Scheme 60

In support of the intermediacy of this ion pair, these workers isolated $[Ph_3PCHPhCH_2NO_2]^+ Br^-$ from the reaction of triphenylphosphine with 1,2-dibromo-1-nitro-2-phenylethane in methanol. Normally α-halogenoacyl halides undergo Arbusov and Perkow reactions with two moles of phosphite (Scheme 61). However, diphenylketen has been prepared by debromination of



$$CH_3CHBrCOBr + 2(EtO)_3P \longrightarrow (EtO)_2P(O)OC\begin{cases} {=}CHMe \\ {-}P(O)(OEt)_2 \end{cases}$$

Scheme 61

α-bromodiphenylacetyl bromide with triphenylphosphine,[179] a procedure which it is claimed has many advantages over all others for the preparation of diphenylketen.

E. Reactions with *N*-Halogenoamides. Conversion of Alcohols into Alkyl Bromides and of Amides into Nitriles.—It has been reported that ethyl bromide is formed when ethanol is added to a mixture of triphenylphosphine and *N*-bromosuccinimide.[180] Reaction between tervalent phosphorus compounds and *N*-halogenoamides has been shown to involve attack at halogen[181] and the formation of the alkyl bromide can be rationalized in terms of the reaction of the

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[179] S. D. Darling and R. L. Kidwell, *J. Org. Chem.*, 1968, **33**, 3974.

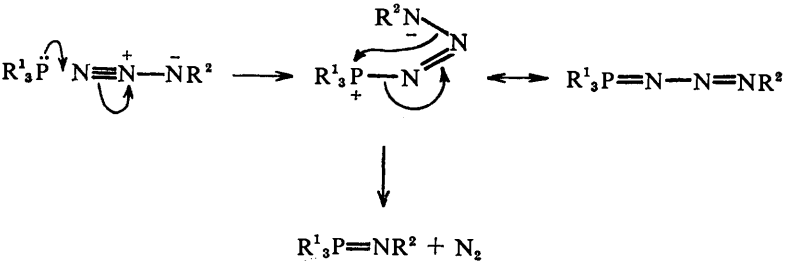
[180] S. Trippett, *J. Chem. Soc.*, 1962, 2337.

[181] A. K. Tsolis, W. E. McEwan, and C. A. van der Werf, *Tetrahedron Letters*, 1964, 3217.

alcohol with the intermediate Ph_3PBr^+ ion. The reaction has application in carbohydrate and nucleoside chemistry since amide ester and acetal functions are unaffected.[182] The use of trialkyl phosphites with *N*-halogenoamides, on the other hand, leads to a mixture of the parent amide and the corresponding nitrile.[183]

6 Miscellaneous Reactions

A. Reactions with Azides: Formation of Imines and their Use in Synthesis.—Both tertiary phosphines[184] and triesters[185] react with azides by loss of nitrogen to give imines. In some cases isolation of the intermediate has been achieved.[186] The displacement reaction has been shown to proceed as in Scheme 62.[187]



Scheme 62

The phosphinimines are particularly useful synthetic intermediates because they react readily with a wide variety of unsaturated compounds (Scheme 63). The Wittig reaction, which followed later, is closely related in type to these reactions, which all probably proceed *via* four-membered cyclic intermediates.[146]

An interesting variation on the intermolecular reaction of phosphinimines and carbonyl compounds outlined in Scheme 63 is Zbiral's synthesis of tetrazoles from phosphinimines and acyl halides,[188a] followed by reaction with sodium azide (Scheme 64). The corresponding acylation using acyl cyanides leads to iminonitriles (Scheme 64). Intermolecular condensation of phosphinimines containing a β-carbonyl group, on the other hand, leads to pyrazines (Scheme 65).[188b]

Several useful syntheses of heterocyclic compounds have resulted from intra-

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[182] M. M. Ponpipom and S. Hanessian, *Carbohydrate Res.*, 1971, **18**, 342.

[183] J. M. Desmarchelier and T. R. Fukoto, *J. Org. Chem.*, 1972, **37**, 4218.

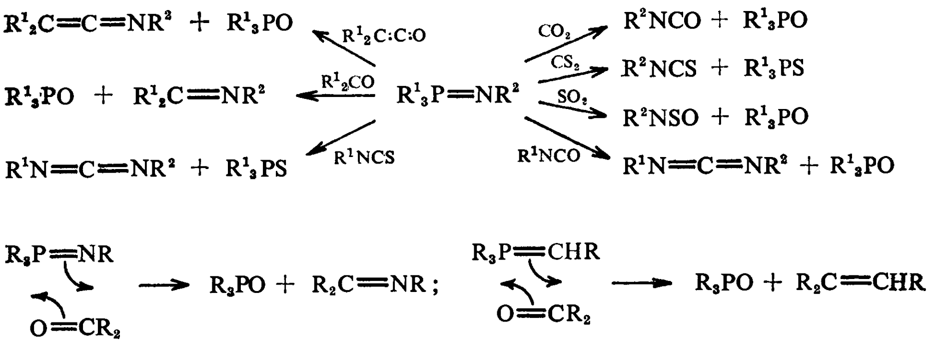
[184] (*a*) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, 1921, **4**, 861; (*b*) H. Staudinger and J. Meyer, *ibid.*, 1919, **2**, 635; (*c*) *ibid.*, 1919, **2**, 619.

[185] M. I. Kabachnik and V. A. Gilyarov, *Izvest, Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk*, 1956, 790 (*Chem. Abs.*, 1957, **51**, 1823).

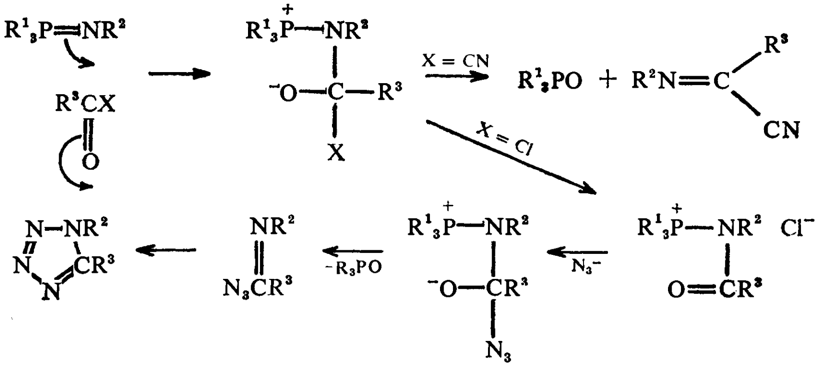
[186] L. Horner and A. Gross, *Annalen*, 1955, **591**, 117.

[187] J. E. Leffler and R. D. Temple, *J. Amer. Chem. Soc.*, 1967, **89**, 5235.

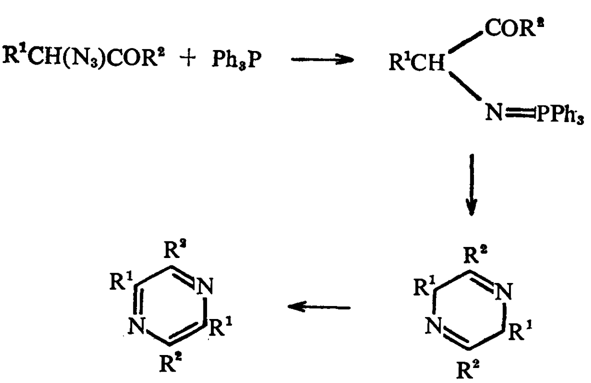
[188] (*a*) E. Zbiral and J. Stroh, *Annalen*, 1969, **725**, 29; (*b*) 1969, **727**, 231.



Scheme 63

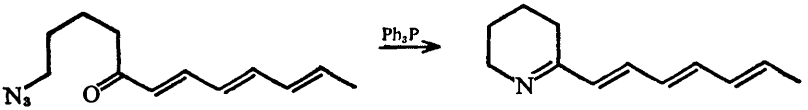


Scheme 64

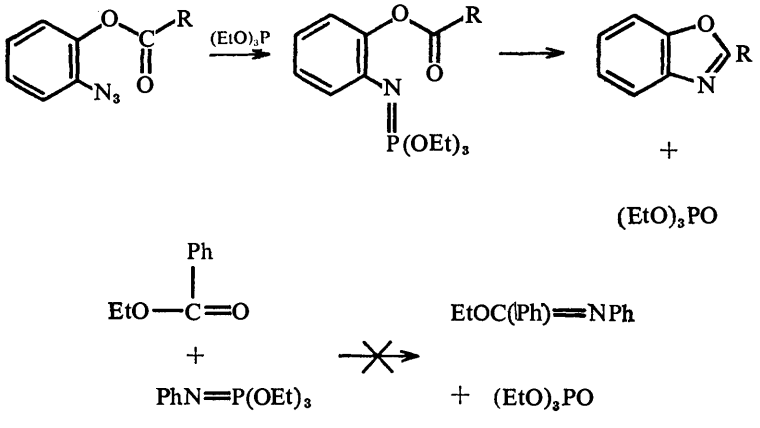


Scheme 65

molecular reactions of suitably substituted phosphinimines and triethyl phosphorimidates. The alkaloid nigrifactine, for example, has been neatly synthesized from the azidotrienone shown in Scheme 66.[189] The reaction with the greatest potential is possibly Leyshon and Saunders' demonstration[64] that the phosphorimidates, derived from reaction of *o*-azidophenyl benzoate or acetate with triethyl phosphite, cannot be isolated at 20 °C but rapidly eliminate triethyl phosphate to give the corresponding 2-phenyl- or 2-methyl-benzoxazole (70%) (Scheme 67). This is a particularly interesting demonstration of anchimeric acceleration, because intermolecular reaction of triethyl *N*-phenylphosphorimidate with ethyl benzoate does not occur (Scheme 67). It is synthetically useful because the experimentally simpler, direct, deoxygenation of the parent nitro-compounds with triethyl phosphite[63] works well only in the case of 2-arylbenzoxazoles.



Scheme 66



Scheme 67

Reaction of 2-azidocinnamates with triethyl phosphite under photochemical conditions similarly gives an entry to the quinoline ring system (Scheme 68).[190] No reaction of the intermediate phosphorimidate occurs in the dark, so photo-

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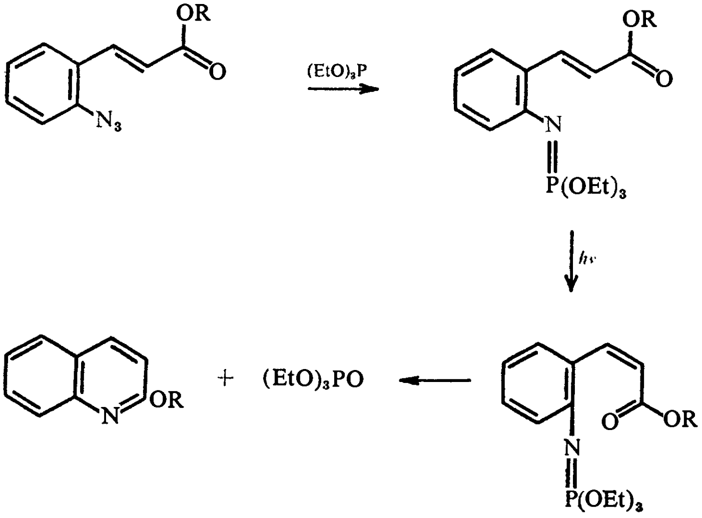
[189] M. Pailer and E. Haslinger, *Monatsh.*, 1970, **101**, 508.

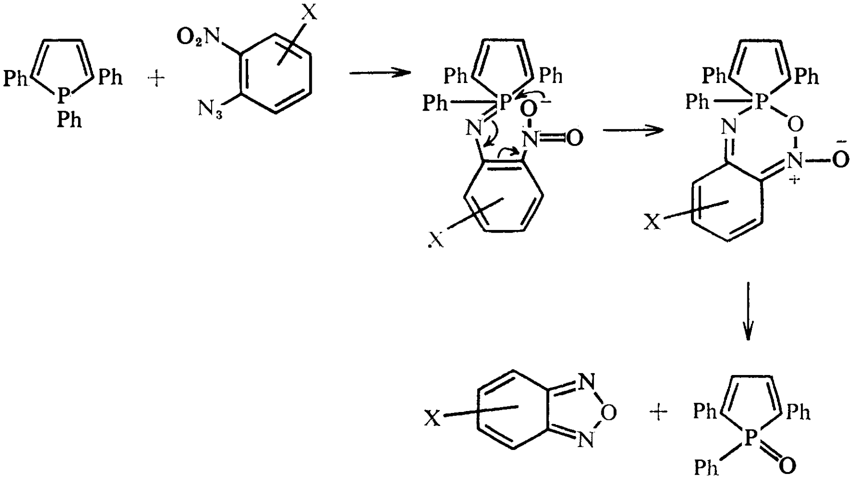
[190] S. A. Foster, L. J. Leyshon, and D. G. Saunders, *J.C.S. Chem. Comm.*, 1973, 29.



Scheme 68

chemical activation is needed to isomerize the *trans*- to the *cis*-form, thus bringing the reacting ester carbonyl and phosphorimidate groups close enough for reaction to occur.

Benzofurazans can be prepared *via* a related reaction of *N*-(*o*-nitro-aryl)-1,2,5-triphenylphospholimines, obtained by the reaction of 1,2,5-triphenylphosphole

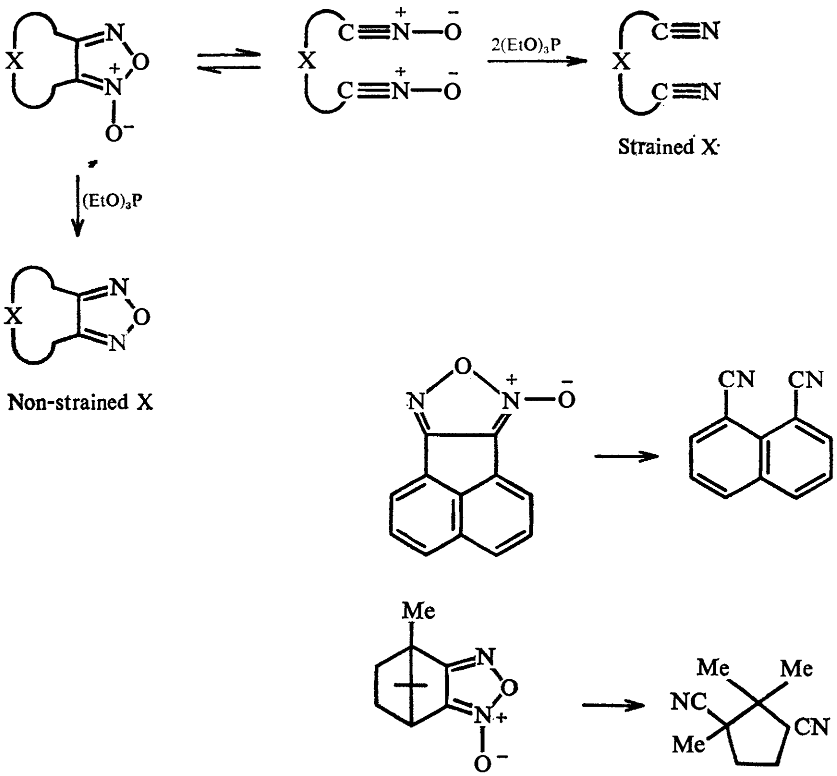


Scheme 69

and suitable *o*-nitro-aryl azides (Scheme 69),[191] the driving force being release of ring stain in the pentaco-ordinate intermediates.

B. Reactions with Diazoalkanes: Formation of Methylenephosphoranes.—Diazoalkanes react with tertiary phosphines[184c] to give phosphazines, which give methylenephosphoranes on thermolysis. These, the well-known Wittig reagents, have a well-known versatility in organic synthesis but this route is not as experimentally useful as the alternative route *via* phosphonium salts.

C. Fragmentation Reactions.—Normally furoxans are readily reduced to furazans[50,192] but strained furoxans undergo cleavage to give dinitriles (Scheme 70),[193] presumably *via* the tautomeric form. In a closely related reaction, certain



Scheme 70

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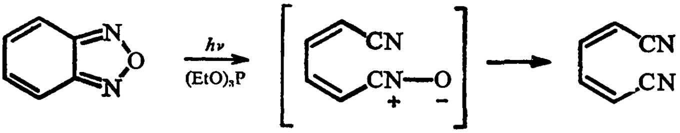
[191] J. I. G. Cadogan, R. Gee, and R. J. Scott, *J.C.S. Chem. Comm.*, 1972, 1242.

[192] T. Mukaiyama, H. Nambu, and M. Okamato, *J. Org. Chem.*, 1962, **27**, 3651; C. Grundmann, *Chem. Ber.*, 1964, **97**, 575; A. S. Bailey and J. N. Evans, *Chem. and Ind.*, 1964, 1424.

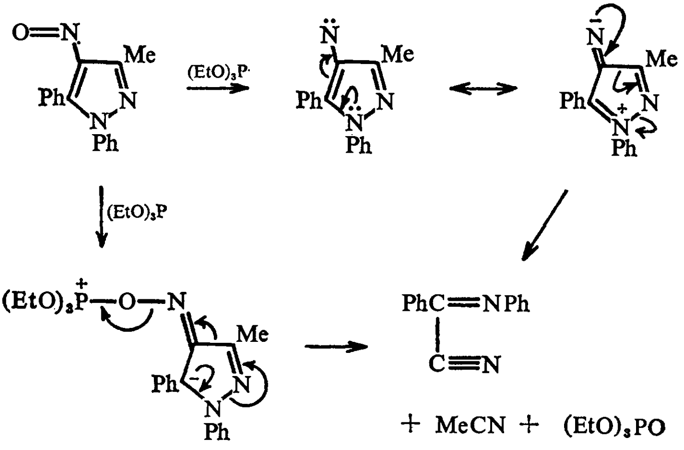
[193] M. Altaf-ur-Rahman and A. J. Boulton, *Chem. Comm.*, 1968, 73; J. Ackrell, M. Altaf-ur-Rahman, A. J. Boulton, and R. C. Brown, *J.C.S. Perkin I*, 1972, 1587.

fused furazans, normally resistant to phosphites, undergo clean, deoxygenative, cleavage to dinitriles on photolysis with phosphites[194] (Scheme 71).



Scheme 71

Nitriles are also produced by exocyclic deoxygenation of 4-nitrosopyrazoles,[195] pathways *via* a nitrene or a nitrene precursor being possible (Scheme 72).



Scheme 72

D. Reactions with αβ-Unsaturated Compounds.—In general these proceed *via* nucleophilic addition of the phosphorus reagent to the α,β-system. Thus triphenylphosphine reacts with diphenylcyclopropanone to give an ylide which, although it does not react with aldehydes and ketones, does react with isocyanides to give a derivative of cyclobutenedione (Scheme 73) with elimination of triphenylphosphine.[196] Related to this is the reaction of 1,3-diphenyl-4-benzylidene-

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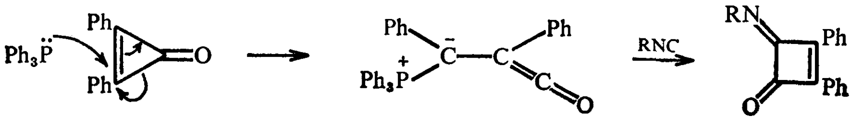
[194] T. Mukai and M. Nitta, *Chem. Comm.*, 1970, 1192.

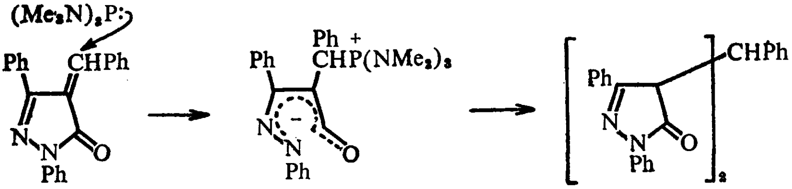
[195] J. B. Wright, *J. Org. Chem.*, 1969, 34, 2474.

[196] A. Hamada and T. Takizawa, *Tetrahedron Letters*, 1972, 1849.



Scheme 73

pyrazolin-5-one with $(Me_2N)_3P$, which gives an adduct which apparently decomposes in most solvents to give a bis(diphenylpyrazoline) (Scheme 74).[197]



Scheme 74

Both triphenylphosphine[198] and triethyl phosphite[199] have been used to produce telomers of activated olefins, again by addition to the α,β double bond. The postulated intermediate betaine in this reaction is also invoked to explain the catalysis by triphenylphosphine of the Michael addition of 2-nitropropane to activated olefins (Scheme 75).[200] The possibility that the phosphine is acting as a

$$Ph_3P + RCH{=}CH_2 \rightleftharpoons Ph_3\overset{+}{P}CH_2\overset{-}{C}HR$$
$$Ph_3\overset{+}{P}CH_2\overset{-}{C}HR + Me_2CHNO_2 \rightarrow Ph_3\overset{+}{P}CH_2CH_2R + Me_2CNO_2^-$$
$$Me_2CNO_2^- + RCH{=}CH_2 \rightarrow Me_2CNO_2CH_2\overset{-}{C}HR$$
$$Me_2CNO_2CH_2\overset{-}{C}HR + Me_2CHNO_2 \rightarrow Me_2CNO_2CH_2CH_2R + Me_2CNO_2^-$$

Scheme 75

base, *i.e.* by abstracting a proton rather than by adding to the double bond, is discounted on the grounds of the apparent independence of the reaction on the pK of the phosphine used.[201] A similar reaction is probably occurring in the triphenylphosphine-catalysed ring expansion of substituted cyclopropyl ketones to 4,5-dihydrofurans.[202]

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[197] B. A. Arbusov, E. N. Dianova, and V. S. Vinogradova, *Zhur. obshchei Khim.*, 1972, **42**, 750 (*Chem. Abs.*, 1972, **77**, 126777).

[198] L. Horner, W. Jugeleit, and K. Klupfel, *Annalen*, 1955, **591**, 108.

[199] V. A. Kukhtin, G. Kamai, and L. A. Sinchenko, *Doklady Akad. Nauk. S.S.S.R.*, 1958, **118**, 505 (*Chem. Abs.*, 1958, **52**, 10956).

[200] D. A. White and M. M. Baizer, *Tetrahedron Letters*, 1973, 3597.

[201] K. Issleib and H. Bruchlos, *Z. anorg. Chem.*, 1962, **316**, 1.

[202] E. E. Schweizer and C. M. Kopay, *Chem. Comm.*, 1970, 677; *J. Org. Chem.*, 1971, **36**, 1489.