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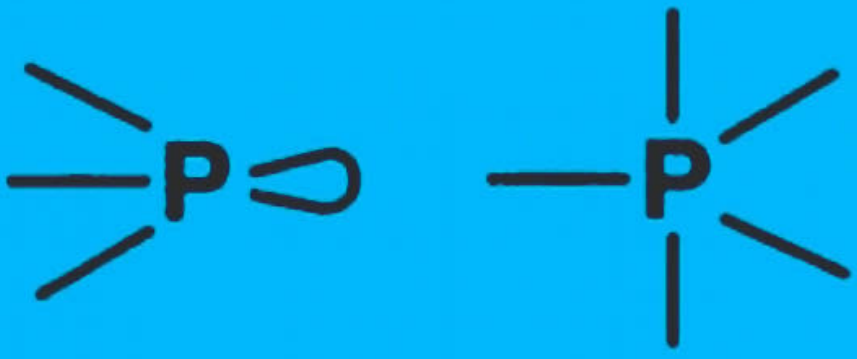
The chemistry of functional groups

The chemistry of organophosphorus compounds

Edited by
Frank R. Hartley

Volume 4 Ter- and quinque-valent phosphorus acids and their derivatives



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The chemistry of
organophosphorus compounds

Volume 4

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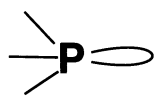

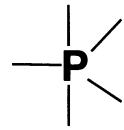

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Edited by

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Foreword

The chemistry of organophosphorus compounds is a multi-volume work within the well established series of books covering *The Chemistry of Functional Groups*, and is in four volumes.

Volume 1 covers primary, secondary and tertiary phosphines (PR_3H_{3-n}, $n = 1 - 3$), polyphosphines (both P—$(C)_n$—P and $R(P)_nR'$, $n > 1$) and heterocyclic compounds containing phosphorus.
Volume 2 covers phosphine oxides, sulphides, selenides and tellurides.
Volume 3 covers phosphonium salts, phosphonium ylides and phosphoranes.
Volume 4 covers phosphinous, phosphonous, phosphinic and phosphonic acid compounds and their halogen derivatives R_2PY, RPY_2 and $R_2P(X)Y_2$, where Y = halogen and X = O, S or Se.

For many years the nomenclature used in organophosphorus chemistry was extremely frustrating, with different compounds being given the same name by different authors. The nomenclature has, however, now been rationalized and is summarized in Volume 1, Chapter 1, Section IV.

In common with other volumes in *The Chemistry of the Functional Groups* series, the emphasis is laid on the functional group treated and on the effects which it exerts on the chemical and physical properties, primarily in the immediate vicinity of the group in question, and secondarily on the behaviour of the whole molecule. The coverage is restricted in that material included in easily and generally available secondary or tertiary sources, such as *Chemical Reviews* and various 'Advances' and 'Progress' series, as well as textbooks (i.e. in books which are usually found in the chemical libraries of universities and research institutes) is not as a rule repeated in detail, unless it is necessary for the balanced treatment of the subject. Therefore, each of the authors has been asked *not* to give an encyclopaedic coverage of his or her subject, but to concentrate on the most important recent developments and mainly on material that has not been adequately covered by reviews or other secondary sources by the time of writing of the chapter, and to address himself or herself to a reader who is assumed to be at a fairly advanced post-graduate level. With these restrictions, it is realized that no plan can be devised for a volume that would give a complete coverage of the subject with no overlap between the chapters, while at the same time preserving the readability of the text.

The publication of the Organophosphorus Series would never have started without the support of many people. This volume would never have reached fruition without the help of Mr Mitchell and Mrs Perkins with typing, and the efficient and patient co-operation of several staff members of the Publisher. Many of my colleagues in England, Israel and

elsewhere gave help in solving many problems, especially Professor Saul Patai, without whose continual support and encouragement this work would never have been attempted,

Finally, that the project ever reached completion is due to the essential support and partnership of my wife and family, amongst whom my eldest daughter provided both moral support and chemical understanding in the more difficult areas of the subject.

Cranfield, England FRANK HARTLEY

Contents

List of abbreviations used

abd	azobisisobutyl diacetate
Ac	acetyl (MeCO)
acac	acetylacetone
Ad	adamantyl
aibn	azobisisobutyronitrile
all	allyl
an	acetonitrile
An	anisyl
Ar	aryl
ATP	adenosine triphosphate
bipy	2,2′-bipyridine
bpr	Berry pseudorotation
BSA	bovine serum albumin
btsa	*N*,*O*-bis(trimethylsilyl)acetamide
Bu	butyl (also *t*-Bu or Bu^t)
Bz	benzyl
CD	circular dichroism
CI	chemical ionization
cod	cycloocta-1,5-diene
cp	cyclopentadienyl
mCPBA	*m*-chloroperoxybenzoic acid
CP-MAS	cross-polarization magic angle spinning
Cy	cyclohexyl
dbn	1,5-diazabicyclo[5.4.0]non-5-ene
dbso	dibenzoyl sulphoxide
dbu	1,8-diazabicyclo[5.4.0]undec-7-ene
$DDPN^+$	deamino diphosphopyridine nucleotide
diop	2,3-*o*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane
dme	1,2-dimethoxyethane
dmf	dimethylformamide
dmg	dimethylglyoximate
dmpe	bis(1,2-dimethylphosphino)ethane
dmso	dimethyl sulphoxide
DNA	deoxyribonucleic acid

$dpbO_2$	$Ph_2P(E)(CH_2)_nP(E)Ph_2$
$dpbS_2$	b, $n = 4$
$dpbSe_2$	e, $n = 2$
$dpeO_2$	m, $n = 1$
$dpeS_2$	p, $n = 3$
$dpeSe_2$	E = O, S, Se
$dpmO_2$	
$dpmS_2$	
$dpmSe_2$	
$dppO_2$	
$dppS_2$	
$dppSe_2$	
dpmPS	$Ph_2P(S)CH_2PPh_2$
dpmPSe	$Ph_2P(Se)CH_2PPh_2$
DPN^+	diphosphopyridine nucleotide
DPNH	dihydronicotinamide adenine dinucleotide
dppb	bis(1,4-diphenylphosphino)butane
dppe	bis(1,2-diphenylphosphino)ethane
dppm	bis(1,1-diphenylphosphino)methane
dppp	bis(1,3-diphenylphosphino)propane
dpso	diphenyl sulphoxide
DTG	differential thermal gravimetry
ECE	electron transfer followed by chemical reaction followed by further electron transfer
edta	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron impact
EPR	electron paramagnetic resonance
ESR	electron spin resonance
FAB	fast atom bombardment
FAD	flavine adenine dinucleotide
FDMS	field desorption mass spectrometry
FMN	flavine mononucleotide
FT	Fourier transform
GLC	gas–liquid chromatography
Hba	benzoylacetone
Hbfa	benzoyltrifluoroacetone
Hdbm	dibenzoylmethane
H_2dehp	di(2-ethylhexyl)phosphoric acid
H_2dmg	dimethylglyoxime
H_2dz	dithizone (3-mercapto-1,5-diphenylformazan)
Hex	hexyl
Hhfa	hexafluoroacetylacetone
HMDE	hanging mercury drop electrode
hmpa	hexamethylphosphoramide
hmpt	hexamethylphosphorotriamide
HOMO	highest occupied molecular orbital
Hox	8-hydroxyquinoline
HPLC	high-performance liquid chromatography

Hpmap	1-phenyl-3-methyl-4-acylpyrazol-5-one
Hpmbp	1-phenyl-3-methyl-4-benzoylpyrazol-5-one
Hpmbup	1-phenyl-3-methyl-4-butyrylpyrazol-5-one
Hpmdbp	1-phenyl-3-methyl-4-(3,5-dinitrobenzoyl)-pyrazol-5-one
Hpmop	1-phenyl-3-methyl-4-octanoylpyrazol-5-one
Hpmsp	1-phenyl-3-methyl-4-stearoylpyrazol-5-one
Hpmtfp	1-phenyl-3-methyl-4-trifluoroacetylpyrazol-5-one
Hpva	pivaloyltrifluoroacetone
Hpvta	dipivaloylacetone
Htbfa	thiobenzoyltrifluoroacetone
Htfa	trifluoroacetylacetone
Htfma	1,1,1-trifluoro-5-methylhexane-2,4-dione
Htta	1,1,1-trifluoro-3-(2-thenoyl)acetone
IP	ionization potential
LC_{50}	concentration causing lethality to 50% of the population
LD_{50}	dose causing lethality to 50% of the population
lda	lithium diisopropylamide
lp	lone pair of electrons
LUMO	lowest unoccupied molecular orbital
M	metal
Me	methyl
mibk	methyl isobutyl ketone
MIS	metal–insulator semiconductor
MNDO	modified neglect of diatomic overlap
MS	mass spectrometry
NADP	nicotinamide adenine dinucleotide phosphate
nba	*N*-bromoacetamide
NCI	negative ion chemical ionization
NHN	nicotinamide ribose monophosphate
Np	naphthyl
OAc	acetate
ORD	optical rotatory dispersion
PCI	positive ion chemical ionization
Pe	pentenyl
Pen	pentyl (C_5H_{11})
PES	photoelectron spectroscopy
Ph	phenyl
phen	1,10-phenanthroline
ppa	polyphosphoric acid
ppm	parts per million
Pr	propyl (also *i*-Pr or Pr^i)
R	any radical
RNA	ribonucleic acid
SCE	saturated calomel electrode

SCF	self-consistent field
SIMS	secondary ion mass spectrometry
tbap	tetra-*n*-butylammonium perchlorate
tbp	trigonal bipyramid (when referring to a structure) or tertiary butyl peroxide (when referring to a chemical)
tbpo	tri-*n*-butyl phosphate
TCNQ	tetracyanoquinone
tfa	trifluoroacetic acid
tfb	tetrafluorobenzobicyclo[2.2.2]octatriene
TG	thermogravimetric
thf	tetrahydrofuran
tht	tetrahydrothiophene
TLC	thin-layer chromatography
tmeda	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
tmpo	2,2,6,6-tetramethylpiperidine-1-oxyl
Tol	tolyl ($CH_3C_6H_4$)
topo	tri-*n*-octyl phosphate
tos	tosyl
tp	tetragonal pyramid
TPN	triphosphopyridine nucleotide
tr	turnstile rotation
t_r	relative retention time (in GLC)
TSP	thermospray
VSEPR	valence shell electron pair repulsion
X	halide
XRD	X-ray diffraction

CHAPTER 1

The preparation and properties of tervalent phosphorus acid derivatives

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I. INTRODUCTION

Tervalent phosphorus acid derivatives (**1**) are compounds with three covalent bonds to phosphorus and at least one electronegative atom bound directly to the phosphorus atom. Such compounds are able to undergo a diversity of reactions since they are nucleophiles due to the lone pair on phosphorus and also electrophiles because of the presence of a leaving group X. They are generally reactive towards water and often easily oxidized. They are therefore mainly used as intermediates for the preparation of more stable phosphorus compounds, such as phosphine oxides, phosphates and phosphonates.

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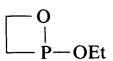
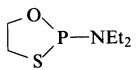
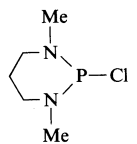
TABLE 1. Names of representative compounds

Formula	Name (i)	Name (ii)
$P(OH)_3$	Trihydroxyphosphine	Phosphorous acid
PCl_3	Trichlorophosphine	Phosphorus trichloride[a]
$MeOPCl_2$	Dichloro(methoxy)phosphine	Methyl phosphorodichloridite
$(MeO)_2PCl$	Chlorodimethoxyphosphine	Dimethyl phosphorochloridite
$P(OMe)_3$	Trimethoxyphosphine	Trimethyl phosphite
$P(SMe)_3$	Tri(methylthio)phosphine	Trimethyl phosphorotrithioite
$P(NMe_2)_3$	Tris(dimethylamino)phosphine	Hexamethylphosphorous triamide
$MeOP(NMe_2)_2$	Bis(dimethylamino)methoxyphosphine	Methyl tetramethylphosphorodiamidite
$(MeO)_2PNMe_2$	(Dimethylamino)dimethoxyphosphine	Dimethyl dimethylphosphoramidite
$MeOP(Cl)NEt_2$	Chloro(diethylamino)methoxyphosphine	Methyl diethylphosphoramidochloridite
$MeOP(SEt)_2$	Methoxydi(ethylthio)phosphine	*O*-Methyl *S*,*S*-diethyl phosphorodithioite
$EtP(OH)_2$	Ethyldihydroxyphosphine	Ethylphosphonous acid
$EtPCl_2$	Dichloro(ethyl)phosphine	Ethylphosphonous dichloride
EtP(OMe)Cl	Chloro(ethyl)methoxyphosphine	Methyl ethylphosphonochloridite
$EtP(OMe)_2$	Ethyldimethoxyphosphine	Dimethyl ethylphosphonite
EtP(OMe)(SPh)	Ethylmethoxy(phenylthio)phosphine	*O*-Methyl *S*-phenyl ethylphosphonothioite
$HP(OBu)_2$	Dibutoxyphosphine	Dibutyl phosphonite[b]
$PhP(SEt)_2$	Di(ethylthio)phenylphosphine	Diethyl phenylphosphonodithioite
$EtP(NMe)_2Cl$	Chloro(dimethylamino)ethylphosphine	*P*-Ethyl-*N*,*N*-dimethylphosphonamidous chloride
$EtP(OEt)NMe_2$	(Dimethylamino)(ethoxy)ethylphosphine	Ethyl *N*,*N*-dimethyl-*P*-ethylphosphonamidite
$EtP(NMe_2)_2$	Bis(dimethylamino)ethylphosphine	*N*,*N*,*N*′,*N*′-Tetramethyl-*P*-ethylphosphonodiamidite
MePhPOH	Hydroxy(methyl)(phenyl)phosphine	Methylphenylphosphinous acid
Me_2PCl	Chlorodimethylphosphine	Dimethylphosphinous chloride
Me_2POEt	Ethoxydimethylphosphine	Ethyl dimethylphosphinite
Me_2PSEt	Ethylthiodimethylphosphine	Ethyl dimethylphosphinothioite
Me_2PNEt_2	(Diethylamino)dimethylphosphine	*N*,*N*-Diethyl-*P*,*P*-dimethylphosphinous amide
PhP=O	Oxo(phenyl)phosphine[c]	
MeP=S	Methylthioxophosphine[c]	
PhP=NMe	(Methylimino)(phenyl)phosphine[c]	

When the tervalent phosphorus group is not the principal group, prefix names have to be used. IUPAC does not give such names, but they may be constructed in analogy with the phosphine nomenclature:

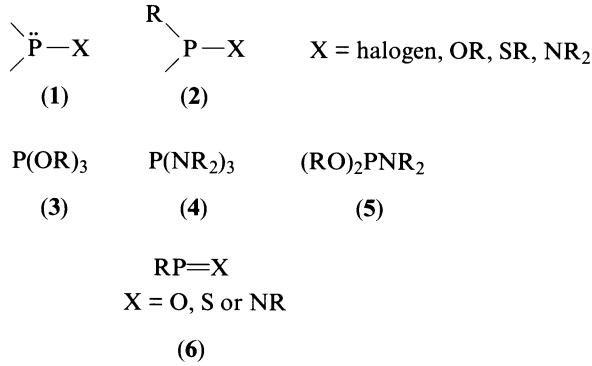
Cl_2P—	Dichlorophosphino-
$(EtO)_2P$—	Diethoxyphosphino-
$Me_2N(PhO)P$—	(Dimethylamino)(phenoxy)phosphino-
Cl(Me)P—	Chloro(methyl)phosphino-
	Chlorophosphinediyl-
	Methoxyphosphinediyl-

Ring compounds are named by the oxa-thia-aza replacement nomenclature from the parent phosphorus-containing ring:

	2-Ethoxy-1,2-oxaphosphetane
	2-Diethylamino-1,3,2-oxathiaphospholane
	2-Chloro-1,3-dimethyl-1,3,2-diazaphosphorinane

[a]This is the inorganic name commonly used.
[b]The IUPAC name. H-phosphonites is suggested as a common name for $HP(OR)_2$.
[c]Not found in the IUPAC list, but constructed in accordance with the phosphine nomenclature.

This chapter will be limited to the preparation and properties of compounds (**2**) with one or two P—C bonds, since only these compounds contain functional groups of phosphorus in the sense of the Patai series. Thus, important classes of tervalent phosphorus acid derivatives with three electronegative groups, e.g. phosphites (**3**), tris(dialkylamino)phosphines (**4**) and phosphoramidites (**5**), will only be included for illustration of a reaction or property which is common to tervalent phosphorus acid derivatives but has not been sufficiently studied for compounds with a P—C bond. The chapter will cover the highly reactive, dicoordinated derivatives **6**, but not diphosphines **1** (X = PR_2) or diphosphenes **6** (X = PR).

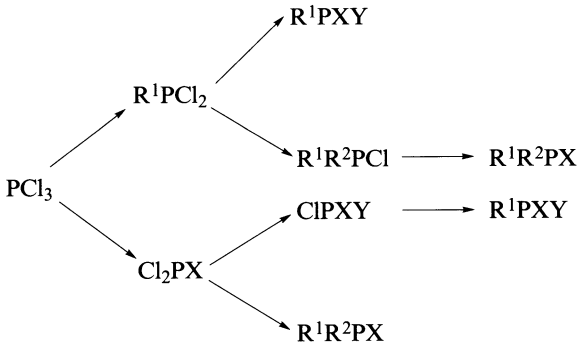


The nomenclature of tervalent phosphorus acid derivatives is difficult, and the literature abounds with ambiguous or misleading names. The IUPAC rules[1] allow three methods to name the compounds: (i) as substitution products of phosphine; (ii) as derivatives of the parent acid; or (iii) as coordination compounds of phosphorus. Of these, only the first two methods are in common use, and Table 1 gives the names of representative examples of compounds according to (i) and (ii), with the name which will be used in this chapter underlined.

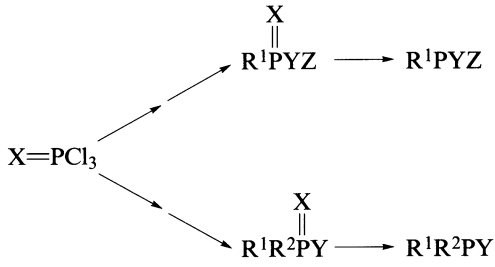
Methods for the preparation and properties of tervalent phosphorus acid derivatives with one or two P—C bonds were reviewed in detail by Sasse in *Houben-Weyl*, Vol. 12/1 (published 1963)[2] and by Regitz in *Houben-Weyl*, Vol. E1 (published 1982)[3]. Another valuable review on this subject is Vol. 4 in Kosolapoff and Maier's *Organophosphorus Compounds* (published 1972)[4], which contains lists on all known compounds up to ca 1970. These should always be consulted for information of the preparation of compounds known before the above publication times. Yearly reviews on the preparation and chemistry of halophosphines and tervalent phosphorus acid derivatives are published in *Specialist Periodical Reports, Organophosphorus Chemistry* (from Vol. 1, 1970)[5].

II. PREPARATION

With few exceptions, derivatives of tervalent phosphorus acids are prepared from phosphorus trichloride by nucleophilic substitution of one or two of the chloro groups with organometallic compounds, followed by substitution of the remaining chloro groups with alkoxy, amino, alkylthio groups, etc., or *vice versa* (Scheme 1). Occasionally a tervalent compound is best obtained by reduction of a (thio)phosphoryl derivative which is prepared from (thio)phosphoryl chloride (Scheme 2), or from a P—H compound and an electrophilic reagent, e.g. Scheme 3.

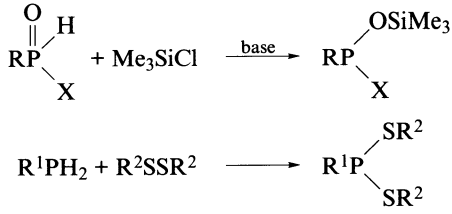


SCHEME 1



X = O or S

SCHEME 2



SCHEME 3

A. Preparation of Halophosphines (Mostly $RPCl_2$ and R_2PCl)

The preparation of these compounds was thoroughly reviewed up to 1970 by Kosolapoff and Maier.[4] Aliphatic compounds are best prepared in the laboratory from PCl_3 and organometallic compounds with reduced reactivity, such as R_4Pb, Bu_3SnR or R_2Cd, unless the alkyl group is highly branched, in which case also the more reactive Grignard or alkyllithium reagents can be made to substitute only one or two of the chlorine atoms of PCl_3. Representative examples are given for the preparation of dichloro(ethyl)phosphine (equation 1)[6], *tert*-butyldichlorophosphine (equation 2)[7], several chlorodialkylphosphines (equation 3)[8,9] and the very hindered dichloro[tris (trimethylsilyl)methyl]phosphine (equation 4)[10]. Unsymmetrical dialkylchlorophosphines, RR'PCl, are obtained by stepwise

$$2PCl_3 + Et_4Pb \xrightarrow{\text{reflux}} 2EtPCl_2 + Et_2PbCl_2 \quad (1)$$
89%

$$PCl_3 + Bu^tMgCl \xrightarrow[-20 \text{ to } -10\ ^\circ C]{Et_2O} Bu^tPCl_2 \quad (2)$$
44–50%

$$PCl_3 + 2RMgCl \xrightarrow[-25\ ^\circ C\text{–r.t.}]{Et_2O} R_2PCl \quad (3)$$
R = Pr^i, Bu^i, Bu^s, Bu^t 45–80%

alkylation with R_4Pb[11] or by the Grignard route if one of the alkyl groups is branched[12,13]. Methylenebis(dichlorophosphine) is easily obtained from dichloromethane, Al and PCl_3[14], but ethylenebis(dichlorophosphine), prepared from ethylene, P_4 and PCl_3 at 200 °C[15], is probably better purchased. Functionalized dichloro(alkyl)phosphines or chlorodialkylphosphines may be obtained from the trialkyltin compounds (equations 5–7)[16–18]. Dichloro(methyl)phosphine (equation 8)[19] and chlorodimethylphosphine (equation 9)[20] are best obtained by other routes as shown.

$$PCl_3 + (Me_3Si)_3CLi \xrightarrow[0\ ^\circ C]{THF} (Me_3Si)_3CPCl_2 \quad (4)$$
67%

$$PCl_3 + n Bu_3SnCH_2COOR \longrightarrow Cl_{3-n}P(CH_2COOR)_n \quad (5)$$
n = 1 or 2; R = Me, Et ~80%

$$PCl_3 + Bu_3SnCH_2CN \longrightarrow Cl_2PCH_2CN \quad (6)$$
23%

$$PCl_3 + Bu_3SnCH_2SMe \longrightarrow Cl_2PCH_2SMe \quad (7)$$
61%

$$PCl_3 + MeI + AlCl_3 \longrightarrow Me\overset{+}{P}Cl_3\ AlCl_3I^- \xrightarrow{Fe\text{–}KCl} MePCl_2 \quad (8)$$
70–80%

$$Me_2P(S)—P(S)Me_2 \xrightarrow[86\%]{SO_2Cl_2} MeP(S)Cl \xrightarrow[73\%]{Bu_3P} Me_2PCl \quad (9)$$

The preparation of chlorophosphines or bromophosphines from (dialkylamino)phosphines and dry HCl or HBr is an indirect method which is occasionally used, e.g. to obtain chlorodicyclopropylphosphine (equation 10)[21], 1-chlorophosphorinane (equation 11)[22], the bisdibromophosphines **7** (equation 12)[23], and the dihalo(trifluoromethyl)phosphines **8** (equation 13)[24]. Reduction of dialkylphosphinothioic chlorides, as in equation 9, or alkylphosphonothioic dichlorides with phosphines is a method which is convenient in some cases, e.g. for the preparation of 1-adamantyldichlorophosphine (equation 14)[25]. The photoinitiated addition of PBr_3 to alkenes or alkynes may be preparative by useful, e.g. to obtain 2-bromocyclohexyldibromophosphine (equation 15)[26]. More useful is that PCl_3 in the presence of catalytic amounts of PBr_3 gives the product of addition of PCl_3 to e.g.

butadiene (equation 16)[27] and phenylacetylene (equation 17)[28]. However, in the presence of triethylamine, PCl_3 and phenylacetylene gave a substitution product (equation 18)[29]. Functionalized alkyldichlorophosphines (**9**) are obtained by the uncatalyzed addition of PCl_3 to silylated ketene acetals (equation 19)[30]. Preparation of chloro- or dichlorophosphines by chlorination of secondary or primary phosphines is only useful when the phosphine is easily obtained, e.g. dichloro(2-cyanoethyl)phosphine (equation 20)[31].

$$Et_2NPCl_2 + 2\ \triangleright\!\!-Li \xrightarrow[61\%]{} \left(\triangleright\!\!-\right)_2 PNEt_2 \xrightarrow[67\%]{HCl} \left(\triangleright\!\!-\right)_2 PCl \qquad (10)$$

$$Et_2NPCl_2 + BrMg(CH_2)_5MgBr \xrightarrow[54\%]{} \text{P(cyclohexyl)—NEt}_2 \xrightarrow[93\%]{HCl} \text{P(cyclohexyl)—Cl} \qquad (11)$$

$$2\,(Et_2N)_2PCl + XMg(CH_2)_nMgX \longrightarrow (Et_2N)_2P(CH_2)_nP(NEt_2)_2 \qquad (12)$$

$n = 4\text{–}10$

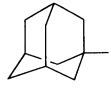
$(Et_2N)_2P(CH_2)_nP(NEt_2)_2 \xrightarrow[76\text{–}90\%]{HBr} Br_2P(CH_2)_nPBr_2$ (**7**)

$$CF_3P(NEt_2)_2 + 4HX \longrightarrow CF_3PX_2 + 2\,Et_2NH_2^+X^- \qquad (13)$$

X = F, Cl, Br, I (**8**)

$$1\text{-Ad—Br} \xrightarrow[(ii)\ H_2O]{(i)\ PCl_3\text{–}AlBr_3} 1\text{-Ad—}\overset{\overset{O}{\|}}{P}Cl_2 \xrightarrow[\text{reagent}]{\text{Lawesson's}} 1\text{-Ad—}\overset{\overset{S}{\|}}{P}Cl_2 \qquad (14)$$

$1\text{-Ad—}\overset{\overset{S}{\|}}{P}Cl_2 \xrightarrow[75\%]{Ph_3P} 1\text{-Ad—}PCl_2$

1-Ad = 

$$PBr_3 + \text{(cyclohexene)} \xrightarrow{O_2} \text{(cyclohexyl)}(PBr_2)(Br) \qquad (15)$$

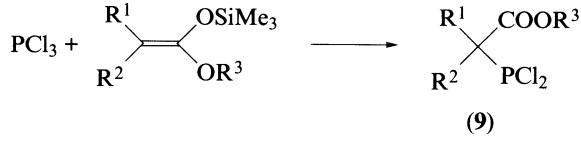
$$PCl_3 + \text{(allyl)} \xrightarrow[\substack{h\nu \\ 45\%}]{\text{cat. } PBr_3} Cl\text{(allyl)}PCl_2 \xrightarrow[50\%]{Et_3N} \text{(allyl)}PCl_2 \qquad (16)$$

$$PCl_3 + PhC{\equiv}CH \xrightarrow[h\nu]{\text{cat. } PBr_3} PhC(PCl_2){=}CHCl \qquad (17)$$

92%

$$PCl_3 + PhC{\equiv}CH \xrightarrow{Et_3N} PhC{\equiv}CPCl_2 \qquad (18)$$

42%



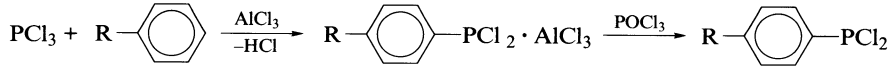
(19)

(9)

$$NCCH_2CH_2PH_2 + 2COCl_2 \longrightarrow NCCH_2CH_2PCl_2 \quad (20)$$

75%

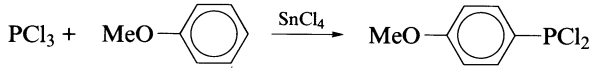
Aromatic dihalophosphines are often prepared by a Friedel–Crafts reaction from PCl_3 or PBr_3 and an arene, with $AlCl_3$, $FeCl_3$, $SnCl_4$ or $ZnCl_2$ as the catalyst. Dichloro(phenyl)-phosphine and chlorodiphenylphosphine [from the thermal disproportionation of dichloro(phenyl)phosphine] are obtained from benzene in this way and are commercially available and cheap; a variety of substituted aryl and heterocyclic derivatives can be similarly made in the laboratory, although mixtures of isomers are often obtained. The reaction fails for aromatic ketones, esters and nitriles. Representative examples are 4-alkylphenyldichlorophosphines (equation 21)[32], dichloro(4-methoxyphenyl)phosphine (equation 22)[33], dichloro (2-thienyl) phosphine (**10**)[34], dibromo(5-methyl-2-furanyl)-phosphine (**11**) and the bromodifuranylphosphine **12**[35], and dibromo(*N*-methyl-2-pyrrolyl)-phosphine (**13**)[36]. The substituted furans and pyrroles are reactive enough to give **11**–**13** with PBr_3 without a Friedel–Crafts catalyst. The same holds for the reaction of PCl_3 with *N*,*N*-dimethylaniline (equation 23)[37] or with diphenylamine (equation 24). The product of the latter reaction, 10-chloro-5,10-dihydrophenophosphazine (**14**), is unstable, but may be generated just before use from the hydrolyzed product as shown[38].



R = Me, Et, Pr^i, Bu, Hex

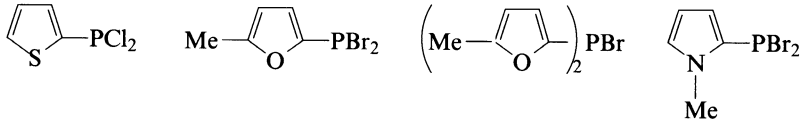
39–69%

(21)

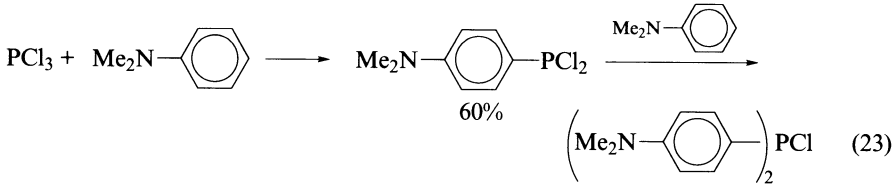


91%

(22)

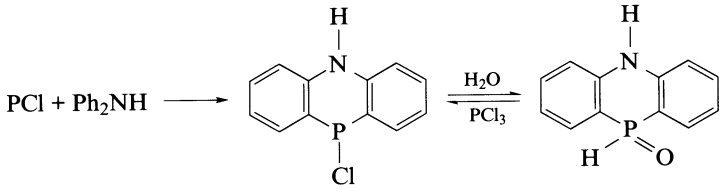


(10) **(11)** **(12)** **(13)**

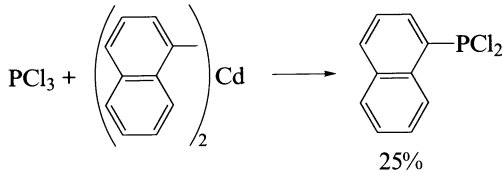


60%

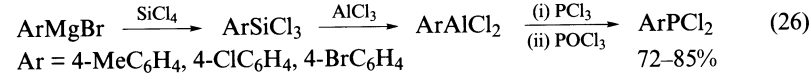
(23)



(14) (24)



(25)



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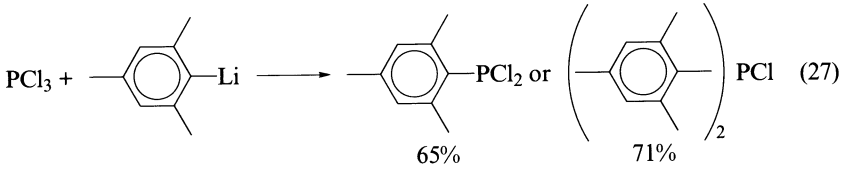
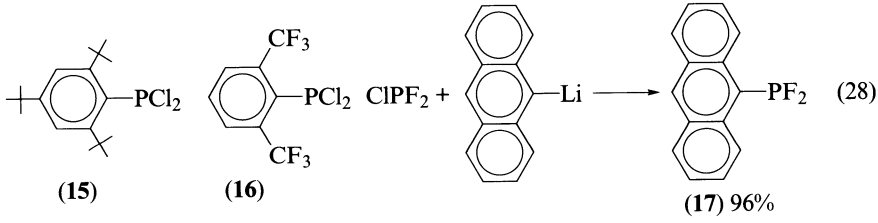


(27)



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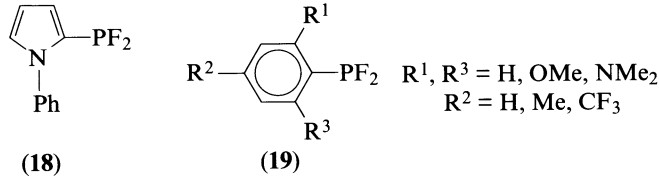
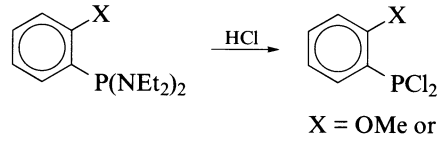


An alternative method to prepare aromatic halo- or dihalo-phosphines is the reaction of a phosphorus trihalide with an arylmetal compound. Like the alkyl compounds, the metal must be a less electropositive one to avoid the formation of a tertiary phosphine, unless the arylmetal compound is sterically hindered. Older examples of syntheses by this method are the preparation of dichloro(1-naphthyl)phosphine (equation 25)[39] and some dichloro(4-substituted-phenyl)phosphines (equation 26)[40]. More recently, hindered aryllithium compounds have been treated with PCl_3 to give dichloro(mesityl)phosphine[41] or chlorodimesitylphosphine[42] (equation 27), dichloro (2,4,6-tri-*tert*-butylphenyl)phosphine (**15**)[10] and dichloro[2,6-bis(trifluormethyl)phenyl]phosphine (**16**).[43] Aryldifluorophosphines have

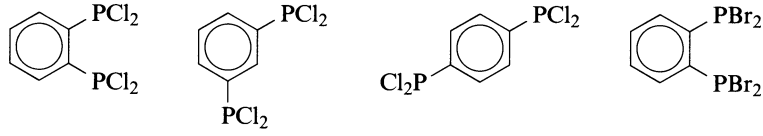
been obtained from the aryllithium and $ClPF_2$, e.g. **17** (equation 28)[44], **18**[45] and **19**[46]. Some diaryl and dialkylfluorophosphines were similarly prepared from Cl_2PF[47].

Other methods to prepare aromatic halo- or dihalo-phosphines are occasionally used. Arylbis(dialkylamino)phosphines have been converted into aryldihalophosphines with dry HCl or HBr, e.g. dichloro(2-methoxy- or 2-dimethylaminophenyl)phosphine (equation 29)[48], the *o*- and *m*-phenylenebis(dichlorophosphine)s **20** and **21**[49] and the *p*-phenylenebis(dichlorophosphine) **22**[50]. The *o*-phenylenebis(dibromophosphine) **23** has been prepared similarly[51]. Aryldiazonium tetrafluoroborates with PCl_3 give chlorophosphonium salts, which can be reduced to aryldichlorophosphines (equation 30)[52]. Primary and secondary phosphines may be chlorinated with phosgene to give chlorophosphines, e.g. hexamethylenebis[chloro(phenyl)phosphine] (equation 31)[53] and **20**[54].

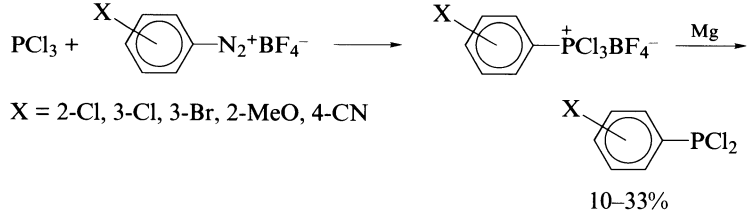


(29)

X = OMe or NMe_2



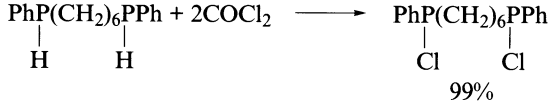
(20) **(21)** **(22)** **(23)**



X = 2-Cl, 3-Cl, 3-Br, 2-MeO, 4-CN

10–33%

(30)



99%

(31)

Halophosphines other than chlorophosphines are often made from the chlorophosphine by halogen exchange. Fluorophosphines are best prepared by exchange with NaF in a dipolar aprotic solvent, e.g. sulpholane, and bromophosphines by exchange with PBr_3 without a solvent; the labile iodophosphines can be obtained from exchange with LiI or Me_3SiI. Several examples are given in *Houben-Weyl* [2,3].

B. Preparation of Aminophosphines [$RP(NR_2)_2$ and R_2PNR_2] and Aminohalophosphines [Mostly $RP(Cl)NR_2$]

Aminophosphines are mostly prepared by one of two routes: the reaction of halophosphines (normally chlorophosphines) with amines or silylated amines (equation 32), or the

reaction of aminohalophosphines with organometallic compounds (equation 33). Of these, the first method normally gives the highest yield because organometallic compounds displace amino groups nearly as fast as halo groups at a tervalent phosphorus centre.

$$R_nP(NR_2)_{3-n} \xleftarrow[-Me_3SiCl]{R_2NSiMe_3} R_nPCl_{3-n} \xrightarrow[-R_2NH_2{}^+Cl^-]{R_2NH} R_nP(NR_2)_{3-n} \quad (32)$$

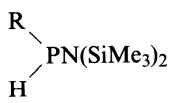
$$Cl_nP(NR_2)_{3-n} + nRM \longrightarrow R_nP(NR_2)_{3-n} + nMCl \quad (33)$$

A great number of aminophosphines were known prior to 1970 and were listed by Kosolapoff and Maier[4]. Derivatives with no substituents on the nitrogen atom are stable only when the phosphorus substituents are very bulky or highly electronegative, e.g. the amino-*tert*-butylphosphines **24**[55] and **25**[56] and the amino(trifluoromethyl)phosphines **26**[57] and **27**[58]. Derivatives with one N—H bond are more common, although eliminations (equation 34) or further reactions (equation 35) may complicate their preparation. A few aminophosphines which contain a P—H bond are known, e.g. **28**[59], **29** and **30**[60]; they are prepared by complex hydride reduction of the corresponding aminochlorophosphines.

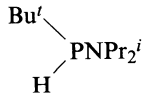
$Bu^tP(NH_2)_2$ (**24**) $Bu^t{}_2PNH_2$ (**25**) $CF_3P(NH_2)_2$ (**26**) $(CF_3)_2PNH_2$ (**27**)

$$RPCl_2 + R'NH_2 \longrightarrow \underset{\displaystyle Cl\ \ H}{RP{-}NR'} \longrightarrow (RP{=}NR')_n \quad (34)$$

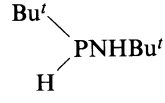
$$R_2PCl + R'NH_2 \longrightarrow R_2PNHR' \xrightarrow{R_2PCl} (R_2P)_2NR' \quad (35)$$



(**28**)



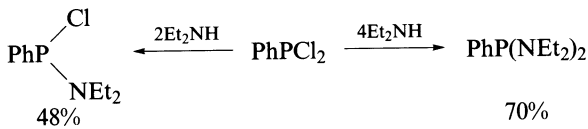
(**29**)



(**30**)

R = Pr^i, Bu^t, CH_2SiMe_3, Ph

The preparation of aminophosphines from chlorophosphines and an amine is usually straightforward. Two equivalents of the amine or the addition of one equivalent of a tertiary amine per chloro group is necessary to neutralize the acid formed, unless a trimethylsilylamine is used; good yields of aminochlorophosphines are obtained from dichlorophosphines and 2 mol of an amine or 1 mol of a trimethylsilylamine. Representative examples are the preparation of aminophosphines from dichloro(phenyl)phosphine (equations 36[61] and 37[62]) and the preparation of some functionalized aminophosphines (equations 38[18] and 39[36]). Examples of reactions with trimethylsilylamines are given in equations 40[63] and 41[64]. Hydrazinophosphines are known and may be prepared from chlorophosphines, e.g. 2,2-dimethylhydrazinodiphenylphosphine (equation 42)[65].



(36)

$$PhPCl_2 \xrightarrow[Et_3N]{Pr^iNH_2} PhP(NHPr^i)_2 + PhP(NHPr^i)N(Pr^i)PPh(NHPr^i) \quad (37)$$

ca 1 : 1

$$MeSCH_2PCl_2 \xrightarrow{Et_2NH} MeSCH_2P(NEt_2)_2 \quad (38)$$

80%

$$PBr_3 + \text{N-Me-pyrrole} \longrightarrow \text{N-Me-pyrrole-PBr}_2 \xrightarrow{Et_2NH} \text{N-Me-pyrrole-P(NEt}_2)_2 \quad (39)$$

74%

$$MePCl_2 + MeN(SiMe_3)_2 \longrightarrow MeP(Cl)N(Me)SiMe_3 \quad (40)$$

73%

$$C_6F_5PCl_2 + 2Me_2NSiMe_3 \longrightarrow C_6F_5P(NMe_2)_2 \quad (41)$$

81%

$$Ph_2PCl + 2H_2NNMe_2 \longrightarrow Ph_2PNHNMe_2 \quad (42)$$

85%

The reaction of aminochlorophosphines with organometallic compounds is the other main route to aminophosphines. The method is convenient since aminochlorophosphines are easy to prepare, either from PCl_3 and the calculated amount of secondary amine, or from commercially available $P(NMe_2)_3$ or $P(NEt_2)_3$ and the calculated amounts of PCl_3 (equation 43 and 44)[66–68]. Grignard reagents tend to give low yields, e.g. of (dimethylamino)- dimethylphosphine (equation 45)[69], and organoaluminium compounds seem not to be better (equation 46)[70]. However, alkyllithium reagents at low temperatures give high yields (equation 47 and 48)[66], probably because the more reactive organolithium compounds do substitute chloro groups but not readily amino groups at low temperatures. More recent examples are the preparation of bis(diethylamino)ethynylphosphine (equation 49)[71] and other compounds shown before (equations 10–12). Some functionalized aminophosphines have also been prepared by this method, e.g. methyl *P*,*P*-bis(dimethylamino)phosphinoacetate (equation 50)[72] and some arylbis(diethylamino)phosphines (equations 51 and 52)[48].

$$PCl_3 + 2(Me_2N)_3P \xrightarrow{r.t.} 3(Me_2N)_2PCl \quad (43)$$

92%

$$2PCl_3 + (Me_2N)_3P \xrightarrow{r.t.} 3Me_2NPCl_2 \quad (44)$$

82%

$$Me_2NPCl_2 + 2MeMgBr \longrightarrow Me_2PNMe_2 \quad (45)$$

48%

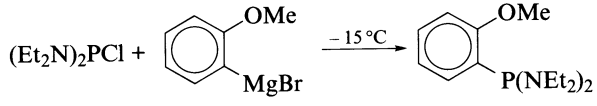
$$(Me_2N)_2PCl + Et_3Al \longrightarrow EtP(NMe_2)_2 \quad (46)$$
45%

$$Me_2NPCl_2 + 2BuLi \xrightarrow{-78\,^\circ C} Bu_2PNMe_2 \quad (47)$$
80%

$$(Me_2N)_2PCl + BuLi \xrightarrow{-78\,^\circ C} BuP(NMe_2)_2 \quad (48)$$
83%

$$(Et_2N)_2PCl + HC{\equiv}CMgBr \xrightarrow{0\,^\circ C} HC{\equiv}CP(NEt_2)_2 \quad (49)$$
72%

$$(Me_2N)_2PCl + LiCH_2COOMe \xrightarrow{-68\,^\circ C} MeOCOCH_2P(NMe_2)_2 \quad (50)$$
63%



(51)

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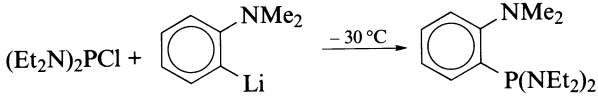
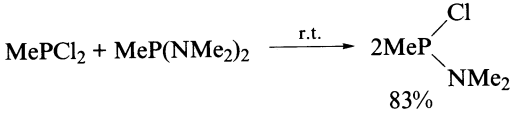


(52)

64%

Aminohalophosphines can be prepared from dihalophosphines and 2 mol of an amine (equation 36) or simply by mixing a diaminophosphine with a dihalophosphine. The latter method gives a pure product in high yield, e.g. equations 53[73] and 54[74].



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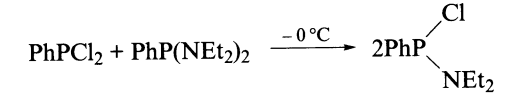
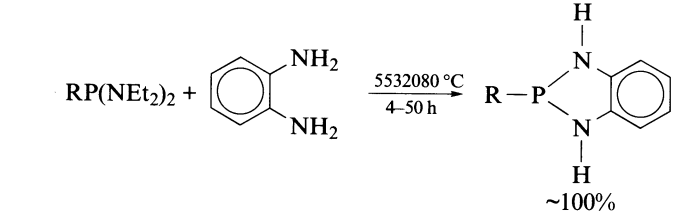


(54)

Aminophosphines can be converted into other aminophosphines by transamination. The reaction is probably acid catalyzed and an equilibrium is established which can be displaced by distilling off the lowest boiling amine. A recent example is shown in equation 55[75,76]. Other methods to obtain aminophosphines have occasionally been used. Reduction of some phosphinic amides with phenylsilane have been described (equation 56)[77] and a

thiophosphinic amide with potassium gave an aminophosphine in low yield[78]. A simple method to prepare bis(diethylamino)trifluoromethylphosphine (equation 57)[24] seems a useful route to other trifluoromethyl-substituted tervalent compounds, e.g. **31** and **8**. Some α-haloalkylbis(diisopropylamino)phosphines were obtained by halogenation of alkylbis-(diisopropylamino)phosphines with CCl_4 or $CBrCl_3$ to give halophosphoranes, which rearranged to the aminophosphines (equation 58)[79].



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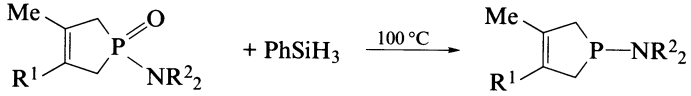
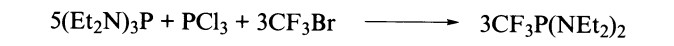


(56)

R^1 = H, Me
R^2 = Me, Et

62–69%



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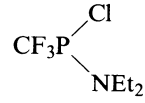

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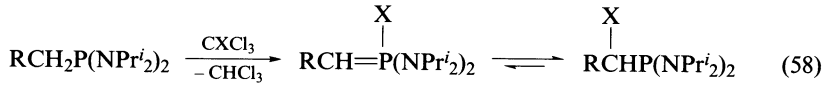


(58)

R = H, Me, Pr, Pr^i
X = Cl, Br

C. Preparation of Phosphinites (R_2POR), Phosphonites [$RP(OR)_2$], Phosphonohalidites [Mostly RP(Cl)OR] and Phosphonamidites [$RP(OR)NR_2$]

Tervalent phosphorus compounds which contain one to three alkoxy or aryloxy groups are mostly prepared by one of three routes: the reaction of a halophosphine with an alcohol or a phenol in the presence of a base (equation 59), the reaction of an amino-phosphine with an alcohol or a phenol (equation 60) or the reaction of a phosphite, a phos-phorochloridite, a phosphorodichloridite, or a phosphoramidochloridite with an organometallic compound (equation 61). The first two methods generally give high yields, whereas the last method gives variable yields because alkoxy/aryloxy groups or amino groups may be substituted in addition to the substitution of the chloro group(s). Phosphinites, phosphonites, phosphonohalidites and phosphonamidites known up to 1970 were listed by Kosolapoff and Maier[4].

$$\text{P—Cl} + \text{ROH} \xrightarrow[-\text{HCl}]{\text{base}} \text{P—OR} \tag{59}$$

$$\text{P—NR}^1_2 + \text{R}^2\text{OH} \xrightarrow[-\text{R}^1_2\text{NH}]{} \text{P—OR}^2 \tag{60}$$

$$\text{Cl—P—OR}^1 + \text{R}^2\text{M} \xrightarrow[-\text{MCl}]{} \text{R}^2\text{—P—OR}^1 \tag{61}$$

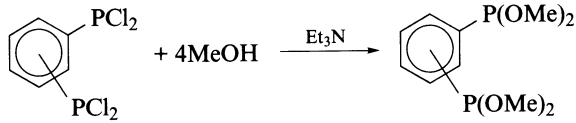
The reaction of a halophosphine with an alcohol in the presence of a base, often triethylamine, is the method mostly used to obtain alkyl phosphinites, phosphonites and phosphonohalidites. Without a base the alcohol is transformed into an alkyl halide because an intermediate alkoxyphosphonium ion is dealkylated by an S_N1 or S_N2 reaction (equation 62). Since an analogous dearylation does not occur, halophosphines can be treated with phenols to give aryl phosphinites, etc., in the absence of a base. Representative examples are the preparation of diethyl methylphosphonite (equation 63)[80], tetraalkyl and tetraaryl methylenediphosphonites (equation 64)[81], tetramethyl ethylenediphosphonite[82], and tetramethyl *o*-phenylene-[51] and *m*-phenylene-diphosphonite (equation 65)[83]. Phosphinites are similarly obtained[2] or prepared from the chlorophosphine and an alkoxide[84], e.g. some alkyl di-*tert*-butylphosphinites (equation 66)[85,86]. No base is required for the preparation of aryl phosphinites or phosphonites[2] or dialkyl trichloromethylphosphonites (equation 67)[87]. Ethyl diphenylphosphinite has been obtained from chlorodiphenylphosphine and triethyl orthoacetate, also without a base (equation 68)[88]. The reaction of epoxides with halophosphines to give 2-chloroalkyl phosphinites or phosphonites (equation 69) does not require a base either[2,3]. Phosphonohalidites are easily obtained from dichlorophosphines and 1 mol of an alcohol plus 1 mol of a base (e.g. equation 70) or 1 mol of a trimethylsilyl ether if a base cannot be tolerated[2,3]. Phosphonamidites can be prepared from an aminohalophosphine and an alcohol or phenol plus a base (e.g. equation 71)[89], from a phosphonohalidite and an amine (e.g. equation 72)[90] or from a dihalophosphine and an amino alcohol (e.g. equation 73)[3].

$$\text{P—Cl} + \text{ROH} \longrightarrow \text{P—OR} + \text{HCl} \rightleftharpoons \left[\text{H—P}^{+}\text{—OR}\right] \text{Cl}^- \longrightarrow \text{H—P(=O)} + \text{RCl} \tag{62}$$

$$\text{MePCl}_2 + 2\text{EtOH} \xrightarrow{\text{PhNMe}_2} \underset{91\%}{\text{MeP(OEt)}_2} \tag{63}$$

$$\text{Cl}_2\text{PCH}_2\text{PCl}_2 + 4\text{ROH} \xrightarrow[\text{Py}]{\text{Et}_3\text{N or}} (\text{RO})_2\text{PCH}_2\text{P(OR)}_2 \tag{64}$$

R = Me, Et, Ph, *p*-tolyl 45–70%



(65)

o : 32–73%

m : 92%

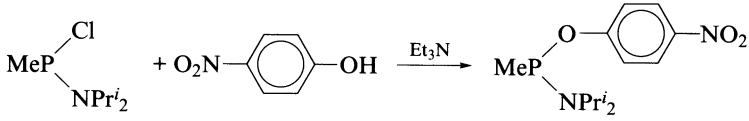
$$Bu^t_2PCl + RONa \xrightarrow{ROH} Bu^t_2POR \quad (66)$$
$$R = Me, Et, Pr^i \qquad 43\text{–}88\%$$

$$CCl_3PCl_2 + 2ROH \xrightarrow[-2HCl]{vacuum} CCl_3P(OR)_2 \quad (67)$$
$$R = Me, Bu, Pen \qquad 66\text{–}78\%$$

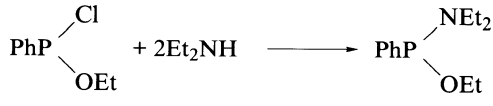
$$Ph_2PCl + CH_2C(OEt)_3 \longrightarrow Ph_2POEt + EtCl + CH_3COOEt \quad (68)$$
$$78\%$$

$$RPCl_2 + 2 \text{ (epoxide)} \xrightarrow{0\,^\circ C} RP(OCH_2CH_2Cl)_2 \quad (69)$$

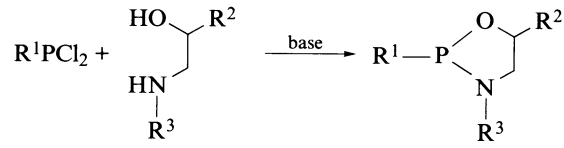
$$PhPCl_2 + BuOH \xrightarrow[-30\,^\circ C]{PhNEt_2} \text{PhP(Cl)(OBu)} \quad (70)$$
$$62\%$$



(71)
95%



(72)
65%

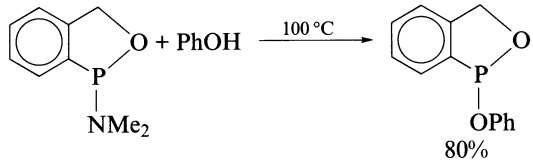


(73)

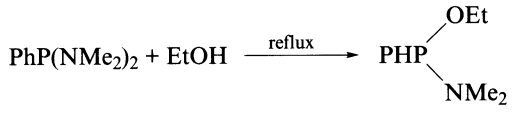
The reaction of an aminophosphine with an alcohol or a phenol can give rise to phosphinites, phosphonites or phosphonamidites. No reaction occurs unless a weak acid is present ($R_2NH_2^+Cl^-$, tetrazole, phenols, etc.)[91], but since aminophosphines are usually contaminated with ammonium halides, the reaction will normally take place in the absence of added acid catalyst, at least on heating. In the presence of molar amounts of catalyst, however, the reaction is usually fast at room temperature. Representative older examples of preparations where no catalyst was added are the preparation of butyl diphenylphosphinite and dibutyl phenylphosphonite (equation 74)[92], dimethyl methylphosphonite (equation 75)[73] and 1-phenoxy-3*H*-2,1-benzoxaphosphole (equation 76)[93]. Bis(dialkylamino)phosphines with 1 mole of an alcohol give high yields of phosphonamidites, e.g. equation 77[70]. With 2-aminoethanol or 2-aminophenol, diaminophosphines give 1,3,2-oxaphospholidines, e.g. equation 78[94]. Catalyzed reactions at room temperature have been used mainly to prepare phosphonites and phosphonamidites of sensitive natural products, e.g. nucleosides. A representative example is shown in equation 79[95,96].

$$Ph_nP(NEt_2)_{3-n} + BuOH \xrightarrow{\text{reflux}} Ph_nP(OBu)_{3-n} \quad (74)$$
$n = 1$ or 2 — 94–95%

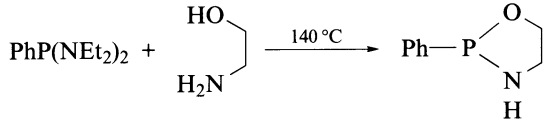
$$MeP(NMe_2)_2 + MeOH \xrightarrow{70\text{–}90\ ^\circ C} MeP(OMe)_2 \quad (75)$$
76%



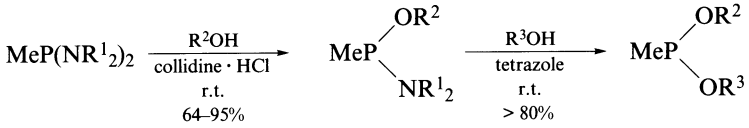
(76)
80%



(77)
81%



(78)
68%



(79)

R^1 = Me, Pr^i
R^2OH, R^3OH = nucleosides

The reaction of a phosphite, a phosphorochloridite, a phosphorodichloridite or a phosphoramidochloridite with an organometallic compound constitutes the third commonly used method to obtain phosphinites, phosphonites or phosphonamidites. As mentioned before, a chloro group is a better leaving group than an alkoxy, a phenoxy, or a dialkylamino group at a tervalent phosphorus atom, so a stochiometric amount of an organometallic compound can yield products which are the result of substitution of only the chloro groups. The yields, however, are generally not as high as those for the previous two methods, partly also because of difficulties in obtaining pure phosphorochloridites, phosphorodichloridites or phosphoramidochloridites as the starting materials[97]. Convenient methods to prepare 96–99% pure phosphorochloridites from trialkyl phosphites (equation 80)[98], methyl or ethyl phosphorodichloridite from the dialkyl phosphites (equation 81)[99] or from trimethyl phosphite (equation 82)[100] and a series of alkyl phosphorodichloridites from the alcohol and a large excess of phosphorus trichloride in acetonitrile (equation 83)[101], however, makes this route more attractive. Representative examples are the preparation of diethyl methylphosphonite (equation 84)[80] and a series of diethyl phosphonites (equation 85)[102] and ethyl phosphinites (equation 86)[102] from diethyl phosphorochloridite or ethyl phosphorodichloridite. Triethyl phosphite or tributyl phosphite

with 1 mol of a Grignard reagent gave reasonable yields of dialkyl phosphonites, e.g. equation 87[102], but 2 mol of a Grignard reagent gave a mixture of dialkyl phosphonites and tertiary phosphines and no alkyl phosphinite[102]. Functionalized phosphonites have been obtained from diethyl phosphorochloridite and lithium enolates at low temperatures, e.g. an organolithium ester (equation 88)[72] and several α-lithiated ketones and esters[103]. In the latter cases, the phosphonates were isolated in 32–93% yield after air oxidation. Two 2, 1-benzoxaphospholes have been prepared from *o*-lithiobenzyl alcoholate and dichloro-(phenyl)phosphine or dichloro(dimethylamino)phosphine (equation 89)[93]. The cyclic phosphorochloridite **32** has been prepared in 79% yield from 2-phenylphenol, PCl_3 and $ZnCl_2$[104].

$$(RO)_3P + Ph_3PCl_2 \xrightarrow[\text{reflux}]{CH_2Cl_2} (RO)_2PCl + Ph_3PO + RCl \quad (80)$$

R = Me, Et, Pr, Pr^i, Bu; 38–71%

$$(RO)_2PHO + PCl_3 \xrightarrow{\text{r.t.}} ROPCl_2 \quad (81)$$

R = Me, Et; 53–72%

$$(MeO)_3P + PCl_3 \xrightarrow{\text{r.t.}} MeOPCl_2 \quad (82)$$

55%

$$PCl_3 + ROH \xrightarrow[CH_3CN]{\text{r.t.}} ROPCl_2 \quad (83)$$

93–100%

R = $R_1SO_2CH_2CH_2$, $NCCH_2CH_2$, $C_{16}H_{33}$, $PhCH_2$, fluorenylmethyl

$$(EtO)_2PCl + MeMgI \xrightarrow{-10 \text{ to } 0\,^\circ C} MeP(OEt)_2 \quad (84)$$

61%

$$(EtO)_2PCl + RMgX \xrightarrow{10\,^\circ C} RP(OEt)_2 \quad (85)$$

R = Et, Bu, $PhCH_2$, Ph; 47–63%

$$EtOPCl_2 + 2RMgCl \xrightarrow{0\,^\circ C} R_2POEt \quad (86)$$

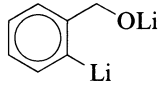
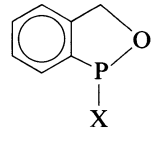
R = Et, Bu, Hex, octyl, $PhCH_2$, Ph; 15–63%

$$(EtO)_3P + RMgX \xrightarrow{65\,^\circ C} RP(OEt)_2 \quad (87)$$

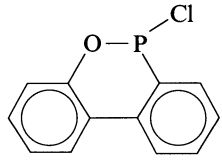
R = Et, Bu, $PhCH_2$, Ph; 31–54%

$$(EtO)_2PCl + LiCH_2COOEt \xrightarrow{-68\,^\circ C} EtOCOCH_2P(OEt)_2 \quad (88)$$

69%

$$XPCl_2 + \text{  } \xrightarrow{-78\,^\circ C} \text{  } \quad (89)$$

X = Ph, Me_2N; 30–50%



(32)

Other methods than those above are sometimes used to prepare phosphinites, phosphonites, phosphonohalidites or phosphonamidites. Trimethylsilyl phosphinites or phosphonites are obtained in high yield from dialkyl(or aryl)phosphine oxides or monoalkyl(or aryl)phosphinic acids, respectively, and chlorotrimethylsilane plus a base, or aminosilanes. Examples are the preparation of trimethylsilyl diphenylphosphinite (equation 90)[105], bis(trimethylsilyl)phenylphosphonite (equation 91)[106] and some bisphosphinites (equation 92)[107]. Phosphonohalidites may be prepared by exchange between dihalophosphines and phosphonites, e.g. ethyl phenylphosphonochloridite was obtained in good yield in this way (equation 93)[90]. Transesterification of phosphonites with a higher boiling alcohol or phenol is catalyzed by acids or bases (see Section V); this method, with sodium as the catalyst, has been used to prepare dibutyl butylphosphonite from diethyl butylphosphonite[102] and ethyl phenyl ethylphosphonite from diethyl ethylphosphonite (equation 94)[108]. Dialkoxyphosphines (H-phosphonites) can be alkylated by compounds containing activated C=C bonds, e.g. acrylonitrile (equation 95)[109], or by aldehyde derivatives, e.g. (butoxymethyl)dialkylamines (equation 96)[110] to give functionalized alkylphosphonites. The preparation of phosphinites and phosphonites by reduction of phosphinic or phosphonic acid derivatives requires a selective reduction which is difficult to perform. $LiAlH_4$ reduces phosphinates and phosphonates to the secondary or primary phosphines, respectively[111], and sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) seems to remove alkoxy groups in preference to the phosphoryl oxygen[112]. A few phosphinites have been obtained in low yields by reduction of a thiophosphinate with Na[78], a cyclic thiophosphinate with a Ni complex (equation 97)[113] and a phosphinate by alkylation with triethyloxonium tetrafluoroborate followed by reduction with Mg[114]. An optically active phosphinite has been prepared by methylation of an optically active thiophosphinate and removal of the methylthio group with tris(dimethylamino)phosphine (equation 98)[115].

$$Ph_2PHO + Me_3SiCl \xrightarrow{Et_3N} Ph_2POSiMe_3 \quad 81\% \qquad (90)$$

$$PhP(H)(=O)-OH + (Me_3Si)_2NH \xrightarrow{125\,^\circ C} PhP(OSiMe_3)_2 \quad 90\% \qquad (91)$$

$$MeP(H)(=O)-(CH_2)_n-P(H)(=O)Me + 2M_3SiNMe_2 \xrightarrow{90\,^\circ C} MeP(OSiMe)-(CH_2)_n-P(OSiMe)Me \quad 71\% \qquad (92)$$

($n = 2$ or 3)

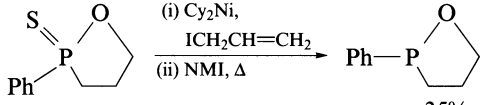
$$PhPCl_2 + PhP(OEt)_2 \xrightarrow{0\,^\circ C} 2PhP(Cl)(OEt) \quad 74\% \qquad (93)$$

$$EtP(OEt)_2 + PhOH \xrightarrow[\text{reflux}]{\text{cat. Na}} EtP(OPh)(OEt) \quad 72\% \tag{94}$$

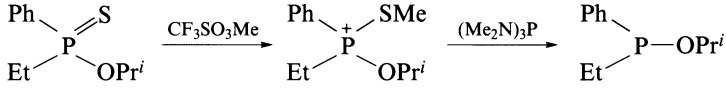
$$(BuO)_2PH + CH_2{=}CHCN \xrightarrow{\text{r.t.}} NCCH_2CH_2P(OBu)_2 \quad 54\% \tag{95}$$

$$(BuO)_2PH + BuOCH_2NR_2 \xrightarrow{\text{r.t.}} R_2NCH_2P(OBu)_2 \quad 81\text{–}85\% \tag{96}$$

R = Me, Et, Pr



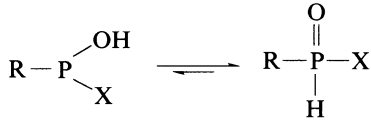
35% (97)



78% (98)

D. Preparation of Tervalent Phosphinous and Phosphonous Acids

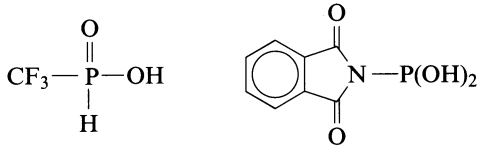
Phosphinous and phosphonous acids normally exist in the tetracoordinated form (equation 99). This is shown by the presence of P—H and P=O vibrations in the IR spectra and large $^1J_{PH}$ coupling constants and low δ_P chemical shift values in the ^{31}P NMR spectra and by the fact that phosphinous acids are very weak acids and phosphonous acids are only monovalent acids in water. The anions derived from these acids, however, are ambident, and hard electrophiles may react at oxygen to give tervalent derivatives (equations 90–92). The only well characterized tervalent phosphinous acid is bis(trifluoromethyl)phosphinous acid, prepared from the anhydride (equation 100) in 1960[116]. The tervalent tautomer structure was shown by the absence of P—H and P=O stretching vibrations in the IR spectrum and the presence of a strong O—H stretching band[117]. Later ^{31}P NMR data (δ_P 78 ppm)[118] confirmed the tervalent structure. The reason for the tervalent structure being the stable tautomer in this case is probably the presence of the two strongly electron-attracting trifluoromethyl groups, which reduces the basicity of the phosphorus atom sufficiently to place the proton on oxygen instead of on phosphorus.



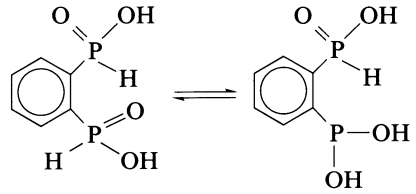
X = R, Cl, OR, NR_2 (99)

$$(CF_3)_2POP(CF_3)_2 \xrightarrow{HCl} (CF_3)_2P{-}OH + (CF_3)_2PCl \quad 92\% \tag{100}$$

No tervalent phosphonous acids are known; one trifluoromethyl group, as in trifluoromethylphosphonous acid (**33**)[119], does not promote the tervalent structure according to IR evidence. Phosphinous, phosphonous and phosphorous acid or derivatives should not be assigned a tervalent structure without proper evidence. For example, a diphosphonous acid was claimed to exist as a mixture of two tautomeric forms (equation 101)[51], the postulated structure with a tervalent phosphorus atom is unlikely since both isomers had phosphorus chemical shifts in the usual range for tetracoordinatated compounds. Recent examples of the elusive tervalent acids are some phosphorous amides, e.g. **34**[120], which lack P=O stretching bands in their IR spectra and have phosphorus chemical shifts in the region expected for tervalent compounds.



(**33**) (**34**) δp 142.5

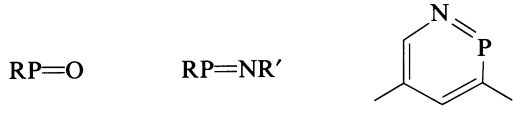


(101)

δp 14.3 δp 17.2 and 11.0

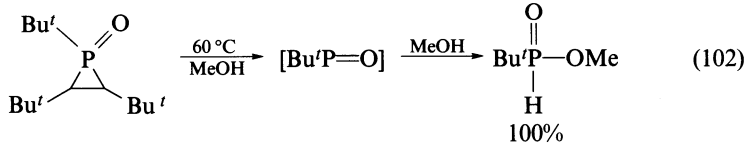
E. Preparation of Two-coordinated Tervalent Compounds

Oxophosphines (**35**) and iminophosphines (**36**) are in general highly reactive compounds which can be generated and trapped by dienes, alcohols, etc., before they oligomerize or polymerize. Iminophosphines are the least reactive and can be isolated if they contain sterically demanding groups at phosphorus and/or nitrogen. The iminophosphine moiety may also be stabilized by being part of an aromatic ring, e.g. **37**[121]; such heterocyclic iminophosphines will not be covered here.

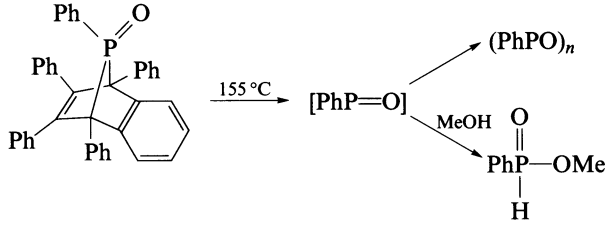


(**35**) (**36**) (**37**)

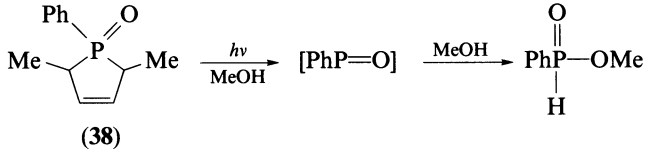
Oxophosphines have been generated by pyrolysis of cyclic phosphine oxides, e.g. *tert*-butyloxophosphine (equation 102)[122] and oxophenylphosphine (equation 103)[123]. The thermally stable dihydrophosphole **38** gave oxophenylphosphine upon irradiation (equation 104)[124]. Another route to oxophosphines is the dehalogenation of phosphonic dihalides with magnesium, e.g. oxophenylphosphine from phenylphosphonic dichloride



(102)

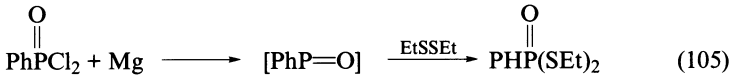


(103)



(38)

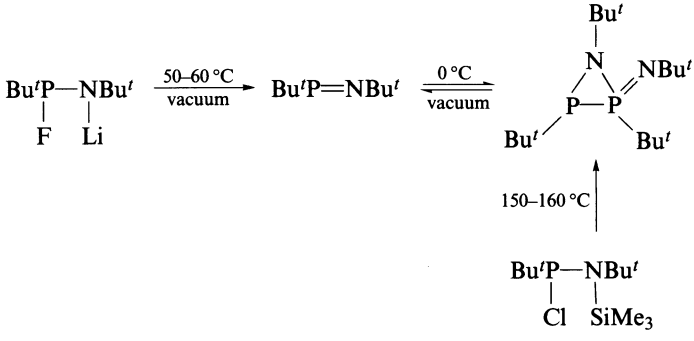
(104)



(105)

(equation 105)[125]. In no case has a monomeric oxophosphine been detected, but its existence has been inferred from trapping experiments.

The first iminophosphine was isolated in 1981; it was prepared by two routes (equation 106) and was stable below – 40 °C[126]. Two years later an iminophosphine was prepared which could survive distillation at 110 °C (equation 107)[127]. Several other iminophosphines (**39**) have been prepared by the route of equation 107 or from chloro(silylamino)phosphines on heating (equation 108)[128]. These iminophosphines are kinetically stabilized by large groups on both the phosphorus and the nitrogen atom. With small groups at phosphorus even the large *N*-substituent 2,4,6-tri-*tert*-butylphenyl does not prevent dimerization of **40** at low temperatures (equation 109),[129] although **40** (R = isopropyl) is stable[130].



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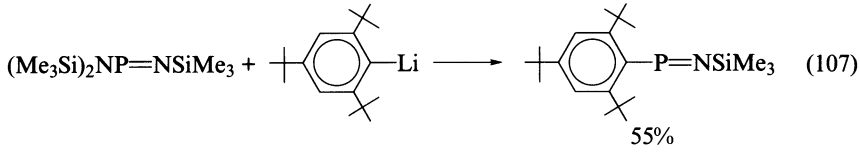
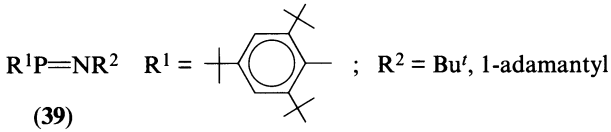
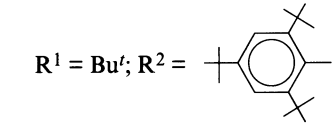
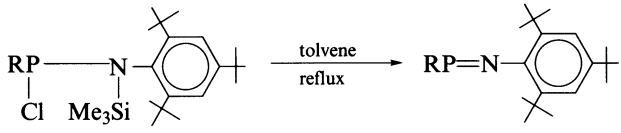


(107)



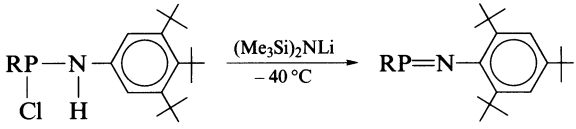
(39)



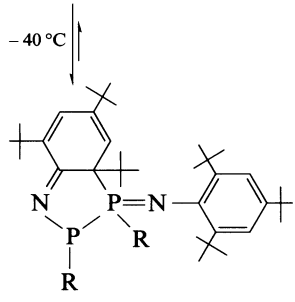


(108)

R = Bu^t, Ph, mesityl ~100%



R = Me, Et **(40)**

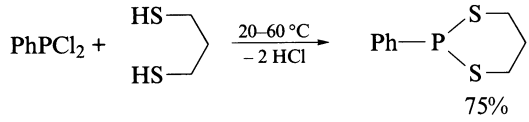


(109)

E. Preparation of Thio and Seleno Analogues

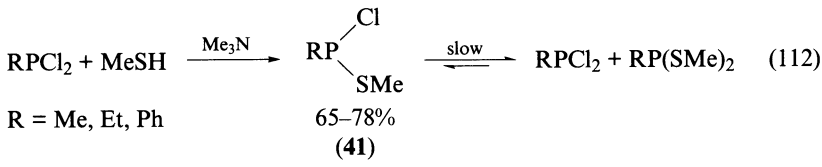
Thio analogues of phosphinites, phosphonites, phosphonohalidites and phosphonamidites have been known for a long time, and are often prepared in an analogous way to the oxygen compounds[2-4]. Representative examples are 2-phenyl-1,3,2-dithiaphosphorinane, prepared from dichloro(phenyl)phosphine and propane-1, 3-dithiol without a base (equation 110)[131], butyl diphenylphosphinothioite from chlorodiphenylphosphine and butyl trimethylsilyl sulphide (equation 111)[132], some labile methyl phosphonochloridothioites (**41**) prepared from dichlorophosphines and methanethiol (equation 112)[133] and

2-methyl-1,3,2-thiazaphospholidine from bis(diethylamino)methylphosphine and 2-aminoethanethiol (equation 113)[134]. Seleno analogues have also been prepared by similar routes, e.g. dimethyl phenylphosphonodiselenoite (equation 114)[135] and the phosphinoselenoite **42** (equation 115)[136]. A useful synthetic route which has no counterpart in the oxygen compounds is to heat primary or secondary phosphines with disulphides, e.g. equation 116[137]. Two optically active phosphinothioites have been prepared by reduction with tris(dimethylamino)phosphine of the corresponding methylated phosphinodithioate (cf. equation 98)[115].

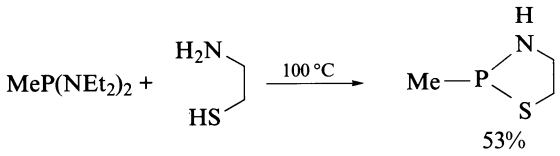


(110)

$$Ph_2PCl + BuSSiMe_3 \longrightarrow Ph_2PSBu \quad 43\% \qquad (111)$$

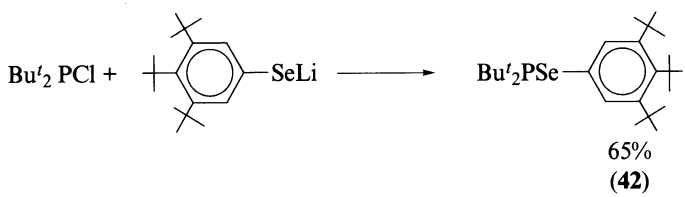


(112)

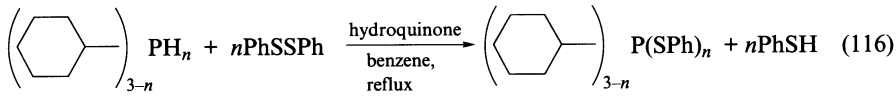


(113)

$$PhPCl_2 + 2MeSeSiMe_3 \longrightarrow PhP(SeMe)_2 \quad 99\% \qquad (114)$$



(115)



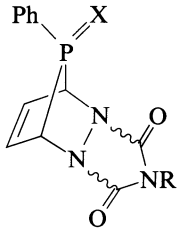
(116)

n = 1 or 2 90–92%

Thiophosphorous acids exist in the tetracoordinated from, except bis(trifluoromethyl)-phosphinothioic acid (**43**)[138]. Two-coordinated thioxophosphines and selenoxophosphines appear to be kinetically more stable than oxophosphines. They have been generated by pyrolysis (X = S) or photolysis (X = Se) of **44** (equation 117)[139] and the first stable thioxophosphines (equation 118)[140] and a moderately stable selenoxophosphine (equation 119)[141] have recently been isolated.

$(CF_3)_2P—SH$

(43)



(44)

X = S or Se

$$Ph_3P{=}CPCl_2 \xrightarrow{Na_2S} Ph_3P{=}CP{=}S \qquad (118)$$

R = Me, Et, Ph, *m*-tolyl; 68% (R = Et)

$$ArP{=}PAr \xrightarrow{Se} ArP(=Se)_2 \xrightarrow{(Me_2N)_3P} ArP{=}Se \qquad (119)$$

Ar =

III. HANDLING; PHYSICAL PROPERTIES

Tervalent phosphorus acid derivatives are normally liquids or low-melting solids which can be purified by distillation, or sometimes by recrystallization from a non-polar solvent. Most are oxidized in contact with the atmosphere, and many are easily hydrolyzed, so they must be kept under an inert atmosphere (N_2 or Ar) during all manipulations. Flasks should be predried and solvents dried and deoxygenated before use. Tervalent phosphorus acid derivatives are, with few exceptions, thermally stable and can be kept indefinitely in ampoules under an inert gas (many halophosphines dissolve stopcock grease and should not be kept in stoppered flasks for prolonged periods). Inert solvents are hydrocarbons, ethers and, for most compounds, dichloromethane, ethyl acetate and tertiary amines. Aminophosphines react vigorously with tetrachloromethane and slowly with trichloromethane, and most tervalent phosphorus acid derivatives are oxidized by dimethyl sulphoxide and react with alcohols.

Physical properties such as boiling points, melting points and refractive indices and also molar weight determinations and IR spectra are useful to characterize and sometimes prove the structure of a compound, but the most valuable information comes from NMR, in particular ^{31}P NMR. Phosphorus is an ideal nucleus for NMR, since it exists as a pure isotope with spin 1/2, the sensitivity is high (7% of ^{1}H) and the chemical shift region is large (more than 500 ppm). Tervalent phosphorus acid derivatives have characteristic chemical shifts in the low-field region, whereas likely impurities (hydrolysis or oxidation products) most often have chemical shifts in the 0–50 ppm region. In addition, it is easy to decide whether an impurity is the result of hydrolysis or of oxidation, since only a hydrolysis product singlet will split to a widely separated doublet when ^{1}H decoupling is removed owing to the large $^{1}J_{PH}$ coupling constant (typically 300–600 Hz) of the $\diagdown\!\!\diagup$PHO product.

^{31}P NMR chemical shift values are normally given in all more recent publications on the preparation of phosphorus compounds. Compilations of phosphorus chemical shifts can be found in two older books, covering literature values up to 1966[142] and the period 1966–69[143], and in a newer book which gives selected values up to 1987[144]. Table 2 gives selected ^{31}P chemical shift values for different types of tervalent phosphorus acid derivatives. The chemical shifts are relative to 85% H_3PO_4 and positive shifts are towards the low field (to the left) of the standard (the older literature has the opposite sign!); shifts may vary by a few ppm according to the solvent.

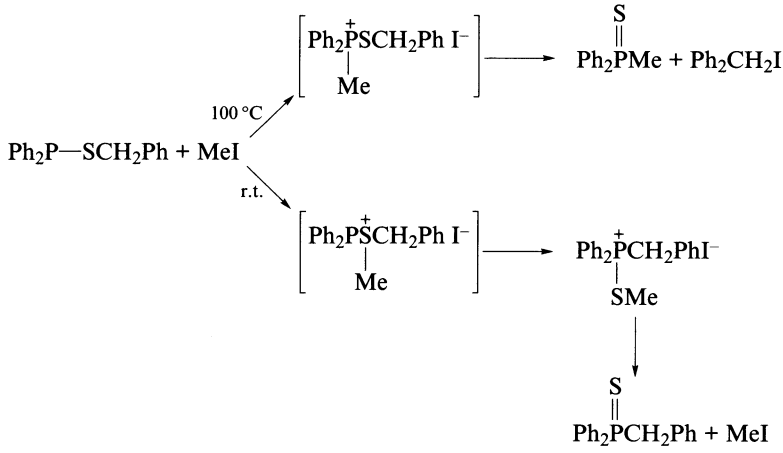
TABLE 2. Selected ^{31}P chemical shifts for different types of compounds

Compound	δ_P (ppm)	Compound	δ_P (ppm)
$MePX_2$	245 (F), 191 (Cl), 184 (Br), 131 (I)	$PhP(OEt)NMe_2$	154
$PhPX_2$	207 (F), 161 (Cl), 152 (Br)	$MeP(NR_2)_2$	86 (Me), 79 (Et), 39 (Pr^i)
Me_2PX	186 (F), 96 (Cl), 91 (Br)	$PhP(NMe_2)_2$	100
Ph_2PX	81 (Cl), 71 (Br)	Me_2PNMe_2	39
MeP(Cl)OMe	205	Ph_2PNMe_2	65
$MeP(OMe)_2$	201	MeP(Cl)SMe	156
$PhP(OMe)_2$	159	$MeP(SMe)_2$	75
Me_2POMe	124	Me_2PSMe	8
Ph_2POMe	116	$Bu^tP{=}NBu^t$	472
R_2POEt	111 (Ph), 137 (Et), 150 (Pr^i), 160 (Bu^t)	$Ph_3P{=}C(Et)P{=}S$	488
$MeP(Cl)NMe_2$	151		

IV. NUCLEOPHILIC REACTIONS

All tervalent phosphorus acid derivatives have a lone pair on phosphorus and are therefore nucleophiles, but their reactivity depends on the electronegativity of the group(s) bound to phosphorus. Aminophosphines are the most reactive and chlorophosphines the least reactive, with the phosphinites, phosphonites and thio analogues in between. In principle they are ambident nucleophiles because there are lone pairs both on the heteroatoms and on phosphorus, but apart from the thio analogues these heteroatom lone pairs do not participate in the common reactions discussed below.

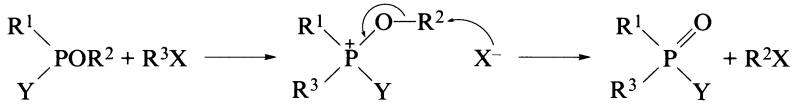
Aminophosphines, phosphinites and phosphonites from quasi-phosphonium salts with alkyl halides in normal S_N reactions. The aminophosphonium salts and the salts derived from aryl phosphinites and diaryl phosphonites are stable, but the majority of the quasi-phosphonium salts which contain alkoxy groups are dealkylated during the reaction with the alkyl halide (the Arbuzov reaction, see below). Thio analogues of phosphinites and



(120)

phosphonites react with alkyl halides to give products derived from *P*-alkylation and/or *S*-alkylation (equation 120), depending on the conditions[145].

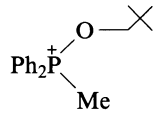
The Arbuzov reaction is an important method for preparing phosphine oxides and phosphinates from phosphinites or phosphonites, respectively[146]. The reaction requires only one alkoxy group in the reactant, so phosphonamidites and phosphonothioites also react (equation 121); phosphonohalidites, apart from fluoridites, are unreactive unless a Lewis acid catalyst, e.g. BF_3 or $FeCl_3$, is added[147,148]. The reaction conditions are milder than those required for the preparation of phosphonates from trialkyl phosphites, the reactivity order being $R_2POR > RP(OR)_2 > (RO)_3P$. Primary alkyl halides react faster than secondary alkyl halides, and tertiary alkyl halides usually fail to react or give elimination products, although trityl halides do react by an S_N1 mechanism. Aryl halides react at 150–160 °C in the presence of nickel salts[149]. Vinyl halides also require metal salt catalysis, preferably copper(I) bromide[150], but 1-alkynyl halides react without a catalyst[151], probably by an addition–elimination mechanism. Acyl halides are very reactive and give 1-oxoalkylphosphine oxides or phosphinates. α-Halo ketones are reactive but give varying amounts of vinyl esters (the Perkow reaction) in addition to the 2-oxoalkylphosphine oxides or phosphinates[152].



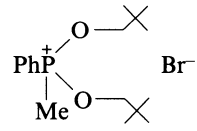
(121)

X = halogen
Y = halogen, OR, SR, NR_2

The first step in the Arbuzov reaction is normally rate determining, but the quasi-phosphonium salt intermediate has been isolated in several cases where the alkyl group on oxygen is difficult to remove, e.g. **45** and **46**, and shown to be salts and not pentacoordinate species by ^{31}P NMR and X-ray crystal structure evidence[153]. The *O*-alkyl group that is removed in the second step can be primary, secondary or tertiary, the *tert*-butyl group being particularly easily removed[154]; the same holds for *O*-trimethylsilyl groups. The alkyl halide formed should be removed by a stream of inert gas if it is able to compete with the reactant alkyl halide, otherwise a mixture of products is obtained. The alkyl halide from a



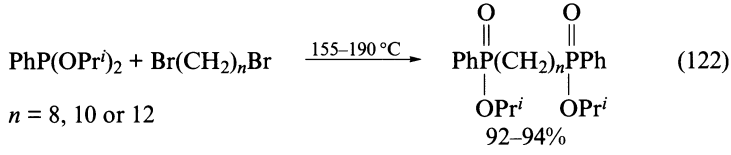
(45)



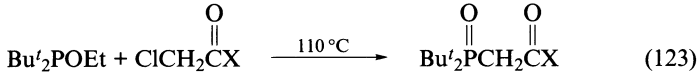
(46)

secondary or tertiary alkyl phosphinite or phosphonite or chlorotrimethylsilane from a trimethylsilyl derivative will normally not compete and such compounds give the purest product.

Representative examples of Arbuzov reactions with alkyl phosphinites and phosphonites are the preparation of some bisphosphinates (equation 122)[155], functionalized trialkylphosphine oxides (equation 123)[86] and phosphorylated sarcosine analogues (equation 124)[156]. Examples involving aryl halides (equation 125)[149], a vinyl halide (equation 126)[150], an alkynyl halide (equation 127)[151] and an acyl halide (equation 128)[157] illustrate the diversity of the reaction. Arbuzov reactions that involve trimethylsilyl phosphinites or phosphonites occur under very mild conditions, usually at or below room temperature, e.g. equation 129[158].



(122)



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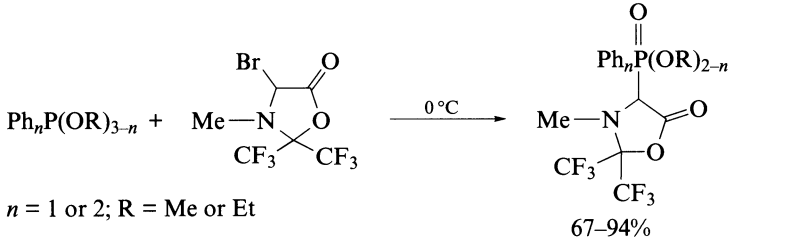
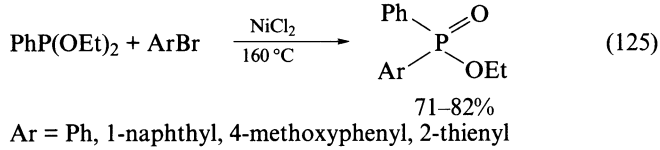


(124)



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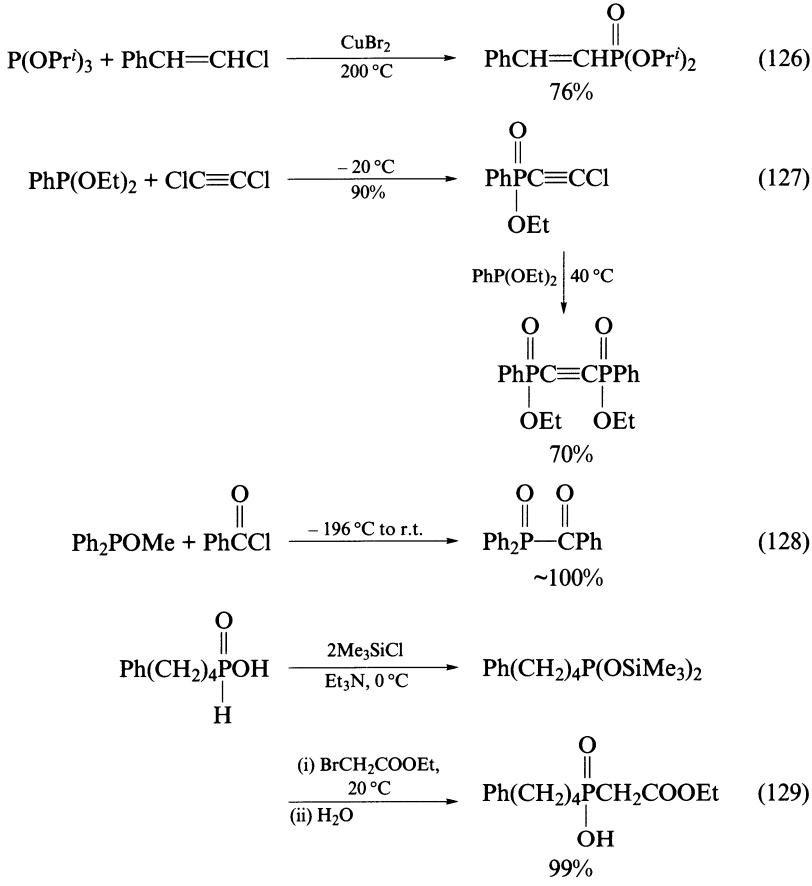
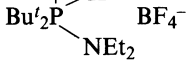


Tervalent phosphorus acid derivatives react readily with hydrogen halides and other strong acids. The most basic derivatives, the aminophosphines, from isolable salts when the anion is a weak nucleophile, with the proton bound to phosphorus, e.g. **47**[159]. Hydrogen halides normally cleave the N—P bond(s) to give halophosphines (equation 10–13). With one equivalent of an dialkylammonium chloride, one of the amino groups of a diaminophosphine can be replaced to give an aminochlorophosphine in good yield, e.g. equation 130[74]. Phenyl or neopentyl phosphinites and phosphonites form phosphonium salts with dry HCl, e.g. **48**, which can be observed by ^{31}P NMR at low temperatures, but undergo dealkylation or substitution reactions on heating[160]. Normal phosphinites and phosphonites react with aqueous acids to give secondary phosphine oxides and alkyl phosphinates or phosphinic acids, respectively, e.g. equation 131[102].



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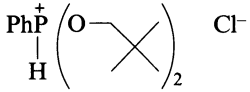


(48)

$$EtP(NEt_2)_2 + Et_2\overset{+}{N}H_2Cl^- \xrightarrow{90\text{–}140\,^\circ C} EtP(Cl)NEt_2 \quad (130)$$

73%

$$BuP(OEt)_2 + H_2O \xrightarrow[\text{r.t.}]{\text{cat. HCl}} BuP(=O)(H)OEt \xrightarrow[\text{reflux}]{\text{conc. HCl}} BuP(=O)(H)OH \quad (131)$$

85%

Some tervalent phosphorus acid derivatives, particularly phosphinites and phosphonites, are useful nucleophiles in Michael addition reactions. Examples are reactions of methyl diphenylphosphinite with acrolein or methyl vinyl ketone in the presence of chlorotriethylsilane to quench the enolate (equation 132)[161] and the reaction of some trimethylsilyl phosphonites with acrylic acid, methyl acrylate or acrylonitrile (equation 133)[162]. Dichlorophosphines may also add to vinyl ketones in the presence of acetic anhydride to give cyclic phosphinates which can be opened to γ-oxoalkylphosphinates (equation 134)[163,164]. Dichlorophosphines with 2 mol of ketones give similar cyclic phosphinates, e.g. equation 135[165], and monochlorophosphines may give phosphine oxides with some dicarbonyl compounds (equation 136)[166]. The reaction of phosphites with aldehydes (the Abramov reaction, equation 137) proceeds in high yield when R^2 is trimethylsilyl; similar reactions with phosphinites or phosphonites seem feasible but no example has been found. With imines, trimethylsilyl phosphinites and phosphonites gave 1-aminoalkylphosphine oxides and 1-aminoalkylphosphinic acid esters, respectively, in high yields, e.g. equation 138[167].

$$Ph_2POMe + CH_2{=}CHC(=O)R + Et_3SiCl \xrightarrow{\text{r.t.}} Ph_2P(=O)CH_2CH{=}C(OSiEt_3)R \quad (132)$$

R = H, Me

~100%

$$Ph(CH_2)_4P(OSiMe_3)(OR) + CH_2{=}CHX \xrightarrow{\text{r.t.}} \xrightarrow{H_2O} Ph(CH_2)_4P(=O)(OR^1)CH_2CH_2X \quad (133)$$

R = Et, $SiMe_3$

X = COOH, COOMe, CN

61–97%

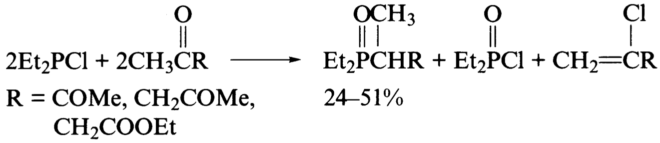
R^1 = Et or H

$$R^1PCl_2 + R^2CH{=}CHC(=O)R^3 \xrightarrow{Ac_2O} \xrightarrow[\Delta]{R^3OH} R^1P(=O)(OR^3)CHR^2CH_2CR^3(=O) \quad (134)$$

$$RPCl_2 + 2EtC(=O)Et \longrightarrow \quad (135)$$

R = Et, Ph

44–53%



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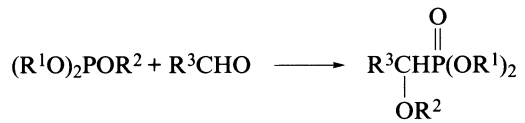

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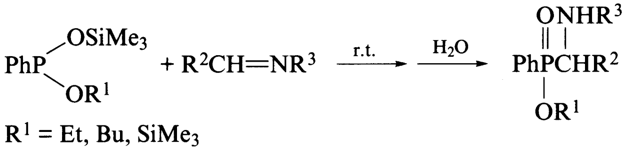
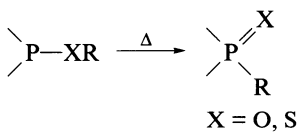


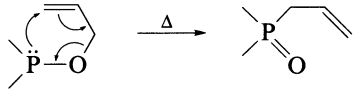
(138)

Phosphinites, phosphonites and their thio analogues are potentially thermolabile and may rearrange on heating to the isomeric (thio)phosphoryl compounds (equation 139). The rearrangement is strongly catalysed by alkyl halides, acids, iodine and other compounds which can initiate an Arbuzov-type reaction and since crude products may contain alkyl halides, rearranged products are often reported after distillation at elevated temperatures. The more nucleophilic phosphinites are more prone to rearrangement than phosphonites, but pure alkyl phosphinites, apart from the benzyl esters, do not rearrange at 190 °C[84], so they can usually be distilled at reduced pressures.



(139)

Phosphonochloridites normally contain acid impurities and therefore are prone to rearrange or decompose on heating. The thio analogues are in general thermally rather labile, some rearranging at room temperature[168,169]. Some phosphinites and phosphonites with 2-alkenyl or 2-alkynyl groups on oxygen are thermally labile (equation 140 and 141). The alkenyl esters require heating, but alkynyl esters may rearrange spontaneously; an example is the spontaneous rearrangement of a 2-alkynyl diphenylphosphinite at – 78 °C (equation 142)[170]. *N*-2-Propynylaminophosphines also rearrange in a similar way, but with cleavage of the P—N bond to give tertiary phosphines (equation 143)[171].



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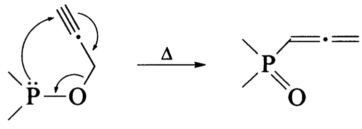

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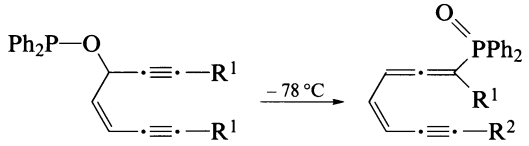

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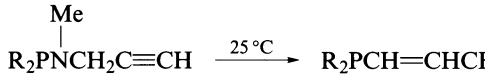
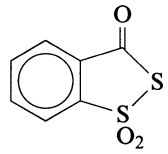


(143)

Tervalent phosphorus acid derivatives are, with some exceptions, readily oxidized in contact with air. The rate of oxidation is $R_2PX > RPX_2 > PX_3$ for compounds with analogous substituents, and compounds with amino or alkoxy groups are more easily oxidized than compounds with chloro groups. Thio analogues often react strongly exothermically with air, and rearrangements are common. Consequently, although trialkyl phosphites, tris(dialkylamino)phosphines and phosphorus trichloride can be handled without special precautions in the atmosphere, similar derivatives with one or two P—C bonds should always be kept under an inert atmosphere. For preparative purposes, oxidation is often performed with dry oxygen, N_2O_4[172], dimethyl sulphoxide[173], *tert*-butyl hydroperoxide[95], bis (trimethylsilyl) peroxide[174] or active MnO_2[175]. Addition of halogens in the presence of water is a useful alternative if hydrolysis of the dihalophosphorane or halophosphonium salt can be made without hydrolysis of the remaining electronegative groups, and if Arbusov-type reactions are not induced. Methyl phosphonites are commonly oxidized with I_2–H_2O–lutidine–THF to methylphosphonates during the preparation of methylphosphonate analogues of DNA, although the water content should be kept low in order to reduce the extent of hydrolysis[176].

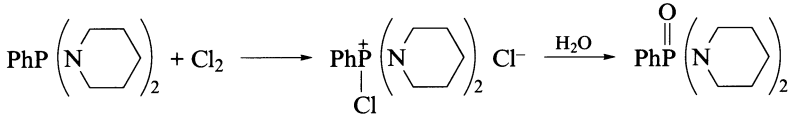
Oxidation with elemental sulphur converts tervalent phosphorus acid derivatives to the corresponding P=S compounds. The reaction occurs spontaneously or on gentle heating, the reactivity order for phosphinites and phosphonites being $Ph_2POR > PhP(OR)_2 > P(OR)_3 > Ph_3P$[177]. Several compounds (mainly diacyl disulphides) which, in contrast to elemental sulphur, are soluble in ordinary solvents and are able to oxidize phosphites to phosphorothioates, have been developed for use in the automated synthesis of DNA analogues; one of these (**49**) has been used successfully to oxidize DNA-methylphosphonites to methylphosphonothioates[178]. The halogens normally react exothermically with tervalent phosphorus acid derivatives. The primary products are phosphoranes or halophosphonium halides, which are stable when formed from halophosphines and aminophosphines, e.g. methyltrichlorophosphonium chloride (equation 144)[179] and chlorodipiperidinophenylphosphonium chloride (equation 145)[180], although they are hydrolysed to phosphoryl compounds by water. Products from alkyl phosphinites and phosphonites are unstable with respect to Arbuzov-type dealkylations, but may be solvolysed before they have time to dealkylate, e.g. equation 146[181].



(**49**)

$$MePCl_2 + Cl_2 \longrightarrow Me\overset{+}{P}Cl_3\ Cl^- \quad (144)$$

94%



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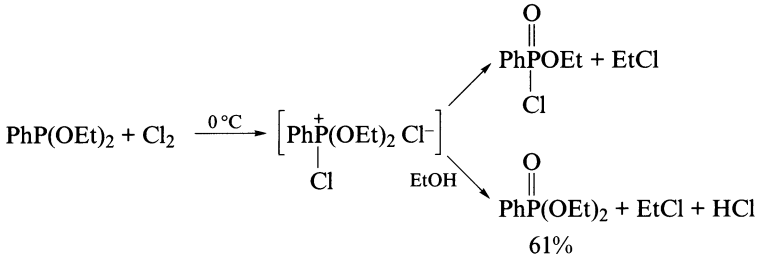
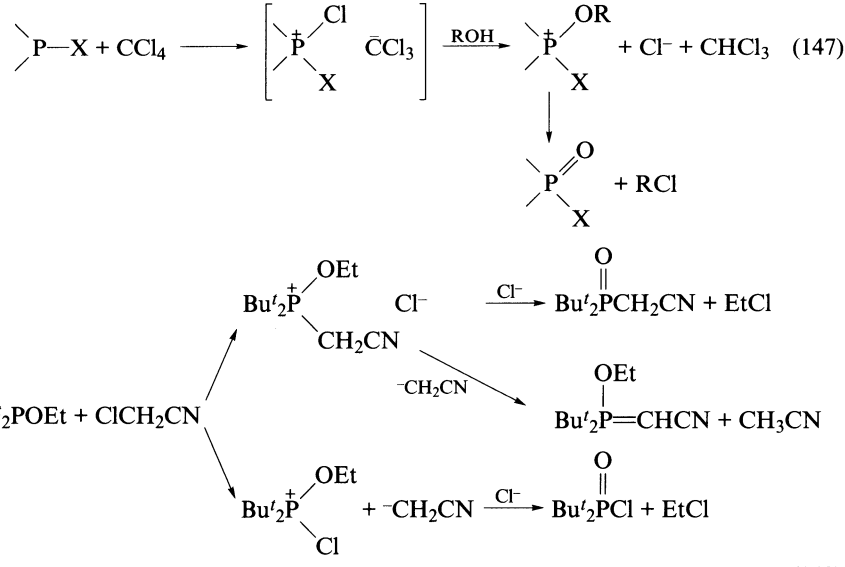


(146)

Nucleophilic attack of tervalent phosphorus acid derivatives on the carbon atom of alkyl halides is the normal process, but sometimes the attack occurs at the halogen atom instead. This reaction is most pronounced when a stabilized carbanion may be formed, e.g. in the reaction with tetrachloromethane (equation 147)[182]. The extent of debromination of α-bromo ketones has been found to decrease in the series $R_2POR > RP(OR)_2 > P(OR)_3$[152]. Ethyl di-*tert*-butylphosphinite has been shown to react preferentially at the halogen atom of chloroacetonitrile, 1,2-dibromoethane and diiodomethane, to give in each case a mixture of products, e.g. equation 148[86]. Aminophosphines are also very reactive in this respect



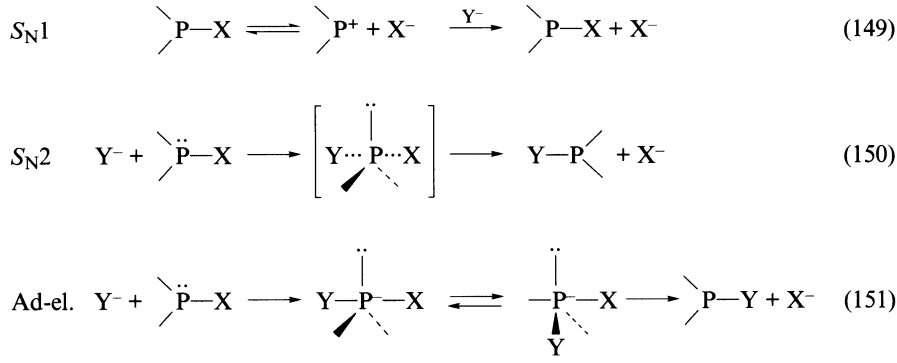
(147)

(148)

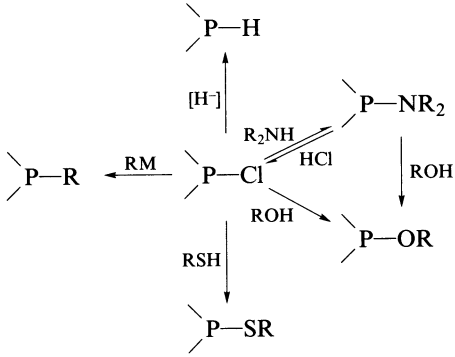
and abstract chlorine atoms from terachloromethane (e.g. equation 58) and even from trichloromethane[183]. Tervalent phosphorus acid derivatives, in particular aminophosphines, abstract sulphur from many compounds, e.g. alkylthiophosphonium salts (equation 98) and disulphides[184,185].

V. ELECTROPHILIC REACTIONS

Tervalent phosphorus acid derivatives contain one to three potential leaving groups bound to phosphorus and electrophilic reactions, where a nucleophile substitutes one or more of these groups, are very common. The best leaving groups are the halogens (I > Br > Cl >> F), but amino groups are also good leaving groups in the presence of weak acids. Even alkoxy and phenoxy groups are reasonably good leaving groups (PhO > alkylO) that can be substituted by strong nucleophiles (R^-,F^-); weaker nucleophiles, e.g. alcohols, may substitute alkoxy and phenoxy groups in base-[102] or acid-catalyzed reactions[186]. Several mechanisms may be envisaged for substitution reactions at a tervalent phosphorus centre, viz. S_N1 (equation 149), S_N2 (Equation 150) or addition-elimination pathways (equation 151). Although the intermediates of the S_N1 mechanism (phosphenium ions) are known[187], and the intermediates of the addition–elimination mechanism (phosphoranide anions, or phosphoranes from a Y—H nucleophile) have been observed during substitution reactions[188–190], the stereochemical results (predominant inversion in most cases[191]) points to the S_N2 mechanism as the most likely. However, a classical in-line S_N2 process has been shown not to be the preferred pathway in one case[192], so several mechanisms probably operate, depending on the system. Substitution reactions are much faster at tervalent phosphorus centres than at phosphoryl or thiophosphoryl centres and normally take place under mild conditions and give high yields. They are therefore often used to introduce phosphorus groups into sensitive molecules, such as DNA and RNA, sugar phosphates, phosphoproteins, phospholipids and their analogues. This is done by phosphitylation of natural alcohols with phosphorochloridites or, better, phosphoramidites[193–196], followed by oxidation to the phosphates. Similar reactions with phosphonochloridites[197] or phosphonamidites[95], to give phosphonate analogues of phosphate-containing natural products have not been much studied, but their use is expected to increase in the future.



Electrophilic substitution reactions (Scheme 4) in many cases convert one derivative of a tervalent phosphorus acid into another and numerous examples have been given in Section II. Therefore, the following discussion will be limited to electrophilic reactions which are not treated in Section II because they give products that are not tervalent phosphorus acid derivatives, or because the reactions are of limited preparative value.



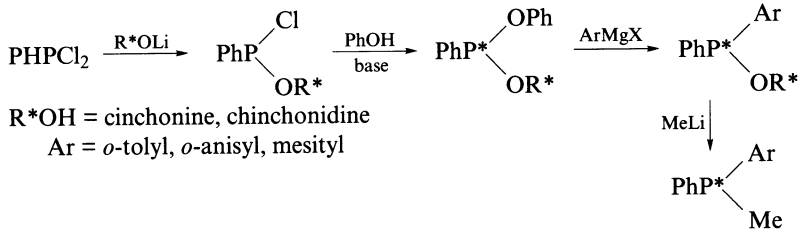
SCHEME 4

Primary, secondary and tertiary phosphines are often prepared from trivalent phosphorus acid derivatives and complex hydrides or organometallic reagents. The leaving group on phosphorus is most often a chloro group, but alkoxy and in particular phenoxy groups are also easily displaced. The complex hydride is commonly $LiAlH_4$, but silanes such as $HSiCl_3$ or Ph_2SiH_2 are also able to remove chloro groups and are more selective. Examples are the reduction of chlorophosphines with $LiAlH_4$ (equation 152)[198,199] or silanes (equation 153)[200] and the reduction of phosphonites with $LiAlH_4$ (equation 154)[201]. The organometallic reagent is mostly a Grignard or an organolithium reagent. Numerous examples of the preparation of tertiary phosphines from chloro- or dichlorophosphines can be found in *Houben-Weyl*[2,3] and Vol. 1 of this series[202]. The preparation of tertiary phosphines from phosphinites, phosphonites or phosphonochloridites is particularly suited to give phosphines with different alkyl or aryl groups on phosphorus, because stepwise substitution is easily controlled. Thus chiral phosphines have been prepared in high optical purities from dichloro(phenyl)phosphine via chiral phosphonites and phosphinites, the stereoselectivity being induced by the use of chiral alkaloid alcohols (equation 155)[203,204].

$$\begin{matrix} RPCl_2 + LiAlH_4 \longrightarrow RPH_2 \\ R = Bu^t, \text{ Ph, mesityl} \qquad 86\text{–}94\% \end{matrix} \tag{152}$$

$$\begin{matrix} Ph_nPCl_{3-n} \xrightarrow[Ph_2SiH_2]{HSiCl_3 \text{ or}} Ph_nPH_{3-n} \\ n = 1 \text{ or } 2 \qquad 55\text{–}82\% \end{matrix} \tag{153}$$

$$\begin{matrix} (EtO)_2P(CH_2)_nP(OEt)_2 \xrightarrow{LiAlH_4} H_2P(CH_2)_nPH_2 \\ n = 4 \text{ or } 6 \qquad 42\text{–}66\% \end{matrix} \tag{154}$$



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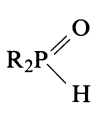
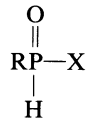


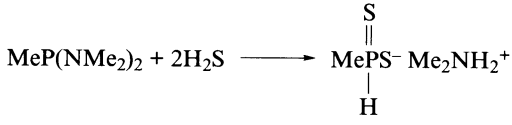
(50)



(51)

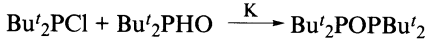
X = Cl, OR, OH, NR_2

The hydrolysis of tervalent phosphorus acid derivatives with two P—C bonds leads to secondary phosphine oxides (**50**) and with one P—C bond to phosphonus acid derivatives (**51**). Chlorophosphines react rapidly with water, but aminophosphines, phosphinites and phosphonites often survive a short wash with aqueous $NaHCO_3$, an effective way to remove contaminating ammonium salts in the crude products[67]. However, aminophosphines with small substituents, e.g. dimethylaminodimethylphosphine, aryl phosphinites and phosphonites and trimethylsilyl phosphinites and phosphonites are hydrolysed too quickly for such a treatment. The hydrolyses are catalysed by acids (the hydrolyses of phosphinites and phosphonites are also catalysed by OH^-) and are much faster than hydrolyses of the corresponding phosphoryl compounds [up to a factor of 10^{12} for acid-catalysed hydrolysis of $(MeO)_3P$ compared with $(MeO)_3P{=}O$[205]]. Dialkyl phosphonites are rapidly hydrolysed to the monoalkyl esters (**51**, X = OR) in weakly acidic water, whereas hydrolyses to phosphonous acids require reflux with strong acid or base, e.g. equation 131[102]. Bis-(dialkylamino) phosphines may also be partially hydrolysed to phosphonous acid amides (**51**, X = NR_2)[206]. Tervalent phosphorus acid derivatives with hydrogen sulphide give secondary phosphine sulphides or phosphonodithious acids, e.g. equation 156[207].



(156)

Several types of anhydrides of tervalent phosphorus acids are known and have been prepared by electrophilic substitution reactions at phosphorus. Examples are the phosphinous acid anhydrides **52** (equation 157)[208], **53** (equation 158), prepared from a chlorophosphine [209] or an aminophosphine[210], and **54** (equation 159)[211]. Aminophosphines react with carbon disulphide to give ionic addition compounds at low temperatures, but dithiocarbamate anhydrides (**55**) at room temperature (equation 160)[212,213]. Aminophosphines form analogous carbamate anhydrides with carbon dioxide[212], but isothiocyanates give ionic addition products, not insertion products[214].



(**52**)
73%

(157)

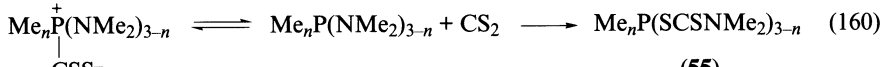
(**53**)

(158)

$R^1 = Bu^t$, Ph
R^2 = Ph, MeO

(54)

(159)



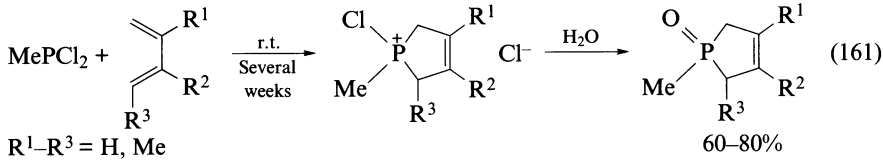
n = 0–2

(55)

(160)

VI. OTHER REACTIONS

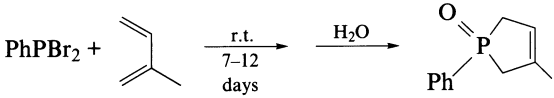
Tervalent phosphorus acid derivatives undergo electrocyclic reactions with 1,3-dienes, 1,2-diones, 2-alkenones and similar compounds with a conjugated 4π electron system. The reaction of dihalophosphines with 1,3-dienes (the McCormack reaction) to give dihydrophosphole derivatives is probably the best synthetic method to obtain phospholes. The reaction is rather slow, but gives fair to high yields of 2,5-dihydrophosphole 1-oxides after hydrolysis, e.g. equation 161[215]. 4,5-Dihydrophosphole 1-oxides are also formed, and are the sole products from dichloro(phenyl)phosphine and isoprene[216]; the amount of this isomer can be kept small when the reaction is performed at room temperature, preferably with the more reactive dibromophosphines (equation 162)[217]. The halophosphonium intermediate can be reduced with magnesium to dihydrophospholes[215] or dehydrohalogenated with bases (preferably 2-methylpyridine[218]) to phospholes (equation 163). Not unexpectedly for a cycloaddition reaction, the rate of the McCormack reaction is pressure dependent, and the reactions can be completed in hours at 7 kbar[219]. Iminophosphines (equation 164)[220,221] and phosphenium ions (equation 165)[222] react in an analogous way with 1,3-dienes. With 1,2-diketones and 2-alkenones, phosphonites give phosphoranes, e.g. equations 166[223] and 167[224]. The unstable oxophosphines, and phosphenium ions, react similarly with o-quinones (equations 168[122] and 169[225]).



R^1–R^3 = H, Me

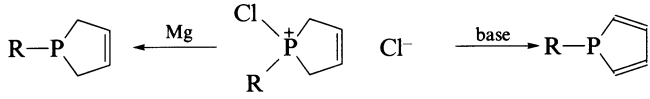
60–80%

(161)

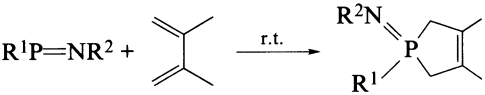


79%

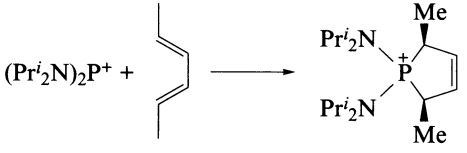
(162)



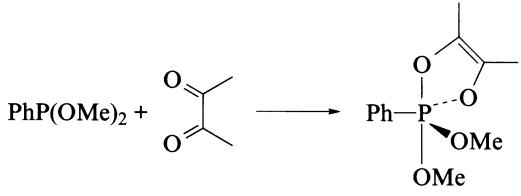
(163)



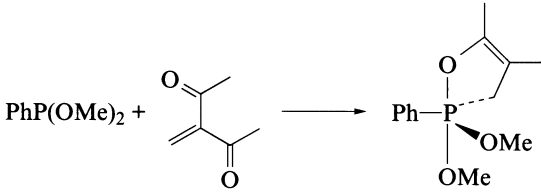
(164)



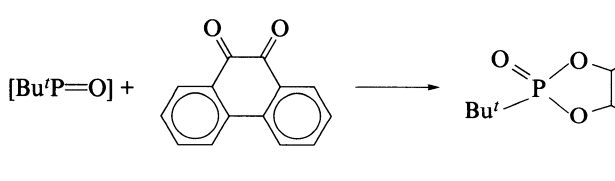
(165)



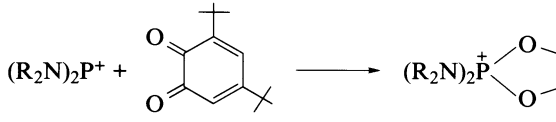
(166)



(167)

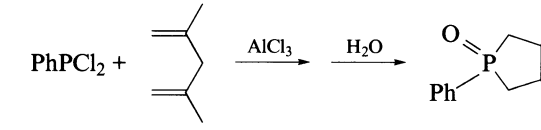


(168)

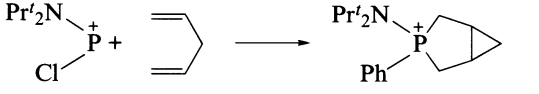


(169)

Other electrocyclic reactions of tervalent phosphorus acid derivatives are known. These include the previously mentioned rearrangements of 2-alkenyl and 2-alkynyl phosphinites or phosphonites (equations 140–142), The rearrangements of (2-alkynylamino)phosphines (equation 143) and some reactions of 1,4-dienes with dichlorophosphines (equation 170)[226] or phosphenium ions (equation 171)[222].



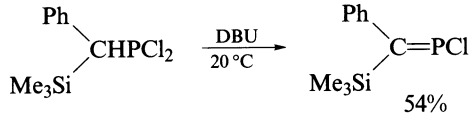
(170)



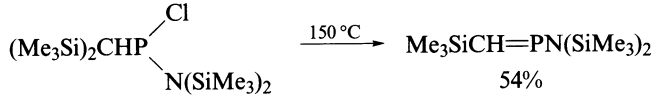
(171)

Free-radical reactions of tervalent phosphorus acids have been covered to some extent in Section II (addition of PX_3 to alkenes, equation 15–17) and in Section IV (oxidations with molecular oxygen). Several other reactions occur via radicals, e.g. reactions with peroxides, certain disulphides and certain halogen compounds. However, these reactions are the subject of chapters by Bentrude and Dankowski in Vol. 1 of this series[227,228] and will not be covered here.

Chlorophosphines with an α-hydrogen atom may eliminate hydrogen chloride to give methylenephosphines. With large and carbanion stabilizing groups the elimination take place at room temperature in the presence of a tertiary amine, e.g. equation 172[229]. Chlorophosphines with an α-trimethylsilyl group eliminate chlorotrimethylsilane on heating, e.g. equation 173[230]. Simple chlorophosphines, e.g. dichloro(methyl)phosphine, only eliminate hydrogen chloride at very high temperatures[231].

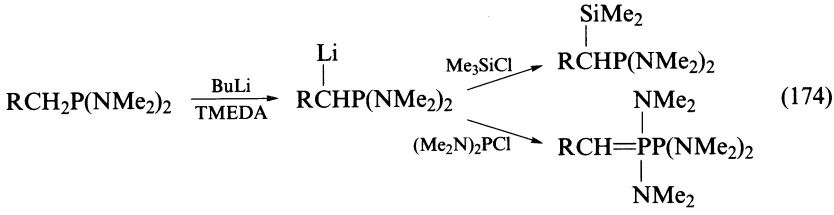


(172)



(173)

Reactions in the alkyl or aryl part of tervalent phosphorus acid derivatives (halogenation, nitration, functional group interconversion, etc.) are in general not possible without destroying the sensitive tervalent phosphorus groups. Only a few reactions which occur under anhydrous neutral or basic conditions, such as hydrogenation of C=C bonds or conversion of esters in to amides, may have any chance of success. Very few reactions of this type has been studied, and the strategy for the synthesis of compounds with functional groups apart from the phosphorus group is either to prepare a tervalent phosphorus compound with the functional group already in place, or to introduce the functional group after the tervalent phosphorus group has been converted in to a less reactive phosphorus derivative. Among the few examples of reactions in the alkyl part of tervalent phosphorus acid derivatives are the α-halogenation of some aminophosphines with CCl_4 or $CBrCl_3$ described earlier (equation 58)[79] and the α-metallation of a few aminophosphines with BuLi + TMEDA and subsequent reactions with some electrophiles (equation 174)[232].



(174)

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CHAPTER 2

The synthesis of phosphonic and phosphinic acids and their derivatives: Non-functionalized acids

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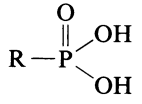
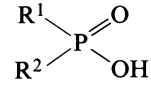
1. INTRODUCTION

Phosphonic acids (**1**) and phosphinic acids (**2**) possess one and two carbon–phosphorus bonds, respectively, and represent structurally intermediate stages between on the one hand, phosphoric acid and, on the other, a tertiary phosphine oxide. As such, members of the two series of acids possess many properties common to each other and also to some extent with those of phosphoric acid and phosphine oxides. Each series of acids provides a wide array of derivatives—halides, esters, amides, and many more—whose properties are



(**1**)



(**2**)

the result of the interaction of the functional group at phosphorus with the specific type of carbon moiety present.

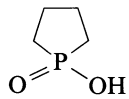
In principle, the three main approaches to the synthesis of phosphonic and phosphinic acid derivatives consist in (i) the generation of phosphorus–carbon bonds in the presence of other functional groups at phosphorus which, themselves, very often act to block the formation of a second (or third) phosphorus–carbon bond; (ii) modifications in the phosphonic or phosphinic carbon moieties; or (iii) modifications, at phosphorus in tetracoordinate compounds which already possess phosphorus–carbon bonds; reactions of this last type are considered in Chapter 6.

Phosphonic and phosphinic acids are rarely synthesized directly. Much more frequently, they are obtained initially as derivatives, in particular as esters or acid halides, the latter most frequently the chlorides, and some methods of synthesis can be adapted, with slight modifications, to yield either type of derivative. Of the classical methods used to obtain compounds which possess phosphorus–carbon bonds, the interaction of alkyl halides and PCl_3 in the presence of $AlCl_3$ (the Clay–Kinnear–Perren reaction) and that of alkyl halides with phosphorus(III) esters (the Michaelis–Arbuzov–Kaehne reaction) remain popular for the synthesis of acid derivatives with P—C(sp^3) bonds, as does the Michaelis–Becker modification (using alkyl halides and sodium dialkyl phosphites) of Michaelis–Arbuzov procedure. Reactions between PCl_5 and alkenes or alkynes are still valuable for the formation of systems with P—C(sp^2) bonds, and the use of aryl diazonium salts with PCl_3 and of the Friedel–Crafts reaction, in its many guises, are still used to obtain compounds in which phosphorus is bonded to an aromatic system. However, recent years have seen many advances in new reactions and modifications to old ones including, particularly, the use of rare metal catalysts to aid reaction between phosphorus-containing species and compounds which would normally be considered to possess less reactive sites.

This chapter is concerned with the synthesis of those phosphonic and phosphinic acids which, with certain exceptions, do not possess functional groups as part of the carbon moieties of the acids; those exceptions consist essentially of common functional groups attached to an aromatic ring. A consideration of the synthesis of those acids which possess the common functional groups such as hydroxyl, oxo, or amino, is deferred to Chapters 3 and 4, whilst syntheses and properties of sulphur- and selenium-containing acids are described in Chapter 5. The reactions of phosphonic and phosphinic acids, many of which lead, of course, of new acids and are therefore often of value in synthesis, are dealt with in Chapter 6.

The chemistries of phosphonic[1–5] and phosphinic[5–8] acids have been previously reviewed with extensive listings of compounds know at the time of publication. In addition, the area is reviewed annually[9], and bibliographies for specific compounds, including key references to syntheses and to spectroscopic and other characteristics, have been presented[10].

There are very many compounds based on simple phosphorus-containing ring systems, such as those represented by structures **3** and **4**, which are essentially of the phosphonic or phosphinic acid types. To the extent that they are also heterocyclic compounds of phosphorus, their chemistry has also been considered separately[11–14].



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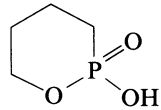


(4)

In compiling this chapter, the literature has been reviewed up to the spring of 1994.

II. THE FORMATION OF P—C(sp^3) BONDS. SYNTHESES OF ALKYL, CYCLOALKYL AND ARALKYL PHOSPHONIC AND PHOSPHINIC ACIDS

A. Through the Michaelis–Arbuzov–Kaehne Reaction

The Michaelis–Arbuzov–Kaehne reaction is probably the most widely used reaction in organophosphorus chemistry for the preparation not only of phosphonic and phosphinic acids (as their esters), but also of tertiary phosphine oxides. The reaction, discovered by Michaelis and Kaehne in 1898, and extensively developed by A. Arbuzov in the early years of this century, consists essentially in the interaction of phosphorus(III) acid ester with a reactive carbon-based species, generally an alkyl halide, and can be represented in very general terms as in equation 1; the reaction has been extensively reviewed[15–18].

$$\underset{\textbf{(5)}}{R^1R^2POR^3} + RX \longrightarrow \underset{\textbf{(6)}}{[\text{Intermediate}]} \longrightarrow RR^1R^2P{=}O + R^3X \quad (1)$$

Compounds **5** may thus be a phosphorus(III) phosphite ester, in which R^1 and R^2 are alkoxy or aryloxy groups, not necessarily identical, and R^3 is alkyl, or it may be the ester of a phosphorus(III)) phosphonous acid, in which R^1 is alkyl or aryl, R^2 is alkoxy or aryloxy, with R^3 once again alkyl. The product from a phosphinous ester (R^1, R^2 are alkyl or aryl) would be a tertiary phosphine oxide, but such application of the Michaelis–Arbuzov–Kaehne reaction (henceforth referred to simply as the Michaelis–Arbuzov reaction for the sake of brevity, but also to distinguish it from the Michaelis–Becker reaction) falls outside the scope of this chapter, and has been considered elsewhere[19]. When $R = R^3$, the reaction becomes one of mere isomerization, a process which can be brought about through the treatment of the ester with iodine[20] or by the mere application of heat or, rarely, of light. The reaction can be viewed as consisting of nucleophilic attack by phosphorus(III) at positive carbon, and proceeding through an intermediate (**6**) which, partly because of the presence therein of bonds other than those between phosphorus and carbon, and partly because of early doubts as to its exact nature, has been described as a pseudo- or quasi-phosphonium species.

The scope of the Michaelis–Arbuzov reaction has been so widely examined that it is useful to consider separately the various aspects of the procedure, noting that, from the practical viewpoint, such reactions are carried out either by heating a mixture of reactants to a temperature sufficiently high to initiate and complete the reaction or by the addition of one reactant (usually the alkylating agent) to the second, pre-heated reactant.

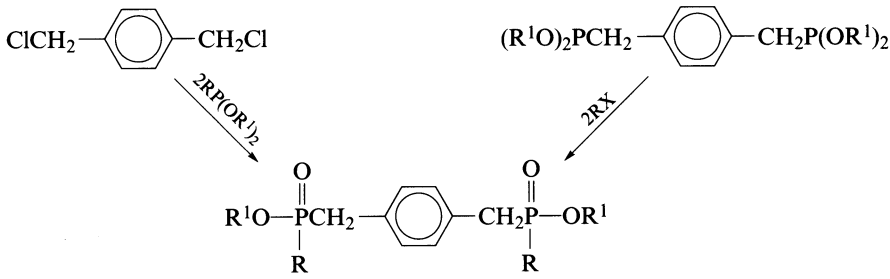
1. The nature of the phosphorus(III) reactant

The acyclic trialkyl phosphite esters used may possess primary, secondary or, very occasionally, tertiary alkyl groups (particularly when the phosphite molecule is of a cyclic nature, although tri-*tert*-butyl phosphite has also been successfully employed), the reactivity decreasing in this order. Triaryl phosphites, although shown to interact with alkyl halides to yield phosphonium species (of some interest because studies of their structures have shed light on the nature of the reaction intermediate), do not undergo the Michaelis–Arbuzov reaction under normal conditions. The choice of the trialkyl phosphite to be used in the preparation of a particular phosphonic diester (or of the phosphonous ester for a particular phosphinic derivative) is of some practical significance since self-alkylation, resulting in the formation of product mixtures which might be difficult to resolve, then becomes a distinct possibility. Thus, in the reaction between a primary haloalkane and trimethyl phosphite, competition between the reactant RX and the

released MeX for the phosphite occurs, and leads to a mixture of the dimethyl methylphosphonate, $MeP(O)(OMe)_2$, and the desired ester, $RP(O)(OMe)_2$. In such a case, it is desirable to use an ester which releases a less reactive halide, e.g. an isopropyl halide from triisopropyl phosphite, so eliminating a significant competitive reaction[21,22].

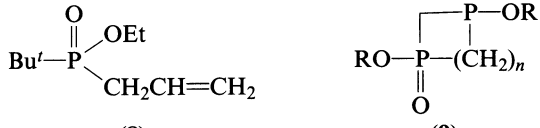
The use of trialkyl phosphites in the Michaelis–Arbuzov reaction has been so widespread during the decades following its discovery that it is almost impossible to select individual examples worthy of separate comment. Some examples of the preparation of benzylic phosphonic diesters may be noted; these are of some interest since they are useful reactants in the Wadsworth–Emmons modification of the Wittig reaction, and are extensively used in the synthesis of alkenes[23–37]. It may also be noted that when the phosphite ester possesses different alkyl groups, some selectivity of reaction is possible[38].

The use of acyclic phosphonite esters, $R^1P(OR)_2$, to prepare esters of phosphinic acids, $R^1R^2P(O)OR$ (R^1 and R^2 may, or may not, be identical) is not so widely exemplified, but it may again be noted that there are always two routes, theoretically, to a target compound, as for example, in the case of the 1,4-phenylenebis(methylene)bisphosphinic esters **7**[39–41].



(7)

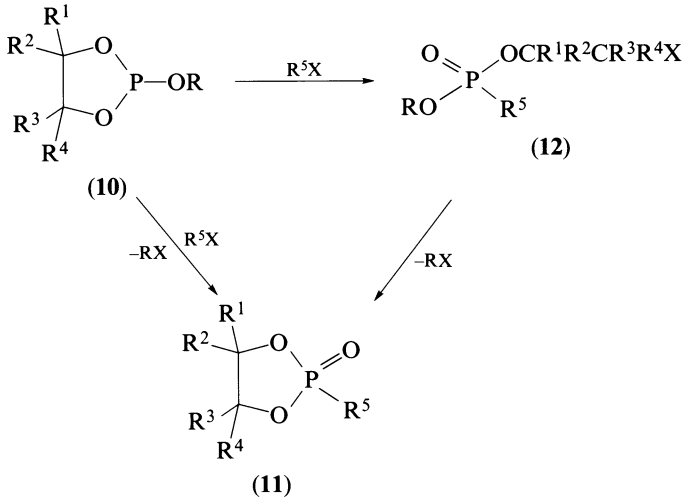
Consideration should always be given to the choice of route when planning a synthesis; thus, ethyl *tert*-butylallylphosphinate (**8**) is best prepared from allyl bromide and diethyl *tert*-butylphosphonite, rather than from *tert*-butyl chloride and diethyl allylphosphonite[42]. Several α,ω-alkanediylbismethylbisphosphinic esters have been obtained from diisopropyl methylphosphonite and the appropriate dibromoalkane[43], whilst analogous reactions between methylenebisphosphonous esters, $(RO)_2PCH_2P(OR)_2$, and such dibromoalkanes have been used to obtain the cyclic compounds **9**[44].



(8) (9)

The outcome of the reactions between alkyl halides and cyclic phosphite triesters depends on the ring size and the degree and type of substitution on ring carbon atoms, but the behavior of any given ring compound can also depend on the nature of the co-reactant. Rate studies have indicated that simple five- and six-membered ring phosphites react with iodoethane more slowly than do triethyl and triisopropyl phosphites[45]. Simple tertiary phosphites (2-alkoxy-1,3,2-dioxaphospholanes) (**10**) derived from alkane-1,2-diols tend to react with ring opening, although ring retention to give the phosphonic cyclic ester **11** becomes more important with increasing ring substitution[46–50]. It is evident that a rise in

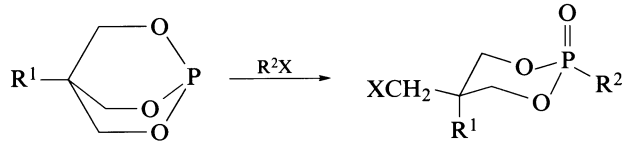
reaction temperature can also bring about the cyclization of a ring-opened product (**12**) to give **11**. However, with the more reactive benzyl and triphenylmethyl halides, ring retention occurs for both five- and six-membered phosphite rings even in the complete absence of ring substituents[51,52].



However, opening of six-membered phosphite rings [2-alkoxy-1,3,2-dioxaphosph(III)-orinanes] occurs in reactions with simple, and less reactive, alkyl halides (MeI, EtBr)[53] and also with other, more reactive, halides[54]. In their studies on stereochemical aspects of the Michaelis–Arbuzov reaction, Bodkin and Simpson[55] noted the duality in behaviour of 2-alkoxy-4-methyl-1,3,2-dioxaphosph(III)orinanes towards $Ph_3C^+BF_4^-$, while Segi *et al.*[56] relied on complete ring opening in the regioselective reactions between (2*S*,4*S*)-2-methyl-4-phenyl-1,3,2-dioxaphosph(III)orinane (**13**) with lower alkyl halides and also with benzyl and triphenylmethyl chlorides, to give optically active 3-halo-1-methylpropyl alkylphenyphosphinates (**14**).

Several studies have concentrated on the reactions of polycyclic phosphite systems. In their reactions with more reactive halides (this description being, very often, related merely to the reaction temperature achieved under normal experimental conditions), 1-phospha-2,6,7-bicyclo[2.2.2]octanes (**15**) undergo stereospecific ring opening to give the phosphonic esters (**16**) (X = Cl or Br; R^2 = aralkyl) with *cis*-oriented CH_2X and P=O groups[57–59]. Berlin *et al.*[60] carried out a similar stereospecific ring opening of 1-phospha-2,8,9-trioxaadamantane (**17**) to give structures of type (**18**).

It is perhaps not surprising that, should competition be possible between five-, six- and seven-membered rings in Michaelis–Arbuzov reactions, the six-membered ring tends to be retained at the expense of the other rings. Thus, the 2,7,8-trioxa-1-phosphabicyclo-



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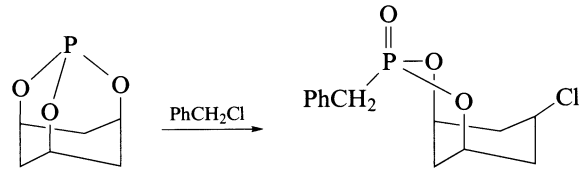
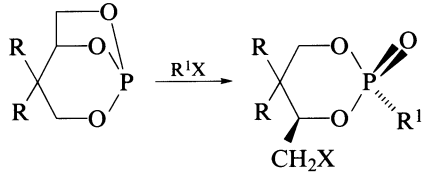


(17) (18)

[3.2.1]octanes **19** (R = H or Me) undergo stereospecific ring opening to give the 1,3,2-dioxaphosphorinane 2-oxides **20**[61,62], and the carbohydrate bicyclic phosphite **21** behaves in a similar way[63]. In similar reactions involving 2,8,9-trioxa-1-phosphabicyclo[4.2.1]-nonane, the products are phosphonates with retained seven-membered ring (1,3,2-dioxaphosphepane 2-oxides)[64].



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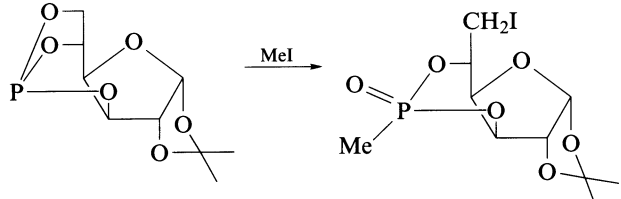
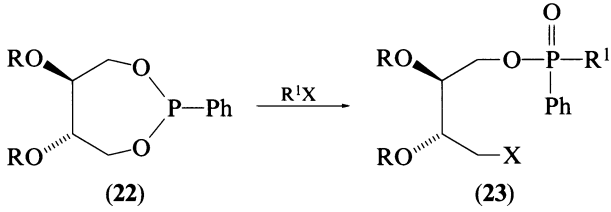


(21)

Nevertheless, isolated seven-membered rings, as in the optically active phosphonites **22** (R = Me, or RR = CMe_2), are also subject to ring opening when acted upon by the benzylic halides 4-$YC_6H_4CH_2X$; the products are the esters **23**, which may be obtained with diastereoisomeric excesses ranging from 24% (X = I, Y = Me) to 99% (X = I, Y = CN, or NO_2); no reaction occurs with X = Br and Y = CN or NO_2, and the diastereoisomeric excesses for X = Br, Y = H or Me are 20–30%[65].

A conspicuous feature in such studies is the behaviour of five-membered cyclic phosphites (**24**), derived from 1,2-dihydroxybenzene, towards alkylating agents; in all cases thus far examined, and independent of the nature of R^1 and R^2, the ring is retained, an



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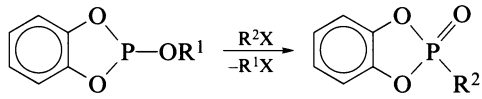
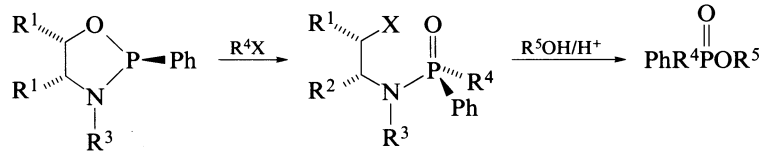


(24)

indication of the stability of this ring system towards cleavage in a pentacoordinate intermediate or in an ionic intermediate (Section II.A.3)[53,66].

Normal valence expansion has also been observed when the esters $(RO)_2PCN$ are treated with R′X to give $R'(RO)P(O)CN$[67] and an analogous reaction leads to the phosphonic isocyanates $R'(RO)P(O)NCO$[68].

A few reactions have been reported for phosphoramidous diesters, $R_2NP(OR)_2$, and for phosphorodiamidous esters $(R_2N)_2POR$, but for the most part these have not involved simple alkyl halides, but rather functionalized alkyl halides and polyhalogenated compounds. In these circumstances, reactions occur which compete with the normal Michaelis–Arbuzov reaction, the principal one being that attributed to Perkow[69]. Nevertheless, successful ring opening reactions have been carried out on the phosph-(III)olidines **25**; the products are of the form **26**, aqueous acid hydrolysis of which then affords the phosphinic acid $PhR^4P(O)OH$ (e.g. benzylphenylphosphinic acid[70]), whereas in other examples, the intermediate **26** has been subjected to acid-catalysed methanolysis to give methyl esters of mixed phosphinic acids[71].



(25) (26)

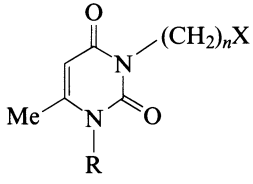
To conclude this section, it must be mentioned that there are phosphite esters which do not take part in the Michaelis–Arbuzov reaction. Many such esters possess cyanoalkyl groups, or are heavily halogenated at the alkyl β-carbon atom, and their nucleophilic character is thereby reduced considerably[15]. The presence of a similarly sited nitro group appears to inhibit the reaction; 4-nitro-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane does not react with aralkyl halides under the conditions sufficient for the 4-alkyl analogues[72].

2. *The nature of the alkylating agent*

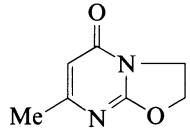
Essentially, the Michaelis–Arbuzov reaction proceeds well with primary alkyl halides and at least moderately well with secondary halides, the reactivity of the halogen being in the order I > Br > Cl, alkyl fluorides normally being unreactive (the reactive polyfluoroalkanes and alkenes do undergo reactions with trialkyl phosphites and afford halogeno-

alkylphosphonic acids, and are therefore considered in Chapter 3). The rate of reaction depends on steric hindrance within the alkyl halide and also within the phosphite ester. In MeCN at reflux temperature, trimethyl phosphite reacts with iodobutane to give a mixture of dimethyl methylphosphonate and dimethyl butylphosphonate, the former being in the greater amount, but no mixed products are obtainable from iodoethane and tributyl phosphite under these conditions[73]. The rate of reaction of triethyl phosphite with isopropyl iodide at 100–200 °C is about 1/60th of the rate of its reaction with iodoethane; *tert*-butyl chloride does not react, even at high temperature and under pressure[74]. Whereas triisopropyl phosphite and isopropyl bromide do not react together under normal conditions, or in MeCN at room temperature, they do so very slowly in hot MeCN[75].

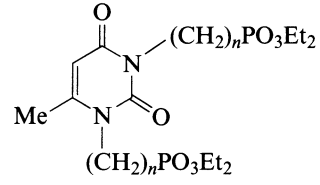
Mono-, di- and tri-arylmethyl halides are all very reactive[24–26,28–31,33–36,40,46–48,51–54,57,59–61,64,66,70], as are allylic halides[42,51,76–78] in Michaelis–Arbuzov reactions. Recent examples of the use of more complex benzylic-like halides include halogenomethylpyridines and halomethylquinolines[23,32], halomethyl–oxygen heterocyclics[24,37,79], halomethylquinoxalines[27,80–82] and other halomethyl hetereocyclic systems[26,80]. Unusual results were obtained with the pyrimidinediones **27**; these (R = H, X = Cl) react with triethyl phosphite to give **28**[83] but the presence of the substituent R = $(CH_2)_nX$, X = Cl or Br in **27** allows the expected formation of the diphosphonic acid esters (**29**)[83,84].



(**27**)



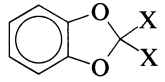
(**28**)



(**29**)

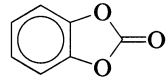
Reactions involving 3-haloalk-1-ynes should be included at this point to complete the range of halides in which halogen is bonded to sp^3 carbon, although this in turn is linked to other carbon atoms possessing another degree of hybridization. Further discussion of this area is deferred, however, since the products do not possess P—C(sp^3) bonding but rather that of a P—C(sp^2) or P—C(sp) nature, depending on experimental circumstances.

gem-Dihalogen compounds take part in the Michaelis–Arbuzov reaction, sometimes producing novel results. The dichlorobenzodioxole **30** affords a very moderate yield of the *gem*-diphosphonic tetraethyl ester **31** together with a larger yield of the cyclic carbonate **32**, whose production has been formulated as occurring through the formation of a pseudoquaternary salt followed by elimination of EtCl and $(EtO)_2PCl$[85–87]. Monodebromination to **34** occurs in the reactions between the gem-dibromopropanes **33** [R^1 = H, R^2 = Hex, Ph or Me_3SiCH_2; $R^1R^2 = (CH_2)_4$] and triethyl phosphite, in the presence of Et_3N, but may be accompanied by phosphonation to give the corresponding **35**, although the success here would appear to depend critically on the dryness of the reactants[88]. On the other hand, the dihalopropenes **36** (X = Cl or Br; R^1 = Me or Ph) readily undergo diphosphonation when they react with triakyl phosphites or dialkyl phenylphosphonites[89]. The participation

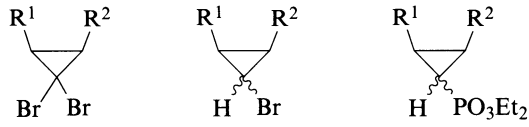


(**30**) X = Cl

(**31**) X = $P(O)(OEt)_2$

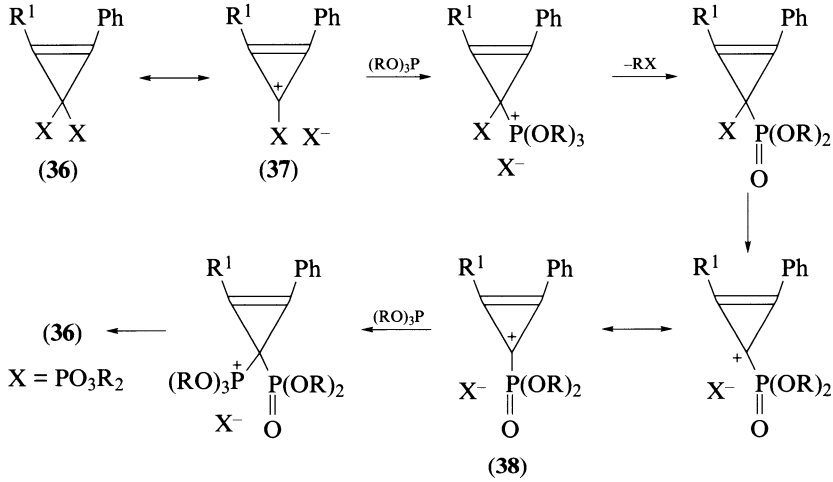


(**32**)



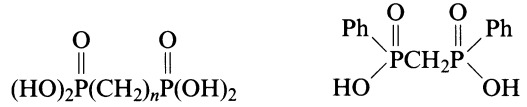
(33) (34) (35)

of the cyclopropenium carbocations such as **37** and **38** (Scheme 1) explains the remarkable ease of reaction under such mild conditions (in dichloromethane at 40 °C).



SCHEME 1

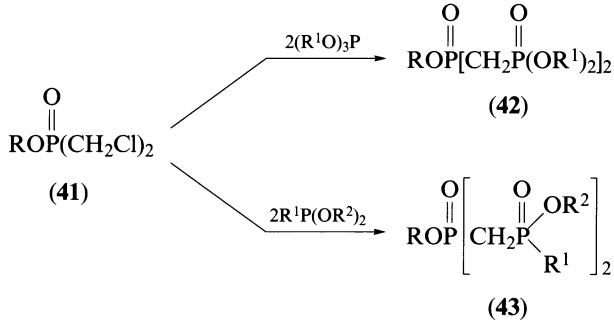
A particularly important example of a *gem*-diphosphonic acid is, in fact, the simplest, namely methylenebisphosphonic acid (**39**) ($n = 1$). The interaction of diiodomethane with excess triisopropyl phosphite at 150–160 °C has provided 50–60% of tetraisopropyl methylenebisphosphonate[90], but marginally better yields are reported to be obtainable if dibromomethane is employed[91]. Lower yields of the tetraethyl ester are obtainable using triethyl phosphite, and it should also be noted that a difference in the ratio of reactants is liable to provide dialkyl (halomethyl)phosphonates (Chapter 3, Section II.A). A similar procedure has provided the tetraethyl esters of α,ω-alkanebisphosphonic acids (**39**) ($n = 1$–10)[92,93]. In a like manner, Dahl and Block[94] have obtained methylenebisphenylbisphosphinic acid (**40**) via its diisopropyl ester (not isolated) from diiodomethane and diisopropyl phenylphosphonite.

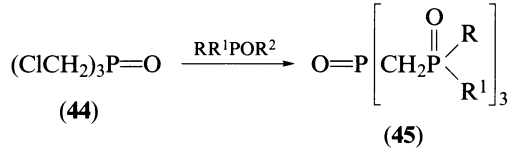


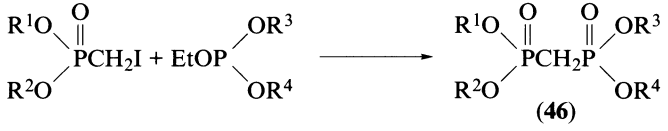
(39) (40)

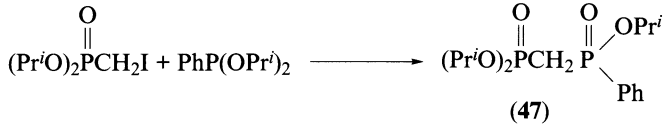
Maier[95] and others[96] have carried out Michaelis–Arbuzov reactions between alkyl bis(chloromethyl)phosphinates (**41**) and trialkyl phosphites to give alkyl bis[(dialkoxyphosphinyl)methyl]phosphinates (**42**), and with alkylphosphonous diesters to give bis[(alkoxyalkylphosphinyl)methyl]phosphinic esters (**43**). Analogous reactions with bis-

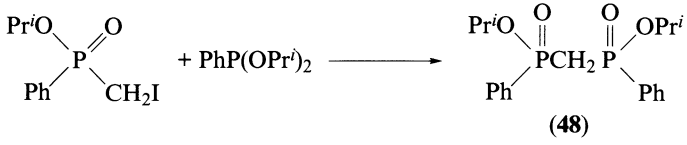
and tris-(chloromethyl)phosphine oxides have led to tris[(dialkoxyphosphinyl)methyl]- and tris[(alkoxyphenylphosphinyl)methyl]-phosphine oxides, e.g. **45** from **44**[96–98], and yet a further communication concerns the analogous synthesis of alkyl bis[2-(dialkoxyphosphinyl)ethyl]phosphinates[99]. More recent publications have been concerned with the synthesis of mixed esters of methylenebisphosphonic acid (**46**) from (halomethyl)-phosphonic diesters[100] and isopropyl esters of the mixed phosphonic–phosphinic acid **47** and methylenebisphenylphosphinic acid (**48**)[101] starting from esters of (iodomethyl)phosphonic acid and [(bromomethyl)phenyl]phosphinic acid in combination with diisopropyl phenylphosphonite. Triethyl phosphite also reacts with (α-bromoaralkyl)phosphonic diesters with the formation of arylmethylenebisphosphonic tetraesters[102].











3. The reaction mechanism

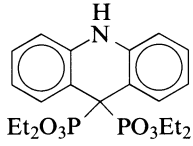
The feature of this which might first be considered is the nature of the intermediate. It is evident that a true intermediate is obtained during the course of the reaction. Thus, the treatment of tri-*tert*-butyl phosphite with methyl iodide at 5–10 °C yields a crystalline solid with the evolution of heat; within 15–20 min the solid begins to disappear, and it disappears completely in 30–40 min resulting in the formation of di-*tert*-butyl methylphosphonate[103]. When a mixture of iodoethane and diethyl ethylphosphonite is heated a 50 °C, crystals appear which at 105 °C, afford ethyl diethylphosphinate. Iodomethane also gives crystalline 1:1 adducts from esters of diethylphosphinous acid[104] and ethylphosphonous and isopropylphonous acids[105], and from esters of allylic phosphonous acids[106,107]. Most of these adducts melt in the range 40–60 °C. Those isolated from trineopentyl phosphite and halomethanes melt at about 85 °C[108]. When heated, such adducts decompose into esters of phosphonic or phosphinic acids. The adducts are soluble in chloroform and in dichloromethane, and in solution provide ^{31}P NMR data consistent with an ionic structure—probably as ion pairs in keeping with the term 'pseudophosphonium salt' applied to them.

The examples just quoted are thus true intermediates in the Michaelis–Arbuzov reaction. However, many other similar adducts have been prepared, including those from triphenyl phosphite and methyl halides and which have the structure $[(PhO)_3P^+Me][X^-]$, but which do not break down under normal Michaelis–Arbuzov conditions: nevertheless, they have some significance in synthesis, since in the presence of alcohols, ROH, they decompose with the generation of the alkyl halides, RX, and formation of diphenyl methylphosphonate[109]. In general, the salts $[(PhO)_3P^+R][X^-]$ will also act as a source of the esters $(PhO)_2P(O)R$[108–111], but only when heated at 140–180 °C for extensive periods, and they therefore cannot be considered as typical Michaelis–Arbuzov intermediates. It might be added that mixed alkyl phenyl esters do take part in the true Michaelis-Arbuzov process[112]. Trifluoromethylsulphonate salts have also been shown by ^{31}P NMR spectroscopy to be ionic (as opposed to being non-ionic and pentacoordinate)[113], whilst a series of tetrafluoroborates, obtained by reaction of the phosphorus(III) esters with $[Ph_3C^+][BF_4^-]$, or with $[Et_3O^+][BF_4^-]$, have been prepared and they, also, decompose in the presence of NaOR or $NaHCO_3$ into phosphonic esters[114]. It is of interest also that, when heated with $NaBPh_4$ at 90–120 °C, trimethyl phosphite isomerizes into dimethylmethylphosphonate, but the process does not extend to higher trialkyl phosphites[115]. The chemistry of the various types of pseudophosphonium salts has been extensively reviewed[116]. Other types of phosphonium salts will be encountered in connection with some variants of the Michaelis–Arbuzov reaction, to be discussed later.

It is evident that the interaction of a phosphorus(III) triester and the alkylating species RX can be pictured as an S_N2 process (reaction 2) or, for those alkylating reagents capable of forming a carbocation, as an S_N1 process (reaction 3). Several reactions testify to the importance of carbocationic carbon for the Michaelis–Arbuzov reaction in pursuance of its normal course; they include the ease of reaction of cyclopropene dihalides, already encountered, and the ready formation of complexes with species having particularly weakly nucleophilic counter ions. Phosphonic acid formation also takes place with cyclic azonium salts and related ions. 9-Chloroacridine reacts with triethyl phosphite to afford a product thought to be the bisphosphonic acid ester **49**[117]. The related phosphonic esters **51** are obtainable when the onium salts **50** (X = NH, NR, O or S) are treated with trimethyl

$$R^1{}_2POR^2 + RX \longrightarrow [R^1{}_2R\overset{+}{P}OR^2][X^-] \quad (2)$$

$$R^1{}_2POR^2 + R^+ + X^- \longrightarrow [R^1{}_2R\overset{+}{P}OR^2][X^-] \quad (3)$$



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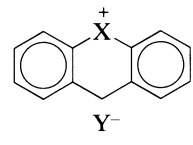

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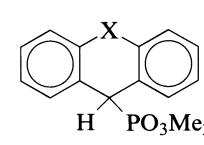
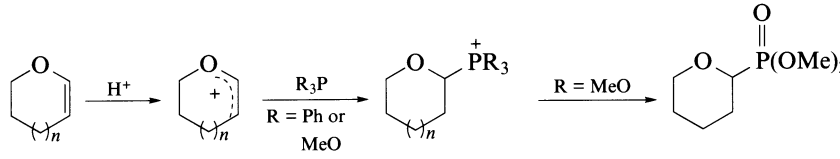


(51)

phosphite and NaI[118], and other similar phosphonic acids are obtainable from quaternary acyl salts from heterocyclic systems[119,120].

The interaction of an ethenyl ether and a trialkyl phosphite (trimethyl phosphite was actually used) under dry acid conditions (HCl gas in MeOH) leads to a phosphonic diester according to Scheme 2. Little dealkylation of the phosphite triester appears to occur, and the reaction appears therefore not to involve addition of dialkyl hydrogenphosphonate (the product of phosphite dealkylation), all the more so since triphenylphosphine also reacts under the same conditions to give related triphenylphosphonium salts. Ethenyl ethyl ether, 2,3-dihydrofuran and 2,3-dihydropyran were used as substrates[121]. The ease of reaction under mild conditions, coupled with high yields, testifies to the importance of a cationic intermediate species.



n = O or 1

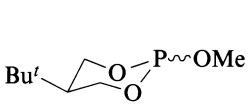
SCHEME 2

Following a comparison of the behaviours of trialkyl phosphites, mixed alkyl phenyl phosphites and triphenyl phosphite towards iodomethane and, in the last case, the breakdown of the phosphonium salt when treated with an alcohol, Landauer and Rydon[109] considered that all the reactions involve a stage identical with that of the normal Michaelis–Arbuzov reaction. The absence of any rearrangement during the decomposition of complexes from neopentyl phosphites, and the configurational inversion which occurs when optically active 2-halooctanes are produced from optically active phosphite triesters (themselves obtained from optically active octan-2-ol), suggest that the mode of breakdown of the intermediate complexes is of S_N2 character.

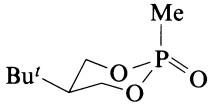
Triethyl phosphite reacts extremely easily with benzoyl chloride to give diethyl benzoylphosphonate; in dioxane at 30 °C, the time for half completion of the reaction is about 4 min. On the other hand, benzoyl fluoride is recoverable to the extent of 90% after 90 h, from which it may be inferred that the rate-determining step in the Michaelis–Arbuzov reaction is not necessarily the first step consisting in the approach of nucleophilic phosphorus to positive carbon[122]. Further, whilst simple trialkyl phosphites are highly reactive towards iodomethane, a bicyclic phosphite such as **15** (R^1 = Me) is unreactive to boiling iodomethane[59], the implication then being that the nucleophilicity of the phosphorus in the bicyclic ester is much reduced, being subject to stereoelectronic influences (a term coined by Taira and Gorenstein[122]).

In spite of the large volume of evidence for the participation of ionic intermediates in the Michaelis–Arbuzov reaction, there is also considerable evidence for the formation and breakdown of other species during the course of the same reaction; such participation occurs together with, or in place of, that of ionic species.

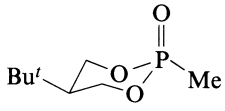
When treated with iodomethane, initially at room temperature, a mixture of conformers of 5-*tert*-butyl-2-methoxy-1,3,2-dioxaphosph(III)orinane (**52**) of conformational (at phosphorus) composition 77:23 yielded a mixture of 5-*tert*-butyl-2-methyl-2-oxo-1,3,2-dioxaphosphorinanes (**53**) of composition 71:29, the principal component being the conformer with *P*-methyl sited axially (**53a**)[123]. This high degree of stereospecificity was not found with similar reactions involving 2-alkoxy-4-methyl-1,3,2-dioxaphosph(III)orinanes (**54**) and simple alkyl iodides. In reactions of the latter phosphites with trityl tetrafluoroborate followed by treatment of the intermediates with I^-, stereospecificity in the formation of the phosphonates **55** was essentially complete although, however, ring retention was accompanied by ring fission to give **56** (or an isomer)[55].



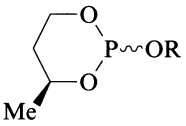
(**52**)



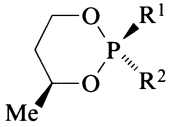
(**53a**)



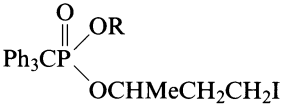
(**53b**)



(**54**)



(**55**)

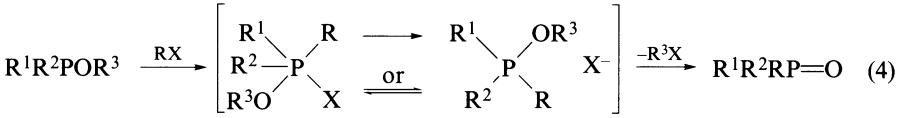


(**56**)

(**a**) $R^1 = CPh_3$, $R^2 = =O$

(**b**) $R^1 = =O$, $R^2 = CPh_3$

On the basis of such evidence, it now seems to be widely accepted that the intermediates in valence expansion reactions of the Michaelis–Arbuzov type can have either an ionic, or a non-ionic, pentacoordinate structure, or both can be involved, possibly sequentially, or through equilibration, the choice being dependent on the ligands surrounding the central phosphorus atom, i.e. on the nature of the reactants. Thus reaction 1 might well be written as reaction 4.



(**6**)

4. *Side-reactions*

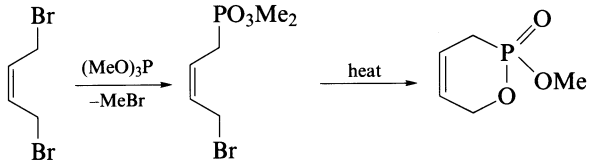
Several possible reactions may give rise to impurities in the preparation of phosphonic or phosphinic acid esters by the Michaelis–Arbuzov reaction, and it is possible that, in some cases, such reactions become preponderant. Triethyl phosphite, for instance, has been successfully used as a dehalogenating agent, in particular, for debrominations[124]. Isomerization of allylic groups may occur through S_N1'-type processes (reaction 5)[76] or be induced thermally (reactions 6 and 7)[125,126].

$$(EtO)_3P + MeCHClCH{=}CH_2 \longrightarrow (EtO)_2P(O)CH_2CH{=}CHMe \qquad (5)$$

$$EtP(OCHMeCH{=}CH_2)_2 \xrightarrow{120\ ^\circ C} EtP(O)(OCHMeCH{=}CH_2)(CH_2CH{=}CHMe) \quad (6)$$

$$EtP(OCH_2CH{=}CHMe)_2 \xrightarrow{140\ ^\circ C} EtP(O)(OCH_2CH{=}CHMe)(CHMeCH{=}CH_2) \quad (7)$$

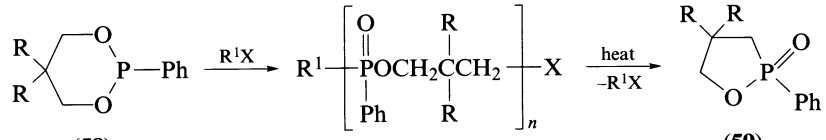
The later stages of reactions involving α,ω-dihaloalkanes and related compounds may be accompanied by cyclization, particularly at higher temperatures (equation 8)[127]. The two-stage reactions between trialkyl phosphites and 1,4-dibromo- or 1,5-dibromoalkanes give rise to 1,2-oxaphosph(V)orinanes (**57**) (n = 1)[128] or 1,2-oxaphosph(V)epanes (**57**) (n = 2)[129] accompanied by monodehydrobromination during the formation of a linear ester.



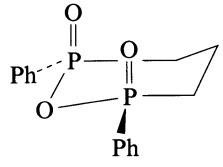
(8)

(**57**)

Reactions between cyclic phosphonites (**58**) and alkyl halides have been employed to prepare linear (ring-opened) polymeric phosphonates which, when heated more strongly, undergo depolymerization and furnish 1,2-oxaphosph(V)olanes, e.g. **59**; when R = H, a second product has been shown to be the phosphinic anhydride (**60**)[130,131].



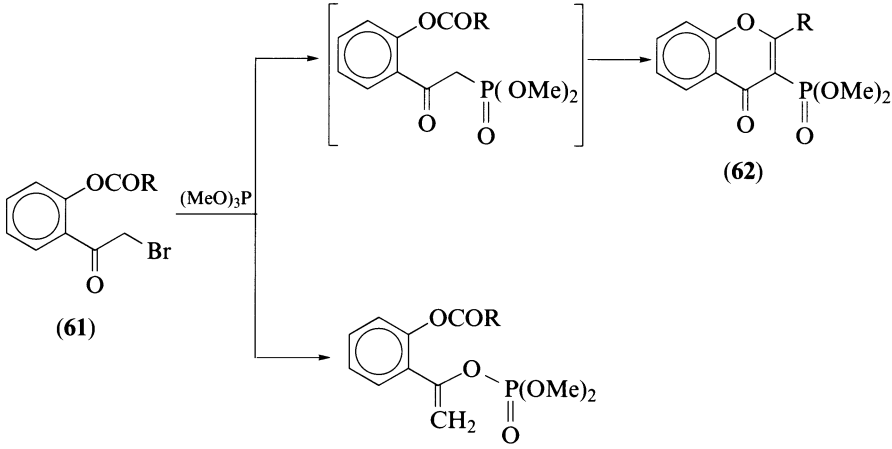
(**58**) (**59**)



(**60**)

A further, and more important, difficulty occurs in attempted Michaelis–Arbuzov reactions involving certain halogenated carbonyl compounds. In these cases, a reaction in

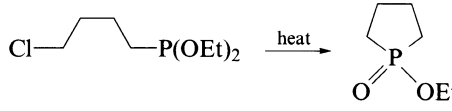
competition with the 'normal' process gives rise to phosphate esters, and in some cases these may be the only products. For these reasons, the Perkow reaction (which has been recently extensively reviewed[69]) will be considered further, although briefly, in Chapter 3 in connection with the synthesis of functionalized acids. At the moment, however, it should be pointed out that the main difference between the Perkow and Michaelis–Arbuzov reactions lies in the point of attack in the carbonyl compound by the phosphite ester. One recent example illustrates a typically final outcome in which both phosphonate (**62**) and phosphate (**63**) esters were obtained from the bromomethyl ketone **61**[132].



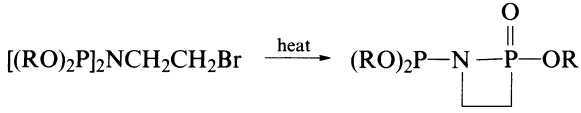
5. Variations

Many variations in the Michaelis–Arbuzov reaction have been observed; they range from slight changes in the nature of the alkylating species to a recognition that certain reactions, of an apparently totally different type, are in essence of the same mechanistic type, and give rise to similar products.

The reaction can be of an intramolecular nature; such possibilities (reaction 9) were explored by Helferich and Aufderhaar[133] and were also adapted by Aksnes and Bergesen[134] in the synthesis of 1,2-oxaphosph(V)epanes. Reaction 10 illustrates the formation, in an analogous fashion, of *N*-phosphitylated 1,2-azaphosphetidines[135].



(9)



(10)

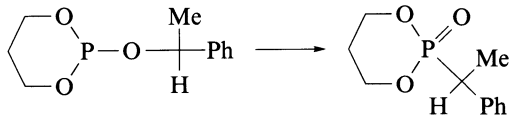
Variations in the alkylating species include the use of benzylic ethers in conjunction with $AlCl_3$[136] and of alkyl sulphonates, particularly alkyl *p*-toluenesulphonates. The latter can

give very high yields of phosphonic esters, particularly if the alkyl groups of both reactants are identical; if they are not, a process of cross-alkylation occurs, resulting in the formation of esters of more than one phosphonic acid[41,137]. Reactions involving sulphonic esters and the bicyclic phosphite esters **14** have also been carried out successfully[59].

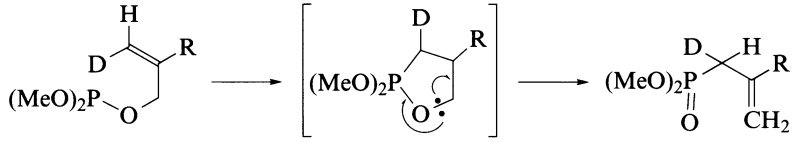
Boyd and coworkers[138–140] investigated the reaction which occurs between PCl_3 and triphenylmethanol and isolated a substance which they described (incorrectly) as the phosphorodichloridite **64** and a further substance to which they gave the (correct) structure **65**, suggesting that the conversion of **64** into **65** involved the valence expansion process. Hatt[141] pointed out that Arbuzov and Arbuzov had meanwhile suggested what was to be recognized as the true structure of **64**, and he later presented further chemical evidence in support of the phosphonic dichloride structure **66**[142]. Further examples of such phosphonic dichlorides and the triarylmethylphosphonic acids obtainable therefrom have since been described[143] and the first spectroscopic (IR) evidence for the structure was eventually presented[144]; subsequently the structure has also been confirmed by X-ray analysis, as was that of the corresponding difluoride[145]. It was Halmann *et al.*[144] who, it appears, first suggested that the reaction might proceed through the species **67**; attack by HO^- on P^+ with displacement of Cl- is comparable to the decomposition of the pseudoquaternary salts formed in the Michaelis–Arbuzov process.

Ph_3COPCl_2	$Ph_3CP(O)(OH)_2$	$Ph_3C\overset{O}{\overset{\|}{P}}Cl_2$	$[Ph_3C\overset{+}{P}Cl_3][HO^-]$
(64)	**(65)**	**(66)**	**(67)**

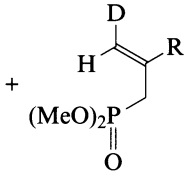
The isomerization of low molecular weight trialkyl phosphite into dialkyl alkylphosphonates merely on heating has been attributed to the presence of impurities which catalyse the process but, even at room temperature, the exposure of trimethyl phosphite to light radiation results in a 32% yield of the isomeric phosphonate, together with the formation of smaller amounts of trimethyl phosphate and dimethyl hydrogenphosphonate[146]. Triphenyl phosphite, diphenyl ethylphosphonite, phenyl diethylphosphinite and analogous ethyl esters fail to isomerize under the same conditions. However, the photoinduced isomerization of benzylic[147,148] and allylic[149,150] phosphites occurs at room temperature, high-yield conversions being achievable. These isomerizations are totally regioselective with regard to the benzyloxy and allyloxy groups. The former rearrangement is intramolecular and occurs with retention of configuration at the benzylic methylene carbon (reaction 11)[146]. The use of *cis*- and *trans*-2-benzyloxy-5-*tert*-butyl-1,3,2-dioxaphosph-(III)orinanes demonstrated that the reaction also proceeds with retention of configuration at phosphorus[147,148]. The rearrangement of a deuterium-labelled allyl phosphite is depicted in reaction 12; when irradiated, the phosphite **68** affords a mixture of **69** (> 95%) and **70** (< 5%), the labelling becoming completely scrambled if the rearrangement is carried out in cyclohexane as solvent. The replacement of an alkene hydrogen by a methyl or phenyl group can result in a slower isomerization and the formation of more than one phosphonate product, and if the allyloxy group is bonded to a 1,3,2-dioxaphospholane or 1,3,2-dioxaphosphorinane ring, the rearrangement can become totally inhibited[149]. The mechanism of the benzophenone-sensitized photorearrangement of allyl phosphite substrates is mechanistically different from rearrangements sensitized by other means, and



(11)



(68) (69)



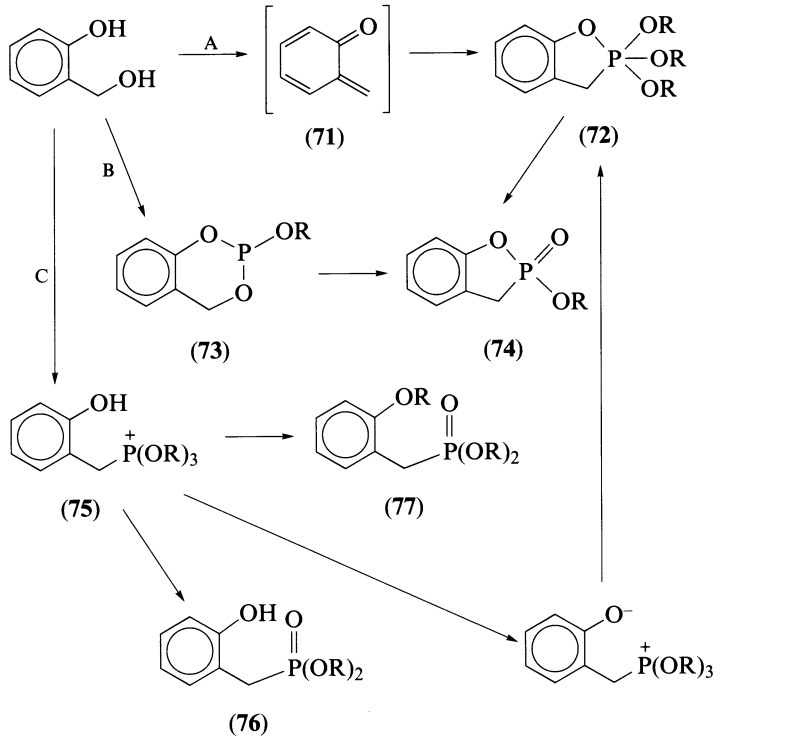
(70)

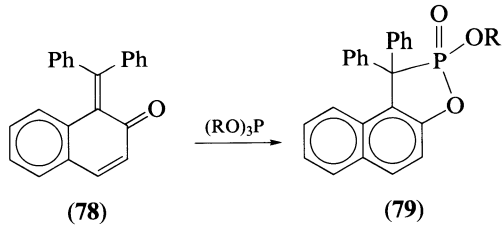
(12)

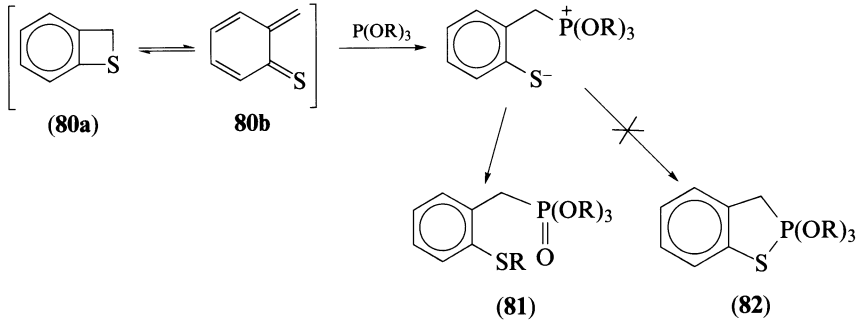
when a 0.02 M solution of dimethyl 2-phenylprop-2-enyl phosphite in MeCN saturated with 9,10-dicyanoanthracene is irradiated, a 70–75% conversion of phosphite to the isomeric phosphonate **70** (R = Ph) is achievable on a 75–100 mg scale during 12 h[150].

Heat is generated when a trialkyl phosphite is mixed with 2-hydroxybenzyl alcohol, but the reaction is best completed by heating the reactants in a solvent, usually dmf, to about 150 °C. Among the products of the interaction are 2,2,2-trialkoxy-2,3-dihydrobenzoxaphospholes (**72**), 2-alkoxy-2,3-dihydrobenzoxaphosph(V)oles (**74**), dialkyl (2-hydroxybenzyl)phosphonates (**76**) and their ethers (**77**). Three reaction pathways have been considered[151–155]. The first of these (A) requires the intermediate formation of a quinonemethide (**71**) and the assumption that such a species would react with a trialkyl phosphite as indicated. Some known quinone methides do behave in this way; thus **78** reacts in this way to give the 1:1 adduct **79** directly[156]. Benzothiete (**80**) is thought to be capable of undergoing reaction through its tautomeric form (**80b**); with a trialkyl phosphite it affords a dialkyl (2-alkylthiobenzyl)phosphonates (**81**), but there are no indications of the formation of the pentacoordinate species **82**[157]. No evidence has been forthcoming for the direct formation of benzodioxaphosphorins (**73**) (pathway B). The intermediacy of **75** affords a rationale for the formation of both **76** and the ethers **77**, and is consistent with the later preparation of **81**. In addition, the action of heat on esters of type **76**, synthesized by alternative means[152], causes their cyclization to the respective **74**. The isolation of the oxyphosphoranes **72** might be the result of betaine formation from **75** and ensuing cyclization. ^{31}P NMR evidence has more recently been advanced in favour of the direct conversion of **76** into **74**[158].

2-Hydroxybenzyl alcohols react, on slight warming, with the series of phosphorus(III) amides **83–85**; the products from these interactions include ethanol and diethyl phosphite (from **83**), together with **86** (from **83**) and **87** in addition to **88** (X = OEt or NEt_2)[159]. The conversion of gramine salts (**89**) (X = I or $MeOSO_2O$) into the phosphonic diester **90** when heated with triethyl phosphite[160] [one of surprisingly few recorded examples of the value of quaternary ammonium salts in the synthesis of non-functionalized phosphonic acids; others are encountered in the preparation of functionalized phosphonic acids (see Chapter 3]. The reactivities of acetates, hydrochlorides and methiodides of 2-hydroxybenzylamines (**91**) (R′X = CH_3COOH, HCl, MeI) towards trialkyl phosphites, affording **74**[161], render possible a comparison, and creation of a link, between the behaviour of phosphite triesters towards 2-hydroxybenzyl alcohols and to 2-hydroxybenzylamines (Scheme 3). Many other studies have been concerned with these and similar reactions with phosphorus(III) ester–amides which have led to derivatives of the 2,3-dihydrobenzoxaphosph(V)ole system[162–164].


OH
OH
A
O
O
OR
P—OR
OR
(71)
(72)
B
C
O
P
OR
O
(73)
O
P
O
OR
(74)
OH
+
P(OR)3
(75)
OR O
P(OR)2
(77)
OH O
P(OR)2
(76)
O⁻
+
P(OR)3


Ph
Ph
O
(78)
(RO)3P
O
Ph
Ph
P
OR
O
(79)


S
(80a)
S
80b
P(OR)3
+
P(OR)3
S⁻
P(OR)3
SR O
(81)
P(OR)3
S
(82)

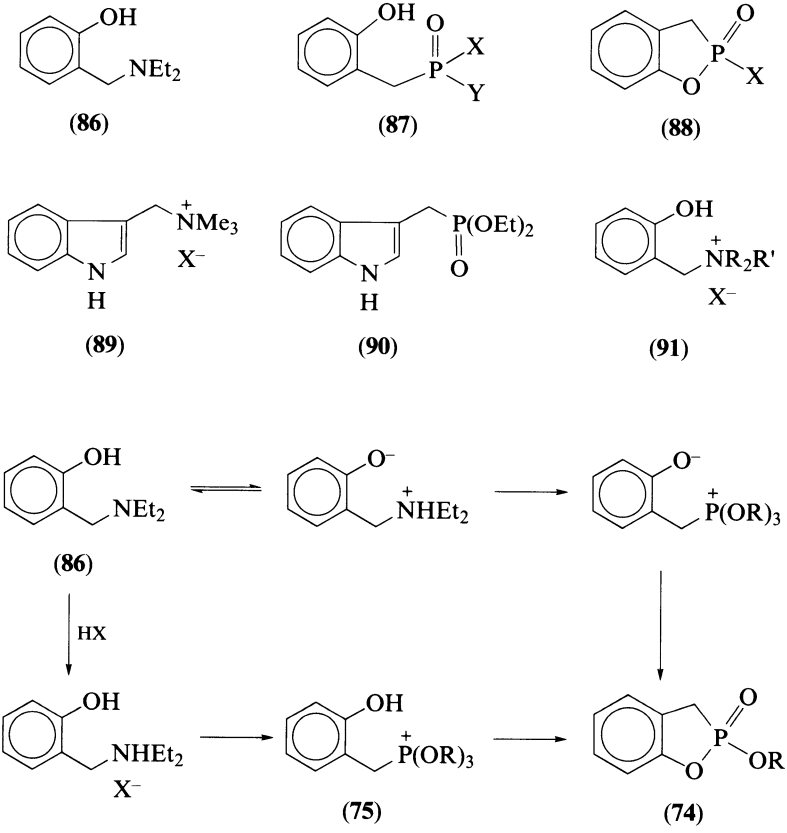
It was McCormack who, in 1953, in the patent literature, first reported the cycloaddition of phosphorus(III) halides to 1,3-dienes[11,12,14]. As then represented, the sequence took the form depicted in reaction 13 (X = Cl or Br). The careful addition of water to the crystalline 1:1 adduct, formulated as a halogenophosphonium salt (**92**), gave the unsaturated phosphinic chloride (**93**, R = Br or Cl) or acid (**93**, R = OH). Since the original publication of the procedure, the application of modern spectroscopic techniques has demonstrated that the final products in such reactions are mixtures of the 3-phospholene (**93**) and 2-phospholene (**94**) isomers, conveniently represented, when admixed and in unknown proportions, as **95**. It has since become apparent that the relative proportions of the isomeric forms **93** and **94** of any derivative depend on the nature of the halogen X and on the manner of work-up; thus, in an acidic work-up medium, the products tend to have the structure **94**, but neutralization during the hydrolysis step leads to derivatives of the isomeric **93**. The reaction consists simply in mixing the reactants at room temperature and

Et_2NPXY

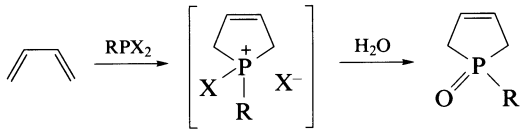
(**83**) X = Y = OEt

(**84**) X = NEt_2, Y = OEt

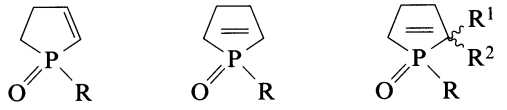
(**85**) X = Y = NEt_2



SCHEME 3



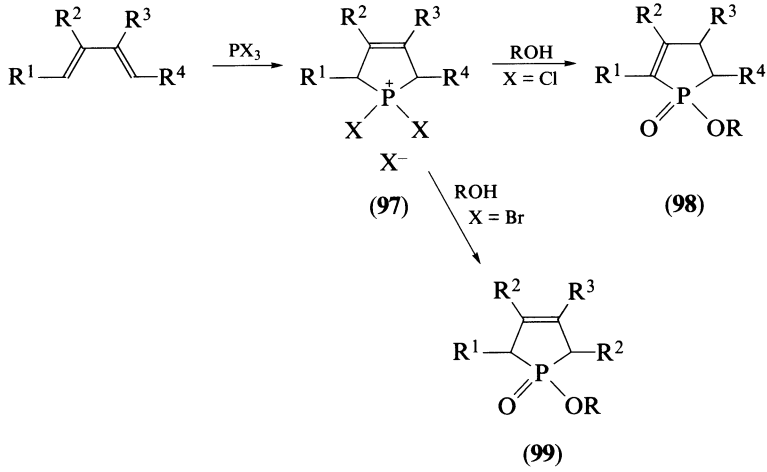
(92) (93) (13)



(94) (95) (96)

allowing the formation of the crystalline adduct to proceed in the presence of a trace of a polymerization inhibitor such as copper stearate. Substitution on the diene skeleton increases the rate of reaction considerably, and a *trans*-diene reacts faster than does its *cis* isomer. In addition, the dibromides $RPBr_2$ are more reactive than the corresponding dichlorides. Further, the use of an appropriately substituted diene can result in mixtures of stereoisomeric products such as (**96**).

The reaction which occur through the use of the phosphorus trihalides, PX_3, have been studied primarily by two groups. Hasserodt and coworkers[165,166] have observed that the reaction rate can vary enormously; thus, the 1:1 adduct from 2,3-dimethylbutadiene and PBr_3 is formed in 85% yield in 1 h at –10 °C, whereas at the other extreme, the reaction between buta-1,3-diene itself and PCl_3 yields only 27% adduct in 22 days at room temperature, and even after 60 days the yield is still only 73%[165]. Hydrolysis or alcoholysis of the adduct **97** (X = Cl) yields the 2-phospholene derivative **98** (R = H or alkyl), but the extent of prototropic change can be reduced considerably through the use of PBr_3, when the 3-phospholenes **99** are the main products. The pattern of unsaturation in purified isomers is demonstrable by ozonolysis. Both 2- and 3-phospholene derivatives are converted into equilibrium mixtures of isomers by the action of strong bases such as alcoholic KOH, sodamide or KOBu^t. Decomposition of the 1:1 adducts with SO_2 or acetic anhydride affords the respective phosphinic acid halides. The results obtained by the Russian work-

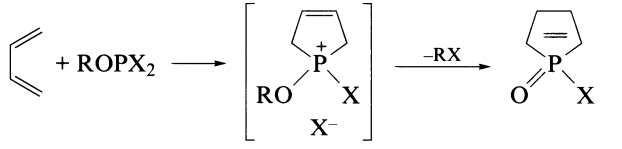


(97) (98)

(99)

ers are essentially the same as those just described[167–169]; but they[170] have also shown that the reactions afford the cyclic phosphinic chlorides directly when carried out in acetone. Improved procedures have been worked out for the synthesis of 1-methoxy-3-methyl-2-phospholene 1-oxide (**98**) (R = Me = R^2, R^1 = R^3 = R^4 = H) from isoprene employing a multivariate optimization analytical procedure[171] and for reactions between butadiene and PCl_3[172].

PBr_3 is thus the preferred reagent for the preparation of the cyclic unsaturated phosphinic acids with only P—C(sp^3) bonding, but the formation of the 1:1 adducts is by no means restricted to those from phosphorus(III) trihalides, or phosphonous dichlorides (dichlorophosphines, which yield 2-alkyl- or 2-aryl-phospholenes (R = alkyl or aryl in reaction 13) and therefore fall outside the scope of this chapter). Other useful reactants include alkyl phosphorodichloridites, $ROPCl_2$[173], and the corresponding difluorides[174], dialkyl phosphorofluoridites, $(RO)_2PF$[174] and aryl phosphoro-dichloridites and -dibromidites, $ArOPX_2$[175], the reactions then taking the forms depicted in equations 14 and 15. Also of considerable interest are the comparable reactions which have been carried out using cyclic phosphorus(III) halides and other derivatives; they include 2-fluoro-[176–179], 2-chloro-[180–182] and 2-bromo-[183,184] 1,3,2-dioxaphosph(III)olanes, and their 2-substituted-1,3,2-dioxaphosph(III)orinane counterparts[182–184]; such reactions are depicted in equation 16 (X = F, Cl or Br, n = 0 or 1), and have also been noted for cyclic isothiocyanates (X = NCS)[185,186], cyclic phosphorus triesters[187,188] and their thio analogues[189] and mixed anhydrides[190,191]. In all cases the reactions were carried out by heating the reactants together at 80–150 °C in sealed tubes. Once again, it is worth noting that absent from this listing are



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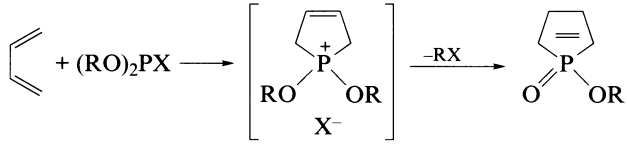

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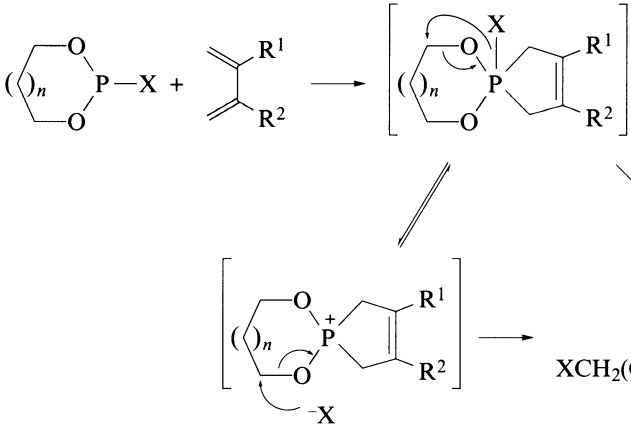
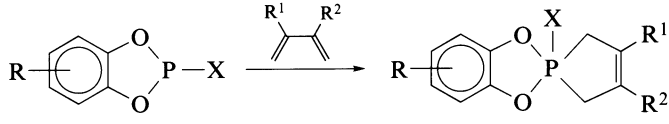


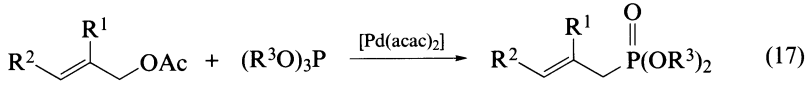
(16)

the cyclic phosphorus(III) compounds derived from 1,2-dihydroxybenzene and its derivatives; these include **100** (X = F[192], Cl[182,193], Br[182,192] or OMe[194]). The products **101** derived from such compounds possess true non-ionic pentacoordinate structures which fail to undergo fission to the monocyclic phospholenes, as do those from dienes and cyclic esters of phosphonous acids[195]. The addition reaction has been discussed in general terms[196]; a progressive increase in reaction rate is in the order X = R_2N < RO < F < SR < Cl < NCS, Br, with increased substitution on the diene system also increasing the rate. As in all cases discussed thus far, the nature of the reaction intermediate depends on the ligands around phosphorus, and structures obviously range from the extremes of true ionic character to a fully non-ionic pentacoordinate nature.



(100) **(101)**

Although not an example of the true Michaelis–Arbuzov reaction, the formation of a phosphonic diester from a trialkyl phosphite and an allylic acetate in the presence of [Pd(acac))$_2$] in dioxane at 145–160 °C (reaction 17) bears some resemblance. When R^1 = R^2 = H, the main product is the dialkyl (1-propenyl)phosphonate. In all examples, trialkyl phosphate is concomitantly produced[197].



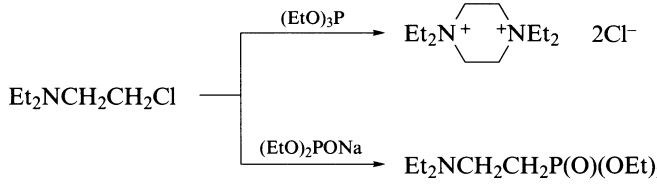
(17)

B. Through the Alkylation of Hydrogenphosphonates and Hydrogenphosphinates

Within this area, the most recent developments in the synthesis of esters of phosphonic acids have been the direct alkylation of hydrogenphosphonates using diazoalkanes in the presence of copper-containing catalysts in benzene as the solvent[198,199]. Of those catalysts examined, the most effective seem to be [Cu(acac)$_2$] and [Cu(OTf)$_2$], with Cu, Pd and Rh acetates and [Ni(acac)$_2$] being less effective[200]. The overall reaction is that represented in equation 18, in which R^1 and R^2 may be H, Ph or a simple alkyl group, but they may also consist of a functionalized alkyl group in reactions catalysed by trifluoromethanesulphonic acid[201]. A similar procedure has been applied to the hydrogenphosphinate Ph(MeO)P(O)H[200].

$$(RO)_2P(O)H + R^1R^2CHN_2 \xrightarrow[C_6H_6]{-N_2} (RO)_2P(O)CHR^1R^2 \qquad (18)$$

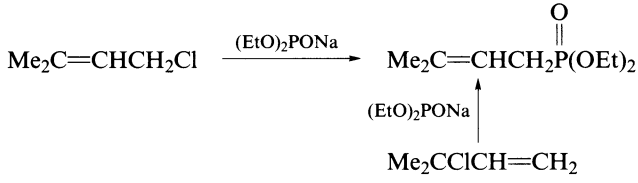
The classical procedure, and the one still extensively employed, consists in the alkylation of compounds containing the P(O)H moiety, as an appropriate metal salt, with an alkyl halide or similar type of compound; such a procedure can sometimes be a successful alternative when the classical Michaelis–Arbuzov reaction fails, one such example being illustrated in equation 19. No reaction takes place between triethyl phosphite and 3-chlorocyclopentadiene at below 120 °C, above which the main reaction is then dehydrochlorination; the use of sodium dialkyl phosphites leads, however, to the desired dialkyl cyclopent-2-enylphosphonates[202].



(19)

As most commonly applied, a dialkyl hydrogenphosphonate is converted into its sodium salt by reaction with NaOEt, $NaNH_2$ or NaH, in thf, of as the lithium salt following a reaction with BuLi, and the solution of the alkali metal derivative is then treated with an organohalogen compound. The technique is attributable to Michaelis and Becker and was reported in 1897. The reaction conditions are much milder than those associated with the Michaelis–Arbuzov reaction, since very strong heating is not required—indeed, many reactions can be carried out at, or only at a slightly above, room temperature, and so thermolytically initiated side-reactions may be avoided. As with the Michaelis–Arbuzov procedure, the reactions are here restricted to the use of alkyl chlorides, bromides or iodides; primary organohalides react most readily, secondary organohalides less so, and the reaction most often fails with tertiary organohalides when dehydrohalogenation tends to occur because of the very basic nature of the phosphorus reactant[203–209]. As in the Michaelis–Arbuzov reaction, complications arise when the substrates consist of 1-haloalk-3-ynes; prototropic isomerization in the initial product then leads to esters of alka-1-2-dienephosphonic acids or of alk-1-ynephosphonic acids.

Examples of the high reactivity of benzylic halides[210] and of allylic halides[211–213] have been reported. In the latter case, the well established S_N1' rearrangement occurs when a secondary or tertiary allyl halide is used, and this leads to the same products as are obtained from the isomeric primary halide (equation 20), Surprisingly, 3-phenylprop-2-enyl halides afford only low yields in sluggish reactions[214].



(20)

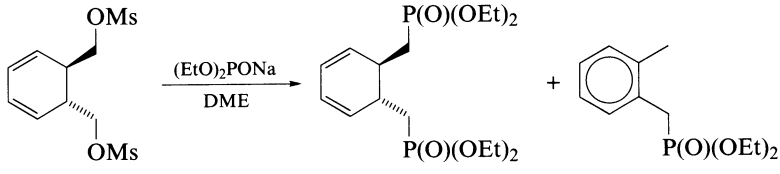
Although it might be expected that reactions which employed triarylmethyl halides would occur very readily, such reactions are rendered potentially more complex by the known nature of the halides and their propensity for involvement in free radical reactions. Whereas normal alkylation proceeds between sodium diethyl phosphite and diphenylmethyl halides, success, or otherwise, in the use of the triphenylmethyl halides depends to some extent on the individual halide and on the metal in the phosphite salt. Thus, in an early study (in 1939), Arbuzov found that in reactions between silver dialkyl phosphites and triphenylmethyl bromide, dialkyl triphenylmethylphosphonates were indeed formed, but the use of the corresponding alkyl chloride provided the phosphite triester instead (metal dialkyl phosphites possess ambident anions[215]). A later study[216] confirmed the behaviour of the silver salts towards the chloride, but also showed that, whereas dialkyl phophites with primary alkyl groups yielded phosphonic diesters (as had already been found), those with secondary alkyl groups afforded phosphite triesters; moreover, the presence and nature of aromatic substituents were also able to control the course of the reaction. Reactions which involve triarylmethyl halides and sodium dialkyl phosphites may well be of a free radical nature since repeated studies have demonstrated the forma-

tion of bistriarylmethyl peroxides and hexaarylethanes, often in substantial yields, alongside the triarylmethylphosphonic diesters[217–219].

Those Michaelis–Becker reactions between even relatively simple primary or benzylic-type halides and sodium dialkyl phosphites are not without their unwanted side-reactions. Halomethylfurylcarboxylic esters, for example, undergo concomitant dehalogenation or Michaelis–Becker phosphonation (the two processes may also occur side by side) depending on the relative positions in the furan nucleus of both carboxylic ester and halomethyl groups and on the halogen. Chlorides react normally, bromides do not[220].

Reactions between dialkyl hydrogenphosphonates and haloalkanes have been performed under phase-transfer conditions; some initial experiments[221] used diethyl and diisopropyl hydrogenphosphonates with either non-functionalized (e.g. alkyl, allyl or benzyl) halides, or functionalized halides, and employed K_2CO_3 as base in the presence of tetrabutylammonium salts or 18-crown-6. Other workers have also reported successes in their use of the same or similar systems[222], but more recent work has raised doubts about the value of the potassium salt, and has illustrated the evident superiority of Cs_2CO_3 as base[223].

Variations in the type of alkylating agent include dialkyl sulphates[203] and *p*-toluenesulphonates[224]. During the synthesis of the 4,5-bisphosphonic acid analogue of *myo*-inositol 4,5-bis(dihydrogenphosphate), the dimesylate **102** and sodium diethyl phosphite were found to provide the target diphosphonate (**103**) together with the monophosphonic diester (**104**) (compare this reaction with those of halomethylfurancarboxylic esters[220])[225]. Other, more novel, co-reactants include phosphonium salts of types **105** and **107**, for example, which provide the (heteroarylmethyl)phosphonic diesters **106** and **108**[226]. The successful synthesis of methylenebisphosphonic acid tetraalkyl esters has also proved possible using a combination of dibromomethane and sodium dialkyl phosphite (1:2) in liquid ammonia or other solvent[227,228] or of sodium dialkyl phosphite and dialkyl (chloromethyl)phosphonate (1:1)[229].

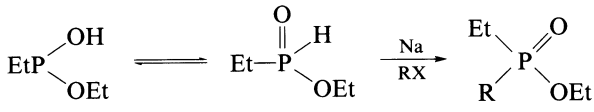


(102) **(103)** **(104)**

(105) X = Ph_3P^+ Br^- **(107)** X = Ph_3P^+ Br^-

(106) X = P(O)(OEt)$_2$ **(108)** X = P(O)(OEt)$_2$

The procedure has been adopted for the preparation of alkyl dialkylphosphinates from alkyl alkylphosphinates (monoalkyl alkylphosphonites) as depicted in equation 21[230] and of the bisphosphinic esters and acids **109** (n = 1 or 2)[231] and **110**[232].



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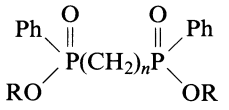

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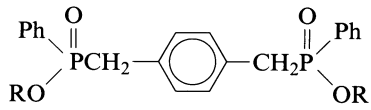
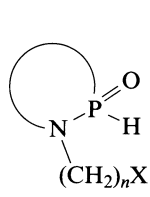


(110)

Trimethylsilyl esters of both functionalized and non-functionalized phosphinic acids, $R_2P(O)OSiMe_3$, have been prepared from the respective alkyl halides and bis(trimethylsilyl) alkylphosphonites, $RP(OSiMe_3)_2$, (Michaelis–Arbuzov alkylation) as part of a novel sequence in which the latter are obtained *in situ* from alkyl halides and bis(trimethylsilyl) hypophosphite $[HP(OSiMe_3)_2]$ in the presence of Et_3N (Michaelis–Becker-like alkylation)[223].

Novel cyclic *N*-(ω-haloalkyl)phosphinic amides of the general type **111** cyclize when treated with NaH[234] and the hydrogenphosphonic diamides **112** have also been alkylated[235]. In this way, a one-pot, but four-step, procedure[236] for the synthesis of (2-pyridinylmethyl)phosphonic acid via its di(4-methylphenyl) ester (Scheme 4) seems unnecessarily long by one step.



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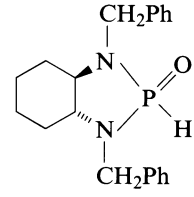

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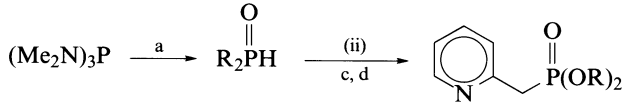

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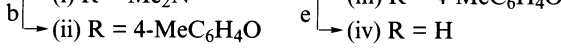
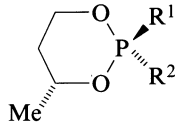


Reagents: a, H_2O; b, 4-MeC_6H_4OH; c, NaH, toluene; d, 2-$(C_5H_4N)CH_2Cl$; e, H_3O^+

SCHEME 4

The kinetics of the reaction between dineopentyl phosphite anion and alkyl halides is second order and thus supports a simple $(S_N2)_P$ mechanism with the implication of configurational inversion at phosphorus in appropriate substrates. However, by using a 1:1 mixture of the epimeric hydrogenphosphonates **114a** and **114b** (R = H), Lesiak *et al.*[237] found the stereochemical changes to be dependent on the manner in which the experiment was carried out. The addition of NaH to a 1:1 mixture of **114** and MeI resulted in retention of the configuration at phosphorus, whereas inversion was observed if the MeI was added to the preformed phosphite salt (in spite of the fact that each phosphite yielded the same sodium derivative with equatorially sited PONa) and, independent of the original phosphite conformation, a 92:8 *trans–cis* (relative spacing of the methyl groups) mixture of

cyclic methylphosphonates. Relevant here is the observation by Reiff and Aaron[238] that the formation of the sodium salt from (*R*)-(–)-isopropyl methylphosphinate (**115**) results in complete loss of optical activity.



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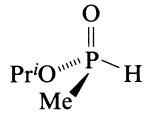

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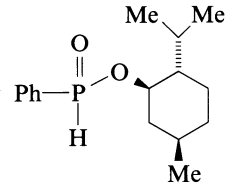


(116)

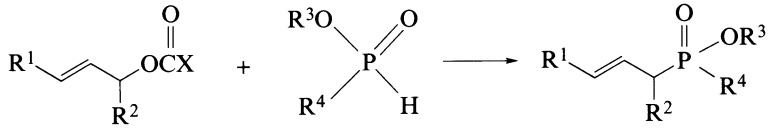
(a) R^1 = =O, R^2 = Me
(b) R^1 = Me, R^2 = =O

Using diastereoisomerically enriched samples of menthyl phenylphosphinate (**116**) (purified samples of diasteroisomers have since been prepared[239]) Farnham and *et al.*[240] have shown that methylation using MeI–NaH–dmf proceeds stereospecifically and with retention of configuration, although the stereolability of the anion was a factor to be taken into consideration, as had been found by the Polish workers[237]. On the other hand, Cram's group[224] showed that the interaction of optically active alkyl tosylates (e.g. that from optically active 1-methylheptanol) with the sodium salt of butyl phenylphosphinate yielded a 1:2 mixture of the diastereoisomeric butyl (1-methylheptyl)phenylphosphinates, implying some retention of chirality in the sodium salt.

From the experimental point of view, it is worth noting that when dimethyl hydrogenphosphonate is treated with NaH in thf, some disproportionation to dimethyl methylphosphonate and monomethyl phosphinate occurs; this property is not important with diethyl hydrogenphosphonate, nor does it occur even with dimethy hydrogenphosphonate if the anion is generated from either NaH or BuLi in benzene or in thf at a low temperature[206].

Michaelis–Becker reactions have been carried out in two-phase systems; even under such mild conditions, isomerization of prop-2-ynylphosphonic diesters occurs to give a 90% combined yield consisting of a mixture of diethyl propadienylphosphonate and diethylpropy-1-nylphosphonate (85:15). Some of the allylic halides furnish small amounts of phosphonic esters, but others, and also benzyl halides, only undergo reaction in the presence of a long-chain tertiary amine hydrochloride catalyst[241]. Dialkyl hydrogenphosphonates and tertiary benzylamines react together to give dialkyl benzylphosphonates[242].

Reaction 22 is analogous to that depicted in equation 17. The compounds **117** (X = Me or OEt; R^1, R^2 = H or Ph) undergo reaction with dialkyl hydrogenphosphonates[243] or alkyl hydrogenphosphinates (and secondary phosphine oxides)[244] in the presence of btsa and 5 mol% of $[Ni(cod)_2]$; the yields of phosphonates **118** (R^4 = OR^3) were 22–90%. The isomeric **117** (X = Me; R^1 = Me, R^2 = H, or R^1 = H, R^2 = Me) and **117** (X = OEt; R^1 = H, R^2 = Ph, or R^1 = Ph, R^2 = H) react with a dialkyl hydrogenphosphonate to give identical



(22)

(117) **(118)**

esters **118** (R^1 = Me or Ph, R^2 = H)[244], implying that the phosphorus nucleophile attacks at the unsubstituted carbon in the metal complex in a regiospecific fashion.

C. Synthesis from Alkyl Halides and Phosphorus(III) Halides

The discovery that a mixture of an alkyl halide, $AlCl_3$ and PCl_3 yields a complex which, when hydrolysed under carefully controlled conditions, gives a phosphonic dichloride seems to be attributable to Clay[245], although the development of the procedure was made slightly later, following independent discovery, by Kinear and Perren[246]. Clay observed several important features which were crucial to experimental success ; these included (i) a correct order of mixing of reactants; (ii) careful control of temperature at the onset of reaction; (iii) careful drying of the reagents; and (iv) the addition, after complete formation of the intermediate complex, of the correct amount of water, which should be a 7–11 molal ratio. The reaction sequence can conveniently be represented as that in equations 23 and 24.

$$RX + PCl_3 + AlCl_3 \longrightarrow [RPCl_3^+][AlCl_4^-] \quad (23)$$

(118)

$$[\overset{+}{R}PCl_3][AlCl_4^-] + 7H_2O \longrightarrow AlCl_3.6H_2O + 2HCl + R\overset{O}{\overset{\|}{P}}Cl_2 \quad (24)$$

(119)

Primary, secondary and tertiary alkyl chlorides, bromides or iodides all undergo reaction (vinyl halides and alkyl fluorides do not), as do cycloalkyl[246,247] and benzyl[246,248] halides. Apart from the compilation of examples by Kinnear and Perren[246], other examples are spread very widely and rather thinly throughout the literature. Some isomerization is to be found when using certain alkyl halides; for example, *n*-propyl and *n*-butyl halides afford the isopropyl- and (1-methylpropyl)-phosphonic dichlorides, and isobutyl chloride yields *tert*-butylphosphonic dichloride[246]. Whilst Me_3SiCH_2Cl affords the expected phosphonic dichloride, neopentyl chloride yields (1,1-dimethylpropyl)phosphonic dichloride[249]. 1,5-Dichloropentane reacts but affords only (4-chloro-1-methylbutyl)phosphonic dichloride[246]

Several syntheses have been performed in the adamantane series. With PCl_3–$AlBr_3$, 1-bromoadamantane gives 1-adamantylphosphonic dichloride[250] and using the same reagent, 1,3-dibromoadamantane yield the corresponding 1,3-di(phosphonic dichloride) and with $AlBr_3$–PBr_3 the corresponding 1,3-di(phosphonic dibromide)[251]. Surprisingly, 2-bromoadamantane with PCl_3–$AlBr_3$ yields a mixture of di-2-adamantylphosphinic chloride and the corresponding bromide, together with some (1-adamantyl)(2-adamantyl)phosphinic chloride[252].

Kinnear and Perren[246] also examined, in a very limited way, the behaviour of alkylphosphonous dichlorides, $RPCl_2$. Here, the reaction (equation 25) would be expected to afford phosphinic chlorides, with either identical or non-identical organic groups, but their experiments did not yield entirely satisfactory results and, evidently, the procedure has not been further developed for such cases.

$$R^1PCl_2 + R^2X + AlCl_3 \longrightarrow [^-R^1R^2PCl_2^+][AlCl_4^-] \longrightarrow R^1R^2P(O)Cl \quad (25)$$

(120)

The importance of the carbocationic character of the alkylating species has been repeatedly demonstrated in instances such as the remarkable ease of reaction of the *tert*-butyl halides, and the ease of formation of 1-adamantylphosphonic dichloride when 1-bromo-, 1-hydroxy- or other 1-substituted adamantanes are dissolved in sulphuric acid and treated with PCl_3[253–255] or when 2-hydroxyadamantane is similarly treated[256]. In the latter case, the use of $PhPCl_2$ yields (1-adamantyl)phenylphosphinic chloride, also similarly obtainable from 1-hydroxyadamantane.

In the light of their high melting points and electrical conductivity in $MeNO_2$, Cade[257] suggested that the intermediate complexes possessed the chlorophosphonium tetrachloroaluminate structures **119** and **120**. The formation of tetrahaloaluminate complexes has been widely recorded throughout organophosphorus chemistry and some have been characterized crystallographically (see Section II.E), and structures **119** and **120** are now widely accepted. The difficulty lies in explaining how such complexes are formed. There is little evidence to indicate any reactivity of RX towards PCl_3 alone, or of PCl_3 towards $AlCl_3$ alone, and all three have to be present together (in spite of the earlier comments about the order of mixing). The mechanism must also allow for the isomerization of the organic moiety, the lower reactivity of polyhalohydrocarbons (to be considered in the following chapter) and vinyl halides, and also for the ability of alkyl dichlorophosphites, $ROPCl_2$, to replace the PCl_3. The intermediate formation of the carbocation R^+ resulting from mixing of RX and $AlCl_3$ is not consistent with the fact that initial mixing of these two reactants, followed by addition of the PCl_3 produces poor yields, and yet Cade accepted the idea of a loose association of the two leading to $[R^+][AlCl_4^-]$, followed by association of the carbocation to give the chlorophosphonium cation. Certainly, comparisons may be made with the Friedel–Crafts reaction but the great difference is the degree to which isomerization may occur; this tends to be complete in the present reaction but only partial in aromatic substitution. Later, Lindner and Granbom[258] suggested an equilibration between PCl_3 and $AlCl_3$ which leads to $[PCl_2^+][AlCl_4^-]$; this is then subjected to attack by the phosphorus(III) chloride. Phosphenium cations of the type $[(R_2N)R'P^+]$, in which R′ is Cl or R''_2N are known but, as yet, there appears to be no evidence for the dichlorophosphenium cation[259,260]. Thus, at present, the fine details of the mechanism remain something of a mystery.

As for all reactions which generate chlorophosphonium cations, in addition to furnishing phosphonic dichlorides by hydrolysis, the work-up can be modified to give other phosphonic acid derivatives and, for example, alcoholysis yields first the chloride esters, $RP(O)(OR')Cl$, and then the diesters, $RP(O)(OR')_2$[247].

D. Synthesis from Hydrocarbons and Phosphorus(III) Halides

1. *The oxidative phosphonation of alkanes*

This procedure, although not widely used since it does indeed have some severe restrictions, has nevertheless proved useful in a few cases. The reaction involves bubbling oxygen or air through a mixture of the hydrocarbon and PCl_3 and the results accord with equation 26. The case most widely reported and one which has always provided excellent results is that of cyclohexane[261–263], and it has been claimed that a second dichlorophosphonylation step can occur[263]. Ethyl or methyl dichlorophosphites can be used to replace the PCl_3[264].

$$2PCl_3 + RH + O_2 \longrightarrow RP(O)Cl_2 + POCl_3 + HCl \qquad (26)$$

Although the reaction requires no catalysis, and is not catalysed by $AlCl_3$, I_2, iron or BF_3, the drawbacks to the procedure are (i) a large wastage of the trichloride as $POCl_3$; (ii) a lack of regiospecificity clearly demonstrable in the reactions of linear or non-symmetrical

hydrocarbons when mixtures of phosphonic dichlorides are obtained; and (iii) the formation of other types of products in certain cases. Nor is the reaction adaptable to the use of PBr_3 as a potential source of phosphonic dibromides. Ethane yields largely $EtOP(O)Cl_2$, with only a much smaller yield of ethylphosphonic dichloride[262]. The mixtures of isomeric phosphonic dichlorides, not always separable, are sometimes accompanied by alkanebis-(phosphonic dichlorides)[261,265–268]. The procedure has been applied to the phosphonation of waxes[269] and also to aromatic hydrocarbons with alkyl side-chains; thus, 1,4-dimethylbenzene yields about 40% of (4-methylbenzyl)phosphonic dichloride[270].

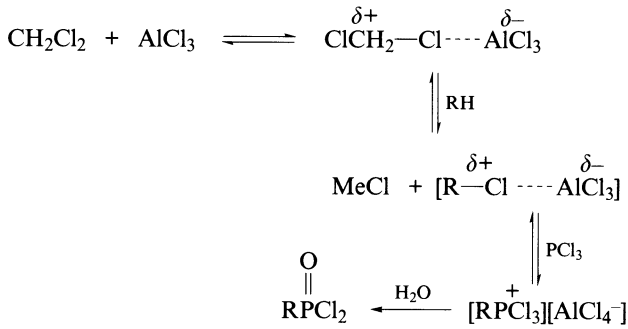
To a very limited degree, the procedure has been applied to the preparation of selected phosphinic chlorides; of these, reactions involving methyl- and ethylphosphonous dichlorides[271] and $PhPCl_2$[272], in conjunction with cyclohexane, successfully lead to the phosphinic chlorides, CyRP(O)Cl (R = Me, Et, or Ph).

The reaction often fails if the reactants, particularly the hydrocarbon, are purified to a high degree, and it has therefore been suggested that the mechanism of the reaction is one involving free radicals, on the assumption that purification of the hydrocarbon removed peroxide impurities. The substitution occurs most readily at a teriary carbon site and least easily at a primary carbon. Radical mechanisms were proposed by Soborovskii *et al.*[273] and later by Flurry and Boozer[274].

2. *Catalysed phosphonations of hydrocarbons*

a. Reactions involving saturated hydrocarbons. The formation of a tetralin phosphonic dichloride when tetralin comes into contact with PCl_3 in the presence of $AlCl_3$ was recorded several decades ago[275]. A more recent study with more accessible results concludes that whilst monocyclic and acyclic saturated hydrocarbons react with PCl_3–$AlCl_3$ mixtures in the proportions 1:1.1 :1.3 to give 10–20% yields of their phosphonic dichlorides, the use of saturated polycyclic hydrocarbons, e.g. adamantane and diadamantane, can lead to 40–65% yields of derivatives using dichloromethane as the specific solvent[276].

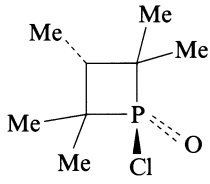
In the light of earlier comments on the lack of interaction of PCl_3 with $AlCl_3$, it may be surmised that the seat of reactivity probably with the $AlCl_3$ and the solvent, specifically dichloromethane. The evolution of chloromethane during the course of the reaction led Olah *et al.*[276]. to suggest a mechanism which involves weakening of the C—Cl bond in solvent molecules by the $AlCl_3$ and further reaction as indicated in the summary given in Scheme 5.



SCHEME 5

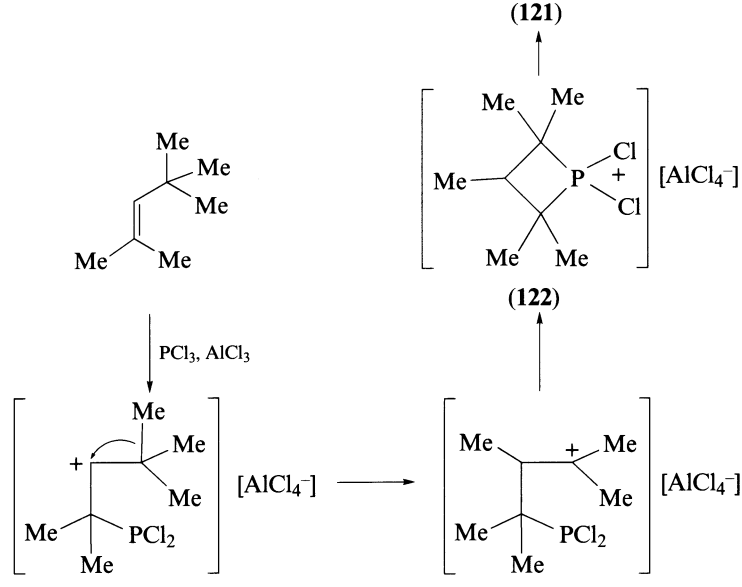
b. Reactions involving unsaturated hydrocarbons. The work of Jungerman and coworkers[277,278] in the early 1960s on the reactions that occur between alkenes and PCl_3 in

the presence of $AlCl_3$ proved to be a milestone, since ready access was thereby provided to a carbon–phosphorus heterocyclic system which was to be widely studied in later years in relation to the mechanism of nucleophilic substitution at phosphorus. Here, the simple procedure involves the treatment of a mixture of alkene and PCl_3 (1:1) with $AlCl_3$ (1 mol per alkene bond) in dichloromethane as solvent. The particular alkene then examined in some detail was 2,4,4-trimethyl-pent-2-ene; hydrolysis of the reaction complex afforded a crystalline compound, $C_8H_{16}POCl$, to which the 1-chloro-2,2,3,4,4-pentamethylphosphetane 1-oxide structure was assigned. A later structural analysis confirmed this and fully determined the stereochemistry of the molecule, showing that the chloro and 3-methyl groups are *trans* to each other as in structure **121**[279]. The corresponding phosphinic bromide was later obtained using the same alkene, PBr_3 and $AlBr_3$[280].



(121)

The isolation and characterization of chloroaluminate complexes of the type $[C_8H_{16}P^+ClR]\,[AlCl_4^-]$, by other workers[281] from reactions which involved phosphonous dihalides, $RPCl_2$, seemed to confirm suggestions as to the reaction mechanism, and which are summarized in Scheme 6. As originally envisioned, the mechanism required the initial complexation of PCl_3 and $AlCl_3$, a point in doubt, but it may be noted that the proposed intermediate **122** possesses a chlorophosphonium structure similar to that encountered in the McCormack reaction.



SCHEME 6

None of the chlorophosphetane is produced in the absence of the $AlCl_3$, and the amount of the latter employed has a marked influence on the product yield; thus if the ratio of the three reactants alkene, PCl_3 and $AlCl_3$ was 1:1:0.75 the yield was about 50%, the yield was about 80% if the ratio was 1:1:1 and > 95% if it was 1:1:1.25. Replacement of the dichloromethane solvent by either a pure aliphatic or aromatic hydrocarbon prevented phosphetane formation, and the use of 1,2-dichloroethane gave some phosphetane together with some dimerized alkene.

No phosphetane was obtained from 2,4,4-trimethylpent-1-ene; 3,3-dimethylbut-1-ene afforded a 92% yield of a mixture of 16% *cis*- and 84% *trans*-1-chloro-2,2,3-trimethylphosphetane 1-oxide[281].

As with so many other organophosphorus reactions in which ionic intermediates have been proposed, the results and conclusions reached from the study of reactions involving one type of substrate (in the present case $RPCl_2$, with $R \neq Cl$) may not, with any degree of certainty, be capable of extrapolation to the case of other substrate types ($RPCl_2$, R = Cl)[282]. This has been amply demonstrated in conductivity studies using 2,4,4-trimethyl-pent-2-ene and 3,3-dimethylbut-1-ene in solution in the methylene dihalides CH_2X_2 (X = Cl or Br) with AlX_3 and either PX_3 or $PhPCl_2$; here, phosphorus trihalides give solutions which are non-conducting until the alkene is added, whereas the solution of $PhPCl_2$ is conducting prior to the addition of the alkene[281]. This would seem to suggest a fundamental difference between the actual attacking species derived from PX_3 and RPX_2, and casts some doubt on proposed ionic structure for the attacking species from PCl_3 and $AlCl_3$ (cf. the work of Olah *et al.*[276]).

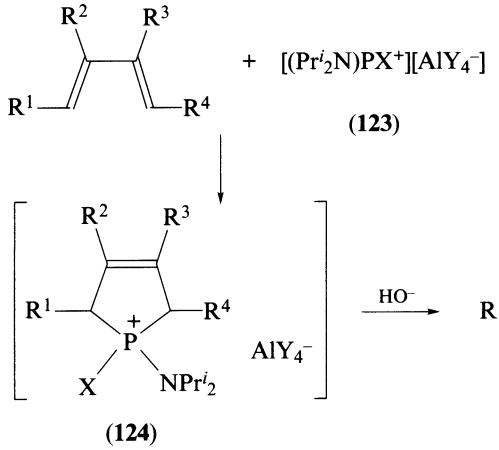
E. Synthesis from Hydrocarbons and Phosphenium Salts

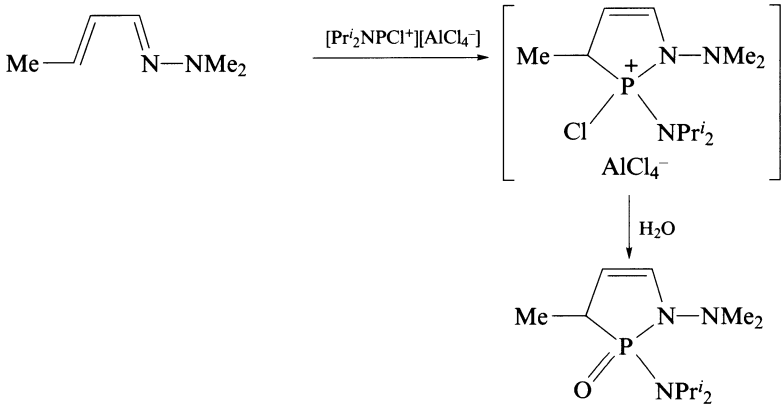
A further method for the synthesis of cyclic compounds in the phosphinic acid series, and investigated within the last decade, is the clearly not unrelated cheletropic reaction which takes place between alka-1, 3-dienes and phosphenium salts. The latter are based on dicoordinate phosphorus, $[R^1R^2P^+]$, the commonly encountered counter ion being the tetrachloroaluminate anion. Such salts are obtained *in situ* through the interaction of $AlCl_3$ and a phosphorus(III) chloride R^1R^2PCl, for which R^1 = Cl, $R^2 = R_2N$, or $R^1 = R^2 = R_2N$[259,260].

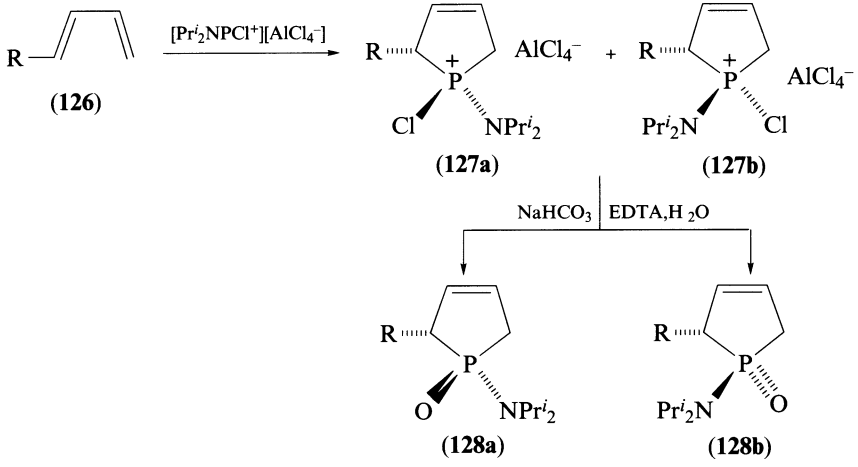
Investigations by Cowley and coworkers[283,284] and by Soottoo and Baxter[285] have revealed that the reactions between 1,3-dienes and the phosphenium salts **123** ($X = NPr^i_2$ or Cl) proceed easily in dichloromethane at 0 °C, to give intermediate cyclic chlorophosphonium salts (**124**) (compare structures **97**, **119**, **120** and **122**), several of which were characterized spectroscopically and crystallographically. The highest yields of **124** ($X = NPr^i_2$) were achieved when $R^2 = R^3$ = Me and $R^1 = R^4$ = H, and the lowest with the reverse pattern of substitution. The hydrolysis of the salts **124** ($X = NR_2$), using NaOH in aqueous dioxane, yields the cyclic phosphinic amides **125** ($X = NR_2$).

A similar cheletropic condensation occurs between a phosphenium cation and a hydrazone from crotonaldehyde (equation 27) to give a cyclic phosphonic diamide derivative[286].

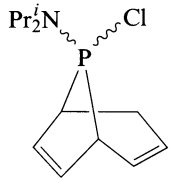
Using penta-1,3-diene and 5-phenylpenta-1,3-diene (**126**) (R = Me or $PhCH_2$), both of *E*-geometry, and in reactions carried out at 0 °C, Polniaszek[287] obtained mixtures of stereoisomeric aminophosphonium tetrachloroaluminate salts, e.g. for **127** (R = Me) in the ratio of 5:1 and for **127** ($R = PhCH_2$) in the ratio 10:1. Hydrolysis of the salts **127** with $NaHCO_3$–edta then gave the separable cyclic phosphinic amides **128** [stereoisomeric 2-methyl(or benzyl)-1-amino-3-phospholene 1-oxides] which were then reduced (5% Ph–C, H_2) to give the corresponding substituted phospholanes (effectively tetramethylenephosphinic acid derivatives). The compound (*E*)-**126** (R = Bu^t) gave only a single salt **127** and single amide **128**. The saturated amides could be acidolysed to the corresponding free phosphinic acids.


R2 R3
R1 R4
+ [(Pri2N)PX+][AlY4−]
(123)
HO−
AlY4−
X NPri2
(124)
(125)

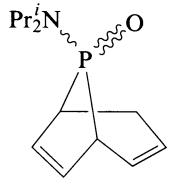

Me N—NMe2
[Pri2NPCl+][AlCl4−]
Cl NPri2
AlCl4−
H2O
O
(27)


R
(126)
[Pri2NPCl+][AlCl4−]
AlCl4−
Cl NPri2
Pri2N Cl
(127a)
(127b)
NaHCO3 EDTA,H2O
O NPri2
Pri2N O
(128a)
(128b)

Weissman and Baxter[288] have also recorded the successful addition of a phosphenium salt to cycloheptatriene; the mixture of stereoisomeric aminochlorophosphonium salts (**129**) then afforded a mixture of phosphinic amides (**130**) when hydrolysed.



(**129**)



(**130**)

For a discussion of the mechanism of the initial cyclization process, the original papers should be consulted[284,287].

F. Synthesis from Hydrocarbons and Hydrogenphosphonates or Related Compounds

1. The hydrophosphonation of alkenes

This is an area in which the syntheses of functionalized acids (as their esters) has predominated (Chapter 3, Sections VI and VII). Nevertheless, the procedure is not without its uses in non-functionalized systems, and it has also received attention as a means for the synthesis of polyphosphonic acids (as their esters).

The interaction of a hydrogenphosphonate diester and an alkene occurs under free radical conditions, arising either through the use of peroxide or azo catalysts, or by exposure to appropriate radiation. Cadogan[289] has summarized some early examples of the procedure, although at the time, there appeared to be very few examples in which non-functionalized systems were used. The commonly accepted mechanism for homolytic addition seems to be that given in Scheme 7.

$$(R'O)_2P(O)H \longrightarrow (R'O)_2PO^{\cdot}$$

$$(R'O)_2PO^{\cdot} + RCH{=}CH_2 \longrightarrow R\dot{C}HCH_2P(O)(OR')_2$$

$$R\dot{C}HCH_2P(O)(OR')_2 + (R'O)_2P(O)H \longrightarrow RCH_2CH_2P(O)(OR')_2 + (R'O)_2PO^{\cdot}$$

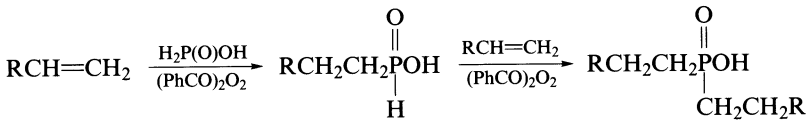
SCHEME 7

Rabillour[290] presented an extensive list of C_5–C_{10} phosphonic acids (as their dimethyl or diethyl esters) produced using γ-radiation from Co^{60}; in certain cases, e.g. in the use of the disubstituted alkenes $Me(CH_2)_nCH{=}CHMe$, mixtures of esters of isomeric phosphonic acids were obtained, the formation of which had apparently not been noticed in an earlier study[291]. Cyclohexene has served as an extensively investigated substrate, additions taking place readily in the presence of dibenzoyl peroxide[292].

Two recent studies have examined the addition of dimethyl hydrogenphosphonate to cyclopropylalkenes in the presence of azobisisobutyronitrile or dibenzoyl peroxide[293] and the addition of a range of dialkyl hydrogenphosphonates to cyclopentene and its methyl-substituted derivatives; in the last case reactions with 1-methylcyclopentene proceeded regiospecifically and to some extent stereoselectively[294].

Reactions involving the addition of hypophosphorous acid (phosphinic acid) to alkenes occur in two stages, the first product being the alkyl phosphinic acid (**131**) which reacts

further to give the phosphinic acid (**132**)[295,296]. The radiation-initiated addition of (*R*)-(–)-isopropyl methylphosphinate to heptene affords (*S*)-(+)-isopropyl heptylmethylphosphinate[238]. Additions of phosphorous acid (phosphonic acid) proceed in a similar fashion to give only alkylphosphonic acids.

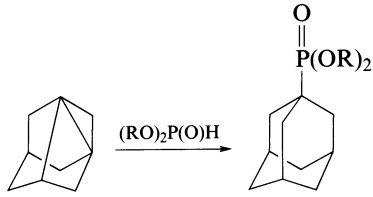


(**131**) (**132**)

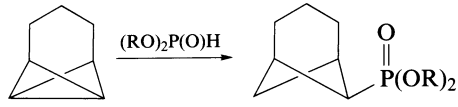
2. *The hydrophosphonation of saturated hydrocarbons*

The photophosphonylation of cyclohexane has been successfully carried out using radiation from a mercury source. With dialkyl hydrogenphosphonates yields of dialkyl cyclohexylphosphonates reaching 75–80% were obtainable within one day, and the esters (EtO)RP(O)H produced similar, or at least acceptable, yields of mixed phosphinic esters CyRP(O)OEt (R = Et, Ph, or Cy) under similar conditions[297].

High reactivity is shown towards hydrogenphosphonates by highly strained hydrocarbon molecules. Thus, 1,3-dedihydroadamantane (**133**) reacts to give esters of 1-adamantylphosphonic acid under non-homolytic conditions[298,299], and tricyclo[4.1.0.0^{2,7}]heptane similarly affords the phosphonic esters **134**[300].



(**133**)



(**134**)

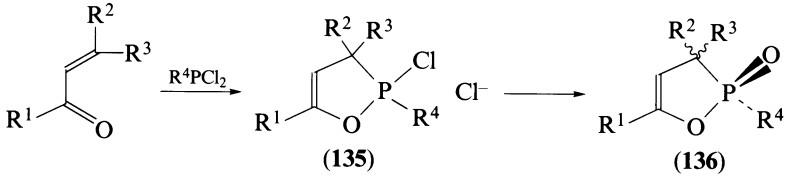
G. Synthesis from Phosphorus(III) Compounds and Carbonyl Compounds

Reactions between simple carbonyl compounds and simple phosphorus(III) halides or esters have been studied periodically throughout more than a century of organophosphorus chemistry and still surface periodically for further examination. This is perhaps not surprising in the light of uncertainties still surrounding the mechanisms of combination, and also the wide variety of products which have been obtained from simple starting materials.

The behaviour of aldehydes and ketones towards dialkyl and trialkyl phosphites will be considered later in connection with the synthesis of (1-hydroxyalkyl)phosphonic acids and

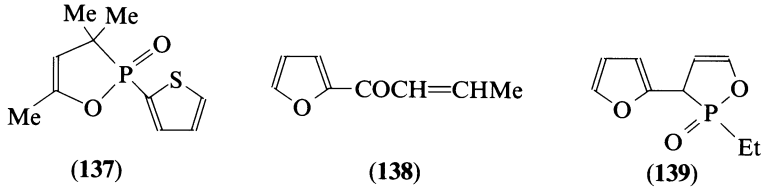
their ethers (Chapter 3, Section III.A), as will their behaviour towards PCl_3 in relation to the preparation both of (1-hydroxyalkyl)phosphonic acids and of (1-chloroalkyl)-phosphonic acids (Chapter 3, Section II.C). However, certain combinations of reactants have received attention for the synthesis of non-functionalized phosphonic and phosphinic acids with P—C(sp^3) bonding.

The reactions between α,β-unsaturated ketones $R^1COCH{=}CR^2R^3$ and phosphorus(III) halides R^4PCl_2 were investigated initially by Conant, who isolated compounds described (using a modern nomenclature) as 1,2-oxa-4-phosph(V)olenes (**136**); such structural conclusions were corroborated by Kabachnik and Medved in 1952[301], although the two groups differed in their interpretations as to the manner of formation of the products.

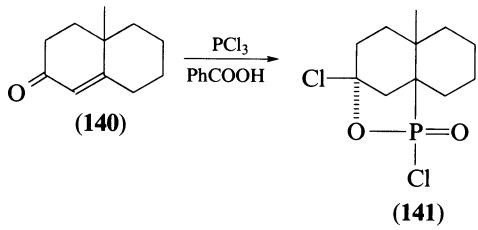


(135) (136)

The procedure involves reaction in acetic anhydride, or in another solvent, followed by the addition of acetic anhydride to decompose the intermediate complex. The procedure has been extensively examined in relation to the 5-methyl- and 4,5-dimethyl-substituted compounds derived from ethenyl methyl and methyl isopropenyl ketones[302–305], and with mesityl oxide[302,306,307], which gives the 3,3,5-trimethyl-substituted compounds. Amongst the phosphorus reactants, the trichloride itself[301,37,308] and methyl-[307,308], ethyl-[303,306,308,309] and phenyl-[303,308] phosphonous dichlorides have been employed, as have ethyl[306] and phenyl[308] dichlorophosphites, $ROPCl_2$. The use of 2-thienylphosphonous dichloride to give **137** is recorded[305], as is that of the unsaturated ketone **138** to give **139**[309]. A more novel conversion is that of **140** into **141** in 25% yield with a similar conversion (15%) being observed for cholest-4-en-3-one[310].



(137) (138) (139)

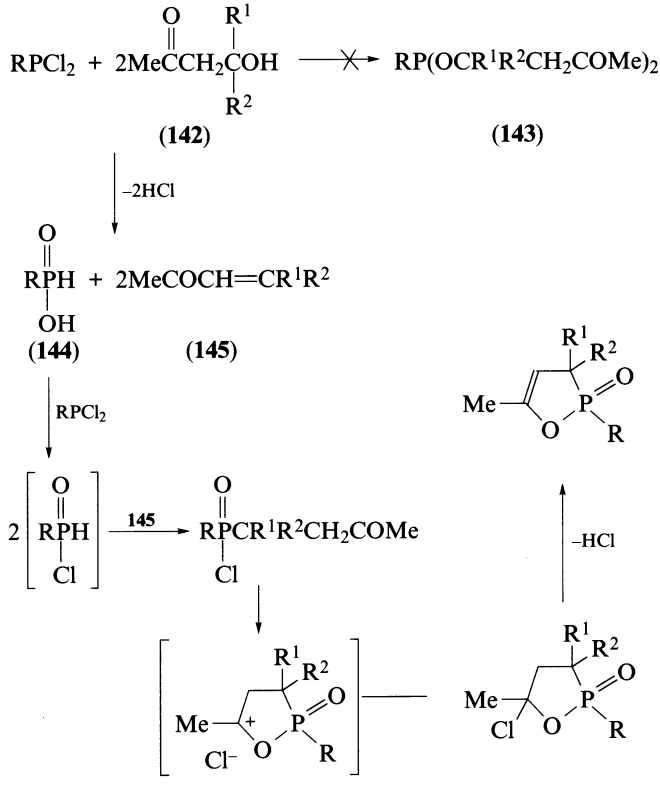


(140) (141)

It is of historical interest to note that 2-chloro-3,5,5-trimethyl-1,2-oxaphosphol-4-ene 2-oxide has sometimes been referred to as the 'Michaelis chloride', having been first reported by Michaelis in 1885, who had prepared the compound from acetone with PCl_3 and $AlCl_3$, a procedure confirmed by Anschutz in 1944. Given the close chemical connection

between acetone, diacetone alcohol (2-methyl-4-oxopentan-2-ol) and mesityl oxide (2-methyl-4-oxopent-2-ene); it should not be surprising that all three are sources of the 1,2-oxaphospholene system (**136**). Several descriptions have been forthcoming on the reactions of simple ketones[311,312] or β-keto alcohols[304,313,314], but in the latter case the process is not initiated by simple dehydration.

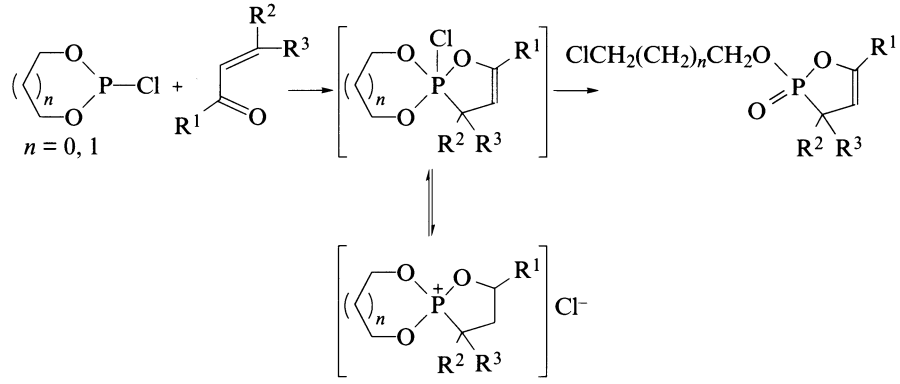
The formation of the 1,2-oxaphosph(V)ol-4-enes as the principal products from *tert*-3-oxoalkanols (**142**) in their reactions with phosphorus(III) chlorides is perhaps surprising; the expected phosphorus(III) esters **143** are not produced, but the respective phosphonous acid **144** is isolable, being formed concomitantly with the α,β-unsaturated ketone **145**. It is envisaged that **144** reacts with dichloride $RPCl_2$ to give a phosphinic chloride; the latter, by virtue of its reactive P—H bond, adds to the ketone to give an intermediate which cyclizes through several stages (not necessarily exactly as depicted) and also with eventual dehydrochlorination to afford the observed product (Scheme 8)[304].



SCHEME 8

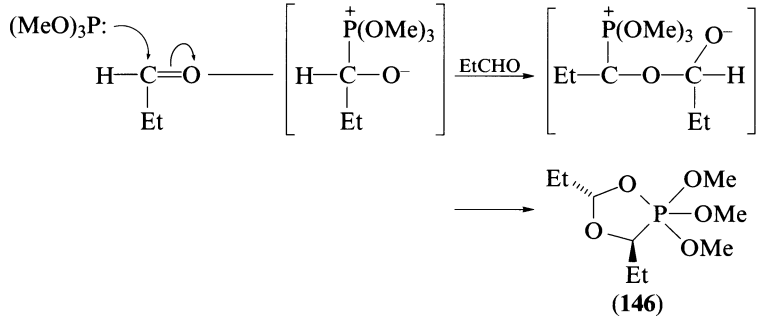
The use of α,β-unsaturated ketones in combination with cyclic phosphorus(III) chlorides[315] takes place through intermediates (Scheme 9) reminiscent of those described for the interactions of phosphorus(III) halides and 1,3-dienes and, indeed, the process seems to be a very general one[316].

In connection with the possible synthetic utility of reactions between simple carbonyl compounds and phosphorus(III) triesters, it is of interest to note that, when heated under



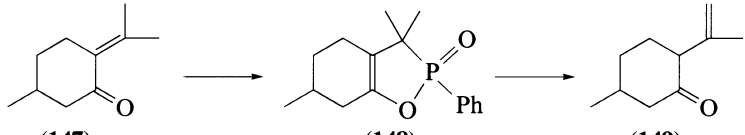
SCHEME 9

reflux for long periods with triisopropyl phosphite, aldehydes or ketones (the former being the more reactive) undergo complete reduction to the hydrocarbon, $R^1R^2CH_2$, if the acetone coproduct is removed continuously[317]. On the other hand, trimethyl phosphite is reported to react with propanal at room temperature to give the 1,4,2-dioxaphosph(V)-olane **146**[318].



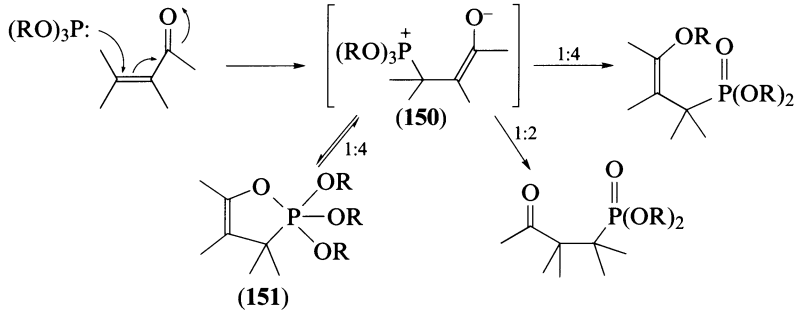
(146)

The product (**148**) obtained by the direct interaction of $PhPCl_2$ and pulegone (**147**) is identical with that obtained from **149** and $PhPCl_2$ in the presence of $AlCl_3$, the result of the prior isomerization of **149** into **147** by the $AlCl_3$[319]. Such reactions are not restricted to the use of α,β-unsaturated ketones but have also been developed for β,γ- and γ,δ-unsaturated ketones, from which phosphine oxides are obtainable[319].



(147) **(148)** **(149)**

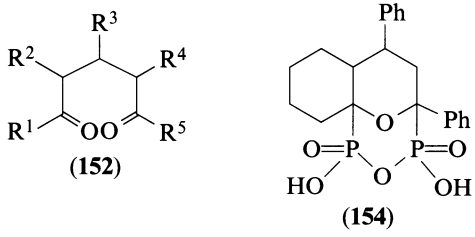
In summary, the interaction of a phosphorus(III) triester and an α,β-unsaturated ketone appears to follow one of the pathways indicated in Scheme 10, proceeding through the dipolar adduct **150** which is in equilibrium with, or converts irreversibly into, the oxyphosphorane **151**, of which many examples are known[320–322]. Alternatively, an alkyl group can

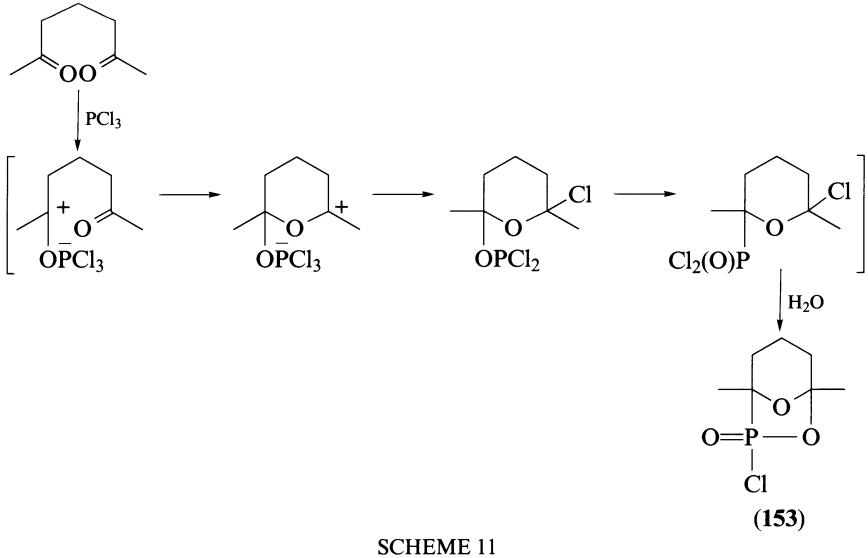


SCHEME 10

be translocated in one or both of two possible ways to give linear functionalized phosphonic esters, and such processes will be considered in Chapter 3.

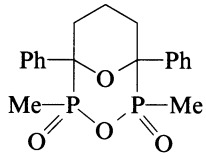
Vysotskii *et al.*[323] reported that PCl_3 reacts with 1,5-diketones to give cyclic compounds of a phosphonic acid type. Following the examination of the reaction for a variety of 1,5-diketones (**152**) [R^1–R^5 = H or Ph, or $R^1R^2 = (CH_2)_4$], they obtained products which were shown to possess the general structure **153**, and they proposed the pathway for the cyclization which is summarized Scheme 11. Later work resulted in the isolation of the



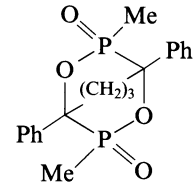


SCHEME 11

phosphonic anhydride **154** from **152** [$R^1R^2 = (CH_2)_4$, $R^4 = H$, $R^3 = R^5 = Ph$][324]. Rudi and coworkers[325,326] examined the behavior of 1,5-diphenylpentane-1,5-dione in acetic acid towards $MePCl_2$ and obtained two isomeric products, both of a phosphinic acid anhydride nature, whose structures were shown by crystallographc analysis to be **155** and **156**.



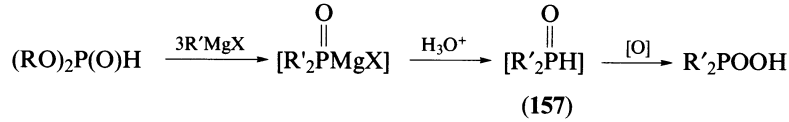
(155)



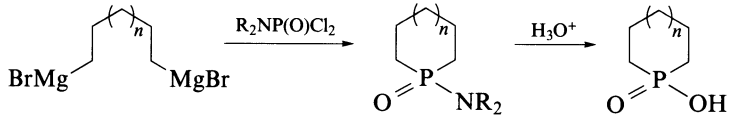
(156)

H. Synthesis Using Organometallic Reagents and Tetracoordinate Phosphorus Compounds

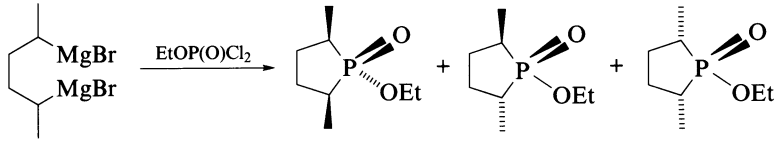
Earlier studies on the reactions of tri- and tetra-coordinate phosphorus compounds with organometallic reagents have been summarized[327]. The reactions originally employed in the synthesis of phosphonic acid esters generally consisted in the treatment of a dialkyl hydrogenphosphonate with a Grignard reagent; this affords a secondary phosphine oxide (**157**), which is subsequently oxidized to a symmetrical phosphinic acid, conveniently with hydrogen peroxide. Alternatively, the use of the sodium dialkyl phosphite requires only two equivalents of the more expensive reagent. The direct, but limited, replacement of halogen in, for instance, $POCl_3$, with the intention of stopping the substitution at the second stage to give a phosphinic chloride, is always difficult, and low yields of the desired compound are the result of the formation of much of the tertiary phosphine oxide, compounded by practical difficulties of physical separation. The introduction of phosphoramidic dichlorides, $R_2NP(O)Cl_2$, was an advance in respect of the former feature since, to a large extent, the third stage of replacement is blocked, and the resultant phosphinic amide, $R_2P(O)NR_2$, can be acidolysed to the free acid, R_2POOH. Reactions between phosphonic dichlorides and Grignard or organolithium reagents are also restricted in the potential preparation of mixed phophinic acids (initially as their chlorides) to reactants with bulkyl organic groups[328,329]. Kosolapoff[330] carried out the reactions indicated in Scheme 12 ($n = 0$ or 1) with some success, and the process was later shown to operate in two distinct stages[331]. Other di-Grignard reagents were employed to prepare substituted phospholane derivatives; a reaction between $EtOP(O)Cl_2$ and the reagent from 2,5-dibromohexane gave a mixture of the three stereoisomeric 1-ethoxy-2,5-dimethylphospholane 1-oxides (**158–160**) in the ratio 1:2:1, and separable by medium-pressure liquid chromatography[332].



(157)

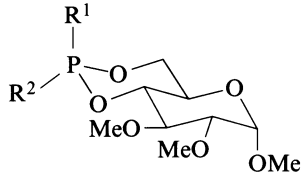


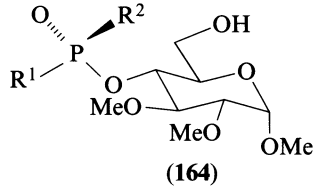
SCHEME 12



(158) (159) (160)

In order to examine the stereochemical implications in the synthesis of (largely) phosphinic acids (but also tertiary phosphine oxides), Inch and coworkers[333,334] employed carbohydrate frameworks as chiral templates. As primary substrates, the cyclic phosphorochloridate **161** and the corresponding phosphorofluoridate **162** were prepared from methyl 1,2,3-di-*O*-methyl-α-D-glucopyranoside, each phosphoryl halide being obtained as a mixture of diastereoisomers, anomeric at phosphorus, and from which, in each case, the major component (thought to have an equatorial P=O bond) was isolated. Configurations in both substrates and reaction products were assigned with the aid of proton and ^{31}P NMR spectroscopy and infrared spectroscopy ($\nu_{P=O}$). Each phosphoryl halide generated a mixture of methylphosphonates (**163a** and **b**) in which the isomer with an axial P—Me bond predominated; the ratio of products from **161** was ca 5:1 and from **162** ca 4:1.





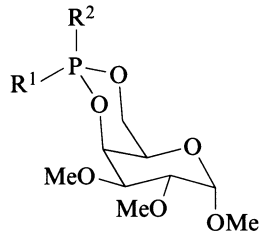
(164)

(**161**) R^1 = Cl, R^2 = =O
(**162**) R^1 = F, R^2 = =O
(**163**) (**a**) R^1 = Me, R^2 = =O
(**b**) R^1 = =O, R^2 = Me

(**a**) R^1 = Me R^2 = Et
(**b**) R^1 = Et, R^2 = Me

The diastereoisomeric phosphonates **163a** and **163b** each undergo further reaction with a Grignard reagent. When heated with EtMgBr in benzene–diethyl ether, isomer **163a**, of (*R*)p configuration, afforded 53% of the $(S)_P$-ethylmethylphosphinate ester (**164a**), and likewise the isomer **163b** gave 44% of the $(R)_P$-phosphinate ester (**164b**), representing ring opening largely with retention of configuration at phosphorus[334,335].

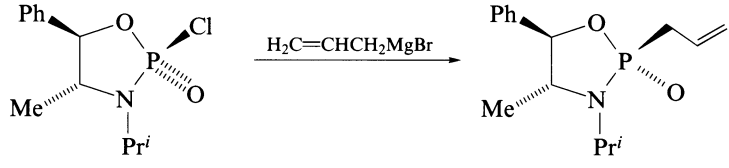
It is of interest to note that, although the Grignard substitution and ring-opening reactions involving the *trans*-fused system **163** occurred under relatively mild conditions, potential reactions based on the *cis*-fused system **165** (in which R^1 and R^2 have the same significance) failed to occur.



(165)

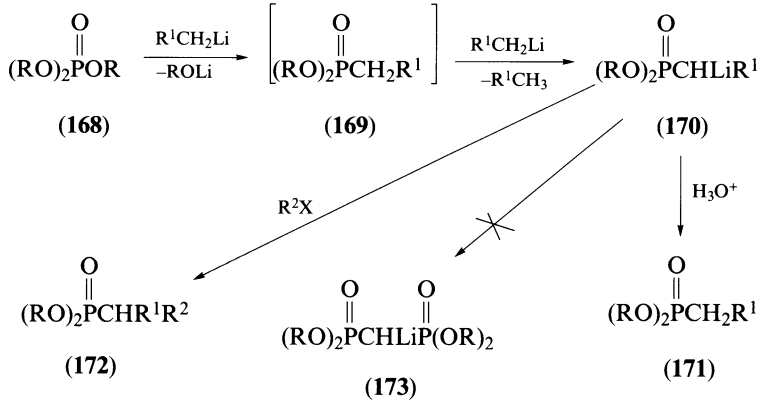
For a full discussion on the mechanisms by which Grignard reactions and other nucleophilic displacements occur in carbohydrate-based bicyclic systems and in particular the role of stereomutation processes which allow reaction with retention only, or with retention and inversion, the reader should consult the review by Hall and Inch[335].

The use of a chiral template of an entirely different nature also provided useful stereochemical data; the phosphoroamidic chloride **166** and prop-2-enylmagnesium bromide provide a product which consists entirely of $(2S)_P$-3-isopropyl-4-methyl-5-phenyl-2-(prop-2-enyl)-1,3,2-oxazaphospholidine 2-oxide (**167**)[336].



(166) **(167)**

In an attempt to secure a procedure for the synthesis of dialkyl alkylphosphonates, which, unlike that due to Michaelis and Arbuzov, would not be prone to so many possible side-reactions, Teulade and Savignac[337] investigated reactions between trialkyl phosphates (**168**) and organolithium reagents ($R^1 \neq H$). The neutral phosphonic diester **169** was never present in the reaction mixtures, whatever the ratio of substrate to reagent, and completion of the process required a second equivalent of reagent which yielded the ultimate, lithiated, product (**170**). In principle, the reaction sequence could be stopped at this point, when acidification would provide the diester **171**, but in practice the salt **170** was generally alkylated to give the esters **172**. Because the lithiated product **170** is a weaker nucleophile than is the organolithium reagent, further reaction between the phosphate triester and **170** does not occur, and the lithiated methylenebisphosphonic ester **173** is therefore not formed.

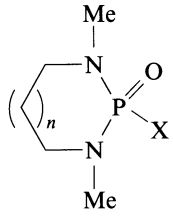


(168) **(169)** **(170)** **(172)** **(173)** **(171)**

The alkylation procedure is salt dependent and is retarded by lithium salts. In the absence of the latter, the reaction between BuLi and triethyl phosphate in thf is 85% complete after 0.5 h at 40 °C whereas, in the presence of LiBr, only 5% of the phosphate ester is consumed under similar conditions; the effect is particularly marked in the use of MeLi, when lower reactivity is probably a consequence of the polymeric nature of the reagent[337,338]. In the absence of lithium salts, even the more highly hindered tributyl and

triisobutyl phophates react rapidly with MeLi. The alkylation of $(EtO)_2P(O)SEt$, results in loss of the SEt group, and is complete after 0.5 h at –20 °C in a salt-free medium[338].

The ester–amide $EtOP(O)(NMe_2)_2$ undergoes no displacement reaction at phosphorus when treated with BuLi; by contrast, $(Me_2N)_2P(O)Cl$ undergoes displacement of Cl with an organolithium reagent to give, once again, the alkylated product as the lithio derivative, $(Me_2N)_2P(O)CHLiR$, from which aqueous hydrolysis affords the phosphonic diamide $RCH_2P(O)(NMe_2)_2$. Also of interest is the contrast in the outcome of reactions when cyclic diamide of different ring sizes are employed. The ester–diamide **174** ($n = 0$) reacts in much the same manner as does its acyclic analogue just discussed[338], but the homologue **174** ($n = 1$) is not alkylated by BuLi whether or not lithium salts are present. However, the diamidic chloride **175** ($n = 1$) is alkylated by BuLi, and even by MeLi in the presence of lithium salts[339]. Such differences in reactivity are due to difference in electron density at phosphorus brought about by changes in steric crowding, i.e. by changes in ring size.



(174) X = OEt
(175) X = Cl

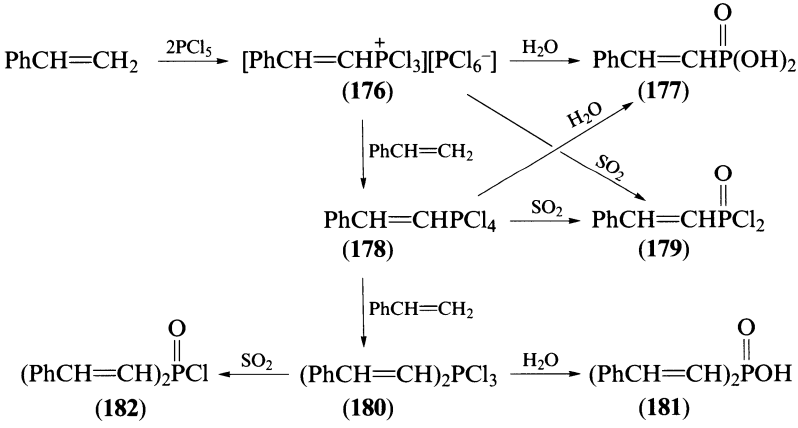
Alkylation of the chlorides of quinquecovalent phosphorus acids has also been achieved using organolead compounds (particularly $PbEt_4$ at 125 °C) and on rare occasions with organotin compounds; that of $POCl_3$ with $PbEt_4$ afforded 40% $EtP(O)Cl_2$ together with 20% $Et_2P(O)Cl$, and other similar experiments produced comparable yields of product mixtures, but the difficulties with the safe handling of such agents do not lend these reactions to general applicability[340].

III. THE FORMATION OF P—C(sp^2) BONDS. SYNTHESES OF ALKENYL AND ALKADIENYL PHOSPHONIC AND PHOSPHINIC ACIDS

A. Through the Reactions between PCl_5 and Alkenes or Alkadienes

The study of phosphorus–carbon bond formation in the reactions which take place between PCl_5 and alkene goes back many years. As far back as 1895, Marsh and Gardner carried out such a reaction with camphene and obtained a substance which, in modern terminology, was a phosphonic acid. Several similar reactions were carried out in the very early years of this century, and examples were listed by Thiele, but experimental details were lacking, and it was Bergmann and Bondi who, in the early 1930s, carried out the first serious study of the reaction. For a survey of the early work, refs 341 and 342 should be consulted. The substrates used by Bergmann and coworkers were aliphatic alkenes; these underwent the reaction with retention of HCl, and it is now recognized that in such cases, the products are the dichlorides of (2-chloroalkyl)phosphonic acids. The formation of such compounds by this means will be considered further in the next chapter in connection with the synthesis of halogen-substituted alkylphosphonic acids. These features of the chemistry of alkenes were corroborated by Kosolapoff and McCullough[341], as was the formation of (2-arylethenyl)phosphonic acids from styrene and its ring-substituted derivatives[342]. The case of indene was also investigated at about the same time[343].

The reaction between PCl_5 and phenylethene has been repeatedly studied in considerable depth, and this substrate may be considered a model for those alkenes in which the double bond occupies a conjugated position, since this appears to exert a pronounced effect on the ultimate course of the reaction, which normally occurs at low temperatures in an appropriate solvent, generally benzene but sometimes CCl_4 or even diethyl ether. Depending on the relative amounts of substrate and reagent, the resulting intermediate is then decomposed with SO_2 to give a phosphonic or phosphinic chloride, or hydrolysed to yield a free acid. For the preparation of a phosphonic acid or its dichloride, the ratio of reagent to substrate should be 2:1 and the resulting intermediate then consists of a chlorophosphonium hexachlorophosphate (**176**), a species insoluble in cold non-polar solvents, and only slightly soluble at the boil; such salts react violently with water, alcohols and amines, and decompose at 110–130 °C to give HCl, PCl_3 and non-characterized hydrocarbons. The hydrolysis of the salt **176** yields the phosphonic acid **177**, and with more styrene **176** affords the tetrachlorophosphorane **178**, distinguishable, through its crystallinity and ready solubility in non-polar solvents, from the salt **176**; the hydrolysis of **178** also yields the phosphonic acid **177**, and the treatment of either **176** or **178** with SO_2 gives the same phosphonic dichloride **179**. With more alkene at 90 °C, **178** yields the trichlorophosphorane **180**, which, in the usual manner, can be used to provide the symmetrical phosphinic acid **181** or the phosphinic chloride **182**[344,345]. Details of the synthesis of the phosphonic dichloride **179** have also been published in a more accessible source[346].

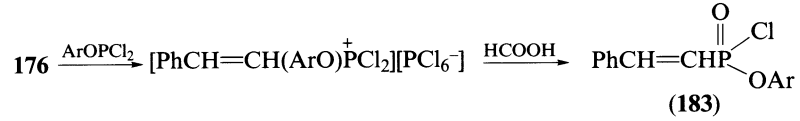


As normally represented, the decomposition of the intermediate chlorophosphonium salts by SO_2 proceeds according to equation 28, and the decomposition is also achievable through the use of phosphoric oxide (reaction 29). Other reagents which have been shown to effect the conversion of the salt into the acid dichloride are boric acid[347], $Na_2S_2O_5$[348], $NaHSO_4$[349], KOH[349], $Na_2S_2O_3$[350], carboxamides[351] and various phosphorus(III) halides. The use of alkyl dichlorophosphites, $ROPCl_2$, in $MeNO_2$ affords moderate to good yields of the phosphonic dichloride, but a change in solvent to one of low polarity then results in reduction of the complex to $PhCH{=}CHPCl_2$[351,353]. Modification to the intermediate through its reaction with $ArOPCl_2$ and subsequent decomposition of the new intermediate

$$3\ \mathbf{176} + 6SO_2 \longrightarrow 3\ \mathbf{179} + 3POCl_3 + 6SOCl_2 + 3HCl \qquad (28)$$

$$3\ \mathbf{176} + P_4O_{10} \longrightarrow 3\ \mathbf{179} + 7POCl_3 + 3HCl \qquad (29)$$

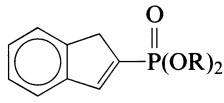
with HCOOH yields the half chlorides (**183**)[354]. When treated with oxirane in the presence of $TiCl_4$, the chlorophosphonium salts give the corresponding di(2-chloroethyl) ester[355].



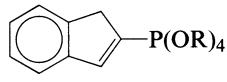
176

(**183**)

Amongst the features of the reaction which have caused concern are the relative roles of chlorophosphonium salt and/or phosphorane intermediates, and the reason(s) for the retention, or otherwise, of 1 mol of HCl within the intermediate species. Russian work had already differentiated between the chlorophosphonium salt and the true tetrachlorophosphorane when styrene was used as the substrate. A new study of the phosphonylation of styrene and indene has shown that esters of the respective phosphonic acids are obtainable by the alcoholysis of the intermediate(s) from each substrate; however, for indene, the esters **184** were obtained only by the use of MeOH, Pr^{i}OH or 2-methylpropanol, and EtOH, PrOH, BuOH, pentanol and isopentanol each yield the tetraoxyphosphorane **185**[356].



(**184**)



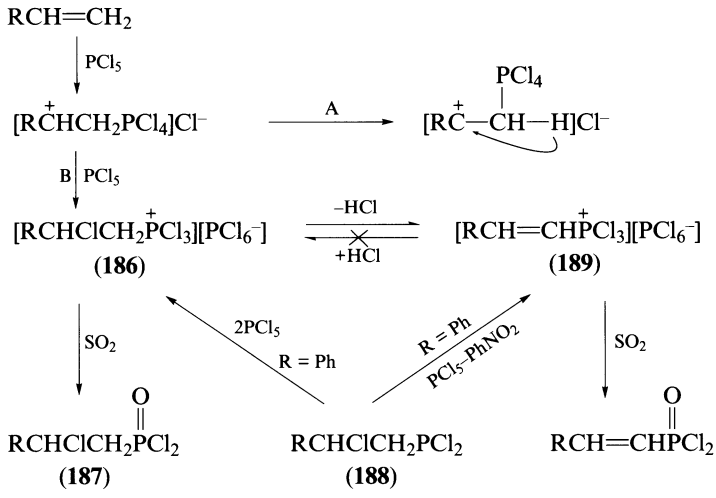
(**185**)

The nature of the solvent can sometimes influence the outcome of the reaction[357,358], but the latter is more significantly controlled by the nature of the alkene substrate. Whereas styrene retains unsaturation following phosphonylation, 3-arylprop-1-enes retain the HCl to form (2-chloro-3-arylpropyl)phosphonic dichlorides[359]. (2-Propeny)trimethylsilane also reacts with retention of the HCl to give a phosphonic dichloride, which subsequently loses Me_3SiCl to liberate (prop-2-enyl)phosphonic dichloride. Chloro(prop-2-enyl)-dimethyl- and dichloro(prop-2-enyl)methyl-silanes each yield an unsaturated phosphonic dichloride following the liberation of HCl, even at low temperatures; the same study also showed some dependence of the success of the reaction on the quality of the PCl_5 reagent[360].

A later investigation drew attention to the lack of characterization of the intermediates **186** along pathway B (Scheme 13), although liberation of HCl at this stage is irreversible, and a structure approaching **186** must be envisioned to account for the formation of the (2-chloroalkyl)phosphonic dichlorides **187**, observed particularly when R = alkyl. Although perhaps of no direct relevance, it is of interest to note that the different trichlorophosphonium salts **186** and **189** are each obtainable from the dichlorophosphine **188** and PCl_5, although under different conditions. Finally, it may be noted that treatment of the salt **189** with SO_2 yields the unsaturated phosphonic dichloride[361].

Crystalline adducts have also been obtained from alka-1,3-dienes, although views differ as to whether the addition occurs across the 1,2- or 1,4-positions, corroborative evidence being available for each conclusion. Both buta-1,3-diene and isoprene undergo addition with PCl_5 and retain the HCl which has to be removed in a separate stage; these reactions will therefore be considered again in Chapter 3, but one example (**190**) has been forthcoming in which phosphorus becomes unequivocally bonded to sp^2 carbon[362].

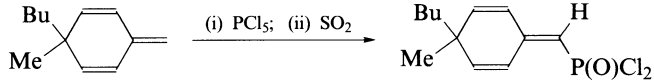
The use of a tetrachlorophosphorane in place of PCl_5 in reactions with alkenes has already been referred to earlier in this Section. A similar series of experiments was carried out using tetrachlorophenylphosphorane, $PhPCl_4$[345]; this reacts with styrene at 85 °C to give about 30% of unstable trichlorophenyl(2-phenylethenyl)phosphorane, which dispro-



SCHEME 13

portionates into $PhPCl_4$ and (**191**). $EtPCl_4$ is also said to be less reactive than PCl_5 in similar reactions[359].

The trichlorophosphorane (**192**) has been claimed as a product from the reaction between 1-phenyl-1,3-butadiene and PCl_5; the corresponding phosphinic acid and its dichloride were obtainable through the usual steps. The phosphinic acids (**193**) and (**194**) were prepared in the same way[363].



(**190**)

$Ph(PhCH{=}CH)_2PCl_2$ (**191**)

$(PhCH{=}CHCH{=}CH)_2PCl_3$ (**192**)

$Ph(PhCH{=}CHCH{=}CH)PO_2H$ (**193**)

$(PhCH{=}CH)(PhCH{=}CHCH{=}CH)PO_2H$ (**194**)

B. Through Rearrangements of Phosphorus(III) Esters and Halides

The reactions which occur between PCl_3 and acetylenic alcohols of the general type $HC{\equiv}CCR_2OH$ were originally reported in the patent literature during the 1950s, with the claim that the products were the corresponding acetylenic phosphites (see ref. 368 for a bibliography). A clue as to their probable true structure followed from the observation that a Michaelis–Arbuzov reaction using the acetylenic halides **195** and **196** resulted in the formation of the allenic phosphonates **197** (R^1 = Me) and **197** (R^1 = H), respectively (the second of these products can undergo further rearrangement[364,365]. The phosphonate **197** (R = Et, R^1 = H) is also formed from triethyl phosphite and the quaternary ammonium salt **198**, but not from the analogous phosphonium salt **199**, reaction with which yields **200** first and subsequently **201**[366].

$Me_2CClC{\equiv}CH$ (195)

$BrCH_2C{\equiv}CH$ (196)

$(RO)_2\overset{O}{\overset{\|}{P}}CH{=}C{=}CR^1{}_2$ (197)

$Me_3\overset{+}{N}CH_2C{\equiv}CH\ Br^-$ (198)

$Ph_3\overset{+}{P}CH_2C{\equiv}CH\ Br^-$ (199)

$Ph_3\overset{+}{P}CH_2CH{=}CHP(OEt)_2\ Br^-$ (200)

$Ph_3\overset{+}{P}CH{=}CHCH_2P(OEt)_2\ Br^-$ (201)

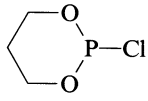
Examples of the rearrangement of phosphorus(III) triesters derived from PCl_3 at low temperatures in the presence of an organic base were soon to follow (reaction 30)[367,368].

$$3\ HOCH_2C{\equiv}CH \xrightarrow[Et_3N]{PCl_3} P(OCH_2C{\equiv}CH)_3 \longrightarrow (HC{\equiv}CCH_2O)_2\overset{O}{\overset{\|}{P}}CH{=}C{=}CH_2 \qquad (30)$$

When reactions between other phosphorus(III) chlorides and acetylenic alcohols are carried out in a similar fashion at 0 °C or slightly lower, the acetylenic phosphite may indeed be obtained, particularly if the base (e.g. Et_3N) hydrochloride is filtered off immediately after completion of the initial mixing; removal of the solvent (generally diethyl ether) allows distillation of the phosphite ester in a high vacuum, to leave a residue which will contain some allenephosphonate. The rearrangement of phosphite to allenephosphonate occurs slowly in solution at room temperature but with a high degree of isomerization being achievable during 15–25 h[369–372]. If the solvent is removed, isomerization becomes spontaneous, and in the event of a rapid rise in temperature, sometimes to as high as 200 °C, a further isomerization occurs which yields an acetylenic phosphonate[373,374]. The first step, in a sequence which leads ultimately to allene phosphonate (reaction 31), can be pictured as an intramolecular valence expansion of the Michaelis–Arbuzov type in the intermedi-

$$HOCR^1R^2C{\equiv}CH \xrightarrow{(RO)_2PCl\text{–}Et_3N} \left[\begin{array}{c} H \\ C \\ \equiv C \\ (RO)_2P \quad CR^1R^2 \\ O \end{array}\right] \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}CH{=}C{=}CR^1R^2 \longrightarrow (RO)_2\overset{O}{\overset{\|}{P}}C{\equiv}CCHR^1R^2 \qquad (31)$$

(202)



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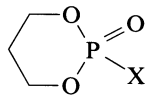
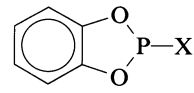
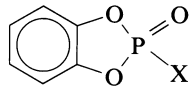


(204) X = CH=C=CH$_2$
(205) X = C≡CCH$_3$

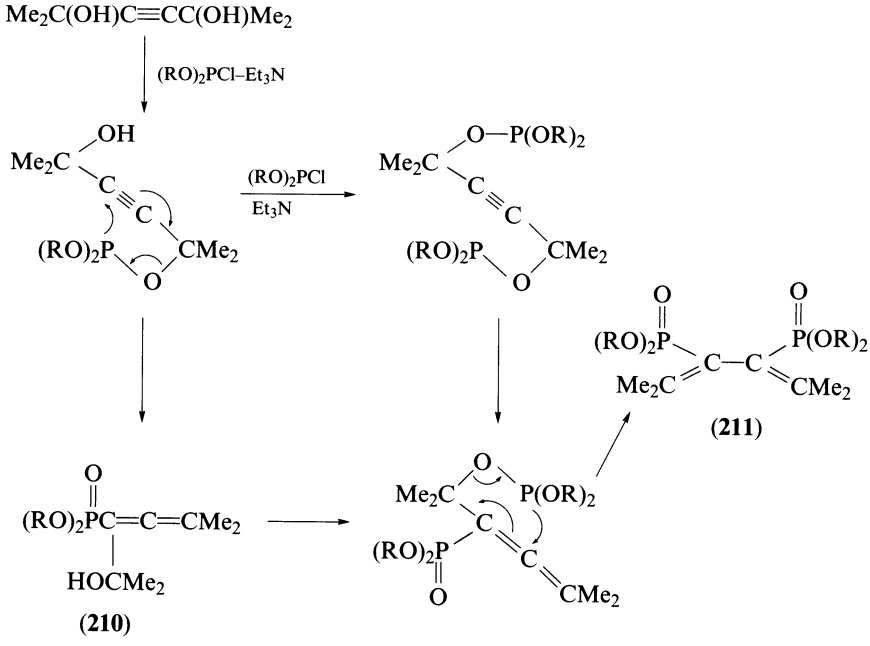


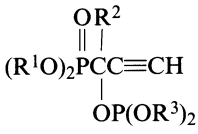
(206) X = Cl
(207) X = OCH$_2$C≡CH



(208) X = CH=C=CH$_2$
(209) X = C≡CCH$_3$

ate **202**, whilst the second stage is purely prototropic[375,376]. The cyclic phosphochloridite **203** reacts with prop-2-ynol to give a mixture of products **204** and **205** separable by chromatography[377]. In another case, **207**, prepared from **206** at –40 °C, rearranges in a kinetically first-order process; in boiling benzene, the equilibrium proportions of 30% **207** and 70% **208** are reached from **207** after 6 h, whereas in boiling toluene **209** is the sole product within 4 h[378]. A slightly more complex case is illustrated by the use of 2,5-dimethylhex-3-yne-2,5-diol; this reacts with a chlorophosphite in stages, and gives first the expected allenic phosphonic diester **210** after the initial phosphitylation, to be followed, after the second phosphitylation step, by the formation of 3,4-bis(dialkoxyphosphinyl)-2,5-dimethylhexa-2,-4-dienes (**211**)[379]. A further novel rearrangement is that of **212** into **213**[380].





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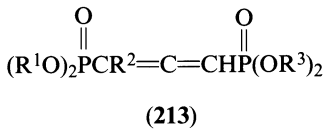
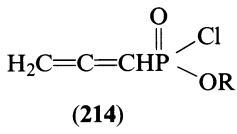


(213)

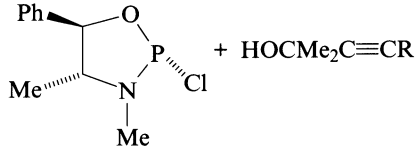


(214)

Differentiation between the types of reaction products is made easy through the application of ^{13}C, ^{1}H and ^{31}P NMR spectroscopy and infrared spectroscopy. Infrared stretching frequencies for the C=C=C system fall within the range 1945–1950 cm^{-1} and for C≡C and ≡CH groups are in the ranges 2040–2090 and 3165–3300 cm^{-1}, respectively[368,376]; a brief listing of ^{13}C chemical shifts has been given for allenic phosphonic acid derivatives[381].

If the reaction between prop-2-ynol and PCl_3 (3 : 1 ratio) is carried out in the absence of a tertiary amine, the liberated HCl dealkylates the tris(prop-2-ynyl) phosphite before it is able to undergo rearrangement, and the product is bis(prop-2-ynyl) hydrogenphosphonate[382].

Reactions between PCl_3 or PBr_3 and an alk-2-yn-1-ol (1:1 ratio) in the presence of a tertiary amine initially afford the acetylenic dichloro- (or dibromo-) phosphite and these also undergo very rapid rearrangement to the corresponding allenic phosphonic dichloride (or dibromide)[370,371,383,384]. The rearrangement of prop-2-ynyl phosphorodichloridite does not occur in diethyl ether, but is evidently so rapid in the neat state as to be potentially explosive, and it should therefore be carried out in hot benzene[385]. The rearrangement of appropriate phosphorus(III) halide esters from alkyl dichlorophosphites leads to alkyl allenephosphonochloridates (**214**)[386]. The use of $(Me_2N)_2PCl$ in the initial reaction stage ultimately provides the allenephosphonic bis(dimethylamide)[387]. Reactions between acetylenic alcohols and chiral phosphorus(III) halides such as the 2-chloro-1,3,2-oxazaphosph(III)olidine (**215**)[388,389] and separate deuterium-labelling experiments[385] have demonstrated the intramolecular nature of the acetylenic phosphite–allenephosphonate rearrangement, the structure of the final product (**216**) (R = CH=CH_2) being confirmed by crystallographic methods[388,389].



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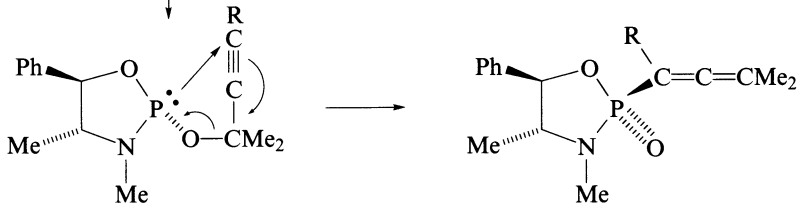
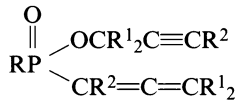


(216)

Several allenic phosphinic esters of the type **217** have been prepared from the appropriate acetylenic alcohol, $HOCR^1{}_2C{\equiv}CR^2$, and a phosphonous dichloride, $RPCl_2$[368,390–392], or $H_2C{=}CPhPBr_2$[393].



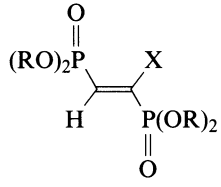
(217)

There are other reactions which lead from prop-2-ynyl compounds to allenic phosphonic acid derivatives. The alkylation of diethyl hydrogenphosphonate with 3-bromopropyne under phase transfer conditions yields a mixture of diethylpropadienyl- and (prop-1-ynyl)-phosphonates in 85:15 ratio[241]. The action of heat on a mixture of prop-2-ynol and a phosphoramidous ester, $(RO)_2PNR'_2$, results in elimination of R'_2NH followed by its re-addition to the rearranged residue to afford a dialkyl (2-amino-prop-1-enyl)-phosphonate[394].

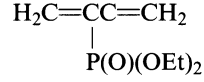
C. Through the Michaelis–Arbuzov and Related Reactions

As has already been indicated, simple vinyl halides, $H_2C{=}CHX$ (X = F, Cl, Br or I) do not normally undergo the Michaelis–Arbuzov reaction when heated with a trialkyl phosphite. However, in the presence of nickel(II) halides (3–10 mol%), and at 150–190 °C, reactions do take place between the halides RCH=CHX (R = H or Ph; X = Cl or Br) and trialkyl phosphites which lead to dialkyl ethenyl- or (2-phenylethenyl)-phosphonates. 1-Bromo-1-phenylethene is similarly reactive to triethyl phosphite in the presence of $NiBr_2$. Under the same conditions, *trans*-1,2-dichloroethene yields, initially, dialkyl *trans*-(2-chloroethenyl)phosphonate, followed by tetraethyl *trans*-(1,2-ethenediyl)diphosphonate (**218**) (R = Et), but *cis*-1,2-dichloroethene fails to react. Evidently, and by complete contrast, a 1:1 mixture of *cis*- and *trans*-1,2-dibromoethene affords only *trans*-(1,2-ethenediyl)diphosphonic acid ester[395]. 1,1,2-Trichloroethene suffers dechlorination at some stage in its reaction with triethyl phosphite; the products are the esters **218** (R = Et) and **219** (R = Et), in approximately 2:1 ratio[396].

The scope of the normal Michaelis–Arbuzov procedure in the synthesis of polyunsaturated phosphonic acids has not been widely explored, but it has been reported that 2-chlorobuta-1,3-diene and triethyl phosphite react together to give about 10% of the ester **220**[397].



(218) X = H
(219) X = Cl



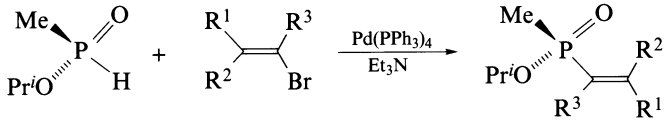
(220)

In contrast to the general lack of reactivity of ethenyl halides under Michaelis–Arbuzov conditions, except in catalysis by nickel(II), the formation of bonds from phosphorus to sp^2-carbon is observed when polyfluoroalkenes take part in Michaelis–Arbuzov reactions,

but the products retain fluorine and the reactions will therefore be considered as syntheses of halogen-containing phosphonic acids (Chapter 3, Section II.A).

Michaelis–Becker reactions between sodium dialkyl phosphites and halogenated alkenes, seem to occur only with polyhalogenated alkenes, but the course of the reaction is then complicated by elimination and addition steps. Thus sodium dialkyl phosphites and 1,1,2-trichlorophenylethene react to give, ultimately, esters of (1-phenyl-1,2,2-ethane)trisphosphonic acid[398]. Such reactions have been reviewed[399].

The importance of catalysis in the Michaelis–Becker reaction has also become apparent in significant advances during recent years. With particular regard to the preparation of alkenephosphonic acids, reactions between dialkyl hydrogenphosphonates and 1-haloalkenes in toluene solution have been shown to be catalysed by $[Pd(Ph_3P)_4]$ in the presence of Et_3N[400]; a 10:90 mixture of (*Z*)- and (*E*)-2-trimethylsilylethenyl bromide afforded 75–80% yields of dialkyl [(2-trimethylsilyl)ethenyl]phosphonate in only the *E*-form[401], and dialkyl (1-trimethylsilyl-1-alkenyl)phosphonates were similarly obtained[402]. The use of enantiomerically pure (*R*)- or (*S*)-isopropyl methylphosphinate leads to optically active forms of the alkenyl(methyl)phosphinic esters **221** (R^1, R^2 and R^3 = H, Me or Ph) with very high enantiomeric excesses[403]. These reactions, and also those of phenylphosphinic acid (monoesters of phenylphosphonous acid), occur with retention of geometry at the double bond and with $[Pd(Ph_3P_2)Cl_2]$ as catalyst[404]. The same catalyst was employed by the same workers to effect a cyclization indicated in reaction 32 in which for **222**, n = 2, 3 or 4[405].



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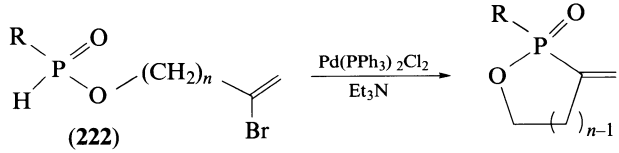


(222) (32)

IV. THE FORMATION OF P—C(sp) BONDS. SYNTHESES OF ALKYNYL PHOSPHONIC AND PHOSPHINIC ACIDS

Few synthetic reactions are available for the direct formation of derivatives of phosphonic and phosphinic acids which possess a P—C(sp) bond. The phosphonylation of an alk-1-yne by PCl_5 does not provide the alk-1-ynephosphonic derivative directly but, in analogy to the procedure for alkenes, the product retains chlorine. Thus phenylethyne with PCl_5 affords a complex which, when decomposed by SO_2, gives a high yield of (2-chloro-2-phenylethenyl)phosphonic dichloride[343,345]. The conversion of this into (2-phenylethynyl)phosphonic dichloride represents a 'modification synthesis' of a type to be discussed later in this chapter (Section VI.D).

The formation of alkynephosphonic diesters through the isomerization of alkynyl phosphorus(III) esters and subsequent prototropic rearrangement of the propadienylphosphonic acid derivatives has already been discussed. An early listing of alkynyl-phosphonic and -phosphinic acid derivatives (and also related types of organophosphorus compounds) is available[376].

A. Through the Michaelis–Arbuzov Reaction

Early attempts to synthesize phosphonic diesters with P—C(sp) bonding met with little success. Nevertheless, reactions of type 33 have been performed with R^1 = Ph or substituted ethenyl[406,407]. Fluoroacetylene is said to react with triethyl phosphite to give a low yield of diethyl ethynylphosphonate; for the phenylethynyl halides, PhC≡CX, the chloride reacts more slowly with triethyl phosphite than does the bromide, and the iodide fails to react[408]. In a later study[409], reactions using **223** (R^1 = Bu^t, X = Cl) were found to be catalysed by $AlCl_3$, and proceeded normally for R = Et or Pr^i, but failed for R = Me.

In efforts to prepare the ethynylphosphonic diesters **224** (R^1 = H), reactions have been carried out with **223** (R^1 = Me_3Si, X = Cl)[410] and with **223** (R^1 = Et_3Sn)[411]. Thermolysis of the silicon-containing esters afforded the corresponding **224** (R^1 = H)[410], and the trialkyltin group could more easily be removed by acidolysis using acetic acid[411].

$$(RO)_3P + R^1C{\equiv}CX \longrightarrow (RO)_2P(O)C{\equiv}CR^1 \qquad (33)$$

(**223**) (**224**)

$$ClC{\equiv}CCl \xrightarrow{(RO)_3P} (RO)_2PC{\equiv}CCl \xrightarrow{(RO)_3P} (RO)_2PC{\equiv}CP(OR)_2$$

(**225**)

$$R^1C{\equiv}\overset{+}{C}IPh\ TsO^- \longrightarrow (RO)_2PC{\equiv}CR^1$$

(**226**)

The reaction between a trialkyl phosphite and dichloroacetylene proceeds in two stages, the initial product being the dialkyl (2-chloroethynyl)phosphonate, which reacts further to give a tetraalkyl ethynediyl)bisphosphonate (**225**)[380,408,412].

The iodonium tosylates **226** have received some attention as alternative substrates in the Michaelis–Arbuzov reaction, with yields in their reactions with trialkyl phosphites of between 35 and 90% for R^1 = Pr^i, Bu^t, EtMeCH, cyclopentyl, Ph, or 4-methylphenyl[413].

B. Through the Michaelis–Becker Reaction

Sturtz *et al.*[414]. have prepared several (alk-1-ynyl)phosphonic acids as their dialkyl esters from sodium dialkyl phosphites and 1-bromoalkynes. The course of this process (reaction 34) may well be one of addition followed by elimination. As an alternative to this procedure, the treatment of (2-bromoalk-2-enyl)phosphonic esters (**227**) (prepared through a normal Michaelis–Arbuzov reaction[415]) with NaH under diethyl ether also affords esters of (alk-1-ynyl)phosphonic acids.

$$R^1C{\equiv}CBr \xrightarrow{(RO)_2PO^-} R^1\bar{C}{=}CP(OR)_2 \longrightarrow R^1C{\equiv}CP(OR)_2 \qquad (34)$$

Br

Other reported examples of the Michaelis–Becker reaction have been complicated by further reactions between product and reagent. A normal Michaelis–Becker reaction between a dialkyl sodium phosphite in thf and either Bu^{t}C≡CCl or Bu^{t}CH=CCl_2 is

complicated by the formation of the hexaalkyl ester of (3,3-dimethyl-1,1,2-butane)triphosphonic acid[409], but such complications seem to be obviated by using the iodonium salt **228** as substrate; a new intermediate (**229**) is formed, which is the active species immediately preceeding formation of the desired alkynylphosphonic diester[416].

$$BrCH_2CBr{=}CHR \xrightarrow{(EtO)_3P} (EtO)_2P(O)CH_2Br{=}CHR \xrightarrow[Et_2O]{NaH} (EtO)_2P(O)C{\equiv}CCH_2R$$

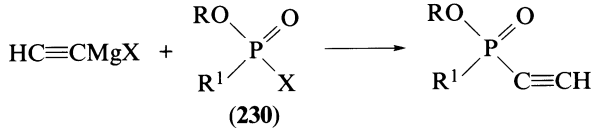
(**227**)

$$PhI^{+}(OH)(TsO^{-}) \xrightarrow{(RO)_2PO^{-}} (RO)_2P(O)I(OH)Ph \xrightarrow{R^1C{\equiv}CH} (RO)_2P(O)C{\equiv}CR^1$$

(**228**) (**229**)

C. Through the Use of Organometallic Reagents

Information in this area is particularly sparse[377]. Even when reverse addition methods are employed, low yields of dialkyl ethynylphosphonates are obtained for a dialkyl phosphorochloridate and ethynylmagnesium bromide (reaction 35; R^1 = RO, X = Cl). The use of a dialkyl phosphorofluoridate (**230**) (R^1 = RO, X = F) with the same organometallic reagent obviates the need for reverse addition, and the overall yields are then improved[417]. One more recently recorded example consists in the interaction of ethynylmagnesium chloride with methyl methylphosphonochloridate (**230**) (R = R^1 = Me; X = Cl) to give methyl ethynylmethylphosphinate[418].



(35)

(**230**)

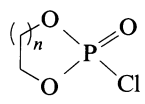
V. THE FORMATION OF P—C(AROMATIC) BONDS. SYNTHESES OF ARYL PHOSPHONIC AND PHOSPHINIC ACIDS

A. Through the Use of Organometallic Reagents

Undoubtedly, reasonable yields of arylphosphonic diesters are obtainable through the interaction of an arylmagnesium halide and appropriate phosphoryl halide. The normal addition of diethyl phosphorochloridate to PhMgBr (1 or 2 mol) affords largely diethyl phenylphosphonate (the product of the first stage in the stepped substitution pattern), together with small amounts of triphenylphosphine oxide, but no ethyl diphenylphosphinate (the second stage) seems to be present. With 3 mol of Grignard reagent, substantially more triphenylphosphine oxide is obtained. The reverse addition procedure is advantageous for the formation of diethyl phenylphosphonate. When PhMgCl is employed, even in substantial excess, the product is mainly diethyl phenylphosphonate with small amounts of triphenylphosphine oxide, irrespective of the manner of addition[419]. Heteroarylphosphonic diesters have been prepared using this procedure; the yield of diphenyl (2-thienyl)phosphonate from the Grignard reagent and $(PhO)_2P(O)Cl$, was much greater than those of the 'less aromatic' diphenyl (2-furanyl)phosphonate and diphenyl (*N*-Methyl-2-pyrrolyl)phosphonate in corresponding reactions[420]. In the case of a sterically hindered Grignard reagent, the use of $P(O)Cl_3$ itself has proved feasible; dimesitylphos-

phinic chloride, for example, is obtainable from mesitylmagnesium bromide[421]. Classically, the Grignard reaction has been employed in the preparation of diarylphosphinic acids through the interaction of diethyl hydrogenphosphonates with ArMgX (3 mol); the intermediate, $Ar_2P(O)MgX$, is hydrolysed to the secondary phosphine oxide, $Ar_2P(O)H$, and oxidized *in situ*, using hydrogen peroxide or bromine. The amount of Grignard reagent required can be reduced by prior conversion of the hydrogenphosphonate into its sodium salt. High yields of products may be expected[422,423]. The reaction between an aryl Grignard reagent and $Et_2NP(O)Cl_2$ has been employed for Me- and MeO-substituted diarylphosphinic acids, following acid hydrolysis of the reaction intermediates[424]. In order to prepare 2-biphenylylphenylphosphinic acid, biphenylylmagnesium bromide was allowed to react with $PhPCl_2$, and the product of the reaction was then oxidized (H_2O_2)[425].

Cyclic phosphoryl chlorides seem to be particularly prone to the complication of ring opening. The addition of PhMgBr (2 or 3 mol) to the chloride **231** ($n = 1$) furnished only 2-hydroxyethyl diphenylphosphinate (**232**) ($n = 1$); neither the cyclic phenylphosphonate **233** ($n = 1$) nor triphenylphosphine oxide was detected, and the excess Grignard reagent could be accounted for. After the use of PhMgCl (1 mol), small amounts of 2-hydroxyethyl diphenylphosphinate could be isolated; 3 mol of the reagent gave **232** ($n = 1$) together with some $Ph_3P(O)$. In reactions between the chloride **231** ($n = 2$) and PhMgCl, the products included both **232** ($n = 2$) and **233** ($n = 2$), together with $Ph_2P(O)OH$. Diphenylphosphinic acid is an important product from reactions between the phenylphosphonate cyclic ester **233** ($n = 1$) and lower molar ratios of PhMgBr or PhMgCl, but is not produced in the case of the ester **233** ($n = 2$). For both cyclic phenylphosphonate esters, the ω-hydroxyalkyl esters are formed and since they can be largely recovered following further treatment with the Grignard reagents, they are therefore not the immediate precursors to $Ph_3P(O)$. Several features of the reaction scheme remain to be explained[419]. 2-Chloro-1,3,2-benzodioxaphosphole 2-oxide undergoes ring opening under the influence of ArMgX (2 mol) to give the 2-hydroxyphenyl diarylphosphinates **234**[426].



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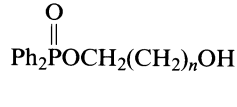

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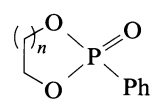

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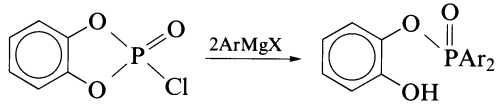
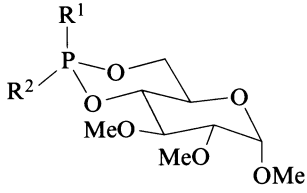


(234)

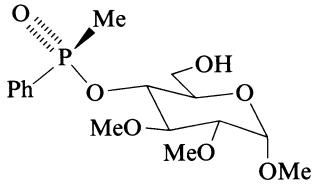
Inch and coworkers extended their studies[335] to include an examination of the action of aryl Grignard reagents on carbohydrate-derived phosphonate esters[335,427]; with the observations that the methylphosphonate **163a** reacted with PhMgBr to give the (*S*)-methylphenylphosphinate **235**, and that **163b** afforded the corresponding (*R*)-phosphinate, they concluded that ring opening occurs with inversion of configuration at phosphorus.

The course of ring opening in the 1,3,2-oxazaphospholidine series, a reaction also widely explored in the synthesis of phosphinic esters of predictable chirality, is different. The (2*S*)-substrate **236** (Ar^1 = Ph) (whose structures was confirmed by X-ray methods) undergoes ring opening when treated with the Grignard reagent Ar^2MgBr (Ar^2 = 2-methoxyphenyl) to give the (2-methoxyphenyl)phenylphosphinic amide **237**, with the (2*S*)-form (net retention of configuration at phosphorus) predominating[428,429]. The (2*S*)-2-methyl



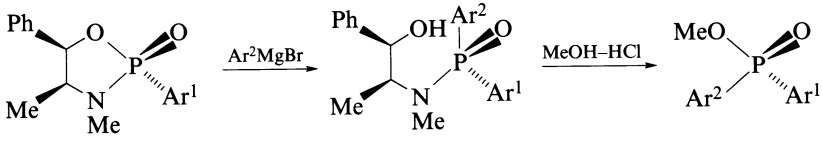
(163)

(a) R^1 = Me, R^2 = =O
(b) R^1 = =O, R^2 = Me



(235)

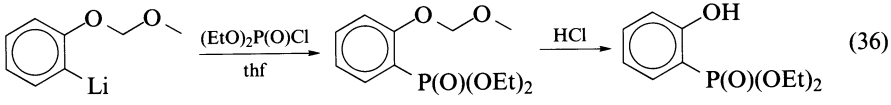
analogue of **236** undergoes 78% P—O bond cleavage when treated with PhMgBr to give a ring-opened product with 98% retention of configuration at phosphorus; the (2*R*)-2-methyl analogue reacts with PhMgBr with 68% ring opening but giving no preponderant isomer[335]. Reactions between the (2*S*)- or the (2*R*)-2-phenyl compounds and MeMgBr proceed with 80% and 60% inversion[335]. Acid-catalysed methanolysis of the product phosphinic amides to give the chiral methyl diarylphosphinate **238** occurs largely with inversion, the loss of stereochemical integrity being about 2–4%.



(236) (237) (238)

A sterically hindered arylithium may react with $POCl_3$ to give the diarylphosphinic chloride; a specific example of one such synthesis is that of bis(2,4,6-triisopropylphenyl)phosphinic chloride[421]. Reactions 36[430] and 37[431] exemplify the use of monolithiated species. The use of 2,2′-dilithiobiphenyls leads to dibenzophospholes (**239**)[432] and the procedure has been extended to include the use of appropriately lithiated quaterphenyls[433].

Once again, the stereochemistry of reactions involving organolithium reagents has been investigated using substrates based on the 1,3,2-oxazaphospholidine skeleton[335]. The reactions between the diastereoisomeric 2-methyl-1,3,2-oxazaphospholidine 2-oxides



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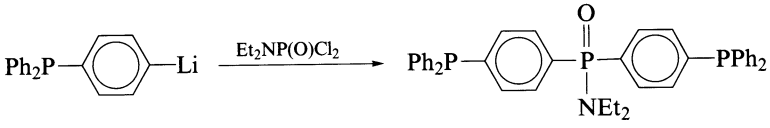

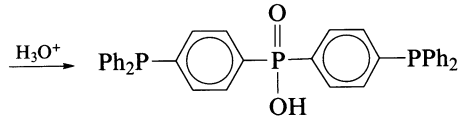

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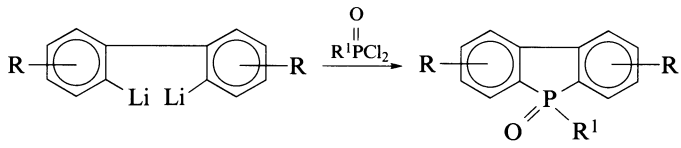


(239)

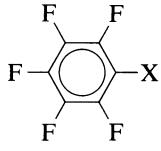
analogous to **236** react with PhLi with reduced ring opening and preponderant, but by no means exclusive, retention of stereochemistry. The degree of stereochemical retention is very much higher in analogous reactions between the 2-phenyl diastereoisomers and MeLi.

B. Through Reactions Between Substituted Arenes and Phosphorus(III) Esters

1. Nucleophilic replacement of an aromatic substituent by a phosphorus(III) ester without catalysis

When heated with triethyl phosphite, 4-nitrochlorobenzene gives traces of diethyl (4-nitrophenyl)phosphonate, and a low yield of the same product is obtainable from 1,4-dinitrobenzene; 2,4-dinitrochlorobenzene similarly yields 11% of diethyl (2,4-dinitrophenyl)phosphonate. The best yields of phosphonate esters were obtained using 1,2-dinitrobenzene in MeCN, when the yields could reach 80%. Reactions involving 1,2,4-trinitrobenzene were sufficiently exothermic to require exterior cooling and the yields of dialkyl (2-4-dinitrophenyl)phosphonate were moderate to good[434]. Other workers have also carried such reactions using aromatics in which the halogen site is activated by one or two nitro groups, together with CF_3[435,436], Cl[436], CN[436] or COOR[436]. A reaction between 1,2-dinitrobenzene and diethyl methylphosphonite[434] or diethyl phenylphosphonite[437] yields the corresponding phosphinic ester $[(2\text{-}O_2NC_6H_4)R]P(O)OEt$ (R = Me or Ph).

The displacement of halogen activated by halogen has also been widely observed. Manninen[438] quotes an earlier observation of the formation of diethyl (4-fluorophenyl)-phosphonate from triethyl phosphite and 1,4-bromofluorobenzene. Markovskii and coworkers[439,440] have studied the reactions between triethyl phosphite and several polyfluoroaromatics (**240**). Low yields of phosphonic acid products were obtained with X = Cl, F, Br, H or OMe. Better yields resulted with X = CF_3 or NO_2. Typically, pentafluorobenzonitrile at 140–150 °C gave diethyl (4-cyano-2,3,5,6-tetrafluorophenyl)phosphonate in about 25% yield. The diphosphonic ester **241** was obtainable from perfluorobiphenyl. In general, such reactions yield complex mixtures of phosphonylated aromatics and triethyl phosphate, together with other products which suggest that the reaction proceeds through a fluorophosphorane (**242**), which is then able to breakdown along several pathways[441].



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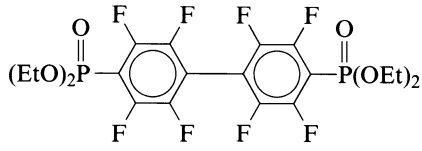
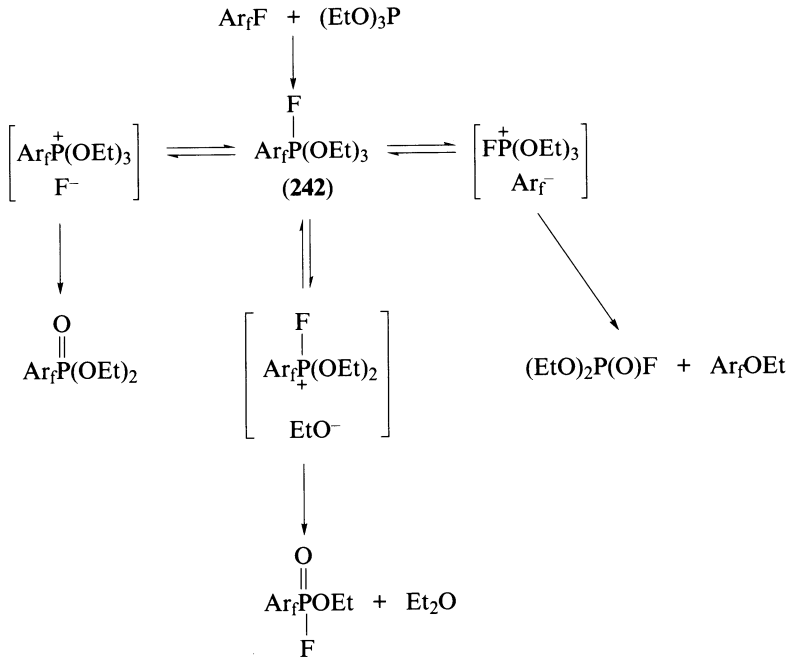
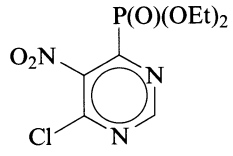


(241)

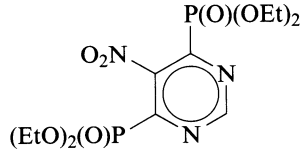
The formation and decay of phosphoranes during reactions between trialkyl phosphites[441–443] or dialkyl methylphosphonites[444] and pentahalogenopyridines, particularly the perfluoro compound, have been discussed. Although diethyl and diisopropyl esters of (2,3,5,6-tetrafluoro-4-pyridinyl)phosphonic acid are formed in such reactions, the corre-



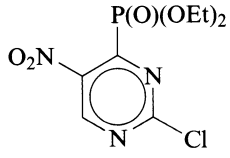
sponding dimethyl ester is not[443]. 4,6-Dichloro-5-nitropyrimidine is able to react with a trialkyl phosphite (in MeCN) in stages to produce a mono- (**243**) followed by the diphosphonic derivatives (**244**); 2,4-dichloro-5-nitropyrimidine reacts also in a stepwise fashion, initially at $C_{(4)}$ to give **245**, followed by **246**[445].



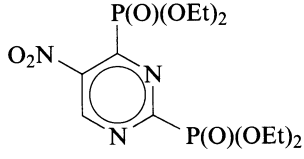
(**243**)



(**244**)



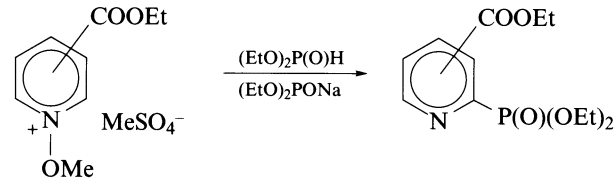
(**245**)



(**246**)

Replacement of iodine *ortho* to NH_2, OH, COOH, COOEt, $CONH_2$ or CSOEt is possible on reaction of the 2-substituted iodobenzene with diethyl hydrogenphosphonate[446]. The 2-position is also sufficiently activated in the quaternary salts **247** [COOEt at $C_{(4)}$, $C_{(5)}$

or $C_{(6)}$] for direct phosphonation[447]. A further reaction available is the replacement of NO_2 in the pyrimidines **248**[448].



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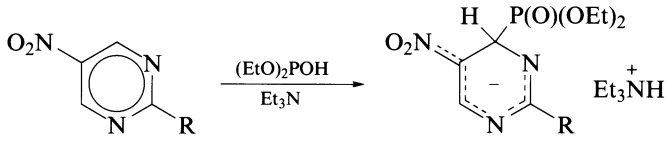


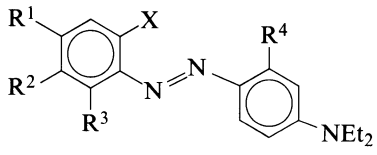
(248)

A claim for the successful replacement of chlorine in pentachlorobenzene using sodium diethyl phosphite to give diethyl (2,3,5,6-tetrachlorophenyl)phosphonate (together with triethyl phosphate and 1,2,4,5-tetrachlorobenzene) is based on the ultimate isolation of an impure product thought to be (2,3,5,6-tetrachlorophenyl)phosphonic acid[449].

Much more successful is the use of sodium dialkyl phosphites in conjunction with diaryliodonium salts to give dialkyl aryphosphonates in yields of 81–93%[450].

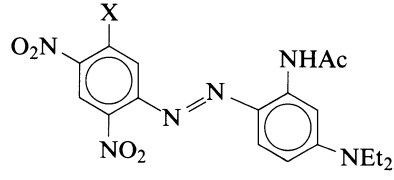
2. *Reactions under metal catalysis*

Some of the earlier examples of such procedures concern the use of Cu or copper-containing catalysts. Tavs and Korte[451] reported the catalysis of reaction between aryl halides (bromides or iodides), RC_6H_4X (R = H, 4-Me, 4-Cl or 4-EtOOC), by copper bronze; the yields were in the range 17–66%. Elsewhere 5 mol% of CuCl was employed (yields for R = H, Me or Cl were 52–76%)[452] whilst copper(II) acetate catalysed the formation of the phosphonic esters **249b** from **249a** (R^1, R^2 and R^3 = H, Br, Me, Et or NO_2; R^4 = H or NHAc)[453]. Interesting observations were made during the study of the formation of **250b** from **250a** using mixtures containing diethyl hydrogenphosphonate, CuI, NaOAc and an alcohol as solvent; irrespective of the particular hydrogenphosphonate (aryl or alkyl), the acid ester groups were determined by the individual alcohol ROH acting as solvent, and it was found to be generally convenient to use diphenyl hydrogenphosphonate[454].



(249)

(a) X = Br
(b) X = P(O)(OEt)$_2$



(250)

(a) X = Br
(b) X = P(O)(OEt)$_2$

CuI was later found to catalyse the phosphonation of aryl halides (bromides or iodides) by dialkyl hydrogenphosphonates in hmpa[455].

Tavs[456] also reported the catalytic effect of 5–10 mol% of nickel(II) halides in reactions between aryl halides and triethyl phosphite at 150–16 °C; yields of products for a wide variety of aromatic substituents could be as low as 11% (2-EtOOC) or greater that 80% (for 4-hydroxy-3,5-di-*tert*-butylphenyl halide, 2-thienyl-, 2-naphthalenyl- or 4-biphenylyl halides). Chinese workers extended the list of arylphosphonic diesters preparable by the method[457]. Free carboxyl groups are esterified during the phosphonation[458]. Russian workers have used the procedure to phosphonylate benzo-crown ethers[459–461] and also to obtain 5-phosphono-indoles and -indolines[462]. Similar reactions between aryl halides and tris(trimethylsilyl)phosphite[463–465] have employed nickel halides or $[Ni(CO)_4]$ as catalysts, whilst dialkyl trimethylsilyl phosphites yield mixtures of dialkyl, alkyl trimethylsilyl and bis(trimethylsilyl) aryphosphonates which are difficult to separate; the explanation for this phenomenon might well lie in the observed disproportionation of $(RO)_2POSiMe_3$ into $(RO)_3P$ and $ROP(OSiMe_3)_2$, catalysed by nickel(II)[466]. The preparation of the bis-(trimethylsilyl) esters offers advantages over the more conventional dialkyl esters in ease of de-esterification, by mere aqueous methanolysis, to the free acid[467].

$NiCl_2$ also catalyses the phosphonation of halothiophenes[468,469] by phosphite and phosphonite esters. Under $NiCl_2$ catalysis, 2-bromoacetanilide and diethyl methylphosphonite afford 98% of ethyl [(2-acetamidophenyl)methyl]phosphinate[470].

Detailed studies of the catalysis by nickel(II) halides in aromatic phosphonation by trialkyl phosphites have revealed the complexity of the process[471–474]. The steps are considered here only briefly, since the phenomenon of Arbuzov isomerization within metal complexes has been considered fully elsewhere[475]. Initial work demonstrated the formation, from nickel(II) salts (in the absence of aryl halide), of nickel(0) species detectable by ^{31}P NMR and EPR spectroscopy. The essential features of the processes involved are indicated in reactions 38–41. The initial stages represent the gradual build-up of a series of nickel(II) halide–ligand [i.e. phosphorus(III) ester] complexes, culminating in the formation of the square-planar diamagnetic complex $[Ni^0L_4]$ (**251**). In the presence of the aryl halide, ArY, the complex **251** undergoes an oxidative-addition reaction leading to a paramagnetic, tetrahedral nickel(II) complex (reaction 41); further interaction of this with more ligand regenerates the nickel(0) complex **251** and, at the same time, generates the 'true' Michaelis–Arbuzov complex **252**, which breaks down by intramolecular dealkylation to give the dialkyl arylphosphonate **253**.

$$NiX_2 + L \rightleftharpoons NiLX_2 \overset{L}{\rightleftharpoons} NiL_2X_2 \overset{L}{\rightleftharpoons} NiL_3X_2 \rightleftharpoons [NiL_3X]X \quad (38)$$

$$NiL_3X_2 \rightleftharpoons NiL_4X_2 \rightleftharpoons [NiL_3X]X \rightleftharpoons [NiL_4]X_2 \quad (39)$$

$$Ni^{II}L_nX_2 + (5-n)L \rightleftharpoons \underset{(\mathbf{251})}{Ni^0L_4} + X_2L$$

$$\downarrow \; Ni^{II}L_nX_2$$

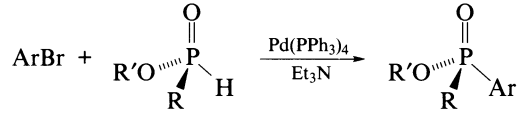
$$2\,Ni^{I}L_nX_2 + (4-n)L \quad (40)$$

$$\underset{(\mathbf{251})}{Ni^0L_4} + ArY \longrightarrow ArNi^{II}L_2Y + 2L \quad (41)$$

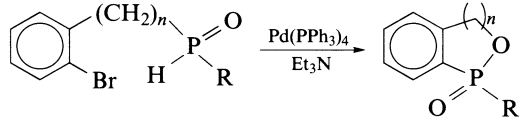
$$ArNi^{II}L_2Y + 3L \longrightarrow \underset{(251)}{Ni^0L_4} + \underset{(252)}{[ArL^+]Y^-}$$

$$\mathbf{252} \equiv [Ar\overset{+}{P}(OR)_3]Y^- \longrightarrow \underset{(253)}{ArPO_3R_2} + RY$$

Similar equilibria exist in systems containing a phosphorus(III) ester and, for example, $PdCl_2$, and equilibria involving palladium(0), palladium(I) and palladium(II) species have all been detected in multi-step processes[476]. Species containing palladium(0), such as $[Pd(Ph_3P)_4]$, catalyse reactions between dialkyl hydrogenphosphonates and aryl bromides (and also vinyl bromides)[400]. $[Pd(Ph_3P)_4]$ catalyses the arylation of alkyl alkyl(or aryl)phosphinates to alkyl alkylarylphosphinates[477,478] or alkyl diarylphosphinates[479], in a process (reaction 42) which may also be intramolecular (reaction 43; n = 1–3; R = alkyl or Ph)[480]. Moreover, by the use of phosphinic esters (monoalkyl phosphonites) and two different aryl halides, stepwise arylation is possible (reaction 44). In this particular case it has to be stated that the use of aryl iodides with $Pd(OAc)_2$ in systems containing *N*-methylmorpholine and Ph_3P in MeCN–$HC(OMe)_3$ produce marginally better yields than those containing $[Pd(Ph_3P)_4]$; aryl bromides and aryl triflates also give rise to lower yields[481]. The direct cleavage of the C(aryl)—O bond and its replacement by C(aryl)—P^V was observed a few years earlier using aryl triflates[482] or other aryl polyfluoroalkanesulphonates[483], with yields in the range 65–95%.



(42)



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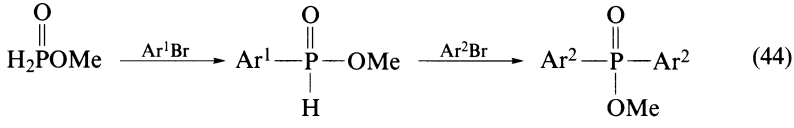


(44)

Examples have been recorded of phosphonation on the benzenoid ring in 1,3-benzothiazoles, quinolines and benzimidazoles[484].

3. *Phosphonation of aryl halides under photostimulation*

Following the (apparently) initial observations by Griffin and coworkers on the irradiation of mixtures of aryl iodides and trialkyl phosphites, it was evident that the procedure held great promise for synthesis; although it was found necessary to employ 3–5 molar excess of phosphite ester (to allow for competitive photostimulated Michaelis–Arbuzov isomerization to dialkyl alkylphosphonate), nevertheless yields were very high, sometimes

almost quantitative for *ortho*- and *para*-substituted compounds, if the reactions were performed at or around 0 °C[485–487].

A detailed study of the mechanism and scope of the process has been carried out over a period of several years by Bunnett and coworkers[488–495]. Using 350 nm radiation, it has been found that while the reaction between ArI and metal dialkyl phosphite takes place during 45–200 min in liquid NH_3[488], other solvents, including dmso, MeCN and dmf are also highly suitable[489] and that the potassium dialkyl phosphite is often more suitable than the corresponding sodium salt[490]. The procedure is complicated by the propensity of certain aryl halides to undergo disubstitution, and this, which leads to phenylenediphosphonic tetraalkyl esters, occurs particularly with bromo and iodo substituents *meta* or *para* to each other[491–493]. In the absence of irradiation, the normal reaction course is that of monodehalogenation[494].

Savignac and coworkers drew a comparison between the transition metal-catalysed and the photostimulated phosphonation reactions and concluded that the latter process produced more uniformly good results[496], and also showed that the addition of one equivalent NaI to mixtures of aryl bromide and metal dialkyl phosphite greatly accelerated the phosphonation process[497].

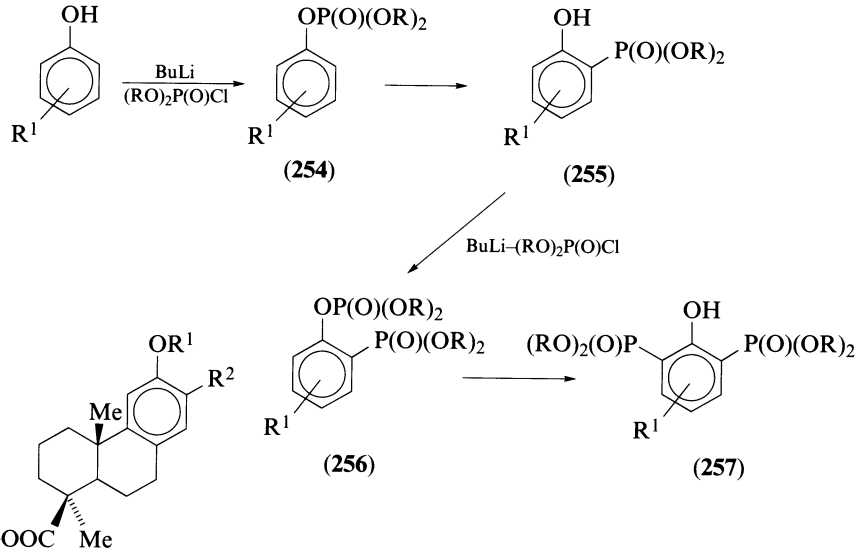
4. Oxidative phosphonylation of aromatic compounds with phosphorus(III) esters

The formation of dialkyl arylphosphonates, in high yields, from methyl- or methoxy-substituted arenes and trialkyl or dialkyl phosphites is also achievable through either anodic oxidation[498] or chemical oxidation. The chemical oxidation procedure has been investigated by Effenberger and coworkers[499,500]. Initially arylphosphonates were obtained from arene–phosphite mixtures in aqueous MeCN or aqueous acetic acid containing peroxidisulphate–$AgNO_3$; an increase in the relative amount of Ag^+ increased the yields of phosphonate substantially. A detailed study was made of a system containing mesitylene and triethyl phosphite in proportions which ranged from 1:5 to 5:1 and with no added metal salts, when the yields of dialkyl mesitylphosphonate varied from 28 to 58%, with $(EtO)_2POOH$ as the main co-product. When the phosphite(III) ester was replaced by diethyl hydrogenphosphonate, the yields of phosphonate were 45–70% with the formation of appreciable amounts of mesityldiphosphonic ester. Apart from the use of added $AgNO_3$, other species which helped to generate appreciable amounts of the dialkyl mesitylphosphonate were $[(Bipy)_2Ag]S_2O_8$ (48% yield), and $[(Bipy)_2Fe](PF_6)_2$ (38% yield), but cerium(IV) ammonium nitrate was chosen as potentially the best generally available salt of those examined. Unfortunately, the process exihibits a very low selectivity in the choice of reaction site on the aromatic nucleus.

C. Through the Rearrangement of Aryl Phosphates

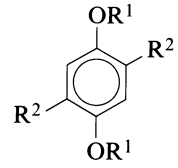
The rearrangement of the aryl phosphate esters **254** into esters **255** of (2-hydroxyaryl)-phosphonic acids under the influence of a strongly basic agent was discovered by Melvin[501], who employed lda and independently, and almost by accident, by Cambie and Palmer[502], who treated the phosphate ester **258** with BuLi and so obtained the phosphonate ester **259**.

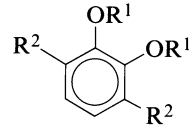
Dhawan and Redmore[503,504] have explored the scope of the isomerization. Thus, the (2-hydroxyaryl)phosphonate ester **255** may itself be *O*-phosphorylated and a second rearrangement carried out, with the resultant formation of **257** from **256**; in addition, the rearrangement of **260** into **261** and that of **262** into **263** were carried out. The diaryl phosphates **264** rearrange to the bis(2-hydroxyaryl)phosphinates **265**[505], whilst the use of mixed alkyl aryl phenylphosphonates (**266**) affords mixed diarylphosphinates



(**258**) $R^1 = P(O)(OEt)_2$, $R^2 = H$
(**259**) $R^1 = H$, $R^2 = P(O)(OEt)_2$

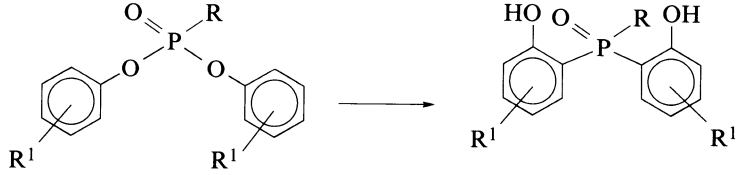
(**267**)[506]. Rearrangements in the naphthalene series are exemplified by that of dialkyl 1-naphthalenyl phosphates into dialkyl (2-hydroxynaphthalenyl)phosphonates and, more surprisingly, that of dialkyl 2-naphthalenyl phosphates into dialkyl (3-hydroxy-2-naphthalenyl)phosphonates[507]. The most recent extension of the rearrangement is in the pyridine series. In a series of diethyl pyridinyl phosphates, phosphoryl migration occurred from oxygen on $C_{(3)}$ to $C_{(4)}$, or if the latter position was blocked, to $C_{(2)}$, and from oxygen on $C_{(2)}$ to $C_{(3)}$[508].

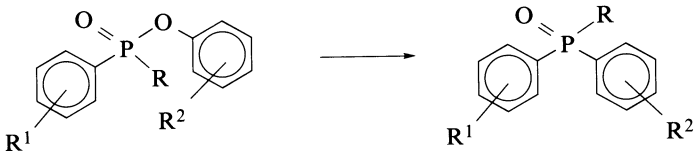




(**260**) $R^1 = P(O)(OR)_2$, $R^2 = H$
(**261**) $R^1 = H$, $R^2 = P(O)(OR)_2$

(**262**) $R^1 = P(O)(OR)_2$, $R^2 = H$
(**263**) $R^1 = H$, $R^2 = P(O)(OR)_2$





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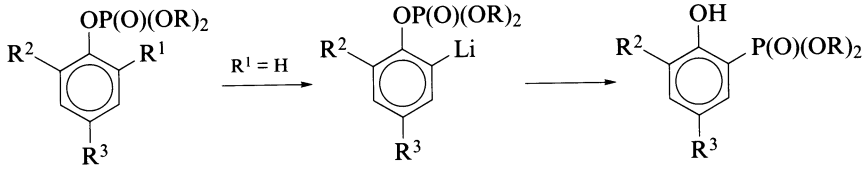
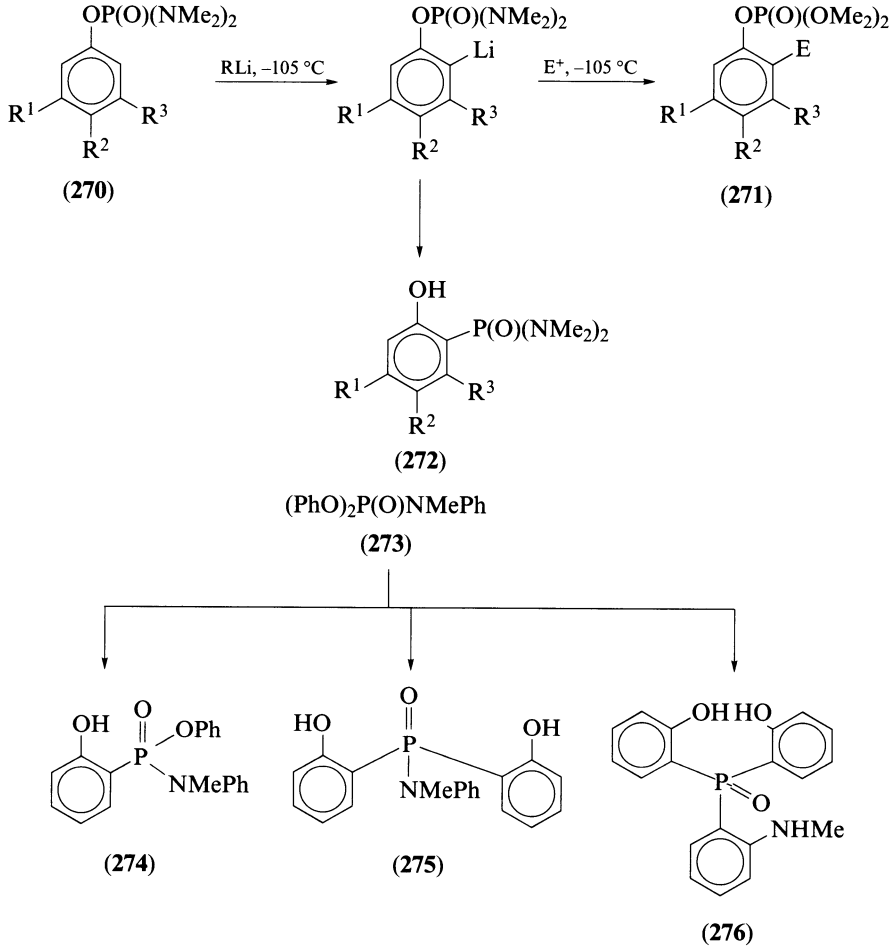


(268) (269)

A useful development from the point of view of synthesis of the free acids is the use of di-*tert*-butyl phosphorylating agents in the preparation of the phosphate esters; the rearrangement products, di-*tert*-butyl (2-hydroxyaryl)phosphonates, can be thermolysed to the free aromatic phosphonic acids, or alternatively acidolysed in trifluoroacetic acid[509,510]. However, according to other workers, di-*tert*-butyl esters do not rearrange as easily as diethyl esters and, moreover, the presence of an electron-withdrawing group *para* to the phosphate ester bond hinders the process, whilst electron deactivation coupled with steric hindrance completely suppress the reaction[511].

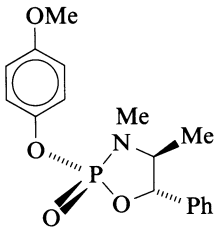
No incorporation of deuterium was found when the ester **268** ($R^1 = R^2 = H$; $R^3 = COOH$, R = Et or Bu^t) was initially treated with lda and then quenched with D_2O, implying the non-formation of the corresponding carbanion (**269**), and in this particular case no rearrangement actually occurred. When R^1 = H, Me or Br, R^2 = H and R^1 = Br, the action of BuLi caused rearrangement to occur readily, but once again, with $R^1 = R^2$ = Br and R^3 = COOBu^t, no rearrangement took place. The rearrangement was consequently considered to take place through an *ortho*-stabilized carbanion[511].

The formation of the *ortho*-lithiated species was corroborated by Watanabe *et al.*[512], who, after showing that the rearrangement of diethyl phenyl phosphate to (2-hydroxyphenyl)phosphonate was catalysed by EtCMeLi in thf at –105 °C, treated the aryl tetramethylphosphorodiamidates **270** (R^1, R^2, R^3 = H or MeO) with the same alkyllithium under identical conditions, and were able to trap the lithiated intermediate, following the addition of an electrophilic agent such as Me_3SiCl, MeI, ArCOCl, PhSSPh or an aldehyde or ketone, to give **271**. When the reaction temperature was allowed to rise to –78 °C, rearrangement proceeded rapidly to yield the tetramethyl (2-hydroxyaryl)phosphonic diamide **272**. The rearrangement of naphthalenyl tetramethylphosphorodiamidates was later described[513]. These observations on the rearrangements of aryl phosphorodiamidates were by no means the first such to be reported. The conversion of diethyl *N*-methyl-*N*-phenylphosphoramidate into diethyl [2-(methylamino)phenyl]phosphonate had already been demonstrated by Jardine *et al.*[574], who also showed that diphenyl phosphoramidates and phenyl phosphorodiamidates rearrange to products the nature of which depends on the relative proportions of substrate and agent (lda); thus, diphenyl *N*-methyl-*N*-phenylphosphoramidate (**273**) treated with 1, 1–10 and 10 mol of lda affords **274**, **275** and **276** successively. It is worth noting that in these reactions, N-to-C migration occurs only after O-to-C migrations have been completed.



The scope of the reaction has been extended to include sulphur-containing substrates (*S*-aryl phosphorothiolates). When treated with lda, diethyl and diisopropyl *S*-phenyl phosphorothiolate yield diethyl and diisopropyl (2-mercaptophenyl)phosphonates in yields of 16 and 60%, respectively[515].

For the determination of any stereochemical changes at phosphorus which might occur during the rearrangement, one can, once again, turn to substrates based on the 1,3,2-oxazaphosph(V)olidine system[516]. An inseparable 95:5 mixture of the (2*S*) and (2*R*) forms of 2-(4-methoxyphenoxy)-3,4-dimethyl-5-phenyl-1,3,2-oxazaphoph(V)olidine (**277a** and **277b**), derived from pseudoephedrine, affords 38% of a single rearranged product, (2*R*)-(2-hydroxy-5-methoxyphenyl-1,3,2-oxazaphospholidine 2-oxide (**278**). Use of the ephedrine-based substrate (2*R*)-(4-methoxyphenoxy)-1,3,2-oxazaphospholidine 2-oxide (**279a**) gives the single rearranged (2*S*)-phosphonic amide **280** in 85% yield; unexpectedly, the corresponding (2*S*)-phosphoramidate **279b** produces the (2*R*)- and $C_{(5)}$-epimerized phosphonic amide **281** in 14% yield together with 34% of the ring-opened material **282**. For all those cases for which the oxazaphosph(V)olidine ring remains intact, however, the phosphate–phosphonate rearrangement occurs with retention of configuration at phosphorus.



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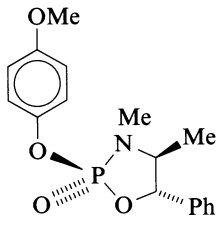

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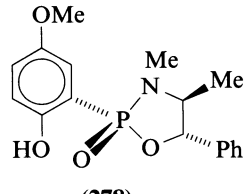

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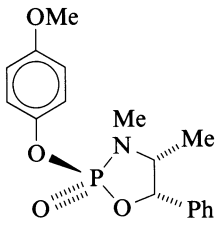

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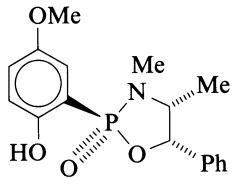

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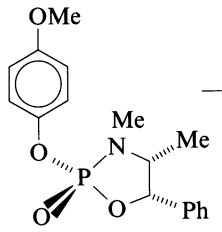

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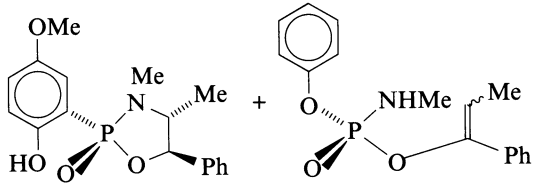


(281) (282)

Finally, it may be noted that the treatment of dialkyl 2-chlorophenyl phosphates with metallic sodium and the formation of the Grignard reagent from dialkyl 2-bromophenyl phosphates both yield dialkyl (2-hydroxyphenyl)phosphonates after work-up; in the case of dialkyl 2,4-dibromophenyl phosphate, the elimination of bromine is restricted to the 2-position[517].

D. From Diazonium Salts and Phosphorus(III) Halides

Two important syntheses of aromatic phosphonic and phosphinic acids are based on classical aromatic chemistry. The use of aryldiazonium salts has the distinct advantage over Friedel–Crafts reactions in that the entering phosphorus is placed in a position of certainty and, additionally, only one step is required in the final stage, whereas two are sometimes needed in the Friedel–Crafts procedure.

The diazonium salt procedure consists in a reaction between a dry aryldiazonium tetrafluoroborate[518] with PCl_3 in a solvent, generally an acetic acid ester, and in the presence of a copper(I) salt. Very rarely, aryldizaonium hexafluorosilicates have been employed but appear to offer no particular advantages[519]. The procedure involves the conversion of the diazonium tetrafluoroborate into the diazonium adduct (**283**) followed by liberation of nitrogen and generation of the aryltrichlorophosphonium salt which is hydrolysed. A wide

$$[ArN_2^+][BF_4^-] \xrightarrow{PCl_3} [ArN_2PCl_3^+][BF_4^-] \xrightarrow{-N_2} [ArPCl_3^+][BF_4^-]$$

(283)

$$[ArPCl_3^+][BF_4^-] \xrightarrow{H_2O} ArPO_3H_2$$

range of substituted-aromatic phosphonic acids—halo[519–526], alkyl[522,523,527–529], alkoxy[520,521,530], aryloxy[531], cyano[532], nitro[59,521,522], aryl[533], trifluoromethyl[536] and carboxy[520,522]—have been prepared in addition to many similar acids with mixed functionality on the benzene ring[520–523,526,528,530,534–539]. The yields of phosphonic acids also vary considerably, from as high as 60% to several for which the yields are approximately 10%. Occasionally, as with 2- and 3-ethylphenyldiazonium tetrafluoroborates, which are not very stable, the conversion into the respective phosphonic acid fails[527]. In nearly all cases the formation of phosphonic acid is accompanied by that of the symmetrical phosphinic acid with aryl groups idential with that in the phosphonic acid; the yields of these acids sometimes reach 20%. Studies have been made of the efficacy of different solvents and different copper(I) salts, but only slight variations are to be found in the ultimate yields[522,524].

The use of *m*- or *p*-phenylenebisdiazonium fluoroborates to obtain phenylenebisphosphonic acids has not met with success. The *meta* salt with PCl_3 yields (3-chlorophenyl)-phosphonic acid (in 80% yield !) together with a smaller amount of the 3-fluorophenyl acid. On the other hand, the yield of (4-chlorophenyl)phosphonic acid is only 10%, and is accompanied by only traces of the 4-fluorophenyl acid[540]. Other side-reactions may include the loss of the ester group when an aromatic substituent is COOMe[535] and a reaction between 2-nitrobenzenediazonium tetrafluoroborate and PCl_3–EtOAc–CuCl has been reported to give 10% of (2-amino-5-chlorophenyl)phosphonic acid[536].

The formation of small amounts of symmetrical diarylphosphinic acids in the reactions between aryldiazonium salts and PCl_3 is complemented by the use of phosphonous dichlorides, the products being the non-symmetrical diarylphosphinic acids, ArAr'P(O)OH[520,523].

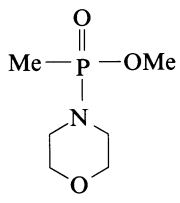
A review exemplifies further the reactions discussed above, and also summarizes other reactions leading to aromatic phosphonic acids[541].

VI. SYNTHESES OF PHOSPHONIC AND PHOSPHINIC ACIDS BY MODIFICATION PROCEDURES

The purpose of this section is to summarize those reactions which lead to phosphonic and phosphinic acids or their derivatives, either through chemical modification to pre-formed phosphonic and phosphinic acids or their derivatives, or through appropriate manipulations of some phosphorus(III) compounds which already possess P—C bonds.

A. Through the Alkylation or Phosphorylation of Carbanions

Given a sufficiently strong base, the activation produced by the phosphoryl group next to an adjacent C—H bond will allow deprotonation and the generation of a highly reactive carbanion. Butyllithium has been commonly used for this purpose, but a preference has been shown in recent work for lda. Treatment of the anion from methyl methyl(4-morpholinyl)phosphinate (**284**) with farnesyl chloride yields **285**, which, on acidolysis, affords the phosphonic acid **286**, employed in the synthesis of a pyrophosphonate analogue of farnesyl pyrophosphate[542]. Alkylation of the carbanion from the chiral phosphonic diamide **287** (X = Me or higher alkyl) leads to the diastereoisomeric phosphonic



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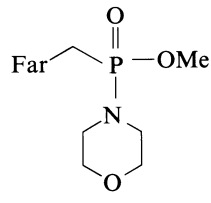

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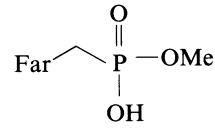
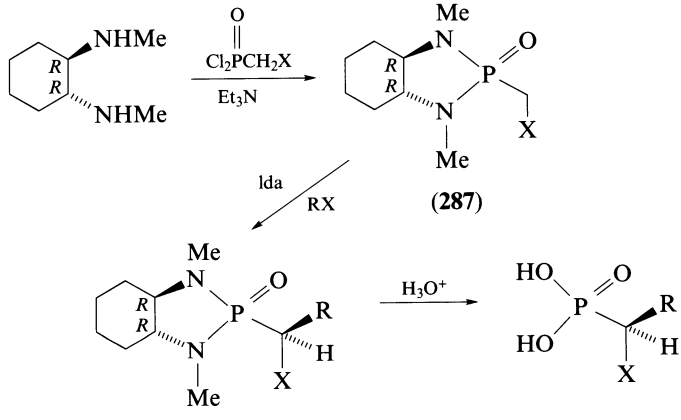


(286)

diamides **288**; these are separable by chromatographic means, and their acid hydrolysis then yields enantiomeric forms of the branched-chain alkylphosphonic acids **289** with little racemization in the last stage. The alkylation step proceeds with high diastereoselectivity at –78 °C using EtI or prop-2-enyl bromide, and reactions carried out at –100 °C show even greater selectivity. A reasonable interpretation of these experimental results lies in the preferential attack by the carbanion lone electron pair in the site of lower steric hindrance by the *N*-methyl groups as shown in the representation **290**, and which leads to the major product enantiomer[543].



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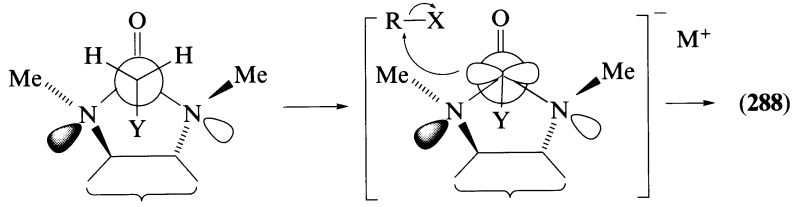
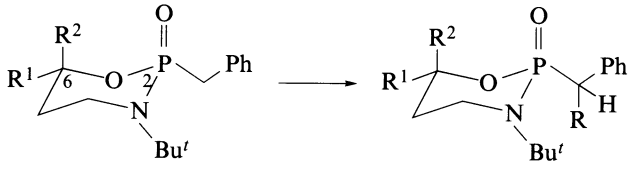


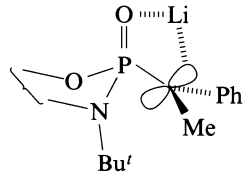
(290)

A closely similar explanation has been provided for the results obtained for the alkylation of the (2*R*)-2-benzyl-3-*tert*-butylperhydro-1,3,2-oxazaphosphorine 2-oxides **291** (R^1, R^2 = H or Me), (this ring system is now also described by the term 1,3,2-oxazaphosphinine); generation of the carbanion at about –70 °C was carried out with Bu^{t}Li or $(Me_3Si)_2NK$ in thf, dme, or Et_2O, and alkylation occurred readily using MeI, Me_2SO_4,

benzyl bromide and prop-2-enyl iodide. Alkylation of the anions from racemic **291** (R^1 = R^2 = Me) is highly selective, [although less so for **291** (R^1 = R^2 = H, or R^1 = Me, R^2 = H) with alkylation by MeI or $PhCH_2Br$] and independent of additives and of the nature of the solvent or base. The assignment of configuration within the side-chain was evidently aided by an X-ray analysis of (6*S*)-**292** (R = $PhCH_2$, R^1 = Me, R^2 = H) and found to be *R*; the main product from the substrate epimeric at phosphorus had the *S* configuration, and it was argued that the course of the alkylation step was controlled by the carbanion lone electron pair. Protonation or deuteriation of the carbanion(s) from the diastereoisomeric **292** (R = R^1 = Me, R^2 = H) leads to a mixture of diastereoisomeric phosphonates of identical stereochemical composition irrespective of chirality of starting compound, and the stereoisomeric carbanions must therefore, possess a common structure (**293**) with a low rotational barrier[544].

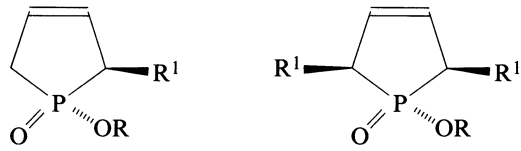


(**291**) (**292**)

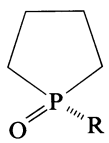


(**293**)

Alkylation of the lithiated anions from the oxides of 2-alkoxy-3-phospholenes (**294**) (R = Me or Pr^i, R^1 = H) and lda, followed by MeI or $PhCH_2Br$, was both regiospecific and stereospecific and afforded only the corresponding monosubstituted products (**294**) (R^1 = Me, $PhCH_2$); unusually, a similar alkylation using benzyloxymethyl chloride additionally give substantial amount of the dialkylated product (**295**) (R^1 = CH_2OCH_2Ph)[545]. By contrast, the high-yield alkylation of the 1-oxides of 1-alkoxyphospholanes **296** (R = OEt or OPr^i) by benzyl bromide (R^1 = CH_2Ph), using lithium tetramethylpiperidide in thf as base, is not stereospecific; the **297/298** product ratio varied from 23:77 to 75:25, depending on the presence of additives to the solvent and on the alkoxy group; for a given alkylating group R, the product ratio could be reversed by the addition of hmpa. The further alkylation (benzylation) of **298**, using the same reagents, gave a mixture of the stereoisomers (**299** and **300**), the proportions of which could again be significantly altered upon addition of hmpa. There was no *gem*-dialkylation[332].



(**294**) (**295**)



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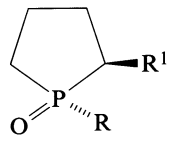

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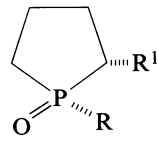

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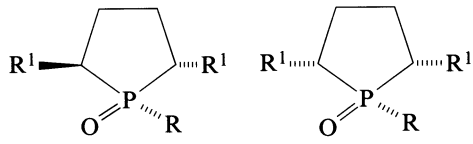
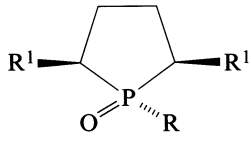


(299) (300)

The stereochemical outcome of the alkylation process also depends on the nature of the base used to generate the carbanion. Use of the substrates **297** (R = NPr^i_2, R^1 = Me or $PhCH_2$) with lda–thf–R^1X gave 86–94% of the *meso* compound **301**. On the other hand, the benzylation of **298** (R = NPr^i_2, R^1 = $PhCH_2$) gave only **302** when lithium tetramethylpiperidide was used, but mixtures of **299** and **302** in the ratio 18:82 (lda used) or 80:20 (BuLi used)[287].



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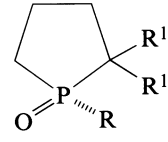
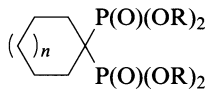


(302)

The anions from simple dialkyl alkylphosphonates and lda in thf have been mono- and di-silylated[546] and stannylated[547].

Esters of methylenebisphosphonic acid are readily alkylated following the easy generation of the carbanions using metallic sodium or potassium, NaH or more conveniently BuLi in solution but, unfortunately, exclusive monoalkylation seldom occurs; 80% yields of the monoalkylated products are often accompanied by 10–15% of dialkylated compounds (reaction 45)[548,549]. The same anions react with α,ω-dibromoalkanes to give the esters **303** (*n* = 0 or 1), and **304** similarly provides **305** followed by **306**; **307** is obtainable from 2,2′-bisbromomethylbiphenyl[550]. Such dialkylations can also be performed under phase-transfer conditions[551]. Hutchinson and Thornton[552] found a superior procedure to consist in the use of the tetraisopropyl ester of methylenebisphosphonic acid and to generate its carbanion with TlOEt; its treatment with 2-[(2-tetrahydropyranyl)oxy]ethyl iodide, followed by the conventional sequence (**308a** to **308d**) and second anion generation, led to the ester **309** (R = Pr^i), and thence to the free acid. The sequential alkylation of methylenebisphosphonic esters with 3-bromoprop-1-yne and then with a 1-bromoalk-3-ene allowed the construction of the cyclopentane ring in cyclopentane-1,1-diylbisphosphonic acid esters through an enyne cycloisomerization process[553].

$$H_2C[P(O)(OR)_2]_2 \longrightarrow R^1CH[P(O)(OR)_2]_2 \longrightarrow R_2{}^1C[P(O)(OR)_2]_2 \quad (45)$$



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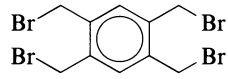

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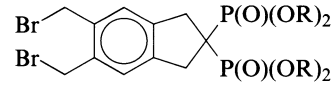

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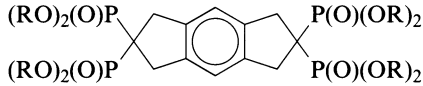

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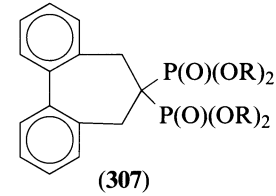

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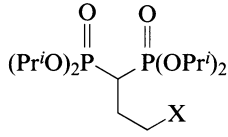

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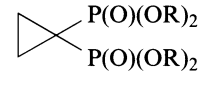
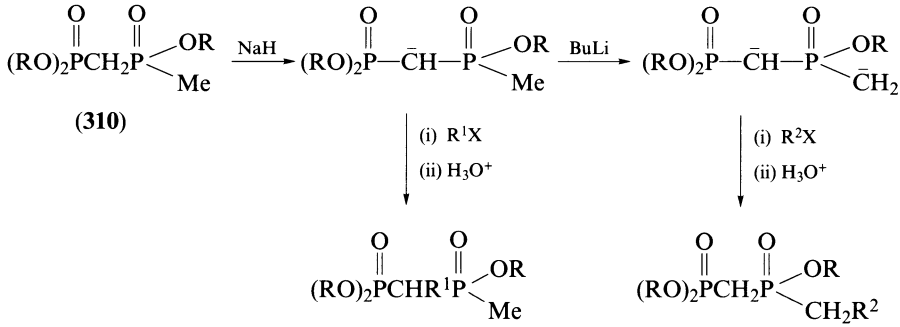


(309)

(a) X = OTHP
(b) X = OH
(c) X = Otos
(d) X = I

The behaviour of bisphosphoryl compounds such as **310** towards strong bases is reminiscent of that of analogous carbonyl compounds. Initial carbanion formation occurs at the more acidic site, but treatment of the initial anion with a stronger base generates a dianion, which may then be selectively monoalkylated at the more reactive site[554].



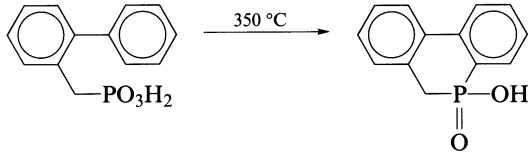
(310)

The well established alkylation of phosphorylated benzyl carbanions has been complemented by the arylation of purely alkyl species. Thus, diethyl (chloromethyl)phosphonate reacts with aryllithium reagents to give the diethyl esters of benzylic phosphonic acids[555].

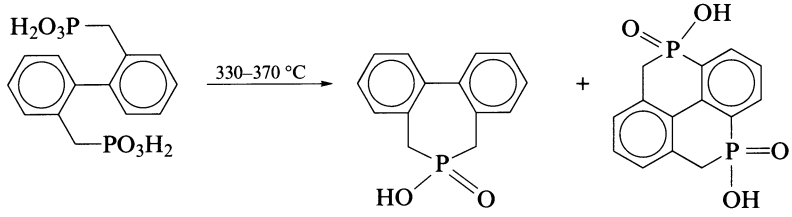
The alternative procedure has been adopted in a synthetic route to isoprenyl (phosphinylmethyl)phosphonates[556]. Here, a lithiated dialkyl alkylphosphonate is acylated using an ester of the phosphonochloridic acid, $R^1P(O)(OH)Cl$, where R^1 is an isoprenoid residue. The acylation process has also been carried to with $(RO)_2P(O)Cl$ or $(Me_2N)_2P(O)Cl$[557].

B. Aromatic Compounds Through Intramolecular Electrophilic Substitution

A simple example to illustrate the procedure is the thermal dehydration of 2-biphenylmethylphosphonic acid (**311**) to the cyclic acid **312**[425], whilst the thermolysis of the di(phosphonomethyl)biphenyl (**313**) yields two cyclic phosphinic acids in 30% overall yield with **314** as the major product[558]. 2-Biphenylyl- and 2-phenoxyphenyl-phosphinic acids fail to cyclize under a variety of conditions[559], nor does (2-biphenylyl)phenylphosphinic acid cyclize with H_2SO_4 or polyphosphoric acid, although the corresponding phosphinic chloride does so in nitrobenzene.

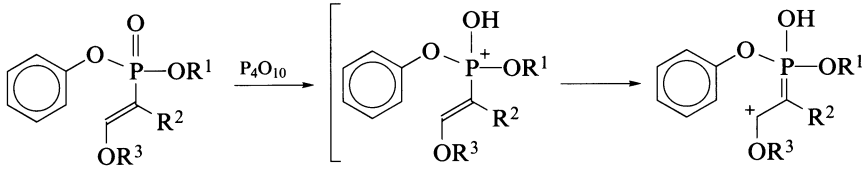


(**311**) (**312**)

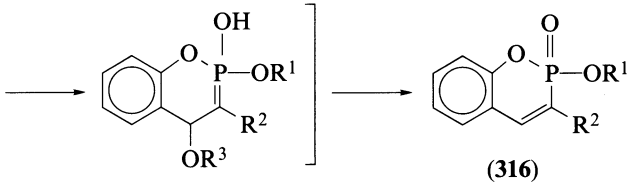


(**313**) (**314**)

When a vinylphosphonic ester (**315**) ($R^3 = CH_2CH_2R^4$) is heated with polyphosphoric acid or with phosphoric acid in toluene, cyclization occurs with the elimination of $R^4CH_2CH_2OH$. The reaction, thought to proceed through the steps illustrated, provides 17–70% yields of 2*H*-1,2-benzoxaphosphorin 2-oxides (**316**)[560].



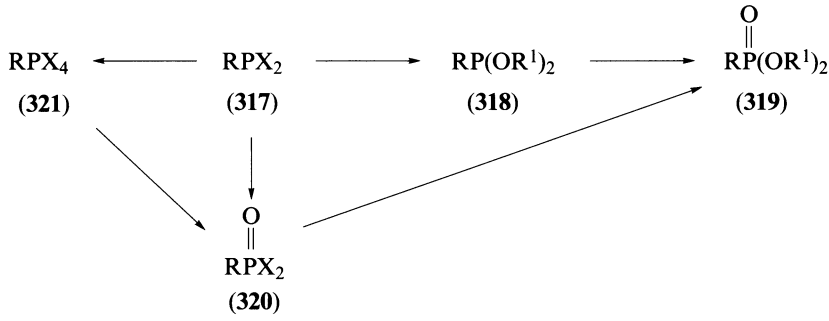
(**315**)



(**316**)

C. By the Oxidation of Phosphorus(III) Compounds

In principle, any phosphorus(III) compound possessing one (phosphonous acid derivative) or two (phosphinous acid derivative) P—C bonds may be oxidized to the corresponding derivative of the quinquevalent phosphonic or phosphinic acid. In practice, this might be difficult to achieve because of the extremely high reactivity of the phosphorus(III) compound in oxidation under both anhydrous or aqueous conditions, and it might also prove inconvenient because of difficulties in the synthesis of the phosphorus(III) compound. Alternative synthetic routes are always available. A phosphonous dichloride (dichlorophosphine) (**317**) may be converted into the phosphonic diester **319** by way of the phosphonous diester **318**; alternatively, the original dichloride **317** may be first oxidized to the phosphonic dichloride **320** before esterification to **319**; a similar sequence exists for the phosphinous–phosphinic series.



In practice, the conversion of the dihalophosphines **317** initially into the more easily handled **320** is the method of choice but, because of the very high reactivity of the former, the conversion is more easily carried out indirectly. The readily available phosphorus(III) chlorides[561–564] are halogenated and the tetrahalophosphorane **321** is then treated with SO_2 or alternatively, and more conveniently, the phosphorus(III) chloride is treated with sulphuryl chloride for a one-step conversion. The method has not been widely adapted for the alkylpolychlorophosphorane series, although alkyltetrachlorophosphoranes, as their complexes with $AlCl_3$, are convertible into the corresponding alkylphosphonic dichloride after removal of $AlCl_3$ with KCl[565]. Analogous alkyltetrafluorophosphoranes have afforded the alkylphosphonic difluorides when treated with alkoxysilanes[566] or hydrolysed at a low temperature[567]. Potassium fluorosulphinate converts $MePCl_2$ and Me_2PCl each into separable mixtures of the phosphonic (phosphinic) (di)fluoride and the corresponding thio compounds[567].

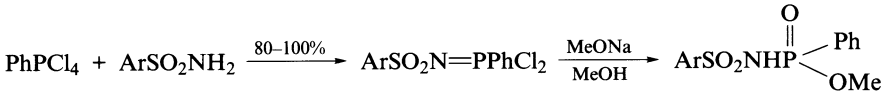
In a novel procedure, trichloroacetic acid acts on phosphorus(III) chlorides with the formation of the corresponding phosphorus(V) chloride together with dichloroacetyl chloride[568].

The conversion of an aryldichlorophosphine into the phosphonic dichloride, directly or indirectly, has been widely described[569–572]. Aryltetrafluorophosphoranes are converted into the corresponding phosphonic difluorides with hexamethyldisiloxane or other similar silicon compounds[573–575]. A constant-boiling mixture of $PhP(O)F_2$ and $PhP(S)F_2$ is obtained from KSO_2F and $PhPCl_2$[567]. Trichlorodiphenylphosphorane and $MeOPCl_2$ give diphenylphosphinic acid in 92% yield[576].

Reactions between alkyl iodides and red phosphorus with iodine or P_2I_4 afford the phosphoranes R_2PI_3, which on hydrolysis yield the dialkylphosphinic acids[577,578].

At this juncture, it may be noted that aryltetrachlorophosphoranes have been used to provide a wide range of derivatives of arylphosphonic and diarylphosphinic acids, as

illustrated in reactions 46[579] and 47[580,581]; there are many more. An aliphatic example is shown in reaction 48[582].



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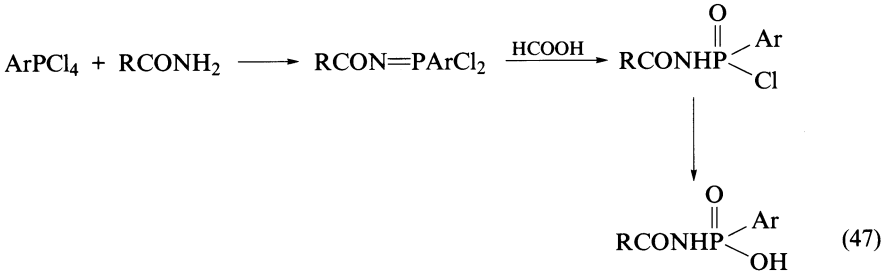

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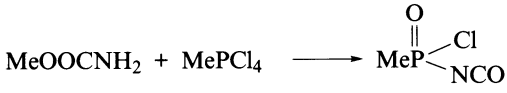
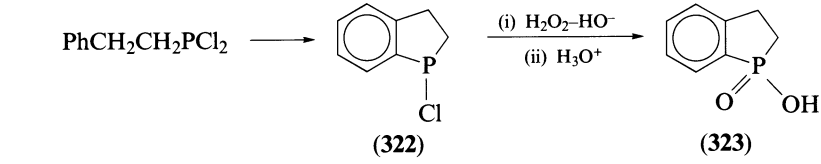
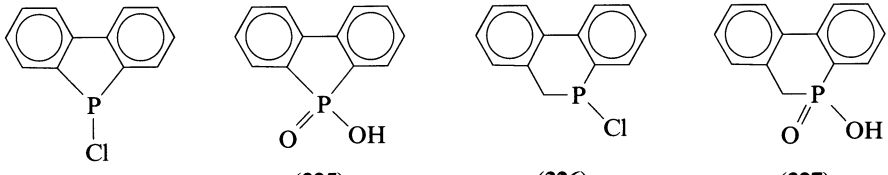


(48)

In the aromatic series, the required arylphosphorus(III) chloride is very often obtained through a Friedel–Crafts type of reaction, which may be inter- or intra-molecular in nature. Typical of an intramolecular sequence is the conversion of dichloro(2-phenylethyl)phosphine into the cyclic phosphinous chloride **322** by the action of $AlCl_3$, and convertible into the cyclic phosphinic acid **323** through an oxidative-hydrolytic sequence[583]. 5-Chloro-5*H*-dibenzophosphole (**324**) is convertible into the phosphinic acid **325**, as is **326** into **327**, using the same oxidative procedure[559]. Apart from the relatively few examples of intramolecular nature, reactions involving arenes–PCl_3–$AlCl_3$ are subject to restrictions sometimes encountered in normal Friedel–Crafts reactions, particularly the lack of regiospecificity in substitution, and the necessity for ring activation. A mixture of diphenyl ether, PCl_3 and $AlCl_3$ (1:1:0.15) yielded 13% of 4-phenoxyphenylphosphonous dichloride convertible, by way of the corresponding tetrachlorophosphorane into (4-phenoxyphenyl)phosphonic acid[584].

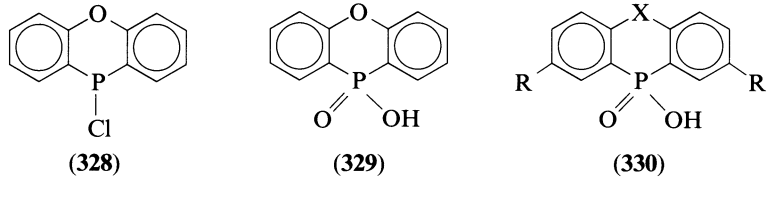


(322) (323)

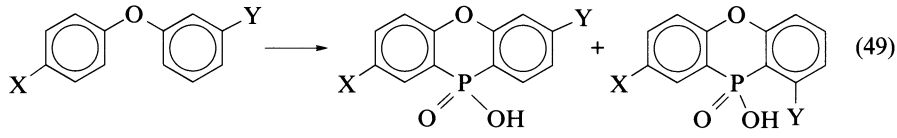


(324) (325) (326) (327)

Another study of the same system succeeded in the isolation of phenoxaphosphinic acid (**329**) after oxidation–hydrolysis of the intermediate chlorophosphine (**328**), but the overall yield of the phosphinic acid was only 2%[585]. Freedman *et al.* carried out the same reaction with other di-*para*-substituted-aryl ethers to give alkylated phenoxaphosphinic acids[586] and they also were able to obtain the corresponding phenothiaphosphinic acid (**330**) (X = S, R = Me) in 25% yield from di-*p*-tolyl-sulphide[587]. Many substituted phenoxaphosphinic acids have been synthesized from diaryl ethers which, depending on their substituents, can provide mixtures of products (reaction 49)[588–590]. The formation of phenazaphosphinic acid (**330**) (X = NH, R = H) and its derivatives has been discussed elsewhere[591].



(**328**) (**329**) (**330**)



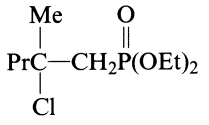
(49)

During the interaction of 2,6-di-*tert*-butylphenol and PCl_3 without added catalyst, either *O*-phosphitylation or reaction at $C_{(4)}$ may occur, the latter particularly when the reaction is performed in the presence of Et_3N. Appropriate manipulation of the aryldichlorophosphine leads to the corresponding phosphonic acid[592].

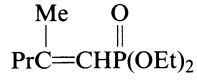
D. Synthesis Through Elimination Reactions

The early literature describes examples of elimination reactions of a rather forcing nature which have not been explored further. For example, the elimination of HCl from (2-chloroethyl)phosphonic dichloride occurs over $BaCl_2$ at 330 °C[593] and dechlorination of (1,2-dichloroethyl)phosphonic diesters occurs on heating with zinc dust[594]. Dehydrochlorination of a (2-chloroalkyl)phosphonic acid occurs on simple pyrolysis[595], but the preferred procedure consists in the treatment of the acid diester with Et_3N in warm benzene[596], a procedure also used for analogous (2-chloroethyl)phosphinic esters[597–599]. The dehydrohalogenation of isopropyl (2-haloethyl)phenylphosphinate by a chiral tertiary amine, such as quinine, quinidine, 1-phenylethylamine or *N*-methylephedrine, in a less than equivalent quantity, affords an enrichment of one enantiomer of the ethenylphenylphosphinic ester[600].

The elimination of HCl from the diester **331** with base afforded a mixture of the diesters **332** and **333**, both as *E–Z* mixtures, together with **334**. During the course of contact with the base, the composition of the product mixture was determined by proton NMR spectroscopy and GLC. For the α,β- and β,γ-unsaturated esters, plots of composition vs time cross, showing their interconvertibility. Formation of the product **332** is kinetically controlled, and both **333** and **334** are the thermodynamically controlled products. At final equilibrium, the mixture of unsaturated esters **332–333–334** had the composition 12:84:4[601]. Similar prototropic changes had been observe earlier during the dehydrochlorination of diethyl (2-chloropentyl)phosphonate[602].



(331)



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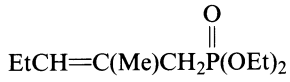
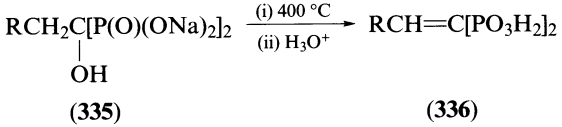


(333)

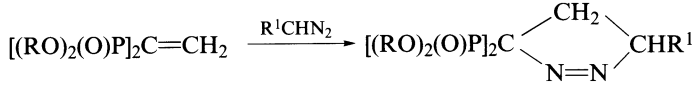
(334)

The addition of PCl_5 to alka-1,3-dienes has already been discussed, and attention has been drawn to the disputed nature of the products. Irrespective of whether, in the product phosphonic dichlorides, chlorine resides on $C_{(2)}$ or on $C_{(4)}$, their reaction with Et_3N results in dehydrochlorination to the (alka-1,3-dienyl)phosphonic dichloride[603–605]. If the phosphonic dichloride is initially converted into the phosphonic diester, the dehydrochlorination can be carried out with KOH in ROH[606–608]. Dehydrochlorination of (2-chloroethenyl)-phosphonic and -phosphinic acids or their esters to generate the alkynylphosphonic or -phosphinic derivatives also employs alcoholic alkali solutions[609–611].

Dehydration of the sodium salts of 1-hydroxyalkylbisphosphonic acids (**335**) occurs at 400 °C to give alken-1,1-diylbisphosphonic acids (**336**)[612]. Esters of this last acid have been prepared through the base-catalysed reaction of the corresponding methylenebisphosphonic esters with HCHO, followed by *p*-toluenesulphonic acid-catalysed dehydration of the resulting (hydroxymethylene)bisphosphonic ester. The reaction of **337** with diazomethane and distillation of the pyrazolinebisphosphonate product leads to loss of nitrogen and the formation of a homologue (**338**) of **337**[613]. Deacetyloxylation, either thermolytic or by $NaNH_2$ in liquid ammonia, is sometimes the preferred procedure[614]. Similar results are achievable through the aminomethylation of esters of methylenebisphosphonic acid with $(Et_2N)_2CH_2$; on attempted distillation, the products lose diethylamine to yield ethenylidenebisphosphonic esters (**337**)[615].



(335) (336)



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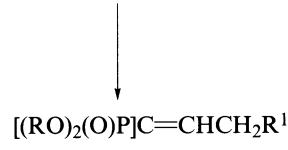
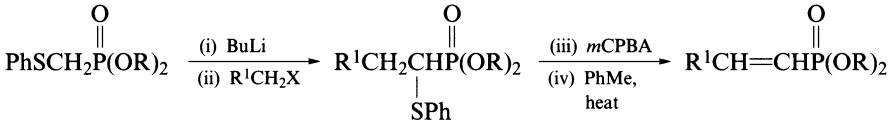
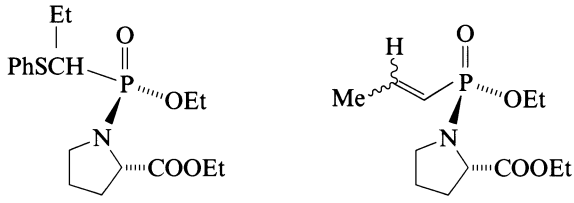


(338)

Pyrolysis (in boiling toluene) of the sulphoxide obtained from a dialkyl (1-phenylthioalkyl)phosphonate (**339**) and 3-chloroperoxybenzoic acid affords an alkenephosphonic diester[616], and subsequent work showed that the sequence was adaptable to the production of chiral esters of alkenylphosphonic diester with optical purities of not less than 93%. Use of the $(S)_P$-phosphonic amide **340** afforded a mixture of the (E)-$(S)_P$- and (Z)-$(S)_P$-stereoisomers (**341**), separable by chromatographic methods[617].

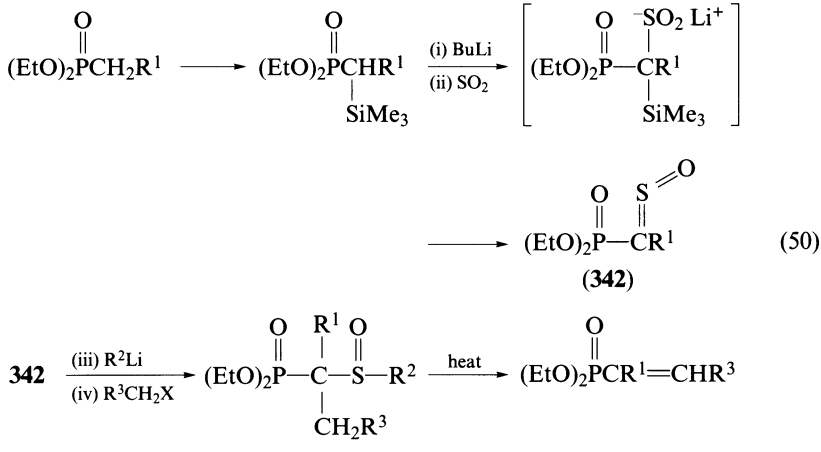


(**339**)



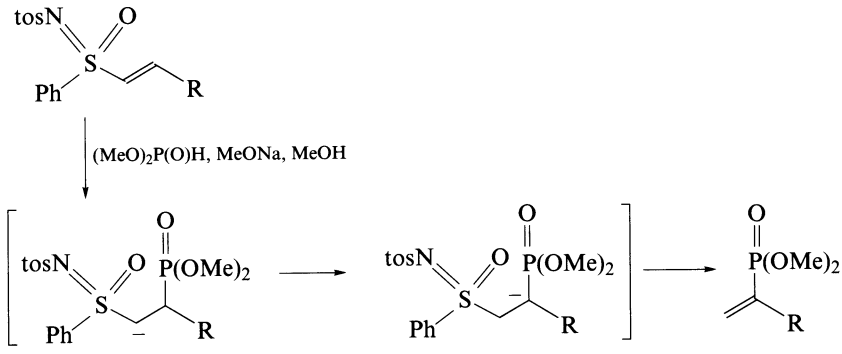
(**340**) (**341**)

[2-(2-Pyridinylsulphinylmethyl)alkyl]phosphonic diesters have likewise been used[618]. The sulphoxides may also be obtained from the compounds **342** (prepared as indicated in reaction 50) by their further treatment with an alkyllithium and alkyl halide[619]. A further



(**342**) (50)

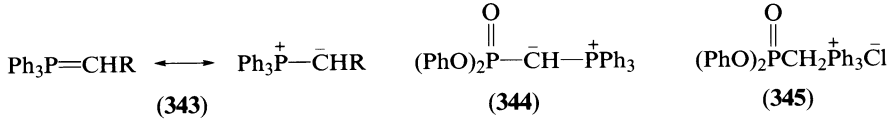
variation uses reactions of *N*-(*p*-toluensulphonyl)ethenyl sulphoximines to obtain dialkyl (1-substituted-1-ethenyl)phosphonates by the base-catalyzed β-elimination from the initial Michael adduct (Scheme 14)[620].



SCHEME 14

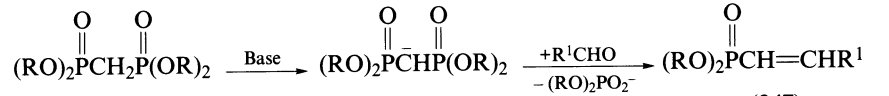
E. Synthesis of Alkenylphosphonic Acids Using the Wittig Reaction

The Wittig reaction involves the interaction of an aldehyde or ketone with a phosphorus-containing carbanionic species, in which the phosphorus is bonded directly to the carbanionic site. At the time of discovery of the reaction, that specification described the triphenylphosphonium alkylides **343**; later developments employed the anions from *tert*-phosphine oxides, the use of which has been described elsewhere in this series[621], and also from a wide variety of phosphonic and phosphinic esters. This latter application will be considered more fully in Chapter 6. An early application of the reaction to the synthesis of alkenephosphonic acids, and which involved an ylide, employed the stable compound **344**, generated from **345** by the action of a strong base. Reactions between **344** and aliphatic or aromatic aldehydes at 100 °C in toluene or dmso gave the diphenyl esters of (alk-1-enyl)phosphonic acids or (2-arylethenyl)phosphonic acids[622].

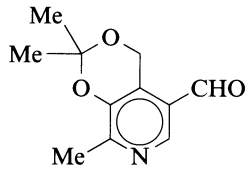


(343) **(344)** **(345)**

The use of esters of a (substituted-methyl)phosphonic acid to provide the carbanion site next to phosphoryl phosphorus was a natural step forward. The most successful development has been the use of the carbanion **346** derived from esters of methylenebisphosphonic acid (or its monoalkylated derivatives). The anion **346** reacts with an aldehyde to afford the alkenylphosphonic diester **347** (R = Et, Ph, PhCH=CH, 2-thienyl, 2-pyridinyl, etc,)[623,624]. Use of the protected 3-pyridinylcarboxaldehyde **348** allowed the preparation of the ester **349**, which, after reduction of the C=C bond and hydrolysis, afforded the phosphonic acid **350**[625]. Such reactions have also been carried out under phase-transfer conditions[626]. Reactions between the lithium salt of the ester **351** and benzaldehyde or but-2-enal give the (alk-1-enyl)phosphonic esters **352** and **353** in the ratio 1:4; the lithium salts **354** and **355** are formed concomitantly in the ratio 4:1[627].



(346) **(347)**



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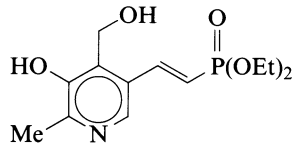

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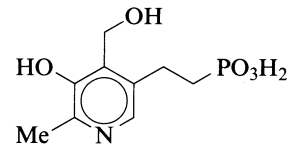

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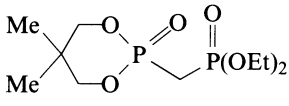

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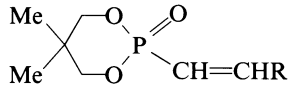

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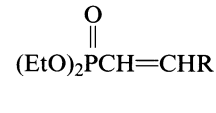

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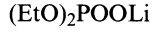

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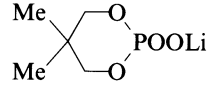
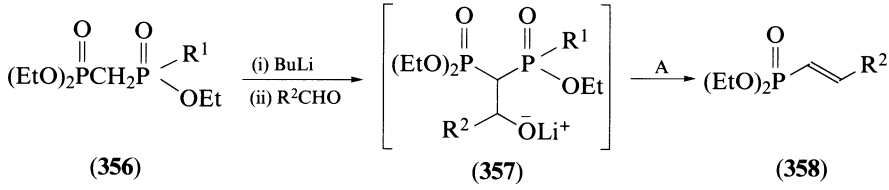
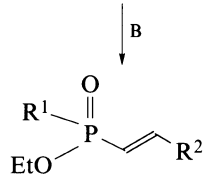


(355)

Other workers have tried to demonstrate selectivity in the breakdown of phosphonomethylphosphinates under Wittig conditions. In the reaction between the anion from **356** and an aldehyde, the initially formed intermediate **357** can break down along pathways A or B to give the alkenyl phosphonic diester **358** or the analogous-phosphinic ester **359**. Using Pr^{i}CHO and **356** (R^1 = Et, Cy, Ph or other aryl), it was shown that the course of the elimination could be directed by modifications in steric and electronic factors. With yields of the esters **359** in the range 10–70%, those of the diesters **358** were 70–10%[628]. Prashad[629] found that, in the reactions of **356** (R^1 = Me) with a range of aldehydes, elimination was in favour of pathway B.



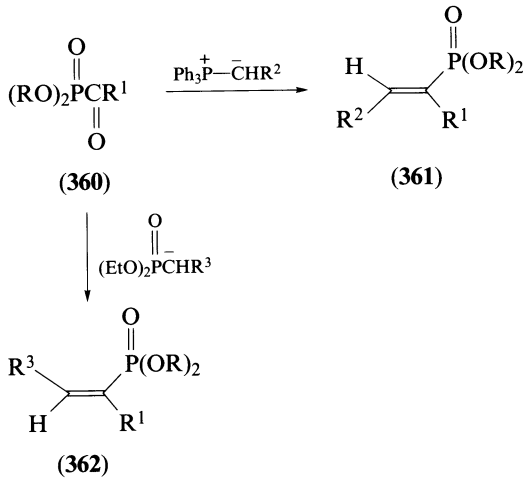
(356) (357) (358)



(359)

In a novel adaptation of the Wittig reaction, the use of the (1-oxoalkyl)phosphonic diesters **360** (R = Me or Et, R^1 = Me, Et, Ph or PhCH$_2$) (Chapter 3, SectionVI.A.1) and a triphenylphosphonium ylide afforded largely the (*E*)-alkenes **361** (R^3 = Ph, CN or

COOEt), whereas the use of the phosphonate (Wadsworth–Emmons) reagent gave largely the (*Z*)-alkenes **362**[630].

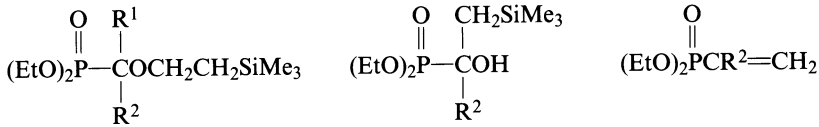


(**360**) (**361**) (**362**)

Some steric control in alkenephosphonic acid formation was achieved using the stannylated phosphonic diesters **363**, generated *in situ* from the lithiated phosphonic diester and $R^2{}_3SnCl$, and from which the (*E*)- and (*Z*)-alkenephosphonic diesters were, respectively, the thermodynamically controlled and the kinetically controlled products, the stereochemistry of the reaction appearing to be governed by R^2 [631]. Purified trimethylsilyl analogues of **363** may be similarly employed[632].

(**363**)

Stepwise alkylation of the diester **364**, obtained conventionally using the Michaelis–Arbuzov reaction, leads to **365**, from which the *O*-(2-trimethylsilylethyl) protecting group may be removed with HF in MeCN. A Peterson reaction on the deprotected alcohol **366** (R^2 = prenyl) results in the formation of the unsaturated phosphonic diester **367** (R^2 = prenyl)[633].



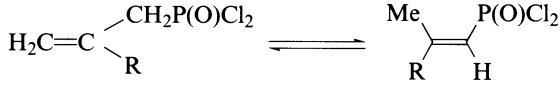
(**366**) (**367**)

(**364**) $R^1 = R^2 = H$
(**365**) $R^1 = Me_3SiCH_2$

Further discussion of the Wadsworth variant of the Wittig reaction is deferred to Chapter 6.

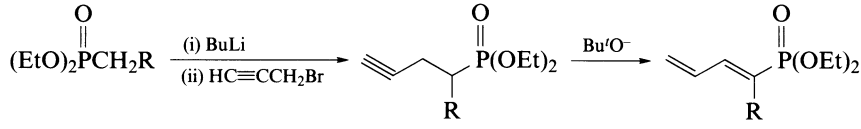
F. Synthesis Based on Prototropic Rearrangement

A simple example of this type of reaction is that in which prop-2-enylphosphonic dichloride is converted into the prop-1-enyl isomer by the action of Et_3N. In reality, equilibrated mixtures of the tautomers are produced; those obtained from the phosphonic dichlorides **368** (R = Me or Ph) contain 20% **368** and 80% **369**[634]. The conversion of 1-chloro-3-methyl-3-phospholene 1-oxide into its 2-phospholene isomer is catalysed by phosphorus(III) chlorides or by metal chlorides, the efficacy of the latter decreasing in the order $ZnCl_2 > PCl_3 > SnCl_4 > TiCl_4$; the presence of oxygen is said to inhibit the rearrangement, and freshly distilled samples are more easily rearranged than are old samples[635].



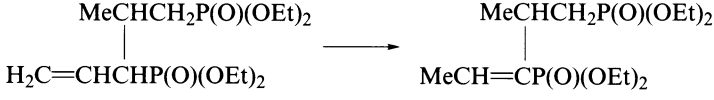
(368) **(369)**

When treated with potassium *tert*-butoxide, the [1-(prop-2-ynyl)alkyl]phosphonic diesters **370** (R = H, Me, Ph, etc.) undergo prototropic isomerization to the (1-R-buta-1,3-dienyl)phosphonic diesters (**371**)[636].



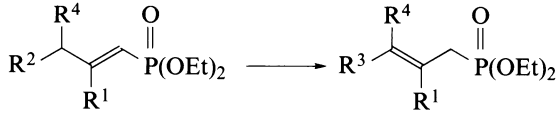
(370) **(371)**

An early report claimed that the treatment of diethyl prop-2-enylphosphonate with NaOEt brings about its isomerization to diethyl prop-1-enylphosphonate, which is followed by the addition of sodium diethyl phosphite (present in the Michaelis–Becker synthesis of the original substrate) to give tetraethyl (1,2-propanediyl)phosphonate[76]. A later communication claimed that diethyl prop-2-enylphosphonate undergoes dimerization when treated with NaOEt; the exothermic reaction was pictured as the addition of the substrate to diethyl prop-1-enylphosphonate (which itself does not dimerize) produced by rearrangement. Finally, the initial adduct (**372**) itself rearranges to **373**[637].



(372) **(373)**

Phosphorylation with $(EtO)_2P(O)Cl$ of the mesomeric anion obtained from diethyl prop-2-enylphosphonate and $LiN(SiMe_3)_2$, leads to the bisphosphonic derivative **338** (R = H)[638].



(374) **(375)**

A further indication of equilibration as the result of deprotonation is the reverse isomerization of the diethyl alkenylphosphonates **374** into the alk-2-enylphosphonates **375** [R^1 = H, R^3 = R^4 = Me, R^3 = H; R^4 = pentyl or Ph, R^4 = H, R^3R^1 = $(CH_2)_4$][624].

G. Miscellaneous Synthetic Reactions for Alkenyl and Alkynyl Phosphonic Acids

Esters and other derivatives of alkenyl- and alkynyl-phosphonic acids, and of the correspondingly unsaturated phosphinic acids, undergo a wide range of addition and cycloaddition reactions which will be considered more fully in Chapter 6. These reactions include applications of the Diels–Alder reaction to yield carbocyclic phosphonic acids based on mono- and poly-cyclic ring systems, some of which are precursors to other aromatic phosphonic acids. A typical example of this procedure is the addition of dimethyl (bromoethynyl)phosphonate to 2,3-dimethylbutadiene; elimination of HBr from the 1:1 cycloadduct, using Et_3N, affords dimethyl (2,3-dimethylphenyl)phosphonate[639]. The addition of carbenes to alkenylphosphonic derivatives yields those of cyclopropylphosphonic acids[640].

Other addition reactions include those of dialkyl hydrogenphosphonates to alkynylphosphonic esters under basic catalysis, observed by Saunders and Simpson[417] and by others (reaction 51)[641], but also of some interest are those additions of hydrogenphosphonates to acetylenic alcohols such as **376** (Scheme 15)[642]. The addition of hypophosphorous acid to the alcohols **380** affords the alka-1,2-dienephosphinic acids **381** which, when treated with acid, cyclize to the acids **382**[643,644].

$$(R^1O)_2P(O)H + (R^2O)_2P(O)C{\equiv}CR^3 \longrightarrow [(R^1O)_2(O)P]_2CR^3CH_2P(O)(OR^2)_2 \quad (51)$$

$$HC{\equiv}CCH_2OH + (EtO)_2PONa \longrightarrow HC{\equiv}CCH_2ONa + (EtO)_2POH$$

(376)

$$HC{\equiv}CCH_2ONa + (EtO)_2POH \longrightarrow (EtO)_2P(O)CH_2\underset{\displaystyle P(O)(OEt)_2}{\underset{|}{C}}HCH_2ONa$$

(377)

$$\mathbf{377} + (EtO)_2POH \longrightarrow (EtO)_2P(O)CH_2\underset{\displaystyle P(O)(OEt)_2}{\underset{|}{C}}HCH_2OH$$

(378)

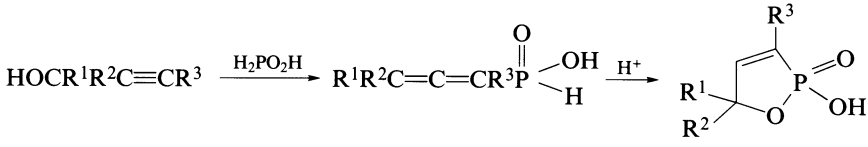
$$\mathbf{378} \xrightarrow{-H_2O} (EtO)_2P(O)CH_2\underset{\displaystyle P(O)(OEt)_2}{\underset{|}{C}}{=}CH_2$$

(379)

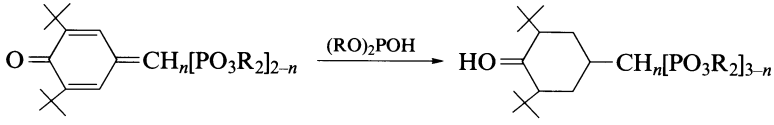
$$\mathbf{379} \xrightarrow{(EtO)_2POH} [(EtO)_2P(O)CH_2]_2CHP(O)(OEt)_2$$

SCHEME 15

Addition of hydrogenphosphonates to the 1,4-quinonemethides **383** to give the 4-hydroxyphenyl polyphosphonic acids as their esters **384** is well established[645,646], and that of hydrogenphosphonates to *p*-benzoquinone itself is reported to give the 2,5-dihydroxyphenyl-1,4-bisphosphonic acid derivative[647].

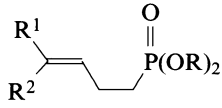


(380) **(381)** **(382)**



(383) **(384)**

The conjugate addition of alkyl or vinyl copper complexes to (alk-1-enyl)phosphonic diesters occurs readily, and that of $R'CuMgX_2$ to diethyl ethenylphosphonate affords $R'CH_2CH_2P(O)(OR)_2$ in 70–80% yields; additionally the use of the complexes $R^1R^2C{=}CHCuMgBr$ gives 25–90% yields of the phosphonates **385**[648].

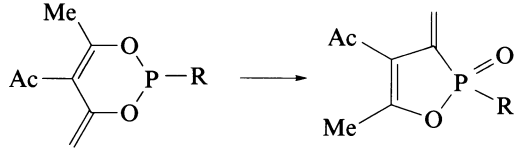


(385)

Vinylation or arylation at $C_{(2)}$ in dialkyl (alk-1-enyl)phosphonates may be performed with vinyl bromides or aryl (substituted phenyl, naphthalenyl, thienyl) bromides in systems which contain $Pd(OAc)_2$–$(2\text{-}MeC_6H_4)_3P$–Et_3N[649] and, interestingly, the same catalyst system used in conjunction with iodobenzene and dialkylprop-2-enylphosphonates affords products which then isomerize into dialkyl (3-phenylprop-1-enyl)phosphonates[214].

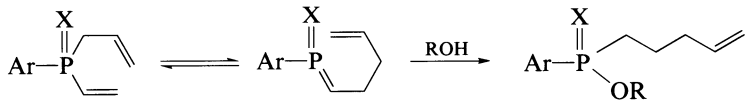
The thermally initiated isomerization of dialkyl alk-2-enyl phosphites leads to phosphonic diesters (reaction 52)[125] and is also to be found in cyclic systems when, for instance, the 1,3,2-dioxaphosph(III)orin **386** gives the 1,2-oxaphosph(V)olene **387**[650].

(52)



(386) **(387)**

Of an equally novel nature is the thermally catalysed rearrangement of the phosphine oxides (or sulphides, or selenides) **388** into the equilibrated system also containing the corresponding **389** and which, on addition of an alcohol, gives rise to the phosphinic esters **390**[651].



(388) **(389)** **(390)**

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NOTE ADDED IN PROOF

The following short selection of relevant publications extends the literature coverage to mid-1995.

Section II

Michaelis–Arbuzov reactions have been carried out with tribenzyl phosphite and mixed alkyl dibenzyl phosphites $(PhCH_2O)_2POR$. A trace of an alkyl halide causes the former to isomerize to the predicted dibenzyl benzylphosphonate, but when the mixed phosphites are treated with the halide R′X, loss of benzyl halide occurs with the formation of $(PhCH_2O)(RO)P(O)R'$. The high reactivity of the systems led to the formation of several oligophosphonates[652]. Carbohydrate-like 1,2-oxaphosphorinanes have been prepared from 2,3-dimethoxybutane 1,4-dihalides and $PhP(OEt)_2$ as mixtures of diastereoisomers (compare the formation of **57**)[653].

Diarylcarbenes, for example, Ph_2C: in sensitized (with benzophenone) or unsensitized form, may be inserted into the P—H bond of dialkyl hydrogenphosphonates to yield dialkyl (diarylmethyl)phosphonates under neutral conditions[654].

Many further examples of the interaction of PCl_3 or dichlorophosphines $RPCl_2$ in sulphuric acid with a wide range of adamantane substrates, variously substituted, have been reported when the products are the adamantylphosphonic dichlorides or [adamantyl(R)] phosphinic chlorides, respectively.

However, the use of PBr_3 under the same or similar conditions results in halogenation of the adamantane substrate rather than phosphorylation[655].

The hydrophosphonation of 1-methylcyclohexene by the addition of a dialkyl hydrogenphosphonate in the presence of an organic peroxide proceeds regioselectively to yield the (2-methylcyclohexan-1-yl)phosphonic diester. Additions to 1,2-dimethylcyclohexene proceed stereoselectively with *trans* addition, and those to 4-methylcyclohexene occur to give mixtures of regioisomers[656].

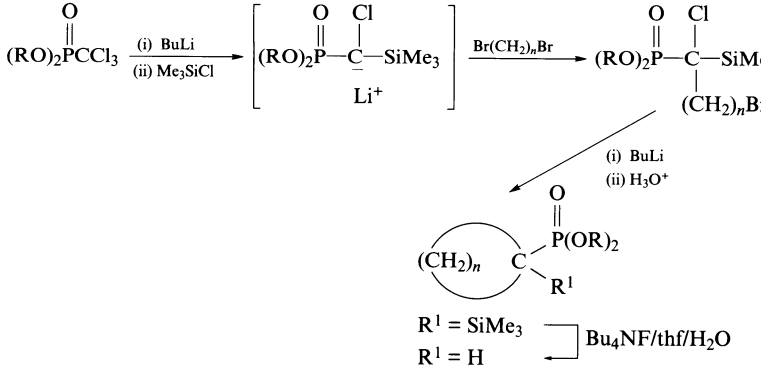
Section V

The rearrangement of dialkyl 3-pyridinyl phosphates and thiophosphates under the influence of a base (lda) at low temperatures has been shown to be remarkably regioselective. In the case of the diethyl phosphate ester, the sole product is diethyl (2-hydroxy-4-pyridinyl)phosphonate; with the corresponding thiophosphate *O,O,O*-triester, diethyl (3-hydroxy-2-pyridinyl)phosphonothioate is formed in a large excess over the (2-hydroxy-4-pyridinyl)phosphonothioic diester[657].

Section VI

A convenient synthesis of diethyl (2-arylethenyl)phosphonates starts with readily available diethyl methylphosphonate; this is converted into its carbanion (BuLi) and the latter acted upon by an appropriate aldehyde or ketone. The resultant (2-substituted-2-hydroxyethyl)phosphonate is phosphorylated and, without isolation of the phosphate ester, a treatment with KOBu^t eliminates diethyl phosphate and yields the desired product[658]. Other diethyl (2,2-disubstituted-ethenyl)phosphonates have been prepared by the addition of organomagnesium–copper reagents to diethyl ethynylphosphonate[659].

A general synthesis of cycloalkylphosphonates, starting from diethyl(trichloromethyl)phosphonate, has been outlined by Savignac *et al.*[660]. The important steps are indicated in Scheme 16, but each is accompanied by other reactions leading to linear products, particularly when $n = 2$; the yields of the cyclophosphonic diester products ($n = 3$–6) are said to be in the range 18–75%.



SCHEME 16

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CHAPTER 3

The synthesis of functionalized phosphinic and phosphonic acids and their derivatives. Part A: halo, hydroxy, epoxy, mercapto, carboxy and oxo functionalized acids

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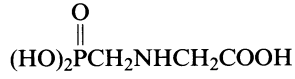
The chemistry of organophosphorus compounds, Volume 4, Ter- and quinque-valent phosphorus acids and their derivatives. Edited by Frank R. Hartley. ISBN: 0-471-95706-2

I. INTRODUCTION

Functionalized phosphonic and phosphinic acids and their derivatives are obviously of interest to the organophosphorus chemist, but the importance, both actual and potential, in other areas, particularly in the biological sphere, cannot be overemphasized. Prominent amongst the many important compounds are, for example,the insecticide dipterex (**1**) and the herbicide glyphosate (**2**)[1], both synthetic compounds. Several phosphonic acid antibiotics have been isolated from *Streptomyces* species. (2*S*)-2-Amino-4-(hydroxymethylphosphinoyl)butanoic acid (**3**), otherwise known as phosphinothricin, and a substance which also possesses herbicidal activity, is a component of the peptide γ-(hydroxymethylphosphinoyl)-L-α-aminobutanoyl-L-alanyl-L-alanine, also present in the same organism. (1,2-Epoxypropyl)phosphonic acid, [(3-methyloxiranyl)phosphonic acid] as the (2*R*,3*S*)-diastereoisomer (**4**), also known as phosphonomycin, is important from the pharmaceutical standpoint as a broad spectrum bactericide, and it is produced commercially.

(1)



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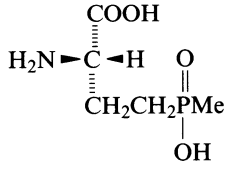

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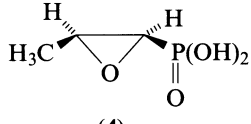
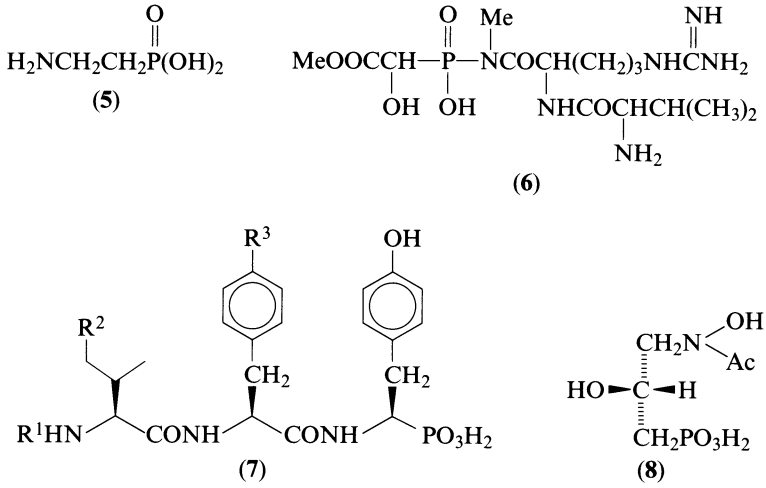


(4)

(2-Aminoethyl)phosphonic acid (**5**) occurs as various *N*-substituted derivatives in several lower organisms [2,3]. Compounds **6**[4], **7** and **8**, are all antibiotics. Further details of these compounds can be found in ref. 18.

Much recent interest has centred around the synthesis of compounds of potential pharmacological interest. Essentially,this area of interest is based on the premise that



(5)

(6)

(7)

(8)

(a) $R^1 = R^2 = R^3 = H$
(b) $R^1 = R^2 = H$, $R^3 = OH$
(c) $R^1 = Ac$, $R^2 = Me$, $R^3 = OH$

carbon–phosphorus bonds are stable to enzymatic activity and that the $P(O)CH_2$ group and, more particularly, the $P(O)CF_2$ group, are isosteric to the P(O)OC group found in biologically active phosphate esters. Even if P—C bond fission were to occur, it would be expected to proceed much more slowly than that of the P(O)OC system in phosphate esters. Thus, many analogues, both isosteric and non-isosteric, of naturally occurring phosphorus compounds have been prepared and subjected to pharmacological assessment. In point of fact, C—P bonds are cleavable under biological conditions[5,6].

The position of the functional group(s) in the carbon moieties,particularly with regard to the carbon–phosphorus bond, can have a profound effect on the chemical properties of that bond; excellent examples are the presence of an OH on the α-carbon atom, or of an oxo group in the α-position, both of which weaken the P—C bond Other properties of a group are consequent upon its position, for example, the pronounced acidity of a hydrogen atom sited on a carbon atom immediately adjacent to the phosphoryl group, and even more so in the presence of a second electron-withdrawing group, either phosphoryl, as in methylenebisphosphonic acid, or,for example, COOR, as in phosphonoacetic acid and its derivatives.

The previous chapter surveyed the methods available for the synthesis of various types of phosphonic and phosphinic acids and their derivatives classified simply by the types of carbon skeletal structures—structures which, with the exception of the aromatic acids, lack carbon-bonded functional groups. This chapter now extends the survey to include those phosphonic and phosphinic acids which possess one or more of the more important functional groups. As in the previous chapter, the literature is surveyed up to early 1994, and an overlap is made with the earlier reviews included in the series edited by Kosolapoff and Maier[7–9] and in the Houben–Weyl volumes[10,12] from which, in general, other references to the earlier literature should again be sought, except in so far as work of particular historical or synthetic importance is concerned.

At the time of publication, Kosolapoff and Maier's review included coverage of the rather sketchy knowledge of the functionalized acids then known, but since the early 1970s our knowledge of the types of functionalized acids and their chemistry has grown enor-

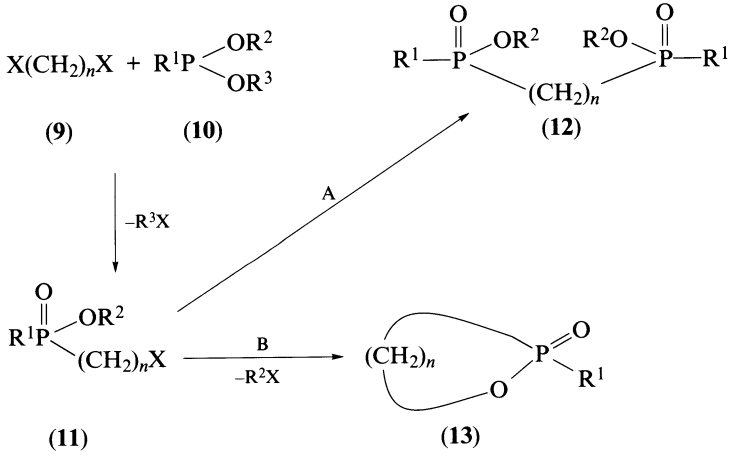
mously. Some aspects of these developments have been surveyed recently[13], and other volumes have described the biological chemistry of many functionalized quinquevalent phosphorus acids[14–16]. The organic chemistry of these same acids is surveyed annually[17], and literature surveys are available for individual acids[18].

II. HALO-PHOSPHONIC AND -PHOSPHINIC ACIDS

A. Syntheses Through Phosphorus–Carbon Bond Formation

1. From haloalkanes through the Michaelis–Arbuzov and Michaelis–Becker reactions

In principle, the reaction between a dihaloalkane (**9**) and a phosphorus(III) ester (**10**; (R^1 = alkyl, aryl or alkoxy) initially affords the haloalkyl compound **11**; the use of a trialkyl phosphite would thus lead to an (ω-haloalkyl)phosphonic diester **11** (R^1 = alkoxy, R^2 = alkyl), whilst that of a phosphonite diester (**10**; R^1 = alkyl, aryl) would afford an (ω-haloalkyl)alkyl(or aryl)phosphinic ester. Depending on the ratio of reactants, further reaction might then take place (pathway A), resulting in the formation of the compounds **12**. Depending also on n, and on the reaction temperature, the alternative pathway B may be followed; the products are then cyclic phosphonic or phosphinic acid derivatives **13**, and examples following both reaction pathways have been discussed (chapter 2, Section A).



As in all Michaelis–Arbuzov and Michaelis–Becker reactions, the usual order of decreasing reactivity at the carbon–halogen bond, I > Br > Cl > F, applies with carbon–fluorine bonds tending to be unreactive, other than in exceptional circumstances. Even for diiodomethane, the most reactive dihalomethane, reactions with trialkyl phosphites can be made to yield esters of (iodomethyl)phosphonic acid (**11**; R^1 = O-alkyl, R^2 = alkyl, n = 1, X = I)[19,20] or in the presence of more phosphite ester, the methylenebisphosphonic ester **12** (R^1 = O-alkyl, n=1)[20]; in the same way, diethyl phenylphosphonite affords **11** (R^1 = Ph, R^2 = Et, n = 1, X = I). Bromoform and iodoform, although reactive to trialkyl phosphites, tend to yield alkyl halide, dialkyl hydrogenphosphonate and dialkyl phosphorohalidate, but (halomethyl)phosphonate esters are not obtained. With tetrahalomethanes, particularly those based on two or more different halogens, a more interesting picture is presented. Triethyl phosphite and tetrabromomethane are reported to yield EtBr quantitatively[21], but

reactions between phosphite or phosphonite esters and carbon tetrachloride have been examined extensively and have a usefulness in the preparation of esters of (trichloromethyl)phosphonic acid and analogous phosphinic acids. However, the reaction is not completely general since, for example, trimethyl phosphite reportedly yields hexachloroethane and dimethyl phosphorochloridate, and indeed, these are by-products in many of the examples of the reaction[21]; triphenyl phosphite does not react with tetrachloromethane, and when the latter is heated with tris(2-chloroethyl) phosphite at a temperature higher than 140 °C, the result is mere isomerization of the phosphite[22] . Free radical mechanisms have been advanced to account for the formation of dialkyl (trichloromethyl)phosphonate, dialkyl phosphorochloridate and hexachloroethane in peroxide–catalysed reactions between phosphite triesters and polyhaloalkanes[23–25] . Bis(2-chloroethyl) phenylphosphonite and CCl_4 react together to give 2-chloroethyl phenyl (trichloromethyl)phosphinate in the expected manner[22] and other aryl(trichloromethyl)-phosphinic esters have been similarly obtained[23–28].

By contrast to carbon tetrabromide, bromotrichloromethane reacts with phosphite esters, including tris(2-chloroethyl) phosphite, to give the corresponding diester of (trichloromethyl)phosphonic acid[22,23]; fluorotrichloromethane likewise affords esters of (dichlorofluoromethyl)phosphonic acid[22]. In other cases, for example, CF_3I[29], CF_2Br_2[29–32] and $CFBr_3$[32–34], it is always the halogen other than fluorine that is displaced. Thus far, (difluoroiodomethyl)phosphonic diesters have been obtained by the action of iodine on the zinc reagents from dialkyl (bromodifluoromethyl)phosphonates[30]. A slightly more unusual example which might be quoted is the formation of triethyl fluorophosphonoacetate, $(EtO)_2P(O)CHFCOOEt$, in the reaction between triethyl phosphite and ethyl bromofluoroacetate[35,36].

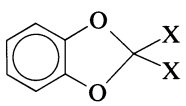
It has already been indicated that the course of any reaction may depend, to some extent, on the nature of the phosphite (or phosphonite) ester (phosphinite esters yield phosphine oxides). Thus, tris(perfluoroalkyl) phosphites do not undergo a Michaelis–Arbuzov reaction with perfluoroiodoalkanes, although reports on the outcome of any reaction between triethyl phosphite and CF_3I, under normal conditions, are conflicting; reactions do appear to proceed under photostimulation[37]. A normal reaction does take place at high temperatures between polyfluorinated trialkyl phosphites and methyl iodide, when the product, $MeP(O)(OR_f)_2$, is accompanied by oxidation of the phosphite to phosphate[38]. Either elimination or alkylation accompanies the formation of unidentified phosphorus-containing products in the reactions between trialkyl phosphites and the halides $Cl_3C(CF_2)_nCl$ ($n = 2$, 4 or 6)[39].

The greater nucleophilic reactivity of silyl phosphites towards organohalogen compounds results in a greater complexity in product composition; thus, dialkyl trimethylsilyl phosphites and CCl_4 afford the dialkyl (trichloromethyl)phosphonates in yields of 50–60%, together with various halogenated silicon-containing products and a dialkyl phosphorochloridate (in up to 30% yield)[40].

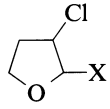
(Trichloromethyl)phosphonic diesters themselves undergo Michaelis–Arbuzov reactions with trialkyl phosphites to give esters of (dichloromethylene)bisphosphonic acid, although in the presence of alcohols such reaction mixtures then afford diesters of (dichloromethyl)phosphonic acid, presumably through the alcoholysis of the Michaelis–Arbuzov intermediate[41]. In a similar vein, the *gem*-dihalide **14** yields the bis(phosphonic diester) **15**, although in low yields only, the main reaction being one of oxidative dehalogenation and the formation of phosphorus(III) acid chlorides together with *o*-phenylene carbonate[42].

The failure to obtain an ester of (2-bromoethyl)phosphonic acid from trimethyl phosphite and 1,2-dibromoethane is due partly to competitive reaction between the evolved methyl bromide and the phosphite and partly to debromination. On the other hand, the use of higher trialkyl phosphites is more successful, although it still becomes necessary

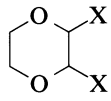
finally to separate the required ester, $BrCH_2CH_2P(O)(OR)_2$, from the by-product, $RP(O)(OR)_2$[43,44]. Depending on the choice of phosphite ester, the halogen in the dihaloethane and the reaction conditions, esters of type **12** may also be formed as by-products. With the more reactive halogens on vicinal carbon atoms, the possibility of dehalogenation, leading either to simple alkenes or to alkenylphosphonic diesters, must be taken into consideration. However, in its reaction with triethyl phosphite, loss of halogen occurs only at the more reactive site in **16** to give **17**, whereas under similar conditions, **18** affords **19**[42].



(**14**) X = Cl
(**15**) X = P(O)(OEt)$_2$



(**16**) X = Cl
(**17**) X = P(O)(OEt)$_2$



(**18**) X = Cl
(**19**) X = P(O)(OEt)$_2$

Continuous monitoring of density and refractive index for mixtures of trialkyl phosphites and the dihalides **20** indicates a two-stage interaction, the outcome of which, at room temperature, is the formation of the esters **21**. No reaction occurs between **20** (X = Cl, Y = COOMe) and phosphite (R = Et or Bu), even at 60 °C[45], but otherwise the products have the composition **21** (Y = O-alkyl[46–49], CN[45] or COOMe[45,48]) for X = Br. In certain cases, the Michaelis–Arbuzov reaction proceeds further to give **22** (Y = OR)[46].

$$\underset{\textbf{(20)}}{XCH_2CHXY} \xrightarrow{(RO)_3P} \underset{\textbf{(21)}}{(RO)_2\overset{\overset{O}{\|}}{P}CHYCH_2X}$$

$$\underset{\textbf{(22)}}{(RO)_2\overset{\overset{O}{\|}}{P}CHYCH_2\overset{\overset{O}{\|}}{P}(OR)_2}$$

The reactions between phosphite esters and longer chain polyhalogen compounds, particularly polyfluorinated compounds, can be complex and the resultant phosphonate esters are based on dehalogenated carbon moieties. With triethyl phosphite, the polyhalides **23** (n = 2, 4, or 6) initially yield the alkenes **24**, and further reaction with phosphite ester leads to the phosphonates **25** accompanied by fluoroethane (and not by iodoethane); the only polyhalide examined which did not give rise to a phosphonate ester was $ICl FCCClF_2$, the product then being $F_2C{=}CFCl$[50]. Similar dehalogenations by trialkyl phosphites have already been encountered for iodine-free polychlorofluorocarbons[39]. On the other hand, the halides **26a–c** do afford the corresponding **27**[51].

Although monohaloalkenes do not normally undergo the Michaelis–Arbuzov reaction, they may do so under conditions of metal catalysis or photostimulation; the two-stage

$$\underset{\textbf{(23)}}{I(CF_2)_nCFClCF_2Cl} \qquad \underset{\textbf{(24)}}{I(CF_2)_nCF{=}CF_2} \qquad \underset{\textbf{(25)}}{I(CF_2)_nCF{=}CF\overset{\overset{O}{\|}}{P}(OEt)_2}$$

$RCH_2CH{=}CHCH_2Cl$

(26)

(**a**) R = CCl_2CF_3
(**b**) R = $CCl_2CF_2CFCl_2$
(**c**) R = $CCl_2CF_2CF{=}CFCFCl_2$

$RCH_2CH{=}CHCH_2P(O)(OEt)_2$

(27)

reactions between phosphorus(III) esters and 1,2-dichloroethene, and which were described in Chapter 2 (Section III.C) can be interrupted to afford the dialkyl (2-chloroethenyl)phosphonate[52]. Tetraethyl (1-chloroethene-1,2-diyl)bisphosphonate is the product from trichloroethene and triethyl phosphite in a reaction carried out under catalysis by $NiCl_2$[53]. Reactions have been shown to occur between fluorinated alkenes **28** and trialkyl phosphites or dialkyl alkylphosphonites to give phosphonates or phosphinates, apparently directly; the phosphonates **29** ($R^1 = R^2O$) have been described with X = F or Cl[54], I[55] and CF_3[54]. Further reaction with trialkyl phosphite can then occur to give the diphosphonates **30** as *E–Z* mixtures[55,56]. Using the more reactive diethyl trimethylsilyl phosphite[56–59] or tris(trimethylsilyl) phosphite[57–59], similar esters **30** (R = Et or Me_3Si), and also the phosphonate **31** (from $F_5SCF{=}CF_2$)[57,58], have been prepared. In several other cases, reactions between trialkyl phosphites and heavily fluorinated alkenes have been shown to proceed through isolable phosphoranes (or pseudophosphonium compounds), but an increase in reaction temperature then results in their breakdown to phosphonic esters. A mixture of triethyl phosphite and perfluoroisobutene, prepared at –70 °C, reacts at –30 °C to give the phosphorane **32** which, at 125 °C, is converted into the phosphonate **33** together with **34**[60]. Perfluorocyclobutene undergoes a similar sequence of reactions. On the other hand, the phosphoranes **35**, prepared in the cold from trialkyl phosphites and the esters $F_2C{=}C(CF_3)COOR$, decompose, when heated, with the expulsion of alkyl difluorophosphites[61,62]. Relatively few examples of analogous phosphinates, preparable from dialkyl alkylphosphinites, have been recorded[54,63].

$R^1P(OR^2)_2 + CF_2{=}CFX \longrightarrow R^1(O)(R^2O)P{-}CF{=}CFX$

(28) **(29)**

$(RO)_2P(O)CF{=}CFP(O)(OR)_2$

(30)

$(RO)_2P(O)CF{=}CFSF_5$

(31)

$(F_3C)_2C{=}CFP(OEt)_3F$

(32)

$(EtO)_2P(O)CF{=}C(CF_3)_2$

(33)

$(F_3C)_2C{=}CFP(O)(F)(OEt)$

(34)

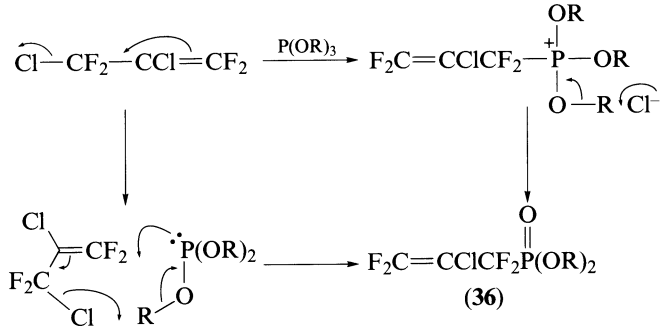
$(R^1O)_3P(F)CF{=}C(CF_3)COOR^2$

(35)

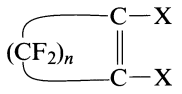
Reactions between fluorine-containing compounds and phosphorus(III) nucleophiles have been reviewed[64].

The two-stage reactions between dichloroethyne and trialkyl phosphites (also described in Chapter 2, Section IV.A) can also be interrupted and the dialkyl (2-chloroethynyl)-phosphonates isolated[65–67].

Several examples are known which demonstrate the greater reactivity of chlorine vs fluorine in unsaturated compounds in their behaviour towards phosphorus(III) esters. Thus, the interaction of 2,3-dichlorotetrafluoropropene and trimethyl phosphite proceeds through an allylic displacement, by either an ionic or a concerted mechanism (Scheme 1) to give the phosphonate **36**[68]. The 1,2-dichloroperfluorocycloalkenes **37** (n = 2, 3 or 4) also react with phosphite or phosphonite esters to give the phosphonates **38** or phosphinates **39**[69,70].



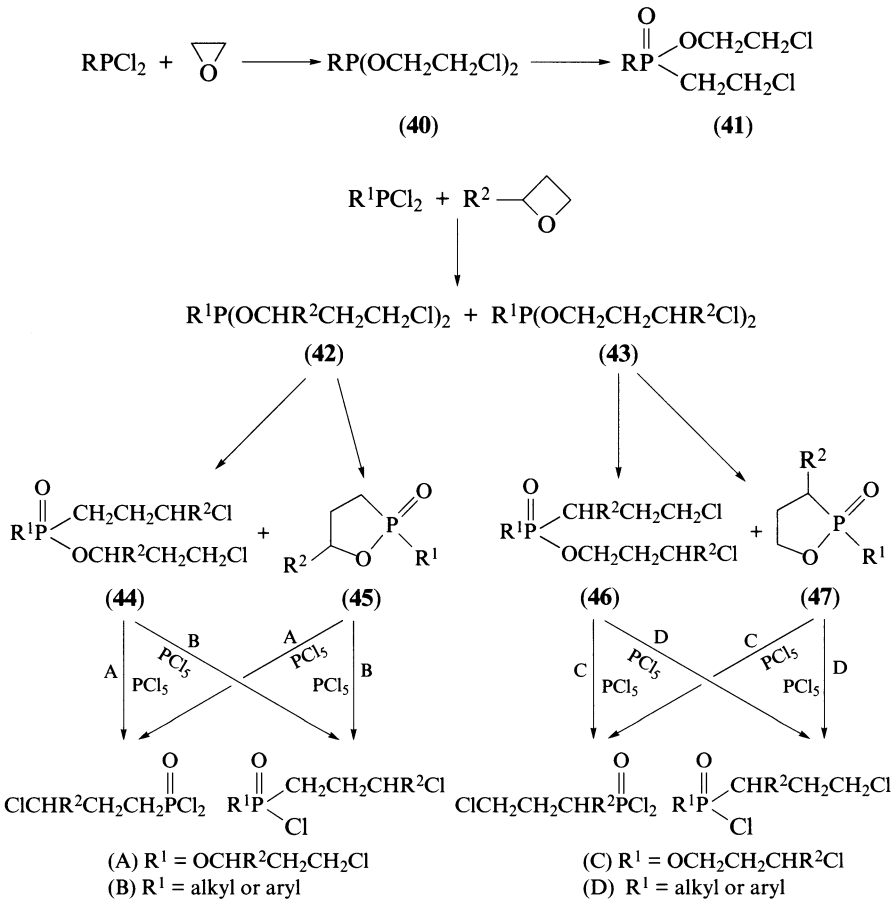
SCHEME 1



(**37**) X = Cl
(**38**) X = P(O)(OR)$_2$
(**39**) X = P(O)(OR^1)R^2

The involved chemistry of fluoroalkenylphosphonic acid derivatives has been reviewed[71].

An interesting example of the Michaelis–Arbuzov reaction, and one which is valuable in the laboratory and also has some commercial interest, is the intramolecular, thermally initiated, isomerization of ω-haloalkyl esters of phosphorus(III)acids, these being conveniently obtainable from phosphorus(III) halides and oxiranes. The simplest example of this rearrangement is that of tris(2-chloroethyl) phosphite, (**40**; R = $ClCH_2CH_2O$), best carried out in a high-boiling solvent (e.g. cumene at 150 °C)[72]; the product is di-2-chloroethyl (2-chloroethyl)phosphonate (**41**; R = $ClCH_2CH_2O$), particularly valuable in view of the ease with which it can be dehydrochlorinated to the corresponding diester of vinylphosphonic acid (Chapter 2, Section IV.D). Other examples have been noted, using halogenated phosphites derived from epichlorohydrin and PCl_3 or a dichlorophosphine[73], or oxirane and a dichlorophosphine[74–81]. The products from alkyl- or aryl-dichlorophosphines are the 2-chloroethyl esters of the (2-chloroethyl)alkyl(or aryl)phosphinic acids. 3-Chloropropyl phosphorus(III) esters are likewise obtained from phosphorus(III) halides and oxetanes (Scheme 2), two isomers, **42** and **43**, being theoretically obtainable from a 2-substituted oxetane. When heated, each of these esters is then capable of yielding a linear phosphorus(V) ester, **44** or **46**, together with a cyclic phosphorus(V) ester, **45** or **47**, the formation of which is accompanied by the elimination of a 1,3-dichloroalkane. Oxetane itself affords tris(3-chloropropyl) phosphite; this, when heated to 160 °C gives 70–80% of



(A) $R^1 = OCHR^2CH_2CH_2Cl$
(B) R^1 = alkyl or aryl
(C) $R^1 = OCH_2CH_2CHR^2Cl$
(D) R^1 = alkyl or aryl

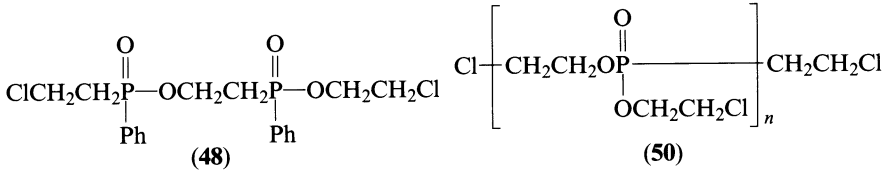
(**a**) $R^1 = OCHR^2CH_2CH_2Cl$, $R^2 = H$
(**b**) $R^1 = OCHR^2CH_2CH_2Cl$, $R^2 = Me$

SCHEME 2

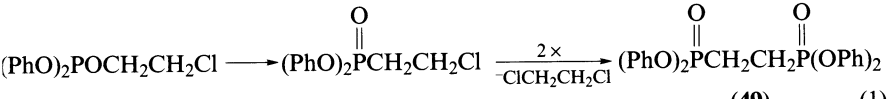
the bis(3-chloropropyl) (3-chloropropyl)phosphonate **44a** and 20–30% of the 1,2-oxaphospholane **45a/47a**[81]. The ester from 2-methyloxetane and PCl_3 is largely the isomer **42b** (R^2 = Me), obtained together with some **43b**. The products of the isomerization of **42a** at 150 °C are largely (64%) the 1,2-oxaphospholane **44b** together with some **45b**[81]. Alkyl- and phenyl-dichlorophosphines, leading to products with R^1 = Me, Et or Ph, behave in a similar fashion, but practical difficulties may be experienced in the separation of the final products[82,83].

The liberation of 1,2-dichloroethane during the isomerization of 2-chloroethyl esters of phosphorus(III) acids is of mechanistic interest and is coupled with the formation of oligomeric phosphonates and Gefter and Rogacheva[84] observed the formation of the compound **48** and liberation of 1,2-dichloroethane during the isomerization of bis(2-chloroethyl) phenylphosphonite. According to Kabachnik, after whom the rearrangement of chloroalkyl phosphorus(III) esters has been named, the action of heat on 2-chloroethyl

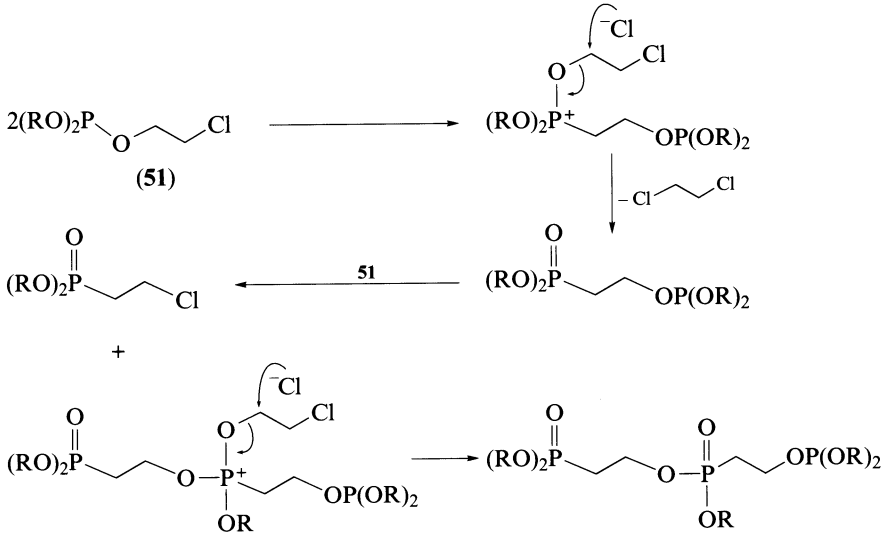
diphenyl phosphite initially yields diphenyl (2-chloroethyl)phosphonate followed by the tetraphenyl (1,2-ethanediyl)bisphosphonate **49** with the liberation of 1,2-dichloroethane (reaction 1).Gloede and Gross[85] observed the formation of the oligophosphonates **50** (n = 2–6) during the isomerization of tris(2-chloroethyl) phosphite and accounted for the liberation of 1,2-dichlorethane with a reaction mechanism, the initial stages of which are indicated in Scheme 3.



(48) **(50)**



(49) (1)

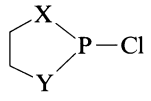


SCHEME 3

The course of isomerization of chloroalkyl alkylene (i.e. cyclic) phosphorus(III) esters is complex, being a function of ring size, the presence of substituents on carbon atoms, the nature of the ring hetero substituents (other than phosphorus), the chloroalkyl chain length and the experimental conditions. In general, 2-chloroethyl and 4-chlorobutyl esters require higher temperatures for the isomerization to occur than do 3-chloropropyl esters[86–88]. The isomerization of the corresponding bromoalkyl esters also occurs at a temperature lower than that required for the chloroalkyl analogue[89].

Mixtures of isomeric 2- or 3-chloroalkyl phosphorus(III) esters (**54**, major isomer); **55**, (minor isomer) are obtained when the cyclic phosphorus(III) chlorides **52** (X, Y = O, S or N-alkyl) react with oxiranes or oxetanes **53**. The isomers **55** do not isomerize when heated,

or do so at a much slower rate than do **54**, and are not considered further. The compounds **54** isomerize to **56** in a manner which is dependent upon the nature of X and Y. The 1,3,2-dioxaphospholane **57a** (R^1, R^2 = H or Me) isomerizes with complete ring retention yielding only the corresponding **58** (X = O)[86], and the ring is also retained for the ester **57b**[87], but for **57c** and **d** a mixture of the corresponding **58** (X = O) and the 1,2-oxaphospholane 2-oxide **59** (X = O) is obtained in relative amounts which depend on the temperature of the process; at temperatures up to 170 °C the main product is **59** (X = O), but thereafter the proportion of **58** (X = O) increases[87]. When $n = 2$, as in **57e** and **f**, the predominant reaction is that of ring opening to give the 1,2-oxaphosphorinane 2-oxide **60** (X = O), although it may be noted that **57g** behaves differently in that it gives the corresponding **58** (X = O)[88]. In the case of 1,3,2-oxazaphospholidines, the direction of isomerization is dependent on group A and the alkyl group on nitrogen as well as on R; thus, **61a** and **61b** isomerize with ring opening to give the corresponding **59** (X = N-alkyl), whilst **61c** and **d** isomerize with ring retention to **58** (X = N-alkyl). The compounds **61e** yield one or other type of product,



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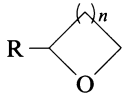

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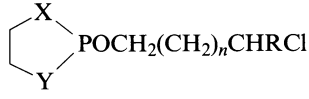
(54)



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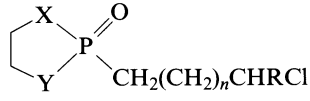
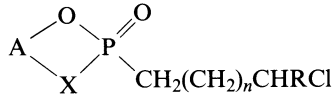


(56)

(57)

(**a**) A = R^1CHCHR^2, $n = 0$
(**b**) A = MeCHCHMe, $n = 1$
(**c**) A = $MeCHCH_2$, $n = 1$
(**d**) A = $(CH_2)_3$, $n = 1$
(**e**) A = $(CH_2)_3$, $n = 2$
(**f**) A = $MeCHCH_2$, $n = 2$
(**g**) A = MeCHCHMe, $n = 2$



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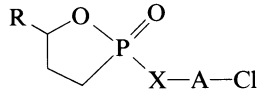

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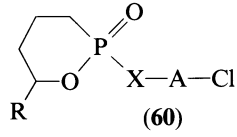

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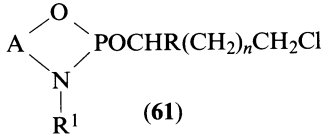
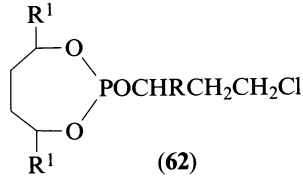


(61)

(a) A = CH_2CH_2, R = Me, R^1 = C_1–C_4
(b) A = CH_2CH_2, R = H, R^1 = Me
(c) A = MeCHCHMe, R = H or Me, R^1 = Me
(d) A = CH_2CH_2, R = H, R^1 = Bu
(e) A = CH_2CH_2, R = H, R^1 = Et, Pr^i or Bu^i

or a mixture, depending on the reaction conditions[90]. For the 1,3,2-dioxaphosphepanes **62**, ring retention is more important than ring opening when R^1 = H, but the reverse is true when R^1 = Me[91]. Finally, it has been found[92] that 1,3,2-thiazaphospholidines (**54**; X = S, Y = NMe) and 1,3,2-diazaphospholidines (**54**; X = Y = NMe) isomerize in the expected manner to give products with the ring intact, whereas 1,3,2-oxathiaphospholanes (**54**; X = O, Y = S) yield mixtures of products. The synthetic value of these rearrangements lies in the fact that, like those reactions outlined in Scheme 2, separation of the products is not always necessary prior to any further reaction; thus, when acted upon by PCl_5, both **58** (X = O, n = 1) and **59** (X = O) yield the identical phosphonic dichloride **63** (n = 1) or, if X = NMe, the product is the phosphonamidic chloride **64** (X =NMe)[88–90,92].



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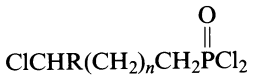

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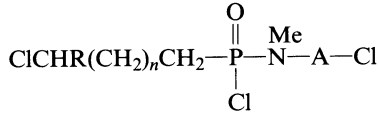
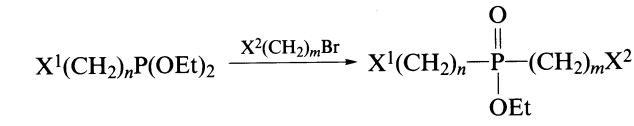


(64)

Esters of bis(ω-haloalkyl)phosphinic acids (**65**) are conveniently obtained through the use of an intermolecular Michaelis–Arbuzov reaction[93].



(65)

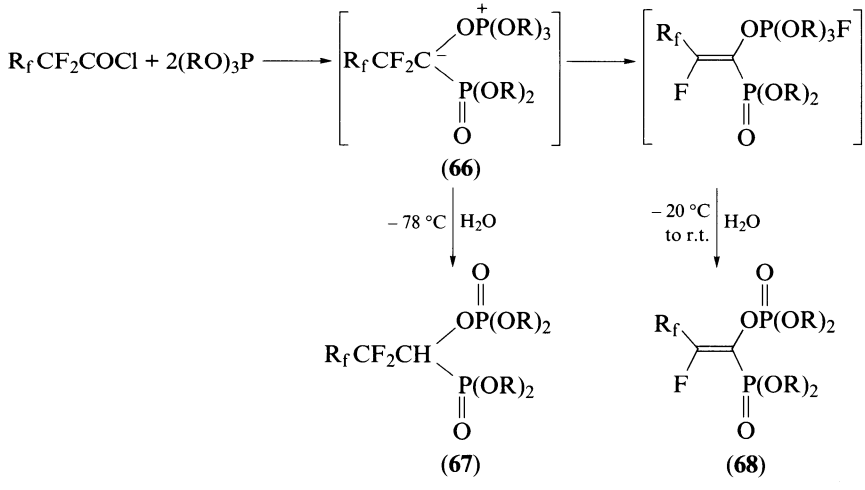
Other examples of modification in the Michaelis–Arbuzov reaction in the formation of phosphorus–carbon bonds in compounds other than esters are reactions between dichlorophosphites[94] or difluorophosphites[95] and organic halogen-containing compounds in the presence of iron(III) chloride (reactions 2 and 3). A similar reaction takes place with diethyl fluorophosphite[95]. A further variation is that of the photoinitiated reaction, a

$$Br_3CNCO + ROPCl_2 \longrightarrow Cl_2P(O)CBr_2NCO \quad (2)$$

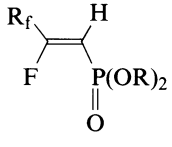
$$R^2OOCCCl_2CHClOR^1 + ROPF_2 \longrightarrow F_2P(O)CH(OR^1)CCl_2COOR^2 \quad (3)$$

technique operation satisfactorily when the normal procedure might fail; triethyl phosphite and trifluoroiodomethane under 350 nm radiation produce diethyl (trifluoromethyl)phosphonate in about 50% yield[37].

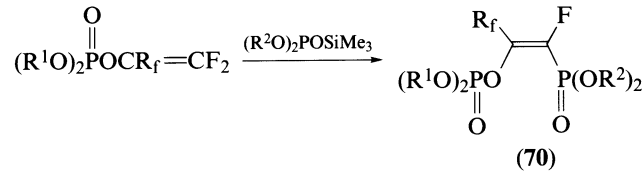
Although those Michaelis–Arbuzov reactions which involve acyl halides and phosphorus(III) esters are yet a further route to phosphorus–carbon bond formation and will be discussed later in Section VI, the use of halogenated acyl halides has led to some unusual results which, conveniently, can be summarized here. The products obtained from reactions between trialkyl phosphites and perfluoroacyl chlorides contain both phosphonate and phosphate moieties and are structurally dependent on reaction temperature. The initial product (Scheme 4) is thought to be the ylide **66**. In an ethereal solvent at low temperature, decomposition of the ylide yields [1-(dialkoxyphosphinoyl)oxy-1*H*-perfluoroalkyl]phosphonates (**67**) exclusively, but at –20 °C and above, and in the absence of a solvent, the products consist of (*Z*)-[1-(dialkoxyphosphinoyl)oxyperfluoroalkene]phosphonates (**68**)[96,97].The treatment of the compounds **67** with lda yields **68**, and the action of BuLi–CuI on **68** results in loss of the phosphate moiety to give the esters **69**[96,97] The structural isomers **70** of the compounds **68** have been obtained as illustrated in equation 4[98].



SCHEME 4



(**69**)



(4)

(70)

The Michaelis–Arbuzov and Michaelis–Becker reactions have both been used widely with monohaloalkanes as substrates, and the latter can sometimes offer certain advantages over the former. However, the Michaelis–Becker reaction has been applied only to a limited extent in the synthesis of esters of (haloalkyl)phosphonic and related acids since, by and large, it is less successful, partly as a result of the ease of replacement of the second halogen atom, and partly as the result of hydrogen halide elimination under the influence of the reagent. Sodium diethyl phosphite and dichloromethane afford tetraethyl methylenebisphosphonate in addition to diethyl (chloromethyl)phosphonate[99], and diiodomethane or dibromomethane each provides only methylenebisphosphonic ester[100,101], and although the dichloroalkanes $Cl(CH_2)_nCl$ (n = 2, 3 or 4) react with sodium phenylphosphinate with replacement of both chlorine atoms[102].

Greater separation of the two halogen atoms in dihalogenated substrates seems generally to increase the feasibility of replacing only one, as in the preparation of diethyl (4-iodobutyl)phosphonate using 1,4-diiodobutane[103], and dialkyl (3-bromopropyl)phosphonates from the dialkyl hydrogenphosphonate and 1,3-dibromopropane under phase-transfer conditions[104]. Selectivity in the site of reaction is also sometimes possible. In its reactions with sodium alkyl phenylphosphinates, it is the chloromethyl group of 2-chloroethyl chloromethyl ether which is selectively attacked, but with more of the sodium salt, halogen-free products can then be obtained[105]. Low yields of products identical with those obtained in Michaelis–Arbuzov reactions are isolable from reactions between sodium diethyl phosphite and 1,2-dichloroethyl alkyl ethers[106]. Successful applications of the procedure have been recorded more recently in reactions which, once again involve fluorine-containing halides. Thus, sodium dialkyl phosphites with FCH_2Br[107], $ClCH_2F$[108] or $CHClF_2$[109] yield dialkyl (fluoromethyl)- or (difluoromethyl)-phosphonates in moderate yields. The choice of dialkyl hydrogenphosphonate is sometimes critical, and the use of diisopropyl hydrogenphosphonate seems to have general advantages over other esters, for example in the preparation of an ester of (chlorofluoromethyl)phosphonic acid[109].

On the other hand, similar reactions with CF_2Cl_2[110,111], CF_3Br[111] or CBr_2F_2[33] lead directly to tetraalkyl (difluoromethylene)bisphosphonates. Reactions between sodium diethyl phosphite and $CFCl_3$ initially give diethyl (dichlorofluoromethyl)phosphonate in very low yield. The formation of methylenebisphosphonic acid esters from methylene dihalides has already been commented upon, and it is therefore not surprising that the formation of such esters also occurs with the polyhalomethanes just mentioned. The fact that the products are very often not the predicted ones is surprising. For instance, the reaction between sodium diethyl phosphite and $CFCl_3$[112], and those reactions between the initial monophosphonated species and an excess of metal phosphite, e.g. between diisopropyl (dibromofluoromethyl)phosphonate and sodium diisopropyl phosphite[33], or between sodium diethyl phosphite and diethyl (dichlorofluoromethyl)phosphonate[111], yield not the respective esters of (bromofluoromethylene)- or (chlorofluoromethylene)-bisphosphonic acids, but rather esters of (fluoromethylene)bisphosphonic acid; tetraalkylpyrophosphates are also isolable. In the same way (bromodifluoromethyl)phosphonic esters initially afford those of (difluoromethyl)phosphonic acid (high yields being isolable), but with an excess of metal phosphite, (difluoromethylene)bisphosphonic esters are obtainable in moderate to good yields[112]. This dehalogenation process is thought to occur through the loss of positive halogen.

Recorded examples of Michaelis–Becker reactions which involve haloalkenes are very few in number and tend to lead to halogen-free adducts considered earlier (Chapter 2, Section IV.B).

2. *From haloalkanes through the Kinnear–Perren–Clay reaction*

The application of this reaction to the preparation of non-functionalized phosphonic and phosphinic acid chlorides, involving the interaction of an alkyl halide with PCl_3 in the presence of $AlCl_3$, and its mechanism, have both been discussed in earlier (Chapter 2, Section II.C). In their experiments, Kinnear and Perren[113] included an examination of the behaviour of several di- and poly-halogen substrates; the resultant yields of (haloalkyl)-phosphonic dichlorides varied from 10 to 90%, being dependent on the substrate, and on the ratio of reactants, In the simplest cases, the dichlorides of (chloromethyl)- and (dichloromethyl)-phosphonic acids are best obtained from CH_2Cl_2 or $CHCl_3$ and although CCl_4 also gives an excellent yield of (trichloromethyl)phosphonic dichloride[114], an even better yield has been reported by the use of $CBrCl_3$. According to Maier[115], the formation of (2-chloroethyl)phosphonic dichloride, in low yield, from 1,2-dichloroethane is accompanied by even smaller amounts of the 1-chloroethyl isomer (ratio 87:13). In an alternative synthesis, the formation of (2-chloroethyl)phosphonic dichloride from bis(2-chloroethyl) (2-chloroethyl)phosphonate and PCl_5 is variable in its success. However, 1,1-dichloroethane did afford (1-chloroethyl)phosphonic dichloride in 100% purity using the Kinnear–Perrens procedure. Interestingly, (2-chloroethyl)phosphonic dichloride was also reported to be the product derivable in a similar way from 1,2-chlorofluoroethane, although in lower yield[113]. The yields of (α-chlorobenzyl)phosphonic dichloride from $PhCHCl_2$ and of (α,α-dichlorobenzyl)phosphonic dichloride from $PhCCl_3$ are also relatively poor. The use of 2,2-dichloropropane provided the dichloride of (1-chloro-1-methylethyl)phosphonic acid[116]. Isomerization within a carbon moiety may be an advantage or disadvantage; thus, 1,5-dichloropentane yields (4-chloro-1-methylbutyl)phosphonic dichloride[113]. The methodology has also been used to make halides of bromoalkylphosphonic acids; the combination of PBr_3, $CHBr_3$ and $AlBr_3$ yields derivatives of (dibromomethyl)phosphonic acid[117]. Equally, careful hydrolysis of the complex derived from aluminium chloride, an alkyl halide and a dichlorophosphine $RPCl_2$ affords a phosphinic chloride (e.g. $Me(Cl_3C)P(O)Cl$ from $MePCl_2$ and CCl_4) or esters on alcoholysis[118].

3. *By the oxidative phosphonation of haloalkanes*

In principle, the passage of oxygen through a mixture of an alkyl chloride and PCl_3 yields the phosphonic dichloride $RP(O)Cl_2$ through a free-radical process[119]. In practice, the reaction is non-selective and attack occurs at all points on a carbon chain, and the several products may be separable only with difficulty, if at all. For example, 1-chlorobutane affords all possible isomers of the chlorobutylphosphonic dichloride. Sometimes the yields are extremely small, e.g. 1,1-dichloroethane gives only 2% of (2,2-dichloroethyl)phosphonic dichloride; 1,1,1-trichloroethane gives a 'low' yield of (2,2,2-trichloroethyl)phosphonic dichloride, while other halides, e.g. iodobutane, fail to react[120]. Nevertheless, several haloalkylphosphonic dichlorides may be obtained in worthwhile yields using the procedure which, however, like all such oxidative phosphonations, is very wasteful in reagent.

4. *Through the use of organometallic reagents*

Some of the difficulties in the use of reactions between Grignard reagents and quinquevalent phosphorus ester-halides or amide-halides have been pointed out already (Chapter

2, Section II.H). The presence of further halogen atoms or other reactive sites in the reactants adds a further complicating feature. Diethyl phosphorochloridate reacts with several polyfluoroalkylmagnesium iodides to give diethyl (polyfluoroalkyl)phosphonates, which include the perfluorohexyl, the ω-chloroperfluoroalkyl series $Cl(CF_2)_n$ ($n = 4$, 6 or 8) and $FO_2S(CF_2)_2O(CF_2)_4$[121].

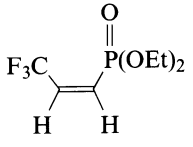
A single example for a recently reported reaction may well be a prelude to a reaction of wide applicability, and is conveniently included here. The interaction of dibutyl phosphorofluoridate and trimethyl(trifluoromethyl)silane give a 93% yield of dibutyl (trifluoromethyl)phosphonate, together with Me_3SiF[122].

5. *By the hydrophosphonation of halo-alkenes and -alkynes*

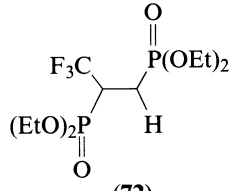
The addition of dialkyl hydrogenphosphonates to tetrafluoroethene occurs in the presence of di-*tert*-butyl peroxide to give the series of polyfluoroalkyl phosphonic diesters, $H(CF_2CF_2)_nP(O)(OR)_2$ (n = 1–3); the free acids with n = 1–5 and the corresponding phosphonic dichlorides with n = 1–9 have also been recorded[123].

The alkenes $ClFC{=}CX_2$ (X = Cl or F)[122] react with dialkyl hydrogenphosphonates, under the influence of γ-radiation, to give the phosphonic esters $(RO)_2P(O)CFClCHX_2$, the general order of reactivity being R = Pr > Et > Me.

Exposure to Co^{60} γ-radiation also catalyses the addition of hydrogenphosphonates and analogous phosphinates to polyfluoroalkenes, e.g. $ClFC{=}CX_2$ (X=Cl or F) to give the esters $(RO)_2P(O)CFClCHX_2$[124], and to $F_2C{=}CFCF_3$[125]. An earlier account seemed to indicate that hydrogenphosphonates do not add to $HC{\equiv}CCF_3$, but it has since been shown that the addition of a trace of triethylamine brings about a rapid exothermic addition which leads to **71** and **72**, albeit in low yields[126].



(**71**)



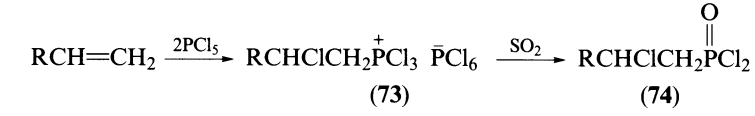
(**72**)

6. *By the chlorophosphonation of alkenes and alkynes*

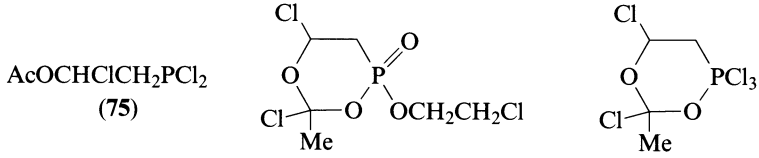
Two procedures are available for the dichlorophosphonation of alkenes and alkynes. The first of these, namely the use of PCl_3 and oxygen, has already been mentioned briefly in connection with reactions which involved phenylethene. The second procedure involves the interaction of an unsaturated hydrocarbon with PCl_5 and this, too, has been discussed to some extent in connection with those reactions which particularly involve arylethenes (Chapter 2, Sections III.A and VI.D).

The interaction of a alk-1-ene and phosphorus pentachloride to form a complex of the general composition $RCH{=}CH_2{\cdot}2PCl_5$, now recognized as having the phosphonium salt structure **73**, has been known for some time. Very many examples are now known of the decomposition of such complexes with SO_2 (or in some cases with P_4O_{10}[127]) under controlled conditions when the products are (2-chloroalkyl)phosphonic dichlorides (**74**) or derivatives thereof. The acids from but-1-ene[128] and pent-1-ene[127], hex-1-ene and hept-1-ene[129] and oct-1-ene and dec-1-ene[130] have all been reported. The stability of the initial adducts appears to very considerably, and dehydrochlorination may occur readily if the reaction is carried out with insufficient control. Vinyl and isopropenyl esters of carboxylic

acids yield the phosphonic dichlorides, $R^1COOCR^2CHClCH_2P(O)Cl_2$ (R^2 = H or Me) in high yields[131]. A further study of the reaction involving vinyl acetate itself with PCl_5 in PhMe–MeCN at –30 °C involved the decomposition of the intermediate with oxirane to give the phosphonous dichloride **75** and the 2,4-dioxaphosphorinane 2-oxide **76**, the latter possibly being obtained through the intermediate **77**[132].

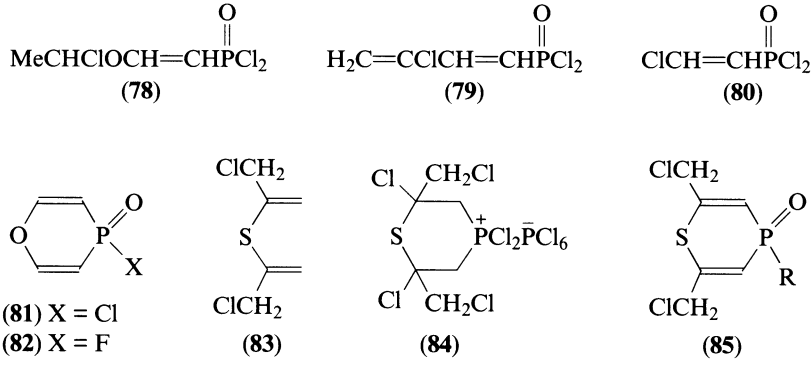


(73) (74)



(75) (76) (77)

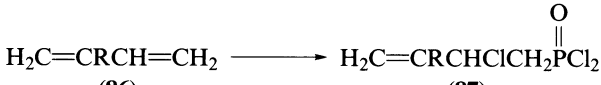
Divinyl ether itself presents a fairly complex case; one detailed study claimed that the decomposition of the ether–phosphorus pentachloride complex with SO_2 yields the phosphonic dichlorides **78–80** together with vinyl dichlorophosphate[133], whilst a more recent study[134] demonstrated that treatment of the intermediate complex with SO_2 yielded **81**, and with AsF_3 yielded **82**; in each case, a co-product was [2-(1-chloroethoxy)vinyl]phosphonic dichloride (**78**). The action of phosphorus pentachloride on the sulphide **83** presumably proceeds through **84**, although in the work-up procedures thus far adopted, dehydrohalogenation occurs to give **85** (R = Cl)[135].



(78) (79) (80)

(81) X = Cl
(82) X = F (83) (84) (85)

The reaction has been extended to include buta-1,3-dienes. Thus **86** affords the phosphonic dichlorides **87** (R = H or Me) (reaction carried out in benzene with decomposition of the complex by SO_2), apparently confirmed through ozonolysis to give formic acid[136,137]. Conflicting reports[138,139] suggest that the addition to buta-1,3-diene (but not isoprene) occurs in the presence of Ac_2O to give (4-chlorobut-2-enyl)phosphonic dichloride, a result



(86) (87)

apparently confirmed by the conversion of the dichloride into the corresponding diethyl ester, and a comparison of this with the ester obtainable by reaction between triethyl phosphite and 1,4-dichloro-2-butene.

Simple alkynes react under the usual conditions to give the (2-chloroalkenyl)phosphonic dichlorides **88** (R = Ph[140,141] and R′O(CH$_2$)$_4$[142], R′ = Ph or Et). The enynes **89** (R = H or Me) afford the phosphonic dichlorides **90** (R = H or Me)[143,144] but, once again, a conflicting report[145] suggests that the product from **89** (R = H) is (2,4-dichlorobut-2-enyl)phosphonic dichloride, recognized by the ability of the derived phosphonic diethyl ester to undergo a further Michaelis–Arbuzov reaction with triethyl phosphite. Other enynes react across the triple bond in the expected manner[146].

$$RC{\equiv}CH + PCl_5 \longrightarrow [complex] \longrightarrow RCCl{=}CHP(O)Cl_2$$
(88)

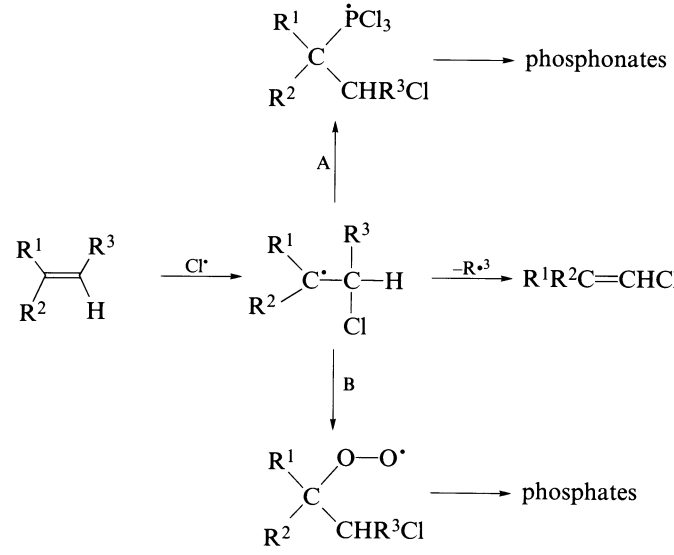
$$H_2C{=}CRC{\equiv}CH \longrightarrow H_2C{=}CRCCl{=}CHP(O)Cl_2$$
(89) **(90)**

The products from the interaction of an alkene and oxygen in the presence of a large excess of PCl_3 are chlorinated phosphonic dichlorides and phosphoryl dichlorides (chloroalkyl phosphorodichloridates). Although a large amount of PCl_3 is required for reasonable conversion of the alkene into phosphorus-containing compounds, the required amount does depend on the alkene substituents; for a terminal alkene and donor substituents, there should be a 3–5-fold molar excess of PCl_3, whereas a 5–10-fold excess is needed for an alkene which possesses electron acceptor groups, and a symmetrical alkene requires an even greater proportion of the trichloride[147]. It has long been recognized that the reaction is a radical process and that two types of phosphorus-containing products are formed, together with halogenated alkanes. A recent study has attempted to relate structural features of the alkene to the nature of the chlorophosphonation products

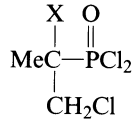
It has been suggested that two types of radical intermediate are formed (Scheme 5). Alkenes with donor groups tend to give rise to radical intermediates with nucleophilic character, which, in turn, (pathway A) lead to products which possess a P—C bond. Thus, propene, 2-methylpropene and 2-methylbut-2-ene yield mixtures of chloroalkylphosphonic dichlorides **91** (X = H or Me) and **92**, together with smaller quantities of chloroalkyl phosphorodichloridates, which are the products from electrophilic peroxidic radicals (pathway B). The phosphoryl dichlorides **93** (X = COOMe or CN) are the main products reached via pathway B for alkenes with electron-withdrawing groups, such as propenoic esters and nitrile[147]. The oxidative phosphonation of ethene with PCl_3–O_2 is an alternative procedure for the preparation of (2-chloroethyl)phosphonic dichloride (yield 38–40%)[148].

Similar reactions with haloalkenes lead to simultaneous halogenation at the C=C bond. Vinyl chloride reacts at –40 to –20 °C to give a 70% combined yield of (1,2-dichloroethyl)- and (2,2-dichloroethyl)-phosphonic dichlorides, which can be separated in an indirect fashion which results in the loss of the latter[149]. The reaction has also been applied to vinyl fluoride[150] and vinyl bromide[151]. Prop-2-enyl chloride gives a good yield of (2,3-dichloropropyl)phosphonic dichloride[149] and 1,2-dichloroethene yields (1,2,2-trichloroethyl)phosphonic dichloride[151]. Other halogenated alkenes, $H_2C{=}CHR$, where R is CCl_3 or C_nF_{2n+1} (n = 4, 6, 8 or 10), yield only the phosphorodichloridates RCH(CH$_2$Cl)OP(O)Cl$_2$[152].

The oxidative phosphonation of the 4-chloroalk-1-enes **94** (R^1 = H or Me; R^2 = Bu^t or Ph) yields mixtures of the phosphonic dichlorides **95** and **96** together with the chloroalkyl



SCHEME 5



(91)

(92)

(93)

phosphorodichloridates **97**, with **95** being the main product for **94a** and **b**. The chemoselectivity in the reaction is reduced by the presence of Ph or Bu^t groups; the presence of two bulky substituents on $C_{(4)}$ raises the regioselectivity of reaction[153–155].

$H_2C{=}CHCH_2CClR^1R^2$

(94)

(a) $R^1 = H$, $R^2 = Ph$
(b) $R^1 = Me$, $R^2 = Ph$
(c) $R^1 = Me$, $R^2 = Bu^t$

$ClCH_2CHCH_2CClR^1R^2$
$P(O)Cl_2$

(95)

$Cl_2P(O)CH_2CHClCH_2CHClR^1R^2$

(96)

$ClCH_2CHCH_2CClR^1R^2$
$OP(O)Cl_2$

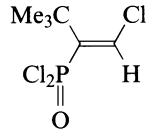
(97)

The chlorophosphonation of simple alkynes is said to give (2-chloroalk-1-enyl)phosphonic dichlorides[156]. The indications are, however, that certain acetylenes are rather unstable under the reaction conditions, and suffer cleavage between the sp and sp^3 carbon

atoms; thus, **98** yields *tert*-butylphosphonic dichloride together with **101** (the major product) and its *Z* isomer, and the chlorophosphonation of **99** similarly yields *tert*-butylphosphonic dichloride, methylphosphonic dichloride and **101** in the ratio 80:5:15[157]. A series of buta-1,3-dienes (**102**) has provided the (4-chlorobut-2-enyl)phosphonic dichlorides **103** together with small amounts of phosphates and chlorination by-products[158]. The enyne **100** follows the trend demonstrated by **98** and **99** in yielding *tert*-butylphosphonic dichloride admixed with other products; other enynes do not suffer such cleavage, but still provide product mixtures which demonstrate preferential chlorophosphonation at the triple bond[159]. The chlorophosphonation of 1,4-dichlorobut-2-yne yields 1,3,4-trichloro-2-dichlorophosphinylbut-2-ene[160].

$Me_3CC{\equiv}CR$

(**98**) R = H
(**99**) R = Me
(**100**) R = $CH{=}CH_2$



(**101**)

$R^1CH{=}C(R^2)C(R^3){=}CH_2$

(**102**)

$ClCHR^1C(R^2){=}C(R^3)CH_2P(O)Cl_2$

(**103**)

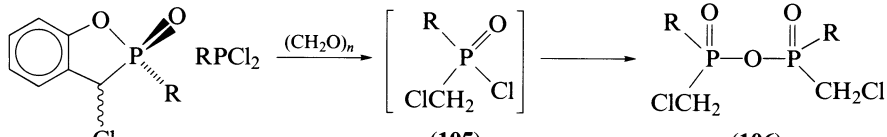
7. From phosphorus(III)halides and aldehydes or ketones

Observations during the early 1880s by Fossek on the preparation of (hydroxyalkyl)-phosphonic acids by the hydrolysis of the products from reactions between aldehydes and PCl_3 in the molar ratio 3:1 seemed to suggest an intermediate stage based on the corresponding (chloroalkyl)phosphonic acid, possibly as its bis(chloroalkyl) ester. Further work by Conant's group in the early 1920s led to the successful isolation of some (α-chloroalkyl)phosphonic acids following reaction of the products [presumably (hydroxyalkyl)phosphonic compounds] from aldehydes or ketones with PCl_3–acetic acid and the HCl liberated under the experimental conditions. Decomposition of the reaction product under aqueous conditions could give rise to (α-hydroxyalkyl)phosphonic acids (see Section III.A.3).Kabachnik and Shepeleva, during 1946–51, showed that an (α-chloroalkyl)phosphonic dichloride is the product when an aldehyde or ketone is heated with PCl_3 in a sealed vessel (i.e. under conditions where the initially liberated HCl could not escape and was therefore available for further reaction)[161]. Good yields of products could be obtained from aromatic aldehydes and ketones (with certain exceptions, e.g. those such as the nitrobenzaldehydes which might have oxidative properties under reaction conditions), but with the exception of formaldehyde, yields from aliphatic carbonyl compounds tended to be poor, possibly because of aldol-type condensations. Well established examples of the procedure include the formation, from PCl_3 and paraformaldehyde at 240 °C, of (chloromethyl)phosphonic dichloride, possibly via the phosphorus(III) derivative, $ClCH_2OPCl_2$, by an 'internal' Michaelis–Arbuzov reaction (which might in practice be an intermolecular process) followed by further reaction with the aldehyde[162]. Trichloroacetaldehyde is also an exception in the sense that it fails completely to react. Phosphonous dichlorides proceed to the phosphinic chlorides, $(ClCH_2)RP(O)Cl$, R = Et (36%) or Ph (47%)[163], R = CF_3 or C_2F_5[164]. Maier[165] also used the same procedure to convert $MePBr_2$ into $Me(BrCH_2)P(O)Br$ in 16% yield, and the use of PBr_3 with formaldehyde affords a very poor yield of (bromomethyl)-phosphonic dibromide[161]. Kabachnik and Shepeleva[161] also described the conversion of

chlorophosphite aryl esters, both cyclic and acyclic, into corresponding esters of the (1-chloroalkyl)phosphonic acid.

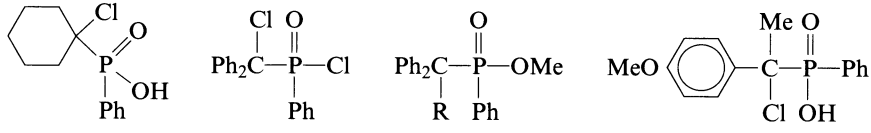
The product isolable from a reaction involving 2-hydroxybenzaldehyde consists of a stereoisomeric mixture of 2,3-dichloro-2,3-dihydro-1,2-benzoxaphosphole 2-oxide (**104**; R = Cl)[161,166,167], and the reaction allows ready access to other derivatives of this ring system.

Occasionally, a side reaction occurs which consists in the formation of anhydrides of the desired acid, for example those of the (chloromethyl)phosphinic acids **106** alongside that of the phosphinic chloride **105**[168]. The same process, presumably consisting in the interaction of acid and acid halide, occurs in the reaction between $BrCH_2PBr_2$ and formaldehyde to give bis(bromomethyl)phosphinic anhydride[169].



(104) **(105)** **(106)**

Reactions with certain ketones also proceed satisfactorily, although, in general, ArCOR or RCOR (R = alkyl, Ar = aryl) furnish complex mixtures of products[170], and reactions which involve acetone presumably proceed through mesityl oxide to give halogen-free main products (Chapter 2, Section II.G), and presumably similar reactions occur with other simple dialkyl ketones, On the other hand, $PhPCl_2$ and cyclohexanone afford **107** (42% yield) after hydrolysis of the acid chloride[170], and the (chloroalkyl)phosphinic chloride **108** has been isolated from reactions between benzophenone and PCl_3 in the presence of moist $AlCl_3$[171]. The corresponding methyl ester **109** (R = Cl) was obtainable through a Michaelis–Arbuzov reaction between $PhP(OMe)_2$ and Ph_2CCl_2, but could not be obtained by the direct halogenation of **109** (R = H)[171]. Acetic acid was used as the solvent for the reaction between $PhPCl_2$ and 4-methoxyphenyl methyl ketone, and X-ray analysis of the product confirmed the structure **110**[172].



(107) **(108)** **(109)** **(110)**

The formation of (α-chloroalkyl)phosphonic acids and of the corresponding (α-hydroxyalkyl)phosphonic acids in systems consisting of an aldehyde or ketone and PCl_3 are obviously interconnected. Such a system which has been extensively investigated is that comprising benzaldehyde and PCl_3 or another phosphorus(III) chloride[173–177]. Under the sealed-tube conditions employed, Kabachnik and Shepeleva[174] isolated and characterized one product as (α-chlorobenzyl)phosphonic dichloride. The exact mechanism of the interaction and the nature of the intermediates depend on the reaction conditions. Consistent with the general behaviour of aldehydes towards PCl_3 is the formation of bis(1-chloroalkyl) ethers and 1,1-dichlorohydrocarbons according to Scheme 6, and it is also known that *gem*-dichlorohydrocarbons react to form (α-chloroalkylphosphonic) dichlorides under Kinnear–Perren conditions. In a detailed study of the benzaldehyde–PCl_3 system over a wide range of temperatures, it was found that at around 70 °C a 92% yield of

$PhCHCl_2$ could be obtained; as the temperature was raised, the yield of this decreased, and there was an increase in yield of the (α-chlorobenzyl)phosphonic dichloride, which could reach 85% before isolation[175]. A variety of products are formed from benzaldehyde and $(PhO)_2PCl$ including the corresponding phosphorus(V) chloride and the compound **111**[177]. When the reaction conditions are changed, for example, by the inclusion of the solvent–reactant Ac_2O, isolation of (α-hydroxybenzyl)phosphonic acid becomes feasible (see Section III.3).

$$2RCHO \xrightarrow[-(POCl)_n]{PCl_3} (RCHCl)_2O \xrightarrow{-RCHO} RCHCl_2 \longrightarrow RCHClP(=O)Cl_2$$

SCHEME 6

$(PhO)_2P(=O)CHPhOCHClPh$

(111)

B. Syntheses Through Modification at Phosphorus in Compounds with Carbon–Phosphorus Bonds

1. By the oxidation of phosphorus(III) compounds

Although this methodology, in which phosphonous acid derivatives **112** give rise to those of phosphonic acids **113** (X = halogen, pseudohalogen, amino or ester group, Y = O, S or Se) and phosphinic acid derivatives **115** are similarly derived from those of phosphinous acids **114**, might in principle, be considered as being of such importance as to be almost ideal, there are practical drawbacks, particularly with a view to direct oxidation; sulphurization and selenation are manifestly easier from the experimental standpoint (Chapter 5). With oxidants under aqueous conditions, there is always the possibility of hydrolysis of the bonds to phosphorus. With many oxidants there is equally the possibility, under anhydrous conditions, of too vigorous a reaction which might result in the thermal decomposition of reactant or product. There is additionally the question of availability of the phosphorus(III) compound. Consequently, few phosphonic and phosphinic acid compounds are normally obtained in this manner.

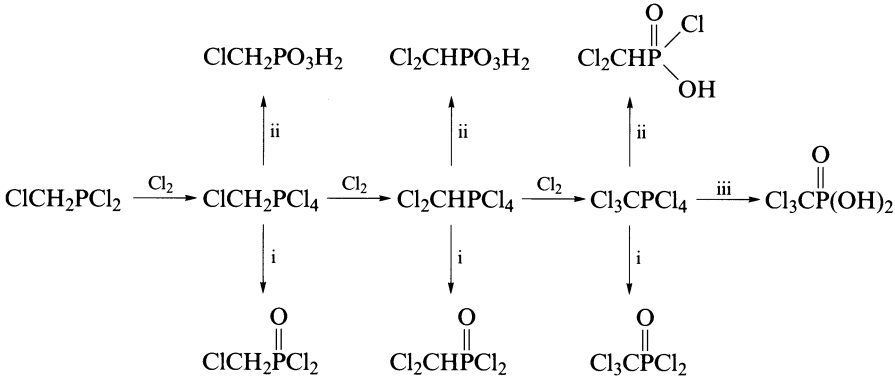
$RPX_2 \longrightarrow RP(=Y)X_2$ **(112)** **(113)**

$R_2PX \longrightarrow R_2P(=Y)X$ **(114)** **(115)**

One successful example is the preparation of (trifluoromethyl)phosphonic dichloride from the dichloro(trifluoromethyl)phosphine by oxidation with N_2O_4[178]. The interaction of tetraethyl pyrophosphite and polyhalogen compounds evidently proceeds through phosphorus(III) esters, subsequently oxidized by *tert*-butyl hydroperoxide to poly- or perfluoroalkyl phosphonic diesters[179,180]. Simultaneous hydrolysis and oxidation might be the outcome of choice; (trifluoromethyl)phosphonous and bis(trifluoromethyl)phosphinous chlorides and iodides are oxidatively hydrolysed (H_2O_2) to the corresponding phosphonic and phosphinic acids[181]. Hydrogen peroxide and $C_3F_7PCl_2$ afford (perfluoropropyl)phosphonic acid[182]. The oxidation of dialkyl (trifluoromethyl)phosphonites to the corresponding phosphonates has been performed with active MnO_2 or SeO_2.

2. *From phosphoranes or other phosphine derivatives*

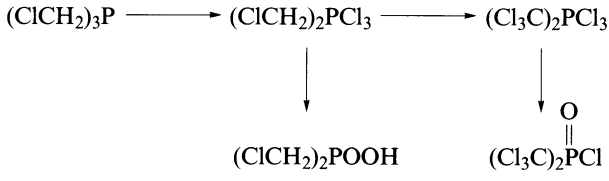
The reactions between the halophosphines **112** and **114** (X = Cl or Br, generally) and halogen, X_2, yields the phosphoranes RPX_4 and R_2PX_3. A useful feature of the chemistry of such compounds is their ease of conversion into phosphonic dihalides or phosphinic halides when treated with SO_2, and their ease of hydrolysis to the corresponding phosphonic and phosphinic acids. A range of polychloromethylphosphonic acids and acid chlorides have been prepared from dichloro(chloromethyl)phosphine using the sequence indicated in Scheme 7[183].



Reagents: i, SO_2; ii, H_2O; iii, dil. HCl

SCHEME 7

It is worth noting that the chlorination of tris(chloromethyl)phosphine (Scheme 8) results, at an intermediate stage, in cleavage of a P—C bond and formation of the phosphorane, $(CCl_3)_2PCl_3$, usable in the synthesis of bis(trichloromethyl)phosphinic acid and its acid chloride[184]. The use of SO_2 following addition of halogen (the reaction may be completed in one step from **112** or **114** by their treatment with SO_2Cl_2) thus offers an alternative, and indirect, procedure for the oxidation of halophosphines. The decomposition of $BrCH_2PBr_4$ with SO_2 likewise gives (bromomethyl)phosphonic dibromide[169]. The decomposition of tetrachlorophosphoranes can also be achieved through their treatment with alkyl nitrites when esters of (trichloromethyl)phosphonic acid are the products[183].

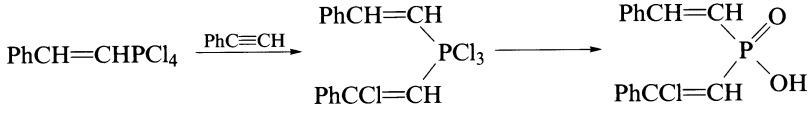


SCHEME 8

Hydrolysis of Cl_3CPCl_4 can proceed in a stepwise fashion depending on the medium; water allows hydrolysis to the half-way stage, $Cl_3CP(O)(OH)Cl$, whilst aqueous alkali results in complete hydrolysis to $Cl_3CPO_3H_2$[183,185], and $(Cl_3C)_2PCl_3$ is stable to boiling water and requires aqueous alkali for its decomposition[184,186]. On the other hand, the phosphorane $(C_3F_7)_2PCl_3$ is decomposed in water to give bis(perfluoropropyl)phosphinic acid[182]. The use of stronger hydrolysis agents may result in P—C bond cleavage. When acted upon

by aqueous NaOH, the phosphoranes $(C_nF_{2n+1})_3PF_2$ (n = 3 or 4) yield the (perfluoroalkyl)phosphonic acid $(C_nF_{2n+1})P(O)(OH)_2$[187]. (Trifluoromethyl)phosphonic difluoride has been obtained as a by-product in the preparation of F_3CPF_4 from F_3CPCl_4 and SbF_3[188].

The behaviour of tetrachlorophosphoranes resembles that of phosphorus pentachloride itself, in spite of fundamental differences in structure. The interaction of alkyl vinyl ethers, $R^1OCH{=}CH_2$, with R^2PCl_4 affords the phosphinic chlorides, $R^2(ClCH{=}CH)P(O)Cl$, by elimination of the ether alkyl group as R^1Cl[189,190], and tetrachloro(2-phenylethenyl)phosphorane adds to phenylacetylene to give the phosphorane **116**, hydrolysable to the phosphinic acid **117** (see Chapter 2, Section III.A)[191]. Bearing in mind that phosphorus pentachloride is ionic in both solution and the solid state, it is perhaps not surprising that mixing PCl_5 and Cl_3CPCl_4 which carries the electron-withdrawing CCl_3 group results in the formation of the trichlorophosphonium salt, $[Cl_3CPCl_3]^+PCl_6^-$, decomposable by either water or SO_2 to give (trichloromethyl)phosphonic dichloride[192]. This phosphonium salt is obviously closely related to the salts, $[RCCl_2PCl_3]^+PCl_6^-$, obtained by the action of PCl_5 on phosphonic dichlorides, $RP(O)Cl_2$, and which, with SO_2 yield the dichlorides of (1,1-dichloroalkyl)phosphonic acids[193,194]. The treatment of such complexes derived from (2-chloroalkyl)phosphonic dichlorides with AsF_3 provides (2-chloroalkyl)phosphonic difluorides[194]. It is also worth noting that the action of an excess of PCl_5 on phosphonic dichlorides can result in their complete decomposition by P—C bond cleavage[186,194].



(116) **(117)**

Tris(heptafluoropropyl)phosphine oxide undergoes methanolysis to yield methyl bis(heptafluoropropyl)phosphinate, but it should be noted that this itself, is, reactive as an alkylating agent, since with excess methanol it then affords MeOMe[195]. Other tris(perfluoroalkyl)phosphine oxides are also cleaved by nucleophiles, including ammonia or primary or secondary amines, to give complex mixtures based on the successive cleavage of one and two P—C bonds. It may also be noted that, when acted upon by dimethylamine, the phosphinic halide $(C_4F_9)_2P(O)F$ affords $(C_4F_9)(Me_2N)P(O)F$ as the main product[196].

C. Syntheses Through Modifications to Carbon Ligands

1. By replacement of hydroxy groups

Although there were early reports that phosphorus pentachloride converts (hydroxymethyl)phosphonic acid into (chloromethyl)phosphonic dichloride, it later became evident that an insufficiency of the reagent leads to the isolable tetrachloride **118**, which is convertible into (chloromethyl)phosphonic dichloride dichloride by the action of more PCl_5[197]. The esters **119** are similarly converted into $RCHClP(O)Cl_2$ when acted upon with sufficient PCl_5[198]. However, the same reagent leads to extensive dehydration of (1-hydroxycycloalkyl)phosphonic diesters, as occurred using SO_2Cl_2–pyridine[199]. In spite of an early report that the use of thionyl chloride was not satisfactory, $SOCl_2$–pyridine has now been

(118)

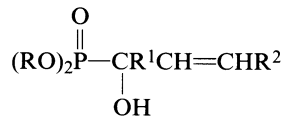
(119)

deemed a satisfactory reagent for the conversion of dialkyl (1-hydroxyalkyl)phosphonates into the corresponding dialkyl (1-chloroalkyl)phosphonates[200].

Phosphorus pentachloride has been reported on extensively as a reagent for the conversion of bis(hydroxymethyl)phosphinic acid and its homologues into bis(1-chloroalkyl)-phosphinic chlorides[186,201–203]; the principle reaction is accompanied by some P—C bond cleavage and formation of (chloromethyl)phosphonic dichloride, the proportion of which increases with increasing reaction temperature. At 95–100 °C further reaction between (chloromethyl)phosphonic dichloride and excess PCl_5 produces CCl_4, $POCl_3$, PCl_3 and HCl, all of these also being formed, in addition to Cl_3CPCl_2, when bis(chloromethyl)phosphinic chloride is similarly treated[186]. A reaction between bis(hydroxymethyl)phosphinic acid and PBr_5 yields only ca 8% of bis(bromomethyl)phosphinic bromide[169].

The use of triphenylphosphine in combination with CX_4 (X = Cl[204] or Br[205]) or Ph_3PBr_2–pyridine in MeCN[205] converts (1-hydroxyalkyl)phosphonic diesters into those of (1-chloroalkyl)- or (1-bromoalkyl)-phosphonic acids, respectively. The transformation of (α-hydroxybenzyl)phosphonic diesters into the (α-fluorobenzyl)phosphonic esters by diethylaminosulphur trifluoride (dast) with commencement of reaction at –78 °C seems now to be a standard practice[105,206]. The same reagent may be used to convert (1-hydroxy-2-alkynyl)phosphonic diesters into the corresponding 1-fluoro compounds, and thence by hydrogenolysis into *cis*-(1-fluoroalk-2-enyl)phosphonic diesters, with no cleavage of the C—F bond[207]. An even more novel reagent which has been used for the same purpose is Et_2NCF_2CHFCl[208]. The stability of the P—C bond in hydroxyalkyl-phosphonic and -phosphinic acids to hydrogen halides, even under aqueous conditions, allows the use of, for example, 57% aqueous HI with red phosphorus to obtain (iodomethyl)phosphonic acid from (hydroxymethyl)phosphonic acid[209], and HCl gas in known to bring about a similar conversion into the corresponding (1-chloroalkyl) acids.

Allylic rearrangements are observed when the esters **120** are treated with $SOCl_2$ to give the (3-chloroalk-1-enyl)phosphonic esters **121**[210,211], but the similar treatment of the esters **122** affords the corresponding (3-chloroalk-1-enyl)phosphonic diesters, without rearrangement, although accompanied by some dehydration products if the group R^3 is a fragment of more than two carbon atoms[212]



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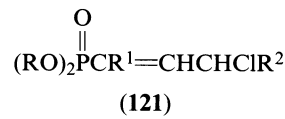

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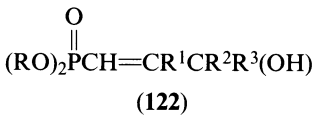
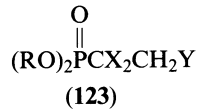


(122)

2. By direct halogenation at carbon

Bromination at the 1-position in alkylphosphonic diesters has been achieved using nbs–dibenzoyl peroxide[213], or at the α-hydrogen in a benzylphosphinic ester using bromine[214], whilst the esters **123** (X = H, Y = CN, COOEt or COOMe) react with 1,3-dibromo-5,5-dimethylhydantion to give the corresponding **121** (X = Br)[215]. (Dihalomethylene)bisphosphonic and related acid esters are formed from the parent ester through reaction with NaOCl[216–218], NaOBr[216–218] and AcOF[219]. The direct monohalogena-

tion of methylenebisphosphonic esters appears not to be feasible, and the (monohalomethylene)bisphosphonic esters have generally been obtained by the dehalogenation of a dihalo compound using Na_2SO_3 or $SnCl_2$[216–218] or KF or KOH in MeCN in the presence of 18-crown-6 ethers[220]; the same series of halogenation/dehalogenation reactions has been carried out on triethyl phosphonoacetate[221]. (1-Cyclohexenyl)phosphonic diesters (**124**; R^1 = H) are chlorinated or brominated in the α-allylic position by ncs or nbs with very high yields[199]. Chlorine gas and SO_2Cl_2 have been widely adopted for the chlorination of (2-oxoalkyl)phosphonic diesters in the α-position[222–224].



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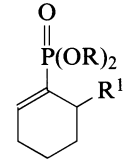
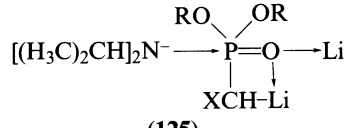


(124)

3. *From phosphorylated carbanions*

The use of a phosphoryl carbanion may be more appropriate than the neutral substrate, particularly in reactions which involve reagents of low electrophilicity. Thus, the carbanions $(RO)_2P(O)CH^-R'$ [R′ = H[106], $S(O)_n$SPh (*n* = 1 or 2)[225] and $P(O)(OR)_2$[226]] have been monofluorinated using perchloryl fluoride; under the correct conditions, the fluorination becomes continuable to the difluorinated stage. More recently, *N*-fluoroimides have come to be regarded as the reagents of choice, eliminating the potential dangers in the use of perchloryl fluoride. Of such imides, $(R^2SO_2)_2NF$, with either $R^2 = CF_3$[227] or R^2 = Ph[228], have been employed. Other reagents, e.g. XeF_2 or *N*-fluorocollidinium triflate, tend to give poor yields of fluorinated products. Chlorination of phosphoryl carbanions has been achieved using $PhSO_2Cl$[229] or CCl_4 or derivatives of trichloroacetic acid[230,231].

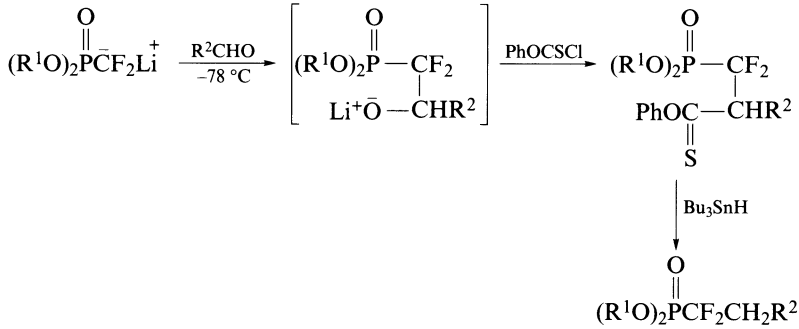
In addition to the use of phosphoryl carbanions as substrates for the introduction of halogen atoms, the halogen-containing phosphoryl carbanions may be modified in the carbon skeleton. Most of the earlier interest in the generation of halogen-containing phosphorylated carbanions not surprisingly concentrated on the use of lithium bases, but the exact composition of the base is of some importance. In the alkylation of carbanions from (chloromethylene)bisphosphonic esters, not only is the nature of the ester alkyl group influential (yields of alkylated products being much less from the tetramethyl or tetraethyl esters than from the tetraisopropyl ester), but P—C bond cleavage is observable when BuLi is used as base, although the extent of this is less when Bu^t Li is employed, and the use of TlOEt is advantageous[232,233]. Butyllithium continues to be used for general purposes in spite of demonstrations that the anions derived using Li-amide bases, $LiNR_2$, appear to be more stable[234]. Lda has been widely used in the generation of the carbanions from esters of (fluoromethyl)- and (difluoromethyl)-phosphonic acids[105,106] for subsequent alkylation or acylation, and their greater stability over that of the corresponding ion generated from BuLi in an ethereal solvent (and which can decompose quite rapidly even at –50 °C) is attributed to the stabilization (1 h at –10 to 0 °C) represented in the formula **125**[234]. The



(125)

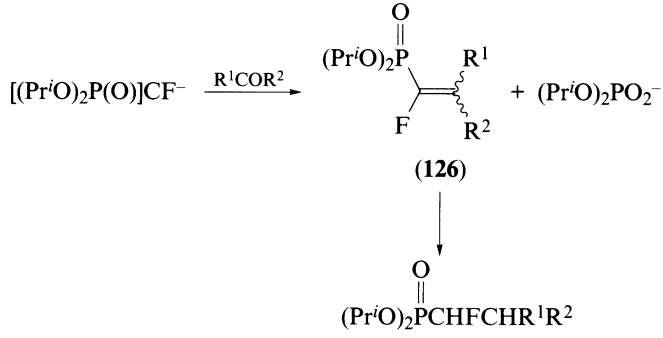
stability of a halogenated phosphoryl carbanion also depends on the individual halogens; the carbanions prepared using lda appear to have stabilities in the order $CHF^- > CF_2^- > CFCl^-$[106].

Diethyl (difluorolithiomethyl)phosphonate is proving valuable for the preparation of homologous (1,1-difluoroalkyl)phosphonic derivatives, either by direct alkylation[235] or by acylation, using PhOC(S)Cl, of the product from the interaction of the phosphorylated carbanion and an aldehyde, and the subsequent treatment of the resultant diethyl [(1,1-difluoro-2-phenoxythiocarbonyloxy)alkyl]phosphonate with Bu_3SnH (Scheme 9)[236].



SCHEME 9

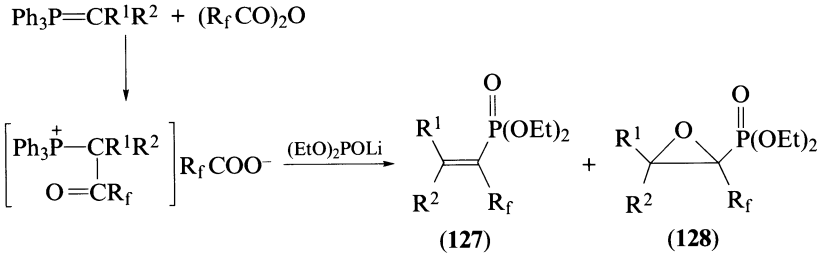
Yet another way to obtain a 1-monohalogenated alkylphosphonic diester is based on the application of the Wadsworth–Emmons adaptation of the Wittig reaction (Scheme 10). Here, the anion from tetraisopropyl (fluoromethyl)bisphosphonate reacts with a carbonyl compound to give the (1-fluoroalk-1-enyl)phosphonic esters **126** as an *E*–*Z* mixture (80–95: 20–5); hydrogenolysis of these mixtures yields (1-fluoroalkyl)phosphonic esters[237]. In a review of the literature[238], the authors pointed out the widely different results experienced by other workers in their attempts to alkylate carbanions derived from fluorinated alkylphosphonic diesters and, as a result of their own work, advocated the use of alkyl triflates, which appear to react with lithiated carbanions very quickly and cleanly.



SCHEME 10

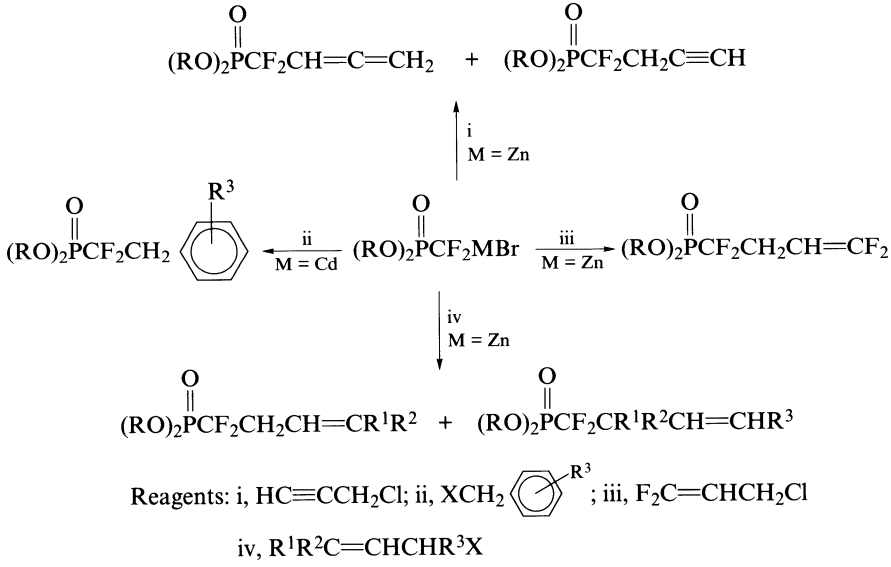
Scheme 11 indicates the usefulness of salts derived from Wittig ylide reagents and anhydrides of perfluorocarboxylic acids in the synthesis of fluorinated alkenylphosphonic diesters (**127**), often together with (epoxyalkyl)phosphonic diesters (**128**)(R_f = CF_3 or

C_2F_5); the reaction is useful for the preparation of the unsaturated phosphonic diester **127** [R^1 R^2 = $(CH_2)_4$], when the epoxide, is not formed, but in other cases, the latter tend to be in excess[239].



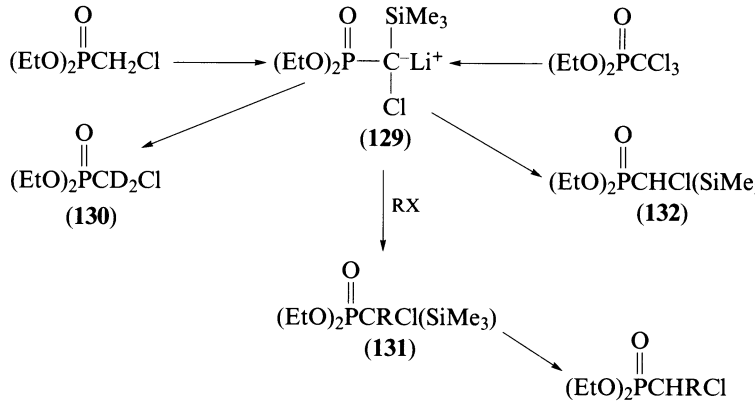
SCHEME 11

The zinc[27,240] and cadmium reagents[241,242] $(RO)_2P(O)CF_2MBr$ have also proved useful as alkylation substrates for particularly reactive species, e.g. allylic, benzylic or propargylic halides; with the last type, some rearrangement to allenic compounds is observed. Scheme 12 illustrates the use of such reagents in the synthesis of α-fluorinated alkylphosphonic acid derivatives.



SCHEME 12

Both diethyl (chloromethyl)phosphonate and diethyl (trichloromethyl)phosphonate, when treated with chlorotrimethylsilane (Scheme 13) followed by BuLi, generate the species **129**, evident from the regeneration of diethyl (chloromethyl)phosphonate under aqueous conditions, and the observed formation of **130**. The alkylation of **129** leads to **131** which, in the presence of EtO^-, loses the silyl group, while the treatment of **129** with formic acid leads to another reactive silicon-containing species, **132**[243]. Loss of chlorine from the



SCHEME 13

lithiated carbanion from (dichloromethyl)phosphonic diethyl ester has been observed during acylation[244,245].

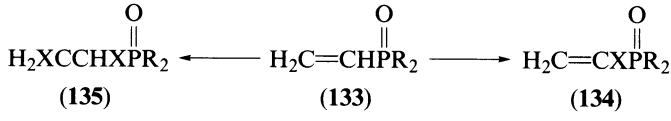
4. *From acylphosphonates*

Two fairly recently announced procedures allow the synthesis of fluorinated phosphonic esters from acylphosphonic diesters. In the first of these, aroylphosphonic diesters are treated with dast reagent at room temperature and in the absence of a solvent, when the products are dialkyl (α,α-difluorobenzyl)phosphonates[246].

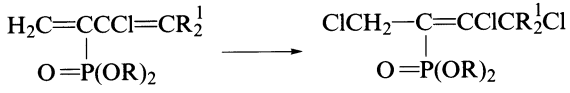
In the second procedure, the dehydration of dialkyl [(perfluoroacyl)methyl]phosphonates (through their enol forms) with trifluoromethanesulphonic anhydride–R_3N leads to dialkyl (perfluoroalk-1-ynyl)phosphonates[247].

5. *By modification through addition reactions*

Early reports on the addition of chlorine or bromine to diethyl vinylphosphonate (**133**; R = EtO)[248] and to vinylphosphonic dichloride (**133**; R = Cl)[249] suggest a lack of predictability even in such simple cases. The addition of bromine in chloroform to **133** (R = EtO) leads to **134** with smaller amounts of **135**; chlorination of the same ester in CCl_4 also leads to a mixture of the two types, in this case in roughly equal amounts. On the other hand, the bromination of vinylphosphonic dichloride yields (1,2-dibromoethyl)phosphonic dichloride (**135**; R = Cl, X = Br), which is sufficiently stable to allow hydrolysis to (1,2-dibromoethyl)phosphonic acid. The ready loss of HBr followed the addition of 2 mol of bromine to phenyl(4-phenylbuta-1,3-dienyl)phosphinic acid; the product consisted almost exclusively of $Ph(PhC_4H_3Br_3)PO_2H$[250].

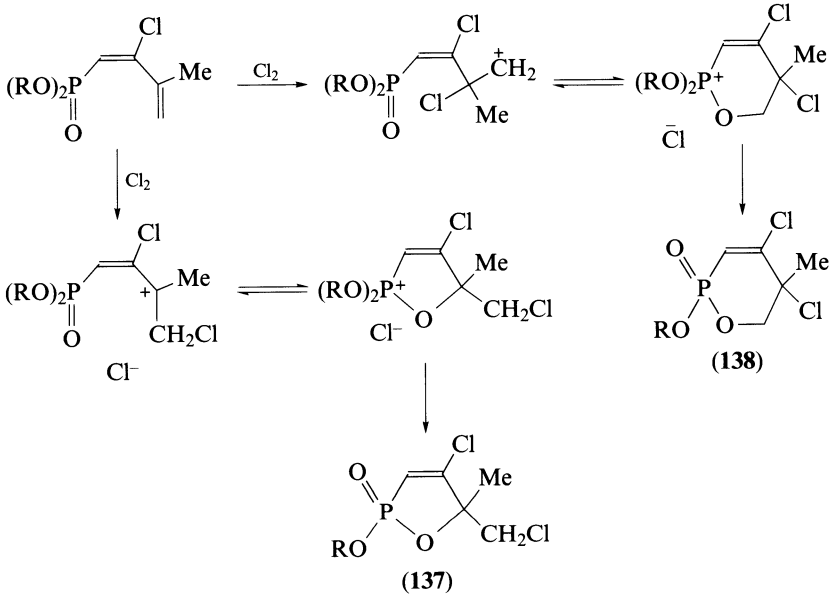


The chlorination of (3-chlorobuta-1,3-dien-2-yl)phosphonic diesters (**136**) proceeds by 1,4-addition, the products being identical with those derived from the phosphonic dichlo-



(136)

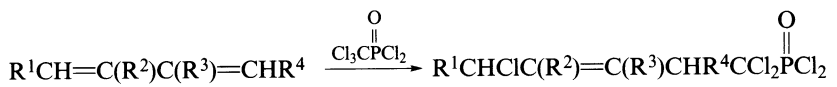
ride obtained through the oxidative dichlorophosphonation of 1,4-dichlorobut-2-yne. However, the chlorination or bromination of certain other buta-1,3-dienes can take a different course. The formation of linear products is observed when the diene has *E* geometry, and (*Z*)-(buta-1,3-dienyl)phosphonic diesters tend to give 2,5-dihydro-1,2-oxaphospholes (**137**)(Scheme 14) or dihydro-2*H*-1,2-oxaphosphorins (**138**), either singly or as a mixture[251–253].



(137) (138)

SCHEME 14

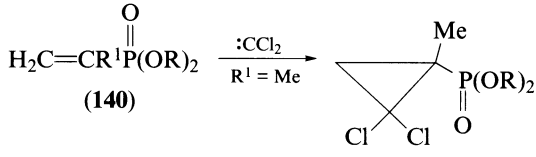
Yet another form of addition reaction is that of (trichloromethyl)phosphonic dichloride, as a consequence of its highly polarized C–Cl bonds, to buta-1,3-dienes in the presence of CuCl; addition is 1,4, with the formation of (1,1,5-trichloropent-3-enyl)phosphonic dichlorides (**139**) as *Z*–*E* mixtures[254].



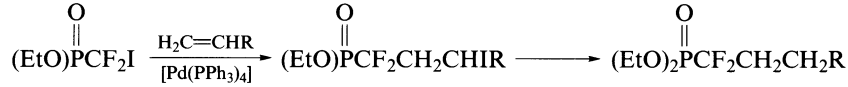
(139)

The classical addition of a dihalocarbene to an alkene to form a *gem*-dihalocyclopropane has been adapted to the formation of halogenated cyclopropylphosphonic diesters. A brief description[255] indicated fundamental differences in behaviour towards dichlorocarbene of esters of ethenylphosphonic acid (**140**; R^1 = H) when the products are

dialkyl (3,3,3-trichloropropyl)phosphonates, whereas for **140** (R^1 = Me) the product is **141** (R^1 = Me, X = Cl). This unusual behaviour of dichlorocarbene towards esters of vinylphosphonic acid has also been demonstrated for reactions in two-phase systems, and yet dibromocarbene reacted in the expected manner to give **141** (R^1 = H, X = Br). A further interesting and confusing feature is the expected course of addition of dichlorocarbene when the latter is generated from sodium trichloroacetate. On the other hand, both dichlorocarbene and dibromocarbene react with dialkyl (prop-2-enyl)phosphonates to give the expected dialkyl [(2,2-dihalocyclopropyl)methyl]phosphonates[256]. Free radical addition of perfluoroalkyl iodides, R_fI, to the carbon–carbon double bond in diethyl (prop-2-enyl)phosphonate occurs in a two-phase system containing $Na_2S_2O_4$; the products are the esters **142**[257].



(140) **(141)**



(143)

(142)

The addition to terminal alkenes of diethyl (difluoroiodomethyl)phosphonate fails to occur in the absence of any catalyst, and is very slow in the presence of copper powder (15 mol%) at 70–90 °C, although the yields are then good (75%) for hex-1-ene, for example, but are accompanied by 15–20% of diethyl (difluoromethyl)phosphonate. When the catalyst is is $[Pd(Ph_3P)_4]$, the reaction occurs, often at room temperature, with yields at least as good if not better[258]. In a more recently announced procedure, diethyl (bromodifluoromethyl)phosphonate is employed in a reaction initiated by a cobalt(III)–zinc redox system containing bromo(pyridine)cobaloxime and zinc powder under ethanol, the mixtures being stirred for several days at ambient temperature[259]. Both of the esters series, **142** and **143**, can be de-iodinated by their treatment with Zn–$NiCl_2$. A variety of functional groups in the alkene (R = alkyl, Me_3Si, hydroxyalkyl, $MeCOCH_2CH_2$, $EtOOCCHMeCH_2$) tolerate the metal-catalysed reaction conditions in the formation of the esters **143**.

III. HYDROXY-PHOSPHONIC AND -PHOSPHINIC ACIDS

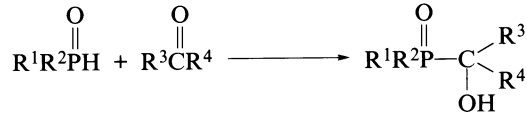
The remarkable ease with which (α-hydroxyalkyl)phosphonic acids and analogous phosphinic acids are produced through a very simple procedure engendered much early interest in these acids, all the more because of the extraordinary ease with which these acids could be returned to their precursors through cleavage at the phosphorus–carbon bond under mild conditions. Less readily available and, as a consequence, less extensively examined, but nevertheless more important from the viewpoint of their potential biochemical

role, are those relatively few acids which possess one or more hydroxyl groups at positions other than, or in addition to, the α-carbon atom.

A. Syntheses of α-Hydroxy Acids and Their Derivatives Through Phosphorus–Carbon Bond Formation

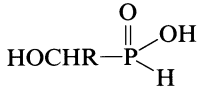
1. From monocarbonyl compounds and hydrogenphosphonates or related compounds

The most important reaction for the formation of those acids carrying the hydroxy group on an α-carbon atom consists in the addition of compounds possessing the P(O)H moiety across the carbonyl group (1,2-addition) of an aldehyde or ketone (reaction 5)—the so-called Abramov reaction[260].

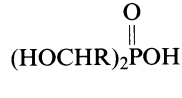


(5)

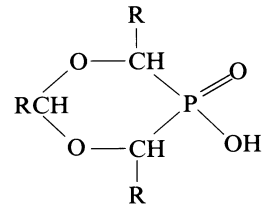
In the simplest form of the Abramov reaction, the phosphorus-containing reactant is hypophosphorous acid (phosphinic acid) or an ester thereof, and in the reactions between the acid and formaldehyde[261] or benzaldehyde[261,262] the initial product is the phosphinic acid **144** (R = H or Ph.). However, the reaction can proceed further to give the bis(1-hydroxyalkyl)phosphinic acid (**145**; R = H or Ph); the latter (R = Ph) reacts readily with yet more benzaldehyde to give its benzylidene derivative, 5-hydroxy-2,4,6-triphenyl-1,3,5-dioxaphosphorinane 5-oxide (**146**; R = Ph)[262]. When acted on by a second mole of cyclohexanone in the presence of acetyl chloride, (1-hydroxycyclohexyl)phosphinic acid (**147**) gives the novel phosphinic chloride **148**, characterized as the free acid **149** following ready hydrolysis[263]. A reaction between a phosphinic acid (**150**) and a second (non-identical) carbonyl compound leads to an unsymmetrical phosphinic acid (**151**)[264]. Esters of symmetrical 1,1′-dihydroxy-substituted phosphinic acids are preparable from hypophosphite esters, $H_2P(O)OR$[265].



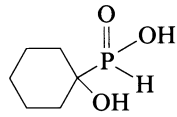
(**144**)



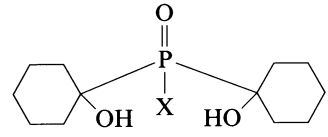
(**145**)



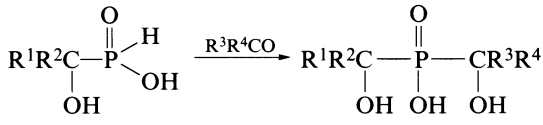
(**146**)



(**147**)

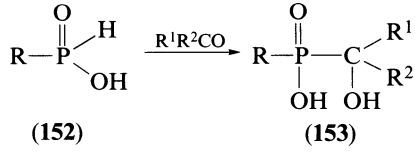


(**148**) X = Cl
(**149**) X = OH

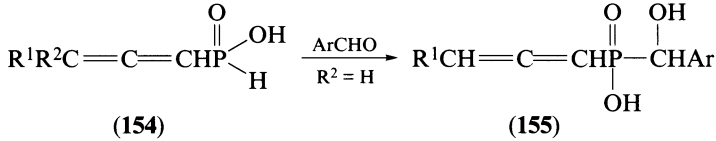


(150) (151)

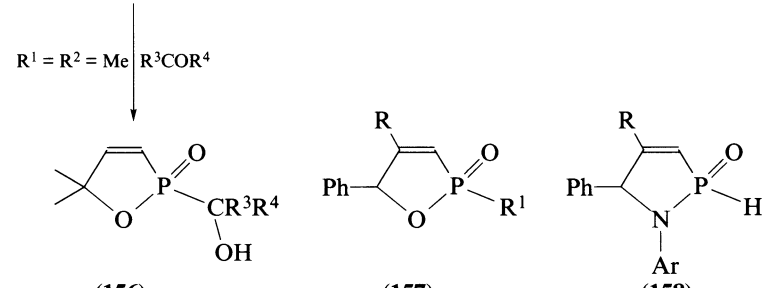
Other simple phosphinic acids (phosphonous acids) **152** react with simple carbonyl compounds, in the absence of a catalyst at room temperature, or on slight warming, to give the acids **153** (R = alkyl[266–271], alkynyl[272] or aryl[269,271,273–276]). The carbonyl reactants have here included esters of α-oxo acids[270–272,275,276] and diesters of (1-oxoalkyl)phosphonic acids (but see later for complications which may ensue)[275,276]. Allenylphosphinic acids present an interesting case; whilst phosphinic acids **154** in which the γ-carbon position is unsubstituted, or at most only monosubstituted, react with (aromatic) aldehydes to yield the expected unsymmetrical hydroxyphosphinic acids (**155**)[277], the addition of (aliphatic)aldehydes or ketones to (3-methylbuta-1,2-dienyl)phosphinic acid (**154**; $R^1 = R^2 = Me$) results in products which sequentially cyclize and dehydrate to give the 2,5-dihydro-1,2-oxaphosph(V)oles (**156**; e.g. $R^3 = H$, $R^4 = CCl_3$; $R^3 = R^4 = Me$)[278–280]. In reactions between hypophosphorous acid and the cinnamaldehydes PhCH=CRCHO, the addition step is also followed by cyclization and further steps to give the dihydro-1,2-oxaphosph(V)oles **157** [R^1 = PhCH=CRCH(OH)][281]. The 1,2-azaphospholines **158** result from the interaction of an aromatic amine with the initial adducts from the aforementioned cinnamaldehydes and hypophosphorous acid. A final step, in which compounds **158** may react with more aldehyde or ketone[282], is paralleled by that which involves the carbonyl compound and the 2-amino-1,3,4,2,-oxadiazaphosph(III)oles (**159**), via their phosphorus(V) tautomers, to give the (α-hydroxyalkyl)phosphonimidic amide derivatives (**160**)[283].



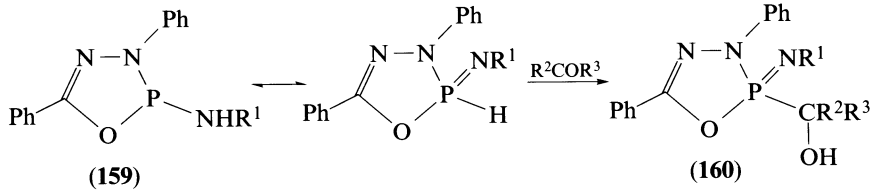
(152) (153)



(154) (155)

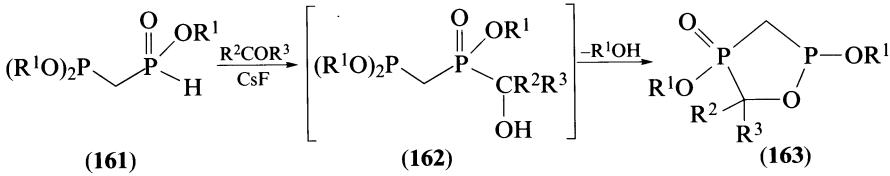


(156) (157) (158)

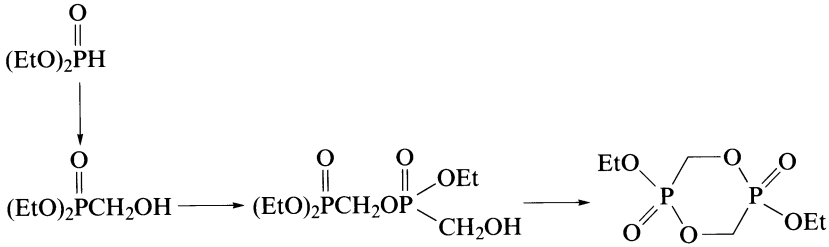


(159) (160)

The hydroxyalkylphosphinic esters **162** are unstable and readily cyclize to 1,2,4-oxadiphospholanes (**163**) which, consequently, are the products from the interaction of **161** and aldehydes or ketones[284]. (Hydroxymethyl)phosphonic acid was originally synthesized from PCl_3 and paraformaldehyde by Page in 1912, and bis(hydroxymethyl)phosphinic acid by the hydrolysis of tetrakis(hydroxymethyl)phosphonium chloride by Hoffman in 1930. In more recently described syntheses of both of these compounds, phosphorous acid (phosphonic acid) has been used as the phosphorus source[285]. Full details have been provided for the preparation of diethyl (hydroxymethyl)phosphonate and its 2-tetrahydropyranyl ether from diethyl hydrogenphosphonate and formaldehyde[286]. When the initial reaction is carried out in the presence of sodium methoxide, other products may be detected and, indeed, are isolable; amongst them are **164** and the 1,4,2,5-dioxadiphosph(V)orinane **165**[287]. The reactions which occur between dialkyl hydrogenphosphonates and aldehydes or ketones were originally investigated by Abramov, and the literature is replete with variations on this theme[288].In general, however, such reactions tend to be less vigorous than those involving phosphinous acids, very often requiring the presence of a basic catalyst (alkoxide ion generally, but sometimes a tertiary amine), also sometimes aided by heat, although even then the reactions can sometimes be sluggish.



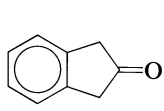
(161) (162) (163)



(164) (165)

In the many recorded examples of the reaction, and because of its very nature, reports have tended to concentrate on compounds derived from a range of simple carbonyl compounds and a single (or at most two) dialkyl[289–294], diaryl[295] or diheteroaryl[296] hydrogenphosphonate or, alternatively, on combinations of a selection of hydrogenphosphonates with a relatively few carbonyl compounds, including propanal[297], benzenoid aldehydes[294–301], furan and thiophene aldehydes[302], 3-formylindole[303], 2- and 3-formylchromones[304,305], diethyl oxomalonate[306] and others[307–309]. It is worthy of comment that

whilst the ketones **166**[310] and **167**[311] yield the expected 1:1 adducts, the diones **168** (R = H[311] and Me[312]) give rise only to 1:1 adducts, which are relatively unstable.



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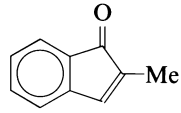
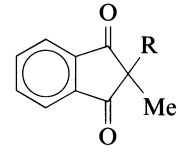


(167)



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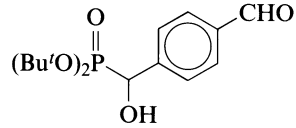
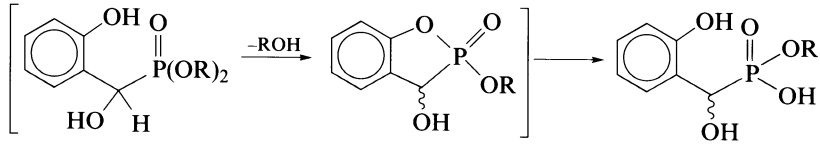


(169)

The use of trichloroacetaldehyde is also to be particularly noted. Although reactions between this aldehyde and various dialkyl hydrogenphosphonates have been reported[269,274,294,295], it is the dimethyl ester of (1-hydroxy-2,2,2-trichloroethyl)phosphonic acid which has received particular attention, and which has been studied widely from the structural point of view in the light of its commercial importance as the powerful insecticide dipterex (also known as trichlorphon and chlorophos)[313–317]. Polyfluoroalkyl esters of the related alkyl(1-hydroxy-2,2,2-trichloroethyl)phosphinic acids have been prepared by the unusual combination of chloral hydrate and the bis(polyfluoroalkyl) alkylphosphonite ester[318].

In the light of the ease of dealkylation of di-*tert*-butyl esters of quinquevalent phosphorus acids, either thermally or under acid catalysis, the reaction between di-*tert*-butyl hydrogenphosphonate and 4-(diethoxymethyl)benzaldehyde has been employed to yield, after deprotection of the *para* substituent, the (α-hydroxybenzyl)phosphonic diester **169**, useful for classical development at the aldehyde group[300,301].

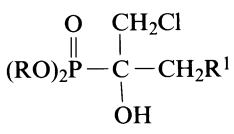
The Abramov reaction proceeds normally with polycyclic aromatic aldehydes[319] but of other, monocyclic, benzenoid aldehydes, the behaviour of 2-hydroxybenzaldehyde is anomalous; here, the reaction product **172** is evidently formed by hydrolysis of the dihydrobenzo-1,2-oxaphosph(V)ole **171**, in turn the result of the expulsion of 1 mol of the alcohol ROH from the initial 1:1 adduct **170**[320].



(170) **(171)** **(172)**

The addition of hydrogenphosphonates to chloroketones, and also to other mono halogenated carbonyl compounds, is aided by the presence of Al_2O_3, yields of 78–96% being achievable[321]. However, reactions between dialkyl or diphenyl hydrogenphosphonates and chloroacetone[294,295,322–324], *sym*-dichloroacetone[294,295,324] or *asym*-dichloroacetone[324] do occur in the absence of a catalyst when mixtures of reactants are heated to 100–120 °C; the products are the phosphonates **173** (R^1 = H or Cl). Aryl trichloromethyl ketones are monodechlorinated by the action of trialkyl phosphites or dialkyl hydrogenphosphonates[325], and both further dechlorination[326] and the formation of phosphate esters[327] have been

reported for ω,ω-dichloroacetophenones. A particularly unusual case is that of the reactions which involve 7,7-dichlorobicyclo[3.2.0]hept-2-en-6-one (**174**); the products from acyclic dialkyl hydrogenphosphonates in the presence of Et_3N catalyst have the structure **175**, and it is only with cyclic hydrogenphosphonates that the expected hydroxy derivatives, e.g. **176** (R = H or Me), are formed[328].



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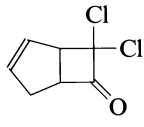

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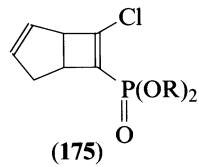

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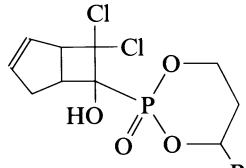
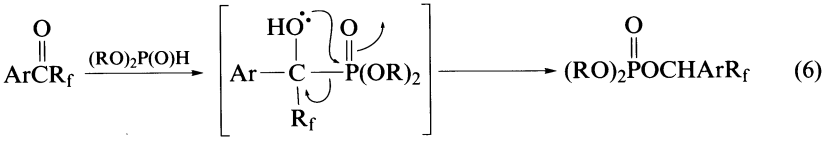


(176)

The mode of addition of hydrogenphosphonates to fluorinated ketones can also be complex. The addition of dialkyl, diphenyl or bis(trimethylsilyl) hydrogenphosphonates to methyl trifluoromethyl ketones occurs in the expected manner[329], but this contrasts with the behaviour of aryl perfluoralkyl ketones in the presence of triethylamine at room temperature, when the products, obtained even under such mild conditions, are phosphate esters (reaction 6), a situation which represents lack of stability of the hydroxyphosphonate rather than novelty of the reaction[330]; under identical conditions, the corresponding alkyl aryl ketones fail to react. The same reaction with mixed-halogen ketones is still more involved, and the nature of the products depends on the reaction conditions; if these are of a mild nature, and with catalysis by triethylamine or pyridine (depending on the particular ketone), the product is the expected (hydroxyalkyl)phosphonate **177**, whereas with



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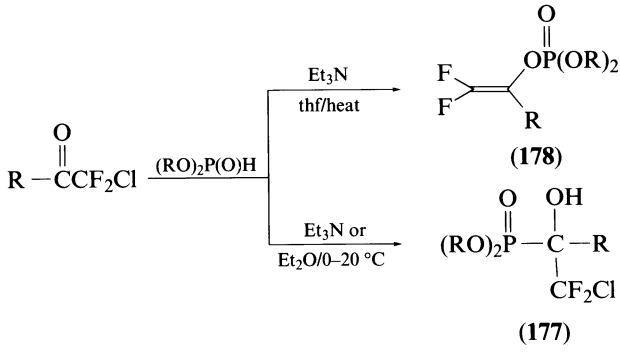
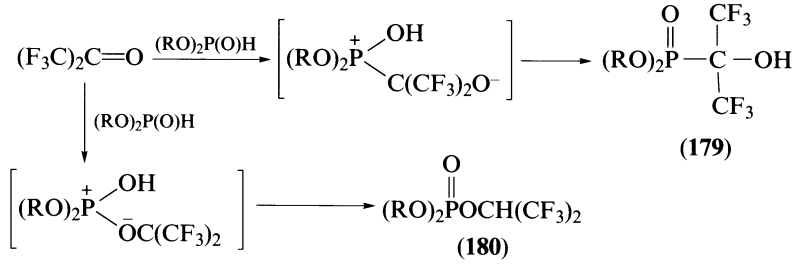


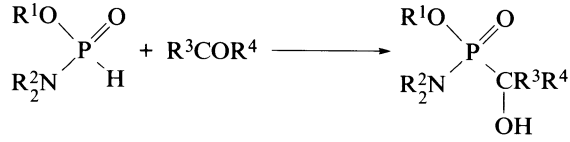
(178)

(177)

triethylamine in boiling thf, the ethenyl phosphate **178** is obtained directly. In the absence of a basic catalyst, the slow reaction yields a mixture of **177** and **178**. The use of sodium dialkyl phosphite leads to mainly phosphate. A further complicating feature is the dependence of the product on catalyst; when R^1 = Ph, the use of pyridine leads, mainly, to **177**, whereas with triethylamine it is mainly **178**[331]. Reactions between hydrogenphosphonates and hexafluoroacetone give mixtures of hydroxyphosphonate (**179**; $R^1 = R^2$ = Me or Me_3Si, $R^1R^2 = CMe_2CMe_2$) and phosphate (**180**; $R^1 = R^2$ =Et or Ph; $R^1 = Me_3Si$, R^2 = Me, Et, or Me_3Si; $R^1R^2 = CMe_2CMe_2$) through direct attack at either the carbon or oxygen of the carbonyl group, the product proportions being dependent on the experimental conditions[332].



Because of the increased electron input to phosphorus from nitrogen, an increase in reactivity towards carbonyl compounds is to be expected for reactions between the latter and phosphonic amides (reaction 7), and such expectations are fulfilled[333].

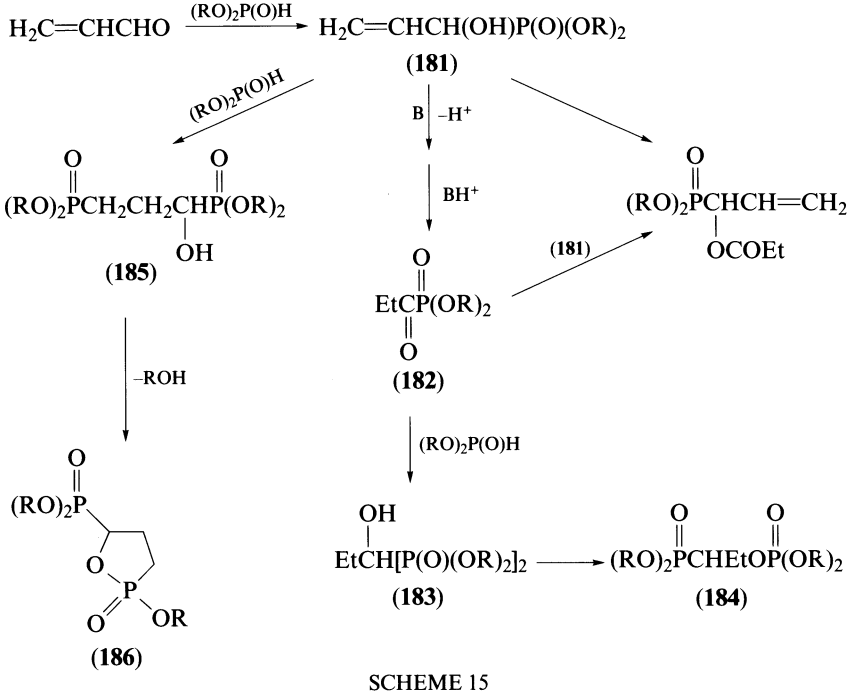


(7)

Experimental conditions and substituents of sp^2 carbon govern reactions between α,β-unsaturated aldehydes or ketones and dialkyl hydrogenphosphonates. Summaries of the field have been presented[287,334], as also has an extensive compilation of reactions and products[335].

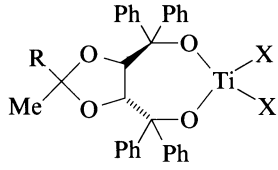
For α,β-unsaturated aldehydes, RCH=CHCHO (R = Me, Ph, 2-furanyl)[321,336], the reactions are catalysed by traces of the sodium phosphite salt, and occur regioselectively across the carbonyl group, although for propenal itself regioselectivity is lacking and the sequence of reactions is more involved; a summary of the reactions observed for propenal is given in Scheme 15. Depending on the relative amounts of hydrogenphosphonate and its sodium salt, various products can be detected and most are isolable; they include the expected (1-hydroxyprop-2-enyl)phosphonate (**181**), which, through loss followed by re-addition of a proton, provides the (1-oxopropyl)phosphonic diester **182**, and the well known acylating properties of (1-oxoalkyl)phosphonic acids and their derivatives account for the formation of the propanoyl derivative of **181**. In a further sequence, the reactants combine to form the (1-hydroxypropylidene)bisphosphonic tetraalkyl ester **183**, known to undergo rearrangement to the phosphate **184**. Addition of the hydrogenphosphonate also occurs at C=C to afford the esters **185** which, when distilled, cyclize with loss of ROH to give the phosphorylated 1,2-oxaphosph(V)olanes **186**.

In most instances the Abramov reaction generates an α-substituted chiral centre, but all syntheses have been considered to lead to the racemic product. Various (α-hydroxyalkyl)phosphonic acids have been resolved through salts of a monoalkyl ester with, for



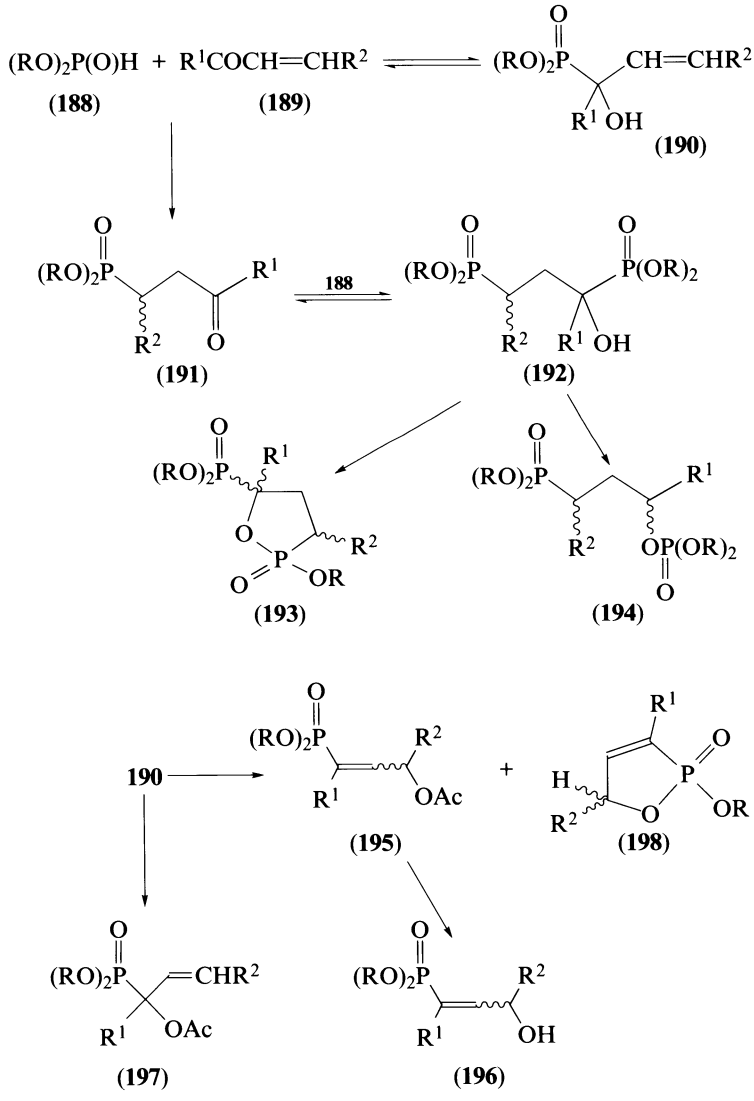
SCHEME 15

instance, ephedrine or 1-phenylethylamine[337,338]. However, it is interesting that low enantioselectivity (10–20%) has been observed in reactions based on *ortho*-substituted benzaldehydes[339]. Some enantioselectivity has also been achieved through the use of a chiral catalyst. The reaction between dimethyl hydrogenphosphonate and 3-phenylpropenal in the presence of 10 mol% of a catalyst consisting of a combination of $LaCl_3$ and dilithium (*R*)-binaphthoxide in thf at –70 °C yields an optically active product whose properties are consistent with a 41% enantiomeric excess of the *S*-form of dimethyl (1-hydroxy-3-phenylprop-2-enyl)phosphonate[340]. The same catalyst was employed for reactions which involved aromatic aldehydes; the products (with yields greater than 90%) were obtained with enantiomeric excesses dependent on the electronic nature of the substituent in the *para* position, and were as high as 82% for the 4-MeO group[341]. Some success has been achieved in the use of chiral catalysts based on chiral titanium alkoxides. In a reaction between benzaldehyde and diethyl hydrogenphosphonate in the presence of $Ti(OPr^i)_4$, racemic diethyl (α-hydroxybenzyl)phosphonate was obtained in 87% yield. In the presence of the catalyst **187** (R = Me or Ph; X = OPr^i), the same product is obtained in 75% yield but with an optical activity corresponding to a 53% e.e.[342].



(187)

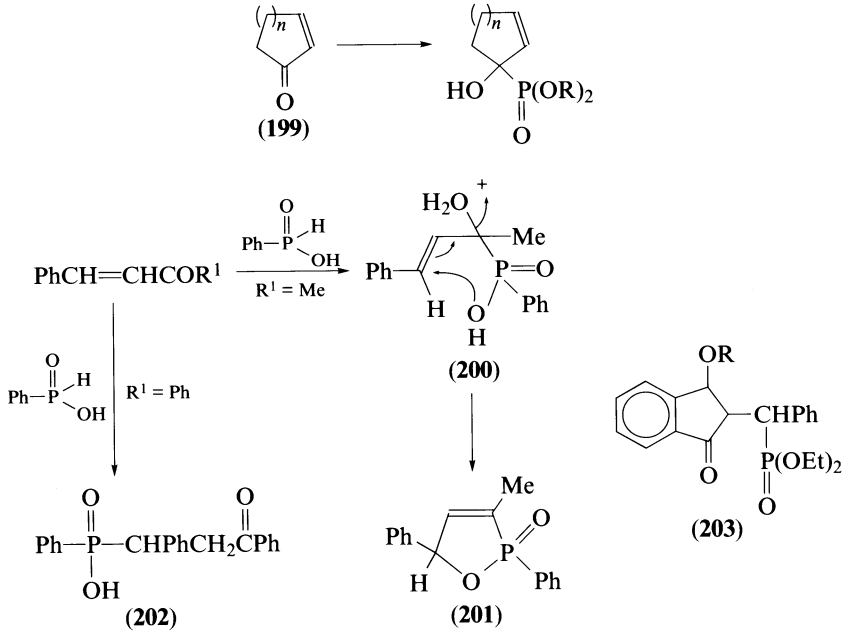
Reactions of hydrogenphosphonates with the α,β-unsaturated carbonyl compounds **189**, both aldehydes and ketones, proceed regioselectively and in high yield, in the presence of KF but with alkoxide or amine catalysis the regioselectivity may be catalyst dependent. Thus, a reaction between dimethyl hydrogenphosphonate and benzalacetone in the presence of diethylamine proceeds by 1,2-addition to give the α-hydroxy adduct, whereas the use of sodium methoxide as catalyst results in 1,4-addition to give dimethyl (3-oxo-1-phenylbutyl)phosphonate. In other cases, the course of the reaction may depend on the amount of added base, with the addition proceeding under either kinetic control to give 1,2-addition, or thermodynamic control to give 1,4-adducts. Treatment of the ketones **189** [R^1, R^2 = H, Me, or Ph; $R^1R^2 = (CH_2)_n$, n = 2, 3 or 4] with **188** (R = Me) in diethyl ether at



–35 °C gives the [1-hydroxy-2-(cyclo)alkenyl]phosphonates **190** in 70–88% yields; 5α-cholest-1-en-3-one gives 76% of a mixture of the $C_{(3)}$ α- and β-epimeric adducts in the ratio 6:1, separable chromatographically. Acetylation of the products **190** (R^1, R^2 = H) gives the γ-acetyloxy compounds **195** and the 1,2-oxaphosph(V)olene **198**, sometimes accompanied by the isomers **197** which, depending on experimental conditions, may become equally important to or more important than **195**[345]. The isomerization of dialkyl (1-acetyloxyprop-2-enyl)phosphonates into dialkyl (3-acetyloxyprop-1-enyl)phosphonates has been shown to occur also in the presence of Pd(0)[344]. No rearrangement occurs during the alcoholysis of **195** with MeONa in MeOH to give the γ-hydroxy adducts **196**[343].

An alkoxide–catalysed reaction between an unsaturated ketone and two equivalents of **188** (R = Me) gives **192** by way of the thermodynamically controlled (20–40 °C) initial formation of **191**. Depending on R^1 and R^2, further transformations of **192** lead to either **193**, as a diastereoisomeric mixture, or **194**, the latter an example of a product from a facile phosphonate–phosphate transformation[345].

A further study, by the same workers, using the cyclic enones **199** (*n* = 1 or 2) showed that the addition occurs regioselectively across the carbonyl group[346]. The addition of phenylphosphonous acid (through its tautomeric phosphinic acid form) to **189** (R^1 = Me, R^2 = Ph) occurs in boiling benzene to give the dihydro-1,2-oxa-4-phosph(V)olene **201** (R^2 = Me), produced by acid-catalysed cyclization within **200**. When R^1 = Ph, a linear product (**202**) is the result of 1,4-addition, and is again accompanied by the product **201** (R^2 = Ph) of the cyclization of the 1,2-adduct[347].

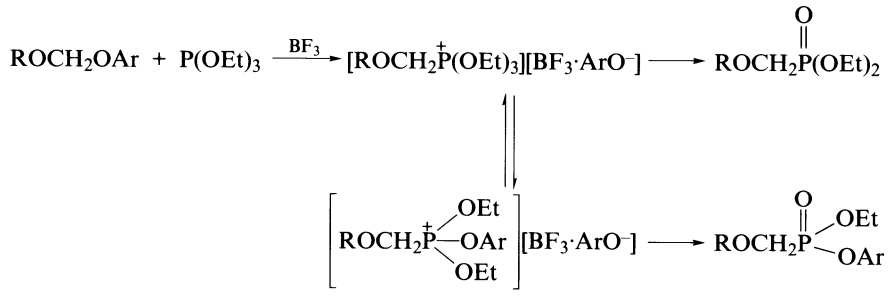


In the reactions between diethyl hydrogenphosphonate and indantrione or 2-benzylideneindan-1,3-dione, the former substrate yields phosphate adducts,but in the latter case, addition affords the phosphonate **203**[348]. The additions of hydrogenphosphonic diesters to propynal and ethynyl methyl ketone[268], and to the ketones RC≡CCOMe (R = Me or Ph)[349], give 1,2-adducts.

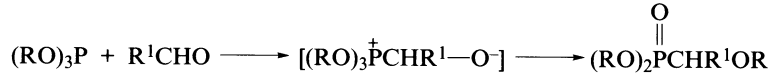
2. From monocarbonyl compounds or their derivatives and phosphorus(III) anhydrides or triesters

Simple derivatives of (α-hydroxyalkyl)phosphonic and analogous acids have been obtained directly by procedures analogous to those adopted for the parent compounds. Thus, *O*-acetates of (2,2,2-trichloro-1-hydroxyethyl)phosphonic acid esters have been prepared through the interaction of the appropriate halogenated acetaldehyde and phosphorous–acetic acid anhydrides[350–353]. An aromatic aldehyde and dialkyl phosphoroisocyanatidite in the presence of water or an alcohol yields analogous *O*-carbamoyl derivatives of (α-hydroxybenzyl)phosphonic diesters, probably through cyclic intermediates[354].

Alkyl ethers of dialkyl (hydroxymethyl)phosphonic acid have been obtained by a modified Arbuzov procedure: in the presence of $BF_3{\cdot}Et_2O$, triethyl phosphite reacts with the formals $ROCH_2OAr$ according to Scheme 16[355]; the reactions are best carried out in the presence of $TiCl_4$ at –78 °C, but the Lewis acid catalyst and the experimental conditions have to be chosen carefully, otherwise mixed alkyl aryl esters are produced. Boron trifluoride etherate also catalyses the interaction of acetals of 4-substituted benzaldehydes with triethyl phosphite to give diethyl (α-alkoxybenzyl)phosphonates[356]. Both aliphatic and aromatic aldehydes are reported to react with trialkyl phosphites at 100 °C to give the ethers **204**[357].



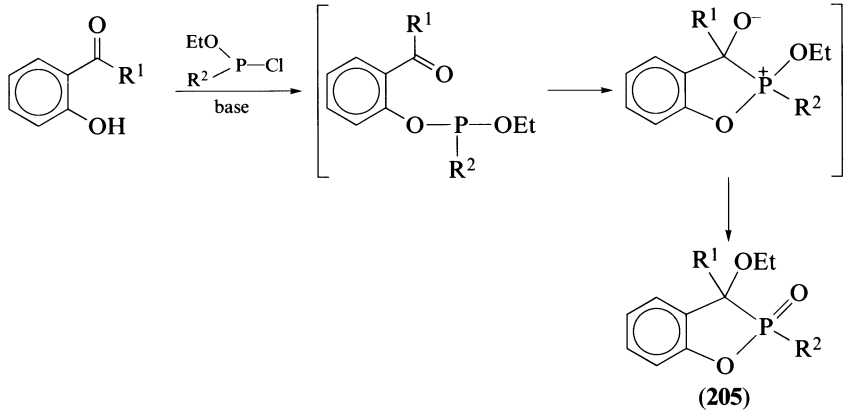
SCHEME 16



(204)

Simple aliphatic aldehydes are also said to yield products which contain the equivalent of 2–3 mol of RCHO per phosphorus atom, some of which have been shown to have an oxyphosphorane structure. (For an introductory account of this fascinating area of phosphorus chemistry, the reader should consult early reviews by Ramirez[358,359].) The phosphite ester obtained from 2-hydroxybenzaldehyde and diethyl chlorophosphite cyclizes with rearrangement to the 1,2-benzoxaphosph(V)ole derivative **205** (R^1 = H, R^2 = EtO), and a similar process was observed in the case of phosphites and phosphonites derived from 2-hydroxyacetophenone to give **205** (R^1 = Me)[360].

The useful reaction which involves a phosphorus(III) ester amide (presumably more reactive than an ester) is based on catalysis with $BF_3{\cdot}Et_2O$– LiI in thf and at low temperature. Under these conditions a mixture of the cyclic phosphoramidite **206** and an aldehyde leads to a diastereoisomeric mixture of (1-hydroxyalkyl)phosphonic amides (**207a** and **b**); the former of these (of (1′ *R*) configuration) exceeds that of latter, sometimes by as much



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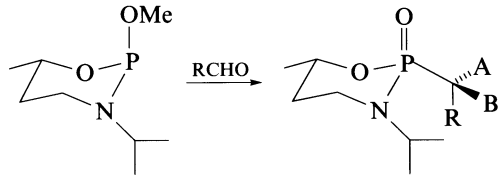
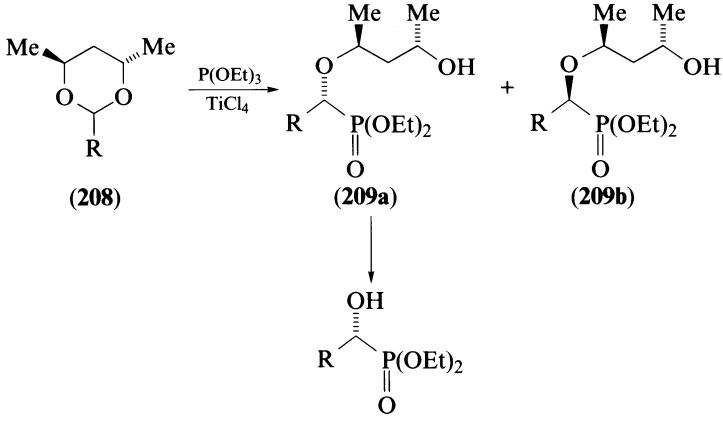


(206) (207)

(a) A = H, B = OH
(b) A = OH, B = H

as 2:1 (R = Ph). Diastereoisomeric excesses tend to be low (8–18%) for the series R = Me, Et, Pr^i and Bu^t, but in a wider range (4–40%) for reactions with aromatic aldehydes[361].

Under catalysis by $TiCl_4$, the 1,3-dioxanes **208**, derived from the aldehyde RCHO (R = Pr^i, Bu^i or CH_2Ph) and (2*S*, 4*S*)-pentanediol, undergo ring opening by the action of phosphorus(III) triesters; Swern oxidation of the major products **209a** (in excess over the minor products **209b** by 91–94:9–6 for R = Pr^i, Bu^i or CH_2Ph) removes the *O*-protecting group to give the (α-hydroxyalkyl)phosphonic acid with enantiomeric excesses greater than 95%[362].



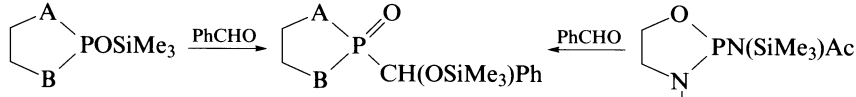
(208) (209a) (209b)

Much attention has been devoted to the conversion of aldehydes into the trimethylsilyl ethers of (α-hydroxyalkyl)-phosphonic acids **210** or analogous -phosphinic acids, or of the corresponding (α-hydroxyalkyl)phosphonic diamides **211** by the use of dialkyl trimethylsilyl phosphite[363–367] or $Me_3SiOP(NEt_2)_2$ (or other phosphorodiamidite)[364,368]. It is a reaction which occurs very readily, even at room temperature, and the ready methanolytic or hydrolytic removal of the silyl protecting group makes the procedure an attractive alternative to the direct synthesis of the (α-hydroxyalkyl)phosphonic acids from dialkyl hydrogenphosphonates and carbonyl compounds. Silyl-protected hydroxy-phosphonic and -phosphinic acid derivatives are useful for further synthetic development[369].

$$R^1_2POSiMe_3 + R^2CHO \longrightarrow R^1_2\overset{\overset{O}{\|}}{P}CHR^2(OSiMe_3)$$

(210) $R^1 = RO$
(211) $R^1 = R_2N$

From the experimental viewpoint, the direct preparation of the same silyl ethers from a mixture of the aldehyde, triethyl phosphite and chlorotrimethylsilane, is a useful shortcut[370]. The reaction occurs much more readily for cyclic esters and amides of phosphorus(III) acids than for their acyclic analogues, and examples are illustrated in Scheme 17[364]. The reaction between diethyl trimethylsilyl phosphite and 2,5-diacetyl-4-methylphenyl trimethylsilyl ether at 180 °C evidently proceeds through **212** on the pathway to **213**; the former of these two products is obtained as a mixture of diastereoisomers, as evidenced from the four appropriate ^{31}P NMR signals, with only one signal being observed for **213**; other signals could be assigned to the by-products **214** and **215**[371]. Diethyl trimethylsilyl phosphite also reacts with acetals of aromatic aldehydes in the presence of $SnCl_4$ to give the diethyl esters of (α-alkoxybenzyl)phosphonic acids[372]. A novel reaction (9) leads to a multi-functionalized product with the potential for much further modification[373].

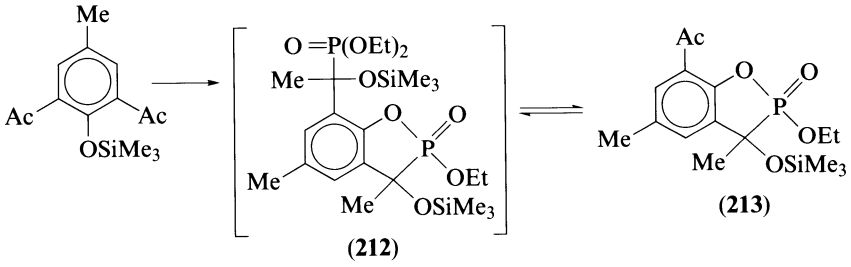


(a) A = B = O or NR
(b) A = O, B = NR

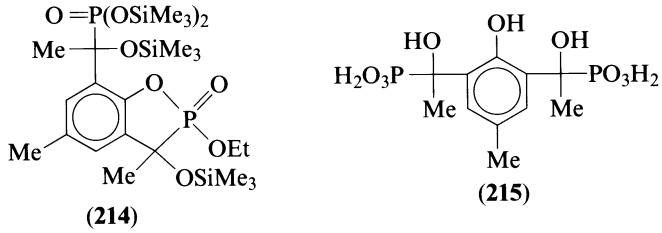
SCHEME 17

Various approaches are currently being made to the asymmetric synthesis of silyl ethers of (α-hydroxyalkyl)phosphonic acids. One approach consists of the use of chiral 1,3,2-oxazaphospholidines (**216**; R^1 = Et or Ph, R^1_3 = Bu^tMe_2), as a mixture of diastereoisomers, which react smoothly at room temperature with an aldehyde to give the diastereoisomeric silyl ethers **217** with retention of configuration at phosphorus[374]. In a second approach, the reaction between benzaldehyde and $(EtO)_2POSiMe_2Bu^t$ was carried out in the presence of the chiral Lewis acids **187** (R = Me or Ph, X = Cl); a higher reaction yield accompanied a lower enantiomeric excess in the product, and vice versa, but the enantiomeric excess was never higher than about 25%[342].

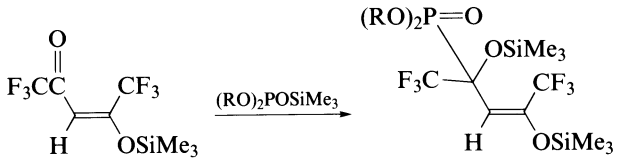
The combination of 1 mol of bis(trimethylsilyl) hypophosphite, 2 mol of an aldehyde or ketone and 1 mol each of chlorotrimethylsilane and triethylamine, affords bis[1-(trimethylsilyloxy)]phosphinic acids (**218**) according to Scheme 18, and subsequent ethanolysis then liberates the free hydroxyalkyl acids[375]. The same hypophosphite ester is reactive towards halogenoacetones, $RCOCX^1X^2X^3$(Scheme 19); the initial stage is a Perkow type of process yielding a trimethylsilyl alkenyl phosphinate ester, **219**. This latter ester is reactive to chlorotrimethylsilane–Et_3N to yield the bis(trimethylsilyl) alkenyl



(212) (213)



(214) (215)



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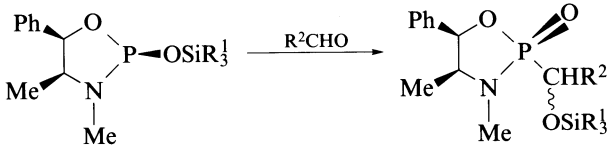
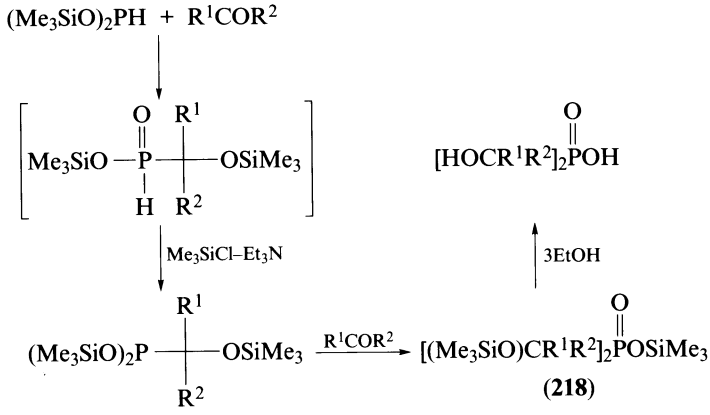


(216) (217)



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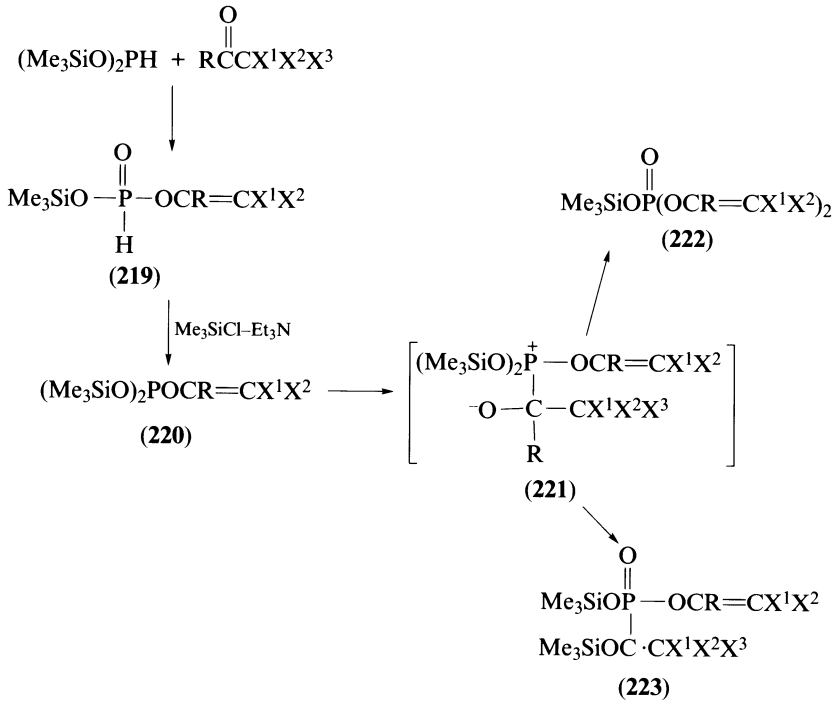
SCHEME 18



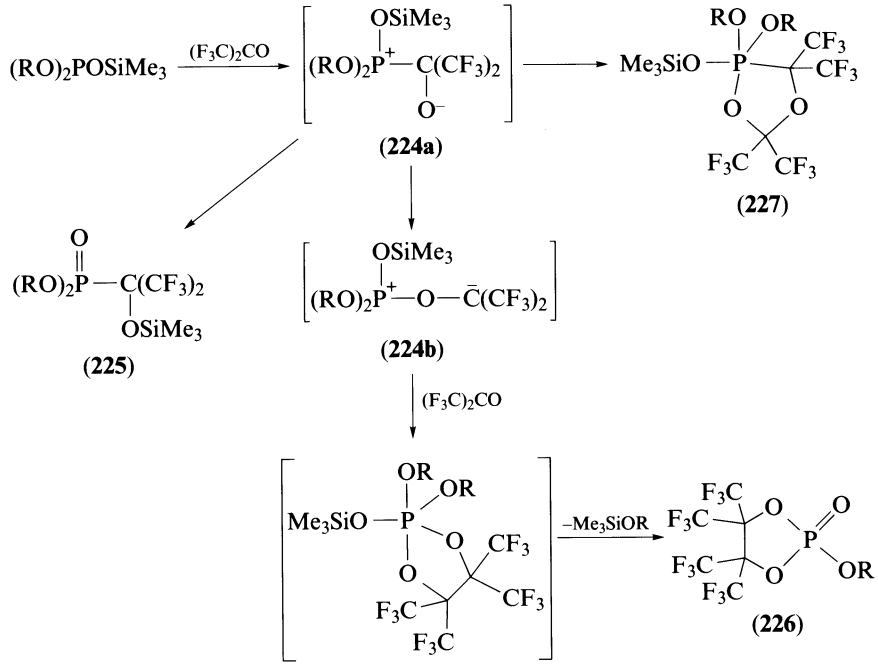
SCHEME 19

phosphite ester **220**, and the conversion of this into either the Perkow ester **222** or the phosphonate ether **223** is considered to proceed through rearrangements within the structure **221**[376].

A further illustration of the difference in behaviour of fluorinated carbonyl compounds (in contrast to those containing other halogens) towards phosphorus(III) esters, consists in the interaction of dialkyl trimethylsilyl phosphites with hexafluoroacetone (Scheme 20). Here, the expected silyl ethers **225**, formed by the rearrangement of **224a**, may be accompanied by the 4,4,5,5-tetrakis(trifluoromethyl)-1,3,2-dioxaphosph(V)olanes **226**, depending on the reaction conditions, and obtained from **224b** with a second equivalent of the ketone. On the other hand, when RR = CH_2CH_2 or CMe_2CMe_2, further reaction occurs through **224a** leading to the stable phosphoranes **227**[377].

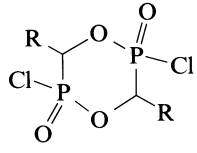
3. From monocarbonyl compounds or their derivatives and phosphorus(III) halides

Reactions between simple carbonyl compounds and phosphorus(III) halides have already been considered in connection with the synthesis of (α-halogenoalkyl)phosphonic acids (Section A.7), and the historical importance of the process (Fossek 1884–86; Michaelis, 1896; Conant, ca 1920–25) has been emphasized. Michaelis also investigated reactions which involved dichloroarylphosphines, $ArPCl_2$. A later study[173] suggested that the interaction of an aldehyde, RCHO, and PCl_3 in the presence of acetic anhydride proceeded through $RCHClOPCl_2$ to $RCH(OAc)PCl_2$, which then underwent a self-condensation with elimination of AcCl to give the 1,4,2,5-dioxadiphosph(V)orinane **228**, recognizable as the dimer of the precursor to the (α-hydroxyalkyl)phosphonic acid pro-



SCHEME 20

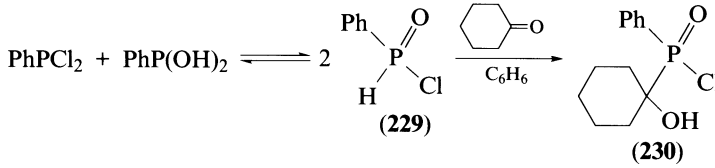
posed by Conant. In a further investigation of the behaviour of PhCHO towards PCl_3, the catalysis of formation of $PhCH(OAc)_2$ from PhCHO and acetic anhydride by PCl_3 has been observed, as has the further reaction of the diacetate with PCl_3 to give PhCHCl(OAc) together with the very unstable $AcOPCl_2$. The latter is thought to be the precursor to the reactive intermediate $(POCl)_n$, which, in combination with PhCHCl(OAc), furnishes **228** (R = Ph)[176].

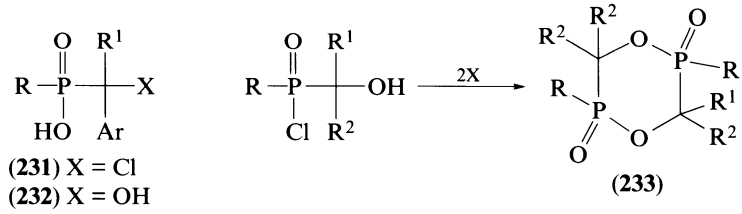


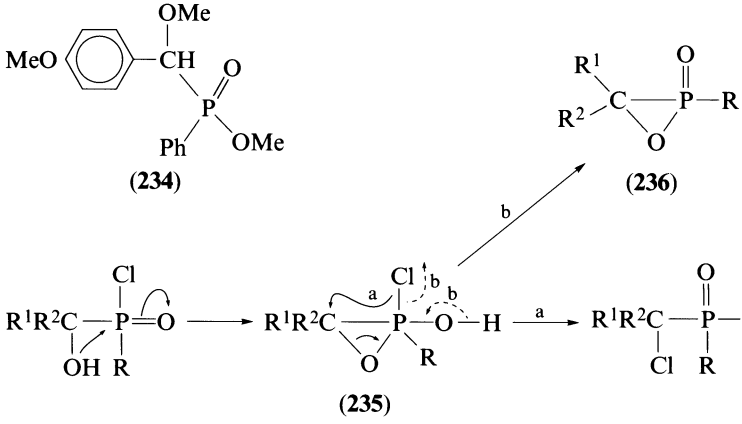
(228)

Reference has also already been made (Chapter 2, Section A.7) to the reaction which takes place between cyclohexanone and $PhPCl_2$, and through which (1-chlorocyclohexyl)phenylphosphinic acid was obtained as an illustration of this synthetic route to a (1-chloroalkyl)phosphinic acid[170]. Mixtures of the same reactants which also contain water[378], or an alcohol[379] or a mixture of cyclohexanone, acetyl chloride and phenylphosphonous acid[380] yield the isomeric (1-hydroxycyclohexyl)phenylphosphinic chloride **230**[374]. The same compound was also formed when a 1:1 mixture of phenylphosphonous dichloride and phenylphosphonous acid (phenylphosphinic acid) was allowed to interact with cyclohexanone, no addition occurring between the acid and the ketone in the absence of the $PhPCl_2$. The formation of **230** was therefore depicted as the addition of the cyclohexanone

to the phosphinic chloride **229**, postulated as the product of equilibration between the phosphonous acid and its dichloride[381]. Confirmation of the structure of this acid chloride was obtained by its conversion into the ethyl ester of the corresponding acid, and the alternative synthesis of the latter from cyclohexanone and ethyl phenylphosphinate, Ph(H)P(O)OEt[382], and also by crystallographic analysis[379,383]. Although these reactions are by no means restricted to cyclohexanone, there are exceptions, the principal one of which consists of certain methyl aryl and diaryl ketones with methoxy substituents, when the product from the ketone R^1 COAr and the chloride $RPCl_2$ (R = Me or Ar) consists of the isolable α-chlorophosphinic acid **231**, and from which the α-hydroxy acid **232** may be obtained by hydrolysis[384]. In some cases, a further reaction, which consists in intermolecular esterification, has been observed for the reactions between $PRCl_2$ and a ketone in acetic acid, and from which the 1,4,2,5-dioxadiphosphorinanes **233** [e.g. R = Ph, $R^1R^2 = (CH_2)_5$] have been isolated[385–387]. The characterization of products **230**–**233**, here isolated from reactions performed under conditions comparable to those of Conant's original experiments, is consistent with his results. Furthermore, the addition of methanol to a reaction mixture containing $PhPCl_2$, propanoic acid and 4-methoxybenzaldehyde resulted in the isolation of the ester **234** with, evidently, no formation of α-chloro acid or



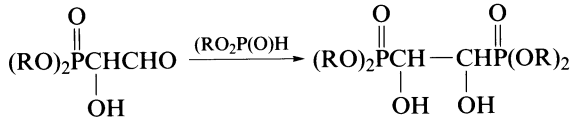




of α-methoxy acid chloride[384]. Also, as has also been mentioned earlier, the interaction of $PhPCl_2$ and 4-methoxyacetophenone in acetic acid provided [1-chloro-1-(4-methoxyphenyl)ethyl]phenylphosphinic acid[172]. The suggestion has therefore been made that the rearrangement of hydroxy acid chloride into chloro acid possibly proceeds through **235**, or through **236** (the latter may exist as a dimer with structure **233**, also comparable to **228**) into the hydroxy acid. Reactions between cyclohexanone, benzaldehyde or 4-methoxybenzaldehyde, and mixtures made up from PCl_3 and acetic acid or water, or H_3PO_3, have led to α-hydroxyphosphonic dichlorides $R^1\ R^2\ C(OH)P(O)Cl_2$, a very surprising and probably unstable structure, yet confirmed by X-ray analysis of the cyclohexanone-derived compound[388].

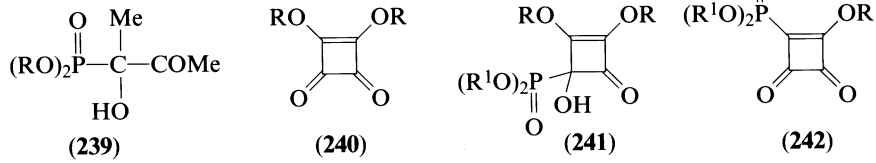
4. *From dicarbonyl compounds*

Perhaps surprisingly, the reaction between glyoxal and a dialkyl hydrogenphosphonate proceeds normally and in two stages, the first of which yields the dialkyl (1-hydroxy-2-oxoethyl)phosphonate **237**, characterized by its reaction with urea, whilst the second stage leads to the *vic*-diol **238**, this characterized through its reaction with 2 mol of PhNCO[389,390]. The *R,R* (*threo*) and *R,S* (*erythro*) diastereoisomers of the dihydroxy compounds have been identified by their ^{31}P, ^{1}H and ^{13}C NMR spectra[391], and each form has also been characterized chemically through its conversion into the respective (*E*)- or (*Z*)-1,2-diphosphonoethene, and of these into ethynediylbisphosphonic acid and 1,2-ethanediylbisphosphonic acid[392].



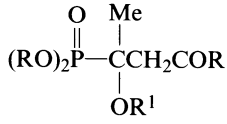
(237) **(238)**

Biacetyl reacts with a dialkyl hydrogenphosphonate in a manner identical with that observed in the first stage for glyoxal, and gives the esteis **239**[393]. A reaction between lithium diethyl phosphite and the 1,2-dioxocyclobutene **240** affords the hydroxy phosphonate **241** only (75% yield) when carried out at –70 °C, but admixed with the phosphonic ester **242** when performed at –20 °C[394].



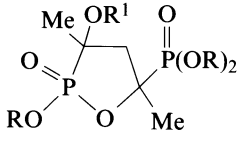
(239) **(240)** **(241)** **(242)**

According to Abramov *et al.*,[393] acetylacetone (as a simple example of a 1,3-dicarbonyl compound) gives **243** when treated with a dialkyl hydrogenphosphonate. Others[395,396] have isolated only the dehydration products **245**, together with, as the major product, 2-alkoxy 5-dialkoxyphosphinoyl-3,5-dimethyl-2-oxo-1,2-oxaphospholan-3-ol (**246**), formed through an initial double 1,2-addition reaction[396]. The structure of the minor product was confirmed by independent synthesis[395]. Exposure of the inital reaction product **248** from acetylacetone and ethylphosphonous dichloride to moist air furnished the analogous 1,2-oxaphosph(V)olane **249**[397]. Dimethyl trimethylsilyl phosphite and acetylacetone are said to react to give initially **244**, with the silyl ether of the phosphorylated 1,2-oxaphospholane 2-oxide **247** as the result of further reaction of **244** with more phosphite triester[398].

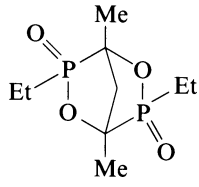


(243) R^1 = H
(244) R^1 = $SiMe_3$, R = Me

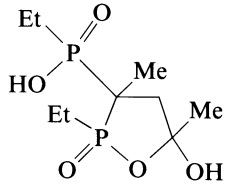
(245)



(246) R^1 = H
(247) R^1 = $SiMe_3$, R = Me

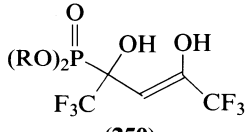


(248)



(249)

Hexafluoroacetylacetone, through its enol form, (*Z*)-1,1,1,5,5,5-hexafluoro-4-hydroxypent-3-en-2-one, undergoes, as might be expected a complex reaction with a dialkyl hydrogenphosphonate with, initially, the formation of **250** (R = Me) or **251** (R = Et or RR = CMe_2CMe_2). For those compounds with R = Me, further steps lead to diastereoisomeric pairs **252** and **253** of 2,5-dialkoxy-2-oxo-3,5-bis(trifluoromethyl)-1,2-oxaphospholan-3-ol via the phosphorane intermediates **254a** and **b**[399].



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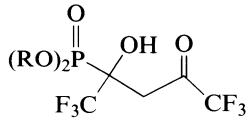

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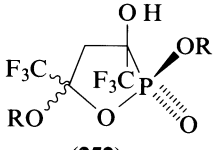

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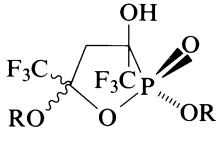

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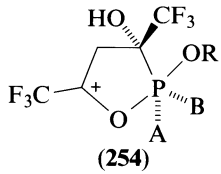
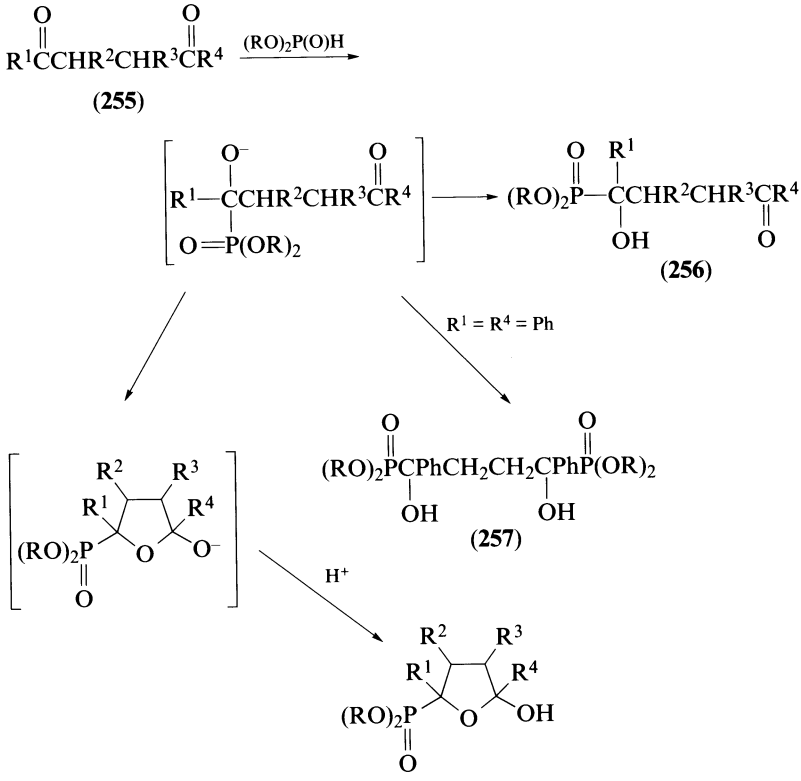


(254)

(**a**) A = OR, B = O^-
(**b**) A = O^-, B = OR

Analogous reactions which involve a 1,4-diketone **255** in the presence of EtO^- occur initially at the more reactive carbonyl site to give **256**, and not at both sites, even in the presence of a large excess of phosphite; an exception to this rule appears to be **255** (R^1 = R^4 = Ph, R^2 = R^3 = H), when both **256** and the corresponding **257** are obtained. In other cases, intramolecular attack at the free carbonyl group leads to phosphorylated tetrahydrofurans[400].

Many other studies have been concerned with reactions between other 1,4-diketones[401–403] or 1,5-diketones[404–407] and a variety of phosphorus-containing reactants including phosphine[401], hypophosphorous acid[402,406] and hypophosphorous esters, either alkyl or

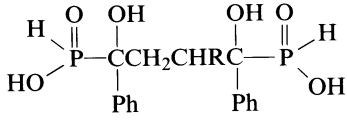


(255)

(256)

(257)

trimethylsilyl[403–407]. These reactions often give rise to linear products accompanied by cyclic compounds, all of which carry a hydroxy group on carbon adjacent to phosphorus(V). Typical products are the linear bisphosphinic acid **258** and the dihydroxyphospholanic ester **259** from bis(trimethylsilyl) hypophosphite and 1,4-diphenylbutane-1,4-dione, and the phosphorinanes **260** produced, along with the linear phosphinic esters **261**, from 1,5-diketones.



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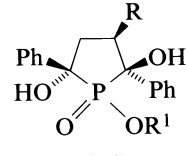

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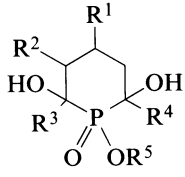

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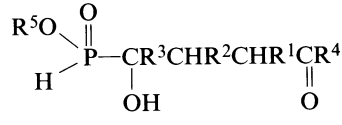
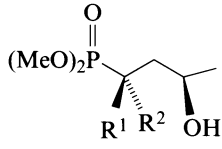


(261)

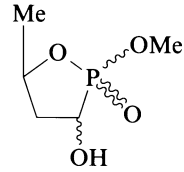
5. *From hydroxyketones or hydroxyaldehydes*

The reaction between dimethyl hydrogenphosphonate and 3-hydroxybutanal produces a mixture of diastereoisomeric dimethyl (1,3-dihydroxybutyl)phosphonates, **262a** and **b**, in the proportions 3:7; the relative configurations at the $C_{(1)}$ and $C_{(3)}$ chiral centres in individual isomers were ascertained through ^{13}C NMR analysis of the benzylidene derivatives. When NaOMe was employed as catalyst in the initial reaction, the formation of **262** was accompanied by that of significant amounts of the 3-hydroxy-1,2-oxaphosph(V)olanes **263**, again as mixtures of diastereoisomers. The latter are also obtained through the triethylamine-catalysed intramolecular transesterification of the linear esters **262**[408]. Mixtures of linear and cyclic acylated phosphonic esters, e.g. the acetates of **262** and **263**, result when 4-acetyloxybutan-2-one is acted upon by a dialkyl hydrogenphosphonate[409].



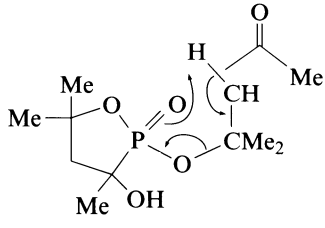
(262)

(a) $R^1 = OH$, $R^2 = H$
(b) $R^1 = H$, $R^2 = OH$



(263)

The treatment of 1,1-dimethyl-3-oxobutanol (diacetone alcohol) with PCl_3 in the presence of Et_3N leads, even at low temperature, to the formation of much 4-methylpent-3-en-2-one (mesityl oxide) together with moderate amounts of the phosphonic diester **264**; when this material is stored, or when it is heated *in vacuo*, elimination of mesityl oxide occurs and the acid **265** (R = H) results[410]. The outcome of this reaction is somewhat different in the absence of the triethylamine, when the final product is the cyclic phosphinic chloride **266**.



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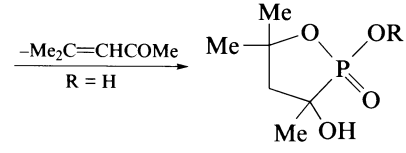

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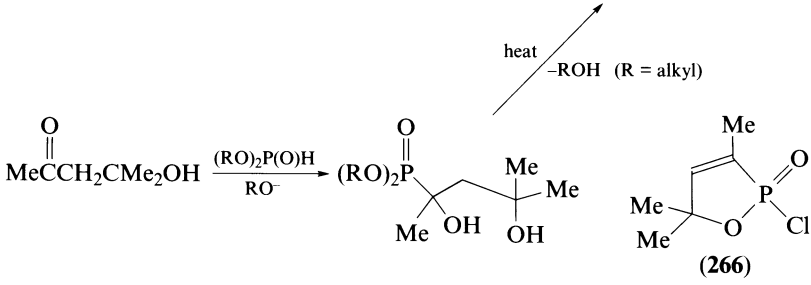
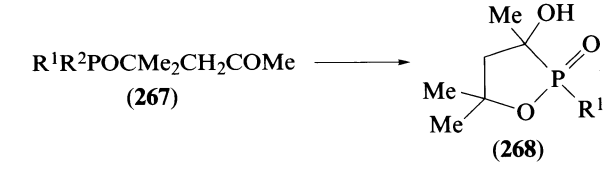


(266)

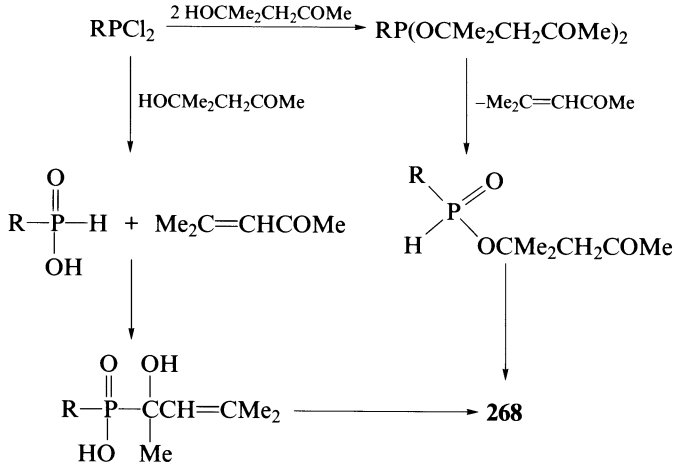
3-Alkoxy-1,2-oxaphosph(V)olanes (**265**) have been prepared following the initial 1,2-addition of a hydrogenphosphonate diester at the carbonyl group of mesityl oxide[411], and the structure of **265** (R = Me) has been confirmed crystallographically[412]. An alternative, and widely developed, procedure for the synthesis of the same, and other, 2-substituted-1,2-oxaphospholan-3-ol 2-oxides is based on the transesterification or hydrolysis of appropriate and linear phosphorus(III) esters or amides. The initial reaction between diacetone alcohol and (1) a chlorophosphite ester, $(RO)_2PCl$, $ROPCl_2$, or $(RO)(Et_2N)PCl$ (with removal of HCl by triethylamine), (2) a phosphorus(III) amide, $(RO)_2PNR_2$ or $ROP(NR_2)_2$, or (3) a phosphorus(III) triamide (with loss of R_2NH) gives rise to the phosphorus(III) esters or amides **267** (R^1, R^2 = RO or NR_2), which may be isolable. More commonly, however, cyclization to the 1,2-oxaphosph(V)olan-3-ols (**268**) occurs rapidly, particularly when the reaction mixtures are heated[413], although failures to cyclize under such conditions have also been reported (in spite of confirmation of the tervalent status of the crude initial products[414]). If the initial mixing is carried out in acetic acid, the 1,2-oxaphospholan-3-ols (**268**)(R^1 = RO or NR_2) are obtained directly under milder conditions and in much better yields[415–417]. In this case, stepwise mechanisms have been outlined which involve the intermediate formation of mixed phosphorus(III) acid–acetic anhydrides which then react with the diacetone alcohol selectively at the anhydride bond. Cyclization also occurs when the intermediate phosphorus(III) ester amide is hydrolysed, since this affords secondary phosphites which tautomerize to hydrogenphosphonates[418–423]. The hydrolysis of dimethyl 2-methyl-3-oxobutyl phosphite yields mixtures of diastereoisomeric 2-methoxy-3,4-dimethyl-2-oxo-1,2-oxaphospholan-3-ols, not all of which may be produced in the initial reaction[421], and the same reaction with the ester from $(MeO)_2PCl$ and 4-hydroxypentan-2-one gave four diastereoisomeric 2-methoxy-3,5-dimethyl-2-oxo-1,2-oxaphospholan-3-ols together with two linear $C_{(3)}$ epimeric phosphonates[424]. Analogous reactions have also been carried out with phosphonous dichlorides $RPCl_2$[425–428]. The configurations of the various diastereoisomers of these compounds have been studied by X-ray methods[424,429] and in some detail by infrared[426,430,431] and NMR[422–427,432,433] spectroscopic methods.



The invariable production of much mesityl oxide during the course of those reactions which involved diacetone alcohol and phosphonous dichlorides, and the successful isolation of phenylphosphonous acid following a reaction with $PhPCl_2$, are testimony to the potential complexity of a reaction scheme, being indicative of two (at least) reaction pathways, both of which involve, in part, internal Abramov steps (Scheme 21)[417,427,434].

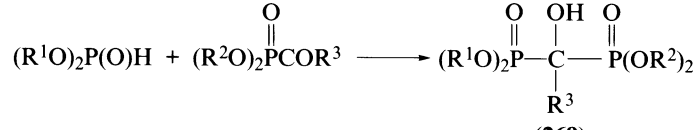
6. *From (1-oxoalkyl)phosphonic acid derivatives*

Reactions between dialkyl hydrogenphosphonates and (1-oxoalkyl)phosphonic diesters in the presence of a trace of basic catalyst, normally triethylamine or sodium alkoxide, give rise to tetraakyl esters of (1-hydroxyalkylidene)bisphosphonic acids (**269**) in a manner similar to the behaviour of the hydrogenphosphonates towards simple aldehydes or ketones[435,436]. However, following the initial observations of this interaction, it soon became apparent that, based on ^1H NMR evidence, the isolated compounds did not possess the stated alkylidenebisphosphonate structure but were, in reality, the products of a

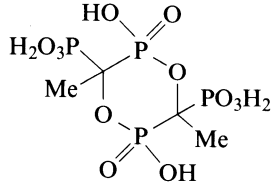


SCHEME 21

P—C—O to P—O—C rearrangement induced by the action of heat (during distillation) or of the base used as catalyst[437]. The acetates of (1-hydroxyalkylidene)bisphosphonic acids (as their esters) are more stable than the free hydroxy esters, and are obtainable through the thermal rearrangement of dialkyl acetyl phosphites, a process that involves the initial rearrangement of the phosphite into dialkyl acetylphosphonate, followed by reaction between this and more acetyl phosphite[438]. Under carefully controlled, neutral conditions, and particularly when purification of the desired compound does not require the application of intense heat, esters of a desired (1-hydroxyalkylidene)bisphosphonic acid can be isolated[439,440]. (1-Hydroxyethylidene)bisphosphonic acid (1-hydroxyethane-1,1-bisphosphonic acid) was evidently first prepared by von Baeyer and Hofmann in 1897, and has more recently been prepared from mixtures derived from acetic acid, water and PCl_3 at 120 °C, phosphorous acid and acetic anhydride at 80–90 °C, or acetyl chloride and phosphorous acid at 120 °C; in such procedures, the essential process probably involves the addition of phosphorous acid to intermediary acetylphosphonic acid[441]. Also isolable from such reaction mixtures is the cyclic tetraphosphonic acid **270**, derived in principle by the dehydration of the ethylidenebisphosphonic acid[441,442], also obtained slightly earlier but assigned an isomeric but incorrect structure[443].



(269)



(270)

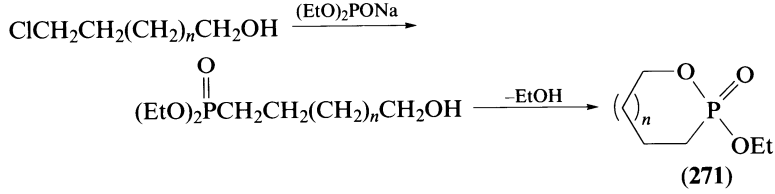
The synthesis of homologues of (hydroxymethylene)bisphosphonic acid may be achieved through reactions between other carboxylic acids, PCl_3 and water at 130 °C[441], and the use of carboxylic esters is also feasible[444]. (Hydroxymethylene)bisphosphonic acid and its ethers are obtainable from tetraalkyl pyrophosphites and alkyl formates in the presence of BF_3 at 20–130 °C[445]. Yet a further reactant combination consists of an alkanoic ester, and P_4O_6–BF_3, which produces glasses, but from which the bisphosphonic acid may be extracted with boiling dilute HCl[444].

(1-Hydroxyalkyl)phosphonic diesters are obtainable more simply by the $NaBH_4$ reduction of esters of (1-oxoalkyl)phosphonic acids; alkalinity in the medium has to be avoided since this causes decomposition of the product into aldehyde and dialkyl hydrogenphosphonate[446].

B. Syntheses of β-and Higher Monohydroxy-phosphonic and -phosphinic Acids

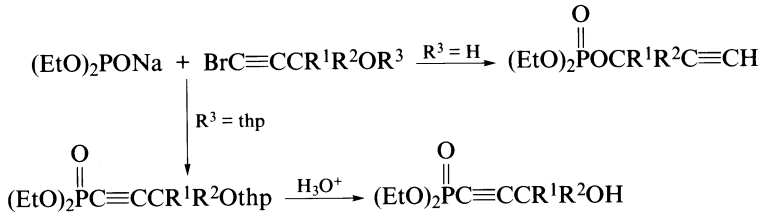
1. *Through the Michaelis–Arbuzov and Michaelis–Becker reactions*

Drawbacks in the application of the Michaelis–Becker reaction for the synthesis of (2-hydroxyalkyl)phosphonic diesters have been revealed in the study of the interaction of sodium diethyl phosphite and ω-chloroalkanols in a procedure which, in principle, might be adaptable to prepare such acids with any carbon chain length possessing an ω-hydroxyl group. However, the yield of diethyl (2-hydroxyethyl)phosphonate from 2-chloroethanol was low (<10%), a mixture of products being obtained, and the preparation of the esters from haloalkanols of longer carbon chain length fared little better since, on attempted isolation, cyclization occurred to give 1,2-oxaphosphorinane 2-oxides **271** ($n = 1$)[447–449] or 1,2-oxaphosphepane 2-oxides **271** ($n = 2$)[447,449]. Elsewhere, the nature of the products from such reactions has been shown to be temperature dependent, and the complexity of the product mixtures cast some doubt, in this case, on the synthetic value of the reaction[450].



(271)

More successful has been the application of the Michaelis–Arbuzov reaction using hydroxyalkyl halides in appropriately *O*-protected form. Reactions which involve non-protected acetylenic alcohols afford rearranged products (Scheme 22), and it is necessary initially to protect the OH group, conveniently with the 2-tetrahydropyranyl moiety[451].

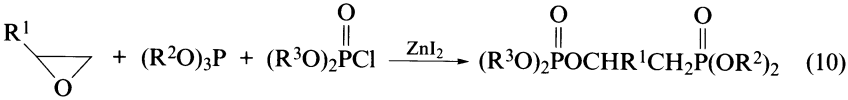


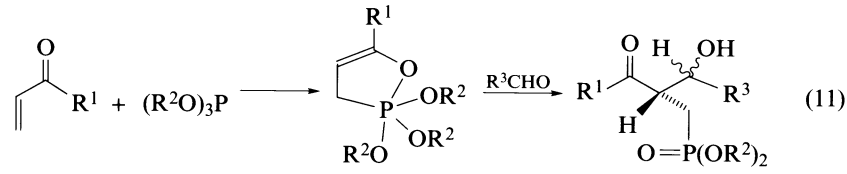
SCHEME 22

(2-Benzyloxypropyl)phosphonic[452] and (2-trimethylsilyloxyethyl)phosphonic[453] diethyl esters are obtained from the appropriate alkyl bromide and triethyl phosphite. Deprotection at the side-chain substituent (debenzylation with H_2, Pd–C; desilylation with MeOH–HCl) leaves the diethyl (2-hydroxypropyl)- and (2-hydroxyethyl)-phosphonates from which the free acids are readily obtainable by acid hydrolysis. Both procedures were adapted by Hammerschmidt for the preparation of deuterium-labelled compounds of known chirality for biosynthetic studies[453,454]. The acetyl group can also be used for protection purposes[455].

2. *Miscellaneous methods based on phosphorus–carbon bond formation*

The use of oxirane together with Na_2HPO_3 to prepare (2-hydroxyethyl)phosphonic acid as its disodium salt is of historical interest. Other poorly exploited, yet interesting and potentially valuable, reactions include the combination of a trialkyl phosphite and dialkyl chlorophosphate with an oxirane to yield *O*-phosphorylated derivatives of (2-hydroxyalkyl)phosphonic diesters (reaction 10)[456] and, following the initial reaction of an α,β-unsaturated ketone with a phosphorus(III) triester to give the cyclic phosphorane **272**, the subsequent further reaction of the latter with an aldehyde followed by hydrolysis (reaction 11)[457]. Dialkyl acetyl phosphites are reported to react with oxirane through anionic intermediate species with the formation, albeit in low yields, of dialkyl (2-acetyloxyethyl)phosphonates[458], hydrolysable with concentrated HCl, to give (2-hydroxyethyl)phosphonic acid[459,460].



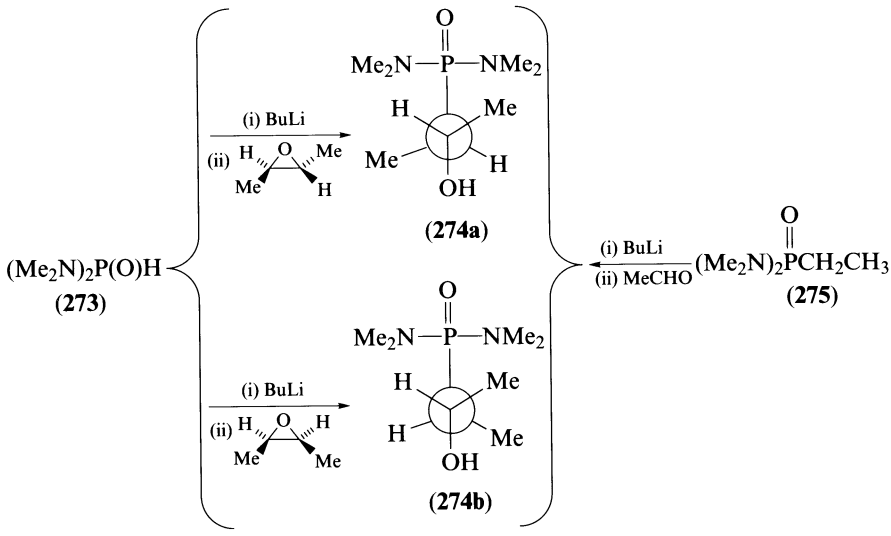


(272)

The opening of the monosubstituted oxirane ring by dialkyl phosphite anions or those from phosphonic diamides, $(R_2N)_2PO^-$, is regiospecific and gives esters or diamides of (2-hydroxyalkyl)phosphonic acids, under mild conditions, in accord with S_N2 reactions of epoxides[461,462]. The reaction is also *trans* stereoselective; thus, the reaction between phosphonic bis(dimethylamide) anion, from **273** and BuLi, and *trans*- or *cis*-2,3-epoxybutane yielded the individually pure diastereoisomeric 2*RS*, 3*SR* and 2*SR*,3*SR* pairs, **274a** and **b**, of (2-hydroxy-1-methylpropyl)phosphonic bis(dimethylamide) (Scheme 23)[463]. This procedure was originally developed by Corey and coworkers as an alternative methodology to the Wadsworth–Emmonds variation of the Wittig alkene synthesis (see the following section and also Chapter 6, Section III.c).

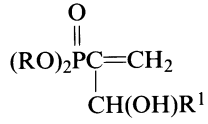
3. *Through modifications to compounds with phosphorus–carbon bonds*

Such methods are scarce. The addition of aldehydes to dialkyl vinylphosphonate occurs in the presence of 1,4-diazabicyclo[2.2.2]octane to give good yields of (2-hydroxy-1-



SCHEME 23

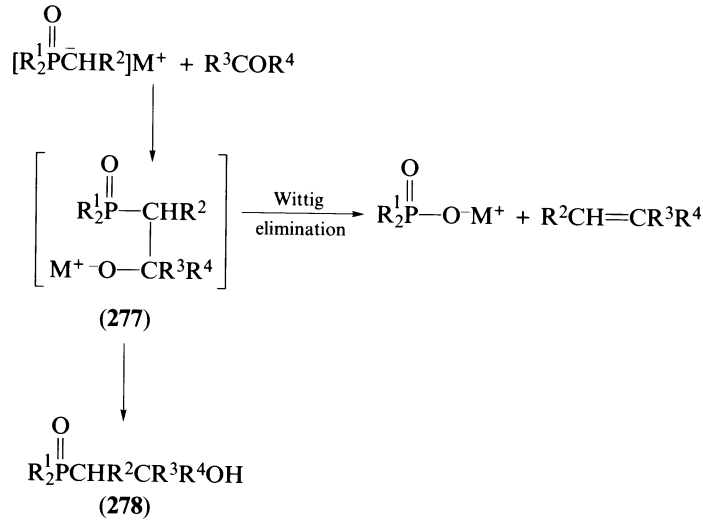
methylenealkyl)phosphonates (**276**), although the reaction proceeds very slowly, requiring several days, if not weeks, at room temperature to ensure reasonable yields[464].



(276)

The most important reaction in this area is that which occurs between a phosphorylated carbanion and an aldehyde or ketone (Scheme 24), and is most commonly used for the preparation of alkenes; the modification which employs anions from tertiary phosphine oxides has been considered elsewhere[465].

Normally, the proposed intermediate **277** (R^1 = EtO or Ph) fragments rapidly, particularly under acidic conditions, and this leads easily to an alkene (in a pure geometric form or as a mixture of *Z* and *E* forms) and a phosphorus-containing acid as a water-soluble salt. The adducts from aldehydes are generally more stable than those from ketones and, in general, increased electron input to carbon from R^3 and R^4 leads to greater attraction of O^- to P^+ and thus easier breakdown. On the other hand, reduced positive electronic character at phosphorus would help to stabilize to intermediate and facilitate the isolation of the (2-hydroxyalkyl)phosphonic derivative **278**. Historically, success in achieving this result came only relatively recently. In practice, it can be, and was initially, achieved with R^1 = Me_2N and, by using the carbanion $[(Me_2N)_2P(O)CHAr]^-$ (Ar = Ph or 4-ClC_6H_4), generally as the lithium salt; reactions have been performed with benzaldehydes[466–468], dialkyl ketones including cycloopentanone and cyclohexanone[468], acetophenone and benzophenone[468], or isobutyraldehyde[466]. Using this procedure, the resultant 2-[bis(dimethylamino)-phosphinyl]alkanols consist of mixtures of *erythro* and *threo* forms, the latter being in excess by a factor of 2–3, and from which the diastereoisomeric forms have sometimes been isolated in the pure state.

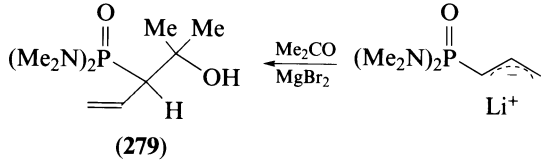


SCHEME 24

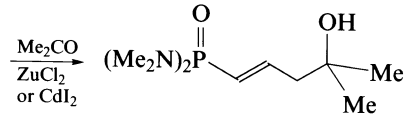
Even the carbanions from less stabilized methyl- or ethyl-phosphonic bis(dimethylamide)s can be successfully employed[469]. In the latter case, the reaction with acetaldehyde (Scheme 23) provides a mixture of the two diastereoisomeric alkanols **274a** and **b**, exemplifying an alternative synthesis of (2-hydroxyalkyl)phosphonic bis(dimethylamide)s.

The reaction between a lithiated dialkyl 2-propenylphosphonate and an aldehyde at −78 °C furnishes a mixture of the α- and γ-adducts; thus, diethyl prop-2-enylphosphonate and 4-nitrobenzaldehyde give a mixture of the α- and γ-adducts in the ratio of 2:5, the former being the kinetically controlled and the latter the thermodynamically controlled product. Deprotonation allows the α-adduct to isomerize to the γ-form[470,471].

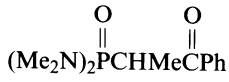
The α-(**279**) and γ-(**280**) adducts from the reaction between lithio(prop-2-enyl)phosphonic bis(dimethylamide) and acetone have been separated by TLC, and each can be obtained separately by the addition to the reaction mixture of a different Lewis acid[463]. In contrast to the 2-hydroxy compound, the 4-hydroxy isomer is thermally stable.



(**279**)



(**280**)



(**281**)

As an alternative to the manner in which the stability of the intermediate species **277** is raised by increasing electron input to phosphorus, a reduction in nucleophilic character of the original carbonyl oxygen might be contemplated. In this respect, it may be noted that a reaction between the lithium salt of diisopropyl (fluoromethyl)phosphonate and the ketones R^1R^2CO affords both the alkene (s) predicted from the Wittig mechanism, but also the alcohols $(Pr^iO)_2P(O)CHFC(OH)R^1R^2$ as mixtures of diastereoisomers, distinguishable spectroscopically but not separable[108].

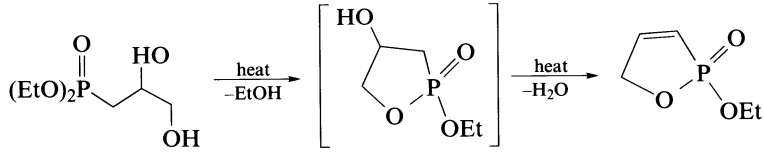
In a further development, explored very little from the stereochemical aspect, the reduction of (oxoalkyl)phosphonic bis(dimethylamide)s, e.g. **281**, with $NaBH_4$ (or $LiBH_4$, H_2–Raney nickel, Al–Hg, B_2H_6 or an organoborane) gave an 80% yield of one diastereoisomer of **278** ($R^1 = Me_2N$, $R^2 = Me$, $R^3 = H$, $R^4 = Ph$) of 98% stereoisomeric purity; since this, on decomposition, gave pure *trans*-1-phenylpropene, the alcohol must have had the 2*RS*,3*SR* (*threo*) configuration[469].

Oxirane rings also suffer rupture when acted upon by phosphorylcarbanions. The products are then dialkyl (3-hydroxyalkyl)phosphonates[472,473]. Reactions between dialkyl (lithiomethyl)phosphonate and α,β-unsaturated aldehydes yields dialkyl (2-hydroxyalk-3-en-1-yl)phosphonates[474].

C. Syntheses of Polyhydroxy-phosphonic and -phosphinic Acids

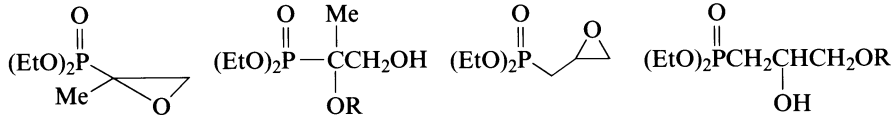
For the purposes of this chapter, the term 'polyhydroxy phosphonic (or phosphinic) acid' is used in the widest possible context, and some discussion is therefore directed towards those carbohydrate analogues, both isosteric and non-isosteric, of true natural carbohydrate molecules, and which include at least one direct phosphorus–carbon bond[475].

Conventional organic synthesis procedures are sometimes employed to prepare the simpler types of those molecules included here. Thus, (*vic*-dihydroxyalkyl)phosphonic diesters are obtainable through the hydroxylation of the corresponding unsaturated acid esters using OsO_4 and standard techniques[476,477]. The isolation and purification of a diol may prove to be difficult because of possible intramolecular transesterification, sometimes accompanied by dehydration (reaction 12)[477].



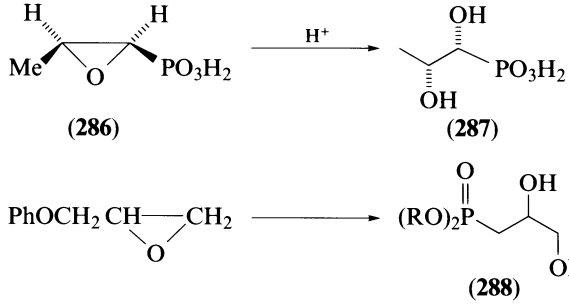
(12)

Within a specific system of reactants, the ring opening in a phosphoryl oxirane by an alcohol may be regarded as occurring regiospecifically. Two examples illustrate the potential for a change in the manner of ring opening. The conversion of **282** into **283** by ROH (R = alkyl or benzyl) occurs in the presence of an acid catalyst or of $BF_3{\cdot}Et_2O$, but not by the use of a basic catalyst. On the other hand, the formation of **285** from **284** requires a basic catalyst and acid catalysts are ineffective. Both reactions occur with phenols under basic conditions[478]. Not only is the ring opening of phosphorylated oxiranes regiospecific, but it can also be stereospecific. For example, (2*R*, 3*S*)-(1,2-epoxypropyl)phosphonic acid



(phosphonomycin; **286**) undergoes acid catalyzed ring opening to (1*R*, 2*R*)-(1,2-dihydroxypropyl)phosphonic acid (**287**)[479].

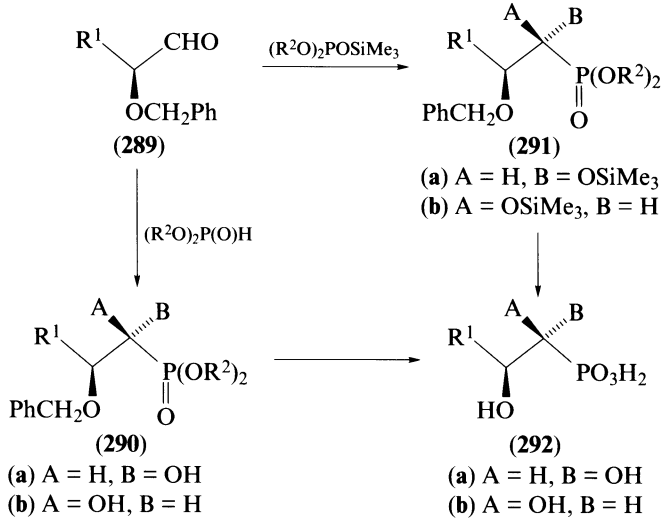
Deprotection procedures are readily available when, for example, in **283** and **285**, R is benzyl, and removal relies on simple hydrogenolysis, and yields a dialkyl (2,3-dihydroxypropyl)phosphonate; the product **288**, from phenylglycidyl ether and a hydrogenphosphonate ester, may likewise be deprotected in an appropriate manner to afford esters of the same phosphonic acid[480].



(**286**) (**287**)

(**288**)

Similar deprotection procedures have been applied in the last stages of Abramov syntheses, and are illustrated in Scheme 25 with particular reference to the (1,2-dihydroxypropyl)phosphonic acid derivatives (R^1 = Me). Dimethyl (2-benzyloxy-1-hydroxypropyl)phosphonate is obtainable as a mixture of stereoisomeric forms **290a** and **b** from $(MeO)_2P(O)H$ and (*S*)-2-benzyloxypropanal (**289**). The aldehyde **289** also reacts with dialkyl silyl phosphites to afford a mixture of the fully protected compounds **291a** and **b**, which may be selectively desilylated or completely deprotected to give the diastereoisomeric forms of (1,2-dihydroxypropyl)phosphonic acid, **292a** and **b**, also obtainable by the debenzylation of the respective **290**[479,481]. Dimethyl (1,2-dihydroxyethyl)phosphonate has likewise been obtained in racemic form as its 2-*O*-benzyl derivative, and also in optically active forms as its 1-*O*-(*tert*-butyldimethylsilyl) and 2-*O*-benzyl-1-*O*-(*tert*-butyl-



(**289**)

(**291**)

(**a**) A = H, B = $OSiMe_3$

(**b**) A = $OSiMe_3$, B = H

(**290**)

(**a**) A = H, B = OH

(**b**) A = OH, B = H

(**292**)

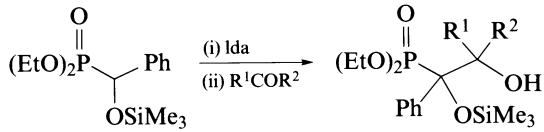
(**a**) A = H, B = OH

(**b**) A = OH, B = H

SCHEME 25

dimethylsilyl) derivatives, and the syntheses have been developed by Hammerschmidt and Vollenkle [482] for the preparation of isotopically labelled hydroxy phosphonic acids.

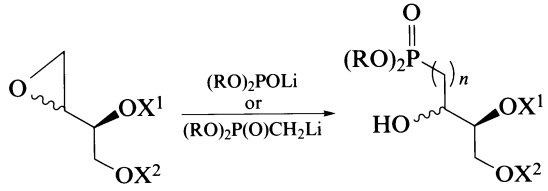
The successful preparation of (2-hydroxyalkyl)phosphonic acid derivatives by the treatment of an appropriately phosphorylated carbanion with an aldehyde or ketone, has been further extended to the formation of **294** from **293**[483].



(293) **(294)**

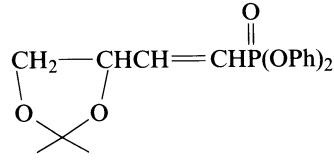
Yet another standard reaction which has been employed for the preparation of dihydroxyalkyl phosphonic acids is an adaptation of that due to Wittig, and exemplified by the synthesis of (3,4-dihydroxybutyl)phosphonic acid; the interaction of 2,3-isopropylideneglyceraldehyde and diphenyl [(triphenylphosphoranylidene)methyl]phosphonate, $Ph_3P{=}CHP(O)(OPh)_2$ yields **295**, which, on hydrogenolysis, affords the target acid[484].

Esters of (2,2-difluoro-3,4-dihydroxybutyl)phosphonic acid have been obtained through an epoxide ring-opening reaction[242], and such a procedure has also been successfully applied to the preparation of mono-, di- and tri-hydroxy acids depending on the nature of the oxirane substituents (reaction 13)(X^1, $X^2 = CH_2Ph$ or *p*-toluenesulphonyl, or X^1, $X^2 = CMe_2$). Ring opening is obtained through the use of sodium dialkyl phosphite (to yield products for which $n = 0$), or with dialkyl (lithiomethyl)phosphonate (to give products for which $n = 1$), in a process catalysed by $BF_3{\cdot}Et_2O$. The yields in this procedure are very high, but the reaction operates very poorly using diethyl trimethylsilyl phosphite $-ZnI_2$[485].



(13)

Many of the aforementioned reactions have been extended to the preparation of tri- and more extensively hydroxylated phosphonic acids. Perhaps the simplest example of this consists in the reaction between dibenzyl hydrogenphosphonate and 2,3-*O*-isopropylidene-D-glyceraldehyde to give, after appropriate deprotection, (1*RS*, 2*R*)-(1,2,3-trihydroxypropyl)phosphonic acid[484]. The opening of the epoxide ring in **296** by diethyl



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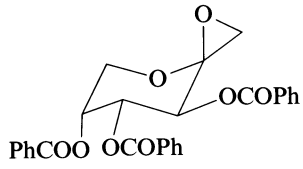

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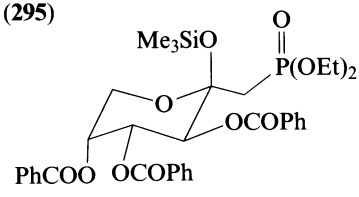
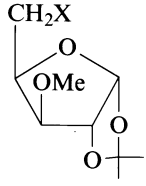


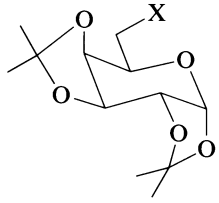
(297)

trimethylsilyl phosphite affords **297**, a surprising result in view of the result presented in the previous paragraph; deprotection then gives 1-deoxy-D-fructose-1-phosphonic acid as a mixture of the α- and β-forms[486].

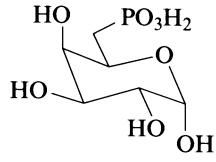
Typical applications of the Michaelis–Arbuzov reaction include the conversion of the 5-deoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose derivative **298** into **299** with triethyl phosphite[487,488] or with diethyl ethyl- or butyl-phosphonite to give **300** (R = Et or Bu)[489]; protection at $C_{(3)}$ is also feasible with acetyl or benzoyl moieties[490]. Another example is the conversion of **301** with $(MeO)_3P$ into **302** (R = Me) in only 30% yield, but with sodium dibenzyl phosphite into **302** ($R = CH_2Ph$) in 80% yield, and thence via **303** to **304**[491]; other similar applications may be noted[492–494].



(**298**) X = Br or I
(**299**) X = $P(O)(OEt)_2$
(**300**) X = P(O)(OEt)R

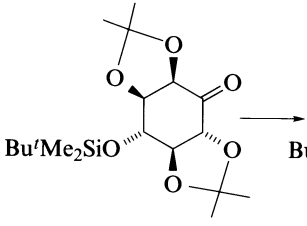


(**301**) X = I
(**302**) X = $P(O)(OR)_2$
(**303**) X = PO_3H_2

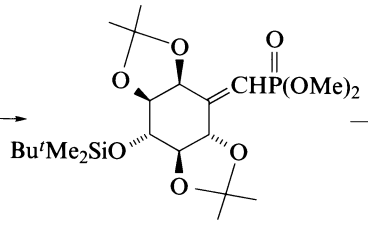


(**304**)

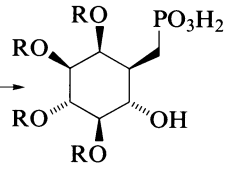
In a typical Wittig process, the lithium salt of tetramethyl methylenebisphosphonate acts upon the cyclic ketone **305** to give **306**; further steps which consist essentially in reduction (PtO_2, H_2), de-esterification at phosphorus (Me_3SiBr) and further deprotection (aq. F_3CCOOH), give racemic *myo*-inositolmethylphosphonic acid (**307**; R = H)[495], also obtainable through a reaction between the epoxide **308** and a dialkyl (lithiomethyl)phosphonate[496].



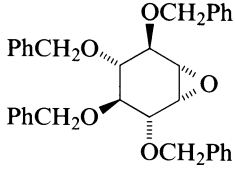
(**305**)



(**306**)



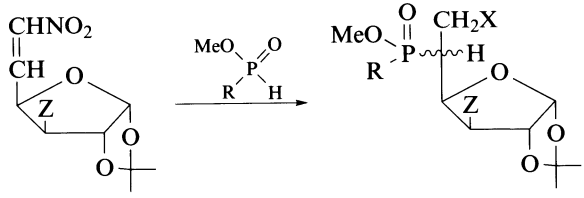
(**307**)



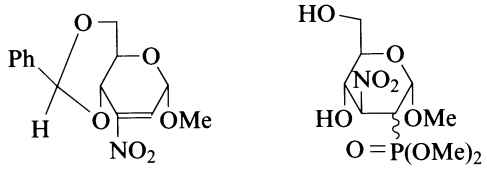
(**308**)

Hydrogenphosphonates and related hydrophosphoryl compounds undergo many addition reactions, including addition to activated alkenes. In the presence of Et_3N, dimethyl hydrogenphosphonate adds to the nitro sugar **309** (Z = H) to give **310** (Z = H, R = OMe) convertible, through **311**, into **312** (Z = H, R = OMe)[497,498]; other synthetic sequences have commenced with **309** (Z = OAc) for R = Et[499] or R = Ph[500]. The initial addition of the hydro-

genphosphonate across an activated C=C bond is also to be observed in the different environment found in **313** when the product is the nitro sugar phosphonic diester **314** and its $C_{(2)}$ epimer, and in which the nitro group may be replaced by OH as for the example **310**[501].



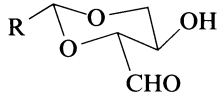
(309) **(310)** X = NO_2
(311) X = NH_2
(312) X = OH



(313) **(314)**

Although the reactions between hydrogenphosphonates and simple aldehydes or ketones have been so widely examined, there have been very few examples of asymmetric synthesis. Apart from the few instances of this phenomenon associated with simple monocarbonyl substrates (see Section III.A.1), other examples include the reaction between dimethyl hydrogenphosphonate and 3-hydroxybutanal, which was discussed earlier (Section III.A.5), and that between dibenzyl hydrogenphosphonate and 2,3-*O*-isopropylidene-D-glycerol when asymmetric induction leads to products in the ratio 4:6[484]. The last substrate represents the group of triose sugars, and indeed most of the known stereochemical preferences have come to light during examinations of the Abramov reaction using tetrose and higher carbohydrate substrates in relation to the synthesis of polyhydroxy phosphonic and phosphinic acids. Within the tetrose series, reactions between dimethyl hydrogenphosphonate and 2,4-*O*-ethylidene-D-erythrose (**315**; R = Me) in the presence of NaOMe, and with the benzylidene derivative **315** (R = Ph) in the presence of Et_3N, both gave 1:1 mixtures of the 1*R* and 1*S* products **316** (R = Me, R^1 = Me or Ph); only the benzylidene derivatives proved useful from the viewpoint of ease of deprotection. On the other hand, the 2,4-*O*-benzylidene derivative of D-threitol, **318**, yielded a mixture of the 1*R* and 1*S* forms of **319**, with a 9:1 preference for the former isomer, and both forms could be deprotected to give the stereochemically corresponding (1,2,3,4-tetrahydroxybutyl)-phosphonic acid[502,503]. This asymmetric preference was explained by considering Newman projections **317** and **320** along the (O=)C—$C_{(3)}$ bonds of the representations **315** and **318** of the substrates, which reveals a restriction in approach from one side of the carbonyl group in **320** (i.e. for **318**), not apparent for **317** (i.e. for **315**)[503]. An earlier study of ethylidene derivatives in the same system, had shown a slight preference for one (unidentified) form of the adduct[504].

Both linear and cyclic forms in the pentose series have been examined. In their reactions with a dialkyl hydrogenphosphonate, both 2,4:3,5-di-*O*-ethylidene-L-xylose (in its reaction with diethyl hydrogenphosphonate in the presence of KF)[505] and 2,3:4,5-di-*O*-isopropylidene-D-arabinose[506], single products were obtained to which the 1*S* configuration was assigned, based on NMR studies on the [(pentaacetyloxy)pentyl]phosphonic



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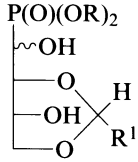

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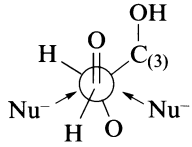

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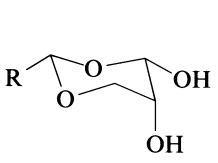

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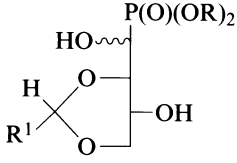

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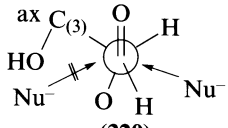
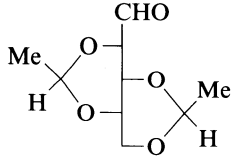
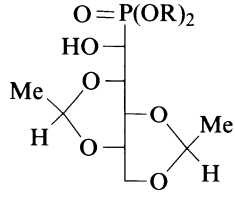


(320)

acids. However, the aldehydo-L-xylose derivative **321** displayed a distinct preference for the 1*R* form (97:3) of the adduct **322**[507]. In other cases in which the substrates were carbohydrates in ring form, the individual hydrogenphosphonate appeared to be a feature controlling the degree of asymmetric synthesis[508,509]. This type of study has been carried out through the hexose series, including ketohexoses[504,507,509–514] and also higher[515] carbohydrates. In some cases, asymmetric induction has been observed, but not in others.



(321)

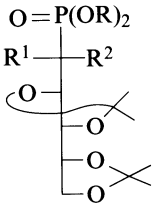


(322)

Chain extension of an aldose by the use of dimethyl (lithiomethyl)phosphonate provides a further route to polyhydroxyphosphonic acid esters. 2,3:4,5-Di-*O*-isopropylidene-D-arabinose reacts with the lithiated ester to give a mixture of the Abramov 1:1 adducts having the *gluco* (**323**; R^1 = H, R^2 = OH) and *manno* (**323**; R^1 = OH, R^2 = H) configurations; spectroscopic examination of the derived monoacetates indicated the two configurations to be present in the ratio 69:31[516].

The interaction of a dialkyl hydrogenphosphonate with a 3-hydroxyalkanal to afford mixtures of diastereoisomers of the linear dialkyl (1,3-dihydroxyalkyl)phosphonate and derived 1,2-oxaphospholane 2-oxides has already been discussed. Lack of protection at appropriately sited hydroxy groups in carbohydrate molecules allows a similar reaction to occur. With D-erythrose, the 1:1 adduct is obtained as a mixture of epimers **324** (R^1, R^2 = H, or OH); on acid-catalysed cyclization, these yield the phosphorus epimeric analogues of D-ribo and D-arabino-furanosides with phosphorus in the epimeric position; **324** (R^1 = H, R^2 = OH) affords **325** as a mixture of the 2*R*, 3*S*, 4*R*, 5*R* and 2*S*, 3*S*, 4*R*, 5*R*, forms in the ratio 2:1, and **324** (R^1 = OH, R^2 = H) also yields the phosphorus epimeric **321** in the same ratio[517].

The involvement of ketoses in the Abramov and related reactions gives rise to linear phosphonic acids in which the phosphinoyl group is sited on a carbon atom other than at position $C_{(1)}$. The dimethyl phosphite ester **327**, derived from 1,3-di-*O*-benzyl-D-



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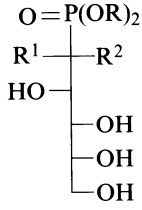

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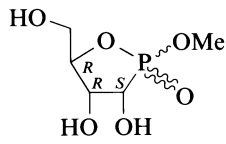

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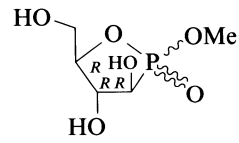
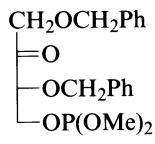


(326)

glycerotetrulose, undergoes controlled hydrolysis to give 22% of a mixture of the $C_{(2)}$ epimers of **328**, together with 23% of a mixture of the (2*R*)-1,2-oxaphospholane 2-oxide (**329**) and its 2*S*-epimer in the ratio 2:1. The latter, and in the identical ratio, are obtained when **328** is treated with Et_3N[502].



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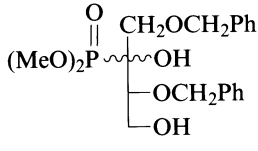
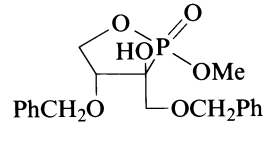


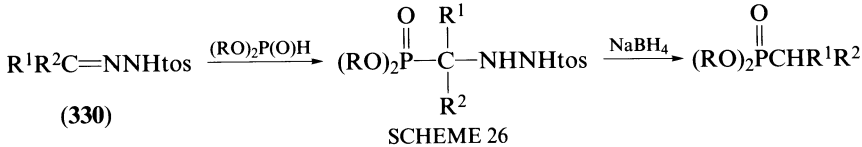
(328)



(329)

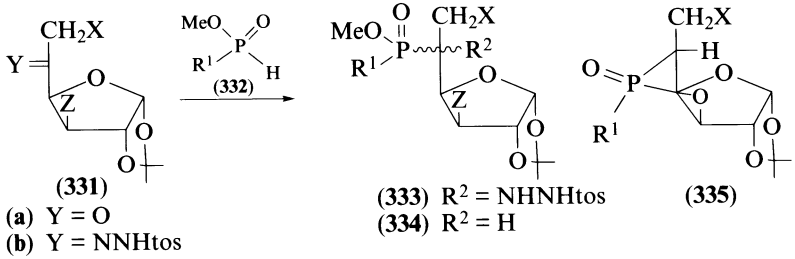
It is thus apparent that the formation of 2-oxo-1,2-oxaphospholanols makes an important contribution to the chemistry of the Abramov reaction when it involves aldoses, but the formation of 2-oxo-1,2-oxaphosphorinanols from appropriate substrates has also been observed[518,519].

A useful method for the introduction of phosphorus-containing moieties on to the carbonyl position of furanose forms of ketohexoses is based on a modification to the Abramov reaction consisting in the addition of a hydrophosphoryl compound to a hydrazide **330** (Scheme 26)[520]. Thus, **331b** (X = H, Z = OMe) (derived from the corresponding **331a**) was allowed to react with **332** (R^1 = OMe[521] or Ph[521–523]) to give the corresponding adducts **333**; reduction of these with $NaBH_4$ yielded **334**. The hydrogenolysis (with Raney nickel or Pd–C) of **333** (X = Z = OCH_2Ph) yielded the bicyclic 1,2-oxaphospholane **335** (X = OH, R^1 = Et)[524], although in later experiments it was found difficult to remove the benzyl protecting groups[525].



(330)

SCHEME 26

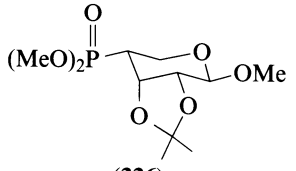


(331)
(**a**) Y = O
(**b**) Y = NNHtos

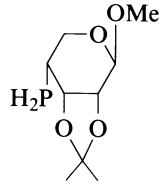
(333) R^2 = NHNHtos
(334) R^2 = H

(335)

A final group of compounds which are formally polyhydroxy phosphinic acids, and which therefore should be mentioned, are those compounds in which phosphorus is the only ring heteroatom and which are thus true phosphorus-containing analogues of carbohydrate molecules. This field has been reviewed up to about 1983[526], but most of the compounds described up to that time were, effectively, phosphine oxides. Even now, very few phosphinic acid derivatives are known. Reduction of the anomeric mixture **336** with lithium aluminium hydride or sodium dihydro(2-methoxyethoxy)aluminate (sdma) yields the anomeric mixture of primary phosphines **337**; acidolysis of this, followed by successive oxidation steps, ultimately yields 2,4-dideoxy-4-hydroxyphosphonoyl-D-*erythro*-pentofuranose† (**338**). From a detailed NMR study of peracetylated derivatives of the methyl ester (prepared using CH_2N_2), an analysis of the stereoisomeric composition of **338** was possible[527,528]. A similar acidolysis and oxidation sequential treatment of the primary phosphine **339**, obtained by reduction (sdma or $LiAlH_4$) of the phosphonate ester **299**, affords the 1,2-oxaphosphorinane 2-oxide **340**[498].



(336)



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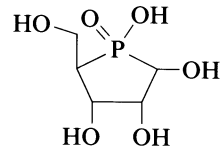

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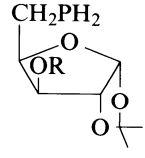

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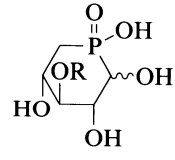


(340)

IV. EPOXY-PHOSPHONIC AND -PHOSPHINIC ACIDS

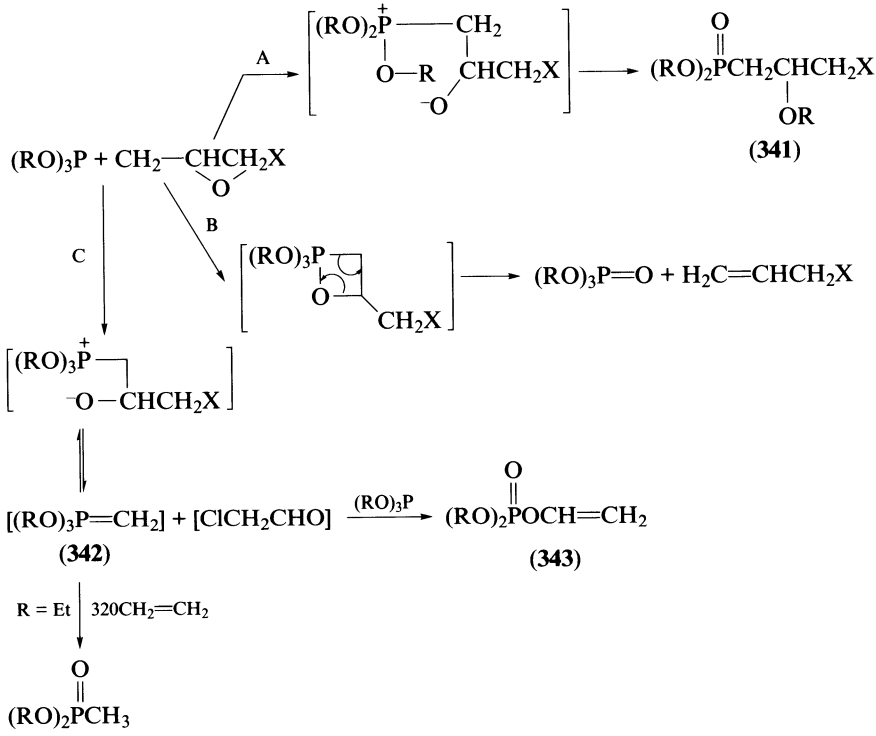
In comparison with several other groups of functionalized phosphonic and phosphinic acids, the chemistry of the epoxy acids has been poorly explored. Up to about 1970[529], the few known epoxy acids had been obtained, for the most part, through the Darzens reaction or through a halohydrin, although the most important example of the class, (1,2-epoxypropyl)phosphonic acid, was produced by the direct epoxidation of (prop-1-enyl)-phosphonic acid.

A. Syntheses of (Epoxyalkyl)-phosphonic and -phosphinic Acids Through Phosphorus–Carbon Bond Formation

In spite of the apparent simplicity of the procedure, the formation of epoxyalkylphosphonic acid derivatives through the Michaelis–Arbuzov reaction is very poorly exempli-

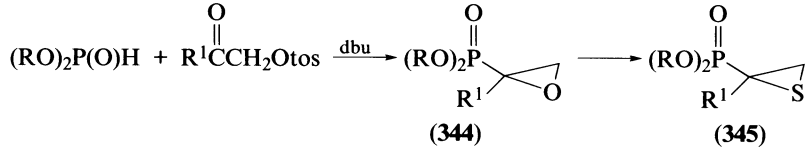
† This form of nomenclature attempts to relate the structure to that of an analogous carbohydrate, and has been widely adopted by those working in the area. Nevertheless, it is not consistent with the customary manner of naming heterocyclic phosphorus compounds. A more systematic way of naming the substance would be either 1,3,4,5-tetrahydroxy-1-oxo-2-phospholanemethanol or 1-hydroxy-2-hydroxymethyl-3,4,5-phospholanetriol 1-oxide.

fied. The formation of diethyl (2,3-epoxypropyl)phosphonate from triethyl phosphite and bromomethyloxirane in acceptable yields (60%)[530,531] might need no further comment were it not for the fact that other workers, who also employed simple trialkyl phosphites[532] or diethyl ethylphosphonite[533] with chloromethyloxirane, obtained the same ester in yields of only about 4%. Three possible reaction pathways (in addition to the normal Michaelis–Arbuzov pathway) were considered by the Russian workers (Scheme 27); they were unable to detect **341** and obtained prop-2-enyl halide in only very small quantity, suggesting that pathways A and B were not of importance. Diethyl ethenyl phosphate (**343**; R = Et) was isolated in 24% yield, consistent with the formation of chloroacetaldehyde, and this was accompanied by diethyl methylphosphonate (also in 24% yield), suggestive of the initial formation of the ylide **342** (R = Et)[532,533].



SCHEME 27

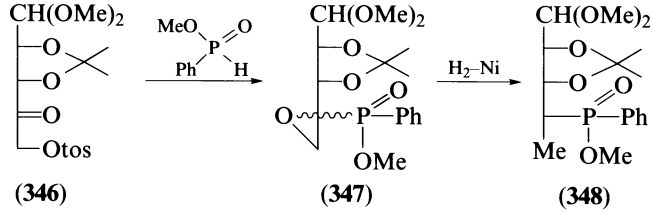
Application of the Abramov reaction has received little more attention, but it has been used in conjunction with toluenesulphonyl derivatives of hydroxyketones in the presence of dbu (Scheme 28); when acted upon by thiourea in MeOH at room temperature, the oxiranes **344** (R = Me or Et, R′ = Me or Cy) are converted into the corresponding thiiranes **345**[534]. The reaction between the protected oxoacetal **346** with methyl phenylphosphinate in the presence of dbu provides the epoxide **347** as a mixture of the diastereoisomeric 4*RS* and 4*SR* pairs in the ratio 7:3. Reduction of the product with H_2 and Raney nickel yields the linear phosphinate ester **348**[535]. Similarly, the reactions between the ketose **349** (R = Me or CH_2Ph) with either dialkyl hydrogenphosphonate or alkyl phenylphosphinate, again in the presence of dbu, gave the epoxides **350** (R = Me or CH_2Ph; $R^1 = R^2 = MeO$; $R^1 = Ph$,



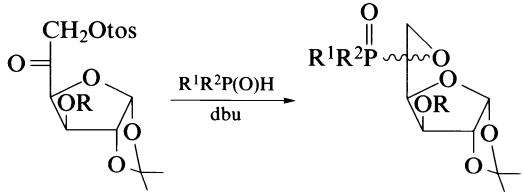
(344) (345)

SCHEME 28

R^2 = MeO or EtO), each mainly in the form of a single stereoisomer at $C_{(5)}$[536,537]. The absolute 5*R* configuration of one of these products, **350** (R = CH_2Ph, $R^1 = R^2$ = MeO), has been confirmed by X-ray crystallographic measurement[538].



(346) (347) (348)



(349) (350)

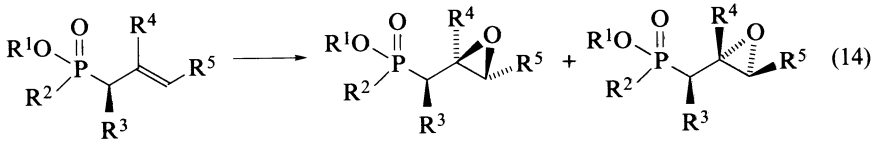
A novel procedure, illustrated in Scheme 11, involves the interaction between a metal dialkyl phosphite and the phosphonium perfluorocarboxylate formed from a Wittig reagent and a perfluorocarboxylic anhydride (R_f = CF_3 or C_2F_5). Although alkenylphosphonic diesters are important coproducts in yields which approach 50%, useful yields of the (1,2-epoxyalkyl)phosphonic diester **128** (also up to 50%) are obtainable when both R^1 and R^2 are Me, but the formation of epoxyalkylphosphonic esters fails completely when $R^1R^2 = (CH_2)_4$[239].

B. Syntheses Based on Modifications to Preformed Phosphonic or Phosphinic Acids or Their Derivatives

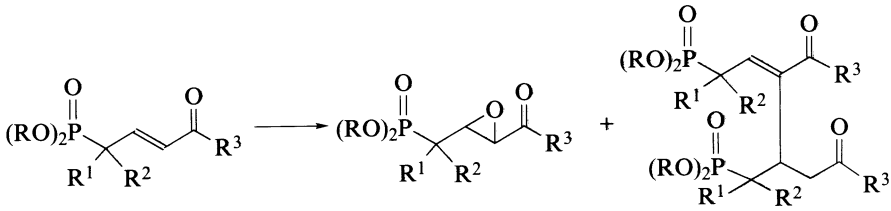
1. By the epoxidation of alkenylphosphonic acids

(Alk-1-enyl)phosphonic esters have been shown to be rather unreactive towards peroxyacetic acid in diethyl ether[539] or in ethyl acetate[530] and towards trifluoroperoxyacetic acid in dichloromethane[530]. Hydrogen peroxide in methanol at pH 9.5 – 10 afforded low yields of epoxy products, and more satisfactory results have been achieved through the use of Bu^{t}OOH in benzene in the presence of Triton B[530]. Diethyl ethenylphosphonate with 85% hydrogen peroxide in the presence of maleic acid gave only 10% of diethyl (epoxyethyl)phosphonate, the yield being increased to 21% through the use of peroxide with perfluoroacetic anhydride in the presence of Na_2HPO_4[540]. The epoxidation of prop-1-

enyl)phosphonic acid has been carried out with hydrogen peroxide in the presence of Na_2WO_4, and thence allowed the isolation of a product (phosphonomycin) which had 92% optical purity[541]. Hydrogen peroxide in the presence of sodium carbonate is a reagent combination which has been used to convert (3-oxoalk-1-enyl)phosphonic esters, both acyclic[542] and cyclic[346], into the epoxy compounds. Peroxyacetic acid[543,544] or trifluoroperoxyacetic acid buffered with sodium acetate[545] has been employed to peroxidize (alk-2-enyl)- and (4-chloroalk-2-enyl)-phosphonic esters. Elsewhere, *m*-chloroperoxybenzoic acid was used[546], when both *erythro* and *threo* forms were recognized in the product, one form generally being in great excess over the other (reaction 14)[547,548]. Once again, epoxidation has been carried out successfully on (4-oxoalk-2-enyl)phosphonic esters, either acyclic[549,550] or cyclic[346], but the required product may be accompanied by a 'dimer' (reaction 15)[549].

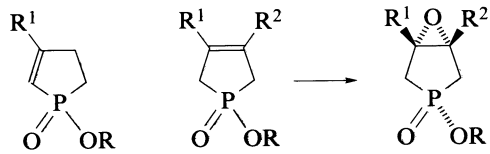


(14)



(15)

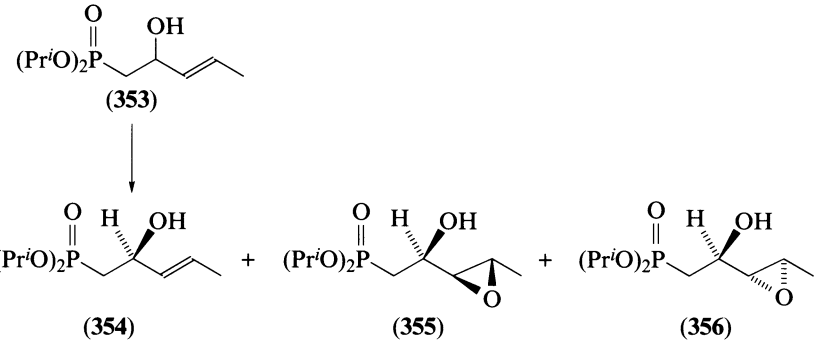
Attempts at the peroxidization of 2-phospholenes (**351**; R = alkyl, R^1 = H or Me) have so far met with little success, in contrast to the positive behaviour of 3-phospholenes (**352**; R = alkyl or Ph; R^1, R^2 = H or Me)[551,552].



(**351**) (**352**)

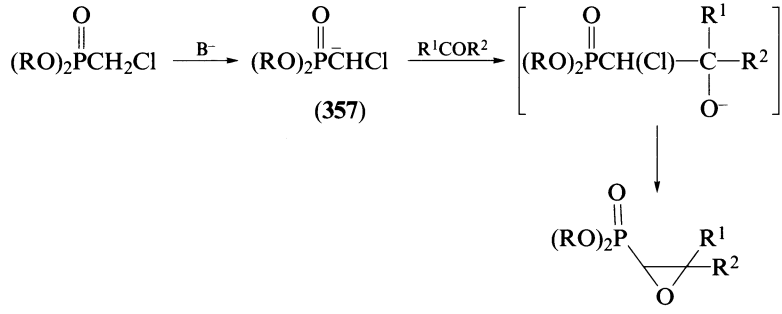
The epoxidation of (buta-1,3-dienyl)phosphonic diesters with peroxytrifluoroacetic acid occurs across the 3,4-double bond[553]. A form of kinetic resolution occurs during the epoxidation of diisopropyl (2-hydroxypent-3-enyl)phosphonate with *tert*-butyl hydroperoxide in dichloromethane at –25 °C. In the presence of diisopropyl D-tartrate–$Ti(OPr^i)_4$, the products from the (2*RS*)-ester **353** are unreacted (2*S*)-ester **354** (63% e.e.) together with the stereoisomeric epoxides **355** and **356**. A similar reaction using diisopropyl L-tartrate gave the epoxide **356** together with unreacted 2*R* substrate[474].

The epoxidation of ethene-1,1-diylbisphosphonic acid esters with 30% H_2O_2 in $NaHCO_3$ buffered solution yields esters of 2,2-oxiranediylbisphosphonic acid[554].



2. Through the Darzens reaction

The simplest application of the Darzens reaction is outlined in Scheme 29. The production of the phosphoryl carbanion has been normally carried out with a metal alkoxide; in this respect, *tert*-butoxide is better than ethoxide, some reactions proceeding only with the former base[555,556]; butyllithium or lda has also been employed. The carbanion **357** is also available through the chlorination of dialkyl methylphosphonate carbanion with $PhSO_2Cl$[229].



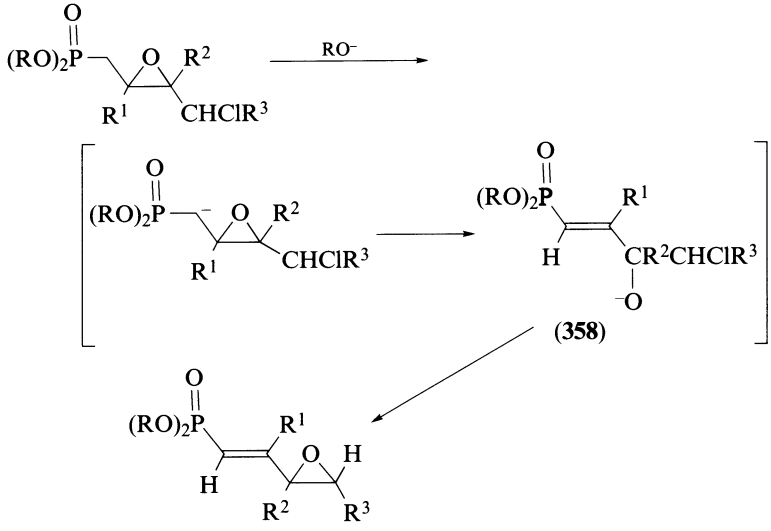
SCHEME 29

Scheme 30 illustrates a novel rearrangement process brought about through participation of the Darzens procedure[212,557].

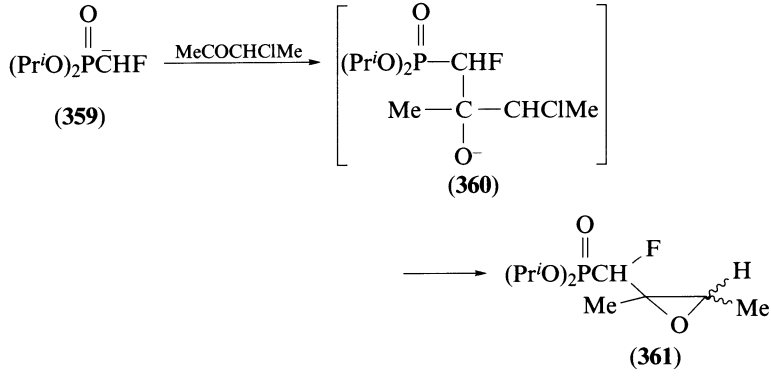
Variations in the Darzens procedure include the generation, from one phosphorylated carbanion, e.g. **359**, of a second carbanion, **360** (similar to **358** already encountered in Scheme 30), as a prelude to the Darzens displacement to give **361**[108]. When treated with tetrabutylammonium cyanide, the ester **362** yields both the epoxide **363** and the cyanooxo ester **364**[476].

3. From halohydrins

Mixtures of halohydrins with (dihaloethyl)phosphonic derivatives are obtained by the appropriate additions to ethenylphosphonic derivatives. Under phase-transfer conditions in the presence of tetrabutylammonium hydroxide, the direct formation of (epoxyethyl)-phosphonic acid derivatives has been observed[558]. However, several earlier reports describe the conversion of isomeric halohydrins (Scheme 31) into the corresponding epoxides[322,323].

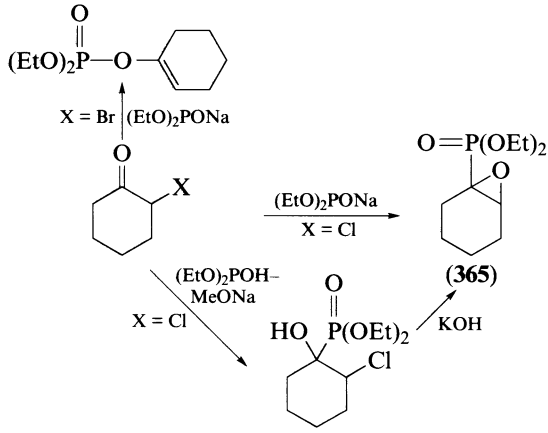


SCHEME 30

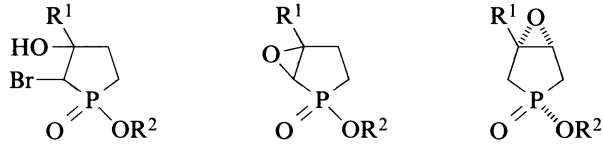


SCHEME 31

The reaction between equimolar amounts of sodium diethyl phosphite and 2-chlorocyclohexanone is reported to yield diethyl (1,2-epoxy-1-cyclohexyl)phosphonate directly, whereas diethyl hydrogenphosphonate, in the presence of a trace of NaOMe in methanol, yields diethyl (1-hydroxy-2-chloro-1-cyclohexyl)phosphonate, convertible into the epoxide **365** by the action of KOH[559]; evidently combinations of triethyl phosphite and 2-chlorocyclohexanone and of 2-bromocyclohexanone and sodium diethyl phosphite yield diethyl 1-cyclohexenylphosphate. On the other hand, diethyl (epoxyalkyl)phosphonates are formed from sodium diethyl phosphite and bromo- or chloro-acetone, 1-chlorobutan-2-one and 3-bromobutan-2-one through initial addition followed by intramolecular displacement of halogen[560,561]. Epoxide formation was also observed in the treatment of dialkyl (4-acetyloxy-3-bromo-1,1-difluorobutyl)phosphonate with KOH at room temperature[242].

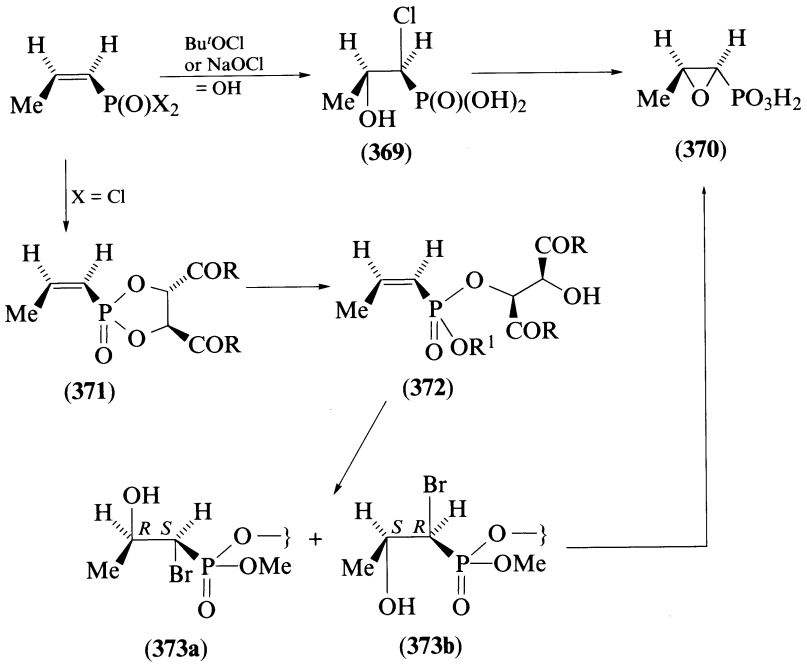


The lack of success in the preparation of 2,3-epoxy derivatives from 2-phospholenes has been obviated by the use of the halohydrin procedure[552]. Thus, the treatment of the 2-phospholene **351** (R = Et, R^1 = Me) with nba yields a stereoisomeric mixture of the halohydrins **366** which, when treated with KOAc in acetone, in turn, yields a mixture of two stereoisomers of the epoxide **367**. The product from the same reaction with the corresponding 3-phospholene is identical with that obtained by the direct oxidation of the phospholene, and is therefore thought to have structure **368**[552].



(366) **(367)** **(368)**

The halohydrin reaction has been used in the synthesis of (1*R*, 2*S*)-(1,2-epoxypropyl)-phosphonic acid (phosphonomycin)(**370**) and its derivatives. One such synthesis (Scheme 32) was devised[562] soon after this substance was originally described[563]. The treatment of (*Z*)-(prop-1-enyl)phosphonic acid with *tert*-BuOCl or NaOCl affords (1*RS*, 2*SR*)-(1-chloro-2-hydroxypropyl)phosphonic acid (**369**), which was resolved by the use of (–)-$PhCHMeNH_2$. When treated in turn with 10 M NaOH, the (+)-chlorohydrin afforded the desired compound **370**. In a second and more recent synthesis, (*Z*)-(prop-1-enyl)-



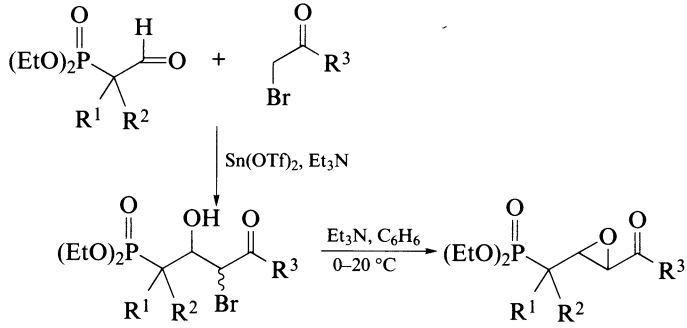
SCHEME 32

phosphonic acid was converted into its dichloride, from which, following interaction with the appropriate tartaric acid derivative (as a chiral auxiliary) in the presence of Et_3N, the 1,3,2-dioxaphospholanes **371** (R = OMe, NHMe, NMe_2, etc.) were obtained. These suffered hydrolytic ring opening to **372** (R^1 = H), readily convertible into **372** (R^1 = Me) with diazomethane; the products, of which that with R = Pr^i proved to be the most useful, underwent highly chemoselective, regiospecific and stereospecific reaction with nba giving the bromohydrins(1*S*, 2*R*)-**373a** and (1*R*, 2*S*)-**373b**, which were separable; the ratio of **373b** to **373a** varied from 51:49 for R = OMe to 70:30 for R = NHMe, $NHPr^i$ and NHBn. In the final step, **373b** (R = $NHPr^i$) was treated with aqueous HBr to liberate the free (1*R*, 2*S*)-(1-bromo-2-hydroxypropyl)phosphonic acid, which was acted upon by NaOMe to give the desired compound **370**[564].

In a later development, it was found that tin(II) triflate catalyses the interaction of a bromomethyl ketone and a (1-formylalkyl)phosphonic diester to give the (3-bromo-2-hydroxy-4-oxoalkyl)phosphonic ester; this is convertible into the epoxide with Et_3N in benzene (Scheme 33)[549,550].

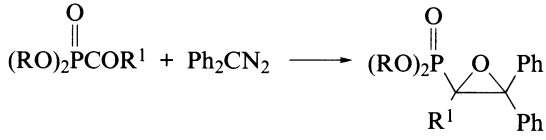
4. From (oxoalkyl)phosphonic esters and diazoalkanes

Diazoalkanes are well known as reagents for carbon insertion reactions through the intermediacy of carbenes. Here, diethyl acetylphosphonate has been shown to react with diazomethane to give a mixture of 2-(diethoxyphosphinoyl)-2-methyloxirane (the major product) together with traces of diethyl (2-oxopropyl)phosphonate[539]; the reaction between dimethyl acetylphosphonate and diazoethane[565] and that between diethyl benzoylphosphonate and diazomethane[539] both afford only the (2-oxoalkyl)phosphonic



SCHEME 33

diester. In spite of these disappointments, the procedure has its usefulness, in that dialkyl acetyl- and aroyl-phosphonates afford high yields (62–98%) of 2-substituted-2-(dialkoxyphosphinoyl)-3,3-diphenyloxiranes (**374**) on reaction with diazodiphenylmethane[566].



(**374**)

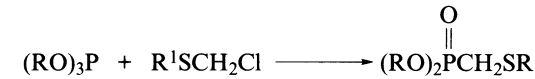
V. MERCAPTO-PHOSPHONIC AND -PHOSPHINIC ACIDS

A. Syntheses Through Phosphorus–Carbon Bond Formation

Both the Michaelis–Arbuzov and the Michaelis–Becker reactions have served to obtain thio ethers in the phosphonic and phosphinic acid series.

Several thioketones, including cyclohexanethione, butane-2-thione and thioacetophenone, react with sodium dialkyl phosphites or similar reagents, or with the hydrogenphosphonates in the presence of Et_2NH at room temperature, or in the absence of a catalyst at 100 °C, to give (α-mercaptoalkyl)-phosphonic or -phosphinic esters[567], although in some cases, including that of thiobenzophenone[568], the initial 1:1 adducts rearrange rapidly to dithiophosphoric triesters.

The Michaelis–Arbuzov procedure, illustrated in general terms in reaction 16, has been used extensively to prepare dialkyl [alkyl(or aryl)thiomethyl]phosphonic diesters[569–573]. (2-Alkylthioethynyl)phosphonic diesters (**375**) were prepared from RSC≡CCl[574], whilst the esters **376**[575] and **377** were obtained in an analogous fashion, the latter being a useful

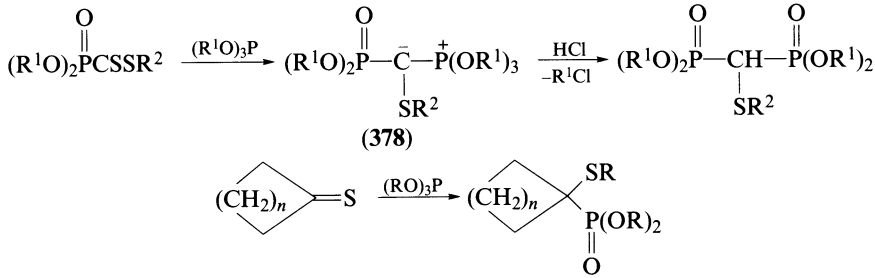


(16)

(**375**) (**376**) (**377**)

intermediate, since its reaction with sodium ethoxide constitutes an improved preparation of diethyl (mercaptomethyl)phosphonate[576,577]. The initial bromination of $MeSCH_2SiMe_3$ and subsequent treatment with triethyl phosphite affords diethyl [(trimethylsilyl)-(methylthio)methyl]phosphonate[578].

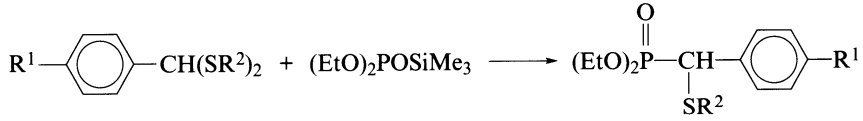
The novel stabilized ylides **378** are obtainable from trialkyl phosphites and dialkoxyphosphinyldithioformic esters, and on acidolysis yield (alkylthiomethylene)bisphosphonic esters[579]. Trialkyl phosphites are also reactive towards cycloalkanethiones, when the products are the (1-mercapto-1-cycloalkyl)phosphonic diesters **379** and their thio ethers **380**[580].



(378)

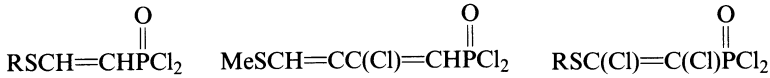
(379) R = H
(380) R = alkyl

Yet another synthesis which employs phosphorus(III)triesters is the reaction which occurs between diethyl trimethylsilyl phosphite and bis(alkylthio)ketals; more specifically, such acetals of aromatic aldehydes react in the presence of a Lewis acid ($SnCl_4$ was actually employed) to give diethyl (α-alkylthiobenzyl)phosphonates (reaction 17)[581].

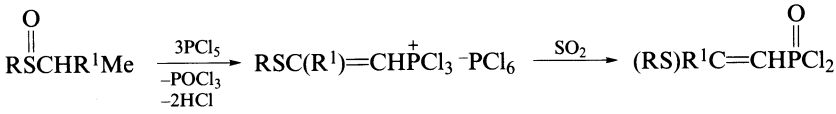


(17)

The reactions between PCl_5 and alkenes or alkynes have already been discussed extensively in connection with the synthesis of a variety of phosphonic acid types (as their acid dichlorides). Successful applications have also used alkenyl alkyl sulphides (to give the dichlorides **381**)[582], to an enyne (to give the dichloride **382**)[583] and to RSC≡CCl (to give **383**)[584,585]. A variation of the Pummerer reaction consists in the interaction of PCl_5 and a dialkyl sulphoxide, during which a trichlorophosphonium salt intermediate is decomposed with SO_2 to yield a (2-alkylthioethenyl)phosphonic dichloride (Scheme 34)[586].

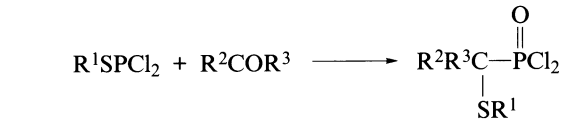


(381) **(382)** **(383)**



SCHEME 34

One further reaction may be noted, although not extensively explored. In the initial report, aldehydes or ketones react with dichlorothiophosphites, when the products are ethers of (1-mercaptoalkyl)phosphonic dichlorides (reaction 18); reactions which involved benzaldehyde or acetone proceeded with only moderate yields[587]. In a second report, use is made of combinations of carbonyl reactant, thiol and phosphorus(III) chloride, and it is conceivable that the actual reactants are essentially those mentioned in the first report[588].

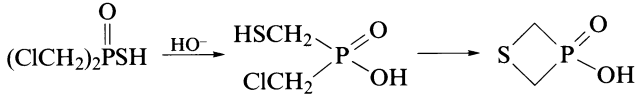


(18)

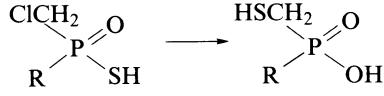
B. Syntheses Through Modification Procedures

1. Modifications at carbon

Simple modifications to substituents on carbon include the replacement of the hydroxy group in dialkyl (1-hydroxyalkyl)phosphonates through the use of PhSH in the presence of diethyl azodicarboxylate–Ph_3P to give dialkyl [(1-phenylthio)alkyl]phosphonates[589], the replacement of chlorine in (chloromethyl)phosphonic acid (or its esters) by the alkylthio group through the use of RSH–NaOEt[590], and the removal of a *p*-tosyloxy group from carbon, also through the action of a thiol[580]. Diethyl (acetylthiomethyl)phosphonate (**377**), already mentioned as being obtainable through the Michaelis–Arbuzov reaction can also be prepared from diethyl (iodomethyl)phosphonate and tetramethylammonium thioacetate, and can be deacetylated with aqueous sodium carbonate[591]. Thiourea was used to convert bis(chloromethyl)phosphinic acid into the unstable bis(mercaptomethyl)-phosphinic acid[592] and [(chloromethyl)alkyl]phosphinic acids into [(mercaptomethyl)-alkyl]phosphinic acids[593]. Following from the earlier observations on the rearrangement accompanying the conversion of **384** into **385** by base, preparatory to the formation of 3-hydroxy-1,3-thiaphosphetane-3-oxide, the analogous change represented in reaction 19 has been developed[593–595].



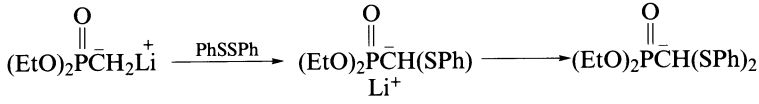
(**384**) (**385**) (**386**)



(19)

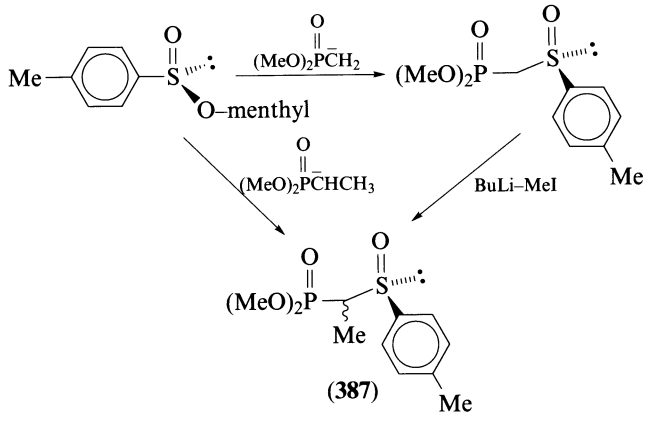
The synthesis of *C*-phosphorylated sulphides has been approached from opposite directions. Thus, the phosphorylation of sulphur-containing carbanions[578,596] complements the modification, by sulphur-containing reagents, of phosphorylated carbanions. The latter, generally generated using BuLi or lda, are reactive to $MeSO_2SMe$[597] and to dialkyl disulphides, the use of which can lead to mono- or di-substitution (Scheme 35)[598], but the addition of sulphur, under carefully controlled conditions, leads directly to (1-mercaptoalkyl)phosphonic diesters in good yields[591].

The reactions of phosphorylated carbanions have been extended to include those with sulphinate esters as a route to phosphoryl sulphoxides[599,600]. The interaction of dimethyl



SCHEME 35

lithiomethylphosphonate and (*S*)-menthyl *p*-tolylsulphinate, and of dimethyl (*p*-toluenesulphinylmethyl)phosphonate and iodomethane, both, proceed (Scheme 36) to a mixture of the diastereoisomeric forms of the sulphoxide **387**, the major diastereoisomer having the S_CS_S configuration[601,602].

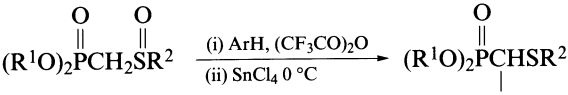


SCHEME 36

The additions of thiols and sulphenyl chlorides to alkenylphosphonic derivatives to yield (2-alkylthioethyl)phosphonic compounds are reactions which have already been noted[43].

Dialkyl (alkylthiomethyl)phosphonates yield α-chloro derivatives when treated with ncs in CCl_4[603]; the resultant dialkyl (1-alkylthio-1-chloromethyl)phosphonates undergo Friedel–Crafts arylation with benzene, alkylbenzenes or other activated aromatics in the presence of $SnCl_4$ or $TiCl_4$[603,604]; yields are said to be good.

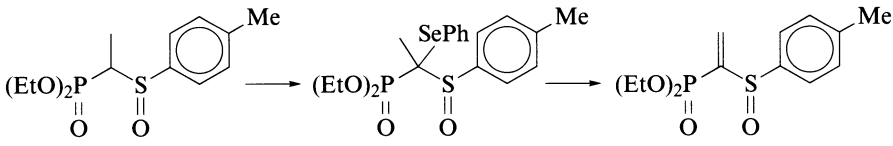
Arylation at a carbon atom attached to phosphorus also occurs when [(dialkoxyphosphinoyl)methyl] sulphoxides are treated sequentially with an arene, trifluoroacetic anhydride and $SnCl_4$ (reaction 20), the product resulting through a Pummerer rearrangement[605].



(20)

The change in bonding from P—C(sp^3) to P—C(sp^2) has been noted following the phenylselenation of the carbanion derived from $(S)_S$-α-(diethoxyphosphinoyl)ethyl *p*-tolyl sulphoxide, and a subsequent oxidative elimination step (Scheme 37) with retained stereochemistry at sulphur[606].

The treatment of the cadmium reagent from a dialkyl (difluoroiodomethyl)phosphonate with SO_2 affords the sulphinic acid derivatives $(RO)_2P(O)CF_2SO_2H$, isolated as their sodium salts[30]. The product isolated from the reaction between diethyl (2-bromoethyl)-phosphonate and Na_2SO_3 is believed to be $(EtO)_2P(O)CH_2CH_2SO_3Na$, from which,



SCHEME 37

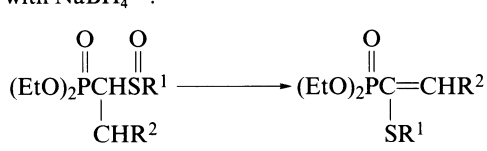
following acidolysis, the free acid $HO_3SCH_2PO_3H_2$ has been obtained[44]. The corresponding sulphonyl fluoride and *N,N*-dialkylsulphonamides, prepared by alternative means, have been known for some time[607], and the phosphonoacetic acid has also more recently been obtained from phosphonoacetic acid when the latter is acted upon by a $ClSO_3H$–$POCl_3$–PCl_5 mixture[608].

2. *Modifications involving sulphur*

Simple alkylation at sulphur in mercaptomethyl moieties occurs with alkyl halides–alkali and also with trialkyl phosphites[609], and the resultant dialkyl (alkylthiomethyl)-phosphonates are oxidized to the corresponding sulphoxides by $KMnO_4$[570], *m*-chloroperoxybenzoic acid[578], Br_2–CCl_4–$KHCO_3$–H_2O[610] or $NaIO_4$[581,605,611], or to the corresponding sulphone by $KMnO_4$[572,612], 50% $KHSO_5$[573], *m*-chloroperoxybenzoic acid[578] or H_2O_2[590,613]; in respect of the last reagent, it is worth noting that its use in an acidic alcohol medium leads to improved yields of the phosphorylated sulphoxide[614]. The above-mentioned phosphorylated methanesulphinic acid may be oxidized to the corresponding sulphonic acid and isolated as $H_2O_3PCF_2SO_3H$[30].

3. *Miscellaneous modifications*

Two further reactions might be included here, since they involve modification at both carbon and sulphur. In the first reaction, dehydration of the sulphoxides **388** (R^1 = Me or aryl; R^2 = H, Me, ethenyl or Ph) to the diethyl [(1-alkylthio)alk-1-enyl]phosphonates **389** is said to result following the action of trimethylsilyl trifluoromethanesulphonate[615]. The second reaction constitutes a new and improved synthesis of an ester of (mercaptomethyl)phosphonic acid, and consists in the treatment of methyl (diisopropylphosphinoyl)dithioformate with $NaBH_4$[616].



(**388**) (**389**)

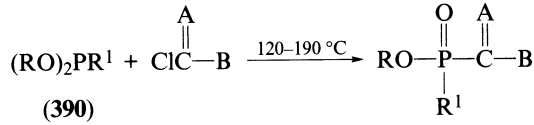
VI. PHOSPHONOYL- AND PHOSPHINOYL-ALKANOIC ACIDS AND THEIR DERIVATIVES

A. Syntheses Through Phosphorus–Carbon Bond Formation

1. *Through the Michaelis–Arbuzov reaction*

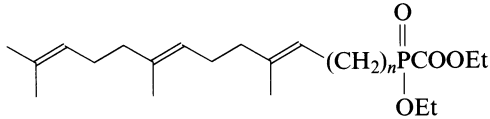
A simple modification to the general Michaelis–Arbuzov procedure, in which the phosphorus(III) esters **390** (R^1 = OR, alkyl, or aryl) and derivatives of chloroformic acid

interact (reaction 21), has provided the derivatives (**391**) of phosphonoyl (or phosphinoyl) formic acid. Examples of such preparations are those of the phosphinoylformic esters **391a** (R^1 = Me, Cy or Ph; R = Et or Me_3Si)[617] and, of a more interesting nature, the phosphonates **392** (n = 2–4), synthesized as potential inhibitors of squalene synthetase[618]. Derivatives of *N,N*-dialkyl- or *N*-phenyl-formamides (**391b**) have been available for many years[619–621] and, through the use of reaction 21, may be obtained in yields of about 50%; exceptionally, reactions which involve $(MeO)_3P$ proceed less satisfactorily. The phosphonoyl and phosphinoyl thioformamide series **391c** are both established[622,623]; reactions have also been carried out with $ClCSOR^2$ and diethyl *N*-substituted phosphoramidites, when the products are the phosphonic amides **391d** (R = Et; R^2 = Me or Et; R^1 = NEt_2 or NHPh)[624]. Trialkyl phosphites and the *N*-chloroformyl derivatives of phenoxazine and phenothiazine provide the amides **393** (Z = O or S; n = 0)[625].

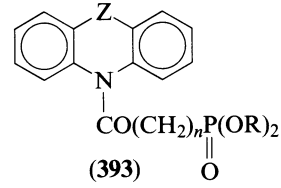


(390) (391)

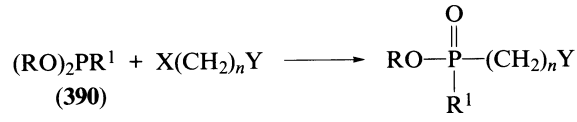
(**a**) A = O, B = OR^2
(**b**) A = O, B = NR^2
(**c**) A = S, B = NR^2_2
(**d**) A = S, B = OR^2



(**392**)



(**393**)



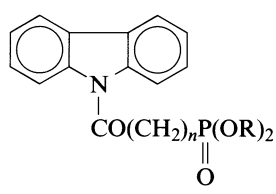
(390) (394)

(**a**) Y = CN
(**b**) Y = $COOR^2$
(**c**) Y = $COSR^2$
(**d**) Y = $CONR^2_2$

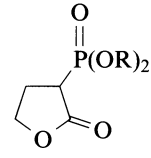
More generally, the compounds **394** have been obtained through the application of reaction 22, in which X = Cl or Br. The interaction of a trialkyl phosphite and chloroacetonitrile yields a dialkyl (cyanomethyl)phosphonate [(dialkoxyphosphinoyl)acetonitrile] (**394a**; R^1 = OR, n = 1)[626–628], and analogous reactions have also been carried out with chloro- or bromo-acetic acid derivatives to give **394b** (R^2 = alkyl[629–633] or aryl[634]), **394c** (R^2 = Et or Ar)[634], and **394d** (*N*-monoalkyl or *N*-phenyl, or *N,N*-dialkyl)[634,635], all with n = 1. Other reactions afforded the amides **393** (Z = O; n = 1)[636], **393** (Z = S, n = 1)[637,638] and **395**

(n = 2)[639]. The bromine in an alkyl bromofluoroacetate is replaced highly selectively[35,36,640,641]. Unusually, the reactions between the esters **390** and those of chlorothioacetic acid fail to result in the formation of the phosphorus–carbon bond, but proceed in accordance with equation 23[642].

(23)



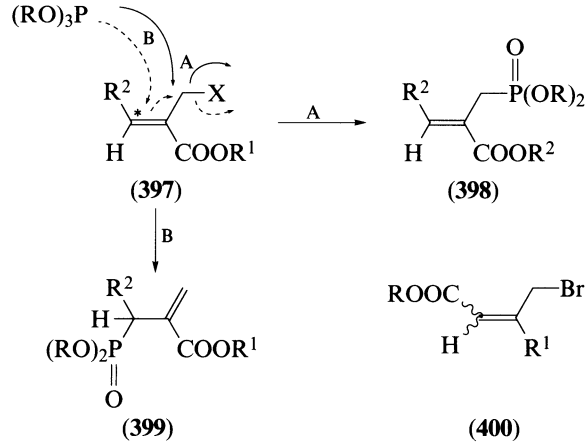
(**395**)



(**396**)

In principle, reaction 22 may be extended to the preparation of the products **394** with n having any value >1, and conventional reactions have thus been carried out with 3-halopropanoic[643–645], 4-halobutanoic[646–649], 5-chloropentanoic[649], and 6-bromohexanoic[650] acid derivatives. Triethyl 3-phosphonopropanoate has also been obtained from triethyl phosphite and β-propiolactone[651], although a 'normal' Michaelis–Arbuzov reaction occurs between trialkyl phosphites and α-bromobutyrolactones (3-bromotetrahydrofuran-2-ones) from which the anhydrides **396** (R^1 = H or Me) have been obtained[652,653]. Difficulties may be encountered should the carbon chain of the acid derivative be branched; for example, whereas Michaelis–Arbuzov reactions proceed satisfactorily with primary alkyl halides, and generally also with secondary alkyl halides[645,647,654–656], the use of tertiary alkyl halides is rarely, if ever, satisfactory. Compounds branched on the α-carbon atom may also be prepared, in principle, by the alkylation of trialkyl phosphonoacetates.

A study by McFadden *et al.*[657] examined the behaviour of several 2-halomethylpropenoic acid derivatives **397** towards simple trialkyl phosphites under a variety of experimental conditions. Two reaction pathways were discernible (Scheme 38), the first of



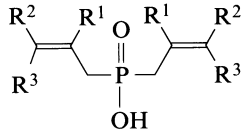
SCHEME 38

which consists in the typical and direct S_N2 displacement of halogen (pathway A) to give the 'normal' Michaelis–Arbuzov product **398**. In the second mode of attack, phosphite approach to C* leads (pathway B) to **399** through an allylic shift. The extent to which product formation occurs through each reaction pathway is controlled by experimental conditions, steric factors at C* and also by the electron density at C*. Reactions carried out with neat reactants at 120 °C, but also in benzene or diethyl ether, tend to occur completely, or extensively, with the formation of the products **399**; those performed in MeCN with added KI tend to proceed with very little rearrangement to give **398**. Even then, the nature of the leaving halogen atom can also influence the outcome; whereas **397** ($R^2 = CCl_3$, X = Cl) reacts with trimethyl phosphite to give >99% of **399**, the reaction fails to so proceed when X = Br, both with KI in MeCN. The choice of the group R has little influence on the outcome. Triethyl 4-phosphonocrotonate [ethyl 4-(diethoxyphosphinoyl)but-2-enoate][658–660] and related esters[661] as mixtures of *E* and *Z* isomers, and separate isomers of methyl [4-(diethoxyphosphinoyl)-3-methylbut-2-enoate][661,662] (or mixtures of isomers[663,664]) have been in widespread use as reagents in the Wadsworth–Emmons variation of the Wittig reaction, and are readily available through phosphite attack on **400** (R^1 = H or Me) without rearrangement; on the other hand, **397** ($R^2 = COOR^1$, R^1 =Me; X = Br) reacts through an allylic shift to give the corresponding **399**. The reaction between **397** (X = R^2 = Br, R^1 = Me) and trimethyl phosphite in boiling benzene results in 50% conversion into **398** [R = R^1 = Me, $R^2 = P(O)(OMe)_2$], presumably through a double allylic shift involving **399** (R^2 = Br, R = R^1 = Me) and attack by phosphite at the terminal double bond.

The use of bis(trimethylsilyl) hypophosphite (phosphonite) continues to provide more unusual compounds. In its reactions with methyl chloroacetate (in the reactant ratio 1:2) in the presence of an HCl acceptor (in this case hexamethyldisiloxane), the initial product **401** undergoes a Michaelis–Arbuzov reaction to yield **402**, from which the acid **403** is readily obtainable after standard manipulations[665]. The acids **404** and **405** have been prepared using the same methodology[666], and similar reactions have also been carried out with alkyl alkylphosphinates[667].

$(Me_3SiO)_2PCH_2COOMe$ **(401)**

$ROP(CH_2COOMe)_2$ **(402)** R = Me_3Si **(403)** R = H

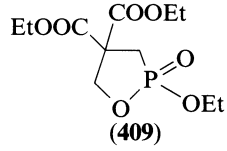


(404) R^1 = EtO, R^2 = COOEt, R^3 = H
(405) R^1 = COOEt, R^2 = R^3 = H

Michaelis–Arbuzov reactions are not restricted to the use of the alkyl halide but may also be carried out with a corresponding ester or alcohol. On reaction with triethyl phosphite or a phosphorus(III) amide, the ester $NCCH_2CH_2Z$ (Z = OAc)[668,669] and ethers (with Z = OPh or OEt)[668] afford the corresponding derivatives of (2-cyanoethyl)phosphonic acid [3-(dialkoxyphosphinyl)propanenitrile]. The same products are obtainable from 2-cyanoethanol[669]. These reactions, and the conversion of **406** into **408** and of **407** into **409**[670], are reminiscent of those which take place between phosphorus(III) esters and 2-hydroxybenzyl alcohols, and indeed they may be formulated in a similar manner (Chapter 2, Section II.A). Yet a further variation in reaction 22 is the involvement of substrates in

$(EtOOC)_2CR(CH_2OH)$
(406) R = H
(407) R = CH_2OH

$(EtOOC)_2CHCH_2P(OEt)_2$
(408)



(409)

which X is a quaternary ammonium function[671], a methodology used more particularly for the preparation of (3-oxoalkyl)phosphonic acid derivatives.

As noted in the previous chapter, the reaction between a phosphorus(III) ester and an alkenyl halide with halogen-carrying (sp^2) carbon atom requires that the latter be activated through the presence of (an)other appropriate functional group(s), or that the system be stimulated either photolytically or by a metal salt catalyst. Here, it is interesting to note that both methyl (*Z*)- and (*E*)-3-chloropropenoate react with triethyl phosphite at 130–150 °C to give only methyl (*E*)-[3-(diethoxyphosphinoyl)propenoate][672], but that the reaction with ethyl (*Z*)-3-chlorobut-2-enoate appears to proceed with retention of geometry[673]. More unusually, however, ethyl 2-bromopropenoate (reaction with the chloro analogue proceeds less successfully) and triethyl phosphite afford a good yield of ethyl [3-(diethoxyphosphinoyl)propenoate][645]. These results, and also the formation of 3-(diethoxyphosphinoyl)propenenitrile from α-bromoacrylonitrile[674], are consistent with initial attack of phosphorus(III) at the terminal carbon atom.

It should be noted that, unlike the reactions between phosphorus(III) esters and monohaloalkanoic acid derivatives which, almost without exception, lead to the expected Michaelis–Arbuzov products, similar reactions which involve derivatives of polyhalogenoalkanoic acids tend strongly to yield enol phosphate esters as the major, if not the sole, product[675].

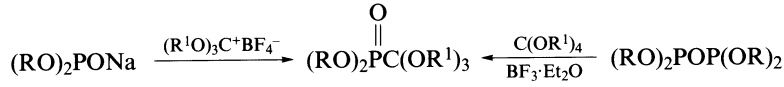
2. Through the acylation or alkylation of hydrogenphosphonates and related compounds

Classically, both acylation and alkylation of dialkyl hydrogenphosphonates have been achieved by adoption of the Michaelis–Becker procedure (Chapter 2, Section II.A). The formation of the compounds **391**, either from the sodium dialkyl phosphite or alternatively, by use of the hydrogenphosphonate in the presence of Et_3N, may be exemplified: **391a** (R^1 = OR)[676]; **391b**[619,620] (R = R^1 = Et)[677]; **391c** (R^1 = OR, R = Me_3Si)[678]. There are reports that, as in the case of the Michaelis–Arbuzov reaction, the use of methyl esters of the phosphorus acid, in this case dimethyl hydrogenphosphonate, is unsatisfactory[619], and that reactions which potentially lead to **391c** can fail[622].

Alkylation at phosphorus under Michaelis–Becker conditions has been widely practised. Triethyl phosphonoacetate, and also other phosphonoacetic esters, have often been made this way[215,679–681]; chlorine is selectively removed from esters of chlorofluoroacetic acid to give trialkyl fluoro(phosphono)acetate[682]. Longer chain ω-haloalkanoic esters afford highly satisfactory yields of phosphonic products[683]. However, unlike the Michaelis–Arbuzov reaction, the use of secondary halides is not very satisfactory and the halides RCHBrCOOEt with sodium dialkyl phosphites are said to lead to diastereoisomeric mixtures of the acids $(CHRCOOH)_2$ [R =Et (30%), R = Hex (10%) and R = Ph (5%)][680].

As a novel example of the use of sodium dialkyl phosphites, Scheme 39 indicates the preparation the phosphonoyl orthoesters **410**, also obtainable from tetraalkyl diphosphites[684].

There are also examples of the use of phase-transfer procedures for the preparation of phosphonoacetic derivatives[685–688] with catalysis by tetraalkylammonium salts or 18-crown-6, and also of the synthesis of analogous phosphinic acid derivatives from

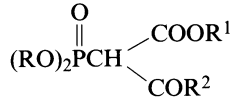


(410)

SCHEME 39

chloroacetic esters and alkyl phenylphosphinates, also in the presence of tetraalkylammonium salt catalysts[689].

Latterly, attention has been turned to the alkylation of the hydrogenphosphonates themselves under essentially neutral conditions, thus obviating the several possible side reactions. The formation (in 38% yield) of triethyl phosphonoacetate from diethyl hydrogenphosphonate and ethyl diazoacetate has been known for some time[690], and the synthetically useful methyl (di-*tert*-butoxyphosphinoyl)acetate (in 40% yield) has been similarly and more recently obtained[691]. Steps have been to try to improve yields under photoinitiation in the presence of copper salts or complexes[692–694], or through catalysis by trifluoromethanesulphonic acid[695]. Such procedures allow the ready synthesis of the esters **411** (R^2 = alkyl or RO).



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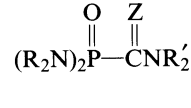


(412)

3. Through addition reactions of hydrogenphosphonates and related compounds

The simplest of these reactions consists in the addition of hydrogenphosphonate esters to isocyanates or isothiocyanates, when the products are the amides **391b** (R^1 = RO) with R^2 = alkyl[619,620] or aryl[620,696], or **391c** (R^1 = RO) with R^2 = alkyl[697,698] or Ph[699]. Differences in reactivity on the part of the isocyanate are to be noted; the use of MeCNO requires the presence of a catalysis, unlike that of PhNCO. Hydrogenphosphonic bis(dialkylamides) also react with isocyanates[700] or isothiocyanates[700–702] when the products are the triamides **412** (Z = O or S).

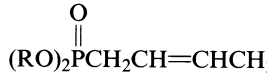
Much more commonly encountered, however, are the additions of hydrogenphosphonic esters or hydrogenphosphinic esters to α,β-unsaturated nitriles, esters, or amides, and generally carried by the addition of a small amount of base catalyst, usually an alcoholic alkoxide solution (with the same alkyl group to be found in the phosphorus ester), to a mixture of the reactants. The reader is referred to reviews[288,355] for the older literature pertaining to the procedure. In the general reaction illustrated in equation 24, some of the more commonly encountered substrates, and the products derived from them are indicated. The substrates include acrylonitrile (which gives **413**); methyl propenoate (which gives **414**)[703]; alkyl 2-methylpropenoates (which give **415**)[703]; 2-methylpropenoamides (which lead to **416**); but-2-enoic esters (which give **417**)[703]; and 3-phenylpropenoic esters (which furnish **418**). Reactions which employ alkyl ethyl- or phenyl-phosphinates, $R^1(R^2O)P(O)H$ (R^1 = Et or Ph), yield the phosphinic analogues of several of the products **413–418**. The yields in such addition reactions tend to be moderate to good, except for the amides, and for the compounds **417** when the group R is large (C_6–C_8). The results obtained for the additions of hydrogenphosphinate esters suggest similar tendencies.

Several slightly more unusual examples are worth presenting. The very vigorous reaction between a dialkyl hydrogenphosphonate and penta-2,4-dienoic acid proceeds to the phosphonic diester **419** initially but which, with more reagent, affords the diphosphonic

$$(RO)_2P(O)H + R^1CH{=}CR^2Z \xrightarrow{RONa} (RO)_2\overset{\overset{O}{\|}}{P}CHR^1CHR^2Z \qquad (24)$$

	R^1	R^2	Z
(413)	H	H	CN
(414)	H	H	COOMe
(415)	H	Me	$COOR^3$
(416)	H	Me	$CONR_2^3$
(417)	Me	H	$COOR^3$
(418)	Ph	H	$COOR^3$

acid ester **420**; ethyl sorbate initially yields **421** followed by **422**; the structures of the unsaturated adducts were confirmed by ozonolysis[704]. The furan derivatives **423a** and **b**[705] and the thiophene derivative **423c**[706] afford the corresponding adduct **424**, and an analogous reaction has been carried out with benzylidenemalononitrile[707].



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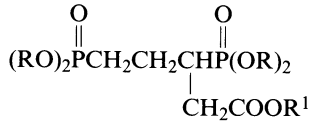
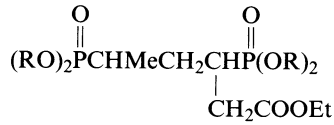


(420)

(421)



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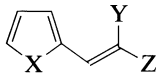
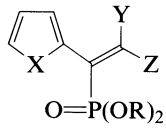


(423)

(a) X = O, Y = COOEt, Z = COMe
(b) X = O, Y = Z = COOEt
(c) X = S, Y = Z = CN



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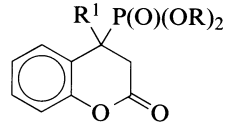
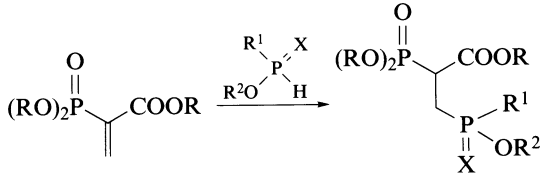


(425)

The dihydrocoumarinylphosphonic diesters **425** are obtained in the predictable manner from the appropriate coumarin[708]. Additions to a 2-phosphonoylpropenoic ester {[1-(alkoxycarbonyl)ethenyl]phosphonic diester} are exemplified by the alkoxide-catalysed additions of dialkyl hydrogenphosphonates (or thiophosphonate)[709] and of the methoxide-catalysed addition of methyl phenylphosphinate[710] to 2-(dialkoxyphosphinoyl)propenoic esters (R = Et or Me) according to equation 25. The addition of hydrogenphosphonic esters to (*E*)- or (*Z*)- but-2-enedioic esters yields esters of 2-phosphonobutanedioic acid[711] and several polycarboxy polyphosphonic acids have been prepared by this and related procedures[712].

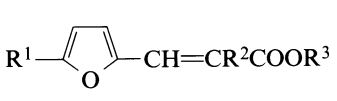
One example of the study of electronic effects on reaction 24 is that of the *tert*-butoxide-catalysed addition of diethyl hydrogenphosphonate to diethyl *p*-substituted-benzylidene-



(25)

malonates, additions which normally proceed rapidly to yield the products **426** and which are activated by halogen substituents, but which suffer the reverse effect when the substituent is the Me_2N group[713]. The addition of diethyl hydrogenphosphonate to the furans **427** in the presence of sodium diethyl phosphite yields the products **428** (R^1, R^2 = H or Me) in yields of 25–55% (R^3 = C_2–C_4), but the reaction is retarded for the amides, when yields may be as low as 13–19%[714].

(426)



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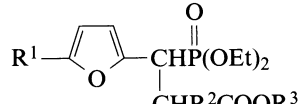
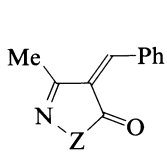


(428)

Reports of the additions of hydrogenphosphonates to heterocyclic systems, effectively unsaturated carboxylic acid derivatives, abound. As examples, the addition of dimethyl hydrogenphosphonate to **429** (Z = O)[715] and to **429** (Z = NPh)[716] yield the corresponding **430**. Dimethyl hydrogenphosphonate and **431** (R = Ph, Z = O) react initially give the enol **432**, which tautomerizes to **433**, a sequence which, in the presence of Et_2NH or Et_3N, occurs even in low-boiling hydrocarbons[717]; similarly, the interaction of diethyl hydrogenphosphonate and **431** (R = Me, Z = S) or analogues occurs in the presence of Al_2O_3–KF under microwave irradiation and in high yields[718].



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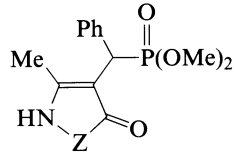

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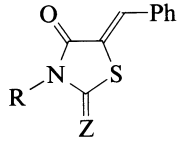

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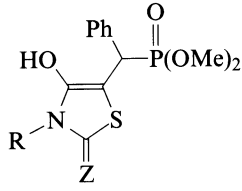
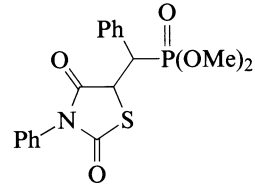
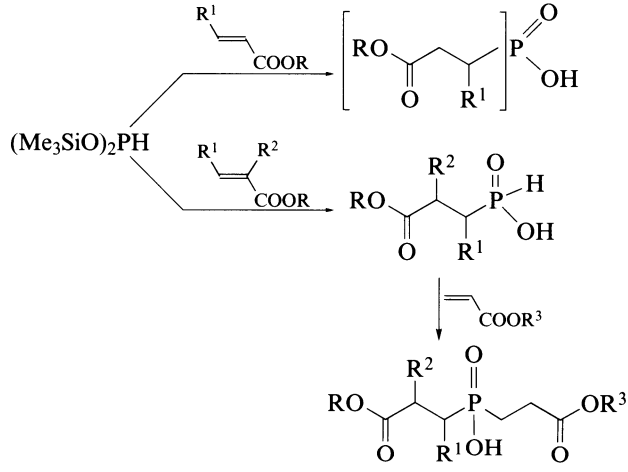


(432)

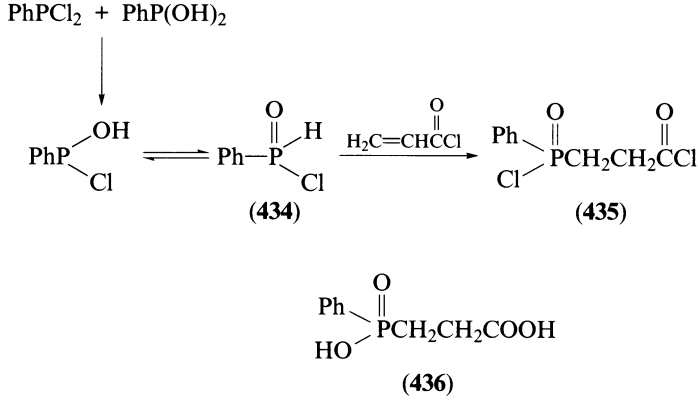


(433)

An important feature of the utility of bis(trimethylsilyl) hypophosphite in synthesis consists in its capability to undergo addition reactions, and which has been exploited in several ways to provide phosphinic acids which possess carboxy groups; these reactions are summarized in Scheme 40[719] (the structures indicated here represent the final products following the acidolytic removal of trimethylsilyl groups). An equimolar mixture of phenylphosphonous dichloride ($PhPCl_2$) and phenylphosphonous acid (phenylphosphinic acid) behaves as the phosphinic chloride **434**, and so adds across carbonyl activated carbon–carbon multiple bonds by virtue of the presence of the P—H bond; propenoyl chloride thus affords the acid dichloride **435**, which may be hydrolysed to 3-(hydroxyphenylphosphinoyl)propanoic acid (**436**)[720].



SCHEME 40



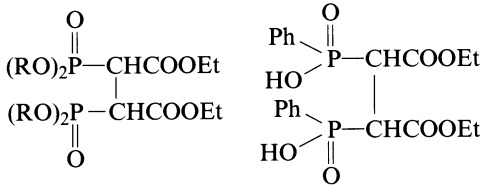
The addition of hydrogenphosphonic diesters to ethenylphosphonic or ethenylphosphinic derivatives follows equation 26, and that of the hydrogenphosphonates to the (1,2-butadiene)phosphonic system is represented by equation 27.

Additions of hydrogenphosphonates to sp carbon bonded systems also occur rapidly[288,355]. Those to diethyl butynedioate give the esters **437**; the phosphinic chloride **434**

$$H_2C{=}CHP(O)(OR)_2 \xrightarrow{(R^1O)_2P(O)H} (R^1O)_2P(O)CH_2CH_2P(O)(OR)_2 \quad (26)$$

$$Me_2C{=}C{=}CHP(O)(OR)_2 \xrightarrow{(R^1O)_2P(O)H} Me_2C{=}C(O{=}P(OR^1)_2)CH_2P(O)(OR)_2 \quad (27)$$

behaves similarly at 90 °C and affords **438**[347]. Additions to the esters **439** (R^1 = H)[709,712] and to **439** (R^1 = Ph), both in excess, can, it seems, be stopped at the half-way stage **440**, as can the additions of hydrogenphosphinates[721].



(437) **(438)**

$$R^1C{\equiv}CCOOR^2 + (RO)_2P(O)H \longrightarrow R^1C(O{=}P(OR)_2){=}CHCOOR^2$$

(439) **(440)**

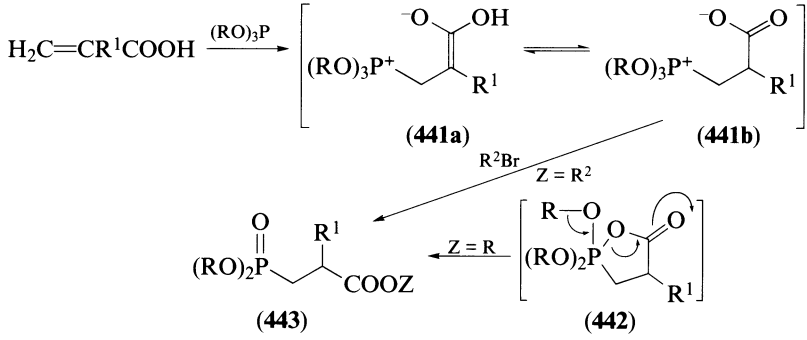
$$\longrightarrow [(RO)_2P(O)]CR^1CH_2COOR^2$$

4. Through the additions of phosphorus(III) triesters or amide esters to α,β-unsaturated carboxylic acids and their derivatives

The reactions between α,β-unsaturated carboxylic acids and phosphorus(III) triesters or mixed amide esters parallel those which have already been noted to occur between the triesters and aldehydes to the extent that, depending on the experimental circumstances, *O*-alkylation may occur along with phosphorylation at carbon.

The interaction of a trialkyl phosphite or related phosphorus(III) triester with an unsaturated carboxylic acid (or derivative) occurs readily. Propenoic acid reacts with phosphite triesters at room temperature, although such a reaction with 2-methylpropenoic acid requires initiation by slight warming. Phosphorus(III) esters also react vigorously with maleic anhydride, again at room temperature. The reactions are promoted by the use of a highly polar solvent ($PhNO_2$ or Me_2CO) or retarded in one of lower polarity (diethyl ether, pyridine)[722]. The reactions between propenoic or 2-methylpropenoic acid and phenylphosphonous[723] or ethylphosphonous[724] esters proceed even more vigorously but are, nevertheless, generally carried out in the neat state. The addition is not retarded by the presence of large (aromatic) substituents on $C_{(3)}$[725].

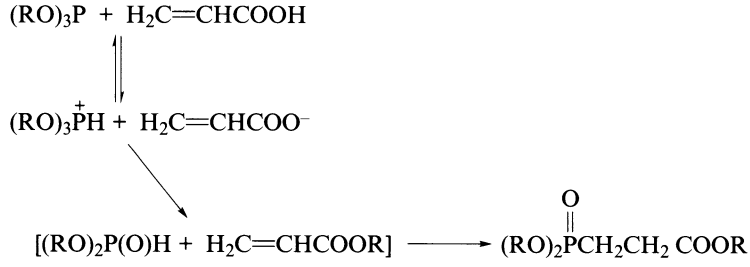
One plausible mechanism (due to Kukhtin and coworkers[726,727]) for the addition of a trialkyl phosphite to propenoic acid, or a simple α-substituted derivative thereof, is outlined in Scheme 41, and this might be compared (when R^1 = CH_2Hal) with Scheme 38.



SCHEME 41

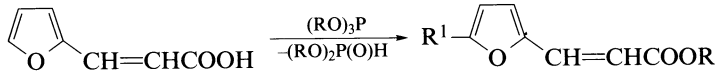
Following the nucleophilic attack of phosphorus(III) at the β-carbon [$C_{(3)}$], the resultant intermediate may have a linear dipolar structure, **441a** (with tautomerization to **441b**), or a cyclic (oxyphosphorane) structure **442**. Whatever the true nature of the intermediate, its breakdown leads to an alkyl [3-(dialkoxyphosphinoyl)propanoate] (**443**). In addition to solvent effects on reaction rate, just noted, a further indication of the probable participation stems from an examination of reactions in which an alkyl halide is added to effect competition with the translocation of an alkyl group from the POR grouping. For a discussion of the very detailed experiments, the original paper should be consulted, but it might be added that, as the authors pointed out, when the added alkyl halide is a particularly reactive one, e.g. iodoethane, the reaction then becomes one between the unsaturated carboxylic acid and a pseudophosphonium salt, $(RO)_3P^+R\ I^-$; in this case the various isolable products uppear to be consistent with a further mechanism which involves attack by COO^- on P^+, a theme developed to account for the addition reactions of other phosphorus(III) species. No further account was taken of the possible role of an oxyphosphorane intermediate, nor indeed, was there any evidence that such an intermediate is actually formed; at the same time, however, there seems to be no evidence to the contrary, and many of the experimental results are equally explicable through the participation of either type of intermediate.

The alternative addition mechanism, introduced briefly in the paragraph immediately preceding, seems to have arisen from observations on the comparative behaviour of propenoic and 3-phenylpropenoic acids towards dialkyl chlorophosphites, $(RO)_2PCl$[728], and involves attack on the protonated ester molecule by the acid anion, a sequence which liberates the dialkyl hydrogenphosphonate (and isolated in some experiments[729]) and alkyl propenoate (Scheme 42); the overall reaction sequence is then terminated by the addition of dialkyl hydrogenphosphonate to the alkyl propenoate to give the observed product.



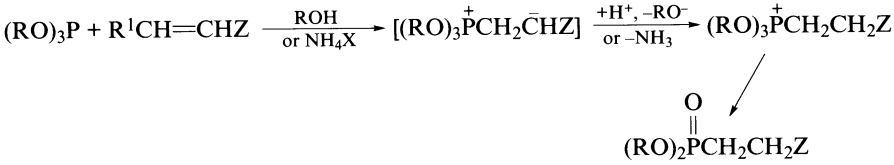
SCHEME 42

The intermediate step in this proposed mechanism is consistent with the well known alkylating activity shown towards saturated carboxylic acids by trialkyl phosphites, during which dialkyl hydrogenphosphonates are formed. With triethyl or triisopropyl phosphite, 2-furancarboxylic acid yields the corresponding ester, and it does not behave (in the light of the reduced aromaticity and enhanced alicyclic character of the furan ring) as an unsaturated carboxylic acid. It is therefore of interest that 3-(2-furanyl)propenoic acid undergoes a similar alkylation to give **444**, but additionally yields the nuclear phosphorylated product **445**[730].



(**444**) R = Et or Pr^i, R^1 = H
(**445**) R = Et, R^1 = $(EtO)_2P(O)$

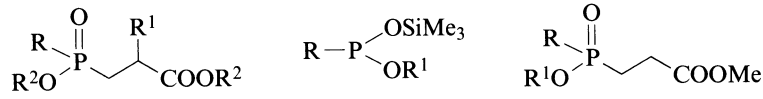
Although the combined additive phosphonylation and esterification of an α,β-unsaturated carboxylic acid by a trialkyl phosphite can thus easily, although not necessarily accurately, be envisaged, that of a similarly unsaturated ester, nitrile, or amide is perhaps not so readily apparent. Harvey[731] showed that successful reaction between triethyl phosphite and such a substrate (Scheme 43) occurs in a protic medium. In this respect, the reactions proceed faster in methanol than in ethanol, but reactions are, in general, (including those of structurally analogous unsaturated ketones) much cleaner and faster when carried out in phenol, and also afford much higher yields in this solvent. It has also been shown[732] that ammonium salts will also act as a proton source to allow completion of addition without alkylation. The later Russian workers used acetic acid with successful results[729].



Z = COO-alkyl, CN or $CONR_2$

SCHEME 43

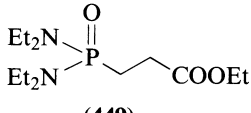
As already mentioned, phosphonous esters, $RP(OR^2)_2$, are extremely reactive to propenoic and 2-methylpropenoic acids, and the products have the structure **446** (R^1 = H or Me)[723,724]. Reactions have also been performed with silyl phosphonite esters (**447**; R^1 = alkyl or Me_3Si) which, with methyl propenoate, yield the products **448** (R^1 = alkyl or H) after hydrolytic removal of the silyl group[733].



(**446**) (**447**) (**448**)

The reactions between α,β-unsaturated carboxylic acids and phosphoramidous diesters or phosphorodiamidous esters are, as might be expected, more complex than those with phosphorus(III) triesters. The products from propenoic acid and $EtOP(NEt_2)_2$ include the amides **449** and **450** (in 21% total yield), the phosphonic amide **451** (26%) and *N*,*N*-

diethylpropenamide[643]; 2-methylpropenoic acid behaves similarly. Anilides of phosphorus(III) acids appear to behave differently. With $(EtO)_2PNHPh$ in the presence of EtO^-, propenoic and 2-methylpropenoic acids yield the analogous products **452** (3-phenylpropenoic acid affords the carboxanilide and diethyl hydrogenphosphonate)[734]; the reactions between diethyl butenedioate and $(EtO)_2P(O)NHC_6H_4R$–4(R = H, Me, MeO, or Cl) all proceed in a solvent at room temperature to give the stable and isolable phosphonimidates **454**, presumably via the dipolar ion **453**[735].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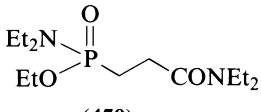
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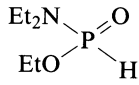
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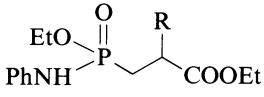
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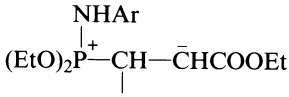
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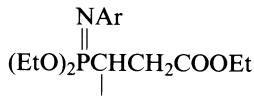
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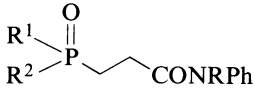
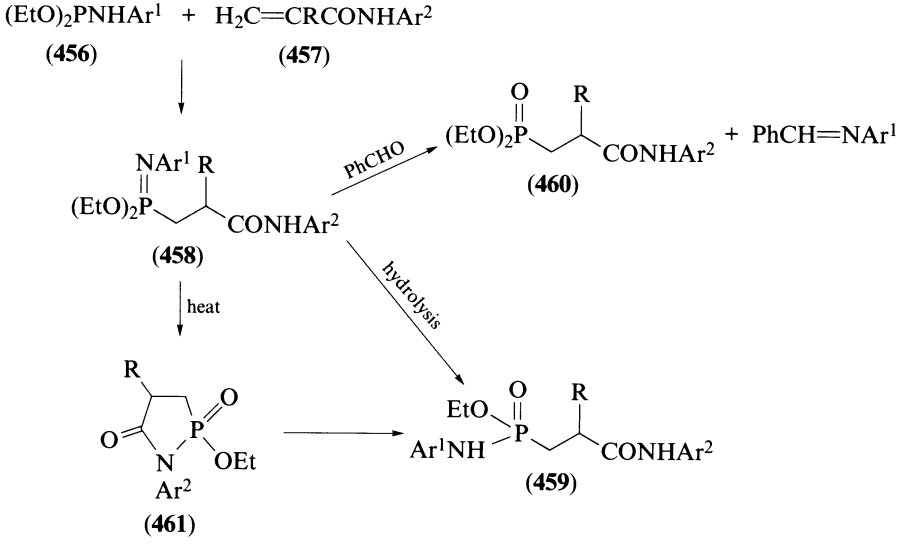

(455)

Reactions between propenoic anilide and phosphorus(III) esters or amides appear to follow a pathway comparable to that given in Scheme 42 and yield *N*-alkylated products **455** ($R^1 = R^2 = OR$, R = Et; $R^1 = RO$, R=Et, $R^2 = NEt_2$; $R^1 = R^2 = NEt_2$, R = Et) and, indeed, separate additions of dialkyl hydrogenphosphonates to the appropriate propenamides yield the same products in not dissimilar yields[736,737].



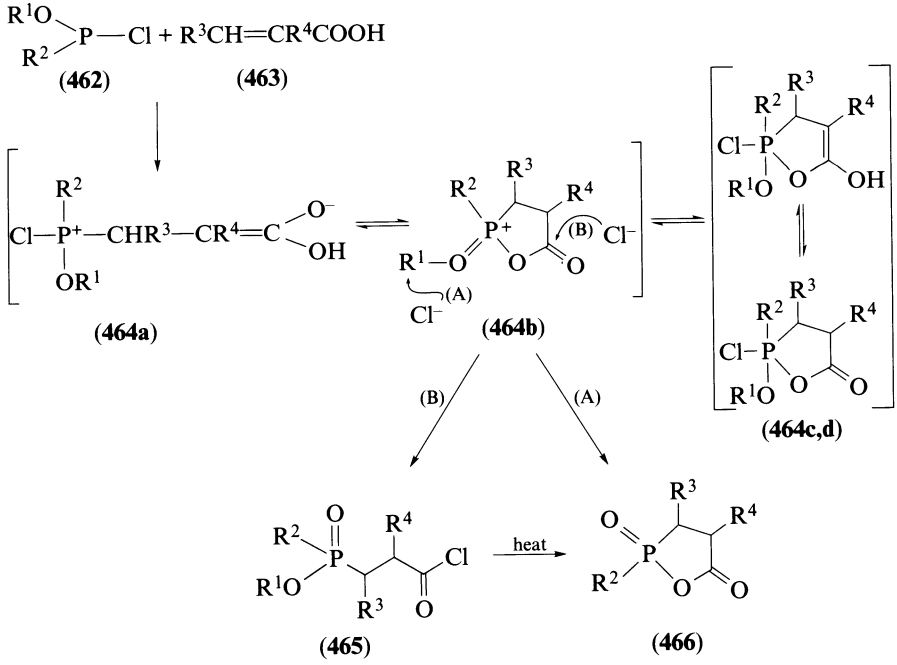
The combination of a propenoic anilide (**457**; R = H or Me) and dialkyl phosphorus(III) anilides (**456**) together affords the *N*-arylphosphonimidates **458** (compare the formation of **454**), the structures of which were confirmed by hydrolysis to be phosphonic monoamides **459**, and by reaction with benzaldehyde to yield the [3-(dialkoxyphosphinoyl)propanamide] **460** together with an appropriate aldimine; when heated, the imidates **458** yield the 1,2-azaphosph(V)olidin-5-ones **461**[738].

Analogous reactions between phosphorus(III) triesters or amide esters and various unsaturated derivatives of heterocyclic systems, e.g. benzylidene derivatives of pyrimidinetriones[739,740] or of other systems, e.g. **429**, proceed through dipolar intermediates and lead to appropriately tautomeric *O*- or *N*-alkyl derivatives[715,741], or even, in the case of benzylidenemalonodinitrile, to *C*-alkylation[707].

The addition of a trialkyl phosphite to an acetylenic acid requires no catalyst. In the case of butynedioic acid, the products are stated to be dialkyl 2,3-bis(dialkoxyphosphinoyl)butanedioates[742]. As for propenoic acid and its derivatives, more than one mechanism can be formulated to account for the overall addition reaction.

5. Through the additions of phosphorus(III) chlorides to α,β-unsaturated carboxylic acids and their derivatives

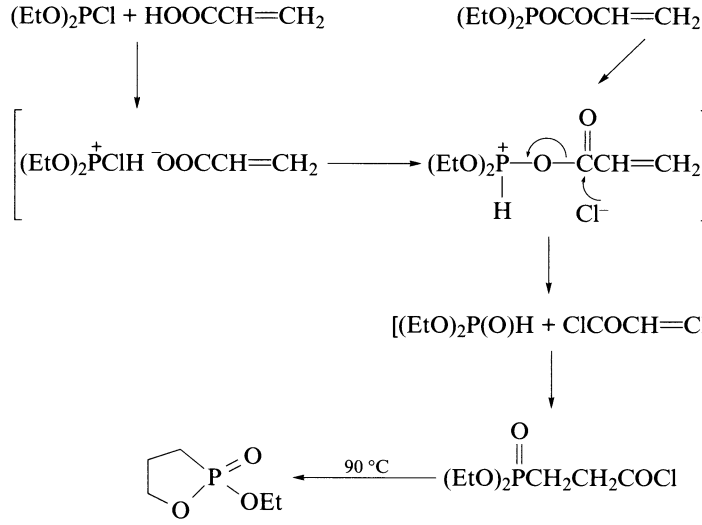
In outline, the reaction between a phosphorus(III) chloride **462** and an α,β-unsaturated carboxylic acid **463** might be formulated in a way (Scheme 44) similar to that between the same acids and a phosphorus(III) ester (Scheme 41); a linear dipolar intermediate adduct **464a** leads to, or is in equilibrium with, a cyclic chlorophosphonium salt **464b**, which, in turn, might be in equilibrium with a pentacoordinate (phosphorane) structure in its tau-



SCHEME 44

tomeric forms, although, once again, no evidence has yet been presented in support of the last suggestion. Breakdown of the intermediate(s), of whatever nature, leads to the linear **465** or the cyclic **466** product.

Very few reports have been concerned with phosphorus chlorides of the types $(RO)_2PCl$ or $ROPCl_2$. For the former (R = Et), the product from propenoic acid consists of the linear ester **465** ($R^2 = OR^1$, R^1 = Et; $R^3 = R^4$ = H)[718], although readily transformed, when heated comparatively gently, into the corresponding 2-ethoxy-2-oxo-1,2-oxaphospholan-5-one (**466**), and that from 2-methylpropenoic acid consisted of the corresponding 4-methyl derivative **466** (R^4 = Me)[743]. However, a detailed study of the reaction between $(EtO)_2PCl$ and propenoic acid, using ^{31}P NMR spectroscopy, showed that the gradual disappearance of the chlorophosphite is accompanied by the slow formation of diethyl hydrogenphosphonate; later, the NMR signal for the linear product **465** ($R^2 = R^1$ O, R^1 = Et; $R^3 = R^4$ = H) increases as that for the hydrogenphosphonate decreases. As a consequence of this study, the proposed mechanism (Scheme 45) received support following the observed formation of the same compound from diethyl propenoyl phosphite and HCl[728]. Additionally, the mechanism appears to be consistent with some observations on reactions between dichlorophosphines and certain derivatives of propenoic acid (see later).

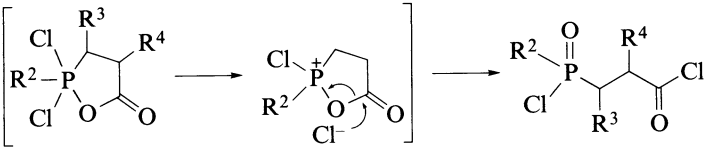


SCHEME 45

Some reactions have been carried out with the ester chlorides **462** (R^2 = alkyl[744] and aryl[745]) when the phosphinic acid derivatives **465** were isolated in essentially pure form, but these also, when distilled, afford 1,2-oxaphospholanes **466**[746,747].

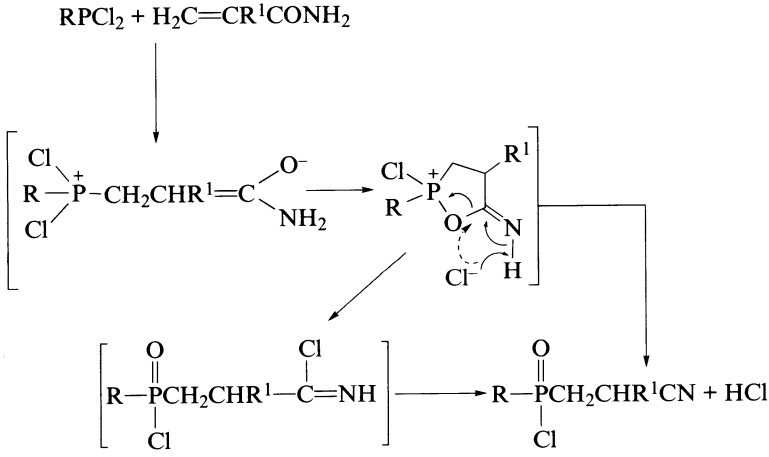
By far the most extensively investigated reaction is that in which phosphonous dichlorides (dichlorophosphines) take part. In these cases, the reaction cannot proceed through **464b**, but most probably does through **464f**, which breaks down to **467**. Such reactions have involved $MePCl_2$[748–752], $ClCH_2PCl_2$[753], $EtPCl_2$[745–757], $H_2C{=}CHPCl_2$[758], $Me_2C{=}CHPCl_2$[759], $PhPCl_2$[760,761], *p*-$TolPCl_2$[757] and 2-thienyl PCl_2[762]. The general order of decreasing reactivity is $RPCl_2 > ArPCl_2 > ClCH_2PCl_2$ and in all cases the products are of the form **467** (R^3, R^4 = H or Me), but conversion of these into the cyclic anhydrides **466** may be achieved following their reaction with acetic anhydride. In some instances the simple carboxylic acid chloride is a by-product of the reaction, but in very few cases, it may

even become the main product as, for example, in the reactions between *p*-TolPCl$_2$ and but-2-enoic acid, and between EtPCl$_2$ and 3-phenylpropenoic acid, when the yields of **467** approach 5% only[757].



(**464e**) (**464f**) (**467**)

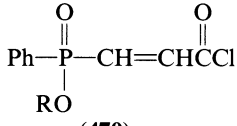
It should be no surprise that reactions which involve phosphorus(III) chlorides and propenamides may yield nitriles as the principal products (Scheme 46), the nitrile being potentially derivable from two possible intermediates. Amongst the phosphorus(III) dichlorides used here have been MePCl$_2$[763,764], ClCH$_2$PCl$_2$[765], EtPCl$_2$[766], PhPCl$_2$ and *p*-TolPCl$_2$[767]. 3-Chloropropanenitrile (from propenoic acid) and Me$_2$CClCN (from 2-methylpropenoic acid) are also produced in the same reactions, but the main by-products are the anhydrides **468**. Analogous 3-phosphinoylpropanenitriles have been obtained from Ar(RO)PCl[768,769].



SCHEME 46

Reactions between ClCH$_2$PCl$_2$[770], EtPCl$_2$[771–773] or PhPCl$_2$[774] and propynoic acid afford the 3-phosphinoylpropenoyl chlorides **469**, whilst the chlorides Ph(RO)PCl similarly yield the phosphinic esters **470**[775]. With acetic anhydride, **469** produce the unsaturated cyclic anhydrides **471**, hydrolysable, as is **469**, to the acids **472**. When heated, **470** also yields **471**.

(**468**) (**469**)



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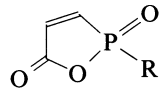
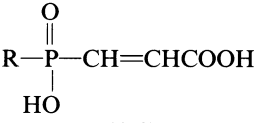


(471)



(472)

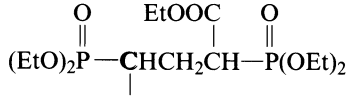
B. Syntheses Through Modification Procedures

In addition to the two general processes described here, namely (1) the introduction of the COOH group, or further COOH groups, or other groups derived therefrom, through acylation of a phosphonoyl carbanion, and (2) the phosphorylation of a substrate lacking such functionalization, many other synthetic procedures entail the modification of appropriate substrates through classical organic procedures. Such procedures as, for example, the Knoevenagel and Stobbe reactions, are essentially concerned with modification without further functionalization, and are therefore considered more fully under discussions of the properties (Chapter 6) of phosphonoyl alkanoic acids.

1. From phosphonoyl carbanions by acylation or alkylation

Lithiated phosphonoyl carbanions are readily acylated with chloroformic esters[776–778], as are the lithiated carbanions from phosphonic diamides[779]. The lithiated carbanions from halogenated phosphonic diesters have been acylated with diethyl carbonate[780] or carboxylated using CO_2[781,782] and, depending on the individual substrate, a lithiated carbanion can yield the dithio derivative $(RO)_2P(O)CXYCSSMe$ when treated with CS_2 followed by MeI[781], also available through the use of the phosphonate copper complex with ClCSSMe[783]. Alternatively, a zinc complex, e.g. $(EtO)_2P(O)CF_2ZnBr$, may be acylated with ClCOOEt–Cu(I) or with $ClCONEt_2$–Cu(I)[31].

The alkylation of a phosphorylated carbanion is not always successful as a preparative procedure, For example, the methylation of the carbanion from a trialkyl phosphonoacetate with one equivalent of MeI yields a mixture of mono- and di-methylated products together with unreacted substrate, and which is very difficult to resolve by distillation, although the introduction of a single alkyl group has been claimed through the use of phase-transfer techniques[784] and the same technique has been applied to the alkylation of phosphonic diamides[785]. The sodium salt from triethyl phosphonoacetate is alkylated with $ClCH_2SMe$, and the expected product undergoes sequential elimination and addition to yield diethyl [1,3-bis(diethoxyphosphinoyl)pentanedioate] (**473**) in 56% overall yield[786]. Greater success has been claimed for the alkylation of the carbanions from methylenebisphosphonic and *N*-substituted diethoxyphosphinoylacetamides with *N*-substituted chloroacetamides in the search for new complexing agents such as **474** and **476**[787,788], and a similar procedure with the respective esters has given esters of 2-phosphonobutanedioic acid (**475**)[789,790]. Acylation with oxalic esters yields phosphorylated *β*-oxoalkanoic esters.



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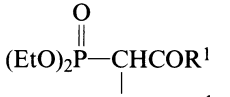
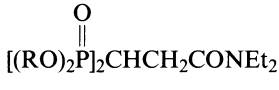


(474) $R^1 = NEt_2$
(475) $R^1 = OR$



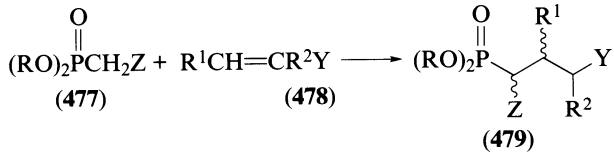
(476)

2. Through the phosphorylation of carbanions

This procedure has not been seriously adopted in view of the very marked tendency of active methylene carbanions and appropriate phosphorylating agents, for example, $(EtO)_2P(O)Cl$, to form phosphate esters derived from the enol tautomers. One useful example appears to such phosphorylation of the anions derived from the species RCH_2Z, with R = H, Me, Et or prop-2-enyl, and Z = CN or COOMe (and also NO_2, but not MeO)[791].

3. Through the use of the Michael reaction

An important procedure in which the carboxyl-derived group is introduced into a phosphonoyl moiety is based on the Michael addition of appropriate phosphonoyl or phosphinoyl carbanions (effectively) to sp^2 or sp bonded systems. Once again, the synthesis of a desired compound can be approached from two different directions, essentially (1) the addition of the phosphorus-containing carbanion to a phosphorus-free substrate or (2) the addition of an active methylene compound to an α,β-unsaturated phosphonic or phosphinic acid derivative. Alternatively, both reactants may possess a phosphonic acid or related moiety. Using this methodology, a wide variety of structural types are theoretically attainable. The addition of the carbanion from **477** to the alkene **478** leads to a potential mixture of stereoisomers of the adduct **479**. The addition of carbanions **477** to esters of propenoic acid **478d** in thf at –78 °C lead to mainly the *anti* stereoisomeric product[792]. Reactions between **477a**[679,712,789], **477b**[626,679] or **477c**[712,793] to propenoic esters **478d**[626,679,712,793] or **478e**[793] or to those of butenedioic acid **478g**[711,789] proceed readily to give the mono adduct which, since a second labile proton is available, can undergo further reaction to give a 1:2 adduct **480**. A recent report[794] indicates that tetraethyl methylenebisphosphonate and electron-deficient alkenes (e.g. acrylonitrile and methyl propenoate) yield cyclopropane derivatives in the presence of Al_2O_3/KF.



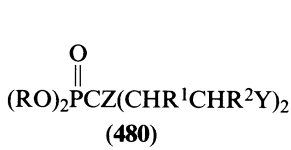
(477) **(478)** **(479)**

(a) Z = COOR′
(b) Z = CN
(c) Z = P(O)(OR)$_2$
(d) R^1 = H, R^2 = H, Y = COOR′
(e) R^1 = H, R^2 = H, Y = CN
(f) R^1 = H, R^2 = H, Y = P(O)(OR)$_2$
(g) R^1 = COOR′, R^2 = H, Y = COOR′

The reaction between lithiated diethyl propenylphosphonate and ethyl propenoate leads to carbon–carbon bond formation involving either $C_{(1)}$ or $C_{(3)}$ of the phosphonate ester[795]. Thus, ethyl but-2-enoate or but-3-en-2-one yielded **481** and **482**, respectively, and the esters **483** were obtained from coumarin, all by simple addition, but addition-elimination and multiple addition processes were also described.

The additions of **477a** or **477c** to butynedioic esters **484** yield *E–Z* mixtures of the 1:1 adducts **486**; the reaction between **477** (R = Me, R′ = Me) and **485** gives a mixture with these isomers in the ratio 3:1[796]. The addition of **477c** (R = Me) to **484** affords a 35:65 mixture of *E–Z* isomers of the product **486**, but the ratio is reversed when R = Et[796]. Additions of **477** to **485** yield **487**[797].

Lastly, it may be mentioned that similar reactions occur between phosphonoylated carbanions **477** and isocyanates, R′ NCO, when the initial products have the structure $(RO)_2P(O)CHZCONHR'$[798].



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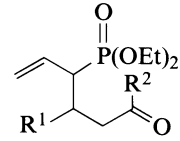
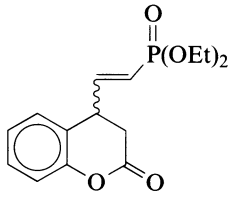


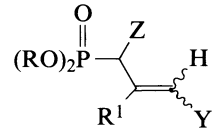
(481) R^1 = Me, R^2 = EtO
(482) R^1 = H, R^2 = Me



(483)

$R^1C{\equiv}CY$

(484) R^1 = COOMe, Y = COOMe
(485) R^1 = $(RO)_2P(O)$, Y = Me



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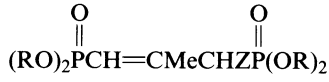


(487)

VII. OXOALKYL-PHOSPHONIC AND -PHOSPHINIC ACIDS

The (oxoalkyl)-phosphonic and -phosphinic acids form a remarkable group of compounds whose ease or formation, stability and versatility in use depend to a high degree on the relative positions of the oxo and phosphoryl groups. From the points of view of both synthesis and reactivity, the (1-oxoalkyl) compounds, also termed acylphosphonates, stand apart from the remaining compound types, and they have been considered separately in this volume and elsewhere[799]; the discussion here is designed to offer a comparison between syntheses of acylphosphonic acids with those of other important oxoalkyl phosphonic and phosphinic acids.

Many of the reactions applied to the synthesis of phosphonoyl and phosphinoyl alkanoic acids described in the previous section can also, in principle, be applied to the synthesis of oxoalkyl-phosphonic and -phosphinic acids. A notable exception, however, is the synthesis of those compounds in which the oxo group is in the β-position relative to phosphorus, when important syntheses lead not to phosphonate or phosphinate esters, but rather to enol esters of phosphoric acid through what is now referred to as the Perkow reaction[675,800].

A. Syntheses Through Phosphorus–Carbon Bond Formation

1. Through the Michaelis–Arbuzov reaction

Equation 28 represents the formation of oxoalkyl phosphonic acid esters (**488**; R^1 = OR) or phosphinic esters (**488**; R^1 = alkyl or aryl) from phosphite or phosphonite esters and appropriate halogen-containing ketones ($n \geq 1$) or acyl halides ($n = 0$), and supplements the formation of the phosphonoylated or phosphinoylated alkanoic acids through reactions 21 and 22 in the previous section.

$$(RO)_2PR^1 + Cl(CH_2)_nCOR^2 \longrightarrow RO-\underset{\underset{R^1}{|}}{\overset{\overset{O}{\|}}{P}}-(CH_2)_n\overset{\overset{O}{\|}}{C}R^2 \quad (28)$$

(488)

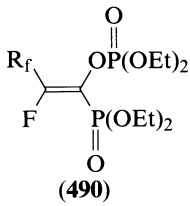
$$(RO)_2\overset{\overset{O}{\|}}{P}COR^1$$

(489)

The formation of esters of (1-oxoalkyl)phosphonic acids (**489**) through the interaction of alkanoic acid halides (the chlorides are generally employed) and trialkyl phosphites is widely documented, and the products are generally isolable with little difficulty[801–807]. Other compounds are derived from the appropriate phosphorous triester and a propenoyl halide[807–810], whilst (α-oxobenzyl)phosphonic esters are obtainable from aroyl halides[805,807,811–814]. Silyl phosphites[369,815], particularly diethyl trimethylsilyl phosphite[816] and tris(trimethylsilyl) phosphite[817–819], which afford diethyl acylphosphonates and bis-(trimethylsilyl) acylphosphonate, respectively, have the advantages of an increased phosphite nucleophilic activity relative to other phosphorus(III) esters and of the ease of removal of the ester protecting groups, generally achievable through methanolysis[817–819]. Benzyl esters of acylphosphonic acids also act as sources of the free acylphosphonic acids through complete debenzylation by hydrogenolysis[802], or monodebenzylation using NaI in acetone[802], a procedure used also for the monodemethylation of the dimethyl esters[807].

The reaction between tris(trimethylsilyl) phosphite and a perfluoroacyl chloride proceeds without any apparent difficulty to give the predicted phosphonate diester **489** [R = Me_3Si, $R^1 = CF_3$ or $(CF_3)_2CH$][820] but the use of longer chain polyfluorinated acyl halides[96,97] or other heavily halogenated acyl chlorides leads to complications; with such substrates, the initially formed acylphosphonate reacts with more phosphorus(III) ester to give the (*Z*)-enol phosphate **490** (Scheme 47). The halides, XCH_2COX (X = Cl or Br) afford only the esters **491** (X = H)[821].

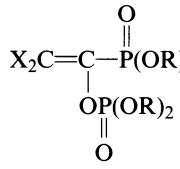
$$R_fCF_2COCl \xrightarrow{(EtO)_3P} (EtO)_2\overset{\overset{O}{\|}}{P}COCF_2R_f \xrightarrow{(EtO)_3P}$$



(490)

SCHEME 47

Very vigorous reactions also occur between phosphorus(III) esters and CCl_3COCl in diethyl ether, from which a dialkyl (trichloroacetyl)phosphonate has been isolated in appreciable yield; however, this process may be accompanied by rearrangement and dechlorination, steps which constitute the main reaction pathway when the reaction is carried out in the absence of a solvent when the products is then **491** (X = Cl)[821,822]. Reactions with other chloroacyl chlorides RCHClCOCl (R = MeCHCl or Me_2CCl) are reported to give mixtures of products, presumably acyl phosphonate and halovinyl phosphates[807]. Other substrates include monoacyl chlorides from alkanedioic acids[802,823], protected aminoacyl halides, which yield dialkyl [(acylamino)methyl]phosphonates (**492**; R^1 = Me or Ph)[824], and the acyl chlorides $X(CH_2)_nCHRCOCl$ (R = H or Me, X = phthalimido or fmocNH)[825] or RCHXCOCl (R = Me or Me_2CHCH_2, X = phthalimido)[826] as the first stage in the synthesis of the free aminoacylphosphonic acids. Heterocyclic reactants include



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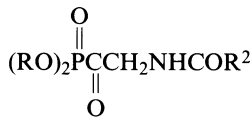
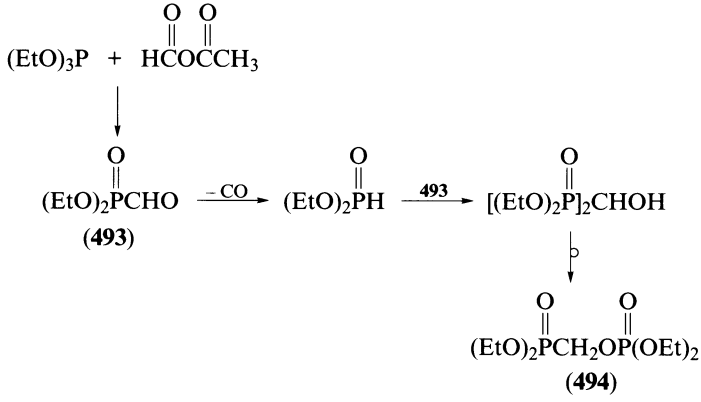


(492)

acid chlorides derived from pyrrolidine-2-carboxylic acid[825], pyridinecarboxylic acids[827], coumarin-3-carboxylic acid[828], and chromone-2- and -3-carboxylic acids[829].

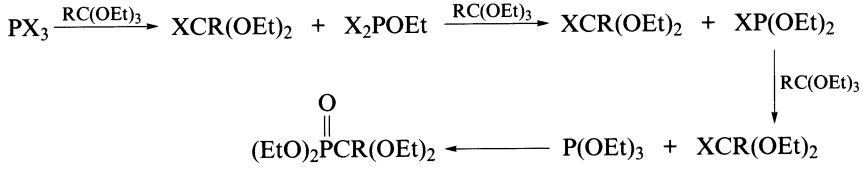
Variations in the phosphorus reactant include the use of phosphonous diesters, $RP(OR^1)_2$, which lead to the monoacylphosphinic esters (**488**) (R^1 = alkyl or aryl, R^2 = alkyl, alkenyl or aryl; n = 0)[830,831], and phosphoramidous diesters, $Et_2NP(OR)_2$ and $(Et_2N)_2POR$, which with R^2COCl yield the monoamides **488** ($R^1 = NEt_2$, R^2 = alkyl or Ph; $n = 0$) and diamides, $R^2COP(O)(NEt_2)_2$[832]. Well characterized products have been obtained from 2-methoxy-4,4,5,5,-tetramethyl-1,3,2-dioxaphospholane in which the five-membered ring is retained[439,440].

The Michaelis–Arbuzov reaction is unable to provide the simplest of the acylphosphonic acids, namely (oxomethyl)phosphonic acid, the diethyl ester of which, **493**, has been obtained from triethyl phosphite and formic–acetic anhydride at –10 °C; at a higher temperature, decomposition sets in with the liberation of CO and formation of diethyl hydrogenphosphonate. Ensuing reactions lead ultimately to **494**[833].

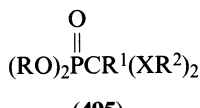


Although esters of (oxomethyl)phosphonic acid have proved to be so elusive, derived acetals (**495**; R^1 = H, X = O) have been prepared with relatively little difficulty from the acid-catalysed interaction of dialkyl hydrogenphosphonates and orthoformic esters[834], and from mixtures of phosphorus(III) chlorides and orthoformic esters when heated in sealed tubes[835,836]; the reaction is included here since the ultimate stage is presumably of the Michaelis–Arbuzov type. The current view (Scheme 48)[835,836] appears to be that the phosphorus(III) chloride reacts with triethyl orthoformate in a stepwise fashion where appropriate, and with the formation, in the penultimate step, of a phosphorus(III) triester and $ClCH(OEt)_2$. Such reactions were observed in a highly detailed study, by ^{31}P NMR spectroscopy, of the very slow reaction, even at 150 °C, between triethyl orthoformate and the chloride **496**, from which the phosphinic ester **497** was isolated; the reaction between the chloride **498** and triethyl orthoformate was much faster, but even so, took place over an

extended period at room temperature to give **499**[837]. The use of other orthocarboxylic esters leads to ketals of (1-oxoalkyl)phosphonic diesters[836,838]. According to another report[839], the same derivatives of dialkyl (oxomethyl)phosphonate are obtainable from the phosphorus(III) compounds $(RO)_2POZ$ (Z = OR, Me_3Si, Ac, or $(RO)_2P$) and a trialkyl orthoformate in the presence of BF_3 etherate. The reaction between a dialkyl trimethylsilyl phosphite and a 2-alkoxy-1,3-dioxolane in the presence of $ZnCl_2$ yields the cyclic acetal **495** (R^1 = H, X = O, $R^2_2 = CH_2CH_2$)[839]. $MePCl_2$ and triethyl orthoformate interact readily at 0–10 °C to produce **500** in very high yield[840], and the compounds **501** likewise from chloromethyl- and dichloromethyl-phosphonous dichlorides[841]. The formation of ketals from higher (1-oxoalkyl)phosphonic or analogous phosphinic esters occurs from their reaction with triethyl orthoformate under conditions of acid catalysis[842].



SCHEME 48



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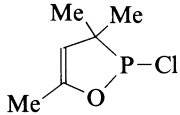

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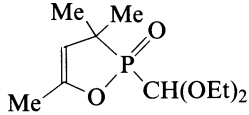

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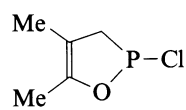

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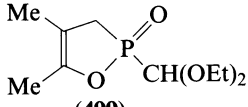

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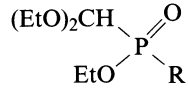
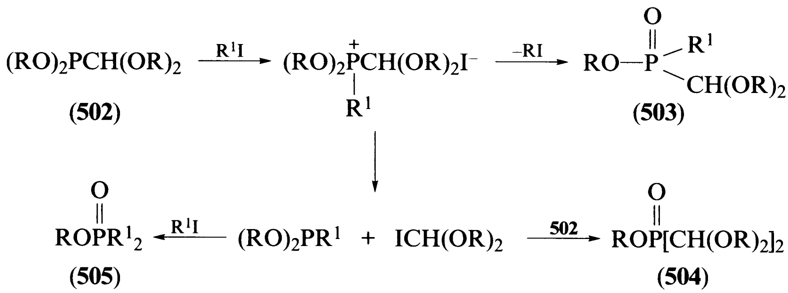


(500) R = Me
(501) R = CH_nCl_{3-n}

The plausibility of the mechanism in Scheme 48 is supported, to some extent, by the formation of the dithioacetals of (oxomethyl)phosphonic diesters (**495**; R^1 = H; X = S) from trialkyl phosphites and $ClCH(SR^2)_2$, also synthesized by other procedures such as exchange of the acetal groups[843]. Other procedures are available for the synthesis of acetals with non-identical R^2 groups[844] or two different chalcogen atoms (O, S; S, Se)[845–848] or with X = Se[849]. These and other synthesis procedures will be considered in more detail later, Unfortunately, the acetals of (oxomethyl)phosphonic diesters do not liberate the free (oxomethyl)phosphonic esters under acidic conditions, but instead, tend to decompose with the formation of dialkyl hydrogenphosphonate.

Attempts to obtain (oxomethyl)phosphinic esters (**503**) through the Michaelis–Arbuzov procedure are not altogether straightforward (Scheme 49)[850,851]. The expected phosphinate **503** may be accompanied by 10–20% (in total) of the symmetrical phosphinates **504** and **505**, but their combined yield may also reach 60% when, for example, $R^1 = MeOCH_2$; the acetals of bis(oxomethyl)phosphinic acid (**504**) have also been prepared by others[834].

Preparations of (3-oxoalkyl)phosphonic diesters through the Michaelis–Arbuzov reaction appear to have been limited to the use of trialkyl phosphites in combination with the methiodides[852], hydrochlorides[852–854] or acetates[855] derived from Mannich bases (reaction 29).

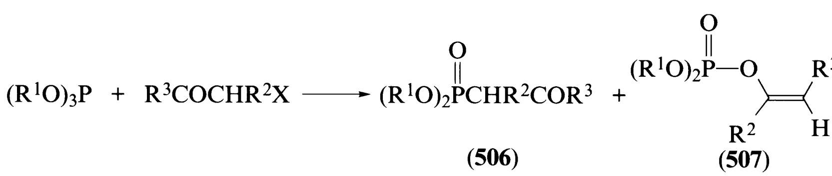


SCHEME 49

$$(R^1O)_3P + R^2COCH_2CH_2\overset{+}{N}Et_2MeX^- \xrightarrow[-NEt_2Me]{-R^1X} (RO)_2\overset{O}{\overset{\|}{P}}CH_2CH_2COR^2 \quad (29)$$

Far more important from the point of view of the utility of the Michaelis–Arbuzov reaction in the synthesis of oxoalkyl phosphonic or phosphinic acids is the behaviour of phosphorus(III) esters towards α-monohalogenated aldehydes and ketones, and the outcome of such reactions is often in marked contrast to that experienced with monohalogenated alkanoic acid derivatives. Almost without exception (for example, the acyl halides), reactions between derivatives of monohalogenated alkanoic acids and phosphorus(III) esters proceed in the expected Michaelis–Arbuzov manner, which is not complicated, to a significant extent, by any important side reaction. On the other hand, it has to be recognized that in many cases, the Michaelis–Arbuzov formation of (2-oxoalkyl)phosphonic esters may make only a minor contribution to the overall reaction, and indeed, it may even take no part at all. The principal competing process, or 'abnormal Michaelis–Arbuzov reaction' as it has sometimes been referred to in the past, was characterized by Perkow *et al.*[856], although it had been reported many times during earlier years that certain attempted Michaelis–Arbuzov reactions led to unusual experimental results; these are now known to have been the result of simultaneous and competitive reactions which resulted in mixtures of products.

Trialkyl phosphites are very reactive towards α-monohaloketones, and even more so towards unprotected α-monohaloaldehydes. Almost invariably, the latter give rise to ethenyl esters of phosphoric acid. The reactivity increases with an increase in the number of halogen atoms at the carbon atom adjacent to the carbonyl group, and also with the halogen order Cl < Br < I. The two principal and potential products of such an interaction (equation 30) are the (2-oxoalkyl)phosphonic diester **506** and an enol phosphate ester **507**, the latter, again potentially, as a mixture of *Z* and *E* isomers. Although the chemistry of the latter compounds is of great interest and commercial importance, it does not form the subject matter of the present chapter, and accordingly the mechanism of formation is not discussed here in detail; it is sufficient to state that the initial step consists in the attack by a phosphorus(III) ester at the carbonyl group rather than at the halogen-carrying carbon atom—the site of the normal Michaelis–Arbuzov displacement.



(30)

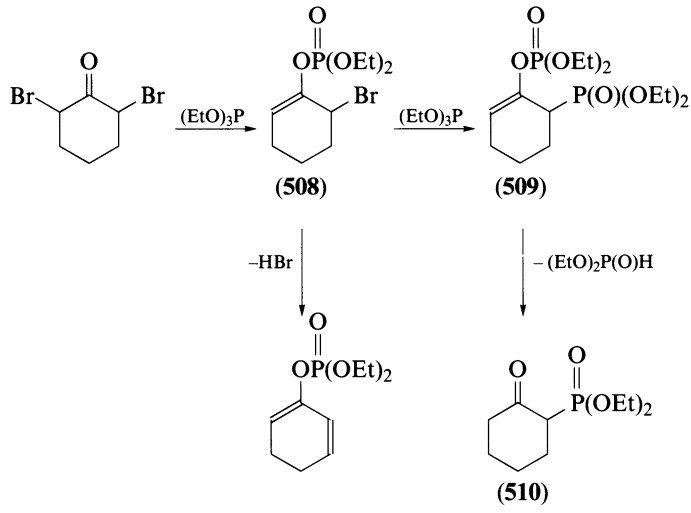
Lichtenthaler's excellent survey[675] lists enol phosphate esters reported up to about 1960. Even by that date, many of the structural requirements within the reactants required for successful formation of the (generally) more important Perkow product were already known. Although the structural features of the carbonyl reactant are of considerable importance with regard to the course of the reaction, the nature of the phosphorus(III) ester is not without some influence. In the reactions between trialkyl phosphites (reaction 30), with R^1 = Me, Et, Bu or Bu^i, and chloroacetone within the temperature range 110–145 °C, with overall reaction yields of 80,60,61 and 78%, the (percentage) proportion of the (2-oxopropyl)phosphonic diester was 16.5, 6.1, 13.7 and 6.3, and, in general, this proportion increased if the reaction temperature was raised[857]. The behaviour of cyclic phosphorus(III) esters, with the customary dependence of reactivity on ring size and degree and type of substitution on ring carbon atoms, appears to be consistent with that described earlier for other Michaelis–Arbuzov reactions, the unsubstituted 1,3,2-dioxaphospholane ring being prone to ring opening[858–860], whilst the (six-membered) 1,3,2-dioxaphosphorinane ring, particularly if substituted on carbon, is retained during a reaction with the more reactive iodoacetone to give the cyclic ester of (2-oxopropyl)phosphonic acid[861]. Triaryl phosphites do not participate in the interaction to give either type of product, but alkyl diphenyl or dialkyl phenyl phosphites react with displacement of an alkyl group[862–864].

The nature of any solvent and the reaction temperature can also be of some importance. For the reaction between trimethyl phosphite and bromoacetone, carried out in diethyl ether at 30 °C, in MeOH or thf at 60 °C or in the absence of a solvent at 110–120 °C the yields of dimethyl (2-oxopropyl)phosphonate were 35, 28, 55 and 45%, whilst those of dimethyl ethenyl phosphate were 30,55,30 and 55%, respectively[865]. The proportion of oxoalkylphosphonate to enol phosphate for the reaction between triethyl phosphite and bromoacetone at 150 °C is 20:80, and this ratio is reversed if the reaction is carried out in boiling diethyl ether. Sometimes a change in both solvent and halogen produces a pronounced beneficial effect with regard to phosphonate formation; thus the 80:20 advantage just noted for bromoacetone in diethyl ether is raised to 90:10 for chloroacetone at 150 °C, but for iodoacetone in boiling diethyl ether it is only 10:90[865].

By far the greatest influence on the course of the interaction is the structure of the carbonyl component in combination with the nature of the halogen. The formation of (2-oxoalkyl)phosphonic diesters from monohaloketones[861–866] occurs to at least some extent, and takes place through 'normal' phosphonium salts[867–869]; no rearrangement occurs within the phosphonium species such as to generate, on decomposition, an enol phosphate. Di- and tri-haloketones and haloaldehydes, irrespective of the degree of halogen substitution, provide only enol phosphate esters through the Perkow process, or at most, only small amounts of (2-oxoalkyl)phosphonic derivatives.

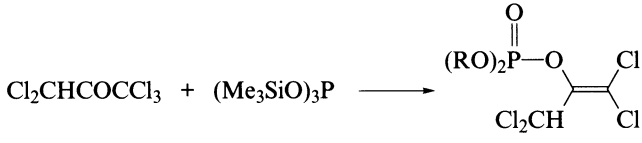
Both 2-chloro-[870–872] and 2-bromo-cyclohexanone[872,873] react with phosphorus(III) esters to yield the enol (1-cyclohexenyl) esters. 2,6-Dibromocyclohexanone yields initially the enol phosphate ester **508**, which reacts with more phosphite ester to give **509**. The thermal decomposition of **508** liberates HBr, which dealkylates some triethyl phosphite, and the resultant diethyl hydrogenphosphonate then reacts with **509** to give 2-(diethoxyphosphinoyl)cyclohexanone (**510**); 2,6-dichlorocyclohexanone does not behave in this complex fashion and furnishes only an enol phosphate[874] The 2-halocyclohexanones represent examples of secondary haloketones, from which only enol esters are obtained directly on reaction with triethyl phosphite. Other secondary halides, e.g. PhCOCHBrR (R = Me or Ph)[675], or bromocamphor[873] yield mixtures of oxoalkyl phosphonates and enol phosphates. Tertiary halides, as exemplified by 2-halo-2-methylcyclohexanones[872,873], $MeCOCMe_2Br$[873] and $PhCOCMe_2Br$[875], yield only enol phosphate esters.

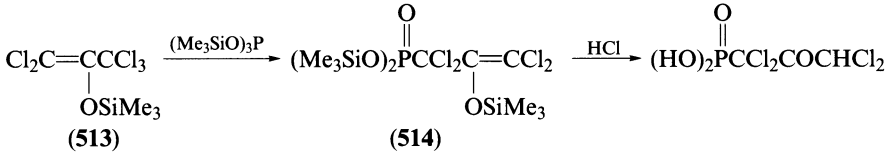
Steric hindrance at the carbonyl group restricts the Perkow reaction and facilitates direct Michaelis–Arbuzov displacement of the halogen to result in increased yields of the (2-oxoalkyl)phosphonate; thus, 2,4,6-trimethylphenylacetyl halides yield only the



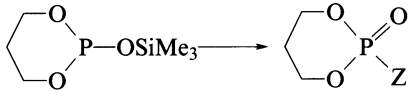
phenacylphosphonates **506** (R^2 = H, R^3 = 2,4,6-$Me_3C_6H_2$), in experiments in which the bromide reacted 21 times faster than the chloride[876,877].

Although it has been stated that di- and tri-haloketones and α-haloaldehydes (irrespective of the degree of halogen substitution) tend to yield only enol phosphate esters, further qualification of this statement is appropriate. The formation of silyl ethers from aldehydes or ketones and silyl phosphites has already been noted (see section III.A). Reactions between silyl phosphites and trifluoroacetaldehyde[365] or perfluoroacetone[377] and other similar compounds[369] initially lead to silyl ethers of (α-hydroxyalkyl)phosphonic diesters in which all the fluorine is retained, although subsequent change leads to fluorinated enol phosphate esters. Sekine *et al.*[878] also observed the formation of (α-silyloxyalkyl)phosphonates and enol phosphate esters only. In the same way, pentachoroacetone and tris(trimethylsilyl) phosphite yields the enol phosphate **511**, which, with HCl, affords the free phosphoric monoester **512**. However, a similar reaction with the pentachloroacetone enol trimethylsilyl ether **513** yields the phosphonic diester **514**, from which the free acid is readily available; dialkyl esters of the latter are also available from **513** and trialkyl phosphites[879].





In a further interesting study[880], the silyl phosphite **515** reacted with haloacetones in the absence of a solvent to give the products **516–518**. The main product from chloroacetone was the silyloxyphosphonate **518** (70%) accompanied by a small amount (14%) of the enol phosphate **517**, but with the change of X from Cl to Br to I, **518** was eliminated entirely, and the proportion of **517** increased for X = Br but then decreased for X = I; the amount of (2-oxopropyl)phosphonate (**516**) increased from 0% (X = Cl) to 24% (X = Br) to 41% (X = I). In hot MeCN the yield of phosphonate increased to 50% with little change in the amount of enol phosphate, but in MeCN at room temperature or below, the amounts of **516** and **517** both decreased, but there was no formation of the corresponding **491** (X = H).



(**515**)

(**516**) Z = CH_2COMe
(**517**) Z = $OCMe{=}CH_2$
(**518**) Z = $C(CH_2X)(OSiMe_3)Me$

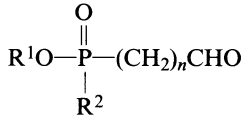
Two further complicating features may be noted. The first is of little, if any, practical consequence with regard to the formation of oxoalkyl phosphonates, but is to be found in the formation of enol phosphates from α-polyhaloketones, when the latter may be accompanied by simple dehalogenation of the carbonyl reactant[881], when treated with phosphorus(III) esters[325], particularly when reactions are carried out in protic solvents[865]. This is coupled with the second feature, which consists in the formation of (1-hydroxyalkyl)phosphonic acid esters from a trialkyl phosphite and the substituted α-monohaloacetophenone also in the presence of a protic solvent[865,882].

Reactions between haloketones and phosphonite esters, $R^1P(OR)_2$, produce enol esters of phosphonic acids or esters of the phosphinic acids, $R^1(R^2COCH_2)P(O)OR$, depending on the halogen involved[675,883], whilst phosphinite esters, R_2POR^1 yield the phosphinic acid esters $R_2P(O)OCPh{=}CHBr$ when treated with α,α-dibromoacetophenone[675,884].

Two promising observations consist of the activation of the interaction of haloketones and phosphorus(III) esters towards phosphonate formation by the presence of silver salts[865,885], and also a two-step process in which a silyl ether $ArC(OSiMe_3){=}CHR$ is first treated with $PhIO–BF_3{\cdot}Et_2O$ at –40 °C, and the resultant complex is then treated with a trialkyl phosphite, again at –40 °C, when the products are the expected oxo phosphonic diesters, $(EtO)_2P(O)CHRCOAr$[886].

It is evidently not possible to prepare the (ω-oxoalkyl)-phosphonic (**519**; $R^2 = R^1O$) or -phosphinic diesters through direct reaction between a phosphorus(III) ester and an ω-haloalkanal. However, the corresponding acetals (**520**; $n = 1$ or 2) are readily available in this way[887–892]; precautions have to be taken to avoid overheating which can result in the loss of ethanol (when $n = 1$) and the formation of the enol ether **521**, a process which becomes more prevalent in the synthesis of the secondary compounds **522**[888]. Gentle hydrolysis of the acetals **520**, using very dilute HCl[887,888,893] or an ion-exchange resin in the acid form[892], or simply the calculated amount of cold water[889], liberates the free aldehyde **519**. The methodology based on acid cleavage of aldehyde acetal was adopted in the successful preparation of 4-(diethoxyphosphinyl)but-2-enal, required for the synthesis of component moieties in the plumbemycin antibiotics[894]. Alternatively, procedures in which the oxo function is protected by a nitrogen function, e.g. the use of an acetimidoyl halide[895], or reaction 31, in which protection is afforded by a hydrazide group[896], may be followed.

In general, enol ethers of the type **521** are more easily obtained through yet another procedure (see Section 3), as has phosphonoacetaldehyde itself. Some (2-oxoalkyl)phosphonic diesters have been obtained, free from enol phosphate byproducts, through



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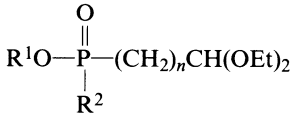

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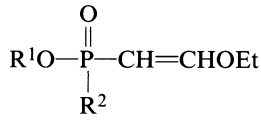
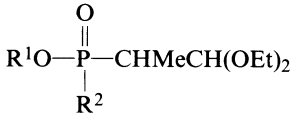


(521)



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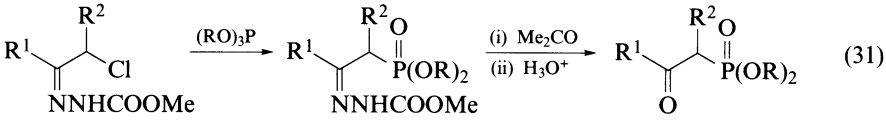
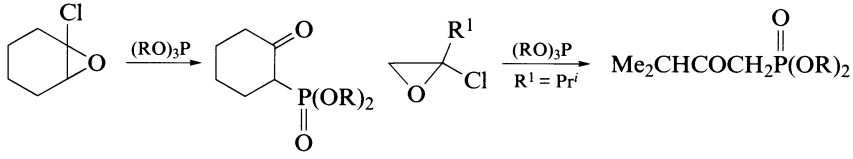


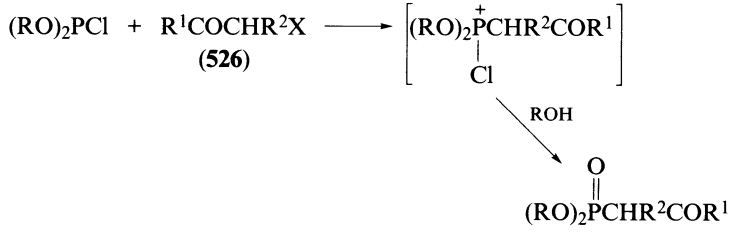
(31)

reactions between phosphorus(III) triesters and epoxides; 2-(diethoxyphosphinoyl)cyclohexanone was thus prepared from **523**, and whereas the epoxide **524** (R = Pr^i) gave only the diester **525**, **524** (R = CH_2Cl) initially yielded a mixture of enol phosphate and dialkyl (3-chloro-2-oxopropyl)phosphonate, which reacted with more phosphite to give **491**[897]. In general terms, the formation of products of the type **491** may not be too great a setback, since careful hydrolysis procedures are able to cleave the system at the enol P—O—C bonds to leave the oxoalkyl phosphonic moiety intact.



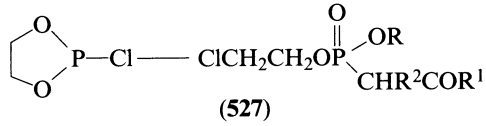
(523) (524) (525)

Variations in the types of reactants have been noted which are a reminder of those variations described in the previous chapter for the basic Michaelis–Arbuzov reaction. In this case, a α-haloketone reacts with a phosphorous chloride; the reaction is envisaged as proceeding through a phosphonium intermediate which, when decomposed through alcoholysis, yields a (2-oxoalkyl)phosphonic derivative (Scheme 50). The usual pattern of



SCHEME 50

phosphite reactivity is evident; with the ketones **526** ethylene chlorophosphite yielded the ring-opened esters **527** of phosphonic acids, whilst *o*-phenylene chlorophosphite provided the products **528** in which the five-membered phosphorus-containing ring is retained[898]. In the reactions between biacetyl and the halides $RPCl_2$ (R = Me or Et[899] or Ph[900]), the intermediate steps lead to the 2,3-dihydro-1,2-oxaphosph(V)oles **529**, which on alcoholysis furnish esters of the [(*R*)-(2-chloro-3-oxobutyl)]phosphinic acids **530**.



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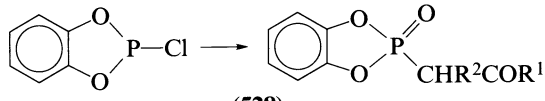

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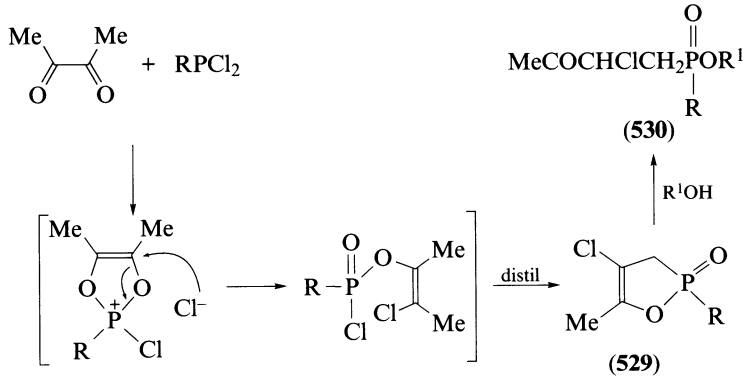


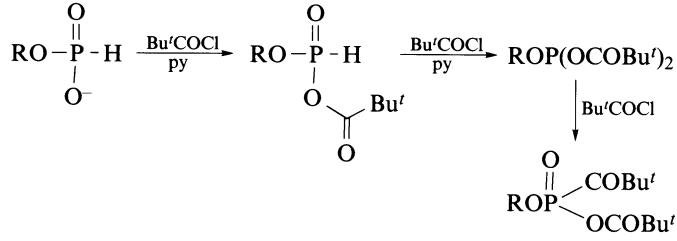
(530)

(529)

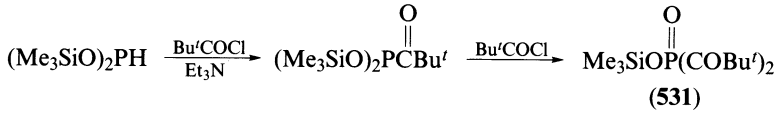
2. Through the alkylation of dialkyl hydrogenphosphonates or related compounds

The direct alkylation of hydrogenphosphonic diesters with a diazoketone has been recorded alongside that with diazoalkanoic esters, and explored particularly with methyl 2-diazo-3-oxobutanoate[692,693], but also for several chloroacetones. Reactions involving 1-chloro-3-diazo-2-propanone are effectively catalysed by $[Cu(acac)_2]$[694], but more heavily chlorinated substrates suffer stepwise dechlorination. Thus 1,1,1-trichloro-3-diazopropan-2-one initially yields the expected dialkyl (3,3,3-trichloro-2-oxopropyl)phosphonate, but under the experimental conditions, dechlorination then proceeds to give the dialkyl (3,3-dichloro-2-oxopropyl)phosphonate; only the monochloroketone undergoes a reaction in which the original halogen content is retained in the final product[901].

The more customary Michaelis–Becker reaction has not been widely adopted for the synthesis of oxoalkyl-phosphonic or -phosphinic esters, and only isolated examples are to be noted, sometimes in combination with a Michaelis–Arbuzov step. The steps in Scheme 51 were adopted to furnish acylphosphorus(V) derivatives of a carbohydrate nucleus (R = a carbohydrate moiety)[902], and a similar sequence (Scheme 52) starts with bis(trimethylsilyl) hypophosphite and can provide novel bis(1-oxoalkyl)phosphinic acids, e.g. **531**[903].

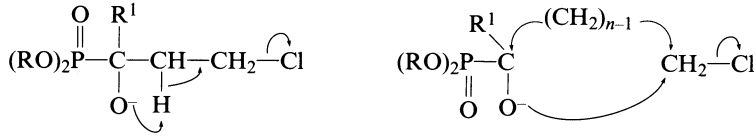


SCHEME 51



SCHEME 52

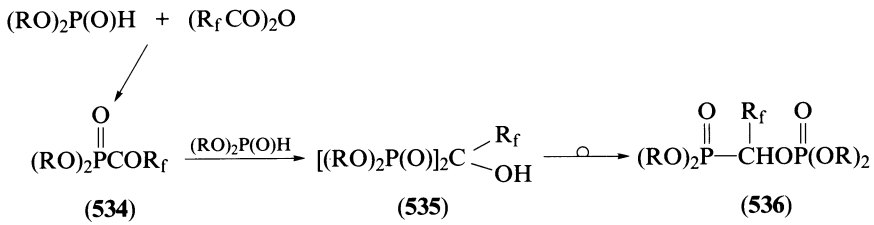
Rare examples of normal Michaelis–Becker reactions which involve ω-chloroalkanal diethyl acetals are to be found[904], and although the formation of dialkyl acylphosphonates from sodium dialkyl phosphites and, for example, benzoyl chloride, is to be observed at −85 °C, the system is further complicated, even at −10 °C, by further addition steps followed by rearrangements which would seem to render the process of little value for the synthesis of oxoalkyl phosphonic esters[905]. On the other hand, in a more detailed and systematic study of reactions between sodium dialkyl phosphites, $(RO)_2PONa$(R = Et or Bu), and the ketones $R^1CO(CH_2)_nCl$, Sturtz[561] and others[906] have observed the formation of epoxides when n = 1 and (1-hydroxyalk-2-enyl)phosphonic diesters when n = 2 (R^1 = Me or Pr^i), according to the displacement in **532**, and of derivatives of tetrahydrofuran or tetrahydropyran, according to **533** (n = 3 or 4); when R^1 = Et, the formation of the cyclic ethers was accompanied by low yields of the expected (oxoalkyl)phosphonic diester, but otherwise the latter were isolated as a single product only for R^1 = Me, n = 5, and R^1 = Et or Pr when n = 2.



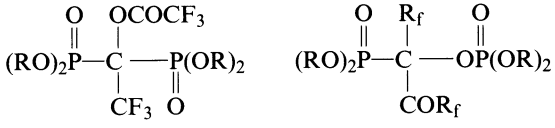
(532) **(533)**

The phosphinic esters **503** have been obtained through the alkylation of the phosphinic esters, $(RO)_2CHP(O)(OR)H$, as their sodium salts, with R^1X[907].

It should perhaps not be surprising that dialkyl hydrogenphosphonates, like phosphorus(III) triesters, are very reactive towards perfluorocarboxylic acid anhydrides, but these reactions, as with those with the perfluoroacyl chlorides, can be complex, and although it seems highly likely that the first stage in the reaction consists in the formation of a dialkyl (perfluoroacyl)phosphonate (**534**)(and more than one mechanism for this step can be postulated), the initial product rapidly undergoes further reaction(s). Two groups of workers have isolated different final products depending on reactant ratios. The first group[908] has provided evidence to suggest the eminently plausible sequence **534** → **535** →**536**, already well established for many other related, but fluorine-free compounds, and coupled with the isolation, under certain experimental conditions, of **537**. Aleinikov and coworkers used the reactants in a 1:1 ratio, and suggested that the products have the structure **538**[909–911].

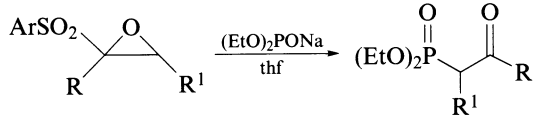


(534) (535) (536)



(537) (538)

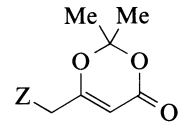
The formation of the dialkyl (2-oxoalkyl)phosphonates (**539**) illustrates the regioselective nucleophilic attack by phosphite anion, with rearrangement and displacement of sulphinate anion, applicable when R = C_1–C_5 alkyl and R^1 = H, Me or Ph; in the single case when Ar = Ph, R = H and R^1 = Ph, the product was diethyl (2-phenylethenyl)phosphonate[912].



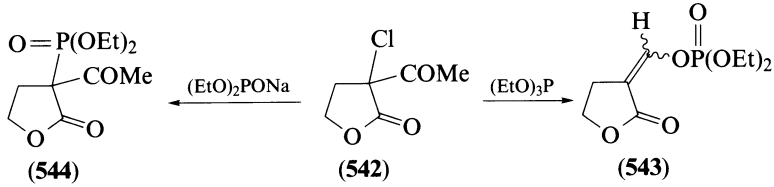
(539)

The formation of compounds **495** from phosphorus triesters and orthoalkanoic esters has already been referred to, and the same compounds are also obtainable when mixtures of hydrogenphosphonate or phosphonous acids [RP(O)(OH)H] and orthoalkanoic esters are heated in sealed tubes[913,914].

Two examples serve to show the relative usefulness of the Michaelis–Becker and Michaelis–Arbuzov procedures. In the first, **540** (Z = Br) suffers debromination when heated with triethyl phosphite, and **541** was prepared only from **540** (Z = Cl) and sodium or potassium diethyl phosphite[915,916]. In the second example, the formation, from **542**, of the enol phosphate **543** in the Michaelis–Arbuzov case, is obviated by the use of sodium diethyl phosphite when the desired phosphonate **544** was obtained[917].



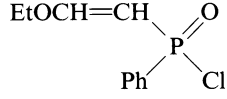
(**540**) Z = halogen
(**541**) Z = $P(O)(OEt)_2$



(544) (542) (543)

3. From PCl_5 and unsaturated ethers, esters or ketones

The synthesis of alkenylphosphonic dichlorides and (2-chloroalkyl)phosphonic dichlorides through reactions between terminal alkenes and PCl_5, followed by decomposition of the resultant chlorophosphonium salts, $RPCl_3^+ PCl_6^-$, with SO_2, was discussed in the previous chapter; the alkenylphosphonic dichlorides arise through the dehydrochlorination of those salts. The treatment of ethenyl ethers with PCl_5, and subsequent work-up of the intermediate phosphonium salts, likewise yields (2-alkoxyethenyl)phosphonic dichlorides, readily convertible into dialkyl (2-alkoxyethenyl)phosphonates through reaction with an alcohol in the presence of an appropriate base, such as Et_3N or pyridine, or by direct alcoholysis of the chlorophosphonium salt[116,117,918–923]; analogous (2-aryloxyethenyl)phosphonic derivatives[922–926] and thioether analogues[582–586] are similarly obtainable. Many examples have been quoted by Gefter[927]. The same products are available from the interaction of alkyl ethyl ethers with PCl_5 and work-up in the usual way[928]; the reaction is here thought to take place via the alkyl 1-chloroethyl ether, and indeed such compounds, also, furnish the same unsaturated phosphonic dichlorides[929]. Polychlorophosphoranes may be used in place of PCl_5; thus, ethenyl ethyl ether and $PhPCl_4$ yield a crystalline chlorophosphonium salt which, following its decomposition with SO_2, affords a product recognizable as [(2-ethoxyethenyl)phenyl]phosphinic chloride (**545**)[930].



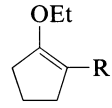
(545)

(2-Alkoxyethenyl)phosphonic dichlorides are, additionally, the products from unsymmetrical acetals $MeCH(OR)(OR')$ and PCl_5; although two similar products are theoretically capable of being produced, the reaction does tend to be selective. If R = Et, and R′ = Bu, Ph, $ClCH_2CH_2$, etc., the main product is $EtOCH{=}CHP(O)Cl_2$, but for R = Et and R′ = Pr^i, it is $Pr^iOCH{=}CHP(O)Cl_2$[931]. Symmetrical acetals, $MeCH(OR)_2$, furnish the [2,2-di(alkoxy)ethenyl]phosphonic dichlorides[932].

The addition of $H_2C{=}CHCOR$ (R = H or Me) or $Me_2C{=}CHCOMe$ to PCl_5 in benzene yields dichlorophosphates in low yields; however, a change in the order of mixing results in *C*-phosphorylation and, for example, but-3-en-2-one yields a complex which, on decomposition with acetic anhydride, gives (2-chloro-3-oxobutyl)phosphonic dichloride[933].

The (2-alkoxyethenyl)phosphonic diesters are, of course, the enol ethers of the dialkyl esters of phosphoacetaldehyde, $(HO)_2P(O)CH_2CHO$, and as such should be capable of hydrolysis to the latter. The reaction between vinyl acetate and PCl_5, and decomposition of the resultant complex with SO_2, yields the phosphonic dichloride **546**, careful hydrolysis of which does, indeed yield almost quantitatively phosphonoacetaldehyde, which can be stabilized as its dilithium salt[934,935]. Using the same methodology, **547** (R = H) can be converted sequentially into **547** ($R = POCl_2$) and **547** ($R = P(O)(OEt)_2$), acid hydrolysis of which yields 2-(diethoxyphosphinoyl)cyclopentanone, not otherwise obtained by the use of the methods thus far discussed[936]. Diethyl phenacylphosphonate [diethyl (2-phenyl-2-oxoethyl)phosphonate] is similarly obtainable from $PhC(OEt){=}CH_2$[937].

(546)



(547)

4. *Through the phosphorylation of mesomeric anions*

The phosphorylation of the mesomeric anion from a ketone or other active methylene compound forms a standard route to enol phosphates[675]; the process is illustrated in equation 32 with the formation of the phosphate esters **548** (R^1 = Me or Ph, R^2 = H, COMe or COOEt) from appropriate ketonic compounds; yields tend to be moderate to good.

$$R^1COCH_2R^2 \xrightarrow[\text{(ii) } (RO)_2P(O)Cl]{\text{(i) BuLi or lda}} (RO)_2\overset{\overset{O}{\|}}{P}OCR^1{=}CHR^2 \qquad (32)$$

(548)

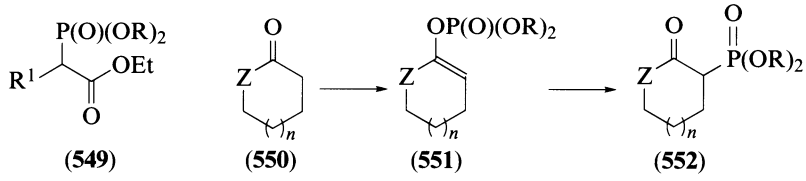
Two approaches have been made to the modification of such a procedure to enable the *C*-phosphorylated product to become the major reaction product. In the first such approach—an umpolung approach, and complementary to the classical Michaelis–Arbuzov reaction—a dianion is generated from an α-bromo carbonyl compound through sequential treatment with two bases (Scheme 53), the first to bring about enolization and the second to remove the bromine, and the dianion is then monophosphorylated at –110 °C. Yields tend to be lower if the reaction is carried out even at –78 °C, but were otherwise in the range 30–80%[938]. The sequence is of particular value since it allows the synthesis of desired compounds from secondary halides when the Michaelis–Arbuzov and Michaelis–Becker reactions might afford only low yields, or even fail completely, and it also allows the use of phosphorus species containing electron-withdrawing alkyl groups, e.g. CF_3CH_2O, when again, the classical procedures might be expected to perform poorly. Some regioselectivity has been noted elsewhere[939] in the phosphorylation of the dianion from 1-phenylpropan-2-one, when phosphorylation at each carbon site adjacent to carbonyl was accompanied by some *O*-phosphorylation; the phosphorylation of the ambident anion from the Schiff base from MeCOR (R = Me or Ph) and cyclohexylamine resulted in predominant reaction at carbon.

$$R^1\overset{\overset{O}{\|}}{C}HR^2Br \xrightarrow[\text{(ii) } Bu^tLi]{\text{(i) } (Me_3Si)_2NLi} R^1\overset{\overset{OLi}{|}}{C}{=}CR^2Li \xrightarrow{(RO)_2P(O)Cl} (RO)_2\overset{\overset{O}{\|}}{P}CHR^2\overset{\overset{O}{\|}}{C}R^1$$

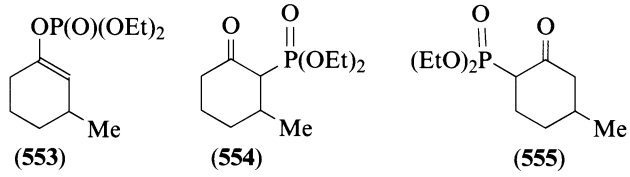
SCHEME 53

Low to moderate yields of the *C*-phosphorylated compounds **549** (R^1 = Me, Et, Pr^i or Ph) have been obtained through the phosphorylation of the mesomeric anion generated from a carboxylic ester and lda in thf–hmpa, followed by further treatment with lda; this procedure works far more satisfactorily for lactones **550** (Z = O) and cyclic ketones **550** (Z = CH_2), when yields can reach 80%[940,941]. The basis of this procedure, the second of the approaches indicated earlier, consists in the initial production of a mixture (presumably) of *O*-phosphorylated (enol phosphate) and *C*-phosphorylated compounds, **551** and **552**, followed by the base (lda)-catalysed rearrangement of enol phosphate to oxo phosphonate. The presence of substituents on the cyclic ketone ring resulted in the formation of isomeric phosphinoylcycloalkanones, and, for example, **553** affords **554** together with **555**. A detailed study of the regioselectivity in this rearrangement has been carried out[942]. In further studies, Wiemer's group also noted that enol phosphates of the type **556**, which contain an unprotected carbonyl group, fail to rearrange in the presence of lda, in contrast to the corresponding ketals, e.g. **557**, which itself yields **558**; in general, regioisomerically formed compounds in the cyclohexanone and decalone systems can be isolated[943].

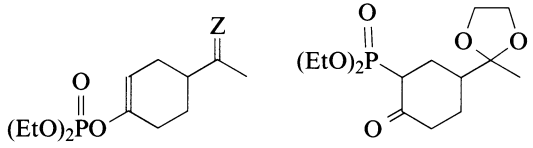
In a modification to the latter procedure, phosphorylation of lithium enolates may be carried out with a phosphorus(III) acid chloride (phosphitylation) and the resultant



(549) (550) (551) (552)



(553) (554) (555)

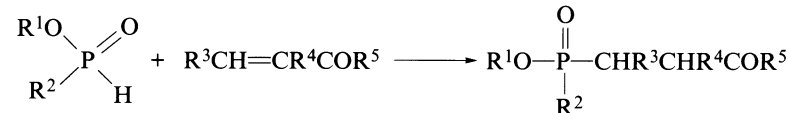


(556) Z = O
(557) Z = OCH_2CH_2O (558)

phosphonite ester subjected to oxidation, conveniently with H_2O_2[944] or by exposure of the product to air[945]. Achievable yields for alkanones, cycloalkanones and cycloalkenones were good to excellent.

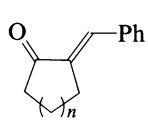
5. Through the addition of hydrogenphosphonates or related compounds to enones

In Section VII.A, the 1,2-addition of a hydrogenphosphonic diester or related compound to an α,β-unsaturated aldehyde[336,340,343,345] or analogous ketone[343,345,346,348] was discussed in relation to the synthesis of (1-hydroxyalkyl)phosphonic diesters. The latter are formed under condition of kinetic control whereas 1,4-addition (the so-called Pudovik reaction), which leads to the (2-oxoalkyl)phosphonic diester occur under thermodynamic control[343,345]. In general, reactions which involve ethylenic aldehydes, or acetylenic aldehydes or ketones, tend to result in adduct formation across the carbonyl group, whilst ethylenic ketones tend to take part in 1,4-additions and afford 3-oxoalkyl phosphonic (or phosphinic) acid systems **560**[334,946–949] consistent with Markovnikov predictions. Such statements are a broad oversimplification, however, at least with regard to the formation of the oxoalkyl phosphonates. In practice, the manner of addition depends on experimental circumstances, the nature and even amount of catalyst and other factors[334,950,951]. For instance, for the additions of dimethyl hydrogenphosphonate to the ketones **561** (n = 1 or 2) and **559** (R^4 = H, R^3 = 2-furyl, R^5 = Me), carried out by the addition of a trace of saturated MeONa–MeOH solution to a mixture of reactants in diethyl ether, yielded (within 5 min) the respective 1,2-adducts (1-hydroxyalkylphosphonates) in yields of 64,69 and 52%;

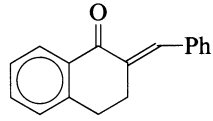


(559) (560)

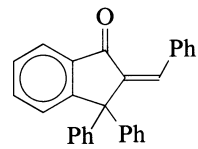
if the reactions were carried out in the presence of an equimolar amount of Et_2NH, again in diethyl ether,the yields of 1,2-adducts were 100, 100 and 31%. The same reactions, when carried out in the presence of a trace of methoxide catalyst but in benzene, afforded the 1,4-adducts (oxoalkylphosphonates) in yields of 48, 79 and 63%; under the same conditions, the ketones **559** (R^4 = H, R^3 = R^5 = Ph), **562** and **563**, gave 1,4-adducts in poor yields[950]. Several examples are known[949] to illustrate the generalization that a rise in reaction temperature tends to increase the extent of 1,4-addition.



(561)

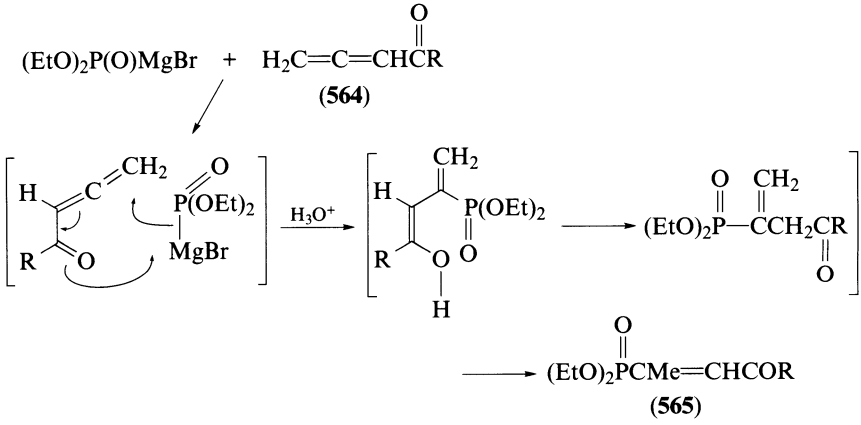


(562)



(563)

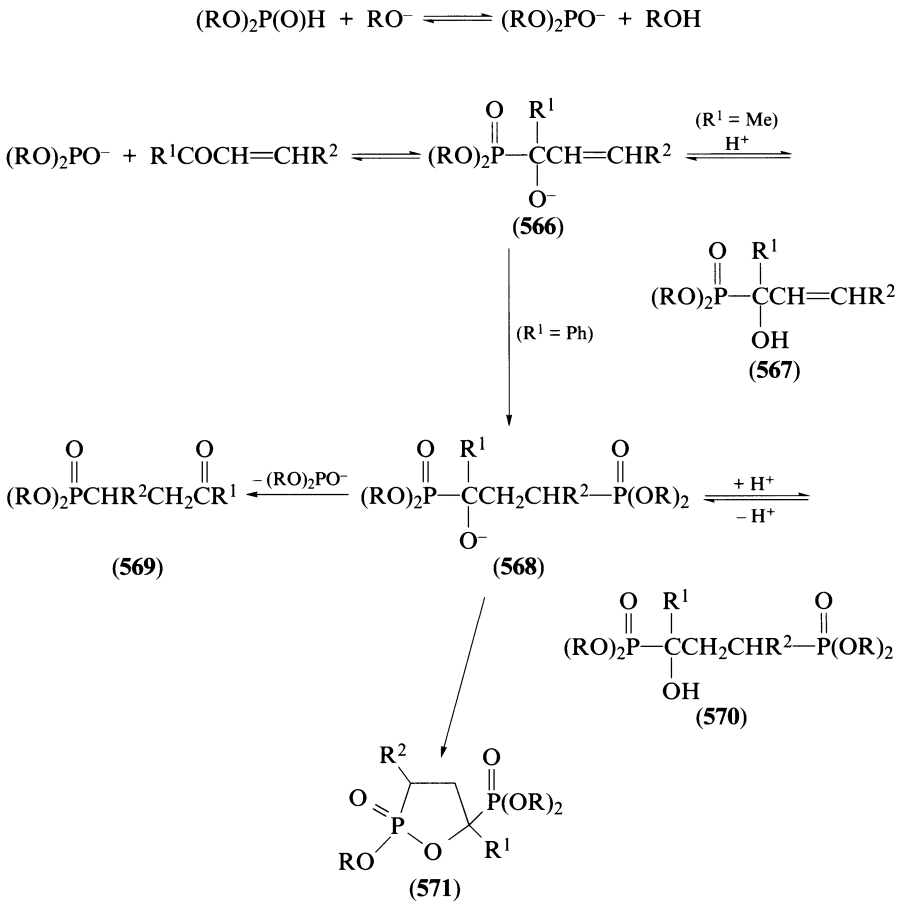
The addition of a hydrogenphosphonate to a symmetrical di(α,β-unsaturated)-ketone occurs very readily, but is controllable to the extent that it occurs across only one of the C=C bonds[952]. The addition of a dialkyl hydrogenphosphonate, in the form of its bromomagnesium salt, to the ketones **564** (R = Me, Et or Pr^i) leads to the oxoalkenyl phosphonic diesters **565** according to a mechanism suggested[953] in Scheme 54.



SCHEME 54

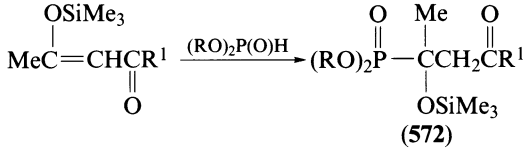
A detailed mechanistic study of the addition of a dialkyl hydrogenphosphonate to benzylideneacetone and to related compounds[954] indicated a kinetically controlled attack of the phosphite anion at the substrate carbonyl group, followed by protonation (by ROH) of the intermediate **566**. The direction of further reaction (Scheme 55) is then a function of the stability/reactivity of this intermediate, and thus governed, at least to some extent, by the nature of the group R^1. When the ion **566** is sufficiently basic, with R^1 = H or Me, protonation (by ROH) occurs to give the 1,2-adduct **567**—the kinetically controlled product. Increased delocalization of the anionic charge in the intermediate **566** e.g. when R^1 = Ph (as in benzylideneacetophenone, with R^1 = R^2 = Ph, or for dibenzylideneacetone, for which R^1 = Ph, R^2 = CH=CHPh)) the intermediate **566** is evidently acted upon by more hydrogenphosphonate to give **568**, whose stability is again controlled, at least partly by the substituent R^1. In certain circumstances, e.g. when the reaction mixture contains a large amount of base catalyst (thus preventing protonation of **566** to give **567**), the ion **568** can

be stabilized through the three pathways indicated to give an oxoalkyl phosphonate (**569**), hydroxyalkyldiphosphonate (**570**) or 1,2-oxaphosph (V)olane (**571**); all three pathways have been realized for benzylideneacetone, and for propenal and but-2-enal.

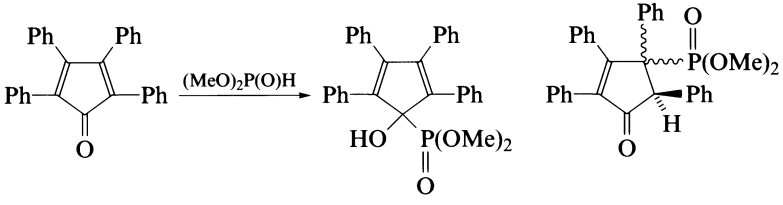


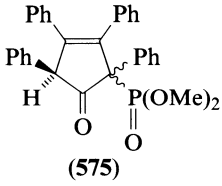
SCHEME 55

The addition of dialkyl hydrogenphosphonates to enol silyl ethers affords good yields of the adducts **572** (R^1 = Me or OEt)[955]. The addition of hydrogenphosphonates to the nitroalkenes ArCH=CR(NO_2) is reported to yield intermediates which, when acted upon by 3-chloroperoxybenzoic acid, give the phosphonates $(R'O)_2P(O)CHArCOR$[956].



A very popular area for study has been the reactions which occur between hydrogenphosphonates or phosphonous monoesters (hydrogenphosphinates) and substituted cyclopentadienones. The resultant picture is a complex one. Pudovik and Konovalova[948] have presented a very brief summary of the earlier work, much of which concentrated on the reactions of the tetraphenyl derivative (tetracyclone). Depending on the reaction conditions, dimethyl hydrogenphosphonate reacts with tetracyclone at the carbonyl group (1,2-addition, to give **573**), or by 1,4- and 1,6-addition to give conjugated or non-conjugated oxo phosphonic products, **574** and **575**, whilst the formation of enol phosphates is also observed. The picture is complicated further by the potential for further prototropic changes. It would be impossible in a reasonably small space to detail further the nature of the reactions involved, which have been studied in detail using proton NMR spectroscopy, IR spectroscopy and X-ray crystallographic techniques. Some more recent studies have been concerned with tetracyclone and its reaction with dimethyl hydrogenphosphonate[957], tetracyclone with phenylphosphonous monoesters[958,959], 2-methyl-3,4,5-triphenylcyclopenta-2,4-dienone with dimethyl hydrogenphosphonate and methyl hydrogen phenylphosphinate[960] and reactions using dimethyl 3,4-diphenylcyclopenta-2,4-diene-2,5-dicarboxylate[961,962].

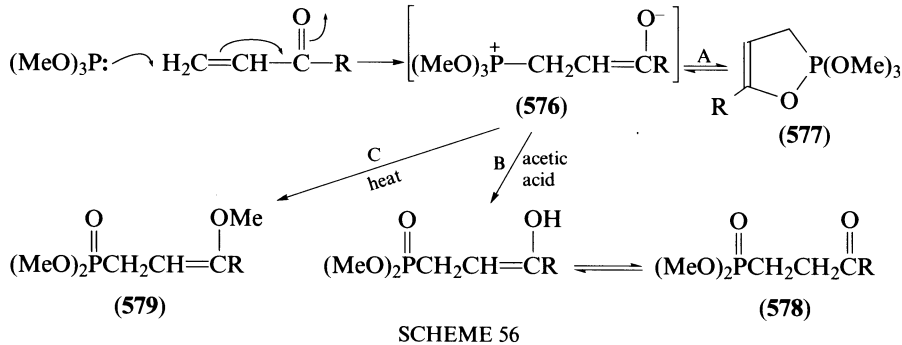




6. Through the addition of phosphorus(III) esters to enones

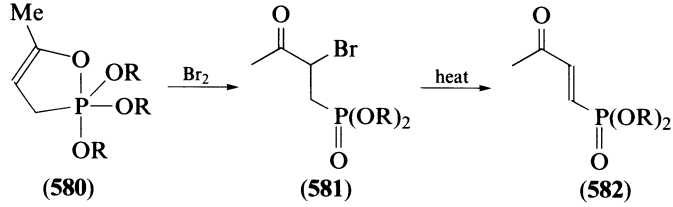
The study of the reactions between conjugated unsaturated carbonyl compounds and phosphorus(III) esters has proceeded alongside that of hydrogenphosphonates and related species, generally with the same substrates.

The interaction of an enone with a trialkyl phosphite proceeds through nucleophilic attack by phosphorus at the β-carbon atom of the carbon–carbon double bond, a step which results in the formation of a dipolar ion **576**; this may then be stabilized (Scheme 56) by cyclization to the oxyphosphorane **577** or, if the initial reaction is carried out in a medium containing acetic acid, the ion is protonated and then undergoes dealkylation to give the phosphonic diester **578**. The third possibility, namely stabilization by translocation of an alkyl group from phosphorus to oxygen to give the enol alkyl ether **579**, is known to be feasible even under very mild conditions as in a low-boiling solvent such as dichloromethane[963]; such a route would apply in the absence of protonation (choice of solvent) or through resistance to cyclization, for steric or other reasons.



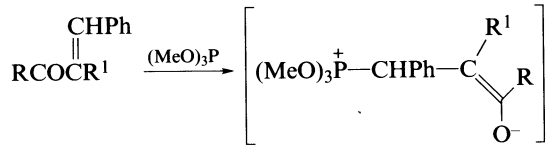
SCHEME 56

The routes A[964] and C[965] have both been considered for the reaction between propenal (R = H) and trimethyl phosphite, and hydrolysis of the oxyphosphorane yielded 3-(dimethoxyphosphinoyl)propanal. The phosphorane, **580** (R = Et), obtained from triethyl phosphite and but-3-en-2-one[966] has been mentioned earlier in connection with the synthesis of phosphonic diesters possessing both oxo and hydroxy groups[457]; as an example of its further usefulness through treatment with an electrophile, its reaction with bromine yields the bromo ester **581** and this, when heated, undergoes dehydrobromination to give diethyl (3-oxobutenyl)phosphonate (**582**), also obtained when **580** is heated with nbs[967].

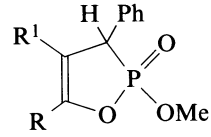


The formation of diethyl (3-oxobutyl)phosphonate from triethyl phosphite and 3-oxobutyl acetate[968,969] can be formulated also as taking place through a phosphorane intermediate. As further examples, the phosphoranes **587** have been prepared from the benzylidene derivatives **583**[970], **584**[971], **585**[972] and **586**[973]. Careful hydrolysis of the phosphoranes **587** with one equivalent of water in diethyl ether leads to the corresponding **588**, which in turn tautomerize to the ketonic alkylphosphonic dimethyl esters **589**, which can also be obtained independently by the addition of dimethyl hydrogenphosphonate to the original benzylidene compounds; the latter, when heated, generate the dihydro-1,2-oxaphosph(V)oles **590**. In the same way, the esters **593** have been obtained from the ethylidene compounds **591** via the respective oxyphosphoranes **592** (R = Me, Et, or EtO)[974].

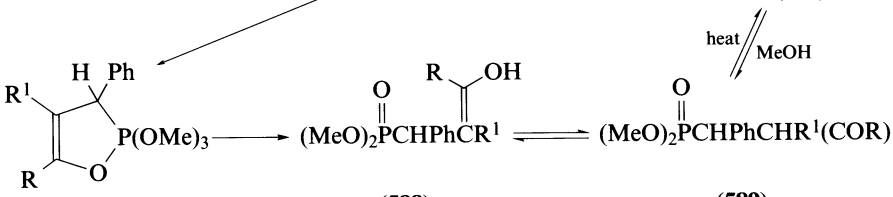
Phosphoranes are also formed when mixtures of trimethyl phosphite and benzylideneacetophenone or 2-benzylidene-1-tetralone are heated at 50–60 °C for long periods[975]. Spirocyclic phosphoranes are commonly the isolable products from five-membered ring phosphites[950], but are also obtainable from six-membered ring phosphites[976]. The 1:1 adduct from propenal and 2-methoxy-5,5-dimethyl-1,3,2-dioxaphosphorinane has been shown to have a pentacoordinate structure and to undergo opening of the five-membered ring upon treatment with acetic anhydride to yield the enol acetate **594**[976]. On the other hand, phosphoranes could not be obtained from trimethyl phosphite and 2,5-dibenzylidenecyclopentanone or 2-benzylidene-3,3-diphenylindan-1-one (**563**)[977]. However, in accordance with Scheme 56, when such reactants are allowed to react in acetic acid, the



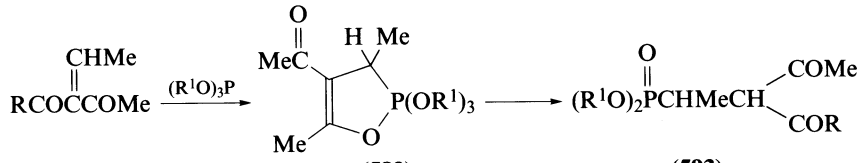
(583) R = Me, R^1 = COOMe
(584) R = Ph, R^1 = COOMe
(585) R = Ph, R^1 = COMe
(586) R = PhCH=CH, R^1 = H



(590)

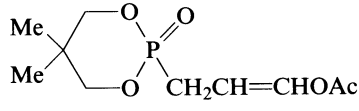


(587) (588) (589)

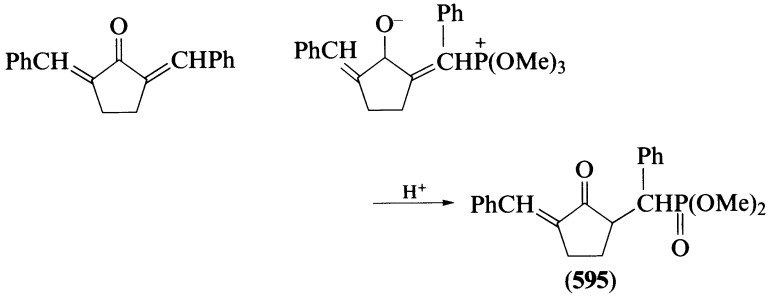


(591) (582) (593)

dimethyl esters of linear oxoalkyl phosphonic acids are formed; 2,5-dibenzylidenecyclopentanone thus yields the keto compound **595**, but on the early introduction of acetic anhydride to the reactants mixture, the enol acetate of **595** is obtained[977].

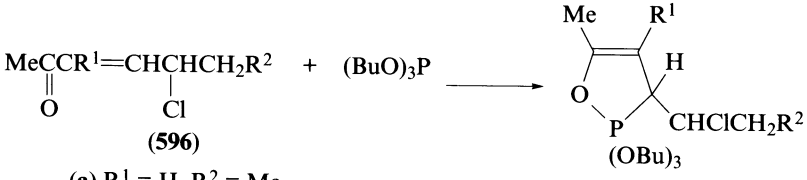


(594)



(595)

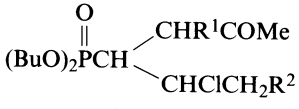
On a more novel note, the formation of the phosphoranes **597a** and **b** illustrates the greater electrophilicity of the unsaturated carbonyl system in capturing nucleophilic phosphorus(III) then would be displayed in a normal Michaelis–Arbuzov displacement of the chlorine. The phosphoranes undergo acid-catalysed hydrolysis to the phosphonic diesters **598**, and on thermolysis **596a** yields the enol ether **599**, possibly suggesting an equilibrium between phosphorane and dipolar ion structures in Scheme 56[978]. In connection with this latter point, it is interesting to note that when **580** (R = Me) is treated with Me_3SiCl, it is possible to isolate the enol ether **600**[979].



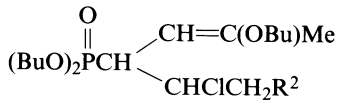
(596)

(a) R^1 = H, R^2 = Me
(b) R^1 = Me, R^2 = H

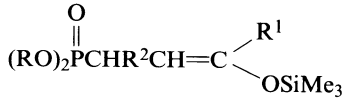
(597)



(598)



(599)



(600) R = R^1 = Me, R^2 = H
(601) R = Me_3Si

(602)

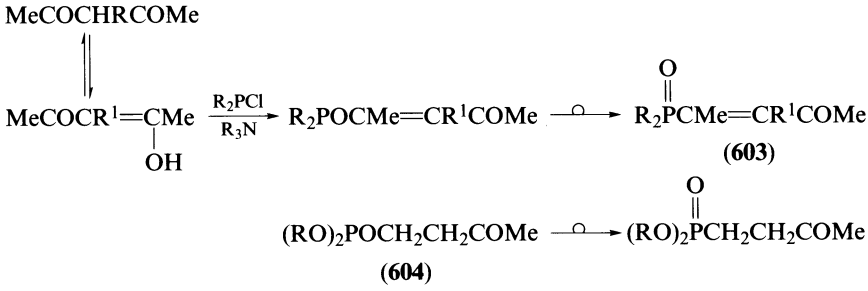
The potential use of silyl phosphites is a natural extension to the scope of the Pudovik reaction. Sekine *et al.*[980] showed that, with regard to α,β-unsaturated carbonyl compounds, aldehydes and $(Me_3SiO)_3P$ yield 1:1 adducts at room temperature, whereas under the same, or similar, conditions, the ketones, $R^1COCH{=}CHR^2$ afford the 1:4 adducts **601**, readily hydrolysed in aqueous thf to the acids **602**. Later studies illustrated some restrictions in the potentiallity for 1:4 addition through the use of the silicon reagents R_3SiOPZ_2 (R = Me or Et); although both 1:2 and 1:4 addition were observed for reactions at 0–55 °C for Z = OMe[979,981] or OEt[981], only 1:2 addition was found when Z = Me_2N[979]. An experimental feature which might be of value in an alternative context is the exact manner of use of the reagent; the use of pure reagent to provide 1:1 mixture of 1:2 and 1:4 adducts contrasts with the formation of only the 1:2 adducts when the reagent is prepared *in situ* (from Me_3SiCl and $ROPZ_2$), although to render the prediction of outcome of any reaction even more difficult, it might be noted that but-3-en-2-one[979] and 3,3-dimethylbutan-2-one[982] both add pure reagent to give only 1:4 adducts. For a series of cyclohexenones, to which addition of the silyl reagents is more difficult, 1:4 adducts are nearly always formed in greater amounts than the 1:2 products[981].

It is also interesting that other mixed phosphorus(III) esters may react with α,β-unsaturated aldehydes or methyl ketones in a similar fashion. Diethyl acetyl phosphite (but not

diethyl benzoyl phosphite) thus adds to give the acetate of the enol phosphonate ester, or across the carbonyl group, depending on the structural features of the carbonyl substrate[983].

7. Through the isomerization of phosphorus(III) esters

The phosphitylation of a ketone through its enol form leads to the phosphorus(III) esters carrying a conjugated unsaturated carbonyl moiety; their isomerization to the phosphonic diesters **603** (R = EtO) occurs reasonably readily, but other compounds in which, for example, $R_2P = (Pr^iO)(Et_2N)P$, isomerize with greater difficulty, during distillation, or during an extended period at room temperature[984]. Other phosphite esters, **604**, isomerize when heated at 160 °C[985] or in the presence of a trace of metallic sodium at the same temperature[986]. The formation of dialkyl (4-oxopentyl)phosphonates by similar means has also been reported[987].



When the reaction is carried out in the presence of a trace of a Lewis acid, e.g. $FeCl_3$, the phosphitylation of an α-hydroxyketone, e.g. benzoin, leads not to a phosphite ester, but to a (2-oxoalkyl)phosphonic diester; there appears to be, as yet, little information on the scope of this procedure[988].

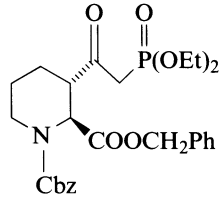
B. Syntheses Through Modification Procedures

In complete contrast to the (1-oxoalkyl)phosphonic acids, for which essentially only one synthesis is available, based on the Michaelis–Arbuzov or Michaelis–Becker reactions, there are several procedures available for the synthesis of those acids with the oxo group at $C_{(2)}$ or at a carbon atom site even further from the phosphoryl centre. Historically, esters of (2-oxoalkyl)phosphonic acids were also obtained through application of the Michaelis–Arbuzov and Michaelis–Becker reactions, but it soon became apparent that complications occur, the major one being the concomitant formation, in many instances, of enol phosphates and, in some cases, this reaction became the main one, indeed, sometimes the only one. Several other procedures are now available for the preparation of oxoalkyl acids which place the oxo group accurately and with no side reactions of any importance, and these are therefore considered first in the following survey.

1. Syntheses from alkylphosphonate carbanions

Carbanions have been generated from dialkyl (generally diethyl) alkylphosphonates by the action of an appropriately strong base, such as BuLi itself, but which, however, has drawbacks[989], or sometimes in combination with CuI, potassium *tert*-butoxide or, preferably, with lda[989], and all have all been used. Acylation of the carbanions leads to (2-

oxoalkyl)phosphonic esters, and may be carried out straightforwardly with an acid chloride, either saturated or α,β-unsaturated[990–993] or with an acid anhydride, as in the reaction between lithiated diethyl methylphosphonate and the anhydride from *cis*-*N*-cbz-piperidine-2,3-dicarboxylic acid to give, after benzylation, the ester **605**, and from which the acid **606** was obtainable[994]. The silyl phosphonoyl carbanion **607**, generated as indicated in Scheme 57, can be acylated at $C_{(1)}$ and acidolysed to yield a silicon-free, (1-substituted-2-oxoalkyl)phosphonic diester[995]. Various acyl chlorides (alkyl, aryl) were employed to acylate the zinc complex from dialkyl (bromodifluoromethyl)phosphonates, the products then being dialkyl [(1,1-difluoro-2-oxo)alkyl]phosphonates[996]; trifluoroacetic anhydride similarly affords esters of (2-oxo-1,1,3,3,3-pentafluoropropyl)phosphonic acid.



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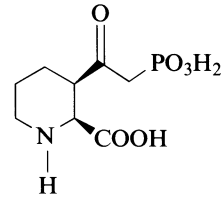

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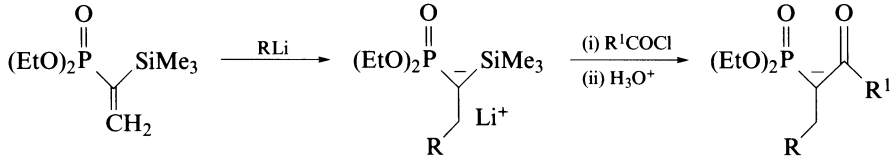
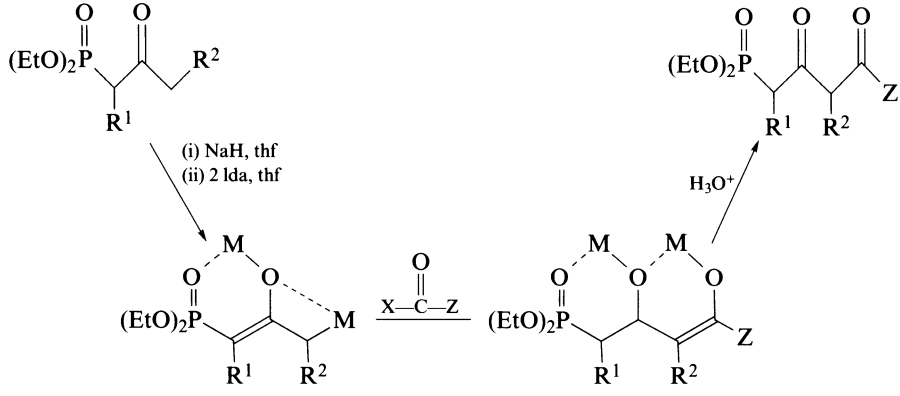


(607)

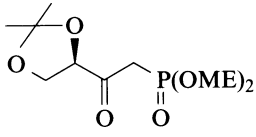
SCHEME 57

The acylation of the dianion from a diethyl (2-oxoalkyl)phosphonate can be designed (Scheme 58) to furnish esters of either (2,4-dioxoalkyl)phosphonic acids (Z = H, alkyl or Ph) or 4-phosphonoylbutanoic acids (Z = OEt)[997].



SCHEME 58

The acylation of phosphonic carbanions with carboxylic esters is a procedure which has received widespread attention[998–1001] and employed to prepare the protected dimethyl (3,4-dihydroxy-2-oxobutyl)phosphonate **608**[1002] and dimethyl [(3*S*)-3-methyl-2-oxo-5-octynyl]phosphonate (**609**), intermediates required in natural product synthesis[1003]. An example of intramolecular acylation is the formation of **610** by the action of potassium *tert*-butoxide on ethyl 2-[(ethoxy)methylphosphinoyl]benzoate[1004]. Acylations of lithiated phosphonoyl carbanions provide dialkyl [(1-formyl)alkyl]phosphonates[1005].



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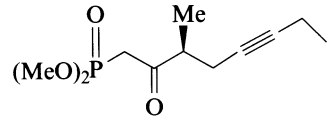
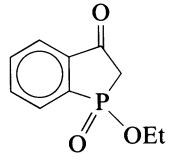
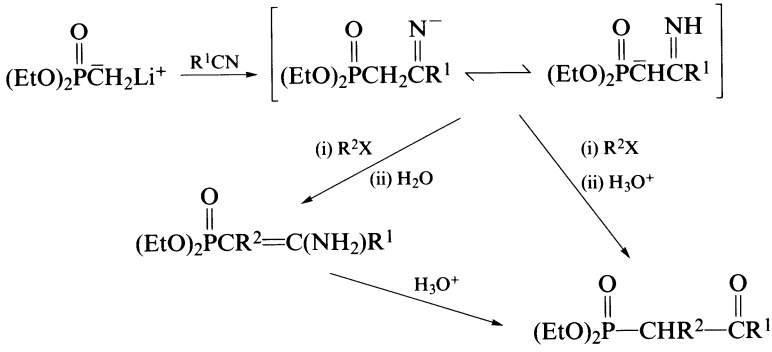


(609)



(610)

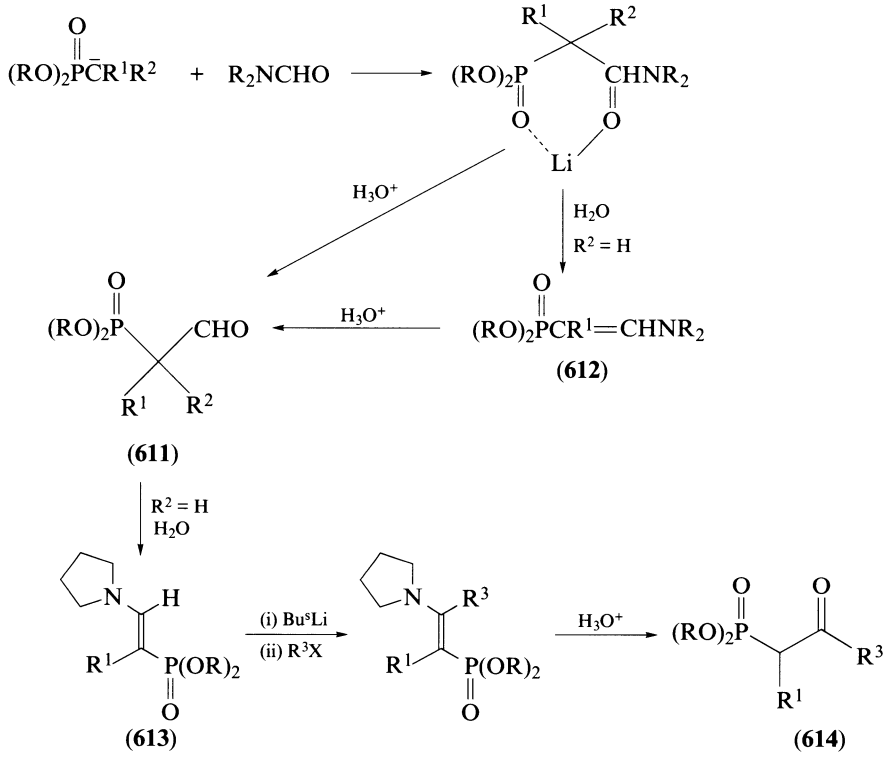
Lee and Oh[1006–1008] employed nitriles in conjunction with lithiated phosphonate carbanions. Careful hydrolysis of the anionic ketimine adducts under acidic conditions gave the (2-oxoalkyl)phosphonic esters, but it was also possible, when the hydrolysis was performed under essentially neutral conditions, to isolate phosphorylated enamines, which themselves are hydrolysable to a corresponding ketone (Scheme 59); the procedure also allows the introduction of other groups into the $C_{(1)}$ position when, for example, R^1X = PhSCl, PhSSPh, PhSeBr, $PhSO_2Cl$ or $MeSSO_2Me$[1009].



SCHEME 59

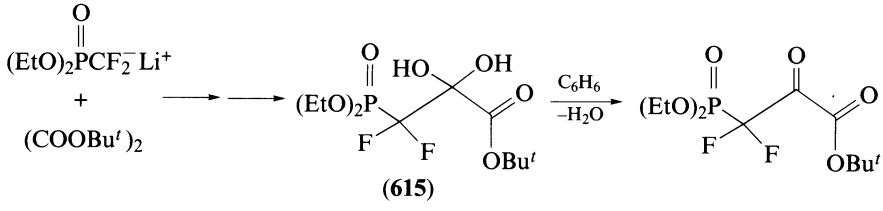
The reaction between carbanion and a formamide, R_2NCHO [R = Me or R_2 = $O(CH_2CH_2)_2$] yields a complex (Scheme 60, which again, depending on the hydrolysis medium, may be hydrolysed to β-phosphorylated acetaldehyde (**611**) or to the enamine **612**, and as before, **612** may be acidolysed to **611**[998,1010,1011]. Azeotropic removal of water from the phosphorylated acetaldehyde and a secondary amine such as pyrrolidine affords the enamine **613**; the treatment of this with a base (1-methylpropyllithium was used)

followed by an alkyl halide results in alkylation at the β sp^2 carbon, when hydrolysis (using oxalic acid in wet silica, or EDTA) gives the ketone **614**.[1011] The method has been used for the preparation of 2-phosphonoylated cycloalkanones[1012]. The ready availability of enamine phosphonates from a variety of starting compounds makes this method of synthesis of oxoalkylphosphonic diesters particularly attractive[1013,1014].



SCHEME 60

Two other examples are of interest in that they lead to phosphonoylated oxoalkanoic esters, In the first, the acyl halide BrCOCOOEt was used as an acylating agent for the synthesis of $(EtO)_2P(O)CH_2COCOOEt$ as the first stage in a preparation of phosphonopyruvic acid[1015]. The second case concerns the acylation of diethyl (difluoromethyl)-phosphonate carbanion with di-*tert*-butyl oxalate[1016]; here when worked up with aqueous $NaHCO_3$–MeCN, the initial product is the hydrated form **615** of the keto ester, from which water is removed by azeotropic distillation with benzene.



2. From phosphonoalkanoyl halides

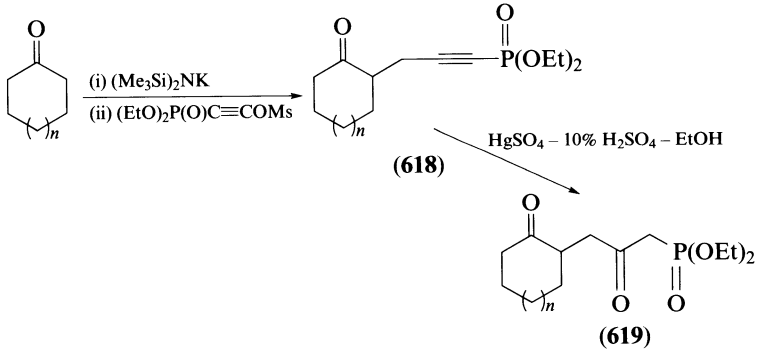
In the reverse of the above sequence, and yet one which initially employs alkylphosphonic diester carbanions, the carboxylation of the carbanion with CO_2 leads to the phosphonoacetic acid **616**, convertible with thionyl chloride into its acid chloride **617** (R^1 = H, Me, Ph, SPh, Cl or F)[1017,1018]. The latter is acted upon by an appropriate alkylating species, e.g. R^2Li, R^2MgBr, $R^2{}_2CuLi$ or $R^2{}_2CuMgBr$, in THF at –78 °C. In the case of the α-fluoro compound, the final alkylation step evidently works well only with Me_2CuLi.

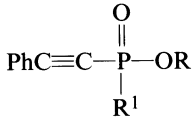
$$(EtO)_2PCHR^1COZ$$

(616) Z = OH
(617) Z = Cl

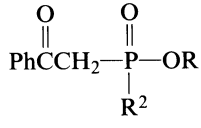
3. By the hydration of acetylenic phosphorus acids

Like the classical conversion of acetylene into acetaldehyde, the treatment of a (2-substituted-ethynyl)phosphonic diester with sulphuric acid in the presence of mercury(II) sulphate, with subsequent drenching, affords the 2-oxo compound through hydration and a prototropic shift. Sturtz *et al.*[451] were thus able to convert a series of diethyl (alk-1-ynyl)phosphonates into diethyl (2-oxoalkyl)phosphonates. The conversion of a cycloalkanone into the 2,5-dioxoalkyl species **619** following the neat generation of the side-chain in **618**[1018] and the conversions of **620** into **621** and of **622** into **623** are further examples of the same process[1019]. Sulphuric acid itself is able to convert the series **624** into the corresponding **625** (Z = OH, OMe or OEt)[1020].





(620) R^1 = Ph
(622) R^1 = PhC≡C



(621) R^2 = Ph
(623) R^2 = $PhCCH_2$ (=O)

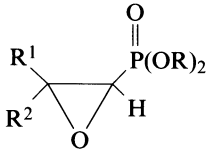
$(PhCCl{=}CH)_nP(O)Z_{3-n}$
(624)

$(PhCOCH_2)_nP(O)Z_{3-n}$
(625)

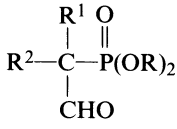
Esters of (2-oxopropyl)phosphonic acid result from the treatment of the corresponding esters of propadienylphosphonic acid with aqueous ammonia, or by the addition of amines to the same esters or those of (prop-1-ynyl)phosphonic acid, followed by mild acid hydrolysis of the resultant eneamine phosphonic diesters[1021].

4. *From (epoxyalkyl)phosphonic acids*

The rearrangement of (1,2-epoxyalkyl)phosphonic acid esters [**626**; R^1, R^2 = H, Me or Ph, $R^1R^2 = (CH_2)_5$] into esters of the (formylalkyl)phosphonic esters (**627**) is initiated thermally, but is also brought about very rapidly under the influence of BF_3 etherate; there was no evidence for the formation of the esters $(RO)_2P(O)COCHR^1R^2$ through hydrogen migration[556].



(626)

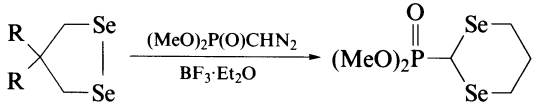


(627)

The epoxidation of halogenated alkenylphosphonic esters with trifluoroperoxyacetic acid yields unstable halogenated (epoxyalkyl)phosphonic esters, which isomerize rapidly by a 1,2-shift of halogen. The isomerization occurs for both 1,2-epoxyalkyl and 2,3-epoxyalkyl compounds, but in some cases the rearrangement is not regiospecific and affords both ketonic and aldehydic products[1022].

5. *Through derivative formation*

The indirect introduction of an oxo group to an otherwise 'functionless' phosphonic acid derivative is a relatively new development which has not yet been explored to a fully satisfactory conclusion, but the potential of the procedure is exemplified by the treatment of methylenebisphosphonic esters and triethyl phosphonoacetate with methyl methanethiosulphonate, $MeSSO_2Me$, in the presence of Al_2O_3–KF, when the products have the composition $(EtO)_2P(O)C(SMe)_2R$, where R = $P(O)(OEt)_2$ or COOEt[1023]. More commonly, however, *gem*-alkylthio groups, either identical or non-identical, have been introduced in a stepwise fashion through the treatment of a phosphonic ester carbanion with a disulphide[591,598] or sulphenyl chloride[1024], or through the use of methyl methanethiosulphonate[1025]. In particular several procedures have already been described for the preparation of derivatives of (oxomethyl)phosphonic acid[844–848]. The preparation of a bisselenide, $(EtO)_2P(O)CH(SePh)_2$, has also been mentioned in the same connection, but a more unusual route has been adopted for the cyclic analogue **628**[1026].



(628)

A second example of derivative formation is that of oximes through the nitrosation of *C*-phosphorylated active methylene compounds. Dialkoxyphosphinoyl and [alkyl(or

aryl)(alkoxy)]phosphinoylacetic acid esters[1027], chlorides[1028] and amides[1029] react with NOCl in the presence of aluminium isopropoxide to give the oximes, $R(R^1O)P(O)C(=NOH)COR^2$ (R^2 = OEt, Cl or NHMe). Many other examples of this process have been reported, particularly in the phospholane series.

The extent to which derivatives, such as those described, can be successfully deprotected to give the parent oxo compounds appears not to have been examined systematically.

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NOTE ADDED IN PROOF

A further selection of advances and new methods reported in this section has been made from the literature published between mid-1994 and mid-1995.

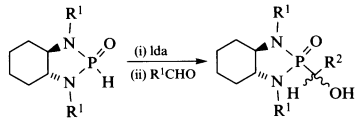
Section II

Details have been provided for an improved synthesis of diethyl (bromomethyl)phosphonate from triethyl phosphite and CH_2Br_2[1030]; dibromodifluoromethane is extremely reactive in Michaelis–Arbuzov reactions, although it is possible to prepare the phosphinic esters $R(BrCF_2)P(O)OEt$ from that halide and $RP(OEt)_2$, where R = Et or Ph[1031]. Reactions between the dihalides $X(CF_2)_nY$ and tetraethyl diphosphite yield bisphosphonites or phosphonate–phosphonites (for n = 3, 4, 6)[1032]. It might be noted that when n = 2, no reaction at all occurs when X = Y = I, and if X = Y = Br, the only observed process is that of elimination to give tetrafluoroethane; on the other hand, tetraethyl diphosphite and $BrCF_2CF_2I$ gives the phosphonite diester $(EtO)_2PCF_2CF_2Br$ which can be oxidized to the corresponding phosphonate diester[1033].

In a polar solvent, adamantane reacts with $P(O)Cl_3$ to give (3-chloroadamant-1-yl)phosphonic dichloride, but should the solvent be non-polar, the product is then bis(3-chloroadamant-1-yl)phosphinic chloride[1034].

Section III

New developments in the synthesis of α-hydroxy phosphonic acids and their derivatives have concentrated on their asymmetric formation. The chiral phosphonic diamides (**629**) (in which R^1 = isopropyl, 2,2-dimethylpropyl, or benzyl or a derivative thereof) in either racemic or optically active forms were converted into their anions and allowed to react with aldehydes to give the products (**630**); the diastereoisomeric composition of the latter could be ascertained by the use of ^{31}P NMR spectroscopy, and after acidic hydrolysis and subsequent methylation (diazomethane) it was possible to isolate optically active forms of the dimethyl esters of (1-hydroxyalkyl)phosphonic acids, the (*R*,*R*)-diamide giving rise to the (*S*)-acids as their esters. The best results were achieved when $R^1 = Bu^tCH_2$, and enantiomeric excesses were generally above 85%[1035].



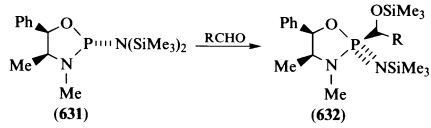
(**629**) (**630**)

The treatment of an acylphosphonic diester with borane in the presence of a chiral 1,3,2-oxazaborolidine has produced the (α-hydroxyalkyl)phosphonic diester, very often in considerable enantiomeric excess[1036]. Moderate enantiomeric excesses have also been observed as the result of the hydrolysis of the acetates of racemic (1-hydroxyalkyl)phosphonic diesters by the lipase from *Aspergillus niger*[1037].

The enantiomeric composition of the free (1-hydroxyalkyl)phosphonic acids, or derived diesters, may be conveniently ascertained by means of ^{31}P NMR spectroscopy, through an examination of the derived and optically active α-methoxy-α-(trifluoromethyl)phenylacetates (Mosher esters). The ^{31}P chemical shift differences may be used to assign absolute configurations to the phosphonic acids or esters[1038].

A further, very detailed study of the condensation reactions between the 1,3,2-oxazaphospholidines (**631**) and aldehydes as a means of preparing silyl ethers based on (1-hydroxyalkyl)phosphonic acids; diastereoselectivities were very high and the configuration at phosphorus in the products (**632**) was determined by a combination of NMR spectroscopic and X-ray crystallographic methods. The Abramov condensation was found to occur with retention of configuration[1039]. In another study, analogous 1,3,2-diazaphospholidines were employed[1040]. This and other work[1041] have been directed towards the design of reagents capable of catalysis of the binding together of the phosphoprus reagent and an aldehyde into a transition state which would lead to the Abramov product.

The chemistry of the reactions of phosphorus-containing carbanions with carbonyl compounds may be revisited (Section III.B.3); those between diethyl (aryllithiomethyl)phosphonates and ketones have been used to prepare diethyl (1-aryl-2-hydroxy-2,2-disubstituted-ethyl)phosphonates, formed with high *syn*-stereoselectivity[1042]. Modro *et al.* have extended their studies on the interaction of aldehydes with diethyl prop-2-enylphosphonate carbanion; when the reaction products are warmed, dissociation of the kinetically



(631) (632)

controlled α-adducts (which are isolable as mixtures of enantiomers) into starting materials occurs, to be followed by their recombination to give the thermodynamically controlled γ-adducts which subsequently fragment into *E*-1,3-dienes[1043].

Complexes from (*S*) or (*R*)-BINAP and Ru(II) are said to be excellent for the enantioselective hydrogenation of β-oxo phosphonate esters leading to the β-hydroxy compound with high enantiomeric excess and in high yield[1044].

The hydroxylation of esters of alk-1-enylphosphonic acids using OsO_4 has been carried out under conditions which result in asymmetric addition, and the stereoisomeric composition of the (1,2-dihydroxyalkyl)phosphonic esters was determined through derived 1,3-dioxolanes (largely of 4*S*,5*S* stereochemistry) using ^1H NMR spectroscopy[1045].

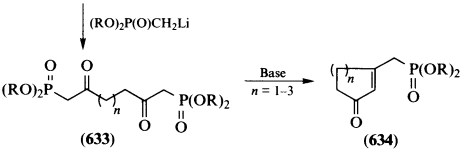
Section IV

The treatment of dimethyl (2-oxopropyl)phosphonate with H_2O_2–HBr leads to the α-bromo derivative; asymmetric hydrogenation of the latter in the presence of Ru(II) and either (*S*) or (*R*)-BINAP affords dimethyl [(1*R*, 2*S*)-1-bromo-2-hydroxypropyl]phosphonate, a convenient source of phosphonomycin (fosfomycin)[1044].

Section VII

In addition to the displacement of sulphinate anions from aryl 2-oxiranyl sulphones recorded earlier, the displacement of nitrite from 2-nitroepoxides by hydrogenphosphonate anions has now been reported[1046].

The condensation between dimethyl (lithiomethyl)phosphonate and methyl glycouronides yields carbohydrate-derived β-oxo phosphonates[1047]. The anion from diethyl (but-2-en-1-yl)phosphonate and lda reacts with ethyl formate to give 4-(diethoxyphosphinyl)-2-methylbut-2-enal[1048]. The di-β-oxo phosphonates (**633**) were prepared in a similar fashion, and when these are acted upon by a base, they undergo intramolecular cyclization to give the unsaturated and functionalized phosphonate esters (**634**)[1049].



(633) (634)

The lithiated carbanion from diethyl (methylthiomethyl)phosphonate reacts with Ph_2S_2; the product, $(EtO)_2P(O)CH(SMe)(SPh)$, is reactive to more BuLi and Ph_2S_2 with loss of PhSSMe and formation of $(EtO)_2P(O)CLi(SPh)_2$[1050]. Other examples have been prepared from $(EtO)_2P(O)CH_2S(O)Ph$ and thiols under Pummerer rearrangement conditions[1051].

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CHAPTER 4

The synthesis of functionalized phosphinic and phosphonic acids and their derivatives. Part B: diazo, nitro and amino functionalized acids

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I. INTRODUCTION

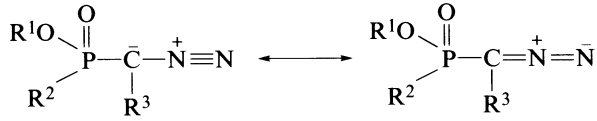
The preceding chapter examined various procedures for the synthesis of phosphonic and phosphinic acids which possess halo, hydroxy, mercapto, epoxy, carboxy (and derivatives) or oxo substituent groups, singly or in combination, in the organic moieties. This chapter is a continuation of this review, and is concerned with the synthesis of those acids, and their derivatives, which possess a common nitrogen-containing functional group, namely, diazo, nitro or amino. Azido acids are also briefly considered alongside the amino- and diazo-substituted acids, since their syntheses and reactions are so closely linked.

Many of the general remarks made in the Introduction to the previous chapter apply equally here. Since the appearance of the original volumes on organophosphorus chemistry in the Houben–Weyl series, and even during the two decades since the publication of Kosolapoff and Maier's survey, an explosive growth has been seen in both the number of known compounds and our knowledge of methods for their synthesis. Nowhere has this growth been more apparent than in the chemistry of the amino-functionalized phosphonic acids, for which some degree of systematic study appeared even before 1950. The enormous increase in interest in the latter was boosted with the discovery that such phosphonic acids occur naturally and possess interesting biochemical roles.

As in the two previous chapters, the surveys edited by Kosolapoff and Maier[1,2] and those in Houben–Weyl[3–5] should be consulted for early references. Some older references are included here only if they are considered to be of particular relevance or historical importance. Other related aspects have been reviewed elsewhere[6], and short bibliographies have been provided for many individual compounds mentioned herein[7]. The present survey is concerned mainly with the literature from about 1960 to mid-1994, and which is also reviewed annually[8].

II. DIAZOALKYL-PHOSPHONIC AND -PHOSPHINIC ACIDS

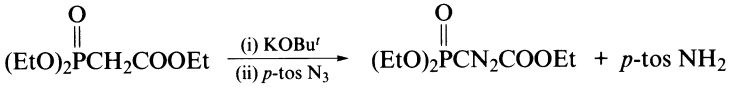
The first successful syntheses of phosphorus-containing diazoalkyl compounds (**1**) appear to have been reported independently by two groups of workers. Petzold and Henning[9] employed a method presently described as that of diazo transfer, in which an active methylene compound, as its anion, is treated with an aromatic sulphonyl azide. Seyferth *et al.*[10], on the other hand, reported on a development to the Bamford–Stevens reaction, in which a carbonyl *p*-toluenesulphonylhydrazone is treated with a base. Both methods thus depend on modifications to compounds with existing phosphorus–carbon bonds, as do other procedures which have since been developed.



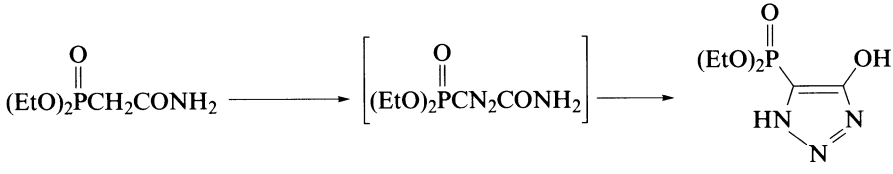
(**1**)

A. Synthesis Through Diazo Transfer

In this procedure, the *C*-phosphorylated active methylene compound is first converted into its anion, through its reaction with KOBu^t, BuLi, PhLi, NaH or even Et_3N, and the anion is then acted upon by a sulphonyl azide; the latter has been *p*-toluenesulphonyl azide in most recorded examples of the reaction. The first example of the adoption of this procedure to the synthesis of a phosphonic acid derivative appears to have been the conversion of triethyl phosphonoacetate into the diazo derivative (**2**)[9]. Since then, the procedure has been used to obtain *N*-substituted derivatives of the phosphonoacetamide corresponding to structure **2**, but the primary amide itself undergoes further reaction to afford the *C*-phosphorylated 1,2,3-triazole (**3**)[11]. Tetraethyl methylenebisphosphonate yields tetraethyl

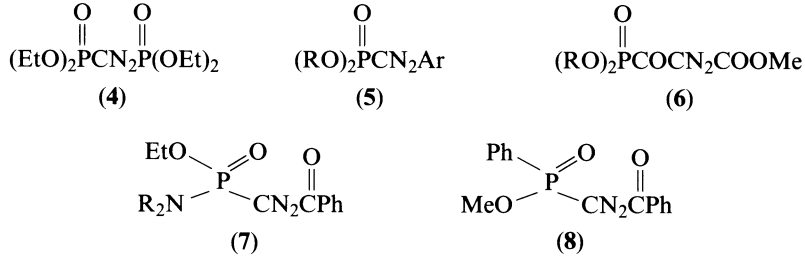


(**2**)



(**3**)

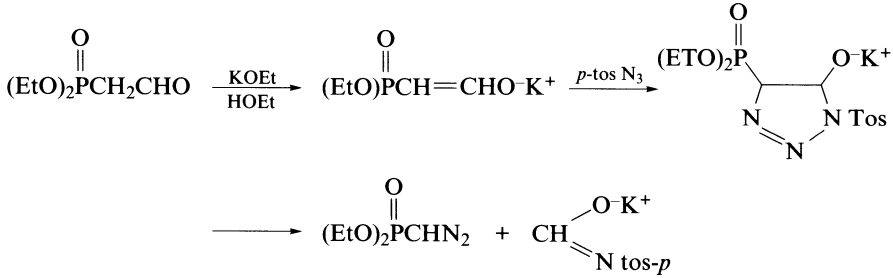
(diazomethylene)bisphosphonate (**4**)[12] and the (arylmethyl)phosphonic diesters afford the products **5**[12]. Such compounds tend to be highly coloured and relatively stable and, in many cases, are isolable through distillation. On the other hand, the β-diazo esters **6** are very unstable[13]. Stability is thus seen to be associated not merely with the presence of two adjacent electron-withdrawing groups, but also with the close proximity of the phosphoryl group as in, for example, the isolable phosphonic monoamides **7**[14] and the phosphinic esters **8**[15, 16].



(**4**) (**5**) (**6**)

(**7**) (**8**)

A mechanism (Scheme 1) has been considered by Regitz and Anschutz[17] for the interaction of diethoxyphosphinylacetaldehyde and *p*-toluenesulphonylazide which depends on addition of azide to the enolate anion followed by an elimination which, in this case, yields diethyl (diazomethyl)phosphonate.



SCHEME 1

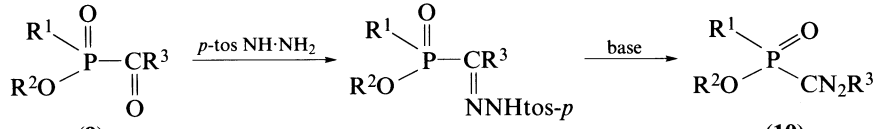
2-Naphthalenylsulphonyl azide has been advocated as a diazo transfer reagent of a capability superior to that of *p*-toluenesulphonyl azide[18].

B. Synthesis Through the Bamford–Stevens Reaction

Should the oxoalkyl phosphonic or phosphinic acid corresponding in structure to a desired diazoalkyl acid be available, an adaptation of the Bamford–Stevens reaction becomes potentially useful.

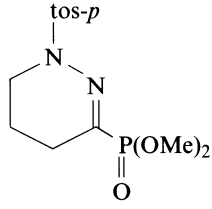
A (1-oxoalkyl)phosphonic diester (**9**; $R^1=R^2O$), generally available through a Michaelis–Arbuzov reaction using the acyl chloride R^3COCl and the phosphorus(III) ester $(R^2O)_3P$, is converted into its *p*-toluenesulphonylhydrazone (Scheme 2), and the latter is then decomposed by the action of a base, very often simply aqueous KOH or Na_2CO_3. The method was originally applied to esters from acetyl- and benzoyl-phosphonic acids[10, 11, 19], and has since been applied to a wide range of dimethyl (1-oxoalkyl)phosphonates [20,21], and also to analogous phosphinic esters (**10**; R = Ph or substituted phenyl)[15], to (1-oxoalk-2-enyl) phosphonic diesters[22, 23] and to (3-oxoalk-1-enyl)phosphonic diesters[23]. An exception

to the general procedure is the case of dimethyl (4-chloro-1-oxobutyl)phosphonate, whose *p*-toluenesulphonylhydrazone, when treated with base, yields **11**[20]. Should the diazo group be introduced on to a carbon which is adjacent to an α—C—H bond, then loss of nitrogen and migration of a hydrogen atom occur with the formation of esters of (alk-1-enyl)phosphonic acids[20]. In methanol, sodium borohydride converts *p*-toluenesulphonylhydrazones of oxoalkylphosphonic diesters into the diazoalkylphosphonic derivative, although in different experimental circumstances the same hydrazone can yield alkylphosphonic diesters[24].



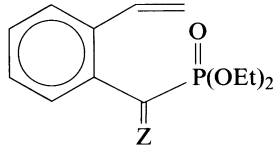
(9) **(10)**

SCHEME 2

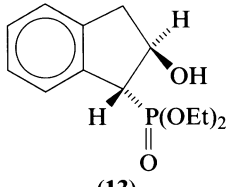


(11)

An incorrect choice of base with which to carry out the decomposition of the hydrazide may also lead to unwanted reactions. Whilst the treatment of the hydrazide **12a** with NaOEt in dme affords the diazo ester **12b** (but which then undergoes a further intramolecular reaction), the use of aqueous Na_2CO_3 leads to the phosphorylated secondary alcohol **13**. Compound **12b**, however, undergoes cyclization to **14** and this, under the influence of more ethoxide, tautomerizes to **15**[23].



(12)
(a) Z = NNHtos-*p*
(b) Z = N_2



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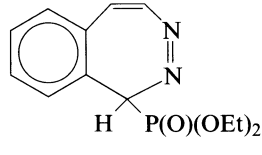

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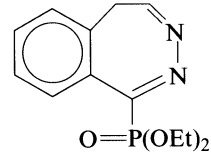
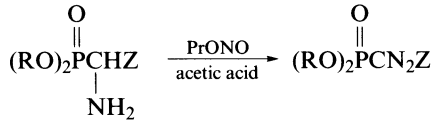


(15)

C. Synthesis Through Diazotization

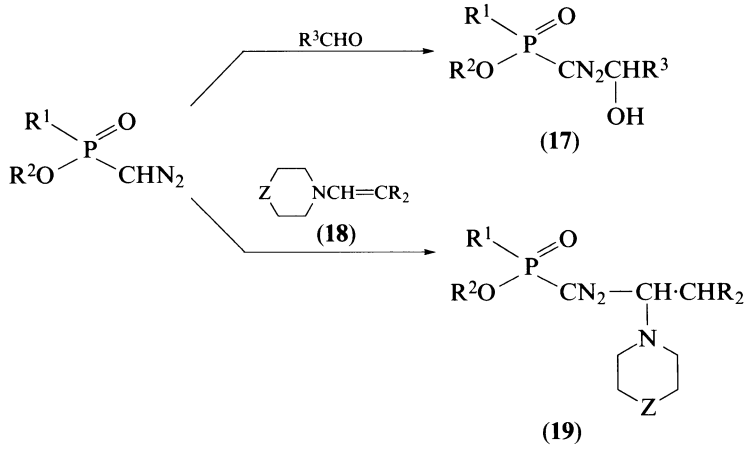
The third procedure for the synthesis of phosphorylated diazoalkyl compounds is that of diazotization of the correspondingly substituted amino compounds, As a result of the ready availability of dimethyl and diethyl (aminomethyl)phosphonates, these form the most convenient starting materials for conversion into the dialkyl (diazomethyl)phosphonate by the use of $NaNO_2$–acid[21]. Latterly, the customary reagent combination has been that of propyl nitrite in acetic acid, and successful conversions have been described for **16** (Z = COOR[25], $CONHR^{26}$ and CN^{27}). In the case of the last substrates, the diazo transfer procedure is said to be unsuitable, because of extensive side reactions which lead to phosphorylated 1,2,3-triazoles. Most reports have been concerned with the preparation of 1-diazoalkyl compounds, and the syntheses of compounds in which the diazo group is sited elsewhere on the carbon skeleton are very rare[28].

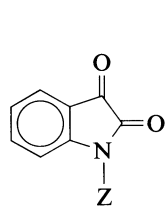


(16)

D. Syntheses Through Modification Procedures

Esters of (diazomethyl)phosphonic acid, or of analogous phosphinic acids, are valuable compounds, in that not only do they act as sources of *C*-phosphorylated carbenes, but they are also potentially capable of modification without loss of the diazo group. Thus, dimethyl (diazomethyl)phosphonate [and also the analogous (diazomethyl)diphenylphosphine oxide] undergoes aldol reactions with aromatic aldehydes to yield the dimethyl (2-diazo-3-hydroxyalkyl)phosphonates (**17**; $R^1 = R^2O$, R^2 = Me)[29]. Dimethyl (diazomethyl)phosphonate [and likewise, again, (diazomethyl)diphenylphosphine oxide] is an active methylene compound and undergoes Michael addition across the carbon–carbon double bond in the enamines **18**(Z = CH_2 or O) to give the adducts **19**[30], and also at the ketone carbonyl group in **20** (Z = H, Me, OH, Ac, or OAc) to give the products **21**[31].

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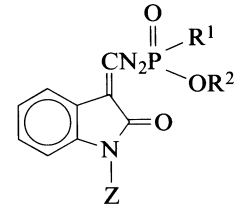
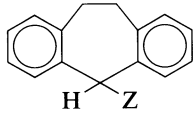
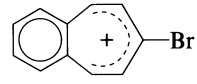

(21)

Diesters of (diazomethyl)phosphonic acid are fairly acidic and metal salts are readily available; the lithium salts from these and the esters of other comparable acids are normally prepared *in situ* through reaction with BuLi, whilst silver salts are normally obtainable from Ag_2O[15,32]. The salts so obtainable are reactive to alkyl halides to give the diesters of homologous (1-diazoalkyl)phosphonic acids[15].

Several electrophilic substitution reactions have employed dimethyl (diazomethyl)-phosphonate, methyl (diazomethyl)phenylphosphinate (**10**; R^1 = Ph, R^2 = Me, R^3 = H) or (diazomethyl)diphenylphosphine oxide, as either a metal salt or the free acid in combination with Et_3N. Thus, **22** Yields **23**[33], **24** gives **25** (Z = Br)[34] and **26** gives a mixture of **25** (Z = OR, R = Me, Pr^i, CH_2Ph, etc.) and **27** (Z = OR)[35], the structural isomer **27** (Z = Br) not being obtained from **24**[34].


(22) Z = Cl
(23) Z = $R^1(R^2O)P(O)CN_2$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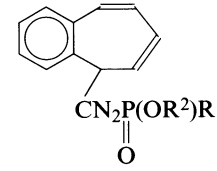
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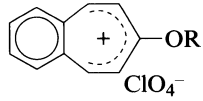
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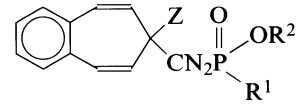
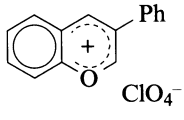

(27)

The benzopyrilium salt **28** yields a mixture of the esters **29** and **30**[36], and **31** (Z = O[37] and S[38]) are convertible into the corresponding **32**. Finally, It has been shown[39] that cyclopropenium salts **33** also react and may form mixtures of the isomeric products **34** and **35**.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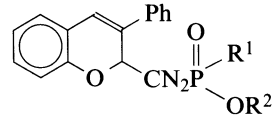
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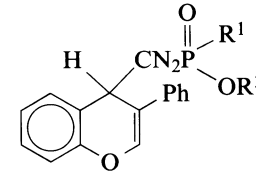
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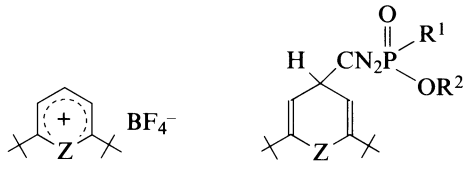
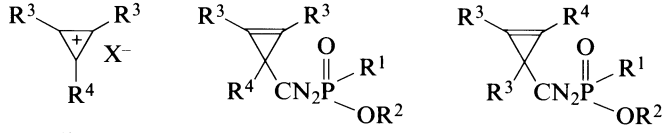


(31) (32)



(33) (34) (35)

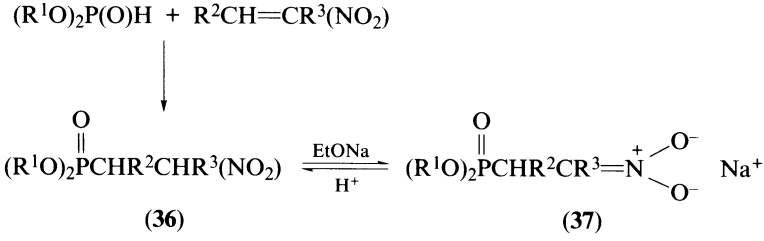
III. NITROALKYL-PHOSPHONIC AND -PHOSPHINIC ACIDS

Developments in the synthesis of (nitroalkyl)phosphonic acids and their phosphinic acid analogues, as a group, have occurred extensively only during the last 10–15 years, and the potential of such compounds in further synthetic procedures is only now becoming apparent. The number of methods available for the synthesis of (nitroalkyl)phosphorus compounds is appreciable and, as for the functionalized phosphonic acids discussed in the previous chapter, can be subdivided into those which depend on the formation of the phosphorus–carbon bonds and those which are based on modification procedures.

A. Syntheses Through Phosphorus–Carbon Bond Formation.

1. Through additions of hydrogenphosphonates or related compounds to nitroalkenes

The addition of a dialkyl hydrogenphosphonate to a nitroalkene takes place when a mixture of the neat reactants is heated at 100 °C for 2 hs, when yields average 50%[40], or in the presence of NaOEt as a catalyst and under much milder conditions, when yields of 30–80% are achievable[41,42]. In the presence of the equivalent amount of ethoxide catalyst, the product then exists in the nitronate form (**37**), from which the nitro form (**36**) may be generated on protonation. Triethylamine (1 mol equiv.) as base catalyst has advantages in that through its use the extent of polymerization is reduced and the yields of adducts consequently increased[43].



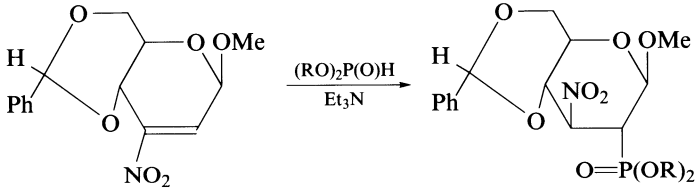
(36) (37)

No nucleophilic displacement of a nitro group from **38** (Z = NO_2) occurs when this is acted upon by dialkyl phosphite anion during 0.5 h at room temperature, and these experimental conditions generate only the corresponding adducts **39** (R = Me, 75%; R = Et,

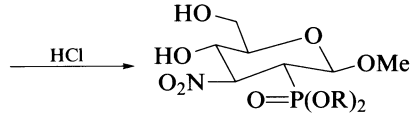
69%); reactions with the analogous thiophosphonate anions produced similar yields of the analogous thiophosphonic diesters[43,44]. With other substrate, the reactions tend to be more complex. For example, when Z = H, both the substrate alkene and the 1:1 (2-nitroethyl)phosphonate adduct react with an excess of phosphite anion to yield 3-(diethoxyphosphinoyl)-2,2-diphenylaziridine. The products from other substrates (e.g. when Z = SBu^t-) may be free of phosphorus, or the 1:1 adduct may lack the group Z (e.g. when Z = SPh)[45].

(38) **(39)**

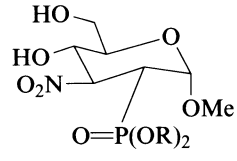
It is surprising that so little has been written about the general scope and other features of this procedure in relation to simple substrates. On the other hand, additions to unsaturated nitro sugars have formed a means through which nitro- and, subsequently, amino- and polyhydroxy-substituted phosphonic and phosphinic derivatives in the carbohydrate field have frequently been obtained. For instance, dimethyl and diethyl hydrogenphosphonates add to methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**40**), in the presence of triethylamine and at room temperature, to give **41** (R = Me or Et); these products may then be deprotected to give the *C*-phosphorylated nitro sugar **42**[46]. It is noteworthy that, under the same conditions, the corresponding α-glycoside yields a mixture of the *gluco* (**43**) and *manno* (**44**) products, in the ratio 1:1[46].



(40) **(41)**



(42)



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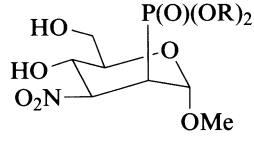
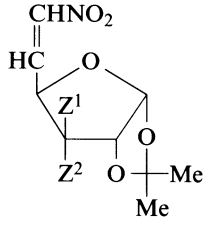
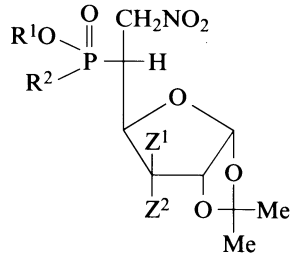


(44)

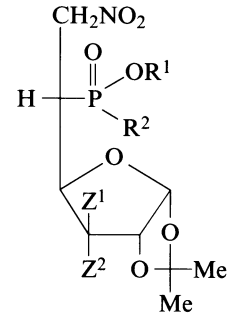
Much more commonly explored have been the additions of hydrogenphosphonates and analogous phosphinates to carbohydrates with exocyclic unsaturation. The addition of dimethyl hydrogenphosphonate to **45** at room temperature with Et_3N catalysis afforded a 89:11 mixture of the *gluco* and *ido* products **48** and **49**, stereoisomeric at $C_{(5)}$; the ratio of products from diethyl hydrogenphosphonate was 84:16. When the reaction is carried out at 100 °C in the absence of a catalyst, the major product from each hydrogenphosphonate has the 5*S* (L-idose) configuration indicated in **49** ($R^2 = R^1O$, R^1 = Me or Et)[46–48], confirmed by a structure determination through the use of X-ray diffraction techniques[49]. An explanation for the selectivity of reaction is based on steric hindrance by the OAc group to the approach by the P(O)H grouping towards that side of the double bond which would lead to the 5*R* (D-glucose) isomer[49]. Similar additions also occur with the hydrogenphosphinates (R^1O)R^2P(O)H (R^1 = Me, R^2 = Et[50] or Ph[51,52]). A greater selectivity towards the *ido* product results from an increase in the size of R^1.



(**45**) Z^1 = OAc, Z^2 = H
(**46**) Z^1 = H, Z^2 = OAc
(**47**) $Z^1 = Z^2$ = H

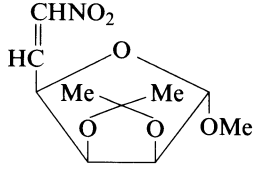


(**48**)

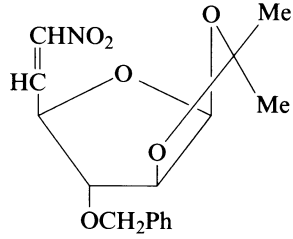


(**49**)

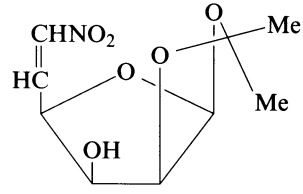
The substrates **46** and **47** also react at room temperature with catalysis by Et_3N[48], a procedure which is preferable since no elimination of nitrous acid then occurs[51]; under such conditions, the substrates **50**–**52** also react, whereas only **50** reacts when heated at 100 °C in the absence of a base catalyst[53]. The absence of the group Z, as in **47**, reduces product selectivity, the ratio of products then being almost identical with that obtained from **46**.



(**50**)



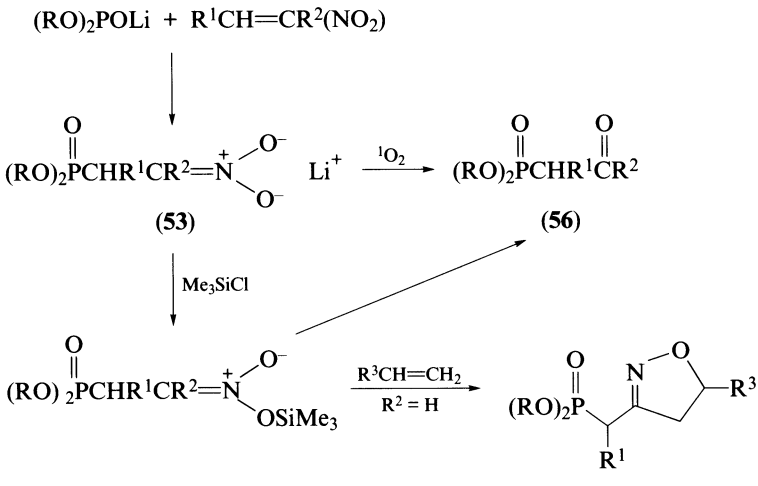
(**51**)

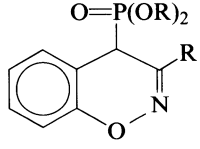


(**52**)

The additions of hydrogenphosphonates to nitroalkenes have served as the first stage in several useful syntheses of other functionally modified phosphonic acids. For instance, an addition in the presence of 1 mol equiv. of BuLi has been employed in a one-pot reaction sequence which leads to [(dialkoxyphosphinoyl)methyl]isoxazolines (**55**; R = Et)[54]; the

oxidation of the silylated nitrones **54** (R = Et, R^1 = aryl) with *m*-chloroperoxybenzoic acid affords diethyl (1-aryl-2-oxoalkyl)phosphonates (**56**; $R^2 \neq H$)[55]. In yet a further sequence, the interaction of the metal nitronates **53** (R = Me) with singlet oxygen also leads to the phosphonic diesters **56** (R^1 = Me, Et, Pr, Pr^i or Ph; R^2 = H)[56]. The adducts from diethyl phosphite anions and the alkenes PhCH=CR(NO_2) are reported to cyclize to the benzoxazines **57** in 85% sulphuric acid[57].

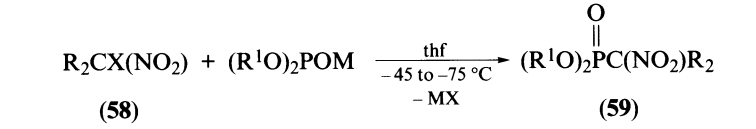




(**57**)

2. *Through the alkylation of hydrogenphosphonates and related compounds*

The displacement of halogen (generally chlorine) or a sulphonate ester group from the compounds **58** by a phosphite (or thiophosphite) anion is of an $S_{RN}1$ nature, being inhibited by oxygen and Bu^{t}NO; when carried out in thf at −45 to −25 °C, the products from **58** (X = Cl or 4-Me$C_6H_4SO_2$) are the (1-nitroalkyl)phosphonic diesters **59** [R = Me or R_2 = $(CH_2)_5$] in 60–80% yields; the yields from thiophosphite anions tend to be lower. The mechanism of the displacement is thought to be that outlined in Scheme 3. When X = NO_2, **58** (R = Me) yields a phosphate ester derived from acetone oxime, but thiophosphite anion does afford a nitroalkyl thiophosphonate[58,59].



$$R_2CX(NO_2)^{-\bullet} \longrightarrow R_2C^{\bullet}(NO_2) + X^-$$

$$R_2C^{\bullet}(NO_2) + (R^1O)_2PO^- \longrightarrow (R^1O)_2\overset{\overset{O}{\|}}{P}CR_2(NO_2)^{-\bullet}$$

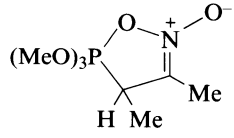
$$(R^1O)_2\overset{\overset{O}{\|}}{P}CR_2(NO_2)^{-\bullet} + R_2CX(NO_2) \longrightarrow R_2CX(NO_2)^{-\bullet} + (R^1O)_2\overset{\overset{O}{\|}}{P}CR_2(NO_2)$$

SCHEME 3

3. *Through the additions of phosphorus(III) esters to nitroalkenes*

The reactions between simple phosphorus(III) esters and nitroalkenes occur very readily, but are complex, and their outcome depends on several factors, including the nature of the ester and the experimental conditions. Several processes, including addition, elimination and oxidation reactions, occur alongside one another. In some respects the reactions of phosphorus(III) esters with nitroalkenes resemble those of the same esters with α,β-unsaturated ketones; evidently equilibration occurs between dipolar adducts and cyclic quinquecovalent intermediates of the phosphorane type, and each may decompose, possibly to give different products.

One of the earliest addition reactions studied is that which takes place between trimethyl phosphite and 2-nitrobut-2-ene, and which illustrates the effect of reactant concentrations on the course of the reaction. When reactant concentrations are high, the phosphorane **60** is isolable, whereas at low reactant concentrations, the product is the oxime **61**, formed from **60** through a process initiated by the transfer of a proton from $C_{(4)}$[60,61].



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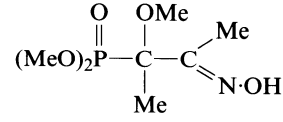
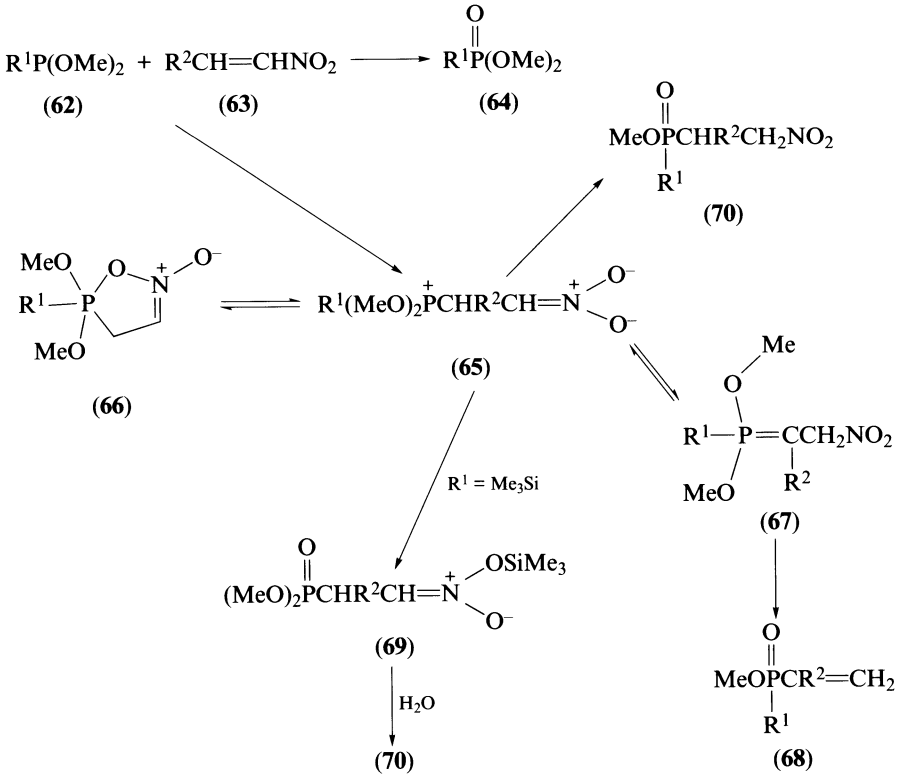


(61)

More generally, the interaction of trimethyl phosphite (**62**; R^1 = OMe) and (*E*)-nitroalkenes (**63**) follows Scheme 4[62]. The formation of trimethyl phosphate (**64**; R^1 = OMe) is the result of direct oxidation, possibly by liberated nitrite ester or through the deoxygenation of a phosphorylated nitrile oxide (see later). In dry diethyl ether at ambient temperature, there is a distinct emphasis on the formation of alkenylphosphonic diesters (**68**; R^1 = OMe) and phosphorane adducts (**66**; R^1 = OMe). An increase in positive inductive effect of the group R^2 results in an increase in the amounts of phosphorane formed relative to unsaturated phosphonate, but there is no change in the amounts of trimethyl phosphate formed. No reaction occurs at –30 °C, and the temperature must reach 25–30 °C before the reaction becomes appreciable. As the temperature is raised still further in an appropriate solvent, the build-up of phosphorane continues, and at 50–60 °C, evolution of methyl nitrite begins; at this stage, the reaction can be stopped and the phosphorane **66** isolated; alternatively, if, at this stage, water is added, the dimethyl (nitroalkyl)phosphonate (**70**; R^1 = OMe) can be isolated.

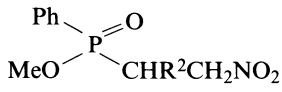
A parallel series of reactions has been observed for tris(2-chloroethyl)phosphite[63,64]. The formation of diethyl (2-oxoalkyl)phosphonates by the oxidation (by *m*-chloroperoxybenzoic acid) of the products from the interaction of triethyl phosphite and nitroalkenes in the presence of $TiCl_4$, is consistent with the intermediate formation of *C*-phosphorylated acinitro complexes[65]. When the phosphite triester species is a dialkyl trimethylsilyl phosphite,



SCHEME 4

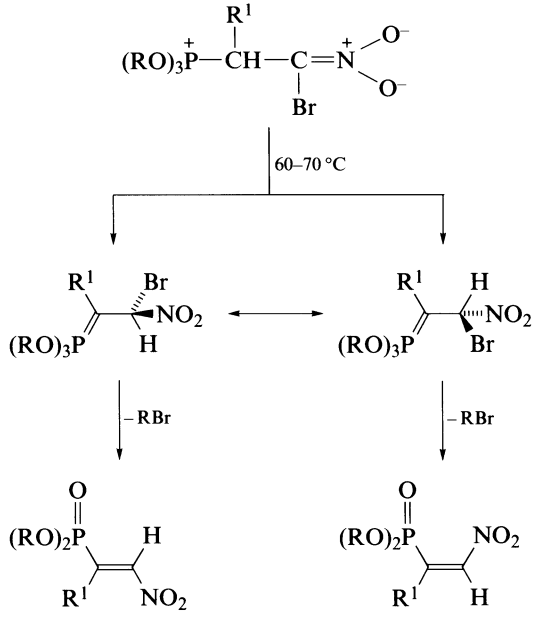
the dipolar intermediate **65** ($R^1 = OSiMe_3$) suffers translocation of the silyl group to give **69**, and hydrolysis of this then affords the target (nitroalkyl)phosphonic diesters, e.g. **70** ($R = Pr^i$)[62,64] The decomposition of the intermediates derived from diethyl trimethylsilyl phosphite and the alkenes $ArCH{=}CHNO_2$ with $TiCl_4$ (initially in reaction at –40 °C but later in the presence of Zn) affords diethyl (α-cyanobenzyl)phosphonates in high yields[66].

A detailed study of the interaction of dimethyl phenylphosphonite (**62**; R^1 = Ph) and (*E*)-**63** ($R^2 = Pr^i$) initially showed that, at –50 °C only traces of unsaturated phosphinate and dimethyl phenylphosphonate are formed, and that the phosphorane **66** (R^1 = Ph, $R^2 = Pr^i$) is the main product[67,68]. In outline, the system of observed reactions resembles that observed for trimethyl phosphite, with the formation of the dipolar species **65** in equilibrium with the phosphorane **66** and with the ylide **67**; the last acts as the immediate precursor to the methyl [(alk-2-enyl)phenyl]phosphinates **68** (R^1 = Ph). Although hydrolysis of the phosphorane could be expected to yield the methyl [(nitroalkyl)phenyl]phosphinates **70**, in practice these could not be isolated directly, but they could be isolated using the initial reaction between the nitroalkene and methyl trimethylsilyl phenylphosphonite, in a procedure analogous to that carried out with dimethyl trimethylsilyl phosphite, and described in the preceding paragraphs[68,69]. Moreover, the reaction between racemic methyl trimethylsilyl phenylphosphonite and the (*E*)-nitroalkene yields the diastereoisomeric phosphinates **71**; the ratios of diastereoisomers from **63** (R = Me and Pr^i) were 45:55 and 35:65[68].

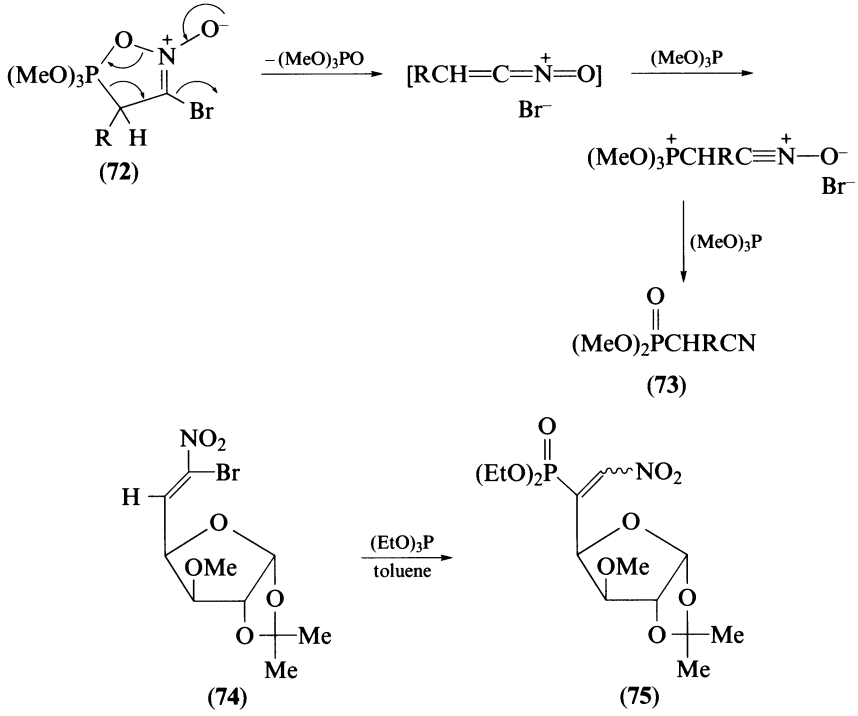


(71)

Several unusual features have been noted for the reactions between trialkyl phosphites and 1-bromo-1-nitroalkenes. Aside from the formation of phosphate ester and following hydrolysis at the intermediate stage, of dialkyl (2-bromo-2-nitro-1-substituted-ethyl)-phosphonate, more conspicuous are the absence of any phosphorane and the decomposition of the dipolar intermediate, not by elimination of alkyl nitrite ester, but of alkyl bromide, to yield dialkyl (2-nitroethenyl)phosphonates (Scheme 5) as a mixture of *E* and *Z* isomers in the ratio of *ca* 1:2[70]. Nevertheless, it is apparent that the liberation of alkyl bromide is not the result of a 'direct' Michaelis–Arbuzov reaction, but rather through a sequence of addition followed by dealkylation as part of an elimination step. The products also included (1-cyanoalkyl)phosphonates **73**, formed by the phosphite deoxygenation of nitrile oxide (and thus generating trimethyl phosphate) which, in turn was thought to be produced by the breakdown of the phosphorane **72**[71]. According to Devlin and Walker[72], the interaction of triethyl phosphite and 1-bromo-1-nitro-2-phenylethene in benzene at room temperature constitutes a worthwhile synthesis of diethyl (cyanophenylmethyl)-phosphonate. However, when the bromonitroalkene **74** is treated with triethyl phosphite in toluene at 0 °C, a 4:1 mixture of *E* and *Z* forms of the phosphonylated alkene **75** is obtained through addition–elimination, whereas in diethyl ether at –65 °C, the same reactants yield a product identical (apart from the ester group) with that obtained from the same **73** with triethyl phosphite and LiI at room temperature[73].



SCHEME 5



4. *Through C-Phosphorylation*

The successful *C*-phosphorylation of aliphatic nitro compounds with a free α-hydrogen has been reported. The treatment of nitroethane or 1-nitropropane with 2 equiv. of lda in thf, followed by the addition of diethyl phosphorochloridate, yields the diethyl (1-nitroalkyl)phosphonates $(EtO)_2P(O)CHRNO_2$ (R = Me or Et)[74]. The failure of such a reaction to occur with smaller amounts of BuLi had been noted some years earlier, but the later success seems not to have been followed through with any more detailed and extensive examination.

B. Syntheses Through Modification Procedures

1. *Through oxidation*

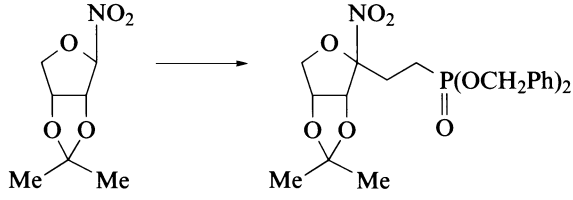
One of the many uses to which (nitroalkyl)phosphonic derivatives are put is their reduction to the corresponding (aminoalkyl)phosphonic compound. The reverse reaction, that of oxidation of the amino compound to the nitro analogue, has rarely been adopted, a suprising observation in view of the multitude of procedures available for the preparation of the amino compounds. The oxidation of amino to nitro on $C_{(1)}$ has employed $KMnO_4$ in acetone or acetic acid, but the yields are low; acidic conditions have to be avoided, since (nitroalkyl)phosphonates then break down according to the Nef reaction[75,76].

The combination of H_2O_2 and Na_2WO_4 oxidizes dialkyl (1-nitro-1-methylethyl)phosphonates to the corresponding nitroso derivatives which, in the monomeric state, exist as bright blue liquids[77].

Oximes derived from (1-oxoalkyl)phosphonic esters have been oxidized to the 1-nitro derivatives in moderate to good yields by means of 3-chloroperoxybenzoic acid in CH_2Cl_2[78]. The use of peroxytrifluoroacetic acid leads to unwanted side reactions.

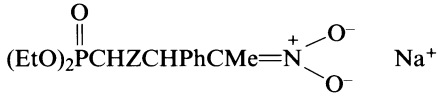
2. Through the Michael reaction

The addition of a nitroalkane to an alkenylphosphonic diester is exemplified by the interaction of nitromethane with diethyl ethenylphosphonate in the presence of NaOEt, when the product is diethyl (3-nitropropyl)phosphonate[79] and by a similar addition to 1,1-bis(diethoxyphosphinoyl)ethane[80]. In the initial stages of a synthesis of (4,5,6-trihydroxy-3-oxohexyl)phosphonic acid, the nitro sugar **76** was made to add to dibenzyl ethenylphosphonate, but the resultant (3-nitropropyl)phosphonic dibenzyl ester **77** was then used without isolation[81].



(76) **(77)**

In the presence of BuLi in thf, the active methylene compounds $(EtO)_2P(O)CH_2Z$ (Z = PO_3Et_2, COOMe, SO_2Me or CN) add to $PhCH{=}CMe(NO_2)$ to give the products **78** as intermediates in a synthesis of *C*-phosphorylated 2-isoxazoline derivatives[82,83]. Other reactions have been performed between 2-aryl-1-nitroethenes and the anions from dimethyl methylphosphonate[84] or dimethyl (difluoromethyl)phosphonate[85] in the initial steps towards syntheses of phaclofen **80**; X = H) and its difluoro analogue (**80**; X = F) by the reduction (H_2–Raney nickel) of the initial adduct **79** (Scheme 6).



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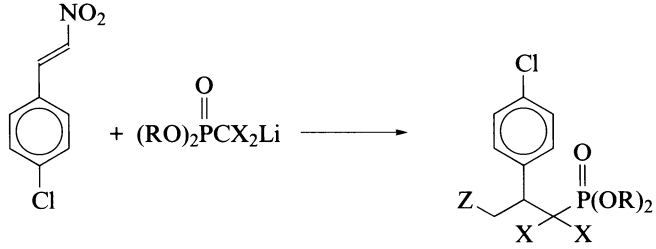
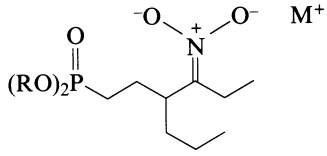


(79) Z = NO_2, X = H or F
(80) Z = NH_2, X = H or F

SCHEME 6

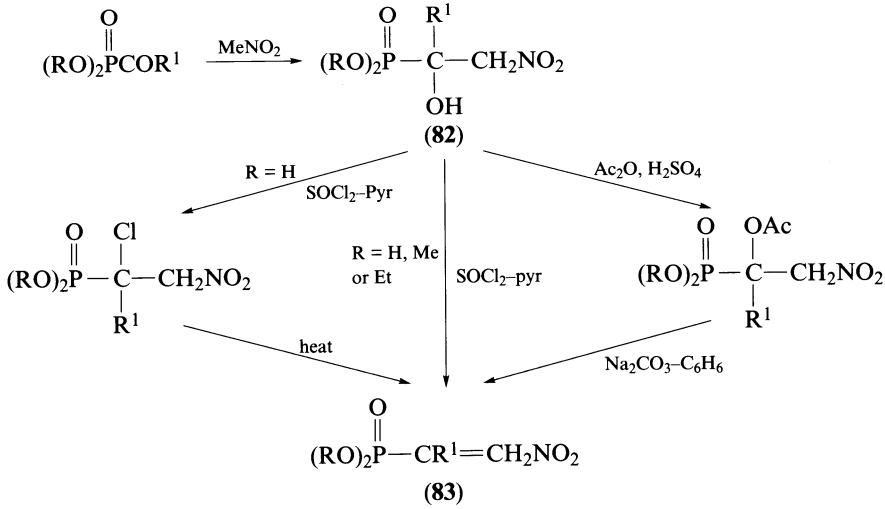
Very high yields have been achieved in the additions of β-Cu/Zn-containing phosphonates to nitroalkenes. The reagents are derived from dialkyl (2-bromoalkyl)phosphonates, $(R^1O)_2P(O)CH_2CHBrR$ (R = H, Me, or Pr), through a stepwise treatment, in thf, with Zn and CuCN. 2LiCl; their addition to 3-nitrohept-3-ene occurs at below 0 °C to give, initially, and in the usual way, the aci-nitro adduct **81**, from which the dialkyl (4-nitro-3-propylhexyl)phosphonate can be liberated under mild aqueous conditions. Other additions to β-nitrostyrene and 1-nitropentene were carried out and the formation of diastereoisomeric product mixtures observed[86]. [It is also worth noting that the aci-nitro intermediates may be cleaved by ozonolysis with replacement of the nitro group by oxo, and that the same Zn–Cu reagents may be employed in reactions with acyl chlorides or aldehydes in syntheses of (3-oxoalkyl)- and (3-hydroxyalkyl)-phosphonates[86].]



(81)

3. *Through aldol reactions*

In the presence of piperidine in benzene, benzaldehyde reacts with diethyl (nitromethyl)-phosphonate to afford at 67% yield of diethyl (2-hydroxy-1-nitro-2-phenylethyl)phosphonate, presumably as a mixture of diastereoisomers. However, a similar reaction with 4-nitrobenzaldehyde leads to phosphorus–carbon bond cleavage and the formation of 1-nitro-2-(4-nitrophenyl)ethane[87]. The converse procedure, i.e. a reaction which involves a nitroalkane and an (oxoalkyl)phosphonic diester, is also subject to certain restrictions. The base-catalysed nucleophilic additions of nitromethane to dialkyl acetylphosphonates (Scheme 7; R^1 = Me) to give dialkyl [(1-hydroxy-1-nitromethyl)alkyl]phosphonates have



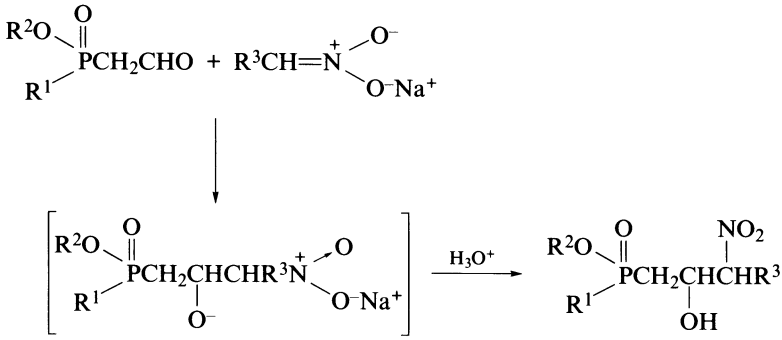
(82)

(83)

SCHEME 7

been reported[88] but, because of destabilization of the phosphorus–carbon bond towards nucleophiles when R^1 = Ph, the reaction then becomes generally inapplicable (cleavage of product occurs to give hydrogenphosphonate and nitroalkyl ketone) and the reaction must then be conducted under acid catalysis[89]; the single recorded instance in which, although R^1 = Ph, the reaction is successful, is apparently due to a steric effect by R (Pr^i)[90]. However, the interaction of a (1-oxoalkyl)phosphonic diester with nitromethane at room temperature in the presence of K_2CO_3–Bu_4NBr under anhydrous conditions does afford the products **82** (R^1 = Me, Et, Pr, Bu, Cy, CH_2Ph or cyclopropyl), often in very high yields[91]. Other examples of attempted aldol reactions in which phosphorus–carbon bond cleavage occurs include the interaction of dimethyl (1-nitropropyl)phosphonate with chloral in the presence of Et_3N[92] and that of dialkyl (trichloroacetyl) phosphonates with nitromethane anion[93].

Salts of 1-nitroalkanes react with β-phosphorylated acetaldehydes to yield dialkyl (2-hydroxy-3-nitroalkyl)phosphonates or analogous phosphinates (Scheme 8)[94].



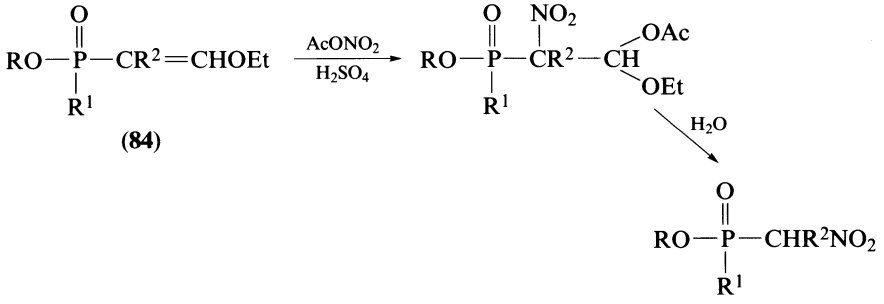
SCHEME 8

The phosphonates **82** undergo *O*-acetylation under conventional conditions, and the products may be deacetyloxylated under basic conditions to give dialkyl (2-nitroethenyl)-phosphonates (**83**); when R^1 = Me or Et, the tertiary alcohols **82** also suffer dehydration to the same **83** when treated wiht pyridine and $SOCl_2$, whereas the secondary alcohols **83** (R^1 = H) suffer dehydration but also furnish the dialkyl (1-chloro-2-nitroalkyl)-phosphonates[95].

4. Through nitration

The treatment of a 2-(dialkoxyphosphinoyl)acetaldehyde with a mixture of acetic anhydride and nitric acid (effectively acetyl nitrate) containing a trace of sulphuric acid leads to very low yields to the dialkyl (nitromethyl)phosphonate, and a better procedure consists in the nitration of an enol ether of the acetaldehyde **84** (R^1 = OR) with R^2 = H[75,96], Me[97] or Et[97];the phosphinate **84** (R = R^1 = Et, R^2 = H) has been similarly modified[98]. An alternative starting material for the preparation of a (nitromethyl)phosphonic diester consists of the diester of (2-oxopropyl)phosphonic acid[99], an observation also consistent with nitration through the addition of reagent to the enol form of the aldehyde (or ketone) or an enol ether (Scheme 9).

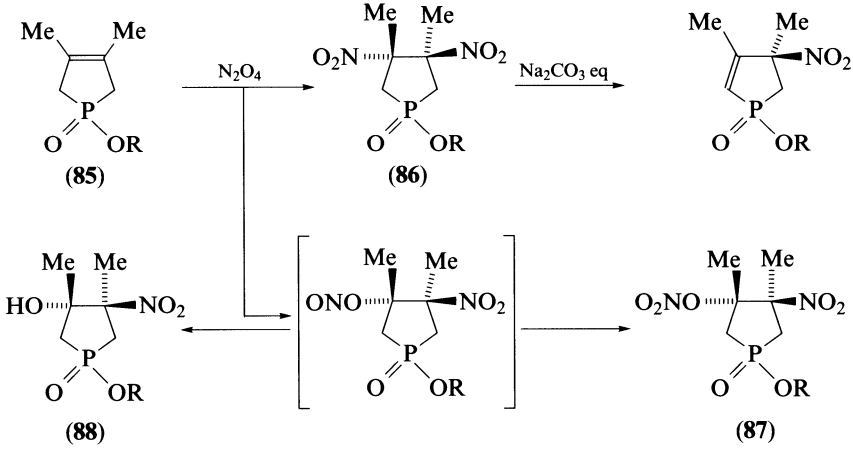
The reaction between dialkyl ethenyl- or (2-phenylethenyl)-phosphonates and N_2O_4 in CH_2Cl_2 was originally stated to generally yield the dialkyl (1-hydroxy-2-nitroethyl)-phosphonate[100], but later work showed that the structure of the product depends on the starting material; thus, esters of ethenylphosphonic acid afford the (1-hydroxy-2-



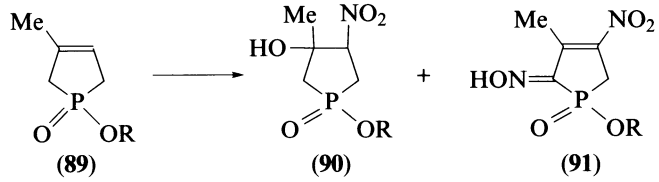
SCHEME 9

nitroethyl)phosphonic diester, whereas dimethyl (2-phenylethenyl)phosphonate yields dimethyl (2-hydroxy-1-nitro-2-phenylethyl)phosphonate[101]. The nitration of ethenylphosphonic diesters with N_2O_5 yields the nitrate esters of (1-hydroxy-2-nitroalkyl)phosphonic diesters, from which the nitrate grouping may be removed under the influence of aniline to give a dialkyl (2-nitro-1-phenylamino)phosphonate diester[102].

Several studies have been carried out on the nitration of phospholenes by N_2O_4 (Scheme 10). The 3,4-dimethyl-3-phospholenes **85** react with N_2O_4 to yield the *trans*-3,4-dinitro derivative **86** when R = H, Me, Et, $ClCH_2CH_2$, Pr or Pr^i, but when R = Me or $ClCH_2CH_2$ compounds **87** and **88** are formed[103,104]. The picture for 1-alkoxy-3-methyl-1-oxo-3-phospholenes (**89**) appears to be more complex in some respects, the products then being mainly the *tert*-alcohol **90** and the oxime **91**; an explanation has been offered regarding the formation of the oximes **91** rather than the isomeric oximes[105,106].



SCHEME 10

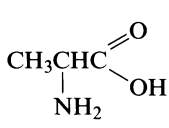


Further examples of the syntheses outlined above, and others which lead to individual compounds of lesser importance, including, for example, (4-nitroalkyl)phosphonic diesters, can be found in a recent review[107].

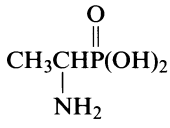
IV. AMINOALKYL-PHOSPHONIC AND -PHOSPHINIC ACIDS

The (aminoalkyl)phosphonic acids occupy a place supreme amongst all the functionalized acids considered in this, and the previous, chapters. The simplest example, (aminomethyl)-phosphonic acid, is said to have been first described in the early 1940s. Nevertheless, by the early 1970s, and at the time of publication of the survey of organophosphorus compounds by Kosolapoff and Maier, only relatively few such compounds had been prepared, even though their natural occurrence and biological importance had already been recognized[108,109]. However, during the last 25 years, there has been a considerable growth in interest in the chemistry of this group of compounds, with the emphasis on their synthesis and potential biological significance in metabolic processes in various life forms. Other areas of activity have been the development of a new area of peptide chemistry and the design of new substances for medicinal purposes.

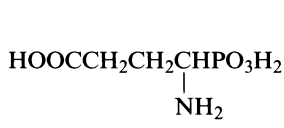
The amino and phosphono groups in an aminophosphonic acid may be sited in any positions relative to each other on the carbon skeleton, but those in which the amino group is sited on a carbon atom α to phosphorus have particular significance in being analogues of the naturally occurring amino carboxylic acids, and reference to the accepted abbreviations for the latter has equal merit in the formulation of the phosphorus-containing analogues. Thus, the phosphonic analogue of alanine **92** is (1-aminoethyl)phosphonic acid (**93**), or in the useful abbreviation, Ala^{P}. This nomenclature can be conveniently extended to more complex cases; thus, **94** is $Glu^{\alpha P}$, whilst **95** is $Glu^{\gamma P}$, with **96** being $Glu^{\alpha\gamma P}$. It is necessary to distinguish clearly between, for example, $Glu^{\alpha P}$, which would be indicative of phosphonoglutamic acid, and **97**, in which the glutamic acid skeleton is retained, but with an added phosphono group, and which could equally be referred to as a phosphonoglutamic acid. Such difficulties are resolvable through the use of a fully systematic name, the customary one of which (*Chemical Abstracts*) is based on the name of the carboxylic acid, rather than on that of the phosphonic acid.



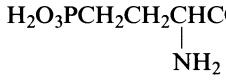
(**92**)



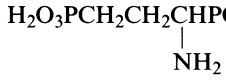
(**93**)



(**94**)



(**95**)



(**96**)

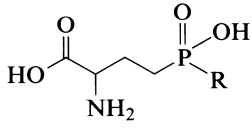
(**97**)

Like the corresponding aminocarboxylic acids, the aminophosphonic acids (and analogous phosphinic acids) are crystalline, high-melting (250–300 °C) solids (and very varied melting point from different syntheses) which possess zwitterionic structures. A comparison of the structural features of the carboxyl and phosphono groups, the former flat, the second much bulkier since it is centred around the tetrahedral phosphorus atom, makes it all the more remarkable that the replacement of —COOH by $—PO_3H_2$ provides a molecule still capable of exerting comparable influences under biological conditions. Although,

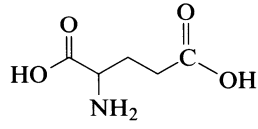
for example, Ala^P has often been regarded as the isostere of alanine, a better comparison is (1-aminoethyl)phosphinic acid (**99**), the more stable phosphoryl tautomer of (1-aminoethyl)phosphonous acid (**98**), and an example of a type of compound which will be considered towards the end of this chapter.

(**98**) (**99**)

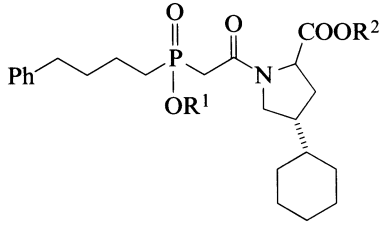
Aminophosphonic acids play an important role in living systems. The first acid to be found naturally, namely (2-aminoethyl)phosphonic acid (also known as ciliatine, 2AEPH, and β-Ala^P)[108,109], has been followed more recently by 2-amino-5-phosphonopent-2-enoic acid, isolated from *Streptomyces plumbens*, and (2-amino-1-hydroxyethyl)phosphonic acid, isolated from *Acanthamoeba castellani*[110–113] and formed through the biological hydroxylation of (2-aminoethyl)phosphonic acid. Many acids are inhibitors of enzymes important in carboxylic acid biochemistry. Ala^P is a potent inhibitor of a racemase from Gram-positive bacteria (the corresponding 'phosphinic' acid **99** is not). Phosphinothricin (**100**), a rare example of a naturally occurring aminophosphinic acid, is an analogue of glutamic acid (**102**) and produced by various *Streptomyces* species; it is a powerful inhibitor of glutamine synthetase (an enzyme which is of prime importance in nitrogen metabolism), as are many of its simple derivatives, and it is worth observing here that the phosphonic acid **101** is of low biological activity in this respect. Consideration given to the way in which the phosphonic acids interact with enzymes and other biological molecules has led to the development of the compound fosinopril (**103**), an effective oral antihypertensive agent which, although inactive itself, acts as a prodrug to **104**, which is a long-lasting and potent inhibitor of angiotensin-converting enzyme.



(**100**) R = Me
(**101**) R = OH

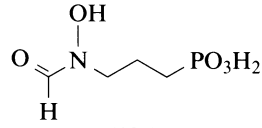


(**102**)



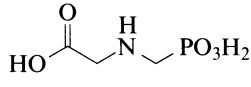
(**103**) $R^1 = CMe_2OCO(CH_2)_2CH_3$, R^2 = Na
(**104**) $R^1 = H = R^2$

The phosphorus-containing antibiotics represent an interesting and even more specialized group of naturally produced, true organophosphorus compounds; many of them are of a peptide nature, the general methods of preparation of which will be considered in more detail in a later section, but fosmidomycin (**105**) is obtainable from *Streptomyces* species and currently undergoing clinical trials in human medicine.



(**105**)

Another area in which aminophosphonic acids have proved to be of great practical value is that of plant growth regulation. The very effective, but non-selective, post-emergence herbicidal activity of glyphosate (**106**) was reported in the early 1970s, and it acts by blocking the shikimic acid pathway. Phosphinothricin (**100**) has also proved to be of value in the same area. Compound **107**, dibutyl (1-butylamino-1-cyclohexyl)phosphonate, is now in widespread use in agriculture.



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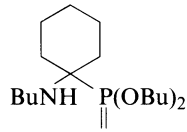
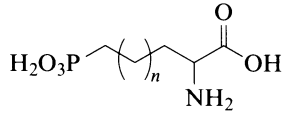
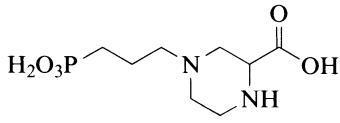


(**107**)

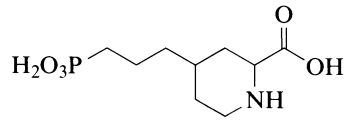
Aside from its other biochemical functions, L-glutamic acid is also a common transmitter in the central nervous system, and is of special importance amongst all the neuromodulators. Compound **101**, a phosphonic acid analogue of glutamic acid, is particularly important as an inhibitor of reactions in several kinds of nervous tissue. Glutamic acid acts through several distinct receptor subtypes, of which N-methyl-D-aspartate (NMDA) and kainate are amongst the best characterized. The first of these connections has led to the synthesis and biological evaluation of a large number of compounds; of these, the homologues **108** ($n = 3$ or 5) of **101**, and several piperazine (**109**) and piperidine derivatives (**110**), have proved particularly interesting.



(**108**)



(**109**)



(**110**)

This short introduction can present only a flavour of the importance, in many respects, of the biochemistry and pharmacology, and hence, by inference, the chemistry, of the aminophosphonic acids. A short, but excellent and thought-provoking account has been

presented by Kafarski and Lejcak[114], who quote many other examples of compounds of actual or potential biological interest. Other interesting reviews are also relevant[115–117].

The literature pertaining to the aminophosphonic acids and, to a lesser extent, to the analogous phosphinic acids, is large (in comparison with that of other areas of functionalized organophosphorus compounds), but the area is well served with reviews of various aspects of the subject[115–128]. Those reviews should be consulted for more examples of compounds and reactions than those given here, and also for descriptions from the less accessible Eastern European and Far Eastern literature.

With the possible exception of the (diazoalkyl)phosphonic acids, all other functionalized phosphonic acids have, at some stage, been employed as precursors in the synthesis of aminoalkyl phosphonic acids, with various degrees of success; many such methods (in the context of Chapter 6, *reactions* of the precursors) will be considered as 'syntheses by modification', and reference should be made to the appropriate sections in this or the previous chapter for the preparation of those precursors.

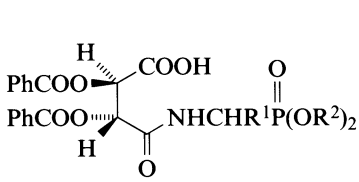
A. Some General Features in Synthesis

Many of the functionalized phosphonic acids and their derivatives described so far in this and the preceding chapter are capable of resolution into enantiomeric forms, through chirality at the carbon atom which carries the functional group. In the case of functionalized phosphonic acids, diastereoisomeric forms become possible as a result of any additional chirality at phosphorus. In practice, few resolutions have been carried out amongst the many types of functionalized acids considered so far, even for those classes of acids in which there is potential biological interest, e.g. the (hydroxyalkyl)phosphonic acids. Two examples of the latter are (1-hydroxy-3-methylbutyl)phosphonic acid, in the form of its monobenzyl ester[129], and (α-hydroxybenzyl)phosphonic acid[130], each of which has been resolved with stereoisomers of ephedrine. Nor have many syntheses been devised in the course of which one stereoisomer is obtained preferentially.

The situation with regard to the (aminoalkyl)phosphonic acids is, however, completely different. Not only have many (aminoalkyl)phosphonic acids, either in the free state or as derivatives, generally esters, been resolved, but also many synthetic procedures have been adapted for potential asymmetric preferment. The latter will be considered under each individual type of reaction, but it is convenient to consider the problem of resolution separately.

The monoaminomonophosphonic acids, either in the free state or, very often, as their diethyl esters, have been resolved by the usual techniques of repeated crystallization of appropriate salts; those of L-(+)-tartaric acid (2,3-dihydroxybutanedioic acid) or its mono- or di-benzoyl derivatives[131–136], or of D-(–)-mandelic acid, have been widely employed; the use of di-*O*-benzoylated L-tartaric anhydride, which is based on the separation of diastereoisomeric amides (**111**), has also been employed to a limited extent[137,138]. In selected cases, such as the monoaminomonophosphonocarboxylic acids or *N*-acylated (aminoalkyl)phosphonic acids, resolution following salt formation with organic bases has also been carried out; ephedrine[139], quinine and both enantiomers of 1-phenylethylamine[140] have all been used. In many cases, only one enantiomer of the (aminoalkyl)phosphonic acid (or diester) has been isolated in optically pure form. Sometimes, the acidity of the substrate, and hence choice of base for resolution, can be modified by using a mono- (as opposed to di-) ester or (or even in addition to) protection of the amino group as, for example, the phthalimido, benzyloxycarbonyl (cbz) or *tert*-butyloxycarbonyl (boc) derivative. Resolved di- and mono-esters can be hydrolysed to the free acids under acidic conditions, and *N*-protection can also be removed through the customary procedures.

Chromatographic resolutions of aminophosphonic acids are a relatively recent innovation. The resolution of phaclofen, [3-amino-2-(4-chlorophenyl)propyl]phosphonic acid



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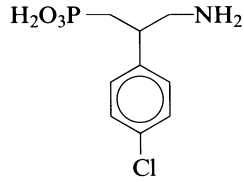
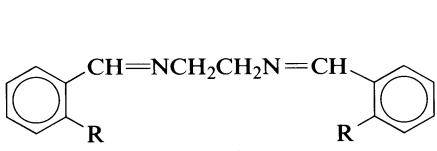
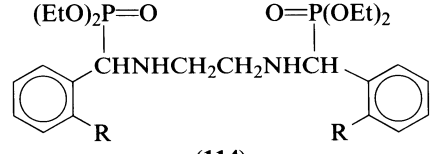


(112)

(112), on a chiral cyclodextrin stationary phase has been reported[141]. Enantiomers of diethyl [α-(phenylamino)benzyl]phosphonate were separated through the use of supported (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine or on a Chiralpak OP(+) colume[142]. The same technique failed to separate either of the compounds **114** (R = H or OMe) following their synthesis from the corresponding **113** by a standard synthesis (see Section IV. B.3), and it was consequently concluded that each of these substances is formed not as a racemic mixture, but rather as a *meso* form[141]. Other HPLC procedures used the commercially available Crownpak support for the separation of 2-amino-ω-phosphonoalkanoic acids[143] or a column prepared with *o*-phthaldialdehyde and a chiral thiol such as *N*-acetyl-L-cysteine[144]. The enantiomeric *N*-1-naphthoyl derivatives of several (1-aminoalkyl)phosphonic acids are separable by HPLC using a column of (*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine bonded to silica gel[145], and resolution of the *N*-(3,5-dinitrobenzoyl) derivative of an aminobenzylic phosphonic diester was carried out successfully by medium-pressure liquid chromatography on a column of silica pretreated with (*R*)-(+)-*N*-2-naphthylalanine undecyl ester[146].



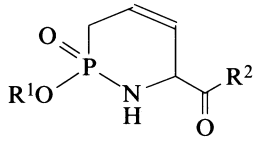
(113)



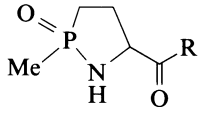
(114)

An alternative approach to the preparation of optically enriched compounds is to utilize enzymic catalysis in the chemical modification of stereochemically different, but chemically identical substrates. The reaction between racemic 2-benzoylamino-4-(diethoxyphosphinyl)butanoic acid with aniline in the presence of papain results in the preferential amidation of the *S*-enantiomer, separation of which from the unchanged *R* isomer thus becomes possible chemically; acid hydrolysis of the separated benzoyl derivatives yields the resolved enantiomers of 2-amino-4-phosphonobutanoic acid[140]. The treatment of racemic triethyl 2-amino-pent-3-enoate with a-chymotrypsin results in preferential hydrolysis of the carboxylic ester group of the *S* enantiomer; when the same enzyme acts on **115**, one diastereoisomer remains unattacked, but the second undergoes deamidation to **116**, which in turn, can be de-esterified through the action of a phosphodiesterase, and the ring then cleaved under acid conditions to afford the L-form of the same aminophosphonic acid[147]; the diastereoisomeric mixture of the esters **117** could also be selectively de-esterified to **116** by chymotrypsin but not by phosphodiesterase I[148]. Natchev[149] used the same methodology in reactions which involved preferential deamidation of the (*S*)-1,2-azaphosph(V)olidine **118** to the acid **119** in the separation of *R* and *S* forms of phosphinothricin. Later work has included the use of penicillinacylase in the resolution of [1-(phenylacetylamino)ethyl]phosphonic acid through the preferential deacylation of the *R* enantiomer[150,151], a similar procedure being used for the resolution of enantiomers of Ser^P

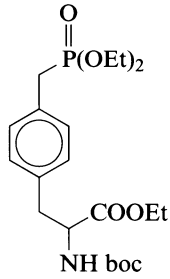
and isoSer^P with the aid of a *Pseudomonas* lipase[152]. Compound **120** has been resolved by the participation of subtilisin Carlsberg esterase[153].



(**115**) R^1 = Et, R^2 = NHCy
(**116**) R^1 = Et, R^2 = OH
(**117**) R^1 = Et, R^2 = OEt

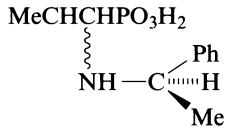


(**118**) R = NHCy
(**119**) R = OH

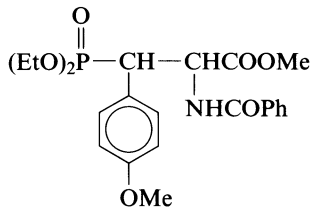


(**120**)

In order to estimate the optical purity of an enantiomerically enriched sample of an (aminoalkyl)phosphonic or related acid, and to assign absolute configurations, it becomes necessary to convert the (partially) resolved forms of the acid into diastereoisomers which can then be distinguished and characterized by an appropriate analytical technique; NMR spectroscopy and X-ray crystallography have complemented each other in this respect. The addition of diisopropyl hydrogenphosphonate to the aldimine from isobutyraldehyde and (*R*)-(+)-1-phenylethylamine yields, after hydrolysis of the product by acid, a 5:1 mixture of diastereoisomeric acids **121**, which showed two signals at 27.2 and 26.7 ppm in the ^{31}P NMR spectrum; an X-ray crystallographic study of the major component demonstrated the *S* configuration at $C_{(1)}$ in the acid carbon moiety[154]. The *RS*/*SR* and *RR*/*SS* diastereoisomers of **122** are distinguishable by X-ray techniques[155]. An X-ray examination of optically inactive **114** (R = H) revealed the presence of two chiral centres with opposite configurations, the molecule as a whole thus being of *meso* configuration[156]. The *S* configuration was assigned to (+)-(1-amino-1-methylpropyl)phosphonic acid as the result of an X-ray crystallographic examination of the salt from the (+)-diethyl ester of the acid and (+)-monobenzoyl tartrate[136].



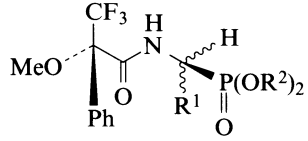
(**121**)



(**122**)

Currently, the most widely practised procedure for the quantitative estimation of diastereoisomeric purity (d.e.) and thus of enantiomeric purity (e.e.) consists in the derivatization of the aminoalkyl phosphonic acid as the *N*-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl) derivative; the latter is prepared from (*R*)-(+)-(3,3,3-trifluoro-2-methoxy-2-phenyl)propanoyl chloride (the so-called Mosher reagent)[157,158]. Although the diastereoisomeric derivatives **123** may also be separable by HPLC (e.g. on Zorbax-Sil) and which can be separately characterized [the derivative from (+)-Val^P was shown by X-ray

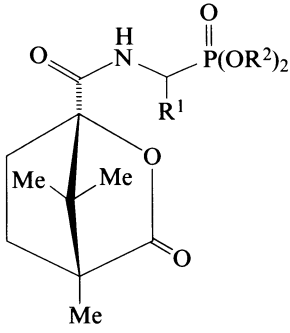
methods to have the *S* configuration at $C_{(1)}$], a quantitative analysis of a mixture of derivatives by ^{1}H, ^{13}C, ^{19}F or ^{31}P NMR spectroscopy is often feasible. Thus, the NMR spectra of the Mosher derivative from racemic diethyl phosphovalinate (**123**; $R^1 = Pr^i$, $R^2 = Et$) show N*H* signals at 7.18 and 6.85 ppm, C*H*$_3$ signals at 3.38 and 3.52ppm and also ^{31}P signals at 24.9 and 24.02 ppm[159]. After its synthesis with the aid of a carbohydrate chiral auxiliary, ^{1}H NMR spectroscopic analysis (C*H*$_3$ signals) of a sample of stereoselectively prepared diethyl (α-aminobenzyl)phosphonate was shown to consist of a mixture of *R* and *S* compounds in the ratio 85.2:14.8, corresponding to a 70% e.e., with C*H*$_3$O signals at 3.36 and 3.47 ppm[160]. In other cases, ^{19}F NMR spectroscopy has additionally been employed[161–163].



(123)

Derivatization through a reaction of the acid or ester with (–)-camphanoyl chloride, followed by spectroscopic characterization of the diastereoisomeric derivatives after their column chromatographic separation on silica gel, has met with variable success. The ^{31}P NMR signals of the diastereoisomers **123** (R = $PhCH_2$) showed little separation, being at 22.84 and 22.76 ppm (in $CHCl_3$)[164]. On the other hand, the *N*-camphanoyl derivatives **124** ($R^1 = Pr^i$, R^2 = H) showed ^{31}P signals at 30.28 and 20.12 ppm[159]. Furthermore, the same reagent has been employed to determine the enantiomeric content in samples of (2-aminoethyl)phosphonic acid monodeuteriated at $C_{(1)}$ through ^{1}H NMR spectroscopic analysis[165].

Peptide formation with an *N*-protected, optically pure aminocarboxylic acid is an alternative means of obtaining diastereoisomeric derivatives of chiral aminoalkylphosphonic acids, the diastereoisomeric products being distinguishable on a quantitative basis by ^{31}P NMR spectroscopy; for example, *N*-boc-L-alanine was used to distinguish the enantiomers of diethyl (α-aminobenzyl)phosphonate[166]. The reaction between an enantiomerically enriched sample of **125** (R = H) and L-leucine methyl ester hydrochloride in the presence of DCC was followed by HPLC separation of the L,L- and D,L-peptides **126** (R = H ratio 95.3:4.7)[167], and essentially the same procedure was applied to an analysis of **125** (R = OCH_2Ph), as prepared using the bislactim ether procedure (see Section IV. C.2.b) when the final product consisted of a mixture of *R*,*S* and *S*,*S* diastereoisomers in the ratio 87.4:12.6[168].



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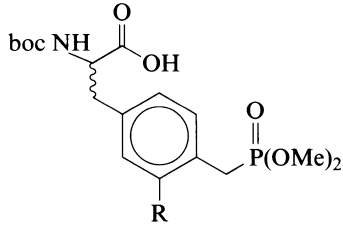

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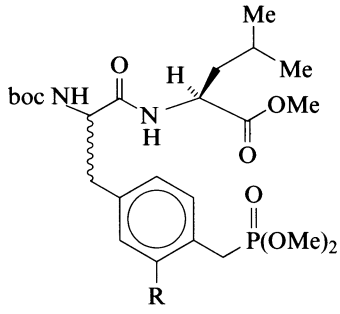

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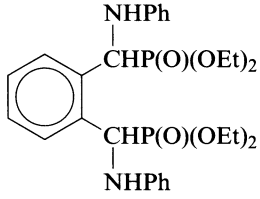
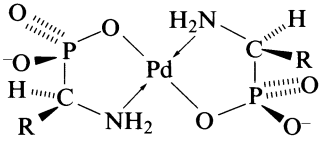


(127)

NMR spectroscopic examination of **127** (produced in the manner used for **114**) showed ^{1}H and ^{31}P signals consistent with the presence of only one of the two possible diastereoisomers (*meso* or *racemic*)[169]

Enantiomeric purity determination is also possible through an examination of the ^{31}P NMR spectra of palladium (II) complexes, $[PdL_2]$, of (1-aminoalkyl)phosphonic acids, after the reaction between the latter and K_2PdCl_4 in D_2O in a 2:1 molar ratio. The largest differences (0.13–0.18 ppm) between the phosphorus chemical shifts of the diastereoisomeric complexes **128** (*R,R*) and **129** (*R,S*) are seen when an aromatic ring is attached to the chiral α-carbon atom. Other acids give a value of ca 0.04 ppm, whilst (1-aminopentyl)- and (1-amino-3-methylbutyl)-phosphonic acids give only one ^{31}P NMR signal[170].



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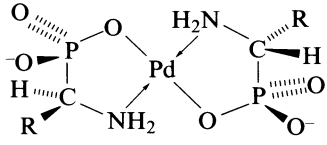


(129)

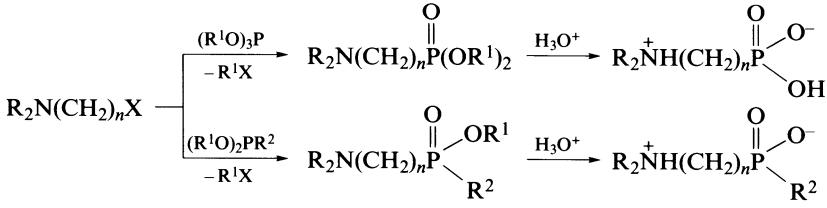
Mention might also be included here of the nature and potential importance of the choice of amino-protection and ester groupings in work on the aminophosphonic acids. The choice of groups for protection at nitrogen is obviously based on experience in conventional amino acid chemistry, and both *tert*-butyloxycarbonyl (boc) and benzyloxycarbonyl (cbz) groups are extensively employed. Most recorded syntheses of aminoalkylphosphonic and -phosphinic acids have relied on diethyl or dimethyl esters, largely as a consequence of the ready availability of the simple trialkyl phosphites and dialkyl hydrogenphosphonates; the same esters are also preparable under mild conditions from the free acids by the action of ortho esters $RC(OR')_3$ (R = H or Me, R′ = Me or Et)[139,147,163,171]. Until the advent of de-esterification through silylation, the complete de-esterification of such simple esters required fairly severe conditions (normally by the action of hot aqueous HBr), although the monodemethylation of dimethyl esters is possible with LiI or LiBr. As an alternative, diphenyl esters (more easily obtainable than the dialkyl esters in those synthetic procedures which involve hydrogenphosphonates) or dibenzyl esters have played a significant role, and both can be de-esterified by hydrogenolysis. Diphenylmethyl esters, obtained by the action of diazodiphenylmethane on the free acids, can be also de-esterified by hydrogenolysis, but also more conveniently by trifluoroacetic acid at 25 °C or even merely in boiling ethanol[130,172,173]. Monoesters derived from *N*-cbz-aminophosphonic acids and secondary alcohols are obtainable in a reaction system containing $SOCl_2$

in dmf at –20 °C[174]. Mono(2-cyanoethyl)esters are prepared from the free phosphonic acid by the action of 2-cyanoethanol in the presence of trichloroacetonitrile, and the further action with diazomethane yields mixed 2-cyanoethyl methyl esters; the latter lose the cyanoethyl group when in contact with ammonia in MeOH, or they can be demethylated with LiBr in pyridine[175]. Selective removal of the 2,2,2-trichloroethyl ester group (introduced with 2,2,2-trichloroethanol in trichloroacetonitrile) in the presence of a second (halogen-free) ester group in a phosphonic acid has been achieved with Zn–Cu in 80% acetic acid or with Zn–*p*-toluenesulphonic acid, but a further means consists in hydrogenolysis with catalysis[139,176].

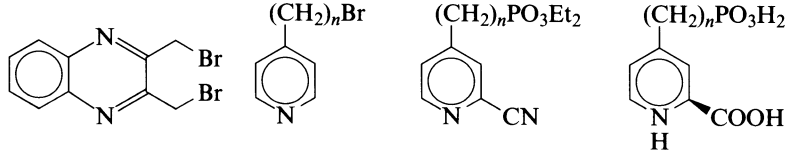
B. Syntheses Through Phosphorus–Carbon Bond Formation

1. *Through the Michaelis–Arbuzov reaction*

In principle, the interaction of a phosphorus(III) ester with an ω-haloalkylamine should lead to an (ω-aminoalkyl)phosphonic diester or a phosphinic acid analogue (Scheme 11). Such examples in the 'classical' Michaelis–Arbuzov mould have been widely reported, but success in their outcome depends on the relative nucleophilicities of nitrogen and phosphorus(III) centres towards the displacement of halogen. The interaction of triethyl phosphite and a halogen-substituted tertiary amine, such as 2-chloroethyldiethylamine, does not lead to a phosphonic diester, and in this particular case the product is a piperazinium diquaternary salt. However, successful Michaelis–Arbuzov reactions have been carried out between the bis(bromomethyl)phthalazines **130** (to both the mono- and di-phosphonic acid stages)[177,178] and the series of [ω-(2-cyano-4-pyridine)alkyl]phosphonic diesters **132** (n = 1–4) have been prepared from the 4-pyridinealkyl bromides **131** as precursors to the phosphonoalkylpiperidinecarboxylic acids **133**[179].



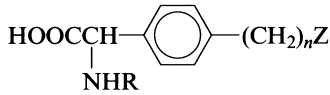
SCHEME 11



(130) **(131)** **(132)** **(133)**

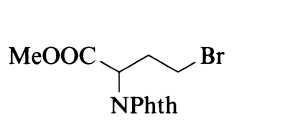
On the other hand, a marked reduction in the nucleophilicity of nitrogen, through acyl protection, allows compounds which possess a primary amino group to be ultimately obtained; *N*-acetylation or *N*-benzoylation fulfils this purpose[180], as in the conversion of the aralkyl halides **134** into the phosphonic esters **135**[181], but a superior methodology relies on a Gabriel-type synthesis (cf. Scheme 11), which uses an appropriate ω-bromoalkylphthalimide to give the (phthalimidoalkyl)phosphonic diester from which the phthalimido group may be selectively removed by hydrazinolysis. Alternatively, the phthalimido and

phosphonic ester groups may be removed in one step by hydrolysis with 48% aqueous HBr (a fast reaction removes ester groups, and slower one removes the phthalimido group). In this way, bromomethyl[182,183], 2-bromoethyl-[183–185] and higher ω-bromoalkyl-phthalimides[183] are precursors to (ω-aminoalkyl)phosphonic acids. The use of a phosphonous diester to give an (aminoalkyl)phosphinic acid is exemplified by the interaction of bromomethyl- and 1-chloroethyl-phthalimides with esters of methyl- or phenyl-phosphonous acids[186].



(134) R = PhCO, Z = Br
(135) R = H, Z = PO_3Et_2

More interesting applications of the procedure include the conversion of **136** into the (1-amino-4-phosphono)butanoic triester **137**[187] and the synthesis of the phosphinic diester **138** from diethyl methylphosphonite; **138** was additionally prepared through the use of the *N*-trifluoroacetyl group for protection purposes[187,188]. The second of these examples constitutes one of very many syntheses of racemic phosphinothricine ($Glu^{\psi PMe}$). The use of 2-phthalimidoalkanoyl chlorides, derived from aminocarboxylic acids of known chirality, allows the preparation of the esters **139** which can be modified as described in a later section[189]. A reaction between bromomethylphthalimide and the ester **140** provides an easy access to the useful intermediate **141**[190]. The course of the reactions between the 2-pyrrolidinones **142** and phosphorus triesters depends on the nature of the latter; thus, the esters EtOPRR′ (R = R′ = NEt_2 or NBu_2; R = EtO, R′ = Et or Ph) yield the expected [2-(2-oxopyrrolidino)ethyl]phosphonates from **142** (n = 2), but reactions between **142** (n = 2 or 3) and cyclic phosphites result only in preservation of phosphorus valence[191].



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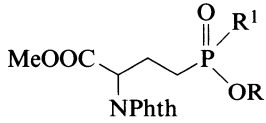
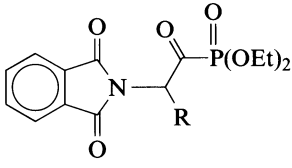


(137) R^1 = OR
(138) R^1 = Me



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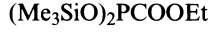

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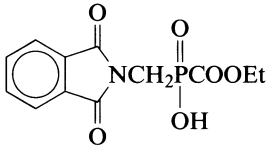

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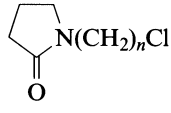
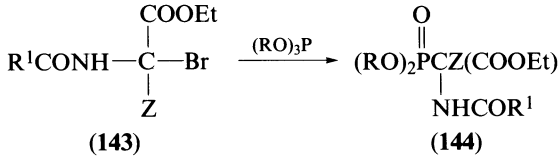
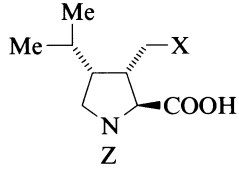


(142)

The useful conversion of the acylaminobromo-acetates and -malonates **143** (Z = H or COOEt; R′ = OBu^t or OCH_2CCl_3) into the corresponding **144** has been effective in the preliminary stages of an aminophosphonic acid synthesis[192]. The phosphonic acid analogue **145** of the powerful neuroexcitant kainic acid **146**, isolated from the marine alga *Digenea simplex*, has been obtained following an initial reaction between **147** and triethyl phosphite[193].

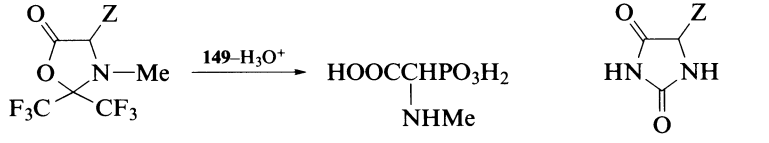


(143) **(144)**



(145) X = PO_3H_2, Z = H
(146) X = COOH, Z = H
(147) X = Br, Z = Cbz

(*N*-Methylamino)phosphonoacetic acid (phosphono sarcosine) **(150)** has likewise been prepared from **148** via the phosphonic diester **149**[194]; the imidazolidin-2,4-diones 151 provide the phosphonic diester **152**[195].



(148) Z = Br
(149) Z = P(O)(OR)$_2$

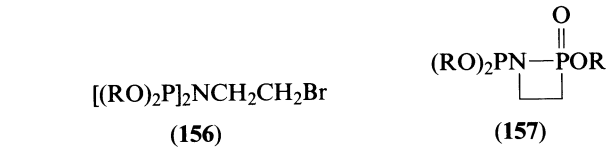
(150)

(151) Z = Br
(152) Z = P(O)(OEt)$_2$

The dialkoxyphosphinoyl group itself has proved useful for *N*-protection. A Michaelis–Arbuzov reaction between a dialkyl *N*-(ω-bromoalkyl)phosphoramidate, **153** (R^1 = Et or Pr^i, R^2 = H), and triethyl phosphite yields the corresponding esters **154**; mild acidolysis of the latter cleaves the P—N bond, and stronger hydrolysis then causes de-esterification to give the corresponding (ω-aminoalkyl)phosphonic acid **155**[196]. The usefulness of this modification lies in the potential for the synthesis of *N*-alkyl derivatives (through the anion from **154**)[197]. *N*-Phosphitylated-1,2-azaphosphetidines (**157**) are obtainable from **156** through an intramolecular Michaelis–Arbuzov reaction[198], and their hydrolysis under mild acidic conditions provides monoesters of (2-aminoethyl)phosphonic acid[199,200].

(153) Z = Br, R^2 = H
(154) Z = P(O)(OEt)$_2$, R^2 = H

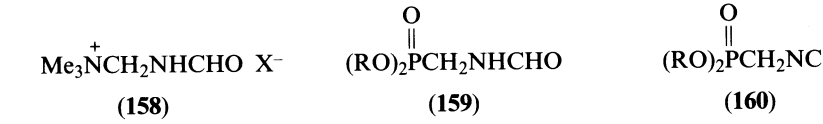
(155)



$[(RO)_2P]_2NCH_2CH_2Br$ (156)

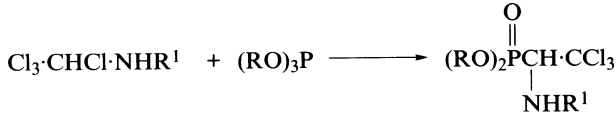
(157)

Esters of (*N*-formylaminomethyl)phosphonic acid (**159**), important as precursors to the corresponding esters of (isocyanomethyl)phosphonic acid (**160**) [themselves useful in further syntheses of (aminoalkyl)phosphonic acids (Section IV.D.1)], have been made through the variation of the Michaelis–Arbuzov reaction which employs quaternary ammonium salts, e.g. **158**[201,202]. The very few examples of this modification include its combination with the Gabriel reaction in a preparation of (phthalimidomethyl)phosphonic diesters[203].



(**158**) (**159**) (**160**)

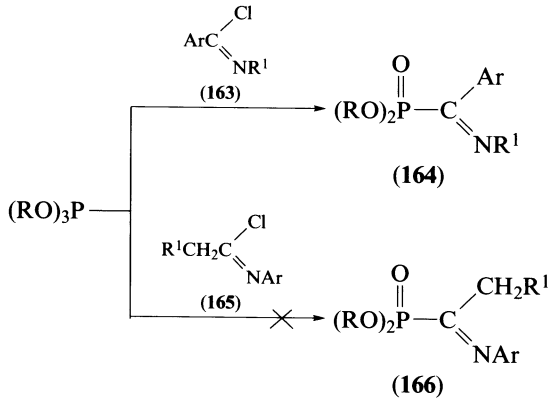
Amongst additionally functionalized aminoalkyl phosphonic acids, of which the hydroxy- and oxo-derivatized compounds are the more important, (haloaminoalkyl)-phosphonic acids have been very seldom reported. In the reactions between trialkyl phosphites and the aminotetrachloroethanes **161**, the integrity of the trichloromethyl group is, surprisingly, retained, with the (1-amino-2,2,2-trichloroethyl)phosphonates **162** as the products[204], e.g. with R^1 = CHO[205]. Such compounds may be reduced by Bu_3SnH, but the nature of the products depends on the presence, or otherwise, of AIBN; in the former case, the products are the esters of the (1-amino-2-chloroethyl)phosphonic acid, whilst otherwise (1-amino-2,2-dichloroethyl)phosphonic acids are formed[204].

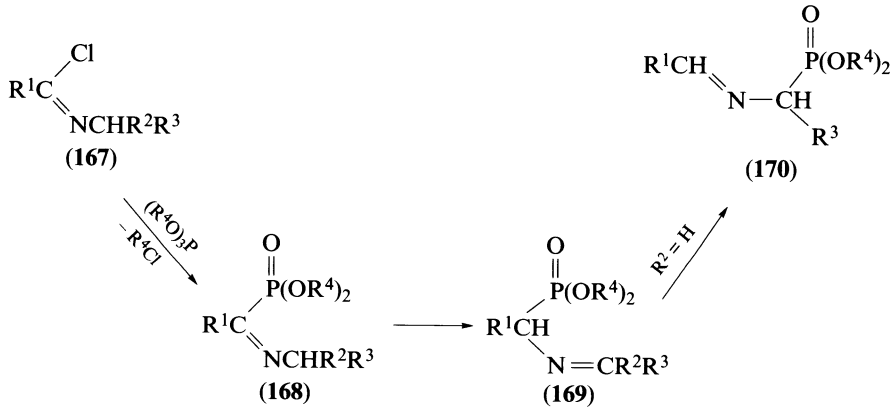


(**161**) (**162**)

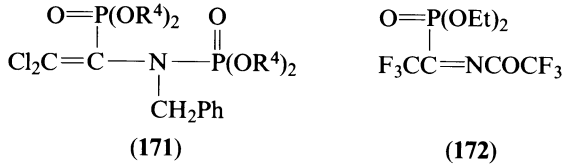
Several studies have been concerned with the Michaelis–Arbuzov reactions of halogen-containing imido compounds and which, in addition to their intrinsic interest, are of potential interest for the preparation of more unusual (aminoalkyl)phosphonic acids. Some of the reactions between trialkyl phosphites and imidoyl chlorides are entirely conventional; thus, the compounds **163** (R^1 = Me or Ph) give the corresponding esters **164**[206]; however, the similar transformation of **165** (R^1 = Ac, PhCO or COOEt) into **166** does not take place[207].

Although the reaction products **164** and **166** are important because of their potential for reduction to (1-aminoalkyl)- or (α-aminobenzyl)-phosphonic diesters, a further feature which may be advantageous or otherwise is the ability of many such compounds to undergo further rearrangement. Some indication of structural influences over prototropic changes for reactions of other imidoyl chlorides is indicated in Scheme 12. The reactions of a trialkyl phosphite (R^4 = Et or Pr^i)[208] or tris(trimethylsilyl)phosphite (R^4 = Me_3Si)[209] with **167a** yields the corresponding Michaelis–Arbuzov products **168**; the latter then undergo irreversible prototropic migration to give **169** only when heated at 160–170 °C and





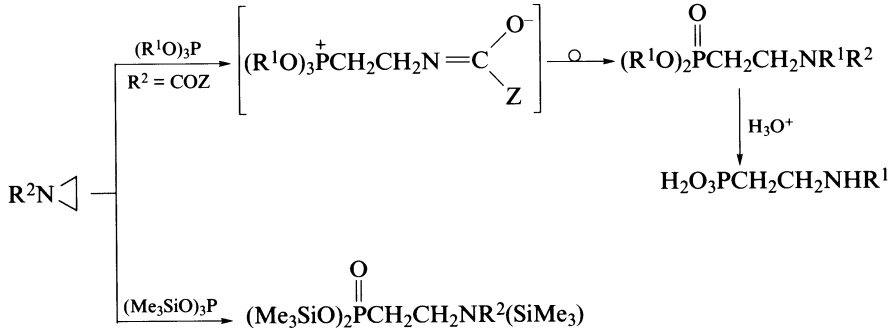
	R^1	R^2	R^3
(a)	Bu^t	H	Ph
(b)	Ph	H	Ph
(c)	$H_2C{=}CMe$	H	Ph
(d)	Cl_3C	H	Ph
(e)	F_3C	Me	Ph
(f)	Cl	Cl	CCl_3



SCHEME 12

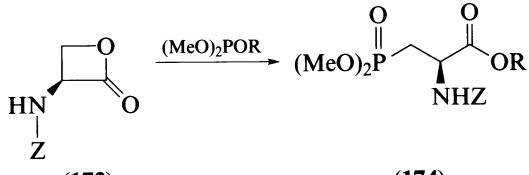
these undergo phosphoryl migration ('phosphorotropy') to give **170** when heated to an even higher temperature[209]. The replacement of alkyl by aryl, as in **167b**, results in failure to isolate the corresponding compound **168b**, and the isolable product is **169b**[210]. For **167c**, the initial reaction to give **168c** is followed by two proton migrations, the first of which gives **168c** followed by the second within the group R^1[211]. For **167d**, the product **169d** undergoes a further reaction with the phosphite ester to give **171**[210]. For $R^1 = CF_3$, the conversion of (–)-**168e** (R^2 = Me, R^3 = Ph) into (+)-**169e** when treated with Et_3N in a non-protic solvent is sterospecific and represents asymmetric induction at the chiral centre formed[212]. The reaction which involves **167f** is complex and involves multi-Michaelis–Arbuzov steps and elimination reactions[213]. Similar migrations have been observed following Michaelis–Arbuzov reactions with dialkyl fluorophosphites[214]. Reactions between *N*-trifluoroacetyltrifluoroacetamide and chlorodiethyl phosphite–Et_3N afford **172** and diphosphorylated species[215].

In addition to the classical form of the Michaelis–Arbuzov reaction, several non-classical variations have proved to be of great use with regard to general applicability and for the preparation of specific compounds. For instance, the ring opening of *N*-acylaziridines, by either trialkyl phosphites or phosphonous diesters[216], or by tris(trimethylsilyl)phosphite[217], leads to dialkyl [2-(*N*-alkylamino)ethyl]phosphonates, or their bis(trimethylsilyl) diesters in *N*-protected forms from which *N*-protection may be removed under aqueous acid conditions (Scheme 13).

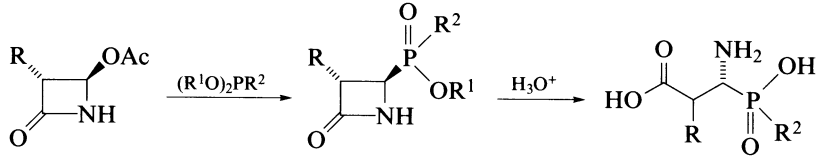


SCHEME 13

The ring opening of the *N*-protected 3-amino-2-oxetanones **173** (Z = cbz[218] or fmoc[219]) yields the esters **174** (R = Me or Me_3Si), hydrolysable under acidic conditions to give (2-amino-3-phosphono)propanoic acid in enantioselective steps with retention of configuration. The acidolytic ring opening of the 4-acetyloxyazetidin-2-ones **175** (R = H[220–222] or acylamino[223]) by phosphorus(III) esters leads to phosphonic[220–223] or phosphinic[221,223] acid analogues of aspartic acid (Scheme 14).



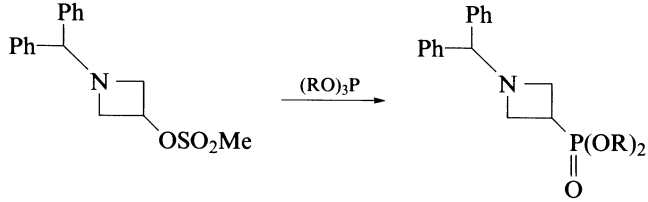
(173) **(174)**



(175)

SCHEME 14

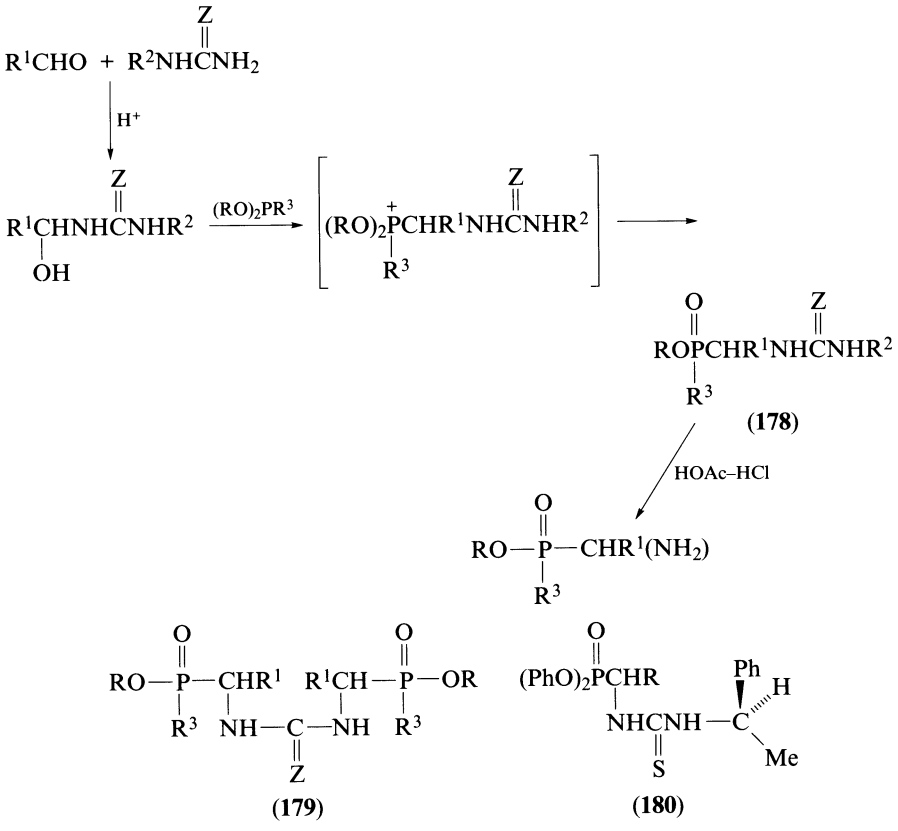
The displacement of a sulphonyloxy group, in this instance from an *N*-protected azetidine (**176**), is yet a further Michaelis–Arbuzov type reaction and yields the product **177** with retention of the ring; deprotection of the latter is achieved by hydrogenolysis[224].



(176) (177)

Reactions such as those outlined in the previous paragraphs are often very limited in their scope, although obviously useful in those specific cases mentioned. One non-classical variant of the Michaelis–Arbuzov reaction which, however, has proved to be extremely useful, is that which involves the three-component system phosphorus(III) ester, aldehyde and urea (or similar substance). When such a mixture in acetic acid (or alternatively in toluene with $BF_3{\cdot}Et_2O$) is heated, the initial product consists of the (α-ureidoalkyl)phosphonic diester **178**[225], the formation of which is thought to occur as shown in Scheme 15 (Z = O, R^2 = H; R^3 = OR). Many minor structural variations (although of some practical importance) include the use of thiourea (Scheme 15; Z = S)[183,225], *N*-phenylurea[226] or *N*-phenylthiourea (or other *N*-arylthiourea)[227–231], with triphenyl phosphite (the preferred phosphite ester)[183,225,227–231] in place of a trialkyl phosphite. The products from the second substitution stage. **179**, have also been isolated from urea or thiourea[225], but they appear not to possess properties of any significant advantage. The decomposition of the ureido compounds to furnish the (α-aminoalkyl)phosphonic acid, is brought about through the action of HCl in acetic acid.

By using (*R*)-(+)- and (*S*)-(−)-*N*-(1-phenylethyl)ureas, derived from the respective amine antipode, Huber and Gilmore[232] were able to isolate optically active samples of (α-aminophenylmethyl)phosphonic acid of low optical activity, and their results regarding the overall stereochemical course of the reaction via the ureides **180** were corroborated by the later work of Oshikawa and Yamashita[233], who actually obtained products with somewhat better optical purity, in some cases with optical yields of up to 35%. In essence, (*R*)-(+)-(1-aminoalkyl)phosphonic acids are derived from the (+)-urea, in turn obtained from the (*R*)-(+)-1-phenylethylamine, whilst the (*S*)-(−)-amine provides the (*S*)-(−)-(1-aminoalkyl)phosphonic acids. Contrary to expectations, the use of tris(2-methylphenyl)-phosphite resulted in no, or little, improvement in optical yields (with the exception of that of (1-aminoethyl)phosphonic acid), which ranged from 8 to 34%. The replacement of a urea with a carbamate ester, H_2NCOOR (R=Et or $PhCH_2$), again for reactions in acetic acid, has also received widespread attention, being used in conjunction with triethyl

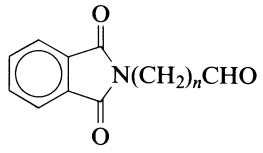


SCHEME 15

phosphite[234] or triphenyl phosphite[138,235–239]; as was previously the case, the protecting group is readily removed by HBr in acetic acid.

Of special interest here is the use of the α-phthalimidoalkanals **181** for the synthesis of the phosphonic acid analogues and their N^1-cbz dervatives **182** (R = cbz), of ornithine (n = 3), lysine (n = 4) and homolysine (n = 5)[238]; the N^2-phthalimido derivative of ornithine was prepared[239] *en route* to a phosphonopeptide thrombin inhibitor. Successful results have been reported when the acetic acid reaction medium is replaced with a cationic exchange resin admixed with the reactants in benzene[240]. Oshikawa and Yamashita[233] employed the carbamates prepared from (–)-menthol (**183**) and (+)-camphor **184**; the former led to (*S*)-(–)-(1-aminoalkyl)phosphonic acids with optical yields of 8–42%, whilst the products from the camphor derivative had the (*R*)-(+)-configuration. In a further variation, the nitrogen is provided by a phosphoric[241] or thiophosphoric[242] amide, and their combination with triphenyl phosphite (or a diphenylphosphonous ester) and an (aromatic) aldehyde occurs in the presence of $BF_3 \cdot Et_2O$; the intermediates, **185** (R = Ph or OPh, Z = O or S), suffer P—N bond cleavage with HBr in acetic acid and de-esterification with aqueous HBr. In yet a further reaction variant, one which is perhaps unexpected, *p*-toluenesulphonamide yields the *N*-*p*-toluensulphonyl derivative of the target (aminoalkyl)phosphonic acid[243].

Evidence is accumulating to support the theory that reactions between phosphorus(III) esters and various nitrogen-containing species, including *N*-hydroxymethyl-carbox-



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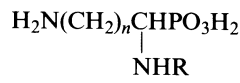

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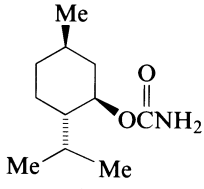

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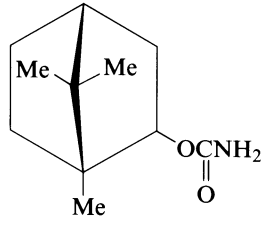
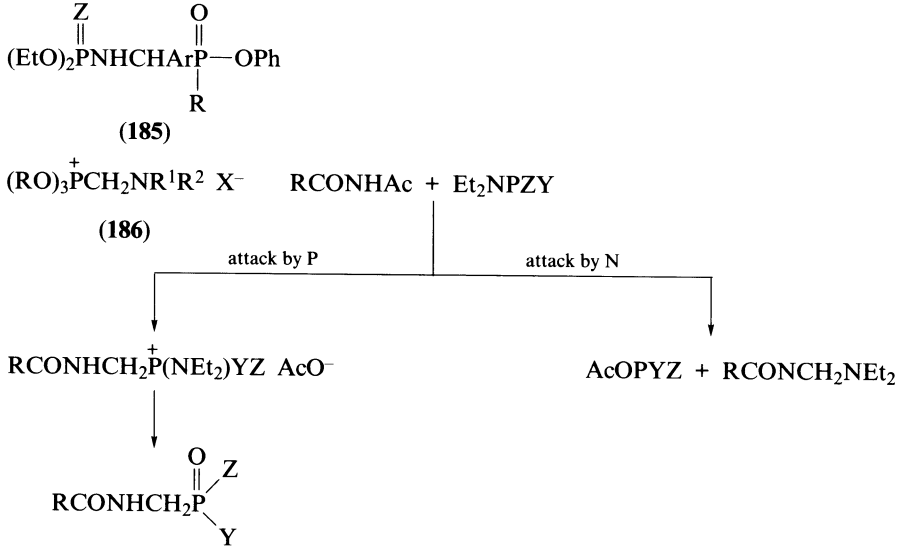


(184)

amides[244–249], *N*-methoxymethyl-amines[250,251] or -amides[252,253]; *N*-acetyloxymethyl-amines[254,255] or -amides[256] or *N*,*N*-dimethylformamide acetals[257–259], all react with phosphorus(III) esters in non-classical Michaelis–Arbuzov fashion. From these and similar reactions, quaternary salts of the type **186** have been isolated. The *N*-methylated dervative may be preformed or produced *in situ* in mixtures containing amide, formaldehyde and phosphite ester. The products of the reactions are *N*-acylated (acetyl, benzoyl, phthaloyl, pyridinecarbonyl or benzyloxycarbonyl) when derived from amides, or *N*,*N*-dialkyl derivatives from hydroxy (or methoxy)methylamines; the use of $Me_2NCH(OMe)_2$ leads to dimethylaminomethyl-enebisphosphonic esters. Ivanov and coworkers[260,261] have made a detailed study of the reactions which occur between phosphorus(III) amides Et_2NPYZ and the substrates, RCONHOAc (Scheme 16). The reagent can attack the substrate by virtue of the nucle-



SCHEME 16

ophilicity of the nitrogen and phosphorus atoms. When R = Me and at least one other group is EtO, the principle products are indicative of attack by nitrogen and phosphorus to roughly the same extent; when Y = Z = NEt_2, the product is largely the quaternary salt. The latter is also the only product for R = Ph, and Y = Z = NEt_2, but when at least one of the other groups is EtO, a mixture of products is obtained.

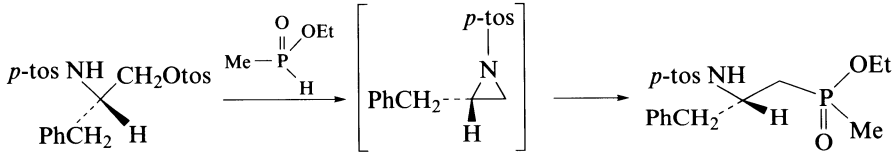
2. *Through the Michaelis–Becker reaction*

The reactions between *N*-(ω-haloalkyl)phthalimides and sodium dialkyl phosphite were reported as early as 1949 by Chavane[2] in the successful sytheses of several (ω-aminoalkyl)phosphonic diesters. The advantage over the Michaelis–Arbuzov reaction in the preparation of (2-aminoethyl)phosphonic diesters with *N*-alkyl or *N*-silyl substituents is worth recalling, and several reports of its successful use may be noted[262-264], including the preparation of nitrogen-functionalized polyphosphonic esters (Scheme 17). Other substrates for the reaction have included 1,3-bis(bromomethyl)benzene and 4-(ω-bromoalkyl)arenes[179,181].

$$N[(CH_2)_nCl]_3 \xrightarrow{3(RO)_2POM} N[(CH_2)_nP(=O)(OR)_2]_3 \xrightarrow{H_3O^+} N[(CH_2)_nPO_3H_2]_3$$

SCHEME 17

The ring opening of aziridines by metal dialkyl phosphites appears to follow a course similar to that followed when trialkyl phosphites are used (Scheme 13)[265]. The reaction between ethyl methylphosphinate (effectively as its sodium salt) and *N*-*p*-tosyl-2-benzylaziridine takes place according to Scheme 18[266].



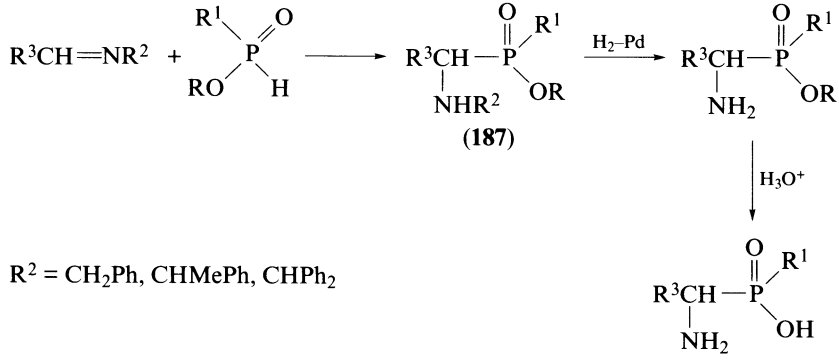
SCHEME 18

The conditions required for the Michaelis–Becker reaction are generally mild, from the point of view of temperature, in contrast to the higher temperatures normally required in the Michaelis–Arbuzov procedure, and this important feature allows its use in the formation of peptides containing terminal (aminoalkyl)phosphonic ester groups. Even so, the alkalinity of the media in which the former reactions take place may result in secondary reactions; when *N*-protection in a substrate is afforded by a phosphoryl substituent, as in a dialkyl *N*-(2-bromoethyl)phosphoramidate, loss of HBr may occur with the formation of dialkyl *N*-ethenylphosphoramidate and 1-(dialkoxyphosphinyl)aziridine[197].

3. *Through additions of hydrogenphosphonates or related compounds to C=N compounds*

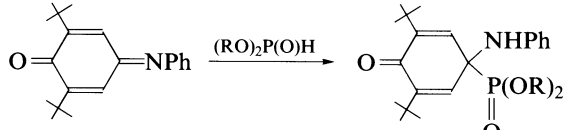
a. To Schiff bases. One of the most widely used reactions for the synthesis of aminoalkyl phosphonic and phosphinic acids consists in the addition of a hydrogenphosphonate or hydrogenphosphinate ester across the C=N bond in imines according to Scheme 19 to give the *N*-substituted α-aminoalkylphosphonic acid **187** (R^1 = OR). In

practice, the additions often occur when the reactants are heated together, but the process is often facilitated by the presence of triethylamine as a base catalyst. The imines which have been examined in connection with this process include very few which lack a substituent on nitrogen[267].



SCHEME 19

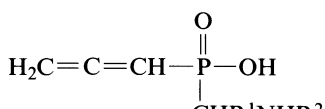
A novel procedure for the preparation of acids which ultimately contain a free amino group consists in the reduction of a nitrile with diisosbutylalane followed by the sequential addition of the hydrogenphosphonate, and hydrolysis[268]. Normally the imines have been derived from aliphatic aldehydes[154,269–273], or ketones[274–276], simple benzenoid aldehydes[131,133,142,146,156,169,277–287] or ketones[288] including fluorenone[285,289,290] or aldehydes based on heterocyclic systems[291–294]. The more unusual of substituents on nitrogen have included SO_2F[273], COOR[275,276] and COPh[276]. The addition of hydrogenphosphonate diesters to the quinoneimines **188** occurs across the C=N bond, like the manner of addition to quinonemethides but unlike that to 1,4-quinones[295].



(188)

Addition reactions have also been carried out with alkyl phenylphosphinates, to give **187** (R^1 = Ph)[296]; with propadienylphosphinic acid[297,298], when the products have the composition **189**. Additions of phosphorous acid (phosphonic acid) lead to the free aminoalkyl phosphonic acid[299].

The addition of dialkyl hydrogenphosphonate or alkyl phosphinate to compounds which possess two C=N bonds is of some mechanistic interest. Such additions to **190** yield **191** (R = OEt[131] and Ph[133]), but no comments seem to have been made about the relative



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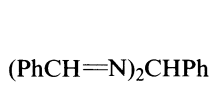

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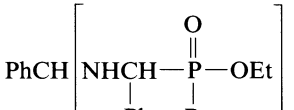
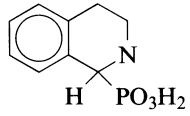


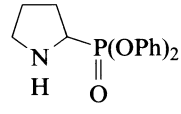
(191)

configurations at the chiral carbon centres. On the other hand, the generation of centres of opposite chirality in **114**[142,156] and **127**[169] following the addition of diethyl hydrogenphosphonate to diimines such as **113** has already been noted. It is not known whether this phenomenon is observed in the like additions to the diimine from 1,4-diaminobenzene and benzaldehyde[296] or in other such cases[279].

The addition of phosphorous acid to 3,4-dihydroisoquinoline gives 1,2,3,4-tetrahydroisoquinoline-1-phosphonic acid (**192**)[299], and that of diphenyl hydrogenphosphonate to 2*H*-pyrroline yields the diphenyl ester of Pro^P (**193**)[300].



(**192**)



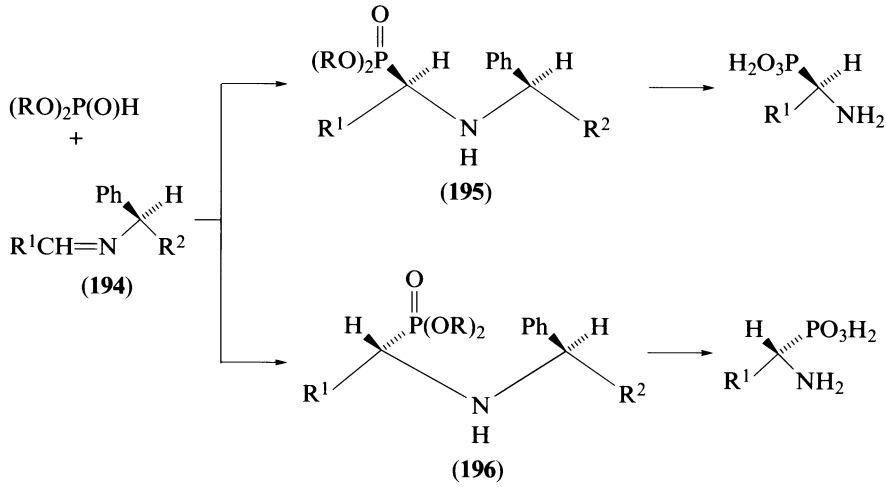
(**193**)

The ready formation of *N*-substituted amino-phosphonic and -phosphinic acids through this route, and the facility with which *N*-substituents, particularly those of the aralkyl group, may be removed, makes the methodology particularly attractive. As already noted, the *N*-(phenylmethyl) (benzyl) substituent is conveniently removed by hydrogenolysis over Pd–C[301,302], as is the *N*-diphenylmethyl (benzhydryl) group which, additionally, is also readily removed during acidolysis (with dilute HBr or HCl) to generate the free phosphonic (or phosphinic) acid[303,304]. Other tertiary aralkyl groups are likewise removable by acidolysis[305], but the use of the triphenylmethyl (trityl) group is not feasible since the Schiff bases are then unreactive to hydrogenphosphonate esters. The 1-phenyl-1-cyclopentyl group appears to have great potential since, after the initial condensation, its removal, as 1-phenylcyclopentene, is achievable on acidolysis with acetic or formic acid; by heating with ethanol or on hydrogenolysis[306,307].

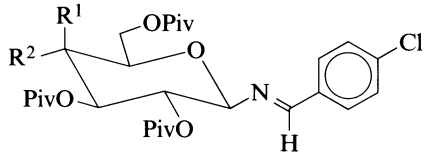
The addition of a phosphorus species containing the P(O)H moiety to an imine is, in principle, readily adaptable to the preparation of an optically active (1-aminoalkyl)phosphonic acid with asymmetric induction. Gilmore and McBride[308] were the first to prepare an optically active (aminoalkyl)phosphonic acid. The route adopted consisted in the initial reaction between diethyl hydrogenphosphonate and the imine **194** from benzaldehyde and either (*S*)-(–)-1-phenylethylamine or its (*R*)-(+) antipode (illustrated) at 140 °C: of the two products esters **195** and **196** (R = Et; R^1 = Ph, R^2 = Me), the major stereoisomer was isolated, hydrolysed and deprotected by hydrogenolysis, when laevorotatory (α-aminobenzyl)phosphonic acid was obtained (Scheme 20). Other workers[309] showed subsequently that the addition step led to the preferred formation of one form of the acid over the other in the ratio of about 2:1, but that better results could be achieved if the addition step was allowed to proceed at room temperature when the ratio could then reach ca 6:1. Poor induction was observed when R^1 = Me or Et, but the results for R^1 = Pr^i (compare ref. 154) were similar to those obtained when R^1 = Ph. A further study[310] showed that the diastereoisomer selectivity in adduct formation from (*R*)-**196** (R^1 = 4-substituted phenyl, R^2 = CH_2OMe or COOMe) was better if thf as solvent was replaced by CH_2Cl_2; the assignments of configurations to products by theoretical means seemed to contradict the results of the earlier work by Gilmore and McBride.

Better results have been obtained in the Lewis acid-catalysed addition of diethyl hydrogenphosphonate to an *O*-pivaloylated *N*-arylidenehexapyranosylamine, acting as a chiral template[160]. The addition of a hydrogenphosphonate to the imine **197** (from *O*-pivaloylated-β-D-galactosylamine; Piv = Me_3CCO) in thf is catalysed by $SnCl_4$ and produces the β-(*S*)-**199a** adduct in excess over β-(*R*)-**199b**.

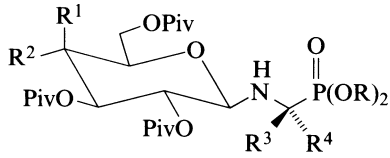
The apparently clear-cut nature of the reaction is complicated by anomerization within the system either during the course of the reaction, or of the initial products by the catalyst.



SCHEME 20



(197) R^1 = OPiv, R^2 = H
(198) R^1 = H, R^2 = Piv

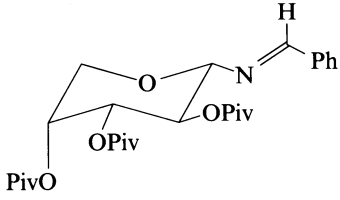


(199)

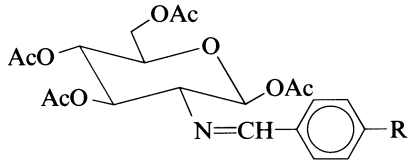
(a) *β-S* R^3 = 4-ClC_6H_4, R^4 = H
(b) *β-R* R^3 = H, R^4 = 4-ClC_6H_4

For the addition of diethyl hydrogenphosphonate, the composition (estimated from the ^{13}C NMR signals for the anomeric carbons) of the reaction product was *β-S*: *β-R*: *α-S*: *α-R* = 83:5.5:10.3:1.2, but this ratio can be altered by a careful choice in the adopted experimental procedure. The major isomer may be isolated by crystallization or HPLC and the cleavage of those adducts by 1 M HCL in MeOH yields the (*S*)-aminophosphonic acid. The Schiff base from D-arabinopyranosylamine, **200**, reacts to form selectively the *R* adduct (the ratio of *R* to *S* products is 5:1). By a careful choice of the carbohydrate nucleus, the major diastereoisomer adduct is formed with a purity sufficient to allow crystallization in pure form, as with the glucosylamine derivative **198** which afforded the adducts in the

(above) ratio of 81:9:6:4, which could be enriched to 96.9:1.2:1.2:0.7 by recrystallization. In the addition of hydrogenphosphonates to the glucopyranosyl imines **201**, an increase in the size of the ester alkyl group results in an increase in the relative proportions of the *R* isomer of the adduct[311].

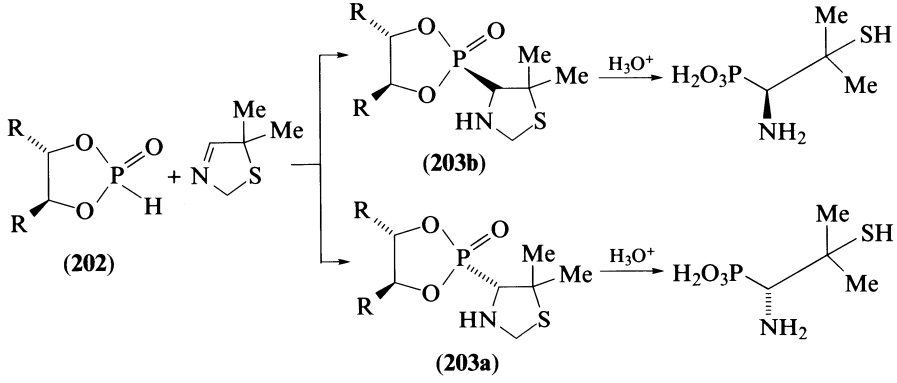


(200)



(201)

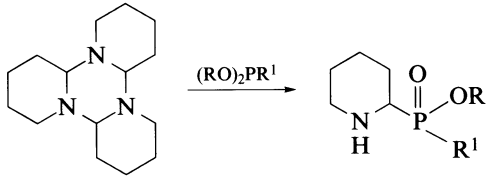
A modified methodology has been adopted in the synthesis of enantiomers of the phosphonic analogue of penicillamine (Scheme 21). Here, an achiral azomethine undergoes a reaction with a chiral hydrogenphosphonate [**202**; R = $CMe_2(OMe)$] to give an easily separable 2:1 mixture of the (*R*)**203a** and (*S*)**203b** diastereoisomeric adducts. Unsatisfactory results were obtained when R = Me or COOEt[312,313].



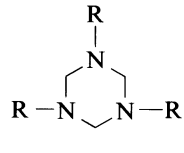
(202) **(203b)** **(203a)**

SCHEME 21

From the practical standpoint, an important variant in this important route to aminoalkylphosphonic acids is the use of the imine trimers—the structurally symmetrical perhydro-1,3,5-triazines. Thus, 2-piperidinephosphonic acid (**205**; R = H, R^1 = OH) (homoPro^P) was obtained, via its diethyl ester, from **204** and diethyl hydrogenphosphonate[314], and other phosphonic acids[315] and analogous phosphinic acids[316] have been similarly prepared. In general, the triamine **206** acts as a source of the phosphonic acids **207** (R = Me[317] or COOEt[318,319]) or the phosphonic acid **208** (R = COOEt)[319].



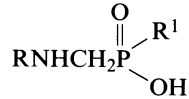
(204) **(205)**



(206)

$RNHCH_2PO_3H_2$

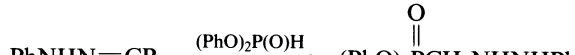
(207)



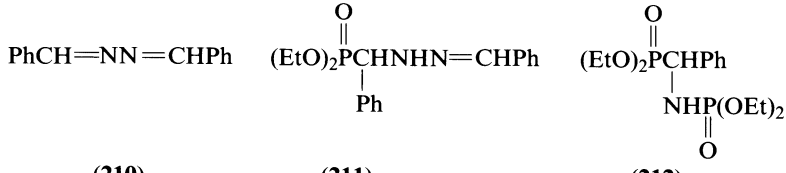
(208)

In addition to aldimines, reactions between dialkyl hydrogenphosphonates and ketoximes are reported to give low yields of (aminoalkyl)phosphonic acids when treated with hypophosphorous acid[320].

Carbonyl hydrazones also participate in reactions with hydrogenphosphonate esters, as is illustrated by the formation of the hydrazine derivative **209**[321]. The outcome of the reaction between diethyl hydrogenphosphonate and an aromatic aldazine, typically **210**, depends on the ratio of reactants. With the reactants in the ratio 1:1, the initial step is the formation of **211**[322,323]; the use of a mixture of the hydrogenphosphonate and sodium diethyl phosphite yields diethyl (α-aminobenzyl)phosphonate and its *N*-phosphorylated derivative **212**[323]. The hydrazine **213** is said to be obtainable from the aldazine and sodium diethyl phosphite at 80–90 °C as well as from **210** and diethyl trimethylsilyl phosphite[323] and, at the same time, to be cleaved by diethyl hydrogenphosphonate to give diethyl (α-aminobenzyl)phosphonate[324]. Aldazines have also been used to prepare aminoalkylphosphinic acids[325–327].



(209)



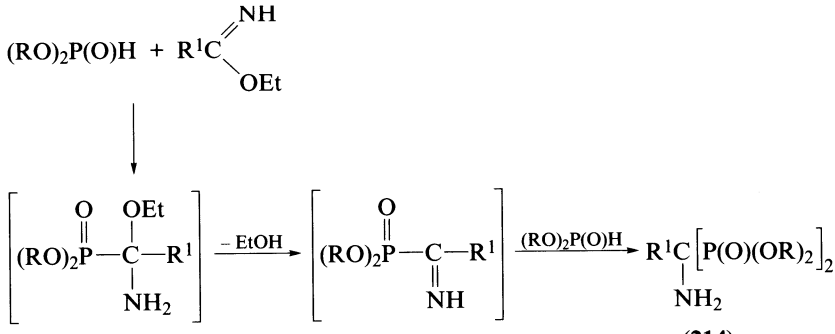
(210) (211) (212)

(213)

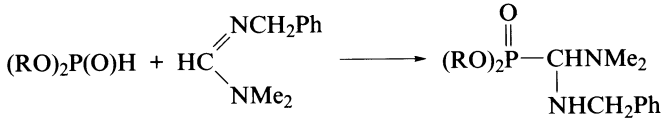
b. To imido ethers, amidines and related compounds. Few examples of such additions have been reported. The initial addition of a dialkyl hydrogenphosphonate to an imido ether is followed by alcohol elimination and a second addition of hydrogenphosphonate, the resultant product being the 1-aminoalkyl-1, 1-bisphosphonic ester **214**[206]. The addition of a hydrogenphosphonate to a fully *N*-substituted formamidine proceeds in the expected fashion as exemplified in the formation of **215**.

4. Through the Kabachnik–Medved'–Fields reaction

It was discovered independently by Kabachnik and coworkers and by Fields, in 1952, that a mixture of dialkyl hydrogenphosphonate, aldehyde or ketone, and ammonia or a

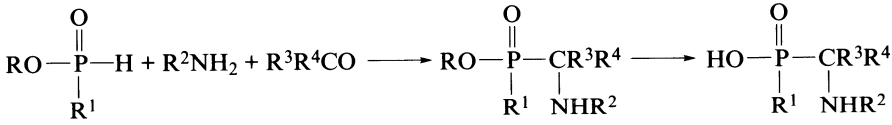


(214)



(215)

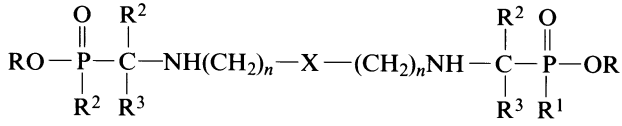
primary amine gave, when heated, the diester of (1-aminoalkyl)phosphonic acid (Scheme 22) ($R^1 = RO$)[328–331]. Although the yields in this procedure tend to be only moderate, there are considerable advantages in the procedure, not least of these being the relative cheapness and availability of starting materials and the extensive scope of the reaction[329–337]. As originally devised, the procedure involved the action of heat on a mixture of reactants



SCHEME 22

(ammonia—the most commonly used source of nitrogen–being present in ethanolic solution) in a sealed tube at 100 °C, but in the case of simple reactants, satisfactory results may be obtained through reaction at room temperature. Analogous phosphinic acids are available through the use of phosphinate esters (Scheme 22; R^1 = alkyl or aryl), although the yields then tend to be unsatisfactory[328,330]. The carbonyl reactant may be an aliphatic aldehyde or ketone (the latter linear or cyclic, aromatic aldehyde or aromatic ketone, although reactions which involve the last of these (and also cyclic ketones) do tend to be sluggish, and result in yields of only 10–20%, whereas, for instance, those with PhCHO are around 40% Fields[331] expanded the scope of the reaction to include several primary and secondary amines, the scope being expanded even further in this respect by other workers[338,339]; the yields in reactions carried out at below 100 °C were in the range 80–95%. The use of α,ω-diaminoalkanes or analogous diamines provides a range of compounds of types **216**[335,340–342] and **217** (*n* generally 2)[343], which are useful as complexones for heavier metal ions. Diphenyl hydrogenphosphonate is more reactive than dialkyl hydrogenphosphonates, presumably because of its greater acidity[344].

The course of the reaction is ambiguous. The presence together, in the reaction mixtures, of hydrogenphosphonate (or phosphinic) esters and carbonyl reactant naturally lends to



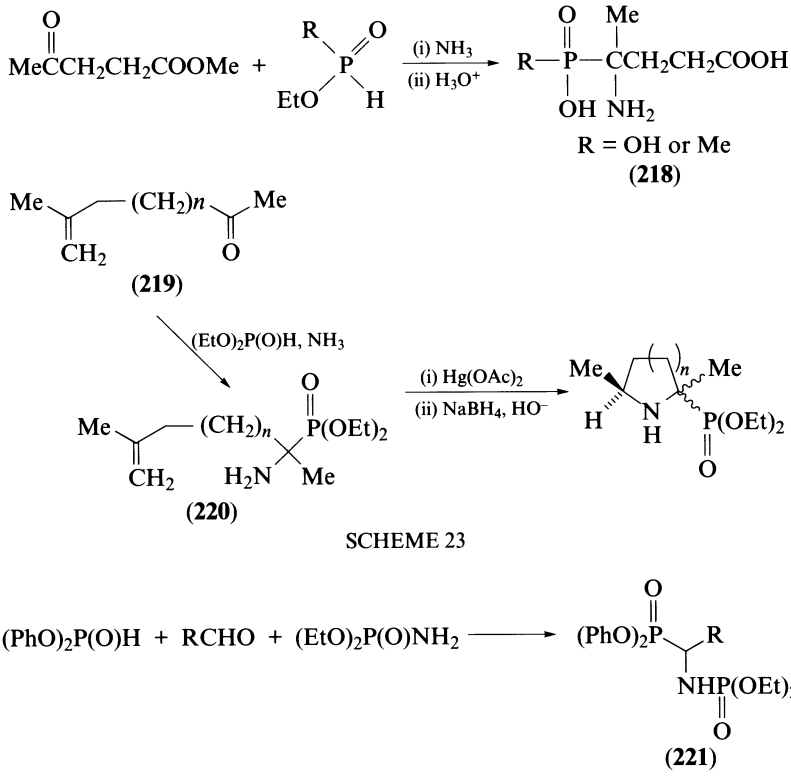
(**216**) X = CH_2
(**217**) X = O, S or NR

the suspicion that the overall reaction might involve the initial formation of an (α-hydroxyalkyl)phosphonic ester (Chapter 3, Section III.A.) which is then acted upon by the ammonia or amine. (Hydroxyalkyl)esters have indeed been isolated as by-products from Kabachnik–Medved'–Fields reaction mixtures, particularly in the cases of cyclohexanone[345] and 4-piperidones[339,346], from which the yields of (hydroxyalkyl)phosphonic ester may approach, or even exceed, those of the (aminoalkyl)phosphonic acid. Reactions with aromatic ketones either fail completely (fluorenone) or, at most, afford very low yields (benzophenone) of desired phosphonic acids; in these cases the reaction between ketones and hydrogenphosphonate ester proceeds 100 times faster than the base-catalysed decomposition of hydroxyphosphonic diester into starting materials, and that the latter reaction is slower, by a factor of 6, than base-catalysed rearrangement of hydroxyphosphonate into a phosphate ester; hence most of the aromatic ketone is used up before the aminophosphonate is formed to any great extent[347,348]. The side reactions in such cases may be obviated by prior formation of the imine reactant[348]. However, the successful conversion of (hydroxyalkyl)phosphonic diester into the corresponding (aminoalkyl)phosphonic diester through the action of ammonia has been observed in very few cases[330]. Moreover, similar attempted amination reactions with aromatic amines do not take place[344]. Nor does the reaction occur through salt formation between the amine and the hydrogenphosphonate[344]. All the evidence seems to point to the initial formation of the imine from amine and carbonyl reactant, and the Kabachnik–Medved'–Fields reaction thus becomes a modification to the sytem considered in the previous section, but without the necessity for the prior isolation of the imine intermediate. The complex nature of the Kabachnik–Medved'–Fields reaction has been commented upon, particularly in relation to the range of possible products obtainable from ammonia and the different types of aldehyde which are able to participate in the reaction[270,347,348].

The reactions between methyl 4-oxopentanoate and phosphinic esters in the presence of ammonia yield the 4-amino-4-phosphinoylpentanoic acids (**218**) (synthesized as analogues of phosphinothricin), although difficulties may be encountered in the purification of these compounds so prepared[349]. The initial adduct formation between the ketones **219**, ammonia and diethyl hydrogenphosphonate can be succeded by the conversion of the products (**220**) into pyrrolidine- and piperidine-2-phosphonic acids (Scheme 23)[350].

A one-pot process has been devised for the synthesis of dialkyl [(α-phenylamino)benzyl]phosphonates from dialkyl hydrogenphosphonate, benzaldehyde and aniline, presumably adaptable for other aromatic amines or aldehydes[351]. To avoid multiple reactions of the Mannich type when using a primary amine and a particularly reactive carbonyl component such as formaldehyde[352], initial silylation of the amine, or the use of diethyl trimethylsilyl phosphite, are valuable moderating variations[353]. The amine can be replaced by a carboxamide[354] or carbamate ester, conveniently the benzyl ester[355,356], and the product can then be selectively deacylated with HBr in acetic acid at room temperature or by hydrogenolysis. Alternatively, even a phosphoric amide may be used to afford an *N*-phosphorylated product (**221**)[357].

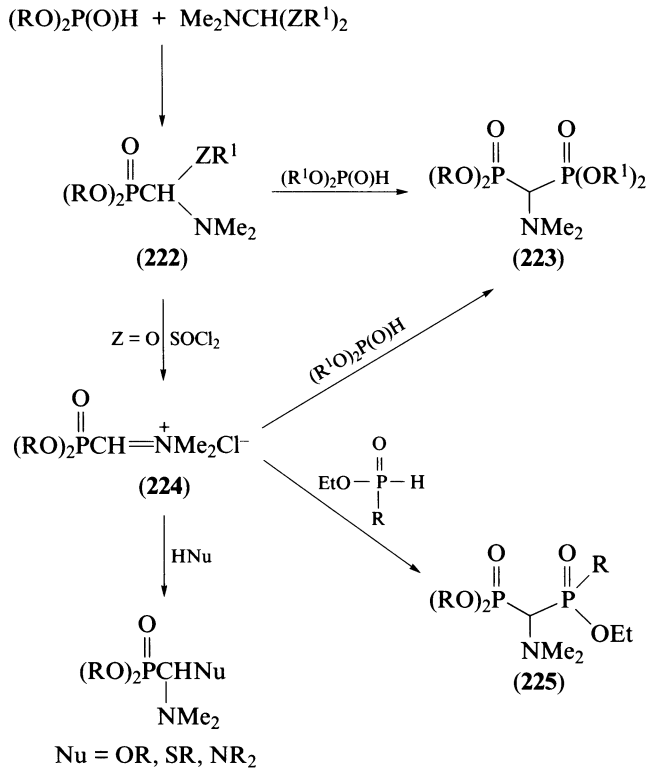
Fields[331] demonstrated that methylenediamines and dialkylaminomethyl ethers also react with dialkyl hydrogenphosphonates with the elimination of alcohol and formation of dialkyl (dialkylaminomethyl)phosphonates. The use of dimethylformamide dimethyl



SCHEME 23

acetal or dimethylformamide dialkyl dithioacetals is illustrated in Scheme 24[358,359]. After the initial formation of **222**, further reaction to yield the (dimethylaminomethylene)bisphosphonic esters (**223**) may occur when Z = O, but not when Z = S. The reactions between **222** and $SOCl_2$ yield the iminium salts **224**, which are themselves of appreciable value in synthesis; their reaction with a dialkyl hydrogenphosphonate yields **223**, whilst the same reaction with an alkyl phosphinic ester affords a 1:1 mixture of the diastereoisomers of **225**. In addition, the iminium salts **224** are reactive to nucleophiles[360,361]. Reagents of the general structure R_2NCH_2Z (Z = OR or NEt_2) react with alkyl hypophosphite esters (alkyl phosphinites) with the formation of phosphonic esters of the type $Et_2NCH_2P(O)(OR)_2$ or the phosphinic esters $(Et_2NCH_2)_2P(O)OR$[362]. Successful reactions between dialkyl hydrogenphosphonates and 4-alkoxyhexahydropyrimidin-4-ones which lead to hexahydro-2-oxopyrimidin-4-phosphonic diesters have also been reported[363].

The reaction between ammonia (or a primary or secondary amine), formaldehyde and phosphorous acid is only one particular case of the Kabachnik–Medved'–Fields reaction, consisting of the aminomethylation of a phosphorus species possessing a reactive P(O)H group, and so is of the Mannich type. The involvement of ammonia leads only to **226** and the intermediate aminomethylphosphonic **227** (R = H) and aminobis(methylene)bisphosphonic acid **228** (R = H) are not isolable although they are detectable by ^{31}P NMR spectroscopy[364]; the sequence can be stopped at the earlier stages if a primary or secondary amine is used[365]. The use of α,ω-diaminoalkanes leads to complexones of type **229**[365–367]. Ethanolamine affords the related bis(phosphonic acid) **230** and diethanolamine yields **231** under similar conditions; acidolysis of the linear compounds brings about their cyclization



SCHEME 24

$$R_{3-n}NH_n + nCH_2O + nHP(O)(OH)_2 \xrightarrow{-nH_2O} R_{3-n}N[CH_2P(O)(OH)_2]_n$$

(226) $n = 3$
(227) $n = 2$
(228) $n = 1$

to the perhydro-1,4,2-oxazaphosphorines **(232)** (Z=PO_3H_2 or OH)[368]. These syntheses are examples of a more general procedure which leads to the derivatives **233** of the same ring system, together with the linear acids **234**, by the reaction between formaldehyde, phosphorous acid and 1,2-amino alcohols[369].

$(H_2O_3PCH_2)_nN(CH_2)_nN(CH_2PO_3H_2)_2$

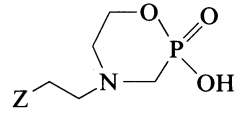
(229)

$HOCH_2CH_2N(CH_2PO_3H_2)_2$

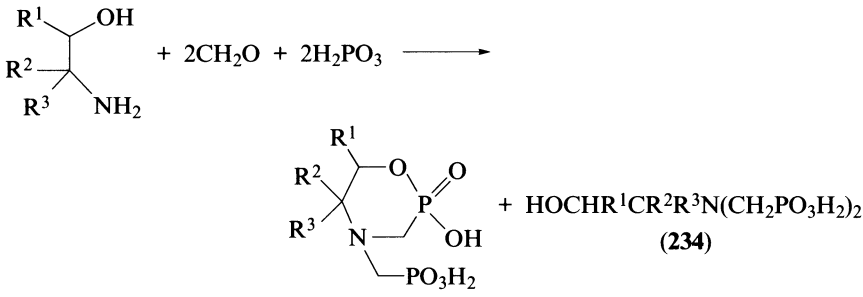
(230)

$(HOCH_2CH_2)_2NCH_2PO_3H_2$

(231)

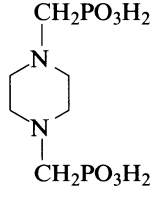


(232)



(233) (234)

A series of di-, tri- and tetra-aza cyclic and macrocyclic poly(methylenephosphonic acids) has been prepared through the Mannich-type process for use as complexones. The simplest is the piperazine-based diacid **235**[370] and the analogous compounds based on 1,4,7-triazacyclononane **236**[370–372], 1,4,7,10-tetraazacyclododecane (**237**)[372,373] and larger ring amines[372,374,375], are derived from the polyamines with formaldehyde and phosphorous acid. Esters of related phosphinic acids have also been prepared[376].



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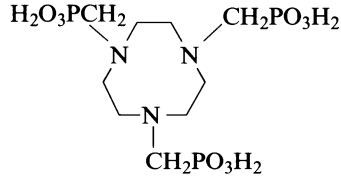

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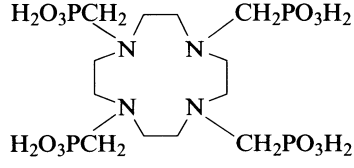
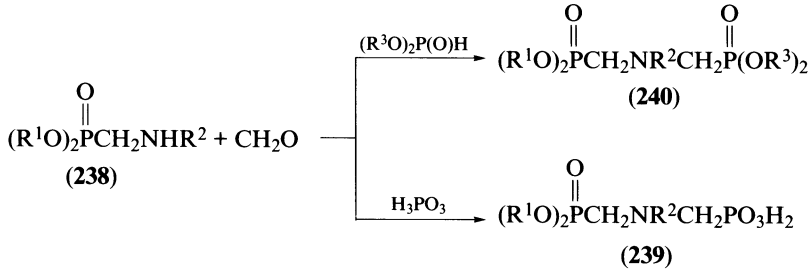


(237)

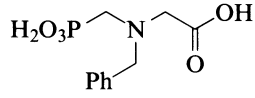
The phosphonomethylation of dialkyl [(alkylamino)alkyl]phosphonates (**238**) in the customary way yields products with mixed phosphoryl functions, e.g. the acids **239** or their esters **240**[377], and **241** are obtained by the phosphonomethylation of alkyl[(alkylamino)-methyl]phosphinic acids[378].

The phosphonomethylation of *N*-benzylglycine yields the phosphonic acid **242**, readily debenzylated by hydrogenolysis to yield glyphosate (**243**; Z = H)[379]. The trimethyl ester of glyphosate was previously obtained in an analogous fashion from glycine methyl ester, formaldehyde and dimethyl hydrogenphosphonate, and was hydrolysed to glyphosate under acid conditions; bearing in mind that this product still has a free NH group, it is not surprising that further reaction can lead to the phosphonic acid **243** (Z = CH_2COOH)[380]. Compound **243** (Z = $NCCH_2CH_2$) is obtainable through the phosphonomethylation of *N*-(2-cyanoethyl)glycine[380]. The phosphonomethylation of aminoacetaldehyde acetals produces the diesters **244**, which undergo single de-esterification when allowed to stand at

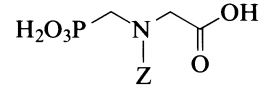
ambient temperature and which, on acidolysis, do not liberate the phosphonic acid **245**. The ester **244** ($R^1 = Me_3Si$; R = Me or Et) is formed from $(Me_3SiO)_2P(O)H$, and when desilyated yields the acid **244** (R^1 = H, R = Me or Et), from which **244** (R^1 = R = H) is obtainable through further acidolysis; like aminoacetaldehyde itself, this latter product remains as the aldehyde 'hydrate'[382].



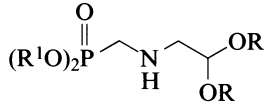
(241)



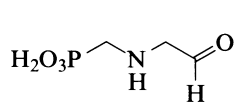
(242)



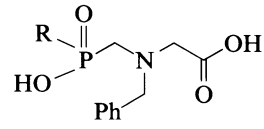
(243)



(244)



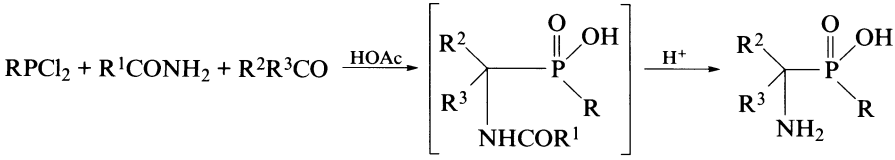
(245)



(246)

Reactions similar to those just described are well known for the phosphinic acid series[383,384]. Maier[385] has described similar aminomethylation reactions which lead to products such as **246** (R = Me, Et, Pr, Bu^t or CH_2OH), and also other reactions, to be discussed later, which afford bis(ω-aminoalkyl)phosphonic acids.

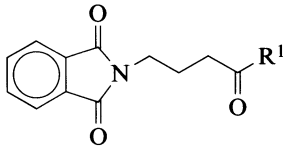
A further development is of importance as potentially time saving, particularly for the synthesis of (aminoalkyl)phosphinic acids, since it does not require the availability of an alkylphosphinic ester. The procedure employs a less reactive nitrogen source (amide[386], urea[387] or carbamate[388]) together with the carbonyl component and, as source of phosphorus, either PCl_3 or a dichlorophosphine, $RPCl_2$, required for the preparation of phosphonic and phosphiinic acids, respectively, all in an acetic acid medium (Scheme 25). The prodcedure has sometimes been referred to as the Oleksyszyn reaction. Almost certainly, the presence of the phosphorus(III) chloride in the acetic acid results in the formation of a species which possesses the P(O)H grouping.



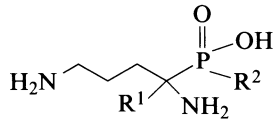
SCHEME 25

The amides used include those of both aliphatic and aromatic carboxylic acids[389]; primary carboxamides and carbamates might react through the initial formation of the species. $R^1CH(NHCOR^2)_2$ from R^1CHO and R^2CONH_2. Of the carbamate esters, the benzyl ester has proved the most popular because of ease of removal of *N*-protection at the ultimate stage by acidolysis of hydrogenolysis[390–394]. In this respect, the use of a secondary carbamic ester $RNHCOOCH_2Ph$ affords the *N*-R amino acid[395]. In place of the added formaldehyde, the use of *N*-hydroxymethylamides[396–401] or *N*-alkoxyureas[402,403], or even aldimines[404,405] has been reported. Other workers[406] have employed mixtures of aromatic aldehydes and phosphorus(III) chlorides with phosphoric amides as the nitrogen source in the presence of $ZnCl_2$ or $AlCl_3$.

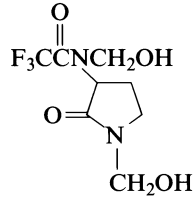
Novel products have been obtained from several of these reactions. Thus the use of 4-chlorobutanal furnished intermediates which could be cyclized, with alkali, to Pro^P or its phosphinic acid analogues[391], and related derivatives of pyrrolidone were prepared from ethyl 4-oxobutanoate and ethyl 4-oxopentanoate[392]. The use of hydroxymethylbenzamide or alternatively, of 1,3,5-tribenzoylhexahydrotriazine led to quantitative yields of (aminomethyl)phosphonic acid without isolation of the intermediate[398]. Phosphonic and phosphinic analogues of ornithine (**248**) have been obtained from the starting compounds **247**[393] and the use of the *N*-hydroxymethyl-3-*N*-hydroxymethylamino-2-pyrrolidones **249** or ring homologues as starting materials leads to the more complex acids **250**[399]. Hydroxymethylated ureas are sources of the 1,3,4-diazaphosph(V)olidin-2-ones **251** ($n = 1$)[402] or analogous phosphorinanones ($n = 2$)[403], which may be readily hydrolysed to the *N*-acylated (aminomethyl)phosphonic acid or (2-aminoethyl)phosphonic acid.



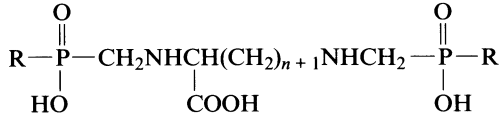
(247)



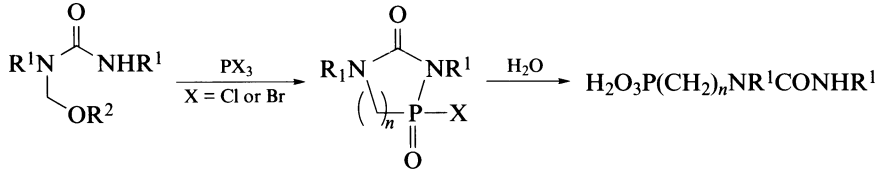
(248)



(249)



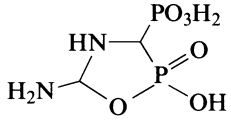
(250)



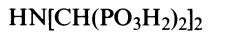
(251)

The combination of amide, phosphorus (phosphonic) acid, water and PCl_3 also provides mixtures of linear and cyclic (aminoalkyl)phosphonic compounds. Such a mixture containing formamide yields aminomethylenebisphosphonic acid together with the oxazaphosph(V)olidine **252**; the course of the reaction, and the effect of changes in reactant

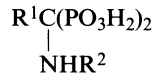
ratios, were studied by ^{31}P NMR spectroscopy and this allowed the optimization of yield (about 30%) in the formation of **252** relative to the other main linear product, imino-bis(methylene)bisphosphonic acid (**253**)[407]. Depending on the reacton conditions, *N*-alkylacetamides and H_3PO_3–PCl_3 with pyridine or tributylamine hydrochloride can give either 1-(alkylamino)ethylidene-1,1-bisphosphonic acids (**254**; R^1 = Me) or the dianhydrides of 1-(alkylamino)butyl-1,1,3,3-tetrayltetrakisphosphonic acids (**255**); mild acidolysis of the latter cleaves one anhydride ring, but not the second, to give **256**, whilst strong acid hydrolysis yields the bisphosphonic acids **257**. When amides, R^1CONHR^2, other than formamide or acetamide are employed, the products are the bisphosphonic acids **254** as well as the cyclic anhydrides **258**[408].



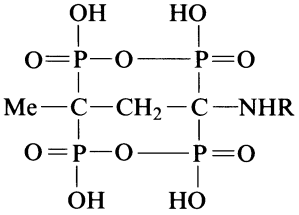
(**252**)



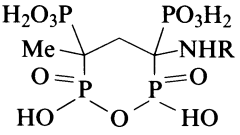
(**253**)



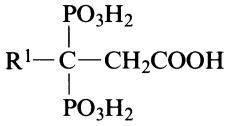
(**254**)



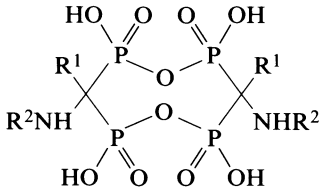
(**255**)



(**256**)



(**257**)

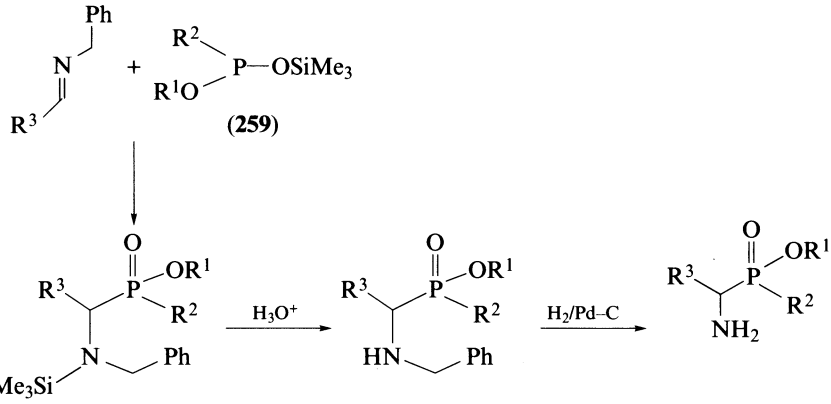


(**258**)

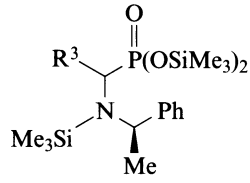
5. *Through additions of phosphorus(III) esters to C=N compounds*

The interaction of a trimethylsilyl phosphorus(III) ester **259** and an imine occurs under mild conditions, and according to the outline in Scheme 26; stepwise deprotection steps remove the silyl group from nitrogen, and in the event that the original nitrogen sp^2-bonded substituent was benzyl, this may be removed in the ultimate stage by hydrogenolysis[409–411]. Deprotection of the diastereoisomeric intermediates **260** (both *O*- and *N*-desilylation by methanolysis and hydrogenolytic removal of the phenylethyl group) obtained from the enantomeric forms of 1-phenylethylamine left enantiomeric forms of the (aminoalkyl)-phosphonic acids, although these had only relatively low optical activities[412].

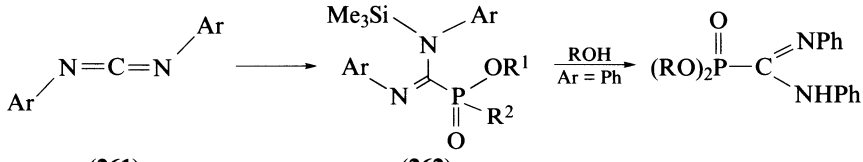
In related reactions, the silyl phosphorus(III) esters **259** add to carbodiimides **261** to give **262**[409,413]. The addition of diethyl *N*-phenylphosphoramidite (**263**) to an aldimine affords the phosphonimidic ester **264**[414]. The preference for attack by an imine at the carbonyl group (rather than at the phosphoryl group) in reactions with phosphorus(III) acid–



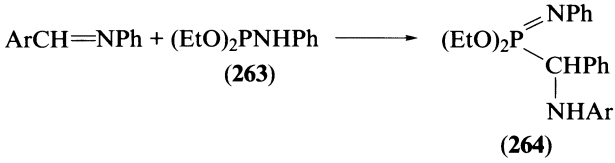
SCHEME 26



(260)



(261) (262)



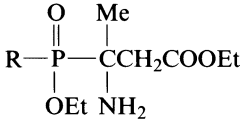
(263) (264)

carboxylic acid anhydrides, and which results in the formation of *N*-acylated (rather than phosphorylated) products[415], is reminiscent of a similar behaviour shown by the anhydrides towards amines.

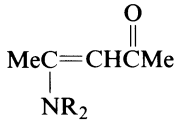
6. Through additions of hydrogenphosphonates to unsaturated compounds

In spite of their potential in synthesis, accounts of additions of hydrophosphoryl compounds to enamines are spread rather thinly throughout the literature. As a contribution towards the synthesis of methylaspartic acid and methylglutamic acid analogues, ethyl esters of phosphinic acids, (EtO)RP(O)H, were shown to add to ethyl 3-aminobut-2-

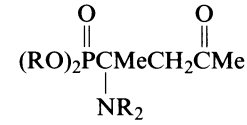
enoate to give (**265**)[349]. Cyclic dialkyl hydrogenphosphonates likewise add to the enamines **266** to give the esters of (2-dialkylamino-4-oxopentyl)phosphonic acid (**267**)[416–419], and to **268** to give **269** in the first step towards a synthesis of phosphonoisohistidine (**270**)[420]. The additions of dialkyl hydrogenphosphonates to the yneamines **271** affords the eneamines **272**, generally as *Z*–*E* mixtures (R^1 = Me) or the *Z* form only (R^1 = Ph)[421].



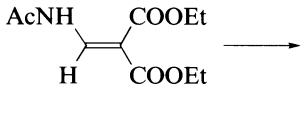
(**265**)



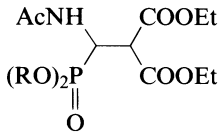
(**266**)



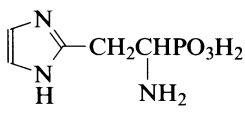
(**267**)



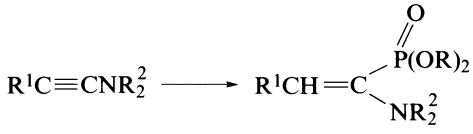
(**268**)



(**269**)

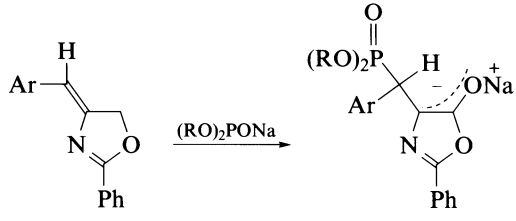


(**270**)

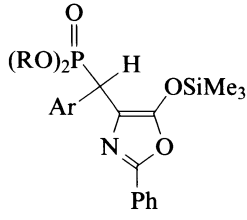


(**271**) (**272**)

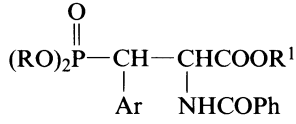
Sodium dialkyl phosphites add to the 4-arylidene-4,5-dihydro-1,3-oxazoles **273** to give the enolate anions **274**; on the other hand, the adducts **275**—the potential products of the silylation of **274**—are more conveniently obtained by additions of dialkyl trimethylsilyl phosphite. The adducts **275** undergo alcoholysis with alcohols, R^1OH, to give the 2-amino-3-phosphinoylpropanoic acid esters **276**, whilst the action of water yields the acids **276**



(**273**) (**274**)



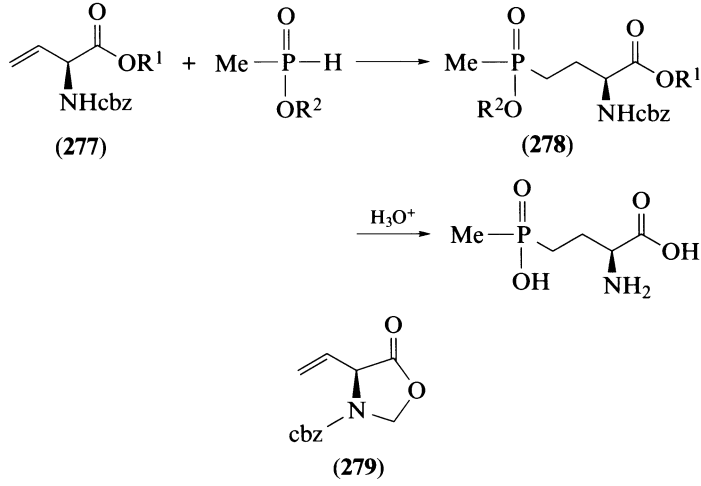
(**275**)



(**276**)

(R^1 = H); the ratio of diastereoisomeric products, recognized by X-ray structure analyses[155], depends markedly on the reaction conditions[422].

The regioselective addition of an alkyl methylphosphinate to the (enantiomerically enriched) vinylglycine esters **277** is catalysed by *tert*-butyl 2-ethylperhexanoate; the adducts **278** are formed in almost quantitative yield and their treatment with 6 M HCl results in de-esterification at both carboxy and phosphinic acid groupings and also removal of the protection on nitrogen. (4*S*)-3-Benzyloxycarbonyl-4-ethenyl-1,3-oxazolidin-5-one **279** also serves as a substrate for the addition of methylphosphinic esters; treatment of the adduct with aqueous NaOH opens the oxazolidone ring and yields the product **278** (R^2 = Bu^i, R^1 = Me) which is deprotected at nitrogen by hydrogenolysis; the d.e. of **278** (R^1 = R^2 = H) obtained after the last step was 97.4%, indicating a maximum of only 2.6% racemization during the series of five transformations starting from L-glutamic acid as the precursor to the oxazolidinone[423].

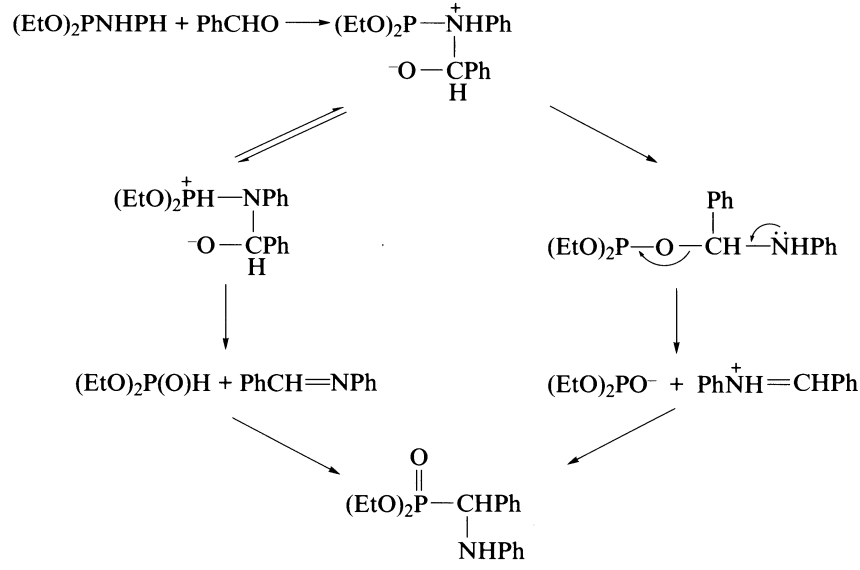


(277) (278) (279)

In general, additions of P(O)H-containing species are carried out with unsaturated esters, amides or ketones, and further standard organic reactions are required to generate the amino function in target compounds. The additions of dialkyl hydrogenphosphonates to systems possessing multiple carbon–carbon bonding have been reviewed in connection with the preparation of oligophosphonic acids containing OH and NH_2 groups[424].

7. Through methylene insertion reactions

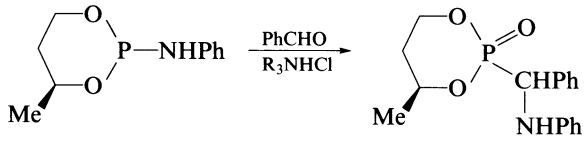
Although not the first to report on the behaviour of ester amides of phosphorus(III) acids towards aldehydes or ketones, it appears to have been Evdakov and coworkers who correctly formulated the products from such interactions[425]. The products from diethyl *N*,*N*-dialkylphosphoramidites and benzaldehyde or cyclohexanone were shown to be (1-aminoalkyl)phosphonic diethyl esters. The phosphonate nature of the products was confirmed by Hudson *et al.*[426], who dismissed earlier suggestions regarding a possible mechanism and suggested that a more likely mechanism (Scheme 27) should be based on the breakdown of an intermediate species into hydrogenphosphonate and aldimine, which recombine in the manner discussed earlier in this chapter. The conclusion seemed particularly likely in view of the isolability of hydrogenphosphonate and imine and also that of (aminoalkyl)phosphonate, and the observation that an increase in the reaction period



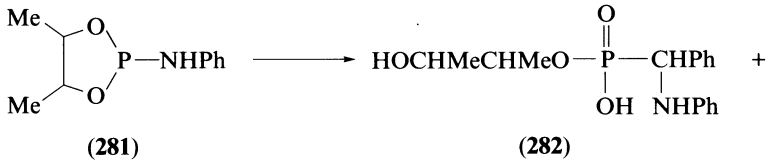
SCHEME 27

resulted in increased yields of the latter at the expense of hydrogenphosphonate and imine; the manner in which the imine is formed remains in question. Thus, the reaction between diethyl *N*-phenylphosphoramidite and cyclohexanone in boiling toluene afforded 52% diethyl hydrogenphosphonate and 58% cyclohexylideneaniline together with only 13% of the (aminoalkyl)phosphonate after 5 h; if the reaction mixture was then allowed to stand for several hours, the yield of the latter could be increased to 69%.

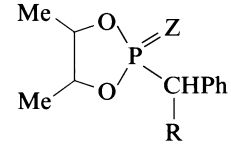
The same phosphoramidite esters have been methylenated by paraformaldehyde to give dialkyl (phenylaminomethyl)phosphonates[427]. An analogous process also occurs when benzaldehyde interacts with 2-phenylamino-1,3,2-dioxaphosph(III)orinanes (to give **280**)[428], but the reaction with a comparable 1,3,2-dioxaphospholane **281** is more complex, and there is formed a mixture of the ring-opened (aminoalkyl)phosphonic monoester **282** and the expected phosphonate with retained ring **283**, accompanied by the hydroxyphosphonimidate **284**[429]. The product obtainable from an analogous benzodioxaphosphole, albeit in low yield, also has retained the phosphole ring but is extremely sensitive to moisture, which causes ring opening[430]. When the cyclic phosphorus(III) substrate possesses an intramolecular P—N bond, as in, for example, a 1,3,2-oxazaphosph(III)olidine, the exothermic reaction (Scheme 28) results in ring enlargement, in this case to give examples of the perhydro-1,4,2-oxazaphosph(V)orine ring system (**285**)[431,432]. Phosphorus(III) hydrazides have also been shown to undergo carbon insertion when treated with aromatic aldehydes[433].



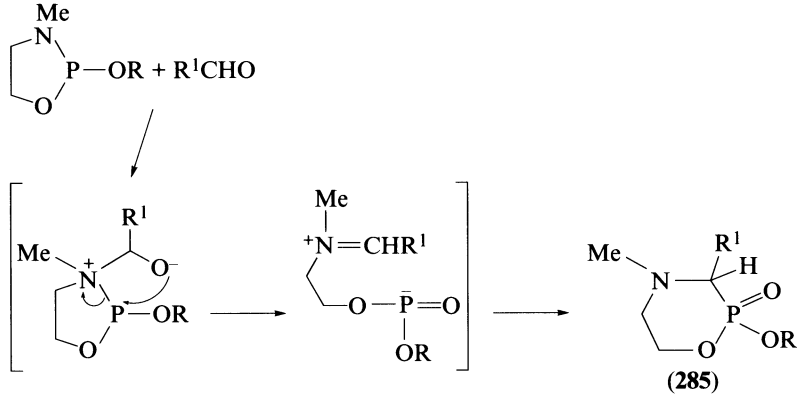
(**280**)



(281) (282)



(283) Z = O, R = NHPh
(284) Z = NPh, R = OH



(285)

SCHEME 28

B. Syntheses Through Modification Procedures

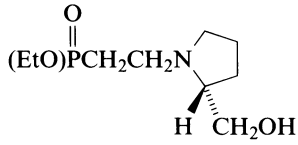
In addition to the very many procedures available for the preparation of aminoalkylphosphonic and -phosphinic acids through phosphorus–carbon bond formation, many of which have just been summarized, the same acids have been obtained through a multitude of procedures which consist in the modification of compounds in which the essential carbon skeleton, and in particular the phosphorus–carbon bond, is already in existence. In the following account, the various types of otherwise functionalized phosphonic and phosphinic acids are considered in the order in which they have so far been listed in this and in the previous chapter.

1. Through Modifications to Functionality

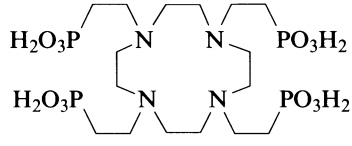
a. From amines and alkenyl- and alkynyl-phosphonates or -phosphinates. The addition of ammonia, or of a primary or secondary amine to a diester of ethenylphosphonic acid occurs in an anti-Markovnikoff manner (Scheme 29). This simple reaction, widely explored in the earlier years of systematic organophosphorus chemistry, occurs readily; the order of amine reactivity, $R_2NH > RNH_2 > NH_3$, is such that simple secondary amines react in the absence of catalyst, under neat conditions or in an aqueous medium[434–437]. Two

examples of greater than passing interest are the addition of L-prolinol to give **286**[435] and that of 1,4,7,10-tetraazacyclododecane to give the novel complexone **287**[436].

SCHEME 29

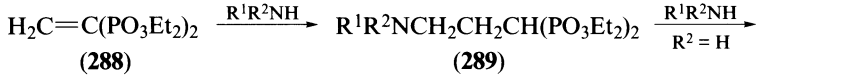


(286)



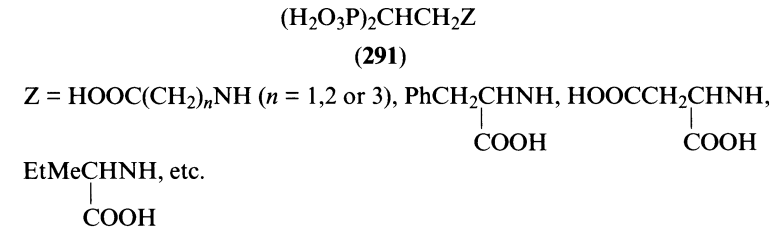
(287)

In general, primary amines require the presence of a catalyst such as an excess of the amine or a metal alkoxide, (often) together with the application of heat. Unfortunately, the presence of alkyl substituents in the carbon ligand may prevent normal addition, and *O*-dealkylation may then occur. However, the addition of secondary amines, including piperidine and morpholine, to dialkyl (1-phenylethenyl)phosphonates occurs only in dmf in the presence of a quaternary ammonium salt[438]. The more basic the amine, the easier is the addition, but steric factors have to be taken into consideration; thus, butylamine adds to a dialkyl ethenylphosphonate in the presence of a trace of alkoxide catalyst, whereas *tert*-butylamine fails to undergo addition. An increase in electron donation to phosphorus also lowers the rate of addition, and higher reaction temperatures and/or extended reaction periods are required for additions to ethenylphosphonic diamides[439] or to alkyl(ethenyl)-phosphinic esters. The addition of an amine to an ethenylidenebisphosphonic ester (**288**) requires the use of a highly polar medium at higher temperatures[440]; if the initial amine is primary, further addition of the resultant secondary amine **289** to **288** produces the tetraphosphonic acid ester **290**[441]. A more recent report by the same authors described several new compounds, **291**, derived by the additions of aminocarboxylic acids to the ethenylidenebisphosphonic acid[442]. The process has been further extended by additions to tetraethyl ethenylidenebisphosphonate described by Sturtz and Guervenou[80], but in



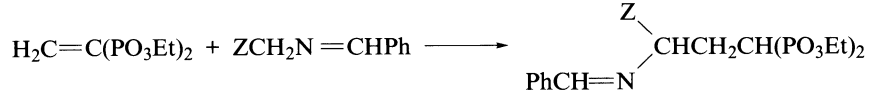
(288) **(289)**

(290)



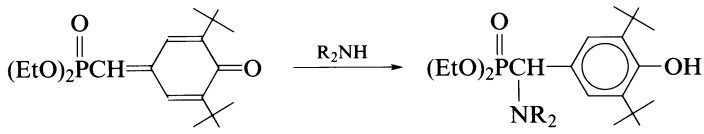
(291)

connection with the synthesis of aminoalkyl phosphonic derivatives, the most useful examples appear to be those illustrated in **292**; a further reaction with *p*-toluenesulphonic acid completes the conversion into the free amino acid.



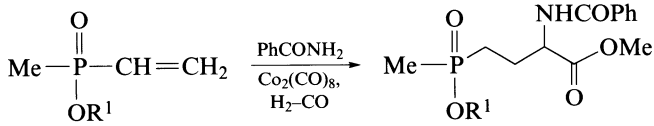
(292) Z = COOEt or PO_3Et_2

Unexpectedly, esters of buta-1,3-dienyl-2,3-diphosphonic acid add diethylamine across only one of the C=C bonds[443]. Amines add to phosphorylated quinonemethides as indicated to give the α-aminobenzylic phosphonic diesters **293**[444].



(293)

A highly novel approach to the synthesis of glufosinate (phosphinothricin) consists in the amidocarbonylation of esters of methylvinylphosphinic acid (**294**) and followed from a study of the simple carbonylation of the same acid esters in the presence of one of a series of metal carbonyl complexes. In the presence of $[Co_2(CO)_8]$, a mixture of hydrogen and carbon monoxide at 140 atm adds to the acid in the presence of benzamide in thf at 120 °C to give the product, mainly as the fully esterified compound, **295**, together with small amounts of free amino acid[445].



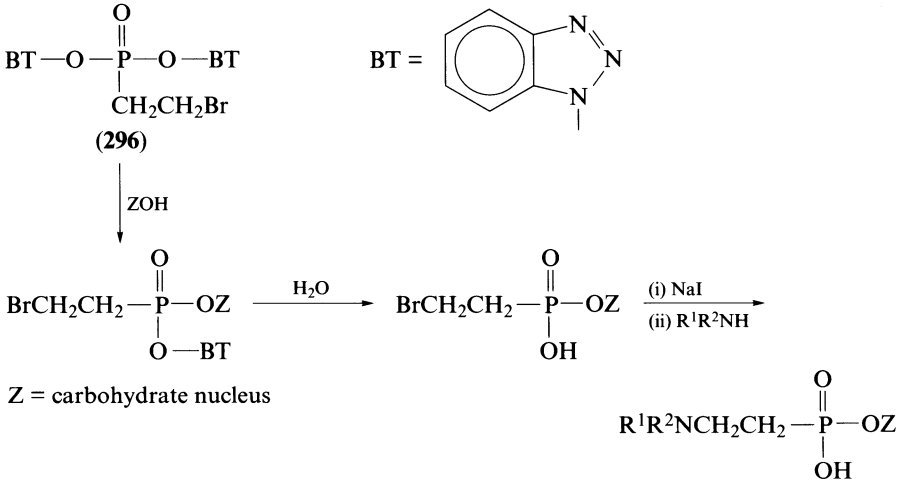
(294) **(295)**

b. From halo- or pseudohalo-alkyl-phosphonic or -phosphinic derivatives. Although Kosolapoff[446] found that diethyl (2-bromoethyl)phosphonate reacted with aqueous secondary amines and afforded good yields of diethyl (2-dialkylaminoethyl)phosphonates, slighly later work by Kabachnik and Medved[447,448] demonstrated that esters of (chloromethyl)phosphonic acid, and even those of the iodo analogue, showed little tendency to allow nucleophilic displacement of the halogen; thus, at room temperature, the preferred reaction with aqueous ammonia was simple ester hydrolysis, and successful ammonolysis required that the ester be heated with concentrated aqueous ammonia in a sealed tube at 100–150 °C when displacement of halogen was still accompanied, of course, by ester hydrolysis.

The direct ammonolysis of (3-bromopropyl)phosphonic acid yields 36% of the 3-amino acid[184]. The reaction between (chloromethyl)phosphonic acid and the less basic aniline requires an extensive period, even at 160–170 °C[449]. Nevertheless, extensive use has been made of the direct displacement of chlorine from (chloromethyl)phosphonic acid by higher boiling primary amines[450], and that in alkyl(chloromethyl)phosphinic esters by glycine[451]. Reactions which involve secondary amines, particularly *N*-substituted glycines[452], and

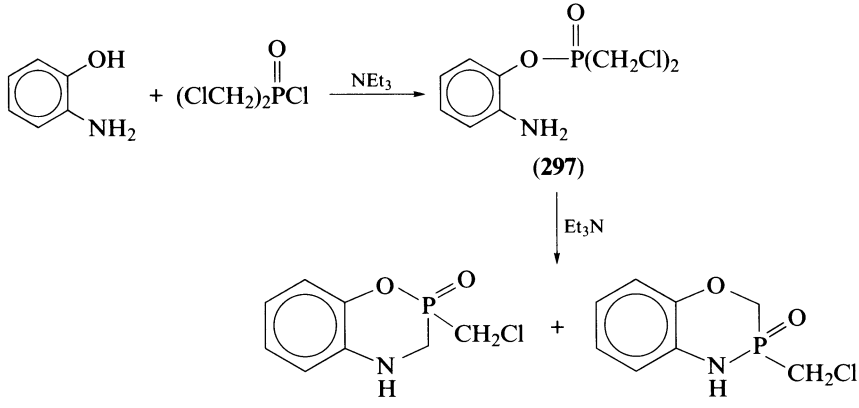
cyclic amines such as piperazine and its homologues, are easier because of more easily reached higher reaction temperatures. In the search for compounds having potential NMDA antagonist activity, such reactions have been extended to include longer chain (ω-haloalkyl)phosphonic esters and larger ring diamines in addition to piperazine[453–455].

Bis(benzotriazolyl) (2-bromoethyl)phosphonate (**296**) has been described as a reagent for the facile preparation of carbohydrate esters of (*N*-substituted-2-aminoethyl)phosphonic acids (Scheme 30); here the introduction of the nitrogen substituent is rendered easier by prior displacement of Br by I[456]. Differences between the reactivities of halogen in ester and acid carbon moieties is readily demonstrable; when 2-chloroethyl bis(2-chloroethyl)phosphinate is heated with 4 equiv. of benzylamine, the product is 2-chloroethyl bis(2-benzylaminoethyl)phosphinate, which is readily hydrolysed and debenzylated to give bis(2-aminoethyl)phosphinic acid[457].



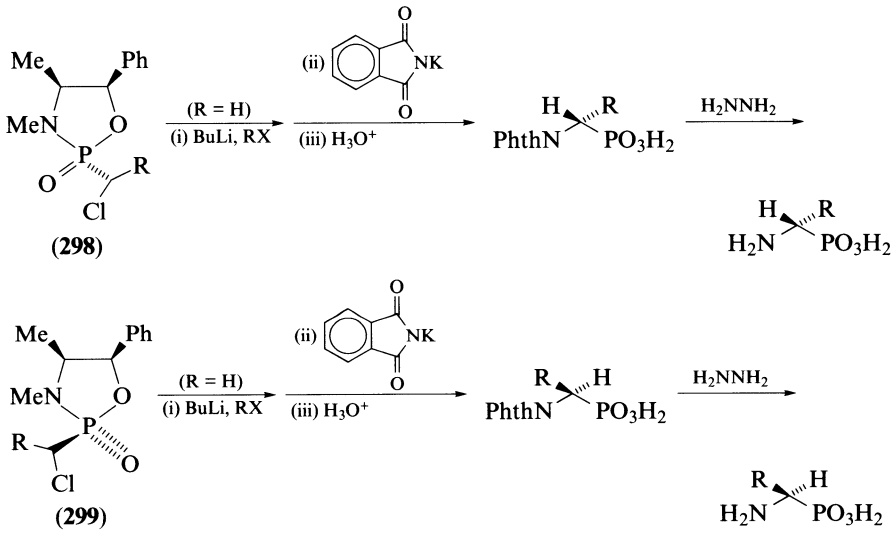
SCHEME 30

A reaction between bis(chloromethyl)phosphinic chloride and *o*-aminophenol at ambient temperature, gives the initial product **297**, which can then be made to undergo intramolecular halogen displacement at a higher temperature[458]. The direct displacement



of chlorine from (chloromethyl)phosphonic acid by a pyrimidone occurs at nitrogen when the reactants are fused together at 200–240 °C[459]. The displacement of bromine in diethyl (2-bromoprop-2-enyl)phosphonate by dimethylamine occurs readily, but is accompanied by prototropic change to give diethyl (2-dimethylaminoprop-1-enyl)phosphonate (other nucleophiles behave similarly)[460]; it might be noted that the ammonolysis of diethyl (2,3-dibromoethyl)phosphonate proceeds via diethyl (1-bromoethenyl)phosphonate (which can be thus prepared) through to diethyl 2-aziridinylphosphonate[461].

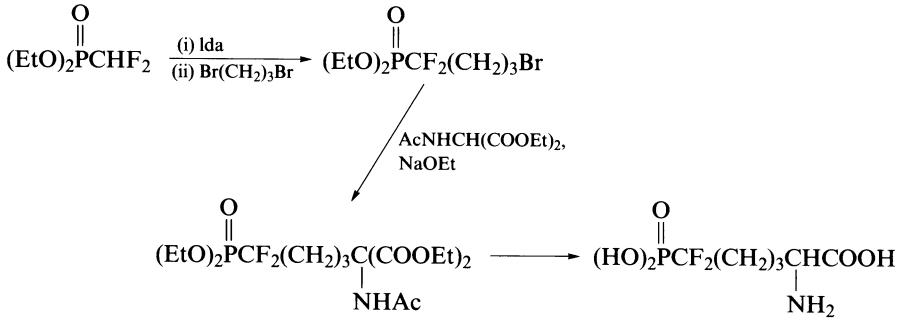
In keeping with the general principles of synthesis in amino acid chemistry, the amino group may also be introduced 'indirectly', although with fewer potential unwanted side reactions, through the application of the Gabriel synthesis; in the example quoted, this has been combined with an attempt to induce enantiomer preferment by the creation and use of chiral templates constructed through the reaction between (chloromethyl)phosphonic dichloride and (–)-ephedrine. A mixture of the (2*S*, 4*S*, 5*R*)- and (2*R*, 4*S*, 5*R*)-2-chloromethyl-1,3,2-oxazaphosph(V)olidines (**298** and **299**; R = H) is formed, which is subjected to alkylation (BuLi–RX). The separated diastereoisomeric 2-(1-chloroalkyl)-1,3,2-oxazaphosph(V)olidines are acted upon by potassium phthalimide and the products worked up according to the usual Gabriel procedures when the separated enantiomeric (1-aminoalkyl)phosphonic acids are obtainable (Scheme 31)[462].



SCHEME 31

Alternatively, the use of acetamidomalonic ester in the classical manner is exemplified by the synthesis of 2-amino-7,7-difluoro-7-(dihydroxyphosphinoyl)heptanoic acid (Scheme 32) in the search for compounds with NMDA antagonist activity[463], and in yet another synthesis of phosphinothricin[464].

c. From (hydroxyalkyl)phosphonic acid derivatives. Although, during the early studies on the Kabachnik–Medved'–Fields reaction, it was recognized that the simpler and more reactive of the (α-hydroxyalkyl)phosphonic acids could be converted into the corresponding α-aminoalkyl compounds through the action of ammonia, it was also shown that the displacement does not occur with primary or secondary amines, and it was therefore thought very unlikely that the hydroxyalkyl acids were formed as intermediates in the



SCHEME 32

reaction. In practical terms, α-hydroxyalkyl-phosphonic and -phosphinic acids are not generally regarded as appropriate precursors to the aminoalkyl acids, even though such conversions are sometimes feasible. However, under Mitsunobu conditions (Ph_3P, diethyl azodicarboxylate, thf, room temperature), (1-hydroxyalkyl)phosphonic diesters afford dialkyl (1-phthalimidoalkyl)phosphonates in 60–70% yields[465].

The most commonly adopted approach to the conversion of (hydroxyalkyl)phosphonic acids into the aminoalkyl analogues is through the intermediate (azidoalkyl)phosphonic acids (see Section IV. C. 1.f) although (aminohydroxyalkyl)phosphonic acids, in many cases readily obtainable through aldol reactions of (nitroalkyl)phosphonic acids, can be dehydroxylated (see Section IV. D.1).

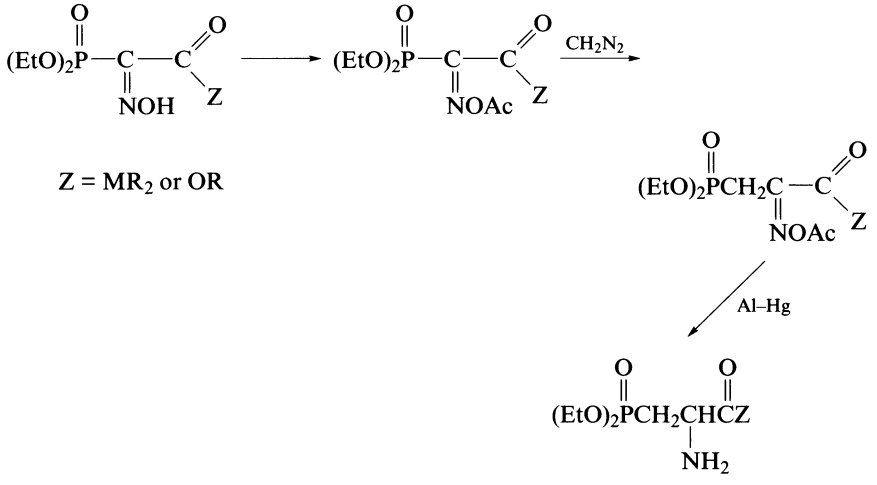
d. From (oxoalkyl)phosphonic derivatives. The ready availability of (oxoalkyl)phosphonic acid esters, particularly those with the oxo group at the α-position through the Michaelis–Arbuzov reaction, but also those with the oxo group at other sites through a variety of other syntheses, makes them attractive starting materials for the preparation of aminoalkyl phosphonic diesters through classical interconversions.

Of these reactions, the simplest direct procedure seems to be that of reductive amination of (1-oxoalkyl)phosphonic acids which occurs when these are treated with NH_3–$NaBH_4$[466,467].

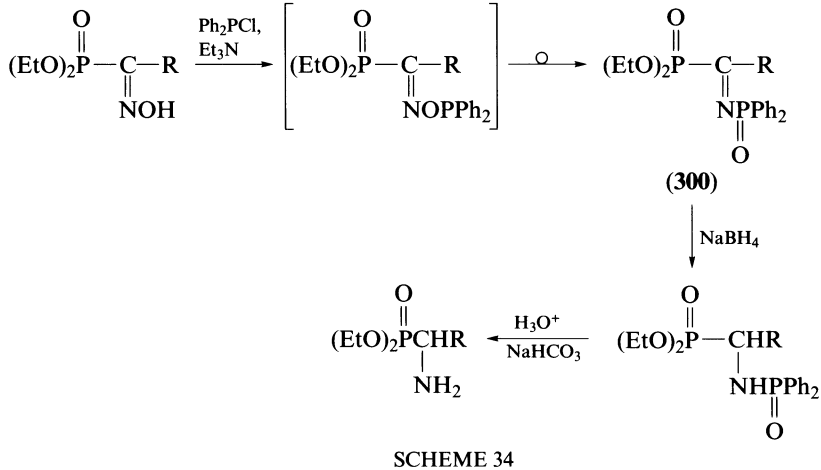
Oximes[468–479] and hydrazones[480] have been widely prepared from the more readily available (oxoalkyl) phosphonic acids (usually in the form of their esters) and their potential for reduction studied. Oximes, the most commonly employed derivatives, are readily converted into the corresponding (aminoalkyl)phosphonic derivative when acted upon by a variety of reducing agents, including aluminium amalgam[472,480]; zinc–copper couple in aqueous ethanol[474]; zinc in formic acid, acetic acid, or trifluoroacetic acid[470,478,479]; Raney nickel–hydrogen[476,477] and diborane[469,475]. Protection of the oxime group of (1-hydroxyiminoalkyl)phosphonic diethyl esters by acylation allows methylene insertion with diazomethane, when subsequent treatment with Al–Hg deprotects and reduces the function to amino (Scheme 33).

The oxime from (4-chloro-1-oxobutyl)phosphonic acid has been cyclized to Pro^{P}[471]. An unusual rearrangement based on valence expansion of phosphorus is of interest; the treatment of an (oxoalkyl)phosphonic oxime with Ph_2PCl initially yields the phosphorus(III) derivative, but this rearranges spontaneously to give a phosphinic amide derivative **300**, reduction of which then affords the [(*N*-diphenylphosphinoylamino)alkyl]phosphonic acid, readily hydrolysable under acid conditions to the free (aminoalkyl)phosphonic diester (Scheme 34)[473].

(Oxoalkyl)phosphonic diesters, through their reactions with primary amines, yield imine derivatives. The reaction between the (oxoalkyl)phosphonate, benzylamine and



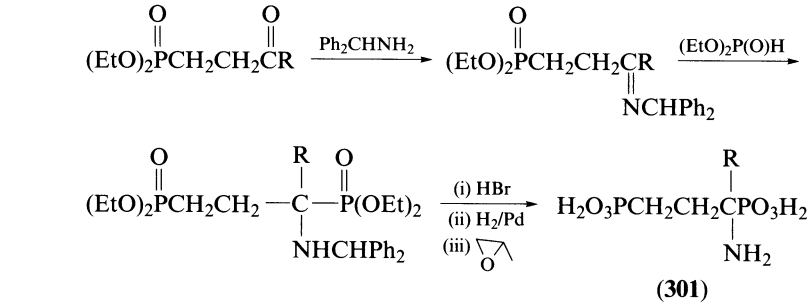
SCHEME 33



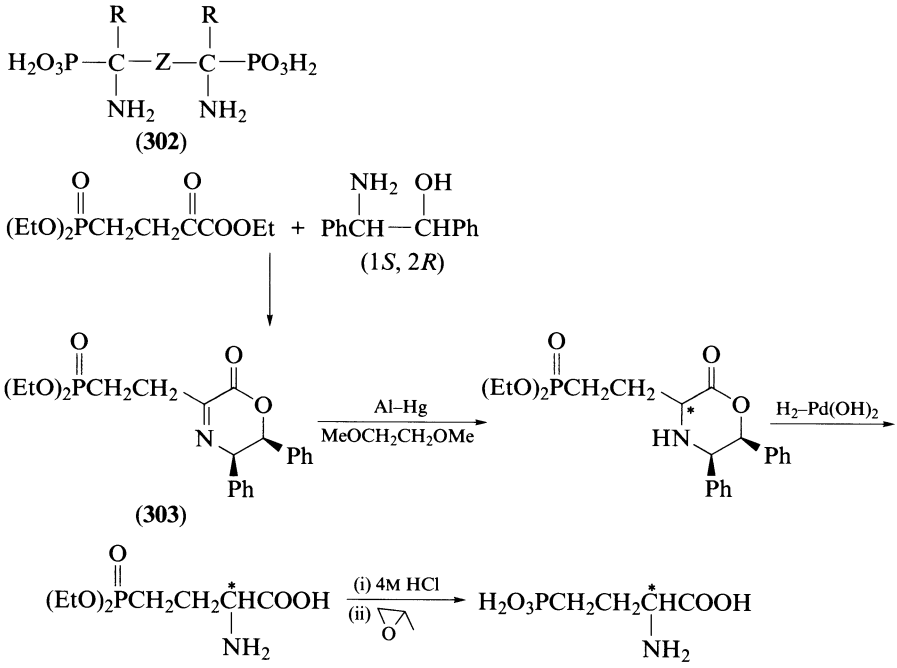
SCHEME 34

$NaBH_3CN$ produces the corresponding (*N*-benzylaminoalkyl)phosphonic diester, from which the nitrogen-protecting group can be removed by catalysed hydrogenolysis. The imines from diethyl (3-oxoalkyl)phosphonates and diphenylmethylamine undergo a reaction with diethyl hydrogenphosphonate in the expected fashion; the *N*-benzhydryl protecting group is removed during the course of de-esterification with aqueous HBr, when the product is the 3-aminoalkane-1,3-diphosphonic acid **301** (Scheme 35), and the procedure is adaptable to the preparation of the symmetrical compounds **302** in which $Z{=}(CH_2)_n$ or 1,4-phenylene[481]. A novel synthesis of 2-amino-4-phosphonobutanoic acid (Scheme 36) relies on the asymmetric reduction of the cyclic imine **303**, controlled by the stereochemistry of the benzyl groups attached to the heterocyclic ring; debenzylation and acid hydrolysis result in a product with 67% e.e.[482].

Hydrocyanic acid adds readily to ω-phosphinoylalkanals **304**, as it does also to the imines derived from the same substrates and amines to produce the aminonitriles **305**, acid



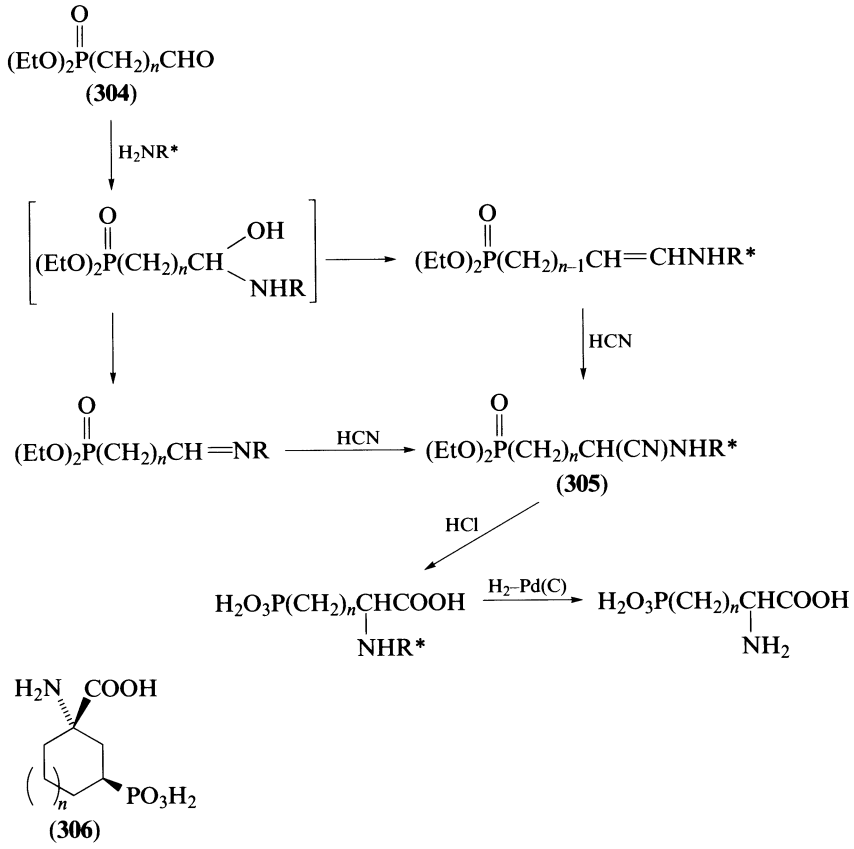
SCHEME 35



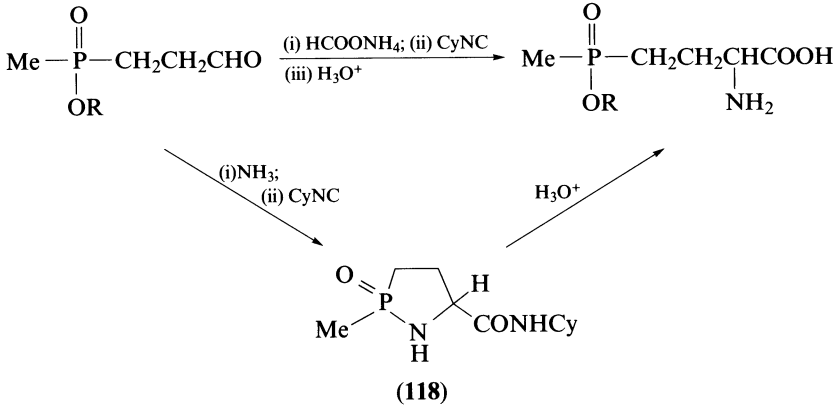
SCHEME 36

hydrolysis of which leads to the desired 2-amino-ω-phosphonoalkanoic acid (Scheme 37); utilization of the pure enantiomers of 1-phenylethylamine in the initial stage results in the products with $n = 1$ or 2, of high optical purities[483]. Cyclic analogues (**306**; $n = 0$ or 1) have been recorded[484].

Leuckart-like reactions have been noted for the ω-phosphinoylalkanals **304** and related compounds[485]. In these reactions, and also for those with analogous ketones[486,487], the carbonyl reactant is subjected to reductive amination with ammonia (as ammonium acetate) or amines and $NaBH_3CN$ in MeOH at pH 7–7.5; the process is very sensitive to steric hindrance and probably proceeds via an enaminophonate intermediate. The sequence is illustrated (Scheme 38) by a direct synthesis of racemic phosphinothricin, but the involvement of the optically active 1,2-azaphospholidine **118** led to an optically active product[149].

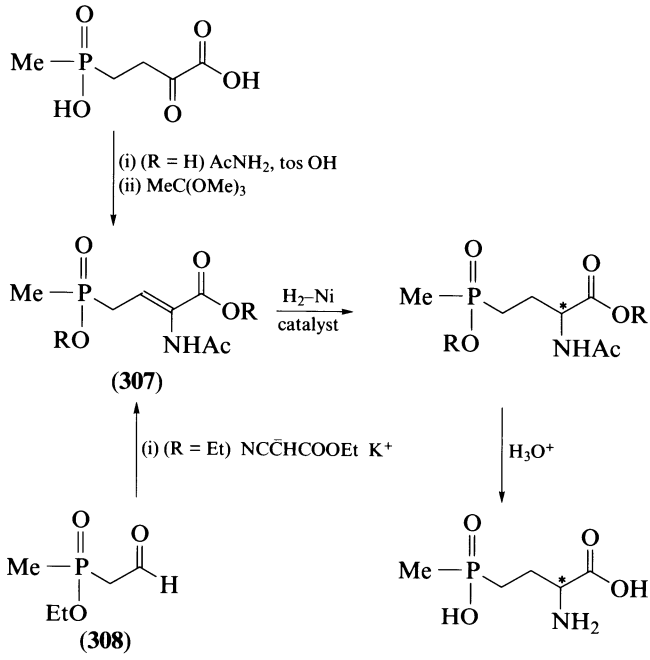


SCHEME 37



SCHEME 38

Asymmetric hydrogenation in the presence of an appropriate catalyst [(*R,R*)-Norphos or (*S,S*)-Chiraphos] of the (*N*-acetyl)enamine **307** derived from 2-oxo-4-(hydroxymethylphosphinoyl)butanoic acid and acetamide (Scheme 39), also obtainable from the 2-phosphinoylated acetaldehyde **308**, afforded phosphinothricin with e.e. ca 91%[488].

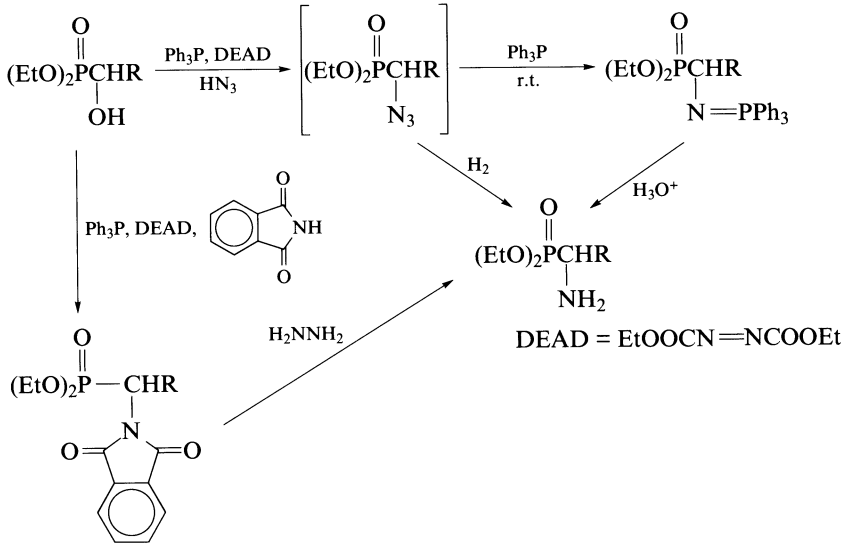


SCHEME 39

e. From phosphonoalkanoic acid derivatives. Classical organic procedures have been used extensively for the conversion of phosphinoylalkanoic acids and their (carboxy) derivatives into aminoalkyl-phosphonic and -phosphinic acids.

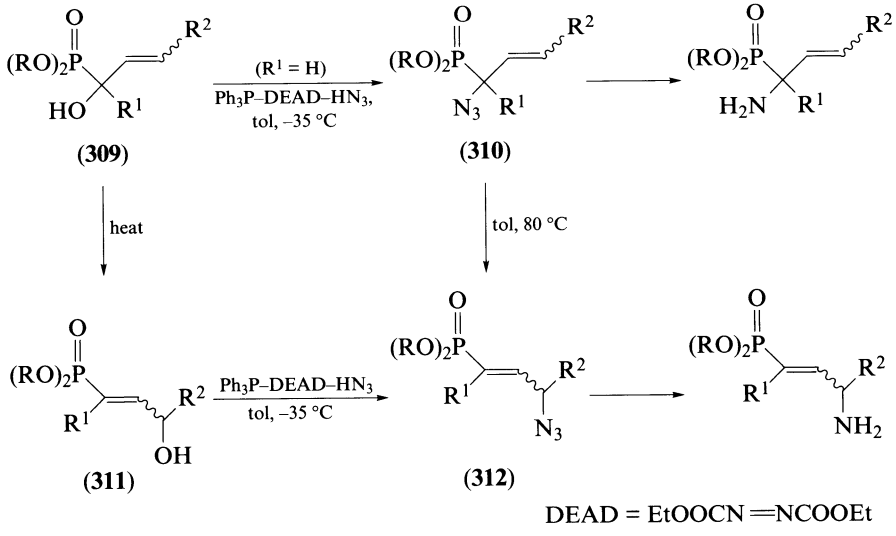
In an application of the Hofmann reaction, triethyl 3-phosphonopropanoate [ethyl 3-(diethoxyphosphinoyl)propanoate] was converted into (2-aminoethyl)phosphonic acid[489], but phosphinoyl carboxamides are also reduced to the amine without loss of carbon through the use of $BH_3{\cdot}SMe_2$ in thf at 0 °C[490]. The Schmidt reaction was employed in a synthesis of phosphonobaclofen, [3-amino-2-(4-chlorophenyl)propyl]phosphonic acid, from ethyl [3-(4-chlorophenyl)-4-(dimethoxyphosphinoyl)]butanoate[491]. However, the most commonly used procedure has been the Curtius reaction, starting with the carboxylic ester via the hydrazide[492–494], or via the acid chloride[495], or by the direct formation of the azide from the carboxylic acid through reaction with diphenyl phosphorazidate, $(PhO)_2P(O)N_3$[496,497].

f. From (azidoalkyl)phosphonic derivatives. The reaction between a (hydroxyalkyl)-phosphonic diester and hydrazoic acid under Mitsunobu conditions leads to the corresponding azidoalkyl phosphonate, which may be isolated[498] and reduced by hydrogenation, but their conversion into the (α-aminoalkyl)phosphonic ester can also be carried out *in situ* through initial reaction with triphenylphosphine at room temperature to give the phosphine imide; the latter is then cleaved under aqueous conditions (Scheme 40)[499]. The replacement of OH by N_3 in the Mitsunobu reaction occurs with inversion of configuration at $C_{(1)}$[500].



SCHEME 40

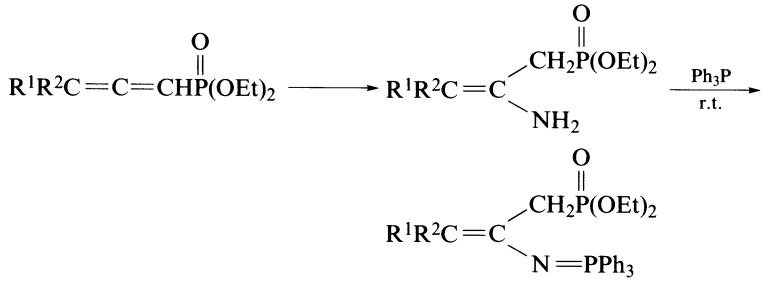
The potential for rearrangement plays an important role (Scheme 41) in the application of the Mitsunobu reaction to the secondary alcohols **309**. Under very mild conditions, the incoming azido group displaces the outgoing hydroxy function to give **310**. Additionally thermal rearrangement of the alcohols leads to the γ-hydroxy compounds **311**, which may be transformed, in the same way, into the azides **312**. Finally, and perhaps most usefully, the rearrangement of the α-azido compounds **309** to their γ-isomers, **312**, is also initiated thermally[498]. In the presence of $[Pd(PPh_3)_4]$ (1-acetyloxy-2-alkenyl)-phosphonic or -phos-



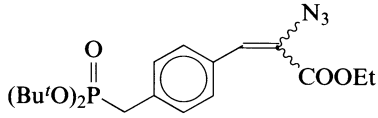
SCHEME 41

phinic esters undergo a reaction with NaN_3 at room temperature with the regioselective formation of the (3-azidoalk-1-enyl)-phosphonic or -phosphinic acids; the isolated yields are very high. Whilst substituents on phosphorus appear to have little influence on the reaction outcome, the nature of the organic ligand certainly does and, for instance, no reaction takes place with diethyl (1-acetyloxy-3-phenylprop-2-enyl)phosphonate[501].

In addition to the conversions of carboxy and ester groupings into the azido function, and the use of the Mitsunobu reaction, as exemplified in the preceding paragraphs, (1-azidoalkyl)phosphonates have been obtained directly from the carbanions (as the magnesium salts) from phosphinoylacetic esters through a reaction with *p*-toluenesulphonyl azide[502] and by the addition of azide to (alka-1,2-diene)phosphonic esters, N_3^- being provided by NaN_3 or tetramethylguanidium azide[503]; the migration of the carbon–carbon double bond (Scheme 42) is to be noted. The condensation between an aromatic aldehyde and ethyl azidoacetate under basic conditions affords the azido ester **313**, reducible to the saturated (aminoalkyl)phosphonic ester[504].

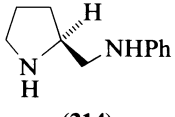


SCHEME 42

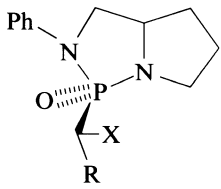


(313)

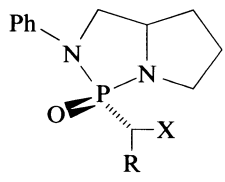
The classical reaction between a (haloalkyl)phosphonic diester and NaN_3, best carried out in a polar solvent, e.g dmf[505], has been developed into an asymmetric synthesis. The reaction between (chloromethyl)phosphonic dichloride and the chiral auxiliary (*S*)-(phenylaminomethyl)pyrrolidine (**314**) is followed by separation of the product 1,3,2-diazaphosph(V)olidines **315** (R = H; X = Cl) and **316** (R = H; X = Cl), obtained in yields of 36 and 45%. Alkylation (BuLi, RX) of the cyclic diamides and reaction between the products and NaN_3, to give **315** and **316** (R = alkyl; X = N_3), is then followed by acidoly-



(314)



(315)



(316)

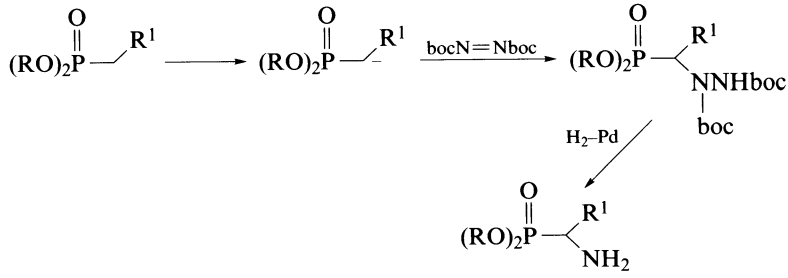
sis of the imide derived from the azide and Ph_3P. The last steps are fast becoming a standard procedure, at least as important, if not more so, than catalysed hydrogenation for the conversion of the azido group into the amino function in the absence of any other reduction requirements, and one which was also used in the final stages of the earlier sequences (Schemes 41 and 42). The reaction sequence is terminated by acidolytic removal of the diazaphospholidine ring and liberation of the (1-aminoalkyl)phosphonic acid[506].

g. From nitroalkylphosphonic derivatives. One of the principal uses of nitroalkyl phosphonic acids in synthesis lies in their catalysed [Ni or $Pd(OH)_2$] reduction to the corresponding (aminoalkyl)phosphonic acid[42,43,79,84,85], a procedure which has been adopted for the preparation of carbohydrate nuclei carrying both amino and phosphinoyl moieties[46,52,53]. Other (aminoalkyl)phosphonic derivatives are available through the similar reduction (Raney nickel[507,508] or Pd–C[509,510]) of (hydroxynitroalkyl)phosphonic acids, themselves readily available through aldol-type reactions (see Section IV. D.1).

Esters and amides of 2-(diethoxyphosphinoyl)-2-nitrosopropanoic acid (presumably in dimer form) are reduced by zinc–acetic acid to the corresponding 2-amino compound[511].

h. By direct amination. Conveniently included here, since a change of functionality is involved, but no change in the molecular carbon skeleton, is the process of direct amination of phosphorylated carbanions. This simple step has been observed with metal salts of trialkyl phosphonoacetates and chloramine (with appropriate hazard warnings)[512] but a much safer procedure uses *O*-diphenylphosphinoylhydroxylamine in thf at –75 °C, the diphenylphosphinic acid coproduct being easily removed under very mildly basic conditions[513,514].

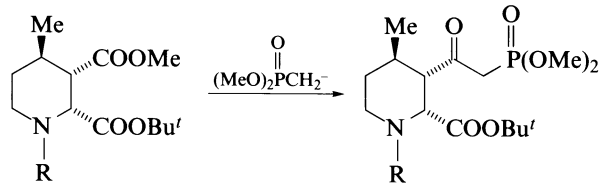
Indirect electrophilic amination is achievable when dialkyl phosphonate carbanions (Li counter ion) reacts with di-*tert*-butyl azodicarboxylate, and the α-hydrazino products (Scheme 43) are then subjected to catalytic hydrogenation which liberates the free amine[515].



SCHEME 43

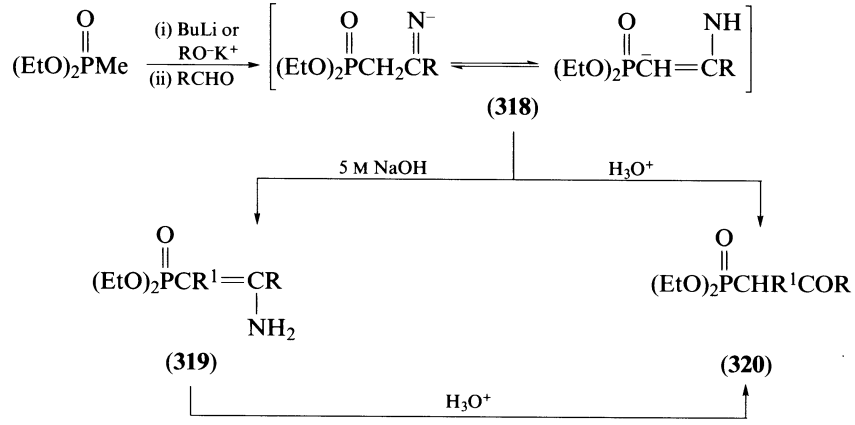
2. Through changes to the carbon skeleton

a. By acylation at carbon. The acylation of phosphoryl carbanions with a variety of reagents (acyl halides or esters) has already been encountered in the previous chapter in the synthesis of (oxoalkyl)phosphonic derivatives. The acylation of such carbanions with *N*-protected amino acid esters leads initially to *N*-protected dialkyl (3-amino-2-oxoalkyl)phosphonates, capable of deprotection or further modification[516]. The preparation of (1-oxo-2-phthalimidoalkyl)phosphonic diesters has already been referred to[189], and the acylation of carbanions by carboxylic esters in the piperidine and tetrahydropyridine series has been explored in the synthesis of competitive NMDA receptor antagonists, as in the preparation of **317**[517,518].



(317)

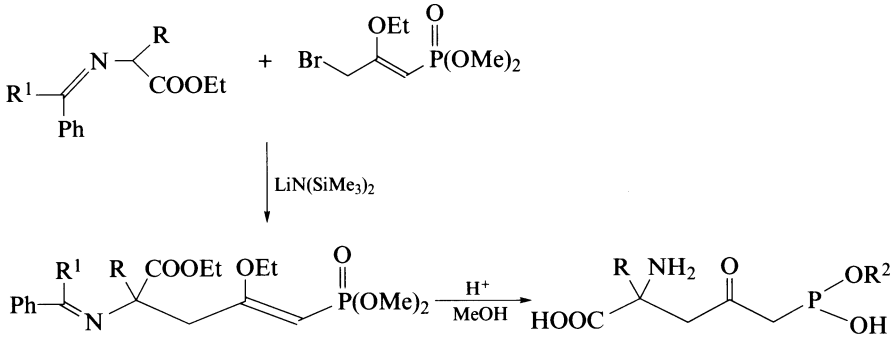
A related process consists initially in the reaction between diethyl methylphosphonate carbanion and a nitrile, RCN, to give the species **318**, and the alkylation (R = Me, $CH_2CH{=}CH_2$, CH_2Ph) of the latter. Work-up of the product under basic conditions leads to the enamines **319**. Work-up with acid conditions affords the (2-oxoalkyl)phosphonic diesters **320**; the latter were also obtained through acidolysis (3 M H_2SO_4) of the enamines **319**. A wide choice of 'alkylating species' is possible; alkyl halides, disulphides RSSR (R = Me or Ph), sulphenyl chlorides RSCl (R = Me or Ph), PhSeBr, $MeSO_2SMe$ and $PhSO_2Cl$ have all been used[519–521].



b. By alkylation at carbon. The modification to a carbon skeleton by alkylation is, from the point of view of synthesis of (aminoalkyl)phosphonic acids, much more important than acylation, and although alkylation of a dialkyl *N*-acyl (benzoyl, benzenesulphonyl, 2,2,2-trichloroethoxycarbonyl) (aminomethyl)phosphonate has been achieved, in an indirect manner, through initial bromination (nbs, radiation)[522–524] followed by reaction of the dialkyl (aminobromomethyl)phosphonate with either a Grignard reagent at –78 °C or with $R_2Cu(CN)Li_2$ in thf, at –78 °C[522], such methodology seems to be unnecessarily complex.

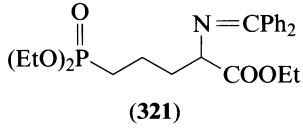
On the other hand, the direct alkylation of appropriate carbanions has been extensively investigated with particular regard to the possibility of enantiomeric preferment at the site of alkylation. In common with so many of the reactions described for the synthesis of functionalized phosphonic esters in which two important reactants come together, two approaches are possible in alkylation methodology.

In the first, little explored, approach, which is useful in the synthesis of compounds which possess additional functional groups, the phosphorus atom is contained within the alkylating species. The alkylation of an additionally functionalized azomethine is exemplified in Scheme 44 (R^1 = H or Ph; R = H or Me; R^2 = H or Me)[525]. The reaction between diethyl

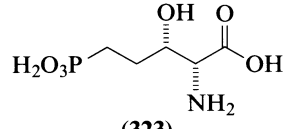


SCHEME 44

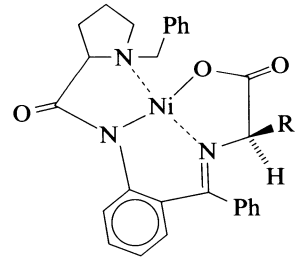
(3-bromopropyl)phosphonate and the Schiff base from ethyl glycinate and benzophenone gives the product **321**, from which racemic 2-amino-5-phosphonopentanoic acid may be obtained by the action of 6 M HCl[526]. The structure **322** [R = $CH(OH)CH_2CH_2PO_3Et_2$] of the alkylation product from **322** (R = H), the nickel(II) complex derived from glycine with (*S*)-2-*N*-(*N'*-benzoylprolyl)-2-aminobenzophenone and diethyl (3-bromo-2-hydroxypropyl)phosphonate, has been confirmed by X-ray crystallography; breakdown of the alkylated complex under the influence of 2 M HCl in MeOH leads to (2*S*, 3*S*)-2-amino-3-hydroxy-5-phosphonopentanoic acid (**323**)[527]. Significant diastereoselectivity (up to 90% d.e.) was observed during the synthesis of (*S*)-phosphinothricin, (*S*)-2-amino-3-phosphonopropanoic acid, (*S*)-2-amino-4-phosphonobutanoic acid and (*S*)-2-amino-5-phosphonopentanoic acid, the chiral reagent being largely recovered[528].



(**321**)

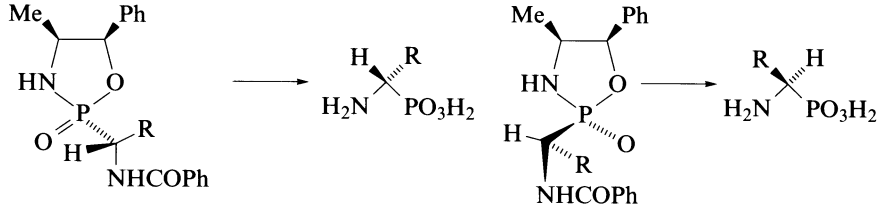


(**323**)



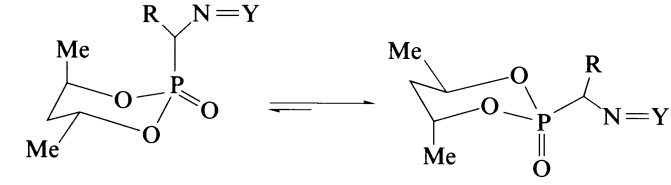
(**322**)

In the second approach, widely used in a variety of syntheses which lead to an enantiomeric preferment, the reaction template already contains the phosphorus, and is designed to control the stereochemical course of the ensuing alkylation through either the chirality of the phosphorus centre, or by other structural means. In a simple example of the first, the chiral intermediates **324** (R = H) and **325** (R = H) from [(benzoylamino)-methyl]phosphonic dichloride and (–)-ephedrine are alkylated (BuLi, RX, –70 °C) to give the (*S*)- or (*R*)-alkyl derivatives which, after separation, are completely degraded by acidolysis to the (*S*)- or (*R*)-(1-aminoalkyl)phosphonic acids; the optical purities of (*R*)- and (*S*)-(1-aminoethyl)- and (1-amino-2-phenyethyl)-phosphonic acids were in the range 83–98% e.e., being higher for the enantiomers of the former acid[529].

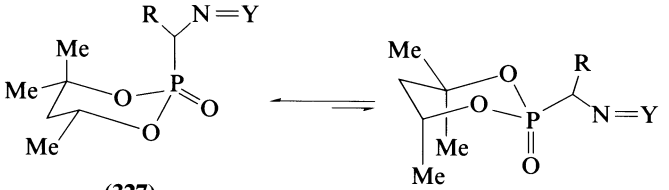


(324) (325)

An attempt to control chirality at the incipient asymmetric carbon atom by conformational means has been described by Bartlett and McLaren[530]. Through a careful choice of ring substituents, 1,3,2-dioxaphosph(V)orinanes were constructed in which the 2-aminomethyl substituent (R = H; Y = H, cbz, CPh_2, CHPh or CH_2) is preferentially equatorial (**326**) or axial (**327**). When alkylated (BuLi, MeI, $PhCH_2Br$), the two series induce asymmetrically in the opposite sense; unfortunately, neither substrate series exhibits a high diastereoisomeric selectivity (≤50%).

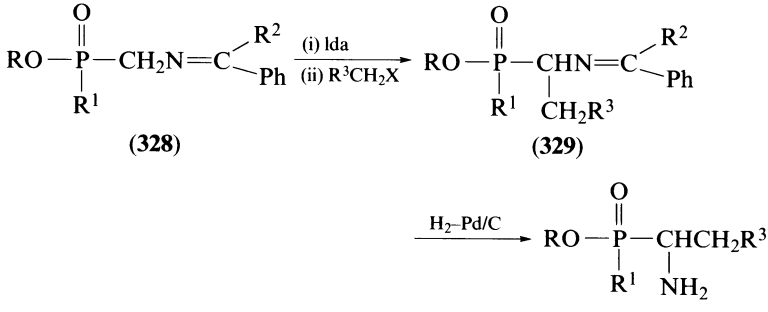


(326)



(327)

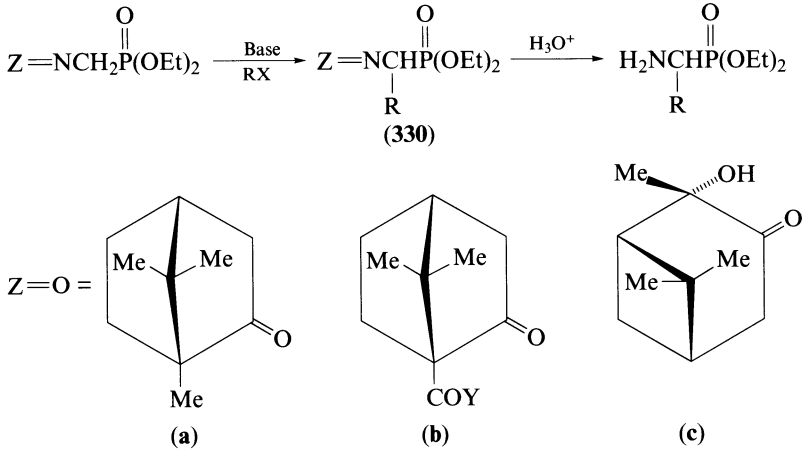
More commonly, a Schiff base from phosphonoglycine (**328**; R^1 = OR, R^2 = H or Ph)[477] or from an analogous phosphinic derivative, e.g. **328** [R^1 = $CH(OEt)_2$, R^2 = Ph][531] is alkylated conventionally, (although phase-transfer conditions may also be used[532]), and the product, **329**, is then hydrogenolysed (R^1 = H or Ph) or acidolysed (10% HCl) (R^1 = Ph) to give the aminoalkylphosphonic diester. When the alkylating species is a dihaloalkane, the



(328) (329)

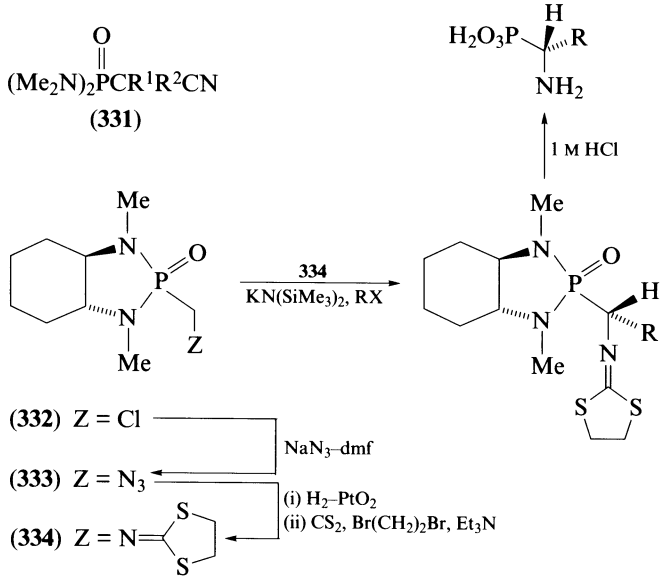
initial alkylation step may be followed by a second such step resulting in the formation of a (1-amino-1-cycloalkyl)phosphonic diester[533]. Genet *et al.*[534] have described [Pd(dppe)]-catalysed allylic alkylations of the Schiff bases.

The use of Schiff bases obtained from phosphonoglycine and several oxo derivatives based on the [2.2.1]bicycloheptane and [3.1.1]bicycloheptane systems as chiral auxiliaries has been an important advance in the methodology. In principle, the bicyclic ketone is converted into a Schiff base through its reaction with diethyl (aminomethyl)phosphonate and, after anion formation with an appropriate base (e.g. BuLi or lda), the Schiff base anion is alkylated with an alkyl halide, RX; acidolysis then cleaves the C=N bond to release the (1-aminoalkyl)phosphonic diethyl ester. Diethyl (1*R*,4*S*)-[(1,7,7-trimethylbicyclo[2.2.1]hept-2-ylideneamino)methyl]phosphonate, from (+)-camphor, gives products **330a** (R = Me, Et or Pr^i) of low to moderate optical purity, the first of which provided (*S*)-(1-aminoethyl)phosphonic acid of 72% optical purity[535]. The alkylation products **330b** from (1*S*,4*R*)-(+)-ketopinic acid [Y = (i) OH], also of (*S*) configuration at $C_{(1)}$, had optical purities of 15, 62, 93 and 92% for R = Me, Et, CH_2Ph and $CH_2CH{=}CH_2$[536]. This dependence of the optical purity of both the alkylated Schiff base and of the released (1*S*)-(1-aminoalkyl)phosphonic acid on the size of the alkylating group R is also found when, in **330b**, Y = (ii) NHPr^i or (iii) NHC_6H_4OH-2. The change in the group Y from (i) to (ii) to (iii) produces very little improvement in the optical purity of product amino acids when R = $CH_2CH{=}CH_2$ or $PhCH_2$ (for which it was already extremely good), but the improvement is marked for R = Et and even more so for R = Me[161]. The Schiff bases derived from (1*R*,2*R*,5*R*)-(+)- or (1*S*,2*S*,5*S*)-(−)-2-hydroxypinan-3-one are at least effective, if not more so, than those from camphor[537], with the diastereoisomeric excesses of the alkylated products **330c** being generally 70–>95% [R = Me, Et, $CH_2CH{=}CH_2$, $CH_2C{=}CH$, $(CH_2)_nI$ (n = 4 or 5)], an exception being when R = $PhCH_2$, for which the diastereoisomeric excess was only 33%. The use of $I(CH_2)_4I$ allowed the synthesis of 2-piperidinephosphonic acid (phosphonohomoproline)[537], and alkylation of the Schiff base by 2-(tetrahydropyranyloxy)ethyl iodide led to phosphonohomoserine[538].



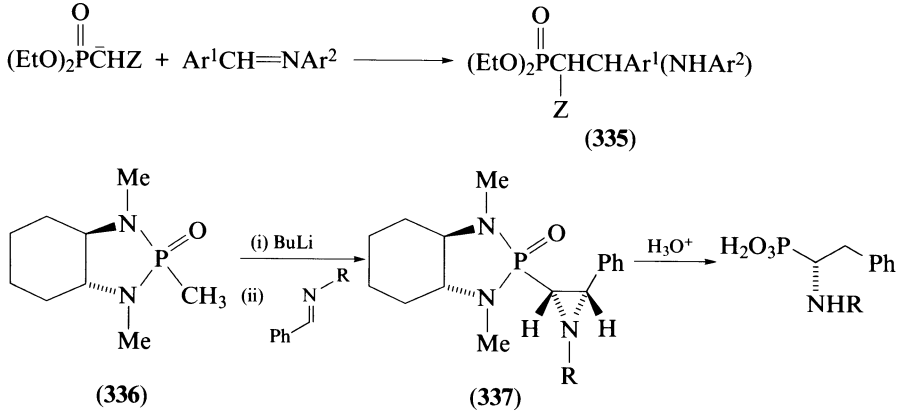
The anion from (cyanomethyl)phosphonic bis(dimethylamide) (**331**; $R^1 = R^2 = H$) may be mono- or di-alkylated, and the products sequentially reduced with H_2–Raney nickel and hydrolysed under acidic conditions to give (2-aminoethyl)phosphonic acid or its $C_{(1)}$ alkylated derivatives[539]. In the search for simple procedures which might lead to better asymmetric induction and so provide products of reasonable optical purity, the

(chloromethyl)phosphonic diamide **332**, obtained from $ClCH_2P(O)Cl_2$ and (1*R*,2*R*)-1,2-bis(methylamino)cyclohexane, is transformed via **333** into **334** (Scheme 45), which, as its carbanion, is then alkylated with RX; mild acidolysis of the products yields the (1*R*)-(1-aminoalkyl)phosphonic acids, said to be of high optical purity[540].



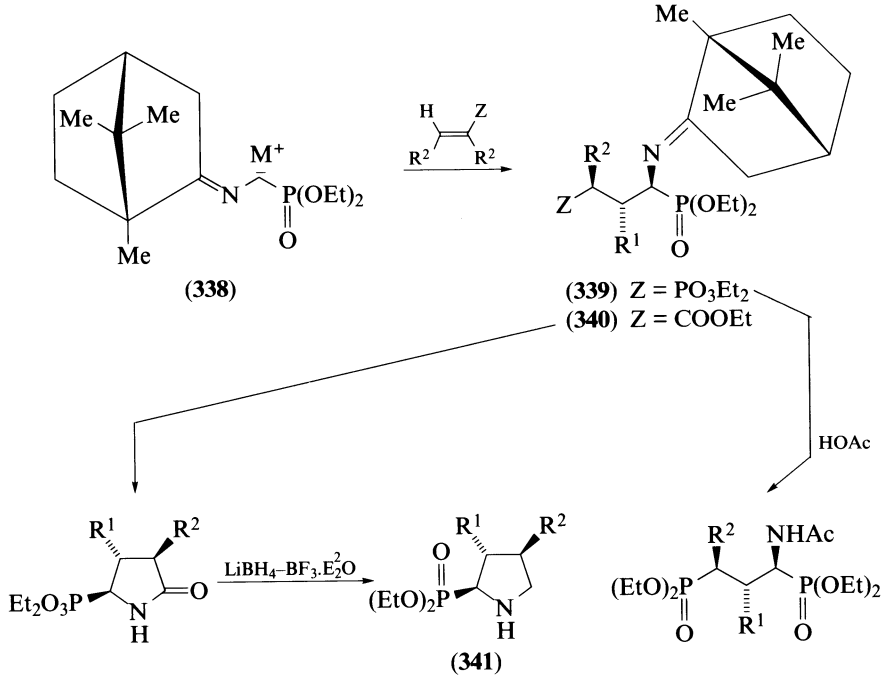
SCHEME 45

The alkylation, with azomethines, of the dialkyl alkylphosphonates $(RO)_2P(O)CH_2Z$ (Z = Ar[541,542], CN or COOEt[543]), either as their carbanions or in the presence of $AlCl_3$[543], gives **335**. The comparable reaction between the carbanion from the (*R*,*R*)-1,3,2-diazaphosph(V)olidine **336** and the benzylideneamines (R = Ar or *p*-tos) yields the 2-(2-aziridinyl)-1,3,2-diazaphosph(V)olidines **337** with a diastereoselectivity of 85:15 for R = Ph or 4-methoxyphenyl, and even 99:1 for R = *p*-toluenesulphonyl, in favour of the (2*R*,3*S*) products **337**, the structures of which were confirmed by X-ray crystallography.



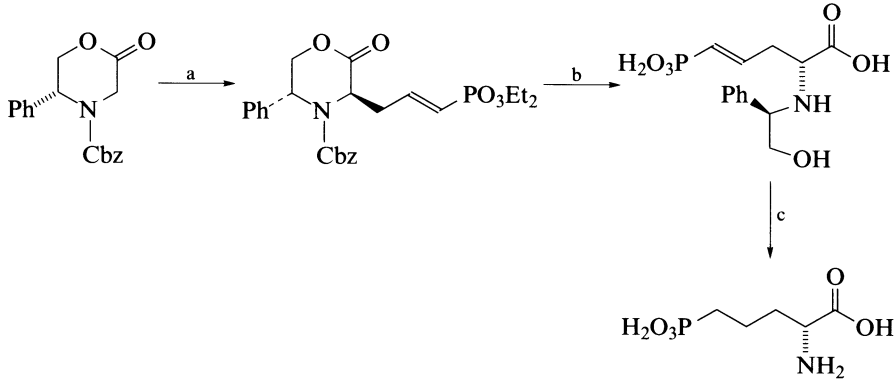
Hydrogenation of **337** (R = 4-methoxyphenyl) opened the aziridine ring without loss of the *N*-aryl group; the diazaphospholidine ring was then removeable with HCl[544]. However, the reaction between the same or analogous Schiff bases and esters of phenylmethyl-(propyl)phosphinic acid is more complex. Only in the case of benzylideneaniline does a reaction (in $NaNH_2$–Et_2O) yield an adduct of type **335**; other Schiff bases fail to react (in this manner) in this system. Reactions carried out with 0.5 M $NaNH_2$ in diethyl ether at –33 °C give yields generally higher, in some cases much higher, than for the same reactions in ether at 10 °C[545].

The anion **338** (as the chlorozincate, copper or magnesium complex, but not as the lithium salt) of the Schiff base derived from phosphonoglycine and (+)-camphor undergoes Michael additions to diethyl ethenylphosphonate or its homologues, and to methyl propenoate or its derivatives, to give **339** and **340**; when treated with aqueous acetic acid, the first of these types yields the enantiomerically pure diphosphono analogue of glutamic acid, whilst the second can be made to furnish Pro^P (**341**; $R^1 = R^2 = H$), the intermediate being obtainable with > 95% e.e.[162,537,546]. It is interesting that, with regard to a Michael addition of the reagent derived from ethyl phosphonoglycine and (1*S*,2*S*,5*S*)-2-hydroxypinan-2-one (**330c**), it is evidently necessary to prepare the anion from $KOBu^t$ and not from NaH or lda, a feature which suggests an important role for the metal counter ion; (*S*)-(+)-phosphinothricin and also its dextrorotatory phosphonic acid analogue have been successfully prepared in this way[547].



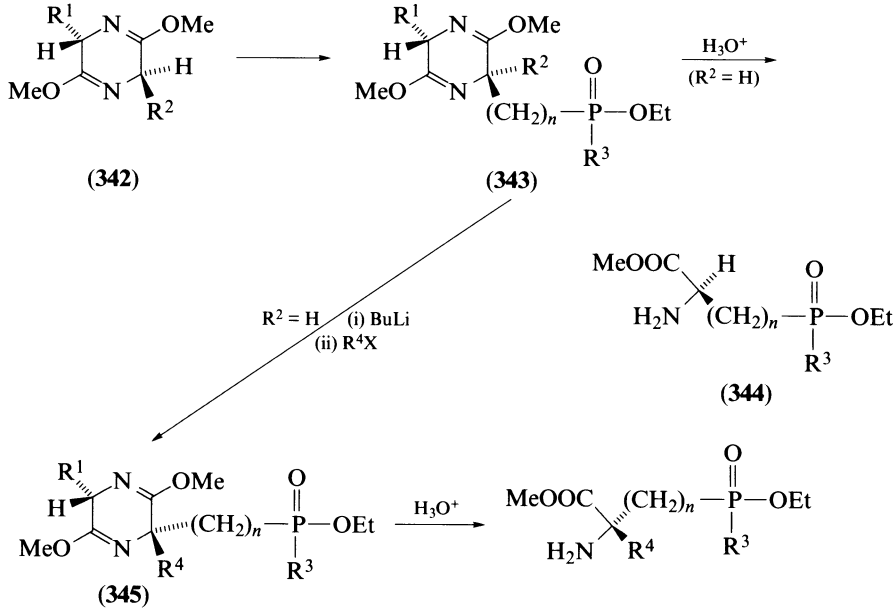
An enantioselective synthesis of (*R*)-(–)-2-amino-5-phosphonopentanoic acid is indicated in Scheme 46 and involves the alkylation of an *N*-protected 2-oxo-5-phenylmorpholine derivative[548]. The idea of stereochemical control in the alkylation of these and similar ring compounds seems to have stemmed from the asymmetric alkylation of the systems **342**

($R^1 = Pr^i$; $R^2 = H$) (Scheme 47) (with BuLi as proton abstractor) with an appropriate diethyl (haloalkyl)phosphonate when **343** ($n = 2$, 3 or 4; $R^3 = OEt$) are formed with d.e.s of 96, 80 and 86%, respectively; cleavage of these products with acid led to the amino esters **344**. It is also possible to alkylate the intermediate **343** further to give **345**, with a preference for the 2*S* configuration; d.e.s of 80, 94 and 94% were recorded for R^4 = benzyl,prop-2-enyl,



Reagents: (a) i, $NaN(SiMe_3)_2$, thf–dme, –75 °C; ii, Br⌒⌒PO_3Et_2, thf–dme, –75 °C. (b) i, Me_3SiBr, CH_2Cl_2, r.t; ii, 6 M HCl. (c) H_2/Pd–C

SCHEME 46



SCHEME 47

and prop-2-ynyl, respectively[549]. The same procedure has been used in the syntheses of (2*S*)-phosphinothricin (93.5% e.e.)[550] and (2*S*)-2-amino-3-(4-hydroxy-3-phosphonophenyl)propanoic acid (3′-phosphono-L-tyrosine)[168], and also that of methyl [2-amino-3-(4-dimethoxyphosphinoyl)phenyl]propanoate, already referred to in connection with peptide formation and the estimation of enantiomeric purity[167].

D. Novel Aminoalkyl- and Related Phosphonic Acids

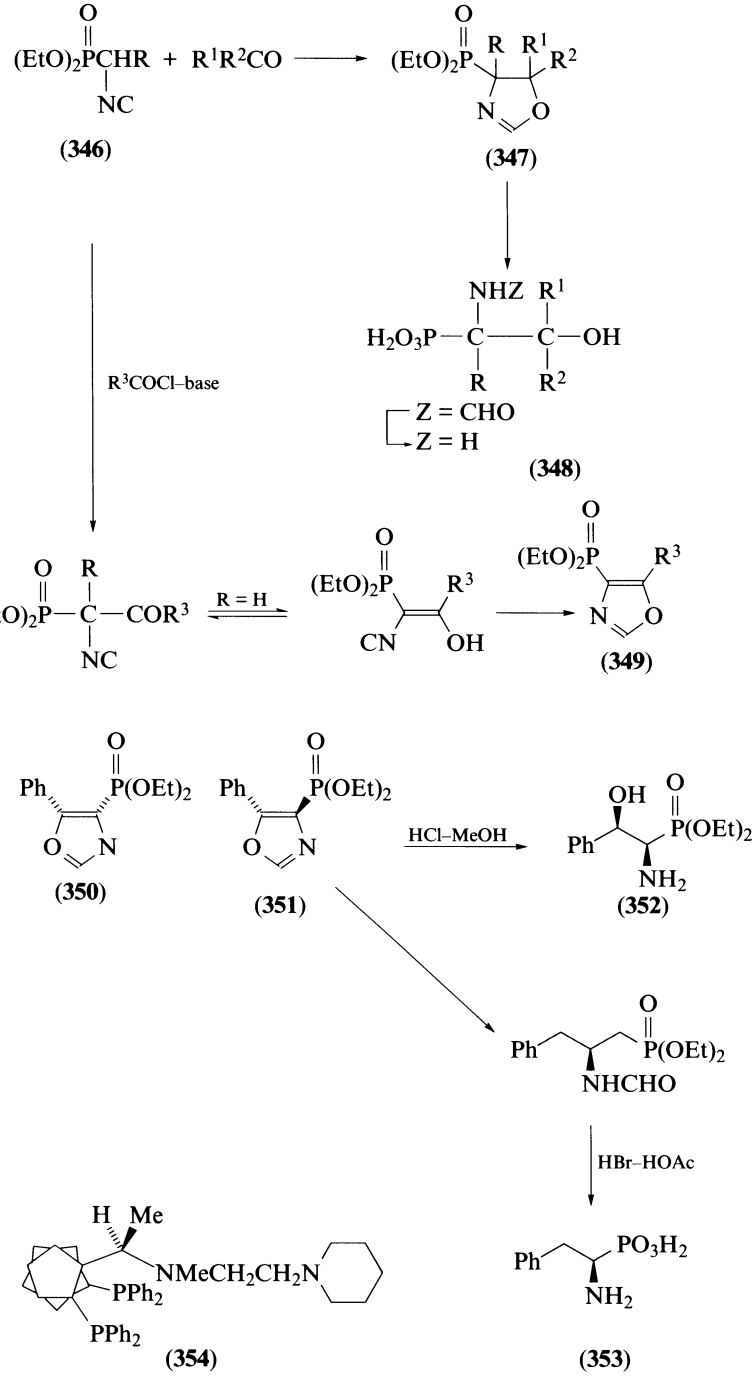
Two groups of compounds, it was felt, warranted a separate survey in the light of their novelty and their relation to several substances which occur naturally. These groups are, first, the amino-hydroxy difunctionalized acids, and second, derivatives, both *O*- and *N*-substituted, of hydroxylamine.

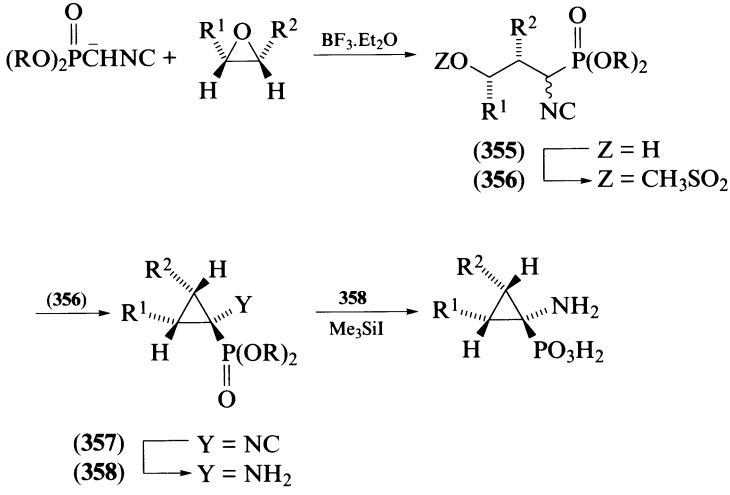
1. (Aminohydroxyalkyl)phosphonic acids

To the several examples of these acids already encountered in the syntheses of aminoalkyl phosphonic acids discussed thus far, and which include (i) aldol formation of (hydroxynitroalkyl)phosphonic acids and their reduction to aminohydroxyalkyl acids[46,52,53,87–91,94,507–509]; (ii) the reduction of *N*-protected-aminooxoalkylphosphonic acids, followed by deprotection[189,510]; (iii) the reduction of amino(phosphono)alkanoic acids or their esters; and (iv) alkylations with hydroxyalkyl halides[527], may be added the utilization of (isocyanoalkyl)phosphonic derivatives. Dialkyl (1-isocyanoalkyl)phosphonates (**346**), obtainable from the [1-(formylamino)alkyl]phosphonic esters by means of successive reactions with $POCl_3$ and Et_3N, react with aldehydes or ketones with the formation of 4,5-dihydro-1,3-oxazoles (**347**); acidolysis of these yields ultimately the [(1-amino-2-hydroxy)alkyl]phosphonic acids (**348**) via their *N*-formyl derivatives[551]. It is interesting that the initial acylation of (isocyanomethyl)phosphonic diester (**346**; R = H) proceeds, through enolization, to the phosphorylated 1,3-oxazole **349**[552]. Moreover, the reaction between **346** (R = H) and benzaldehyde in the presence of $[(CyNC)_2Au]BF_4$ gives the stereoisomeric oxazoles **350** and **351** in the ratio 11:89, which may be increased to 2:98 when the reaction is carried out with admixed bis(diphenylphosphino)ferrocenes[553,554]. Thus, in the presence of (*R*)–(*S*)–**354**, the same reactants furnish (4*R*,5*R*)–**351** which, with HCl in MeOH, gives **352**, readily dealkylated to (1*R*,2*R*)-(1-amino-2-hydroxy-2-phenylethyl)phosphonic acid; on the other hand, hydrogenolysis of **351** leads to the (1*R*)-(1-amino-2-phenylethyl)phosphonic acid **353**[554].

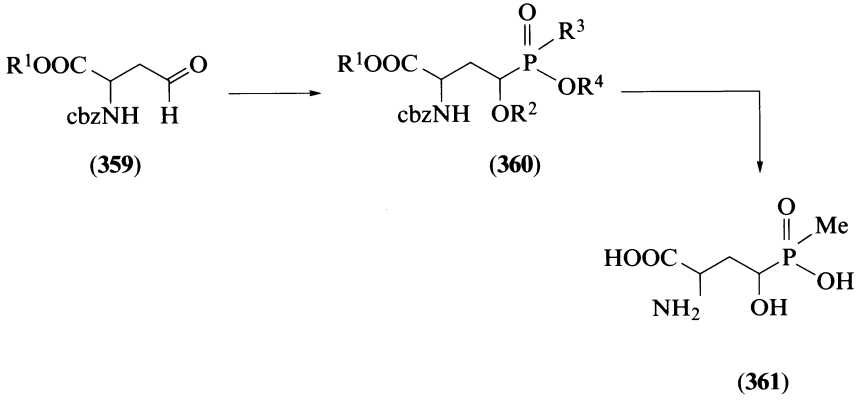
A synthesis of novel (1-amino-1-cyclopropyl)phosphonic acids is initiated by the ring opening of oxiranes by dialkyl (isocyanomethyl)phosphonate carbanions (Scheme 48). The product from the ring opening step is the (3-hydroxy-1-isocyanoalkyl)phosphonic diester **355**, which, through its *O*-mesylate **356**, is convertible into the cyclopropyl isocyanide **357**; this, with HCl in MeOH, yields the racemic (1-amino-1-cyclopropyl)-phosphonic ester **358**[555].

The reactions between appropriately *N*-protected aminoalkanals and dialkyl hydrogenphosphonates or related compounds, further exemplify the Abramov process (Chapter 3), and constitute a facile approach to (aminohydroxyalkyl)phosphonic acid derivatives. Such reactions have been performed with oxophthalimidoalkanes[556] or other *N*-acylated ketones[557] and, after manipulation of the intermediates thus obtained, result in the formation of (1-hydroxy-2-aminoalkyl)phosphonic acids. Two groups of workers have employed the sequence outlined in Scheme 49 to prepare both phosphinothricin itself and also a hydroxy derivative thereof. For the latter[558], the aldehyde **359** ($R^1 = PhCH_2$) reacted with ethyl methylphosphinate and btsa under appropriate catalysis to give **360** ($R^1 = PhCH_2$, $R^2 = SiMe_3$, $R^3 = Me$, $R^4 = Et$); separation of the diastereoisomers of this, and full


(EtO)2PCHR + R1R2CO
NC
(346)
(347)
NHZ R1
H2O3P—C—C—OH
R R2
Z = CHO
Z = H
(348)
R3COCl–base
R = H
(EtO)2P—C—COR3
NC
CN OH
(349)
Ph P(OEt)2
(350)
(351)
HCl–MeOH
OH
Ph
NH2
(352)
NHCHO
HBr–HOAc
PO3H2
NH2
(353)
H Me
NMeCH2CH2N
PPh2
PPh2
(354)



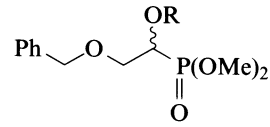
SCHEME 48



SCHEME 49

deprotection, yielded the diastereoisomers of [2-amino-4-hydroxy-4-(hydroxymethylphosphinoyl)] butanoic acid (**361**) (3-hydroxyphosphinothricin). The second group started with (*S*)–**359** (R^1 = Bu^t) and showed that it reacted with a dialkyl trimethylsilyl phosphite to give a 1:1 mixture of the diastereoisomers of **360** (R^1 = Bu^t, R^2 = $SiMe_3$, R^3 = OR^4) from which, unfortunately, methanolysis failed to remove the silyloxy group, but this could be removed in 95% acetic acid at ambient temperature; here, the diastereoisomer mixture was not separated but was dehydroxylated by a well established route which involved Bu_3SnH reduction of the *O*-imidazolylthiocarbonyl derivative[559]. Remarkable diastereoselectivity has been demonstrated in the reaction between 2-*N*-boc-amino-3-cyclohexylpropanal and dimethyl hydrogenphosphonate under base catalysis, and in which the proportions of 2*S* and 2*R* products can reach 12:1[560,561]; the Abramov reaction in which nitrogen is protected as the *N*,*N*-dibenzyl derivative is also diastereoselective, as is the formation of the *O*-silyl ether when the aldehyde is acted on by $(EtO)_2POSiMe_2Bu^t$[562].

(2-Amino-1-hydroxyethyl)phosphonic acid occurs in the plasma membrane of *Acanthamoeba castellani* and the 2*R* isomer is formed, in that organism, by the hydroxylation of (2-aminoethyl)phosphonic acid[563]. This biosynthesis step *in vitro* has been studied by Hammerschmidt[110–113], who synthesized various chiral deuterium–labelled derivatives of both compounds using the isotopically labelled 2-benzyloxyethanal in Abramov reactions to obtain, initially, the dimethyl (2-benzyloxy-1-hydroxyethyl)phosphonate (**362**). This ester was resolved through the diastereoisomeric carbamates **363**; the separated carbamates were sequentially de-1-*O*-protected, silylated at the α-HO group, debenzylated and, by means of the Mitsunobu reaction, converted into dimethyl [2-azido-1-(*tert*-butyldimethylsilyloxy)ethyl]phosphonates. Subsequently, standard reactions were used to transform the latter into the diastereoisomeric, isotopically labelled (2-amino-1-hydroxyethyl)phosphonic acid.

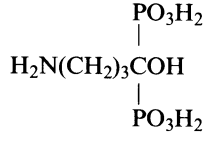


(**362**) R = H

(**363**) R = CONH

The ring opening of 2-R-oxiranylphosphonic diesters (R = H or Me) by primary amines has been described as being regiospecific[564] but, in studies on the biosynthesis of fosfomycin (2-methyl-3-oxiranylphosphonic acid) in cultures of *Streptomyces fradia*, Hammerschmidt et al.[565] treated the isolated fosfomycin samples with ammonia in order to analyse the distribution of the isotope labels; aqueous ammonolysis of (2*R*,3*S*)-(2-methyl-3-oxiranyl)phosphonic acid was found to yield 58% of (1*R*,2*R*)-(–)-(-2-amino-1-hydroxypropyl)phosphonic acid and 23% of (1*S*,2*S*)-(+)-(1-amino-2-hydroxypropyl)-phosphonic acid and so, in this case, the ring opening is far from regiospecific. Stereoisomers of (2*S*)-(2-amino-1-hydroxypropyl)phosphonic acid were obtained through the reaction between dimethyl trimethylsilyl phosphite and *N*-boc-(*S*)-alaninal[565].

Mention might be made of a useful synthesis which is based on the Abramov-type reaction between a hydrogenphosphonate and a dialkyl (1-oxoalkyl)phosphonate, formed *in situ*, to produce tetramethyl (1-hydroxy-4-phthalimido)butane-1,1-bisphosphonate, readily deprotected to give the free amino phosphonic acid **364**[566].



(**364**)

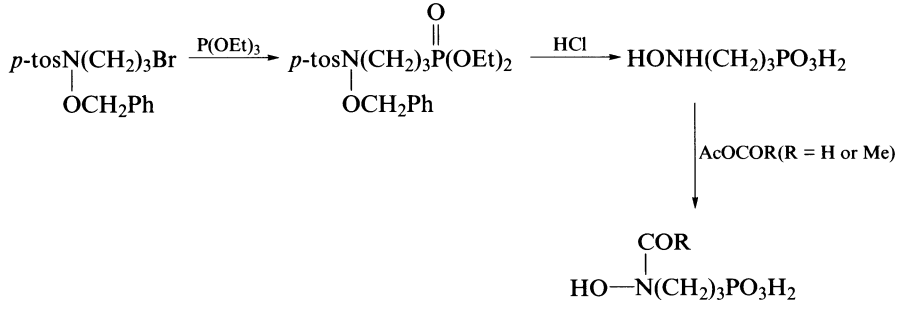
The hydroxylation of diphenyl (1-aminopent-4-enyl)phosphonate, protected as the *N*-cbz derivative yields diphenyl (1-amino-4,5-dihydroxypentyl)phosphonate[567].

It might also be noted that, coupled with the facile formation of an [amino(1-hydroxy)alkyl]phosphonic ester, there exists a tested method for the dehydroxylation of such a system; this consists in acylation [PhOC(S)Cl, R_3N] at OH in the *N*-protected compound, followed by de-*O*-acylation brought about with $(Me_3Si)_3SiH$ in the presence of aibn[568].

2. *[(N-Hydroxyamino)]alkyl phosphonic acids*

These unusual *N*-substituted compounds have been isolated, as derivatives, from natural sources and it is therefore not surprising that an interest has developed with regard to their synthesis and biological role.

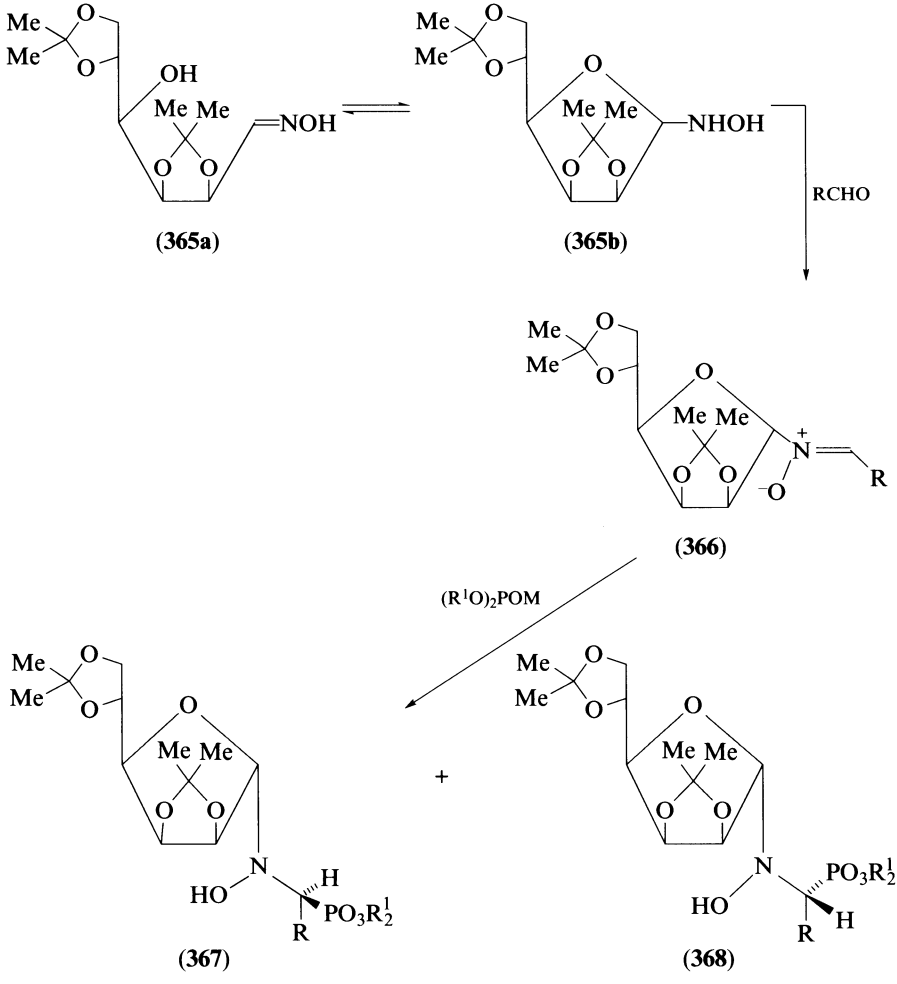
[3-(Formylhydroxyamino)propyl]phosphonic acid (fosmidomycin) (**108**) and the analogous [3-(formylhydroxyamino)prop-1-enyl]phosphonic acid have been isolated from *Streptomyces lavendulae*; in addition, [3-(acetylhydroxyamino)-2-hydroxypropyl]phosphonic acid has been isolated from *Streptomyces rubellomurinus indigo ferris*. All three compounds have antibiotic properties, and their synthesis can be relatively simple, as illustrated in Scheme 50[569]. Another simple procedure which has been developed for the preparation of [1-(hydroxyamino)alkyl]phosphonic acids consists in the reduction of the oximes of (1-oxoalkyl)phosphonic diesters with BH_3–pyridine; yields of the crystalline acids fall within the range 30–90%[570]. *O*-Benzyloximes of (1-oxoalkyl)phosphonic diesters are reduced by Et_3SnH in trifluoroacetic acid[571] or by BH_3–Et_3N[572] to the [1-(benzyloxyamino)alkyl]phosphonic esters, and the debenzylation of such compounds may be achieved with boron tris(trifluoroacetate) or by transfer hydrogenation with $HCOONH_4$ with Pd–C in methanol[573]. Additionally, (*N*-alkyl-*N*-hydroxyaminoalkyl)phosphonic esters are obtained from mixtures of carbonyl compound, dialkyl hydrogenphosphonate and *N*-alkylhydroxylamine[574]. Moderate to good yields of [1-(benzyloxyamino)alkyl]-phosphinic acids are obtainable from *O*-benzyloximes in combination with dichlorophosphines in acetic acid at ambient temperature[575].



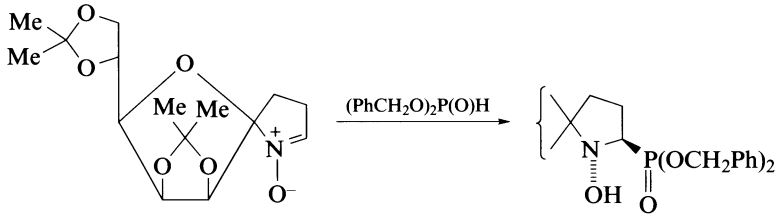
SCHEME 50

Several detailed investigations have been concerned with the potential of the carbohydrate **365** as a chiral template for the synthesis, initially, of *N*-hydroxy products, but ultimately, of aminoalkylphosphonic acids. The oxime **365a** and **b** reacts with the aldehydes RCHO to give the 2-R-(2,3:5,6-di-*O*-isopropylidene)-α-D-mannofuranosylmethanimine *N*-oxides **366**, the group R being determined by the requirements for the target aminophosphonic acid[159]. The nitrones, of *Z* geometry, as evidenced by X-ray crystallography, react with lithium dialkyl phosphites (dimethyl, diethyl, diisopropyl, di-*tert*-butyl or dibenzyl) at –60 °C in CH_2Cl_2 (the use of thf is beneficial in that it yields a higher diastereoisomeric excess in the products) to give the major adducts **367**, isolable by crystallisation, together with the minor adducts **368**, which can be purified, if required, by HPLC. The addition of a lithium dialkyl phosphite to **366** (R = $PhCH_2OCH_2$) under the same conditions yields the corresponding diastereoisomers in high yield with the major product in diastereoisomeric excess by 78–92%. The chiral template is removed with HCl in MeOH and the benzyl group by hydrogenolysis. The diastereoselectivity is even greater (93%) when R^1 = Bu^t, but in order to achieve such high values it is necessary to make a careful choice of the phosphite

counter metal ion; potassium dialkyl phosphites fail to produce such high diastereoselectivities and, indeed, in some cases, for instance when R = Pr^iCH_2, the potassium salts fail completely to react. It is therefore possible to prepare, according to the reactions in Scheme 51, both the (*R*)-(−)- and (*S*)-(+)-(aminoalkyl)phosphonic acids with small alkyl groups, e.g. Ala^P (R = Me) and Val^P (R = Pr^i), in addition to Ser^P (R = CH_2OH), in moderate chemical yields but with high optical purity. In addition, through a careful choice of experimental procedure it is possible to isolate the optically active *N*-hydroxy derivatives of (aminoalkyl)phosphonic acids. The addition of lithium dibenzyl phosphite to the spirocyclic nitrone **369** affords the adduct **370** as a single product, and in greater yield than those obtained with the acyclic nitrones. The structure of **370** has been shown, by X-ray crystallography, to have the P=O group arranged *trans* to the ring oxygen atom and to the *N*-OH group[576]



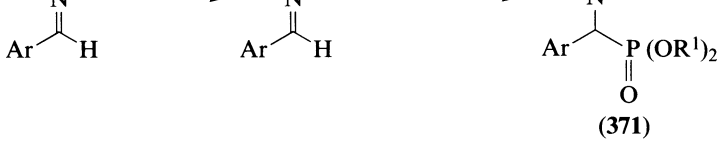
SCHEME 51



(369) **(370)**

No reactions occur between dialkyl phosphite salts and the *N*-glycosyl-*C*-arylnitrones **366** (R^1 = Ph or substituted phenyl)[145]. On the other hand, reactions with tris(trimethylsilyl) phosphite do take place in the presence of a Lewis acid ($ZnCl_2$, $HClO_4$) and proceed smoothly. Some unusual results are to be observed, particularly in relation to the nature of the catalyst; otherwise, the general course of the present reaction is similar to that found for reactions of the nitrones **366** with dialkyl phosphite anions. Thus, the reaction between **366** (R = Ph) and tris(trimethylsilyl) phosphite in the presence of 0.14 equiv. of $HClO_4$ at –50 to 0 °C proceeds via the *N*-trimethylsilyloxy bis(trimethylsilyl) ester of **367/368** (R^1 = $SiMe_3$) which, without isolation, is hydrolysed by 1 M HCl, to give the crystalline (*R*)-(+)-**367** (R = Ph, R^1 = H) the optical purity of which can be raised by recrystallization to 94.8%; when hydrogenolysed, this product gives (*R*)-(+)-phenylphosphonoglycine, in 91% yield and of 87% optical purity; the latter, too, can be raised (to 100%) by recrystallization. The aminophosphonic acid with opposite configuration was obtained when the catalyst was $ZnCl_2$ (0.01 equiv.). Similarly, the $HClO_4$-catalysed addition of the phosphite triester to **366** (R = Pr^i) afforded 77% of (*R*)-(+)-*N*-hydroxyVal^P which was hydrogenolysed to give (*R*)-(–)-Val^P of 95.4% e.e., which could be raised to 100% through recrystallization. Catalysis by $ZnCl_2$ (0,01 equiv.) provided (*S*)-(+)-*N*-hydroxyVal^P of 43.8% e.e. The same procedure was also used to make Ser^P and Meth^P. However, the $HClO_4$-catalysed reaction of the silyl phosphite triester to the nitrone **366** (R = CH_2OCH_2Ph) led, with low selectivity, to the corresponding (*S*)-(+)-Ser^P with an optical purity of only 30% [contrast the previous cases when the (*R*)-aminophosphonic acid was obtained highly selectively]; the result obtained with trace amounts of $ZnCl_2$ was much more encouraging with 87% optical purity of product, but the presence of larger amounts of $ZnCl_2$ reduced the optical purity to almost zero. (*R*)-(–)-Meth^P (R = $MeSCH_2CH_2$) was obtained, using $[Zn(OTf)_2]$ (0.03 equiv.) as catalyst, in about 87% yield and of 76.8% e.e., a value which tended to decrease when attempts were made to raise the value by further crystallization. Also, in this last case, the use of $HClO_4$ or $ZnCl_2$ led to products with lower e.e.s.

The alkylation of *C*-arylnitrones affords oximinium salts which also undergo addition reactions with hydrogenphosphonates or hydrogenphosphinates; the products are *O*-alkylated derivatives of the hydroxyamino acids **371**[577,578]. Although fairly complex examples of such salts could be obtained by the alkylation of the nitrones **366**, much



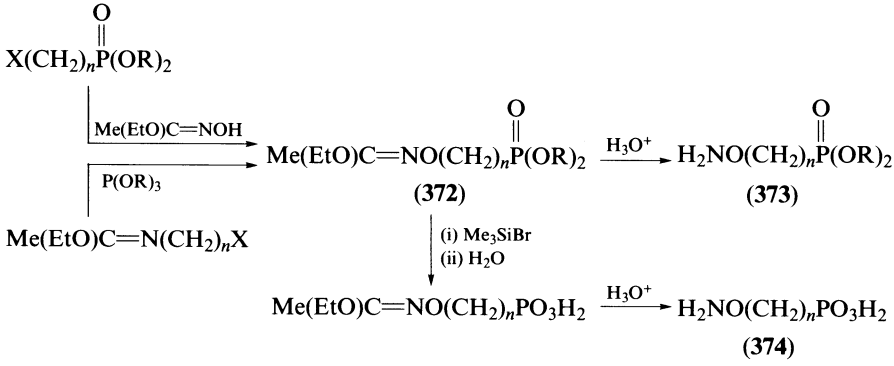
(371)

SCHEME 52

simpler examples have been employed for similar purposes (Scheme 52), although the results have not then been so spectacular. For example, when R = (*R*) or (*S*)-1-phenylethyl, the reaction of **371** (Ar = 4-methoxyphenyl) with diphenyl hydrogenphosphonate yields a mixture of diastereoisomeric products in the proportions 3:2[579]. A similar series of reactions with a series of cyclic oximinium salts provided the means for the synthesis of (1-amino-ω-hydroxy-1-methylalkyl)phosphonic acids.

3. *[(Aminooxy)]alkyl]phosphonic acids*

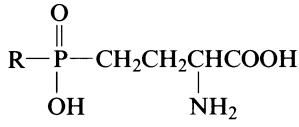
Although this group of compounds is, as yet, very poorly represented, at least three routes for their synthesis already exist. The reactions between acethydroximic acids and (haloalkyl)phosphonic diesters yield the *O*-derivatives **372**, from which selective work-up steps (Scheme 53) lead to the esters **373** or to the free [(aminooxy)alkyl]phosphonic acids **374**[580]. A less conventional approach consists in the reaction between a (1-hydroxyalkyl)-phosphonic[581] or -phosphinic[582] diester with *N*-hydroxyphthalimide in the presence of diethyl azodicarboxylate and Ph_3P under Mitsunobu conditions; the resultant [1-(phthal-imidooxy)alkyl] acid diesters lose the phthalimido group on hydrazinolysis, and a final aci-dolysis provides the [1-(aminooxy)alkyl]-phosphonic or -phosphinic acids.



SCHEME 53

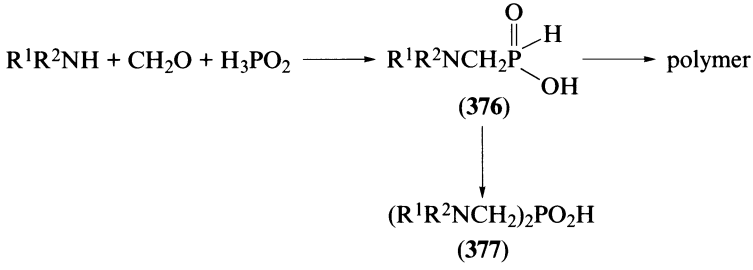
E. (Aminoalkyl)phosphonous Acids [(Aminoalkyl)phosphinic Acids]

This chapter is not concerned with the synthesis or properties of acids of tervalent phosphorus, except in so far that they might impinge on the synthesis of the analogues of quinquevalent phosphorus. The earlier sections in this chapter have included many instances of the reactions of alkyl phosphinates, (RO)R′P(O)H, including additions to compounds which possess C=N bonds[133,278,279,283,290,296–298,302,313,319,325–327,333], and also to alkenes[423]. Structurally, the alkyl phosphinates, thus met with, are the more stable phosphorus(V) tautomers of the monoesters of phosphonous acids, R′P(OH)(OR). Whilst a discussion of the chemistry of (aminoalkyl)phosphonous acids might therefore seem out of place, it has to be said that they are of importance, not only because of their novelty, but also because, structurally, they are based on tetracoordinate phosphorus and, moreover, they are valuable intermediates in several routes which lead to the phosphinic acids, $RR^1P(O)OH$, which possess amino functionalization. Added to these important considerations is their natural occurrence, thus, the acid **375** (R = H), like the phosphinic acid **375** (R = Me), is produced by *Streptomyces hygroscopicus*, and both provide phosphorus acid-based peptides in the same organism[583].



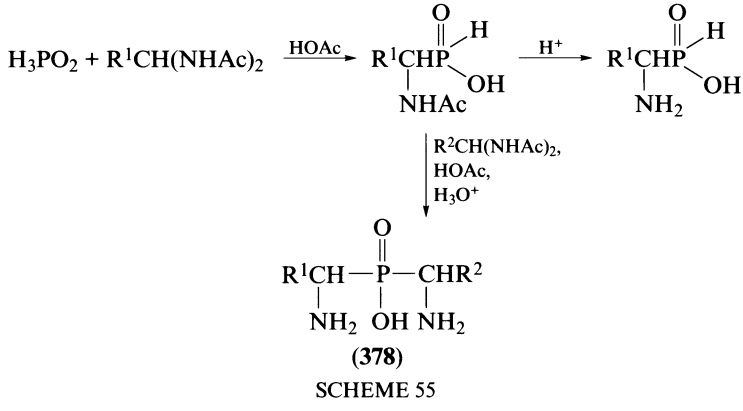
(375)

Many syntheses of (aminoalkyl)phosphonic derivatives have been listed which rely on the participation of phosphorous acid, H_3PO_3; this, like its diesters, exists in the quinquevalent phosphonic acid structure, $(HO)_2P(O)H$. Such reactions include Mannich-type aminomethylations[365–375,379,407,408]. Similar types of reactions with the involvement of hypophosphorous acid and primary amines lead to (aminomethyl)phosphinic acids (Scheme 54) ($R^1 = H$), during which the formation of **376** ($R^1 = H$) undoubtedly occurs initially. However, such products cannot be isolated, and views differ as to the relative importance of the subsequent formation of polymers and that of the bis(aminoalkyl)phosphinic acids (**377**; $R^1 = H$)[584,585], but the latter type of acid is available through reactions with preformed (aminoalkyl)phosphinic acids[586].



SCHEME 54

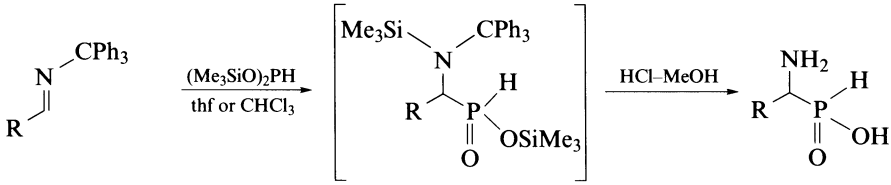
A more easily controlled reaction relies on the use of diamides of the type $RCH(NHAc)_2$ (R = Ph or aryl) with hypophosphorous acid in aqueous acetic acid, when the initial products (Scheme 55) are the [α-(acetylamino)benzyl]phosphinic acid, hydrolysable by mineral acid to the free (α-aminobenzyl)phosphinic acid[587], and which react further with the same amides in acetic acid to give the bis(α-aminobenzyl)phosphinic acid **378**[588]. However phosphonomethylations of secondary amines proceed satisfactorily to give either type of acid **376** or **377**[589].



SCHEME 55

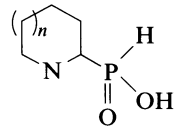
The reactions of phosphorous acid are paralleled still further by the additions of hypophosphorus acid to azomethines; in practice, mixtures of amines and carbonyl reactants may be employed[589–591], but the drawbacks to the procedure found for the synthesis of aminoalkylphosphonic acids may well apply here also. In a valuable publication, Dingwall and coworkers[592] described the syntheses of (aminoalkyl)phosphinic acid analogues of many of the naturally occurring aminocarboxylic acids by the simple treatment of the benzyhydrylimine derivatives of the necessary amines with hypophosphorous acid, formed *in situ* when diphenylmethylammonium hypophosphite is treated with an appropriate aldehyde; this step is followed by removal of the *N*-protection with 48% aqueous HBr, with 18% aqueous HCl or with trifluoroacetic acid in boiling methoxybenzene; any second amino group was protected as the phthalimido derivative.

Diesters of hypophosphorous acid, $(RO)_2PH$ (dialkyl hypophosphites or phosphonites), also add to azomethines; in particular, the bis(trimethylsilyl) ester is of interest in this respect because of the ease of removal of the ester groups and lack of any need to isolate the intermediates **379** (Scheme 56)[593]. This latter procedure also has allowed a synthesis of the phosphinic acids, **380** ($n = 0$, or 2)[594].



(379)

SCHEME 56

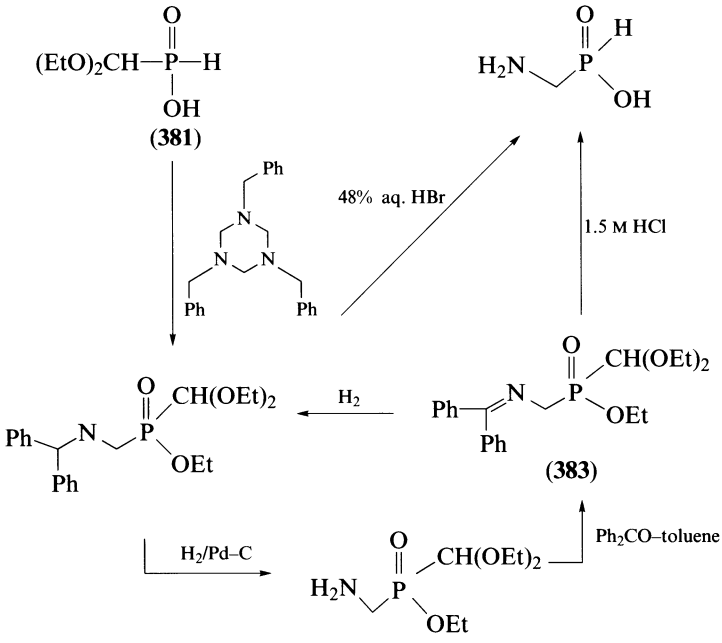


(380)

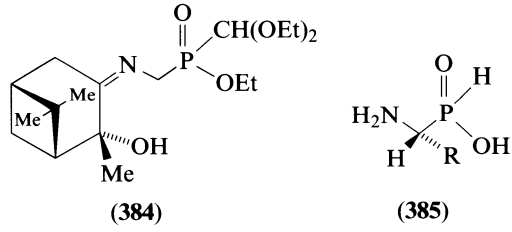
During the last decade, several important advances have been made which have been based on the intermediate **381**, the (aminomethyl)(diethoxymethyl)phosphinic ester **382** and its *N*-benzhydrylidene derivative **383**. The synthetic connection between these compounds is indicated in Scheme 57[531,595]. The importance of **383** lies in its ability to undergo successive alkylations at the aminomethyl carbon following initial anion generation with lda[531]. Moreover, the reaction may be subject to asymmetric control.

The condensation between (1*R*,2*R*,5*R*)-(+)-2-hydroxypinan-3-one and **382** gave a 1:1 diastereoisomeric mixture of products **384**; the alkylation of this product ($PhCH_2Br$, 2 equiv. of lda) and subsequent acidolysis (1.5 M HCl at 100 °C) gave exclusively the (*R*)-(–)-(1-amino-2-phenylethyl)phosphinic acid **385** (R = $PhCH_2$) (e.e. > 99%), and the similar use of the (1*S*,2*S*,5*S*)-(–)-chiral template led to the (*S*)-(+)-aminoalkyl phosphinic acid of similar optical purity. The optical purities of the (1-aminoethyl)phosphinic acids which resulted from the alkylation reactions with MeI were, unfortunately, much lower (ca 50%)[531].

The value of the phosphonite ester **386** in the synthesis of (aminoalkyl)phosphinic acids has been explored. This ester[595] adds to nitroalkenes, acetylaminoalkenes, cyanoalkenes

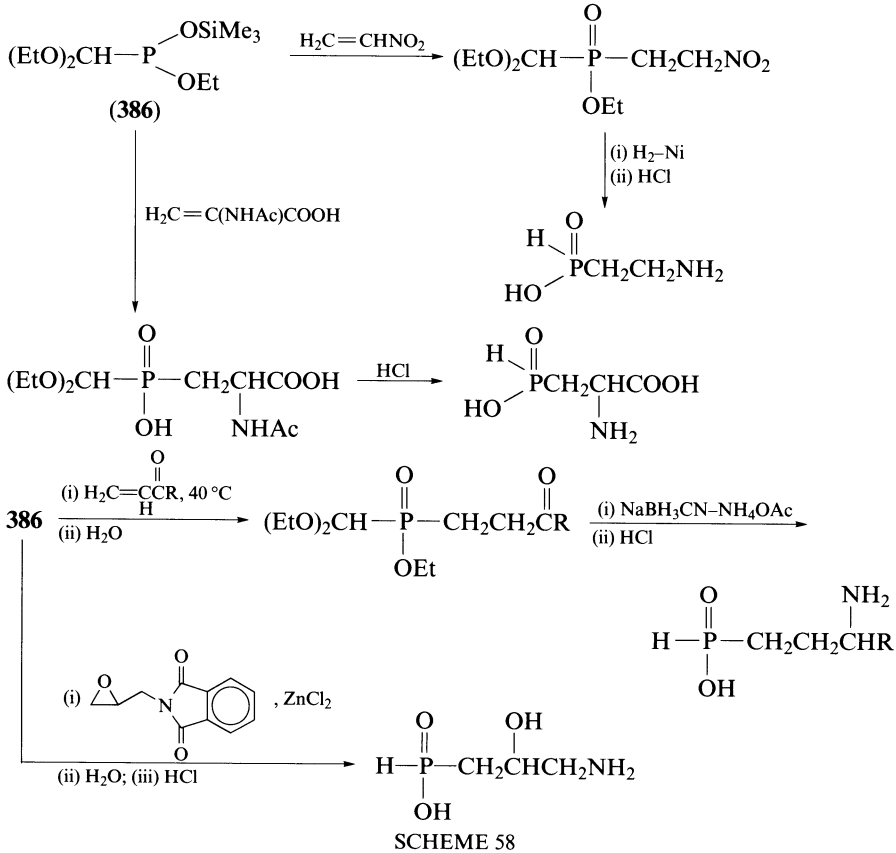


SCHEME 57

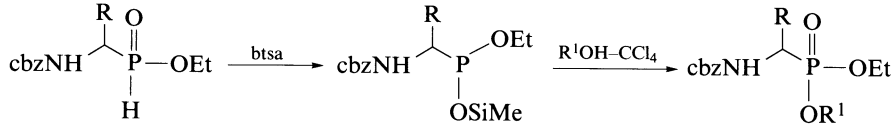


and α,β-unsaturated ketones and reacts also with other compounds to provide intermediates which, after appropriate modification to their functionality, can be made to lose $CH(OEt)_2$ and ester Et groups (1.5 M HCl at 100 °C), to give (aminoalkyl)phosphinic acids; some of these reactions are outlined in Scheme 58.

The synthesis of phosphonic acid derivatives by the direct oxidation of those of the corresponding phosphonous acid has been afforded very little interest (Chapter 2, Section VI.c), unlike the more controllable synthesis of derivatives of the thio- or seleno-phosphonic acid derivatives (Chapter 5, Section II.B.4). In the present instance, the oxidation of *N*-protected (fmoc) (1-aminoalkyl)phosphinic esters has been carried out with $NaIO_4$ with high yields[596]. Quantitative yields of (aminoalkyl)phosphonic acids were obtained in oxidation reactions with bromine water and with $HgCl_2$–H_2O[592]. In an alternative approach (Scheme 59), the *N*-protected (cbz) ethyl(1-aminoalkyl)phosphinate is initially converted into a (1-aminoalkyl)phosphonous acid diester, which is then subjected to the Atherton procedure to achieve change in valence at phosphorus[597].

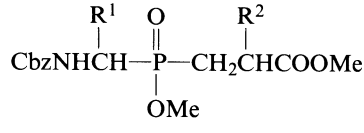


SCHEME 58



SCHEME 59

(ω-Aminoalkyl)phosphinic acids lacking a free N—H bond, undergo aminomethylation to give (ω-aminoalkyl)(aminomethyl)phosphinic acids; their Michael addition to propenenitrile affords the adduct which, when reduced, yields (ω-aminoalkyl)(3-aminopropyl)phosphinic acids[586]. Other Michael additions to esters of propenoic acids lead to unsymmetrical phosphinic esters, e.g. **387** from $H_2C{=}CR^2COOMe$–NaOMe; in the

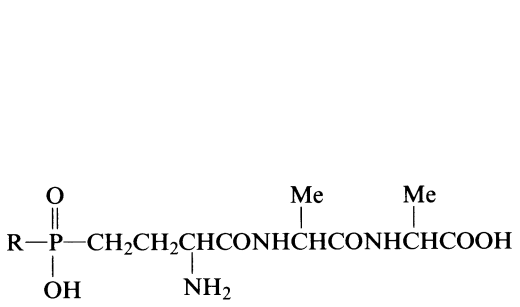


(387)

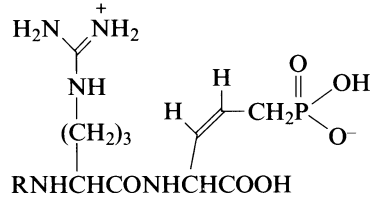
presence of a chiral catalyst, asymmetric hydrogenation can lead to compounds with two chiral carbon centres[598].

F. Phosphonopeptides

Only a brief mention can be made, in the space available, of the rapidly developing area of peptide chemistry in relation to phosphonic and phosphinic acids. Several peptide-like substances constructed by the linkage of an (aminoalkyl)phosphonic acid through its amino group, or of an aminophosphonoalkanoic acid through its carboxy group, to a conventional aminocarboxylic acid have been indicated earlier in this chapter (e.g. structures **103** and **104**). The L-alanyl-L-alanyl peptide from phosphinothricin (**388**; R = Me), also known as bialafos, and its phosphinic (phosphonous) analogue, **388** (R = H), both occur in *Streptomyces hygroscopicus* and *S. viridochromogenes*[583]. *Bacillus subtilis* (ATCC 6633) is a source of L-arginyl-L-2-amino-5-phosphono-*cis*-pent-3-enoic acid (**389**) (rhizocticin A) and the corresponding L-valyl-L-arginyl peptide (**390**) (rhizocticin B) and traces of other related peptides[599].

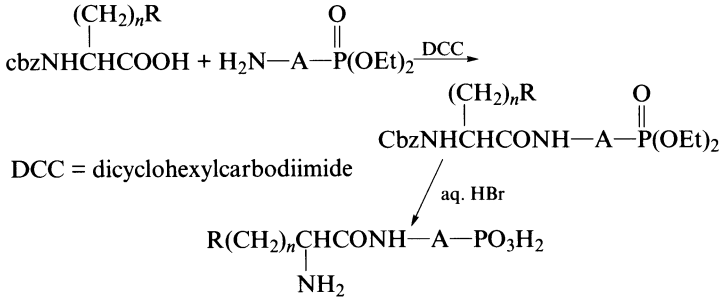


(**388**)



(**389**) R = H
(**390**) R = Pr^{i}CH(NH$_2$)CO

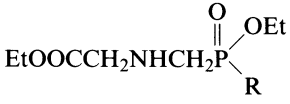
In principle, the reactions employed to bring about peptide formation between an (aminoalkyl)phosphonic acid and an aminocarboxylic acid are similar to those used in conventional peptide chemistry. Thus, a diester of the (aminoalkyl)phosphonic acid is brought into contact with the *N*-protected aminocarboxylic acid in the presence of dicyclohexylcarbodiimide (Scheme 60)[596,600] or the carboxylic acid may be activated by preliminary reaction (mixed anhydride formation) with an appropriate reagent, e.g. Bu^{t}COCl[601], ClCOOEt[602] or ClCOOCHMeEt[603,604], or by the use of *N*-hydroxysuccinimide[603,605]. The



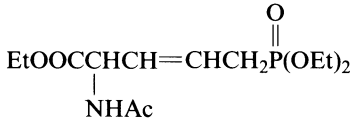
SCHEME 60

condensation between carboxyl-protected amino acids and phosphonic derivatives in the presence of diphenyl phosphorazidate has been noted[606].

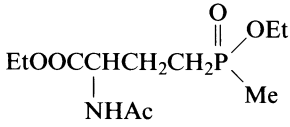
The role of silylated reagents in the formation of oligopeptides has been explored[602]. Here, the bis(trimethylsilyl) ester of the [1-(trimethylsilylamino)alkyl]phosphonic acid is coupled with an activated *N*-cbz-amino acid and the silyl groups are subsequently removed under aqueous conditions; the process can then be repeated. Oligopeptides have also been obtained as the result of enzyme catalysis[607], when the condensations between amino carboxylic esters and (a) *N*-protected (aminoalkyl)phosphonic esters or (b) *N*-protected [(aminoalkyl)methyl]phosphinic esters is brought about in the presence of (a) alkaline phosphatase (E_1) and phosphodiesterase (E_2) and (b) alkaline phosphatase and total bee venom (E_3) (the latter aiding in the removal of both carboxylate ester and *N*-acetyl groups);



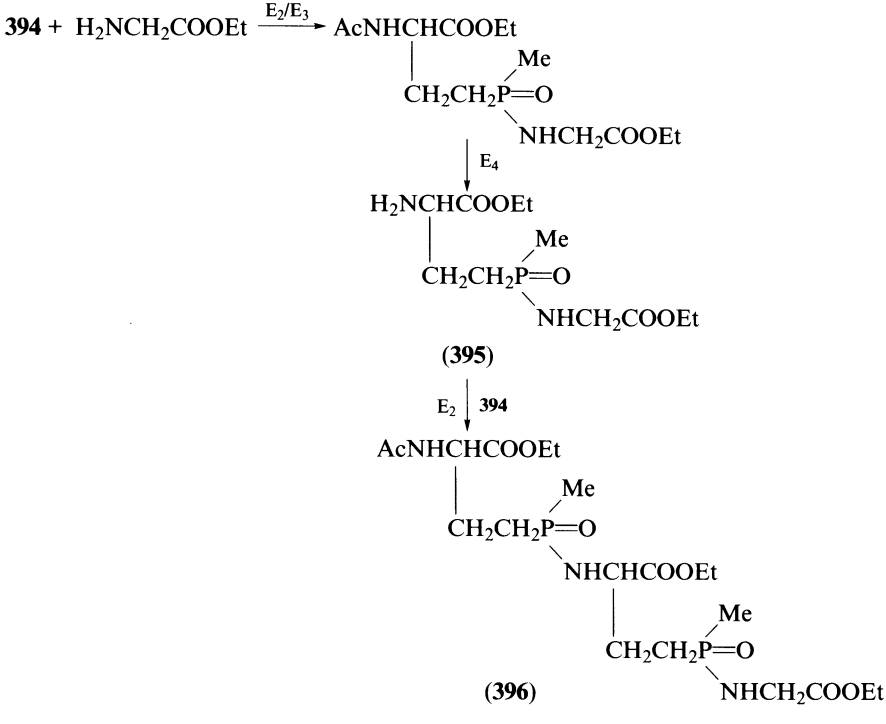
(**391**) R = OEt
(**392**) R = Me



(**393**)



(**394**)



(**395**)

(**396**)

in this way condensations were brought about between each of the two phosphonic substrates **391** or **393**, or the two phosphinic substrates **392** or **394**, and the ethyl esters of glycine, L-alanine, L-methionine or L-histidine. Deacetylation of the *N*-acetyl dipeptide is achieved by means of yet another enzyme, alkaline mesintericopeptidase (E_4); the product, e.g. **395**, is then free to undergo condensation in the presence of phosphodiesterase with a further reactant with free amino group. A further reaction with **384** thus affords **396**.

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NOTE ADDED IN PROOF

The literature coverage of the important groups of phosphonic and phosphinic acids dealt with in this chapter has been extended to mid-1995 with a further selection of publications.

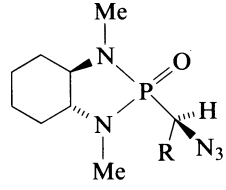
Section IV

A study of the kinetics of the interaction of benzaldehyde together with $PhNH_2$ and a series of hydrogenphosphonates (Kabachnik–Medved'–Fields reaction) has led to the conclusion that the reaction is initiated by the formation of the Schiff base, and this is followed by the addition of the hydrogenphosphonate, although this mechanism was chosen by the elimination of others rather than by direct evidence. The initial formation of the (α-hydroxybenzyl)phosphonate was thought not to occur, at least not to any great extent, because of a lack of catalytic effect by aniline on the interaction of the aldehyde and hydrogenphosphonate[608]. The Strecker-type synthesis of (1-aminoalkyl)phosphonic esters from an aldehyde, NH_3 and hydrogenphosphonate has been improved by the use of an ammonium salt in EtOH, but the very nature of the salt is of some importance, and whereas inorganic ammonium salts fail to participate in the process, ammonium acetate proved useful[609].

In the conversion of derivatives of (1-oxoalkyl)phosphonic diesters into those of the (1-aminoalkyl)phosphonic acid, it may be noted that an improvement to the use of $NaBH_3CN$ involves that of sodium triacetoxyborohydride-$TiCl_3$ in aqueous methanol buffered at pH 4 for the reduction of oximes[610].

Reactions between ω-(diethoxyphosphinoyl)alkanals and *N*-phenylthioureatriphenyl phosphite, followed by acidolysis of the intermediates, afford α-aminoalkane-α,ω-diphosphonic acids[611].

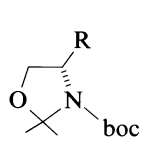
Treatment of the carbanions from *P*-alkyl analogues of compound **336** with 2,4,6-triisopropylbenzenesulphonyl azide yields the azides (**397**) diastereoselectively; acidolytic removal of the 1,3,2-diazaphospholidine ring and catalytic reduction of the azido group affords (1-aminoalkyl)phosphonic acids of known chirality[612].



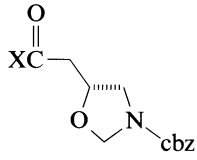
(**397**)

1,3-Oxazolidines and 1,3-oxazolidin-5-ones related to **279** have found favour as sources of amino groups at carbon atoms of known chirality, the former, **398**, through an initial Abramov condensation with an aldehyde to give **399** and subsequent removal of the resultant α-hydroxy group as in a synthesis of *N*-boc-2-amino-4-(diethoxyphosphinoyl)-4,4-difluorobutanoic acid[613], and the latter, **400**, in a sequence which commences with its

reaction with a dialkyl (lithiomethyl)phosphonate to give **401**, and leading ultimately to (*R*)-4-oxo-5-phosphononorvaline[614].

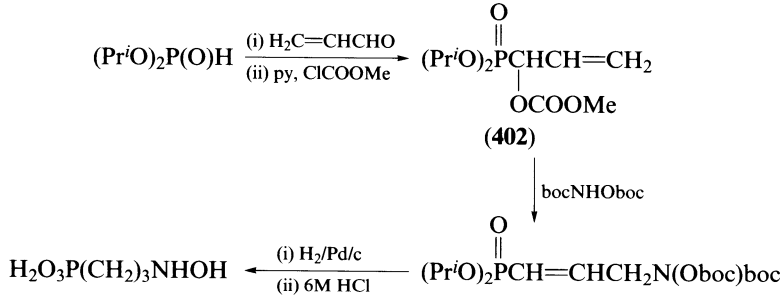


(**398**) R = CHO
(**399**) R = $(EtO)_2P(O)CF_2CH(OH)$



(**400**) X = Cl
(**401**) X = $(EtO)_2P(O)CH_2$

An Abramov condensation between diisopropyl hydrogenphosphonate and propenal and subsequent *O*-methoxycarbonylation to give the intermediate (**402**), forms the first stage in a useful synthesis of an *N*-hydroxy system following a reaction with bocNHOboc (*O*,*N*-di-bochydroxylamine) and subsequent hydrogenolysis and acidolysis[615].



The ready oxidation of (1-aminoalkyl)phosphonous acids (aminoalkylphosphinic acids) with aqueous bromine, to give (1-aminoalkyl)phosphonic acids, raises still further the potential usefulness of the former. In a useful modification to one synthesis, the reaction between an aldehyde and either (*R*)- or (*S*)-1-phenylethylamine hypophosphite salt yields the *N*-substituted (1-aminoalkyl)phosphinic acid which is simultaneously oxidized and deprotected when treated with bromine water[616].

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CHAPTER 5

The synthesis and reactions of thio- and seleno-phosphonic and -phosphinic acids

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I. INTRODUCTION

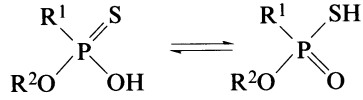
The replacement of one or more oxygen atoms in a phosphonic or phosphinic acid, or a derivative thereof, by an atom of a higher chalcogen affords a series of mono-, di- or even trithio- or -seleno-substituted acids (or their derivatives). Those rare substances which contain tellurium are rather unstable (even if only monoatomic with respect to that element) and cannot be readily purified, but have been characterized spectroscopically.

A complicating feature to be found in the chemistry of the sulphur and selenium compounds (because of their relative rarity, compounds of tellurium will be referred to only in specific contexts) is that of tautomerism within the OPS and OPSe triads. Thus, a monothio(or seleno)-phosphonic acid (**1**) or -phosphinic acid (**2**) (Z = S or Se) exists as an equilibrated mixture of phosphoryl and thio(or seleno)phosphoryl forms, the composition of which depends on the ligand R; this point is illustrated by data for the equilibria illustrated in equations 1–5[1]. For *O,O*-dialkyl hydrogen phosphorothioates ('dialkyl thiophosphoric acids') (equation 3), the thiol contents for the compounds with R = Me, Et, Pr, Pr^i, Bu, Bu^i, or Ph have been estimated as 38–80% in 7% aqueous ethanol or 11–79% in 80% aqueous ethanol. For the thiophosphonic *O*-monoesters (equation 4) with R^1 = Me, Et, Pr, Bu, Bu^i or Ph, the thiol contents (for the two same solvent systems) are 5–19% and 0.2–2.0%, and for the thiophosphinic acids (equation 2) the values are 0–1% and 0–0.1% for R = Et, Pr, Pr^i, Bu, Bu^i or Bu^t. A similar tautomerism exists for the dithio(seleno)phosphonic acids (**3**). There then arise separate series of derivatives dependent on the replacement of hydrogen at the point of attachement to the atomic triad centred on phosphorus: an example of this phenomenon is the series of *O*- and *S*- (or *Se*-) esters, although other derivatives, for example the thiophosphonic dihalides, are derived through replacement of the two OH groups.

(1)

(2)

$$(RO)_2P(S)OH \rightleftharpoons (RO)_2P(O)SH \quad (3)$$



(4)

(3)

(5)

Stereochemical features form a second complicating concern. Because of the tetrahedral geometry of bonding at phosphoryl phosphorus, a non-symmetrical phosphonic diester should, in principle, be resolvable; using conventional procedures, the obtention of such a compound in resolved form might well prove difficult, and in practice would probably be achievable only under special circumstances such as its synthesis under conditions of enantiomer preferment, or the presence, in one of the ester groups, of a functional unit which would act as an anchor for a resolving agent. However, a monoalkyl ester of a monothiophosphonic acid molecule is inherently chiral, and the presence of a free hydroxy (or tautomeric thiol) group allows a facile resolution through diastereoisomeric salt formation, and this presents a convenient route to molecules of potential utility in the study of stereochemical changes in displacements at the central phosphorus atom.

The only comprehensive and readily-available surveys of thio- and seleno-phosphonic and -phosphinic acids appear to be those in the compilation by Kosolapoff and Maier[2–4] which appeared during the 1970s, and those in the Houben–Weyl volumes[5–7]. Some further information relevant to heterocyclic systems which possess endo- or exo-cyclic phosphorus–sulphur bonds has been surveyed by Mann[8]. Gefter[9] has also provided a useful compilation of syntheses and data for unsaturated thiophosphonates and related compounds. As in the preceding chapters concerned with the synthesis of the various classes of phosphonic and phosphinic acids, literature surveys have been presented for individual compounds[10] and the field, as a whole, is surveyed annually[11]. In addition, Hall and Inch[12] reviewed the mechanistic implications of changes in stereochemistry following displacement reactions at phosphorus in cyclic phosphorus(V) esters and amides, and in so doing discussed the reactions of many such thiophosphoryl compounds.

This chapter is intended to survey the literature from the three decades (or so) which lead up to mid-1994, and thus to overlap with the content of the Kosolapoff and Maier reviews. The large range of organophosphorus compounds containing sulphur or selenium finds

widespread use, not only in pure scientific research, but also in technology, with uses, actual or potential, in areas as widely diverse as agricultural pesticides, oil and petroleum technology and metal ore extraction techniques.

A comment on the layout of this chapter is perhaps appropriate at this juncture; the plan does not follow that adopted in the preceding three chapters, which dealt primarily with the synthesis of phosphonic and phosphinic derivatives devoid of the higher chalcogens. This chapter concentrates on those acids and their derivatives that also contain one or more atoms of sulphur or selenium (or, in very rare cases, tellurium), and is concerned not only with the synthesis of such compounds but also, to a certain extent, with their reactions. The chapter commences with a summary of many of the more conventional approaches to the synthesis of compounds which possess only one atom of the higher chalcogen. Relatively few advances have been made in this area during the past two to three decades, and it is in this area that the above-mentioned general information sources should be consulted for more details and further examples. Because of the important role that thiophosphonic and thiophosphinic acid derivatives have played in stereochemical studies of displacement reactions at phosphorus, and continue so to do, there follows a description of procedures for the resolution of appropriate compounds and of the ways in which their optical purity can be ascertained. The description of the reactions of monothio compounds which then follows is in no way intended to be comprehensive but is designed simply to exemplify the stereochemical changes, if any, associated with some of the more fundamental reactions. A discussion of some other aspects of the reactivity of the thio compounds, for example, the stability of P—O and P—N bonds under hydrolysis conditions, is assigned to Chapter 6, where a comparison is made of the reactivities of derivatives of the sulphur-containing phosphonic and phosphinic acids with those compounds which lack the higher chalcogens, and also with the derivatives of (thio)phosphoric acid. The chapter ends with an account of aspects of the chemistry of derivatives of those acids which contain two or more atoms of sulphur or selenium.

II. THE SYNTHESIS OF MONOTHIO- AND MONOSELENO-PHOSPHONIC AND -PHOSPHINIC ACIDS AND THEIR DERIVATIVES

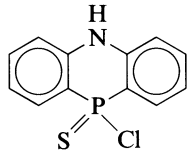
As indicated in earlier chapters, most practicable syntheses of phosphonic and phosphinic acids do not lead directly to the free acids, but rather to derivatives, most often their esters or acid halides, The same situation also obtains for the analogous sulphur- or selenium-containing acids; like the sulphur- or selenium-free acids, the chlorides are the most commonly prepared of the acid halides, but the bromides are fairly widely known and also experimentally convenient to prepare and use; fluorides and iodides are also known, although, in respect of general requirements, they are less valuable. Several preparative procedures are adaptations of those used for the sulphur- and selenium-free acid derivatives. Other syntheses start with the sulphur (or selenium)-free compound to be followed by the replacement of oxygen with the higher chalcogen. The thio- or seleno-acid derivatives are also more conveniently obtainable by the addition of elemental sulphur or selenium to the phosphorus(III) analogue than are phosphonic or phosphinic derivatives through the addition of oxygen.

A. Syntheses through Phosphorus–Carbon Bond Formation

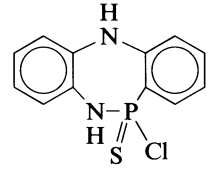
1. Through Friedel–Crafts-like arylation

Several cyclic systems that contain phosphorus as a ring atom and which, structurally, are cyclic esters of phosphonothioic or phosphinothioic acids, are obtainable through

sequences controlled by electron donor substituents on aromatic rings. The substituent effect may be such as to allow further aromatic substitution to proceed without the need for a catalyst. Thus, a reaction between diphenylamine and thiophosphoryl chloride under mild conditions yields the phosphinothioic chloride 10-chloro-5,10-dihydrophenazaphosphine 10-sulphide (**4**)[13], and under similarly mild conditions the reaction between the $P(S)Cl_3$ and *N*, *N*-dimethylaniline evidently proceeds only to the monoarylated stage[14]. In the analogous reaction with 2-aminodiphenylamine, the first step presumably occurs at the primary amino group, and is followed by cyclization of the phosphoramidothioic dichloride; the product is then 6-chloro-6,11-dihydro-5*H*-dibenzo[*c*, *f*][1,5,2]diazaphosphepine 6-sulphide (**5**)[15].

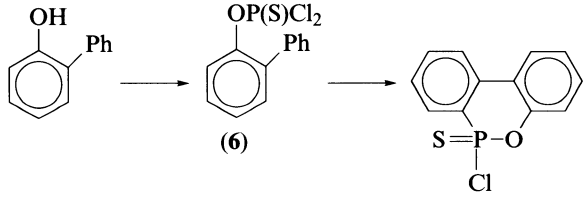


(**4**)

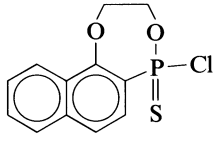


(**5**)

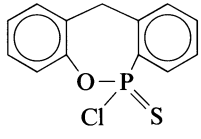
Phenols are attacked by $P(S)Cl_3$ with the initial formation of *O*-aryl phosphorodichloridothioates, $ArOP(S)Cl_2$; under appropriate circumstances, such compounds can be made to cyclize. The passage of the dichloride **6** through a quartz tube at 550–600 °C for 30–40 s affords mainly dibenzothiophene but also about 15% of 6-chloro-6*H*-dibenz[*c*,*e*][1,2]-oxaphosphorin 6-sulphide (**7**)[16]. Much better yields of **7** are achieved if the cyclization step is carried out in the presence of $AlCl_3$[17,18]. Several other analogous systems, **8**–**10**, have been obtained using similar operations[15,19].



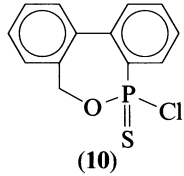
(**6**) (**7**)



(**8**)



(**9**)



(**10**)

Phosphorus–carbon bond formation does not occur when a mixture of an aromatic hydrocarbon and either $P(O)Cl_3$ or $P(O)Br_3$ is treated with $AlCl_3$ because of the strength of phosphoryl–aluminium complexes formed. By contrast, reactions that employ $P(S)Cl_3$ or $P(S)Br_3$ of which the above cyclizations are examples, occur more readily and are clearly of much greater practical use.

The interaction of a thiophosphoryl halide and an aromatic hydrocarbon is catalysed by $AlCl_3$ or $AlBr_3$, but not by other metal halides such as $ZnCl_2$, $FeCl_3$ or $TiCl_4$ [a failure which has been attributed to their inability to complex satisfactorily with the $P(S)X_3$], and proceeds in stages through to the triarylphosphine sulphide **13** (Scheme 1). In this procedure, the sequence may be essentially stopped at the thiophosphoryl dihalide stage, **11**, when $P(S)Br_3$–$AlBr_3$ is used, but for $P(S)Cl_3$–$AlCl_3$ the reaction tends to allow the isolation of the dichlorides only with some difficulty and is best for the preparation of the mononochlorides (**12**; X = Cl)[20,21].

$$P(S)X_3 \xrightarrow[AlCl_3]{ArH} ArP(S)X_2 \xrightarrow[AlCl_3]{ArH} Ar_2P(S)X \xrightarrow[AlCl_3]{ArH} Ar_3P(S)$$

(11) **(12)** **(13)**

SCHEME 1

2. *Through alkylation or arylation with organometallic reagents*

Successful alkylations of thiophosphoryl chloride with lead tetraalkyls and arylations with $PbPh_4$ or $SnPh_4$ have been reported by Maier[22] and others[23]. These reactions are also catalysed by $AlCl_3$, and it should be noted that they take place more easily than for displacements in $P(O)Cl_3$. The rate of reaction depends on the size of the alkyl group attached to the heavy metal, an increase in size resulting in a decrease in reactivity; reduced reactivity is also found when alkyl is replaced by Ph. Thiophosphoryl chloride and $PbEt_4$ at 125 °C yield a product containing 92% of $EtP(S)Cl_2$ and 8% $Et_2P(S)Cl$; reactions with $MeP(S)Cl_2$ or other thiophosphonic dichlorides afford good yields of mixed dialkyl or alkylphenyl thiophosphinic chlorides. Phenylation of $P(S)Cl_3$ with $PbPh_4$ resulted in the preparation of $PhP(S)Cl_2$ and $Ph_2P(S)Cl$, each in yields of 30–35%.

Maier[24] also employed organoaluminium compounds in reactions with $P(S)Cl_3$ under conditions (a 4–7 molar excess of organoaluminium reagent) which led to good yields at the disubstitution stage, i.e. in the formation of $R_2P(S)Cl$; the yields of the dichlorides, $RP(S)Cl_2$, were low, as might have been expected, but more surprising are the low yields of the tertiary phosphine sulphides, $R_3P(S)$. The finding that with essentially equimolar proportions of reactants the yield of phosphine sulphide (R = Et) increased markedly is also of interest. The use of $AlPh_3$ with $P(S)Cl_3$ affords only 17% of $Ph_2P(S)Cl$.

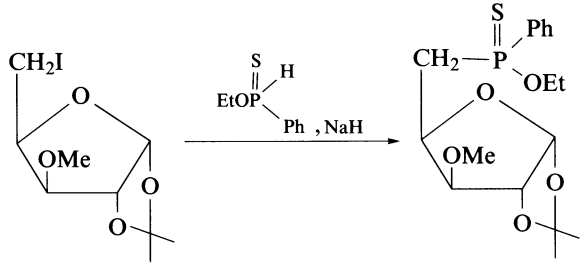
Complications are encountered in the potential use of organomagnesium compounds. The interaction of a Grignard reagent, RMgX, and $P(S)Cl_3$ is a well established route to symmetrical diphosphine disulphides, $R_2P(S)P(S)R_2$, except when R consists of an appropriately branched alkyl group, e.g. isopropyl, *sec*-or *tert*-butyl, when the isolated products are the monohalides, $R_2P(S)Cl$[25]. As will be seen shortly, diphosphine disulphides are themselves of considerable value in the preparation of derivatives of thiophosphinic acids. Some idea of the experimental difficulties that may be encountered in preparative reactions, can be gleaned from studies of the reactions between $MeP(S)Br_2$ and Bu^tMgCl, on the one hand, and between $Bu^tP(S)Br_2$ and MeMgX (X = I or Br) on the other; these apparently simple reaction systems provide complex mixtures of products which include mono- and dithio-phosphinic acid derivatives[26].

3. *Through the Michaelis–Arbuzov and Michaelis–Becker reactions*

Michaelis–Becker reaction between dialkyl thiophosphonates, $(RO)_2P(S)H$, and alkyl halides, R^1X, in the presence of NaOR proceed satisfactorily at 70–80 °C in a few hours to give the diesters, $(RO)_2P(S)R^1$ [27–29]. Under such conditions, or during longer reaction periods or at higher reaction temperatures, the formation of the desired product may be

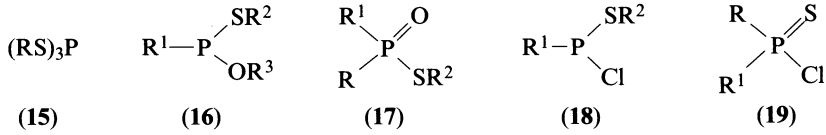
complicated by a further reaction step which involves alkylation at sulphur, a feature of the chemistry of thiophosphoryl compounds that will be discussed more fully later. Recent modifications in technique include the adoption of reaction under phase-transfer conditions through the use of a solid base (KOH or K_2CO_3) in an organic solvent (CH_2Cl_2 or MeCN), or in a CH_2Cl_2–aqueous NaOH medium with an added quaternary ammonium salt, or sometimes in the presence of a crown ether catalyst[30,31].

Thiophosphinoylated carbohydrates are available by means of such procedures. For example, the interaction of 5-deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylofuranose with the sodium salt from ethyl phenylphosphinothioate affords **14** as an inseparable mixture of diastereoisomers (the phosphoryl analogues are separable)[32].

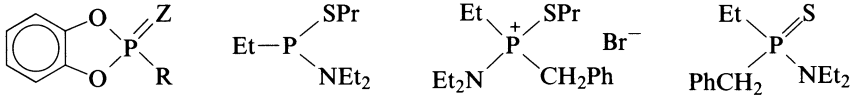


(14)

Classical Michaelis–Arbuzov reactivity has been reported in the behaviour towards alkyl halides, RX, of phosphorotrithioite triesters, e.g. **15** (R = Et), although the reaction is rather slow at room temperature, requiring several days even in the presence of a large excess of RX (MeI)[33]; the phosphonothious esters **16** (R^1 = Et, Bu^t or Ph) yield the *S*-esters of thiophosphinic acids (**17**)[34,35], whilst phosphonothious chlorides **18** give rise to thiophosphinic chlorides (**19**), which may be symmetrical or non-symmetrical[36]. Unusually, the thiophosphite ester **20** (Z = 1.p., R = $PhCH_2S$) when acted upon by MeI rearranges to **20** (Z = S, R = $PhCH_2$) through an initial quaternization at sulphur followed by transfer of charge to phosphorus[37].



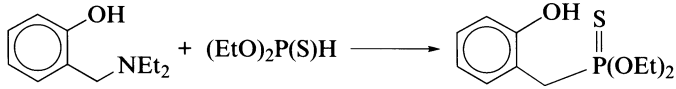
(15) **(16)** **(17)** **(18)** **(19)**



(20) **(21)** **(22)** **(23)**

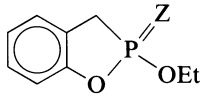
The reaction between the thiophosphorus(III) amide **21** and benzyl bromide is of interest in that it is possible to isolate a pseudoquaternary salt **22**, which decomposes at just above its melting point (92–93 °C) to give the corresponding phosphinothioic amide (**23**)[38].

Non-classical Michaelis–Arbuzov behaviour is exemplified by the reactions between dialkyl hydrogenphosphonothioates and *o*-hydroxybenzylic compounds (equation 6)[39]; the formation of the thiophosphonic ester **24** is accompanied by cyclization to **25** (Z = O



(6)

(24)



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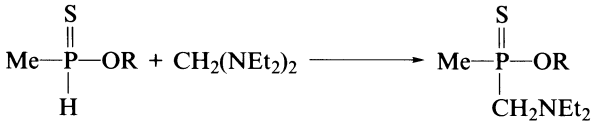
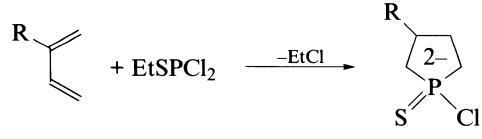


(7)

or S). Equation 7 exemplifies the use of methylenediamines in similar reactions[29,40]. It has also been suggested that the participation of Michaelis–Arbuzov intermediates explains the behaviour of 1,3-dienes towards many acyclic or cyclic esters that possess at least one P—S bond. The product from $EtSPCl_2$ and a 1,3-diene consists of the cyclic phosphinic chloride **26**, the nature of which (i.e. the position of the C=C bond) depends on the presence, or otherwise, of substituents; thus, isoprene affords the symmetrical 3-phospholene 1-sulphide whereas butadiene affords a mixture of 2- and 3-phospholene 1-sulphides, the formulation indicating this point (for a comment, see Chapter 2, section II.A)[41].



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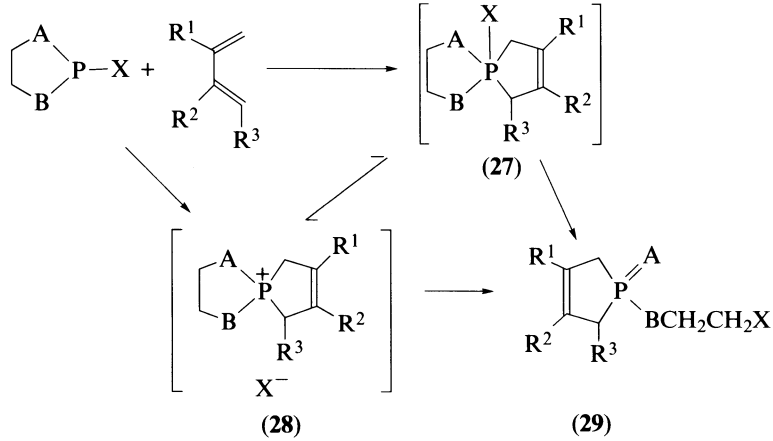


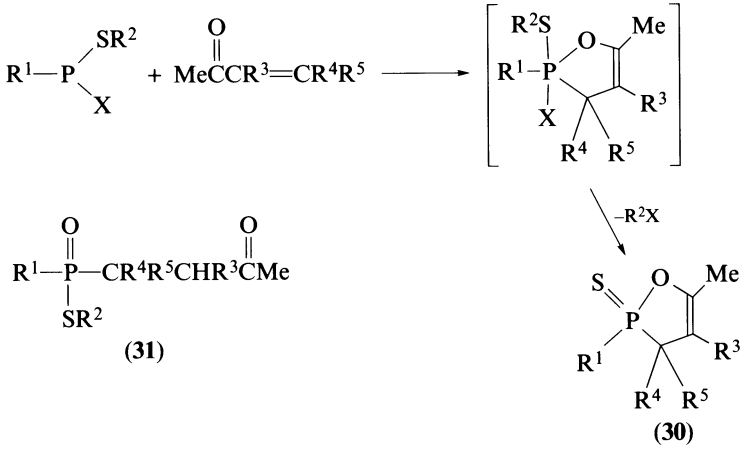
(27)

(28)

(29)

SCHEME 2

Other reactions between cyclic phosphorochloridites or cyclic esters and dienes are summarized in Scheme 2[42–46]; here, A and B are O, S or Se, and may be different or identical, and X = Cl, Br, NCS, or OR, and the conversion is brought about when mixtures of reactants are heated together in sealed tubes for extended time periods. As in the many examples known in which the reacting system, as a whole, is sulphur-free, the nature of the intermediate can be in doubt, and probably depends on the nature of the substituents, particularly those directly connected to phosphorus; thus some reactants may interact through a covalent, pentacoordinate species **27**, whereas others form a pseudoquaternary intermediate **28**. It may also be that one intermediate structure is transformed into the second before the ultimate formation of the 3-phospholene (**29**). Also, in accord with these ideas, thiophosphorus(III) halides have been obseved to react with α,β-unsaturated ketones to give, ultimately, 1,2-oxa-4-phospholenes as their 2-sulphides (**30**) (Scheme 3)[45–48]; from reactions carried out in acetic acid solution the products are said to be the esters **31** and AcCl[49].

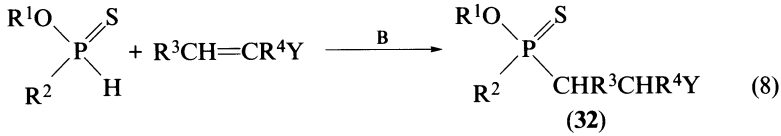


SCHEME 3

4. *The formation of functionalized thio-phosphonic and -phosphinic acids*

Many of the reactions which lead to derivatives of functionalized phosphonic or phosphinic acid derivatives, and which were described in Chapters 3 and 4 have their parallels in the behaviour of the corresponding higher chalcogen-containing species towards the same substrates, Some of the modified reactions are not well exemplified, although other reactions have been widely used for many years; general sources should be consulted for early examples. The following short selection of examples should suffice to indicate how the various reactions have been modified, or could well be adapted in the future.

The older literature, particularly that from the 1950s and surveyed by Pudovik and Konovalova[50] and others[2–7], contains many examples of additions (equation 8), usually



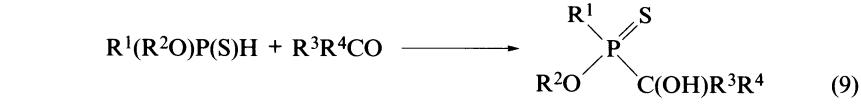
(8)

catalysed by sodium alkoxides, of dialkyl hydrogenphosphonothioates, dialkyl hydrogenphosphonoselenoates or related phosphinates to the esters of α,β-unsaturated carboxylic acids, to the nitriles of the same acids, and to α,β-unsaturated aldehydes or ketones. The yields of **32**[R^3, R^4 = H, alkyl or aryl; Y = COO-alkyl, CO-alkyl, CN, $P(Z)(OR)_2$; R^4 = H, R^3 = Y = COO-alkyl] from such addition reactions tend to be slightly higher than those obtained by the addition of dialkyl hydrogenphosphonates to the same substrates. The addition of the hydrogenphosphonothioates to isocyanates, R^1NCO, proceeds much more easily[51,52], and does not necessarily require the presence of a catalyst; the functionalized products from such interactions have the structure $(RO)_2P(S)CONHR^1$.

The preparation of (dialkoxyphosphinothioyl)alkanoic esters from hydrogenphosphonothioates and bromoalkanoic esters (the Michaelis–Becker alkylation reaction) has been widely used, but the use of diazoalkanoic esters is equally feasible[53].

The reaction between PCl_3 and thioformaldehyde trimer leads to a low yield of (chloromethyl)phosphonothioic dichloride[54], a behaviour qualitatively reminiscent of that of the trichloride towards paraformaldehyde (Chapter 3, Section II.A.7).

The addition of a dialkyl hydrogenphosphonothioate across the carbonyl group of an aldehyde or ketone is an extension of the Abramov reaction, and has been known almost as long as that of the hydrogenphosphonate esters; the reaction occurs easily at room temperature and evidently does not require the presence of a catalyst[29,50,55]; the yields in the comparable additions of alkyl hydrogenphosphinothioates (equation 9)(R^1 = alkyl), carried out at 50–60 °C, were in the range 30–95%[56]. A reaction which, in principle, involves R(EtS)P(O)H, occurs when a tervalent chloride (equation 10)(R = Et or Ph) and carbonyl compound react in the presence of water, and the product is an isomer of that obtained by means of reaction 9[57]. It might be noted, however, that if this procedure is carried out in acetic acid rather than in water, the sulphur is expelled as ethyl thioacetate and the phosphorus-containing products are sulphur-free[58].



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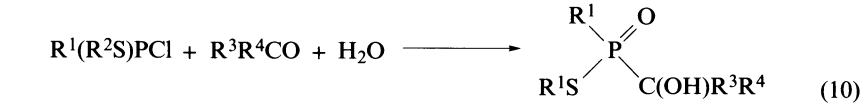
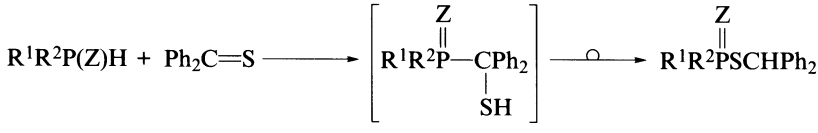


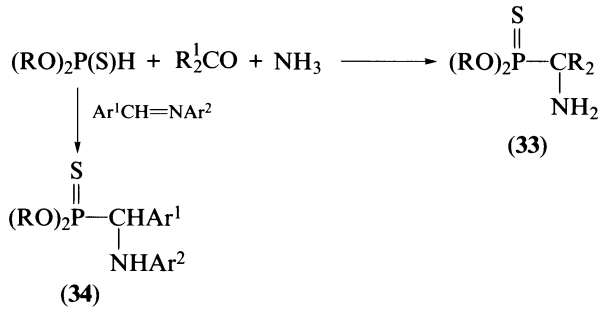
(10)

Reactions take place between thiobenzophenone and hydrogenphosphonothioates or hydrogenphosphinothioates (Scheme 4) (R^1 = R^2 = OEt; R^1 = OEt, R^2 = Et or Ph; Z = O or S) at 110 °C in the absence of a catalyst or, more commonly, at room temperature in the presence of a basic catalyst such as NaOEt or Et_2NH; particularly in the latter circumstances, the initial adducts are non-isolable since they undergo rapid rearrangement to *S*-diphenylmethyl esters[59].

Sodium dialkyl thiophosphites also undergo Michaelis–Becker reactions with acetyl chloride to give dialkyl acetylphosphonothioates, a little explored species, but reactive in the customary way to an excess of hydrogenphosphonothioate[60].



SCHEME 4

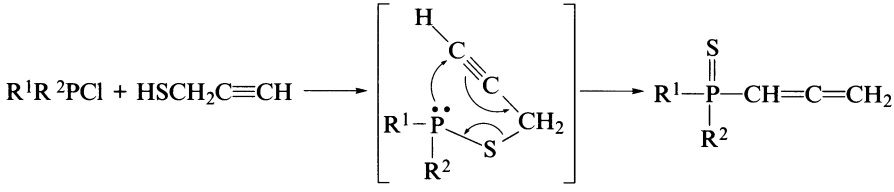


SCHEME 5

The formation of dialkyl (α-aminoalkyl)phosphonothioates (**33**) through the Kabachnik–Medved'–Fields interaction of dialkyl hydrogenphosphonothioates and carbonyl compounds in the presence of ammonia[61] was established in the early days of the study of that reaction, as was the formation of dialkyl [α-(arylamino)arylmethyl]phosphonothioates (**34**) by the addition of $(RO)_2P(S)H$ to anils (Scheme 5)[62].

5. Through the rearrangement of phosphorus(III) thio esters

Leaving aside those rearrangements achievable through the Michaelis–Arbuzov reaction between phosphorus(III) thio esters and alkyl halides with identical alkyl groups (and thus representing a mere isomerization), other rearrangements of phosphorus(III) thio esters do not rely on the presence of added reagent. The rearrangement of *S*-2-alkynyl thiophosphite esters (Scheme 6) parallels that of the sulphur-free esters and the resultant alkadienylphosphonothioic di-*O*-esters, under the influence of a base catalyst, then undergo a further rearrangement to the isomeric 1-propynylphosphonothioic di-*O*-ester. The rearrangement is independent of the nature of the other substituents attached to phosphorus[63,64].



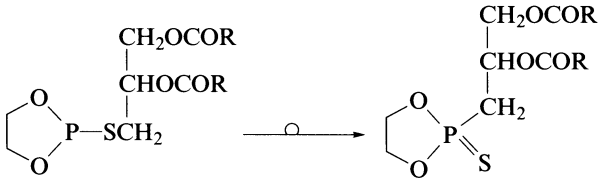
SCHEME 6

S-Benzyl phosphorus(III) esters show a particular propensity to undergo rearrangement (equation 11), even at room temperature, but particularly so when heated in a solvent of even comparatively low boiling point, or during attempted oxidation[65]. In a useful adaptation of this rearrangement, benzylphosphonothioic dibromide is conveniently obtained through an equilibration between tribenzyl phosphorotrithioite and PBr_3 as indicated in equation 12—a probable combination of redistribution followed by rearrangement rather than one of the reverse sequence[66].

The facile, thermally catalysed P—SC → P(S)C rearrangement is further exemplified by the conversion of 2-[2,3-(distearoyloxy)propylthio]-1,3,2-dioxaphospholane (**35**)(R = $C_{17}H_{35}$) into the sulphide (**36**), and allows a ready access to phosphorus–carbon bonded thiophosphatidylcholines and, because of the ease of oxidative removal of the sulphur, to closely related substances[67].

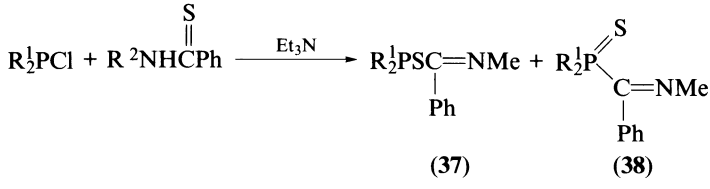
$$(RO)_2PSCH_2Ph \xrightarrow{\text{heat}} (RO)_2P(S)CH_2Ph \qquad (11)$$

$$(PhCH_2S)_3P + 2PBr_3 \longrightarrow 3PhCH_2P(S)Br_2 \qquad (12)$$



(35) (36)

Yet another example of valence expansion through rearrangement occurs after an initial reaction between a phosphorus(III) chloride and a thiocarboxamide in the presence of Et_3N; the relative proportions of the reaction, products, **37** and **38**(R^1 = EtO or Et_2N; R^2 = Me or Ph), may be altered when the mixtures are heated because of the isomerization of the phosphorus(III) compounds **37** to the quinquevalent esters **38** when heated at 80 °C (R = EtO) or at 150 °C (R = E_2N)[68].



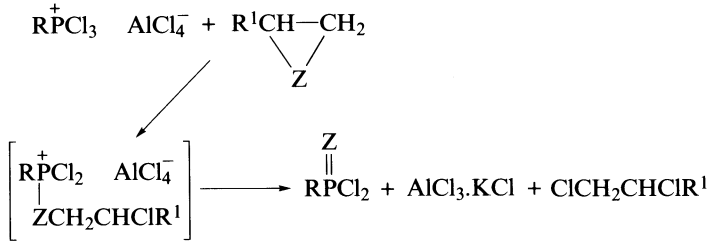
(37) (38)

B. Syntheses Through Modification at Phosphorus in Phosphorus–Carbon Bonded Compounds

1. By chalcogen–halogen exchange

Syntheses of several types organophosphorus compounds proceed through the initial formation of trichlorophosphonium salts. Such syntheses are based on (a) the phosphorylation of alkenes with PCl_5 and (b) the interaction of alkyl halides with PCl_3 in the presence of $AlCl_3$ (the Kinnear–Perren–Clay reaction[69]). The intermediates are now firmly recognized as the salts (a) RPX_3^+ PX_6^- and (b) RPX_3^+ AlX_4^-; normally X = Cl, but analogous tribromophosphonium salts are equally available. The adaptation of these phosphorus–carbon bond-forming reactions to the synthesis of halides of phosphonic and phosphinic acids was discussed in Chapter 2, but the same salts can also act as precursors to the halides and esters of thiophosphonic and thiophosphinic acids.

The tetrachloroaluminate complexes are also derivable from halogenophosphoranes, $RPCl_4$ (in turn preparable, in principle, from $RPCl_2$ and Cl_2[70–74]) and $AlCl_3$. The complex from $EtPCl_4$ reacts very slowly at 90–100 °C with H_2S with the liberation of HCl and the ultimate formation of the species '$EtPS_2$', but the stepwise process can be interrupted to allow the isolation of $EtP(S)Cl_2$[69]. More conveniently, a treatment of the complexes with sulphur, EtSH or KCNS, particularly in the presence of KCl (to remove the $AlCl_3$), leads to the thiophosphonic dihalides, $RP(S)Cl_2$[75,76]; a similar reaction with elemental selenium



SCHEME 7

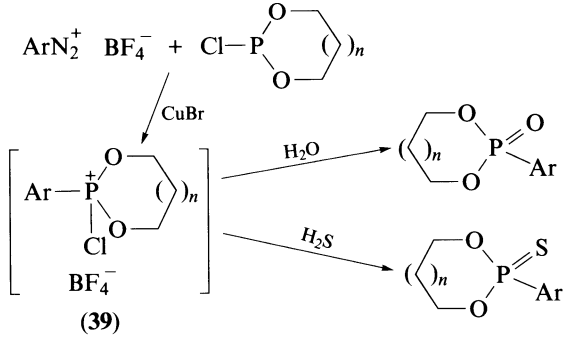
affords the selenophosphonic dichlorides, $RP(Se)Cl_2$[77]. Decomposition of the tetrachloroaluminate complexes to give phosphonic dichlorides is also readily achieved through their reaction with epoxides, and in the same way, the use of thiiranes leads to thiophosphonic dichlorides (Scheme 7). It may be noted that, although the yields of thiophosphonic dichlorides (Z = S) approach those of the corresponding phosphonic dichlorides (Z = O), the amounts of dichloroalkane, produced concomitantly, are significantly smaller in the former reactions[78].

In an analogous fashion, the complexes from alkyl chlorides, R^1Cl, phosphonous dichlorides, R^2PCl_2, and $AlCl_3$, and of the composition $[R^1R^2PCl_2^+][AlCl_4^-]$, are decomposed by sulphur, EtSH, P_4S_{10}, Sb_2S_5, As_2S_5 or even thiourea(S), to give the thiophosphinic chlorides, $R^1R^2P(S)Cl$[79-81].

The most commonly used reagent for the decomposition of the trichlorophosphonium hexachlorophosphates obtained during the phosphorylation of alkenes with PCl_5 has been H_2S[82-87], although thiirane[88] or P_4S_{10}[89,90] have occasionally been used. Decomposition of the chlorophosphonium phosphates with H_2Se affords the selenophosphonic dichloride, $RP(Se)Cl_2$[91].

Purified halophosphoranes, RPX_4 and R_2PX_3, are readily converted into the respective thiophosphonic or thiophosphinic halides (chlorides or bromides[92]), through the action of one of several agents, including S, Sb_2S_3, PbS, SnS_2 and P_4S_6, but, for the preparation of phosphonothioic difluorides from tetrafluorophosphoranes, the best reagent appears to be P_4S_{10}[93]. The difluorides are also available by the addition of sulphur to the phosphoranes, $ArPF_3H$, obtained by the action of KHF_2 on $ArPCl_2$[94].

The chlorophosphonium complexes **39**, produced (Scheme 8) during the synthesis of cyclic esters of arylphosphonic acids from aryldiazonium tetrafluoroborates and cyclic chlorophosphites, are decomposed by H_2S to give the analogous esters of arylthiophosphonic acids[95].



(39)

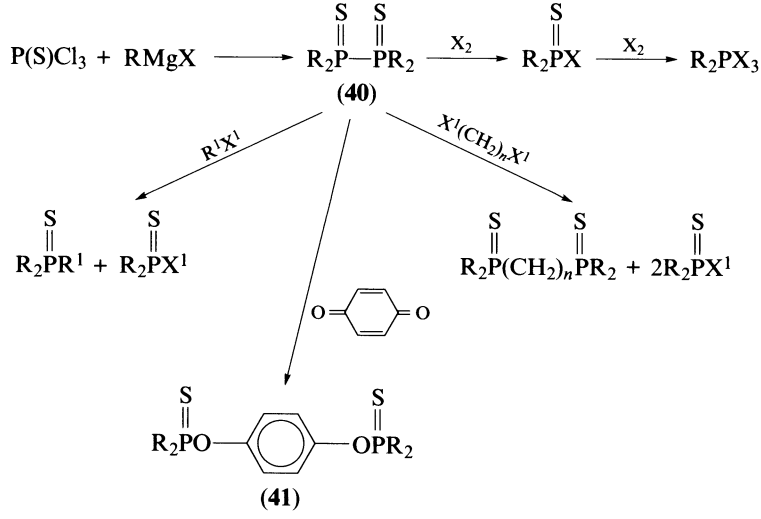
SCHEME 8

2. By phosphorus–phosphorus bond cleavage

The main drawback to the use of Grignard reagents in conjunction with thiophosphoryl chloride or bromide in the synthesis of phosphono- and phosphino-thioic halides is the ready formation (subject to the nature of the group R in the reagent) of diphosphine disulphides, **40** and, indeed, this reaction forms the most widely used process for the synthesis of the latter; this ready accessibility is in contrast to the relative sparcity of data on the corresponding dioxides, by no means so easily obtainable.

Cleavage of the P—P bond in the disulphides has been achieved in several ways, all of which lead to thiophosphinic acid derivatives of a highly useful nature. Particularly useful is the treatment of the diphosphine disulphides with chlorine or sulphuryl chloride[96] ($HgCl_2$ and SCl_2 produce the same qualitative result), bromine[97,98] or iodine in boiling benzene[99], which provide the thiophosphinic halide, $R_2P(S)X$ (X = Cl, Br or I). The use of an excess of the more reactive halogens results in desulphurization of the halides and the formation of trihalogenophosphoranes (Scheme 9)[100]. Cleavage at the P—P bond by phosphorus(III) trihalides, PX_3 (X = Cl or Br), yields the phosphinothioyl chloride or bromide[101].

The action of alkyl halide on diphosphine disulphides (**40**)(Scheme 9)(X^1 = Cl, Br, or I) provides mixtures of phosphine sulphides and thiophosphinic halides, which may be separable[101,102].



SCHEME 9

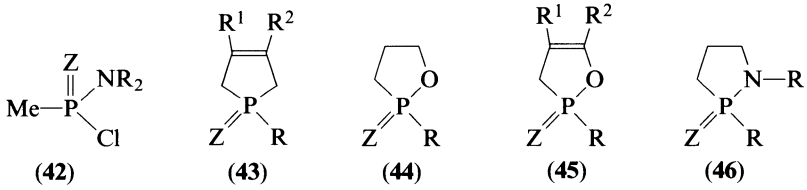
Cleavage of the P—P bond in the diphosphine disulphides **40** is also possible through the action of alkali, but evidently only when R is alkyl. The reaction between tetramethyldiphosphine disulphide and NaOH gives dimethylphosphine sulphide, $Me_2P(S)H$ (which under the influence of the aqueous alkali is converted into the corresponding oxide), and the sodium salt of dimethylphosphinothioic acid, which afforded a 75% yield of the free acid, Me_2PSOH[103]. A more unusual mode of cleavage of the P—P bond is that brought about by the action of a quinone; the 1,4-phenylene diester of dimethylphosphinothioic acid (**41**) is obtained by the action of 1,4-benzoquinone on **40**(R = Me)[104]. *N*-Chlorosulphonamides cleave the P—P bond in tetraalkyldiphosphine disulphides to give the *N*-sulphonyl derivative of dialkylphosphinothioic amides[105].

3. By chalcogen exchange

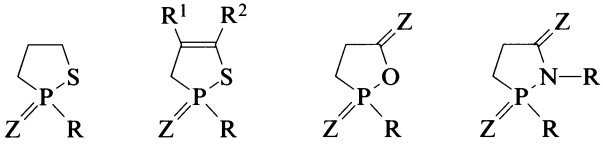
One of the procedures most widely used for the preparation of thiophosphonic and thiophosphinic acid derivatives is that of chalcogen exchange and, in particular, the replacement of the phosphoryl oxygen by sulphur, a step which is conveniently brought about by the action of hot P_4S_{10}, with the liberation of P_4O_{10}. A common application has been the conversion of phosphonic dichlorides into phosphonothioic dichlorides (equation 13)[106–114], and the similar conversion of phosphinic chlorides into phosphinothioic chlorides[115–118]; some arylphosphonothioic difluorides have been similarly obtained[119]. In such straightforward cases, the yields obtainable tend to be at least moderate and, often, they may be said to be good. Transformations of mixed derivatives, e.g. that of the phosphonic amide chlorides **42** (Z = O) into the corresponding **42** (Z = S) with P_4S_{10}, are less satisfactory[120], with yields in the range 10–30%.

$$10\ RP(O)Cl_2 + P_4S_{10} \longrightarrow 10\ RP(S)Cl_2 + P_4O_{10} \qquad (13)$$

In spite of its high bond strength, phosphoryl oxygen in many phosphorus-containing heterocyclic systems may be replaced without any great difficulty; the 3-phospholenes (**43**; Z = O)[121], 1,2-oxaphospholanes (**44**; Z = O)[122,123], 1,2-oxa-3-phospholenes (**45**; Z = O)[124–127] and 1,2-azaphospholidines (**46**; Z = O)[128] are all converted by P_4S_{10} into the corresponding thiophosphoryl compounds (Z = S) under comparatively mild conditions. In the case of **44** and **45**, a further reaction step consists in the replacement of the ring oxygen at a higher temperature and the formation of 1,2-thiaphospholane 2-sulphides (**47**)[123] and 1,2-thiaphosphol-3-ene 2-sulphides (**48**)[126], presumably by a process of ring opening and reclosure, Furthermore, the same reagent with the lactones **49** (Z = O) and the amides **50** (Z = O) brings about the initial conversion of P=O into P=S, followed by C=O into C=S; similar results may be achieved by the action of a 1:1 mixture of red phosphorus and sulphur[129].



(**42**) (**43**) (**44**) (**45**) (**46**)

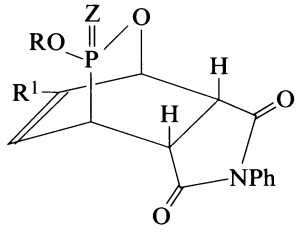


(**47**) (**48**) (**49**) (**50**)

Tetraphosphorus decasulphide was used to convert **51** (Z = O) into **51**(Z = S)[130] (and similarly for **52**[131]) prior to the thermal expulsion of the transient species [EtOP(O)(S)]. With the same reagent, the phosphinic ester **53** (Z = O) yields, initially, the corresponding sulphide (**53**; Z = S), but this is formed alongside the dithio acid **54**[40].

Thiations of phosphoryl groups have occasionally be carried out with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulphide (**55**). This, known as Lawesson's reagent, is a powerful reagent, particularly for the thiation of carbonyl groups, and it has been extensively investigated in this respect (the preparation and properties of

55 and related compounds will be discussed in Section IV.C), but the main drawback in its use lies in the formation and nature of the phosphorus-containing by-products.



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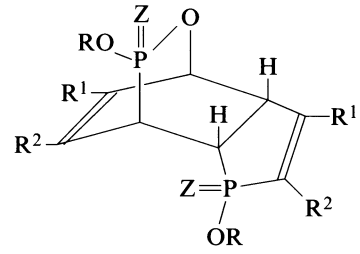

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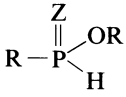
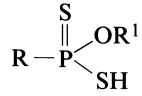


(53)



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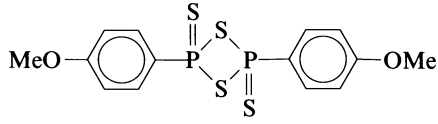


(55)

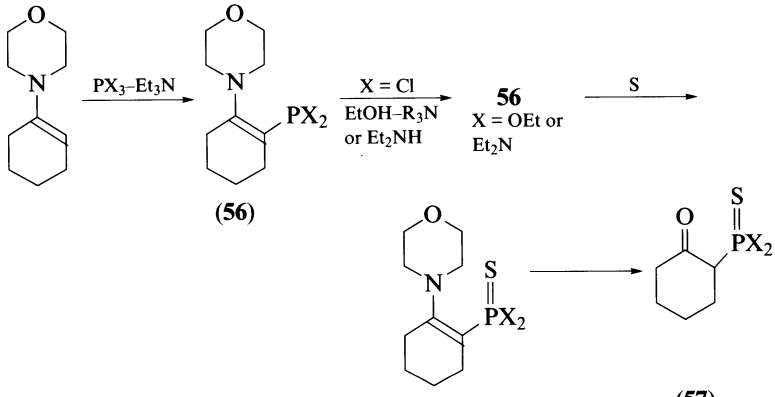
A simple but novel transformation is that of a phosphinic acid into the analogous phosphinothioic chloride in one practical step by the action of thiophosphoryl trichloride[132].

4. By chalcogen addition to phosphorus(III) compounds

Despite statements made in Chapter 2 about the unpopularity of this procedure for the preparation of phosphonic and phosphinic esters from those of phosphonous and phosphinous acids by the addition of oxygen, partly because of the lack of availability of the phosphorus(III) esters, but also because of the high reactivity exhibited by those esters towards oxidizing agents, the reduced reactivity shown towards the higher chalcogens by phosphonous and phosphinous halides (dihalo- and monohalo-phosphines), and even by some of the more reactive phosphorus(III) species, e.g. amides, makes such addition reactions feasible propositions.

The addition of sulphur to a phosphonous or phosphinous chloride is a fairly lethargic process, and although possible at a higher temperature without added catalyst, reactions performed at or near room temperature generally require the presence of a catalyst, and $AlCl_3$ has been widely used, as in the preparation of alkyl and aryl thiophosphonic chlorides, $RP(S)Cl_2$ and $ArP(S)Cl_2$, and thiophosphinic chlorides, $R_2P(S)Cl$ and $Ar_2P(S)Cl$, from the respective chlorophosphines[133–141]. The halides of bis(trifluoromethyl)phosphinous acid present an interesting case with a gradual change in reactivity through the series of four halides; thus $(CF_3)_2PF$ adds only a trace of sulphur after 16 h at 200 °C, but at the same temperature for 48h the addition is much more extensive; the chloride and bromide each afford a reasonable yield of the phosphinothioic halide after reaction at 160–180 °C for 3 days, but $(CF_3)_2PI$ is more reactive towards sulphur and many products are formed after only 16 h at 150 °C; an alternative procedure, consisting in the photocatalysed reaction between iodine and $[(CF_3)_2P]_2S$, is available for the synthesis of bis(trifluoromethyl)phosphinothioic iodide[140,141]. The addition of selenium to the alkyl or aryl chlorophosphines has been applied to give $RP(Se)Cl_2$, $R_2P(Se)Cl$, $ArP(Se)Cl_2$ and $Ar_2P(Se)Cl$, sometimes without added catalyst[142–145]. On the other hand, and in contrast to the requirement for the presence of $AlCl_3$ for chalcogen addition to chlorophosphines, the addition of sulphur to $MePBr_2$ and to Me_2PBr occurs readily in hot toluene, and that of selenium occurs even more easily[146,147].

Not only has thiophosphoryl chloride been successfully employed in the replacement of phosphoryl oxygen by sulphur, but it may also be used as a thiation reagent for tervalent phosphorus, for example for Ph_2PCl and Ph_2PCN[148], and also for other chlorophosphines including compounds as diverse as [(methylthio)methyl]phosphonous dichloride[149] and phenylethynylphosphonous dichloride[150]. The addition of sulphur or other higher chalcogen to phosphorus(III) esters is relatively easy, even without catalysis and may be exothermic[136,142–144,151–156]; the addition of the higher chalcogens is remarkably facile, and becomes easier with greater electron donation to the phosphorus atom, and found for phosphorus(III) amides[157–164]. In a slightly more unusual synthesis of an oxo-functionalized thiophosphonic derivative, the addition of sulphur to the phosphorus(III) derivatives **56** (X = OEt or NEt_2) is followed by mild acidolysis to the ester or bis(diethylamide) of (2-oxo-1-cyclohexyl)phosphonothioic acid (**57**; X = OEt or Et_2N)[165].



Although free thiophosphonic acids may be obtained by the hydrolysis of the corresponding dihalides, a much more convenient procedure, which exploits milder conditions, consists in the conversion of a phosphonous acid into its bis(trimethylsilyl) ester, followed sequentially by the addition of sulphur (and presumably that of selenium would be equally feasible) and hydrolytic removal of the trimethylsilyl groups; the procedure has been used for the preparation of both alkylphosphonothioic acids[166] and their aryl analogues[167].

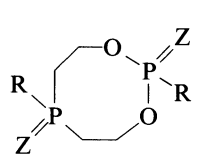
The addition of sulphur or selenium to a free dialkyl phosphite does not occur under normal working conditions (since the latter already exists almost exclusively as its quinquecovalent dialkyl hydrogenphosphonate tautomer), but its conversion into a metal salt (conveniently with a sodium alkoxide, NaH, $NaNH_2$, BuLi, lda or other similar reagent) or to the salt of an organic base allows the addition to proceed because of the reduction in valence at phosphorus. The conversion of a dialkyl hydrogenphosphonate into the halomagnesium salt of a phosphinous acid (through its reaction with a Grignard reagent) can be followed by the addition of sulphur or of selenium as a convenient means for the preparation of a phosphinothioic or phosphinoselenoic acid (Scheme 10)(Z = S or Se)[1,168]. A similar procedure starting with a monoalkyl phosphonite (in its tautomeric phosphoryl form) allows the preparation of a monoalkyl phosphonothioate and phosphonoselenoate[145,169], several of which have been the subject of intensive study from the point of view of resolution and subsequent use in studies on reaction mechanism.

$$(RO)_2P(O)H \xrightarrow{3R^1MgX} \left[R^1_2POMgX\right] \xrightarrow[(ii)\ H_3O^+]{(i)\ Z} R^1_2P(Z)OH$$

SCHEME 10

The three-dimensional structures of many cyclic esters of carbon-bonded phosphorus(III) acids have been studied, by means of ^{1}H, ^{31}P and ^{77}Se NMR spectroscopy and X-ray analytical techniques, after the initial (stereospecific) conversion of the phosphorus(III) compound into the more easily handled thio- (or, to a lesser extent, seleno-) phosphonate. Examples of such cyclic systems (which are merely cyclic esters of phosphonothioic acid) include the *cis* and *trans* forms of the sulphides and selenides of 2,6-dimethyl-1,3,2,6-dioxadiphosphocane (**58**; R = Me, Z = l.p.)[170,171] and a dibenzologue (**59**) of the same primary ring system[172], the 1,3,2-dioxaphospholane dimer 2,7-diphenyl-1,3,6,8-tetraoxa-2,7-diphosphecane **60**[173], the 1,3,2-dioxaphosphorinane phosphonite dimer **61**[174] and the 1,3,2-dioxaphosphepane phosphonite dimer **62**[175]. The formation of **63** by the addition of the chalcogen Z (Z = S or Se) to the phosphorus(III)-containing system allowed the chromatographic separation of phosphorus epimers of the disubstituted 1,3,2-dioxaphosphorinane (six-membered) ring in the carbohydrate system[176]. The addition of one equivalent of tellurium to 1,3-dimethyl-2,4-di-*tert* butyl-1,3,2,4-diazadiphosphetidine (**64**; Z = l.p) yields the fluctional monotelluride **64**(Z = Te) as golden-yellow crystals[177].

Phosphorus(III) thioesters are very air sensitive, and they can become hot even when poured from one vessel to another in the open air, Consequently, it is to be expected that their controlled oxidation to the *P*-oxides would present experimental difficulties. Nevertheless, a few of such oxidations, by MnO_2 or N_2O_4, for example, have been reported.



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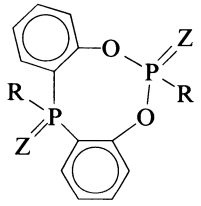

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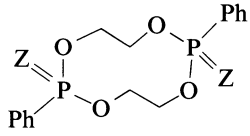

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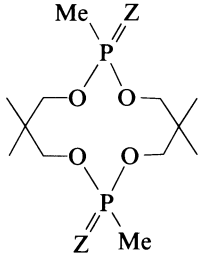

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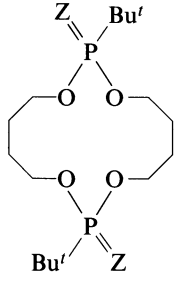

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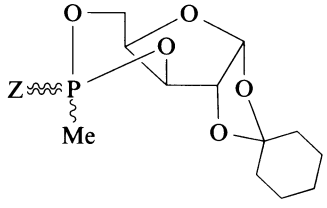

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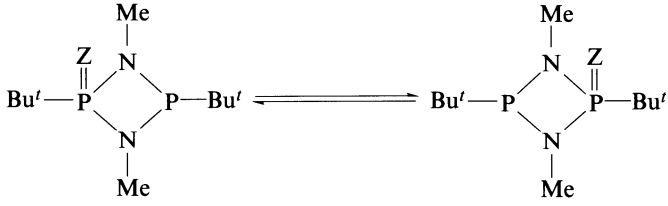
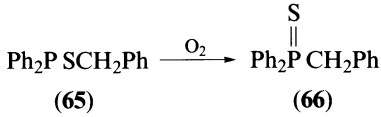


(64)

The esters $EtP(SR)_2$, Et_2PSR and EtPhPSR (R = alkyl)[178,179] and ester amides $RP(SR^1)NR^2_2$[38] have thus been oxidized to the corresponding phosphorus(V) esters. The attempted oxidation of the esters **65** and **67** by elemental oxygen merely results in their isomerization to a phosphine sulphide (**66**) and in the second case to the thiophosphonic diester **68**[180]. The case of **20** (X = 1.p., R = SCH_2Ph) is more unusual still, since such oxidation leads not only to the thiophosphonic ester (**20**; X = S, R = $PhCH_2$), but also to the dithiophosphoric ester (**20**; X = S, R = SCH_2Ph), together with other products[65].



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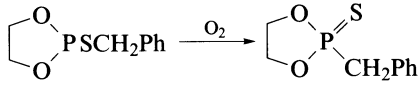
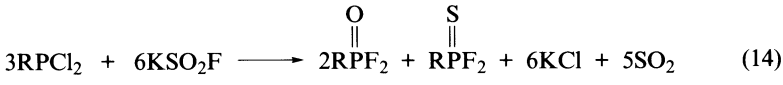


(67) (68)

During an investigation of the potential use of potassium fluorosulphinate, KSO_2F, as a reagent for fluorination by halogen exchange, Schmutzler[181] observed that the products from its interaction with halophosphines consisted of mixtures of the acid fluorides from phosphorus(V) acids according to equations 14 and 15. Separation of the oxo and thio products is sometimes feasible, e.g. when R = Me, but not so in other cases, e.g. for R = Ph in reaction 14 . In the most recent advance in this area, phosphinothioic and phosphinoselenoic chlorides, $Ph_2P(S)Cl$ and $PhBu^tP(S)Cl$ (and also phosphinic and phosphoryl chlorides) are transformed into the corresponding fluorides by the action of benzoyl fluoride or oxalyl fluoride on the derived imidazolides[182].



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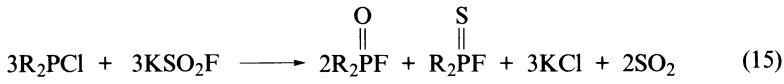


(15)

5. *Miscellaneous syntheses*

Mention might be here of reactions between the sodium salts (or the magnesium equivalent) of secondary phosphine oxides (the diaryl compounds appear to have been exclusively examined) and benzenesulphonyl chloride (reaction 16)[183], and that between chlorodiphenylphorphine and sodium arylsulphinates (equation 17) in DMF[184], when the

neutral products from both reactions are *S*-aryl diphenylphosphinothioates. The same products are obtainable from diarylphosphine oxides through the cleavage of disulphides; in particular, a study of the reactions with Ph_2S_2, from which the co-product is PhSH (equation 18), has demonstrated reaction promotion by the presence of electron-withdrawing groups in the phosphine oxide and by the additon of a suitable base, features which suggest that the phosphine oxide anion is involved in the rate-determining step of the process[185].

$$3Ph_2PONa + ArSO_2Cl \longrightarrow NaCl + 2Ph_2P(O)ONa + Ph_2P(O)SAr \quad (16)$$

$$Ph_2PCl + NaO_2SAr \longrightarrow Ph_2P(O)SAr + NaCl \quad (17)$$

$$Ar_2P(O)H + Ph_2S_2 \longrightarrow PhSH + Ar_2P(O)SPh \quad (18)$$

$$R^1(R^2O)P(O)H + R^3_2Se_2 \longrightarrow R^3SeH + R^1(R^2O)P(O)SeR^3 \quad (19)$$

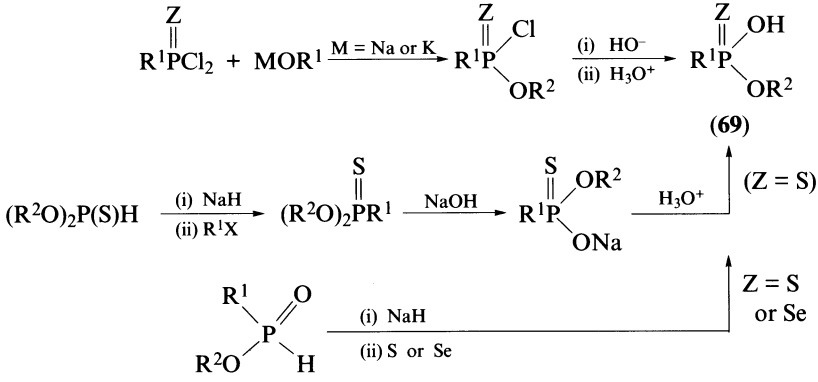
The above use of disulphides was based on earlier results obtained by Petrov and coworkers[186], who indicated the scope of the exchange reaction between disulphides and compounds which possess the P(O)H moiety; unlike dialkyl hydrogenphosphonates and alkyl hydrogenphosphinates, the reactions of both of which require catalysis by added sodium, those of secondary phosphine oxides do not[186,187]. The cleavage reaction is not limited to the use of disulphides, but it also operates for diselenides (equation 19) with no change in configuration at phosphorus[188]. It might also be added that the procedure is equally applicable to hydrogenphosphonothioates.

C. Chirality in Thio- and Seleno-phosphonic and -phosphinic Acid Derivatives

The replacement of oxygen in phosphonic or a phosphinic acid by sulphur or selenium renders it much easier to obtain optically active forms of a simple product possessing a chiral phosphorus centre. As early as 1911, Ephraim failed to resolve anions of the type $R_2P(O)O^-$, and so concluded that the anions were structurally symmetrical. However, the presence of an atom of, for example, sulphur, creates a non-symmetrical environment around the four-coordinate phosphorus atom, and permits the isolation of optical antipodes. Enantiomeric forms of a simple thiophosphonic acid derivative were first obtained by Aaron and Miller[189], who resolved the monoethyl ester of ethylphosphonothioic acid, Et(EtO)P(S)OH, by fractional crystallization of its salts with various alkaloids.

The aim of this section is to present a short summary of the processes used for the resolution of some simple phosphonic and phosphinic acid derivatives, and to indicate how the enantiomeric purity of such preparations, and of other optically active sulphur-containing organophosphorus esters, may be assessed. In most of the work to be described the phosphonic monoesters and phosphinic acids contining sulphur or selenium were prepared from the corresponding acid chloride; this and other preparative routes are indicated in Scheme 11.

The early experimental efforts to separate enantiomeric forms of simple derivatives of phosphono-thioic or -selenoic acids concentrated on the fractional crystallization of quinine, brucine or strychnine salts of the acid monoesters **69** (Z = S or Se); the early work in this area has been summarized[190,191]. It was not long before this tedious procedure, which did not always provide the best results, was superseded by a modification devised by Boter and Platenberg[192] which utlized enantiomers of 1-phenylethylamine. Essentially, (+)-1-phenylethylamine (0.5 mol) is added to the acid monoester in ether and the (+),(+)-salt is allowed to crystallize out, although this does not generally occur quantitatively. The excess



SCHEME 11

base is extracted following basification of the system, and the process then repeated by the addition of (–)-1-phenylethylamine to obtain the (–),(–)-salt. In some cases, a preliminary separation of enantiomers of the thio acid is achieved with the aid of an alkaloid, and the process is completed by the use of 1-phenylethylamine. It cannot be assumed that because an ester of a specific acid is successfully resolved by this, or any other, procedure that a homologue or analogue will also be so resolved and with necessarily equal ease; each potental resolution should therfore be considered on a case by case basis. Table 1 lists phosphonothioic monoesters and phosphinothioic acids (and some seleno analogues) which have been resolved, and which have proved useful, particularly in work on reaction mechanisms.

Reports on the resolution of neutral, racemic thiophosphonic diesters or related compounds by chromatographic means are very few. However, the resolutions of *O*-ethyl *O*-4-cyanophenyl phenylphosphonothioate, (cyanfenfos) and of the analogous *O*-4-nitrophenyl ester (ENP) have been achieved by HPLC on a poly(triphenylmethyl methacrylate) support[215].

Although, in any future use of the resolved compound in the study of changes in configuration at phosphorus, it may suffice to observe only a change in the sign of the optical rotation, it will be of considerable importance in most studies to be aware of the optical purity of any resolved compound and that of any optically active product obtained from it. The estimation of the optical purity fom optical rotation values can sometimes present difficulties, but refined and accurate methods are now available.

Physicochemical techniques do not distinguish between enantiomers in a racemic modification, and in order to provide differentiation, it is necessary to derivatize the enantiomers with a chiral reagent which itself is in resolved form. This may be done through salt formation with an appropriate base (as in the resolution process described above), by placing the substrate in contact with another type of chiral compound (complex formation) or by chemical reaction with a chiral reagent. The distinction between the resultant species has been made, most conveniently, on the basis of physicochemical techniques, particularly those of NMR spectroscopy, but also by structure determination by means of X-ray crystallography. A description of the application of such methods to the determination of enantiomeric purity of aminoalkyl phosphonic derivatives was given in the previous chapter; there follows futther discussion with particular regard to chiral sulphur- and selenium-containing derivatives of quinquecovalent phosphorus acids.

In the earliest example of the application of NMR spectroscopy to the determination of the enantiomeric composition, ^{1}H NMR spectroscopy distinguished between enantiomers of substances which possessed the P(O)H moiety and which were rendered diastereoiso-

TABLE 1. Resolved thio and seleno acids, $R^1R^2P(X)YH$

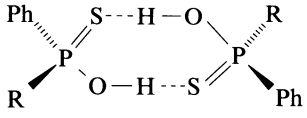
Compound				Resolving base[a]	Salt[a]	[α][b]		Ref.
R^1	R^2	X	Y			Acid: (+)-form	Acid: (–)-form	
Me	MeO	S	O	Q, PE	Q	–136.56 (0.52, MeOH)[c,d]	–146.15 (*c*, 0.52, MeOH)[c]	192, 193
					RPE	+10.04 (3.1, MeOH)	—	
					SPE	—	–10.04 (*c*, 3.1, MeOH)	
					DCH	+6.37 (5, MeOH)	–6.35 (5, MeOH)	
Me	EtO	S	O	B, PE	—	+9.57 (neat)	—	192, 193
					RPE	+10.64 (3.1, MeOH)	—	
					SPE	—	–10.56 (3.1, MeOH)	
					DCH	+8.47 (5, MeOH)	–8.47 (5, MeOH)	
Me	Pr^iO	S	O	Q, PE	—	+13.59 (neat)	–13.92 (neat)	192–195
					RPE	+10.74 (3.1, MeOH)	—	
					SPE	—	–10.74 (3.1, MeOH)	
					DCH	+7.76 (5, MeOH)	–7.72 (5, MeOH)	
Me	BuO	S	O	PE	RPE	+9.98 (3.1, MeOH)	—	192
					SPE	—	–9.97 (3.1, MeOH)	
					DCH	+7.25 (5, MeOH)	–7.21 (5, MeOH)	
Et	MeO	S	O	Q, B	DCH	+4.1 (MeOH)	–7.0 (MeOH)	193
Et	EtO	S	O	PE	—	+14.82 (neat)	–15.45 (neat)	196, 197
					RPE	+12.40 (7.43, MeOH)	—	
					SPE	—	–12.78 (8.13, MeOH)	
Et	EtMeCHO	S	O	PE	—	+8.66,+19.73 (2, EtOH)[e]	–9.13, –20.71 (2, EtOH)[d]	198, 199[f]
					RPE	+13.5 (10, EtOH)	–13.72 (10, EtOH)	
					SPE	–4.30 (10, EtOH)	+4.28 (10, EtOH)	
Pr	EtO	S	O	Q	DCH	+6.5 (MeOH)	–7.0 (MeOH)	193
Pr^i	MeO	S	O	PE	—	+14.67 (neat)	–14.31 (neat)	114
					RPE	+10.5 (1.1, MeOH)	—	
					SPE	—	–11.0 (1.63, MeOH)	
					DCH	+4.30 (1.17, C_6H_6)	–4.20 (1.07, C_6H_6)	
Bu^t	MeO	S	O	PE	—	+13.18 (neat)	–10.52 (C_6H_6)	200

Ph	MeO	S	O	PE	—	+21.72 (neat)	–21.0 (neat)	201–203
					RPE	+17.83 (10.75, MeOH)	—	
					SPE	—	–17.68 (14.5, MeOH)	
					DCH	+9.0 (2–4, MeOH)	–11.8 (2–4, MeOH)	
Ph	EtO	S	O	B	—	+17.2	–16.8	201, 203–205
					B	+12.0 (8.3, $CHCl_3$)	–11.8 (4.5, $CHCl_3$)	
Et	EtO	Se	O	Q, B	—	+11.36 (neat)	–17.54 (neat)	206
Et	EtO	S	Se	Q	—	+4.9 (neat)	–6.7 (neat)	207
					Q	–80 (0.45, C_6H_6)	–85.7 (0.45, C_6H_6)	
					DCH	+2.4 (1.2, C_6H_6)	–3.8 (1.15, C_6H_6)	
Ph	Me	S	O	Q	—	+19.5 (0.5, $CHCl_3$)	–22.3 (1.95, MeOH)	23, 208, 209[g]
					Q	—	–9.22[c]	
					B	+9.25[c]	—	
					RPE	+16.14 (1.5, MeOH)	—	
					DCH	+9.25 (1.75, MeOH)	–8.68 (3.3, MeOH); –9.22 (1.75, MeOH)	
Ph	Et	S	O	Q	DCH	+6.5 (5, MeOH)	–6.6 (6, MeOH)	135
Ph	Bu^t	S	O	PE	—	+28.1 (2.4, MeOH)	–24.9 (2.2, MeOH)	208, 210–212
4-$MeOC_6H_4$	Me	S	O	Q	—	+2.6 (0.04, MeOH)	–2.6 (0.04, MeOH)	213
					Q	–110 (0.04, MeOH)	–127 (0.04, MeOH)	
Ph	1-Np	S	O	Q	—	+112 (C_6H_6)	–113 (C_6H_6)	
					Q	–42 ($CHCl_3$)	–166 ($CHCl_3$)	214
					Et_2NH	+63.8 ($CHCl_3$)	–113 (C_6H_6)	
Ph	Bu^t	Se	O	PE	—	+25.65 (MeOH)	–30.05 (MeOH)	211

[a] PE = 1-phenylethylamine; RPE = (*R*)-1-phenylethylamine; SPE = (*S*)-1-phenylethylamine; DCH = dicyclohexylamine; B = brucine; Q = quinine.
[b] Unless stated otherwise, this is for solutions at 24–26 °C and with Na- D-line radiation.
[c] $[\alpha]_{578}^{25}$.
[d] Concentration, solvent.
[e] From the enantiomers of 1-methylpropanol.
[f] See also ref. 226.
[g] See also ref. 282.

meric through the presence, also, of a menthyl group[216]. Later work relied upon differential complexation between a phosphoryl compound and a chiral solvent such as (+)- or(–)-2,2,2-trifluoro-1-phenylethanol, although it has not proved possible to use this procedure with thiophosphoryl compounds because of a lack of complexation between the solvent and the solute. Nor has the use of chiral shift reagents such as tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium, $Eu(hfc)_3$, attracted much attention, again because of lack of strong complexation with thiophosphoryl compounds, although examples of its use have been reported.

The notion of a chiral agent which complexes simply through hydrogen bonding is both simple and novel, and evidently very effective. The 100 MHz ^1H NMR spectrum of the racemic modification of an asymmetric phosphinothioic acid PhRP(S)OH, (R = Me or Bu^t) show one signal; the purified enantiomers of each acid also show one signal (at positions different from those for the racemic forms). The changes in the positions of the two ^1H NMR signals for mixtures of enantiomers for each of the two acids have been explained in terms of preferential complexation between one enantiomer and itself or between one enantiomer and its antipode through hydrogen bonding in the short-lived (rapidly exchanging) diastereoisomeric dimers **70** and **71**[209]. A study of the ^1H NMR spectra in the analogous complexation between one enantiomer of a phosphinothioic acid and the enantiomeric forms of a non-identical but resolvable compound, e.g. methylphenylphosphinic amide, $MePhP(O)NH_2$, with complexes **72** and **73** then allows the enantiomeric composition of the second molecular species to be determined. In particular, resolved *tert*-butylphenylphosphinothioic acid has been used to determine the enantiomer compositions of a range of phosphoryl compounds with, or lacking, a sulphur content[209]. Magnetic non-equivalence of protons has been observed, for example, in the ^1H NMR signals for the Me protons of *O*-alkyl methylphosphonothioates, (RO)MeP(S)OH, and *O*-methyl alkylphosphonothioates, R(MeO)P(S)OH, in the presence of enantiomerically pure 1-phenylethylamine[191,208,217]. The differences in chemical shifts seen for the methyl protons are greater for the former group (7–19 vs 0.6–4 Hz), and the low non-equivalence sense has been assigned to the acid of *S*-configuration. The sense of the magnetic non-equivalence is not altered by temperature, or by changes in concentration, although these factors may change its magnitude. Magnetic non-equivalence is also observable in the ^{31}P NMR spectra of the same salts with differences in chemical shifts of 1–7 Hz[218]. It should be re-emphasized, however, that stereochemical conclusions based on spectroscopic features can be applied safely only within a series of compounds of one specific type.



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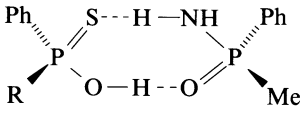

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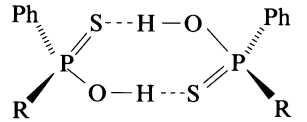

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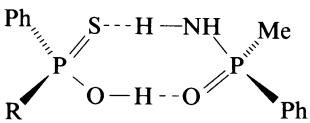
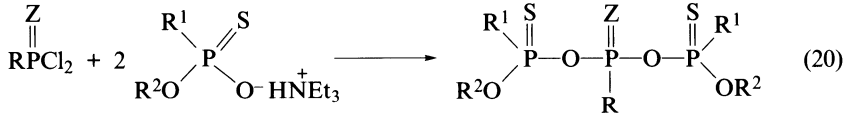


(73)

Another approach to the determination of enantiomeric composition has been offered by Dimukhametov and Ismaev[219,220] based on examination of the NMR spectra of compounds which possess a prochiral phosphorus atom. The rates of reaction 20 are such that

the synthesis of **76** is best achieved by the addition of sulphur to **74**, in turn obtained by the reaction between a dichlorophosphinie and a phosphonothioate ester in the presence of triethylamine. Compounds **74**–**76** are capable of existence in four stereoisomeric forms. Two of these, in which the configurations of the two outer phosphorus atoms are identical, are enantiomeric with respect to each other, and together comprise a racemic modification; in these two forms, the central phosphorus atom is achiral, and the NMR spectra of the two forms are identical. The other two forms, in which the configurations of the outer two phosphorus atoms are antipodal, are both *meso* forms and are diastereoisomers in which the central phosphorus atom is pseudochiral. In the last case, the NMR spectra of the two forms do differ slightly. Thus, the proton-decoupled ^{31}P NMR spectra of **74** (R = Ph; R^1 = R^2 = Et) in benzene consists of two groups of signals, one at ca 95 ppm (for the thiophosphoryl phosphorus atoms) and the other at ca 150 ppm (for the tervalent phosphorus atom); the latter signals consist of a doublet of doublets B (which correspond to the racemic modification) situated between two triplets A and C, which corresponding to the non-equivalent *meso* forms. The signals for the central phosphorus(III) atom in **74** derived from (*S*)-(–)-ethyl ethylphosphonothioate consist of a doublet of doublets indicating, in qualitative terms, that the two thiophosphoryl atoms are magnetically non-equivalent. Again, in qualitative terms, a similar behaviour is seen for **75**, but the nature of the spectrum obtained for the trisulphide **76** is such that it is of very little, if any, use of analytical purposes. In the gradual transition from the racemic form of the phosphonothioic acid ester to an optically active form, the share of the two *meso* forms in the stereoisomeric mixture should decrease from 0.5 (for racemic acid) to 0 (for optically pure enantiomer), with the resultant disappearance of the A and C signals. The integrated values of the A, B and C ^{31}P signals allows a determination of optical purity. NMR examination of a sample of the 1-phenylethylammonium salt from the (–)-base and (–)-*O*-isopropyl ethylphosphonothioate indicated an optical purity of 34.0%; examination by the above method following its reaction with $PhPCl_2$–Et_3N suggested a value of 35.3%.

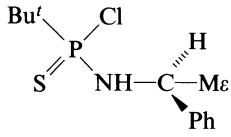


(20)

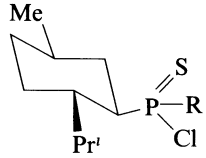
(**74**) Z = l.p
(**75**) Z = O
(**76**) Z = S

Many more examples of the use of ^1H, ^{13}C and ^{31}P NMR spectroscopy in the differentiation between diastereoisomeric sulphur- or selenium-containing organophosphorus ester derivatives are widely distributed throughout the literature. Two further examples are, first, the use of ^{31}P NMR spectroscopy to distingusish between the diastereoisomers of the phosphonothioic chloride **77**, which displays ^{31}P signals at 93.4 and 95.0 ppm in $CDCl_3$, and the products from its reaction with primary amines[221], and second, the phosphorus epimers of the phosphinothioic chloride **78** (R = Bu^t) which exhibit signals at 128.7 and 132.6 ppm[222], the phenomenon being noted for a series of analogous alkyl (L-menthyl)phosphinothioic chlorides[223,224]. The chemical shifts of $C_{(4)}$, $C_{(8)}$, $H_{(8)}$ and the menthyl methyl groups and the coupling constants $^2J_{PC\text{-}2}$, $^2J_{PC\text{-}4}$, $^3J_{PC\text{-}1}$ and $^3J_{PC\text{-}8}$ are stereospecific indicators for the configurations at phosphorus in the phosphorus epimers of such phosphinothioic chlorides.

Mikołajczyk *et al.*[225] have also examined the chiroptical properties of a series of simple phosphono- and phosphino-thioic acids and some of their derivatives. A negative Cotton effect was found to be characteristic for all (*R*)-(+)-alkylphosphonothioic acid *O*-esters,



(77)



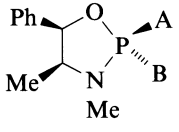
(78)

and a positive effect for the enantiomeric compounds, all of which showed a single intense transition at about 200 nm in non-polar solvents (and almost independent of the solvent) but shifted in water. More complex spectra were observed for the phosphinothioic acids, RPhP(S)OH, with bands at <200, 215–220 and 230–270 nm. Once again, therefore, it should be emphasized that the usefulness of a specific technique depends on the type of compound under consideration.

The configuration at phosphorus in chiral compounds can be determined by an X-ray crystallographic examination of an appropriate derrivative which possesses more than one chiral centre. The procedure is particularly useful for the determination of the chirality of key compounds, such as the resolved acids just described; their conversion into other compounds then allows further structural assignments to be made, provided, of course, that in such transformations bonds to phosphorus are not broken or, if they are, the stereochemical changes involved are then clearly understood. Fukuto and co workers showed that the (–)-enantiomers of each of *O*-ethyl *S*-4-bromophenyl ethylphosphonodithioate and phenylethylammonium *O*-ethyl ethylphosphonothioate[196] and the (–)-1-phenylethylammonium salt of (–)-*O*-methyl phenylphosphonothioate[202] all have the (S_P) absolute configuration. Wustner and coworkers[198,199,226] prepared the *O*-1-methylpropyl esters (from racemic and also from resolved 1-methylpropan-1-ol) of ethylphosphonothioic acid; from the optical rotations of all four diastereoisomers, and the X-ray structure demonstration that the (–)-1-phenylethylammonium salt of (–)-*O*-1-methylpropyl ethylphosphonothioate with $[\alpha]_D = -13.72°$ (in EtOH) had the (R_CS_P)-configuration, they were able to assign configurations to all the diastereoisomers. The structures of some diastereoisomeric 3,4-dimethyl-5-phenyl-1,3,2-oxazaphosph(V)olidines have been confirmed and new ones determined more recently; in the particular context of the present discussion, the structures of the cyclic phenylphosphonothioic amides **79**, epimeric at phosphorus, are of relevance[227]. The same technique has been used for (R_P)-*tert*-butyl(L-menthyl)phosphinothioic chloride[222], and the structure may be compared with that of bis(L-menthyl)phosphinothioic chloride, similarly determined[228]. Sorensen[229] was able to correct an earlier configurational assignment to the methiodide of (+)-*O*-isopropyl *S*-(2-dimethylaminoethyl) methyl phosphonothioate, and showed, by X-ray crystallography, that it was *R*.

The creation of diastereoisomeric molecules which are epimeric at phosphorus presents no fundamental difficulties. Such molecules are readily available by means of reactions between the dichlorides $RP(=Z)Cl_2$ (Z = O, S or Se) and an appropriate chiral difunctional compound. Many reactions that lead to such products were indicated in the previous chapter in connection with the synthesis of enantiomers of, particularly, (1-aminoalkyl)phosphonic acids and related compounds. With regard to the preparation of diastereoisomeric thio- or seleno-phosphoryl compounds epimeric at phosphorus, the chiral reactants first used were modified carbohydrates and, less successfully, simple mono- or di-substituted diols. The latter provided simple monocyclic 1,3,2-dioxaphospholanes and 1,3,2-dioxaphosphorinanes which could provide (a) chiral centre(s) on (a) ring carbon atom(s), but also generated compounds epimeric at phosphorus; their inconvenience often lay in lack of availability of cheap starting materials. In the case of the carbohydrates, the substrates were readily available from cheap starting materials; thus, methyl 2,3-di-*O*-methyl-

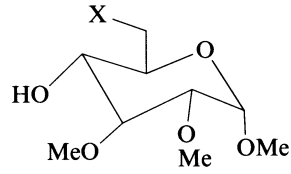
α-D-glucopyranoside and related compounds of the general structural type **80** provided **81** (A, B = Me or Ph, etc.; B, A = =S or =Se; X = O, S or NMe) in which the substituents at phosphorus could be sited axially or equatorially. The assignments of configurations were generally based on infrared, ^{31}P and limited ^{1}H NMR spectroscopic data; in any epimeric pair, the isomer with an axial P=O displays the bond infrared frequency at a higher wavenumber and the ^{31}P signal at a higher field than those shown by the isomer with an equatorial P=O bond; in the case of the selenophosphoryl compounds, the conformation of the P=Se bond, and hence of the second exocyclic moiety, could be determined from a measurement of the $^{1}J_{PSe}$ coupling constant, as well as by a chemical correlation with the phosphoryl analogue, through oxidation with H_2O_2 or *m*-peroxybenzoic acid with retention of configuration at phosphorus. Other chiral 1,3,2-oxathiaphosphorinanes (**82**) were derived from (–)-10-mercaptoisoborneol; the absolute configuration of **82**(Z = O, R = CH_2COOEt) was determined by X-ray crystallography[230].



(79)

(a) A = Ph, B = =S

(b) A = = S, B = Ph

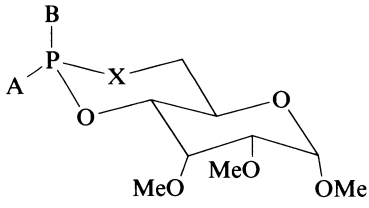


(80)

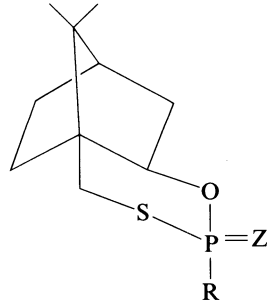
(a) X = OH

(b) X = SH

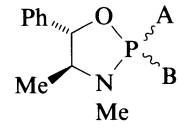
(c) X = NHMe



(81)



(82)



(83)

The bicyclic 1,3,2-dioxaphosphorinanes have lost their popularity and have been replaced, both for mechanistic studies and for synthetic purposes, by the monocyclic and yet diastereoisomeric 3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholidines[12,190]. The most widely employed of these compounds have been those derived from (–)-ephedrine and of 4*S*,5*R* geometry (**79**), from (+)-ephedrine, and so of 4*R*,5*S* geometry, and from (+)-pseudoephedrine, which are of structure **83** with 4*S*,5*R* stereochemistry. Their syntheses with a dichloride $RP(Z)Cl_2$ in the presence of an appropriate HCl acceptor yield mixtures of products, epimeric at phosphorus, and generally separable. A few other compounds have been derived from norephedrine. The stereochemistries of several such compounds have been determined by X-ray crystallography, and reference has just been made to some

of these, but epimers may also be distinguished of the basis of ^{1}HNMR signals for *N*-Me and *C*-Me groups, in addition to their ^{31}P NMR spectra.

Meanwhile, the assignment of configuration at phosphorus by chemical means is still of importance. Generally this is achieved through Walden-type cycles, in which a configurational change in one step of a reaction sequence can be determined from the known changes in the remaining steps; examples of such cycles will be considered in later sections of this chapter. However, a further reaction which has been applied for the same purpose is the oxidation of a thiophosphoryl compound to its phosphoryl analogue by means of a chiral sulphoxide; an assignment of configuration at phosphorus may follow from a consideration of the changes in the stereochemistry of the sulphoxide; this reaction, too, will be considered more fully later in this chapter.

III. INTERCONVERSIONS OF THE MONOTHIO(OR SELENO) -PHOSPHONIC AND -PHOSPHINIC ACIDS AND THEIR DERIVATIVES

In this section, consideration is given to some further, mutually related replacement reactions of monothio- and monoseleno-phosphonic and -phosphinic acids and their simple derivatives and, where appropriate, the stereochemical changes accompanying those reactions, most of which are also of preparative value.

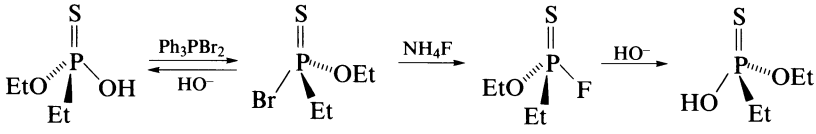
A. Reactions which Proceed with Predominant Configurational Inversion

1. The formation of acid halides

Phosphorus pentabromide was employed to convert *O*-methyl *tert*-butylphosphonothioate into the phosphonothioic monobromide (MeO)Bu^{t}P(S)Br[200] and a similar conversion of *O*-ethyl ethylphosphonothioate into Et(EtO)P(S)Br with triphenylphosphine dibromide has also been described[213].

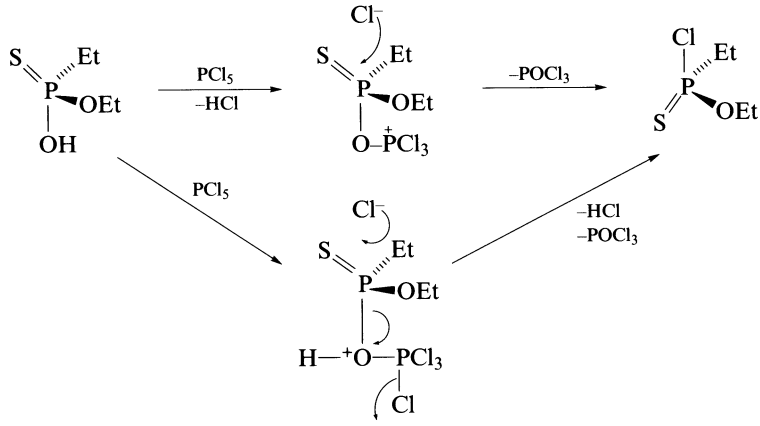
In the second of these reactions (Scheme 12), (*R*)-(+)-*O*-ethyl ethylphosphonothioate yielded the optically stable (+)-bromide, from which, by alkaline hydrolysis (with 2.85 M KOH in aqueous dioxane) the original acid was obtained with only about 6% loss of optical purity. Because the hydrolysis step (at least for the corresponding chloride) is thought to occur with inversion of configuration at phosphorus (Section III.A.3), it follows that formation of the bromide takes place likewise.

Subsequent preparation of the fluoride, (EtO)EtP(S)F, required the use of the thioacid bromide and ammonium fluoride, since the corresponding thioacid chloride displayed only little activity towards NH_4F, and some of the other halogen exchange reagents described in the early literature[2,5–7] [including ZnF_2, NaF, SbF_3, Na_2SiF_6, SbF_3–NaF, MHF_2, (M = Na or K), PhCOF or picryl fluoride] proved unsatisfactory in their behaviour towards either the thioacid chloride or bromide[232]; picryl fluoride is now known to react with a salt of a phosphonothioic acid to give a sulphur-free product.



(*R*)-(+)- (*S*)-(+)- (*S*)-(–)-

SCHEME 12



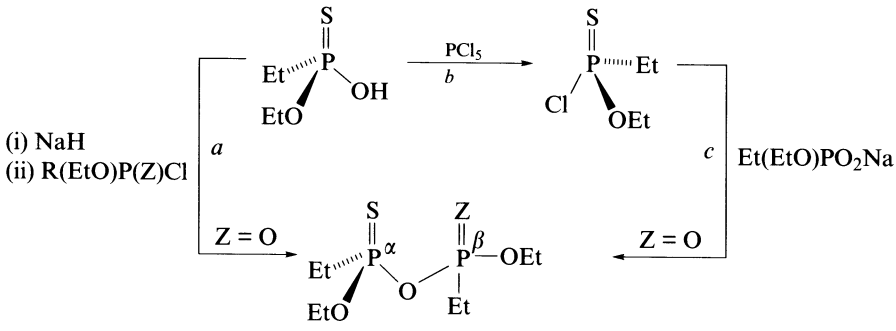
SCHEME 13

The displacement reactions of phosphoryl chlorides sometimes occur without total stereospecificity as a result of racemization brought about by Cl^- [233]. Racemization should not occur in displacements which lead to acid fluorides, particularly under the very mild conditions (in MeCN at room temperature) used with the bromide; here, the thioic (–)-bromide afforded (+)-fluoride in a displacement thought to proceed with at least 90% enantioselectivity. Since hydrolysis of the thioic fluoride resulted in the formation of the (+)-acid, the argument adopted in the previous paragraph would then suggest that the displacement of bromide by fluoride must have occurred with inversion of configuration[232].

The interaction of PCl_5 and a phosphonothioic, phosphinothioic or phosphinodithioic acid affords the corresponding thiophosphoryl (di)chloride[2,5–7]. With neat reactants at room temperature, (–)-*O*-methyl *tert*-butylphosphonothioate gives the (–)-chloride[200]. The reagent and (S)-(–)-*O*-ethyl ethylphosphonothioate in an appropriate solvent at –10 °C (diethyl ether is best) together yield the optically stable (in contrast to the analogous sulphur-free compound) (–)-*O*-ethyl ethylphosphonochloridothioate with very high enantioselectivity, although some racemization by Cl^- might be expected; no *O*-ethyl ethylphosphonochloridate is formed in this reaction and, as a consequence, it has been postulated that the site of attack by the PCl_5 reagent is the oxygen in the acid; two possible modes of interaction are indicated in Scheme 13 [233–235]. Other workers have given accounts of the preparations of optically active *O*-alkyl methylphosphonochloridothioates, (RO)MeP(S)Cl[177,236,237], and also of the ethyl esters of ethyl- and phenyl -phosphonochloridothioic acids, (EtO)RP(S)Cl (R = Et or Ph), obtained in a similar manner[233,238,239]. Yet further compounds based on ethyl- and isopropyl-phosphonochloridothioic acids have been listed by Mikołajczyk *et al.*[237]. Very occasionally, the use of oxalyl chloride has been recommended as an alternative to that of PCl_5; the overall stereochemical result has been claimed to be that of inversion at phosphorus[239], although in the preparation of the chloride **77**, a mixture of diastereoisomers was obtained from from a single enantiomer of the corresponding free acid in diethyl ether[221].

2. *The formation of anhydrides*

Recognition that the formation of a phosphonothioic chloride from the acid occurs with inversion of configuration stems partly from a study of the alkaline hydrolysis of the chloride (with inversion), but primarily on the basis of the formation and structures of the

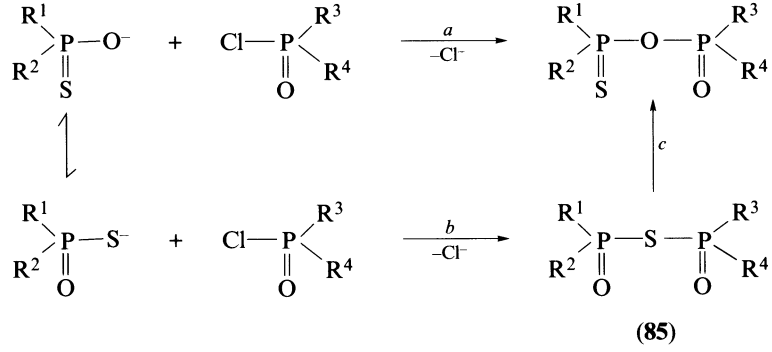


(84)

SCHEME 14

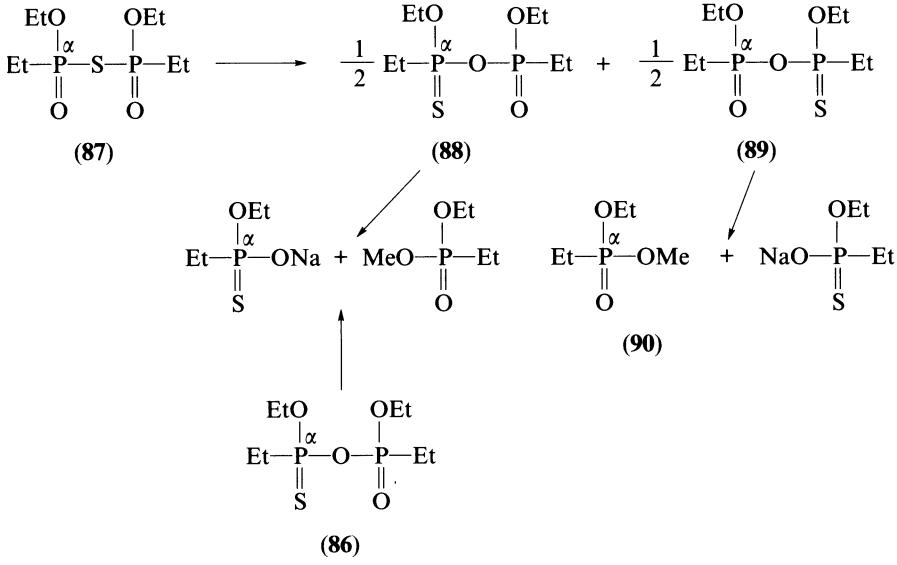
monothiodiphosphonic (monothiopyrophosphonic) diester **84**(Z = O). The two reaction pathways indicated in Scheme 14 need to be considered. In the first (pathway *a*), the (*S*)-(–)-phosphonothioic acid ester is converted into its sodium salt, which is then acted upon by racemic *O*-ethyl ethylphosphonochloridate (Z = O), a step which requires no cleavage of any bond attached to the chiral phosphorus centre. In the second sequence (steps *b* and *c*), the initial conversion of the acid into its chloride is followed by a reaction between the latter and racemic sodium *O*-ethyl ethylphosphonate. The products (**84**; Z = O) from the two routes are identical chemically and, on the basis of sign and magnitude of optical rotations, stereochemically; only a marginal difference in optical rotations for the two samples was observed experimentally, and the values for $[\alpha]^{20}_{D}$ for the routes *a* and *b*/*c* (+29.50° and +28.75°) suggested the degree of stereospecificity to be about 98%. Bearing in mind the possibility of racemization by chloride anion in step *c*, it seems likely that step *a* proceeds with full stereospecificity. The optical activity of the anhydride **84**(Z = O) stems from the thiophosphoryl phosphorus and the configuration of the latter must be identical with that in the original acid; it follows that the steps *b* and *c* must both occur either with retention or with inversion of configuration, the latter being the more likely[235]. The same conclusion was reached from a study of the reactions which involved reacemic Et(EtO)P(S)Cl (step *a*) and racemic Et(EtO)P(S)ONa (step *c*) and which provided **84**(Z = S)[235].

This mode of anhydride synthesis is advantageous in that it defines the stereochemistry at P^{α} as being that of the original acid, with that at P^{β} being inverted relative to the configuration in the precursor chloride. However, these considerations do not take into account the possibility of the preferential formation of an isomeric monothioanhydride. Pathway *a* (Scheme 15) reflects an attack by the harder oxygen centre in the mesomeric ion at phosphoryl phosphorus in the chloride, but the alternative route (steps *b*/*c*) proceeds with the initial formation of the symmetrical compound, followed by its isomerization. Symmetrical monothio anhydrides (**85**) are now known in the phosphoric acid series and, although isolable, they can isomerize rapidly, particularly at higher temperatures. It is also known that the site of attack within the mesomeric phosphonothioate anion depends on the attacking species; thus alkylation leads to *S*-alkyl products (Section III.B.1) whereas reactions with alkanoic chlorides occur at oxygen (Section III.B.2). The possibility of the involvement of pathway *b*/*c* (Scheme 15) has been neatly explored[240]. The unsymmetrical (+)-anhydride **86**(Scheme 16), derived from (–)-phosphonothioic acid and racemic phosphonic chloride, is optically active because of the contribution from P^{α}, and its reaction with sodium methoxide gives rise to racemic ethyl methyl ethylphosphonate together with optically active ethyl ethylphosphonothioate (after acidification). If the initially formed



(85)

SCHEME 15

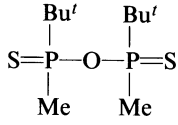


(87) (88) (89) (90) (86)

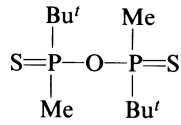
SCHEME 16

anhydride was symmetrical, **87**, it would subsequently isomerize to a mixture of **88**(= **86**) and **89**; because of the formation of the latter, the degradation of **87** with methoxide would lead to the optically active ethyl methyl ethylphosphonate **90**. However, the isolated diester was optically inactive, and it was therefore argued that pathway *b*/*c* plays no part in the reaction Scheme 15[240].

As a variation in experimental methodology, the partial hydrolysis of MeBu^{t}P(S)Cl by aqueous alkali–dioxane (with inversion) affords the symmetrical dithiodiphosphonate; the major product thus isolated had the *meso* structure **91**(indicated by X-ray crystallography) rather than the racemic form **92**; by contrast, when the same phosphinothioic chloride in acetone reacted with preformed MeBu^{t}P(S)ONa at 65 °C, a mixture of the *meso* and racemic modifications in the ratio 1:2 was obtained[241].



(91)



(92)

At this point, the reader is reminded of the considerations given earlier to the anhydrides **74–76** obtained by the reactions between the dichlorides, $RP(Z)Cl_2$ (R = Me or Ph, Z = l.p.,O or S) and optically active mono-*O*-esters of phosphonothioic acids, and their use in the determination of the optical purity of the latter[219,220].

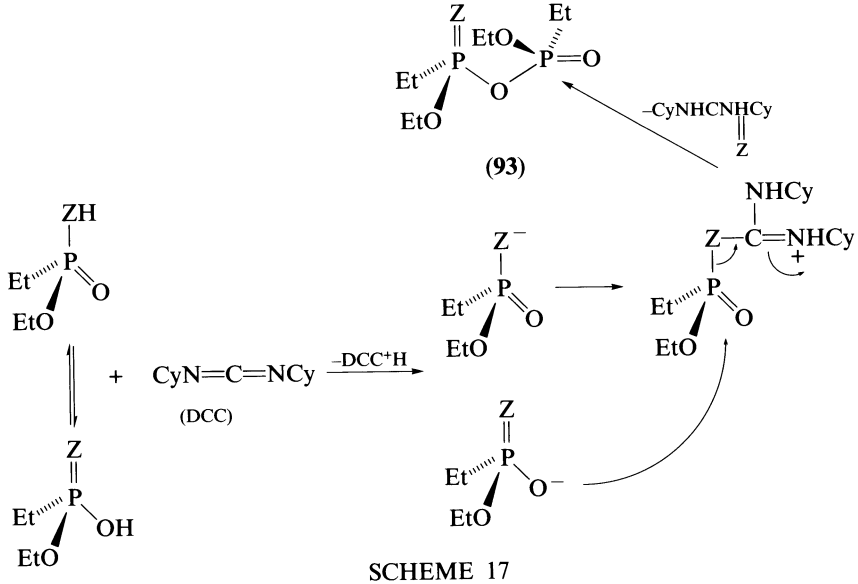
A further route to monothioanhydrides lies in the thermolysis of symmetrical diphosphoryl disulphides[242]. The formation of the disulphides will be discussed in later paragraphs, but it might be pointed out here that, in the context of this particular study, the (+)-disulphide was obtained by the action of sulphuryl chloride on (*R*)-(+)-*O*-ethyl ethylphosphonothioate. The interesting feature with regard to the formation of the anhydrides is that the slow decomposition of the disulphide at 20–25 °C (its complete decomposition required 250 h) yielded a product mixture different from that formed at 120–125 °C. Thermolysis of the (+)-disulphide gave the (–)-anhydride; likewise, the (+)-anhydride was formed from the (–)-disulphide [prepared from the (*S*)-(–)-phosphonothioic acid]. The stereochemistry of each anhydride was determined by degradation with MeONa (with inversion). The ethyl methyl ethylphosphonate isolated (compare Scheme 16) from the low-temperature decomposition was optically inactive, but the (+)-ester was isolated from the anhydride obtained from a high-temperature decomposition. Analysis of the optical activity data suggested that the slow decomposition led to one of two possible mixtures of a *meso* and optically active diastereoisomer depending on the chirality at phosphorus in the starting phosphonothioic ester; the anhydride formed at high temperature consisted of a *meso* form, possibly formed in a free-radical reaction, in contrast to an ionic process at the lower temperature.

Another procedure which should be considered here is one which became particularly important in phosphoric acid chemistry because of its applicability under very mild conditions and its resultant success in nucleotide chemistry; dehydration of the acid to an anhydride is achieved with the aid of a carbodiimide the most widely used of which has been dicyclohexylcarbodiimide (DCC). By analogy with the accepted mechanism for such reactions, the dehydration of a phosphonothioic monoester should take place according to Scheme 17.

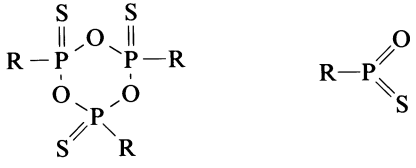
(*S*)-(–)-*O*-Ethyl ethylphosphonothioate with DDC gives the (+)-anhydride **93**(Z = S). From mechanistic considerations, the anhydride should have the *S*-configuration at the thiophosphoryl phosphorus with inverted configuration, i.e. *S*, at the phosphoryl phosphorus[243]. A similar process (Scheme 17)(Z = Se) operates for the dehydration of *O*-alkyl ethylphosphonoselenoates with DCC when (–)-acid esters yield (+)-anhydrides[244].

The hydrolysis of phosphonothioic dichlorides under carful conditions yielded 'trimer' anhydrides of type **94**, 1,3,2-trioxa-2,4,6-triphosphorinane 2,4,6-trisulphides; 'dimer anhydrides', 1,3,2,4-dioxadiphosphetane 2,4-disulphides, do not appear to be formed under normal conditions[245]. Other reports on the hydrolysis of (2-alkoxyethenyl)phosphonothioic dichloride suggest the formation of monomeric oxothioxophosphorane species (at least monomeric in acetic acid solution) (**95**); these react with alcohols, phenols, primary amines or oxiranes to give products of a well defined nature (see Section IV.C.)[246].

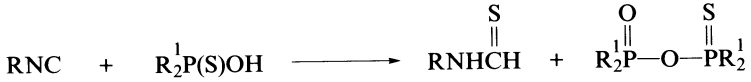
The interaction of a phosphinothioic acid (or a dialkyl phosphorothioic acid) with an alkyl isocyanide yields the corresponding *N*-alkylthioformamide together with a monothio anhydride (reaction 21)[247]. A further interesting sequence commences with the interaction of a diarylphosphine oxide, $R_2P(O)H$ (R = Ph or *p*-Tol) with HCNS. It is known that such



SCHEME 17

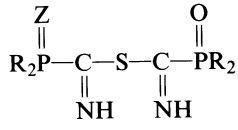


(94) (95)



(21)

phosphine oxides and analogous sulphides react with thiocyanates (in the presence of Et_3N at 70–80 °C) by additon across the N=C bond and formation of the phosphinothioformamides, $R_2P(Z)C(S)NHR'$ (Z = O or S); with HCNS, a second addition step leads to the two compounds **96**(Z = O or S) together with $R_2P(S)NCS$ and the symmetrical dithioanhydride $R_2P(S)OP(S)R_2$. The latter might be formed when the phosphine oxide is sulphurized (by the HCNS) to $R_2P(S)OH$, which then combines with $R_2P(S)NCS$ (from the phosphinothioic acid and more HCNS)[248].

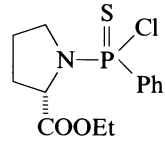


(96)

3. *The hydrolysis and alkoxide displacements of acid halides and anhydrides*

As indicated in Section III.A.1, the evidence for configurational inversion during the formation of phosphonothioic halides is based, at least partly, on the belief that the reverse hydrolysis also occurs with inversion. Mikołajczyk[249] made a special study of the hydrolysis of optically active *O*-ethyl ethylphosphonochloridothioate . In 2 M KOH–dioxane at room temperature, the (–)-chloride is hydrolysed, with high yield, to the (*S*)-(–)-acid; the acid was found to be at least 97.5% optically pure, which suggested that the hydrolysis was 97% stereospecific, the slight loss in stereospecificity being the result of racemization caused by the presence of chloride anions. Thus, the stepwise conversion of the acid into chloride and back into the acid produced acid of configuration identical with that with which the cycle started, probably by two inversion steps.

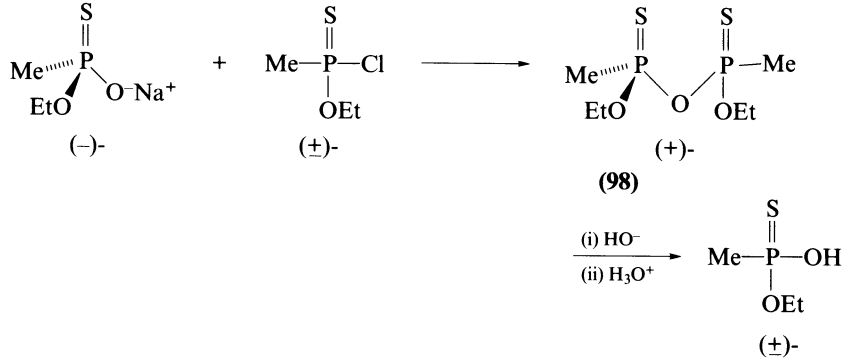
A high degree of stereospecificity with inversion has been reported for several other displacements of thioacid halides, including the reactions between (Pr^{i}O)MeP(S)Cl and NaOMe[236], and between (R_2N)PhP(S)Cl (**97**)(from ethyl prolinate and $PhP(S)Cl_2$) and MeOH–Et_3N[250] or $NaOAr$[250,251].



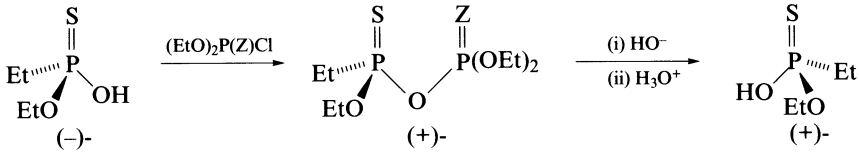
(97)

More convincing evidence for the inversion of configuration at phosphorus during hydrolysis reactions was obtained by studies with phosphonothioic anhydrides. The first observations in this respect (Scheme 18) seem to have been those reported by Green and Hudson[252]; they showed that alkaline hydrolysis of the optically active anhydride **98** yielded racemic *O*-ethyl methylphosphonothioate—the result of hydrolysis with inversion . The cycle represented in Scheme 19 indicates that an optically active acid yields an optically active anhydride (**99**; whose sign of optical rotation is independent of Z = O or S) with retention of configuration (no bond to phosphorus P^z broken); hydrolysis of the anhydride then yields the same acid but of opposite configuration, indicating a reversal in configuration at P^z [253].

The cleavage of the anhydride bond in mono- and di-thio anhydrides of phosphonothioic mono esters (and indeed also of similar anhydrides of phosphinothioic acids), with



SCHEME 18

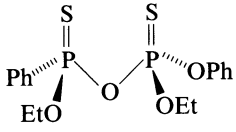


SCHEME 19

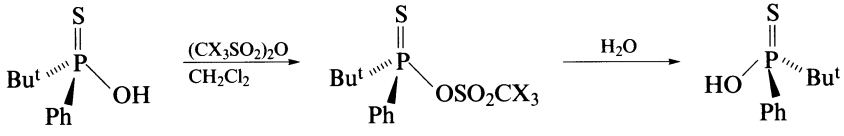
chiral centres at one or both phosphorus atoms, is a reaction of enormous potential for the synthesis of derivatives of chiral phosphorus acids, and the manner of cleavage results from the greater electrophilicity of phosphoryl phosphorus compared with thiophosphoryl phosphorus. Thus the anhydride **84**, chiral at the thiophosphoryl phosphorus, is cleaved by thiolate anions to yield *S*-alkyl *O*-ethyl ethylphosphonothioates[254,255], by alkoxide anions to give *O*-alkyl *O*-ethyl ethylphosphonates[240,255], and by secondary amines[249] or amine anions[255] to give the phosphonamidic esters $Et(EtO)P(O)NR_2$, all the products being in optically active forms with inverted stereochemistry at phosphorus. Displacements have been carried out on the analogous monoseleno anhydrides with similar results[244].

The displacement reactions of the anhydride from *O*-ethyl phenylphosphonothioate and *O*-ethyl *O*-phenyl phosphorothioic acid have been the subject of separate investigation[256]. The (*R*,*R*)-(+)-anhydride **100** was subjected to reactions with a variety of nucleophiles. The latter, which included HO^-, NH_3 and HS^-, all appeared to attack the phosphonothioic phosphorus centre, and the reactions proceeded with inversion of configuration, with the exception of that with HS^-, from which a racemic product was obtained since it consisted of the ion $Ph(EtO)PS_2^-$. The principle difference between this substrate example and those considered earlier is that both phosphorus centres are chiral, and hence the thiophosphoric derivatives, formed concomitantly, are also optically active.

In mixed anhydrides in which thiophosphoryl phosphorus is bonded to another heteroatom other than phosphorus, attack by a nucleophile may be diverted away from the phosphorus should the second reactive centre be more electrophilic. So, in the case of phosphinothioic sulphonic anhydrides, although hydrolysis or acid-catalysed methanolysis of **101**(X = H) proceeds with inversion at phosphorus, attack by HO^- occurs at sulphur with retention of configuration of phosphorus whilst the hydrolysis of the much more reactive **101**(X = F) in aqueous dioxane proceeds with preponderant inversion of phosphorus



(**100**)



(**101**)

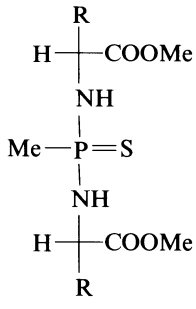
configuration irrespective of pH. In the case of the trifluoromethyl compound, inversion at the phosphorus centre with high stereoselectivity was observed also to occur on reaction with Cl^- (to give Bu^{t}PhP(S)Cl), but the reaction with I^- proceeded with retention of configuration—a completely unexpected result[257–259].

4. *Ammonolysis and aminolysis: phosphonothioic amides and related compounds*

The use of the same optically active halide **97** demonstrated predominant inversion of configuration in its reaction with ammonia[250]. It is highly likely that for most simple phosphono- and phosphino-thioic halides a reaction with a secondary amine proceeds with inversion of phosphorus configuration; on the other hand, the stereochemical outcome of a displacement reaction which involves a halide of the type $(R^1NH)R^2P(S)Cl$ and an amine depends on the basicity of the attacking amine and would appear to occur through an initial elimination of HCl. Such differences in mechanisms will again be referred to later.

The reactions between amines and phosphonothioic or phosphinothioic halides (and even more so the corresponding selenium-containing compounds) are slow, and particularly those reactions with the weaker bases such as aromatic amines require more forcing conditions and the presence of a stronger base as a hydrogen halide acceptor; often the products from these reaction are more easily obtained by the addition of sulphur or selenium to the analogous compounds of tervalent phosphorus. Many examples of the reactions between the general species $R^1R^2P(S)X$ (R^1, R^2 are either, or both, carbon moieties; or one RO, or RR′N etc., X = halogen)[3–9,260] and amines or hydrazines have been listed. In some respects, also, the reactions which involve phospho(i)nothioic halides may proceed more easily than those with the sulphur-free halides as, for instance, in the second, cyclization, stage of the reactions between phosphonothioic dichlorides and 1,2-phenylenediamines[261].

The reactions between $MeP(S)Cl_2$ and amines have been utilized in a novel way; the products from chiral amines, e.g. aminocarboxylic acids, consist of mixtures of diastereoisomeric methylphosphonothioic diamides, two of *meso* structure, **102** and its mirror image, together with the racemic modification **103**; the proton-decoupled ^{31}P NMR spectra of such mixtures display three well separated singlets from which the enantiomeric purity of the amines can be determined[262].



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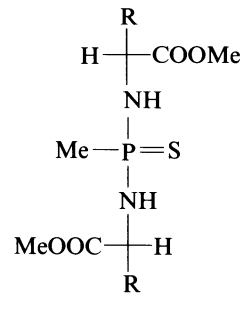
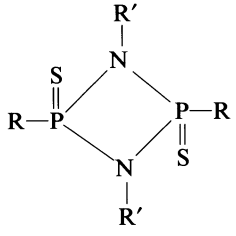


(103)

In many instances, the reactions between the dichlorides, $RP(S)Cl_2$, R = Ph[263–268] or R = alkyl[267,269], and the range of primary amines can yield a variety of products depending on the individual amine and the reaction conditions. Thus when R = C_1–C_7, reactions in MeCN furnish 1,3,2,4-diazadiphosphetidine 2,4-disulphides (**104**), sometimes as mixtures of separable *cis* and *trans* isomers, together with the predicted phosphonothioic diamides,



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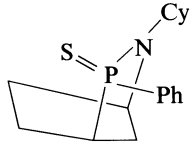

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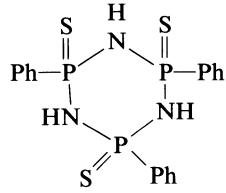


(106)

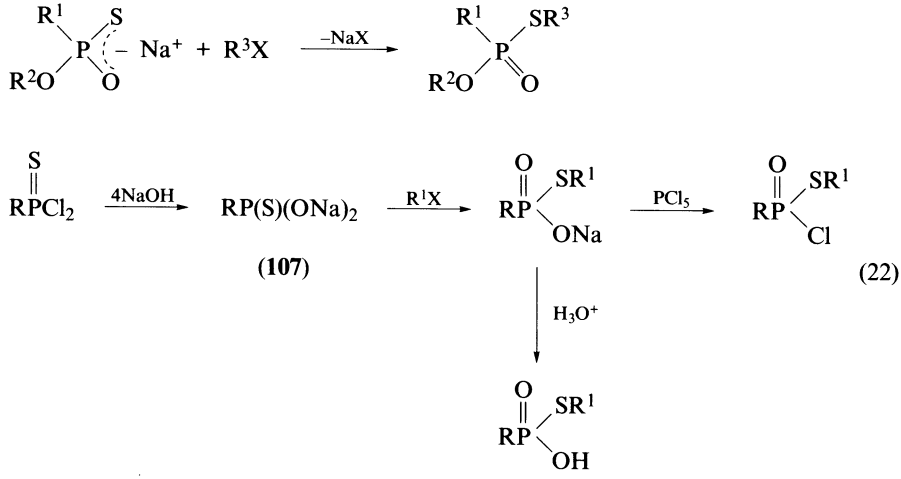
$RP(S)(NHR')_2$ [265,270]. Moreover, the diazadiphosphetidine disulphides are also formed (with the liberation of primary amine) when the phosphonothioic diamides are heated to about 150–250 °C [263,264,266,269]. Several of the diazadiphosphetidines have been characterized in both geometric forms by X-ray crystallography[264,267,271–274]. The action of heat on *N,N'*-dicyclohexyl-*P*-phenylphosphonothioic diamide is unusual, since the cyclization process yields a compound with the structure **105**, as determined by X-ray crystallography[257]. The action of heat on the diamides, $PhP(S)(NHR)_2$, (R = H, Pr^i, Bu^t or CHMeEt) is also known to yield 1,2,3,4,5,6-hexahydro-2,4,6-triphenyl-1,3,5-triaza-2,4,6-triphosphorine 2,4,6-trisulphide (**106**)[269,270].

B. Reactions which Proceed with Predominant Configurational Retention

1. *The alkylation of acids*

The mono-thio, -seleno and -telluro analogues of phosphonic and phosphinic acids are tautomeric (equations 1, 2 and 4). In the case of the sulphur-containing compounds, an attempt has been made to estimate the equilibrium compositions of a variety of acids by means of physicochemical measurements[1]. The alkali metal salts of phosphonothioate and phosphinothioate acids possess anions which are mesomeric and, theoretically, it is possible for such ions to act as sources of both *O*-and *S*-substituted products. The same products can be obtained through reactions between the free acids and diazoalkanes, and because these reactions are relatively fast, it might be expected that the composition of the product mixtures might be a reflection of the tautomer composition of the acids.

The alkylation, with the more reactive of alkyl halides, of the sodium salts of monoesterified phosphonothioic acids (equation 22)[276–279] (see also Scheme 11) or of the disodium salts **107** [280,281] results in preferential *S*-alkylation, and the same situation obtains for the salts of phosphinothioic acid[282–285]; methylation can also be carried out with dimethyl sulphate. Alkylations may also be performed under phase-transfer conditions[286]. From both practical and theoretical perspectives, the subject is more complex, since the course of alkylation reactions depends on the nature of the alkylating agent, on the polarity of solvent and whether this is protic or non-protic and on the concentrations of reactants; a study of these features has been the subject of two reports[287,288]. In non-polar or weakly polar aprotic media, or in EtOH, alkylation occurs almost exclusively on sulphur, but in dipolar aprotic solvents, *O*-alkylation also takes place. The relative yields of sulphur- and oxygen-substituted derivatives, $[Q_S/Q_O]$, depends, for a given solvent, on the nature of substituents on phosphorus, i.e. essentially, whether the substrate is a thiophosphoric, thiophosphonic or thiophosphinic acid. With alkyl tosylates as alkylating agents at 0.02 M in hmpt, the alkylation of sodium *O,O*-dialkyl or diphenyl phosphorothioates results in 100% overall conversions with $[Q_S/Q_O] \approx 5$; the overall yields for sodium diphenyl- or diisopropylphosphinothioates are lower (50–100%) with $[Q_S/Q_O] \approx 1$.

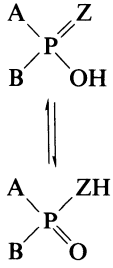


The explanation offered for the observed results is long and involved and centres on the nature of the substrate species present at a given concentration and whether these be contact ion pairs, solvent separated ion pairs or free ions. Dimethylformamide is more favourable for ion pairs than is hmpt, and lower yields of *O*-alkylated derivatives are observed for the reactions in dmf, whereas in EtOH, ions and ion pairs are said to be present, the oxygen end of the OPS triad is blocked by hydrogen bonding or by the counter-ion and, regardless of the degree of dissociation, only *S*-alkylation is then found. The isomeric *O,O*-dialkyl phosphonothioates (or analogous *O*-alkyl phosphinothioic esters) are obtainable through the displacement of chlorine from phosphonothioic dichlorides[2–7,9] (or phosphinothioic chloride[283]) by alcohols in the presence of an HCl acceptor (i.e. as the sodium alkoxide, or with Et_3N) and which may be interrupted at the intermediate stage, and the reader is reminded that such isomers can also be obtained by the addition of sulphur to the phosphorus(III) esters; however, it might be pointed out that a reaction between a phosphonothioic dichloride and an alcohol in the absence of an HCl acceptor leads to the *O,S*-dialkyl esters[280]. The *O*- and *S*-alkyl esters may be differentiated by mass spectrometry[289] but, much more conveniently (and the composition of mixtures thereby estimated), by means of NMR spectroscopy; often, for example, when simple organic groups, e.g. Me, are present, ^{1}H NMR spectroscopy may suffice, but much more superior is the use of ^{31}P NMR spectroscopy, the two isomeric series having different phosphorus chemical shifts[290]. The alkylation of sulphur-containing acids by small-ring ethers appears to follow the same course; thus, the reaction between the monophenyl esters of ethyl- or phenyl-phosphonothioic acids are alkylated by oxetane to give the *S*-3-hydroxypropyl esters[291].

The behaviour of selenium-containing acids might be expected to parallel that of the sulphur acids, but the position is not so clear. *Se*-Alkyl esters are the products of similar alkylations of sodium salts by alkyl halides[292], and are also produced from hydrogenphosphonates and diselenides according to equation 19[188]. The reaction between the triethylammonium salt of (*R*)-(+)-*O*-ethyl ethylphosphonoselenoic acid and Me_3SiCl affords the laevorotatory *O*-silyl ester rather than the *Se*-silyl ester as demonstrated by ^{31}P NMR spectroscopy and also by alternative synthesis[293]. By contrast, the use of the sodium salt of the acid leads to the *Se*-silyl ester[292].

Free phosphonothioic and phosphinothioic acids, and their selenium analogues, are readily alkylated by diazoalkanes, diazo esters or diazo ketones. The early work has been

summarized and potential reaction mechanisms have been examined in some detail[294]. Diazoalkanes react with monothio and monoseleno acids according to S_N1 or S_N2 mechanisms . During the alkylation of acids by diazoalkanes (carried out in a solvent at room temperature or with a neat substrate and slight warming), a proton is transferred from the acid to the diazo compound to form a cation (equation 23), which then attacks the ambient counterion within the ion pair (**108**), with the various ways in which breakdown may then occur through **108** or through **109** after loss of nitrogen, depicted in equations 24–28. Equations 25 and 26 represent attack by the diazo cation at either S or O by the S_N2 mechanism, whereas equations 27 and 28, following equation 24, represent an S_N1 process. The relative amounts of *S*- to *O*-alkylation for the series of thiophosphoric, thiophosphonic and thiophosphinic acids, obtained with diazomethane, show an overall increase (with exceptions, such as Ph_2PSOH) in that order. The relative increase in reaction at Se in each of the three groups of monoseleno acids is not so pronounced as for the sulphur-containing acids. Both *O*-and *S*- (or *Se*-) alkylation also occur with higher diazoalkanes, the main difference in comparison with diazomethane itself being the relatively greater extents of *O*-alkylation, the greatest being for diazoisopropane, >50% with thiophosphates and >40% for thiophosphonates. For diphenyldiazomethane, proton transfer is the rate-determining step and,also, the diphenylmethyl cation is more inclined to undergo S_N1 reaction; the $[Q_S/Q_O]$ values are lower than for diazomethane i.e. the relative yields of *O*-alkylated products are higher. Protonated ions from diazoketones lose their nitrogen during electrophilic attack. Diazoacetone (or diazoacetophenone) and the sulphur acids produce only small amounts of *O*-alkylated products.



$$+ \quad RCHN_2 \quad \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \quad [ABZO^- \; RCH\overset{+}{N}_2H] \qquad (23)$$

(108)

$$\mathbf{108} \xrightarrow{k_2} [ABZO^- \; RCH_2{}^+] + N_2 \qquad (24)$$

(109)

$$\mathbf{108} \xrightarrow{k_3} ABP(O)ZCH_2R + N_2 \qquad (25)$$

$$\mathbf{108} \xrightarrow{k_3'} ABP(Z)OCH_2R + N_2 \qquad (26)$$

$$\mathbf{109} \xrightarrow{k_4} ABP(O)ZCH_2R \qquad (27)$$

$$\mathbf{109} \xrightarrow{k_4'} ABP(Z)OCH_2R \qquad (28)$$

O,O,O-Trialkyl phosphorothioates can be made to isomerize to the *O,O,S*-trialkyl compounds in a process which can be thermally initiated and which may occur during distillation. A similar rearrangement, coupled (evidently) with an allylic rearrangement, occurs

in 10–20 min at 70-80 °C when the *O*-prop-2-enyl esters **110**(R = EtO, NHEt, NEt_2 or SEt) are exposed to $[Pd(PPh_3)_4]$; if diethyl malonate is included in the reaction mixture, about 15% of diethyl allylmalonate is formed, suggesting the intermediary formation of a palladium–allyl complex. No stereochemical studies have been carried out on the system, but it is highly probable that configuration at phosphorus is retained[295]. In contrast to the analogous allyl selenophosphates, *O*-allyl esters of selenium-containing phosphonic or phosphinic acids are thermally stable, and may be distilled without change[296,297].

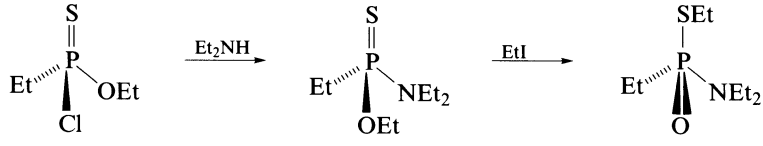
(110)

The configuration at phosphorus should be preserved in the isomerization of *S*- or *Se*-alkyl esters of monothio or monoseleno carbon-bonded quinquevalent phosphorus acids when treated with alkyl halides, a sequence known as the Pishschimuka reaction. When heated with bromobutane at 130 °C, a decreasing order of reactivity is observed for the esters, $Et_2P(Se)OEt > EtP(Se)(OEt)_2 > (EtO)_3P(Se)$, when the products are the respective P(O)(SEt) isomers[298]. The reactions between MeI and (–)- and (+)- (EtO)EtP(S)OMe at 120 °C gave the (+)- and (–)-forms, respectively, of (EtO)EtP(O)SMe having unchanged configurations at phosphorus; the optical purities of the products (about 70%) were consistent with appreciable competitive reaction at sp^3 carbon[299]. The same esters with identical configurations are obtained by the methylation (MeONa, MeI) of (*R*)-(+)- and (*S*)-(–)-*O*-ethyl ethylphosphonothioate, i.e. acid and corresponding ester have indentical configurations; this is yet further evidence for the course of hydrolysis, since (–)-ester hydrolyses to (+)-acid, i.e. a change in configuration occurs[299]. The Pishschimuka reaction has also been noted for thiophosphonic amides (Scheme 20)[299].

The thione → thiol rearrangement of *O*-alkyl phosphinothioic esters is catalysed by acids. In an investigation of the catalysis of isomerization of the esters $Me_2P(S)OPr$ and $Ph_2P(S)OMe$ by trifluoroacetic acid by means of ^{31}P NMR spectroscopy, Bruzik and Stec [300] assigned transient signals to the species **112**.

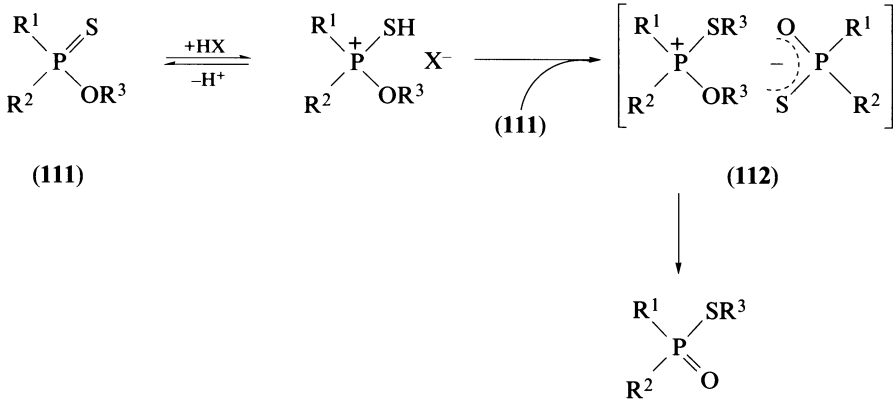
Such species bear comparison with those proposed for the transformation of menthyl phosphinate and phosphinothioate esters (**113**; Z = O or S; R = Me or Et; $ML_n = PF_6$, BF_4 or $SbCl_6$) by other alkylating species (Scheme 21)[301]. The formation of an intermediate quaternary species also allowed the transformation of an (*R*)-(+)-phosphonothioic amide **114**(Ar = 2,4,6-tri-*tert*-butylphenyl) into its *S*-alkyl isomer with retention of configuration (Scheme 22)[302].

A 'retro-Pishschimuka' reaction has recently been reported, in which the quaternary salts from the (*R*)-(+)-*S*-methyl phosphinothioates (**115**; R = Me or Bu^t) and methyl triflate (Scheme 23) are treated with NaSH, which results in the formation of the isomeric *O*-methyl esters of unchanged configuration although with some loss of optical purity[303].

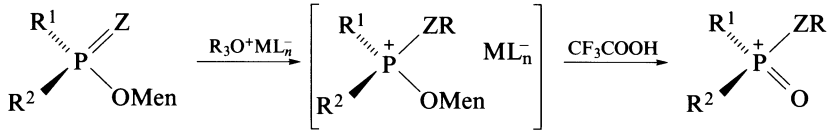


(*R*)-(–)- (*S*)-(+)- (*S*)-(–)-

SCHEME 20

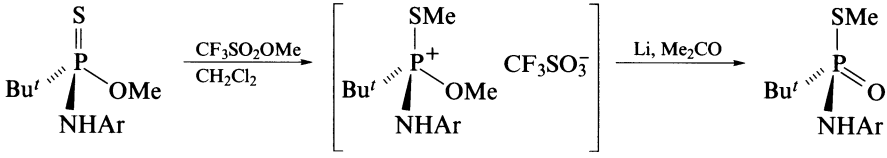


(111) (112) (111)



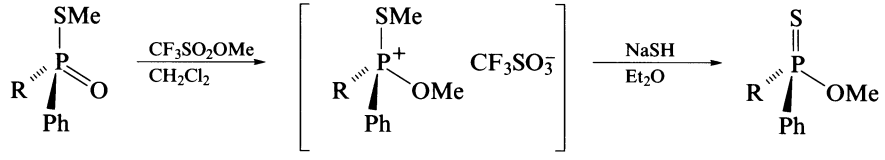
(113)

SCHEME 21



(114)

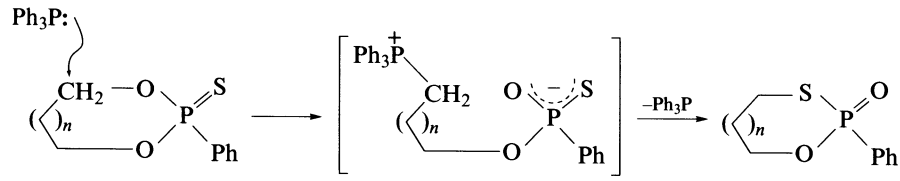
SCHEME 22



(115)

SCHEME 23

Although not strictly relevant to the present considerations, it is interesting that isomerization of cyclic phosphonothioate esters can be achieved when they are treated with triphenylphosphine (Scheme 24)(n = O, 1); this overall reaction takes place with initial ring opening (this step is completely analogous to that observed with trialkylamines)[304]. An analogous ring opening – ring closure sequence has been observed for a cyclic ester of benzylphosphonothioic acid under catalysis by Et_2NH[305].



SCHEME 24

2. The acylation of acids

The almost exclusive *O*-acylation (as opposed to *S*-alkylation) of salts of monothio- or monoseleno-phosphonic or -phosphinic acids by acetyl chloride or bromide or benzoyl bromide proceeds, as might be expected, with retention of configuration at phosphorus. The formation of monothiodiphosphonates as by-products has been reported, but the use of ketene for acetylation purposes allows a cleaner reaction without anhydride formation[306,307].

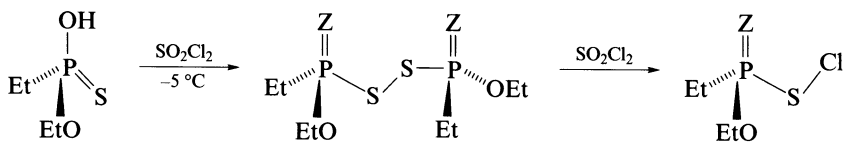
The same types of mixed phosphonothioic-carboxylic anhydrides, $RP(Z)(OOCAr)_2$, are also formed in the reactions between the dichlorides $RP(Z)Cl_2$ (R = Me or Ph, Z = S or Se) and the silver salts of aromatic carboxylic acids[308,309]. In this case, however, since bonds to phosphorus are broken it might well be that, in more structurally appropriate cases, an inversion of configuration might occur. Such mixed anhydrides are powerful acylating (rather than phosphorylating) agents by virtue of the greater electrophilicity of the carbonyl group by comparision to that of the P=X centre.

Although amine salts of dithiocarboxylic acids react with chlorodiphenylphosphine to give the anhydrides $Ph_2PSC(S)R$, no such reaction occurs with $Ph_2P(S)Cl$; on the other hand, the use of metal salts of the dithiocarboxylic acids does afford the anhydrides $Ph_2P(S)SC(S)R$, and the use of $Ph_2P(Se)Cl$ give $Ph_2P(Se)SC(S)R$, e.g. the dark-green R = Ph[310].

Reference has already been made to properties of mixed phosphinic–sulphonic anhydrides. *tert*-Butylphenylphosphinothioic trifluoromethanesulphonic anhydride (**101**) was prepared, in both racemic and optically active forms, from the phosphinothioic acid and trifluoromethanesulphonic anhydride in dichloromethane at –50 °C[258].

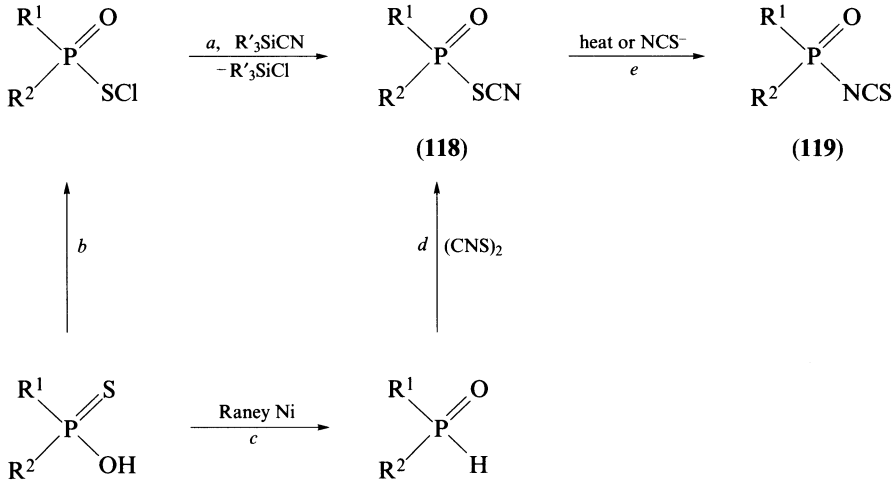
3. Disulphides: their formation and properties

Phosphoryl disulphides, compounds which possess the P(Z)SSP(Z) moiety (Z = O or S), are obtained most readily through the mild oxidation of the sodium thioates RR'P(Z)SNa with iodine in KI solution[3–7]. An alternative synthesis is based in the chlorination of the free thioic acid, conveniently with SO_2Cl_2; the (+)- and (–)-forms of the disulphide **116**(Z = O) are formed from the (*R*)-(+)- and (*S*)-(–)-forms of the precursor acid[263]. Further chlorinolysis with more sulphuryl chloride then cleaves the disulphide bond with the formation of (+)- and (–)-ethoxyethylphosphinoylsulphenyl chloride (**117**; Z = O)[97,311]. A similar



(+)- (+)- (Z = O) (+)- (Z = O)

(116) **(117)**

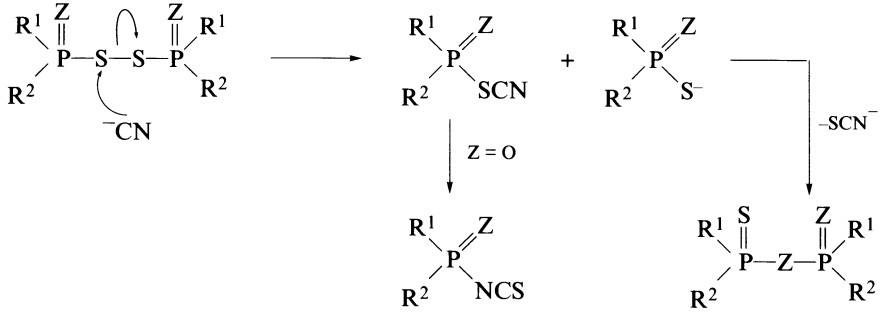


SCHEME 25

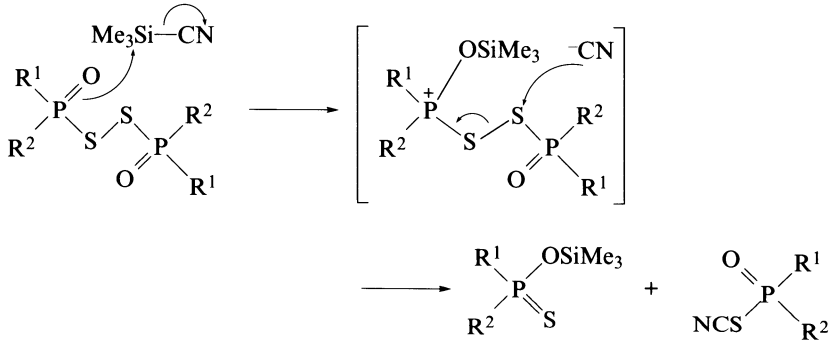
sequence operates for *tert*-butylphenylphosphinothioic acid[312]. Further methods for the preparation of this and related compounds depend on the chlorinolysis of esters or of phosphonothioic chlorides, e.g. Et(EtO)P(S)Cl[313], and also of mixed anhydrides of thiophosphonic or thiophosphinic acids and acetic acid[314]. The tetrasulphides **116**(Z = S) have also been reported[314]. The halogenolytic cleavage of the mixed anhydrides of acetic acid with thiophosphonic or selenophosphonic acids has also made available sulphenyl bromides, selenyl chlorides and bromides[314].

Phosphinoylsulphenyl halides are, as their name might suggest, highly unpleasant compounds and very reactive. The chlorides add across carbon–carbon double bonds to give *S*-(2-chloroalkyl) esters[197,311,315] and they react with amines to give sulphenyl amides; following their reaction with trialkylsilyl cyanides or AgCN, the products are thiocyanates (sulphenyl cyanides). The latter, e.g. **118**(R^1 = Bu^t, R^2 = Ph or MeO), are unstable and isomerize during distillation, but also even at room temperature or in the presence of SCN^-, into the corresponding and thermodynamically more stable phosphinoylisothiocyanate **119**, readily characterized by the usual isothiocyanate reactions with amines or alcohols[312,316,317]. The final thiocyanate to isothiocyanate isomerization was demonstrated, by the use of weakly optically active phosphinothioic substrates, to proceed with inversion of configuration at phosphorus, a fact also concluded from a study of the same isomerization using the geometric isomers of compounds in the 1,3,2-dioxaphosph(V)orinane series. The phosphinoylthiocyanates are also conveniently obtained by the thiocyanation of hydrogenphosphinates and secondary phosphine oxides[317]. Stereochemical studies have shown that, since reactions *a*, *b* and *c* (Scheme 25; R^1 = Bu^t, R^2 = MeO) all occur with retention of phosphorus configuration, then step *d* must also occur in this way[317].

Phosphinoylthiocyanates are also the initial products (along with a monothiophosphonic anhydride) from cleavage of phosphinoyl disulphides by CN^- (Scheme 26; Z = O)[318,319] and also by a similar process with trimethylsilyl cyanide (Scheme 27)[316] when the co-products are *O*-trimethylsilyl esters of the phosphono- or phosphono-thioic acid. An entirely analogous sequence (Scheme 26; Z = S), which proceeds more slowly, is undergone by phosphinothioyl disulphides[316].



SCHEME 26



SCHEME 27

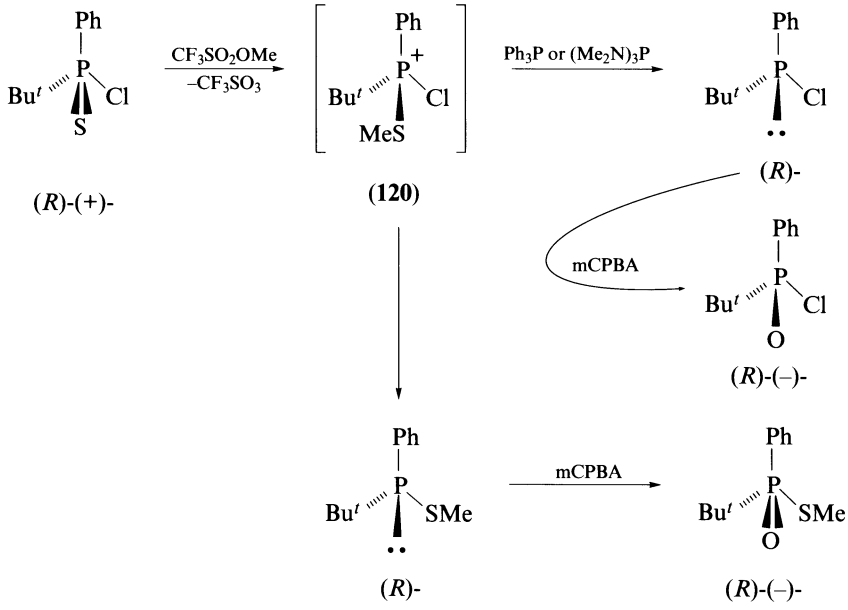
C. Cleavage Reactions with Variable or Undecided Stereochemistry

It should immediately be emphasized that the above heading is merely one of general convenience, and that the stereochemical course of an individual reaction step, herein considered, may be well defined for specific conditions.

1. Desulphurization and oxidative desulphurization reactions

Sulphur in *O*-alkyl alkylphosphonothioates[187] and selenium in *O*-alkyl alkylphosphonoselenoate[320,321] are removable by a treatment of the acids with Raney nickel under ethanol; configuration at phosphorus is retained. Stereochemical features of the eliminations were indicated by (i) the formation of the same (–)-*tert*-butylphenylphosphine oxide from both (*R*)-(+)-*tert*-butylphenylphosphinothioic acid and the (*R*)-(+)-selenoic acid[322] and (ii) the generation of the original *O*-ethyl ethylphosphonoselenoate after initial deselenation followed by the re-addition of selenium, whether starting with the (+)- or the (–)-from[317], and also the similar elimination of sulphur from, and regeneration of, *O*-isopropyl methylphosphonothioate[187].

Thiophosphoryl sulphur is removed from phosphinothioyl chlorides when they are treated with derivatives of tervalent phosphorus, e.g. triphenylphosphine or triphenyl phosphite[323]. A novel procedure for the desulphurization of phosphinothioic chlorides consists in the quaternization of the phosphorus substrate with methyl triflate followed by

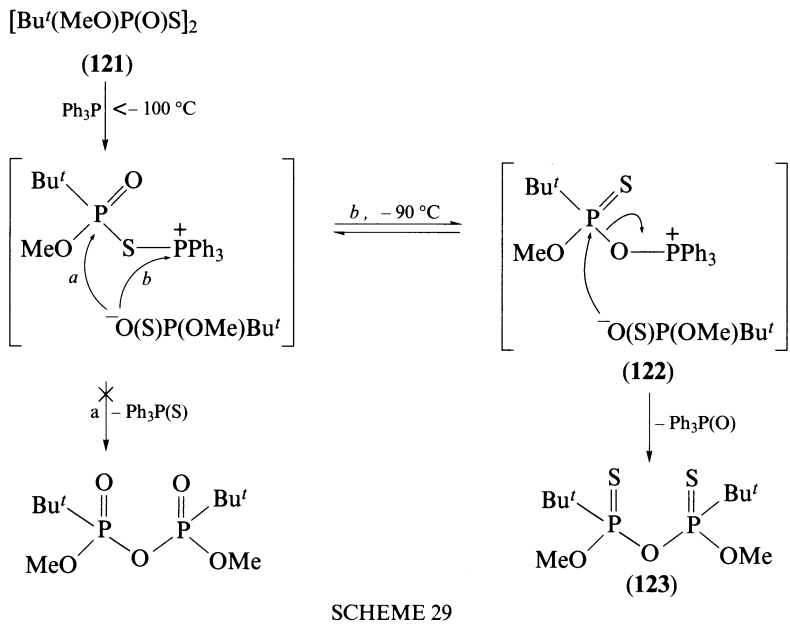


SCHEME 28

a reaction with a thiophilic reagent, again Ph_3P or $(Me_2N)_3P$ (Scheme 28); the nature of the products depends on which of these two reagents is employed, complete desulphurization only being achieved with the phosphorous triamide[324]. Although these steps are those through which an optically active phosphinous chloride was first obtained, and optically active *tert*-butylphenylphosphinous chloride obviously racemizes fairly easily, the oxidation of tervalent phosphorus with 3-chloroperoxybenzoic acid (mCPBA) occurs essentially quantitatively and with stereospecific retention of configuration, the oxidation of the specific phosphinous chloride furnished (*R*)-(−)-*tert*-butylphenylphosphinic chloride in 24% optical purity and the (*S*)-(+)- form with only 1.4% optical purity[324]. A reaction between the quaternary salt **120** and triphenylphosphine in dichloromethane at room temperature to reflux temperature was developed as a practical synthesis of unsymmetrical phosphinous chlorides[325]. The methodology appears to be general; the desulphurization of analogous quaternary salts from *O*-alkyl alkylphenylphosphinothioates with the phosphorous triamide was applied to the preparation of optically active alkyl alkylphenylphosphinites with retention of configuration[326].

There is evidence that desulphurization can occur when phosphinoylsulphenyl chlorides and phosphinoyldisulphides are treated with phosphorus(III) compounds[327] but, in reality, the reactions are much more complex, and sometimes yield unexpected products[328]. Thus, in the treatment of the disulphide **121** with triphenylphosphine, the outcome is uncharacteristically simple (Scheme 29), the result being 100% deoxygenation and the formation of the symmetrical anhydride **123** through the phosphonium salt **122**, detected by its ^{31}P NMR signals at 59.7 (P^+) and 113.1 (P=S) ppm; unfortunately, this result was the only one here[329] relevant, all other experiments being concerned with the reactions of bis (dialkoxyphosphinoyl) disulphides, for which both deoxygenation and desulphuration occurred to various extents.

The same workers also presented the detailed results of an examination of the strongly exothermic reactions (reactivity is demonstrable even at −100 °C) between various phos-

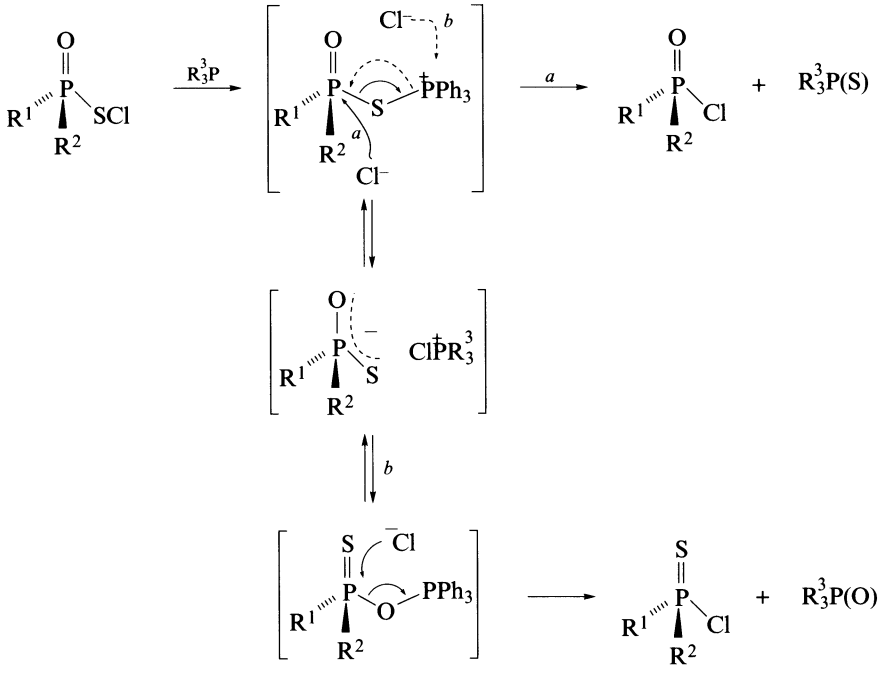


SCHEME 29

phorus(III) compounds and carbon–phosphorus bonded sulphenyl chlorides, and the results can be conveniently summarized by means of Scheme 30, which represents only those reactions which are resistant to dealkylation. Table 2 lists the results of reactions carried out at –20 °C in dichloromethane. What is immediately apparent is the complete, or almost complete, desulphurization of Et(EtO)P(O)SCl by phosphorus(III) esters or amides, and yet the singular deoxygenation of Bu'PhP(O)SCl by Ph_3P[330]. In general, the course of the reaction depends more on the nature of the ligands at tricoordinate phosphorus (PCl_3 also tends to lead to both effects or to largely deoxygenation) than on the ligands attached to tetracoordinate phosphorus; bulky groups in the phosphorus(III) triester result in desulphurization (entry i) but bulky groups at the tetracoordinate atom lead to deoxygenation (entry vi). The reaction between optically active Et(EtO)P(O)SCl and triphenylphosphine produced Et(EtO)P(O)Cl and Et(EtO)P(S)Cl, each formed with inversion of configuration at phosphorus[330].

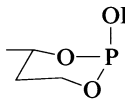
Additional to the possibility of complete elimination of thiophosphoryl sulphur is that of its replacement by oxygen. Many of the reagents used and the reaction conditions are those employed for the oxidation of phosphine sulphides and selenides[331]. Ozone is thought to convert the enantiomers of *O*-4-nitrophenyl methylphenylphosphinothioate into the phosphinate esters with retention of configuration[332]. The use of dialkyl sulphides in combination with Rose Bengal is very good to excellent for the oxidative deselenation of $PhP(Se)(OEt)_2$ and $Ph_2P(Se)OEt$ [better than for $(RO)_3P(Se)$ and generally better than for sulphur-containing esters], but the procedure is very poor for the analogous thio esters[333]; the oxidative desulphurization of Bu'PhP(S)OMe proceeds quantitatively in trifluoroacetic acid, as does the same process for tertiary phosphine sulphides and selenides, and also phosphoro-thioic and -selenoic esters[334].

The elimination of the SCF_2 moiety from *S*-trifluoromethyl esters of phosphorothioic acids proceeds readily at 0–130 °C without the aid of a catalyst and largely with retention of configuration; in the single reported example of a phosphinothioic ester, *S*-trifluoromethyl (*S*)-(–)-*tert*-butylphenylphosphinothioate in the presence of pyridine at 0–20 °C, yields racemic Bu'PhP(O)F[335].



SCHEME 30

TABLE 2. Deoxygenation and desulphurization of sulphenyl chlorides, $R^1R^2P(O)SCl$, by R^3_3P in CH_2Cl_2 at –20 °C

Entry	R^1	R^2	R^3_3P	Deoxygenation (%)	Desulphurization (%)
i	Et	EtO	$(Me_3CCH_2O)_3P$	0	100
ii	Et	EtO		0	100
iii	Et	EtO	$(Et_2N)_3P$	5	95
iv	Et	EtO	$(PhO)_3P$	8	92
v	Et	EtO	Ph_3P	40	60
vi	Bu^t	Ph	Ph_3P	100	0

The reagents of choice for the replacement of P=S(Se) by P=O are hydrogen peroxide, 3-chloroperoxybenzoic acid (mCPBA), and dimethyl sulphoxide (dmso).

Detailed studies on the use of H_2O_2 in the phosphonothioic(and selenoic) and phosphinothioic (and selenoic) acid series (in addition to experiments with derivatives of phosphorothioic and phosphoroselenoic acids) have been carried out, also by Polish workers. It appears that the stereochemical course of oxidative desulphurization (or deselenation) is the same for all three series of esters (retention of configuration) but differs from the reaction for phosphine sulphides (net inversion), whilst the course of the reaction for phosphine

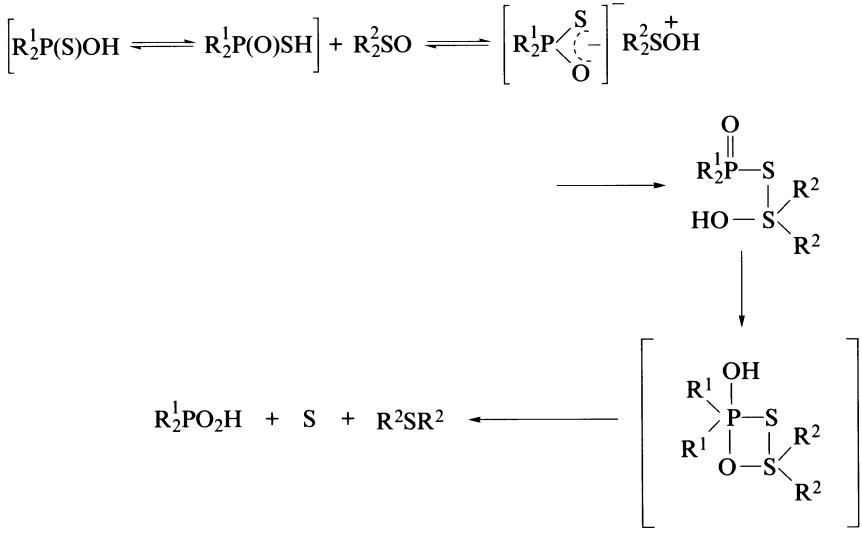
selenides depends on the reaction conditions; the stereoselectivity in the conversion of (*S*)-(–)-*O*-ethyl *O*-Methyl ethylphosphonothioate to the corresponding (*S*)-(–)-phosphonate ester was assumed to be high, despite the low optical activities of the two esters[336]. Inch and coworkers[164] employed H_2O_2 in the assignments of chirality to 2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulphides and 2-selenides through oxidation to the corresponding 2-oxides. Retention of stereochemistry was also demonstrated in the peroxide oxidation of (*Sp*)-(–)-*O*-[(–)-menthyl] ethylphenylphosphinothioate to the sulphur-free ester[337].

Herriott[337] used the phosphorus epimers of *O*-(–)-menthyl methylphenylphosphinothioate to demonstrate the almost quantitative stereospecificity in the reaction with mCPBA; by contrast, the use of trifluoroperoxyacetic acid was less successful, with a retention to inversion ratio of 21:79. A further feature in favour of mCPBA is the independence of its activity relative to solvent. Other extensive correlations were made by Inch and coworkers during investigations into the stereochemistry of displacement reactions at phosphorus in compounds based on a carbohydrate template **81**; by means of structural assignments based on infrared absorption frequencies for the P=O bond together with ^{31}P NMR chemical shifts, they showed that mCPBA oxidation of thiophosphoryl or selenophosphoryl bonds (A or B = =S or =Se, B or A = Me or Ph) occurred highly stereoselectively with the formation of the phosphonate ester with retained stereochemistry[156].

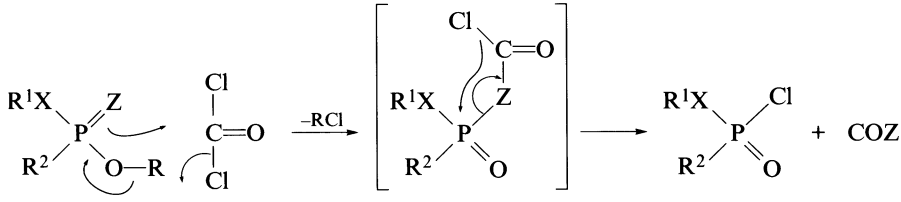
We also owe to Mikołajczyk[338] the observation that, when in contact with dmso, phosphonothioic esters are oxidized slowly (75–80% conversion within 1 week at room temperature)to the corresponding phosphonic ester with the liberation of Me_2S and sulphur . The oxidation is catalysed by acid, and proceeds satisfactorily also for phosphinothioic esters, but even more so (in terms of yields, but still over extended reaction periods) for the analogous phosphono- and phosphino-selenoates[339]. Once again, through the use of (*Sp*)-(–)-*O*-[(–)-menthyl] ethylphenylphosphinothioate, it was demonstrated that oxidation with dmso in the presence of iodine proceeds with inversion of configuration at phosphorus[340]. This result is in contrast to those obtained for the oxidative desulphurization and deselenation of phosphine sulphides, phosphine selenides, and derivatives of $(HO)_3P(Z)$ (Z = S or Se), all of which show retention of configuration at phosphorus.

Earlier, attention was drawn to a novel application of the oxidative desulphurization reaction which occurs between sulphoxides and phosphonothioic acid esters. When 1 mol of the thio acid is allowed to remain in contact with 2 mol of a racemic methyl alkyl sulphoxide for 2 weeks at room temperature, the unreacted sulphoxide is found to be optically active, a result which represents asymmetric deoxygenation of the sulphoxide. The chemical course of the reaction is consistent with Scheme 31. Since the appearance of the initial results, corrections have been made to the configurations of the phosphorus-containing substrates, and hence the stereochemical details and mechanistic arguments require reappraisal; neverthless, the fact remains that (+)-sulphoxides are obtained by the use of the (*S*)-(–)-acids, $R^1(R^2O)P(S)OH$[341], a feature which can be used to determine the chirality of other like acids. Dialkyl and alkyl aryl sulphoxides are also known to form diastereoisomeric complexes with (*S*)-(–)-*tert*-butylphenylphosphinothioic acid, distinguishable by their ^{1}H NMR spectra, and through such complexation it is possible to assess the enantiomeric composition of the sulphoxide[342].

A reaction of greater preparative value is the desulphurization which occurs when *O,O*-dialkyl alkylphosphonothioates are acted upon by carbonyl chloride (Stirling, 1957), a reaction which may be envisioned as a consequence of the pronounced nucleophilic character of the thiophosphoryl group as indicated in Scheme 32, in which either X or Z is sulphur; desulphurization occurs when Z = sulphur[343]. However, the positive results so depicted contrast with the lack of reactivity of phosgene towards both Et(EtO)P(S)OMe and Et(EtO)P(O)SMe reported slightly later[344] and with the novel nature of the interaction of similar esters with $POCl_3$, when the products are of the structure Ph(RS)P(O)Cl[345,346]. The nature of the ligands to phosphorus has a marked effect on the ability of the reaction



SCHEME 31

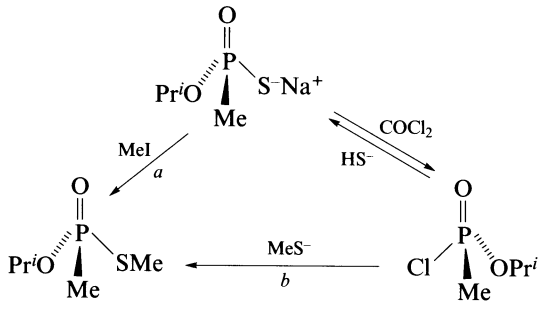


(124)

SCHEME 32

with phosgene to proceed; thus, *O,O,O*-triethyl phosphorothioate is unreactive and *O,O*-diethyl phenylphosphonothioate almost so. The reaction of phosgene with *O*-ethyl diphenylphosphinothioate proceeds satisfactorily to give $Ph_2P(O)OEt$, as the first stage in the sequence which eventually leads to $Ph_2P(O)Cl$[347]. The ready reaction of the same reagent with optically active *O*-ethyl ethylphosphonothioic acid to give Et(EtO)P(O)Cl, but no Et(EtO)P(S)Cl, occurs with complete racemization. Similar reactions occur with the sodium salts of *O*-alkyl alkylphosphonothioic acids; sodium (*S*)-(–)-*O*-ethyl ethylphosphonothioate furnished (*R*)-(+)-Et(EtO)P(O)Cl, the optical activity of which is readily lost under a variety of conditions. The sequence depicted in Scheme 33 suggests that, since steps *a* and *b* occur with retention and inversion respectively, then the desulphurization step also proceeds with inversion of configuration and is initiated by the nucleophilic character of sulphur and the formation of **124** (X = O, Z = S)[339,343,344].

It might also be noted that loss of sulphur occurs when *O,S*-dialkyl methylphosphonothioates react with thionyl chloride or PCl_5[348]. The ability of certain carbonyl-containing compounds, such as amides, aldehydes and some heterocyclic systems, to undergo oxygen–selenium exchange represents an oxidative deselenation of $PhP(Se)Cl_2$, a reagent used for selenation purposes[349].

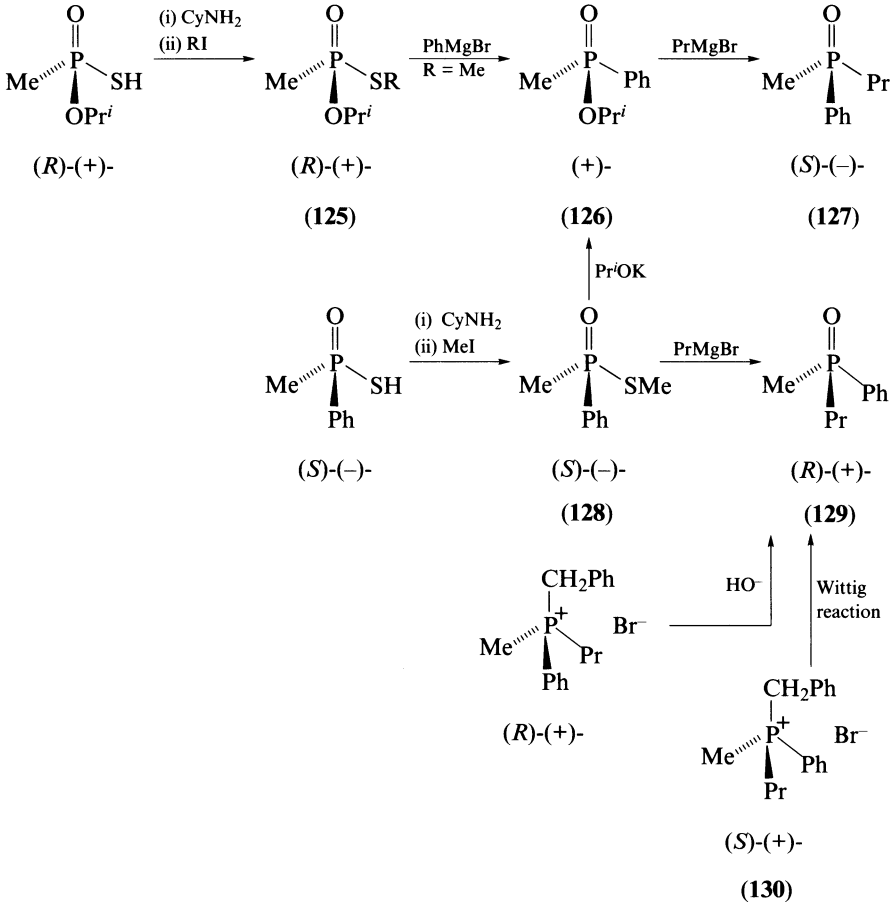


SCHEME 33

2. *The cleavage of P-S bonds*

a. With Grignard reagents. Benschop *et al.*[282] appear to have been the first to report the cleavage of P—S bonds in phosphonothioic esters by Grignard reagents. They found, in preliminary experiments, that (*R*)-(+)-*O*-isopropyl *S*-ethyl methylphosphonothioate (**125**; R = Et)(Scheme 34) failed to react satisfactorily with PrMgBr in thf. However, the cleaner reaction between the corresponding *S*-methyl ester and PhMgBr yielded (+)-*O*-isopropyl methylphenylphosphinate (**126**). In the phosphinothioate series, (S)-(-)-S-methyl methylphenylphosphinothioate (**128**) was converted into the (*R*)-(+) tertiary phosphine oxide **129** by the action of PrMgBr; this observation should be contrasted with the failure of reaction in the phosphonothioic series. The assignments of configurations by chemical means rested on the chirality of **129** (and thus of **127**), since this could be correlated with that of the phosphonium salt **130** (being derived from it with retention of stereochemistry by means of any simple Wittig reaction with an aldehyde or ketone), and also on the configurations of several phosphonothioic derivatives but particularly on that by Sorensen[229], as determined by single-crystal X-ray analysis. If the two steps **125** → **126** → **127** both occur with either retention or inversion, the final phosphine oxide product would have the *R*-configuration; it does not, and therefore the two steps must proceed in a stereochemically opposite sense. If the step **125** → **126** proceeds with retention, then the step **126** → **127** must proceed with inversion (or vice versa) and the step **128** → **126** must also proceed with inversion (as it appears so to do from other evidence). The conclusion thus reached, that retention of configuration occurred in the interaction of a phosphonothioate ester with an aryl (phenyl) Grignard reagent (and thus the phosphinic ester **126** is of *R*-configuration), was confirmed in later work[350]. Moreover, the configuration of the tertiary phosphine oxide, (*R*)-(+)-**129**, obtained from (*S*)-(–)-*S*-methyl methylphenylphosphinothioate, clearly and unequivocally demonstrates the inversion of configuration in the use of PrMgBr with a thiophosphinate ester.

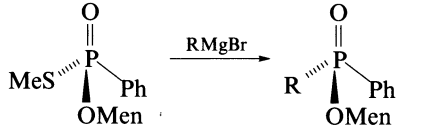
By contrast, a reaction between *O*-(–)-menthyl *S*-methyl (*S*p)-phenylphosphonothioate (**131**) (whose configuration at phosphorus was also assigned through single-crystal X-ray analysis) and MeMgBr (or MeLi) afforded the (*R*p)-methylphenylphosphinate **132**[351]. Moreover (results quoted in ref. 351), a similar reaction of (*S*p)-**131** with PrMgBr gave the phosphinate (*R*p)-**133**, as confirmed by X-ray analysis. Hence the displacement of SMe in a phosphonothioic diester by alkyl Grignard reagents occurs with retention. The conversion of (*R*)-(+)-(MeO)PhP(O)SMe into (*S*)-(–)-(MeO)PhP(O)Me also represents a displacement with retention of chirality at phosphorus[203]. However, an example of the difficulties which may arise has been provided by Moriyama and Bentrude[195] (Scheme 35); here, both phosphinic ester intermediates reacted with a Grignard reagent (steps *b* and *d*)

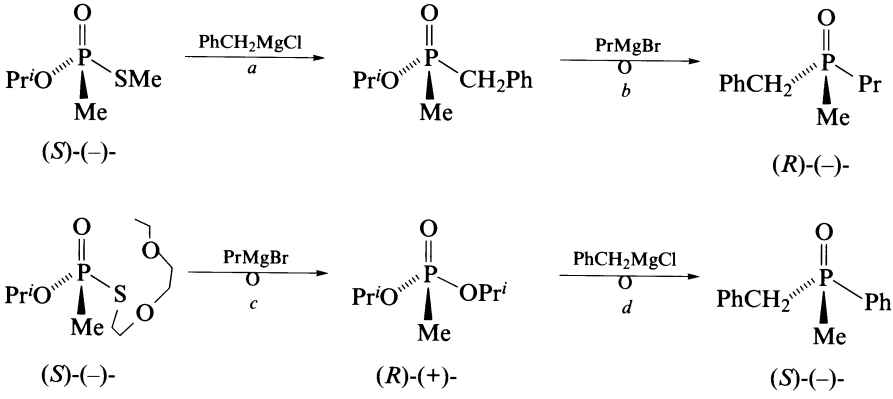


SCHEME 34

with inversion of configuration to give phosphine oxides of known configuration, but in the initial stages, both retention (step *a*) and inversion (step *c*) were observed; moreover, benzylmagnesium chloride took part in reactions *a* and *d* with different stereochemical consequences.

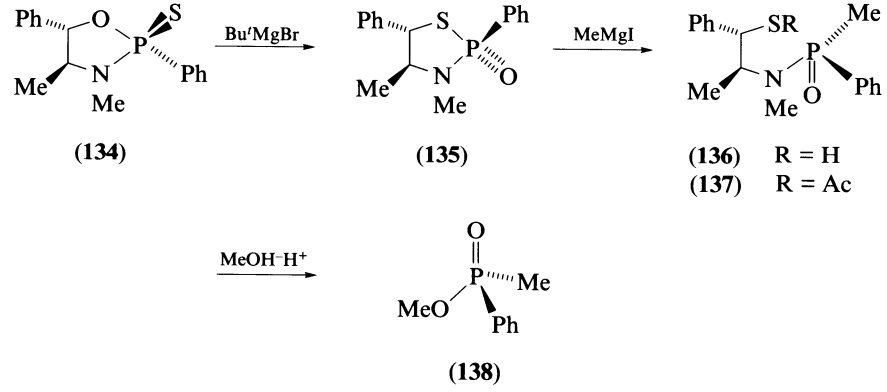
Treatment of **134** with Bu^{t}MgBr, $MgBr_2$ or even better, MgI_2, resulted in isomerization (presumably by ring opening and re-formation) to give the 1,3,2-thiazaphospholidine 2-oxide **135**. When **135** is treated with MeMgI at room temperature, cleavage of the P—S bond occurs quantitatively to give **136**, readily convertible into into its *S*-acetate (**137**). The





SCHEME 35

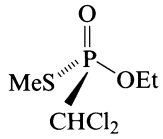
acid-catalysed methanolysis of either **136** or **137** yields (*R*)-(+)-methyl methylphenylphosphinate (**138**), a step known to occur with inversion of configuration; hence the P—S bond cleavage in **135** must have taken place with retention of configuration at phosphorus[352].



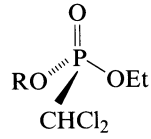
b. By alkoxides. Another widely explored displacement with P—S bond fission is that brought about by alkoxides. (*R*)-(+)-*O*-isopropyl S-methyl methylphosphonothioate (**125**; R = Me) undergoes inversion of configuration at phosphorus when treated with EtO^-; the corresponding (*R*)-(+)-*S*-propyl ester (**125**; R = Pr) behaves likewise[344]. A detailed study of the action of ethoxide ion on *O*,*S*-dimethyl phenylphosphonothioate, in which the competitive displacement of MeO^- also occurs, led to the same conclusion with regard to the displacement of MeS^-[203]. Inch and Lewis[353] also reported P—SMe bond fission by MeO^- with inversion in substrates based upon chiral carbohydrate templates.

In other cases, the course of a simple interaction can be complex, as in, for example, reactions between methoxide and phosphonothioates based an halomethyl phosphonothioic acids. Inch's group[354] examined the behaviour of (*R*)-(+)-*O*-ethyl *S*-methyl (dichloromethyl)phosphonothioate (**139**); this could be dechlorinated with H_2–Pd/C in a stepwise fashion, and so eventually correlated with the methylphosphonothioate diester of identical configuration at phosphorus; furthermore, chlorination of **139** with BuLi–CCl_4

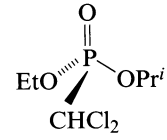
gave the stereoisomerically identical (trichloromethyl)phosphonothioate. In the first place, the course of the reactions with methoxide depends on chlorine content of the phosphonothioic acid; the (trichloromethyl)phosphonothioate diester suffers P—C bond fission, and is not be considered further at this point. The (dichloromethyl)phosphonothioate diester **139** is also very reactive, and because of further possible reaction of the product(s), the reaction with methoxide must be carried out carefully (and may be monitored by ^{31}P NMR spectroscopy). Methoxide displacement of MeS^- from **139** to give **140** occurs with retention of configuration on the other hand, the displacement by Pr^iO^- yields a mixture of (*R*)- and (*S*)-*O*-isopropyl esters, **141** and **142**, in the ratio 4:1, and, after consideration of possible causes of this loss of stereospecificity it was concluded that the result does represent loss of MeS^- with both inversion and retention. For the (chloromethyl)phosphonothioate diester **143**, the chemistry of the reaction was rendered more complex by other processes; P—S bond cleavage occurs with >70% inversion to give (*R*)-**144** and a minor primary product was **145**, although this could not be isolated because of the ease of P—O fission to give dimethyl (chloromethyl)phosphonate. Thus, an increase in chlorine content, i.e. an increase in the electron-withdrawing power of the alkyl group, resulted in a change from P—S bond fission with predominant inversion to one of predominant retention. When chlorine is replaced by fluorine[355], the action of methoxide results in P—C bond fission even in the (difluoromethyl)phosphonodithioate ester; reactions between MeO^- and *O*-ethyl *S*-methyl (fluoromethyl)phosphonodithioate, and also with *S*-methyl *P*-(difluoromethyl)-*N*,*N*-dimethylphosphonothioic amide, occur with predominant inversion of configuration.



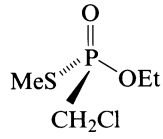
(139)



(140) R = Me
(141) R = Pr^i



(142)



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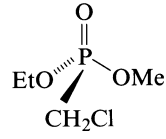

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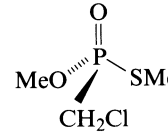
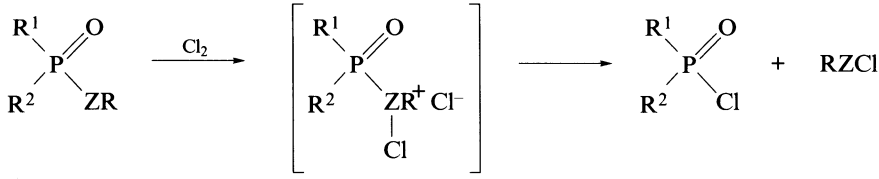


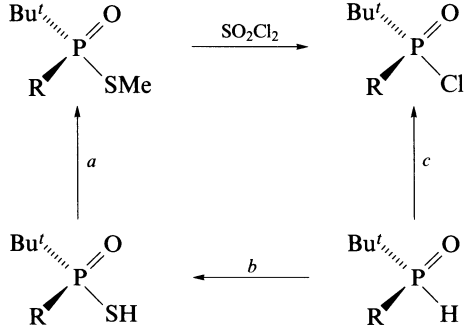
(145)

c. By halogenolysis. It has long been known that thiolate esters are cleaved at the P—S bond when acted on by chlorine or sulphuryl chloride, with the introduction of the P(O)Cl moiety. The literature already reviewed in this chapter includes several references to such reactions (see, for example, refs 294 and 354), but others are known. In its simplest form, the reaction may be formulated as in Scheme 36. Several relatively recent studies have been made of the halogenolysis of phosphinothioates with chlorine or sulphuryl chloride[356], or with bromine and with iodine[357], and the chlorination, bromination and iodination of phosphinoselenoates[358] and phosphonothioates[359], largely based on very detailed ^{31}P NMR spectroscopic work. The two aspects of the chemistry concentrated on were the overall stereochemistry of the reaction and the nature of the several intermediates.

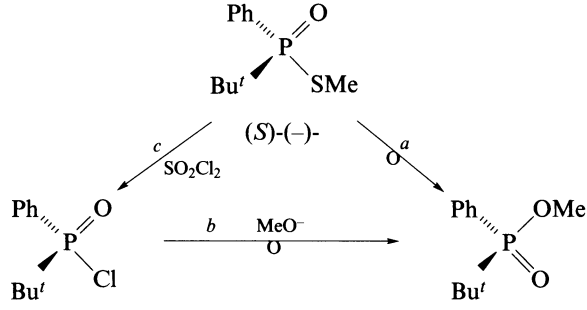


SCHEME 36

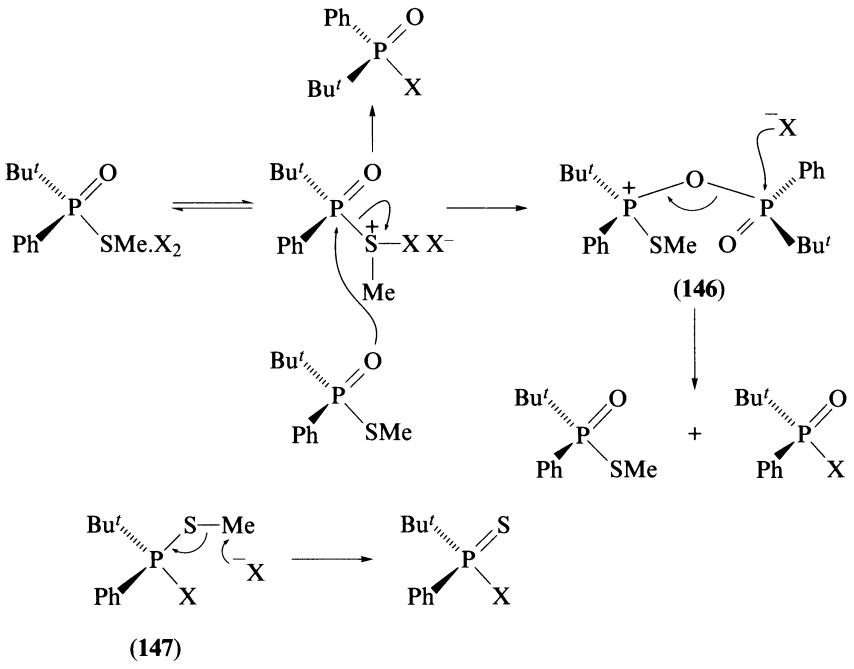
Irrespective of solvent [benzene (highest stereoselectivity), CCl_4 (good stereoselectivity), CH_2Cl_2 or mixtures of these (low stereoselectivity)], the overall reaction between chlorine or sulphuryl chloride and (*R*)-(+)- or (*S*)-(–)-*S*-methyl *tert*-butylphenylphosphinothioate proceeded with retention of configuration, and some similar findings were reported by Inch's group[353]; when $HgCl_2$ was introduced into the mixture, the reaction proceeded with low stereoselectivity but with overall inversion. Evidence for the stereochemistry of the reaction rests in two reaction cycles (Schemes 37 and 38). In the first of these, steps *a*, *b* and *c* all proceed with known retention, and hence the chlorinolysis step must also proceed with retention. In Scheme 38, the two steps *a* and *b* proceed with inversion, and hence the chlorinolysis step must again proceed with retention. The ^{31}P NMR spectroscopic studies were performed for CH_2Cl_2 or toluene solutions of reactants within the temperature range –100 to +20 °C, many of the NMR signals being characterized by reference to earlier work.



SCHEME 37



SCHEME 38

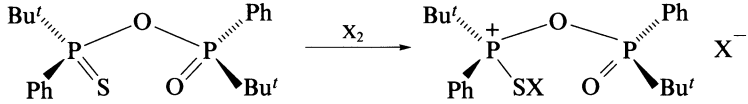


(147)

SCHEME 39

The sequence of steps in Scheme 39 (X = Cl) is evidently initiated by association (in molecular and ionic species) of the halogen with the ester; later NMR signals were linked with the presence of several quaternary phosphonium salts, some with only one, but others with two phosphorus centres. The main product of the reaction sequence is *tert*-butylphenylphosphinic chloride, accompanied by trace amounts of the corresponding phosphinothioic chloride which presumably arise through the collapse of structure **147**; the latter is probably reached by the alternative manner of breakdown of structure **146**.

A similar sequence of reactions was described to account for the behaviour of the same phosphinothioate ester with bromine or with iodine[358]. The intermediates including, for the brominolysis, those with two phosphorus atoms appeared to be more stable at room temperature. In the case of iodination, no phosphinic iodide was formed, and the only products that were detected were the ester–iodine complex(es) and the iodide of **146**; further reaction, which took 1–2 months, gave the thiopyrophosphinate **148** complexed with iodine, as in **149**. The bromination reaction was also slow, and although the complex **149** (X = Br) could readily be detected during shorter reaction periods, di-*tert*-butylphosphinic bromide was obtainable in yields of about 30% only when admixed *S*-methyl di-*tert*-butylphosphinothioate and bromine were stored at room temperature for about 2 months.



(148) (149)

The good donor properties of the selenium atom account for the greater reactivity of *Se*-methyl phosphinoselenoate esters compared with that of an analogous sulphur-containing ester, and the ultimate loss of selenium is a result of the better leaving ability of the $-\overset{+}{S}e(X)R$ group; the participation of diphosphorus intermediates is increased and the overall diastereoselectivity of the sequence reduced[358].

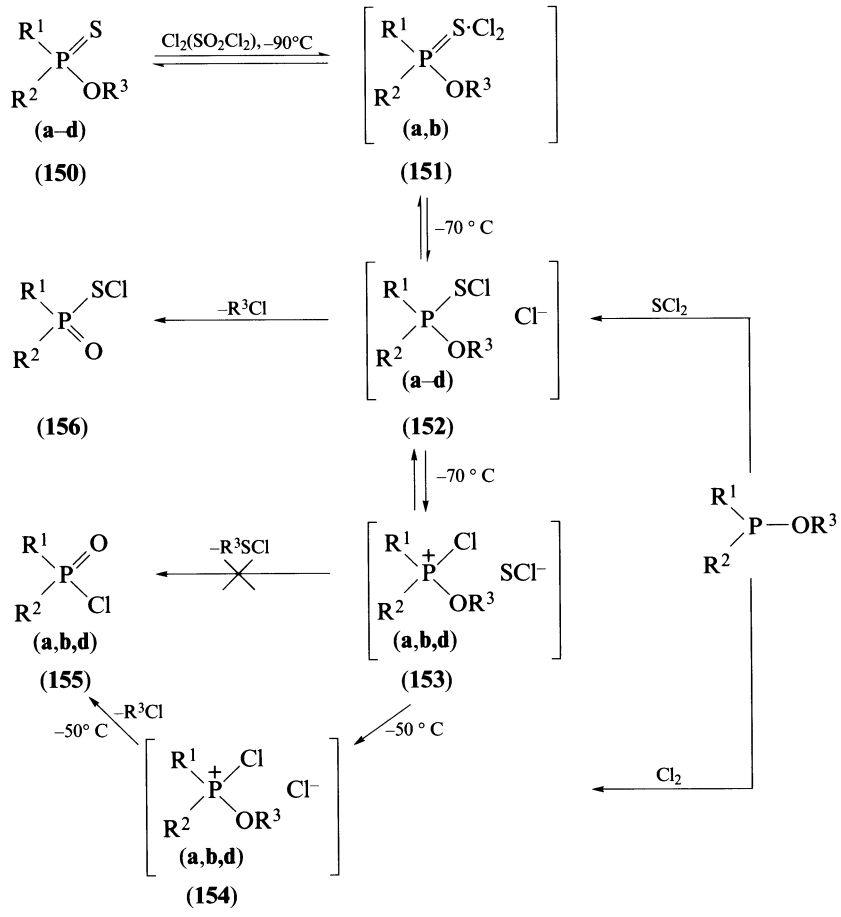
The reaction between (*S*)-(–)-*O*,*S*-dimethyl *tert*-butylphosphonothioate and sulphuryl chloride in benzene (best) or chlorine in CCl_4 (less satisfactory) results in the formation of (*S*)-(–)-methyl *tert*-butylphosphonochloridate (with retention of configuration); however, either SO_2Cl_2 or Cl_2 in CH_2Cl_2 gives the same acid chloride with overall inverted stereochemistry and reduced optical activity[359].

Fundamental differences are to be observed between the halogenolysis of *O*,*O*-dialkyl phosphonothioate or *O*-alkyl phosphinothioate esters, on the one hand, and tri-O-alkyl phosphorothioate esters on the other (Scheme 40)[360]. The chlorination of **150a** at –90 °C affords a complex, indicated as **151**, although there is no particular significance in this manner of representation. A rise in reaction temperature to –70 °C allows the appearance of a phosphonium complex (**152a**), which is accompanied by a second phosphonium complex (**153a**). When the temperature is eventually allowed to rise to –50 °C, the chloridate **155**, elemental sulphur and alkyl halide are formed in a final irreversible step. The process of reversible ligand exchange between structures **152** and **153** is of some importance, and it must be faster than dealkylation which would lead to the phosphinoylsulphenyl chloride **156**; at this stage, the process takes on a course which is essentially different from that found for *O*,*O*,*O*-trialkyl phosphorothioates, which lead mainly to phosphoroylsulphenyl chlorides. The character of the phosphonium salts **152** and **154** has been established by the isolation of hexachloroantimonate salts, stable at ambient temperature, and also by an alternative synthesis through a Michaelis–Arbuzov-like process. The stereochemical path of the chlorination reactions was established as involving an inversion of configuration at phosphorus by means of the steps indicated in Scheme 41[359,361]. Here, step *a* proceeds with retention of configuration and step *b* is known to proceed with inversion; hence step *c* must also proceed with inversion. However, attention should be drawn to the similar chlorination of *O*-trimethylsilyl esters of *O*-methyl *tert*-butylphosphonothioate and *O*-ethyl ethylphosphonothioate (**150e** and **150f**); here, the breakdown of a phosphonium salt (**152**; $R^3 = SiMe_3$) proceeds to the phosphinoylsulphenyl chloride (**156**) with little, if any, ligand exchange and ultimate formation of phosphonochloridate[362].

3. *The cleavage of P–N bonds*

Many of the earlier syntheses of phosphonic and phosphinic acid derivatives relied on the supposition that P—N bonds are stable to the action of organometallic reagents (Chapter 2). However, the P—N bond is not immune from cleavage by such reagents. Thus, 1,3,2-oxazaphospholidine 2-sulphides derived from (–)-ephedrine or (+)-pseudoephedrine undergo P—N bond fission with inversion of configuration, a reaction complicated by accompanying P—O bond fission with retention (Scheme 42)[363]. It is worth noting that the relative extents of P—N and accompanying P—O cleavages depend not only on the nature of R in RMgBr, but also on the overall geometry of the substrate molecules (Table 3). The cleavage of the P—N bond by Grignard reagents is evidently not observed in reactions that involve 1,3,2-thiazaphospholidine 2-oxides[352]. The isomerization of a 1,3,2-oxazaphospholidine 2-sulphide (**134**) into the 1,3,2-thiazaphospholidine 2-oxide (**135**) by the action of Bu^tMgBr (or other reagents), and without fission of the P—N bond, has already been noted[352].

The use of P—N-bonded compounds in the synthesis of phosphonic and phosphinic acids depends ultimately on the removal of nitrogen 'protection' by the cleavage of the P—N bond under aqueous acidic conditions; this procedure remains useful for acid

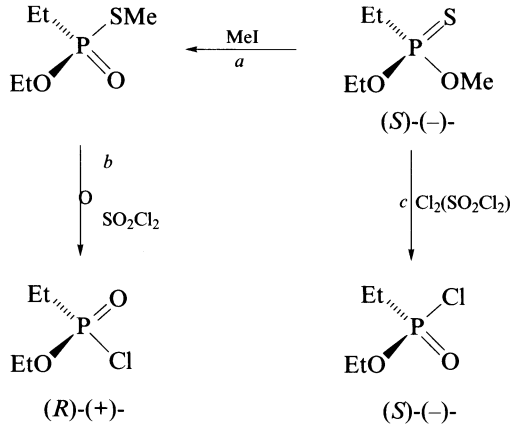


	R^1	R^2	R^3
(a)	Et	EtO	Et
(b)	Bu^t	EtO	Et
(c)	Ph	BuO	Et
(d)	Me	Me	Me
(e)	Bu^t	MeO	$SiMe_3$
(f)	Et	Et	$SiMe_3$

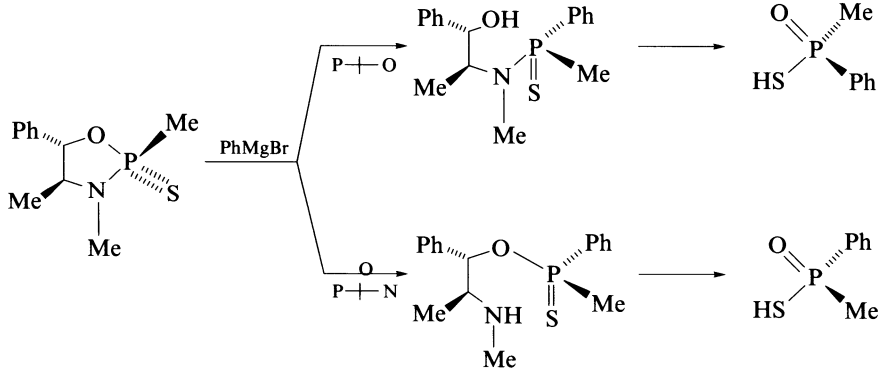
SCHEME 40

synthesis. Equally useful, however, is the acid-catalysed alcoholysis of phosphorus amides. However, such displacements are not peculiar to thiophosphorus compounds and they will be considered again in Chapter 6. Section VI.

Stereospecific P—N bond fission in a non-catalysed process is observed in the fission of amide anions with the substances CXY (X, Y = O or S) (the essential steps involved are

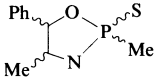


SCHEME 41

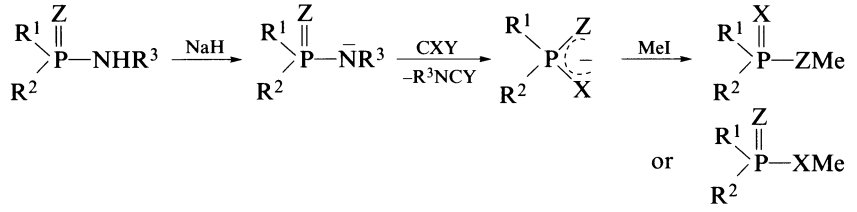


SCHEME 42

TABLE 3. Ring opening in 1,3,2-oxazaphospholidine 2-sulphides by Grignard reagents

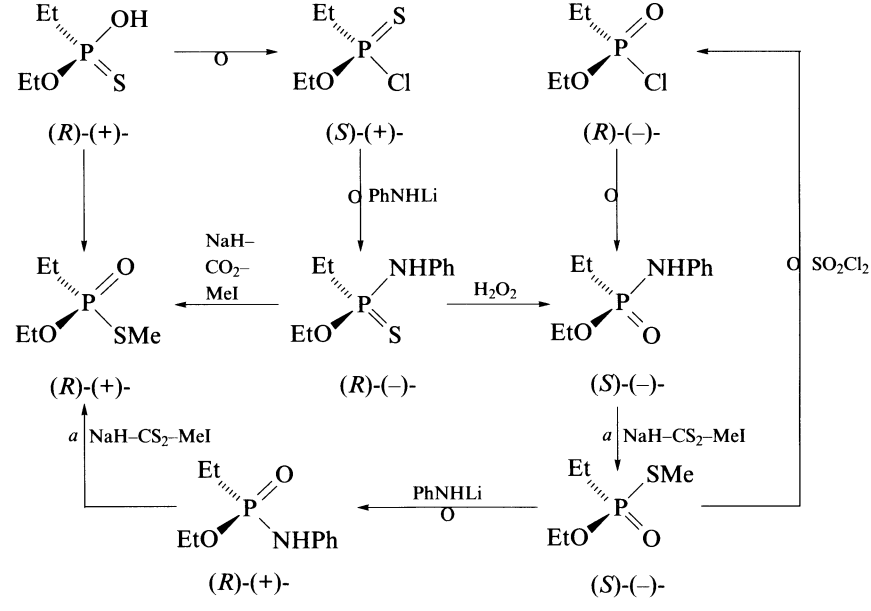
Structure: 	RMgBr: R	Yield (%) (stereochemistry) P—O cleavage	P—N cleavage
2*R*,4*S*,5*R*	Ph	76 (Retn)	Trace
2*S*,4*S*,5*R*	Ph	11 (50% Retn)	36 (Inv)
2*R*,4*S*,5*S*	Ph	30 (Retn)	25 (Inv)
2*R*,4*S*,5*S*	Et	35 (80% Retn)	15 (Inv)
2*S*,4*S*,5*S*	Ph	34 (Retn)	44 (Inv)
2*S*,4*S*,5*S*	Et	61 (60% Retn)	27 (Inv)

[a]Retn = retention; Inv = inversion.

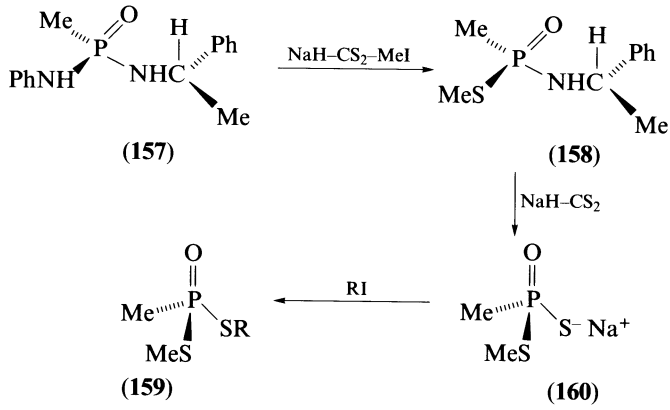


SCHEME 43

indicated in Scheme 43, in which Z = O, S or Se). The sequence can be utilized in various ways, such as the addition of sulphur to molecules which may, or may not, already contain that element, and this may be coupled, but need not be, with a change of P=X (X = S or Se) to P=O. In earlier studies, Stec *et al.*[364] worked on the anilides of various sulphur- and selenium-containing phosphorus acid esters; in addition to employing cyclic tri-*O*-alkyl phosphorus (V) esters, they studied the stereochemistery of the process with the aid of *O*-ethyl *P*-ethyl-*N*-phenylphosphonothioic amide. The latter, as its nitrogen anion, was made to react with CO_2; additionally, the corresponding sulphur-free anilide was used in conjunction with CS_2. The results are incorporated in Scheme 44 in which all stereochemical changes are already known with the exception of those marked *a*; it was concluded that these steps proceeded with high stereoselectivity with retention of configuration. Krzyzańowska and Stec[365] took the methodology a stage further and used phosphorus(V) amides derived from enantiomers of 1-phenylethylamine, and they started the sequence with diastereoisomeric amides such as (S_P,S_C)-**157**; under the usual conditions, this initially lost the anilino group and gave **158**, which could then undergo a second reaction to give chiral dithio acids (**159**) or their esters (**160**). The reaction was also extended to the preparation of S-alkyl esters of chiral phosphinothioic acids.



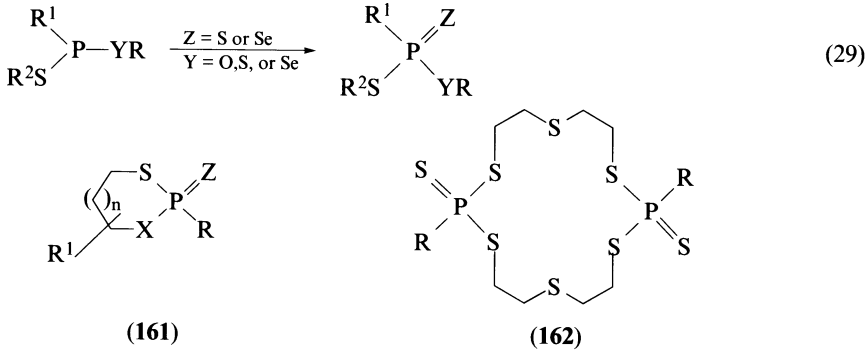
SCHEME 44



IV. SYNTHESES AND REACTIONS OF DI- AND TRI-THIO(SELENO)-PHOSPHONIC ACIDS AND DITHIO(SELENO)PHOSPHINIC ACIDS

A. Syntheses

Many of the syntheses that provide derivatives of polythio- or polyseleno-phosphonic and phosphinic acids are developments of the type of reactions discussed in the earlier sections of this chapter. Such methods include, for example, the addition of sulphur or selenium to phosphonothioite esters and other phosphorus(III) derivatives (equation 29) [2–7,366]. Many (cyclic) esters of phosphonodithioic and phosphonotrithioic acids (or their selenium-containing counterparts) have also been prepared by the addition of sulphur or selenium to the cyclic phosphorus(III) esters **161** (Z = l.p.; n = 0–2; X =O, S or Se; R^1 = H, Me, etc.) or from the dichlorides $RP(Z)Cl_2$(Z = O, S or Se) and a diol or dithiol in the presence of an acid (HCl) acceptor[367–370]. The *cis* and *trans* stereoisomers of the trithiophosphonate **162**(Z = S), so prepared, are separable[371]. The addition of sulphur or selenium to phosphorus(III) esters and amides is successively easier and is almost always exothermic, but successful oxidations with H_2O_2 have been reported, in spite of the excessively high reactivity of sulphur–phosphorus(III) bonded compounds towards oxidizing agents[372]. Tellurium has been added to the species R_2PZ^- to form R_2PZTe^- (R = Ph or Cy; Z = O, S, Se or Te) characterized through their ^{31}P and ^{125}Te NMR spectra, and some of which have been isolated in unstable and impure form[373]. The deoxidative sulphurization of esters of phosphinothioic acids by P_4S_{10}[40,48,123,126] or by Lawesson's reagent (see later discussion) to give the derivatives of phosphinodithioic acids has been widely reported.



(29)

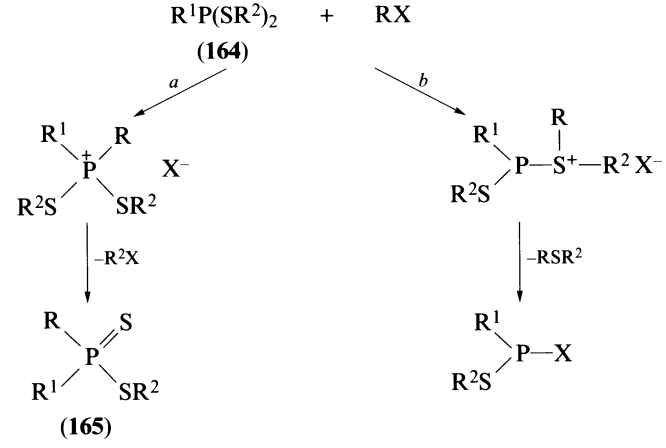
The displacement of halogen from phosphonic dihalides with thiols in the presence of an appropriate base leads to *S,S*-diesters rather than *O,S*-isomers (equation 30 Z = O)[2–7,374,375]. Such a reaction has been employed in the determination of the enantiomer composition of chiral thiols. The ^{31}P NMR spectra for a series of phosphonodithioates **163** (Z = O, R = Me, Ph, $PhCH_2$) and also for analogous trithiophosphonates **163** (Z = S, R = Me or Ph) in which the group R^1 is derived from a chiral thiol, showed that the best separation of ^{31}P NMR signals for the diastereoisomeric forms was achieved when R = Me[376]. Displacement reactions which involve the loss of chlorine from $R_2P(Z)Cl$ (Z = S[110,140] or Se[144]). $RP(O)(SR^1)Cl$[281] and $RP(S)(NHR^1)Cl$[377] by thiols in the presence of a tertiary amine base, and many more, are widely exemplified.

$$RPCl_2(Z) + 2RSH \xrightarrow{-2HCl} RP(SR^1)_2(Z) \qquad (30)$$

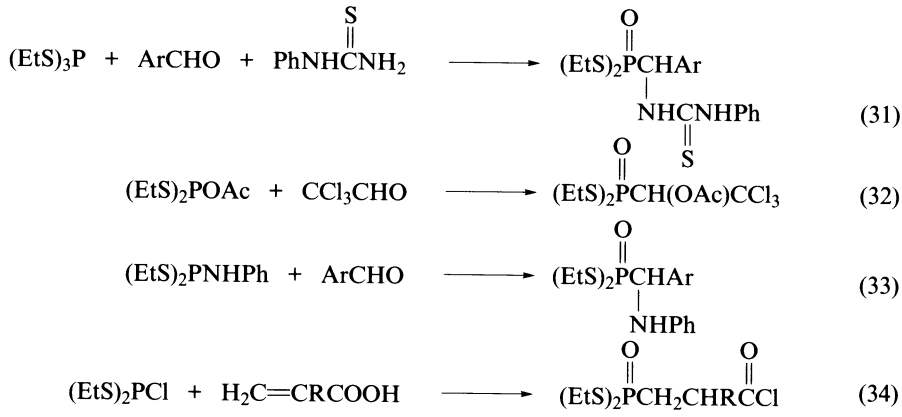
(163)

Classical Michaelis–Arbuzov reactivity towards the alkyl halides RX is exhibited by the phosphorodithious ester $(R^1S)_2POR^2$ and give the *S,S*-phosphonodithioate esters **163** (Z = O)[34], and by $(EtS)_3P$ towards MeI[33]. Crystalline 1:1 adducts have been obtained from alkyl halides and the phosphonodithious esters **164** under very mild conditions[378,379] and which, on decomposition at raised temperatures, may give the phosphinodithioic ester **165**[379,380], although the presence of other products suggests that, during the course of the interaction, quaternization at phosphorus (Scheme 45; pathway *a*) may be accompanied by that at sulphur (pathway *b*) and also by sulphur abstraction[379–382]. Non-classical Michaelis–Arbuzov activity which leads to esters of phosphinodithioic acids is found in the reactions between alka-1,3-dienes and 2-substituted-1,3-dithiaphospholanes[42,44,45]. The reader is also reminded of the cleavage of the P—N bond in compounds of the general form $RP(O)(SR^1)NHR^2$, as their nitrogen anions, in reactions with CS_2; this sequence is capable of yielding chiral phosphonodithioic diesters (**160**) and also, through the analogous formation of a chiral phosphinothioic ester followed by sulphurization, a chiral phosphinodithioic ester[364,365].

Functionalized phosphonodithioic derivatives have been obtained by well established reactions which include, for example, the formation of *S,S*-dialkyl [(α-thioureido) benzyl]phosphonodithioates from trialkyl phosphorotrithioites, aromatic aldehydes and a thiourea (equation 31), a reaction that parallels the formation of the phosphonic analogues



SCHEME 45



(31)

(32)

(33)

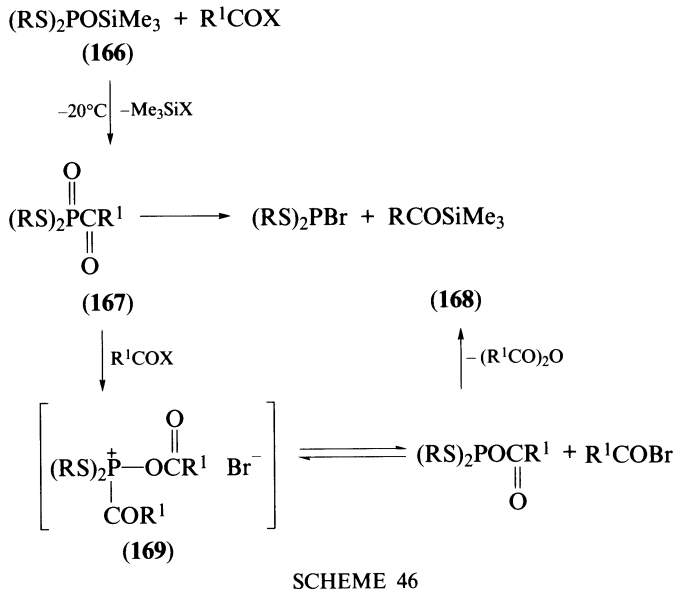
(34)

from trialkyl phosphites[383]. Other such reactions include the formation of the S,S-diethyl (1-acetyloxy-2,2,2-trichloroethyl)phosphonodithioate according to equation 32[384], the insertion of carbon between phosphorus(III) and nitrogen which provides an (α-aminobenzyl)phosphonodithioic diester according to equation 33[385] and the addition of phosphorus(III) chlorides to α,β-unsaturated carboxylic acids according to equation 34[386], which probably takes place through a covalent pentacoordinate intermediate. However, complications arise during attempts to prepare sulphur-containing (1-oxoalkyl)phosphonic diesters from phosphorothioite esters. A recent study[387] has demonstrated the complexity in the interaction of phosphorodithioite esters and acyl halides; the outcome is dependent on temperature and the nature of the halogen (Scheme 46). The esters **166** (R = Et or Pr^i) react at –20 °C with acetyl chloride or benzoyl chloride in the expected fashion to give the phosphonodithioate esters **167**; at the same or a lower temperature, acetyl and benzoyl bromides behave similarly, but if the reaction temperature is raised, the formation of the dithiobromidite eser **168** is observed, and is thought to be initiated by a reaction between **167** and the acyl bromide and to proceed via **169**.

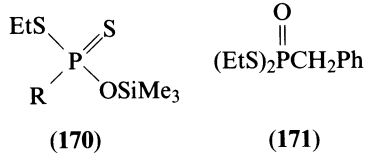
It might be noted that Michaelis–Arbuzov reactions between the esters **166** and MeI or EtI yield the products **170**(R = Me or Et), and whilst benzyl chloride affords the expected Michaelis–Arbuzov ester **171**, the outcome of a reaction with benzyl bromide depends on the experimental conditions, the ester **171** being formed at 100 °C with removal of volatile products at 100 mmHg, but at 130 °C in a sealed tube the product is **170** (R = CH_2Ph)[388].

Reactions have been carried out between aldehydes or ketones and esters of trithiophosphorous acid (equation 35; $R^2 = R^1S$)[389] or those of phosphonodithious acids (R^2 = Et), from which the products are esters with thioether substituents[389,390]. Benzaldehyde dithioacetals, $PhCH(SR)_2$ (R = Et or Pr^i), and the sulphide, P_4S_2 interact in an entirely novel manner to give products which include the perthio-phosphonic and -phosphinic esters **172** and **173**[391,392].

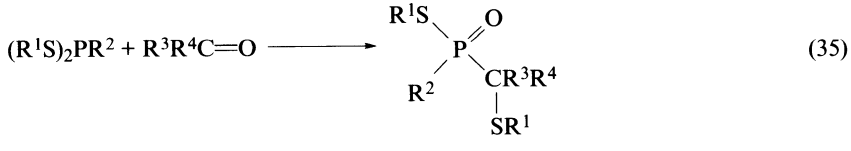
Although Grignard reagents are of comparatively little value in the direct synthesis of phosphono- and phosphino-thioic acids, they are of value in the preparation of the intermediates which themselves may then be converted into mono- or di-thio acids[25]. Thus, the reagent RMgX in diethyl ether reacts with metal salts of hydrogenphosphonothioates, $(R^1O)_2P(S)M$, with the formation of salts of secondary phosphine sulphides, $R_2P(S)M$, to which sulphur, or indeed selenium, may be added, to give the salts R_2PZSM (Z = S or Se), obtainable in moderate to excellent overall yield. Grignard reagents are reactive towards P_4S_{10} when mixtures of dithiophosphinic acids, R_2PSSH, and dithiophosphonic acids, $RP(O)(SH)_2$, are obtained, and which are separable through their nickel salts; those of the phosphinic acids are soluble in diethyl ether and benzene, in contrast to the salts of the phosphonic acids.



SCHEME 46



(170) (171)



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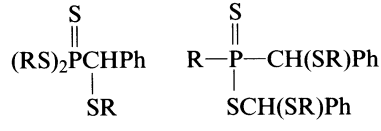


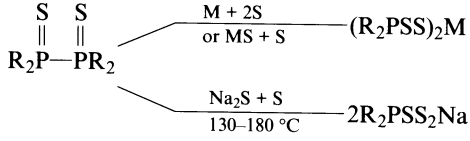
(172) (173)

The Friedel–Crafts-type reaction between an aromatic hydrocarbon and P_4S_{10} in the presence of a catalyst, generally $AlCl_3$ or $AlBr_3$ (the amount of which may inversely influence the final yields), has been useful in the preparation of diphenylphosphinodithioic acid (equation 36), in yields up to 80% and also certain other acids, but obvious difficulties arise in reactions with monosubstituted arenes from which mixtures of isomeric products are formed, although their separation is generally not required for potential technical uses. A similar Friedel–Crafts procedure, which employs the cyclic bisanhydrosulphides of phosphonotrithioic acids (to be considered more fully in later sections) has also been successful in the preparation of unsymmetrical phosphinodithioic acids (reaction 37)[25].

$$8\,C_6H_6 + P_4S_{10} \xrightarrow{AlCl_3} 4\,Ph_2PSSH + 2H_2S \quad (36)$$

$$(RPS_2)_2 + 2C_6H_6 \xrightarrow{AlCl_3} 2\,RPhPSSH \quad (37)$$

The ready availability of diphosphine disulphides, from $P(S)Cl_3$ and Grignard reagents, and their ability to undergo cleavage at the P—P bond when acted on at 130–180 °C by a Group II metal, or a metal sulphide, in the presence of sulphur, is a good option in the synthesis of dithio- and related phosphinic acids, with high yields of metal salts of the desired acids (Scheme 47). The P—P bond in tetraalkyldiphosphine disulphides is cleaved by a mixture of sulphur and Na_2S to give the sodium salt of a dialkylphosphinodithioic acid, R_2PSSH[393–395], and, likewise, a mixture of selenium and Na_2Se affords the salt of the selenothioic acid, R_2PSSeH[395]. The same acids, and the analogous diseleno acid, are also conveniently obtained by reaction 38, in which either, or both, Z and Z′ are S or Se[395,396].

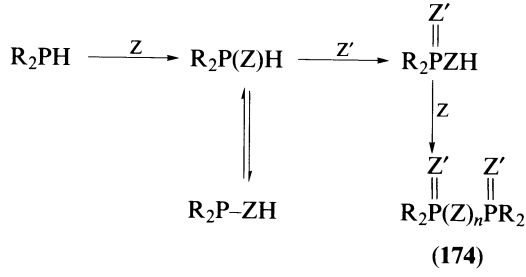


SCHEME 47

$$RR^1P(Z)Cl + NaZ'H \longrightarrow RR^1P(Z)Z'H + NaCl \quad (38)$$

The addition of sulphur to a stoichiometric amount of a secondary phosphine, R_2PH, in a solvent and in a non-oxidizing atmosphere, affords the phosphine sulphide, $R_2P(S)H$[25]. The further addition of sulphur (a less than stoichiometric amount is recommended[397]) which, in principle should provide the phosphinodithioic acid, $R_2P(S)SH$[398], was the method used originally in 1871 by Hofmann, without published details, for the preparation of diethylphosphinodithioic acid, and remains, following modifications, one of the more important means of obtaining such compounds.

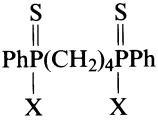
The two principle products from the addition of sulphur to $Et_2P(S)H$ are the phosphinodithoic acid, Et_2PSSH, and the trisulphane, **174** (R = Et, Z = Z′ = S, n = 3)(Scheme 48), which can be separated wthout too much difficulty. In many cases, the phosphinodithioic acids may be isolated as the salt of a heavy metal such as nickel, but a better synthesis procedure consists in the addition of the sulphur to the secondary phosphine sulphide in aqueous alkali (ammonia solution provides better yields than sodium hydroxide), when the polysulphane—the principle by-product—is broken down under the influence of the alkali metal sulphide[396]. A phosphinodiselenoic acid may be obtained in essentially the same



(174)

SCHEME 48

way. Obviously the second step may consist in the addition of a chalcogen non-identical with the first, and it is thus possible to prepare selenothiophosphinic acids. Attempts to purify diethylphosphinodithioic and diethylphosphinodiselenoic acids by recrystallization resulted in the formation of the same trisulphane, and of the yellow crystalline **174** (R = Et, Z = Se, Z′ = S, n = 3) and orange crystalline **174** (R = Et, Z = Z′ = Se, n = 3)[395]; the second of these three compounds was also isolated after the recrystallization of **174** (R = Et, Z = Se, Z′ = S, n = 2) from benzene[399]. As a further example, tetramethylenebisphenylphosphine adds sulphur in boiling benzene to give the symmetrical bisdithiophosphinic acid **175** (X = SH), readily converted into **175** (X=Cl) with PCl_5[400]. In other cases where, for instance, an acid is particularly sensitive to aqueous conditions, e.g. bis(2-cyanoethyl) phosphinodithioic acid, the stoichiometric amount of sulphur may be added to the secondary phosphine in an inert solvent. In practice, the addition of sulphur to a secondary phosphine sulphide is readily carried out following the preliminary reaction between the salt of a dialkyl hydrogenphosphonothioate with a Grignard reagent.

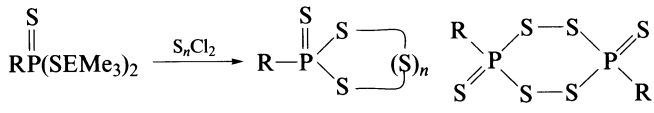


(175)

Several of the procedures employed for the synthesis of dithiophosphinic acids have also been developed for the preparation of a remarkable group of compounds already referred to as phosphonotrithioic bisanhydrosulphides or 'thionophosphine disulphide' dimers but which, structurally, are 1,3,2,4-dithiadiphosphetane 2,4-disulphides. Their importance is such as to warrant separate discussion, and this is to be found in a later section.

Phosphonotrithioic acids are generally not obtainable in pure form because of their ease of hydrolysis, although derivatives are available. In addition to reactions based on those described in the preceding paragraphs, a unique manner for the construction of the phenylphosphonotrithioic nucleus involves a reaction between $(Ph_4P)_2[WS_4]$ and $PhPCl_2$ in acetonitrile; the structure of the reaction product, as ascertained by single-crystal X-ray analysis, has a W_2S_2 core to which are ligated two bidentate $PhP(S)S_2$ groups in the overall structure $(Ph_4P)_2[W_2S_4(S_3Ph)_2]$[401].

Although the phosphonotrithioic acids are themselves poorly characterized, there is an increasing number of substances, often heterocyclic in nature, which are based on the phosphonotrithoic acids and which have been well characterized. Thus, the formation of novel phosphorus–sulphur heterocyclic systems with exocyclic P—C bonding (**177**) is observed when bis(trimethylsilyl) esters (or the corresponding tin compounds) of phosphonotrithioic acids **176**(R = Me or Bu^t, E = Si or Sn) react with the sulphur chlorides S_nCl_2 (n = 3–5). The products are fairly stable in the crystalline state, but disproportionate in solution[402]. When treated with dmso, the same esters **176** yield the tetrathiadiphosphorinanes **178**, which are also reasonably stable in the crystalline state but which, in solution, lose sulphur to give a 1,2,4,3,5-trithiadiphospholane 3,5-disulphide. Moreover, although **178** (R = Me) exists in both *cis* and *trans* forms, only the latter is known when R = Bu^t [403].



(176) **(177)** **(178)**

B. Reactions

A brief consideration follows of some of the more important reactions of the acids, prepared as described in the previous paragraphs, and their simple derivatives—with the exception of the anhydrosulphides which, questionably, are the most important of those derivatives, certainly as far as potential for use is concerned.

Phosphinodithioic acids undergo several unusual reactions with comparative ease. They are readily and completely oxidized to phosphinic acids by powerful reagents such as nitric acid, alkaline hydrogen peroxide or bromine in alkaline solution. Loss of sulphur also occurs when the acids are heated with metallic sodium, by which procedure the sodium derivative of the secondary phosphine is produced (equation 39); removal of sulphur is also brought about when an acid is treated with a reactive trialkylphosphine, tributylphosphine often being employed (equation 40). The conversion of diphenylphosphinodithioic acid into its derived acid chloride (identical with that from diphenylphosphinothioic acid) is best achieved, not by the action of PCl_5 as in the case of the phosphinothioic acid, but rather by the action of HCl at 150–200 °C under anhydrous conditions (equation 41); the action of an elemental halogen is too severe for such a conversion, since the replacement of both sulphur atoms occurs to give trichlorodiphenylphosphorane (equation 42) and, unfortunately, the action of thionyl chloride leads to diphenylphosphinic chloride (equation 43)[2–7,25]. The chlorination of Et(EtO)P(S)SeEt occurs through the cleavage of the more reactive P—Se bond to give Et(EtO)P(S)Cl and EtSeCl, a procedure used to identify the site (sulphur or selenium) of alkylation of $R^1R^2PSSe^-$ ions; it is interesting that a difference in sites for alkylation (at sulphur) and acylation (at oxygen), such as that observed for phosphonothioate anions, is also to be observed here; benzoylation of the phosphinoselenothioate anion occurs on sulphur, and the chlorination (SO_2Cl_2) of the product affords benzoyl chloride and the unstable $R^1R^2P(Se)SCl$[404].

$$Ph_2PSSH + 5Na \longrightarrow 1/2\ H_2 + 2Na_2S + Ph_2PNa \quad (39)$$

$$Ph_2PSSH + 2Bu_3P \longrightarrow Ph_2PH + 2Bu_3P(S) \quad (40)$$

$$Ph_2PSSH + HCl \longrightarrow Ph_2P(S)Cl + H_2S \quad (41)$$

$$Ph_2PSSH + 3Cl_2 \longrightarrow Ph_2PCl_3 + HCl + S_2Cl_2 \quad (42)$$

$$Ph_2PSSH + SOCl_2 \longrightarrow Ph_2P(O)Cl + 3S + HCl \quad (43)$$

Alkyl esters of phosphinodithioic acids and related acids are readily obtained by the alkylation of metal salts of the acid with more reactive alkyl halides, or from a phosphinothioic halide and thiol in the presence of a tertiary amine base, whereas aryl esters are obtainable by the interaction of such metal salts and aryldiazonium salts. Higher alkyl esters are obtainable by the direct reaction between a dithio acid and the alcohol at a high temperature with the elimination of water; thus diphenylphosphinodithioic acid reacts with the normal and tertiary butyl alcohols (but not with 1-methylpropanol) at 80–120 °C over extended periods (16–30 h) to give the corresponding butyl diphenylphosphinodithioates in 60–70% yields. Reactions with secondary alcohols may be successful at higher temperatures e.g. 1-methylheptanol reacts during 6 h at 180 °C. It is notable that in the reaction between diphenylphosphinodithioic acid and phenol the product is not the phenyl phosphinodithioate, but rather *O*-phenyl diphenylphosphinothioate; it has been suggested that this is the result of the initial formation of the 'anhydride' of the dithioic acid followed by a cyclical reaction between the diphenylphosphinodithioic anhydrosulphide and the phenol (Scheme 49). Alkylation of the acids proceeds almost quantitatively when they are acted upon by epoxides or oxetanes; the products are the 2-hydroxyalkyl esters.

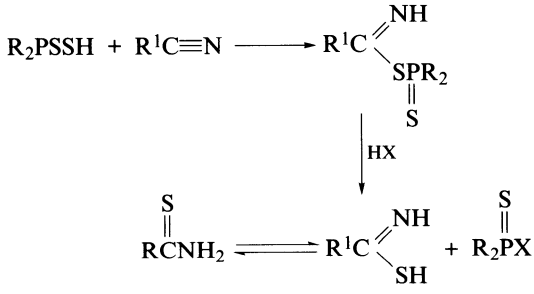
$$2Ph_2PSSH \xrightarrow{PhOH} Ph_2P(S)SPPh_2 \xrightarrow{PhOH} Ph_2P(S)OPh + Ph_2PSSH \xrightarrow{PhOH} \text{etc.}$$

SCHEME 49

In common with simple thiols and *O,O*-dialkyl phosphorodithioates, phosphinodithioic acids add to alkenes according to the Markovnikoff rule (propenenitrile is a possible exception to this behaviour) and even in the absence of a catalyst (equation 44). In the presence of sodium methoxide, anti-Markovnikoff behaviour is often observed as the result of Michael addition of the acid anion (equation 45). Addition of the acids to otherwise saturated nitriles leads, following acidolysis of intermediate species, to thiocarboxamides and the phosphinothioyl halide (Scheme. 50).

$$R_2PSSH + R^1CH{=}CH_2 \longrightarrow R_2P(S)SCHR^1CH_3 \quad (44)$$

$$R_2PSS^- + H_2C{=}CHCN \xrightarrow{H_3O^+} R_2P(S)SCH_2CH_2CN \quad (45)$$



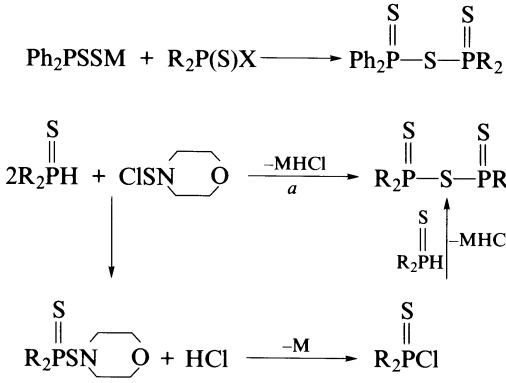
SCHEME 50

C. Anhydrides and Anhydrosulphides; Syntheses and Reactions

1. Syntheses

The anhydrosulphides of polythio-phosphonic and -phosphinic acids occupy a special place in the chemistry of those acids which warrants a separate and more detailed consideration, since this is one area in which true advances have been made during the two past decades both in the discovery of new structures and in the application of organophosphorus chemistry to conventional organic synthesis.

When diphenylphosphinodithioic acid is heated at 170 °C for an extended period, a loss of H_2S occurs with the formation of the anhydrosulphide. Related compounds are also easily prepared by the reactions between salts of dithioic acids (these are more reactive than salts of phosphinic acids) and phosphinothioic halides; obviously, this procedure is capable, in principle, of providing unsymmetrical anhydrosulphides (equation 46), but these tend to disproportionate into a mixture of symmetrical compounds[405].

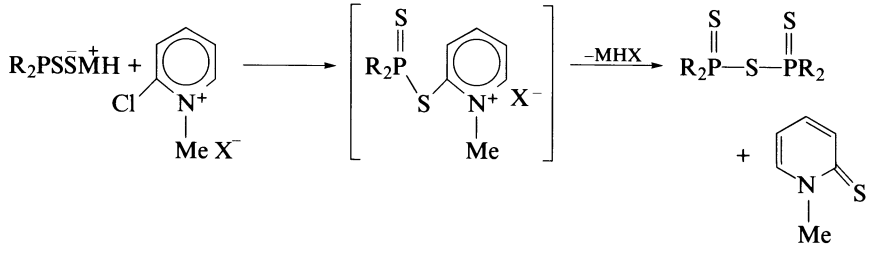


SCHEME 51

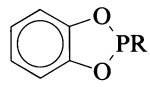
A novel means of obtaining anhydrosulphides consists in the reaction between a secondary phosphine sulphide and a sulphenyl chloride derived from a secondary amine (Scheme 51; step *a*; M = morpholine). The other proposed stages in this reaction scheme, as indicated, have received confirmation in separate studies including synthesis and degradation. The yields for the compounds with R = Me, Et, Pr, Bu, $PhCh_2$ or Ph are in the range 53–80%[406]. A further procedure which, unlike the previous one, is generally applicable to *O,O*-diesters of dialkyl phosphorodithioic acids, but is equally applicable to diphenylphosphinodithioic acid, involves the interaction of a tertiary amine salt of the acid and a reactive pyridinium species (Scheme 52; X = I or *p*-Tos, M = piperidine) in dichloromethane for 1 h at 0 °C[407]. The abstraction of sulphur from bisphosphinothioyl disulphanes (disulphides) is a widely applied method for the preparation of anhydrosulphides of various structural types; with **174** (Z = Z′ = S, *n* = 2) the abstraction is easily achieved by the action of Ph_3P or Bu_3P.

Although probably a process of doubtful synthetic utility, it has been noted that the phosphorus(III) isocyanate **179** reacts with diphenylphosphinodithioic acid to furnish the mixed anhydrosulphide **180**[408].

Cleavage of the P—P bond in a diphosphine by chalcogens forms a useful route to various derivatives of (particularly) selenium or tellurium which might otherwise not easily be obtainable. Such reactions are exemplified by reference to those of tetra-*tert*-butyldiphosphine and outlined in Scheme 53. The ultimate products in the selenation of the diphosphine are the anhydroselenide **182** (*n* = 1) of di-*tert*-butylphosphinodiselenoic acid and the tetraselenide **182** (*n* = 2). The use of tellurium (reaction in boiling benzene) in this investi-

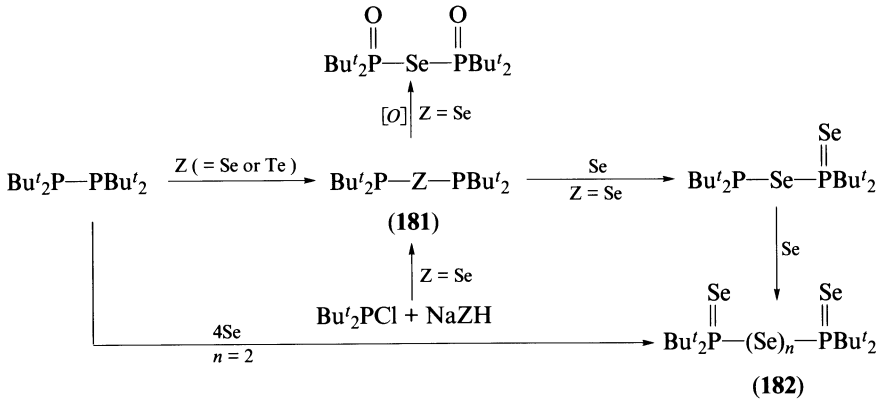


SCHEME 52



(**179**) R = NCO

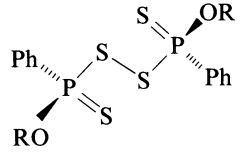
(**180**) R = $SPPh_2$ (S)



SCHEME 53

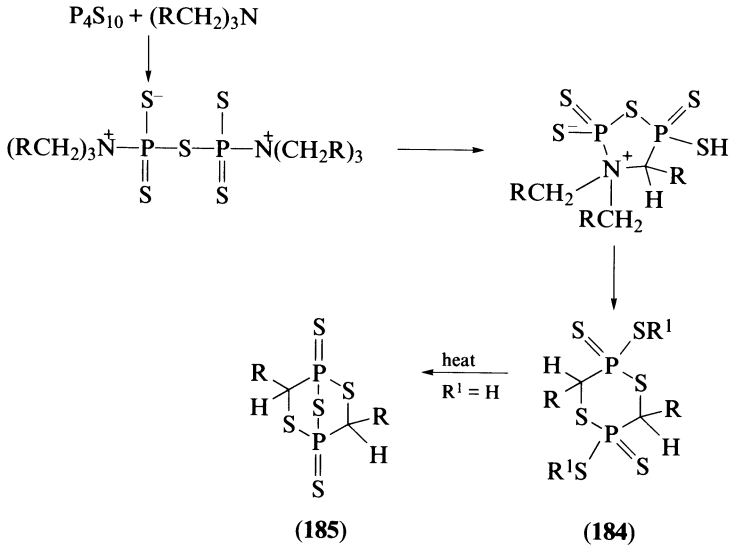
gation was restricted to the preparation of the telluride **181** (Z = Te), the anhydrotelluride of di-*tert*-butylphosphinotellurous acid[409].

Obviously, the anhydrosulphides just described are merely the first members of the series of sulphides **174** (Z = Z′ = S). One of these, **174** (R = Et, n = 3), has already been mentioned as a by-product in the early preparation of diethylphosphinodithioic acid. The disulphanes **174** (n = 2) are most readily obtained when metal salts of the phosphinodithioic acid are oxidized with iodine, but they have also been obtained as by-products in a range of reactions in phosphorus–polysulphur chemistry; non-symmetrical disulphides appear to be more stable to disproportionation than are the comparable anhydrosulphides. An unusual case of steric selection is to be found in the iodine oxidation of the *O*-(–)-menthyl ester of phenylphosphonodithioic acid (as its triethylammonium salt); the product **183** [R = (–)-menthyl] possessed the (S_P,S_P) configuration, a structure based on its single ^{31}P NMR signal and the result of an X-ray analysis[410]. The reaction between the phosphinodithioic acid and sulphur chlorides leads to the polysulphans **174** (n = 3 or 4)[393].



(**183**)

The interaction of tetraphosphorus decasulphide with a trialkylamine is thought to proceed according to Scheme 54 and lead to 2,5-dimercapto-1,4,2,5-dithiadiphosphorinane 2,5-disulphide [**184**; $R^1 = H_2N^+(CH_2R)_2$}, which can be methylated by MeI to yield **184**

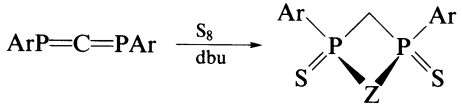


(185) (184)

SCHEME 54

(R^1 = Me). The action of heat on the derivatives **184** is such as to lead to a loss of H_2S and the formation of the anhydrosulphide **185**[411–413]. Tributylphosphine removes exocyclic (thiophosphoryl) sulphur from **185** and the conversion of **184** into **185** is also achieved when the former is treated with $P(S)Cl_3$[414].

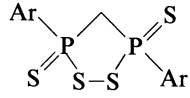
The addition of sulphur to the phosphorus analogue **186** of a carbodiimide (Ar = 2,4,6-tri-*tert*-butylphenyl) in the presence of dbu produces both the *cis*-**187** and *trans*-**189** isomers of the 2,4-diaryl-1,2,4-thiadiphosphetane 2,4-disulphide, together with the *trans* form of the 1,2,3,5-dithiadiphospholane 3,5-disulphide, **190**, the last structure being confirmed by single-crystal X-ray analysis[415]. Under wet conditions, the system also provided the *cis*-1,2,4-oxadiphosphetane **188**, a structure also confirmed by X-ray analysis[416]. The mode of formation of a cyclic anhydrosulphide **191** (a 1,2,5-thiadiphospholane 2,5-disulphide) is indicated in Scheme 55 (Im=1-imidazolyl)[417].



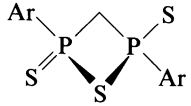
(186)

(187) Z = S

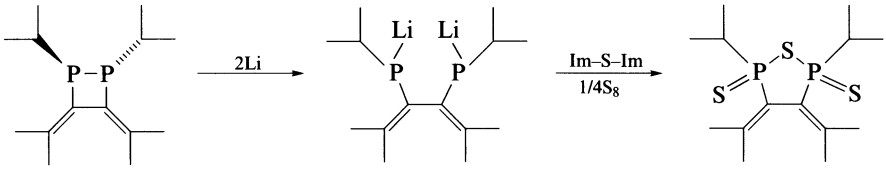
(188) Z = O



(190)



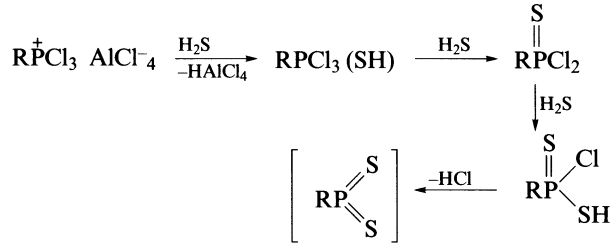
(189)



(191)

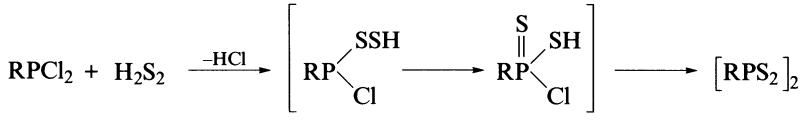
SCHEME 55

In 1952, Kinnear and Perren recorded[69] that the complex from EtCl, $AlCl_3$ and PCl_3 was reactive to H_2S at 130 °C and afforded a substance with the composition $EtPS_2$. This reaction received further attention from Newallis *et al.*[418], and was developed as a general method of synthesis; in its essentials, the synthesis involves the formation of the dichlorides, $RP(S)Cl_2$, which, in the absence of an acid acceptor, react slowly with H_2S even at 160 °C; in the presence of Et_3N, the reactions are much faster (Scheme 56). Indeed, Grishina and coworkers[108,110,111] and also Fukuto's group[18] prepared the same products directly from phosphonothioic dichlorides and H_2S.

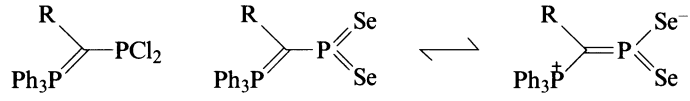


SCHEME 56

Baudler and Valpertz[419] found that dichlorophosphines can likewise act as a source of the same compounds when they undergo a stepwise displacement of halogen by H_2S_2 (Scheme 57). It is much more convenient to treat the dichlorophosphine, e.g. $PhPCl_2$ or Bu^tPCl_2, with K_2S_2 or Li_2S_2[420] to produce derivatives of an analogous composition. Moreover, Li_2Se_2 with Bu^tPCl_2 gives a selenium analogue[420]. On treatment with Na_2Se_2, **192** is converted into the orange **193** (R = Me, Et, or Ph)[421].

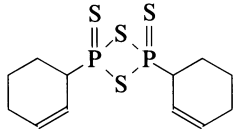


SCHEME 57



(192) (193)

One of the earliest positive demonstrations of the formation of a substance having the composition RPS_2 was that by Fay and Lankelma who (se Ref. 25), in 1952, showed that cyclohexene and P_4S_{10}, when boiled together in the molar ratio 20:1, produced a substance with a dimeric nature $(RPS_2)_2$ (molecular weight determination) and formulated as **194**, although no evidence was presented to indicate actual molecular geometry[25]. The same type of product is also formed from benzenoid compounds, e.g. benzene, toluene, xylene and other alkylbenzenes; each reacts with P_4S_{10} within a specific temperature range. Naphthalene is a particularly interesting case; aside from changes to the composition of the phosphorus sulphides present, several reactions have been observed depending on the molar ratio of reactants and temperature. With a very high ratio of naphthalene to P_4S_{10} at 160–190 °C, pure **195** is isolable. Roesky reported[422] in 1968 that naphthalene could also react with P_4S_{10} to form a 1,8-bridged product, but later work was unable to confirm this. However, when a mixture of P_4S_3 and sulphur is heated in 1-bromonaphthalene at 240 °C, there is formed the 1,8-disubstituted naphthalene **196**, the structure being confirmed by X-ray analysis[423]. The same substance is also obtainable from 1-bromonaphthalene and P_4S_{10} at the same temperatue[424]. Products of the composition $(ArPS_2)_2$ have been obtained from phenols, e.g. 2,6-di-*tert*-butylphenol[425], and from aryl ethers, e.g. the bis(2-phenoxyphenyl) compound from diphenyl ether and P_4S_{10} at 160 °C[426].



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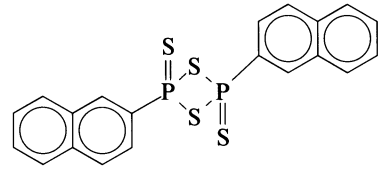
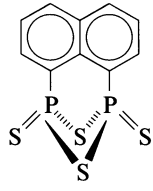
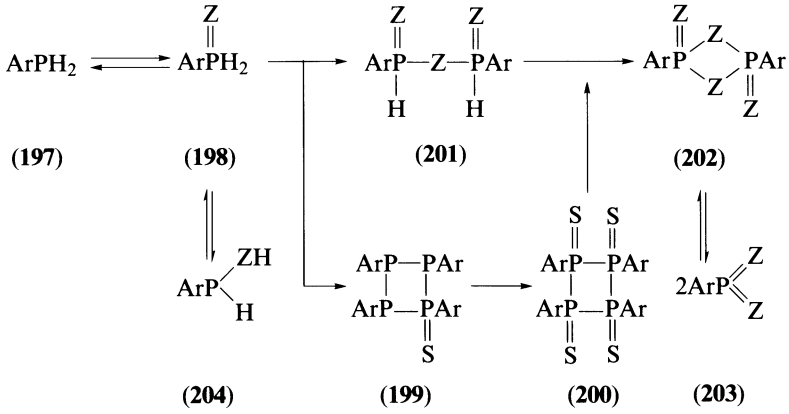


(195)



(196)

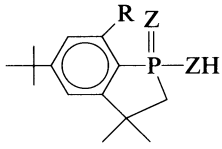
The addition of sulphur or selenium to primary phosphines has also been investigated with some surprising and interesting results (Scheme 58) and, as for the secondary phosphines, the early literature has been reviewed[25]. The addition of sulphur to phenylphosphine (**197**; Ar = Ph) in benzene at 50 °C yields the primary phosphine sulphide **198** (Ar = Ph, Z = S), which is unstable and decomposes, even at room temperature, to regenerate the phosphine and liberate H_2S and also to yield tetraphenyltetraphosphetane monosulphide (**199**) and the tetrasulphide **200**. More generally, the treatment of a primary phosphine **197** with a sufficiency of sulphur, leads in a stepwise fashion, via the primary phosphine sulphide **198** and possibly also via the particular **199**, **200** and/or **201** to the 1,3,2,4-dithiadiphosphetanes 2,4-disulphides **202** (Z = S), drawn here as a *trans* structure; such a compound is structurally the cyclic bisanhydrosulphide of a trithiophosphonic acid, the chemistry of which will be referred to again later. When Ar = 2,4,6-tri-*tert*-butylphenyl, the product **202** can dissociate into the stable,yellow, crystalline aryldithioxophosphorane **203** (Z = S)[427,428]. It had widely come to be expected that the presence of bulky *ortho* groups



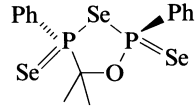
SCHEME 58

was a minimum requirement for the stabilization of the reactive species **203**, and it was therefore of considerable interest when the species **203** (Ar = 2,4-di-*tert*-butyl-6-methylphenyl) was obtained as a bright orange solid, stable for several months under argon[429]. Later work has provided the dithioxophosphoranes[203] with, as *ortho* substituets, NMe_2[430] and OMe[431], the former compound as colourless crystals, and both of reasonable stability, even in solution.

The addition of selenium to **197** (Ar = 2,4-di-*tert*-butyl-6-methylphenyl) led initially to the white product **198**, isolable as a salt of the tautomeride **204**, but the diselenoxophosphorane **203** (Z = Se) was not detected; instead, the isolated product had the cyclic phosphinodiselenoic acid structure **205** (Z = Se; R = Me)[429]. On the other hand, the diselenoxophosphorane **203** (Z = Se; Ar = 2,4,6-tri-*tert*-butylphenyl) has been obtained as thermally stable, green crystals, sensitive to light[432]; in addition, the compounds **202** (Ar = Ph, Z = S or Se) have been reported as the products from the interaction of pentaphenylpentaphospholane with grey selenium or with elemental sulphur, and distinct working-up procedures also yielded **206**, the structure confirmed by single-crystal X = ray analysis[423,433,434].

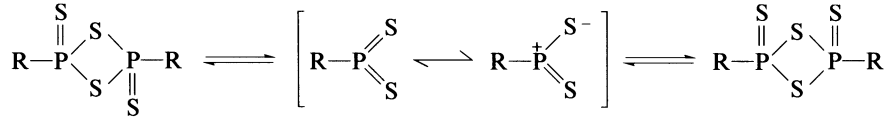


(205)



(206)

Before going on to consider some of the very valuable reactions of anhydrosulphides, both in the general context of organophosphorus chemistry and also from the viewpoint of more conventional organic synthesis, it is worth considering them briefly from the structural point of view. The so-called thionophosphine disulphides are (generally) dimeric and possess the 1,3,2,4-dithiadiphosphetane 2,4-disulphide structure. As normally prepared, the compounds exist in the *trans* form **207**, as evidenced by X-ray analyses of, for example the 2,4-dimethyl[435,436], 2,4-diphenyl (powder structure)[437], 2,4-bis(4-methoxyphenyl)[438] and 2,4-bis(2,4,6-triisopropylphenyl)[439] compounds. Evidence has been obtained which clearly demonstrates the ability of the cyclic structure to dissociate and re-form under varied con-



(207) (208) (209)

ditions. In solution, the isomerization of the *trans* form to the *cis* isomer (**209**) has been shown (by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy) to occur, presumably through a monomeric, dithioxophosphorane form **208** (= **203**) through which the many reactions of this class of compounds are thought to take place; evidence for this suggestion has been forthcoming through the equilibration of non-identical *trans* forms and the formation of mixed compounds which also exist in geometic forms[440,441]. The 2,4-diethyl compound dissociates at 700 °C in the gas phase to give **208** (R = Et)[442]. Moreover, also in the gas phase, a further isomerization to **210** has been detected[443]. In the case of aryl compounds, the presence of

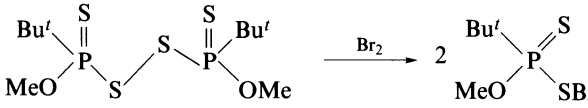
RS—P=S

(**210**)

bulky groups in the 2- and 6-positions sterically destabilizes the dimer and allows the direct isolation of the remarkably stable arylidithioxo- and aryldiselenoxophosphoranes. However, in these structures, the aromatic ring is perpendicular the the $P(=S)_2$ or $P(=Se)_2$ moieties, so preventing any electron delocalization. Molecular structure determinations have actually been carried out on **203** (Ar = 2,4,6-tri-*tert*-butylphenyl and 2,4-di-*tert*-butyl-6-methylphenyl)[439], and a dipolar form is not thought to contribute significantly to the final structure. On the other hand, this is not so for structure **193**; here, the phosphoranylidene and $(P=Se)_2$ moieties are each planar, and can be mutually coplanar with the result that a dipolar form does contribute to the resonance hybrid.

2. Reactions

Relatively few reactions of compounds which possess the P(S)SSP(S) grouping have been reported, but two of the more important might be mentioned; these are the cleavage of the disulphide bond by halogens and desulphurization by tertiary phosphines, already referred to. One example of the first of these is the cleavage of the disulphide bond by bromine to give phosphinoylsulphenyl bromides (equation 47); the products are very reactive towards nucleophiles (alcohols, amines) and also to carbon–carbon double bonds, across which addition occurs[444].



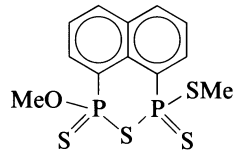
(47)

The cleavage of the P—S—P bonding in anhydrosulphides of phosphinodithioic acids by phenol to give 1 mol of the free phosphinodithioic acid together with 1 mole of an *O*-phenyl phosphinothioic acid has already been noted. Primary or secondary amines react in a similar fashion and give the amine salt of the phosphinodithioic acid together with the phosphinothioic amide. In practice, the anhydrosulphide bonding is readily attacked by nucleophiles.

On the other hand, reactions of the thionophosphine disulphides' (1,3,2,4-dithiadiphosphetane 2,4-disulphides) have been reported in abundance. Many of these reactions have been known for some years and have been reviewed more fully else-

where[445–449], but some of the more important reactions are summarized here. Alcoholysis[450–457] or phenolysis[458] of a bisanhydrosulphide yield the corresponding *O*-alkyl (or *O*-aryl) ester of the phosphonodithioic acid (equation 48); methanolysis of the unusu-

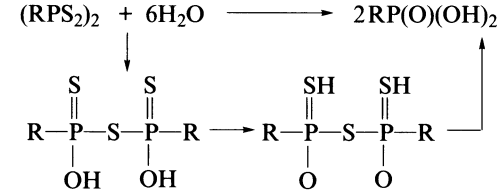
(48)



(211)

al compound **196** yields the diester **211**, the structure of which was confirmed by X-ray analysis[459]. Unusually, a reaction between the bis(2,4,6-tri-*tert*-butylphenyl) compound with *tert*-butyl alcohol yields the acid **205** (R = Bu^t). Likewise, interaction with a thiol[458,460] affords the monoester of a phosphonotrithioic acid; NaHS gives the disodium salt of a phosphonotrithioic acid[461]. Hydrolysis might at first be expected to proceed similarly, but in practice, all the sulphur is lost in the hydrolytic cleavage of P—S bonds both in the bisanhydrosulphide, and also in the product of initial ring opening, **212**, and the final hydrolysis product is a phosphonic acid (reaction 49)[425,456,461]. Reactions with amines afford the amine salts of phosphonamidodithioic acids (reaction 50)[452,462,463], but when such salts are heated in boiling xylene, elimination of H_2S accompanies the formation of phosphonothioic diamides (reaction 51)[463]. The action of tertiary amines affords betaines[464], as does the action of tertiary phosphines[465] (reaction 52). Many metallic salts MX (M = Na, K; X = F, N_3, CN, NCS, etc.) cleave the ring system with the formation of salts (reaction 53)[466]; these are generally not isolated, nor generally is acidification to the acid carried out, but rather alkylation yields the corresponding esters, also obtained by the direct reaction of the reagent R^{1}X (X = halogen) with the anhydrosulphide; α,ω-dibromoalkanes yield cyclic esters of phosphonotrithioic acids[461]; other organohalogen compounds, e.g. aralkyl or alkenyl halides, furnish mixed phosphinothioic halides in reactions at 130–160 °C (reaction 54). The reaction with HF is also worthy of note since the action of heat on the initial product leads to a compound of rare composition (reaction 55). Two reactions, namely with benzene in the presence of $AlCl_3$ (equation 56) and with a Grignard reagent (equations 57 and 58)[467], afford phosphinodithioic acids; in the case of the Friedel–Crafts-like reaction, the yields are comparable to those obtainable when P_4S_{10} is employed.

Also of potential value in synthesis is the halogenolysis process when, depending on reagent (Cl_2, SO_2Cl_2, PCl_5, SCl_2 or S_2Cl_2) and conditions, either phosphonothioic dihalides, $RP(S)Cl_2$. or, tetrahalophosphoranes RPX_4 are formed. The action of sulphur



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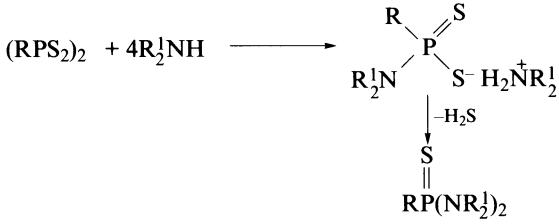
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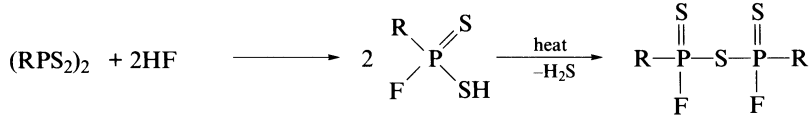
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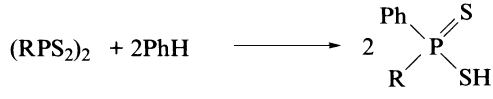
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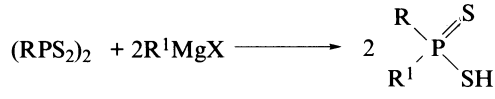
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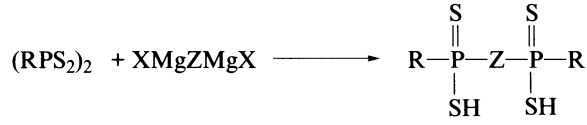
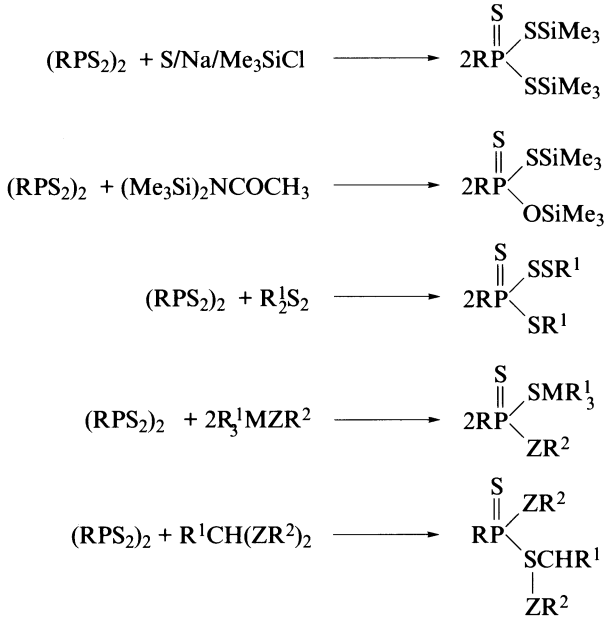

(58)

and sodium on the cyclic bisanhydrosulphide affords the disodium salt of the respective phosphonotrithioic acid which, by the action of chlorotrimethylsilane, is converted into the bis(trimethylsilyl) ester (reaction 59) [the bis(trimethylstannyl esters are obtained in an analogous fashion]; both silyl and stannyl esters react with halogens to give 1,2,4,5,3,6-tetrathiadiphosphorinane 3,6-disulphides (**178**)[468]. *O,S*-Bis(trimethylsilyl) esters of phosphonodithioic acids are obtainable by the use of *N,N*-bis(trimethylsilyl)acetamide (equation 60)[469] and diesters of novel phosphonotetrathioates are obtainable from reactions with disulphides (equation 61)[470]; mixed alkyl trialkylsilyl or alkyl tristannylalkyl diesters have been obtained according to equation 62 (M = Si or Sn, Z = O or S)[471]. The reaction with acetals and dithioacetals proceeds according to equation 63[472].



$$(RPS_2)_2 + S/Na/Me_3SiCl \longrightarrow 2RP(S)(SSiMe_3)_2 \quad (59)$$

$$(RPS_2)_2 + (Me_3Si)_2NCOCH_3 \longrightarrow 2RP(S)(SSiMe_3)(OSiMe_3) \quad (60)$$

$$(RPS_2)_2 + R^1_2S_2 \longrightarrow 2RP(S)(SSR^1)(SR^1) \quad (61)$$

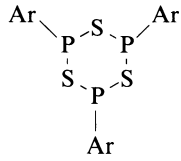
$$(RPS_2)_2 + 2R^1_3MZR^2 \longrightarrow 2RP(S)(SMR^1_3)(ZR^2) \quad (62)$$

$$(RPS_2)_2 + R^1CH(ZR^2)_2 \longrightarrow RP(S)(ZR^2)(SCHR^1ZR^2) \quad (63)$$

The monomeric diselenoxophosphorane **203** (Z = Se, Ar = 2,4,6-*tert*-butylphenyl) is stable in the solid state towards atmospheric oxidation, but decomposes at around 150 °C (slightly above the melting point) to yield the diselenophosphinic acid **205** (Z = Se, R = Bu^t)[429]; this process also occurs with the dithioxophosphorane, and also under the influence of an amine of whatever nature even at room temperature[457]. Dinitrogen tetroxide oxidizes the dithioxophosphorane to the oxygen compound **203** (Z = O, Ar = 2,4,6-tri-*tert*-butylphenyl), which immediately cyclizes to the phosphinic acid **205** (Z = O, R = Bu^t)[473]. Methanolysis of the same dithioxophosphorane yields *O*-methyl (2,4,6-tri-*tert*-butylphenyl)phosphonodithioate. When **202** (Ar = 2,4-di-*tert*-butyl-6-methoxyphenyl) reacts with benzophenone, thiobenzophenone is formed (thiation is one of the principal uses of the compounds **207** in conventional organic chemistry) together with the reactive species ArP(=S)(=O), but the latter immediately reacts with the reagent to give the 2,4-diaryl-1,3,2,4-oxathiadiphosphetane 2,4-disulphide[431].

With Ph_3P, the dithioxophosphorane **203** (Ar = 2,4,6-tri-*tert*-butylphenyl) is desulphurized, evidently to the species ArP=S [also formed from $ArP(S)Cl_2$ and Mg], which manifests itself as its trimer, the 1,3,5,2,4,6-trithiatriphosphorinane **213**[473]. Developments in the formation and properties of the species R P=X (X = O, S or Se) fall outside the scope of this chapter, but it is nevertheless worthwhile noting some new developments which have led to species ArP=X (Ar = 2,4-bis-*tert*-butyl-6-dimethylaminophenyl, X = S or Se), including the observation that the ease of removal of one chalcogen atom from the species $ArP(=Z)_2$ depends on Z itself[474]. Both the monomeric dithioxophosphorane and the dimer bis(anhydrosulphide) add to 1,3-dienes to give the reduced 1,2-thiaphosphorin species **214**[475].

In particular, the chemical reactions and uses of 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulphide (**55**) have been widely investigated during the last two decades. The reagent is conveniently prepared on a large scale by heating together at ca 150 °C a mixture of red phosphorus, sulphur and methoxybenzene in the molar propor-



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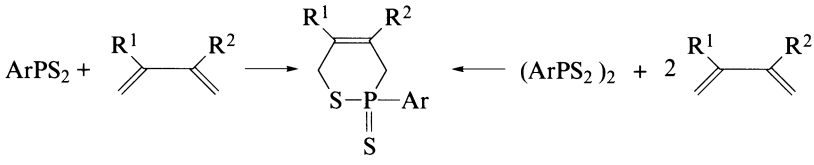
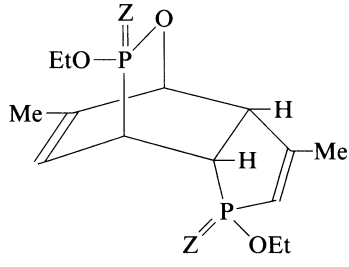


(214)

tions 5:2:2, the yield of product being then about 50%[476], or by the action on methoxybenzene of P_4S_{10}. The reagent was introduced and its usefulness in synthesis investigated extensively by Lawesson (under whose name the reagent is known and marketed commercially) from 1978 onwards. The selenium-containing analogue of **55** could not be obtained by the use of the above methods[477].

The reactions of 1,3,2,4-dithiadiphosphetanes, in general, were reviewed in 1965[25] and again in 1980[447]. The chemistry of Lawesson's reagent, in particular, was further summarized in 1985[448] and again in 1993[449]. The uses to which Lawesson's reagent have been, and are still being, put are increasing rapidly. Analogues,e.g. the bis(4-phenoxyphenyl)[478–480] and bis(4-phenylthiophenyl)[479,480] compounds, and others[480], have occasionally been examined, but it is doubtful whether any offers advantages of a general nature over Lawesson's reagent itself, and the following discussion refers specifically to that reagent.

The most prominent amongst the many reactions of the Lawesson reagent is that of thiation—the simple replacement of oxygen by sulphur—possible in a wide variety of substrates, and also the ability to transfer sulphur with valence expansion in the substrate; in these processes, it is at least comparable, and on some occasions superior, to P_4S_{10}. The use of the latter reagent in connection with the conversion of phosphoryl compounds into thiophosphoryl analogues has been discussed earlier in this chapter; in some of these conversions, Lawesson's reagent was used as the alternative (see, e.g., refs 130 and 131). In one such thiation, that of **215** (Z = O) to **215** (Z = S), the use of the reagent led to a new ring system **216**[131,481]. In another study, the thiation of benzophenone to thiobenzophenone was



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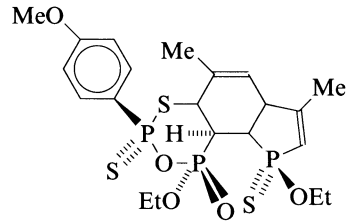

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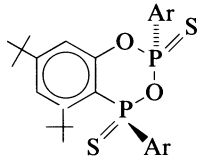

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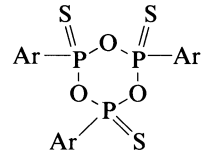


(218)

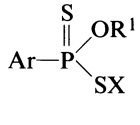
accomplished in 63% yield when the monomeric' **203** (Ar = 2,4-di-*tert*-butyl-6-methoxyphenyl) was used after isolation; without prior isolation, the yield was only 14%, and this was accompanied by much recovered benzophenone, about 5% of the corresponding 1,3,2,4-oxathiadiphosphetane 2,4-disulphide and smaller amounts of a mixture of *trans*- and *cis*-**217**[431].

Dialkyl hydrogenphosphonates are converted into dialkyl hydrogenphosphonothioates[482,483] and these and other phosphoryl thiations have often been shown to be accompanied by the formation of 2,4,6-tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriphosphorinane 2,4,6-trisulphide (**218**; Ar = 4-methoxyphenyl)[484]. The thiation of *S*-methyl *tert*-butylphenyl- and 1-naphthalenylphenyl-phosphinothioates to the corresponding dithioates evidently proceeds largely with stereochemical retention[485]. The abstraction of sulphur from Lawesson's reagent (and from other similar structures) with phosphines represents the means of valence expansion in appropriate phosphorus(III) substrates[486]. With tetraphosphetanes or pentaphospholanes in equimolar quantities, only partial sulphurization may occur[487].

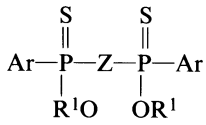
Reactions between Lawesson's reagent (**55**) and nucleophiles further exemplify the chemistry of 1,3,2,4-dithiadiphosphetane 2,4-disulphides[488–492]. Of its reactions, those with alcohols and, to a lesser extent, thiols, are complex and give mixtures of products the compositions of which depend to a large extent on the type of alcohol (or thiol) and conditions. Primary alcohols, R^1OH, yield the *O*-alkyl esters **219** (in structures **219–272**, Ar = 4-methoxyphenyl unless stated otherwise) which, when heated, suffer loss of H_2S and yield the anhydrosulphide **222**. Secondary alcohols (e.g. cyclohexanol) initially yield the *O*-alkyl ester **219**, but further reaction, particularly in boiling xylene, can give the *O*,*S*-dialkyl ester together with the anhydride **223**. A *tert*-alcohol, with or without added tertiary amine catalyst, provides a large yield of the trimeric phosphonothioic anhydride **218**. Thiols and Lawesson's reagent are said to give the trithio esters **224**, although thiophenol and the reagent in benzene at 60 °C yield the anhydrosulphide **225**. The phosphonodithioic chlorides **226** are obtainable from alkyl chlorides, RCl, and a similar reaction with PhSCl yields the chloride **227**. A reaction between the reagent and a carboxylic acid chloride gives a species **228**, which is a powerful acylating agent.

For the most part, however, Lawesson's reagent has been employed in conventional organic chemistry as a versatile reagent for the thiation of carbonyl groups in a large variety of compounds. Reactions with simple saturated ketones lead only to thioketones, the phosphorus being released as the trimeric anhydride **218** of the (4-methoxyphenyl) phosphonothioic acid, formed conceivably through a monomeric oxothioxophosphorane (Scheme 59)[448].

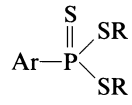
Sterically hindered ketones e.g. di-*tert*-butyl ketone and 2,2,6,6-tetramethylcyclohexanone, are not thiated. However, other cyclic ketones, whilst being thiated also undergo other concomitant transformations; thus, cycloalkanones **229** yield the trithiaphosphorinanes **230** (n = 1 or 2) and enethiols are the products from 2-substituted-cyclohexanones[493]. Many polycyclic ketones, e.g. 9-acridones[494], xanthone and benzanthrone, all are simply thiated[448]. The α,β-unsaturated ketones (chalcones)[231] (X = O; R = Bu^t or Ph) yield the corresponding thiochalcones **231** (Z = S) together with their dimers **232** when reaction occurs



(219) X = H
(220) X = Na
(221) X = R^2



(222) Z = S
(223) Z = O



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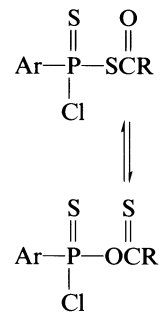

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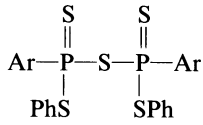

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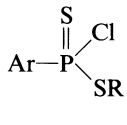

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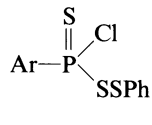

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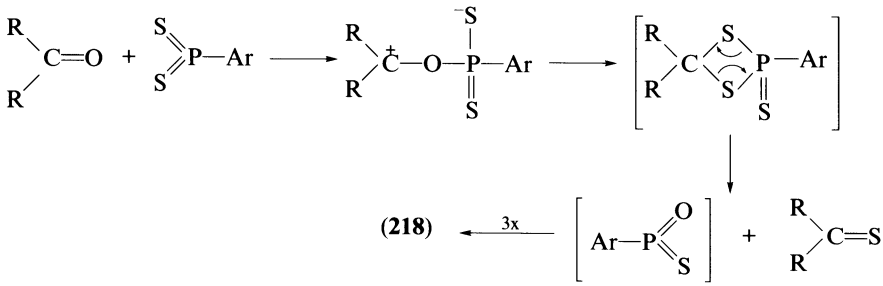
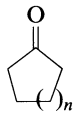


SCHEME 59

in boiling benzene; under other conditions, e.g. at room temperature in MeCN, or through the use of 2 mol of the reagent in boiling xylene, the chalcone **231** (Z = O, R = Ph) yields the two phosphorus-containing ring compounds **233** and **234** through a [4 + 2] cycloaddition; the formation of **236** is thought to occur through the unstable **235**[495–497]. Thiation of the chalcones **231** is also achieved in their reactions with P_4S_{10}, but this is accompanied by the formation of **237**; this species is seen to be derived from the thiochalcone and the thiaphosphole **238**[498]. Accordingly, when compounds **237** are heated with the nucleophiles NuH (N = R'O, Ar'O, Ar'S or R_2N) in the presence of Et_3N, reaction occurs through addition of the nucleophile to **238** to give **239**[498].

A [4 + 2] cycloaddition reaction between Lawesson's reagent and the ketone **240** yields **241**, whilst a reaction with P_4S_{10} give **242**; it might be noted that diphenylphosphinodithioic acid adds to give the ester **243**[499]. The carbonyl groups in pyrones[500], chromones[500,501], their benzologues[501] and related compounds[500] are thiated satisfactorily with Lawesson's reagent (and with the formation of **218**), although not necessarily with analogues of the latter. It might also be pointed out that the unsaturated ketones **244**, and also the epoxides **245**, react with Lawesson's reagent to give the 1,2-dithiolenes **246**; by contrast, the epoxide **247** is said to give a 22% yield of the 1,3,2-oxathiaphospholane **248**[502], a type of reaction also recorded with other epoxides[489].



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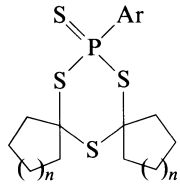

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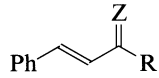

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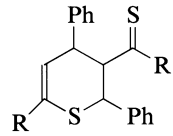

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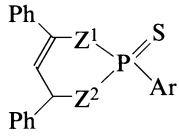
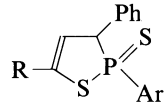


(233) $Z^1 = O$, $Z^2 = S$

(234) $Z^1 = S$, $Z^2 = O$

(235) $Z^1 = Z^2 = S$



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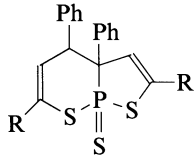

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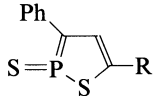

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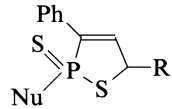

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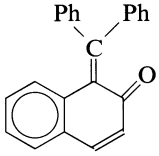

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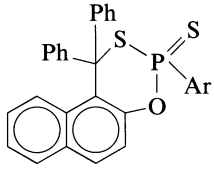

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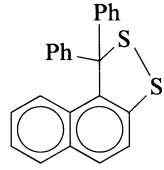

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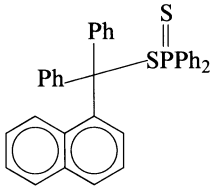

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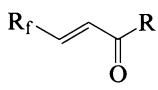

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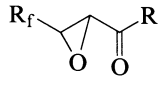

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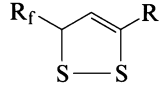

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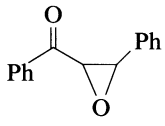

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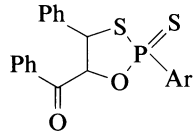
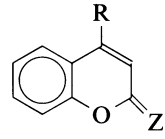


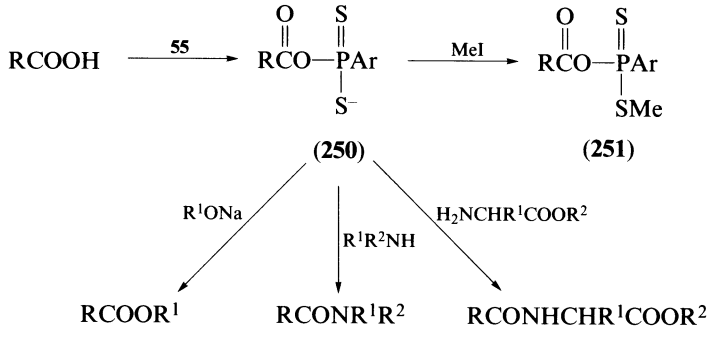
(248)

Thiation of the carbonyl group in carboxylic esters to give the esters RC(S)OR′ requires a moderate excess of the reagent[503], and only mild conditions are required for the conversion of RC(O)SR′ into RC(S)SR′ Lactones are thiated at the carbonyl group in boiling toluene or xylene much more cleanly than is the case with P_4S_{10}, when mixtures of isomerically and partially thiated products also include the fully thiated compounds[504], but the coumarins **249** (R = H, or OH; Z = O) furnish only the corresponding systems with Z = S[505].



(249)

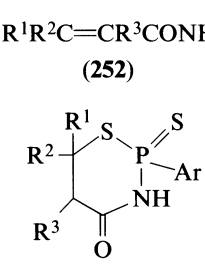
Lawesson's reagent has been shown to act as a coupling agent for the preparation of esters and amides and, in particular, of peptides[506]; the reactions between the reagent and carboxylic acids and amides should therefore be considered in a separate context. Simple carboxamides and lactams, when treated with the reagent in HMPA, are thiated in the usual way to give almost quantitative, yields[448]. Peptides are also similarly thiated, the reaction taking place selectively at the amide carbonyl group[507]. However, carboxylic acids form mixed anhydrides **250**[508] (demonstrated by their methylation to the mixed anhydride **251**), which act as activated species for the preparation of carboxylic esters and for coupling reactions with amino groups and which thus find usage in peptide coupling (Scheme 60).



SCHEME 60

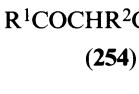
The reaction between Lawesson's reagent and α,β-unsaturated carboxamides present another facet of the chemistry of dithioxophosphorane dimers. Some cases have already

been presented in which such reaction systems lead to heterocyclic systems based on the phosphorus–sulphur bonding in the reagent. These products are, in essence, cyclic esters or amides of acids based on the carbon moiety of the reagent, in this case 4-methoxyphenyl. In this respect, unsaturated primary carboxamides **252** furnish compounds based on the perhydro-1,3,2-thiazaphosphorin-4-one system **253**[503] and the oxocarboxamides **254** yield examples of the related system **255** together with the 3*H*-1,2-dithiol-3-thiones **256**, Herein lies another feature of the chemistry of Lawesson's reagent, namely a propensity to lead to heterocyclic compounds containing sulphur (but lacking phosphorus)[509]; a further illustration of this capability is the conversion of **257** into **258**[510].



(253)

(252)



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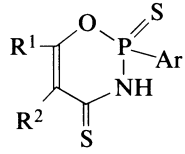

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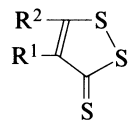

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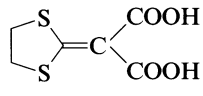

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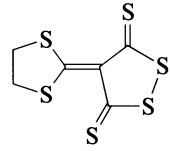
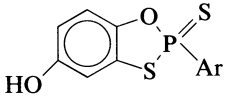


(258)

Phosphorus-containing ring systems are obtainable from some very simple substrates. 1,4-Benzoquinone, 1,4-naphthoquinone and 9,10-anthraquinone supply the 1,3,2-oxathiaphospholes **259** and **260** and the 1,3,2-oxathiaphosphorin **261**, respectively[479]; 1,4-quinonediimides are said to produce analogous 1,3,2-thiazaphospholes[511], and examples of the same ring system, **263**, are also obtainable from the monoanils of benzils, **262**[512]. Reactions with isocyanates Ar'NCO yield the corresponding isothiocyanates in moderate yields, with further reaction to give the 1,3,2,4-thiazadiphosphetidines **264**[513].



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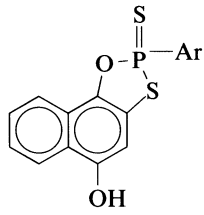
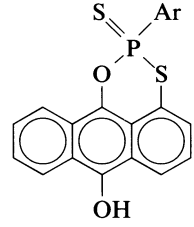


(260)



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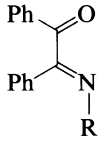

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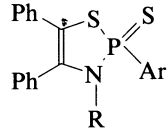
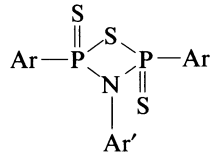
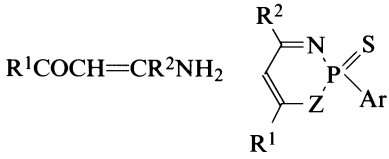


(263)



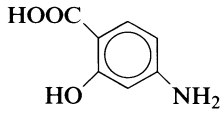
(264)

A slightly more complex case is presented by the amines **265**. In general these undergo normal carbonyl thiation, but they also yield ring-containing products; thus, when $R^1 = R_f$ (R_f = CF_3, C_2F_5, etc.), the reactions with Lawesson's reagent also produce the 1,3,2-oxazaphosphorines **266** (Z = O). By contrast, the isomeric amines **265** ($R^2 = R_f$, R_f as before) suffer thiation, but also provide the two ring compounds, the 1,3,2-oxazaphosphorines **266** (Z = O) and also the 1,3,2-thiazaphosphorines **266** (Z = S). For reactions in dilute solutions, only the thiated amines are obtained, but with an increase in concentration of the reactant solutions the ring compounds are produced in increasingly significant amounts[514,515].

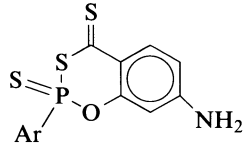


(265) **(266)**

In general, the presence of more than one reactive functional group in a substrate, particularly if adjacent on, for example, a benzene ring, is likely to lead to a phosphorus-containing and thiated ring compound, possibly as the only product, but possibly alongside a thiated but non-phosphorylated product. The conversion of **267** into the heterocycle **268** has been reported and might be taken as illustrative[516]. A variety of products have been prepared from hydrazides[448], but a more recent example is the conversion of the hydrazide **269** into the 1,3,4,2-thiadiazaphosphole **270**[517], and other like reactions yielded the compounds **271**[518], whilst amidoximes give the dihydrothiadiazaphospholes **272**[519].

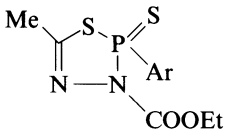


(267)

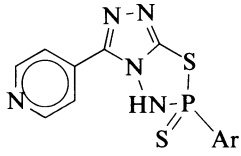


(268)

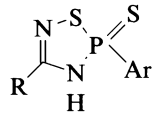
(269)



(270)



(271)



(272)

For many more examples of ring systems obtained through reactions of dithioxophosphorane dimers, the reviews by Maier[447], Cherkasov *et al*,[448] and others[449] should be consulted.

In general, Lawesson's reagent (and, in principle, other dithioxophosphorane dimers) is a powerful agent for simple thiations at both carbonyl and phosphoryl functions, for the preparation of sulphur- and of phosphorus–sulphur-containing heterocyclic compounds (these last being fundamentally derivatives of 4-methoxyphenylphosphono(di, tri)thioic acids and for the coupling of acids and amides, particularly in peptide synthesis.

Further aspects of the chemistry of sulphur- and selenium-containing organophosphorus acids, particularly in relation to the reactivity of P—O and P—N bonds in those compounds, and a comparison of such reactivity with that to be found in compounds which lack the higher chalcogens, will be discussed in the following chapter.

V. REFERENCES

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NOTE ADDED IN PROOF

Section III

In the alkylation of mono-*O*-esters of phenylphosphonothioic acid, (RO)PhPSOH, as their dicyclohexylammonium salts, by alkyl halides R^1X, it has been observed[520] that high yields of S-alkylated diesters are obtained when R = Et or Pr but not when R = Me; this unfortunate result has been ascribed to further reactions between the above salts (R = Me) and the *O,S*-diesters (MeO)PhP(O)SR^1 and which lead to *inter alia* (MeO)PhP(O)SMe.

The cleavage of the disulphide bond in phosphinothioyl disulphides by elemental bromine has provided optically active forms of phosphinothioylsulphenyl bromides (RO)PhP(S)SBr; unusually, however, the action of bromine on $(S)_P(S)_P$-bis[(*O*-(–)-menthyl)phenylphosphinothioyl] disulphide yields a mixture of $(R)_P$- and $(S)_P$-[(*O*-(–)-menthyl)phenylphosphinothioyl]sulphenyl bromide in the ratio of 2:1. The explanation advanced for this phenomenon is based on an equilibration between species possessing P^+(SBr)SSP(S) or P(S)S^+(Br)SP(S) groupings and their attack by Br^-[521].

Section IV

The alcoholysis of 2-alkyl- and 2-aryl-2-thioxo-1,3,2-dithiaphospholanes proceeds with ring opening and has provided a route to mono-*O*-esters of phosphonodithioic acids[522].

Section VI

Although phosphinodithioic esters may be obtained from thiolate anions and a phosphinothioic chloride (compare equation 30) a word of warning needs to be issued with regard to the synthesis of optically active phosphinodithioate esters. The reaction between (*S*)-(+)-*tert*-butylphenylphosphinothioic chloride and EtS^- yields (*R*)-(+)-ethyl *tert*-butylphenylphosphinodithioate and so occurs with inversion of configuration at phosphorus. In some cases, the phosphinothioic bromide might be obtained more conveniently and it might be assumed that it would prove an alternative to the chloride. It is now known that (*S*)-(–)-*tert*-butylphenylphosphinothioic bromide, in the same reaction, provides the (*S*)-(–)-ethyl ester, i.e. the replacement of P–Br by P–SEt occurs with retention, and a two stage mechanism, each stage occurring with inversion, has been proposed to account for this finding[523].

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CHAPTER 6

Properties and reactions of phosphonic and phosphinic acids and their derivatives

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I. INTRODUCTION

The preceding four chapters dealt primarily with the synthesis of phosphonic and phosphinic acids and their derivatives. At the same time, the discussion on the synthesis of the acids containing the higher chalcogens was accompanied by a description of some of their properties and reactions. This chapter concentrates on their properties and reactions. Inevitably, some overlap with the earlier chapters will occur, since the reactions of one compound may form a basis for the synthesis of another. In addition, some comparison needs to be made between the reactivities of those acids and their derivatives which contain sulphur or selenium, and those which do not; the effects on reactivity of replacing P=O by P=S or P—O by P—S are not of theoretical interest but have practical utility and consequences.

With regard to the overlap in the study of synthesis and reactivity, the general sources of information on the synthesis of phosphonic and phosphinic acids[1-8] also contain much information that is of interest to those concerned primarily with reactivity. As has already been indicated for synthesis, progress in the study of the reactivity of the carbon–phosphorus(V) bonded acids is also reviewed annually[9]. Monographs which discuss the reactivity of organic compounds of phosphorus, for example those by Kirby and Warren[10], Emsley and Hall[11] and by Hudson[12], are available, but, advances in new reactions and their interpretations are appearing at an ever increasing rate, and much has happened during the last 2–3 decades. Nevertheless, the older sources should be consulted for background information.

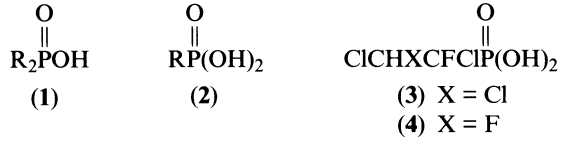
Using the symbolism [C] to represent any organic moiety ligated directly to phosphorus, we can formulate phosphonic acids as [C]P(Z)XY and phosphinic acids as $[C]_2P(Z)X$, where Z = O, S, Se, or Te (or even NR) and X or Y are halogen or pseudohalogen, OR, SR, NR_2 or other similar function. The two groups of acids thus represent intermediate stages between the tertiary phosphine chalcogenides $[C]_3P(Z)$ on the one hand and, on the other, derivatives of phosphoric acid (Z)PXYZ′, where Z′ has the same significance as X or Y. We may predict, therefore, that phosphonic and phosphinic acids will possess properties which overlap, to some extent, those of their 'outer' neighbours, and also, to some extent, with those of each other. The reactions and properties of phosphonic and phosphinic acids are considered in terms of the reactions of the functions Z, [C], X and Y.

Compared with formic acid (pK_a = 3.77 in water, 5.75 in 95% aqueous ethanol), acetic acid (pK_a = 4.76 in water), and benzoic acid (pK_a = 4.17 in water, 7.07 in 95% aqueous ethanol), simple symmetrical dialkylphosphinic acids (**1**) are moderately strong acids[13-16]. Thus, for dimethylphosphinic acid (R = Me), pK_a = 3.08 (in water) and 6.64 in 95% aqueous ethanol, figures which rise to 3.56 for R = Pr^i and 4.24 for R = Bu^t for solutions in water; for R = Ph, pK_a = 5.80 in 95% aqueous ethanol. These values can also be compared with those for the dialkyl phosphoric acids; for dimethyl hydrogenphosphate, pK_a = 0.47 in water and 1.88 in 80% aqueous ethanol. Obviously the phosphorus–oxygen bonded acids are rather stronger, with the simple phosphinic acids closer to the carboxylic acids in their acidity.

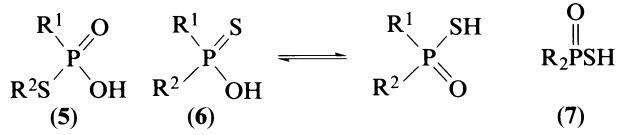
Greater acidity is to be expected for the phosphonic acids (**2**), and through the range R = Me to R = pentyl, including those acids with branched alkyl groups, the pK_{a1} values rise from 2.38 (R = Me) to 2.88 (R = CMe_2Et); the corresponding pK_{a2} values increase from

7.74 to 8.96. When R = Ph, the two values are 1.86 and 7.51 in water, with pK_{a_1} = 3.96 in 75% aqueous ethanol[13,14,16–18].

However, a direct comparison with a structurally similar alkanoic acid is often rendered difficult because of solubility problems, and many of the data are available only for solutions in ethanol–water mixtures with high alcohol content. Nevertheless, the normal electronic effects found for carboxylic acids are also to be found for the phosphonic and phosphinic acids. Electronic withdrawal from the PO_3H_2 moiety results in an increase in acidity as found in, for instance, halogen-containing acids[19,20] and aromatic acids[18]; the branching of an aliphatic chain, particularly when relatively close to the phosphono group, results in the general weakening of acid strength. The pK_{a_1} values for (trichloromethyl)- and (trifluoromethyl)-phosphonic acids are 1.63 and 1.16 with the corresponding pK_{a_2} values of 4.81 and 3.93[21]. It is surprising that the pK_{a_2} values of some polyhalogen-containing acids differ little from those of the halogen-free acids, although differences are to be seen in the pK_{a_2} values for the acids **3** and **4**, pK_{a_1} = 2.4 and 2.2, respectively, with corresponding pK_{a_2} values of 5.2 and 4.9, and these may be compared with the values for ethylphosphonic acid, ca 2.4 and 8.05[22].



The pK_a values for the acids **5** are relatively little influenced by the nature of R^2 when this is a simple alkyl group[20]. The acidity of compounds **6** is influenced markedly by the nature of the solvent, since this affects the balance in the thione–thiol tautomeric equilibrium (see Chapter 5), $MeNO_2$ and 100% ethanol favouring the thione form and 7% aqueous ethanol the phosphoryl-thiol form. In spite of the changes in the nature of R^1 and R^2, e.g. from $(EtO)_2$ to Me(EtO) to Et_2 to Ph_2, this solvent influence seemed to be of a general nature[23]. Over the range of acids examined, changes in R^1 and R^2 produce relatively little variation in pK_a (ca 1.5–3.6 and 6.5–8.5) for the first two solvents as opposed to the larger variation (8.5–13.2) for $MeNO_2$ solutions. The pK_a values of **7** are remarkably independent of the nature of R (alkoxy, aryloxy, alkyl, aryl); when R_2 = Et_2, Ph_2, or Me(PrO), the values are 1.73, 1.75 and 1.74 for solutions in 7% aqueous ethanol[23].

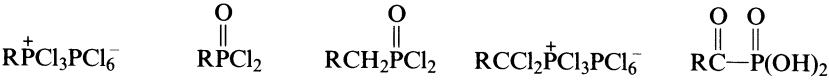


II. THE ROLE OF THE PHOSPHORYL (P=Z) (Z = O, S, Se OR Te) GROUP

The nature of the element Z affects the ability of the 'phosphoryl' group to bring about electron withdrawal from attached ligands by virtue of the polarity $P^+—Z^-$, and also the ability to donate electronic charge to a nearby electrophile because of polarizability in the same direction. From the experimental point of view, these two features, coupled with the relatively great strength of the P=O bond, have been explored in reactions which range from the activation of adjoining methylene functions (in much the same way as is brought about by an adjacent carbonyl or nitro group[24]) and which may result in the cleavage of the P—C bond, to attack on alkylating species; the latter process is more difficult for those compounds with the 'harder' P=O bond, but easier for those with the more polarizable

P=S and P=Se bonds. There is also the question of the ease of removal of the element Z to leave behind a tervalent phosphorus compound. This topic has already been considered in the case of the tertiary phosphine chalcogenides[25].

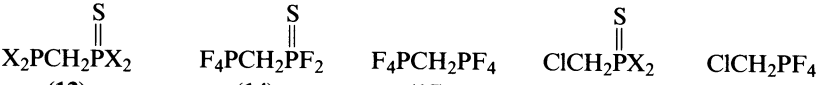
Although the P=O bond is normally considered to be one of the strongest of chemical bonds, with its (re)formation often described as the driving force behind many chemical reactions of quinquevalent phosphorus compounds, there is no shortage of reactions in which that bond can be modified or even removed completely. The phosphorylation of alkenes with PCl_5 leads to chloroalkylphosphonium chlorides (**8**), which are decomposed by SO_2 to generate the phosphonic dichlorides **9** (Chapter 2, Section III. A). Equally, however, certain arylphosphonic dichlorides (e.g. the phenyl, 3- and 4-nitrophenyl and 3-methylphenyl compounds) react with PCl_5 to form such quaternary salts (R = Ar)[26,27]; moreover, the treatment of alkylphosphonic dichlorides (**10**) with PCl_5 yields the salts **11**, hydrolysable to the acylphosphonic acids (**12**)[28].



(8) **(9)** **(10)** **(11)** **(12)**

The removal of the phosphoryl group from phosphonic diesters and dichlorides[29–33], including methylenebisphosphonic derivatives[34,35], has often been achieved through their reactions with $LiAlH_4$, the products being primary phosphines. Phosphinic acids[36–38] have been reduced in a similar way to secondary phosphines, as have their derivatives[32,39,40], sometimes with loss of other functions on phosphorus. The presence of halogen within the carbon ligand of a phosphonic diester can be accommodated in the reduction to a primary phosphine by $LiAlH_4$[41]; the yields in such reductions vary enormously, from as little as 2% to as high as 95%. Lithium aluminium hydride has been used in combination with Me_3SiCl, with resultant high yields[42], but, in contrast to the widespread use of silanes in the reduction of phosphine oxides[25], their value in the reduction of phosphonic and phosphinic derivatives has been but little explored[43,44]. An important development is the use of $AlHCl_2$ in high-yield reductions of (alk-1-enyl)phosphonic diethyl esters, sometimes containing carbon-bonded chlorine, without the removal of either the unsaturation or the chlorine[45].

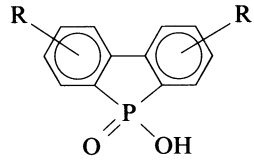
Some chemical reactions which destroy the very nature of the phosphoryl bond P=Z (Z = O), also occur when Z = S or Se. The treatment of [(dichlorophosphino)methyl]phosphonothioic dichloride (**13**; X = Cl) with SbF_5 results in the initial replacement of all the chlorine by fluorine, followed by further fluorine transfer and the formation of the mono(tetrafluorophosphorane) (**14**); this step is then followed by the destruction of the thiophosphoryl group to give **15**[46]; on the other hand, SbF_3 does not convert **16** (X = Cl) into **17**, although **16** (X = F) is formed[47]. The phosphoryl group is not replaced by PF_2 when acted upon by SbF_3 or AsF_3[46].



(13) **(14)** **(15)** **(16)** **(17)**

The phosphoryl group evidently, and not surprisingly, deactivates an attached benzene ring during electrophilic substitution reactions; the sulphonation (with SO_3) of phenylphosphonic acid leads initially to the 3-sulphonic acid, and subsequently at 180–240 °C to the 3,5-disulphonic acid[48,49]. The nitrations of (4-chlorophenyl- or (4-bromophenyl)-phosphonic acids have given products described as the 3-nitro derivatives, but it has also been stated that the nitration of dimethyl phenylphosphonate gives dimethyl (4-nitrophenyl)phosphonate, a pattern of substitution certainly observed in the nitration of

(phenylmethyl)phosphonic acid and its diethyl ester. The nitration of (3-bromophenyl)-phosphonic acid is reported to yield (5-bromo-2-nitrophenyl)phosphonic acid[50]. Many other examples of the nitration of aromatic phosphonic and phosphinic acids, or their derivatives, are to be found, particularly in the older literature[1-8,51,52]. The phosphoryl moiety facilitates nucleophilic substitution; thus, (2-bromophenyl)phosphonic acid in aqueous ammonia gives (2-hydroxyphenyl)phosphonic acid[53]. The synthesis of phosphinic acids derived from 5*H*-dibenzophosphole (phosphafluorinic acids) (**18**) depends on the cleavage of C—Cl bonds in halogenated [1,1′-biphenyl]-2-yl phosphinic acids with KOH[54]. The oxidizing nature of a nitration medium may result in (some) conversion of a thiophosphoryl compound to the sulphur-free nitrated analogue.



(**18**)

Taking into account the known electron-donor effects of alkyl groups R, the acidities of the phosphinoylacetic acids **19** (R = Me, Et, Pr or Bu; n = 1–4) are consistent with an electron-attracting capacity of the P=O group which, when inserted into acetic acid, increases its acidity by a factor of about 10; the compound with R = Et and n = 4 has pK_a (water) = 4.62. The two acids **20** have pK_a values (in 50% aqueous EtOH) of 4.45 (4.83) (Z = O) and 4.76 (4.97) (Z = S) at 25 °C, and the $Ph_2P(O)$ group is thought to have an electron-withdrawing capability comparable to that of EtOOC[55-59].

$$R_2P(CH_2)_nCOOH \qquad (\mathbf{19})$$

$$Ph_2PCH_2COOH \qquad (\mathbf{20})$$

The electron-withdrawing capacity of a group such as $(EtO)_2P(O)$ renders the formation of carbanions from the compounds **21** (Z = O, R′ = Ph, CN, COOEt, for example) and an appropriate base particularly facile and of great synthetic utility; the formation of carbanions from esters of the type **21** (Z = S) is equally feasible but not so widely explored. The formation of a carbanion following the use of $NaNH_2$ and its subsequent reaction with benzophenone was evidently first reported in 1958[60] and eventually formed the basis for an important variant of the well-known Wittig reaction. An ester such as **22** forms a dicarbanion, also of use in synthesis[61]. Phosphoryl carbanions have played an important role, in terms of both the importance in conventional organic synthesis of the Wittig reaction in its several forms, and in classical organophosphorus chemistry; in this context, the outcome of so many of the reactions is that of cleavage of the P—C bond, an area to be discussed in more detail later.

$$(RO)_2PCH_2R' \qquad (\mathbf{21})$$

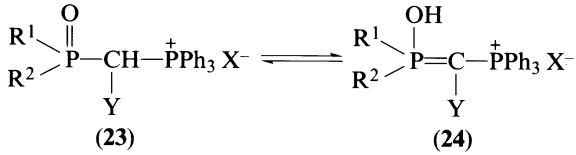
$$(EtO)_2PCH_2CCH_2COOEt \qquad (\mathbf{22})$$

An unusual aspect of the behaviour of the phosphoryl group, which has already been discussed in connection with the chemistry of tertiary phosphine oxides[25], is the potentially tautomeric behaviour of the group, but a more detailed discussion of the phenomenon

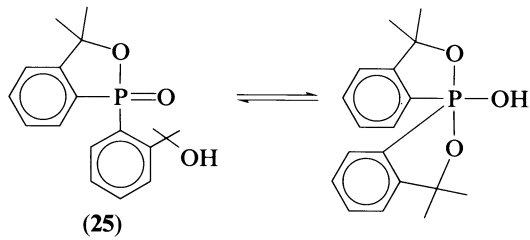
TABLE 1. Phosphoryl tautomerism in [(triphenylphosphonio)-methyl]-phosphonates and -phosphinates (**23**)

R^1	R^2	% Hydroxyphosphorane form (**24**) in CH_2Cl_2	
		X = Br (at −80 °C)	X = ClO_4(at 30 °C)
Bu	Bu	75	29
Bu	EtO	50	12
BuO	BuO	45	<2
EtO	EtO	25	<2
PhO	PhO	<2	<2

in relation to phosphonic and phosphinic derivatives, albeit with a sparsity of available data, is also available[62]. Whereas the equilibria between structures **23** and **24** can be demonstrated by IR and ^{31}P NMR spectroscopy when R^1 and R^2 are alkyl or Ph (Y = COOEt, $CONEt_2$, CN, SO_2tol), no such behaviour is observable when R^1 and R^2 = Oalkyl or OPh, or R^1R^2 = (EtO)Bu for the compounds in the crystalline state, but the equlibria can be detected for solutions of the salts in dichloromethane. Table 1 indicates the phosphoryl–hydroxyphosphorane composition for solutions of bromide and perchlorate salts from various phosphorus (V) esters[63]. Isolated instances occur of the participation of the phosphoryl bond in ring–chain tautomerism; one such example is that which involves the phosphinic acid **25**[64,65].



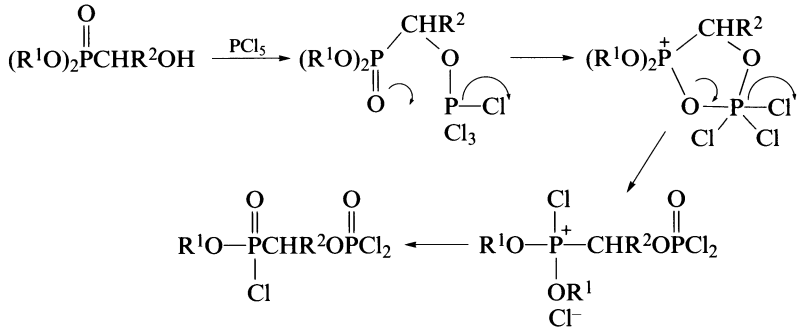
(23) **(24)**



(25)

In very general terms, the importance of the P=Z bond, particularly for Z = O, lies in its strength, and the fact that its formation acts as the driving force for many of the reactions of organic phosphorus(V) compounds, but also and as far as the present chapter is concerned, its polarizability, which allows the setting up of pentacoordinated phosphorus intermediates; this in turn affords an explanation for many of the substitution reactions which can occur at tetracoordinated phosphorus.

Two examples which might simply by mentioned at this stage are the interaction of dialkyl (1-hydroxyalkyl)phosphonates with PCl_5, which proceeds without the liberation of $POCl_3$ according to Scheme 1[66], and the action of an electrophile EBr (E = H or Br) on 1-phosphoryl substituted-2-ethenylcyclopropanes (Scheme 2)[67]; in both cases ring formation occurs, temporarily and permanently, respectively, through the participation of the phosphoryl group.



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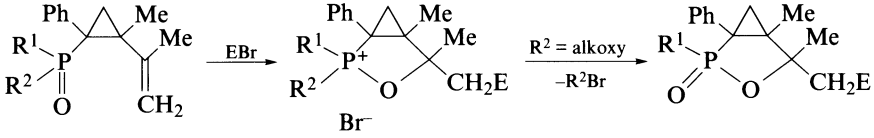
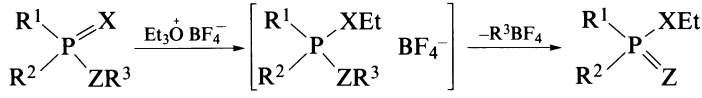


(26)

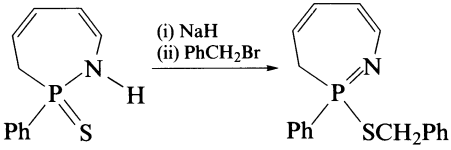
SCHEME 2

In another area, the phosphoryl group 'activates' carbon–carbon multiple bonds towards cycloaddition reactions, as in the Diels–Alder process (Section V.D), in a way reminiscent of carbonyl-containing or other electron-withdrawing functions.

It has been noted (Chapter 5, Section III.B) that thiophosphoryl and selenophosphoryl esters participate in alkylation reactions (Scheme 3); (X = S or Se) with resultant ligand exchange more easily than do phosphoryl esters (X = O) although, in the latter case, such reactions are by no means unknown. A further difference between the P=O and P=S bonds is to be found in relation to their presence in species capable of generating mesomeric anions. The alkylation of the mesomeric anions from the thiophosphinic amides **27**[68], **28**[69] (with R = CN, or COOMe) and **29** occurs at sulphur, although in the last case a further step regenerates the P=S bond[70]. Methylation of the disulphide **28** also yields an *S*-methyl derivative, but interaction of the amide potassium salt and dimethyl sulphate resulted in methylation at both sulphur atoms, and salts of the composition **30** (X = BF_6^-, $SbCl_6^-$ or PF_6^-) were isolated[71]. For the simple thiophosphinic amides **31**, in their reactions (as anions) with Me_3ECl (E = Si or Ge), stabilization of the imide form **33** over the amide form **32** occurs only when R = X = Bu^t [72,73].



SCHEME 3



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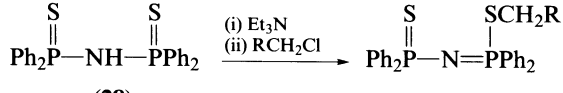

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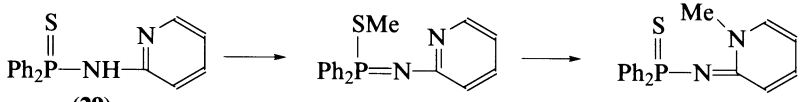

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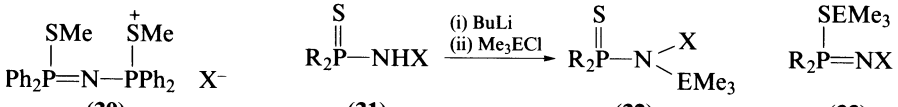


(30) (31) (32) (33)

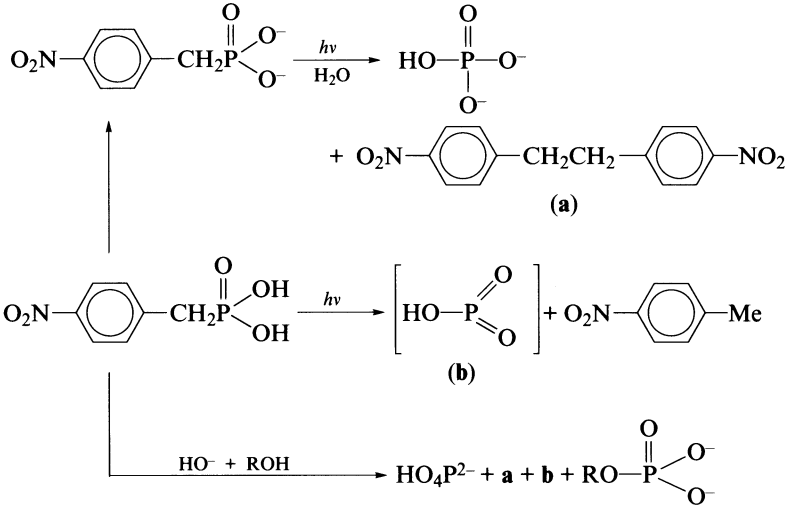
III. CLEAVAGE OF THE PHOSPHORUS–CARBON BOND

Phosphonic and phosphinic acids have been considered for so long to be chemically stable towards a large variety of mild reagents and experimental conditions that the overall term 'chemically stable' seemed to be applicable to them—certainly in contrast to, for example, phosphate triesters. Equally, however, other reactions have also long been known (e.g. modifications in the well known Wittig reaction) in which the fission of phosphorus–carbon bonds is well recognized. At present, however, in spite of the much greater stability (in rather general terms) of the phosphorus–carbon bond, compared with the phosphorus–oxygen, phosphorus–sulphur or phosphorus–nitrogen bonds, in phosphonic and phosphinic derivatives, these compounds can no longer be regarded necessarily as being 'chemically stable'. It is now widely recognized that, in addition to the mobility of other ligands at phosphorus, the phosphorus–carbon bond can be cleaved, often easily, through attack on a variety of compound types by many reagents under a variety of circumstances which include photochemical and biological conditions, homolysis and the action of acids or bases under aqueous conditions.

A. Photochemical Cleavage of the Phosphorus–Carbon Bond

1. *In acyclic phosphonic diesters*

The photochemical cleavage of the phosphorus–carbon bond in many benzylic phosphonic acids occurs through intramolecular electron transfer and gives monomeric metaphosphate together with substituted toluenes and, in many cases, 1,2-diarylethanes. The ultraviolet irradiation of (4-nitrobenzyl)phosphonic acid dianion in solution in aqueous ethanol yields 1,2-bis(4-nitrophenyl)ethane, 4-nitrotoluene, H_3PO_4 and monoethyl phosphate (Scheme 4)[74]. Irradiation of the same acid in the presence of dbu (other tertiary bases have proved to be less satisfactory) and in an excess of an anhydrous alcohol has been developed for the synthesis of monoalkyl (4-nitrobenzyl)phosphonates, obtainable in yields of 30–97%, and which do not, themselves, cleave even at a pH below 10[75]. The success of photochemical P—C bond cleavage is dependent on the pH of the medium, and the rate of reaction reaches a maximum at about pH 9. It might also be noted that, even in the absence of ultraviolet irradiation, (4-nitrobenzyl)phosphonic acid in 0.002 M aqueous NaOH at 70 °C undergoes fission to 4-nitrotoluene to the extent of 25% after 3 h and 90%

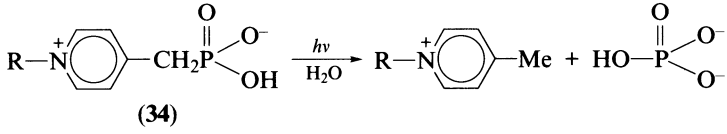


SCHEME 4

after 72 h. Under the same conditions, (2-nitrobenzyl)- and (3-nitrobenzyl)-phosphonic acids undergo much slower breakdown; furthermore, (3-methyl-4-nitrobenzyl)- and (4-methyl-3-nitrobenzyl)-phosphonic acids are almost unreactive. With other nitrobenzylic phosphonic acids, the formation of non-phosphorylated dimer molecules may or may not be observed; thus, [1-(4-nitrophenyl)ethyl]phosphonic acid dianion yields 2,3-bis(4-nitrophenyl)butane and HPO_4^{2-}, whereas [bis(4-nitrophenyl)methyl]phosphonic acid dianion gives bis(4-nitrophenyl)methane but no dimer. Possible mechanisms for these cleavage reactions have been considered, but remain controversial, although various lines of evidence have been presented which appear to preclude a homolysis mechanism[76].

(4-Benzoylbenzyl)phosphonic acid (the 3-substituted isomer behaves in the same fashion qualitatively and almost quantitatively so) in an aqueous alkaline medium also undergoes virtually quantitative decomposition with the formation of 4-methylbenzophenone, the efficiency of the process again depending on the pH of the reaction medium[76].

Photochemical phosphorus–carbon bond fission is also found when (pyridinylmethyl)phosphonic acids at the isoelectric point are irradiated (equation 1); the cleavage at pH > 4 (but best at ca pH 9) has been noted for **34** (R = H[77], $PhCH_2$[78] and C_nH_{2n+1}, n = 0, 7, 9, 11, 13, 15 and 17[79]).

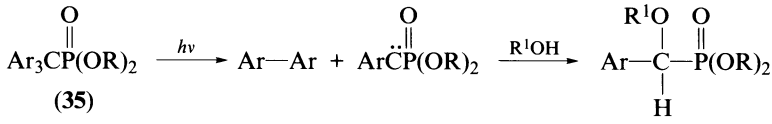


(1)

(34)

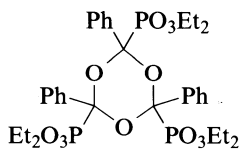
The dialkyl (triarylmethyl)phosphonates **35** seemed to be likely contenders for P—C bond cleavage on photolysis; however, the first step in such treatment is evidently the formation of a phosphorylated carbene together with that of a biaryl; in the presence of an alcohol, the ethers **36** are produced in moderate yields with no cleavage of the phosphorus–carbon bond[80–82].

Equally, the photolysis of aroylphosphonic diesters has received little attention even though they, too, might have been considered potential substrates for bond cleavage at



(35) (36)

phosphorus. Irrespective of the nature of the solvent, the diethyl ester of benzoylphosphonic acid behaves differently from other diesters of the acid; the sole product from the former is the trioxanetriphosphonic derivative **37**. Certain other diesters of benzoylphosphonic acid, e.g. the diisopropyl and dibutyl esters, yield the diol-diphosphonic acid derivatives **38** (R = Pr^i or Bu, R^1 = H) through ketyl radicals produced in aprotic solvents; some 4-substituted benzoylphosphonic diesters behave similarly[83]. Unusual behaviour has also been observed during ultraviolet photolysis of the acylphosphonic diesters **39** (R = Me or Ph) in which the ester groups possess a free tertiary hydrogen atom; in benzene solution, monodealkylation occurs with insertion of the alkyl group between phosphorus and carbon, i.e. P—C bond cleavage is at least involved, the process thus consisting of P—C bond fission and re-formation. When $R^1 = R^2$ = H, irradiation for 20 h produced none of the monoester **40**, but about 25% of dimethyl phenylphosphonate and much polymer; on the other hand, during only 4 h of irradiation, 12% of the insertion compound **40** and 6% of the phenylphosphonic diester were obtained when R^1 = Me and R^2 = H; the respective figures for the substrate **39** ($R^1 = R^2$ = Me) are 83.5 and 2.5% The insertion product **40** was obtained, also in about 75% yield, for **39** (R = Ph, $R^1 = R^2$ = Me), but was not accompanied by the diester **41**[84].



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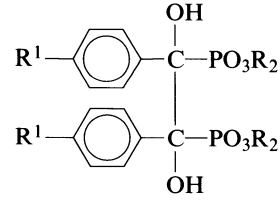

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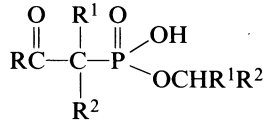

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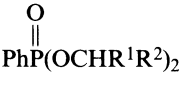
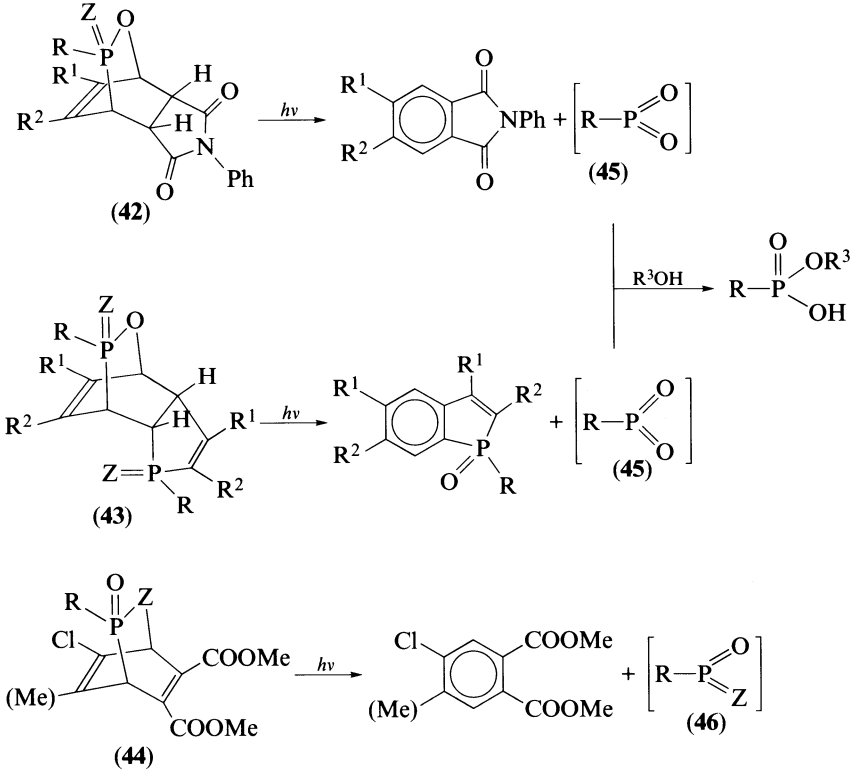


(41)

2. In 2,3-oxaphosphabicyclo[2.2.2]octane derivatives

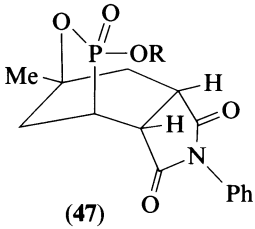
A further type of degradation occurs during the photolysis or thermolysis of derivatives of the 2,3-oxaphosphabicyclo[2.2.2]octene system, formally derivatives of cyclic phosphonic or phosphinic acids. The compounds **42** are obtained by Baeyer–Villiger oxidations, with 3-chloroperoxybenzoic acid, of the 1:1 adducts from monomeric 1*H*-phospholes and *N*-phenylmaleimide, and **43** by the identical oxidation of the products of dimerization of monomeric but unstable 1*H*-phospholes. The simpler substrates **44**, similarly obtained by the oxidation of the Diels–Alder adducts prepared from acetylene dicarboxylic ester, have also been examined. The thermolysis (at 80–110 °C in toluene) or

irradiation (in dioxane with 254 nm radiation) of the compounds **42** (R^1, R^2 = H or Me) results in the formation of *N*-phenylphthalimide and extrusion of the reactive species **45**; compounds of the second type, **43**, behave similarly but with the formation of the phosphindole. The procedure was first reported in 1985 for the generation of ethyl metaphosphate and thus far the metaphosphate species **45** (R = EtO[85–87], 1-adamantoxy[87], 2,2-dimethylpropoxy[87], Me_2N[85], Et_2N[86,88], Bu^{t}NH and 2,4,6-$Me_3C_6H_2NH$[88]) and metathiophosphate **46** (Z = S; R = EtO[86,89] or EtMeCHO[89]), and also for the metaphosphonic monoanhydrides with R = Me or Ph[90,91]. Relatively few compounds of types **43** and **44** have been examined[92]. The intermediate and highly reactive species **45** and **46** have been characterized following their absorption in an alcohol with resultant formation of a phosphate diester (R = EtO), a phosphonic monoester (R = Me or Ph), or a phosphoramidic monoester R = R'_2N). Some later developments in the synthesis and properties of the substrates, and reactions of the metaphosphonate and metaphosphate species, have been reviewed[89], but even since 1991 there have been several detailed reports of interesting developments. Mechanistic aspects of the extrusion process have been studied with particular regard to kinetics (which are first order)[86,89], and also the stereochemistry of extruded fragment[89].



The expulsion of monomeric metaphosphate ester in EtCN at –78 °C can be followed by ^{31}P NMR spectroscopy, and this allowed the detection of a species formed in competition with the elimination process. The second product from **42** (R = 1-adamantoxy, R^1 = Me, R^2 = H) was shown, by single-crystal X-ray analysis, to have the structure **47**, additionally

represented in another way as **48**[87]. The rearrangement has not been observed for phosphonic amides in the bicyclic series, but is thought to occur when R = Ph, although the rearranged product has not been isolated.



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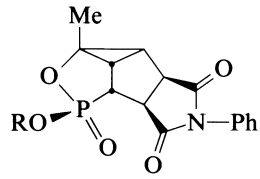
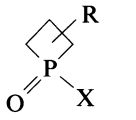


(48)

3. *In phosphinoyl azides*

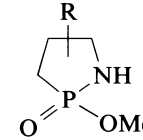
When heated in a vacuum, diphenylphosphinic azide undergoes phosphorus–carbon bond cleavage with formation of a phosphorus–nitrogen bond, an observation which appears to have been first reported by Reichle in 1964[93], although little was presented by way of detail. Since then, the photolysis of phosphinic azides, both acyclic and cyclic, has been examined in some detail, largely by Harger and coworkers. Historically, the topic was carried a stage further by a study of the behaviour of 1-azidophosphetane 1-oxides in MeOH solution towards mercury radiation, and concentrated on the three polymethylated compounds **49a–51a**. In the absence of radiation, these three compounds undergo a very slow solvolysis to give the methyl esters **49b–51b** of the phosphetanic acids. When irradiated at room temperature, the methanolic solutions liberate nitrogen, but otherwise the course of the reaction depends on the molecular symmetry of the substrate. Compound **49a** yielded the 1,2-azaphospholidine 2-oxide, **52**, as the main product (62%), whereas the azide **50a** afforded a mixture of isomeric products, **53** and **54**, obtained in total yield of 40%, and accompanied by smaller amounts of other materials. Potential reaction pathways are exemplified for substrate **49a** in Scheme 5. The manner of formation of the principal reaction product, the 1,2-azaphosph(V)olidine **52a**, is best explained by postulating the participation of a metaphosphonimidate intermediate **55**. Just how the last might be formed was a point of contention, and two possibilities considered were a concerted liberation of nitrogen with cyclization (pathway a), and second, a route by way of a distinct nitrene intermediate **56** (pathway b + c). One argument for the latter rested on the nature of the minor reaction products which, in this particular case included the unsaturated phosphonamidic methyl ester **57**. The substrate **50a** yielded the products **53** and **54**, presumably via the two isomeric metaphosphonamidate intermediates **58** and **59**, respectively[94].

Harger[94] also examined the behaviour of the azide **51a**, from which he obtained a mixture of stereoisomeric 2-methoxy-2-oxo-1,2-azaphospholidines (in total yield 60%) together with 16% of an unsaturated phosphonamidic ester. Meanwhile, Wiseman and Westheimer[95] reported on a more detailed examination of the behaviour of this particular

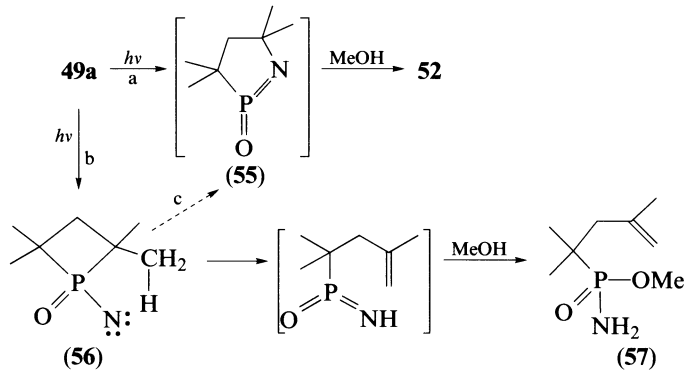


(**a**) X = N_3
(**b**) X = OMe
(**c**) X = NH_2

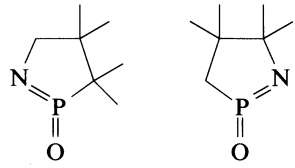
(**49**) R = 2,2,4,4-Me_4
(**50**) R = 2,2,3,3-Me_4
(**51**) R = 2,2,3,4,4-Me_5



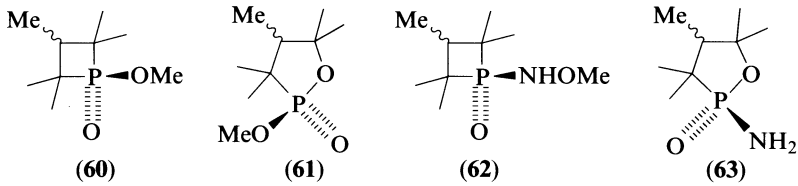
(**52**) R = 3,3,5,5-Me_4
(**53**) R = 3,3,4,4-Me_4
(**54**) R = 4,4,5,5-Me_4



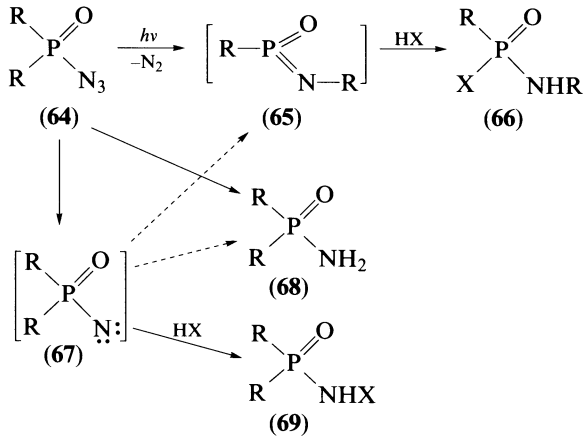
SCHEME 5



substrate and were able to demonstrate the formation of at least ten products. Compelling evidence for a metaphosphonimidate intermediate was based on the fact that the stereoisomeric composition of the main product (67–71% *trans*) was independent of the stereoisomeric composition (pure *trans*, 78% *trans* or 28% *trans*) of the substrate azide **51a**. The minor products included pairs of stereoisomers of (i) unsaturated phosphonamidic methyl esters analogous to **57**, (ii) the methyl phosphetanate **60**, (iii) the 1,2-oxaphospholane **61** and (iv) traces of **62** and **63**.



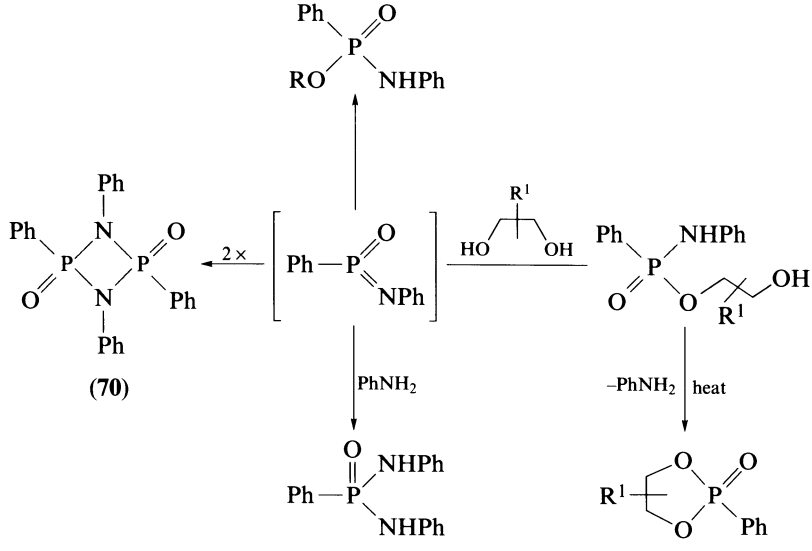
Harger and coworkers observed the migration of groups from phosphorus to nitrogen (i.e. phosphorus–carbon bond cleavage) during the photolysis of both dialkylphosphinic[96] and diarylphosphinic azides[97]. The formation of the phosphonic amide **66** (the major product when R = Pr^i or Bu^t, 71% for a reaction in MeOH) with **69** (R = Bu^t, X = MeO, EtO, Pr^{i}O, Bu^{t}O or Bu^{t}NH) in low yield are consistent (Scheme 6) with the intermediacy of the metaphosphonimidate **65** and also, probably, a nitrene **67** but, as in the case of the photolysis of the phosphetane azides, it is unclear whether **65** is derived from **64** directly or indirectly through **67**. In an effort to observe more fully the steric effects of alkyl groups, diethylphosphinic azide was also examined but was found to be largely solvolysed under the conditions generally used in the study. The direct solvolytic formation of methyl diarylphosphinate (during photolysis of methanolic solutions) appeared to be greater than for the diisopropylphosphinic and di-*tert*-butylphosphinic azides when R =



SCHEME 6

4-methylphenyl or 4-chlorophenyl, but about the same, or lower, when R = phenyl or 4-methoxyphenyl; on the other hand, the yields of phosphinic amides (**68**) then tended to be greater than from the two dialkyl phosphinic azides[97].

In the work just described, the formation of a species thought to be the metaphosphonimidate intermediate was demonstrated by its entrapment with an alcohol, normally MeOH, although Harger and Stephen[96] also used other alcohols and also *tert*-butylamine. Other workers, in an examination of the photolytic breakdown of diphenylphosphinic azide, used a variety of agents to trap the intermediate (Scheme 7), but also observed its dimerization to give the 1,3,2,4-diazadiphosph(V)etidine **70** accompanied by more extensive polymerization[98].

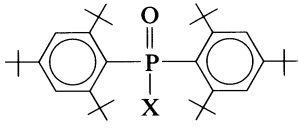


SCHEME 7

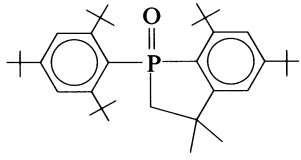
Other aspects of this Curtius-like rearrangement have also been investigated by Harger and by others. For the series $PhRP(O)N_3$ in MeOH, there is a slight preference for the alkyl group to migrate relative to the phenyl group, but this migratory aptitude decreases in the series $Bu^t > Pr^i > Et > Me$; in addition, for the azide $Bu^tMeP(O)N_3$, there is little difference in the ease of migration of the two organic groups. In the breakdown of mixed azides, two intermediate metaphosphonimidates become possible, and provided that these are trapped rapidly and quantitatively by the solvent (MeOH), the relative migratory aptitudes of the two carbon moieties are then indicated by the amounts of the methyl phosphonamidate products[99].

Attempts to stabilize a possible intermediate metaphosphonimidate by the methods used to stabilize dithioxophosphoranes, i.e. by the presence of bulky *ortho* aromatic substituents (Chapter 5, Section IV.C), experienced difficulties with regard to the preparation of the azide substrates; an attempt to prepare bis(2,4,6-tri-*tert*-butylphenyl)phosphinic azide (**72**) from corresponding chloride (**71**) and NaN_3 in pyridine–dmf, yielded the phosphine oxide **73**[98]. However, Harger and Shimmin[100] succeeded in the preparation of other sterically hindered phosphinic azides, including the mixed azide **74**, dimesitylphosphinic (**75**) and bis(2,4,6-triisopropylphenyl)phosphinic azides (**76**). For both symmetrical diarylphosphinic azides under photolysis conditions, Curtius-like rearrangement to give the phosphonamidic esters **77** was accompanied by the insertion of the (supposed) nitrene intermediate into the C—H bond of an *ortho* aromatic substituent to give the dihydrobenzazaphosph(V)oles **78** and **79**. The azide **74** behaved similarly, except that a mixture of two phosphonamidic esters was obtained the composition of which suggested that the relative migratory aptitudes of the Bu^t and mesityl groups are 6:1. It was argued that the presence of the bulky *ortho* substituents stabilized the nitrene, preventing further interaction with external agents (e.g. solvent) and so allowing time for intramolecular reaction to occur[100]. Although experimental details are still lacking, it has been claimed that the symmetrical (*R*,*R*)- and (*S*,*S*)-bis(1-phenylethyl)phosphinic azides in MeOH undergo photo-Curtius rearrangement to give the methyl phosphonamidic esters with essentially quantitative retention of configurations[101].

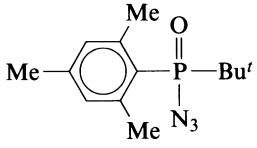
In the above discussion, it was presumed that one of the intermediates involved in the photo-Curtius rearrangement is indeed a phosphinoyl nitrene. Although the formation of the alkyl phosphonamidic esters constitutes one line of evidence for the intermediacy of



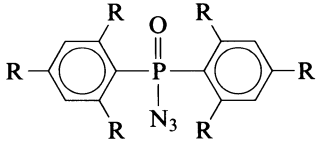
(**71**) X = Cl
(**72**) X = N_3



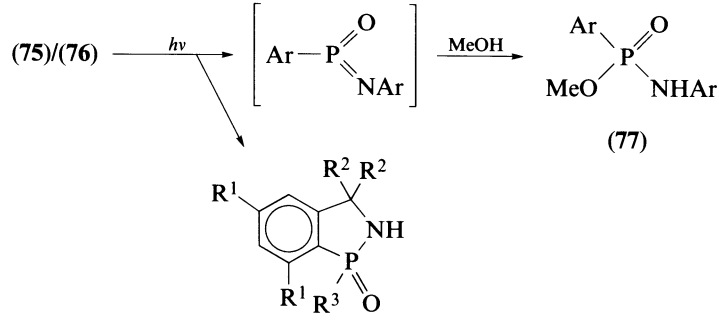
(**73**)



(**74**)

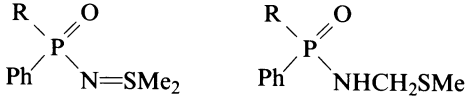


(**75**) R = Me
(**76**) R = Pr^i



(78) R^1 = Me; R^2 = H; R^3 = 2,4,6-$Me_3C_6H_2$
(79) R^1 = Pr^i; R^2 = Me; R^3 = 2,4,6-$Pr^i_3C_6H_2$
(80) R^1 = Me; R^2 =H; R^3 =Bu^t

such a species, it is obviously desirable to have further evidence. An early attempt to trap a nitrene by the incorporation of dmso (effective as a trap for sulphonyl nitrenes) into the reacting system was not successful[97]. However, the incorporation of dimethyl sulphide into a benzene–methanolic solution of an azide $RPhP(O)N_3$ during photolysis led to the isolation of the corresponding sulphilimine **81** with a decrease in the extent of Curtius rearrangement; as the Me_2S content of the system was increased, the yields of methyl phosphonamidates fell, those of the sulphilimines increased but levelled off and those of the phosphinic amides **82** increased steadily. The uncertain conclusion was that as regards the mixed azide, $Bu^tPhP(O)N_3$, the formation of the metaphosphonimidate occurred by a concerted process, but the data for diphenylphosphinic azide left open the possibility of formation of the discrete singlet nitrene[102]. Furthermore, the incorporation of Me_2S into the reacting system containing the azide **74** resulted in the formation of sulphilimine at the expense of nitrene insertion to give the dihydrobenzazaphosph(V)ole **80**[103]. This particular study suggested more clearly that, for this particular example at least, 40% of the azide rearranges concertedly, and 60% proceeds via the singlet nitrene to the insertion product or sulphilimine.



(81) (82)

Finally, it might be pointed out that the photolysis of $Ph_2P(S)N_3$ in MeOH, does not lead to phosphorus–carbon bond fission, the main product being diphenylphosphinic amide[98].

B. Biochemical Fission of the Phosphorus–Carbon Bond

Apart from the results from a very few isolated studies, little is yet known about the breakdown of phosphorus–carbon-bonded compounds in vertebrates or invertebrates[104]. However, a very wide range of bacteria are capable of destroying the phosphorus–carbon bond, often in individual compounds, sometimes in a range of chemically similar structures[104]. The outstanding feature is the way in which many bacteria can utilize phosphonic acids as the sole source of phosphorus, and so catabolize simple phosphonic acids (but not

their esters) under aerobic or anaerobic conditions, to give mixtures of alkanes and alk-1-enes (equation 2) (apart from methylphosphonic acid, which gives methane only) together with inorganic phosphate.

$$RCH_2CH_2P(O)(OH)_2 \longrightarrow REt + RCH{=}CH_2 + P_i \qquad (2)$$

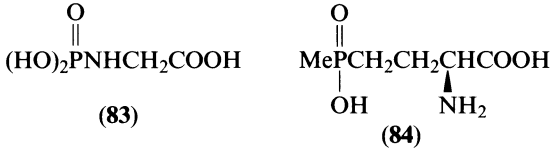
Notable exceptions to this generalization, apart from the lack of activity towards derivatives of the phosphonic acids, are isopropyl- and *tert*-butyl-phosphonic acids and benzylphosphonic acid; (2-methylpropyl)phosphonic acid is cleaved to give very low yields of 2-methylpropene and 2-methylpropane[105,106]. Isotopically labelled (carbon or hydrogen) methylphosphonic acid affords methane possessing the identical distribution of the label[105,107].

Several studies have employed *Escherichia coli*, some strains of which appear to be particularly active in their ability to cause P—C bond fission, and through the use of one of these, a metabolite from ethylphosphonic acid was shown to be α-1-(ethylhydroxyphosphinoyl)ribose[108]; (aminomethyl)phosphonic acid and its *N*-methyl, *N*,*N*-dimethyl and *N*-acetyl derivatives are converted into *N*-methylacetamide, *N*,*N*-dimethylacetamide, trimethylamine and *N*-methylacetamide, respectively[109].

The ratio of alkane:alkene produced enzymically according to reaction 2 varies from ca 30:1 (R = H) to ca 2000:1 (R = Bu)[110] and at least two free-radical mechanisms have been proposed for the breakdown process[108]. In this respect, attempts have been made to draw a parallel between the results of the enzymic process and those from the lead tetraacetate treatment of phosphonic acids, but the ratio of alkane to alkene thus formed is almost independent of the group R and there is a much greater emphasis on the formation of the alkene[105,110]. Amongst the free-radical probes which have been applied were (cyclopropylmethyl)phosphonic acid, metabolized by *Klebsiella oxytoca* and *Kluyvera ascorbata* to but-1-ene and methylcyclopropane, and *cis*-1,2-dideuteriopropene, but the results were not convincing, and the role of homolysis in the cleavage of phosphorus–carbon bonds by bacteria remains undecided[107].

At least two enzyme systems (individual or type) appear to be involved since it has been claimed that the enzyme(s) responsible for P—C bond fission in simple alkylphosphonic acids are not identical with those responsible for the breakdown of phosphonoacetic acid[111] and phosphonoacetaldehyde, in the latter case known as phosphonoacetaldehyde hydrolase (phosphonatase), and which cleaves (2-oxoethyl)phosphonic acid (phosphonoacetaldehyde) into acetaldehyde and inorganic phosphate with retention of configuration at phosphorus[112].

The range of phosphonic acids which can be utilized enzymically (at least by those enzymes present in *Pseudomonas fluorescens*) has recently been extended to include aminoalkyl-, hydroxyalkyl- and oxoalkyl-phosphonic acids, as well as phosphonodipeptides; only slight growth was seen with the herbicide glyphosate (*N*-phosphonomethylglycine; **(83)**, which is metabolized to (aminomethyl)phosphonic acid, and neither phosphinothricin **(84)** nor its dialanyl tripeptide bialaphos supports growth[108,113], in contrast to the behaviour of other bacterial extracts isolated from soil[114].

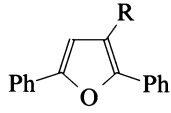


(83) **(84)**

C. Chemical Fission of the Phosphorus–Carbon Bond

Instability in the supposedly stable phosphorus–carbon bond displays itself not only in unfortunate ways, leading as it does to side reactions and the formation, in synthesis, of unwanted by-products, but also in a constructive manner, forming the basis of reaction sequences of outstanding value in synthesis, as for example in alkene-forming reactions. Instability is an inherent property of (α-hydroxyalkyl)phosphonic acids which manifests itself in phosphorus–carbon bond cleavage as a result of the action of heat or of alkali, and which can lead either to dissociation into precursors or to rearrangement to phosphates; (α-oxoalkyl)phosphonic derivatives are susceptible to attack by nucleophiles, a process which also results in carbon–phosphorus bond fission.

Aside from photolytic or biological cleavage, chemical cleavage at the phosphorus–carbon bond is generally associated with the presence of particular functionalizations in the carbon moiety. However, there are exceptions to this. Butyl-, benzyl- and phenyl-phosphonic acids are cleaved to organic products plus inorganic phosphate and CO_2, when placed into contact with irradiated TiO_2[115]. At 240 °C, the phosphonic acids **85** and **86**[116] and also **87**[117] (all with R = PO_3H_2) decompose into the corresponding **85**, **86** and **87** (all with R = H).



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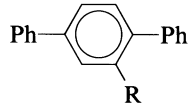

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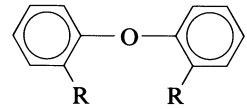
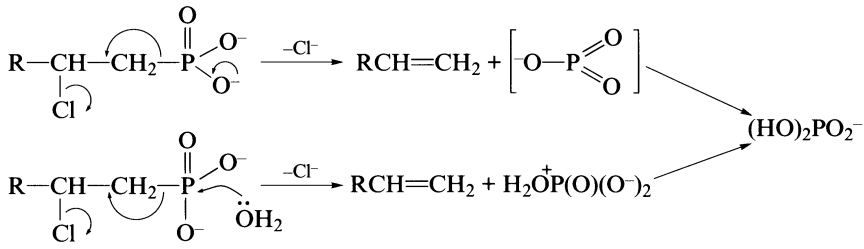


(87)

The presence of one or more halogen atoms on a carbon atom α or β to P=O renders the phosphorus–carbon bond more liable to break under less forcing circumstances. The fragmentation of (2-haloalkyl)phosphonic acids under aqueous conditions (the Conant–Swan reaction) has been known for many years. Conant and coworkers[118,119], in the early 1920s, reported on the instantaneous fragmentation of the acids **88** and **89** in aqueous $NaHCO_3$ into inorganic phosphate, Br^- and PhCOCH=CHPh.

(88) R = OH
(89) R = Ph

The slow destruction of (2-chloroethyl)phosphonic acid (known commercially as Ethephon or Florel) under aqueous conditions with the liberation of its carbon as ethylene (Scheme 8; R = H), a reaction of commercial value in market gardening, results in the liberation of the phosphorus-containing moiety as phosphoric acid, probably via metaphosphate. The phosphonic acid is stable to titration with 0.1 M alkali at room temperature, but decomposes rapidly in 30% aqueous KOH[120]; higher (2-chloroalkyl)phosphonic acids behave similarly[120,121]. Under alkaline conditions, two modes of decomposition can be envisaged (Scheme 8), although later work[122] has indicated that in protic solution (2-haloalkyl)phosphonic acids decompose unimolecularly. The generation of metaphosphate raises the possibility of the use of (2-chloroalkyl)phosphonic acids as phosphorylating agents. Certainly the decomposition takes place readily when the acids are fully neutralized in aqueous solution; (2-chlorodecyl)phosphonic acid decomposes slowly in solution at pH 4.5, and the rate increases rapidly with an increase in pH, being too fast



SCHEME 8

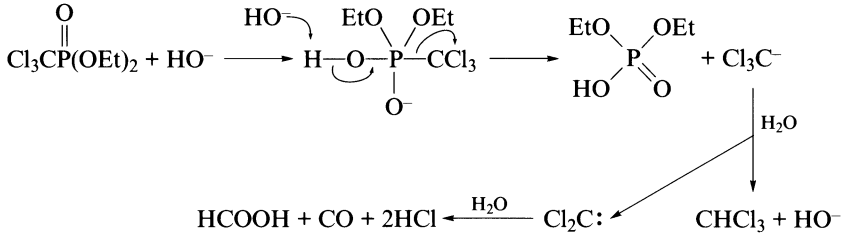
to measure at pH 7. However, monoesters of (2-chloroalkyl)phosphonic acids are stable to hot aqueous 2 M NaOH or KOH–MeOH, although more forcing conditions with the same or similar reagents may result in the elimination of HCl but without phosphorus–carbon bond fission. Evidence for the phosphorylating capability based on the decomposition of (2-chloroalkyl)phosphonic acids is readily available. Thus, (2-chlorodecyl)phosphonic acid with 3 equiv. of cyclohexylamine in EtOH decomposes rapidly to give 89% dec-1-ene together with the bis(cyclohexylammonium) salt of monoethyl phosphate, and other phosphorylations of secondary and tertiary alcohols and phenols have been recorded; (2-chloroethyl)phosphonic acid behaves similarly[120].

A similar breakdown of (2-haloalk-1-enyl)phosphonate dianions into alkynes and inorganic phosphate, again probably via metaphosphate, has been known for many years, being observed both by Conant's group and by Bergmann and Bondi slightly later[123].

Conant and Pollack[119] had originally suggested the participation of a 1,2-oxaphosph(V)olane (phostone) as an intermediate in the breakdown of the acids **88** and **89**, but the arguments for this proposal have been rejected, additionally on the basis of kinetic data[124], and further data have been presented which preclude the intermediacy of a phenonium ion[125].

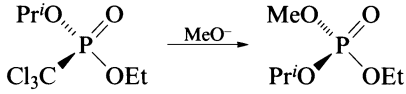
As another example of the remarkable ease of dehydrohalogenation of (2-haloalkyl)phosphonic acids under basic conditions, a solution of *erythro*-(1,2-dibromo-1-phenylpropyl)phosphonic acid in 1 M NaOH at room temperature becomes turbid immediately and gives (*E*)-1-bromo-1-phenylpropene in 85% yield; the *threo* acid behaves similarly to give 97% of the (*Z*)-alkene, and in addition, the acid itself decomposes in boiling aqueous solution to give the same product in 75% yield[126].

Cleavage at the phosphorus–carbon bond in esters of (trichloromethyl)phosphonic acid under alkaline conditions has been known for many years and yields ethanol, phosphoric acid and chloroform[127], and a study of the kinetics has shown that as the concentration of alkali rises, CO, HCl and HCOOH are formed in increasing amounts, possibly through the sequence illustrated in Scheme 9[128]. However, hydrolytic removal of the trichloromethyl group is possible in conditions other than alkaline. At pH 1–10, 4-nitrophenyl phenyl(trichloromethyl)phosphinate is cleaved at the P—C bond to the extent of 90–100%, although this is accompanied by hydrolysis at the POC bonding with the liberation of small



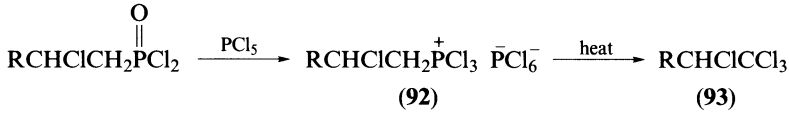
SCHEME 9

amounts of 4-nitrophenol[129]. The displacement of the trichloromethyl group from a chiral ester of (trichloromethyl)phosphonic acid, e.g. the (*R*)-(+)-ester **90**, by MeO^- yields a chiral phosphate ester, **91**, with *inversion* of configuration; such a displacement does not occur for the corresponding ester of (dichloromethyl)phosphonic acid[130]. When boiled with 10% aqueous NaOH solution, (1,2,2-trichloro-1-fluoroethyl)phosphonic acid yields 1,2-dichloro-1-fluoroethene[22].

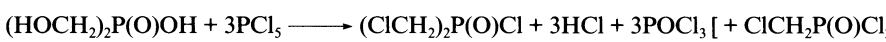


(90) **(91)**

The action of PCl_5 on (2-chloroalkyl)phosphonic dichlorides yields complexes, probably of the composition **92** which, when heated at only moderate temperature, afford the tetrachloroalkanes **93**[131]. Even the reaction between PCl_5 and bis(hydroxymethyl)phosphinic acid, and that between the products therefrom and more PCl_5 represent a complex picture which involves the fission of phosphorus–carbon bonds in several compounds; the reactions are represented, in overall terms, by equation 3 (the yields of the phosphinic and phosphonic chlorides were ca 50% and ca 30% at 0–10 °C, although the former increases at the expense of the latter at 50 °C)[132], and equations 4 and 5 (reactions at about 100 °C)[133]; a further detailed study allowed a mechanism to be proposed (Scheme 10)[134]. A similar situation arises in the treatment of dibutyl (difluoromethyl)phosphonate with PCl_5 (1:1 at 70 °C), when the yield of phosphonic dichloride is about 30%, but with an excess of PCl_5 the products include $BuOP(O)Cl_2$, $POCl_3$, PCl_3, BuCl and CHF_2Cl[135].



(92) **(93)**



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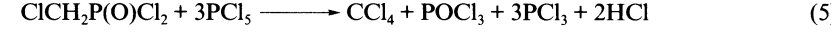

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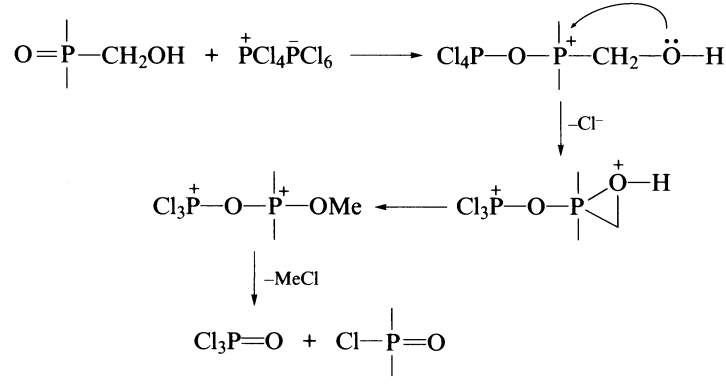
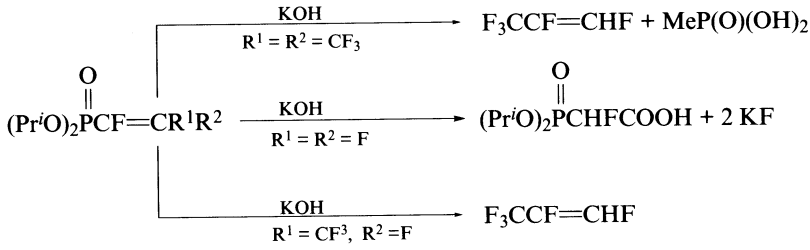
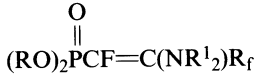


SCHEME 10

Ammonia, $MeNH_2$, and also Me_2NH all cause the breakage of phosphorus–carbon bonds, initially in perfluoroalkylphosphine oxides $(R_f)_3P(O)$, but the products from successive reactions include the respective amides from $(R_f)_2P(O)OH$ and $(R_f)P(O)(OH)_2$[136]. (Polyfluoroalkenyl)phosphonic diesters also break down under strongly alkaline conditions (Scheme 11)[137] and various reagent combinations cause the cleavage of the esters **94** (NR^1_2 = 1-piperidino) to, *inter alia*, the ketones R_fCOCH_2F[138].

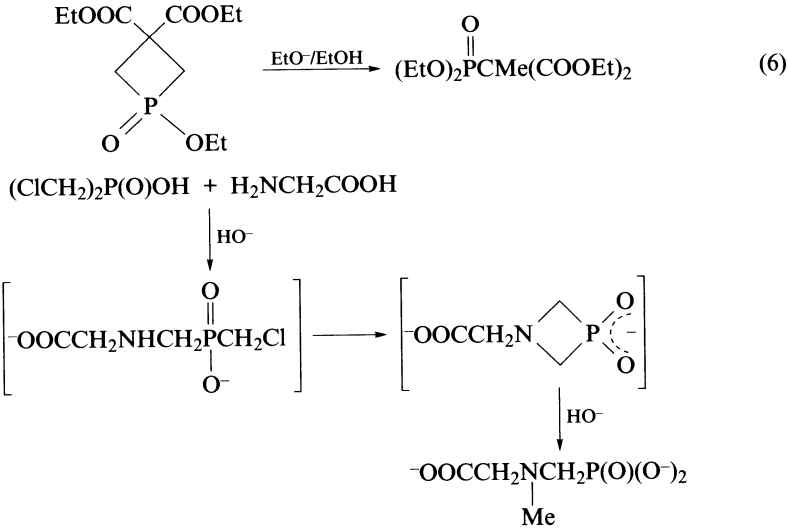


SCHEME 11



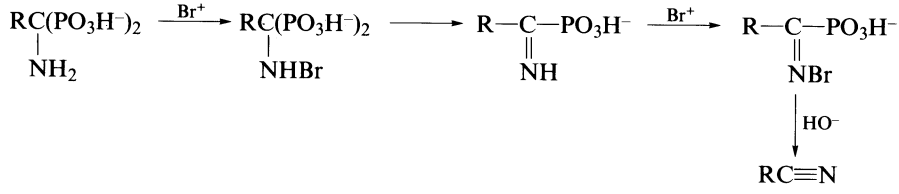
(94)

An unusual example in which the action of ethoxide leads to fission of the bond between phosphorus and carbon (reaction 6) is probably due to loss of ring strain in a pentacoordinate reaction intermediate or transition state (Section 6)[139], but it is also of interest that P—C bond cleavage occurs, probably in a similar species, during the reaction between bis(chloromethyl)phosphinic acid and glycine in the presence of alkali; in this case, the reaction is represented in Scheme 12, in which the P—C bond cleavage occurs via a 1,3-azaphosph(V)etidine[140].



SCHEME 12

Stepwise dephosphorylation occurs during the cleavage of (1-aminoalkylidene)bisphosphonic acids when these are brominated under alkaline conditions (bromine in aqueous HCO_3^-). *N*-Bromination is accompanied by loss of the phosphoryl group in each of two steps (Scheme 13)[141]. The trisphosphonate **95** reacts with either HCl or Me_3SiBr–H_2O by splitting off one phosphoryl moiety to give the bis-acid **96**. The course of the alkylation of **95** depends on the choice of reagent; the use of MeI leads to **97**, but methyl *p*-toluenesulphonate or dimethyl sulphate gives the expected salts **98**. Acid hydrolysis of the latter yields **99**, but a phosphorus–carbon bond is split also during a treatment with alkali which affords the ylide **100**[142].



SCHEME 13

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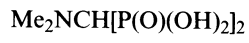

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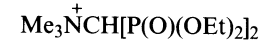

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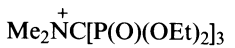

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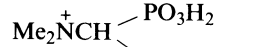

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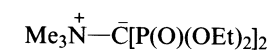
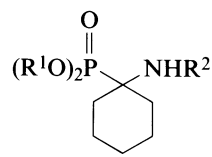


(100)

α-Dephosphorylation has been shown to be mediated by pyridoxal in reactions between the latter and (1-aminoalkyl)phosphonic acids, in particular, (α-aminobenzyl)phosphonic acids which also possess a functional group capable of chelation to a metal catalyst ion; the products from (α-aminobenzyl)phosphonic acid itself are pyridoxamine, 2-hydroxybenzaldehyde and also (2-hydroxybenzoyl)phosphonic acid, the result of accompanying deamination[143].

Compounds of the type **101** seem to possess slightly unusual properties. Thus, the agriculturally important herbicidal compound buminafos (**101**; $R^1 = R^2 = Bu$) is labile under aqueous conditions, and in addition to suffering dealkylation from nitrogen, the fragmentation process also yields cyclohexanone and its butylimine together with monobutyl hydrogenphosphonate[144]. Other chemical behaviour also differentiates between the esters **101** and analogous (α-aminobenzyl)phosphonates; unlike the latter, the treatment of **101** (R^2 = Ph) with chloroacetyl chloride leads to the dialkyl hydrogenphosphonate and a cyclohexene fragment devoid of phosphorus[145,146].



(101)

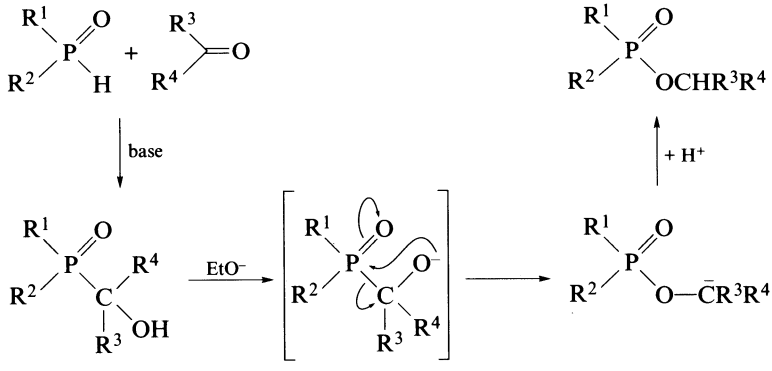
Phosphorus–carbon bond fission by the action of metals or of organometallic reagents is exemplified by that in tetraalkyl methylenebisphosphonates during lithiation (to afford

the desired bisphosphorylated carbanion) with BuLi; this effect can be reduced by using Bu^{t}Li or an organothallium reagent[147]. Dialkyl alkylphosphonates react with an alkali or alkaline earth metal to give a dealkylated product accompanied by low molecular weight gases which may be traced to the formation of radical fragments through the cleavage of phosphorus–carbon bonds; alkanes are formed predominantly, but traces of unsaturated hydrocarbons may also be present. Some esters, however, decompose largely through loss of the phosphonic ester alkyl moiety, a behaviour exemplified by diisopropyl methylphosphonate, and the extent of P—C fission depends on the individual metal, being extensive for sodium but less so for lithium[148].

The presence of electron-withdrawing groups positioned on an aromatic nucleus bonded directly to phosphorus can be a source of instability in the phosphorus–carbon bond. This situation is found particularly in (4-nitrophenyl)phosphonic acids. (2-Methoxy-4-nitrophenyl)phosphonic acid can be demethylated in 40% HBr, but cleavage of the carbon–phosphorus bond becomes more pronounced in a reaction with 48% HBr; moreover, hydrogenation of the same acid over Raney nickel yields the expected (4-amino-2-methoxyphenyl)phosphonic acid, but a similar reduction of (2-hydroxy-4-nitrophenyl)-phosphonic acid results in the separation of 3-aminophenol. These and other, similar, reactions have been surveyed by Freedman and Doak[149].

However, the two groups of compounds in either the phosphonic or the phosphinic acid series which possess the most readily labile phosphorus–carbon bonds are those with hydroxy or oxo functions at the α-carbon atoms. With regard to the former function, the lability of the phosphorus–carbon bonds manifests itself as thermal instability during the purification, by distillation, of (some) dialkyl (1-hydroxyalkyl)phosphonates or related phosphinates, and which takes the form of reversion (the retro–Abramov process) to preparative starting materials (aldehyde or ketone, and hydrogenphosphonate or hydrogenphosphinate)[150–152] or, alternatively, of thermally initiated isomerization[153,154]. Yet a third mode of fission is that which occurs during phosphonate–phosphate isomerization, effected by the action of a base catalyst.

The rearrangement of a (1-hydroxyalkyl)phosphonic or analogous phosphinic ester in the presence of an alkoxide base is visualized (Scheme 14) as proceeding with initial deprotonation from the hydroxy group to give the intermediate **102**, although it is also conceivable that the steps indicated may be synchronized; the product is a phosphate ester, or phosphonate ester from a phosphinate substrate[155,156]. The predicted 1:1 adducts from dialkyl hydrogenphosphonates and diaryl ketones are obtainable only in the presence of a

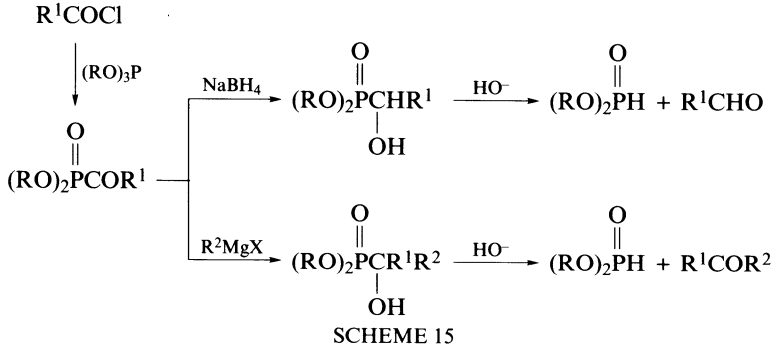


(102)

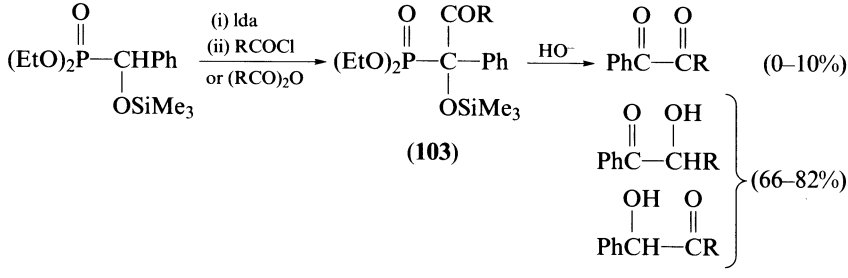
SCHEME 14

small amount of ethoxide catalyst, otherwise rapid, and sometimes exothermic, rearrangement to dialkyl diarylmethyl phosphates occurs; reactions with dialkyl hydrogenphosphonothioates give *S*-diarylmethyl thiophosphates immediately[157].

The degradability of (1-hydroxyalkyl)phosphonic diesters under aqueous alkaline conditions has been utilized in a procedure for the conversion of an acyl chloride into an aldehyde or ketone. Following the $NaBH_4$ reduction of an acylphosphonic diester (Scheme 15; R^1 = aryl or alkyl)[158,159] or, after a reaction with a Grignard reagent (Scheme 15; R^1 = Ph, R^2 = Me or Ph), alkaline cleavage of the products yields acetophenone or benzophenone[159]. The potential in the methodology can be increased still further since the dialkyl (1-hydroxyalkyl)phosphonates can also be obtained from non-functionalized dialkyl alkylphosphonates through oxidative procedures which employ $(Me_3Si)_2O_2$ or 3-chloroperoxybenzoic acid, the latter after initial protection of the hydroxy group with $(MeO)_2BCl$[160], and it is thus possible to convert an alkyl halide RCH_2X into the aldehyde $RCH_2CH{=}O$ or ketone RCH_2COR^1, or, after an initial alkylation of the starting material, into $RR^2CHCH{=}O$ or RR^2CHCOR^1. The cleavage of the silyl ethers **103** by alkali yields 1,2-diketones, or isomeric benzoins (Scheme 16), sometimes as a single product[161]. The reduction of diethyl benzoylphosphonate under Wolff–Kishner conditions gives toluene in 69% yield[159].

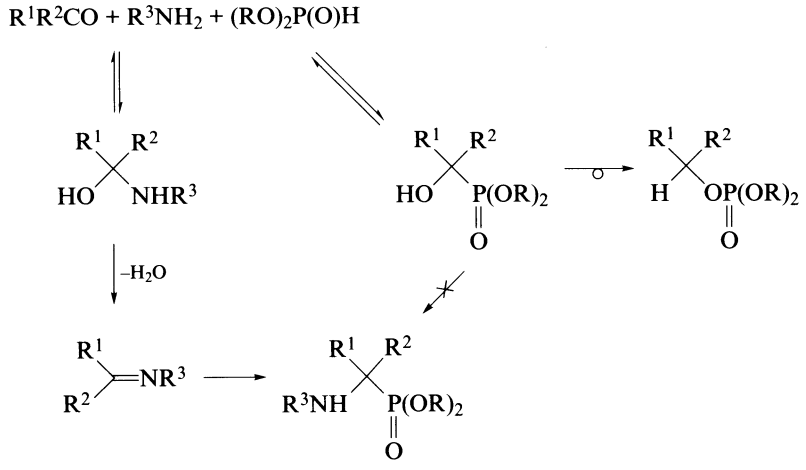


SCHEME 15



SCHEME 16

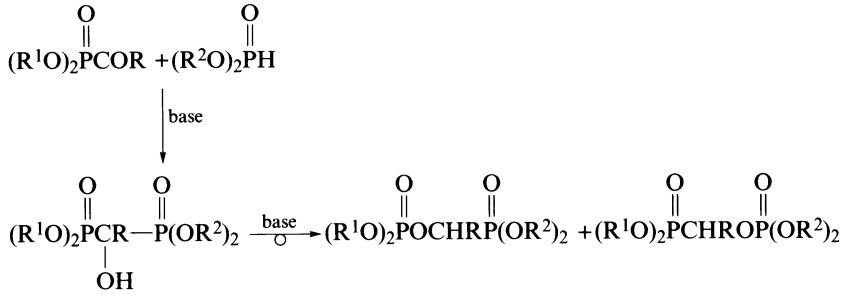
The practical difficulties sometimes encountered in Kabachnik–Medved'–Fields syntheses of (α-aminoalkyl)phosphonic acids from amines, aldehydes or ketones, and dialkyl hydrogenphosphonates, have been traced to the rearrangement of dialkyl (1-hydroxyalkyl)phosphonates to isomeric phosphate esters under the essentially basic conditions; the reactions involved are summarized in Scheme 17. The direct conversion of a (hydroxyalkyl)phosphonic diester into the corresponding (aminoalkyl)phosphonate by the action of the amine is known, generally, not to take place, and it seems much more likely that successful Kabachnik–Medved'–Fields syntheses proceed by the addition of the hydro-



SCHEME 17

genphosphonate to a pre-formed imine (Chapter 4, Section IV.B). With the more unreactive carbonyl substrates such as diaryl ketones, the initial and reversible formation of hydroxy phosphonate is much faster and the equilibrium can be driven forward by removal of the hydroxy phosphonate as phosphate[162,163]. In the presence of a base such as that used in the initial stage of reaction between hydrogenphosphonate and carbonyl compound—and EtO^- and Et_3N have been used very often—a desired (1-hydroxyalkyl)phosphonic diester may rapidly rearrange to a phosphate ester.

NMR spectroscopy has shown that many compounds, previously described as (1-hydroxyalkylidene)bisphosphonic esters, are actually either totally rearranged compounds or mixtures of initial and rearranged compounds. Such was the case with the products from dialkyl hydrogenphosphonates and dialkyl acylphosphonates, for which, when $R^1 \neq R^2$, the potential for confusion is obvious (Scheme 18). Provided that the compounds **104** are not heated above 80 °C, they may sometimes be isolated by crystallization, but others, e.g. **104** (R = Ph or aryl), rearrange very easily and cannot be isolated[164–166]. (1-Hydroxyethylidene)bisphosphonic acid is stable in solution at pH 1.6 up to 125 °C, and in alkaline solutions at pH 8.5–11.5 up to 195 °C; the compound then undergoes thermolysis with fission of the carbon–phosphorus bond to give, initially, acetylphosphonic and (1-hydroxyethyl)phosphonic acids[167,168]



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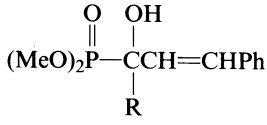
SCHEME 18



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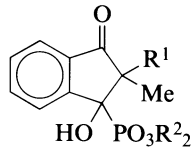

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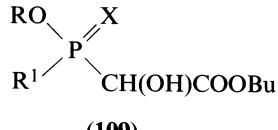

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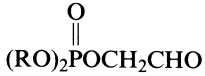

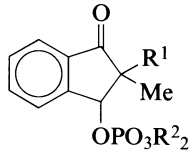

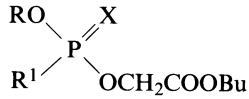

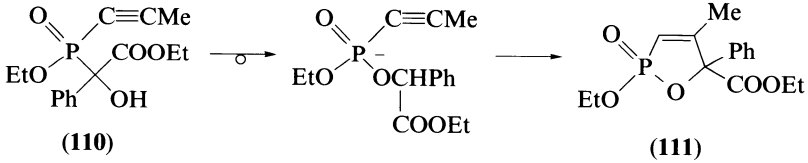

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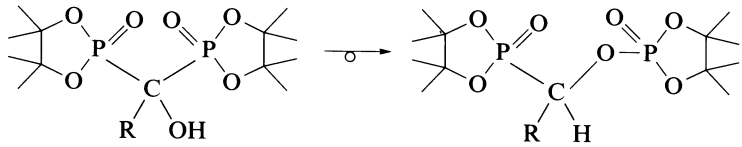

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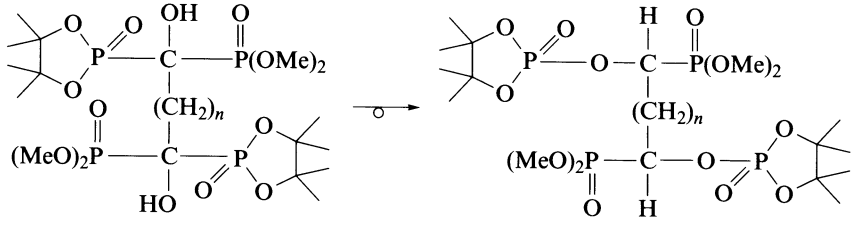
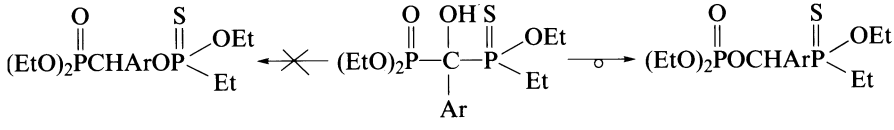


(114)

(115)

The rearrangement of (α-hydroxyalkyl)phosphonate into phosphate ester is not universal: (1-hydroxy-2-nitroalkyl)phosphonic esters do not rearrange under the influence of heat whether aided, or not, by added base[169] and the reaction between $(MeO)_2P(O)H$ and MeCOCH=CHPh at 130–160 °C yields the 1,2-adduct (**105**; R = Me) which is stable to base (MeO^- or Et_3N)[170]. On the other hand, **105** (R = H) partially decomposes in the presence of MeO^- and the products include the phosphate **106** together with methyl cinnamate and cinnamyl alcohol, as might be expected from the action of base on cinnamaldehyde[171]. Other compounds which undergo base–catalysed rearrangements include **107**[172], the indanones **108** (R^1 = H or Me)[173,174], the hydroxy phosphinic esters **109** (X = O or S, R^1 = Et or OR, R = alkyl)[175] and the phosphonate from the rearrangement of **110** undergoes an intramolecular Michael reaction under the influence of the base catalyst to give the 1,2-oxaphosph(V)ol-3-ene **111**[176]. The conventional rearrangement of **112** into **113** is catalysed by Et_3N at room temperature[177], whereas the rearrangement of the esters **114** (n = 3–8) is said to give the products **115** indicated rather than those from an alternative mode of uniform or mixed isomerization[178].

(Hydroxymethylene)bisphosphonic acids or related compounds such as **116** which possess one thiophosphoryl centre undergo a regiospecific rearrangement with the migration of the phosphoryl (as opposed to the thiophosphoryl) group[179]. The action of a base on esters of (2,2,2-trichloro-1-hydroxyethyl)phosphonic or related phosphinic esters **117** brings about rearrangement coupled with dehydrochlorination[180–182]. The action of trifluoroacetic anhydride on dialkyl hydrogenphosphonates in a hydrocarbon solvent at 10–20 °C gives the compounds **118**[183].



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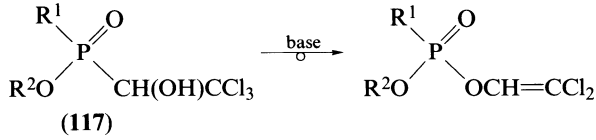

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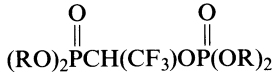
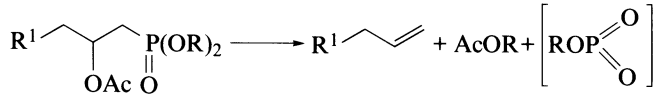


(118)

Little is known about the stereochemical changes which accompany the phosphonate–phosphate rearrangement, and what is known relates only to the carbon moiety. The rearrangement of diethyl (*R*)-(+)- and (*S*)-(–)-(1-phenylethyl)phosphonates in various organic solvents (pure or as mixtures), sometimes containing up to 7% water, and containing KOBu^t–KOH, or dbu as base, proceed with retention of configuration at carbon. The highest enantiomeric excess in the product was observed for aqueous dmso in which the concurrent cleavage of ester into diethyl hydrogenphosphonate and acetophenone predominated and the actual yield of phosphate ester was only about 80%; there is obviously a correlation between the optical purity of the product phosphate and the relative extents by which it is synthesized by rearrangement on the one hand, and cleavage with recombination on the other[184]. It might also be noted that, using the same system of compounds,

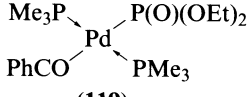
the reverse phosphate-to-phosphonate rearrangement has been shown to occur, once again with retention of configuration at carbon[185].

Dialkyl [(2-acyloxy)alkyl]phosphonates, neat or in solution, undergo a fragmentation–rearrangement process when pyrolysed at ca 220–240 °C; the overall reaction, represented in equation 7, results in moderate to high yields of alkenes and of acetic esters[186,187]. A similar decomposition occurs under ultraviolet irradiation[188].



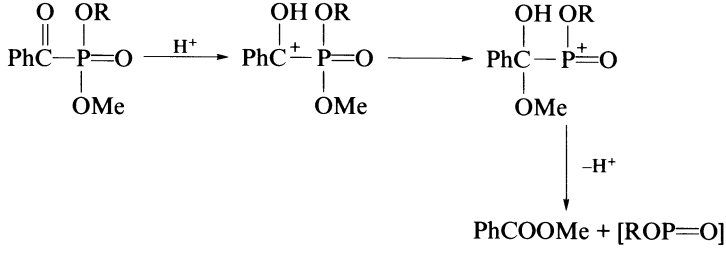
(7)

The decarbonylation of diethyl benzoylphosphonate occurs when the ester, in boiling toluene, is treated with a palladium phosphine complex; those examined and used successfully include $[Pd(PPh_3)_4]$ or were of the general form $[PdR_2(PR^1{}_nPh_{3-n})_2]$. The use of *trans*-$[PdEt_2[(PMe_3)_2]$ allowed the isolation of the crystalline complex **119**, and the product of the reaction was diethyl phenylphosphonate, produced in almost quantitative yield during 10–15 min[189]. A similar reaction for a dialkyl (1-oxoalkyl)phosphonate requires up to 72 h. It is also interesting that if a mixture of two esters $RCOP(O)(OR)_2$ and $R^1COP(O)(OR^1)_2$ is so treated, the product contains the corresponding decarbonylated esters, and also $R^1P(O)(OR)_2$ and $RP(O)(OR^1)_2$[190].



(119)

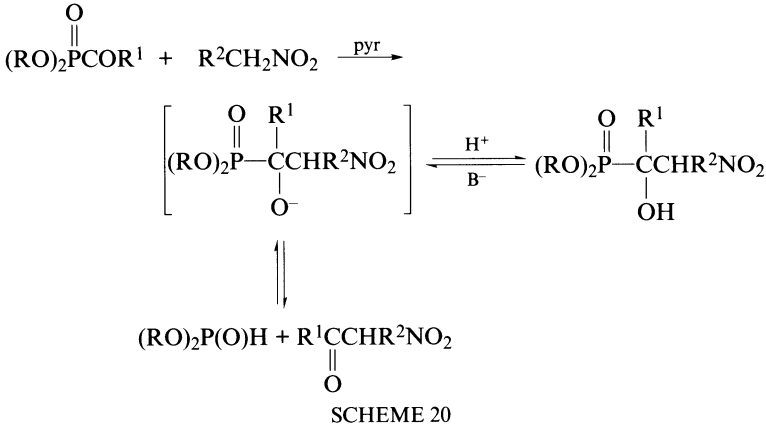
The phosphorus–carbon bond in acylphosphonates is cleaved by simple nucleophiles as the result of their preferential attack at the carbonyl carbon atom; these reactions include attack by ethanol[191], ammonia[192] and simple aliphatic amines[191–194], aniline[195] or hydrazine[196], and in all cases the product is the *O*- or *N*-acylated compound produced alongside the phosphoric acid, $(RO)_2PO_2H$. The phosphorus–carbon bond is cleaved by acids or, better, by alkalis[197–201]; the reaction with alkalis appears to be initiated by hydration of the carbonyl group, and this is followed by deprotonation. Alkyl sulphonates and alkyl carboxylates are produced in reactions with alkanesulphonic acids[202] whereas reactions with mineral acids can be formulated as occurring at phosphoryl[200] or at carbonyl; in the latter case, the leaving group containing the phosphorus would depart as the species ROP=O (Scheme 19), which might then be trapped. Thus, in the reactions between a dialkyl benzoylphosphonate (R = MeO or CH_2CF_3) and alcohols, e.g. MeOH, the products are methyl benzoate and the dialkyl hydrogenphosphonate[203]. In general, the phosphorus–carbon bond is so susceptible to cleavage by a wide range of reagents that



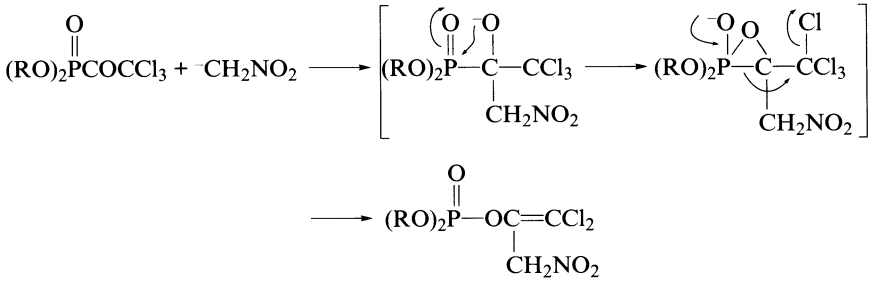
SCHEME 19

especially mild conditions are necessary in order to be able to obtain the free acylphosphonic acids from esters; these conditions include the stepwise demethylation of dimethyl esters by NaI in acetone or LiBr in MeCN[204,205]. In a recently reported example of the reactive nature of acylphosphonates, diethoxyphosphinoylmethanal, $(EtO)_2P(O)CHO$, has been shown to act as a formylating agent[206].

The course of the condensation between an acylphosphonate and a 1-nitroalkane carbanion depends on the nature of the acyl group. Base catalysts are commonly employed, but an acylphosphonate derived from an aromatic acid requires an acidic catalyst otherwise the intermediate anion fragments to hydrogenphosphonate and nitroketone (Scheme 20)[207]. The reaction between a nitroalkane carbanion and a dialkyl (trichloroacetyl)phosphonate results in a rearrangement to phosphate with additional dehydrochlorination (Scheme 21)[208].

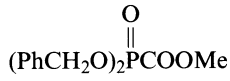


SCHEME 20



SCHEME 21

Under conditions of hydrolysis, methyl (dibenzylphosphinoyl)formate (**120**) loses ester groups from the phosphinoyl moiety (a minor reaction), but this is accompanied by the loss of carbon in the more extensive formation of dibenzyl phosphate and dibenzyl hydrogenphosphonate[209,210].

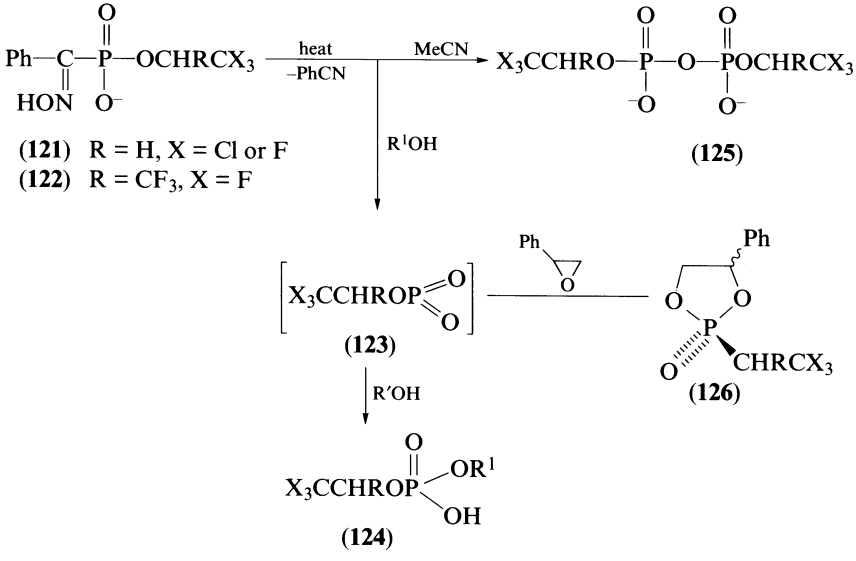


(**120**)

It is possible to obtain derivatives of acylphosphonic diesters when less basic nucleophiles are employed[211] or from preparations carried out in anhydrous media. Thus, the phenylhydrazones[212] and 2,4-dinitrophenylhydrazones of many esters are known[213], and hydrazones and methylhydrazones of diethyl (1-oxoalkyl)phosphonates have been satisfactorily obtained through reactions in acetic acid[214]. Hydrazones of (1-oxoalkyl)phosphonic diesters have been employed in the synthesis of (1*H*-indole-2-yl)phosphonic esters, and the derivatives from dialkyl (2-oxoalkyl)phosphonates have been used to make (1*H*-indole-3-yl)- and [2-(1*H*-indolemethyl)]-phosphonic esters by cyclization in polyphosphoric acid[212].

Oximes, which are valuable intermediates for the conversion of oxoalkyl phosphonic diesters into those of aminoalkylphosphonic acids (Chapter 4, Section IV.C.1.d), are also readily available, although it is necessary to prepare them with some care. Nevertheless, the feature of interest here is their ready degradability, particularly under aqueous conditions, and which has been intensively investigated by Breuer and coworkers. The necessity for care in the preparation of oximes of acylphosphonic diesters, is illustrated by the synthesis of dimethyl [α-(hydroxyimino)benzyl]phosphonate[215]; this compound exists in the thermodynamically more stable (*E*) form which, under the influence of acid is converted into the less stable (*Z*) form, and both forms have been separately characterized by X-ray crystallography. The geometric isomers of the oxime differ in their behaviour under basic conditions: with NaOH–MeOH, the (*E*) form undergoes monodealkylation, whereas the (*Z*) isomer decomposes to dimethyl phosphate and benzonitrile. In aqueous solution, (*E*)-[α-(hydroxyimino)benzyl]phosphonic acid also decomposes into benzonitrile together with phosphoric acid, in a manner which is pH dependent, and consistent with a dissociative mechanism that involves the early formation of monomeric metaphosphate[216].

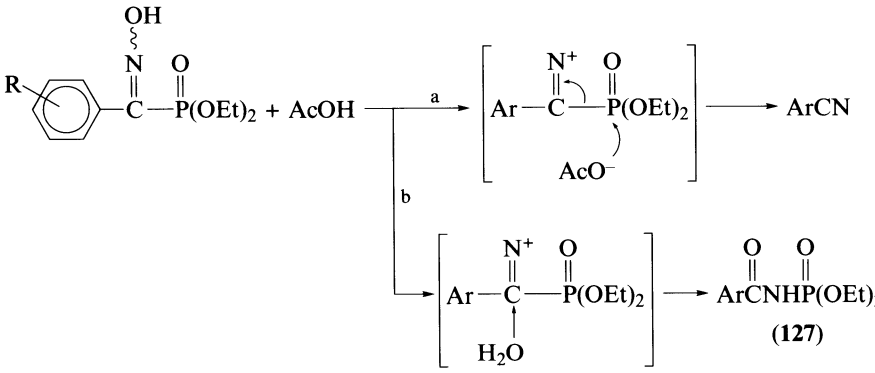
Monoalkyl esters of the same acid likewise decompose under acidic conditions to give benzonitrile and monoalkyl metaphosphates[217]. The nature of the solvent in which degradation occurs can have a profound effect on the course of such degradation; the predominantly (*E*)-oximes from the mono-2,2,2-trihaloethyl esters **121** and **122** of [α-(hydroxyimino)benzyl]phosphonic acid, as their anions, lose benzonitrile in boiling ethanol or propan-2-ol and yield mixed phosphodiesters **124** (R^1 = Et or Pr^i); (*E*)-(**121**) does



not decompose in water or methanol although in boiling aprotic solvents (e.g. MeCN or thf) a diphosphate dianion **125** is formed together with benzonitrile[205]. In the case of the decomposition of **121** (X = F), the intermediate metaphosphate **123** was trapped through its reactions with the alcohol R^1OH to give the unsymmetrical dialkyl phosphate **124**, and with styrene oxide to give the corresponding 1,3,2-dioxaphosph(V)olane **126** as a mixture of stereoisomers[209].

In general, simple monoester anions are stable in boiling MeCN for 30 h, but the corresponding dianions have a tendency to undergo fragmentation; the presence, in the ester grouping, of a strongly electron–withdrawing constituent results in a marked increase in instability of the molecule as a whole.

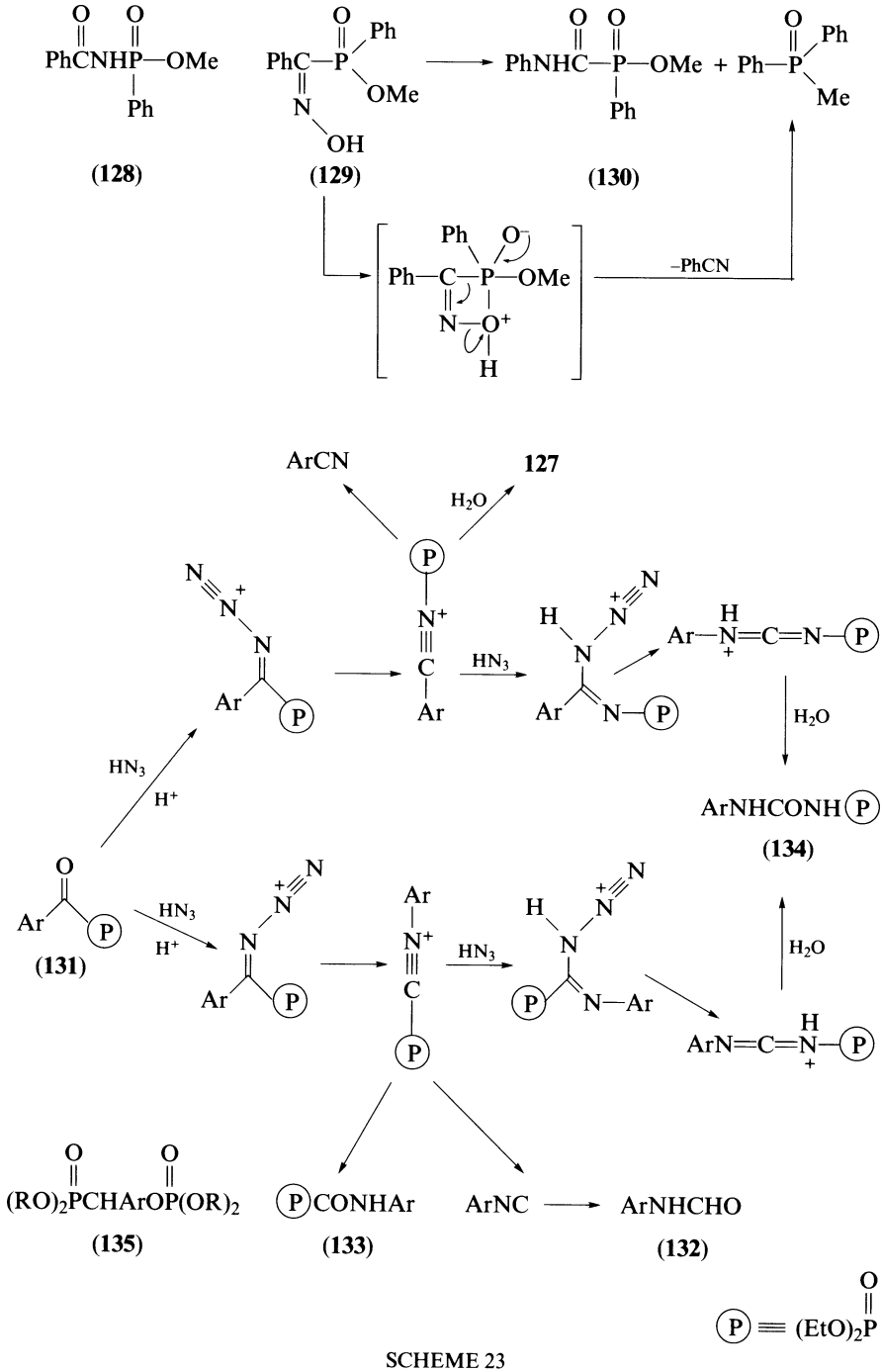
Dimethyl [α-(hydroxyimino)benzyl]phosphonate is stable in mineral acid but decomposes in formic acid containing formate with the liberation of benzonitrile, but otherwise the behaviour is different from that in boiling acetic acid when an additional product, a phosphoramidate ester, is obtained by a Beckmann rearrangement. For the oximes of the (4-methoxybenzoyl)- or (4-chlorobenzoyl)-phosphonic esters, only the phosphoramidate diester **127** is obtained, but for all the substrates examined [additionally the unsubstituted benzoyl- as well as the (4-methylbenzoyl)phosphonic derivatives], the formation of the phosphoramidate ester demonstrates a high migratory aptitude of the phosphinoyl group (Scheme 22)[218].



SCHEME 22

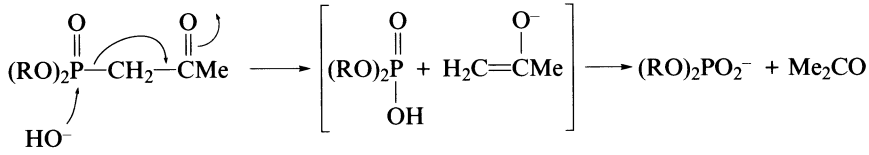
Breuer's group[219] also observed the participation of the Beckmann rearrangement in the decomposition of the (*E*)-oxime of methyl (benzoyl)phenylphosphinate with the formation of the methyl *N*-benzoyl-*P*-phenylphosphonic amide **128** as the sole product; the (*Z*)-oxime **129** decomposed to benzonitrile, methyl hydrogen phenylphosphonate and the carbamylphosphinate **130**.

In spite of the propensity of acylphosphonic diesters and the parent acids to undergo cleavage reactions with a wide range of basic nucleophiles, and under a variety of experimental conditions including those of hydrolysis, it was found possible to observe Schmidt reactions (Scheme 23); these require strongly acidic, and therefore potentially hydrolytic, media. In practice, solutions of the acylphosphonate diester in $CHCl_3$ were treated with an excess of hydrazoic acid in the presence of sulphuric acid. As a result, benzoyl- or substituted benzoyl-phosphonic esters (**131**) yielded the phosphoramidates **127**, **132** (the only substantial product from esters of benzoylphosphonic itself) and ArCN as the main products, although not all three compounds were obtained from all of the substrates examined. Minor products included $ArNH_2$ and the esters **133** and **134**, and the carboxylic acid RCOOH was sometimes a trace product together with an ester **135**, obtained, it was


PhCNHP—OMe
Ph
(128)
PhC—P
Ph
OMe
N
OH
(129)
PhNHC—P—OMe + Ph—P
Ph
Me
(130)
-PhCN
ArCN
127
H2O
HN3
H+
Ar
(131)
ArNHCONH
(134)
(RO)2PCHArOP(OR)2
(135)
CONHAr
(133)
ArNC
ArNHCHO
(132)
(EtO)2P

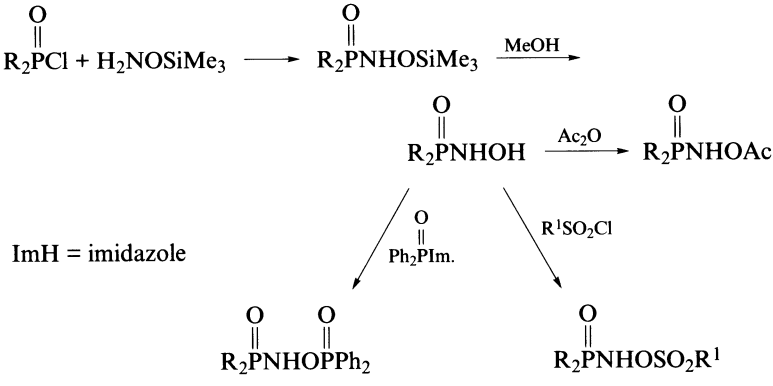
SCHEME 23

suggested, by the rearrangement of the appropriate (1-hydroxyalkylidine)bisphosphonic ester[220]. It should be emphasized that the cleavage of (oxoalkyl)phosphonic derivatives by nucleophiles is by no means restricted to that of the acyl (i.e. 1-oxoalkyl)phosphonic group, but is found also for those of the (2-oxoalkyl)phosphonic series, for which P—C bond fission (Scheme 24) may accompany normal de-esterification at phosphorus[123,221].

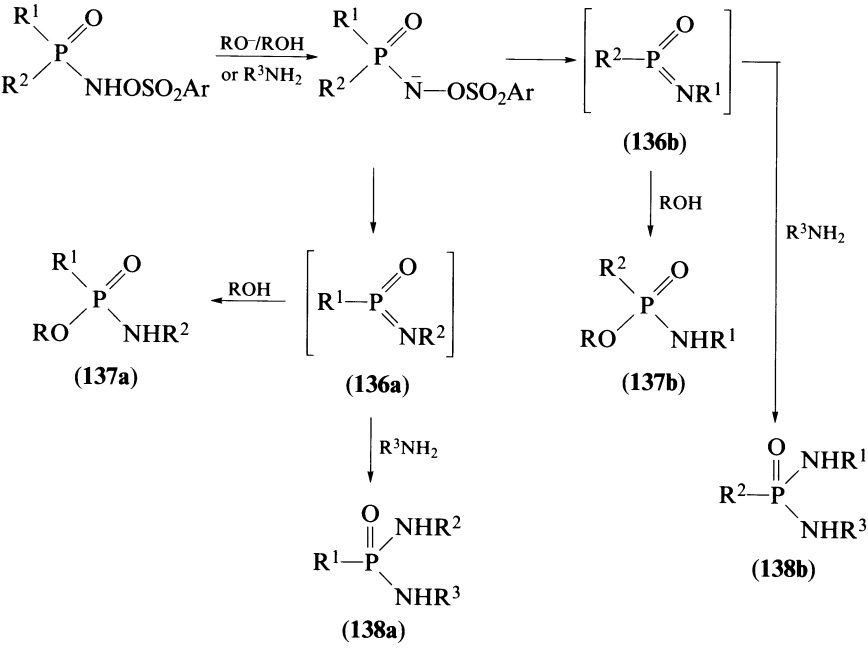


SCHEME 24

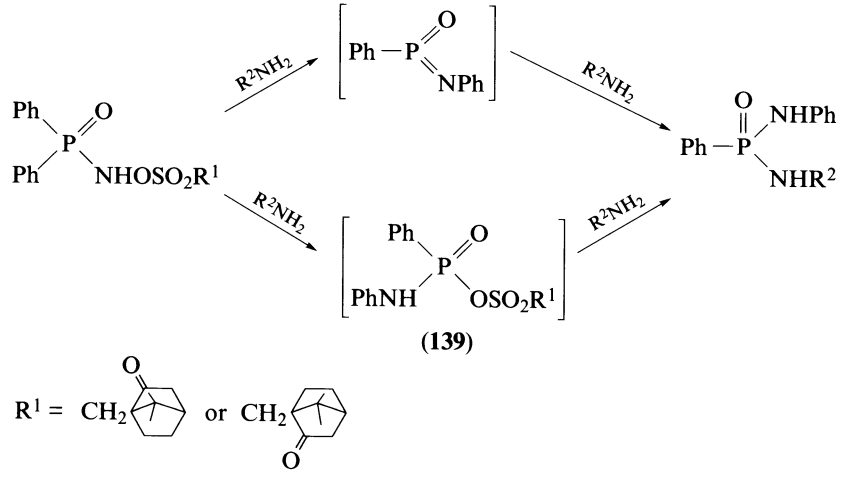
In a further development by Harger and coworkers, phosphorus–carbon bond fission was observed in the Lossen-like base-promoted rearrangement of *O*-sulphonic esters of *N*-phosphinoylhydroxylamines; overall, the picture is reminiscent of that of the photolytic cleavage of phosphinic azides. The substrates have to be prepared through a slightly involved route (Scheme 25)[222–225]; the methodology is general and *O*-acyl and *O*-phosphinoyl derivatives are similarly obtained[222,226]. When the *O*-sulphonyl-*N*-phosphinoylhydroxylamine is treated with an alkoxide base, proton loss is followed by the migration of one of the phosphorus-bonded carbon moieties to nitrogen; the main product from such a rearrangement consists of a phosphonamidic ester **137**. A mechanism based on the formation of a pentacoordinate intermediate has been considered but one based on deprotonation and the intermediary formation of a tricoordinate phosphonimidate species **136** (compare this with the photolysis of phosphinic azides) is preferred (Scheme 26). In principle, a single product is obtained when the organic groups are identical, but otherwise two isomeric phosphonamidic ester products become theoretically possible. The cleavage–rearrangement can also be initiated by an amine in place of alkoxide, in which case the product(s) consist(s) of a phosphonic diamide **138**, either symmetrical or unsymmetrical[227]. The rearrangement of a substrate in the presence of an amine has provided recent evidence that an alternative mechanism might perhaps play a small part in the overall scheme; *N*-(diphenylphosphinoyl)-*O*-(camphor-10-sulphonyl)hydroxylamine, from either the (+)- or (–)-camphor-10-sulphonyl chloride, rearranged in the presence of a primary amine (R^2 = Me or Bu^t) to give a diamide product (Scheme 27) which was found to exhibit a low optical activity. In the event that R^1 is chiral, as it is in the present case, then an optically



SCHEME 25



SCHEME 26

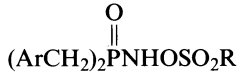


SCHEME 27

active phosphonic diamide product must be derived from a diastereoisomeric intermediate, possibly a mixed phosphonic–sulphonic anhydride **139**, possibly formed from the hydroxylamine-based substrate with a slight imbalance in its stereoisomeric composition[228].

Attention has been focused on two aspects of the reaction, namely the relative migratory aptitudes of different carbon groups and the effect of a change in the sulphonate leaving

group. For a series of *N*-(arylphenylphosphinoyl) *O*-methanesulphonates, preferential migration of the aryl group relative to phenyl is encouraged by electron-releasing substituents (e.g. 4-MeO and 4-Me by factors of 30–35 and 3, respectively and retarded by electron-withdrawing substituents (e.g. 4-Cl and 4-NO_2 by factors of 0.7 and 0.06, respectively)[223]. Benzyl groups appear to migrate less readily than do aryl groups, and consequently non-migratory competing reactions assume a greater significance. Thus, in the presence of R^1O^- (R^1 = Pr^i or Bu^t) in R^1OH, the compound **140** (R = Me, Ar = 4-methylphenyl) yields 70–80% of the expected **141**, but with R^1 = Me or Et, competing solvolyses lead to **142** and **143**, the migration process accounting for much lower yields of phosphonamidic ester products[229]. The observed migration of a benzylic group is of some significance since it demonstrated that the migrating centre can be based on sp^3 carbon, and need not be based on an involvement of π electrons. The substrate **144** (Ar = 4-methylphenyl, R = Me) with methoxide in MeOH underwent solvolysis to **145** and migration of the phenyl nucleus to give **146** (but not **147**) in the ratio of 1:10[225]. The *N*-[(4-nitrobenzenesulphonyl)oxy] derivatives from diethyl- and isopropylmethyl-phosphinic amides rearrange quantitatively with Bu^tO^- in Bu^t OH (the migratory aptitudes of methyl and isopropyl are very close), and the derivative from diisopropylphosphinic acid rearranges readily when R^1 = Bu^t but not when R^1 = Me, Et or Pr^i; however, the migration of alkyl groups cannot compete when an aryl group is also present[230]. The benzyl group has a tenfold preference for migration over all other alkyl groups[231]. The phosphonamidic derivatives **148** (R = 4-nitrophenyl) suffer phenyl migration under the influence of *tert*-butylamine[232]. Also, under the influence of methanolic methoxide, the compounds **149** (R = Me, R'_2 = Ph,H or Me_2) do not undergo phenyl migration, but the amino moiety as a whole suffers transfer from phosphorus to nitrogen[233].



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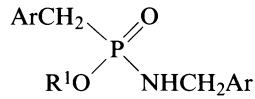

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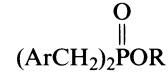

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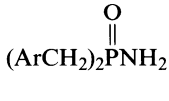

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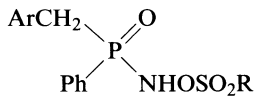

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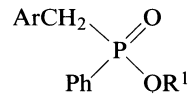

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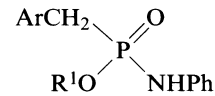

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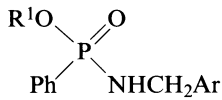
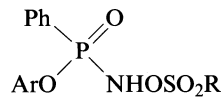


(147)



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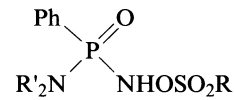


(149)

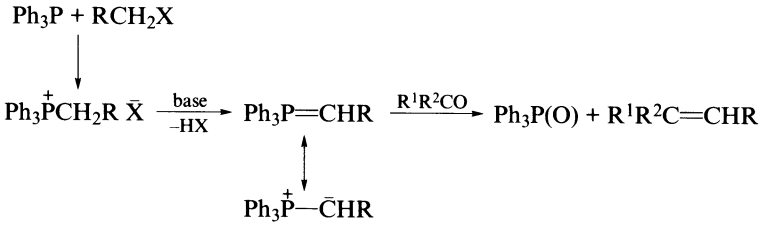
Compound **150** (analogous sulphonate esters are unstable) with NaOMe in MeOH gives diphenylphosphinic amide as the main product, thought to be reached via **151** (tentatively identified) together with diphenylphosphinothioic acid as a minor product[234].

Probably the best known of all the many reactions which result in the cleavage of a phosphorus–carbon bond is one which is based on the Wittig reaction. The Wittig reaction consists in the interaction of a triphenylphosphonium ylide and an aldehyde or ketone, the outcome of the reaction being the formation of a tertiary phosphine oxide together with an

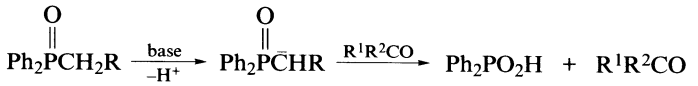
(150)

(151)

alkene. Commonly, the ylides are derived by the action of a base on the quaternary phosphonium salts obtained from triphenylphosphine; the essential practical steps of the reaction are represented in Scheme 28. Since its discovery, the realization of the scope and importance of the original Wittig reaction as a means of creating carbon–carbon bonds in organic synthesis has prompted an apparently never-ending search to discover new variations in attempts to control the outcome of a reaction, particularly with regard to stereochemistry. One such attempt depends on the use of the carbanion **152** from a tertiary phosphine oxide in which the contribution in the ylide of the positive phosphorus is replaced by the polarization ($P^{\delta+}$) in the phosphoryl bond: this particular variation has come to be known as the Horner reaction (reaction 8) and has been discussed elsewhere[25].



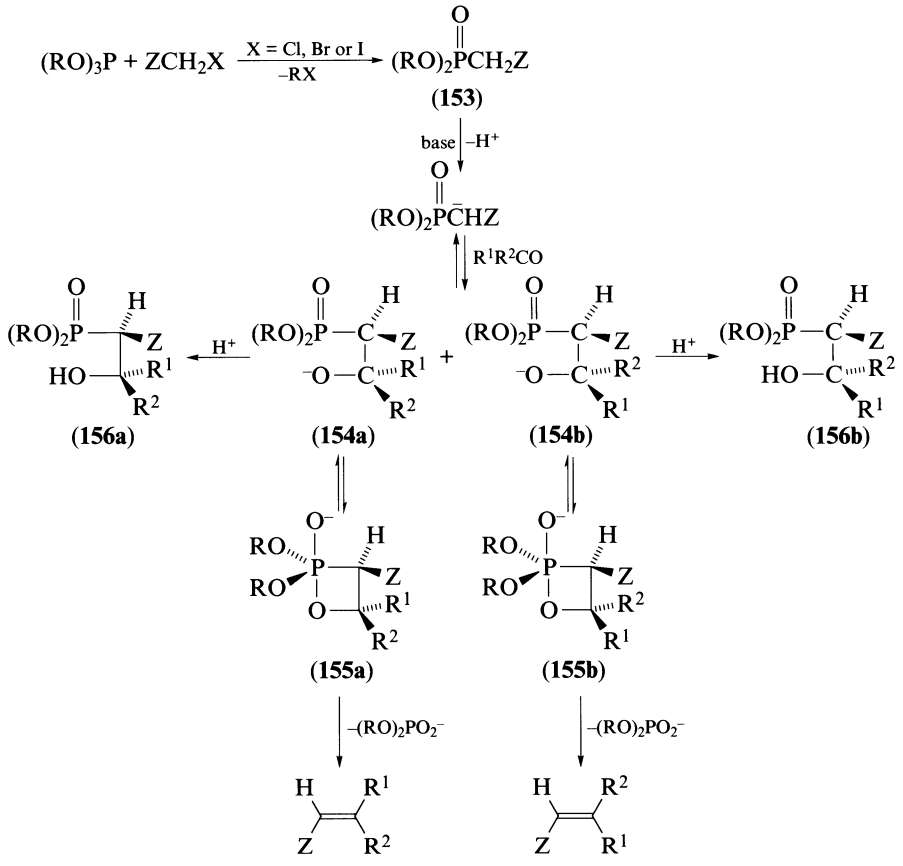
SCHEME 28



(152) (8)

A second variation, although stemming from original observations reported by A. E. Arbuzov and Dunin in 1927[235] that triethyl phosphonoacetate can be deprotonated by a suitable base to give a carbanion, is even more closely linked to a report by Horner *et al.*[236] that the anion obtained from diethyl benzylphosphonate by reaction with sodamide, yielded triphenylethene when treated with benzophenone. It was W. S. Wadsworth and W. D. Emmons[237] (after whom this variation reaction is currently and widely named, although some credit ought to go to Horner) who enlarged the scope of the procedure and drew attention ot its potential in conventional organic synthesis. Although the Wadsworth–Emmons–Horner (henceforth abbreviated to WEH) procedure, together with the original Wittig reaction and the Horner phosphine oxide modification, are regarded first and foremost as means for the construction of alkene bonds, the WEH reaction will be considered here simply as a means by which cleavage of the phosphorus–carbon bonds in a very wide range of phosphonic (and also phosphinic) acid derivatives can be achieved. The extensive uses of the reactions have been repeatedly reviewed[238–242] and, together with those of the Wittig reaction itself and the Horner modification, were also reviewed recently[243] and are reviewed annually[244].

In general (Scheme 29), the phosphorus–containing reactant consists of a phosphonic acid derivative with at least one free α-hydrogen atom on the carbon ligand—generally a diester, although amides and other derivatives have been used, all of which are converted into a carbanion. The phosphorus reactants **153** (Z = H, alkyl, cycloalkyl, aryl, heteroaryl, COR′, COOH, COOR′, COSR′, $CONR'_2$, CN, F, Cl, Br, OR′, CX_3, CHX_2, CH_2X (X = F



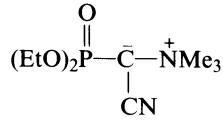
SCHEME 29

or Cl), CH=CHR′, CH_2SiMe_3, SR′, SOR′, SO_2R', $SO_2NR'_2$, SeR′, NHR′ or NHCOR′, etc.) are (generally) readily available by means of reactions between appropriate organic halides and trialkyl phosphites, and lead to products which, very often, are of such a high degree of purity that they are frequently used *in situ*. Of particular interest from the viewpoint of the organophosphorus chemist are the compounds **153** in which Z = $P(O)(OR)_2$ or $P(O)R_2$. The ester, in a solvent (usually diethyl ether, dioxane, thf or benzene), is then deprotonated by a base; this is commonly NaH, BuLi, PhLi or KOBu′, but others, including $NaNH_2$, Et_2NLi, NaOMe, NaOEt, Pr'_2NLi, $(Me_3Si)_2NLi$ and, more recently, LiOH[245], have all been employed. The carbonyl reactant is added at a low temperature (– 78 °C) or at room temperature depending on the reactivity within the system. Later developments include the use of two-phase systems (liquid–liquid or liquid–solid) with tetrabutylammonium salts or crown ethers as phase-transfer catalysts, or with $MHCO_3$ or M_2CO_3 (M = K or Cs) in an organic solvent. The use of an amine as base is not so successful, generally, since other processes (e.g. the Knoevenagel condensation, to be considered later, Section V.B) then tend to occur, although dbu and Et_3N have been more recently, and successfully, employed in the presence of LiCl[246,247]. Other methodologies include the application of ultrasound, and also an electrochemical approach; in the latter, deprotonation occurs at a

platinum or vitreous carbon cathode, and the carbanion reacts in MeCN containing $Et_4N^+Br^-$; the yields of alkenes have been reported to be moderate to good[248].

The initial step in the WEH procedure has long been considered to be the formation of the isomeric adducts **154**, which then yield isomeric 1,2-oxaphosph(V)etanes **155**; the latter subsequently collapse with the generation of stereoisomeric alkenes, and the phosphorus is set free as water-soluble $(RO)_2POO^-$. The evidence for the order of the steps, and the nature of the actual intermediates, is sparse and conflicting, and neither the initial adducts **154** nor the 1,2-oxaphosph(V)etanes **155** have been detected during the course of such reactions (see, however ref. 264 discussed later), although the careful protonation of selected adducts has led to the isolation of stereoisomeric dialkyl (2-hydroxyalkyl)phosphonates **156** (Chapter 3, Section III.B); the latter can also act as sources of the alkenes otherwise available without isolation of the intermediate. The order of the proposed steps has recently been queried, and it has been suggested that the relative positions of oxaphosph(V)etanes and betaines might be interchanged.

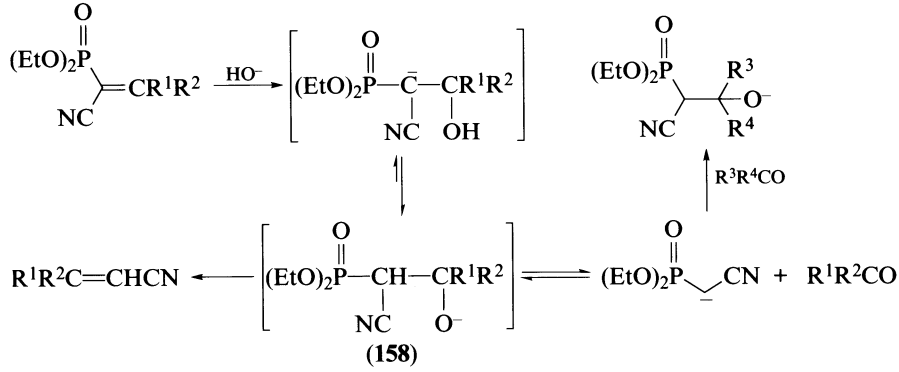
In a minor variation, the possession of an appropriately positioned carbonyl group by the phosphonic derivative, can lead to simultaneous expulsion of the phosphinoyl moiety with carbon–carbon double bond formation coupled with cyclization[249,250]. Although the ylide **157** can be alkylated on carbon (like the carbanion prepared by Arbuzov and Dunin), with simultaneous expulsion of the diethoxyphosphinoyl moiety (unlike the phosphorylated carbanion), no reaction takes place between **157** and an aldehyde or ketone[251].



(157)

The various steps in the overall sequence will here be considered individually, but only briefly, and no attempt will be made to indicate the scope of the WEH procedure which, as has already been indicated, has been widely reviewed. The aldol condensation which leads to the ions **154** is considered to be essentially reversible, a feature which has been observed in the reactions between diethyl (prop-2-enyl)phosphonate anion and aromatic aldehydes[252,253]. Reversibility has also been demonstrated in a variety of other reactions that include crossover experiments, based on the system from benzaldehyde and **153** (Z = CN or COOMe) into which a more electrophilic aldehyde is added; this results in the incorporation of the latter into products in such a way that the dissociation of the phosphonate–benzaldehyde adduct must have occurred[254,255]. The addition of an aldehyde to a deuterium-labelled adduct in the presence of NaOEt–EtOH affords a mixture of labelled and unlabelled alkenes in the ratio of ca 1:1[256]. The product (**158**) from the interaction of HO^- (Na_2CO_3 in EtOH–H_2O) and a dialkyl (α-cyanoethenyl)phosphonate decomposes into the expected alkene, but also dissociates into a carbonyl compound together with a carbanion; the latter can then be trapped by the addition of a different aldehyde or ketone (Scheme 30)[257].

As indicated above, (β-hydroxyalkyl)phosphonic diesters can be obtained by protonation of the ions **154** under carefully controlled conditions, and the formation of such products (unaccompanied by an alkene) has been observed directly in the interaction of benzophenone and the anion from diethyl methylphosphonate, and also from dialkyl (prop-2-enyl)phosphonate anions and aldehydes under kinetic control[252,253]. The ionic intermediates, such as **154** (Z = Ph, CN or COOEt) from PhCHO, are stabilized in the presence of lithium or magnesium ions, so aiding in the isolation of the corresponding (β-hydroxyalkyl)phosphonic diesters[258]. The addition of KOBu^t to **154b**, prepared by an independent route, produces the orange colour characteristic of the ions from **153**; more-

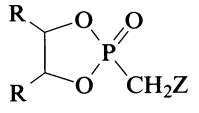


(158)

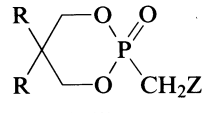
SCHEME 30

over, the hydrolysis of such a mixture not only produces the carbonyl reactant (in this case PhCHO) and the phosphonate **153** (Z =Ph) but also (*Z*)-stilbene, rather than the *E*-isomer expected from the direct decomposition of the adduct **154b**[259].

The ease of collapse of the species **154** to the alkene, either directly or via an oxaphosphetane (**155**) depends, at least partly, on the electrophilicity at phosphorus. This can be reduced by the replacement of the two RO groups by alkyl groups[260], or increased by their replacement by a cyclic system containing the phosphorus atom; for a given group Z (with reaction rates decreasing in the order Z = CN > COOEt > 4-nitrophenyl), compounds based on the substituted 1,3,2-dioxaphospholane **159** (R = Me) and 1,3,2-dioxaphosphorinane **160** (R = Me) rings undergo faster overall reaction with PhCHO–EtO$^-$. An interpretation of the rate enhancement by the dioxaphospholane ring (this particularly) rests on the formation of a pentacoordinate intermediate which releases the inherent strain in the ring (see Section VI for further discussion)[261–263]. It was for such a system that a ^{31}P NMR spectroscopic study of the reaction between **159** (Z = COOEt) and benzophenone revealed signals which could ascribed to the starting material, to the intermediate **154** and the cyclic phosphate decomposition product and, in addition, one ascribable to a pentacoordinate species, possibly **161**[264].



(159)



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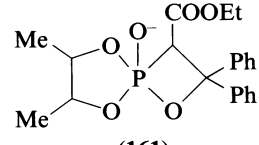
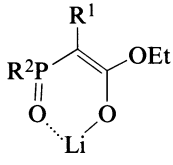


(161)

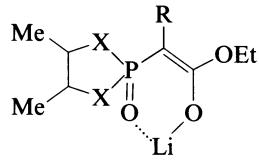
The reduction in electrophilicity of phosphoryl phosphorus in bis(dialkylamides) of phosphonic acids also hinders the collapse of the intermediate ions and facilitates the isolation of (*β*-hydroxyalkyl)phosphonic acids as their diamides, although both normal reactivity as well as a complete lack of reactivity, have been observed[265].

Ultimately, those factors which influence the outcome of the WEH reaction are linked to, and are a measure of, the stability of the phosphorus–carbon bond in equilibria between carbanion and carbonyl reactant. In general, dialkyl phosphonate carbanions (**162**; R = EtO) in their reactions with either aliphatic or aromatic aldehydes yield (*E*)-alkenes, whereas carbanions based on the 1,3,2-dioxaphosph(V)olane **163** (X = O) or the 1,3,2-dioxaphosphorinane ring **164** (X = O) may reverse the relative amounts of the (*Z*)- and (*E*)-alkenes, in this case from ca 1:2 to ca 2:1[262]; no reaction at all was observed in this instance

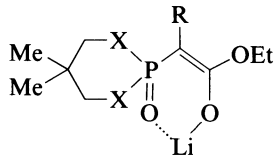
for **162** (R = Me_2N) or for **164** (X = MeN), but **163** (X = MeN) afforded products in the ratio of 3:1[266]. A reduction in the product *Z*:*E* ratio, and even a reversal, has also been observed with bis(2,2,2-trifluoroethyl) esters relative to dimethyl esters[267]. The nature of the group Z also influences the stereochemical composition of the resultant alkene to some extent. Compound **153** (Z = CN) produces more (*Z*)-alkene than does **153** (Z = Ph or COOEt), and the presence of a second substituent on the α-carbon atom of the phosphonate ester tends to lower the total yields of alkene but increase the *Z*:*E* ratio in reactions with branched-chain aliphatic aldehydes[268] although not with ArCHO (the opposite effect is observed for compounds with a single substituent at $C_{(1)}$[262]. Ketones also tend to yield more of the (*Z*)-alkene. A high degree of stereoselectivity is experienced in the use of the enantiomers of the diazaphospholidine **165** (the *R*,*R*-stereoisomer is shown); the anion from (*R*,*R*)-**165** is reactive to (*R*)-3-methylcyclohexanone to give the (*E*) (*R*)- and (*Z*) (*R*)-products in the ratio 93:7, reversed to 15:85 when (*S*,*S*)-**165** is employed[269].



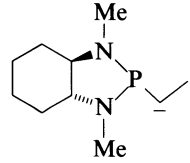
(**162**)



(**163**)

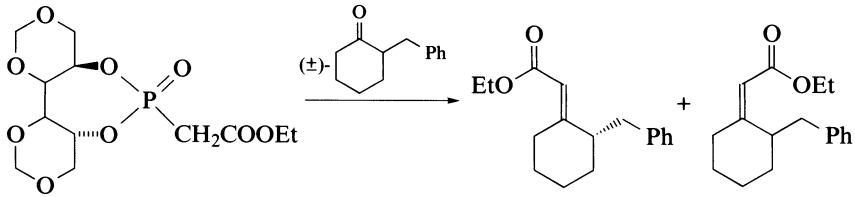


(**164**)

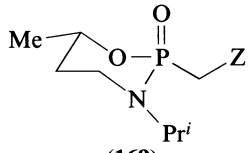


(**165**)

In a substrate such as phosphonoacetic acid, chiral ester groups on either carboxy or phosphono moieties can induce stereoselectivity in reaction products. Enantiomeric ester groups on carboxy in dimethoxyphosphinoylacetic acid produce opposing *E*:*Z* ratios of products[270]; the phosphonate substrate **166**, derived from mannitol, undergoes a WEH reaction with racemic 2-benzylcyclohexanone at 0 °C to give 9–56% of (*S*)-**167** with 39–89% enantiomeric excess, 2–11% of **168**, and 29–89% of (*R*)-2-benzylcyclohexanone with 3–34% enantiomeric excess, depending on the base, solvent, and any additive (e.g. lithium salt or hmpa)[271]. Denmark and Chen[272] employed the carbanion from the phosphonic amide **169** (Z = Ph); the anion from a pure stereoisomer with a 4-substituted cyclohexanone gave the (β-hydroxyethyl)phosphonic amides **170** (R = Bu^t, Me, Ph or $COOBu^t$) in 94–98% yields, which were decomposed by $KOBu^t$, for example, although with poor



(**166**) (**167**) (**168**)



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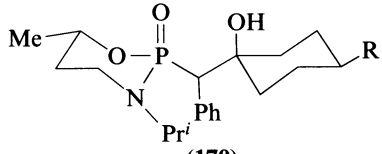
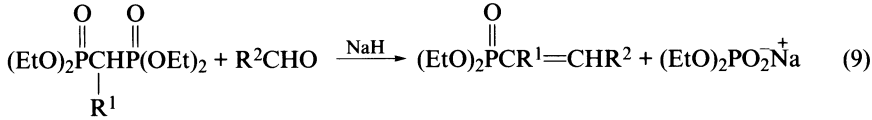


(170)

results, and a much better procedure involved a trityl salt such as Ph_3COTf, when the (*S*)-alkene was obtained with very high enantioselectivity.

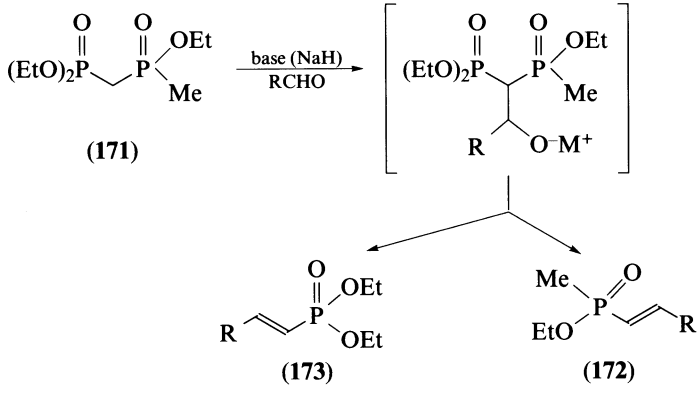
Two other features which have been found to influence the final reaction outcome are the nature of the reaction solvent and the individual metal counter ion. The effects of the first are varied, and the latter is also important since, for example, in reactions which involve dialkyl (2-oxoalkyl)phosphonates, lithium and magnesium ions tend to form complexes[247,273–277] whereas sodium and potassium ions do not. In reactions between acetone and the anion from (prop-2-enyl)phosphonic bis(dimethylamide) and BuLi, the presence of zinc or cadmium ions alters the site of attack from only $C_{(3)}$ to a mixture of $C_{(1)}$ and $C_{(3)}$ in the ratio 3:1[278]. Dialkyl (lithioalkyl)phosphonates which lack complexing functions may be rather unstable, or may dimerize within minutes at 0 °C[279].

As already repeatedly indicated, the WEH reaction is by no means restricted to the use of esters of monophosphonic acids. Esters of alkylidenebisphosphonic acid have proved to be popular in the synthesis of (alk-1-enyl)phosphonic acids according to equation 9[275,280].

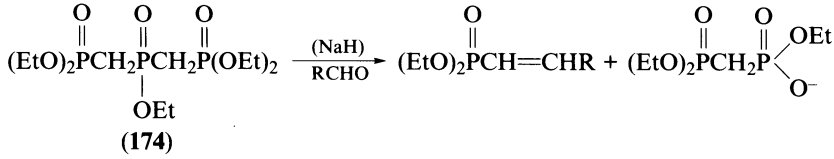


(9)

Diesters of phosphinic acids have also received attention. When both phosphonic and phosphinic ester moieties are present in the same substrate molecule, the question is naturally raised as to which of the two phosphinoyl moieties will be expelled and which will remain attached to carbon. Perhaps the simplest system to be studied is also the most recently reported. Thus, in reactions between **171** and aliphatic aldehydes or benzaldehyde in diethyl ether with $MgBr_2$ and Et_3N, it is the phosphonate moiety which is preferentially eliminated to leave the methylphosphinic esters **172**[281], although with other bases such as NaH, KOBu^t or BuLi, all in thf, the balance of this reaction and that giving the alternative **173** is more equitable. For the slightly more complex case of **174** with RCHO (R = Ph or Pr^i), the preferential fission occurs to liberate the phosphinate moiety[282,283].



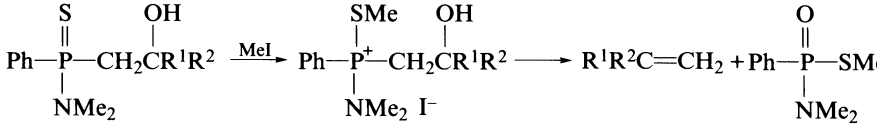
(171) (173) (172)



(174)

The use of carbanions from phosphonothioic esters has been little studied, but one potential advantage, particularly with regard to non-stabilized carbanions, appears to lie in easier elimination therefrom[284,285].

Phosphonic mono- and di-amides have been widely examined as substrates in the WEH reaction with the considerable success in the use of their carbanions in the non-stereoselective synthesis of (β-hydroxyalkyl)phosphonic diamides the result of decreased electrophilicity of the phosphorus atom. The fission of such diamides occurs when they are heated in a high–boiling solvent[278,286–289]; the separated *threo* and *erythro* stereoisomers from, for example, benzylic phosphonic diamides undergo decomposition into (*E*)- and (*Z*)-alkenes, respectively, although the exact mechanism is unclear[288]. The successful release of alkene from the thiophosphinic amide **175** is possible after methylation to **176**; the yields of unsymmetrical disubstituted alkenes are 50–99%, and even for tri- and tetra-substituted alkenes yields of 53–93% are achievable[290].



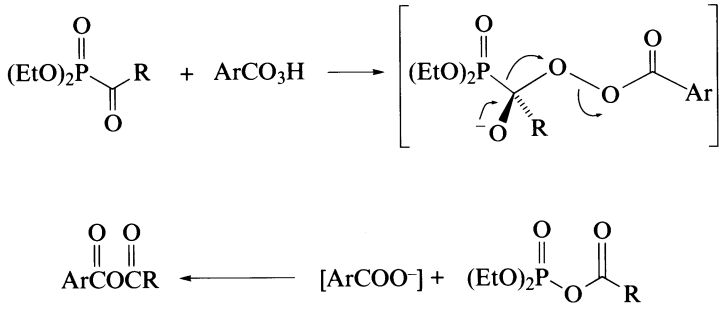
(175) (176)

A long and detailed theoretical analysis of the behaviour of the lithiated anions from both cyclic and acylic phosphonic diamides has recently been presented, and their reactivity has been discussed in terms of relative conformations of nitrogen lone electron pairs, phosphoryl bonding and anionic charge[291].

Although the original Wittig reaction and the WEH modification often have no major stereochemical advantage over each other, occasionally it is otherwise[292], and the two procedures generally serve to complement each other, each reaction having its own advantages. For the WEH reaction, the starting materials are cheap and easy to prepare; the main by-products are water soluble, and so easy to separate; and the phosphonate and phosphinate carbanions are more nucleophilic, and so generally more reactive, than the phosphonium ylides. On the other hand, the phosphonates require stronger bases for the deprotonation step (some ylides require only aqueous carbonate solutions, and many are so stable as to be isolable, and very often commercially available), and the stronger bases may then lead to unwanted side reactions, sometimes of a self-condensation nature.

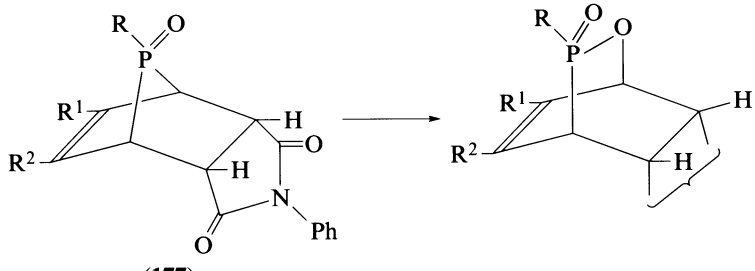
Together with the original Wittig reaction, the WEH modification currently enjoys widespread popularity in the synthesis of a wide range of compound types.

The treatment of diethyl aroylphosphonates with 3-chloroperoxybenzoic acid yields diethyl aroyl phosphates (oxygen insertion) in 70–85% yields together with smaller amounts of mixed carboxylic anhydrides, ethyl benzoate and diethyl hydrogenphosphate (Scheme 31). The main reaction is a typical Baeyer–Villiger oxidation, applied here to an acylphosphonate[293]. The reaction generally has little value in the synthesis of acyclic mixed anhydrides, which are easily obtained by other procedures, but it is of value in some slightly modified but specific cases as, for example, in the synthesis of compounds in the 2,3-oxaphosphabicyclo[2.2.2]octane series (Section III.A.2). The 1:1 adducts of 1*H*-phospholes and *N*-phenylmaleimide (**177**) or dimers of the same phospholes (**178**; R =



SCHEME 31

OCH_2Bu^t, 1-adamantoxy, R'_2N, Me, or Ph; R^1, R^2 = H or Me) undergo an oxygen insertion when treated with the same peroxy acid[87,89,92].



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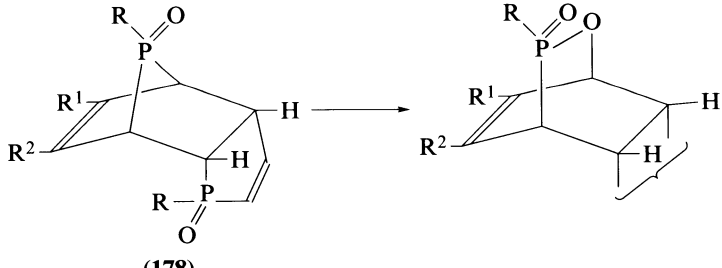
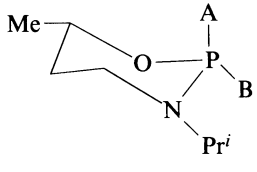


(178)

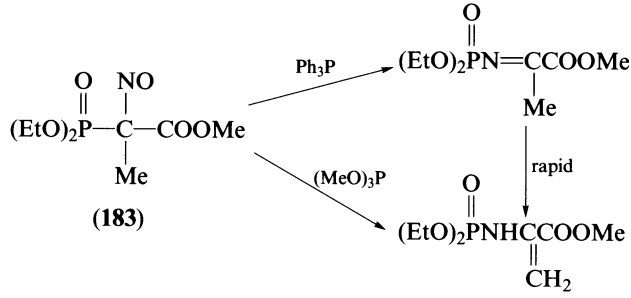
An investigation into the stereochemistry of oxygen insertion into (1-oxoalkyl)phosphonamidic esters was carried out with the aid of derivatives of the perhydro-1,3,2-oxazaphosphorine system. A 92:8 mixture of **179** and **180**, in CH_2Cl_2, when treated with 30% H_2O_2 at –5 °C, gave 98% of a mixture of **181** and **182** of identical composition, indicating



(179) A = =O, B = C(O)Et
(180) A = C(O)Et, B = =O
(181) A = =O, B = OC(O)Et
(182) A = OC(O)Et, B = =O

retention of configuration. A study by ^{17}O NMR spectroscopy of the reaction using ^{17}O-enriched H_2O_2 indicated a scrambling of the isotope into the anhydride and carbonyl oxygens and even, at higher temperatures, into the phosphoryl oxygen. This feature was rationalized by assuming a transfer of the propanoyl group between oxygen atoms, and indicated as being feasible by a crossover experiment which employed a mixture of diethyl acetyl phosphate and dimethyl propanoyl phosphate (4:1) at 90 °C, and which gave diethyl propanoyl phosphate (11%) and dimethyl acetyl phosphate (7%)[294].

Migration of the phosphoryl-containing moiety from carbon to nitrogen occurs in the treatment of the nitroso compound **183** with a tertiary phosphine or trialkyl phosphite, both of which act through oxygen abstraction, and it is of interest that the two products are tautomeric forms[295].

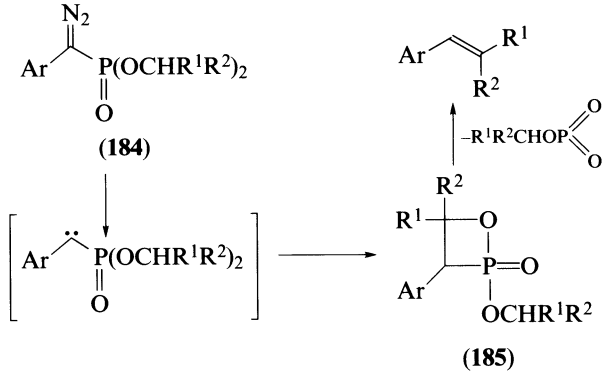


IV. REACTIONS AND PROPERTIES OF THE CARBON LIGANDS: THE FUNCTIONAL GROUPS

Many of the syntheses described in the preceding chapters utilized well known properties of the common functional groups present in the carbon ligands of phosphonic and phosphinic acids. The purpose of this section is to extend the coverage of the chemical properties of several of the functional groups commonly found in what were termed, in Chapters 3 and 4, the functionalized acids,

A. Diazoalkyl Acids

The uses of diazoalkylphosphonic and related acids are based almost entirely on their fragmentation to phosphoryl carbenes, either during thermolysis or under conditions of photolysis, sometimes aided by the presence of an appropriate catalyst. The postulate that a phosphoryl carbene is formed under such conditions is based largely on the nature of the ensuing reactions and a general comparison with the properties and reactions of non-phosphorylated diazo compounds. Direct identification of the carbene, $PhC\ddot{P}(O)(OMe)_2$, followed from its entrapment in an argon matrix during the photolysis of dimethyl (α-diazobenzyl)phosphonate. In argon doped with 20% oxygen, two other species were also identified, dimethyl benzoylphosphonate and dimethyl benzoyl phosphate, thought to be formed via a diradical or possibly a dioxirane[296]. Flash vacuum pyrolysis (350 °C, 10^{-5} mmHg) of the dialkyl (α-diazobenzyl)phosphonates **184** gave alkenes ultimately. This process was envisioned (Scheme 32) as the result of the formation of the 1,2-oxaphosphetane derivatives **185** and their subsequent decomposition with the elimination of a metaphosphate ester, but the overall result depends on the nature of substituents on the benzene nucleus: thus, the reaction proceeded as indicated with the presence of 3-Cl, 4-Cl, 2-Br, 3-Me and 4-MeO substituents, and also when Ar = 1- or 2-naphthalenyl, but no alkene was obtained for compounds with 2-Me, 2-Et or 2-MeO substituents[297].

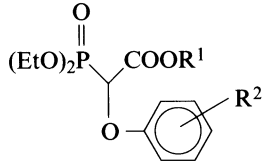


(184)

(185)

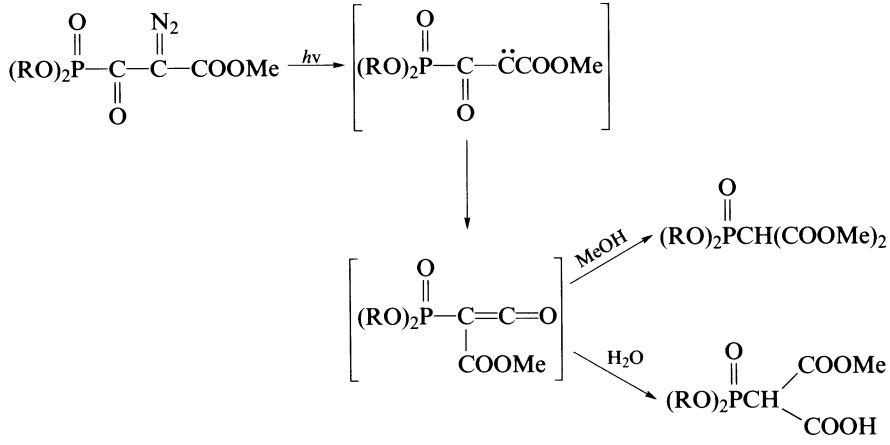
SCHEME 32

The decomposition of diazophosphonoacetic acid triesters in the presence of phenols and $[Rh_2(OAc)_4]$ yields the corresponding α-phenoxy derivative of the triester **186**[298].



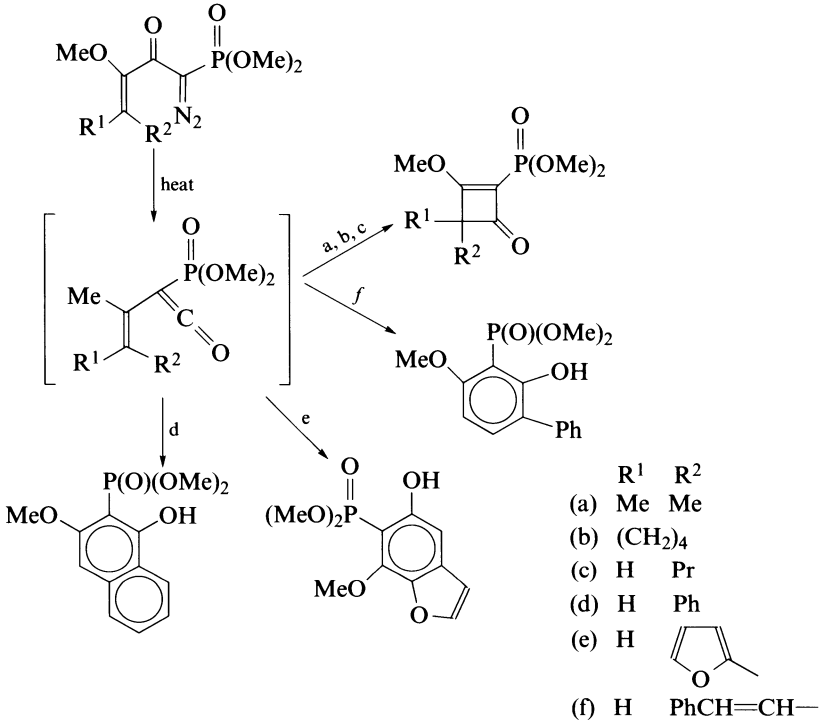
(186)

The photolysis of a methanolic solution of a phosphonic diester with adjacent diazo and oxo substituents occurs with a Wolff rearrangement of the carbene and the capture of the resultant ketene by the alcohol (or by water); the yields are almost quantitative for the examples illustrated (Scheme 33; R = Et or Pr^i)[299]. Similar reactions were observed for (1-diazo-2-oxoalkyl)phosphonic diesters from which the products were then α-phosphonoalkanoic triesters[300].



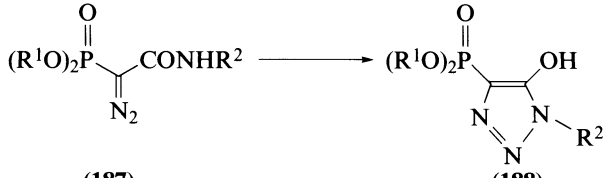
SCHEME 33

(1-Diazo-2-oxoalk-3-enyl)phosphonic diesters have proved to be a valuable source of alicyclic and heterocyclic compounds which result from the various reactions of the derived ketene (Scheme 34)[301]. In the presence of $[Rh_2(OAc)_2]$, (1-diazo-2-oxoalkyl)phosphonates of sufficient alkyl chain length undergo decomposition and cyclization to give α-phosphinoylated cyclopentanones[302].

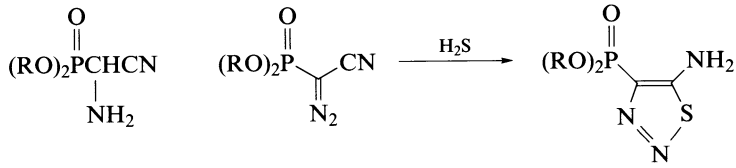


SCHEME 34

Several important reactions of (diazoalkyl)phosphonic esters and related compounds are essentially 1,3-dipolar additions, either inter- or intra-molecular in nature, and as such are considered in Section V.D. The compound **187** (R^2 = H) is unstable and, when prepared, cyclizes spontaneously to the phosphorylated triazole **188**[303], but the same conversion with R^2 = Me or Et is achieved by the action of $KOBu^t$[304]. The nitrosation of the aminoacetonitriles **189** with propyl nitrite does not have the disadvantages that other synthetic routes to the diazoacetonitriles **190** possess[305]; further reaction between **190** and H_2S yields the phosphorylated thiadiazoles **191**[306].

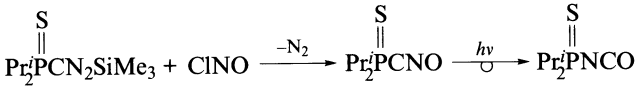


(187) **(188)**

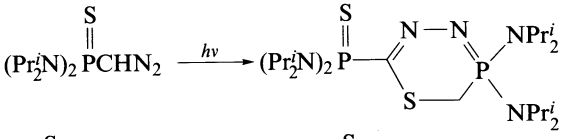


(189) (190) (191)

In a novel interconversion, the phosphine sulphide **192** reacts with nitrosyl chloride to give the phosphinothioic cyanate **193** which, when irradiated, isomerizes to the isocyanate[307]. Two unusual reactions (equations 10 and 11) result from the photolysis of derivatives of (diazomethyl)phosphonothioic diamide derivatives[308]. Yet a further unusual reaction is experienced by the monoanion **194** when irradiated in MeOH, and which is thought to proceed with the cyclization of the carbene intermediate to give an oxaphosphirane, methanolysis of which results in ring opening with phosphorus–carbon bond fission[309].



(192) (193)



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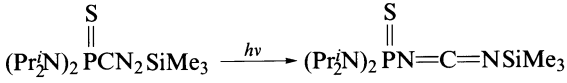

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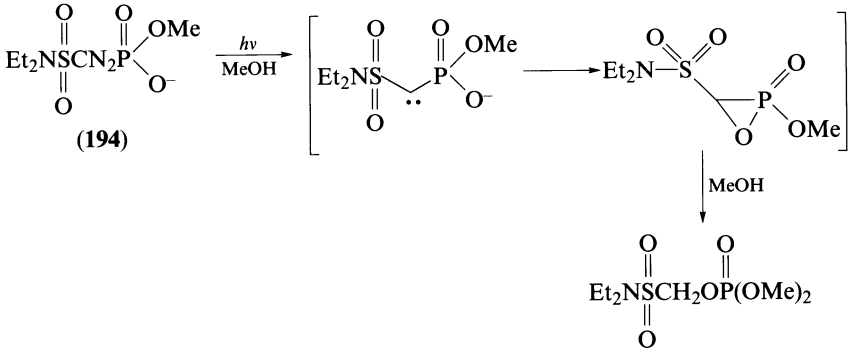
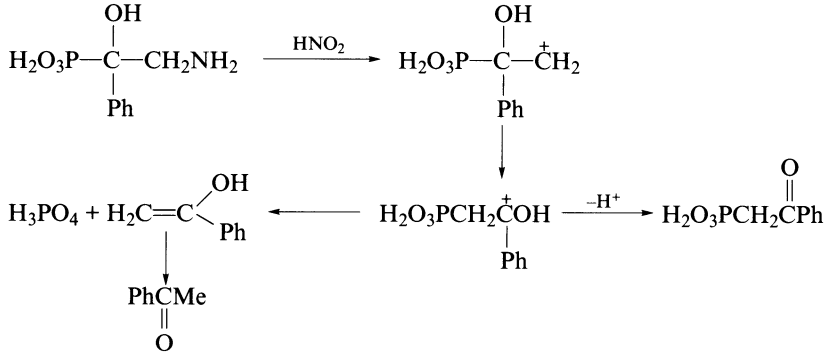


(194)

B. Amino Acids

By contrast, the reactions of the amino group in (aminoalkyl)phosphonic and related acids are, in principle, relatively simple and few in number, interest in the acids, as a class, residing in their biochemical properties. Their diazotization leads to (diazoalkyl)phosphonic derivatives, and the protection of the amino group by acylation (as acetyl, benzoyl

phthaloyl, toluenesulphonyl, benzyloxycarbonyl and *tert*-butyloxycarbonyl derivatives) has been encountered in the syntheses of aminoalkylphosphonic and related acid derivatives (Chapter 4, Section IV). Other reactions are explicable in classical terms; carbocation intermediates are probably involved, for example, in the diazotization of dialkyl (1-aminocyclohexyl)phosphonates, which leads to high yields of dialkyl (cyclohex-1-enyl)phosphonates[310], and in the diazotization of (2-amino-1-hydroxy-1-phenylethyl)phosphonic acid, when the products include acetophenone (7%) and (2-oxo-2-phenylphenyl)phosphonic acid (ca 80%), formed, evidently, by phosphoryl migration within a carbocation (Scheme 35)[311]



SCHEME 35

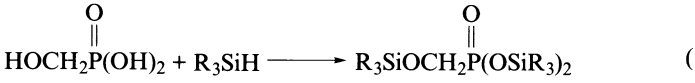
The action of hot alkali on salts of the acids **195** (R = *tert*–alkyl) yields the acids **197**, whereas nitrous acid at 0–5 °C yields the hydroxy acids **196**[312]. (1-Aminoalkyl)phosphonic diesters react with carbonyl chloride to give the corresponding isocyanates, which may be characterized as derived ureas or semicarbazides[313].

(**195**) Z = NH_2
(**196**) Z = OH

(**197**)

C. Hydroxy Acids and Their Esters and Ethers

The known reactions of the hydroxy function in the carbon moieties of phosphonic acids and related compounds are many. When treated with an excess of a silane, R_3SiH, in the presence of colloidal nickel at about 110 °C, (hydroxymethyl)phosphonic and bis(hydroxymethyl)phosphinic acids each undergo silylation at both alcohol and acid OH sites, although equation 12 is a simplification of the overall chemistry. The other main phosphorus–containing product from such reactions is **198** (when R = Et); the 1,4,2,5-dioxadiphosph(V)orinanes (**199**) are also isolable if reaction product mixtures are kept at ambient temperature[314–316]. An excess of an alkoxysilane R_3SiOR^1 also fully silylates



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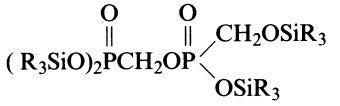

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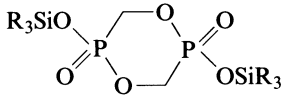
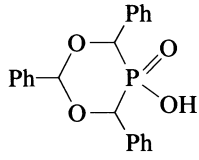


(199)

hydroxyalkyl acids[317]. With smaller amounts of silylating agents, reactions occur preferentially at the acid hydroxy group(s)[318]. The silanes R_3SiOAc acetylate the alcohol OH and silylate the acid OH functions[318,319].

Apart from the preceding processes, the hydroxy group in hydroxyalkyl-phosphonic or -phosphinic esters has been acylated straightforwardly[320–323] or by carboxylic acids in the presence of dicyclohexylcarbodiimide[324,325], a procedure also particularly useful for the *N*-acylation of aminoalkylphosphonic acids for the purpose of enantiomer analysis[326], phosphitylated[327–331], phosphorylated[332,333] and replaced by halogen (Chapter 3, Section II.C.1). Carbamates have been prepared from isocyanates or isothiocyanates[334–336] and hemiacetals formed in reactions with trichloroacetaldehyde[337]; the acetal **200** was prepared from benzaldehyde and the bis(α-hydroxybenzyl)phosphinic acid[338]. Cyclic boron diesters have also been prepared[339].



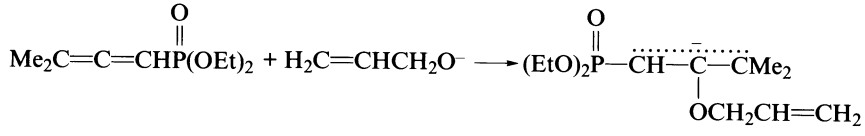
(200)

Simple alkyl ethers are readily available by appropriate alkylation with alkyl halides and, of such ethers, the allyl ethers are of special interest[340]. Allyl ethers from slightly more complex hydroxy acids have been obtained as carbanions by the addition of allyloxy ions to dialkyl (1,2-alkadienyl)phosphonates (Scheme 36), when the main products were the separable ketones **202** (37%) and **203** (19%) formed by Claisen rearrangements within the mesomeric ion **201**[341].

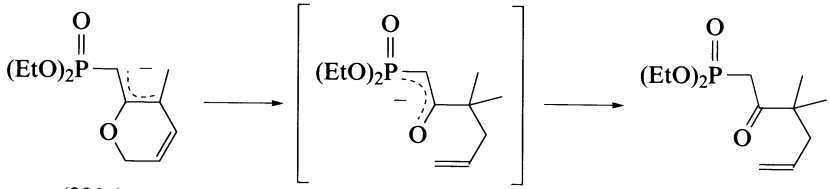
The same manner of synthesis led to the allylic ethers **204** (R = H or Me); the thermal Claisen rearrangement of compounds **204** (R^1,R^2 = H or Me) led to poor asymmetric induction (at the carbons α and β to the carbonyl group) in the products **205**, but this was increased considerably, as was the rate of rearrangement, by the initial generation (with K–dmso) of the carbanion from **204**; the change in level of asymmetric induction with increasing concentrations of added LiCl suggested a competition between the lithium (an similarly potassium) in transition-state complexes[342]. A second study by the same group[343] concentrated on a series of ethers derived from cyclic phosphonic diamides (with five-, six- or seven-membered rings with, as substituents on nitrogen, Me, Pr^i, Bu^t, Ph or CH_2Ph), and identified the 1,3-dibenzyl-1,3,2-diazaphospholidine moiety in, for example, **206** (R^1–R^4 = H or Me) as being the most effective in the ease and stereoselectivity of the rearrangement.

Treatment of the allylic ethers **207** (R^1, R^2 = H, Me or Ph) with lithium diisopropylamide (necessarily 2 equiv.) in thf at a low temperature brings about the Wittig rearrangement to α-hydroxyalkyl phosphonates; the diastereoisomer ratios in the products **208** vary from 1:1 (R^1 = H, R^2 = Me) to 95:5 (R^1 = H, R^2 = Ph)[344].

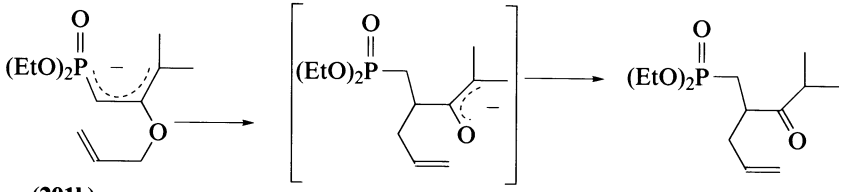
Other interesting rearrangements of ether derivatives of hydroxy phosphonates have been reported, for example the spontaneous formation of **210** from **209**, and the slow



(201)

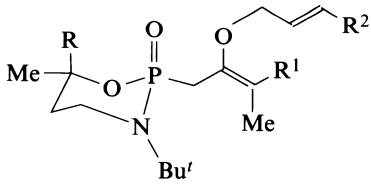


(201a) (202)



(201b) (203)

SCHEME 36



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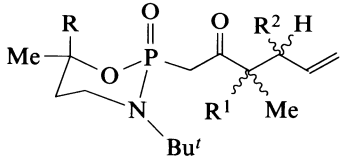

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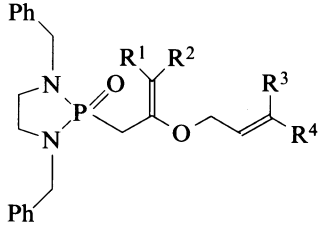
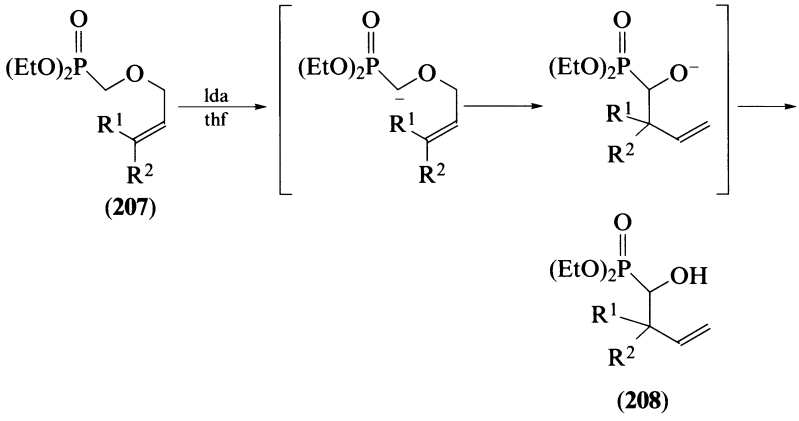
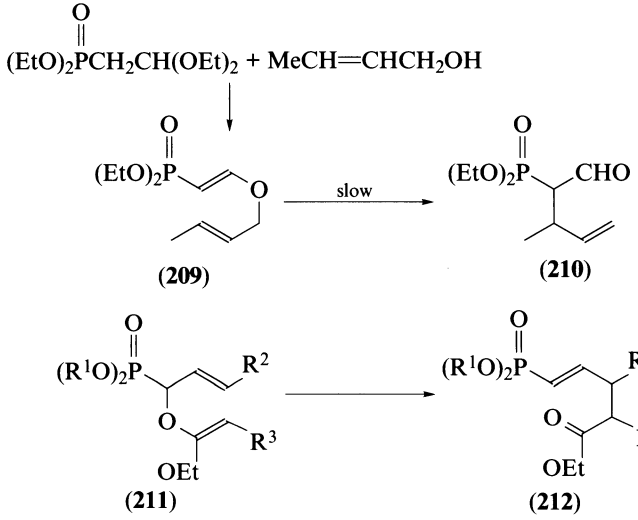


(206)

thermal conversion of **211** into **212**, but α-hydroxyallylic phosphonic diesters do not, themselves, undergo Claisen rearrangements[341].

Other derivatives of the hydroxy group include special ethers such as the 2-tetrahydropyranyl ethers; these are prepared from the hydroxyalkyl acid and 2,3-dihydro-4*H*-pyran. Under aqueous acidic conditions, the tetrahydropyranyl ethers readily revert to the hydroxyalkyl acid, and the group thus acts as a convenient *O*-protecting function[345–347].

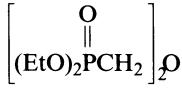




The α-hydroxy group has been replaced by arylthio using ArSH under Mitsunobu conditions[348]. Esters of (hydroxyalkyl)phosphonic acids readily furnish esters of sulphonic acids when acted upon by sulphonyl chlorides–R_3N or sulphonic anhydrides, and which are convenient substrates for many substitution reactions. Thus, the trifluoromethanesulphonate **213** (R = H) is preparable at < – 15 °C, but at temperatures higher than this the ether **214** is formed; **213** (R = H) also undergoes reaction with nucleophiles such as NH_3 and R_2NH under very mild conditions to give (aminomethyl)phosphonic acids, and metal aryloxides afford (aryloxymethyl)phosphonic diesters[349]. The solvolysis of **213** (R = Me) with alcohols (EtOH, CF_3CH_2OH, etc.) gives alkyl ethers[350]. The reaction between diethyl (1-hydroxyalkyl)phosphonates and methanesulphonyl chloride has been developed as a 'one-pot' procedure for the preparation of alkylidenebisphosphonic esters[351]. With NaN_3, dialkyl [α-(*p*-toluenesulphonyloxy)benzyl]phosphonates yield the (α-azidobenzyl)phosphonic diesters[352]; with KSCN, the products are of the form **215**[353].

The mechanistic details in the replacement process for various methanesulphonyl esters have been examined in detail; the structure of the substrate has some control over the

(213)



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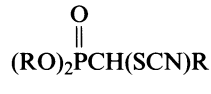
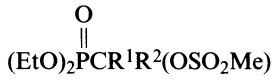


(215)

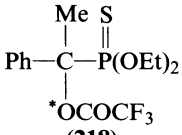
nature of the products. Thus, the reactions with alcohols are facile, and whereas **216** (R = H) undergoes exclusive substitution on trifluoroacetolysis, **216** (R = Me) provides the elimination product, diethyl (1-phenylethenyl)phosphonate, alongside the product of substitution; other esters based on tertiary alcohol groups, such as [**217** ($R^1 = R^2$ = Me, or $R^1R^2 = (CH_2)_n$] yield elimination products, exclusively, when treated with EtOH, HOAc, HCOOH and other solvent nucleophiles[354].

(216)



(217)

The acetolysis of *O,O*-diethyl {1-phenyl-1-[(trifluoroacetyl)oxy]ethyl}phosphonate (**218**) gave the thiol **219** as the minor product (yield 27%) together with, as the major product, its *S*-trifluoroacetyl derivative **220**, in 63% yield. Accompanying these two products were traces of the transacylated compound **221** and the elimination product **222**, both of which retained the thiophosphoryl group. If the starting material is isotopically labelled at O*, the label is ultimately found in **220** in the phosphoryl group (80%) and in the carbonyl group (20%). This novel transformation has been rationalized in terms of the removal of the trifluoroacetyl group with its recombination at phosphorus through either carboxylate oxygen (only one of which is isotopically labelled) in the transition state, **223**, to give the pentacoordinate species **224**; the latter leads to **225**, an obvious potential precursor to both **219** and **220**[355].



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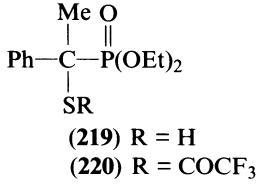
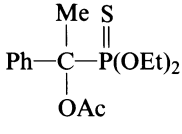


(219) R = H
(220) R = $COCF_3$



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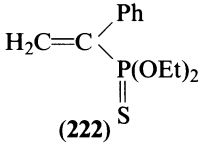

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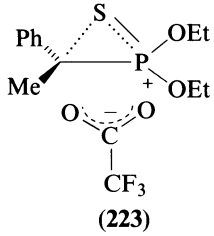

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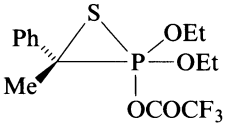

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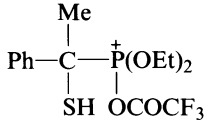
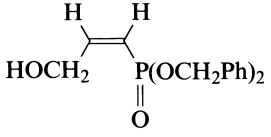


(225)

Appropriately sited hydroxy groups participate in transesterification with nearby alkoxy groups bonded to phosphorus[356]. So, for example, the (*Z*)-ester **226** undergoes spontaneous cyclization to the 1,2-oxaphospholene **227** (R = CH_2Ph) which may be debenzylated, by hydrogenolysis, to the acid **227** (R = H)[357]. The hydroxy group may be present as an enol tautomeride, as with the example **228**[358]. Intramolecular esterification is equally feasible when alcohol and acid OH are correctly sited relative to each other, as in the conversion of the dihydroxybisphosphonic acid **229** into the phosphorylated 1,2-oxaphosphol-3-ene **230**[359].



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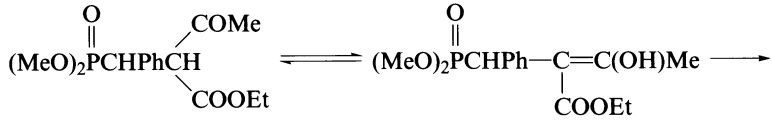
(227)



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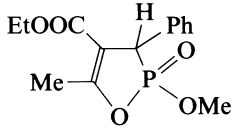
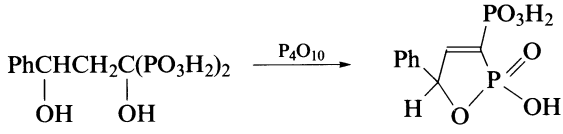
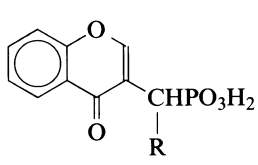


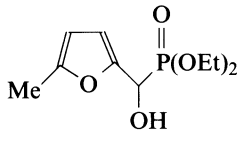


(229) **(230)**

Useful methods for the removal of the hydroxy group from hydroxyalkylphosphonic or related acids are available; three later examples might be quoted. Some hydroxy acids are reducible with HI–red phosphorus, as in the preparation of **232** from **231**[360]. As an even more specific example, dry HCl in ROH converts **233** into **234**[361]. In a more general vein, **235** with NaH, CS_2, followed by MeI, yields **236**, reducible to **237** when treated with Bu_3SnH–aibn[362], and variations in the procedure are exemplified by the treatment of the readily available derivatives **238** (R = Me or Ph, Z = OH) with 4-$MeC_6H_4OC(S)Cl$ in pyridine, with reduction of the product, again with Bu_3SnH[363].



(231) R = OH
(232) R = H



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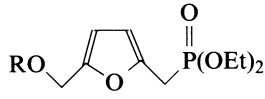

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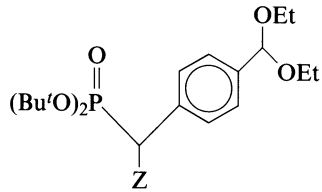
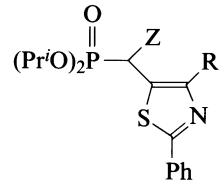


(235) Z = OH
(236) Z = OC(S)SMe
(237) Z = H.



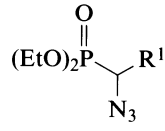
(238)

D. Nitro Acids

Apart from the reduction of (nitroalkyl)phosphonic acid derivatives to give the corresponding (aminoalkyl)phosphonic derivatives, and the participation of the nitro group in its *aci* form during additions of phosphorus(III) nucleophiles to nitroalkenes, the role of the nitro group in phosphonic and related acids is very restricted. It is interesting to note that, in selected examples, the nitro group in (1-nitroalkyl)phosphonic diesters may be completely removed when these are treated with Bu_3SnH–aibn[364] although a partial reduction to hydroxyamino is possible with either Al–Hg in ethyl acetate or $SnCl_2$–HCl[365]. The chemistry of nitro-substituted aliphatic organophosphorus compounds has been reviewed[366].

E. Azido Acids

The relevant chemistry of the azido group is also mainly connected with its reduction to amino (Chapter 4, Section IV.C.1.f), but the 1,3-dipolar cycloaddition of azidoalkyl phosphonic diesters **239** to acetylenes is also of some importance with regard to the synthesis of phosphinoylated 1,2,3-triazoles, and will be considered further (Section IV.D).

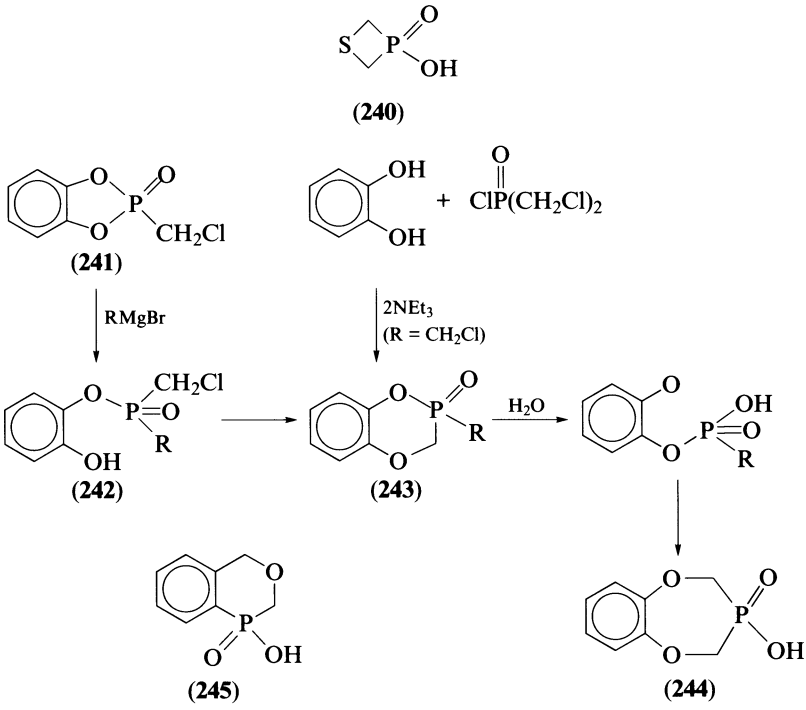


(239)

F. Halogen–containing Acids

Halogen bonded to sp^3 carbon can be subjected to the usual replacement reactions. For instance, the chlorine in bis(chloromethyl)phosphinic amides or esters is replaced by reactions with amines to give bis(aminomethyl)phosphinic derivatives[367,368], by alkoxides to give bis(alkoxymethyl)phosphinic derivatives[369] or by aryloxides to give the bis(aryloxymethyl)phosphinic derivatives[370]. The reactions with amines have been described as being of S_N2 character for stronger bases such as benzylamine, but S_N1 for reactions with more weakly basic amines such as $PhNH_2$[371]. Halogen metathesis occurs in a stepwise manner with KI[372,373], and the reaction between sodium bis(chloromethyl)phosphinate and Na_2S yields the phosphinic acid **240** readily convertible into the usual derivatives[374].

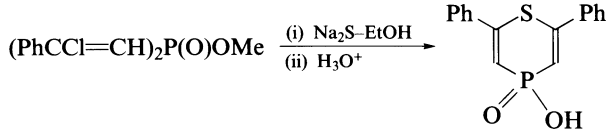
The formation of ethers can also occur with cyclization and the synthesis of heterocyclic phosphorus compounds (Scheme 37). The reaction between the benzodioxaphosph(V)ole **241** and a Grignard reagent (R = alkyl or aryl) followed by a treatment of the product **242** with base affords the dihydrobenzodioxaphosph(V)orin **243**[375], also available from catechol and bis(chloromethyl)phosphinic chloride[376]. The hydrolysis of **243** and cyclization of



SCHEME 37

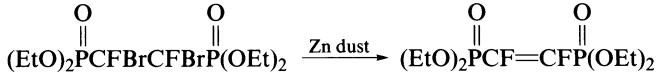
the product (R = CH_2Cl), again with alkali, gives the cyclic phosphinic acid **244**[376,377]. The phosphinic acid **245** was prepared following similar methodology[378]. The nickel-catalysed hydrogenation of bis(chloromethyl)phosphinic acid results in stepwise reductive dechlorination, yielding, eventually, dimethylphosphinic acid[379].

Equation 13 indicates an example of substitution at an sp^2 carbon atom that has been practised in the synthesis of phosphorus–containing heterocyclic systems such as the 1,4-thiaphosphorin illustrated[380].



(13)

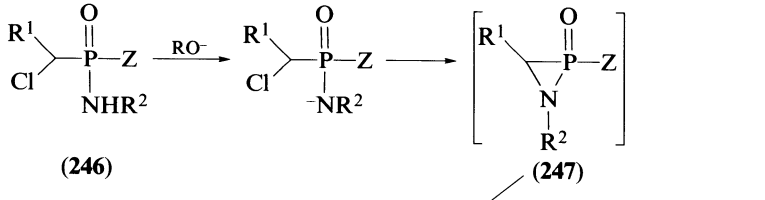
The other main area of reactivity in connection with halogen-substituted acids and their derivatives is that of halogen elimination, already seen to play an important role in phosphorus–carbon bond breakage and the formation of metaphosphate ion. Simple dehalogenation has been employed to produce alkenylphosphonic acid derivatives (equation 14)[381,382], but much more important is dehydrohalogenation, particularly when halogen is sited on $C_{(2)}$; this, also leads to alkenylphosphonic derivatives and as a methodology for the



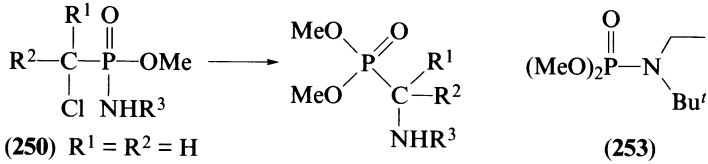
(14)

preparation of such derivatives has been described earlier in this volume (Chapter 2, Section VI.D). Several recent studies on the topic have included those by Modro and co-workers[383,384], who concluded that a group such as $(EtO)_2P(O)$ exerts only a weak stabilizing effect on adjacent, incipient carbon–carbon double bonds, and that a more important factor is the pattern of substitution on those bonds.

Although (α-haloalkyl)phosphonic diamides (**246**; Z = NEt_2) react in the expected manner with secondary amines, their reactions with alkoxides or phenoxides have produced novel results, with rearranged products, the formation of which has been attributed to proton loss and production of an azaphosphiridine intermediate **247** which then, probably through a further intermediate **248** of a pentacoordinate structure, suffers ring opening to give the product **249** (Z = NEt_2)[385]. Harger and Williams[386,387] studied the reaction with the aid of phosphonamidic esters having the structures **250**–**252**; for a given R^3 (Ph or Bu^t) the relative rates of rearrangement were **252** > **251** > **250**. Indeed, the reaction can be very fast [for example, that between **252** (R^3 = Ph) and MeO^- was complete within 2 min at 60 °C], whereas under the same experimental conditions, that for **251** was slower by a factor of 50. One unusual feature was phosphorus–carbon bond cleavage in the reaction between **251** (R^3 = Bu^t) and benzyltrimethylammonium methoxide in thf–MeOH, which gave the phosphoramidate **253** alongside the rearranged (aminoalkyl)phosphonic diester[387], and it is worth noting that the formation of both products can be envisaged as occurring through the same pentacoordinate intermediate **248** with appropriate ligand reorganization. For the reaction of an α-bromo analogue of **246** (R^1 = H, R^2 = Bu^t, Z = O$^-$ menthyl), cleavage of the P—N bond (the major reaction) occurred with inversion of configuration and the cleavage of the P—C bond (the minor reaction) with retention of configuration at phosphorus[388].



(246) **(247)** **(248)** **(249)**



(250) $R^1 = R^2 = H$
(251) R^1 = Me, R^2 = H
(252) $R^1 = R^2$ = Me

(253)

G. Oxo Acids

Dialkyl (1-oxoalkyl)phosphonates (dialkyl acylphosphonates) in the ketonic form, **254**, are actually or potentially tautomeric with the enol form **255**. Such a system possesses two sites capable of attack by a nucleophile, namely carbonyl carbon and phosphoryl phosphorus, and three sites—the oxygen atoms of carbonyl and phosphoryl groups, and also the methylene group—through which it is possible for reaction to occur with an electrophile. The reactions between such esters and acetyl chloride or trimethylsilyl chloride furnish the enol acetate or enol trimethylsilyl ether, and phosphitylation of the latter then affords the phosphorus(III) enol ester[389]. Enol acetates are best obtained by the acetylation of dialkyl hydrogenphosphonates with acetic anhydride (2 equiv.) in the presence of $CoCl_2$ (best) or an iron chloride; the use of 3 equiv. of Ac_2O gives, additionally, smaller amounts of dialkyl acetylphosphonate[390]. According to McConnell and Coover[391], ketene–BF_3 may be employed in place of acetic anhydride in the last reaction, but the similar acetylation of diethyl acetylphosphonate yields the enol acetate in a mixture of products that is difficult to resolve.

$$(RO)_2P(O)CH_2C(O)R^1 \rightleftharpoons (RO)_2P(O)C(OH)=CHR^1$$

(254) **(255)**

The facility with which the phosphorus–carbon bond in acylphosphonic derivatives is cleaved by the action of the more basic nucleophiles has already been commented upon. Those nucleophiles include alkoxides and amines, but it may be noted that thiols undergo normal addition to the carbonyl group. With regard to the latter, diethyl acetylphosphonate yields the monothioacetals **256**[392]; the derivatives may not be stable thermally but their decomposition occurs with cleavage of the phosphorus–carbon bond[393]. Reactions between the same substrate and simple carboxamides in the presence of an acid catalyst under dry conditions furnish the acylated enamides **257**[394].

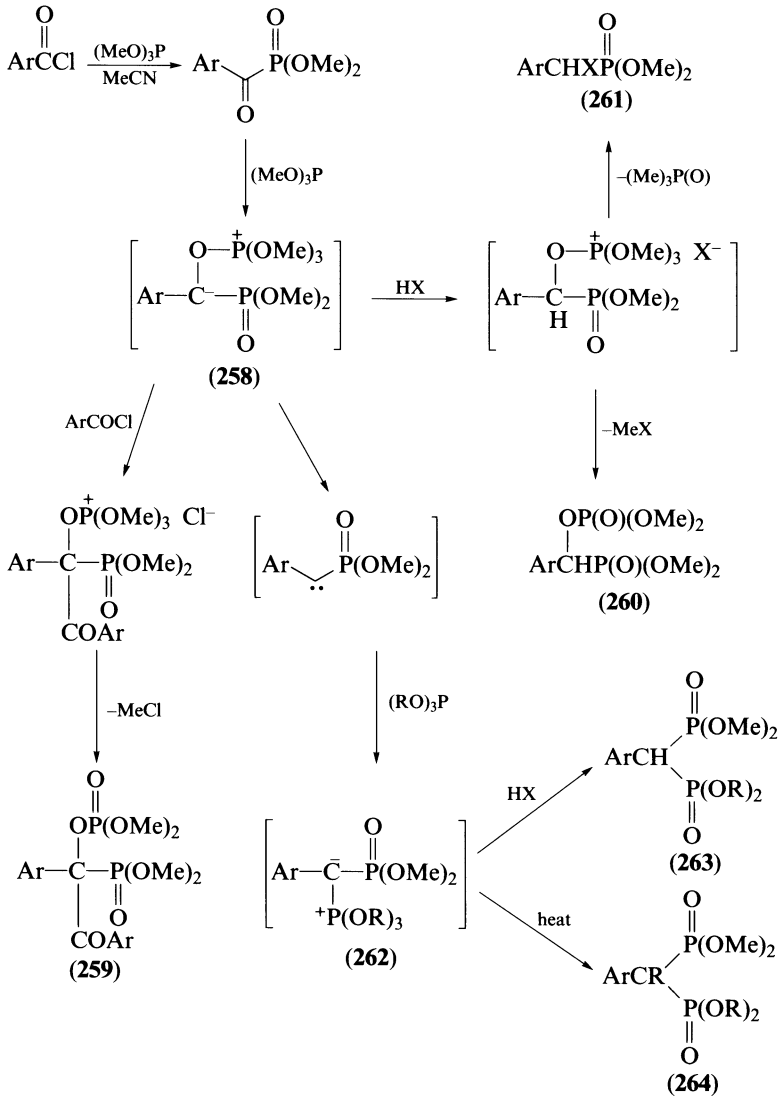
$$(EtO)_2P(O)C(SR)(OH)Me$$

(256)

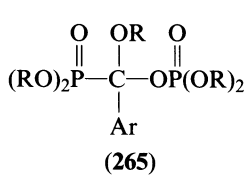
$$(EtO)_2P(O)C(=CH_2)NHCOR$$

(257)

Unlike the reactions with other aroyl chlorides, that between 4-nitrobenzoyl chloride and trimethyl phosphite does not stop at the dimethyl acylphosphonate stage, but a further reaction occurs (Scheme 38) which results in the formation of compound **259** (Ar = 4-nitrophenyl). Other aroyl chlorides are reluctant to engage in this reaction, possibly because of the stability of the relevant betaine intermediate **258**, but do so in the presence of proton donors such as RCOOH or ROH, when the products are **260** (Ar = 4-methoxyphenyl, X = RCOO) or **261** (Ar = Ph, 4-chloro- or 4-methoxy-phenyl, X = RCOO)[395]. In the absence of an electrophile, the betaine intermediate **258** decomposes at > 80 °C to give a carbene fragment which can undergo insertion or be captured by more trialkyl phosphite to give the ylide **262**; the sequence is ended by a further reaction with HX to give benzylidenebisphosphonic esters **263** or, at higher temperatures, by intramolecular alkylation to give **264**[396]. Russian workers have suggested that the species **258** can rearrange to the compounds **265**[397]. The outcome in the reaction scheme depends very much on the number and nature of aromatic substituents. For 4-chlorobenzoyl chloride, a competing reaction is the formation of a 1,3,2-dioxaphosph(V)olane, **266** (Ar = 4-chlorophenyl), but this is not observed for 2,4-dichlorobenzoyl chloride; in the latter case, steric hindrance by the *ortho* chloro group directs **258** to **262** and its subsequent decomposition.



SCHEME 38



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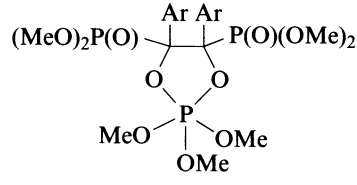
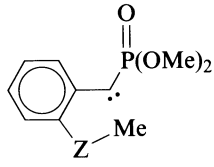


(266)

Evidence for the participation of a carbene intermediate stems from the results of some cyclization reactions. The reaction which involves dimethyl (2-ethylbenzoyl)phosphonate at 100 °C generated dimethyl 1-indanephosphonate (**268**; Z = CH_2) presumably via **267** (Z = CH_2), and similarly, dimethyl ([1,1′-biphenyl]-2-ylcarbonyl)phosphonate gave the fluorenylphosphonate diester **269**, produced very quickly at 90 °C with no sign of the ylide. For the reaction of dimethyl (2-methoxybenzoyl)phosphonate at room temperature, the ratio of the formation of **268** (Z = O) to that of **262** was 1:4, but at 105 °C, the ratio became 3:1; by contrast, dimethyl ([1,1′-biphenyl]-4-ylcarbonyl)phosphonate yielded only the ylide[396].



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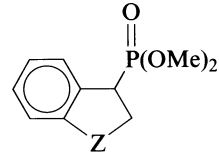

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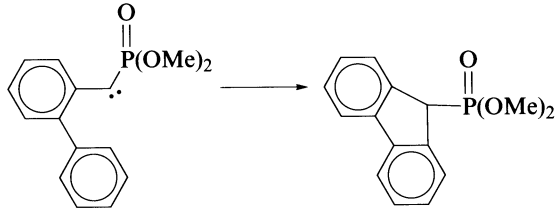
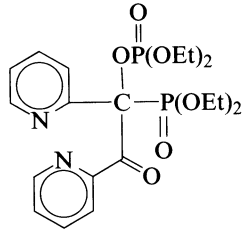


(269)

Similar results have been obtained for some reactions between phosphite triesters and the chlorides from heterocyclic carboxylic acids. The first of these to be reported were for the pyridinylcarbonyl chlorides. Here, **270** from 2-pyridinylcarbonyl chloride, and **271** from the 3- and 4-pyridinyl chlorides, were obtained presumably via the betaines **272**[398]. Similarly, the acylphosphonate **274**, from **273**, reacted with more trialkyl phosphite (R = Me or Et), possibly via structures **275** and **276** (together with, in the latter case, the geometrically isomeric form) to give the isolated products, **277** and **278** (again as geometric isomers)[399]. With 4,4-dichloro-4*H*-benzopyran-2-ylcarbonyl chloride, a similar mechanism was postulated but with the loss of one chlorine atom (as in **279**) to restore electron redistribution within the chromone system[400]; the *E* structure was confirmed by X-ray crystallography[401].

Dialkyl (1-oxoalkyl)phosphonates and aroylphosphonates undergo classical and stereospecific reactions with Wittig reagents **280** (R^3 = CN, Ph or COOR)[402,403] and they also participate in WEH reactions with phosphonate carbanions with a high degree of



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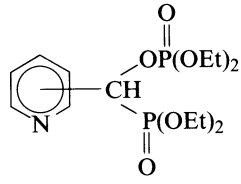

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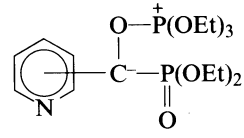
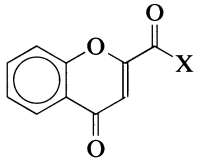
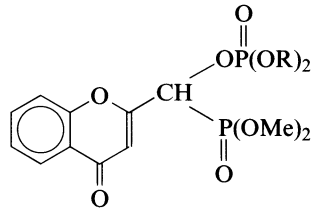


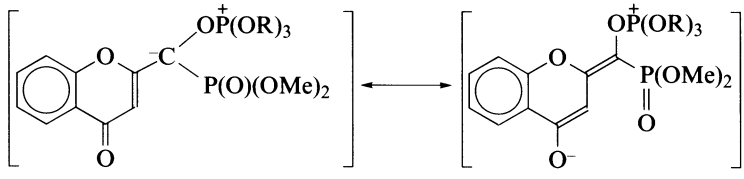
(272)



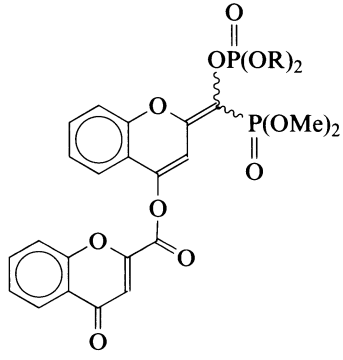
(**273**) X = Cl
(**274**) X = P(O)(OMe)$_2$



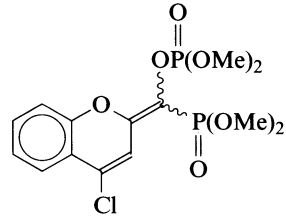
(**277**)



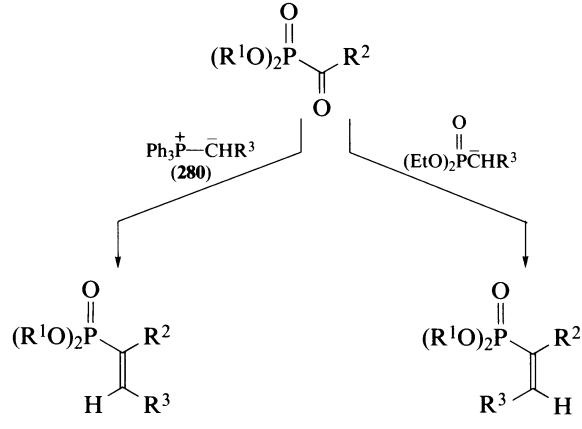
(**275**) (**276**)



(**278**)



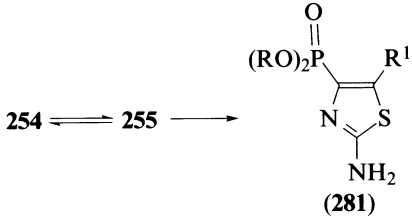
(**279**)



SCHEME 39

stereoselectivity (Section III.C)[403]; the complementary reactions (Scheme 39) lead to stereoisomers of dialkyl (alk-1-enyl)phosphonates, although some restrictions (e.g. lack of reactivity for R^2 = Me or $PhCH_2$) have been noticed in the case of the WEH reaction.

Acylphosphonic diesters take part in condensations very often through the participation of their enol tautomers; with formamidine disulphide, for example, the 1,3-thiazoles **281** can be obtained; analogues of such phosphonic acid products, e.g. **282**, are obtainable from (2-oxoalkyl)phosphonic diesters with the same reagents[404].



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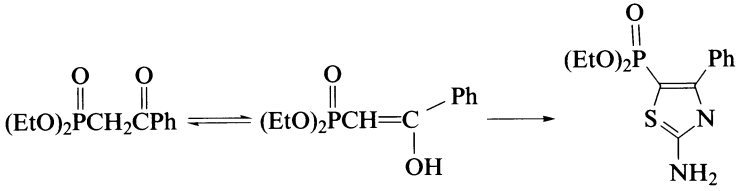
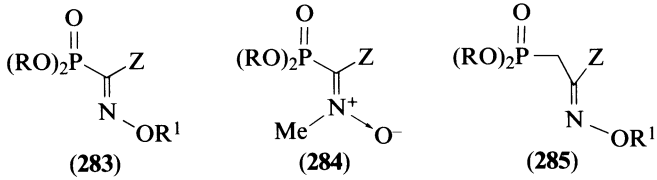


(282)

In addition to (aminoalkyl)phosphonic diesters, several other, well characterized products have been obtained from the oximes, or derivatives of oximes, of acylphosphonic diesters. Methylation of the oximes **283** [Z = CONHR, COOR (R = Et or Pr^i), R^1 = H; of undefined geometry] with MeI–K_2CO_3, or with Me_2SO_4, yields the *O*-methyl oximes **283** (Z = CONHR; R^1 = Me); methylation with diazomethane also yields the latter but together with the phosphorylated nitrones **284** (Z = CONHR or COOR), which have been characterized in *E* and *Z* forms. The interaction of **283** (R^1 = Me) and diazomethane yields the corresponding **285**[405,406]. Methylene insertion also occurs in reactions between diazomethane and *O*-acylated oximes[407,408].

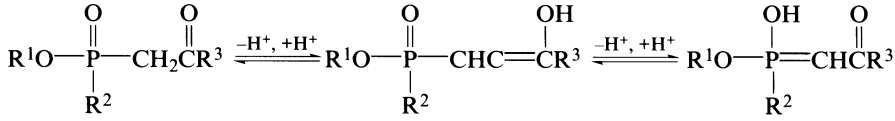


(283) **(284)** **(285)**

In their reactions with BuLi, dialkyl (1-hydroxyiminoethyl)phosphonates are lithiated in both the hydroxy and methyl groups, opening up the way for further reactions including addition to Schiff bases and subsequent cyclization[409]. One important property of the hydroxyimino group is that of its reducibility to amino, or even partially to hydroxyamino. Many of the reagents which, in the past, have been employed for such purposes, have been listed earlier (Chapter 4, Section IV.C.1.d), but new reagents include $LiBH_4$–Me_3SiCl for reduction to amino[410], B_2H_6–pyridine for reduction to hydroxyamino[411] and Et_3SnH–CF_3COOH for the reduction of *O*-benzyl oximes to benzyloxyamino without debenzylation[412]. By contrast, the treatment of oximes of acylphosphonic diesters with 3-

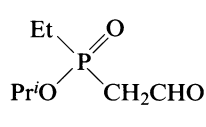
chloroperoxybenzoic acid results in their oxidation to (1-nitroalkyl)phosphonic diesters[413]. Many other reactions of acylphosphonates have been reviewed[414].

(2-Oxoalkyl)phosphonic acids and their acid derivatives are also tautomeric with equilibration between oxo and (carbon) enol forms, and with a potential third contributor in the phosphoryl group (Scheme 40)[61].



SCHEME 40

Although the participation of the phosphoryl group in the tautomeric equilibria of certain esters has been alluded to already (Section II), early determination (by B. A. Arbuzov and co-workers, and reviewed by Mastryukova and Kabachnik[62]) of the enol content of tautomeric mixtures by bromine titration or by UV spectroscopy, indicated, at most, only low percentages (0–10%) of enol content for many compounds and it was felt that such low figures could easily represent the presence of unsaturated compounds as impurities. A relatively high pK_a value, e.g. 11.89 for triethyl phosphonoacetate, is now recognized as characteristic of a compound as a 'CH' acid, and an indication of lack of enolization; equally, a relatively low pK_a is associated with an 'OH' acid to be found as the enol form, as for the acetaldehyde **286** $pK_a = 9.23$[415,416]. The enol form is well recognized, even in the solid state, in 2-phosphorylated-1,3-diketones, e.g. **287**[417,418]. Earlier studies on the tautomerism of β-phosphinoylacetaldehydes employed IR and ^1H NMR spectroscopy, and ^{13}C NMR spectroscopy was used in later work[419]. Mixing β-(diethoxyphosphinoyl)-acetaldehyde with BuLi at low temperatures affords the lithium enolate salt **288** as a stable, crystalline solid, but with BuLi or Zn $(OAc)_2$ at higher tempertures, stable metal enolates of the aldol condensate **289** (Z = Li or Zn/2) are formed[420,421]. Diethyl (3,3,3-trifluoro-2-



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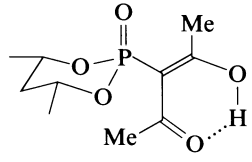

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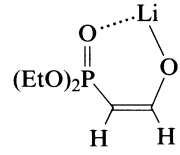

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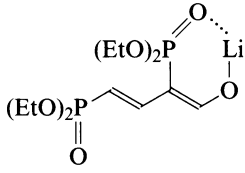

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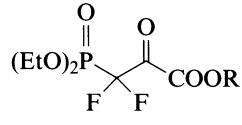

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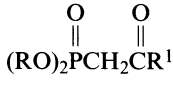

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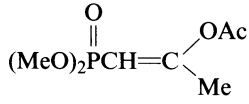
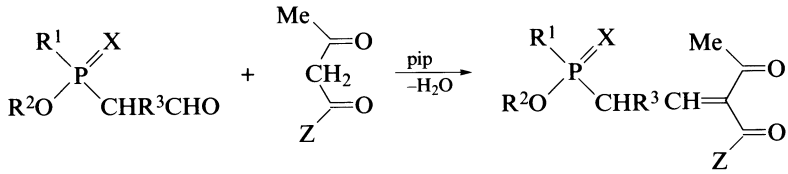


(292)

oxpropyl)phosphonate exists to the extent of 12% in the enol form, but in common with many halogenated ketones, e.g. **290**, is also capable of existence as a hydrate[422,423]. Consistent with the availability of both keto and enol forms, the acetylation (with AcCl) of metal salts can afford either *C*- or *O*-acetyl derivatives; in the acetylation of the sodium salt of **291** (R = Et, R^1 = Me) the product is the *O*-acetyl derivative but the *C*-derivative when R = Me and R^1 = OMe the latter compound then existing almost completely in the enol form. The potassium salt of trimethyl phosphonoacetate gives the same *C*-acetyl compound as is formed from the sodium salt, but additionally accompanied by the enol acetate **292**[424]. Acetylation, in addition to phosphitylation and phosphorylation, is extremely sensitive to several factors and regioselectivity of attack of a reagent at carbon versus oxygen (in which case either or both *E* and *Z* products may be formed) depends on conditions, the nature of ester groups in the substrate and the metal counter ion[425].

The properties of 2-phosphinoylacetaldehydes have attracted much attention[426]. Typically for aldehydes, condensation occurs with active methylene compounds in the presence of piperidine as catalyst (Scheme 41), although side reactions predominate for those aldehydes with unbranched chains and it is then not possible to isolate a dicarbonyl product; in some cases cyclization to 1,2-oxaphosph(V)orin derivatives has been observed[427].

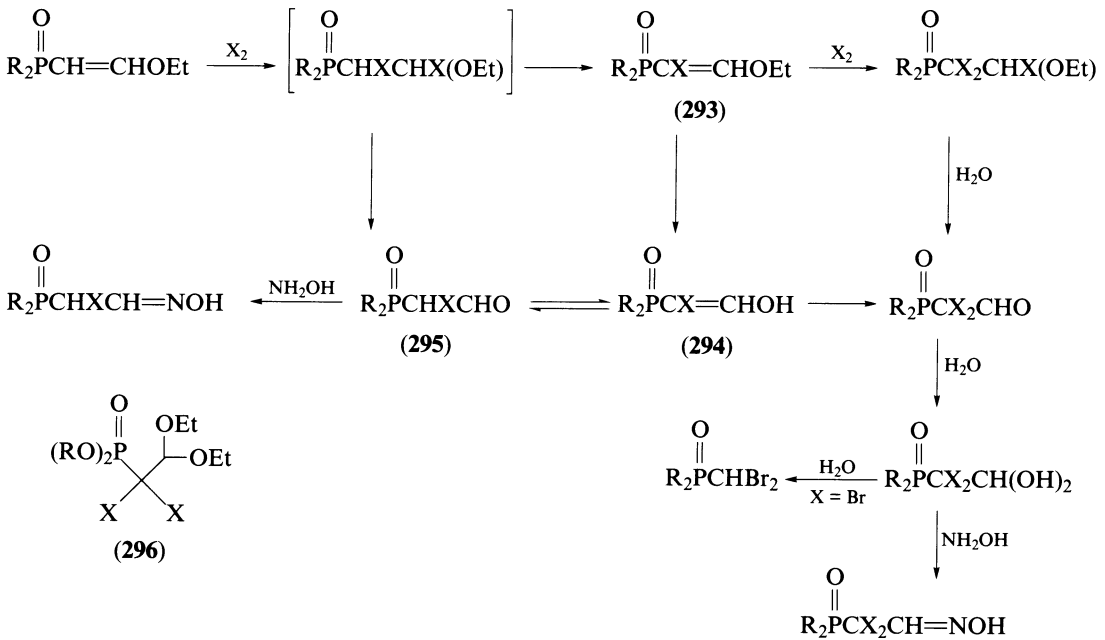


SCHEME 41

Amongst the reactions investigated in considerable detail has been that of halogenation. It might here be mentioned that compounds of the type **291** may be brominated with nbs–CCl_4 (satisfactory for R^1 = Ph but particularly so for R^1 = OCH_2Ph), but other compounds (R^1 = Ar, COOR′, COAr) as their sodium salts may be brominated, reasonably satisfactorily, by elemental bromine[428]. With chlorine in CCl_4 at –10 °C, β-(dialkoxyphosphinoyl)acetaldehydes are successively mono- and di-chlorinated on the carbon α to phosphorus, although at higher temperatures, the chlorination proceeds so rapidly that the dichloro stage is reached very quickly[429,430], and it is now recognized that a more convenient way to obtain the monochloro derivatives is to chlorinate enol ethers of the same system (Scheme 42; R = alkoxy)[431,432] and the same process has been used to chlorinate (and brominate) analogous phosphonic diamides[433].

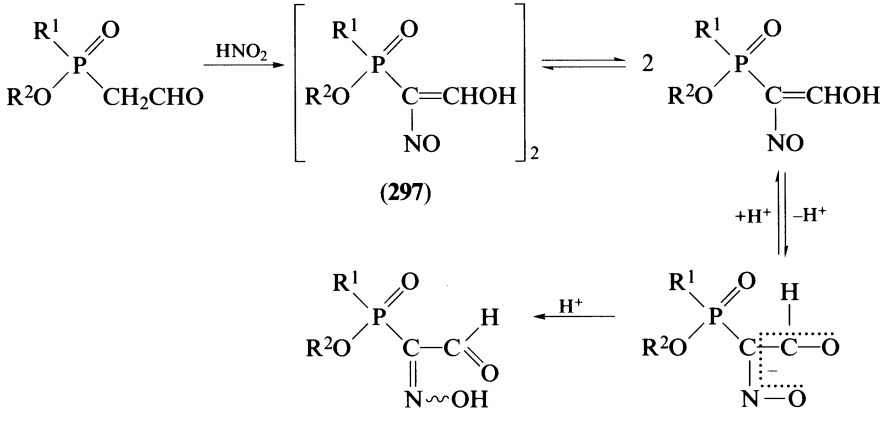
The dibromo- and dichloro-β-(dialkoxyphosphinoyl)acetaldehydes, like chloral, form stable hydrates (the formation of a hydrate from an analogous difluoro compound has already been referred to). The monohalogenated β-[bis(dialkylamino)phosphinoyl]-acetaldehydes enolize much more readily than the dialkoxyphosphinoyl derivatives[433]. A detailed examination of the steps in the chlorination of the enol ethyl ether of β-(dimorpholinyphosphinoyl)acetaldehyde,indicated in Scheme 42 (R = 4-morpholinyl), extended the knowledge gained from similar , but less detailed studies on the analogous dialkoxyphosphinoyl compounds already discussed[434]. Here, both the monobromo and monochloro derivatives (**293**; X = Br or Cl) are sufficiently stable to be isolable, and the monobromo- and monochloro-acetaldehydes each exists in the crystalline state as the (*Z*)-enol **294** but is in equilibrium with the oxo form **295** when in solution[435]. The diethyl acetal of a β-(dialkoxyphosphinoyl)acetaldehyde (**296**; X = H) can readily be chlorinated to give **296** (X = Cl), which is then hydroysed to the free dichloroacetaldehyde[431].

The nitrosation of β-phosphinoylacetaldehydes (with KNO_2–AcOH) occurs at the carbon α to phosphoryl, to provide a system of dimeric nitroso-enol in equilibrium with


R2PCH=CHOEt
X2
R2PCHXCHX(OEt)
R2PCX=CHOEt
(293)
X2
R2PCX2CHX(OEt)
H2O
R2PCHXCH=NOH
NH2OH
R2PCHXCHO
(295)
R2PCX=CHOH
(294)
R2PCX2CHO
H2O
(RO)2P
OEt
OEt
X
X
(296)
R2PCHBr2
H2O
X = Br
R2PCX2CH(OH)2
NH2OH
R2PCX2CH=NOH

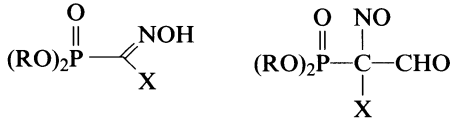
SCHEME 42

the corresponding monomer and with the tautomeric α-oxime of the β-oxo form (Scheme 43)[436]. In the nitrosation of monohalogenated β-(dialkoxyphosphinoyl)acetaldehydes (HNO_2 in aqueous alcohol, or NOCl with $Al(OPr^i)_3$ in toluene at –20 °C), further changes under aqueous conditions lead to the oximes of dialkoxyphosphinoylformyl halides (**298**), thought to exist in the nitroso tautomeric form[432,437,438]; a preference for one geometric form (generally the *Z* form) is realized, but with a decrease in solution concentration, the amount of (*E*)-enol increases. A rise in the temperature leads to the decomposition of the compounds **299** under aqueous conditions also leads to the species **297** in amounts which depend on the individual halogen, chlorine producing just a trace, whereas the yield with bromine is about 20%. The structurally complex nature of compounds **297** and **298** (X = H) has been examined more fully elsewhere by NMR spectroscopy[439,440].



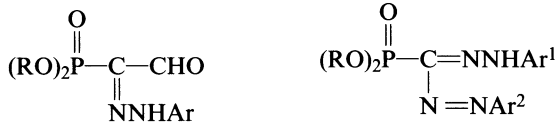
(**297**)

SCHEME 43

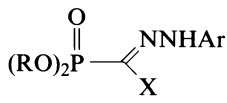


(**298**) (**299**)

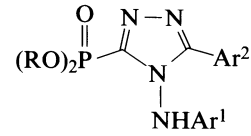
β-(Dialkoxyphosphinoyl)acetaldehydes react with aryldiazonium salts in dilute solution at pH 4–6 to give the arylhydrazones **300**; traces of the compounds **301** (*C*-phosphorylated formazans) may also be formed at the same time. The arylhydrazones **300** are tautomeric and also exist in geometrically isomeric forms[441–443]. Similar reactions with the α-halogenated acetaldehydes lead to the formyl hydrazones **302**, analogous to the oximes **298**[444,445]. When heated in boiling toluene, the *C*-phosphorylated formazans undergo a transformation into phosphorylated 1,2,4-triazoles **303**; other heterocyclic systems are obtained in boiling MeCN[445,446].



(**300**) (**301**)

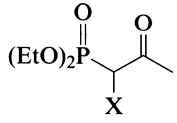


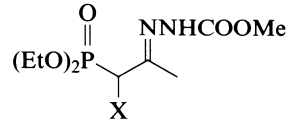
(302)



(303)

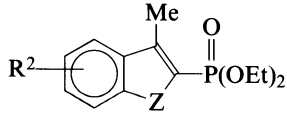
Indeed, one of the main uses of β-phosphorylated ketones is the synthesis of *C*-phosphorylated heterocyclic systems, and in this respect the reactions very often complement those of isomeric acylphosphonates. In the first of the examples chosen, the ketone **304** cannot be converted into **305** in a direct reaction with the appropriate amine; instead, the carbonyl group must be protected as in **307**, when a reaction with the amine then gives **308**; hydrolysis of **308** with 3 M HCl yields **305**. When treated with $ZnCl_2$ under toluene, **305** yields the indolylphosphonic diester **310**[447]. In the same way, a direct reaction between **304** and ArONa fails to give **306**, which must therefore be prepared via **307** and **309** with acid hydrolysis to **306**; when the latter is treated with hot polyphosphoric acid, cyclization occurs to give the benzofuranylphosphonic diester **311**[447,448]. In order to obtain the isomeric compounds **312** and **313**, the bromoketone **314** can be converted directly into **315**, but in order to obtain the ether **316**, it is necessary for a preliminary reaction between the enamine **317** and aryloxide to give **318**, hydrolysis of which gives the desired **316**. Compound **315** with $ZnCl_2$, and compound **316** in hot polyphosphoric acid yield **312** and **313**, respectively[447,448]. Several phosphorylated indoles have been obtained by the polyphosphoric acid cyclizations of arylhydrazones from (1-oxoalkyl)- and (2-oxoalkyl)-phosphonic diesters, and even by simply heating together dialkyl (3-oxoalkyl)phosphonates and phenylhydrazines in ethanolic solution[212]. The ketone **304** (X = Cl) has been used to make the pyrrole

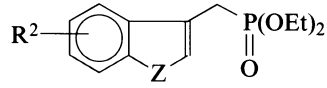




(**304**) X = Cl or Br
(**305**) X = $NR^1C_6H_4R^2$
(**306**) X = OAr

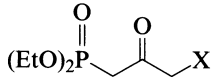
(**307**) X = Cl or Br
(**308**) X = $NR^1C_6H_4R^2$
(**309**) X = OAr

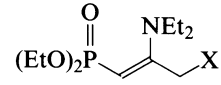




(**310**) Z = NR^1
(**311**) Z = O

(**312**) Z = NR^1
(**313**) Z = O

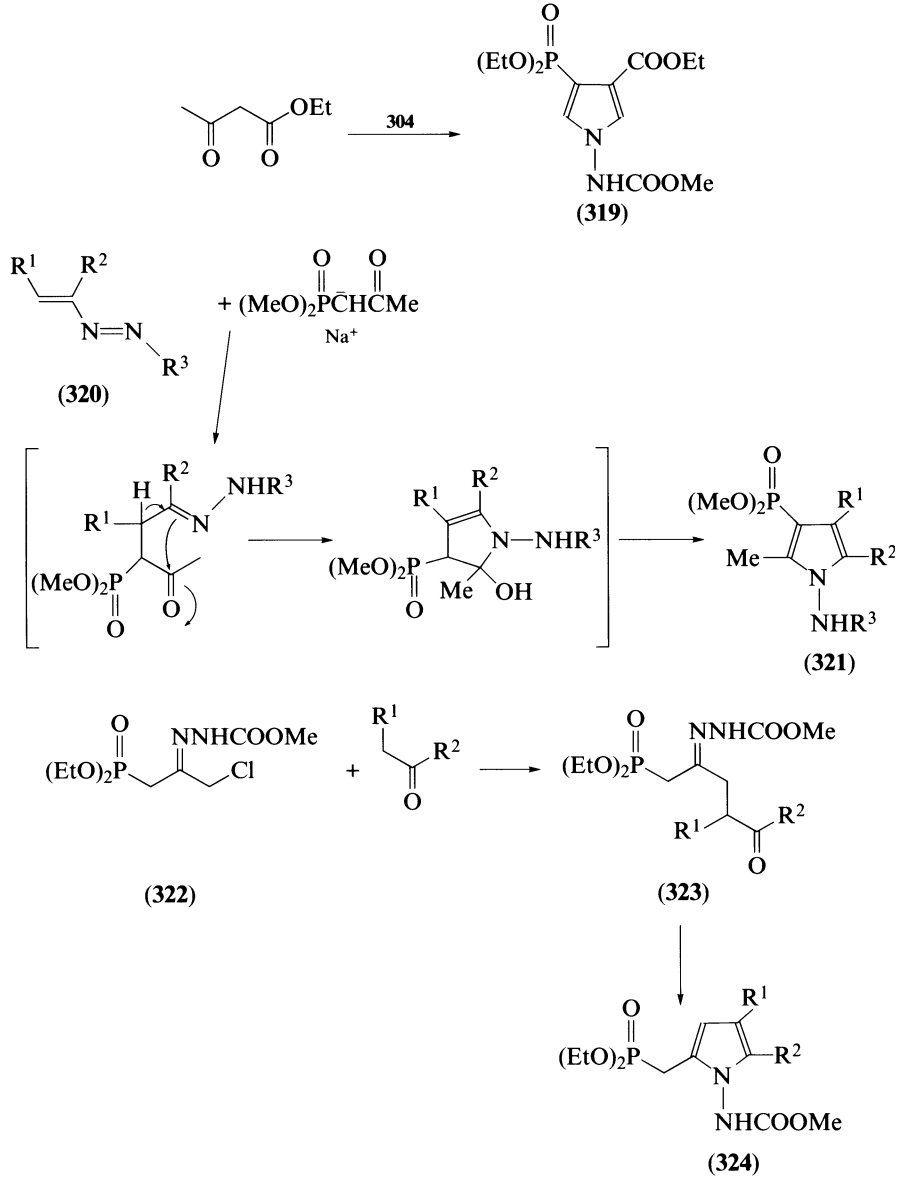


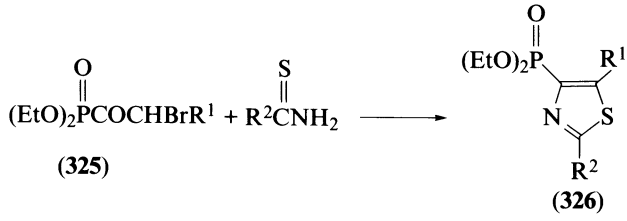


(**314**) X = Br
(**315**) X = NR^1Ar
(**316**) X = OAr

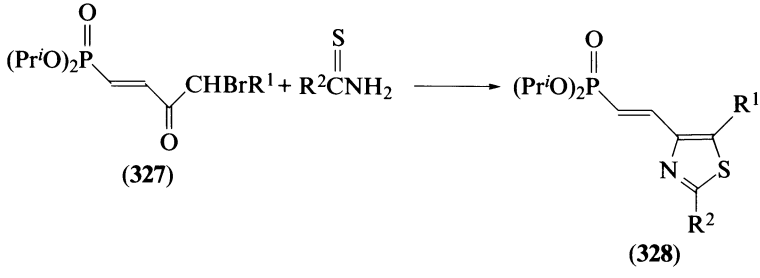
(**317**) X = Br
(**318**) X = OAr

319 through a reaction with ethyl 3-oxobutanoate[449], and related compounds **321** were prepared from the species **320** (R^1, R^2 = COOR, $CONH_2$ or CONHPh)[450]. The hydrazone **322** acts as a source of **323**, the precursor to other pyrroles, **324**[449]. The bromination of a dialkyl (1-oxoalkyl)phosphonate (Br_2–CCl_4) or unsaturated analogue (nbs–aibn) leads to brominated intermediates **325** and **327**, which are precursors to the thiazoles **326** and **328**[451]. A simple transformation is that of di-β-oxo compounds such as **329** into the 4-phosphinoylpyrazoles **330**[452].

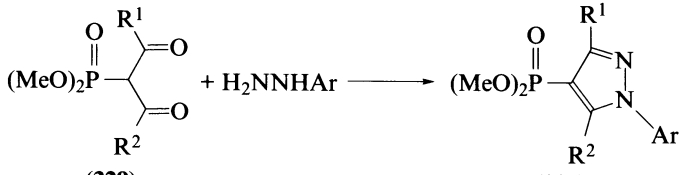




(325) (326)

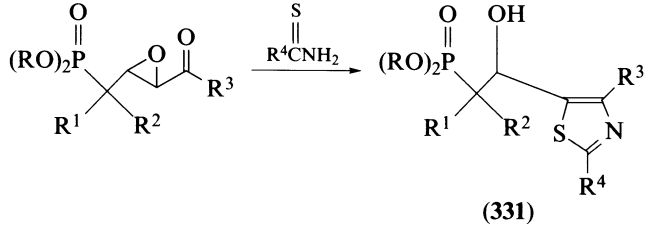


(327) (328)



(329) (330)

In combination with an adjacent oxirane nucleus, the carbonyl group is a valuable starting point for the synthesis of additional heterocyclic systems; reactions which involve thiocarboxamides or thioureas lead to the monocyclic 1,3-thiazoles **331**[453] and **332**[363]. The subsequent removal of the hydroxy function has been described earlier in this Chapter (Section IV.C).



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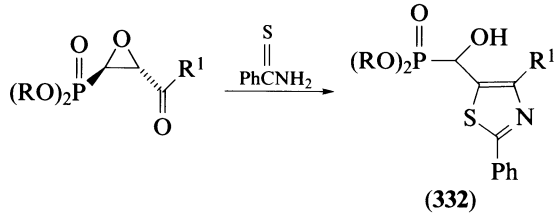
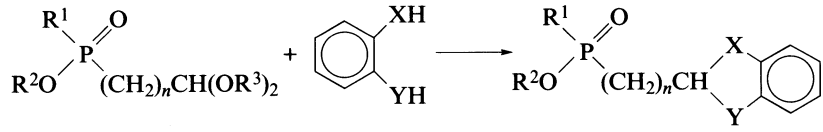


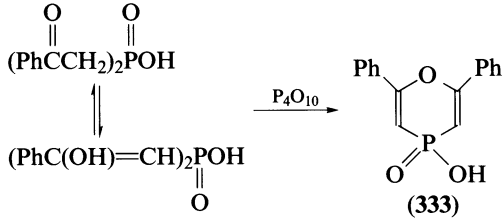
(332)

In addition to acetal formation with simple alcohols, (oxoalkyl)phosphonic diesters afford dioxolanes or dithiolanes from 1,2-diols or 1,2-dithiols[454]. It is possible to transpose oxo protecting groups as illustrated in equation 15 (n = 0, 1 or 2; X, Y = O, S or NH)[455–457].



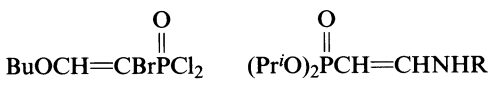
(15)

The reaction between (2-oxoalkyl)phosphonic diesters and triethyl orthoformate in the presence of iron(III) chloride yields the enol ethyl ethers[458], while reactions with amines afford enamines[459]. When heated with P_4O_{10}, enols may undergo dehydration, as in the reaction with diphenacylphosphinic acid in hot toluene, which gives the 1,4-oxaphosphorin **333**[460].



(333)

Enol ethers from (2-oxoalkyl)phosphonic diesters are themselves highly reactive in hydrolysis and addition reactions. (2-Butoxyethenyl)phosphonic dichloride in CCl_4 solution readily adds bromine in the cold, but attempts to distil the resultant (1,2-dibromo-2-butoxyethyl)phosphonic dichloride result in dehydrobromination; the product **334** is unreactive to further attempted bromination, but suffers ready hydrolysis to (1-hydroxy-2-oxoethyl)phosphonic acid, and similarly, hydrolysis of the precursor dichloride yields (2-oxoethyl)phosphonic acid[461]. Reactions between enol ethers and amides, carbamates or phosphoramidates, under acidic conditions, yield the enamides **335** [R = CO-alkyl, CO-aryl, COO-alkyl or $P(O)(OPr^i)_2$][462]. (2-Alkoxyethenyl)phosphonic diisocyanates act as precursors to phosphapyrimidines **336** and analogous phosphapurines[463].



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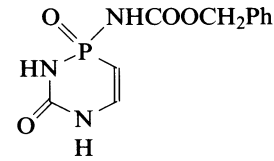


(336)

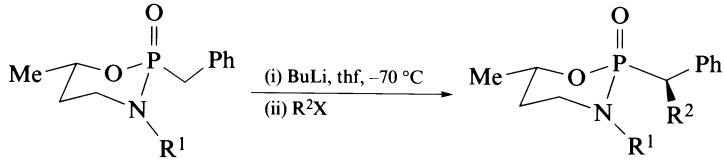
V. REACTIONS AND PROPERTIES OF THE CARBON LIGANDS: THE CARBON SKELETON

The modifications which may be carried out to the carbon ligands in phosphonic and phosphinic derivatives are based on changes in degree of unsaturation through addition or elimination reactions, or the simple branching of a carbon chain through alkylation or acylation. The latter may be carried further through the conversion of a linear structure into a ring, not only through initial substitution reactions but also by means of various cycloaddition reactions. Many examples of reactions which lead to changes in hybridiza-

tion at carbon or to branching have been given in earlier chapters on synthesis in those sections headed 'synthesis by modification', but the topic of modification to the carbon ligand is now developed further.

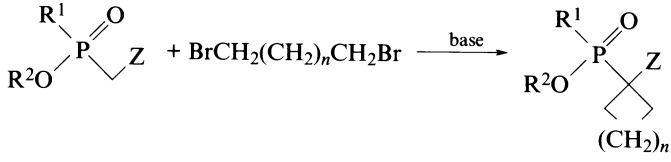
A. Alkylation and Acylation at Carbon

Arguably the simplest modification to the carbon ligand in a phosphonic or phosphinic acid derivative which can be brought about is that of alkylation of the derivative carbanion; although this has been normally carried out with a simple alkyl halide, a dialkyl sulphate or alkyl sulphonate may also be used. As in conventional organic synthesis, alkylation at carbon is rendered easier in the presence of an adjacent electron-withdrawing group; the more powerful the electron withdrawal, (generally) the easier is the alkylation. Alkylation at carbon sited between two phosphoryl groups or between a phosphoryl-containing moiety and a carbonyl group, is thus relatively easy to achieve after the prior generation of the carbanion with an appropriate base (Na, NaH, BuLi, PhLi, $NaNH_2$, lda, etc.). A desired monoalkylation reaction may be accompanied by undesired dialkylation which may then necessitate troublesome separation of products. A recent study which demonstrated a steric effect in alkylation involved the perhydro-1,3,2-oxazaphosph(V)-orines **337** and their stereoisomers **337′** epimeric at phosphorus. In the first of two series of experiments on the substrates **337** (R^1 = Me, Et, Pr^i or Bu^t), the ratio of diastereoisomeric products, **338** and the carbon epimers, remained unchanged at ca 96:4, and only fell to 90:10 for $R^1 = CEt_3$ for alkylation by MeI(and the results were similar for the same series in their reactions with **337′**); for alkylation by benzyl bromide, the stereoisomeric composition was ca 92:8, which fell to 84:16 for $R^1 = Bu^t$ and to 80:20 for $R^1 = CEt_3$. In the alkylation of **337** ($R^1 = Pr^i$) by a variety of alkyl halides R′X, the product diastereoisomer ratios were within the range 100:0 to 94:6 for R′ = Me, Pr^i, Bu, Bu^i, $H_2C{=}CHCH_2$ or $PhCH_2$[464]. Alkylation at carbon adjacent to phosphoryl, even in the presence of chlorine attached to $C_{(1)}$, is possible in the presence of K_2CO_3 under thf[465]. Magnesium under liquid ammonia has also been used in the alkylation (at carbon) or acylation (at oxygen) of **291** (R = Et, R^1 = Me)[466]. Even arylation at a phosphoryl-activated carbon by aryl iodides in the presence of copper (I) iodide has been noted for (diethoxyphosphinoyl)acetonitrile, although the phosphorylated products themselves were not isolated[467].



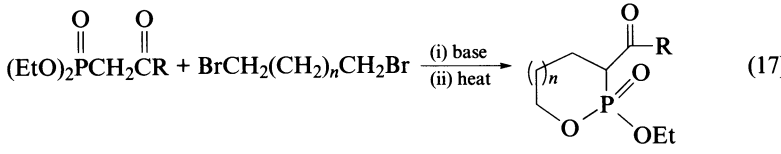
(337) (338)

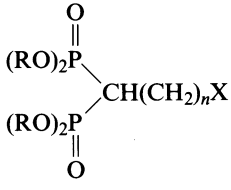
1,2-Dibromoethane has been widely used to prepare phosphonoylated or phosphinoylated cyclopropanes; in this process (equation 16; $n = 0$; Z = CN, COOR)[468–470], the reaction can also be carried out with K_2CO_3–dmso[471,472], or under phase-transfer conditions (with a quaternary ammonium salt–HO^-)[473,474]. Initial mono-*C*-alkylation may be followed by



(16)

cyclization through thermal *O*-alkylation as a result of phosphoryl nucleophilicity; examples of the overall reactions are illustrated in equation 17 (n = 1, R = EtO)[475] and (n = 0 or 1, R = Me)[476]. Alkylation, in accordance with reaction 16, is rendered facile particularly when Z = SO_2R (R = Me or Ph) or Z = aryl, but also when Z = SR (R = Me or Ph)[477]. Reactions between methylenebisphosphonic tetraesters (as their anions) and α,ω-dibromoalkanes or analogous ditosylate esters have also been reported to yield the linear compounds **339** or **340**, or the cycloalkanebisphosphonic acid derivatives [equation 16; Z = Me(RO)P(O) or $(RO)_2P(O)$], depending on the relative amounts of reactants and conditions[478]. Other examples, e.g. **341** (Z = COOEt or PO_3Et_2), have been similarly obtained[478,479].





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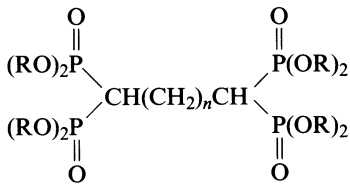
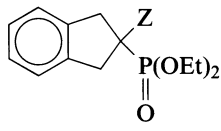
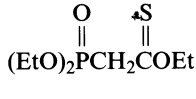


(340)

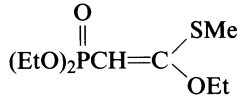


(341)

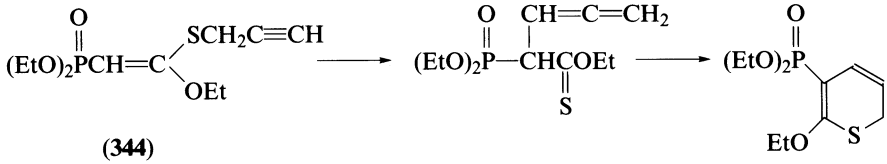
Attempts to alter the carbon skeleton by alkylation are always potentially complicated in the presence of a functional group more nucleophilic than phosphoryl and capable of involvement in tautomerization, thus raising the possibility of alkylation at the heteroatom. Cyclizations similar to those just described have been performed using analogous phosphono- or phosphino-thioates, and it is worth noting that although alkylation might be expected to occur preferentially at sulphur (Chapter 5, Section III.B.1), cyclization through alkylation at sulphur does not appear to have been reported in these reactions (however, see the further discussion about this topic in Section VI)[480]. The simple methylation (Na, MeI) of the ester **342** leads to the phosphonoylated ethene **343**[481]. An unusual consequence of this process is illustrated in Scheme 44; the synthesis of the *S*-propargyl compound **344** is complicated by a sequence of bond shifts which lead to a *C*-phosphorylated 2*H*-thiapyran[481]. Nevertheless, it is often possible to obtain one or the other product



(342)



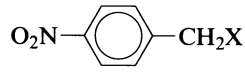
(343)



(344)

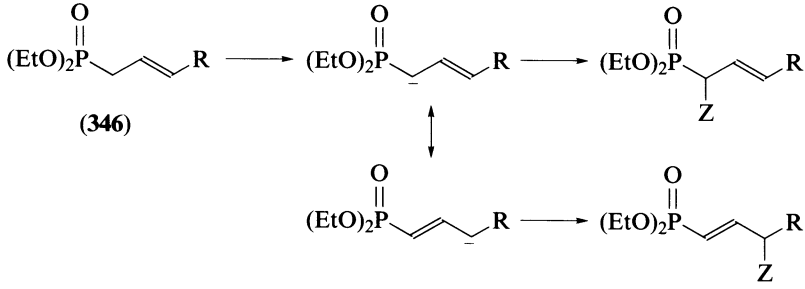
SCHEME 44

under specific experimental conditions and careful choice of leaving group. In the alkylation of triethyl phosphonoacetate anion with 4-nitrobenzyl compounds **345**, S_N2 *O*- and *C*-alkylations are increasingly inhibited with decreasing ability of the leaving group to depart, while at the same time $S_{RN}1$ alkylation at carbon is facilitated[482]. The problem, as a whole, is thus very similar to that of the classical alkylation or acylation of simple active methylene compounds.



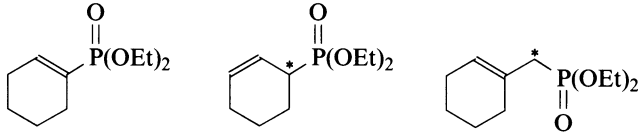
(345)

The special problems associated with the reactivity of allylic phosphonate anions in, for example, their reactions with aldehydes which can occur in a reversible manner at either $C_{(1)}$ or $C_{(3)}$, are also to be found elsewhere (see Chapter 3, Section III, and this Chapter, Section VI). When diethyl allylphosphonate (**346**; R = H) is treated with BuLi in an aprotic solvent at –50 °C, the lithiated species is formed; by using slightly different methods for the generation of the 'anion', the formation of localized lithiated monocarbanions at $C_{(1)}$ or at $C_{(3)}$, together with a delocalized ion of *E* configuration, was observed by means of ^1H, ^{13}C and ^{31}P NMR spectroscopy. Furthermore, at –50 °C in a solvent of low polarity such as diethyl ether or triethylamine, the $C_{(1)}$ localized anion is converted into the $C_{(3)}$ carbanion at a measurable rate[483]. Such properties obviously have implications regarding the reactivity of the carbanions and their value in synthesis, as is seen in the complex picture for the silylation of diethyl allylphosphonate (**346**; R = H) anion prepared with Li–hexamethyldisilazane, when isomeric monosilylated and disilylated products have been recognized[484].



(346)

Although the ester **347** forms a carbanion, this fails to react with simple alkyl halides and does not incorporate deuterium when quenched with D_2O; on the other hand, lithiated anions from **348** and **349** (the former does not form a carbanion with NaH) react with alkyl halides, apparently exclusively at the C* positions[485].



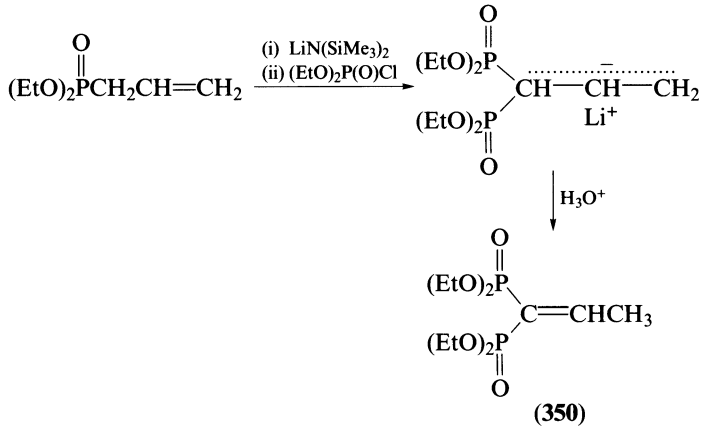
(347) **(348)** **(349)**

The acylation of triethyl 3-phosphonopropanoate with diethyl oxalate and NaH (the Stobbe condensation) is notable in that it occurs at carbon α to the carboxy ester group,

indicating a lesser activation by the phosphoryl group[486–488], a phenomenon found elsewhere in, for example, attack by nucleophiles on mixed anhydrides, particularly in ring structures.

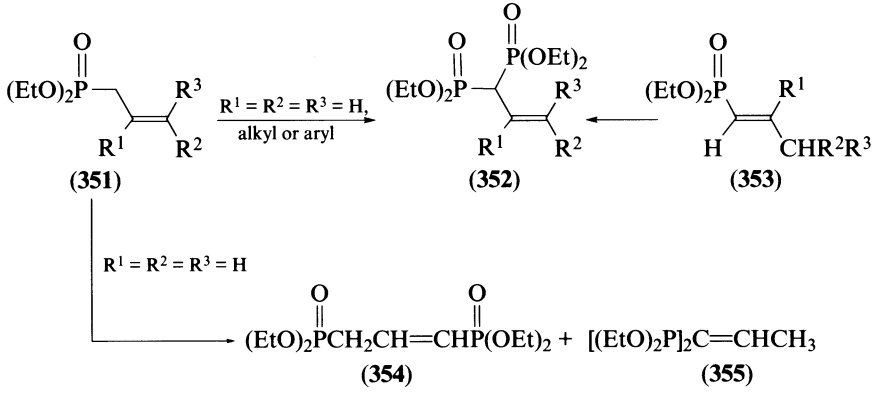
B. Hybridization Modifications to Phosphorus-bonded Carbon Atoms

From the previous paragraphs, it would appear that, under controlled conditions, it might be possible to effect a change in the hybridization of carbon bonded directly to phosphorus through the use of allylic phosphonates or related compounds and, indeed, it has been claimed that the phosphorylation of diethyl allylphosphonate itself can be used to prepare the propenylidene-1,1-bisphosphonic ester **350** (Scheme 45)[489].



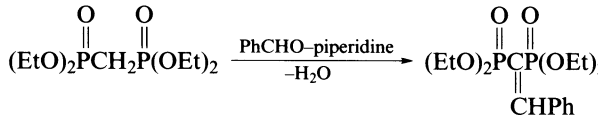
SCHEME 45

This result would appear to be at variance with the more complex picture presented later by Chinese workers. The latter[490] showed that when the allylic phosphonates **351** were converted into their carbanions with lda in thf, and phosphorylated with diethyl phosphorochloridate, the phosphorylation reaction occurred at the α-carbon to give **352**, and the latter were also formed from the similar treatment of **353**; when, however, hmp was added to the solvent for the first of these two reactions, the products then consisted of two different compounds, **354** and **355**, in the ratio 4:1. The difference in the reaction outcome



was ascribed to the removal of lithium into a complex with the hmpa so engendering a difference in carbanion structure.

A simple application (equation 9) of the WEH reaction (Section III.C), in which there is a distinct lack of side reactions, illustrates the potential scope particularly since the methodology may be extended such that the groups R^1 and R^2 may be functionalized[491]. This methodology is receiving increasing attention as a means of preparing phosphonic and phosphinic acids based on P—C(sp^2) bonds. At the same time, it will also be recalled that WEH reactions cannot be carried out satisfactorily if amines are used as the base catalyst, because of the potential for other condensations. The most important of these is the Knoevenagel condensation, the difference in reaction outcome being illustrated in the reaction of tetraalkyl methylenebisphosphonates with benzaldehyde in the presence of piperidine with azeotropic removal of water with xylene (reaction 18)[492].



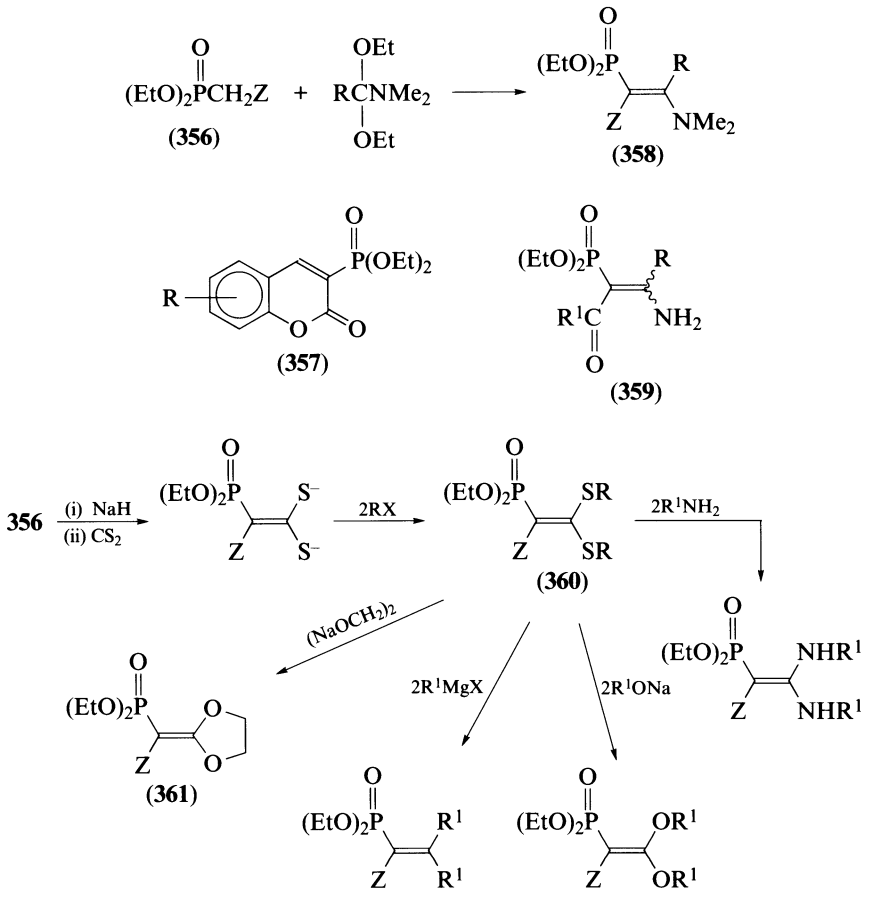
(18)

This particular example is one which requires slightly more forcing conditions that those required for the compounds **356** for which the ease of reaction with benzaldehyde increases in the order Z = COOEt < COMe < CN, and for which water can be removed azeotropically with benzene[493–495], and reactions also proceed with Z = $CONH_2$[496]. The standard procedure is based on the conditions adopted by Patai and Schwartz[497] and by others[498] for reactions between triethyl phosphonoacetate and benzaldehyde in the presence of piperidine–acetic acid catalyst in benzene; the condensation proceeds for simple aliphatic aldehydes and ketones[499–501] but not with benzophenone[497]. Titanium chloride ($TiCl_4$) enhances the catalytic capability of piperidine in condensations between substituted 2-hydroxybenzaldehydes and triethyl phosphonoacetate[502] or tetraethyl methylenebisphosphonate[503] to give diethyl (coumarin-3-yl)phosphonates (**357**). Furthermore, the nature of an added titanium catalyst, and whether this leads to chelated or non-chelated titanium-containing species, has been found to control the stereochemical outcome of the reaction with aldehydes, as typified by benzaldehyde. The latter, in combination with $TiCl_4$–*N*-methylmorpholine yields the *E*-product, whereas the use of NaH–$ClTi(OPr^i)_3$ affords *Z*-product complicated by transesterification at the carboxy group[504,505]. The condensations between **356** (Z = CN, COOMe or $CONH_2$) and aldehydes (both aliphatic and aromatic) are catalysed also by MgO with very high yields, and the high *Z*:*E* ratios for reactions between benzaldehyde and diethyl (cyanomethyl)phosphonate with this catalyst in dmf or dmso are completely reversed on the addition of $HgCl_2$ or $CdCl_2$[506].

The introduction of a phenylseleno group on the α-carbon followed by peroxide oxidation[507] to give the triethyl ester of 2-phosphonopropenoic acid is an alternative to the piperidine–catalysed condensation of triethyl phosphonoacetate with formaldehyde[508] as examples of the conversion of an α-sp^3 -carbon into an α-sp^2 -carbon.

Condensations between members of the series **356** (Z = NO_2, CHO, COR, COOR, $CONMe_2$ or CN) and dimethylformamide dimethylacetal[509,510] or its homologues[511] provides the enamines **358**, readily hydrolysed under acidic or basic conditions to β-carbonyl-containing phosphonic esters; the enamines are a source of pyrazoles, pyrrolidines and pyrimidines bearing phosphonic substituents[509,510]. Condensations between **356** (Z = COMe or COOEt) and RCN (R = CN or CCl_3) in the presence of [$MnAc_2$] or [$Mn(acac)_2$] yield the enamines **359** (R^1 = Me or OEt)[512].

The anions from **356** [Z = $P(O)(OEt)_2$[513,514] or COOMe[515]] react with carbon disulphide to give ethylenic dithiolate anions which may be alkylated to give **360**; the latter (e.g. with R = Me) undergo a variety of displacement reactions (Scheme 46)[513–517] to give compounds



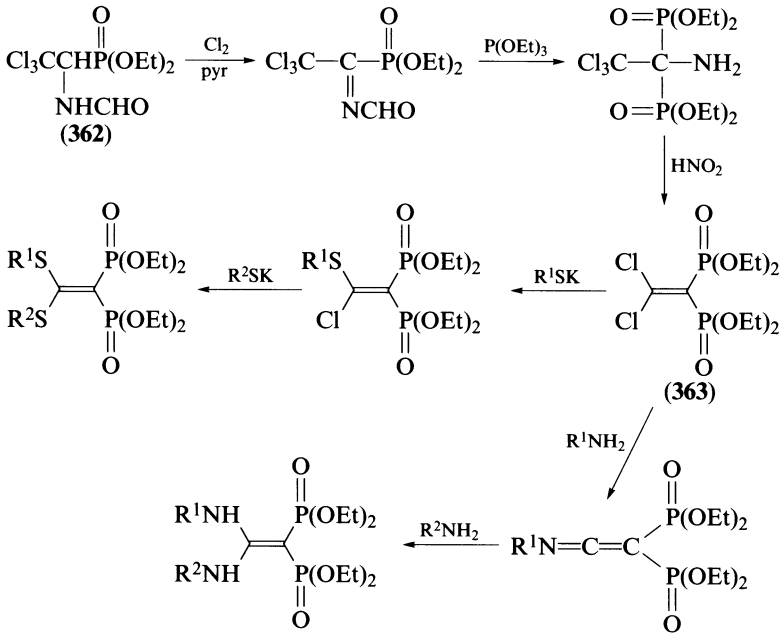
SCHEME 46

with P—C(sp^2) bonding. The 2,2-bis(methylthio) compound **360** (R = Me) has also been prepared through an independent route (Scheme 47) and via tetraethyl (2,2-dichloroethene-1-diyl)bisphosphonate (**363**)[518,519]; its source, the ester **362**, itself appears to be a valuable starting material for the synthesis of a variety of novel compounds including several heterocyclic systems bearing diethoxyphosphinoyl groups[520–522].

Further changes in hybridization are observed in additions to carbon–carbon multiple bonds adjacent to phosphorus; for convenience, these reactions are collected together in a separate section.

C. Some Reactions of Carbon–Carbon Multiple Bonds

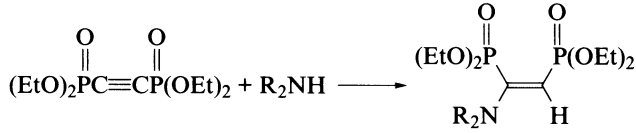
The particular interest here is the reactivity of carbon–carbon multiple bonds when attached to the phosphorus atom. However, there are also reactions of considerable interest in which the phosphorus ultimately participates in reactions which initially occur at carbon–carbon double bonds distant therefrom.



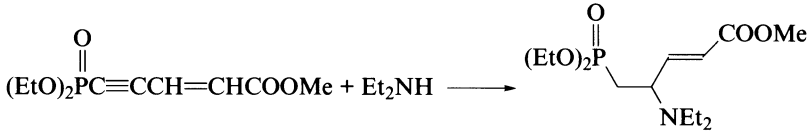
SCHEME 47

1. *The carbon–carbon triple bond*

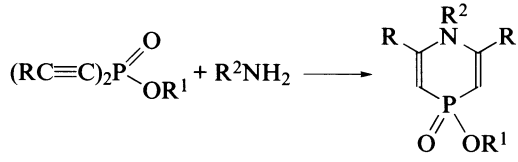
The carbon–carbon triple bond is reducible to the *cis* ethene bond with the aid of the Lindlar catalyst[523]. The triple bond is also highly reactive towards nucleophilic reagents: amines add to give enamines, even when conjugated to double bonds (equations 19 and 20)[524,525] and with diethynylphosphinic derivatives, the addition of ammonia or primary amines yields 1,4-dihydro-1,4-azaphosphorines (equation 21)[526].



(19)

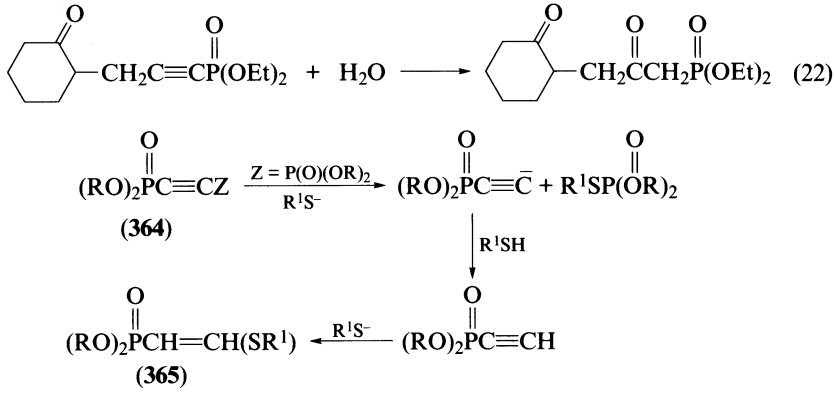


(20)

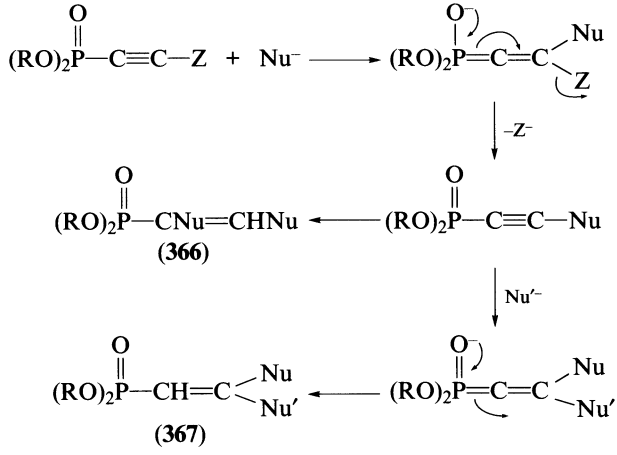


(21)

Hydration in the presence of mercury(II) sulphate yields an (oxoalkyl) compound (equation 22)[527]. The treatment of the phosphonic ester **364** (R = Et, Z= PO_3Et_2) with a thiolate leads, via diethyl ethynylphosphonate, to the ethenylphosphonic diester **365** with the concomitant formation of thiophosphate ester; in this particular case, the product **365** as initially formed, is of *Z* geometry, but isomerizes when distilled[521,528]. In other cases of the reactions with thiols, for instance with **364** (R = Et, Z = Cl), the direct replacement of Z is accompanied by overall displacement plus addition at each carbon to give products of types **366** (as a mixture of *E* and *Z* stereoisomers) and **367**[529]. The same substrate **364** (R = Et, Z = Cl) with the monosodium salt of ethane-1,2-diol represents an alternative route (substitution followed by addition) to **361**, but with more basic nucleophiles such as Bu^tO^-, and even MeO^-, cleavage of the phosphorus–carbon bond occurs, although the extent of this decreases, and the extent of addition (with EtO^- and PhO^-) increases, when R = Me is replaced by R = Et[529]. The additions of arylsulphenyl chlorides to **364** (R = Et, Z = Me) occur stereoselectively to give only the *E* products[530].



In general, a reaction between a basic nucleophile and an ethynylphosphonic diester carrying a displaceable group on an sp-carbon atom can be considered in terms of consecutive addition and elimination steps as indicated in Scheme 48.



SCHEME 48

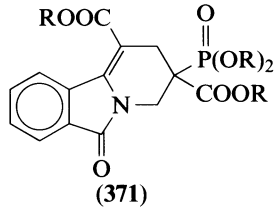
2. The carbon–carbon double bond

The carbon–carbon double bond is activated by adjoining phosphoryl groups to the additions of nucleophiles, as generalized in equation 23. Important amongst these reactions are those of amines, both simple amines which lead to (2-aminoethyl)phosphonic acids or their derivatives (usually the diesters)(Chapter 4, Section IV.C.1.a), and also of functionalized amines as in the addition of aminocarboxylic acids to the double bond in ethenylidenebisphosphonic acid; glycine, for example, yields **368** (Z = $NHCH_2COOH$)[531]. Treatment of the same substrate with an alkanethiol or thiophenol in acetic acid affords the adducts **368** (Z = RS or ArS)[532]. A further example, of potential value in synthesis, is the addition of an organometallic reagent (R^3M = MeMgI, $H_2C{=}CHCH_2ZnBr$ or $LiCuR'_2$) to α-substituted-alkenyl phosphonic diesters, **369** (R^1, R^2 = H, Me or Ph, Z = CN, COMe or COOEt) to give the corresponding **370**[533].

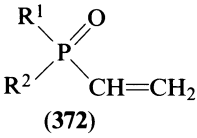
$$H_2C{=}C(PO_3H_2)_2 + ZH \longrightarrow ZCH_2CH(PO_3H_2)_2 \quad (23)$$
(368)

$$(RO)_2\overset{\overset{O}{\|}}{P}CZ{=}CR^1R^2 + R^3M \xrightarrow{(H_3O^+)} (RO)_2\overset{\overset{O}{\|}}{P}CHZCR^1R^2R^3$$
(369) **(370)**

The addition of the phthalimido anion to triesters of 2-phosphonopropenoic acid at room temperature gives an initial adduct, which is unexpectedly inert to benzaldehyde reaction but which adds to a second molecule of the phosphonic diester to form a second carbanion; the latter undergoes an intramolecular WEH condensation to give the heterocyclic system **371**; indolizine and quinolizine phosphonic diesters have been similarly obtained from maleimide, succinimide and glutarimide anions[534]. The ability of piperidine to add to the compounds **372** decreases in the order R^1R^2 = (BuO)H (exothermic reaction) > $(BuO)_2$ > (BuO)Me > Bu_2 (the last requires heat)[534]. Ethenylphosphonic diamides (**372**; $R^1 = R^2 = NR_2$) are unreactive to nucleophiles (by virtue of reduced electrophilic character at phosphorus and thus reduced electron attraction from the carbon–carbon double bond) but are reactive to electrophilic reagents[535].

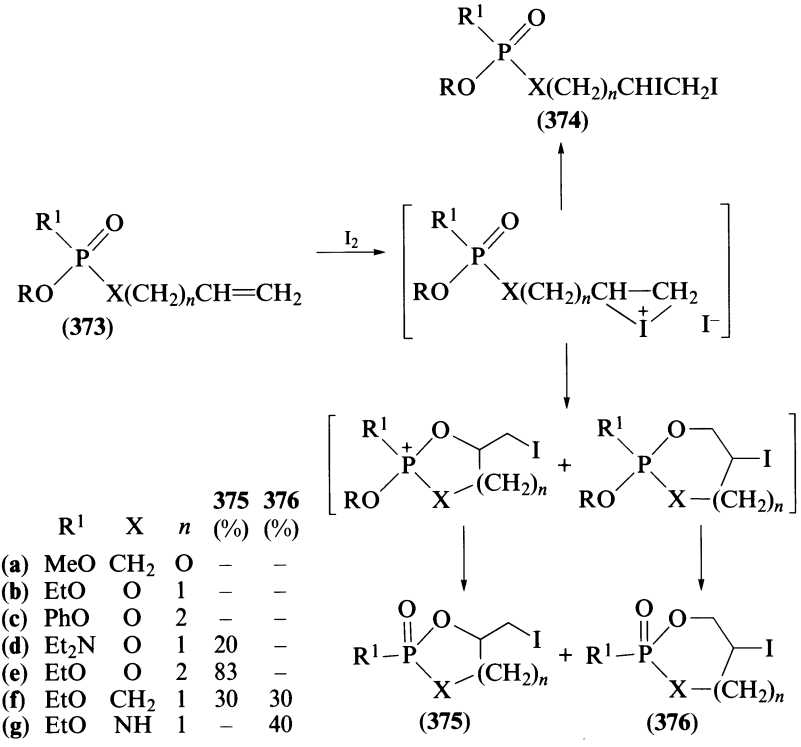


(371)



(372)

Carbon–carbon double bonds, whether attached directly to or are distant from the phosphorus, can undergo some unusual reactions, particularly when treated with electrophilic reagents such as the halogens or pseudo-halogens, a behaviour attributable to phosphoryl nucleophilic character. Ethenylphosphonic acid and its simple derivatives add chlorine or bromine with the expected overall results, but the 'normal' addition of the latter is rapidly accelerated by UV radiation and inhibited by added iodine, suggestive of a homolytic nature[537]. Dialkyl (pent-4-enyl)phosphonates (**373**; R^1 = RO, X = CH_2, n = 2) equally add bromine to give the expected dibromo adducts, but their behaviour towards iodine is more complex (Scheme 49)[536]. In reactions in $CHCl_3$ at ambient temperature, not only are the expected 4,5-diiodo adducts **374** formed, but so is an additional species, probably a quasi-



	R¹	X	*n*	375 (%)	376 (%)
(a)	MeO	CH_2	O	–	–
(b)	EtO	O	1	–	–
(c)	PhO	O	2	–	–
(d)	Et_2N	O	1	20	–
(e)	EtO	O	2	83	–
(f)	EtO	CH_2	1	30	30
(g)	EtO	NH	1	–	40

SCHEME 49

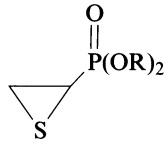
phosphonium salt, and in benzene the formation of yet a further intermediate is observed, which might be of a pentacoordinate nature. The nature of the product(s) of the sequence depends on X and R^1, both of which influence the nucleophilicity of the phosphoryl group. The compounds **373a–373c** yield only the iodine adduct **374**, but when $n = 2$ and R^1 = EtO, the products are ring compounds **375** or **376** with some dependence on the nature of X (CH_2, NMe, NH or O); in some cases, e.g. when R^1 = EtO, X = CH_2 and $n = 1$. mixtures of diastereoisomeric 1,2-oxaphosph(V)orinanes are formed[536,538–541]. A comparison between the ease of cyclization of unsaturated phosphonic diesters and esters of analogous unsaturated carboxylic acids revealed no substantial difference between the nucleophilicity required of the C=O or P=O groups in the rate-limiting step[541].

The further additions of electrophilic reagents to activated carbon–carbon double bonds in phosphonic derivatives include those of sulphenyl chlorides (equations 24 and 25).

$$\underset{\textbf{(377)}}{(RO)_2P(O)CR^1{=}CH_2} + R^2SCl \longrightarrow \underset{\textbf{(378)}}{(RO)_2P(O)CR^1(SR^2)CH_2Cl} + \underset{\textbf{(379)}}{(RO)_2P(O)CR^1ClCH_2SR^2} \quad (24)$$

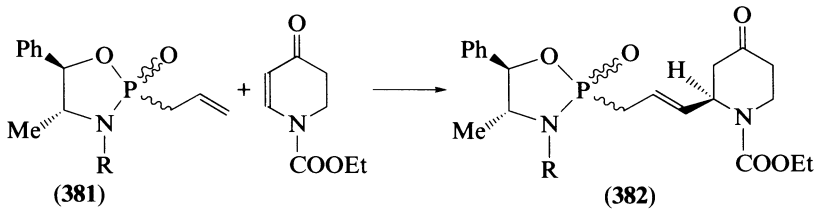
$$(RO)_2P(O)CH_2CH{=}CH_2 + EtSCl \longrightarrow (RO)_2P(O)CH_2CHClCH_2SEt \quad (25)$$

Detailed studies of such reactions are very few, but such a study of the interaction of ethenylphosphonic diesters (**377**; R^1 = H) and PhSCl indicated the simultaneous formation of the two regioisomers **378** and **379** (the Markownikoff product), with the 2-chloro adduct being thermodynamically more stable than the 1-chloro isomer, whereas a similar reaction with esters of (1-methylethenyl)phosphonic acid (**377**; R^1 = Me) gave the single products, **378**[542]. Only an anti-Markownikoff product has been claimed for the addition of EtSCl to diethyl ethenylphosphonate and to diethyl prop-2-enylphosphonate[543]. The ionic nature of the additions is evidenced by the enhanced rates for reactions in polar solvents; the replacement of P=O by P=S also enhances the reactivity towards PhSCl[542]. The ultimate products from acetylsulphenyl chloride and ethenylphosphonic diesters are the esters **380** of thiiranephosphonic acid[544].

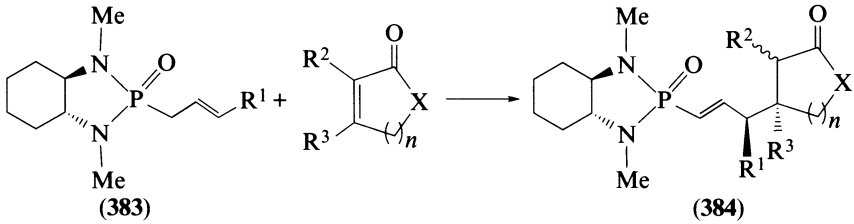


(380)

In the 1,4-addition of carbanions from the diastereoisomeric 1,3,2-oxazaphosph(V)-olidines **381** to cyclopent-2-enone[545], the replacement of R = Me by R = Pr^i increased the enantioselectivity considerably; good enantioselectivity was also achieved in additions to a didehydropiperidone to give **382**[546]. A more fully exemplified study of the conjugate addition of carbanions derived from the chiral phosphonic diamides **383** to cyclopentenones, cyclohexenones, lactones, lactams and conjugated unsaturated carboxylic demonstrated, once again, the high stereocontrol (with product ratios never less than 90:10 and often > 99:1) in the formation of the adducts **384** (*n* = 1 or 2; X = CH_2, O or NR)[547].

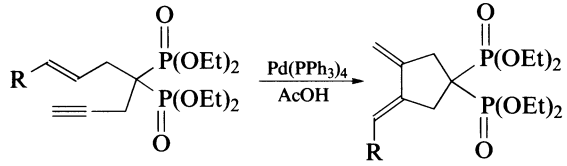


(381) **(382)**

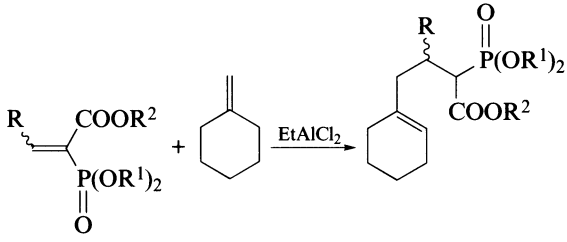


(383) **(384)**

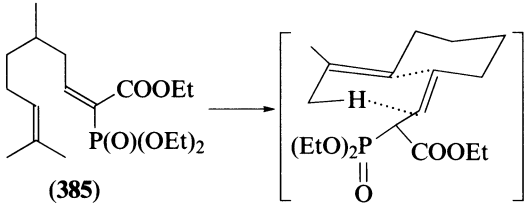
Equation 26 illustrates the rare enyne cycloisomerization process which is feasible under relatively mild conditions (in acetic acid at 80 °C for 6 h) in the presence of a palladium (0) catalyst[548]. In the presence of $EtAlCl_2$, alkenes undergo ene reactions with 2-(dialkoxyphosphinoyl)propenoic esters (equation 27[549]); the same catalyst, and other Lewis acids, catalysed the intramolecular reactions of **385** and **386** (*n* = 0 or 1), which are exemplified by reaction 28[550].



(26)

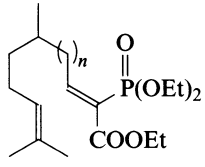


(27)



(385)

(28)



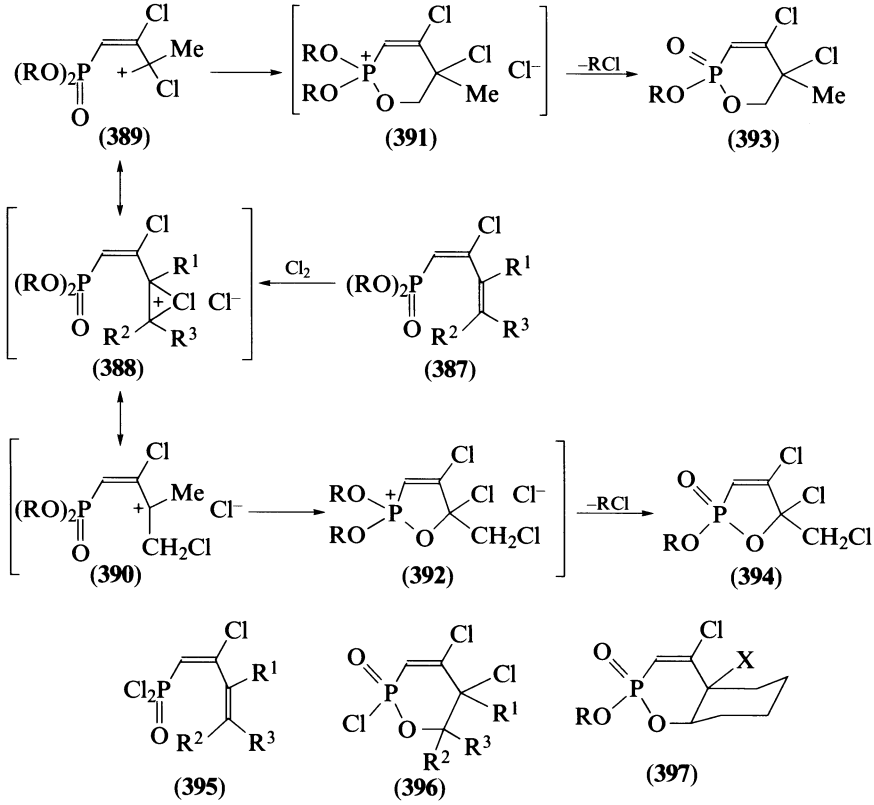
(386)

Many interesting transformations of polyene phosphonic derivatives have been observed, particularly in regard to the reactivity towards electrophilies of derivatives which possess either conjugated unsaturation or cumulative unsaturation in the carbon ligands, as in derivatives of (alka-1,3-dienyl)phosphonic and (alka-1,2-dienyl)phosphonic acids, respectively. One point needs to be (re)emphasized, namely the fact that the carbon–carbon double bonds in the first group are themselves conjugated, but in neither group of derivatives is there conjugation between the phosphoryl bond and a carbon–carbon double bond because of the tetrahedral nature of bonding about the phosphorus.

The hydrogenation, over palladium–$CaCO_3$, of halogenated (buta-1.3-dienyl)phosphonic diesters both removes the halogen and reduces the double bond furthest from the phosphorus centre[551].

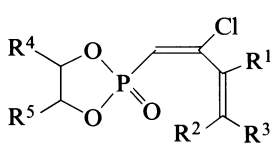
The bromination of (buta-1,3-dienyl)phosphonic acid derivatives (dichloride or diethyl ester) and those of diethyl (*Z*)- and (*E*)-(2-methylbuta-1,3-dienyl)phosphonates occurs across the double bond remote from phosphorus; the products may subsequently be dehydrobrominated with Et_3N[552]. The chlorination (with Cl_2 or SO_2Cl_2) of dialkyl (2-chlorobuta-1,3-dienyl)phosphonates also substituted at either $C_{(3)}$ or $C_{(4)}$, or at both positions, leads to mixtures of acyclic and cyclic products, with ring formation favoured by the *Z* configuration of the diene. In the case of the diesters **387** (R^1 = Me, R^2 = R^3 = H),

for example, attack by electrophilic chlorine leads to the isomeric primary **389** and tertiary **390** carbocations through a chloronium ion **388**; ring closure is rendered feasible by the nucleophilicity of the phosphoryl group and affords the pseudoquaternary phosphonium salts **391** and **392** (evidence for the participation of which stems from other studies with unsaturated phosphine oxides) which, in turn, break down into the isomeric dihydro-1,2-oxaphosph(V)orin **393** and the 5*H*-1,2-oxaphosph(V)ole **394**; in one particular study, these compounds were obtained in the ratio of ca 4:1[553]. In addition, each of the products is capable of existence as diastereoisomers, detectable most readily by NMR spectroscopy, but generally not separated. Chlorination (by SO_2Cl_2) of the phosphonic dichlorides **395** yielded the cyclic phosphonic chloride **396**[554] and chlorination (Cl_2) or bromination (Br_2) of the ester **387** [R^2 = H, R^1 R^3 = $(CH_2)_4$] gave only the bicyclic products **397** (X = Cl or Br)[555,556]. It would appear that the nature of the product(s) depends, at least partly, on the relative stabilities of the two carbocations **389** and **390**, interchangeable through the common ion **388**[557].

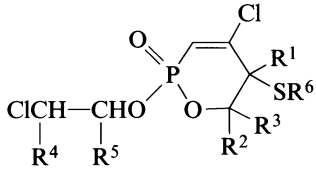


The phosphonic esters **397** (X = SR^4, R^4 = Me, Pr^i, Ph or 4-methylphenyl) are equally obtainable through reactions with the sulphenyl chlorides R^4SCl[558]. In a further development, the 2-chloro-1,3-dienes **398** (R^4, R^5 = H or Me) when acted upon by a sulphenyl chloride behave in a manner which depends on the individual reactants; thus, reactions with an alkylsulphenyl chlorides R^6SeCl (R^6 = Me or Pr^i) lead to products with the six-membered ring, **399**, the reaction intermediate then being of the form **400** (in place of the corre-

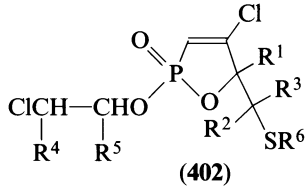
sponding **391** or **392**), or possibly **401**. When R^6 = Ph or 4-methylphenyl, the products are then **402**[559].



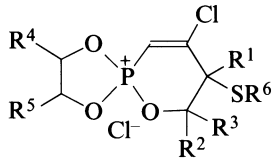
(**398**)



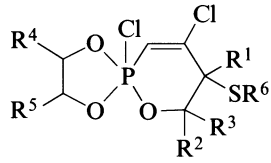
(**399**)



(**402**)

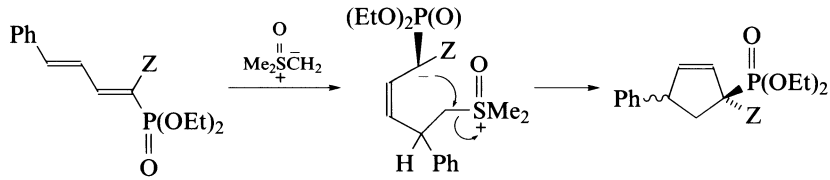


(**400**)



(**401**)

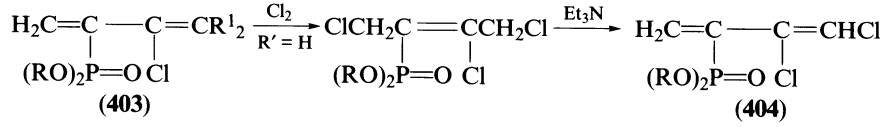
The formation of (cyclopent-2-enyl)phosphonic diesters from (buta-1,3-dienyl)phosphonic diesters by the action of a dmso-derived ylide or a triphenylphosphonium ylide is depicted in Scheme 50 (Z = CN, COOEt or SO_2Me)[560]. The role of esters of ethenyl- and buta-1,3-dienyl)phosphonic acids in organic synthesis has been surveyed[561].



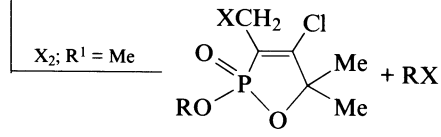
SCHEME 50

Only a few examples are known of reactions which involve isomeric (buta-1,3-dien-2-yl)phosphonic derivatives. The course of chlorination of the esters **403** depends on the nature of the substituent R^1; when the latter is hydrogen, classical 1,4-addition of halogen can be followed by Et_3N-promoted dehydrohalogenation to give the esters **404**, but when R^1 is methyl (i.e. the diene terminal carbon is tertiary), the result is the formation of the 1,2-oxaphosph(V)ol-3-ene **405**, the outcome being dependent, presumably, on the stability of an intermediate carbocation[562].

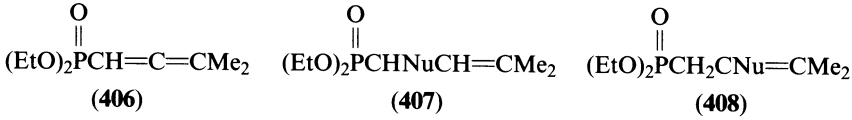
Because of the nature of the bonding in the carbon moiety, derivatives of (alka-1,2-dienyl)phosphonic acids undergo a range of reactions which affect only one of the double bonds, and the simplest of which is the hydrogenation of the esters in the presence of 50% Pd–$CaCO_3$ to produce the esters of (*Z*)-(alk-1-enyl)phosphonic acids[563]. The addition of a nucleophilic reagent XH [RNH_2, R_2NH, RONa–ROH, $(RO)_2PONa$] to diethyl (3-methylbuta-1,2-dienyl)phosphonate (**406**) can provide four theoretically possible products, **407**–**410**.



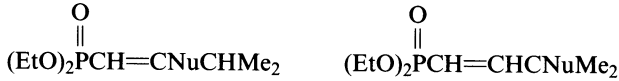
(403) (404)



(405)



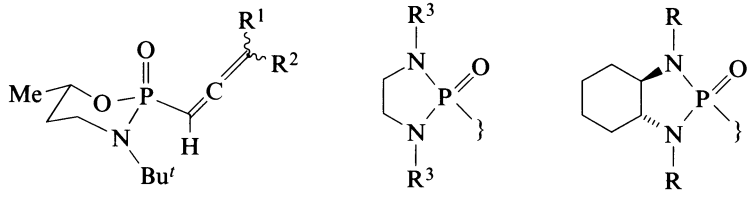
(406) (407) (408)



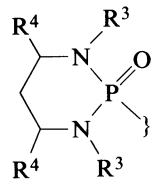
(409) (410)

The regiochemistry of addition was studied by the chemical examination (ozonolysis, $KMnO_4$ oxidation) of the reaction products; these experiments confirmed that additions of the above nucleophiles occur at the central carbon of the double bond system, a process which, by subsequent protonation at $C_{(1)}$ or $C_{(3)}$, limits the possibilities to two, **408** and **409**, of which only the latter was found to be present. The yields in such nucleophilic additions (exothermic with RO^-, but requiring slight thermal assistance but otherwise no catalysis for Et_2NH) could be as high as 60–90%[564–566]. It might be recalled that the addition of allyloxide to diethyl (3-methylbuta-1,2-dienyl)phosphonate occurred through attack at the central carbon, and subsequent protonation yielded a mixture of isomeric products which then rearranged to the ketones **202** and **203**; the initial adducts were not isolated[340]. On the other hand, when the other ligands at phosphorus (apart from the phosphoryl group) were part of the perhydro-1,3,2-oxazaphosphorine ring as in **411**[341] or part of a 1,3,2-diazaphospholidine ring, as in **412** or **413** (R^3 = Me, Pr^i, Bu^t, Ph or $PhCH_2$), or of a perhydro-1,3,2-diazaphosphorine ring, as in **414** (R^3 = Pr^i or $PhCH_2$, R^4 = H or Ph) or (**415**), the addition of allyloxide even at –10 °C gave mixtures of allyl ethers, rearranged ketones and alk-1-ynylphosphonic diamides in proportions which are dependent on the individual phosphonic diamides, the metal counter ion and time of contact[342].

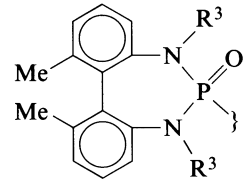
The addition of a thiolate anion to **406** yields an ester of the type **408** (Nu = SR′)[567]. The addition of Et_2NH to dialkyl (1-methoxymethyl propadienyl)phosphonate is slightly



(411) (412) (413)

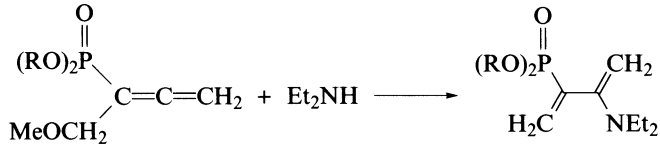


(414)

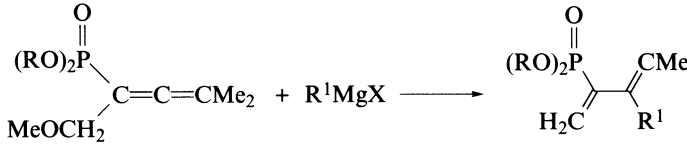


(415)

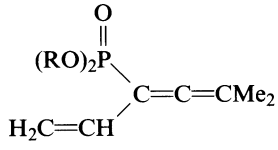
unusual in that the reaction involves the elimination of the methoxy group (equation 29)[568], a feature also to be found in reactions of the esters with Grignard reagents (equation 30)[569,570]. The position of attack is unaffected by the presence of an extra double bond as in reactions of the esters of (penta-1,3,4-trien-2-yl)phosphonic acid (**416**) with Et_2NH which yields **417** (Z = NEt_2)[571] or with alkoxides to give **417** (Z = OR′) as mixtures of *E*-and *Z*-isomers[572,573]. The pyrazolinyl- and indolinyl-phosphonic esters, **418** and **419** respectively, result from 1,4- and 1,2-additions of phenylhydrazine to the esters **416**[574]. The additions of *O,O*-dialkyl phosphorothioic acids[575], *O,O*-dialkyl phosphorodithioic acids[576–578], dithiobenzoic acid[579] and dithiocarbamates[580] appear to follow a similar pattern.



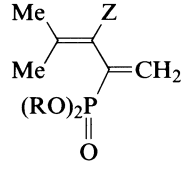
(29)



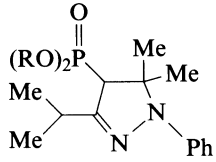
(30)



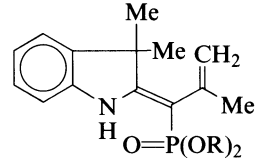
(416)



(417)



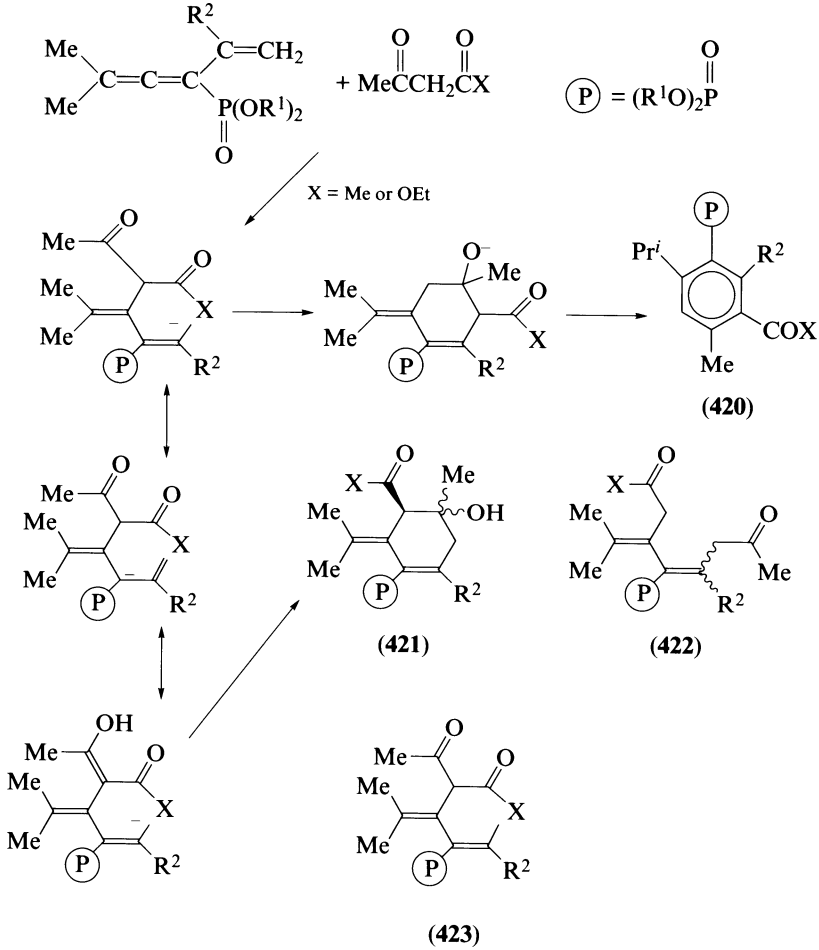
(418)



(419)

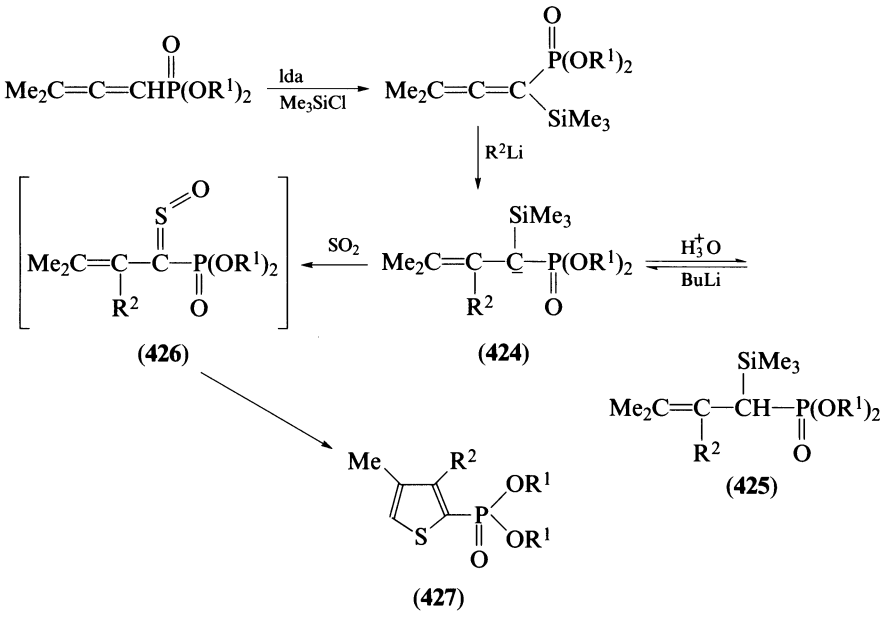
One reaction of particular interest is that which occurs between (alka-1,2-dienyl)-phosphonic diesters and the anions of active methylene compounds. With the anions of

cyanoacetic ester, malonic ester or 3-oxobutanoic ester, the initial site of reaction is again at the central carbon atom in **406** to give **408** (Nu = YCHCOOEt, Y = CN, COOEt or Ac)[567], but the action of such nucleophiles on diesters of (1-ethenylalka-1,2-dienyl)phosphonic acids (shown in much abbreviated form in Scheme 51) affords, from mesomerism in the initial adduct anion and depending on the individual attacking carbanion, complex mixtures of aromatic phosphonic diester **420**, stereoisomeric hydroxycyclohexenylphosphonic esters **421** in yields of up to 45%, together with linear products such as **422** and **423**[581,582].



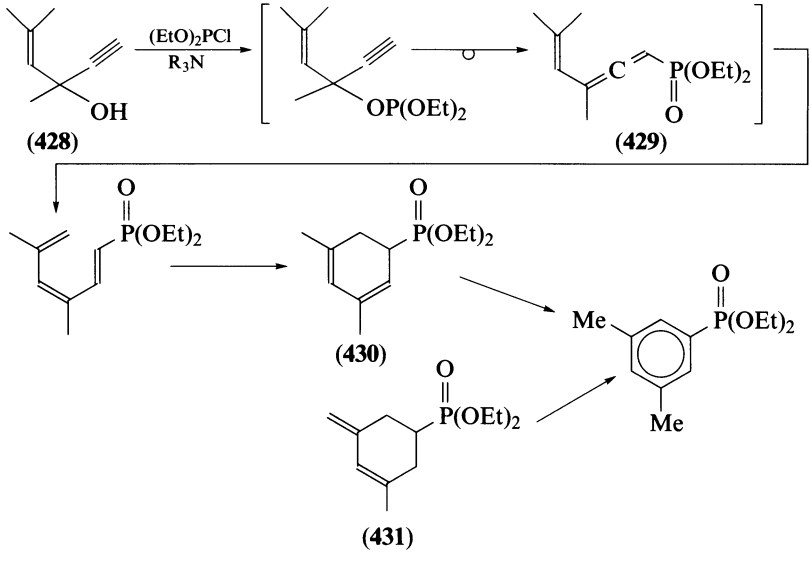
SCHEME 51

Scheme 52 outlines a sequence of reaction steps of an unusual nature in which an alka-1,2-dienylphosphonic diester is subjected to initial lithiation followed by silylation; at this stage the silylated carbanion **424** may be protonated to yield the [1-(trimethylsilyl)alk-2enyl]phosphonate (**425**). However, **424** also reacts with SO_2 to yield the thienyl-2-phosphonic diester **427**; the intermediate in this process has been identified as the sulphine **426**[583].



SCHEME 52

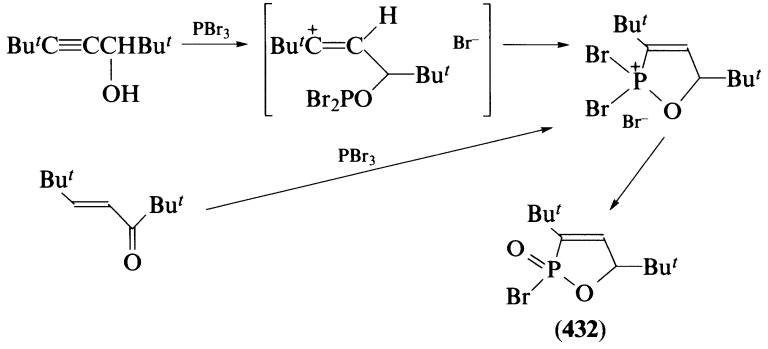
Following the reaction between the acetylenic alcohol **428** and $(EtO)_2PCl$–pyridine, distillation yielded the cyclic products **430** and **431** via **429** together with a subsequent series of hydride shifts (Scheme 53); prolonged heating of the mixture in the presence of palladium-charcoal under nitrobenzene afforded only diethyl (3,5-dimethylphenyl)phosphonate[340].



SCHEME 53

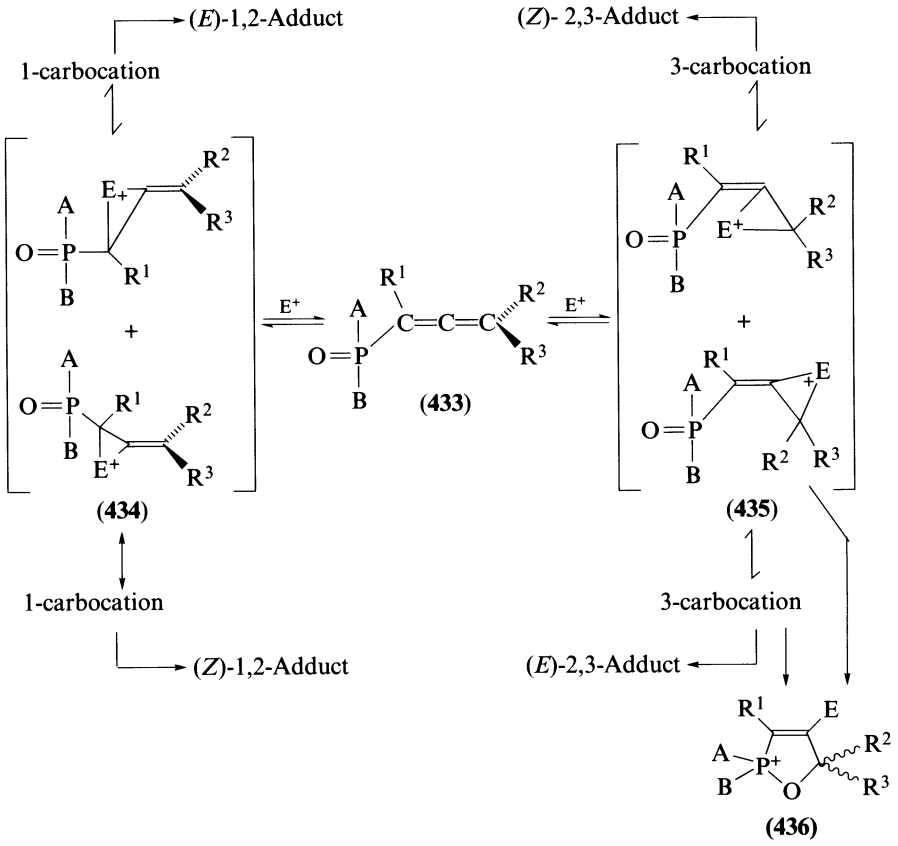
The behaviour of derivatives of the (alka-1,2-dienyl)phosphonic acids, and to a far lesser extent those of analogous phosphinic acids, towards electrophiles, has been examined far more than those of the (alka-1,3-dienyl)phosphonic acids, and indeed is surely one of the most intensely examined of reactions in organophosphorus chemistry–other than those which have found application in more conventional organic chemistry. The literature from the first observations in the mid-1970s to late 1981 has been surveyed in detail[584]; other readily available reviews cover the topic in less detail, and carry the discussion forward only to a relatively small extent[585,586].

This fascinating area of organophosphorus chemistry appears to originate from the first observations on the formation of 1,2-oxaphosphol-3-enes by the action of phosphorus trihalides on propargylic alcohols by Macomber and coworkers[587,588], who demonstrated the formation of a cyclic phosphonic bromide **432**. At this early stage it was felt that **432** was formed directly from the acetylenic alcohol in accordance with the steps indicated in Scheme 54, but a more detailed study of the reactions between PCl_3 and a selection of other propargylic alcohols demonstrated the intermediate isomerization of the propargylic dichlorophosphite to an (alka-1,2-dienyl)phosphonic dichloride (Chapter 2, Section III.B), which then reacted further with the PCl_3 with subsequent heterocyclization[589].



SCHEME 54

Numerous studies have been carried out on the reactions between (alka-1,2-dienyl)-phosphonic and -phosphinic acids and their derivatives with the halogens (Cl_2, Br_2, I_2), SO_2Cl_2, interhalogens (ICl and IBr), alkyl or aryl sulphenyl halides (RSX) and the corresponding selenium compounds (RSeX), and also phosphinoylsulphenyl chlorides and protic reagents. The general pattern in the behaviour of electrophiles towards (alka-1,2-dienyl)phosphonic and -phosphinic derivatives is summarized in Scheme 55. The acid or a derivative thereof, **433**, is attacked by an electrophile E^+ at either the 1,2-bond (**434**) or the 2,3-bond (**435**), giving rise in each case to separate intermediates in equilibrated stereoisomeric forms, which then decompose, probably via individual carbocations, to yield *E*- or *Z*- acyclic reaction adducts. The two most important features which control the outcome of the reactions are the substituents on phosphorus, A and B, and the pattern of substitution on the carbon chain. If the diene moiety is unsubstituted, then the nature of the attacking agent, e.g. R in RSCl (since this then alters the electrophilicity of the group $RS^{\delta+}$), becomes increasingly important; on the other hand, increased substitution at the terminal carbon of the allene chain, so creating a secondary or tertiary carbocation, helps in the stabilization of those ions (**435**) which then lead to the 2,3-adducts in stereoisomeric forms. A further important feature, which may become one of dominance with substrates fully substituted at $C_{(3)}$, is the ability of the 2,3-addition process to lead, via **435** and the



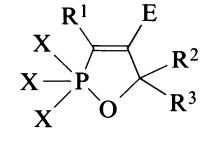
SCHEME 55

quasiphosphonium ion **436**, to 1,2-oxaphosph(V)ol-3-enes, potentially as mixtures of stereoisomers.

The action of elemental chlorine on diethyl propadienylphosphonate yields an inseparable mixture of diethyl (3-chloroprop-1-ynyl)phosphonate (about 30%), diethyl (*E*)- and (*Z*)-(2,3-dichloroprop-1-enyl)phosphonate (in yields of 12% and 9%, respectively) and 4-chloro-2-ethoxy-1,2-oxaphosphol-3-ene 2-oxide (29%)[590]; when a single hydrogen atom on $C_{(1)}$ or $C_{(3)}$ is replaced by a methyl group, the yields of the respective 4-chloro-1,2-oxaphosphol-3-ene 2-oxides are about 75%

The impact of replacing both hydrogen atoms on $C_{(3)}$ by alkyl groups is as great, and in some examples even greater in chlorination or bromination, as it is for trisubstituted alka-1,2-dienylphosphonic diesters[591,592]. The action of iodine and the interhalogens ICl and IBr to give the 4-iodo heterocycles follows the same pattern, but is much slower[593]. In all such cases, the formation of the oxaphosph(V)olene occurs through the halogen dealkylation of the ionic species **436** (A = B = OR) with loss of alkyl halide. In the case of propadienylphosphonic dichloride and homologous compounds, halogenation affords crystalline, insoluble adducts, the structures of which appear to depend, at least partly, on the individual halogen. Thus, the pentacoordinate form **437** appears appropriate when X = Cl, but for bromine an ionic structure **438** seems to more relevant, but the breakdown of

whichever form to give a mixture of (*E*)- and (*Z*)-**439** is most easily visualized as taking place according to **438**[590,594]. The replacement of hydrogen at $C_{(3)}$ in the propadienyl chain yields the salts **440**, which, when stored or heated *in vacuo*, are transformed into the dichlorides of substituted buta-1,3-dienylphosphonic acids; thus, **440** yields 39% **441**[551,595–597]. The reaction between an alka-1,2-dienylphosphonic dichloride and SO_2Cl_2 yields **438** and its decomposition by the liberated SO_2 to give the cyclic phosphonic chloride **442** (R = E = Cl); compare this result with the decomposition by SO_2 of linear trichlorophosphonium salts from the phosphorylation of alkenes with PCl_5[598,599].



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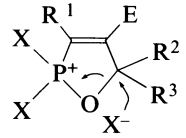
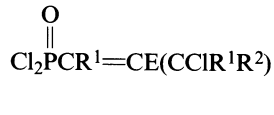


(438)



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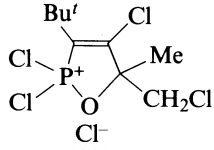

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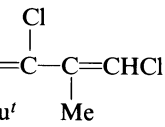

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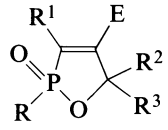
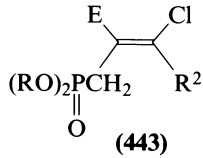


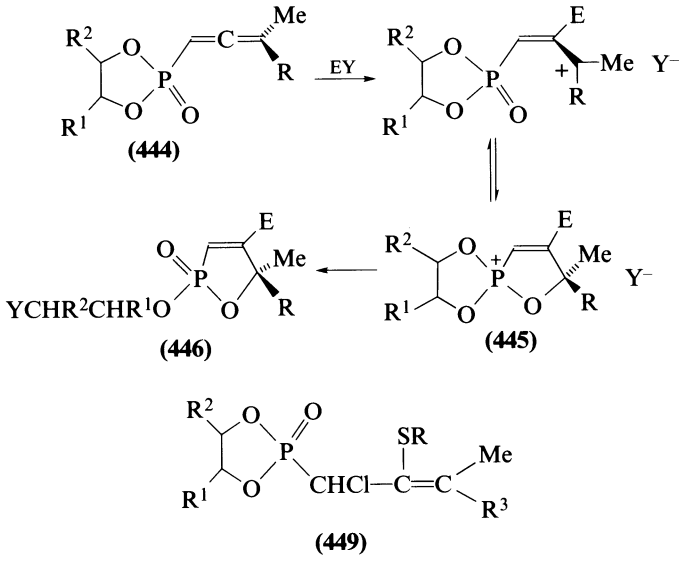
(442)

1,2-Oxaphosph(V)ol-3-enes are not found as products from the interaction of esters or the dichloride of propadienylphosphonic acid itself with MeSCl, PhSCl or the corresponding RSeCl; in such cases the main products were the *E*-2,3-adducts with higher yields reported for RSCl than for the corresponding alkylselenenium chlorides RSeCl[600–605]; the formation from the latter of larger amounts of the *Z*-2,3-adducts has also been reported. Such reactions are thought to take place through episulphonium or episelenonium intermediates. Once again, the presence of multiple substituents in the diene moiety can lead to high yields of 1,2-oxaphosph(V)ol-3-enes as stereoisomeric mixtures[600,602–611]. A further feature which complicates the addition of selenenyl chlorides is that of the 1,3-sigmatropic rearrangement in the formation of the compounds **443** and their geometric isomers obtained from the initial 2,3-adducts and produced when either R^2 or R^3 is H; the quantities of the rearranged products are greater (12–31%) when the $C_{(3)}$ atom is of a primary nature and 1,2-adducts are not formed[604,610].



(443)

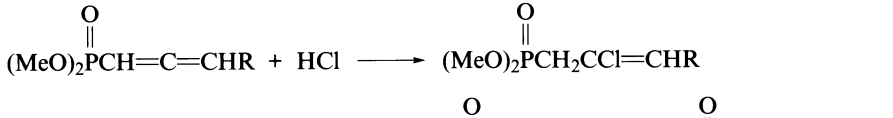
Evidence for the formation of intermediate quasiphosphonium salts comes from the isolation of the ion **436** (A = B = EtO; R^1 = H, R^2 = R^3 = Me; E = SPh) as the hexachloroantimonate[612], and further evidence stems from reactions with cyclic esters of the (alka-1,2-dienyl)phosphonic acids. The reactions of the 1,3,2-dioxaphosph(V)olanes **444**, of known geometry, with Cl_2, Br_2[613] and RSCl or RSeCl[614] are highly stereoselective and would be expected to proceed through the quasiphosphonium salts **445**; such salts have been isolated from other reactions. The 1,2-oxaphosph(V)ol-3-enes **446** have been isolated (66–75%) when EY is RSCl or RSeCl, but in the former case, were accompanied by **449** (65–73%) Phosphonium salts **436** (A = B = alkyl) have been obtained from reactions of propadienyldialkylphosphine oxides[615].



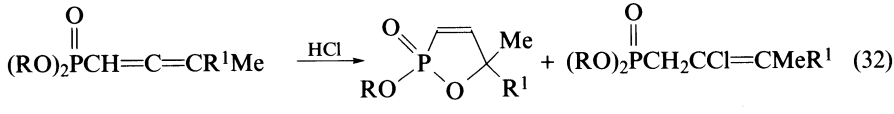
(444) (445) (446) (449)

Reactions between the diesters or dichlorides of (alka-1,2-dienyl)phosphonic acids with additional ethenyl groups at $C_{(1)}$[616–618] or at $C_{(3)}$[619] (pentatrienyl phosphonic acids) and halogens[617–619], SO_2Cl_2 or RSeCl[616] yield 1,2-oxaphosph(V)ol-3-enes[616,618,619], sometimes accompanied by linear products[617,619].

Compounds which bear the alka-1,2-diene moiety attached to phosphoryl phosphorus can undergo spontaneous, although perhaps slow, cyclization to 1,2-oxaphosph(V)ol-3-enes (**442**; R = OR′, E = H)[620], or when subjected to external acidic conditions[621–623]. The extent of cyclization is governed by the polarity of the solvent: the more polar the solvent, the greater is the extent of cyclization as opposed to simple addition[623]. In general, phosphonic and phosphinic acids which are based on 1,2-dienes with primary or secondary carbon at $C_{(3)}$ are unable to undergo cyclization (equation 31), even in strongly acidic media at high temperature, and afford linear addition products[623], and a tertiary carbon is necessary for the cyclization process (equation 32)[620,623]. The steps are essentially as those indicated in Scheme 55 in which E^+ is H^+; in this respect, the esters **444** in sulphuric acid form the quasiphosphonium salts **445** (R^1, R^2 = H or Me, R = Me or Et), identified by ^1H and ^{31}P NMR spectroscopy[624].

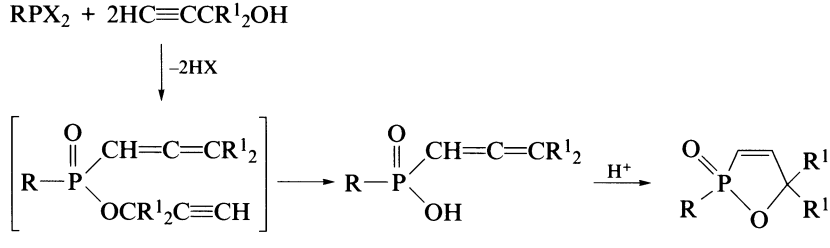


(31)



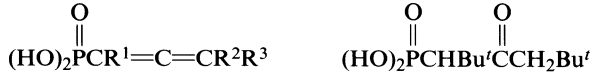
(32)

Macomber and coworkers' original observations[587,589] provide a synthesis of 1,2-oxaphosph(V)ol-3-enes without the necessity for isolation of the (alka-1,2-dienyl)phosphonic intermediates, although it is certain that these are formed during the course of the sequence (Scheme 56)[625]. The acid HX must be efficiently removed from the system (and not simply neutralized), otherwise side reactions lead to non-phosphorus by-products). When $R^1 \neq H$, the products **450**, from dibromophosphines, decompose to the phosphinic acids **451** even at slightly above room temperature, and cyclization occurs when the temperature is raised to about 100 °C[626]. Unusual properties are conferred upon the (alka-1,2-dienyl)phosphonic system by substituent *tert*-butyl groups; the acid **452** (R^1 = Bu^t, R^2 = R^3 = Me) underwent the expected cyclization, and with quantitative yields, when acted upon with trifluoroacetic acid but, by contrast, the acid **452** (R^1 = R^2 = Bu^t, R^3 = H), in a slow reaction with trifluoroacetic acid, yields the acid **453**[627].



(450) **(451)**

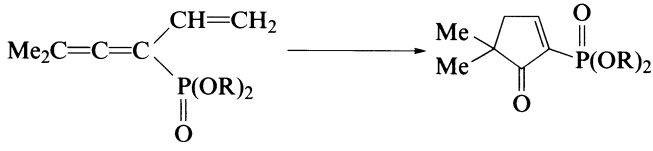
SCHEME 56



(452) **(453)**

Cyclization involving phosphorus(V)-bonded moieties is also brought about by the silver ion[620,624] and by $Hg(OAc)_2$[628]. The addition of Schiff bases to (alka-1,2-dienyl)phosphonic esters occurs in the presence of $BF_3 \cdot Et_2O$ to give, e.g., **442** (R^1 = H, R^2 = R^3 = Me, E = PhNHCHPh)[629].

Amongst several other transformations of the alka-1,2-dienyl moiety in derived phosphonic acid derivatives, is that of the chromyl chloride-assisted conversion of the 1-ethenyl substituted esters into cyclopentenylphosphonic derivatives (equation 33)[630] and the oxidative cyclization (using 3-chloroperoxybenzoic acid) of the free acids to 1,2-oxaphosph(V)olan-4-ones (equation 34)[631].



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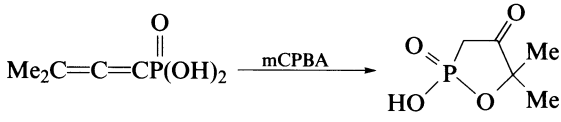
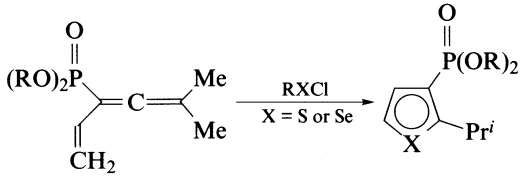


(34)

The addition of sulphenyl or selenenyl chlorides to dialkyl alkatrienylphosphonates has led to the claim that heterocyclic phosphonic derivatives may be formed (equations 35 and 36) admixed with, but inseparable from, the 1,2-oxaphosph(V)ol-3-ene co-products, and also thought to be derived through the 2,3-episulphonium (or analogous selenonium) intermediates[599,632].



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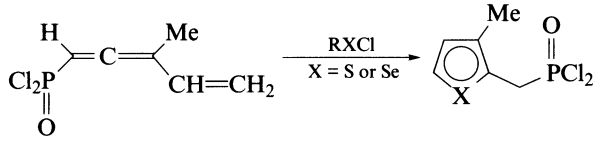
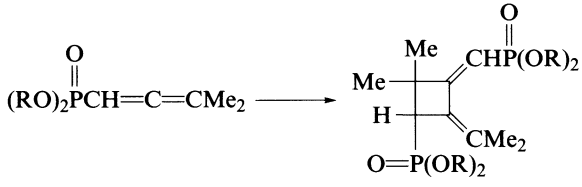


(36)

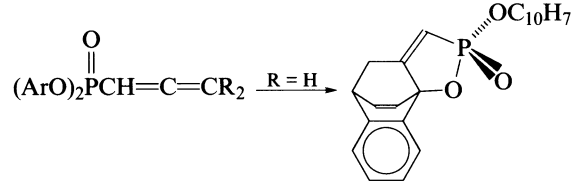
D. Cycloaddition Reactions of Unsaturated Carbon Chains: the Diels–Alder Reaction

The phosphoryl group behaves electronically very much as does the carbonyl group in the activation of unsaturated carbon–carbon bonds towards [4+2] cycloaddition reactions of the Diels–Alder type, and also cycloaddition processes of other configurations.

Simple [2+2] cycloadditions (i.e. dimerizations) have been noted in the formation of a mixture of *cis*- and *trans*-1-phenyltetralin-1,4-diyldiphosphonic acids when (1-phenylethenyl)phosphonic acid (itself obtainable from acetophenone and P_4O_6) is heated at 180–200 °C for 6 h[633]. The action of heat on dialkyl (3-methylbuta-1,3-dienyl)phosphonates produces the dimers **454**[634]. Analogous products were produced by the action of heat on (alka-1,2-dienyl)phosphonic diaryl esters (Ar = Ph or 1-naphthalenyl; R = H or Me)[635]; in one instance, for which R = H and Ar = 1-naphthalenyl, a second product **455** was isolated.

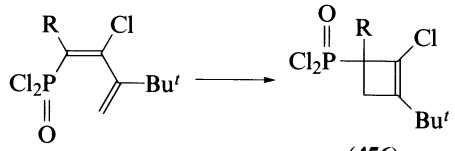


(454)

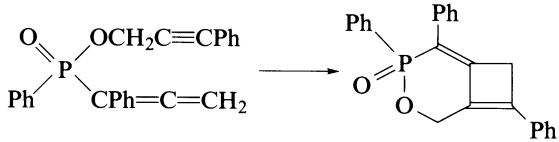


(455)

Cyclobutenylphosphonic dichlorides (**456**) have been obtained by the action of heat on buta-1,3-dienylphosphonic dichlorides and their structures confirmed by X-ray crystallography[636]. The addition of the carbon–carbon triple bond to the 1,2-diene moiety in **457** occurs across the double bond distant from phosphorus[637]. The cycloaddition of cyclopentadiene to the (diethoxyphosphinoyl)ketenes **458** (R = Me or Cl), generated *in situ*, gives the products **459**[638].



(456)



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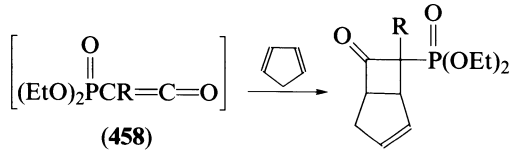
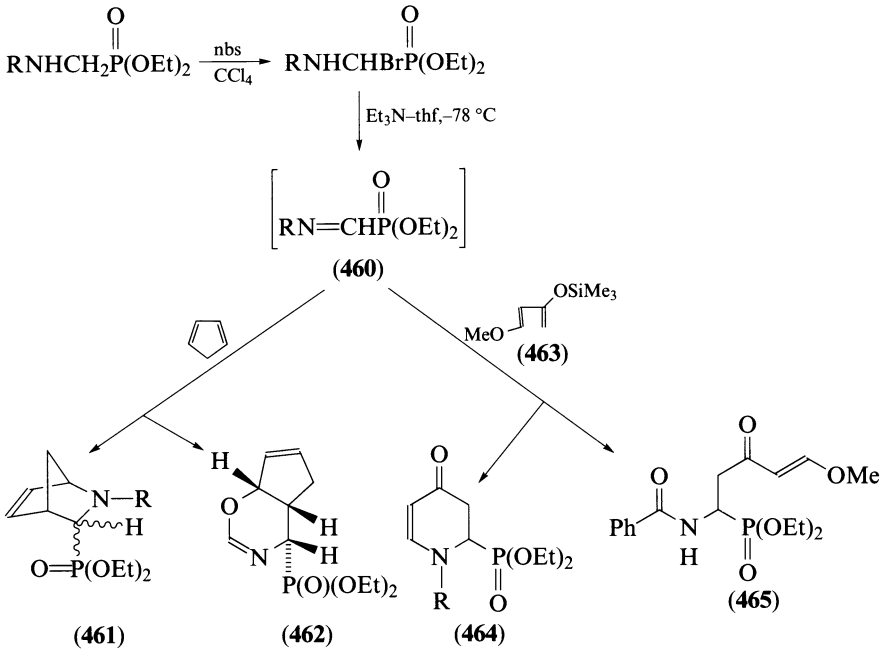


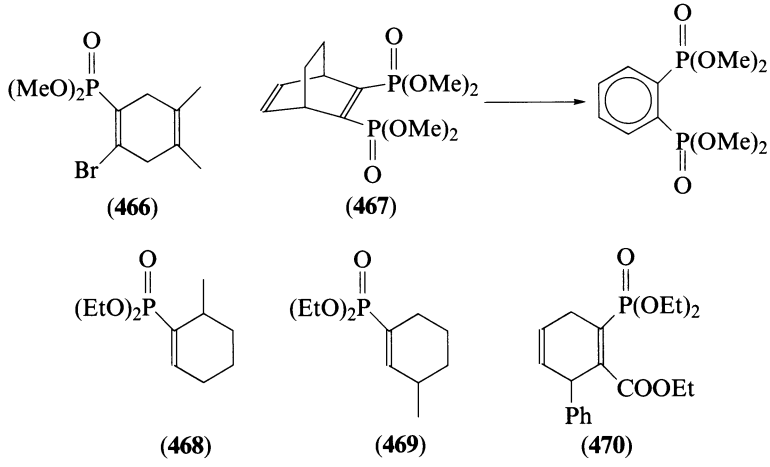
(458) **(459)**

Other similar reactions which might be conveniently included here include the [4+2] additions of iminomethyl phosphonic diesters to 1,3-dienes; reactions between the species **460** (R = PhCO or $PhSO_2$), generated *in situ* as indicated, and cyclopentadiene leads to the two adducts, **461**, as the *endo* (R = PhCO) or *exo* (R = $PhSO_2$) form, and **462** (R = PhCO only). Reactions involving the diendiol ether **463** proceed less satisfactorily to give the phosphonic diesters **464** and **465**. Other dienol silyl ethers tended to give linear products of the type **465** under the same or similar conditions[639]. The cycloaddition of α-nitrosophosphonic esters to 1,3-dienes has provided a synthesis of 2-phosphinoylalkyl-1,2-oxazines[640].

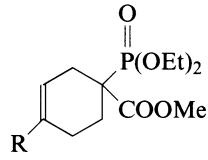
Many reactions between 1,3-dienes and phosphoryl dienophiles were reported in the patent literature during the early 1950s, but in many cases the products, many of which were heavily halogenated, were not thoroughly characterized. Alkyn-1-yl-and alken-1-yl-phosphonic acids, diesters and dichlorides behave as dienophiles. Most of the commonly available dienes—linear and cyclic 1,3-dienes, anthracene, tetracyanoethene, *N*-phenylmaleimide and 1,3-diphenylisobenzofuran—have been shown to be reactive. Most reactions require a few hours at 120–180 °C, whereas those that involve cyclopentadiene are initiated in a solvent at –78 °C, and the reaction temperature is then allowed to rise to ambient; in many cases the yields of products may, at worst, be moderate, and at best, quantitative. The products from acetylenic phosphonic derivatives are sometimes valuable precursors to aromatic systems; thus, the product **466** is dehydrobrominated with Et_3N to give dimethyl 3,4-dimethylphenylphosphonate[641], and in the reaction between tetramethyl ethyndiylbisphosphonate and cyclohexa-1,3-diene, a bicyclic system **467** is formed but is unstable, and immediately undergoes conversion to tetramethyl 1,2-phenylenebisphos-



phonate[642]. Daniewski and Griffin[643] studied the Diels–Alder reactions of diethyl ethenylphosphonate and diethyl (2-chloroethenyl)phosphonate and showed that, in contrast to earlier observations by other workers, the adducts were often formed in a non-regiospecific manner; to illustrate the point, diethyl vinylphosphonate and penta-1,3-diene produced a 1:1 mixture of adducts **468** and **469**, and isoprene gave a 2.3:1 mixture. Such mixtures were successfully aromatized through dehydrogenation, sometimes with cyclohexene, but most often with $PhNO_2$[643]. However, many of the reactions are regiospecific: thus only the one isomer **470** is produced in a direct addition[644]. The cycloaddition reactions of $Bu^t C{\equiv}CP(O)Cl_2$ are slower than those of phenylethynylphosphonic dichloride[645].

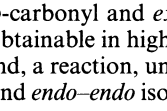


In many of the reactions of alkenylphosphonic derivatives, the potential for the formation of mixtures of regioisomeric and stereoisomeric products is well recognized, but particularly in the latter case, separation of the products, or even their structural characterization without separation, has rarely been attempted[646–649]. The homogeneous product **471** (R = H) was obtained in high yield from buta-1,3-diene and methyl 2-(diethoxyphosphinoyl)propenoate, but it is worth noting that no ring formation was observed in the reactions between methyl 2-(diethoxyphosphinoyl)-3-phenylpropenoate and isoprene or butadiene in attempts to prepare phenyl-substituted derivatives of **471** (R = H or Me)[650].



(471)

Diethyl ethenylphosphonate reacts with cyclopentadiene in boiling toluene during 6 h to give the 1:1 adduct in 85% (combined) yield; the product consists of a 45:55 mixture of diethyl *endo*- and *exo*-(5-norbornen-2-yl)phosphonates, **472** and **473**, respectively, the structures of which were assigned on the basis of their ^{13}C NMR spectra. In the presence of an equimolar amount of Lewis acid catalyst ($AlCl_3$, $FeCl_3$, $TiCl_4$ or $SnCl_4$[651] or $GaCl_3$[652]), similar yields are obtainable at room temperature, but a more interesting feature is the change in the isomer ratio to as high as 85:15[651]. The influence of experimental conditions was ascertained for reactions between cyclopentadiene and the dienophiles **474** (Z = CN or COOMe); changes in temperature and pressure on the system containing **474** (Z = COOMe) in toluene has relatively little effect on the ratio of **475** and **476**, nor is there much change in the ratio of the comparable products when Z = CN, although the two examples produce different ratios of *endo* and *exo* compounds[653]. As a result of the addition of cyclopentadiene to the (*E*)-phosphonates **477** (R = Me, MeO, or Ph) in hot $CHCl_3$, the two isomers **478** (with *endo*-carbonyl and *exo*-phosphoryl) and **479** (with *exo*-carbonyl and *endo*-phosphoryl) are obtainable in high combined yield, with the former always in large excess; on the other hand, a reaction, under the same conditions, with the (*Z*)-dienophile produces the *exo–exo* and *endo–endo* isomers in 55:45 ratio[654].



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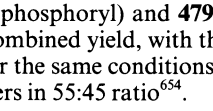
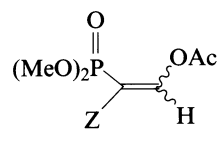


(473)

Chirality in the phosphorus-containing dienophile induces a preferential mode of approach to the diene; the (2*R*,4*S*)-1,3,2-oxazaphospholidine 2-oxide **480** reacts with cyclopentadiene to give a 10:19 ratio (96% total yield) of the *endo* (structure confirmed by X-ray crystallography) and *exo* adducts, and a similar reaction with the (2*S*, 4*S*)-1,3,2-oxazaphospholidine 2-oxide gave *endo* and *exo* products in the ratio 2:3, with considerable diastereoisomeric excesses (80–88%)[655].

The mixed anhydride **481** in its reactions with dienes provides a useful route to the reduced bicyclic systems **482**[656,657]. The phosphinoyl moiety may be part of the 1,3-diene in reactions with tetracyanoethene[658]. When heated to 120–130 °C, diethyl (buta-1,3-dienyl)phosphonate acts both as diene and dienophile and dimerizes to give **483**[659].



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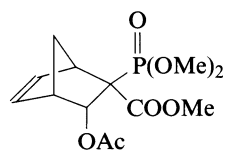

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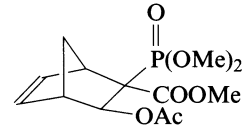

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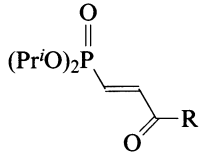

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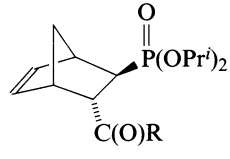

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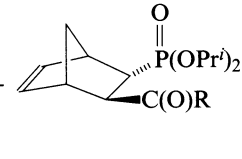

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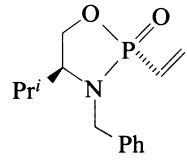

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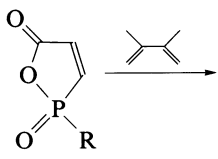

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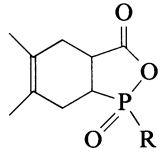

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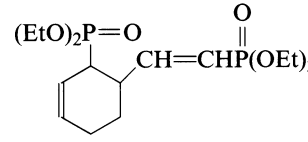
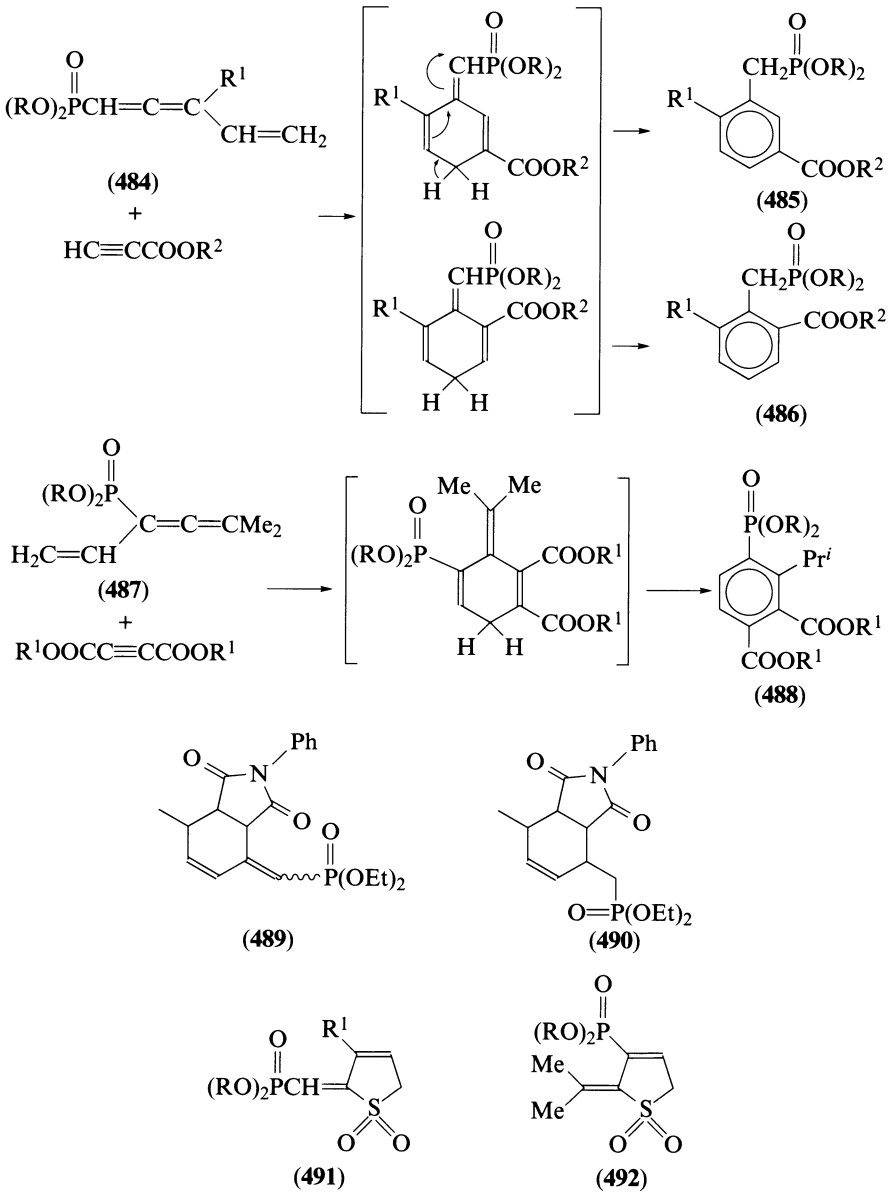


(483)

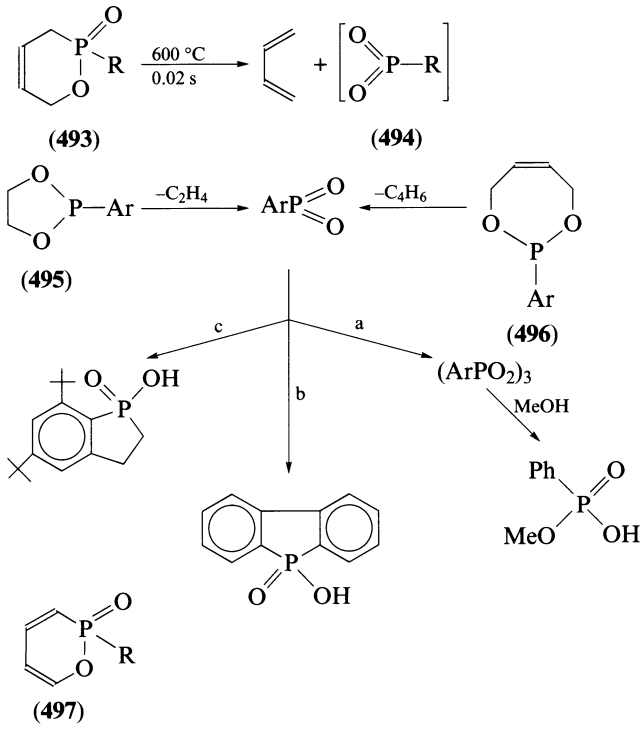
In the additions of acetylenedicarboxylic esters to the (penta-1,2,4-trienyl)phosphonic esters **484** (R^1 = Me), both head-to-head and head-to-tail products are formed. The initial reaction is then followed by 1,5-sigmatropic rearrangements to give isomers of benzylic phosphonic diesters, **485** (R^1 = Me) and **486** (R^1 = Me). The trienyl phosphonic esters **487** simi-larly give rise to aromatic phosphonic diesters **488**[660]. The ester **484** (R = Et, R^1 = H) is reactive towards *N*-phenylphthalimide at room temperature, but the product is not the expected **489** but rather **490**, which aromatized on chromatography over alumina[340]. The same trienyl phosphonic diesters undergo Diels–Alder reactions with sulphur dioxide and yield sulpholene adducts **491** and **492**[661,662].

Several other publications have exemplified the Diels–Alder reaction with phosphorylated dienophiles[663–665].

The well-known retro-Diels–Alder expulsion of SO_2 and liberation of buta-1,3-diene when their adduct is heated has analogies in the phosphorus field. Flash thermolyses of the cyclic phosphonic ester **493** (R = OMe)[666] and of the phosphinic ester **493** (R = 2,4,6-trimethylphenyl)[667] afford buta-1,3-diene and the highly reactive metaphosphate **494** (R = OMe) or metaphosphonate **494** (R = 2,4,6-trimethylphenyl) species. The elimination of phenylmetaphosphonate or an analogous species was observed during the thermolysis of the 1,3,2-dioxaphospholanes **495** [Ar = (a) Ph or (b) (1,1′-biphenyl)-2-yl[668], or (c) 2,4,6-tri-*tert*-butylphenyl[669]] at 700–800 °C ; here the respective metaphosphonates were characterized through the formation of the indicated known products. The compound **496** (Ar = Ph)



also acts as a source of phenylmetaphosphonate by expulsion of buta-1,3-diene[668]. It may be noted that **497** (R = 2,4,6-trimethylphenyl), derivable from the corresponding **493** by bromination and subsequent dehydrobromination, itself undergoes a Diels-Alder reaction with acetylenedicarboxylic ester or with maleic anhydride, but at the temperature of reaction (140–165 °C) a retro-reaction then follows with the liberation of the metaphosphonate and formation of phthalic acid esters or anhydride[667].

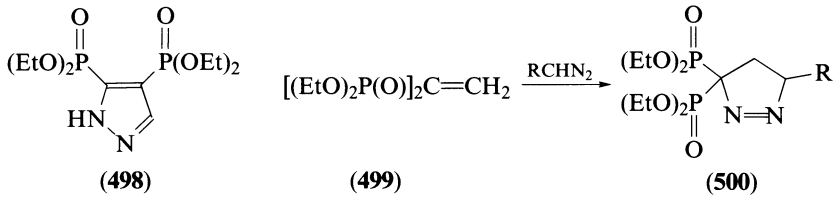


E. 1,3-Dipolar Cycloadditions of Unsaturated Phosphonates and Phosphinates

These reactions include the well known additions to alkynyl- and alkenyl-phosphorus(V) acids of diazomethane and other diazoalkanes, and also of azides, either inter- or intra-molecularly.

The addition of diazomethane to a symmetrical phosphorylated dipolarophile occurs with high yield, even at room temperature, and produces, of course, a single product as exemplified by the 3,4-bis(diethoxyphosphinoyl)pyrazole **498** obtained from tetraaethyl ethynylbisphosphonate[642] and the pyrazolines **500** obtainable from tetraethyl ethenylidenebisphosphonate **499** in reactions at 0 °C not only with diazomethane itself, but also with ethyl diazoacetate (R = COOEt) and with several diazoketones (R = R′CO, R′ = Et, Bu^t, Cy, Ph or substituted phenyl)[670]. Generally, the reactions are accelerated by the presence, in the dipolarophile, of either electron-donor or -withdrawing functions[671–673] and additionally reactions with unsymmetrical dipolarophiles lead to mixtures of products. Reactions between ethyl *tert*-butyl azidoacetate and methyl ethynylmethylphosphinate and between methyl azidoacetate and triethyl phosphonopropynoate afford mixtures of the regioisomers of the *C*-phosphorylated 1,2,3-triazoles **501** [R = Bu^t; X, Y = H, Me(MeO)P(O)][674] and **501** [R = Et; X, Y = COOEt, P(O)(OEt)$_2$][644], respectively. A further example is the use of diazomethane in the preparation of the pyrazole regioisomers **502** [X, Y = (R^{1}O)$_2$P(O), COR^2; R^2 = OMe, Me, Et, or Ph][675].

A quantitative study of the reactions between methyl 3-(dialkylphosphinoyl)-propenoate and diazomethane or 2-diazopropane revealed that the regioselectivity of addition was more dependent on the structure of the diazoalkane than on the nature of the



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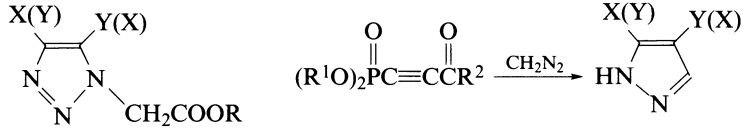
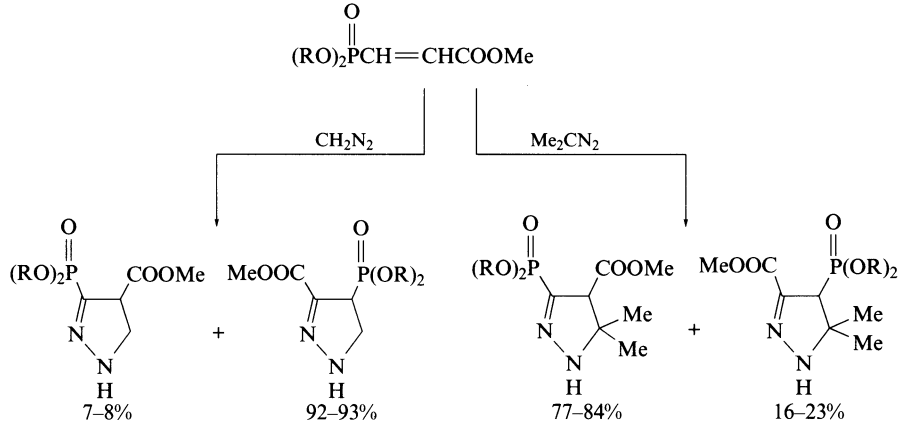


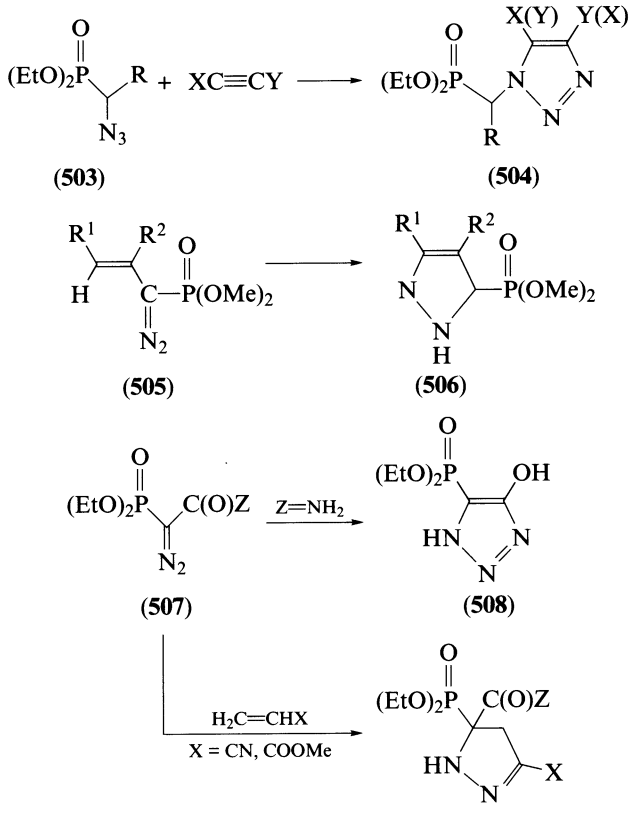
(501) (502)

phosphorus ester group R (Me, Et or Pr^i), the yields of products being those shown in Scheme 57[676].

Diethyl (4,5-dihydro-5,5-diphenylpyrazol-3-yl)phosphonate is produced from diazodiphenylmethane and diethyl ethenylphosphonate in solution at 0–5 °C; the product is still stable at 80 °C and the liberation of nitrogen to give the phosphinoylated diphenylcyclopropane does not take place uniformly until a temperature of about 170 °C is reached. Cyclopropanation occurs almost immediately at room temperature when vinylphosphonic dichloride reacts with Ph_2CN_2, but no reaction between the latter and diethyl prop-2-enylphosphonate occurs up to 80 °C; only at 115 °C does nitrogen begin to be liberated, but even at 150 °C the yield of cyclopropane derivative is only about 13%[677]. The importance of activation by an adjoining phosphoryl group in the cycloaddition process is illustrated by the very poor reaction between diazomethane and dialkyl (prop-2-enyl)phosphonates in ether at room temperature (yields of pyrazoline are ca 5%), in contrast to reactions with esters of ethenylphosphonic acid in the same solvent at –15 °C, when yields approach 50%, although it may be noted that cyclopropanation of (prop-2-enyl)phosphonic diesters occurs to a slightly better extent in the presence of copper(II) salts[678]. Indeed, copper salts assist generally in the quicker expulsion of the pyrazoline nitrogen to leave the cyclopropane derivative, and copper(I) trifluoromethanesulphonate has been



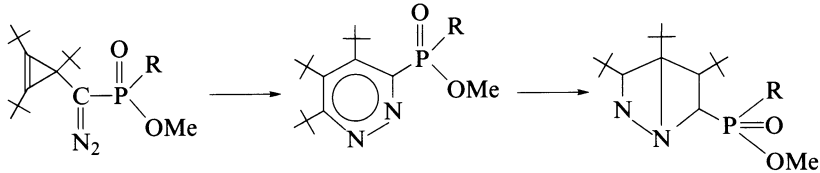
SCHEME 57



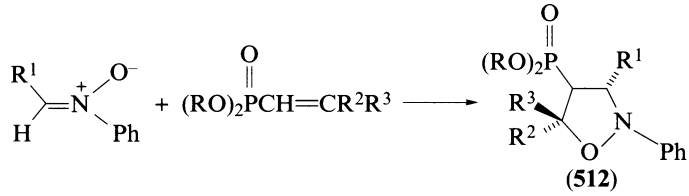
shown to be particularly effective in this respect[679], but irradiation of the pyrazoline is also effective for this purpose[680].

The converse addition of a phosphorus-containing dipolar reactant to a dipolarophile which lacks phosphorus is exemplified by the addition reactions of diethyl (1-azidoalkyl)-phosphonates (**503**) to acetylenic compounds to give the 1,2,3-triazoles **504** [X = H, Me, Ph, COPh, or COOMe; Y = COOMe, COOEt, $P(O)(OEt)_2$, or $P(O)Ph_2$][681]; related reactions have also been carried out with the ester **503** (R = NHR')[682]. The (1-diazoalk-2-enyl)phosphonates **505** readily cyclize to **506**[683] and the diazoamide **507** ($Z = NH_2$) also behaves analogously to give **508**[302], but may (for Z = OMe or OEt) react in an intermolecular fashion[684].

A remarkable sequence, observed by Eisenbarth and Regitz[685], is initiated by the action of heat on the esters **509** (R = MeO or Ph) and yields, first, the phosphorylated diazines **510**, irradiation of which causes isomerization to a Dewar pyridazine (**511**).

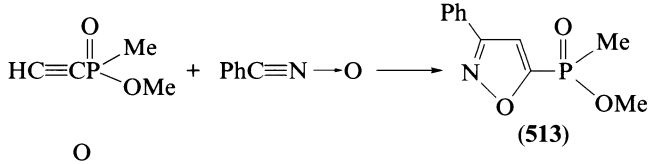


Dimethyl ethenylphosphonate itself[686] and dialkyl ethenylphosphonates with strong electron-withdrawing groups such as CN or COOMe in the β-position[687] undergo cycloaddition reactions with *C,N*-diphenylnitrone to give mixtures of liquid and solid stereoisomeric isoxazolidines (**512**), the molecular geometries of which were studied by NMR, infrared and Raman spectroscopy. Further reactions explored are those between *C,N*-diphenyl-or *C*-benzoyl-*N*-phenyl-nitrones and other β-substituted ethenylphosphonic diesters[688].

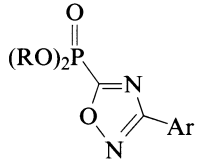


(**512**)

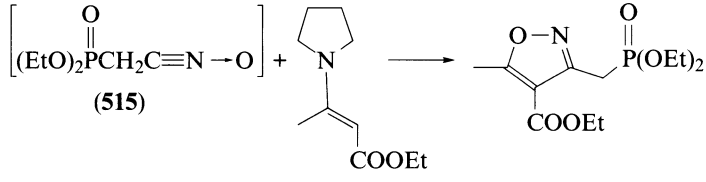
The cycloaddition of an arylnitrile oxide to methyl ethynylmethylphosphinate in an inert solvent at 5 °C produces a $C_{(5)}$-phosphinoylated-isoxazole **513** in high yield[674] and phosphorylated 1,2,4-oxadiazoles **514** are obtainable in a similar addition to $(RO)_2P(Z)CN$ (Z = O or S)[689]. Phosphorylated nitrile oxides, e.g. **515**, are generally prepared by the Et_3N-dehydrobromination of the product from the bromination of the oxime of a β-(dialkoxyphosphinoyl)acetaldehyde, and then used *in situ* in reactions with alkenes to give isoxazolines[690–693] and with alkynes to give isoxazoles[693,694]. The chlorination and subsequent dehydrochlorination of diethyl (nitromethyl)phosphonate yield the nitrile oxides **516** (R = EtO[695], Pr^{i}O[696] or morpholinyl[697]) and these, with unsaturated centres, yield isomerically phosphorylated isoxazolines and isoxazoles.



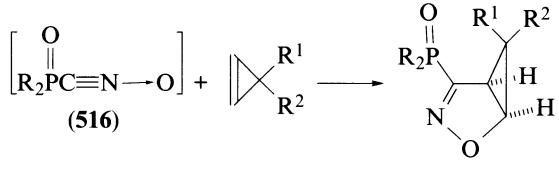
(**513**)



(**514**)

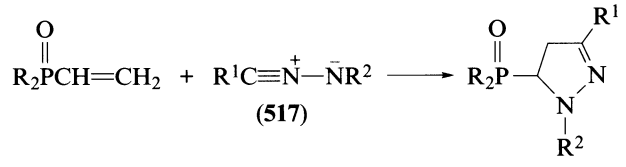


(**515**)

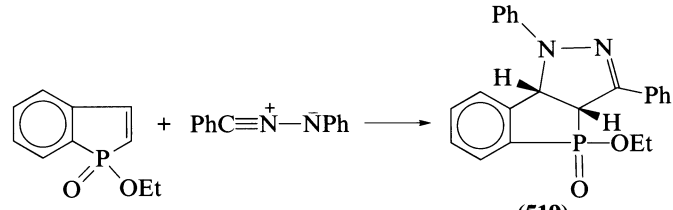


(**516**)

Similar reactions which involve the nitrilimines **517** (R^1, R^2 = Ph or COOEt) in additions to ethenylphosphonic diesters or diamides to give the pyrazolines **518** (R = MeO or Me_2N)[698] and **519**[699] are regiospecific; the reaction of a *C,N*-diphenylnitrilimine with diethyl propadienylphosphonate is regioselective[700]. Mention is included here of the preparation, and study of the reactions of phosphorylated nitrilimines, as exemplified by **520**[701].



(517) **(518)**



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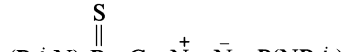
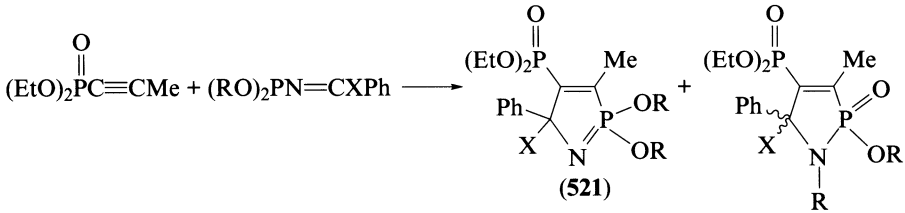
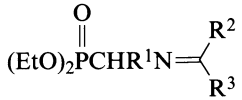


(520)

Mention should also be made of the addition of tervalent phosphorus compounds to alkynylphosphonic and to (alka-1,2-dienyl)phosphonic derivatives [in which addition occurs across the $C_{(1)}$—$C_{(2)}$ bond]. The main product is of type **521** (X = Ph, OR or NR_2), but is normally accompanied by smaller amounts of the isomers **522**. Although this process is formally of a [3 + 2] format, a ^{31}P NMR study of the kinetics suggests that the addition is not a synchronous addition but rather occurs in a stepwise manner[702,703]. On the other hand, the phosphorylated Schiff base **523** undergoes regioselective and stereospecific reaction with α,β-unsaturated esters which, a kinetic study has shown, appears to be concerted[704].



(521) **(522)**



(523)

The literature on the role of organophosphorus compounds in 1,3-dipolar cycloaddition reactions has been reviewed up to about 1976–77[705].

VI. DISPLACEMENT REACTIONS OF NON-CARBON LIGANDS AT PHOSPHORUS

A rapid survey of the contents of the previous four chapters, which dealt primarily with the synthesis of various types of phosphonic and phosphinic acids, is all that is necessary to realize that both classes of acids are synthesized by the direct formation of a limited selection of types of derivatives. Most often these are either esters as, for example, in the Michaelis–Arbuzov reaction, or acid halides, almost invariably the chloride as in the phosphorylation of alkenes with PCl_5. In any multi-step synthesis, the interconversions of acids, acid halides and esters are consequently amongst the most important of translocations of ligands attached to phosphorus, and their success may even become of critical importance.

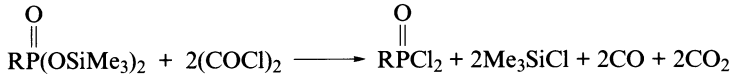
The classical methods for procuring free phosphonic and phosphinic acids include the acid hydrolysis of esters, very often with concentrated aqueous HBr or HCl; alternatively, alkaline hydrolysis of phosphonic diesters generally removes one ester group, leaving the second in place. Phosphinic esters can be hydrolysed to the acid under either conditions. Under favourable circumstances, a phosphonic dihalide or a phosphinic halide can be hydrolysed to the acid under strongly alkaline conditions, and the procedure may be improved by the incorporation of a solubilizing solvent such as dioxane or thf. Of course, such forcing conditions can have adverse effects on other functional groups which might be present in the carbon–phosphorus-bonded ligand. Recent years have therefore seen a search for ever-increasing chemoselectivity in the many transpositions to be accomplished under ever milder conditions. Even under very mild conditions, however, perhaps unwanted reactions might take place; the treatment of phosphonic dichlorides with water can lead to other reactions and, in particular, the formation of the metaphosphonates **524** with a cyclic structure (n = 2 or 3), but their composition is influenced by the group R; the same or similar products are also formed in reactions between the dichlorides and formic acid[706].

$$(RPO_2)_n$$

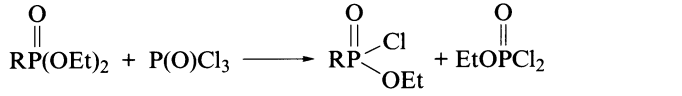
(524)

Silyl esters of phosphonic and phosphinic acids are notable for the ease with which the silyl group can be removed from phosphorus–oxygen bonds, and this property has been developed into the current procedure of choice for de-esterification at phosphorus, and one in which the ester is treated with Me_3SiCl or, better, the bromide or iodide[707–709], or from a more practical viewpoint, the chloride can be used in the presence of a metal bromide or iodide[710]; another variation is the use of the chloride in combination with hexamethyldisilazane[711]. The silyl ester is then hydrolysed in an aqueous–methanolic medium[712,713]; the procedure accommodates a variety of other functional groups including carboxylic ester, carbon–carbon multiple bonding, oxo groups, amide groups and the presence of halogens[707]. *tert*-Butyl esters are dealkylated by thermolysis; both *tert*-butyl[714,715] and diphenylmethyl[716] esters can be dealkylated by acidolysis, conveniently with trifluoromethanesulphonic acid. Diaryl esters of simple alkylphosphonic acids are de-esterified when photolysed in methanol; the ester aryl groups become incorporated into biphenyls, obtainable in moderate to good yields, and into generally smaller amounts of dibenzodioxins[717–719].

Of necessity, the preparation of acid halides involves the cleavage of P—O bonds. Silyl esters can be converted into acid chlorides with oxalyl chloride (equation 37)[720] but, more commonly, phosphonic or phosphinic chlorides are prepared from the acid or ester by the action of $SOCl_2$ or PCl_5. The action of $POCl_3$ (equation 38)[721] or Ph_3PCl_2 (equation 39)[722] on phosphonic diesters yields the monohalides, whilst that of PCl_5 on the diesters gives mono- or di-halides depending on relative amounts of reactants and reaction conditions (equations 40 and 41); the literature is replete with examples of these displacements[723–726] in which, as one possible concern, carboxy ester groups are unaffected by the reaction



(37)



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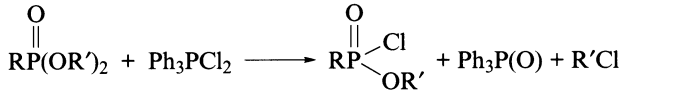

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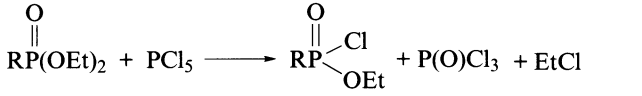

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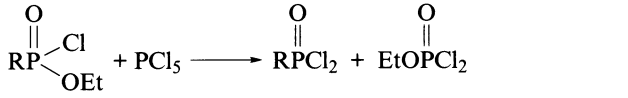
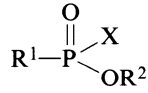


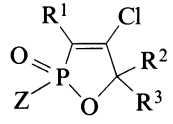
(41)

conditions[727,728]. A mixture of PCl_5 (2.5 equiv.) and $POCl_3$ (1.3 equiv.) has been recommended for the conversion of a phosphonic diester into the dichloride without any affect on halogen substituents or, more importantly, carboxy ester groups[729]. High yields of the phosphonic dichloride are available from diesters and $SOCl_2$ in the presence of dmf or similar *N*-formylated secondary amine, pyridine or hmpa[730]. The replacement of the ester group in **525** (X = F) by the use of PCl_5 is feasible only under carefully controlled conditions since the liberated $P(O)Cl_3$ may participate in a further halogen exchange reaction; other pentacoordinate chlorides, such as $PhPCl_4$, also participate in the partial exchange of F by Cl[731].

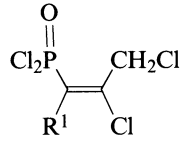


(525)

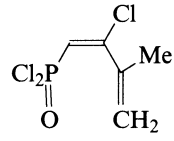
The replacement, by chlorine, of an exocyclic ester group in the presence of an endocyclic phosphorus–oxygen bond often presents a problem, with a choice to be made between $SOCl_2$ and PCl_5 as reagent. Thionyl chloride is useful for this purpose without the rupture of the ring, as in the conversion of **526** (Z = OEt) into **526** (Z = Cl)[590], although the same reagent has no such affect on **527** (Z = OEt) whereas PCl_5 brings about the simultaneous rupture of a ring and the formation of an acyclic phosphonic dichloride, as it does with **527** (Z = OEt) and **528** (Z = OMe), which are converted into **529** and **530**, respectively[551,590,623]. The ester **393** also fails to react with $SOCl_2$, and undergoes ring opening with PCl_5[732]. The



(526) $R^1 = R^2 = H$, $R^3 = Me$
(527) $R^1 = R^3 = Me$, $R^2 = H$
(528) $R^1 = H$, $R^2 = R^3 = Me$



(529)



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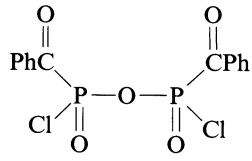
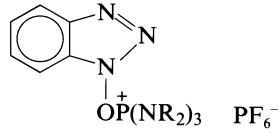


(531)

action of $SOCl_2$ on benzoylphosphonic acid is such that the initial product, the phosphonic dichloride, then leads to the acid anhydride chloride **531**[733]. A reagent which operates under extremely mild conditions for the conversion of phosphonic acids into dichlorides is oxalyl chloride in the presence of pyridine[734] or in dmf[735] at low temperature. Diphenylphosphinic acid is converted into its fluoride with SOF_2–Et_3N[736], but phenylphosphonic acid undergoes the replacement of only one OH group to give the stable PhP(O)(OH)F[736].

Calcium or magnesium salts catalyse reactions between perfluoroalkanols and phosphinic chlorides[737] or phosphonic chlorides[738]. Reactions between $MeP(O)Cl_2$ and chiral alcohols[739] and chiral thiols[740] have been employed in the determination of the stereochemical composition of the alcohol or thiol by an NMR method. Phosphonic monoesters have been esterified by secondary alcohols in the presence of BOP-type reagents, e.g. **532** (R = Me)[741]. After the selective monodemethylation of a dimethyl ester by means of a metal salt, of which LiBr and LiI appear to be the most effective[742,743] the Mitsunobu re-esterification (reaction with an alcohol in the presence of Ph_3P–dialkyl azodicarboxylate) may be followed by a second demethylation and re-esterification by the same means, so allowing the synthesis of a large range of mixed esters (Scheme 58)[744–746]. Esterification in mixtures of acids and alcohols is achieved through dehydration with dicyclohexylcarbodiimide[747]. Phosphonic and phosphinic acids may be esterified by the action of ortho esters, $RC(OR)_3$, and sodium ethenylphosphonates have been esterified by alkyl halides in the presence of quaternary amonium salts[748]. Benzyl esters are more conveniently and cleanly de-esterified by hydrogenolysis[749].



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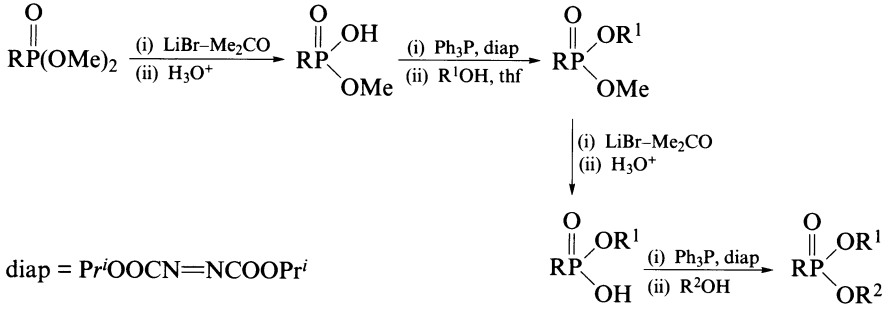
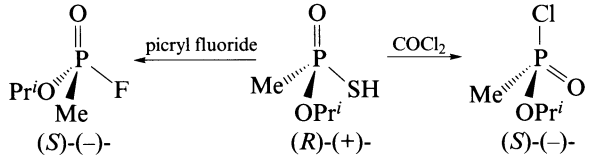
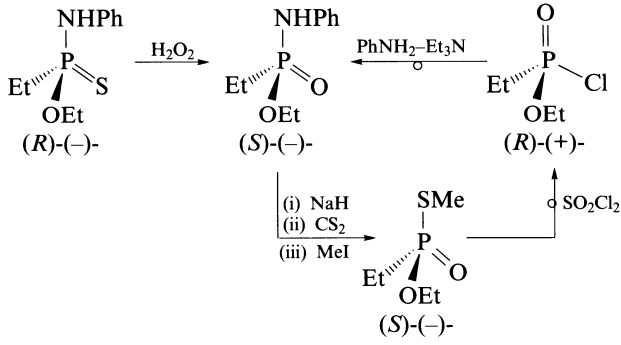


SCHEME 58

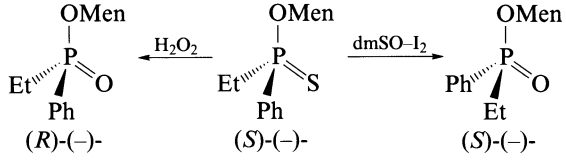
Less appears to be known about the stereochemistry of the processes listed thus far than for the corresponding displacements which involve thiophosphonic and thiophosphinic derivatives (Chapter 5, Section III); in all probability, the aforementioned reactions which involve the cleavage of direct bonds to phosphorus, like the analogous displacements at thiophosphoryl phosphorus, occur through bimolecular displacements of the $S_N2(P)$ type (see below), possibly catalytically assisted. It will also be recalled that it is possible to obtain chiral phosphonic or phosphinic derivatives from their sulphur or selenium analogues. The reader is reminded that some relatively simple ways in which this can be achieved include the formation of compounds **525** (X = Cl) by the desulphurization of phosphinoylsulphenyl chlorides with a phosphite ester (Ph_3P causes deoxygenation)[750]; the preparation of the same phosphonic chlorides by the displacement of SH groups with $COCl_2$ (Scheme 59)[751] and of SMe groups by sulphuryl chloride (Scheme 60)[752,753] with inversion of configuration at phosphorus; the oxidation of thiophosphoryl compounds $R^1R^2P(S)OR$ to $R^1R^2P(O)OR$ by means of H_2O_2[754,755] or 3-chloroperoxybenzoic acid with retention of configuration at phosphorus, and with inversion through the use of dmso–I_2 (Scheme 61)[755] and the displacement of *S*-alkyl groups and halogen groups with Grignard reagents or organolithium compounds[751]. The samples of chiral phosphonic halides produced by these



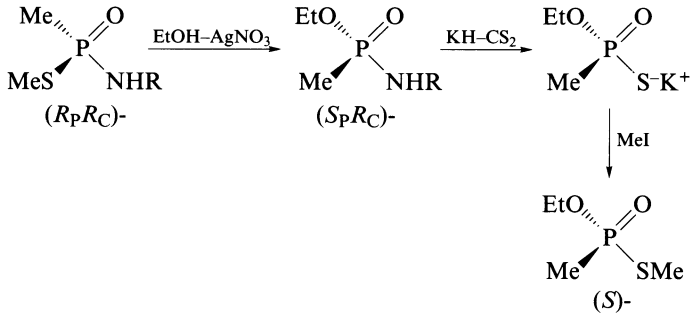
SCHEME 59



SCHEME 60



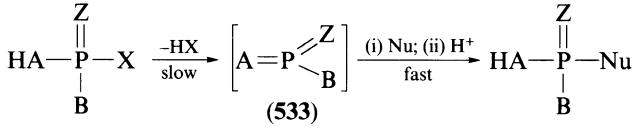
SCHEME 61



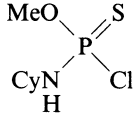
SCHEME 62

methods tended to be of low optical purities, and were, in addition, optically unstable, probably undergoing racemization under the influence of traces of halide ion. The treatment of phosphonic and phosphinic amide anions with CXY (X, Y = O or S) to remove the amide moiety is yet another method (Schemes 60 and 62[756]). All of these procedures were discussed earlier (Chapter 5, Section III).

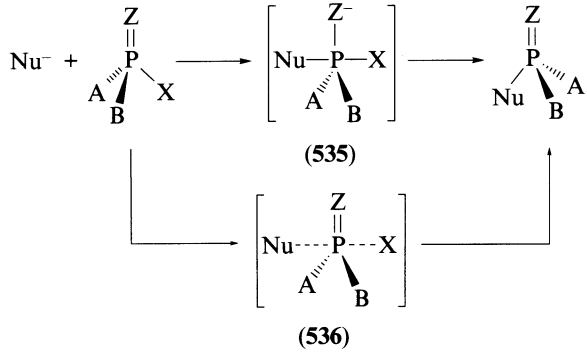
Leaving aside the (thio, seleno)phosphoryl group, it is evident that ligands on tetracoordinate phosphorus, including the directly bonded carbon moieties, may be displaced by nucleophiles through two fundamentally different mechanisms. The first mechanism is commonly referred to as the $S_N1(P)$ mechanism, but should not be confused with the S_N1 displacement process at carbon; it consists of a slow elimination step to give a planar, tricoordinate, quinquevalent species (**533**) followed by a faster addition step (Scheme 63), and hence is simply termed the elimination–addition (EA) mechanism. The present acceptance of such a process owes much to a study by Gerrard and Hamer[757] of the hydrolysis of the phosphoramidic chloride **534**. The second mechanism (Scheme 64), termed the $S_N2(P)$ mechanism, involves the approach of the nucleophile towards the face of the phosphorus tetrahedron away from the group being displaced, but in line with that group, and is reminiscent of the S_N2 displacement at carbon; because of the 'addition–elimination' nature of the process, it is often referred to as the AE mechanism. However, there exists one fundamental difference between the bimolecular displacement at phosphorus and that at carbon. That difference lies in the electronic structures of carbon and phosphorus; the latter is able to support five ligated moieties in a true intermediate **535**, unlike carbon. On the other hand, it is also evident that the formation of such a species does not occur for all displace-



SCHEME 63



(**534**)



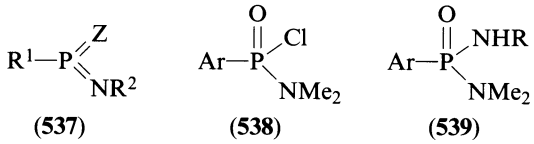
SCHEME 64

ments of tetracoordinate reactants; instead, a trigonal bipyramidal (tbp) transition state species **536** is more appropriate. The difference between these two definitions may be of theoretical interest only for many, if not most, displacements, and represents simply the two extremes of a manner of bond formation prior to bond breakage. Transition states of square pyramidal geometry are considered from time to time for individual reactions but, by and large, the AE mechanism together with the EA approach seem adequate to account for the course of most displacement reactions at (thio, seleno)phosphoryl phosphorus. Also, in very general terms, it seems reasonable to suppose that displacements at phosphorus in acyclic compounds and probably also in organic ring compounds with phosphorus as a ring atom (with the probable exclusion of compounds having five-membered rings) react through transition states, whereas cyclic compounds with the phosphorus atom as part of a five-membered ring system react via intermediate species. Much of the evidence which supports these concepts has been derived from the study of phosphate esters, and so falls outside the scope of this chapter; some of the more fundamental data which support the operation of these mechanisms has been discussed by Kirby and Warren[10], Emsley and Hall[11] and Hudson[12]. Yet a further mechanism has been reconsidered briefly in the recent past for reactions of phosphino- and phosphono-thioic derivatives, which resembles much more closely the S_N1 displacement at carbon, and is said to be based on the intermediacy of a so-called phosphaacylium ion, $R^1R^2P^+{=}Z$.

The purpose of the remaining discussion in this section is to review further developments in the chemistry of nucleophilic displacement reactions at phosphorus in the P=Z bond (Z = O, S or Se) as pertinent to phosphonic and phosphinic derivatives.

The evidence for the participation of planar tricoordinate metaphosphonimidate intermediates in the photolytic cleavage of phosphinic azides, and the liberation of planar metaphosphonate intermediates in elimination reactions of β-halogenated alkylphosphonic acids has been discussed earlier in this chapter. The first of these two examples is further characterized by the cleavage of the phosphorus-carbon bond and migration of a carbon moiety from phosphorus to nitrogen. Compounds of the type **537** (Z = O, S or Se; R^1, R^2 = Bu^t or 2,4,6-tri-*tert*-butylphenyl), although prepared in a totally independent manner, have been recorded as monomers in solution[758], and yet a further reaction for which planar tricoordinate intermediates have been proposed is the fascinating Lossen-like rearrangement of *N*-phosphinoylhydroxylamine *O*-sulphonic esters also discussed earlier.

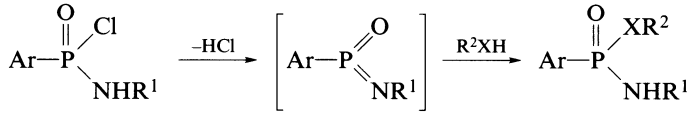
The phosphonamidic chlorides **538** (Ar = Ph, 2-methylphenyl, 2,4,6-trimethylphenyl or 2,4,6-triisopropylphenyl) undergo the expected displacements to give the phosphonic diamides **539** (R = Pr^i or Bu^t) when acted on by Pr^{i}NH$_2$ or Bu^{t}NH$_2$. With increased steric resistance by Ar, the rate of reaction with Bu^{t}NH$_2$ decreases by 70-fold overall, and the



(537) (538) (539)

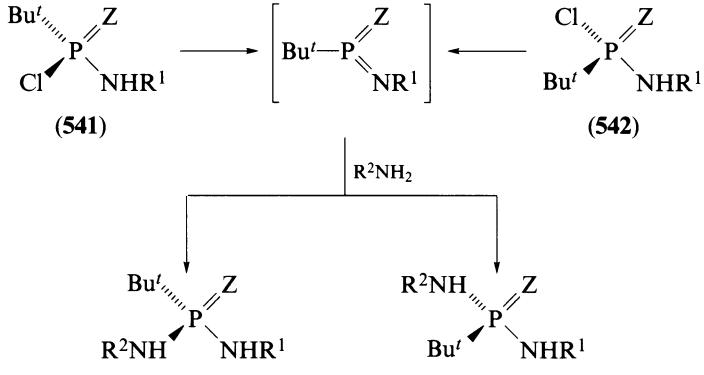
reactions with the less sterically hindered Pr^iNH_2 are faster, by about 100-fold overall; such features are consistent with the rearrangement being of an $S_N2(P)$ process.

However, for the amide **540** ($R^1 = Bu^t$) in its reactions with Bu^tNH_2, the reactivities are similar when Ar = 2,4,6-trimethyl- or 2,4,6-triisopropyl-phenyl, the reactions being about 100 times faster than those of **540** (Ar = Ph or 2-methylphenyl), which are also similar in their reactivity. The critical feature appears to be the presence, or otherwise, of two *ortho* methyl (or larger) groups; moreover, for this series, there is little difference in the reactivities of Bu^tNH_2 and Pr^iNH_2 under competition conditions. Under the circumstances, the EA mechanism (Scheme 65; $R^2 = Bu^t$ or Pr^i, X = NH) is considered to operate. The high reactivity of the reaction intermediate, interpreted through a conformational analysis, allowed the phosphorylation of sterically inhibited substrates, for example, Pr^i_2 NH (X = NPr^i) or Bu^tOH (X = O)[759]. In a further study (Scheme 66)[760], diastereoisomeric phosphonamidic chlorides **541** and **542** (Z = O, R^1 = CHMePh), derived from (*S*)-1-phenylethylamine, were subjected to reaction with Bu^tNH_2 in MeCN at room temperature, and the diastereoisomeric diamides were separated. Each chloride, gave the same stereoisomeric mix (55:45) of the product diamides; the reactions were slower in CH_2Cl_2 but otherwise produced exactly the same result, attributed to asymmetric induction. This prominent lack of stereospecificity found for low concentrations of the amines is reduced with increasing amine concentration. Even when the reaction is carried out with pure amine the reaction is still not stereospecific, but a stereoselectivity limit of about 87:13 is eventually reached



(540)

SCHEME 65



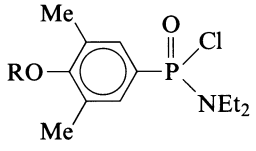
(541) (542)

SCHEME 66

and which is independent of R^2 (Pr^i or Bu^t). The comparable reactions between the stereoisomeric phosphonothioic chlorides (Scheme 66; Z = S) and the same amines are completely non-stereoselective with each giving exactly the same ratio (57:43) of diamides in dilute solution; in this case, an increase in the concentration of amine changes the ratio comparatively little, until the reactions are performed with neat amine, when each phosphonamidothioic chloride produces a slightly different ratio of products. There is a notable difference, by a factor of up to 1000, in the rates of reactions of the phosphoryl and thiophosphoryl substrates[761].

The faster alkaline hydrolysis of the phosphonamidic chloride **543** (R = H) relative to the methyl ether **543** (R = Me) has been attributed to participation of the intermediate phosphonimidic species **544**[762]. The rapid reaction between the phosphonamidothioic chloride **545** and Et_2NH to give **546** has likewise been attributed, in the light of deuterium incorporation experiments, to the intermediacy of the species **547**[763]. On the other hand, the EA mechanism is not considered to play a part in the hydrolysis of the series **548** (R = $PhCH_2$; X = EtO, Et_2N or Ph)[764], **549**[765] or **550**[766]. A further study was unable to decide on the mechanistic significance of the affects of aromatic substituents in the hydrolytic removal of the nitrophenoxy group from the compounds **551**[767].

Many data have been provided in support of addition–elimination characteristic of an $S_N2(P)$ process, and include information from studies of reaction kinetics, isotopic labelling, kinetic isotope effects and stereochemical changes. Green and Hudson[768] demon-



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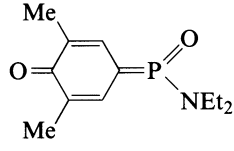

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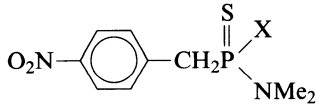
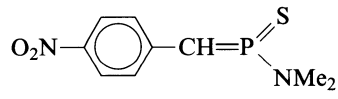


(545) X = Cl

(546) X = NEt_2



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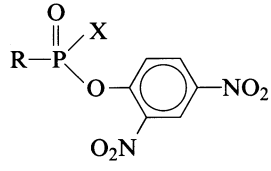

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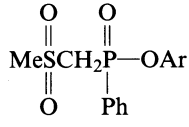

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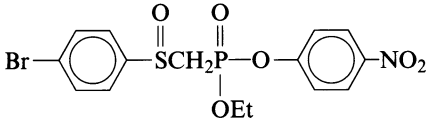

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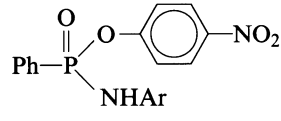
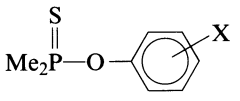


(551)

strated the equilibration between methoxide anion and optically active [^{14}C]methyl methylphenylphosphinate, for which the rate of racemization was twice the rate of exchange of methoxide, a result explicable only in terms of a bimolecular displacement with complete inversion. More recent examples of similar studies are those described by Sigal and Westheimer[769], who showed that the exchange between diphenyl methylphosphonate and [^{18}O]water under acidic conditions resulted in phosphoryl-labelled ester, and by Cook and Metni[770], who demonstrated the labelling of the phosphoryl group during the hydrolysis of *O*-methyl dimethylphosphinothioate in D_2SO_4 at 75 °C to the phosphinothioic acid; this was accompanied by desulphurization to methyl dimethylphosphinate and the sequence ended in hydrolysis to dimethylphosphinic acid. Reaction sequences such as these are explicable in terms of the formation and breakdown of pentacoordinate species, if account is taken of possible ligand redistribution (pseudorotation; see later).

Studies on the alkaline hydrolysis of various phosphonic and phosphinic esters have provided information on the electronic or steric effects of substituents and the effects of changes in reaction conditions; amongst the substrates so extensively examined are the *O*-aryl esters of dimethylphosphinothioic acid (**552**)[771–775], esters of diphenylphosphinic acid[776–779] and *O*-aryl[778,778] and *S*-aryl[779,780] esters of diphenylphosphinothioic acid (**553**; Z, Y = O or S). Other studies have concentrated on aryl esters of diarylphosphinic acids (**554**)[781,782], and the effects of the stepwise replacement of *P*-Me by *P*-Ph in esters of dimethyl-, methylphenyl- and diphenyl-phosphinic acids[783]. The esters **555** (R^1 = EtO, R^2 = Me or Ph, $R^1 = R^2$ = Ph; X = SEt or Cl)[784] hydrolyse under alkaline conditions faster than do the comparable *S*-(4-substituted-butyl) esters. Comparable steric and electronic influences on the hydrolyses of phosphonic and phosphinic fluorides[785], phosphinic chlorides[786–788], the phosphonothioic chlorides **556**[789] and other phosphonic and phosphinic esters[788,790] have been noted. Phosphonic and phosphinic halides are prone to undergo halogen-exchange reactions, a process which, in general, is faster for derivatives of phosphonic than for those of phosphonothioic and phosphonoselenoic acids, and to be particularly important for acid fluorides[791,792].



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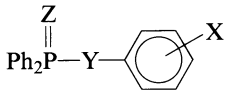
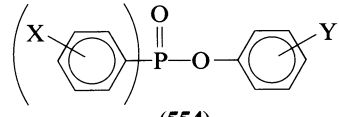
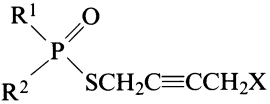


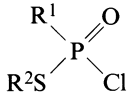
(**553**)



(**554**)



(**555**)



(**556**)

The effect of replacing oxygen by a higher chalcogen in either the P=X bond or in an ester linkage on the rate of alkaline hydrolysis through the $S_N2(P)$ (AE) mechanism is in contrast to that experienced in a reaction known to proceed through the EA mechanism. The pronounced difference in the rates of reaction of the substrates **541** and **542** (Z = O) compared to the rates for the corresponding thiophosphoryl (Z = S) substrates (Scheme 66)[761] has already been commented on. Tables 2–5 summarize, in comparative terms, alkaline hydrolysis rate data for series of phosphinic esters and their mono- and di-thio analogues[793]. Tables 2 and 4 clearly demonstrate a steric effect on the part of the ester alkyl group. The replacement of P=O by P=S (and it is expected that a replacement by P=Se would produce a similar outcome) is seen to cause a decrease in the rate of nucleophilic attack by hydroxide or a primary amine by a small factor only (Table 5); as might be

TABLE 2. Relative rate data for the alkaline hydrolysis of phosphinate, phosphinothioate and phosphinodithioate esters: influence of the alkyl substituents on phosphorus. Reproduced, with modifications, by permission of the Research Council of Canada

	Relative rate data for R=					
Ester	Me	Et	Pr	Pr^i	Bu^i	Bu^s
$R_2P(O)OMe$[a]	10760	808	–	–	31.3	1
$R_2P(O)OME$[b]	515	11	1	–	–	–
$R_2P(S)OMe$[c]	235	2.9	1	–	–	–
$R_2P(O)SMe$[d]	10.6	3.7	1	–	–	–
$R_2P(O)SMe$[e]	550	310	55	1.4	–	1
$R_2P(S)SMe$[f]	13	1.4	1	–	1.7	–
$RC(O)OEt$[g]	21	10	4	2.5	1	–

[a] At 75 °C in water.
[b] At 75 °C in 60% dme–water.
[c] At 50 °C in 60% dme–water.
[d] At 30 °C in 60% dme–water.
[e] At 50 °C in water.
[f] At 50 °C in 60% dme–water.
[g] Ref. 795.

TABLE 3. Relative rate data for the alkaline hydrolysis of phosphinate, phosphinothioate and phosphinodithioate esters; influence of the heteroatom in the leaving group. Reproduced, with modifications, by permission of the Research Council of Canada

Ester	Solvent[a]	Temperature °C	k_S/k_O
$Me_2P(O)YMe$	D	30	1.03
$Et_2P(O)YMe$	D	50	22[b]
$Et_2P(O)YEt$	W	75	77[c]
$Bu^tP(O)YMe$	W	75	126
$Me_2P(S)YMe$	D	30	1.5
$Et_2P(S)YMe$	D	30	13.3
$Pr_2P(S)YMe$	D	30	22

[a] D = 60% dme–water; W = water.
[b] Rate for $Et_2P(O)OMe$ from ref. 796.
[c] Rate for $Et_2P(O)YEt$ extrapolated to 75 °C.

TABLE 4. Relative rate data for the alkaline hydrolysis of phosphinate, phosphinothioate and phosphinodithioate esters: influence of the alkyl group in the leaving group. Reproduced, with modifications, by permission of the Research Council of Canada

	Relative rate for R=					
Ester	Me	Et	Pr	Pr^i	Bu^i	Bu^s
$Et_2P(O)OR$[a]	342	39	26	2.4	15	1
$Et_2P(O)SR$[b]	9	3	3	–	1	–
$Et_2P(S)SR$[c]	10	2.2	1.9	–	1.7	1
$MeC(O)OR$[d]	33	14.3	8.3	2.2	5.5	1
$MeP(O)OR$[e]	600	40	–	1	–	–

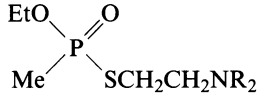
[a] At 75 °C in water.
[b] At 50 °C in water.
[c] At 50 °C in 60% dme–water.
[d] At Ref. 797; at 24.7 °C in 70% acetone–water.
[e] Ref. 798; at 80 °C in water.

TABLE 5. Influence of the P=X bond (X = O or S) on rate of nucleophilic attack on phosphorus. Reproduced, with modifications, by permission of the Research Council of Canada

Compound	Nucleophile	$k_P = O/k_P = S$
$Me_2P(X)OMe$	HO^- [a]	1.1
$Me_2P(X)SMe$	HO^- [b]	1.7
$Et_2P(X)OMe$	HO^- [c]	0.6
	HO^- [d]	1.8
$Et_2P(X)XSMe$	HO^- [b]	8.3
$Et_2P(X)OEt$	HO^- [c]	0.4
$Ph_2P(X)OC_6H_4Me$-4	HO^- [e]	33
$(ClCH_2)_2P(X)SEt$	HO^- [f]	25
$(ClCH_2)_2P(X)OEt$	HO^- [f]	4
$Ph_2P(X)OC_6H_4NO_2$-4	H_2NBu [g]	25
$(EtO)_2P(X)OC_6H_4NO_2$-4	HO^- [h]	9.1
	H_2O [i]	56
$(EtO)_3P(X)$	HO^- [j]	6.6
$PhC(X)OC_6H_4NO_2$-4	HO^- [k]	8.3
	H_2NEt [k]	0.39

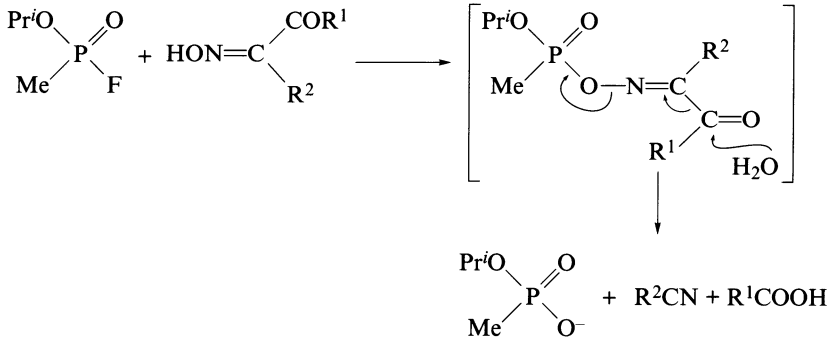
[a] At 50 °C in 60% dme–water.
[b] At 30 °C in 60% dme–water.
[c] At 75 °C in water.
[d] At 75 °C in 60% dme–water.
[e] Refs 777 and 799; at 50 °C in 50% EtOH–water.
[f] Ref. 800; at 25 °C in water.
[g] Ref. 779; at 30 °C in MeCN.
[h] Ref. 801; at 25 °C in water.
[i] Ref. 802; at 37 °C and pH 7.4 in 0.067 M phosphate buffer.
[j] Ref. 803; at 25 °C in water.
[k] Ref. 804; at 25 °C in 20% MeOH–water.

expected, the value of $k_{P=O}/k_{P=S}$ depends, at least partly, on the nature of the leaving group, being small for RO^- but larger for RS^- and even more so for ArO^-. The replacement of P—O alkyl by P—S-alkyl increases the rate of hydrolysis to a moderate extent (Table 3). Differences in reactivity are attributable to differences in electrophilicity of phosphorus in the P=O and P=S bonds and the polarizability of the bonds. Difficulties in attempting to correlate the rates of nucleophilic attack, e.g. alkaline hydrolysis, and the group R of a phosphinic ester $R_2P(O)OR'$ have been attributed to a mixed hydrolysis pattern, i.e. both P—O and O—C cleavage, as was found by Rahil and Haake[794] for methyl diisopropylphosphinate (the relative extents of cleavage of the two bonds were 3:1); this is in contrast to only P—O cleavage in less sterically hindered compounds, which is thought to proceed via TBP transition states. A small difference in the structure of a substrate may make a pronounced difference in the manner of hydrolysis; the compounds **557** (R = Et or Pr^i) both hydrolyse at the P—S bond and at pH below 7 and above 10, but in this intermediate pH range, **557** (R = Et) hydrolyses by cleavage of C—O and P—S bonds, whereas **557** ($R = Pr^i$) hydrolyses through fission of the C—O, P—S and C—S bonds[805].

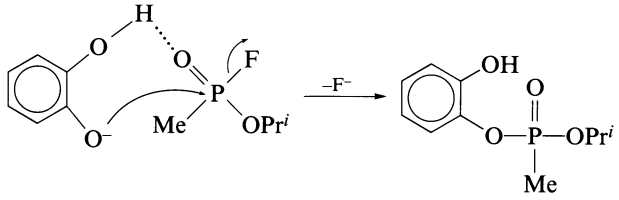


(557)

The bimolecular displacement process may often be subject to catalysis, and this may be either inter-or intra-molecular. A well known example of intermolecular catalysis is the



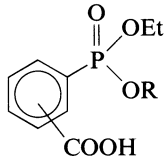
SCHEME 67



SCHEME 68

widespread use of imidazole or its derivatives in the catalysis of phosphorylation processes in general and, in a recent example, its use in conjuction with diphenylphosphinic chlorid in the preparation of allylic esters of diphenylphosphinic acid[806]; tetrazole has been used for the same purpose[807]. A technically important example of intermolecular catalysis is the use of oximes as antidotes to the action of nerve gases, and illustrated (Scheme 67) for the case of sarin (isopropyl methylphosphonofluoridate)[808]. The same phosphorus substrate, in its reaction with catechol, provides an example of acid catalysis (Scheme 68) in which the polarization of the phosphoryl group is enhanced through hydrogen bonding, so increasing electrophilicity of phosphorus[809]. Several examples of intermolecular catalysis, particularly in connection with the hydrolytic removal of the 4-nitrophenoxy group, have been encountered. The displacements of 4-nitrophenoxy groups from various esters by other alcohols (transesterification) is efficiently catalysed by amines[810,811] and particularly by dbu in reactions with primary or secondary alcohols, phenols or other amines[812]. Sodium perborate catalyses the hydrolytic degradation of 4-nitrophenyl esters of phosphoric, phosphonic and phosphinic acids in reactions so fast that the agent has been recommended for decontamination purposes (because of the ease of removal of the nitrophenoxy group under biological conditions with resultant phosphorylation, some nitrophenyl esters, e.g. ethyl 4-nitrophenyl methylphosphonate, are as highly toxic as the better known nerve gas compounds)[813].

As the first reported[814] example of intramolecular catalysis of hydrolysis of a phosphonic diester, the *ortho* isomer of **558** (R = Et) hydrolyses almost 10^8 times faster than the *para* isomer (which, together with the *meta* isomer, behaves in no unusual way), presumably by intramolecular acid catalysis, to give the monoethyl ester of *ortho*-**558** (R = H)[814,815]. Moreover, the sodium salt of *ortho*-**558** (R = Et) is moderately stable under aqueous conditions, but undergoes immediate hydrolysis to *ortho*-**558** (R = H) when acidified[814].



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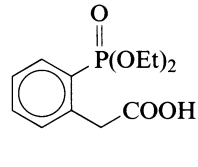

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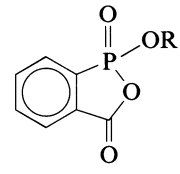

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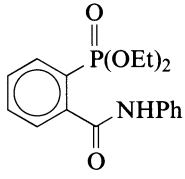

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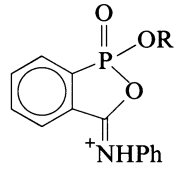

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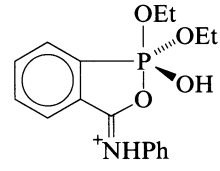
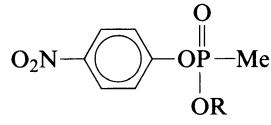


(563)

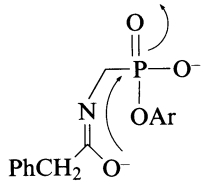
The hydrolysis rate of **559** is 10^5 times slower than that of *ortho*-**558** (R = Et)[815]. It was suggested that **560** (R = Et) might be an important intermediate in the hydrolysis of **558** (R = Et)[815]. Another study has been concerned with the carboxamide **561**; under alkaline conditions, its diethyl ester hydrolysed at a rate which approximated to that of diethyl phenylphosphinate, but under acidic conditions $t_{1/2}$ for loss of both ester groups was about 1 h, whereas the *para* isomer remained almost unchanged for 1 month. The breakdown of **561** was thought to occur by the stepwise loss of the ethyl ester groups and the participation of **562** which then led to **560** and eventually to 2-phosphonobenzoic acid[816,817], although the final picture presented was slightly more complex and involved the participation of a pentacoordinate intermediate **563**[818]. The reverse phenomenon, i.e. the phosphonate-assisted hydrolysis at pH < 4 of the carboxanilido group, is also known, and is thought to proceed through the intermediate **560** (R = H)[819].

The potential for intramolecular catalysis thus appears to depend, to some extent at least, on molecular geometry. The phenomenon has also been seen in the ability of the geometric isomers of 3-(diethoxyphosphinoyl)propenoic acid to hydrolyse; in weakly acidic aqueous media, the stepwise release of both ethyl ester groups, with P—O bond fission, has been observed at a rate 10^6 times faster for the *Z*-isomer than for the release of just one ester group in the *E*-isomer[820]. The participation of an enol form (through hydrogen bonding with the phosphoryl group) might be responsible for the much enhanced hydrolytic removal of the 4-nitrophenoxy group from **564** compared with that from **565**, by a factor of about 9000[821,822].

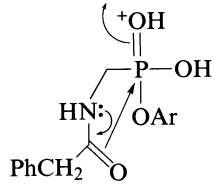


(**564**) R = CH_2COPh
(**565**) R = Et

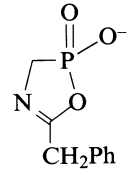
The monoaryl esters of {[*N*-(phenyacetyl)amino]methyl}phosphonic acid hydrolyse at much faster rates under either alkaline **566** or acidic **567** conditions than analogues which lack the acylamino or even acyl substituents, although the potential intermediate **568** could not be detected[823]. A comparison of the rates of hydrolysis of diethyl (aminomethyl)phosphonates with the rates for diethyl phenylphosphonate and tetraethyl methylenebisphos-



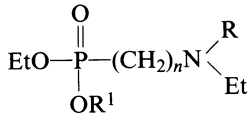
(566)



(567)



(568)



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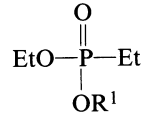


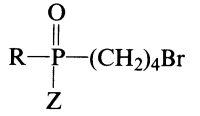
(570)

phonate suggested that the amino group serves to catalyse the hydrolysis; a significant deuterium isotope effect was experienced with D_2O[824]. A study of the triesters **569** (R = Et, n = 2, or 4) has shown that at pH 8.21–11.45, these (R^1 = H or Et) and also **570** (R^1 = Et) lose one ethoxy group to give the corresponding compounds with R^1 = H; in addition, however when n = 2, an elimination process also occurs to give the di- and mono-ethyl esters of ethenylphosphonic acid (when R = Et) or diethyl (2-hydroxyethyl)phosphonate (when R = H). The amino group exhibits intramolecular catalysis of hydrolysis when R^1 = H; when R^1 = Et, general base catalysis takes place[825].

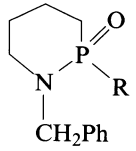
The hydrolysis of alkyl esters of bis(chloromethyl)phosphinic acids is controlled by steric factors within the alkyl group[826], and during the hydrolysis of diethyl (chloromethyl)-phosphonate or ethyl (bromomethyl)(chloromethyl)phosphinate with $H_2{}^{18}O$ at 98 °C, the isolated ethanol contained 93–100% of the isotope label, indicating that nucleophilic attack by the water occurred at the ester α-carbon atom[827]. The presence of a halogen on $C_{(1)}$ increases the rate of alkaline hydrolysis (and also that of hydrolysis in water) relative to that of the same ester of a halogen-free acid, with the effectiveness of the halogen decreasing in the order Cl > Br > I[828–830]. The positive influence is reduced for the halogen at $C_{(2)}$, but when the halogen is sited on $C_{(3)}$, an appreciable accelerating influence can be seen once again, the effect being larger for esters of the bis(ω-haloalkyl)phosphinic acid than for a (ω-haloalkyl)phosphonic diester[831–833].

Disregarding the phosphoryl bonds and the carbon ligands at phosphorus, the remaining non-carbon ligands are subject to countless potential displacement reactions as surveyed elsewhere[1–8]. The literature appertaining to several such displacements has been updated, for instance, for the conversions of OH and OR into Cl and *vice versa* (this section), and the displacements of SR by RO^- or organometallic reagents (Chapter 5). Some displacement reactions are of essentially theoretical interest only, others possess experimental significance and, indeed, may be of commercial importance as, for example, in the manufacture of organophosphorus pesticides. Generally, however, there have been few developments in methodologies associated with displacement processes, e.g. in the development of new reagents or experimental procedures, with certain notable exceptions, as has already been seen, for example, in the interconversions of OH, OR and halogen groups.

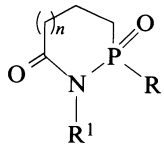
A further nucleophilic displacement of both theoretical and practical significance is that of halogen by an amine. Thus, **571** can be converted, via **572**, into **573**, and **573**, when acted on by NaH (to form the amide anion), then yields the perhydro-1,2-azaphosphorines **574** (R = EtO or Ph)[834,835]; a similar procedure was used to obtain **575** (R = EtO,



(571) Z = EtO
(572) Z = Cl
(573) Z = $NHCH_2Ph$



(574)



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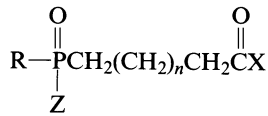

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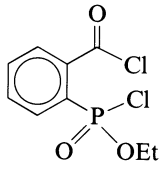

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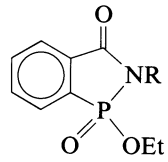
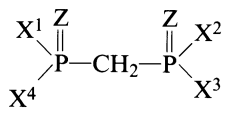


(578)

$R^1 = PhCH_2$) from **576** (n = 1, R = EtO, X = Z = Cl) by a reaction with benzylamine. In a slightly different approach, and with variable results, **576** (n = 1, Z = NHR′, R′ = H, Me or $PhCH_2$; X = EtO) were obtained from **576** (n = 1, Z = Cl, X = EtO); cyclization with $KOBu^t$ provided the corresponding **575** (n = 1)[836] and the 1,2-azaphosph(V)olidin-5-ones **575** (n = 0) have been obtained in a similar manner[837,838] as was **578** from **577**[839].

Reactions between amines and phosphonic dichlorides may not always proceed in the expected manner in spite of the (supposed) high reactivity of the latter; phosphonic dichlorides can be expected to react in a stepwise fashion with amines (at least with secondary amines, but complications may arise with primary amines), but the displacement of only one chlorine atom occurs in a reaction between prop-2-enylphosphonic dichloride and diethylamine[840]. The methylenebisphosphonic tetrahalides **579** (Z = O or S, X^1–X^4 = Cl; Z = S, X^1–X^4 = F) react with Me_2NH is a stepwise fashion with the replacement of the halogen atoms in a symmetrical, rather than an unsymmetrical, way[841] but a similar reaction between **579** (X^1–X^4 = Cl, Z = O) and RNH_2 (R = PR^t or Bu^t) yield the 1,3,4-azadiphosphetidines **580** as mixtures of *cis* and *trans* isomers[842].



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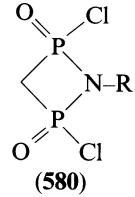
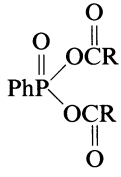


(580)

A further displacement of practical utility is that of halogen in phosphonic[843] and phosphinic[844] chlorides by carboxylate ions (with silver or thallium salts, for example) to give mixed anhydrides, e.g. **581** and **582**. Such anhydride formation provides a system particularly reactive at the carbonyl group towards nucleophiles, and thus preliminary activation of the carboxyl group by the diphenylphosphinoyl group becomes useful in amide or peptide formation[845–847]

The cyclic anhydrides **583** undergo exothermic reactions with nucleophiles as indicated (Scheme 69)[848–855]. Whether a nucleophile attacks carbonyl carbon or phosphoryl phosphorus obviously depends on the nucleophilicity of the attacking reagent (water, an alcohol or amine) and the results were at one time observed to be consistent with the principles



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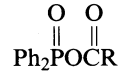

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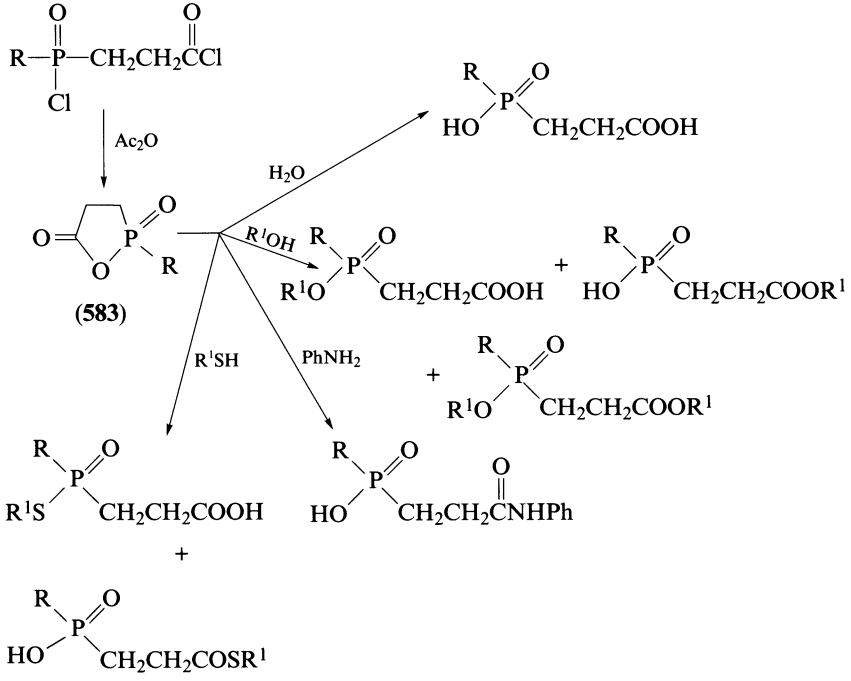
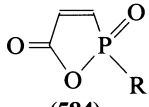


SCHEME 69



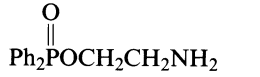
(584)

of hard and soft acids and bases, i.e. attack by an alcohol occurs preferentially at phosphorus whereas that by an amine ($PhNH_2$) occurs at carbonyl. However, alcohols have been found able to attack the carbonyl group, or into both reactive sites concurrently, with the outcome depending on several factors including the nature of the group R, order of addition and other experimental circumstances. The anhydrides **584** behave similarly[856].

Chemoselectivity in the displacement process has been examined by Horner and coworkers[857–859] in order to try to obtain an insight into the potential of the $Ph_2P(Z)$ (Z = O

(585)

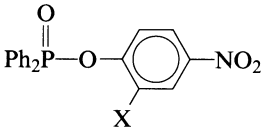
(588)



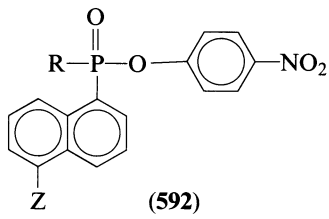
(586)

(589)

(587)



(590) X = NO_2
(591) X = H



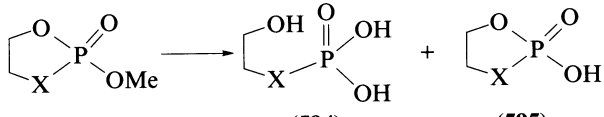
(592)

or S) group for protection purposes. In the reactions between $Ph_2P(O)X$ and 2-aminoethanol, the three possible products of nucleophilic substitution are **585–587**; for X = Cl, the selectivity in product formation is **585** > **586** > **587**, but the reverse is true for $X = N_3$, and for X = F, CN or 4-nitrophenoxy only the ester **586** is obtained[857]. It might be noted that $Ph_2P(O)Cl$ is *O*-selective in its reaction with 2-aminophenol in the presence of Et_3N[860]. With 2-aminoethanethiol, the phosphinic chloride reacts preferentially at nitrogen to give **588** and **589** in the ratio 65:35[858]. In the reactions between the thiophosphinic derivatives $Ph_2P(S)Z$ and the butane derivatives BuXH (X = O, S or NH) as mixtures of two reactants, most of the reactions showed extensive selectivity and those with X = F produced low yields, although the reagent was *O*-selective in the presence of either thiol or amine[857,858]. The chloride was *N*-selective in the presence of alcohol or thiol, but S-selective in the presence of alcohol. When X = CN, the reaction occurred entirely with BuSH in the presence of $BuNH_2$. The selectivity in reactions between the various nucleophiles and $Ph_2P(S)X$ was not greatly different from that shown by the phosphinoyl chloride[857,858]. Other interesting results were obtained with the nitrophenyl esters **590–592**; ester **590** reacted with nucleophiles (BuOH, BuSH or $BuNH_2$, as before) with the displacement of the dinitrophenyl derivative of the nucleophile and liberation of diphenylphosphinic acid, whereas the 4-nitrophenyl esters **591** and **592** (Z = OMe or NMe_2; R = alkyl or aryl) liberate nitrophenol and act as phosphorylating agents for the nucleophile[859]. Tetraalkylammonium fluorides cleave the P—S bond in esters of diphenylphosphinothioic and diphenylphosphinodithioic acids to give the corresponding fluorides[858].

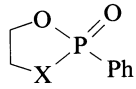
Similar reactions between racemic MePhP(O)X (X = F, Cl, CN or 4-nitrophenoxy) and ROH (R = Me, Pr^i, CF_3CH_2 or $PhCH_2$) in the presence of optically active amines [(*R*)- or (*S*)-1-phenylethylamine, (*R*)- or (*S*)- *N*,*N*-dimethyl-1-phenylethylamine or nicotine] indicated partial induction of optical activity of 1–14% in the resultant esters formed in the

ligand transposition, an observation which received an explanation in terms of complexation of the amine with the phosphinic derivative to give, initially, a pentacoordinate species; the latter is attacked by the alcohol to give a novel hexacoordinate species, which then loses F^- and amine hydrofluoride in a stepwise manner[861].

Reactions which involve displacements at phosphorus in cyclic esters or related compounds have occupied a special position in the development of the theory of ligand replacement at phosphorus. A well known feature of phosphate ester chemistry is the remarkable ease with which, during the solvolysis of cyclic phosphoric triesters under alkaline or acidic conditions, ring fission or cleavage of the exocyclic ester group occur; for methyl ethylene phosphate, **593** (X = O), for example, both processes occur about 10^6 times faster than the hydrolysis of a non-cyclic analogue, e.g. trimethyl phosphate[862], although at pH > 12 hydrolysis is exclusively exocyclic. The rate enhancements for the base-catalysed hydrolyses of the two esters **596** and **597** relative to diethyl phenylphosphonate and ethyl ethylphenylphosphinate, respectively, are 6×10^3 and 1.5×10^6[863].



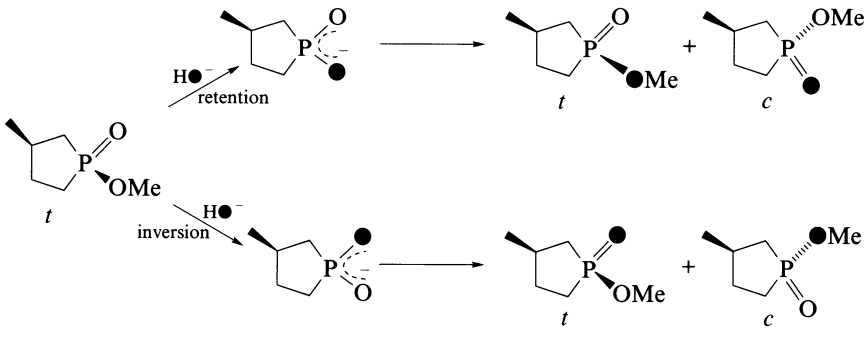
(593) **(594)** **(595)**



(596) X = O
(597) X = CH_2

The currently accepted interpretation of earlier observations such as these was devised and enunciated by Westheimer[864] and is based on the participation of an ionic, pentacoordinate intermediate formed by combination of reactants as required for S_N2 substitution (i.e. in-line approach of reagent towards the phosphorus tetrahedron face opposite the atom or group to be replaced), capable of undergoing, but not necessarily of so doing, one or more ligand exchanges. In essence[11,865,866], the ligand exchanges are restricted in so far that, within the suggested trigonal bipyramidal (tbp) intermediate (Scheme 64), certain rules must hold good; these include (i) the more electronegative an atom, the greater is the tendency for it to occupy an apical position—a position through which the tbp intermediate is set up and also breaks down during the course of the AE reaction; (ii) phosphorus–carbon bonds are unlikely to occupy the apical positions; (ii) in the case of cyclic phosphorus compounds, those with six-membered and larger rings can span either equatorial–apical or equatorial–equatorial positions satisfactorily, whereas those with five-membered or smaller rings can only span equatorial–apical positions, since equatorial–equatorial spanning by a smaller ring would result in a much higher ring strain than is normally to be found within the ring, whereas the setting up of the tbp intermediate with the smaller ring equatorial-apical helps to reduce inherent ring strain (see, however, the finding discussed below). In deciding which atoms or groups are to occupy which positions in the tbp structure, an order of preference for occupation of the apical positions has been drawn up, viz. F > H > CF_3 > OPh > Cl > SMe OMe > NMe_2 > Me > Ph. This order, which consists of the relative apicophilicities[867,868] of the groups, was devised from considerations of the structures of stable, isolable, pentacoordinate compounds.

With regard to phosphonic and phosphinic derivatives, it can clearly be assumed that a P—C bond will be sited preferentially in an equatorial position and, moreover, for cyclic

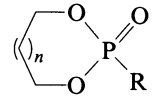


● = ^{18}O ; *c* = *cis* ; *t* = *trans*

SCHEME 70

phosphonic and phosphinic esters, the preferred position for a five-membered ring will be apical–equatorial with (as far as possible) P—O bonds apical and P—C bonds equatorial. However, the exclusion of the phospholane ring in 1-methoxy-3-methylphospholane 1-oxide from the apical–equatorial site has been claimed[869] from a study of the hydrolysis of this compound using $Na^{18}OH$ (Scheme 70); the starting material, largely one diastereoisomer in the *trans* form, was hydrolysed, the resultant dianion remethylated with diazomethane and the isotopic composition of the final methyl esters determined. The label was found to reside largely in the phosphoryl group as the result of a reaction with inversion of configuration at phosphorus and which, in the light of the above reasoning, rules out any ligand reorganization (a single pseudorotational step) and at the same time suggests a direct in-line displacement with a diequatorial ring.

Again with regard to cyclic phosphonic and phosphinic esters, a feature of both theoretical and practical significance is the great difference between the reactivity of esters based on five-membered or smaller rings and those with six-membered or larger rings in terms of both exo- and endo-cyclic P—O—C bond reactivity. The alkaline hydrolysis of the cyclic phosphonic diesters **598** (*n* = 1 or 2) under a various conditions is thought to proceed through an AE mechanism with steric hindrance on the part of the group R when this is branched, and with the probable participation of a tbp transition state **536** rather than intermediate **535**[870–872]. The acid hydrolysis of 2-methoxy-1,2-oxaphospholane 2-oxide (methyl propylphostonate) (**593**; X = CH_2), like that of methyl ethylene phosphate (**593**; X = O) proceeds exceedingly quickly and along two pathways with both ring opening to give **594** (>98%) and with ring retention to give **595** (< 0.2%)[873]. The Westheimer concept therefore requires that endocyclic P—O bond cleavage takes place in the tbp (ring P—OC bond axial, ring P—C bond equatorial), within any rearrangement, whereas the exocyclic P—OC bond fission requires a single pseudorotation step to allow this bond to be positioned apically. On the other hand, the cyclic phosphinic esters **599–601** can hydrolyse only exocyclically and, moreover, do so at rates only slightly faster than the acyclic analogues **602–604**[874–877]. The remarkable ease with which cyclic phosphonate esters based on the



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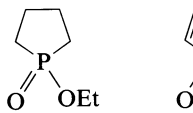
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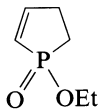
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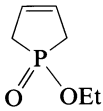
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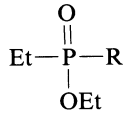
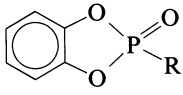
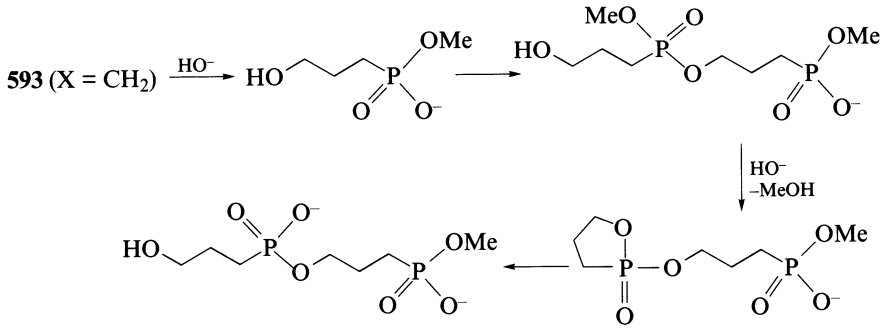

(602) R = Et
(603) R = $CH{=}CH_2$
(604) R = $CH_2CH{=}CH_2$


(605)

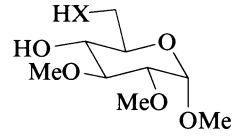
1,3,2-benzodioxaphosph(V)ole ring system, **605**, undergo hydrolysis or alcoholysis through cleavage of the five-membered dioxaphosphole ring[878–881] is a reflection of the ease with which tbp intermediates can be set up with a ring P—OC bond arranged axially; this remarkable property allows their use for phosphorylation purposes. In addition, however, it might be noted that the benzodioxaphosphole ring system plays an important role in stabilizing pentacoordinate covalent compounds (phosphoranes).

Meanwhile, studies on the hydrolysis of cyclic phosphonates (particularly) and phosphinates are becoming ever more detailed. The results of a recent product analysis for the alkaline hydrolysis of methyl propylphostonate are summarized in Scheme 71 and indicate a sequence of ring opening, cyclization and further ring opening[882]. It should be pointed out that not all nucleophilic displacements (ring-opening reactions) occur by the attack of a nucleophile at phosphorus; primary amines, including aniline, react with 2-methyl-1,2-oxaphospholane 2-oxide to give a variety of products, the structures of which are consistent with nucleophilic attack at carbon[883]. While the hydrolysis of an ester to the corresponding acid is of considerable practical importance, the details of the mechanism are of rather specialized interest, and the effort devoted to its study during recent years has been considerable, and only an outline of the salient features has been presented.

As a consequence of the general lack of availability of simple chiral phosphoryl compounds, often the result of difficulties in synthesis which may be associated with problems of optical stability of enantiomeric forms [for example, ethyl ethylphosphonochloridate Et(EtO)P(O)Cl, which has been isolated in optically active enantiomeric forms, racemizes during storage], and also partly by the desire to conduct studies in which ligand reorganization (pseudorotation) in the reaction intermediate or transition state might be restricted, many studies on displacements at phosphorus have employed phosphorus esters and



SCHEME 71

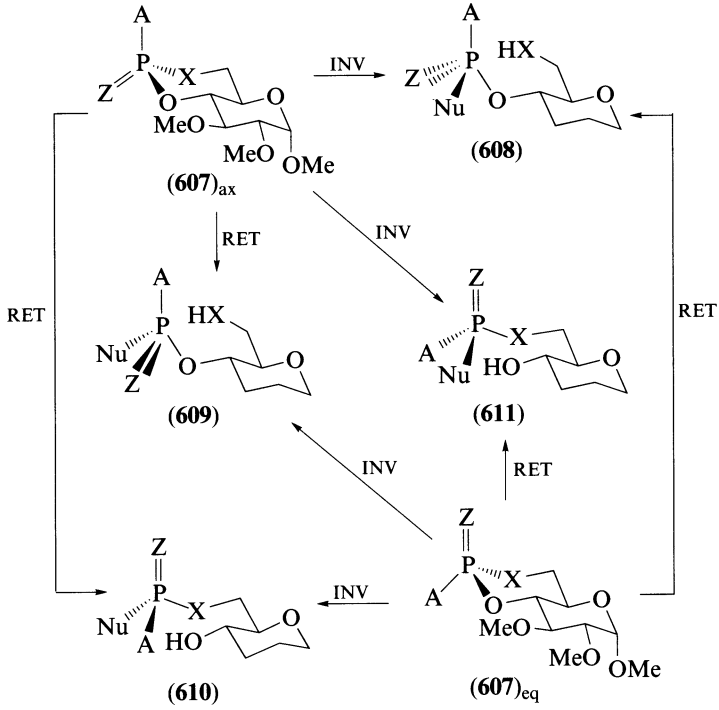


(606)

amides derived from chiral templates such as natural carbohydrates or amino alcohols; these have the advantage of being readily available and therefore cheap, and of being pure. Reactions between $RP(Z)Cl_2$ and the compounds **606** (X = O, S, or NMe) derived ultimately from D-glucopyranose, have provided the diastereoisomeric bicyclic 1,3,2-dioxaphosphorinanes **607** (X = O), 1,3,2-oxathiaphosphorinanes **607** (X = S) and perhydro-*N*-methyl-1,3,2-oxazaphosphorines **607** (X = NMe), in which the P—A bond is axial $(\mathbf{607})_{ax}$ or equatorial $(\mathbf{607})_{eq}$ (phosphorus epimers); a similar series is available from D-galactopyranose. Although much of the work in this area has been concerned with compounds in which A = EtO, EtS, Cl, F, Me_2N or other similar groups and are not of primary concern here, many data are available on reactions of substrates in which A = Me or Ph. Complications have sometimes arisen in these studies, however, because of the formation of one (or more) diastereoisomeric product(s) under conditions of kinetic control, and which then isomerize to thermodynamically more stable products. Fortunately, the phases in the overall reaction scheme proceed at rates which largely allow each to be examined separately; the rates of ring-opening reactions tend to be at least ten times faster than subsequent rearrangements, and both of these are much faster than further reactions undergone by the acyclic products derived from the initial substrates. The course of the displacement reactions which have employed the substrates **607** and very often also the stereochemistry of the products, have been decided on the basis of IR spectroscopy (particularly with regard to the assignments of P=O and P=S), ^1H and ^{31}P NMR spectroscopy, the occasional use of ^{13}C NMR spectroscopy; chemical correlation was achieved by the stereospecific oxidative desulphurization and deselenization of thiophosphoryl and selenophosphoryl compounds into their phosphoryl analogues with 3-chloroperoxybenzoic acid or hydrogen peroxide with retention of configuration at phosphorus[884]. Although the use of the compounds **607** in the synthesis of linear organophosphorus derivative has sometimes been referred to briefly in earlier chapters, their use in the synthesis of chiral acyclic phosphonic and phosphinic derivatives, and those of the sulphur and selenium analogues, will now be illustrated further and the results summarized.

In principal (Scheme 72), the chiral substrate **607** (X = O, S or NMe; Z = O, S or Se; A = a carbon moiety generally Me or Ph) can react with a nucleophile in such a way as to bring about fission of the bond between phosphorus and $C_{(4)}$ or that between phosphorus and $C_{(6)}$. For the cleavage of the P—$XC_{(6)}$ bond in the diastereoisomer with axial P—A and equatorial P=Z bonds, a reaction with inversion yields the acyclic phosphonic ester **608**, whereas a reaction with retention of configuration at phosphorus yields the ester **609**. Similarly, the diastereoisomer epimeric at phosphorus, viz. $\mathbf{607}_{eq}$ will undergo fission at the P—$OC_{(4)}$ bond with inversion or retention to yield the stereoisomeric products **610** and **611**, respectively. The stereochemistry of ring opening of $\mathbf{607}_{ax}$ at P—$OC_{(4)}$ and of $\mathbf{607}_{eq}$ at P—$XC_{(6)}$ follows the pattern indicated in Scheme 72. Whether a reaction proceeds with cleavage of one or other bond P—O or P—X, and with inversion or retention, will obviously depend on the direction of initial attack by the nucleophile (and the nature of the latter), and this might be controlled by any of several factors including, for example, steric forces, the reaction conditions, and relative apicophilicities (but see also later arguments), as well as any constraints to ligand reorganization in an intermediate or transition state.

Most reactions between bicyclic 1,3,2-dioxaphosphorinanes (**607**; X = O, A = Me or Ph, Z = O or S) and Grignard reagents RMgBr (R = Ph or Me) [i.e. both reactions leading to



MeO groups have been omitted from structures **608–611** for the sake of clarity.
INV = inversion; RET = retention

SCHEME 72

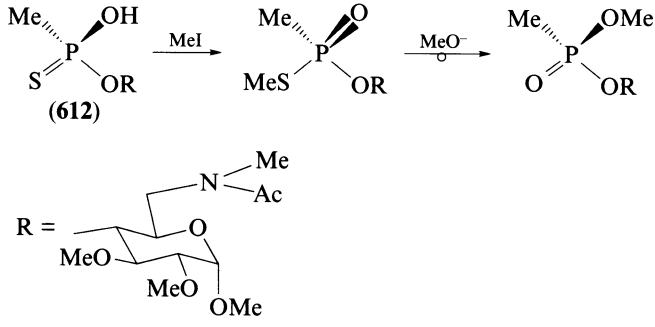
derivatives of methylphenylphosphinic (Z = O) or methylphenylphosphinothioic (Z = S) acids] proceed with the cleavage of the P—$OC_{(6)}$ bond, i.e. the bond to a primary carbon; almost always the stereochemistry of the process is inversion, although some reactions with retention are seen, particularly with **607**$_{eq}$ (Z = S), also when the attacking reagent is PhMgI or when the bond broken is P—$OC_{(4)}$. No more than two products from a given reaction have generally been observed, at least for those reactions with Grignard reagents. Generally, reactions with the organolithium reagents RLi (R = Me or Ph), although poorly exemplified, nevertheless appear to be less satisfactory than those with Grignard reagents, at least in terms of reaction yields, but also in terms of complexity of reaction mixture, but they may offer alternative products. Methylmagnesium iodide and **607**$_{ax}$ (A = Ph, Z = S) yield only the $C_{(4)}$-substituted ester **609** whereas **607**$_{eq}$ (A = Ph, Z = S) and MeLi react with retention to give the $C_{(6)}$-substituted ester **610**. In the case of the bicyclic 1,3,2-oxathiaphosphorinanes (**607**; A = Me, Z = O, X = S), the axial and equatorial stereoisomers each react with PhMgBr with cleavage (and retention of configuration) of the P—SC bond, together with cleavage of the P—$OC_{(4)}$ bond with undecided stereochemistry[885,886].

Ring-opening reactions brought about by alkoxides are more complex. The formation of the initial product(s), i.e. those which are kinetically preferred, may be followed by a phosphoryl migration fromm $C_{(4)}O$ to $C_{(6)}O$ or from sulphur to oxygen. The compounds **607**$_{ax}$ (A = Ph or Me, Z = O or S) react quickly with NaOMe in MeOH; after 2 h the products consist of the 4-substituted esters **608** formed with inversion (a tentative assumption)

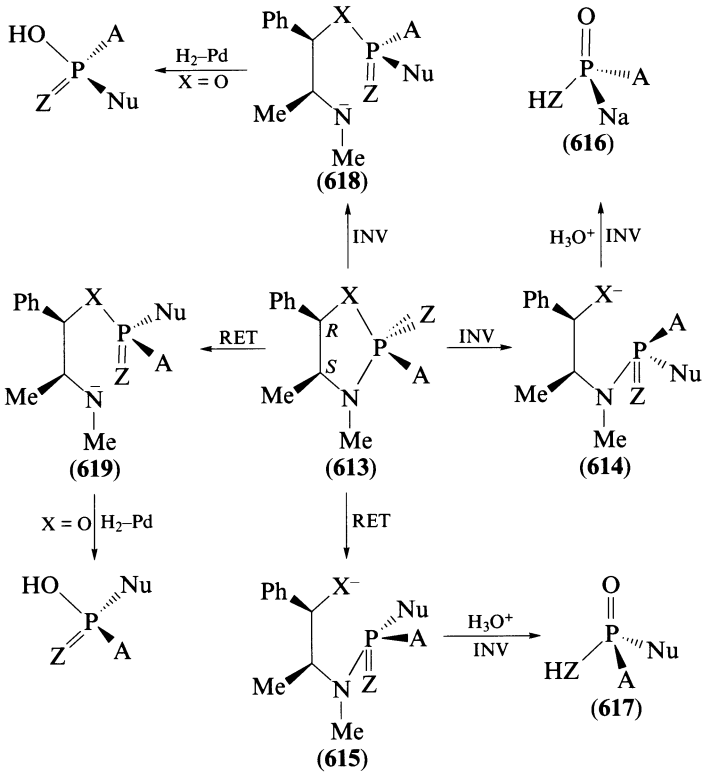
but during the following 16 h appreciable amounts of the derivatives **611** are formed. By contrast, $\mathbf{607}_{eq}$ (A = Ph or Me, Z = O or S) react more slowly; from the outset of reaction both **610** and **611** are formed, but after an extended contact time, only the former was present[885,886]. The alkaline hydrolysis of $\mathbf{607}_{ax}$ (A = Me, Z = S) proceeds with inversion to give largely **608** but containing about 5% of **611**; in the similar hydrolysis of the phosphorus epimer, predominant inversion in the two pathways again occurs but in addition **608** and **611** are present to a combined extent of about 10%.

Reactions between alkoxide anions and bicyclic 1,3,2-oxathiaphosphorinanes are even more complex. The initial remarkable feature in reaction is the preferential cleavage of the P—O bond by MeO^- over the P—S bond. Thus, $\mathbf{607}_{ax}$ (A = Me, X = S, Z = O) yielded (with inversion) **611** in only 10 min at room temperature, but on extended storage cleavage at P—S occurred with the formation of (presumably) dimethyl methylphosphonate and the liberation of the free thio sugar; further, the **611** was also converted, presumably through the re-formation of **607**, to **608** (with inversion) and **609** (with retention) in the proportions 2:1. The interaction of the same substrate with NaOPh in benzene yielded the corresponding **608** and **609** in roughly the same proportions and the same products, but in reversed proportions, were the products from NaOPh and $\mathbf{607}_{eq}$ (A = Me, X = S, Z = O). The preferential cleavage of endocyclic P—OC over P—SC with methoxide is in sharp contrast to the ease of displacement of SMe from acyclic phosphonothioic esters by the same agent (Chapter 5). In general, the very complexity of displacements in the bicyclic 1,3,2-dioxaphosphorinane and 1,3,2-oxathiaphosphorinane series, and the failure, in some cases, to be able to assign configurations to the ring-opened products, has tended to preclude such systems as useful precursors to acyclic esters in high optical purity.

Reactions which involved the bicyclic perhydro-1,3,2-oxazaphosphorinanes **607** (X = NMe) proved to be of greater utility. The interaction of $\mathbf{607}_{ax}$ (A = Me, Z = O) and EtO^- leads to P—OC fission with inversion and the formation of **611** and the HCl-catalysed methanolysis of this affords (*R*)-ethyl methyl methylphosphonate, evidently the first example of a chiral phosphonate ester to be obtained without the intermediate use of a sulphur-containing ester[887]. The P—N bond is particularly prone to cleavage under acidic conditions (and this occurs with inversion of configuration whether the bond is exo- or endo-cyclic), although some fission by base is also observable. The corresponding 2-sulphide $\mathbf{607}_{ax}$ (A = Me, Z = S, X = NMe) is cleaved by dilute aqueous acid to give a product convertible, without further fission of bonds to phosphorus, into the acid **612**, containing the *N*-acetylated carbohydrate moiety, and thence into a sulphur-free diester (Scheme 73)[888]. The alkoxide-promoted cleavage of **607** (Z = S, A = Me, X = NMe), whether axial or equatorial in definition, proceeds with P—O (70%) and P—N (30%) cleavage, the latter to be particularly noted, and both with inversion of configuration at phosphorus.



SCHEME 73

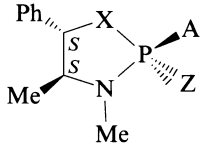


RET = retention; INV = inversion

SCHEME 74

The 1,3,2-oxazaphosph(V)olidines **613** (X = O or S, Z = O, S or Se)—in the case of X = O the general formula illustrates one diastereoisomeric structure (of 4*S*, 5*R* configuration) derived from (–)-ephedrine—do not possess some of the disadvantage of the carbohydrate 1,3,2-dioxaphosphorinanes and 1,3,2-oxathiaphosphorinanes, but like the bicyclic perhydro-1,3,2-oxazaphosphorines, residual P—N bonds are readily cleaved to acids, or converted into esters by HCl-catalysed alcoholysis. A potential advantage in the use of such oxazaphospholidines rather than analogous six-membered ring compounds is that of assignment of ring position within an intermediate structure (it should occupy an apical–equatorial span) with reasonable certainty, thus allowing prediction of stereochemistry. Scheme 74 presents the general picture of ring cleavage at either P—O or P—N bonds with either inversion or retention of configuration at phosphorus. Acidolysis or acid-catalysed alcoholysis of the products of ring cleavage at the P—O bond with inversion (**614**) or retention (**615**) yield the acids (or their esters) **616** or the enantiomer **617**, in both cases with *in*version of configuration; thus the configurations at phosphorus in **613** and **616** are identical, whereas those in **613** and **617** are different. Ring cleavage at the P—N bond with inversion yields **618** and with retention **619**. Alternative to further strong acidolysis or alkaline cleavage of the P—X bond, the products of ring opening by P—N bond fission may be debenzylated by hydrogenolysis[889].

(2*S*,4*S*,5*R*)-**613** (A = Me, X = Z = O) reacts with PhMgBr with 78% cleavage of the P—O bond with 98% retention to give **615**; the substrate epimeric at phosphorus also reacts with PhMgBr largely with P—O fission but with undefined stereochemistry. Reactions between the two analogous 2-phenyl substrates (A = Ph) and MeMgI once again led to much preferred P—O fission, and in both cases with preferential inversion to give **614**[885]. By contrast, X-ray crystallography of both substrate and product confirmed that P—O bond the cleavage in the (2*R*)-phenyl substrate by 2-methoxyphenylmagnesium bromide occurred with retention of configuratin, as did a reaction between 2-(2-methoxyphenyl)-1,3,2-oxazaphospholidine 2-oxide and PhMgCl, a result which was interpreted in terms of the participation of magnesium coordination during the course of the displacements[890,891]. In its reaction with PhMgBr, (2*R*,4*S*,5*S*)-2,3,4-trimethyl-5-phenyl-1,3,2-oxazaphospholidine 2-sulphide (**620**; A = Me, X = O, Z = S) underwent P—O fission with retention of configuration to yield the $C_{(5)}$ epimer of **615**, which is stable and which on acidolysis yielded (*R*)-methylphenylphosphinothioic acid; concomitant P—N bond fission with inversion afforded the intermediate **618**, which is rather unstable and it was necessary to apply preliminary *N*-acetylation (Ac_2O–pyridine) when acidolysis of the product yields (*S*)-methylphenylphosphinothioic acid[885,892]. It might be remarked that whenever P—N fission is the more prominent manner of ring opening, then it is always stereospecific, but this cannot always be said of P—O fission.



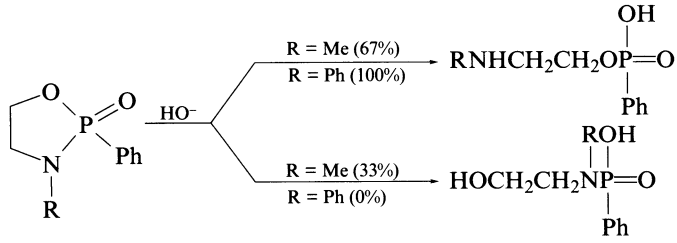
(620)

When treated with MeMgI, **620** (A = Ph,X = S, Z = O) was cleaved at the P—S bond with retention (also found for the 2-EtO substrate) and after the acidolytic methanolysis step furnished methyl (*R*)-methylphenylphosphinate[893,894].

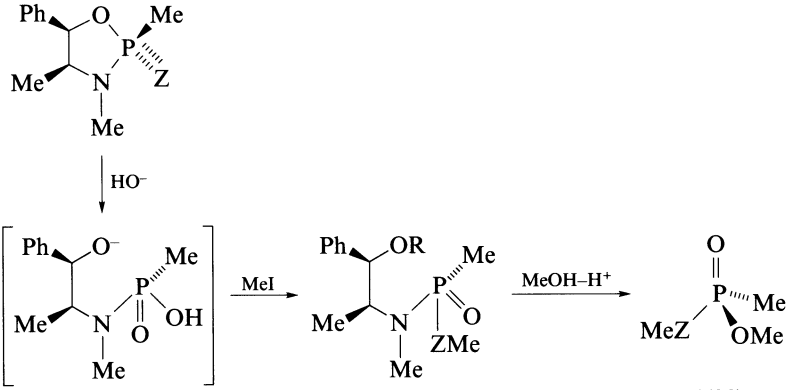
The reactions between the four substrates **613** (A = Me or Ph, X = O, Z = S) and PhLi or MeLi, all of which took place with preferred P—O fission and retention (75–95%) of configuration, the exact extent depending on the nature of R in RLi (R = Me, Et or Ph) for a given precursor[885,895].

In an earlier period of synthetic organophosphorus chemistry, stability of the P—N bond was often relied on for protection purposes in the synthesis, from $(R_2N)_2P(O)Cl$ or $R_2NP(O)Cl_2$ and organometallic reagents, of simple phosphonic and phosphinic acids, since the bond was regarded as being stable to further attack by the reagent and also to bases. but could be cleaved in the ultimate step by acidolysis (Chapter 2). It is therefore interesting to note that in the alkaline hydrolysis of simple 1,3,2-oxazaphospholidine 2-oxides the ring can cleave not only at the P—O bond (expected, at least to some extent, bearing in mind the extreme reactivity of five membered ring esters) but also, unexpectedly, at the P—N bond in a manner dependent on substituents on nitrogen (Scheme 75)[896].

A like behaviour has been found for the ring *C*-substituted substrates such as **613**, although in the case of hydrolysis, the extent of P—N bond fission is not so great. The alkaline hydrolysis of **613** (X = O, Z = S, A = Me) proceeds with P—O fission to give an unstable intermediate; this is first methylated (MeI) to give **621** (Z = S) which is acetylated (Ac_2O-Pyridine) in order to prevent unwanted intramolecular displacements, and the resultant product **622** is then methanolysed under acid conditions to give *O*,*S*-dimethyl methylphosphonothioate **623** (Z = S) as a 2:3 mixture of *R*- and *S*-enantiomers. The implication is that the endocyclic P—O bond was therefore cleaved with preponderant

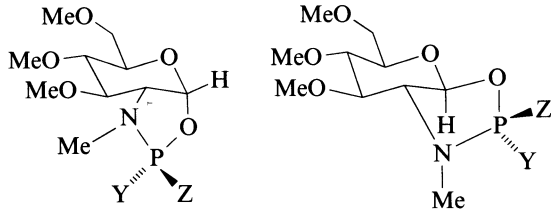


SCHEME 75



inversion. The alkaline hydrolysis also cleaved the P—N bond to the extent of about 5%, which is thus much slower than obtained under acid conditions, but the stereochemical result is the same[897].

Reactions between the 1,3,2-oxazaphospholidines **613** (X = O) and alkoxide ions are even more remarkable in that ring opening occurs with preferential P—N rather than P—O bond cleavage, and with inversion of configuration at phosphorus, cf. **613** → **618**[885,898]. The diastereoisomeric 1,3,2-oxazaphospholidines **624** and **625** (X or Y = O or S, Y or X = Me or Ph) undergo acid hydrolysis first at P—N and then at P—O, but in base, P—N and P—O bonds are cleaved competitively; both are highly stereoselective and occur with inversion of configuration[899]. It has been observed that, in comparable reactions between ethoxide anion and 1,3,2-oxazaphospholidine 2-sulphides from (+)-norephedrine (which therefore lack the *N*-methyl substituent), fission of the ring, including that which takes place at the P—N bond, occurs much more quickly (in qualitative terms) for the ephedrine-derived



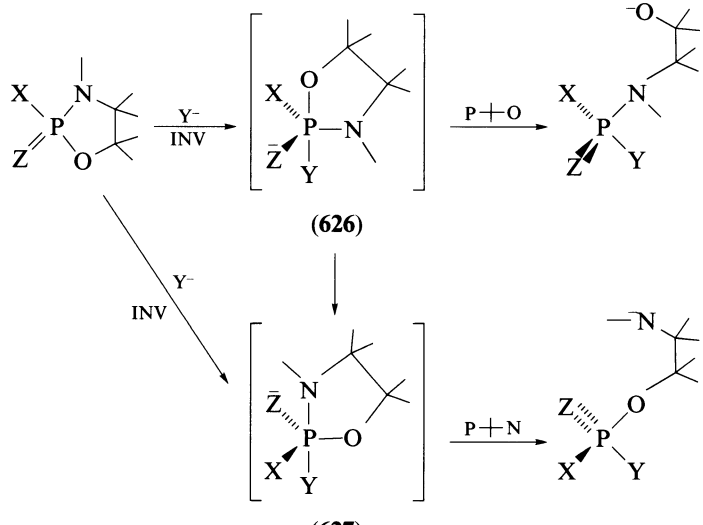
(624) (625)

substrates, and it was therefore proposed that for those substrates with the free NH, the EA mechanism might operate[900].

The oxazaphospholidine-based methodology has been developed to provide syntheses of chiral (chloromethyl)-, (dichloromethyl)-and (trichloromethyl)-phosphonic esters, and those of the corresponding phosphonothioic acids[130], and also chiral derivatives of (fluoromethyl)phosphonic acid and (fluoromethyl)phosphonothioic acid[901].

From this discussion regarding the nature of displacement reactions at phosphoryl phosphorus, it is evident that certain of the reactions of ring systems make the latter stand apart from acyclic compounds; those reactions include, for example, the preferential cleavage by alkoxides of a P—OC bond over a P—SC bond in the 1,3,2-oxathiaphosphorinane ring, and the competitive cleavage of P—N and P—O bonds in 1,3,2-oxazaphosph(V)olidines by nucleophiles such as RMgX, HO^- and RO^-, the stereochemistry of these displacements contrasting with that found for acyclic analogues. An overall mechanistic approach must accommodate these unusual features.

The Westheimer proposals require that incoming nucleophilic reagent (MeMgI, PhMgBr, HO^-, RO^-) and the departing group form apical bonds within a tbp intermediate; the incoming bond is completely formed before the bond to the outgoing group begins to break. If the one follows the other directly, the configuration at the central phosphorus atom is reversed. The outgoing group is likely to be the one with the highest (or at least a high) apicophilicity; if this is not the case, ligand reorganization (pseudorotation) occurs in one or more movements, until that group with the greatest apicophilicity finds itself at the apex opposite the site initially occupied by the incoming reagent, and it then departs. Apart from the apicophilicity itself of any atom or group, there are no fundamental restrictions to the way in which a pentacoordinate intermediate derived from an acyclic phosphoryl compounds can reorganize. In the case of the 1,3,2-oxazaphosph(V)olidine system, the approach of a nucleophile Y^- in line with the P—O bond generates the tbp **626** with the ring apical–equatorial, and organized with the most apicophilic group in the correct position for the cleavage of the axial P—O bond with inversion. The fission of the P—N bond requires that the tbp pseudorotates to position the less apicophilic nitrogen atom at the apex, as in **627**. The situation can apparently be resolved if, rather than considering apicophilicity—a thermodynamic term related to the positional preferences for atoms or



(626)

(627)

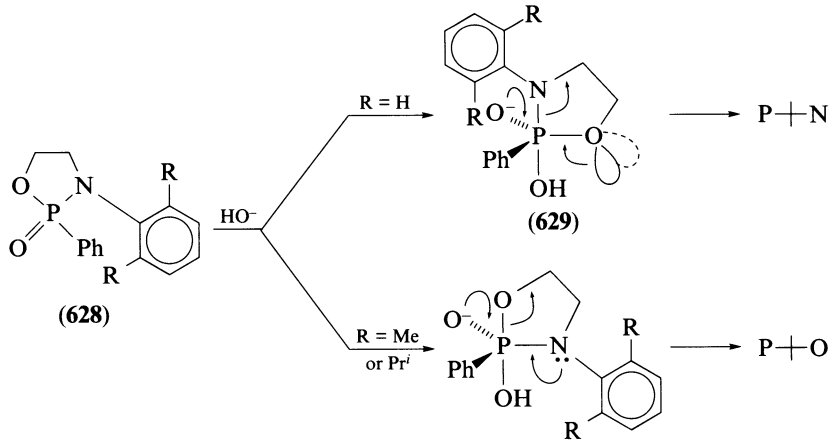
groups in stable, isolable, pentacoordinate compounds—an alternative concept—the ligand apical potentiality[885,897]—is employed. This concept relates to a preference for position within the tbp ionic intermediate.

To explain the preferential cleavage of the P—N bond in this way, it is simply necessary to accept that the reagent approaches that tetrahedron face opposite the nitrogen and in line with the P—N bond, and that the latter is sufficiently weakened to undergo an S_{N^2} displacement. Alternatively, it might be that the apical potentiality of nitrogen is similar to that of oxygen—which the apicophilicity clearly is not, as judged from displacements in acyclic phosphoryl or thiophosphoryl compounds, although if the former concept were to be adopted, a more flexible order of atoms or groups can be envisaged, the exact order which would depend on the remaining groups within the tbp, but also on other factors such as metal counter ions and other experimental variables. The extent of P—N cleavage is often appreciable for many of the reactions discussed in the preceding paragraphs and when the other bonds present in a tbp would include one to two P—C bonds; however, in the reaction between RO^- and 2-aryloxy-1,3,2-oxazaphospholidine 2-oxide[896], any tbp intermediate would lack P—C bonds and would possess, instead, four P—O bonds, in addition to the P—N bond, thus representing an entirely different situation with much opportunity for P—O bond cleavage (4% endocyclic, 91% exocyclic) but little for P—N cleavage (5%), which would require the resiting of nitrogen in opposition to the four oxygen atoms.

In conjuction with an examination of several dialkylphosphinoyl groups for *N*-protection purposes for amino acids, Ramage *et al.*[902] examined and discussed the lability of P—N bonds under acidic conditions and reviewed much literature on the topic; it was felt that, although the original proton addition to a phosphinic amide might occur on oxygen, initial protonation at nitrogen seems more likely.

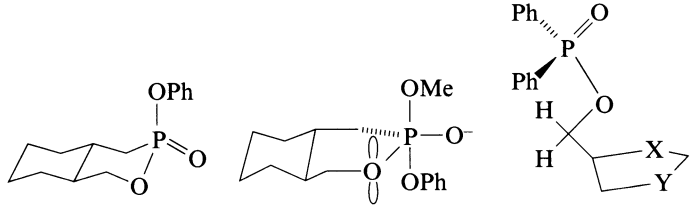
There remains one more important contribution to the concepts relating to S_{N^2} displacements at phosphoryl phosphorus; it is that of electronic interactions ('stereoelectronic effects') which purport to assist in the breakdown of the tbp intermediate in the unpredicted manner. Reference has already been made (Scheme 75) to the unusual cleavage of the P—N bond in 2,3-diphenyl-1,3,2-oxazaphospholidine 2-oxide under alkaline conditions[896]; the behaviour of that compound, **628** (R =H), is to be contrasted with the behaviour of the two compounds **628** (R = Me or Pr^i) which, in 0.01–0.3 M NaOH–50% aqueous dioxane are completely hydrolysed within 20 min with 95–100% P—O bond cleavage[903]. Of the cyclic phosphonic phenyl esters **631**, the axial isomer (shown) undergoes methanolysis (NaOMe–MeOH) to the corresponding methyl ester 5–8 times slower than the equatorial diastereoisomer, each isomer with 100% inversion of configuration at phosphorus[904]. The fact that **597** hydrolyses under alkaline conditions, in the predicted manner, but only 6×10^3 times faster than ethyl ethylphenylphosphinate, whereas, under the same or similar conditions, **596** hydrolyses 1.5×10^6 times faster than diethylphenylphosphonate, is also a remarkable finding[863].

To attempt an explanation of these unusual features, the additional concept of the stereoelectronic effect was introduced. In relation to the hydrolyses of compounds **628**, it has been suggested that when R = Me or Pr^i, conjugation between the nitrogen atom lone pair and the attached benzenoid ring is reduced because of the lack of coplanarity in the system, and so the nitrogen lone pair becomes more available to assist in the cleavage of the axial P—O bond (**630**), presumably aided by the 'correct' order of apicophilicities or apical potentialities of oxygen and nitrogen; when R = H, coplanarity of the benzenoid ring (with free rotation) and nitrogen conjugation become possible and, by contrast to the formation of the intermediate **630**, the formation of **629** by the approach of HO^- to the tetrahedral face opposite to nitrogen and in line with the P—N bond is feasible. The breakdown of the P—N bond in **629** is then strongly assisted by the ring oxygen electron orbitals. A similar explanation is applicable to the relative rates of hydrolysis of **596** and **597**; here, also,

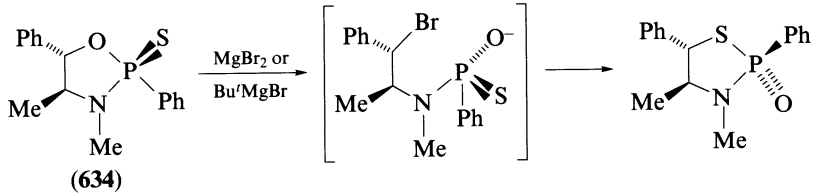


calculations of free energies of activation have suggested that the difference in the rates of hydrolysis of **596** and $(EtO)_2P(O)Ph$ corresponds to a free energy difference of 8.4 kcal mol^{-1}; of this, 5.2 kcal mol^{-1} has been attributed to ring strain, so leaving 3.2 kcal mol^{-1} to be accounted for. Several explanations have been offered to account for this difference (see ref. 863 for a fuller discussion and bibliography), one of which is the existence of the phenomenon of stereoelectronic assistance in the setting-up and breaking down of the pentacoordinate intermediate.

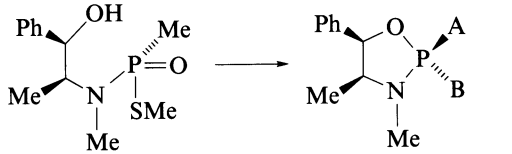
The relative rates of basic methanolysis of the stereoisomers of **631** was attributed to the participation of pentacoordinate intermediates in which the six-membered ring takes up the equatorial–equatorial position and in which that from the equatorial isomer would have an electronic interaction between ring oxygen and oxygen of the exocyclic P—OPh bond implied by structure **632**. A conformational transmission effect was proposed to account for the hydrolyses of the diphenylphosphinic esters **633** (X, Y = O or CH_2)[905,906].



References have already been made to examples of ring-opening reactions which have been followed by reclosure. Such reactions include the action of Bu^{t}MgBr on a 1,3,2-oxazaphospholidine 2-sulphide with the formation of a 1,3,2-thiazaphospholidine 2-oxide, probably dependent on ring opening at the benzylic carbon of **634** followed by intramolecular alkylation at sulphur which results in inversion of configuration at phosphorus[894]. The storage of a 3:2 mixture of stereoisomers of **635** for 24 h at room temperature results in spontaneous cyclization to a 3:2 mixture of the epimers **636** and **637**, and the cyclization was therefore assumed to be stereospecific[897], and the alkoxide induced ring openings of the carbohydrate-based bicyclic 1,3,2-dioxaphosphorinanes are followed by



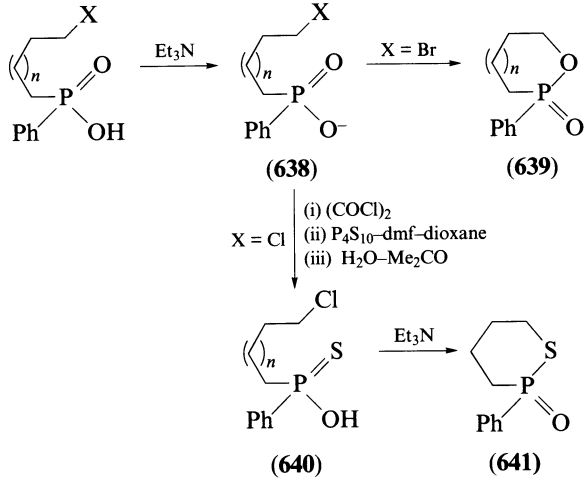
(634)



(635) (636) A = Me, B = =O
(637) A = =O, B = Me

equilibration of two ring opened stereoisomers by participation of ring re-formation[886]. The synthesis of the bicyclic diheterophosphorinanes from **606** and phosphorus(V) dichlorides involves two steps, the second of which is a cyclization step; when the two heteroatoms are different, the difficulty in predicting the initial step has been highlighted by Horner's work. The complexity of the processes possibly involved in the cyclization step, irrespective of the problems associated with choice in initial nucleophile and its attack, have been discussed by Harrison and Inch[907] in connection with cyclic ethyl phosphates.

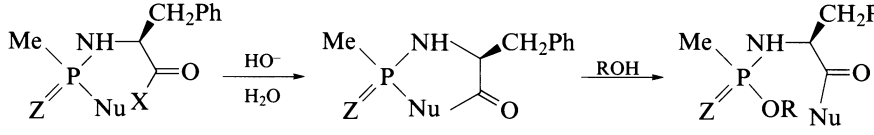
The phosphinic anions **638** cyclize at rates which depend on *n*; at 35 °C, the half-lives for the cyclizations to **639** were 1.1 h for $n = 0$ and 4.7 h for $n = 1$, and so the rates of formation of the five- and six-membered rings differ by a factor of 4.3. Similar cyclizations on to sulphur would be expected to be faster partly, in the case of the five-membered ring, because of the larger size of the sulphur atom and the consequential reduction in resistance to the formation of the smaller ring; the rate difference for the step **640** → **641** is 30 times, thought to be a large factor and so suggestive that factors other than ring strain contribute to ring formation[908].



(638) (639)

(640) (641)

Jacobsen and Bartlett[909,910] studied several transformations at phosphonic phosphoryl and thiophosphoryl centres in which transient cyclic phosphonic-carboxylic imides or anhydrides were characterized by physical techniques but not isolated. Their work indicated the ready transformation of **642a** and **b** into **643a** and **642c** into **643b** during hydrolysis or solvolysis under basic conditions which affords the products **644**, and the extreme sensitivity of **642c** by comparison with **642a** compound **642d** hydrolyses through initial conversion into **642e** prior to removal of phenoxide via the cyclic anhydride **643c** to give **642f** in anionic form. (S_P)-**643b** is formed 2–3 times faster than the R_P-stereoisomer. Solvolytic (ROH) ring opening of the postulated cyclic intermediates occurs with retention of configuration at phosphorus. The cyclic imides appear to be much more reactive than comparable cyclic phosphonic-carboxylic anhydrides referred to earlier. The latter have also been postulated as non-isolable intermediates in the intramolecular phosphono-assisted hydrolysis of 4-nitrophenyl 4-(dihydroxyphosphinoyl)butanoate dianion and the corresponding 3-(dihydroxyphosphinoyl)propanoate dianion, the latter being faster by a factor of 1.5[911].



(642)

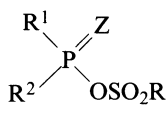
	Z	Nu	X
(a)	O	NH_2	MeO
(b)	O	MeO	NH_2
(c)	O	NH_2	HO
(d)	S	PhO	OMe
(e)	S	PhO	OH
(f)	O	HO	OH

(643)

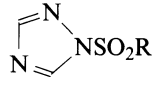
	Z	Nu
(a)	O	NH
(b)	O	O
(c)	S	O

(644)

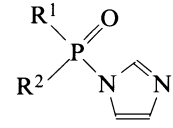
Earlier, reference was made to the potential third mechanism associated with nucleophilic displacements at phosphoryl phosphorus, namely that which might involve the participation of a phosphaacylium cation. Mixed sulphonic–phosphonic or sulphonic–phosphinic anhydrides **645** (Z = O, R = Me or 4-methylphenyl) have been obtained from the free phosphorus(V) acid and the 1,2,4-triazole **646** in the presence of trifluoromethanesulphonic acid, or **645** (Z = O, R = CF_3) from the imidazolides **647** and trifluoromethanesulphonic acid[912,913], and *tert*-butylphenylphosphinothioic acid with trifluoromethanesulphonic anhydride yield the mixed *O*-anhydride **648** (R = CF_3), some reactions of which are illustrated in Scheme 76[914]. Of those reactions, the formation of the iodide **649**, albeit in low yield when the reaction is carried out in MeOH, with stereochemical retention of configuration at phosphorus, contrasts with the inversion of configuration observed for the remainder, and which is normally encountered for $S_N2(P)$ displacements. The reaction of **648** with methoxybenzene to yield the phosphine sulphide **650** in a solvent of high ionizing power (1,1,1,3,3,3-hexafluoropropan-2-ol; a lower yield was obtained in a



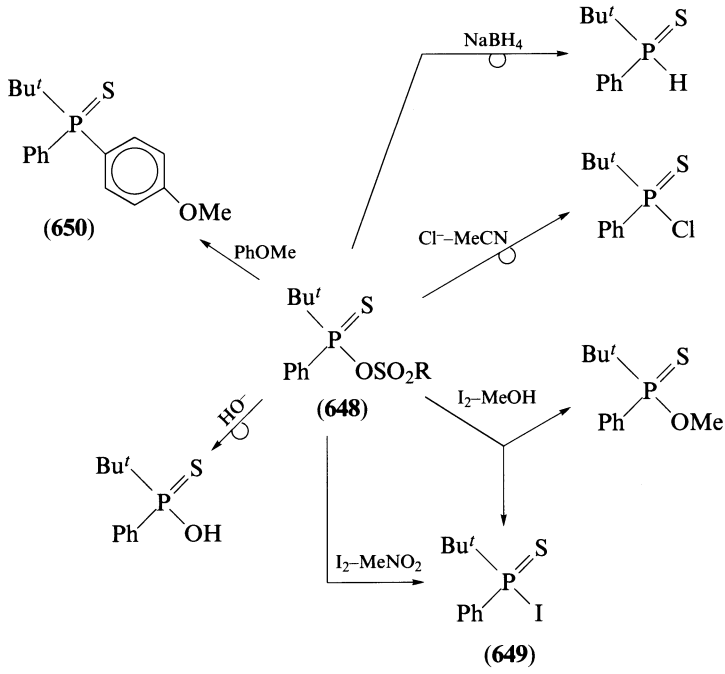
(645)



(646)

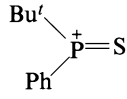


(647)



SCHEME 76

solvent of lower ionizing power, e.g. $MeNO_2$) suggests the intermediacy of ionic species[915] and the same product is obtainable from **649** and methoxybenzene in the presence of $AgClO_4$; moreover, **649** with $AgClO_4$ in $MeNO_2$ produces Ph_3C^+ (not formed in the absence of the phosphorus iodide)[915]. Such evidence has been advanced to suggest the existence of **651** (not necessarily as a totally free ion but probably highly solvated), and for its formation during the course of reactions, particularly solvolyses, of compounds derived from *tert*-butylphenylphosphinothioic acid.



(651)

It will be apparent from the contents of the preceding four chapters that important developments in the synthesis of phosphonic and phosphinic acid derivatives are still taking place, although many 'advances' are of a slight nature. It will also be evident, however, from the contents of this chapter, that the study of reactions which take place at a phosphoryl phosphorus centre is very far from being complete. The recognition that displacements at phosphoryl phosphorus occur through only two (possibly three) fundamental mechanisms was followed by the concept of the participation of pentacoordinate intermediates (as opposed to mere transition states, although the difference may, indeed, be one of a philosophical nature) in some displacements, and which has received much experimental support. This was an important suggestion (arguably the most important advance in the

interpretation of reactions of tetracoordinate quinquecovalent phosphorus), the consequences of which have provided much by way of explanation for the course of many reactions. Nevertheless, in spite of further developments with the ideas of apicophilicity (or apical potentiality) and stereoelectronic control, entirely convincing explanations are still lacking for many reactions.

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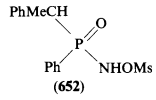
NOTE ADDED IN PROOF

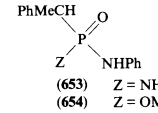
Section III

A further study of the rearrangement of *O*-mesylates of *N*-phosphinoylhydroxylamines employed diastereoisomerically enriched samples of the compound (**652**) (compare this with structure **144**) in reactions with primary amines RNH_2. With both neat $MeNH_2$ and neat Bu^tNH_2, the rearrangements, giving the corresponding **653**, proceed with a high degree of stereospecificity and with retention of configuration at phosphorus, a feature demonstrated by X-ray analyses of both substrate and product having R = Me. Such results rule out the initial direct involvement of a

metaphosphonamidate intermediate **136**. Instead, further arguments have been advanced for an initial rearrangement of the substrate to a mixed phosphonamidic-sulphonic anhydride (**654**) with inversion of configuration, followed by nucleophilic substitution in **654** by RNH_2 and elimination of MsO^-; the latter may occur through the $S_N2(P)$ process with inversion of configuration (exclusively, or almost so, when R = Me, depending on concentration), or through a dissociative pathway (when R = Bu^t, particularly), and dominant when the amine is in high dilution[916].

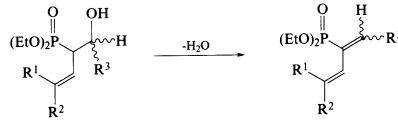


(**652**)

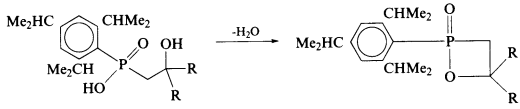


(**653**) Z = NHR
(**654**) Z = OMs

Further studies on the dehydration of (2-hydroxyalkyl)phosphonic esters leading to alkenes[917], and on the dehydration of the (1-substituted-2-hydroxyalkyl)phosphonic esters (**655**)[918], both conveniently with dicyclohexylcarbodiimide, have further confirmed the direct correlation between *Z*/*E* composition of the resultant alkene and the *erythro*/*threo* composition of the substrates. A similar treatment of the sterically hindered *β*-hydroxyalkyl ester (**656**), has provided isolable examples of the 1,2-oxaphosphetanes (**657**) (R = CH_2Ph or other benzylic function). At 50 °C **657** (R = CH_2Ph) decomposes to the expected alkene, $H_2C{=}C(CH_2Ph)_2$ as the major product (60%), together with the expected dehydration products of the alcohol **656** (ca 30%), ethyl methyl (2,4,6-triisopropylphenyl)phosphonate, and smaller amounts of other esters[919]. Such results do not, of course, demonstrate the formation of 1,2-oxaphosphetanes in the WEH reaction.



(**655**)



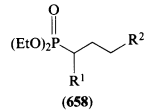
(**656**) (**657**)

Section IV

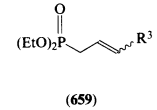
The formation of the compounds **186** by phenolysis of diazophosphonoacetic triesters in the presence of $Rh_2(OAc)_4$, is an example of the more common displacement of the diazo function in such esters and others, $(EtO)_2P(O)CN_2Z$ (Z = COOEt, SO_2Ph or Et_2O_3P) by alcohols and phenols[920].

The formation of aryl ethers of (hydroxyalkyl)-phosphonic or -phosphinic derivatives from the corresponding haloalkyl phosphorus(V) acid derivative and a metal phenate may present unfortunate difficulties depending on the particular halogen, but these have been overcome by the use of sulphonate substrates, in particular the *O*-4-chlorobenzenesulphonyl esters of the phosphonic or phosphinic derivative, in reactions with sodium phenates[921]. A study of the alcoholysis reactions of the *O*-*p*-tosylates of the *cis* and *trans* isomers of diethyl (2-hydroxycyclohexyl)phosphonate, has shown that with a 60° dihedral angle between the two functions, the rate of reaction is sensitive to solvent nucleophilicity, and the evidence supports a bimolecular displacement. When the dihedral angle is 180°, the lack of dependence of rate on solvent and other features, support the involvement of carbocationic intermediates, with their stabilization by the phosphono group[922].

The treatment of diethyl (trichloromethyl)phosphonate with BuLi in thf affords diethyl [lithio(dichloromethyl)]-phosphonate; the latter undergoes reactions with aldehydes or ketones to give, not only dichloroalkenes, $Cl_2C{=}CR^1R^2$, but also, from RCHO, the saturated esters RCH=CAB (A, B = Cl or PO_3Et_2)[923]. The products from the interaction of the (1-haloalkyl)phosphonic diesters, $(EtO)_2P(O)CHXR^1$ (X = Cl, Br or I; R^1 = H or Me) and alk-1-enes, $H_2C{=}CHR^2$ (R^2 = pentyl, OEt, OBu, OAc, CN or Ac) under free radical conditions, are mixtures containing moderate amounts of the esters **658** and **659**, as well as diethyl methylphosphonate, in relative amounts which depend on reaction conditions[924]

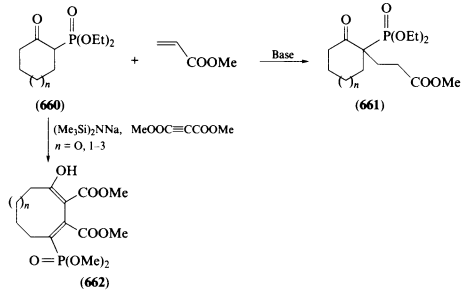


(**658**)



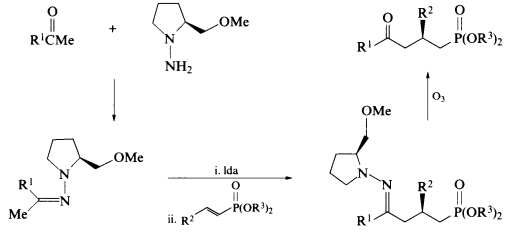
(**659**)

Oxoalkyl-phosphonic and -phosphinic acids and their derivatives continue to provide one of the most widely and deeply investigated groups of compounds. The hydrogenation of (1-oxoalkyl)phosphonic diesters in the presence of $RuCl_2$ and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl results in high yields of (1-hydroxyalkyl)phosphonic diesters in equally high enantiomeric excesses, the (*R*)-ligand providing the (*S*)-(1-hydroxyalkyl)phosphonic derivatives, and the (*S*)-ligand the (*S*)-products[925]. 2-(Diethoxyphosphinoyl)cyclohexanone (**660**; n = 1) undergoes Michael-type additions to activated alkenes in the presence of a base catalyst, to give, for example **661**[926]. In addition, however, such cyclic oxoalkyl phosphonic diesters undergo ring expansion reactions when acted upon with dimethyl but-2-yne-1,4-dioate in the presence of a basic catalyst; the substrates **660** (n = 0, 1–3) afford the systems **662** (n = 0, 1–3) through sequential Michael and aldol interactions[927].



Section V

A further study of additions of nucleophiles to unsaturated phosphonic diesters confirms reaction (23)[928]. The asymmetric Michael addition of a ketone to a dialkyl *E*-(alk-1-enyl)phosphonate has been achieved following the derivatization of the carbonyl substrate as a chiral hydrazone (Scheme 77)[929].



SCHEME 77

Recent examples of 1,3-dipolar addition reactions include the additions of aryl nitrile oxides, ethyl diazoacetate, or *tert*-butyl azidoacetate to dialkyl (perfluoroalk-1-ynyl)phosphonates[930], and further reactions of the nitrilimine (**520**) have been reported[931].

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CHAPTER 7

Acylphosphonates and their derivatives

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I. INTRODUCTION

Acylphosphonates represent a special group among phosphonates. Because of the proximity of the carbonyl and the phosphoryl groups, these compounds are endowed with special physical, chemical and biological properties which make them worthy of separate treatment among phosphonates. These properties are the consequence of the mutual interaction of the two functional groups. The electron-withdrawing nature of both the carbonyl and the phosphoryl groups confers increased reactivity on both groups and on the bond linking them, which have been exploited synthetically in diverse ways. Acylphosphonate diesters show dualistic behaviour. Towards some nucleophilic reagents, e.g. hydroxylamine, they behave as ketones, and lead to the formation of oximes, whereas towards most nucleophiles they act as activated carboxylic acid derivatives, with the dialkylphosphoryl group serving as a leaving group. The proximity between the carbonyl and phosphoryl groups has also been exploited for the design of novel metal chelators and biologically active compounds.

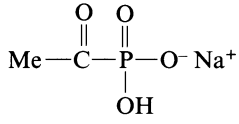
The field of acylphosphonates (α-ketophosphonates) has been reviewed previously[1]. This chapter will deal mostly with the advances made since the publication of the previous review; however, results from the older literature will be included for completeness. This chapter includes functional derivatives of both the phosphoryl and the carbonyl groups. With regard to the phosphoryl group, this refers to acylphosphonic acids esterified to various degrees, and also to acylphosphonoamidates and to acylphosphonic mono-and di-halides. With respect to the carbonyl group, this refers mainly to enolates, enamines, oximes and hydrazones in which the closeness of the phosphoryl function has yielded a wealth of recent results. These are discussed separately in Sections II and IV.

II. ACYLPHOSPHONATES

A. Structure

1. Crystallography

The only acylphosphonate for which the crystal structure has been determined by X-ray study is acetylphosphonic acid monosodium salt (**1**) acetic acid solvate[2].

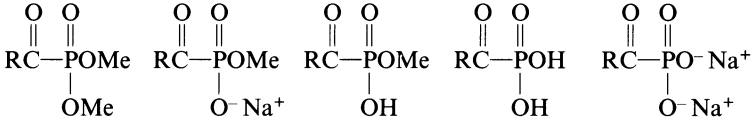


(1)

The structure consist of sodium ions, acetylphosphonate monoanions and acetic acid molecules. The structure of the acetylphosphonate ion is unexceptional. It has three different P—O bond lengths: one long bond of 1.563 Å and two short bonds of 1.489 and 1.505 Å. The C=O bond length is 1.219 Å. The O—P—O angles are 110° and the O—P—C angles are 104.6°, 106.1° and 107.1°, indicating a tetrahedron. The angles around the carbonyl group are P—C—C 118.4° and P—C=O 119.3°. The C=O and P=O groups are nearly parallel, the O=C—P=O torsion angle being 9.1°.

2. *Theoretical aspects*

Semiempirical quantum mechanical calculations, with a modified version of MNDO, have been carried out on a series of benzoylphosphonate derivatives. These include the dimethyl ester **2**, the anion of the monomethyl ester **3**, the monoacid monomethyl ester **4**, The diacid **5** and its dianion **6**[3].



R = Ph	(2)	(3)	(4)	(5)	(6)
R = Me	(7)	(8)	(9)	(10)	(11)

The energies of many rotatory conformers of **2** were calculated by rotating P=O with respect to C=O. This compound was found to be most stable in its *s-trans* carbonylphosphoryl arrangement (ΔH_f = 141.18 kcal mol^{-1}). The *s-cis* conformation is a maximum on the rotational energy coordinate, but only 1.8 kcal above the minimum. The phenyl ring is nearly perpendicular to the average plane of O=C—P=O and has a rotational barrier of ca 5.2 kcal, but it may rotate ± 50° from its minimum with less than 2.0 kcal. Calculated bond lengths, angles and Mulliken atomic charges for **3** are given in Table 1. The calculated dipole moment for the most stable conformation is μ = 2.177 D. These theoretical calculations substantiate previous conclusions regarding free rotation around C—P in

TABLE 1. Calculated structure and charge parameters of dimethyl benzoylphosphonate (**2**)

Bond length (Å)		Bond angle (°)		Atomic charges (e^-)	
O=C	1.203	O=C—P	119.8	C=O	−0.210
C—P	1.861	C—P=O	119.6	C=O	0.291
				P	1.159
P=O	1.497	C—P=O	103.8	P=O	−0.696
P—O	1.614	P—O=Me	126.9	P—O	−0.567
O—Me	1.389				

benzoylphosphonate[4]. The large decrease in the carbonyl IR frequency in the phosphonate (with respect to α-dicarbonyl compounds) was attributed to an interaction between the lone pair of the P=O oxygen and the carbonyl carbon orbital, which is mostly possible in a perpendicular conformation of P=P—C with respect to the P—C=O plane.

The validity of the calculations for the molecular conformation was further tested by combining the results for conformational energy and for dipole moment of 36 conformers (at 10° intervals) around the C—P bond of **2** and calculating the resultant dipole moment from the contribution of each conformer, due to its molar fraction in the mixture. The value of $\mu = 2.934$ D thus obtained for **2** is in striking similarity to the measured value of $\mu = 2.93 \pm 0.05$ D. This corresponds to a mean dihedral angle (O=P—C vs P—C=O) of ca 115°, close to the conformation previously suggested[4].

Additional confirmation of the calculated structure was recently obtained from crystallography of the related α-hydroxyiminophosphonates (see Section IV), in which the phenyl ring was found to be out of the plane of the SP^2 C=N bonds. The barrier to rotation about the C—P bond in the anion of **3** had a similar value to that of **2**. Whereas the optimized structure of the neutral compounds **2**, **4**, and **5** is *s-trans* for the O=C—P=O group, the anion **3** prefers a conformation with the two oxygens, which share the additional negative charge, at an angle of ca ± 130° with respect to the O=C—P plane. This is in contrast with the crystallographic study of monosodium acetylphosphonate mentioned in the previous section, which showed the P=O and C=O groups nearly parallel in the crystal.

Anion **3** has longer C=O and P=O bonds than the neutral compounds **2**, **4**, and **5**. This is reflected in the lower vibrational frequencies (Table 2), and is accompanied by minor shortening of the C—P bond in anion **3**.

3. *Spectra of acylphosphonates*

a. Infrared. The infrared spectra of the various diesters of acylphosphonates have been studied previously[1]. The results, which show that the carbonyl absorptions of acylphosphonates appear at lower frequency than those of the corresponding α-diketones,

TABLE 2. Comparison of IR, ^{1}H NMR and ^{31}P NMR data with results of MNDO/H calculations for benzoylphosphonate

Parameter	**2**	**3**	**4**	**5**	**6**
Calculated length of C=O (Å)	1.2033	1.2213	1.2032	1.2031	1.2277
Calculated length of P=O (Å)	1.4971	1.5096	1.4997	1.5025	1.5260
Observed ν C=O (cm^{-1})	1655	1620	1650	1650	1605
Observed ν P=O (cm^{-1})	1260	1215	1230	1230	1200
Calculated charge on C=O	0.291	0.108	0.297	0.299	0.068
Calculated charge on P	1.159	1.293	1.124	1.093	1.312
δ^{31}P (ppm)	−0.87	2.16	−0.55	−1.29	2.55
Average calculated charge on OMe Hs	0.023	−0.025	0.023	—	—
Calculated charge on OMe C	0.185	0.243	0.185	—	—

served as a basis for speculations regarding the rotational conformation and electronic interactions and conjugation in the acylphosphonic group.

Table 2 records some representative results obtained for a series of benzoylphosphonate derivatives with different degrees of esterification and ionization, along with relevant results from MNDO calculations. It can be seen that anions of acylphosphonate monoesters **3** show lower absorption frequencies for the C=O and P=O bonds than the corresponding diesters, **2**, and acids, **4**. These low C=O and P=O frequencies are consistent with an alteration in the electronic ground state of C=O and P=O. The negative charge, located on the oxygens of the phosphoryl group, interacts with the carbonyl group and shifts the carbonyl stretching absorption to a longer wavelength. Similarly, delocalization of the negative charge on the oxygen results in lowering the stretching frequency of P=O, as in the case of other types of phosphoryl derivatives.

b. NMR

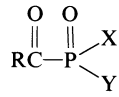
i. Proton. In the ^{1}H NMR spectrum, the P—O—Me protons of dimethyl and monomethyl esters appear as doublets ($^3J_{H-C-O-P}$ = 10 Hz) in the region of δ3.9 ppm. Ionization of the phosphoryl group causes a significant change in the methoxy proton shifts, as can be seen from the values of δ3.6–3.7 obtained for the salt **3**. This shift is caused by electron donation from the negatively charged oxygen which results in an increase in the electron density on the methoxy protons. This is confirmed by MNDO/H calculations, as shown in Table 2. Both ^{1}H NMR spectra and theoretical calculations for the diesters and monoesters (of type **2** and **4**) and also those of anions **3** indicate the existence of free rotation round the C—P bond in these molecules. In contrast to the 3 bond splitting seen in the P—O—C—H protons, in most aliphatic acylphosphonates no splitting of the protons located α to the carbonyl groups (H—C—CO—P) is seen. Acetylphosphonate is an exception in this respect; the *C*-methyl group in dimethyl acetylphosphonate is split by the phosphorus ($^3J_{PH}$ = 5 Hz)[5]. Similar splitting can be seen in the sodium salt of methyl acetylphosphonate (**8**, $^3J_{PH}$ = 4.5 Hz)[6].

ii. ^{31}P. Table 3 summarizes in a comparative manner the ^{31}P chemical shifts of derivatives of representative acylphosphonic acids, variously esterified or otherwise substituted on the phosphorus. The data show that the phosphorus nucleus adjacent to a negatively charged oxygen resonates at lower field by approximatley 2–4 ppm than the phosphorus of an unionized analogue. This is consistent with the results of MNDO/H calculations described in the previous section, which indicate that the phosphorus in mono- and dianions has a larger positive charge than the phosphorus in the unionized derivatives. A similar influence of the ionization the ^{31}P chemical shifts has been observed in the case of orthophosphoric acid[13]. Table 3 also reports ^{31}P NMR data for benzoylphosphonic chloride and dichloride, a pyrophosphonic derivative, representative benzoylphosphonamidates, an oxalylphosphonate and a phosphonoformate.

iii. ^{13}C. The carbonyl carbon appears in the ^{13}C NMR spectra of 3-phosphonopropanoylphosphonic acid at 222 ppm (J_{C-P} = 167 Hz)[14], whereas the carbonyl of phosphonoformates[12] and oxalylphosphonate[15] was reported to resonate at 160–165 ppm and to be coupled to the adjacent phosphorus with $^1J_{C-P}$ = 280–290 Hz.

iv. ^{17}O. The ^{17}O NMR spectra of a series of dialkyl aroylphosphonates were measured along with those of some other acyl derivatives, in order to determine by this method the electrophilicity of the carbonyl groups. From the strong deshielding of the C=O oxygens (values of δ^{17}O in the range 580–608 ppm in a series of dialkyl-substituted aroylphosphonates), it was concluded that the carbonyl group is highly electrophilic. Because there can be no n-electron donation from the phosphorus to the carbonyl in these compounds, they

TABLE 3. ^{31}P chemical shifts of representative acylphosphonic derivatives



R	X	Y	$\delta^{31}P$ (ppm)	Ref.
Me	OMe	OMe	−2.93[a]	3
Me	OMe	OH	−2.51[b]	3
Me	OMe	O^-Na^+	−0.83[b]	3
Me	OH	OH	−2.10[a]	3
Me	OH	O^-Na^+	−0.63[b]	3
Ph	OMe	OMe	−0.87[a]	3
Ph	OMe	OH	−0.55[a]	3
Ph	OMe	O^-Na^+	2.16[b]	3
Ph	OH	OH	−1.29[a]	3
Ph	OH	O^-Na^+	2.13[b]	3
Ph	O^-Na^+	O^-Na^+	2.55[b]	3
Ph	OMe	Cl	14.4[a]	7
Ph	Cl	Cl	28.00[a]	8
Ph	OEt	NEt_2	4.1[c]	9
Ph	OPh	O^-Li^+	2.26[b]	10
Ph	Cl	OP(O)(Cl)COPh	8.00[a]	8
HOC(O)	OH	OH	−1.2[b]	11
EtOC(O)	OEt	OEt	−2.4[a]	11
MeO	OCH_2OCOMe	OCH_2OCOMe	−9[a]	12

[a]Solvent $CDCl_3$
[b]Solvent D_2O.
[c]Solvent not stated.

show very high substituent sensitivity. From the effect of the aromatic substituent on the ^{17}O chemical shift, a δ value of 27.4 was obtained for the $(MeO)_2P(O)$ group (compare with 29.0 obtained for the CF_3 group)[16]. A similar conclusion was reached from the π-coordination ability of acylphosphonates towards nickel (0); see Section II.C.7).

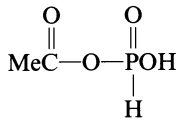
4. *Acidity of acylphosphonic acids*

The pK_a values of methyl hydrogenacetylphosphonate (**9**) and that of the monoanion of acetylphosphonic acid (**10**) were determined by spectrophotometric titration and found to be 0.5 and 5.6, respectively[17]. In another paper[18], a value of 5.2, determined by titration of dilithium acetylphosphonate, was reported.

B. Synthesis of Acylphosphonate Derivatives

1. *Synthesis of acylphosphonic acids*

a. Direct synthesis of acylphosphonic acids. The first known claim for the synthesis of an acylphosphonic acid was by direct acetylation of phosphorous acid[19], and the structure of the product was assigned as acetyl phosphite (**12**). This assignment was revised subsequently to the isomeric acetylphosphonic acid **10** by different authors[20]. The procedure was



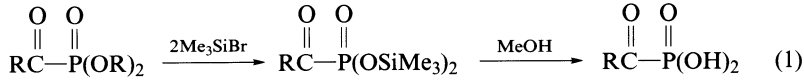
(12)

repeated in the present author's laboratory. Examination of the white solid product obtained by means of ^{1}H and ^{31}P NMR spectroscopy showed that it is composed of at least five major and a larger number of minor components, none of which is identical with authentic acetylphosphonic acid[21].

b. Dealkylation of dialkyl acylphosphonates. This is the most frequently used method to prepare acylphosphonic acids, dialkyl acylphosphonates being the most easily accessible derivatives among the different members of this class. However, because of the hydrolytic instability of the C—P bond in acylphosphonate dialkyl esters, special precautions need to be taken when this kind of reaction is planned.

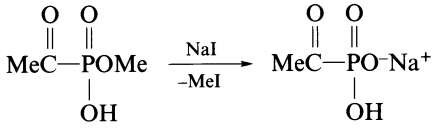
i. Hydrogen bromide. Heating diethyl acetyl- and benzoylphosphonates with dry hydrogen bromide at 95–100 °C was reported to yield the acylphosphonic acids[22]. A modification of this method (hydrogen bromide in acetic acid at 20 °C) was used recently for preparing bromoacetylphosphonic acid[23].

ii. Methods involving silylation. Similarly to dialkyl phosphonates[24], dialkyl acylphosphonates are converted in to bis (trimethylsilyl) esters on treatment with bromotrimethylsilance (equation 1)[3] or iodotrimethylsilane[25]. Alternatively, the same type of bis(trimethylsilyl) esters can be obtained by using the much cheaper chlorotrimethylsilane combined with sodium or lithium bromide or iodide[26]. Bis(trimethylsilyl) esters are cleaved by alcohol or water under mild conditions. Bromotrimethylsilance was used recently for the preparation of a series of bisacylphosphonic acids, $H_2O_3PCO(CH_2)_nCOPO_3H_2$[27].



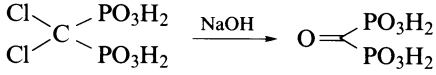
(1)

c. Dealkylation of monoalkyl acyl hydrogen phosphonates. Monomethyl acetyl hydrogen phosphonate was demethylated to acetylphosphonic acid by refluxing with sodium iodide in acetone solution (equation 2)[17]. This method is likely to be applicable mainly to methyl esters, as higher alkyl esters are expected to be far less reactive in such a nucleophilic dealkylation reaction. Sodium salts of monobenzyl esters of a series of acylphosphonates were reported to undergo hydrogenolysis to the monosodium salts of the corresponding acylphosphonic acids over palladium black. Under the reaction conditions (not reported), the keto group was apparently not reduced[28]. This method appears to be limited to benzyl-type esters. An additional method involves boiling monosodium methyl acylphosphonates with 99% formic acid[23]. This simple method was applied to monomethyl acetyl-, isovaleryl- and phenylacetylphosphonates[23]. However, It is not clear whether this method is applicable to esters higher than methyl. Also, the yields reported (44–67%) are lower than those obtainable by other methods.



(2)

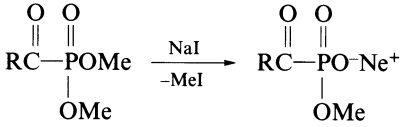
d. Hydrolysis of α,α-dichlorophosphonic acids. Dichloromethylenebisphosphonic acid was hydrolysed by boiling sodium hydroxide to oxomethylenebisphosphonic acid (equation 3)[29]. This method should be equally applicable to other α,α-dichlorophosphonic acids, but not to esters.



(3)

2. Synthesis of acylphosphonate monoesters

a. Monodealkylation of dialkyl acylphosphonates. Monodealkylation of dialkyl acylphosphonates can be carried out most conveniently on dimethyl esters, by treating with sodium iodide in acetone or lithium bromide in acetonitrile (equation 4)[3,17]. The reaction usually gives highly pure products which crystallize out of the reaction solution. When esters of higher alcohols are used, more drastic reaction conditions are required to complete the reaction in a reasonable time. For example, to achieve monodeethylation or monodebenzylation, several hours of reflux are required[28]. This reaction leads to the corresponding alkali metal salts, which can be converted in to alkyl hydrogen acylphosphonates by acidification and extraction in to an organic solvent such as dichloromethane[3,28].



(4)

Arbuzov reaction of mixed phosphites such as ethyl bis (trialkylsilyl) phosphite may lead conveniently to monoalkyl acylphosphonates, since in such reactions one of the trialkylsilyl groups is lost preferentially, leading to an ethyl trialkylsilyl acylphosphonate[30], which can be alcoholysed rapidly.

3. Synthesis of dialkyl acylphosphonates

a. Arbuzov reaction

i. Normal reactions. The standard synthetic procedure for the synthesis of acylphosphonates is the Arbuzov reaction of acyl halides with trialkyl phosphites equation 5)[1,31]. In addition to simple alkanoyl and aroyl halides, this method has been shown to be applicable also to the synthesis of α,β-unsaturated derivatives: dimethyl *trans*-but-2-enoylphosphonate[32] and dimethyl 2,2-dimethylacryloylphosphonate[33] and 3-coumarinylcarbonylphosphonates[34], but not for the synthesis of acryloylphosphonates[32]. In contrast, good yields were obtained when the reaction was used for the preparation of the terminally unsaturated (unconjugated) dimethyl pent-4-enoylphosphonate and dimethyl undec-10-enoylphosphonate[3].

(5)

The Arbuzov reaction is also applicable to the preparation of other haloacylphosphonates, such as dimethyl 2-chloropropionyl-, and 4-chlorobutyrylphosphonate, but it yields

unstable and impure products when used with 2, 3-dichloropropionyl chloride and 3,4-dichlorobutylryl chloride[3]. A series of bisacylphosphonate tetraesters were prepared by the Arbuzov reaction of dicarboxylic acid dichlorides of varying chain length with trimethyl phosphite or 2-methoxy-4,4,5,5-tetramethyl[1.3.2] dioxaphospholane[27,35]. Tetraethyl pyrophosphite was also reported to undergo Arbuzov reaction with acetyl chloride, with the formation of diethyl acetylphosphonate and diethylphosphorochlorodite[36].

Synthesis of mixed dialkyl acylphosphonates by the Arbuzov reaction is of practical value only with mixed phosphites in which there is clear preference of the different alkyl groups to be cleaved. For example reaction of diethyl phenyl phosphite with benzoyl chloride give phenyl ethyl benzoylphosphonate (equation 6)[10].

$$RCCl + PhOP(OEt)_2 \longrightarrow RC(=O)-P(=O)(OEt)(OPh) \quad (6)$$

A recent paper reports the reaction of trimethylsilyl bis (alkylthio) phosphites with acyl halides[37]. This reaction may take two pathways, depending on the nature of the halogen in the acyl halide and the reaction conditions, to give either bis (alkylthio) halophosphites or bis (alkylthio) acylphosphonates [e.g. MeCOP (O) $(SEt)_2$]. The latter compound is formed by reacting MeCOBr with $(EtS)_2POSiMe_3$ at –25 °C, whereas the same reaction at –34 °C gave $(EtS)_2PBr$. Thiobenzoyl chloride also underwent Arbuzov reaction at –5 °C to give dimethyl thionobenzoylphosphonate $(PhCSPO_3Me_2)$[38].

Similarly to trialkyl phosphites, dialkyl phosphorofluoridites also undergo facile Arbuzov reaction to give the corresponding acylphosphonofluoridates (equation 7)[39]. The products, when derived from aliphatic carboxylic acids, are not stable. They undergo facile self-aldol condensation, demonstrating the increased reactivity of the carbonyl group and the relatively high acidity of the α-protons in such compounds, as a result of the strong electron-withdrawing influence of the fluorophosphonyl group.

$$RCCl + FP(OR)_2 \longrightarrow RC(=O)-P(=O)(F)(OR) \quad (7)$$

In contrast, dialkyl chlorophosphites behave differently. They react with acyclic acid anhydrides with the formation of dialkyl acylphosphonates and acyl halides (equation 8)[40].

$$(RCO)_2O + ClP(OR')_2 \xrightarrow{50^\circ C} RCOPO_3R'_2 + RCOCl \quad (8)$$

The Arbuzov reaction proceeds well with tris-(trimethylsilyl) or (triethylsilyl)-phosphites. These phosphites were reacted with acetyl chloride, benzoyl chloride[30] or trifluoroacetyl chloride[41] to give the corresponding bis (trimethylsilyl) trifluoroacetyl-phosphonates (equation 9).

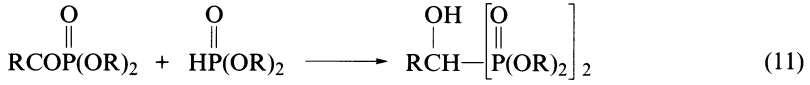
$$F_3CCCl + (Me_3SiO)_3P \longrightarrow F_3CC(=O)-P(=O)(OSiMe_3)(OSiMe_3) \quad (9)$$

This approach was applied subsequently for the preparation of acylphosphonic acids. The bis (trimethylsilyl) esters obtained could be subjected to alcoholysis and the resulting

acylphosphonic acids were isolated as anilinium salts[42]. In reactions using mixed phosphites such as ethyl bis (trialkylsilyl) phosphite, one of the trialkylsilyl groups was lost preferentially, leading to ethyl trialkylsilyl acylphosphonate[30]. Arbuzov reaction of acyl halides with diethyl trimethylsilyl phosphite[43] produces diethyl acylphosphonates while avoiding the complications that occur with triethyl phosphite (see next section, equation 16).

ii. Complications in the Arbuzov syntheses of acylphosphonates. The most common complication in the Arbuzov synthesis of acylphosphonate diesters arises when there are traces of water present in the reaction mixture. Under such conditions, hydrolysis of the dialkyl acylphosphonate may yield dialkyl hydrogenphosphonates (equation 10). The latter compounds may add to the carbonyl group of a molecule of unreacted acylphosphonate with the formation of a geminal bisphosphonate (equation 11). Geminal bisphosphonates may rearrange at 50 °C (or on distillation) to a phosphate phosphonate (equation 12). This can be seen in the ^{31}P NMR spectra of the reaction mixture. The geminal bisphosphonate appears at 21 ppm. In contrast, the product obtained after distillation shows two different phosphorus signals: one at –1 ppm, corresponding to the phosphate phosphorus, and a second at 16 ppm (R = phenyl) or 21 ppm (R = methyl), corresponding to the phosphonate phosphorus[44]. Later work confirmed these data, and supplied P—O—C—P coupling constants (J = 17 Hz) for similar compounds[45].

(10)



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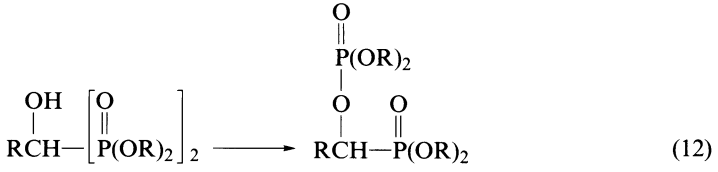


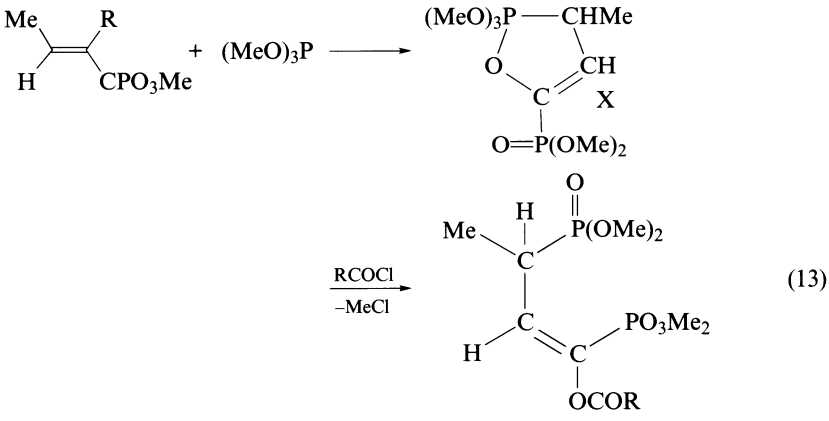
(12)

The reaction of *trans*-but-2-enoyl chloride with trimethyl phosphite can be directed to give a low yield of the expected dimethyl but-2-enoylphosphonate by using excess acid chloride. However, when equimolar amounts of these compounds are reacted, a product containing two different phosphorus atoms is formed[32]. The mode of formation of this (see equation 13) was elucidated and the intermediates were identified.

Reaction of the initially formed acylphosphonate with a second mole of trimethyl phosphite leads to the formation of a cyclic product with one pentacoordinated phosphorus atom. Further reaction of this oxaphospholene with a second molecule of butenoyl chloride, followed by the loss of methyl chloride, leads to the final product[32].

Reactions of chloroacetyl chloride with a two fold excess of trimethyl phosphite[46] or triethyl phosphite[47] were reported to give the corresponding dialkyl choloroacetylphosphonates, which at high temperature underwent a Perkow reaction leading to the tetraalkyl enolphosphonate phosphate (equation 14).

In another study, only the formation of tetraalkyl enolphosphonate phosphate was observed. The mechanism of its formation was elucidated (equation 15)[48]. It was concluded that the initial product, an acylpseudophosphonium salt, added rapidly a second molecule of phosphite to form an ionic species which gave the final product after a carbon to oxygen migration of one of the phosphoryl groups, and the loss of two molecules of ethyl chloride.



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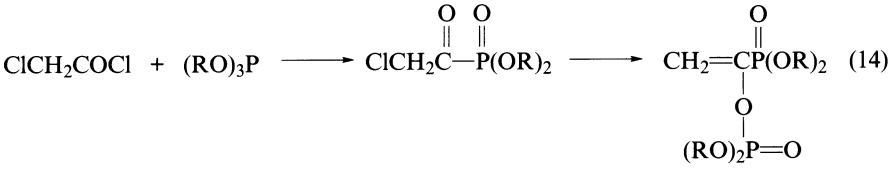

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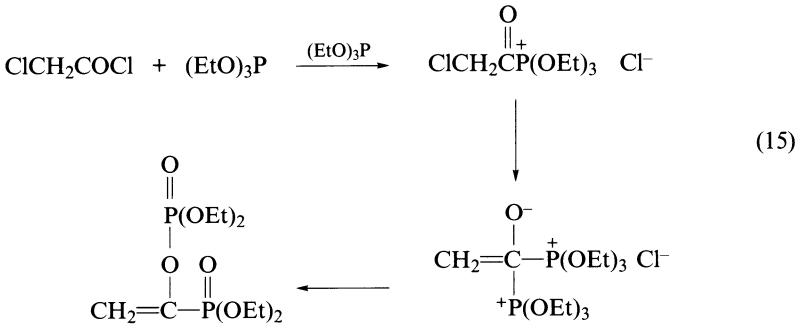
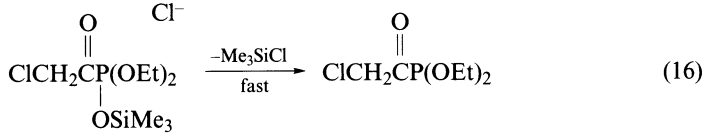


(15)

In contrast, when triisopropyl phosphite was reacted with chloroacetyl chloride, diisopropyl chloroacetylphosphonate was obtained smoothly. Apparently, triisopropyl phosphite is too hindered sterically to react rapidly with the acylpseudophosphonium salt first formed, and the dealkylation can take place without interference.

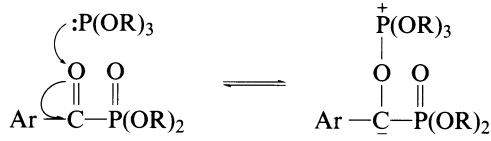
This problem was studied further by reacting chloroacetyl chloride with diethyl trimethylsilyl phosphite. In this case, the acylpseudophosphonium salt initially formed in the reaction contained a rapidly removable trimethylsilyl group. Indeed, the loss of chlorotrimethylsilane was rapid, allowing the formation of diethyl chloroacetylphosphonate (equation 16)[48].



(16)

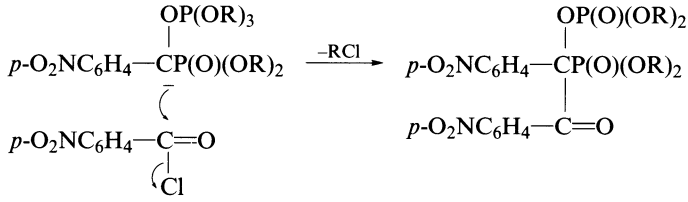
Enol phosphates phosphonates were also obtained by the reaction of perfluoroalkanoyl chlorides with triethyl phosphite[49]. In this case, it was not possible to isolate the putative intermediate perfluoroacylphosphonates. This result is in contrast with the facile formation of bis (trialkylsilyl) trifluoroacetylphosphonates (see previous section), and it indicates that acylphosphonates derived from carboxylic acids with strongly electron-withdrawing groups can be prepared using tris(trialkylsilyl) phosphites. Such silyl phosphites seem to be uniquely suitable for this purpose, by virtue of their high reactivity in the first step and their steric hindrance, which presumably retards the second step.

Side-reactions of a different type may result from zwitterionic carbanionic intermediates formed by the interaction of the freshly formed acylphosphonates with excess trialkyl phosphite (equation 17). Such ionic intermediates may undergo variety of reactions, depending on the nature and the R group, temperature and whether other reactive molecules are present in the reaction mixture. The zwitterionic intermediate may react with electrophiles or lose phosphate to from novel carbene intermediates as shown in the following sections.



(17)

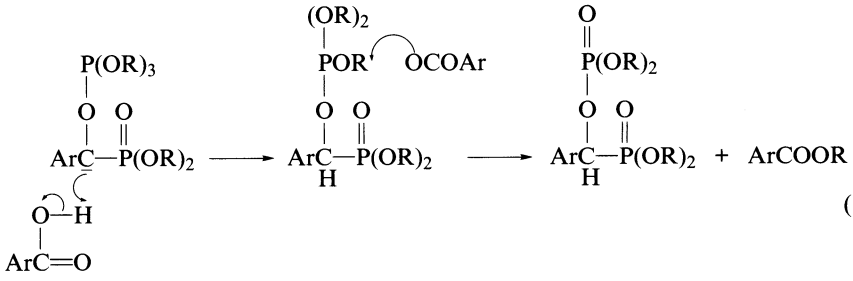
iii. Reaction of phosphonium phosphonate intermediates with electrophiles. When the preparation of dimethyl *p*-nitrobenzoylphosphonate was attempted by Arbuzov reaction of *p*-nitrobenzoyl chloride, the formation of a diphosphorus compound was observed[50]. The formation of this product (shown in equation 18) was rationalized by the nucleophilic attack of the carbanion on the highly electrophilic carbonyl carbon of *p*-nitrobenzoyl chloride. The two phosphorus atoms resonate in compounds of this type in the ranges of –2.2 to –2.5 and 12 to 13 ppm with a J_{PP} of 1.8 Hz.



(18)

On the other hand, when the Arbuzov reactions of aroyl (*p*-nitrobenzoyl, benzoyl, *p*-chlorobenzoyl or *p*-toluoyl) chlorides were carried out in the presence of proton sources (i.e. excess of a carboxylic acid), phosphate phosphonates were obtained as shown in equation 19[51]. The formation of these resulted from protonation of the initially formed carbanion, to form a phosphonate trialkoxyphosphonium ion, followed by nucleophilic dealkylation of the trialkoxyphosphonium moiety. Indeed, the formation of carboxylate esters as additional products was noted in these reactions. The type of products shown in this reaction show characteristic resonances in the ^{31}P NMR spectrum in the ranges 0.8–1.25 and 16–17 ppm with J_{PP} = 29 Hz. Analogous results were observed in the reaction of 2-pyridoyl chloride with triethyl phosphite[52].

In the exceptional case of the reaction of *p*-anisoyl chloride with trimethyl phosphite in the presence of *p*-anisic acid, the product was an unusual monophosphorus compound (equation 20)[51]. The formation of this was also rationalized as proceeding through the common phosphonate phosphonium intermediate, the difference being merely in the mode



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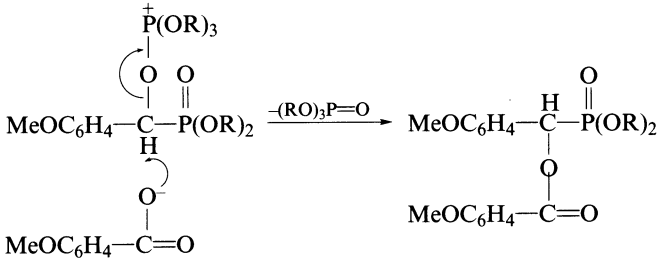
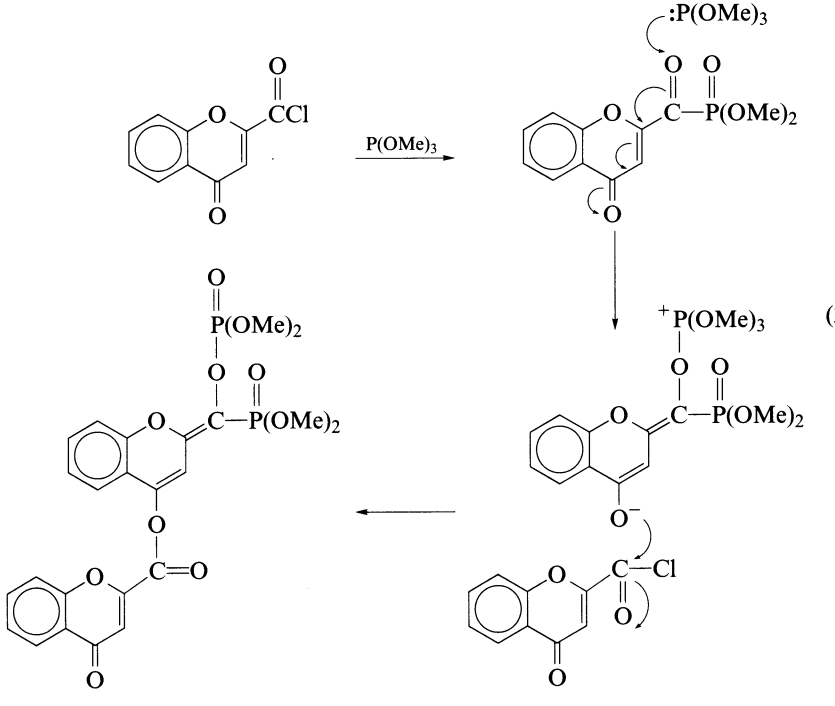


(20)

of the dealkylation. The product in this case is formed by the attack of the anisate anion on the benzyl carbon, with trimethyl phosphate serving as a living group.

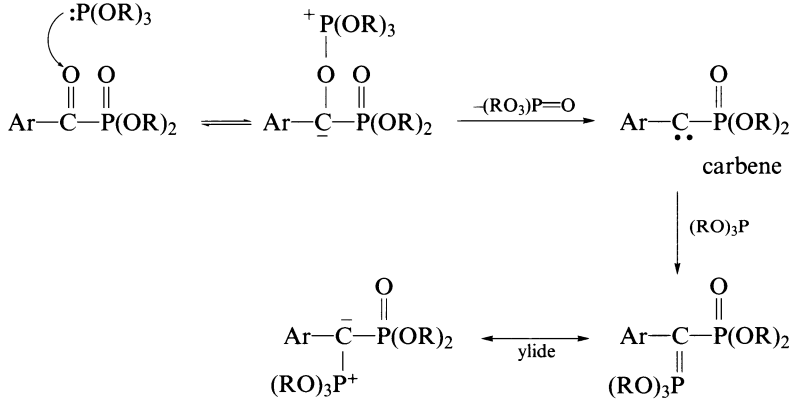
Analogous results were observed in the Arbuzov reactions of chromone 2-carbonyl chloride with trialkyl phosphites (equation 21)[53]. In this case the acyl carbonyl group is



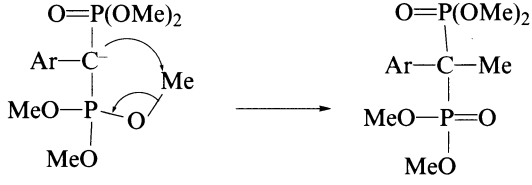
(21)

situated γ,δ to the α,β-unsaturated chromone carbonyl and therefore it is highly activated. Here too the carbonyl oxygen of the initially formed acylphosphonate is attacked by a second molecule of trialkyl phosphite, leading to a zwitterionic intermediate which is acylated by a second molecule of chromone carbonyl chloride on the ring carbonyl to give a mixture of *E*- and *Z*-isomeric final products. When the Arbuzov reaction was carried out in the presence of proton donors or when the final product was treated with water, alcohols or amines, the phosphate phosphonate containing one chromone moiety could be obtained. Chromone 3-carbonyl chloride reacted normally with trialkyl phosphites to afford the expected acylphosphonates.

iv. Formation and reactions of carbenes from phosphonium phosphonate intermediates. While the reactions between trialkyl phosphites and acylphosphonates proceed at room temperature only if an electrophile is present to trap the anionic intermediate, further investigation revealed that at higher temperature trialkyl phosphites react with aroylphosphonates (Ar = Ph, *p*-ClC_6H_4, *p*-MeC_6H_4 or *p*-$CMeOC_6H_4$) to give novel ylidic phosphonates via carbenic intermediates (equation 22)[54]. The ylides could be observed by ^{31}P NMR spectroscopy. They show signals at about 31 and 54 ppm, corresponding to the phosphon and trialkoxyphosphonium moieties, respectively. The coupling constant of the two phosphorus atoms was $J = 96$ Hz.

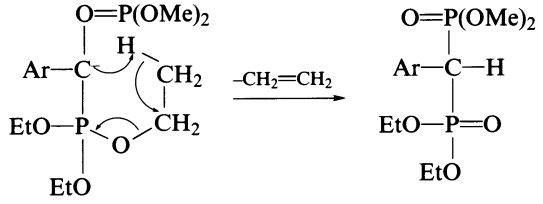


The ylides can be further transformed into bisphosphonates. When the ylide (R = Me) is heated, one of the methyl groups is transferred from the oxygen to the carbon with the formation of the geminal bisphosphonate through the mechanism indicated in equation 23.



On the other hand, when R = Et, one of the ethyl groups is lost with the elimination of ethylene to give a different *gem*-bisphosphonate (equation 24).

When Ar = *p*-ClC_6H_4, a bimolecular addition of the ylide to aroylphosphonate is observed, leading eventually to a dioxaphospholane (equation 25)[54].



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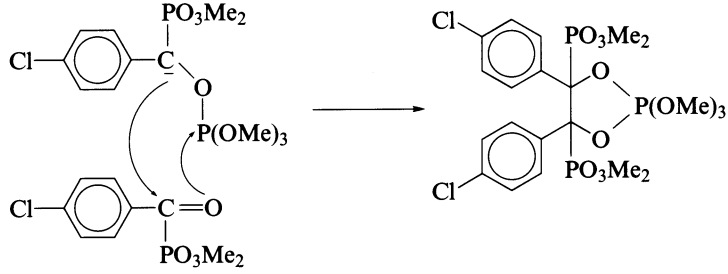


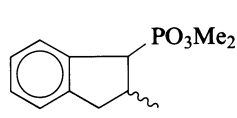
(25)

The conclusive evidence for carbene intermediates is obtained from the results of the reactions of *ortho*-substituted derivatives such as 2-methoxybenzoyl-, 2-ethylbenzoyl- and 2-phenylbenzoylphosphonates, all of which undergo an insertion of the carbene into a C—H bond with the formation of dihydrobenzofuran or indan derivatives (equation 26), although in the first two instances this is accompanied by the formation of ylide in a temperature-dependent manner[55].

(26)

Y = CH_2 or O

The carbene mechanism is to be highly preferred over the anionic mechanism proposed earlier[56] for the formation of the dihydrobenzofuran derivative. Further study revealed that the preferred mode of cyclization in most of the cases is the one which leads to five rather than six-membered rings. Thus *o*-propylbenzoyl- and *o*-phenoxybenzoyl phosphonates give the five-membered ring products **13** and **14**[55]. In the latter case, the reaction involves expansion of the aromatic ring.



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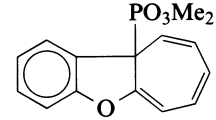
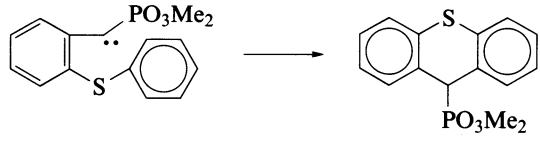


(14)

In contrast to the phenoxy derivative, the carbene derived from *o*-phenylmercaptobenzoylphosphonate inserts to form a six membered ring product (equation 27). This exceptional behaviour is presumably due to the change in the C—S—C angle (respective to that of C—O—C) which might affect the line of attack of the carbene on the ortho substituent[57].

A unique case in this series is that of *o*-benzoylbenzoylphosphonate. The carbene derived from this compound is trapped intramolecularly by the carbonyl group leading to the reactive isobenzofuran system (equation 28)[57].



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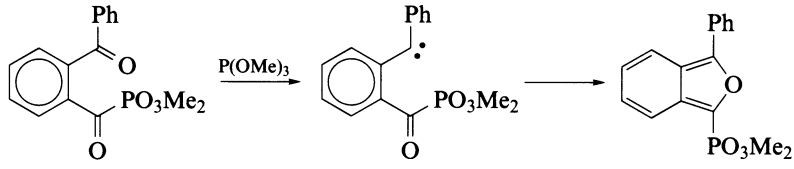
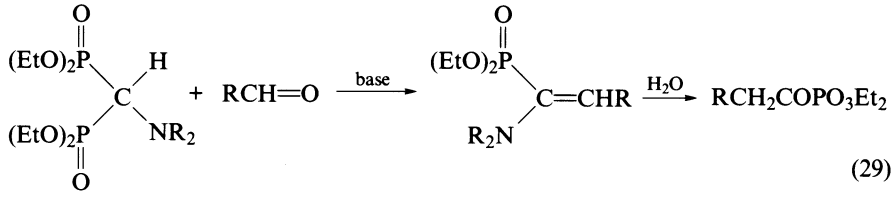


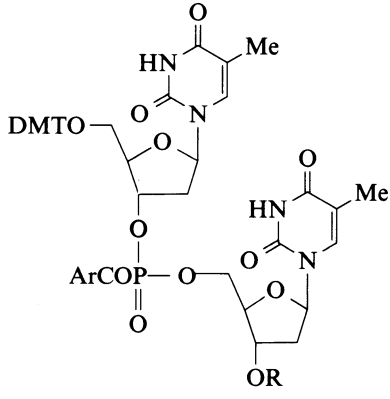
(28)

b. Hydrolysis of enamines. Dialkyl acylphosphonates were obtained by mild hydrolysis of enamines, which in turn were obtained in Horner–Emmons–Witting reaction of *N,N*-dialkylaminomethanebisphosphonates (equation 29)[58].



(29)

c. Condensation of aroylphosphonic acids with nucleoside alcohols. Aroylphosphonic acids were condensed with two different, appropriately protected thymidines to afford dinucleosidyl aroylphosphonates (**15**). In the first step, a 5′-*O*-dimethyltritylthymidine was condensed on the free 3′-OH group with benzoylphosphonic acid using mesitylene-1,3-disulphonyl chloride (MDS) as condensing agent. The mononucleosidyl benzoylphosphonate that resulted was subsequently condensed with 3′-*O*-acetylthymidine in the presence of MDS and nitrotriazole to yield the aroylphosphonate diester. Compounds **15** were stable to chromatography, in contrast to aliphatic acylphosphonate diesters[59].



(15)

d. Oxidative methods

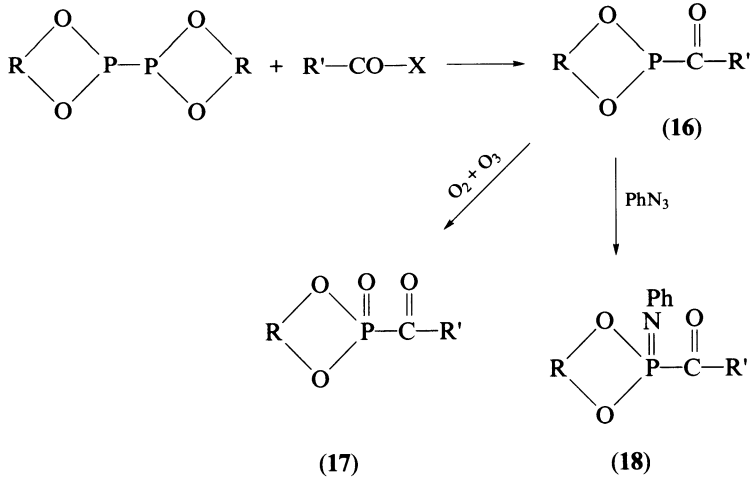
i. Oxidation of α-hydroxyphosphonates. Although α-hydroxyphosphonates are easily accessible by addition of dialkyl hydrogenphosphonates to aldehydes (Abramov reaction), these compounds have not become common starting materials for acylphosphonates. The earliest report of this approach is the oxidation of a hydroxyphosphonate, derived from a 2,4,3,5-di-*O*-ethylidene aldopentose, by dimethyl sulphoxide. The reaction was carried out in acetic anhydride, and the product was isolated as the enol acetate of the expected acylphosphonate in 40% (equation 30)[60]. The latter could be converted directly into the corresponding α-hydroxyiminophosphonate by treatment with hydroxylamine hydrochloride[60].

$$R_2CHCHPO_3Et_2 \xrightarrow[Ac_2O]{dmso} R_2C{=}CPO_3Et_2 \quad (30)$$

(OH; OAc)

A recent paper reports the oxidation of benzylic α-hydroxyphosphonates to aroylphosphonates in good yields, by refluxing them with 10 equiv. of MnO_2 in toluene[61]. The same paper reports that other oxidizing agents, including pyridinum chlorochromate and dichlorodicyanobenzoquinone (DDQ),or the Swern method are also applicable for the oxidation of benzylic α-hydroxyphosphonates to benzoylphosphonates. This approach to acylphosphonates was found, however, to be limited to *tert*-butyl esters[61].

ii. Oxidation of acylphosphonites. Cyclic acylphosphonites (**16**) are obtained by the reaction of hypodiphosphites with acyl chlorides (equation 31)[62]. The acylphosphonites **16** can be oxidized to the acylphosphonates **17** by passing an ozone–oxygen mixture through their solution . Alternatively, on reaction with phenyl azide, the acylphosphonimidates 18 were formed.



(31)

iii. Oxidation of methylenebisphosphonate. A unique case is the synthesis of tetraesters of oxomethanebisphosphonic acid. Such esters were synthesized by halo formylation of the methanebisphosphonates by *t*-BuOCl in formic acid (equation 32)[63].

$$(RO)_2PCH_2P(OR)_2 \xrightarrow[HCOOH]{t\text{-BuOCl},} (RO)_2P(O)C(O)P(O)(OR)_2 \qquad (32)$$

4. *Synthesis of acylphosphon-amidates and -imidates*

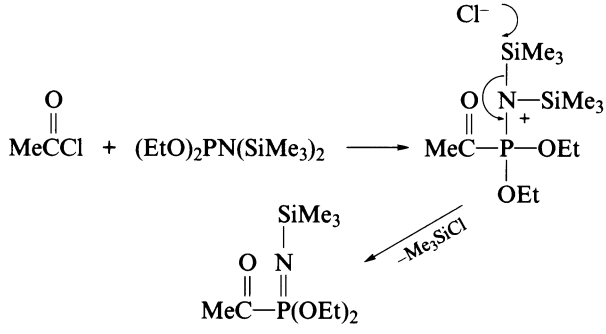
Both alkyl acylphosphonamidates and acylphosphonediamidates have been synthesized by the Arbuzov reaction. Acyl chlorides have been reacted with dimethyl[64] or diethyl[9] *N,N*-diethylphosphoramidite give alkyl acyl-*N,N*-diethylphosphonamidates in medium to fair yields (equation 33).

$$RCOCl + (EtO)_2PNEt_2 \longrightarrow RC(O)P(OEt)NEt_2 \qquad (33)$$
$$R = Me \text{ or } Ph$$

Similarly, ethyl *N,N,N',N'*-tetraethylphosphordiamidite reacted with acyl chlorides to give tetraethyl acylphosphonediamidates in low yield[64]. In such cases, it appears to be advantageous to use highly reactive silyl derivatives. It was reported that reaction of trimethylsilyl *N,N,N',N'*-tetraethylphosphordiamidite reacted smoothly with acetyl chloride at –5 °C to give 95% yield of acetyl-*N,N,N',N'*-tetraethylphosphonediamidate, as determined by ^{31}P NMR examination of the reaction mixture (equation 34). Unfortunately, the isolated yield of this product was reported to be only 41%[65]. A more flexible method of entry to alkyl acylphosphonamidates is the raction of phosphonochloridates with amines (see the next section).

$$MeCOCl + Me_3SiOP(NEt_2)_2 \longrightarrow MeC(O)P(NEt_2)NEt_2 \qquad (34)$$

Exceptional behaviour is seen in the reaction of diethyl *N,N*-bis (trimethylsilyl) phosphoramidite with acetyl chloride. This reaction was reported to give diethyl *N*-(trimethylsilyl) acetylphosphonimidate (equation 35)[66]. Apparently, one of the silicon atoms is attacked preferentially over the phosphorus in the quasiphosphonium intermediate formed in the first step of the Arbuzov reaction, and the product is formed by the loss of chlorotrimethylsilane.

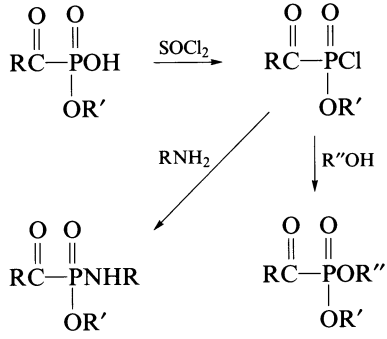


(35)

5. *Miscellaneous methods for the interconversion of phosphorus-substituted derivatives*

This section deals with interconversion of the various types of acylphosphonic derivatives which were not discussed in the previous sections.

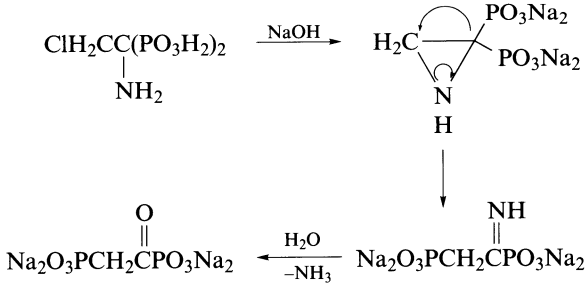
Alkyl hydrogen acylphosphonates have been converted into alkyl acylphosphonochloridates by thionyl chloride (equation 36). The latter are versatile intermediates that have been used for the synthesis of mixed dialkyl acylphosphonates[7,67] or alkyl acylphosphonamidates (equation 36)[68,69].



(36)

6. *Formation of acylphosphonate derivatives in miscellaneous reactions*

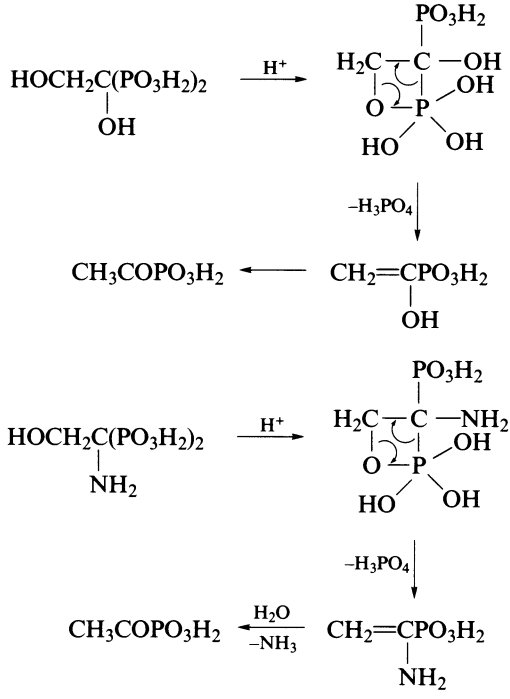
The reaction of chloroacetamide with phosphorus trichloride and phosphorous acid is reported to lead to 1-amino-2-chloroethane-1,1-bisphosphonic acid[70]. Treatment of this compound with base caused loss of ammonia with the formation of phosphonoacetylphosphonic acid as the sodium salt. The reaction has been rationalized by the mechanism depicted in equation 37[71].



(37)

Another interesting case of acylphosphonate formation from a geminal bisphosphonate is presented by the fragmentation of 1,2-dihydroxyethane-1,1-bisphosphonic acid. This compound is stable in base, but fragments in acidic solution to phosphoric and acetylphosphonic acids (equtation 38)[72].

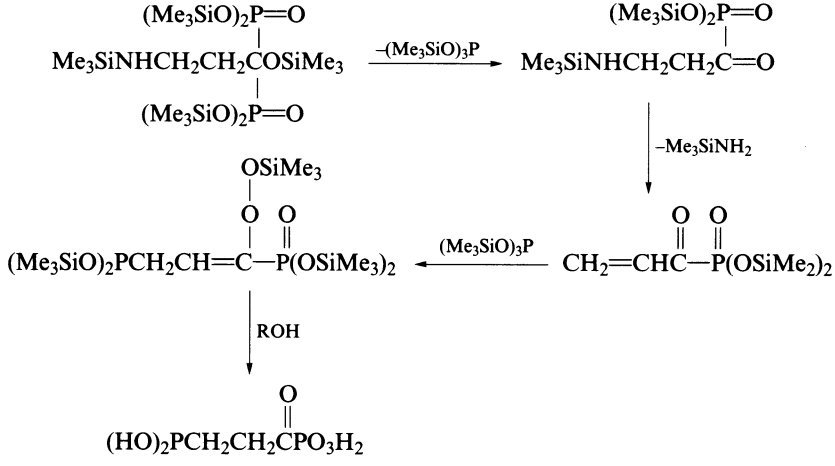
It was proposed that this is a general characteristic of all 2-hydroxyalkane-1,1-bisphosphonic acids. Indeed, a similar result was produced by the product of the reaction of hydroxyacetonitrile with phosphorous acid, 1-amino-2-hydroxy-1,1-bisphosphonic acid, which decomposed on acidification to give acetylphosphonic acid, presumably via the corresponding enamine (equation 39)[72].



(38)

(39)

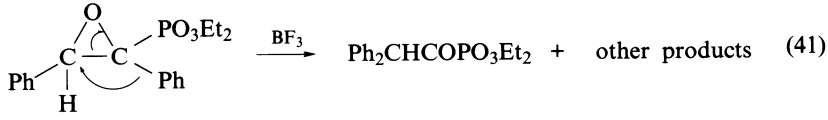
Another case in which a geminal bisphosphonate is converted in to an acylphosphonate is the thermal rearrangement of silylated 3-amino-1-hydroxypropane-1,1-bisphosphonic acid[14]. This reaction yields 3-phosphonopropionylphosphonic acid, along with some byproducts, the formation of which is rationalized in equation 40.



(40)

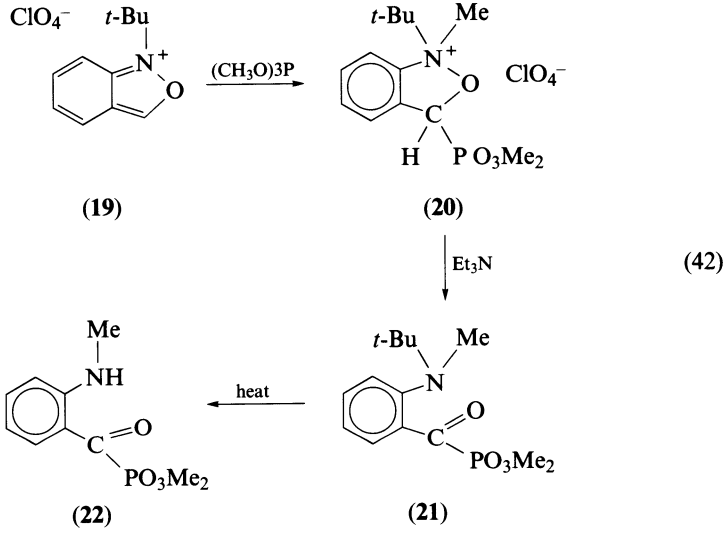
In a study aimed at determining the relative migratory aptitudes of the phenyl versus diethylphosphono groups, it was found that rearrangement of epoxyphosphonate in equa-

tion 41 under the influence of boron trifluoride etherate gave the acylphosphonate, in yields dependent on the stereochemistry of the epoxide[73].



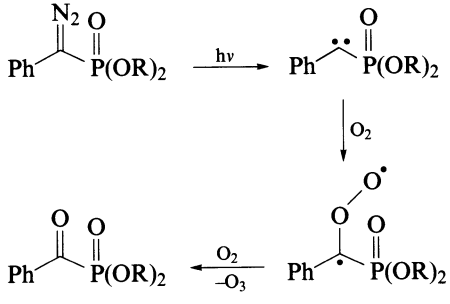
(41)

An unusual reaction leading to an acylphosphonate is that of *tert*-butylanthranilium perchlorate (**19**) with trimethylphosphite[74]. This reaction gives, in the first step, *N*-methyl-*N*-*tert*-butyl-3-(dimethoxyphosphinyl)-2,1-benzisoxazolinium perchlorate (**20**), which on treatment with triethylamine is converted into the unstable *ortho*-substituted benzoylphosphonate **21**. The latter undergoes methanolysis to the methyl ester and dimethyl phosphite when treated with methanol (not shown). On distillation, this compound loses isobutene and gives dimethyl *o*-methylaminobenzoylphosphonate (**22**) (equation 42)[57].



(42)

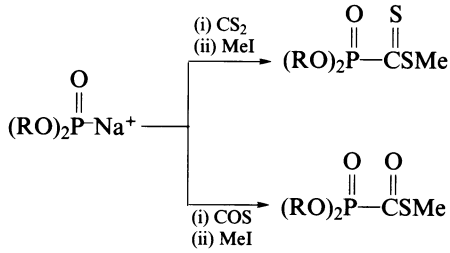
Photolysis of dimethyl α-diazobenzylphosphonate in an argon matrix doped with 20% of oxygen at 10 °C gave dimethyl benzoylphosphonate along with dimethyl benzoyl phosphate (equation 43)[75]. The reaction involves photochemical generation of phenyl-



(43)

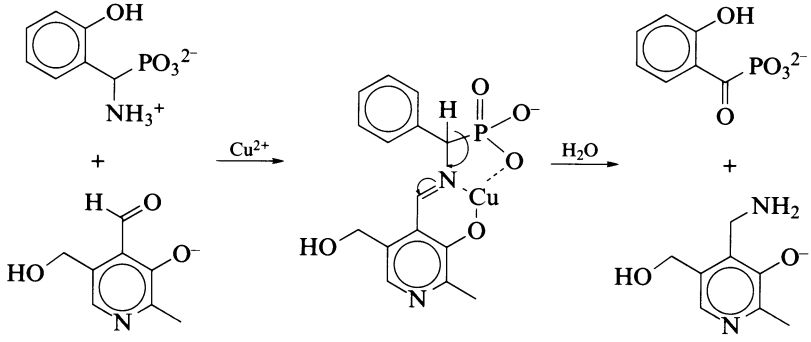
phosphonylcarbene, which reacts with oxygen to from the corresponding carbonyl oxide, which in turn reacts with a second molecule of oxygen to give the ketone and ozone.

The synthesis of the thio analogues of phosphonoformate can easily be achieved by addition of dialkyl phosphite anion to carbon disulphide or to carbonyl sulphide (equation 44)[76].



(44)

In work aimed at elucidating the mode of pyridoxal mediated dephosphonylation of α-aminophosphonic acids, it was found that simple aminophosphonates reacted with pyridoxal to form Schiff bases, which complexed copper(II) ions, but did not react further. In contrast, *o*-hydroxyphenylphosphaglycine did react with pyridoxal at 40 °C with the formation of pyridoxamine, along with *o*-hydroxybenzoylphosphonic acid on the one hand (equation 45), and salicylaldehyde and H_3PO_4 (not shown) on the other[77]. Apparently, the presence of the *o*-hydroxy group is necessary for the success of the reaction, presumably by complexing the copper ion in the fashion indicated. The formation of *o*-hydroxybenzoylphosphonic acid illustrates the capability of α-aminophosphonic acids to participate in transamination (similarly to amino acids), while salicylaldehyde is the result of dephosphonylation (analogous to decarboxylation).



(45)

7. *Putative involvement of acylphosphonic derivatives as intermediates in various reactions*

The reaction of ketene with diethyl hydrogen phosphonate leads to diethyl acetoxyvinylphosphonate (equation 46)[78]. This reaction was assumed to involve the initial formation of acetylphosphonate, which underwent enolization and reaction with a second molecule of ketene to the final product. Infrared spectral examination of the product mixture revealed the formation of an additonal product, presumably a β-lactone ($\nu = 1830$ cm^{-1}) which could be formed through 2 + 2 cycloaddition of a ketene molecule to the C=O group of the acetylphosphonate.

$$CH_2{=}C{=}O + HP(O)(OEt)_2 \longrightarrow MeCOPO_3Et_2 \xrightarrow{CH_2=C=O} CH_2{=}C(OCOMe)PO_3Et_2 \quad (46)$$

The intermediacy of benzoylphosphonic acid was postulated in the reaction of benzoyl chloride with phosphorous acid, which gave α-hydroxybenzylidenebisphosphonic acid as one of the final products[79].

C. Reactions of Acylphosphonates

Because of the strong electron-withdrawing effect of dialkyl phosphoryl groups[16], the carbonyl in dialkyl acylphosphonates is highly electrophilic and therefore reacts rapidly with all types of nucleophiles.

1. *Hydrolysis of acylphosphonates*

Dialkyl acylphosphonates are sensitive to water in neutral[80] and alkaline conditions[1], and hydrolyse rapidly to the corresponding carboxylic acids and to dialkyl hydrogenphosphonate (equation 47)[1,31]. This occurs following the rapid addition of water to the carbonyl group with the formation of stable hydrates[1]. The involvement of stable carbonyl hydrates in the hydrolysis of dimethyl acetylphosphonate[80] and aroylphosphonates[81] was established by ^{1}H NMR and UV spectroscopy, respectively. In the latter case, the rates of formation and decomposition of the tetrahedral carbonyl hydrates were also determined.

$$RCOP(O)(OR)_2 \xrightarrow{H_2O} RCOOH + HP(O)(OR)_2 \quad (47)$$

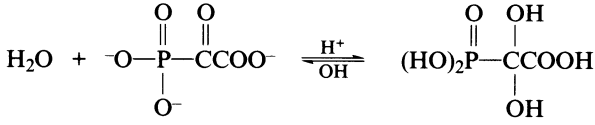
Similarly, oxomethanebisphosphonic[63] and oxophosphonoacetic acid esters[11] (equation 48) interact readily with water. In these compounds the carbonyl groups are situated between the two electron-withdrawing groups, and therefore on addition of stoichiometric amounts of water they are converted quantitatively into the hydrates.

$$(RO)_2P(O)C(O)P(O)(OR)_2 \xrightarrow{H_2O} (RO)_2P(O)C(OH)_2P(O)(OR)_2$$

$$(EtO)_2P(O)C(O)COOEt \xrightarrow{H_2O} (EtO)_2P(O)C(OH)_2COOEt \quad (48)$$

In the case of the fully hydrolysed derivative, the ketone ⇌ hydrate equilibrium depends on the pH. In alkaline medium only the ketone is present, whereas with a decrease in pH there is an increase in the proportion of the hydrate ($\delta^{31}P = 14.5$ ppm), which predominates below pH6 (equation 49)[11].

A similar influence of the pH was seen in haloacetylphosphonic acids. Using the Taft relationship for ketone hydration, the equilibrium constants for hydration of the dianionic



(49)

species: bromoacetylphosphonate (BAP^{2-}) and chloroacetylphosphonate (CAP^{2-}) were estimated to be 0.29 and 0.42, respectively. As expected, for the monoanionic species, $BAPH^-$ and $CAPH^-$, the hydration constants were far larger (148 and 207, respectively)[82].

$BAPH_2$ $CAPH_2$

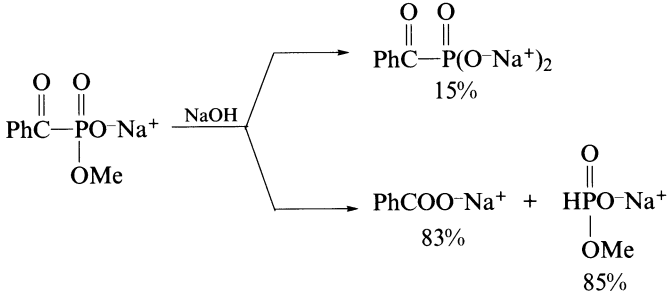
A kinetic study of the alkaline hydrolysis of diethyl benzoylphosphonate was performed and a mechanism of general base catalysis was formulated[83]. This general base catalysis mechanism was subsequently disputed on the basis of a later kinetic study of the hydrolysis of diethyl benzoylphosphonate in neutral and acidic aqueous solutions[84]. Under these conditions, mainly benzoic acid and diethyl hydrogenphosphonate are formed, in addition to small amounts of benzoylphosphonic acid and ethyl hydrogenbenzoylphosphonate. This study formulated the mechanism as involving the formation of the carbonyl hydrate ($\delta^{31}P = 17.9$ ppm) in the first step (stabilized by hydrogen bonding with two additonal water molecules) which collapses to the C—P bond-cleaved products after intramolecular proton abstraction by the P=O group.

The stabilities of dimethyl benzoylphosphonate, methyl hydrogenbenzoyl phosphonate and benzoylphosphonic acid in hydrochloric acid for 96 h at room temperature were examined by ^{31}P NMR spectroscopy[3]. Similarly to previous work[84], it was found that dimethyl benzoylphosphonate hydrolysed (to the extent of 50%) to dimethyl hydrogenphosphonate [$(CH_3O)_2PHO$] as the main product (40%), in addition to methyl dihydrogen phosphonate. In contrast, methyl hydrogenacyl phosphonates and acylphosphonic acids were stable under these conditions. It seems reasonable to assume that the stability of the half ester and of the acid is a consequence of intramolecular hydrogen bonding.

The high reactivity of acylphosphonate diesters in hydrolytic C—P bond fission reactions appears to be the cause of the difficulties in the preparation of prodrugs of the antiviral agent phosphonoformic acid (Foscarnet, $HOCOPO_3H_2$). Triesters of this compound have been synthesized and evaluated, but were found much too unstable to be useful as prodrugs[12,85,86]. A recent paper reported the surprising observation that, in contrast to *P*-bis (alkyloxy) esters of phosphonoformic acid which undergo P—C bond cleavage, the dominant base-catalysed reaction of *P*-bis (aryloxy) esters of phosphonoformic acid, ROCOP(O) $(OPh)_2$ is P—O bond cleavage[87]. This reaction proceeds at a rate 10^6 times faster than the hydrolysis of diphenyl methylphosphonate and 10^4–10^5 times faster than that of diphenyl difluoromethylphosphonate. Such a rate acceleration cannot be accounted for by simple electronic effects. Therefore, other possibilities, such as intramolecular nucleophilic catalysis or stereoelectronic assistance, both originating in the carbonyl group, have been suggested[87]. It would be interesting to examine the behaviour of diaryl esters of acylphosphonates.

In order to gain information regarding the comparative hydrolytic stabilities of the partially or fully unesterified acylphosphonates in base, the stabilities of monomethyl acylphosphonates [RCOP(O)OMeOH] and acylphosphonic acids [RCOP(O) $(OH)_2$] (R = Hex, Ph and MeCH=CH—) were examined as representative compounds by ^{31}P

NMR spectroscopy and high-performance liquid chromatography under three standard conditions: (i) borate buffer of pH 7.4, (ii) borate buffer of pH 9.0 and (iii) 1 M NaOH (pH ≈ 14), at room temperature[3]. It was found that acylphosphonic acids are completely resistant to basic hydrolysis. In contrast, monomethyl acylphosphonates were stable at pH 9 but hydrolysed at pH 14 to give acylphosphonate dianion, sodium carboxylates and methyl sodium phosphonate in the approximate ratio 1:5:5 as determined by high-performance liquid chromatography and ^{31}P NMR spectroscopy (equation 50). The formation of these products indicates that in the molecule of methyl hydrogenbenzoyl phosphonate there are two electrophilic sites at which there is a possibility of nucleophilic attack by a hydroxide anion. Judging by the relative amounts of the products, the more reactive site is the carbonyl carbon which reacts with a hydroxide to give, reversibly a tetrahedral intermediate, which in turn may be protonated and suffer cleavage of the C—P bond to from benzoate and monomethyl hydrogenphosphonate (equation 51).



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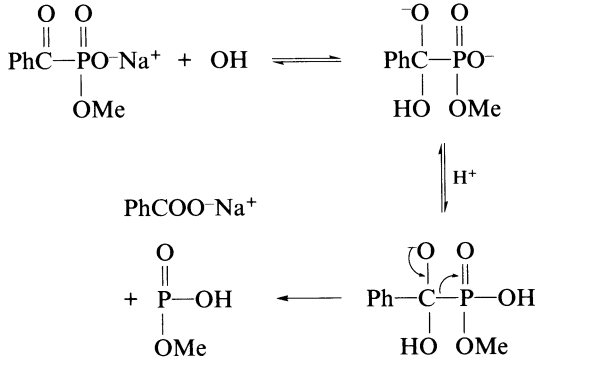
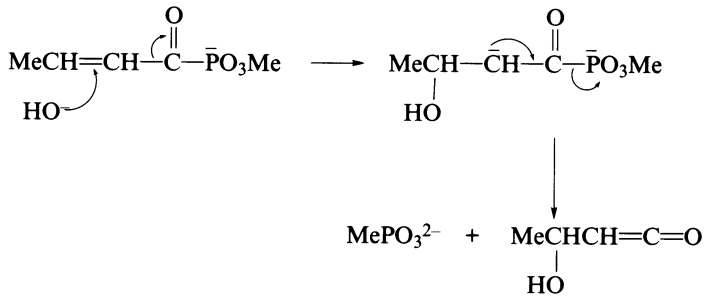


(51)

Alternatively, hydroxide anion may also attack the P—O—Me group and displace benzoylphosphonate, which as a dianion is expected to be a very poor leaving group. Therefore, it is not surprising that this is the less favoured course of the reaction.

Among monoesters that are generally stable at pH 7.4, the crotonoyl derivative is exceptional in its instability at this pH. It was proposed that the decomposition of this compound may be initiated by a Michael-type addition of hydroxide ion to the double bond, to form an enolate anion, which would decompose by analogy with what was observed for α-carbanions derived from acylphosphonates (equation 52).

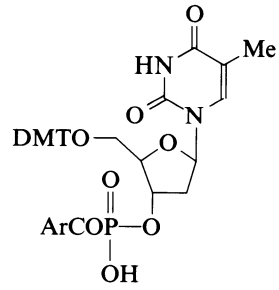
2-Phosphonoacetylphosphonic acid, $H_2O_3PCH_2COPO_3H_2$, was reported to be stable for 2–3 h in water at 70 °C, but decomposed completely when refluxed in water for 48 h[88]. In contrast, it was stable for 'long periods of time to hot aqueous base'[88].



(52)

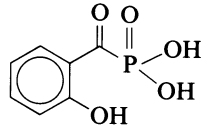
In summary, it can be concluded that acylphosphonic acids and monoesters are far more stable than diesters in alkaline conditions. The former ionize under the influence of base, and then the phosphonyl group cannot act as a leaving group to give the C—P bond fission products.

Results concerning the behaviour of two unique acylphosphonate derivatives under hydrolytic conditions should also be mentioned. The aroylphosphonic group was used as a protecting group in the synthesis of nucleotides[59]. In the course of this work, the stability of this group was determined examining a series of 5′-(dimethoxytrityl) thymidine-3′-aroylphosphonates (**23**) in '1 M sodium hydroxide–pyridine (1:1, v/v)'. These aroylphosphonate monoesters were resistant to hydrolysis. In comparison, methyl sodium benzoylphosphonate under these conditions underwent complete hydrolysis to benzoic acid in 18 h at 25 °C[3].



(**23**)

Another interesting case is that of *o*-hydroxybenzoylphosphonic acid (**24**), which was reported to hydrolyse to the extent of 15% 'at 100 °C, pH 8.8'[77]. In contrast, no decomposition was observed when benzoylphosphonic acid was kept under the same conditions[3]. It appears reasonable to asssume that the excessive stability of the nucleoside derivative **23** is the result of steric hindrance due to the large nucleoside bound to the phosphoryl group. On the other hand, the increased reactivity of *o*-hydroxybenzoylphosphonic acid (**24**) compared with the unsubstituted compound indicates that the *o*-hydroxy group probably participates intramolecularly in the fission of the C—P bond.



(**24**)

2. Reactions with other nucleophiles

a. Alcohols

i. Reactions with alcohols. Examination of solutions of dimethyl acetylphosphonate and dimethyl benzoylphosphonate in a series of alcohols with pKa values ranging from 12 to 16 showed the appearance of new signals in the range 17–23 ppm, depending on the alcohol, indicating the formation of hemiketals (equation 53)[89]. It was found that both the rate of the hemiketal formation and the proportion of the hemiketal in the equilibrium mixture increased with increasing pK_a of the alcohol. MNDO calculations carried out in the same work on the ralationship between the proton affinity of the ionized hemiketal oxygen and the electronic effect of the groups bound to the carbonyl carbon, showed that the σ^+ value of the $(MeO)_2P{=}O$ group is equal to that of the CCl_3 group. (See also Sections II. A. 3. iv and II. C. 7. b for other means of estimating the electron-withdrawing effect of the dialkoxyphosphoryl group.)

(53)

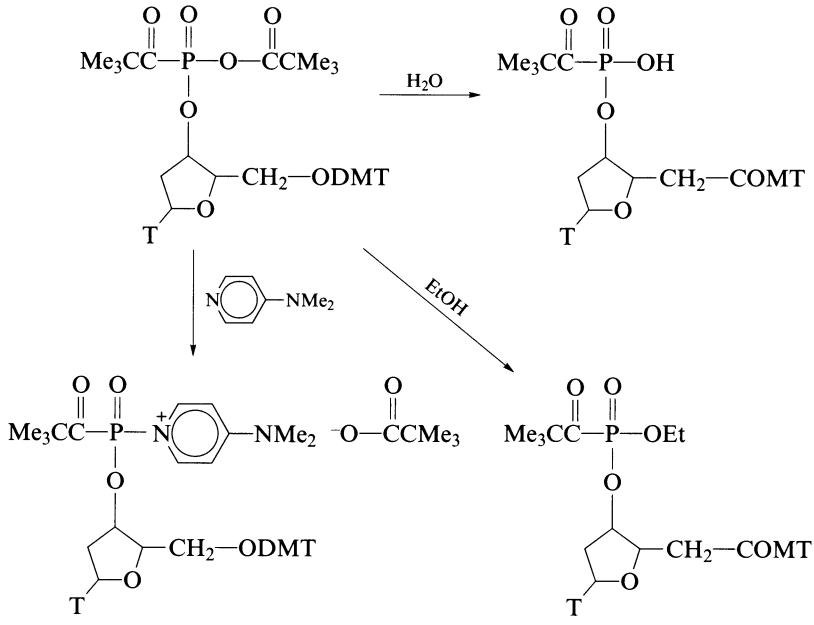
R = Me or Ph

R' = Me, Et, $NCCH_2CH_2$, $MeOCH_2CH_2$, $ClCH_2CH_2$, $HC{\equiv}CCH_2$, Cl_3CH_2

The effect of the P—O—alkyl group on the reactivity of the C=O in acylphosphonates could be evaluated by comparing methanol solutions of dimethyl benzoylphosphonate and methyl 2,2,2-trifluoroethyl benzoylphosphonate[67]. Solutions of the two compounds contained 49 and 61% hemiketals ($\alpha^{31}P \approx 18$ ppm), respectively. The difference in behaviour was more striking in the second step, namely the C—P bond fission reaction. Presumably owing to the better leaving group properties of $(MeO)(CF_3CH_2O)P(O)$– than $(MeO)_2P(O)$, the latter phosphonate underwent, at room temperature, complete alcoholysis in minutes, whereas the dimethyl ester was cleaved only to the extent of about 50% in 5 h. In contrast, in the more hindered propan-2-ol there was only 2 and 4% hemiketal formation after 30 min[67].

An exceptional case of an acylphosphonate in which nucleophiles react at the phosphorus rather than at the carbonyl is that of the mixed anhydride of pivalic acid and pivaloylphosphonyl monoester of 5′*O*-DMT-2′-deoxythymidine (equation 54). In this compound the keto function is especially unreactive, because of steric hindrance, while the phosphorus is unusually electrophilic, being both a mixed anhydride and an acylphosphonyl function at the same time[90]. As a consequence of these structural features, this compound reacts at the phosphorus with nucleophiles, such as water, ethanol or pyridine, to give products resulting from P—O bond cleavage (equation 54).

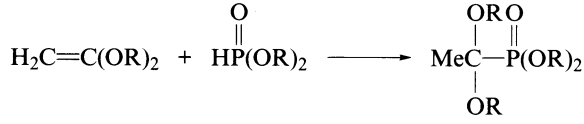
The reaction of acylphosphonate diesters with alcohols was reported early to lead to dialkyl hydrogenphosphonates and carboxylate esters[1]. In a more recent systematic study, conditions were developed to use acylphosphonates for the acylation of alcohols[91]. It was found that 1,5-diazabicyclo [5. 4. 0] undec-7-ene (dbu) is a highly effective catalyst for acylation of alcohols by acylphosphonates. Two special aspects deserve mention: (1) *tert*-butyl alcohol could be acylated with diethyl benzoylphosphonate, in the presence of dbu and 4-dimethylaminopyridine, to give *tert*-butyl benzoate in 57% yield; (2) the primary hydroxy group of a diol (e.g. butane 1, 3-diol) could be acylated fairly selectively in the presence of a secondary hydroxy group by this methodology (ratio of mono to diacyl product = 88:12).



(54)

ii. Acetals of acylphosphonates. As the reaction of acylphosphonates by alcohols under acid catalysis leads to C—P bond cleavage, this method cannot lead to acetal formation. Treatment of dialkyl acylphosphonates with orthoesters might be a reasonable method for these compounds.

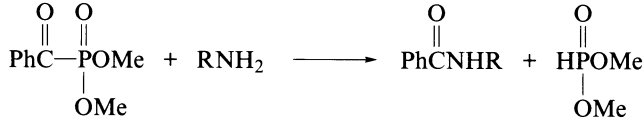
The preparation of acetals of the unknown formylphosphonic acid was reported by treating a dialkyl hydrogenphosphonate[92] or a dialkyl trimethylsilyl phosphite[93] wth trialkyl orthoformate in the presence of boron trifluoride. Another method which is reported to yield acylphosphonate ketals is the addition of dialkyl hydrogenphosphonates to ketene acetals (equation 55)[94]. For dithioketals, see Section II. C. 4. b.



(55)

b. Amines Dialkyl benzoylphosphonates were studied in detail as benzoylating reagents for amines[95]. Aliphatic primary amines cleave the C—P bond rapidly to form substituted benzamides and dialkyl hydrogenphosphonates (equation 56). Hindered and secondary amines react more slowly, and aromatic amines do not react at all under the conditions examined[96].

The aroylphosphonic function was utilized elegantly for the protection of the O=P—H moiety in the synthesis of dinucleoside hydrogen phosphonates. Although dinucleosidyl



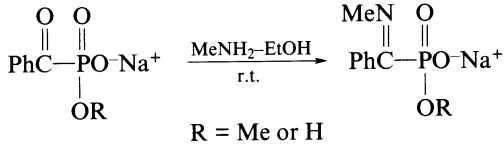
(56)

aroylphosphonates (e.g. **15**) were not cleaved by *n*-butylamine, presumably owing to the steric hindrance exerted by the two large nucleoside residues, in the presence of catalytic amounts of dbu the cleavage was achieved smoothly[59]. The same approach was utilized subsequently for the conversion of dinucleosidyl acylphosphonates into dinucleosidyl phosphorothinates and dinucleosidyl trimethylsilyl phosphites[97,98].

N-Bromomagnesylamines were reported to add to the carbonyl of dimethyl benzoylphosphonates with the formation of stable tetrahedral adducts (equation 57)[96]. Unfortunately, no ^{31}P NMR data have been reported for these compounds.

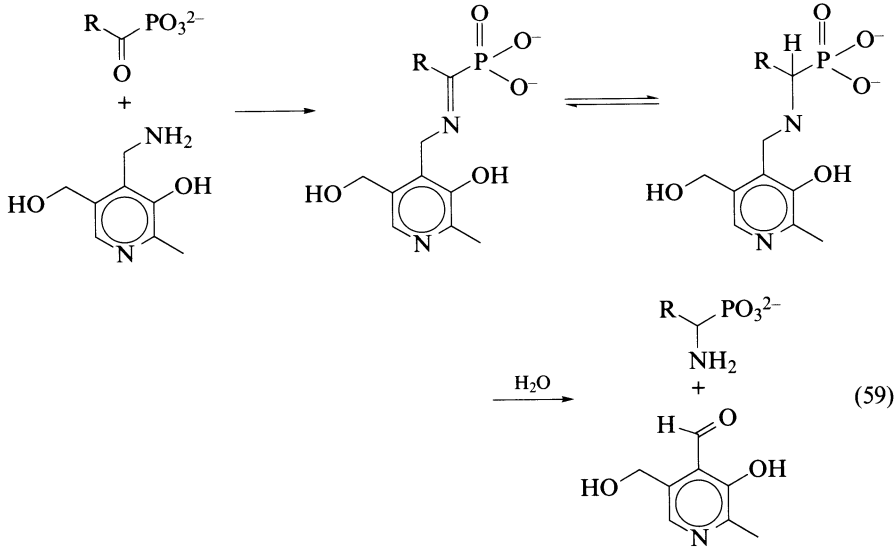
(57)

In contrast to dialkyl acylphosphonates, the reaction of methyl sodium benzoylphosphonate or disodium benzoylphosphonate with methylamine gave the imine without severing the C—P bond, demonstrating that the high reactivity of the carbonyl group is preserved even in the anion (equation 58)[3].



(58)

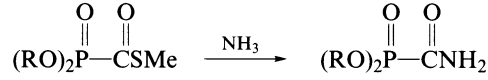
Acylphosphonic acids react with pyridoxamine, which is a coenzyme of transaminases, with the formation of α-aminophosphonic acids (see also reductive amination, Section II. C. 4. c)[28]. The first step of the reaction is addition of the pyridoxamine to the carbonyl of the acylphosphonate, followed by prototropic rearrangement and hydrolysis to pyridoxal and an aminophosphonic acid (equation 59). This reaction is in contrast with the reverse



(59)

process described in Section II. C. 4. c, which however, does not take place with simple aminophosphonic acids. only *o*-hydroxyphenylphosphaglycine could be deaminated—the presence of the the *o*-hydroxy group was deemed to be crucial for the success of the reaction[77].

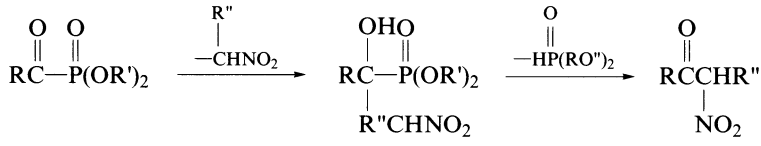
It is interesting to note that reaction of *S*-methyl diethoxyphosphinylthiolformate with ammonia proceeds with breaking of the C—S rather than the C—P bond to give the carboxamide in 75% yield (equation 60)[76]. Apparently, MeS^- is a better leaving group than the phosphite anion.



(60)

c. Carbanions

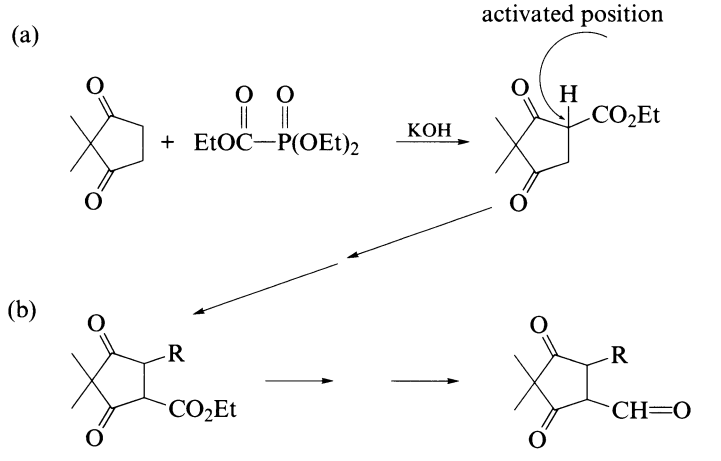
i. Condensation with nitroalkanes. Dialkyl acylphosphonates undergo condensation with nitroalkanes with base catalysis[99]. The resulting 1-alkyl-1-hydroxy-2-nitrophosphonates may lose dialkyl phosphite with the formation of α-nitroketones (equation 61)[100]. Recently, phase-transfer conditions were developed for the addition of nitromethane to a variety of aliphatic and aromatic dialkyl acylphosphonates[101].



(61)

ii. Enolates. Aliphatic and aromatic diethyl acylphosphonates were used for *C*-benzoylation of enolates derived from ketones (acetophenone, cyclohexanone) and esters (ethyl acetate and acetoacetate and malonate). The reactions led to the corresponding di- and tricarbonyl compounds in reasonable yields[102].

Triethyl phosphonoformate served as a tool for the introduction of the ethoxycarbonyl group into the cyclopentanedione ring: (a) for the purpose of activation of a position and (b) as a one-carbon unit for building up a side-chain (equation 62)[103].

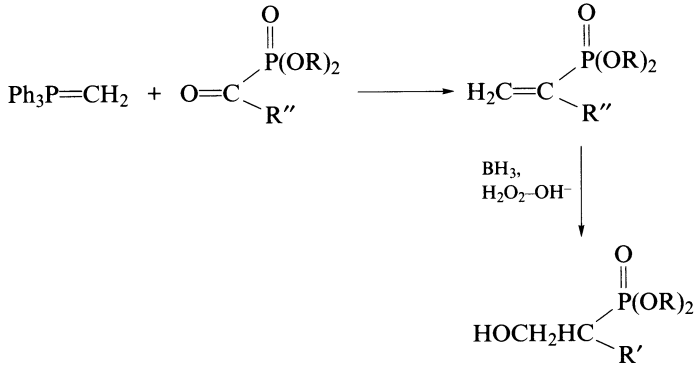


(62)

d. Grignard and Reformatsky reagents. Dialkyl acylphosphonates react with Reformatsky reagents with the ultimate formation of ketones, as a consequence of elimination of phosphite from the initial addition product[1,96].

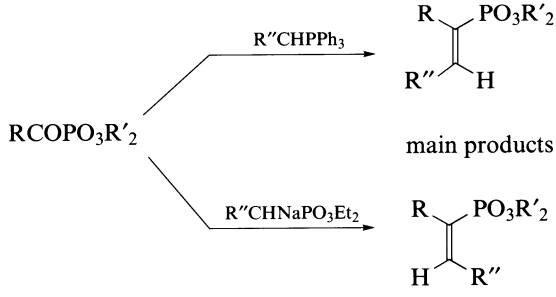
e. Ylides

i. Phosphorus ylides. Several papers report on aspects of Wittig reactions of acylphosphonates. Methylenetriphenylphosphorane reacts with aliphatic and aromatic acylphosphonates with the formation of vinylphosphonates which can be hydroborated to give 2-hydroxyethylphosphonates (equation 63)[104].



(63)

Further work showed that stabilized ylides can also react with acylphosphonates. Ethoxycarbonyltriphenylphosphorane and triethyl phosphonoacetate carbanion (Horner–Emmons reagent) give trisubstituted vinylphosphonates of the opposite stereochemistry as main products (equation 64)[105].

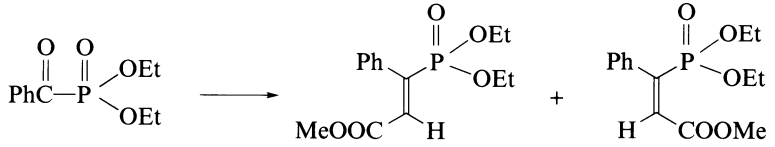


(64)

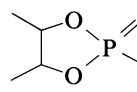
Earlier it was shown that by the use of cyclic phosphonates it is possible to modify the steric course of the Horner–Emmons–Wittig reaction[106]. Treatment of diethyl benzoylphosphonate with an acyclic and a five-membered cyclic phosphonate led to the formation of vinylphosphonates of opposite stereochemistry (equation 65)[107].

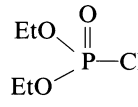
Ketotriphenylphosphoranes give the expected dialkyl 3-oxoalk-1-enylphosphonates **25** on reaction with aliphatic and aromatic acylphosphonates[108].

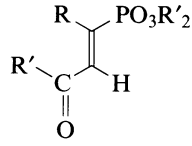
In contrast to saturated acylphosphonates, alk-2-enyl-1-oxophosphonates react with stabilized phosphoranes to yield (*E*)-dienones with a *cis* arrangement of the C=O and



(65)

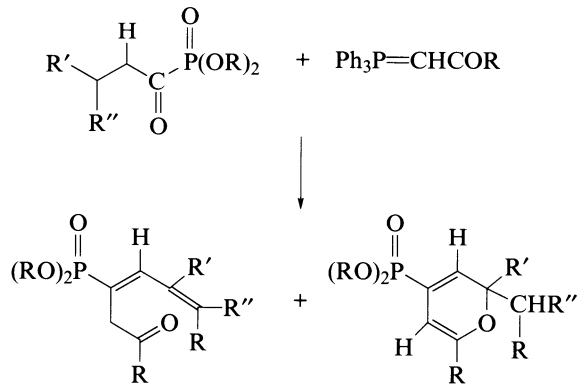
With  CH_2COOMe: 20% 80%

With  : 83% 17%



(25)

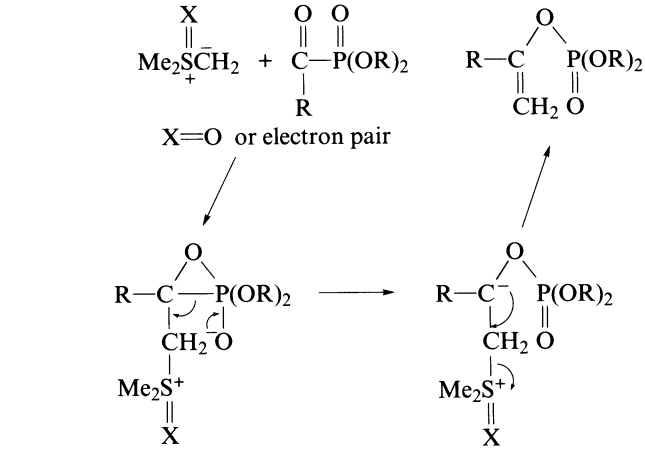
C=C bonds. The valence bond isomeric 2H-pyranylphosphonates are usually isolated, occasionally together with the non-conjugated isomeric dienones (equation 66)[109].



(66)

ii. Sulphur ylides. Acylphosphonates react with both sulphonium and sulphoxonium ylides to give enol phosphates (equation 67) and phosphonophosphates (equation 78). The ratio between the two products is determined by the nature of the acyl group. If the latter is not 'electron withdrawing' (i.e. not aromatic), the phosphonophosphate is the sole product[110].

iii. Azolium ylides. Azolium ylides react with aromatic and aliphatic dialkyl acylphosphonates to form six-membered azine derivatives. This work was described in a series of papers summarized in a review[111]. The work was initiated following a proposal on the mode of involvement of thiamine in the enzymatic decarboxylation of pyruvic acid (see



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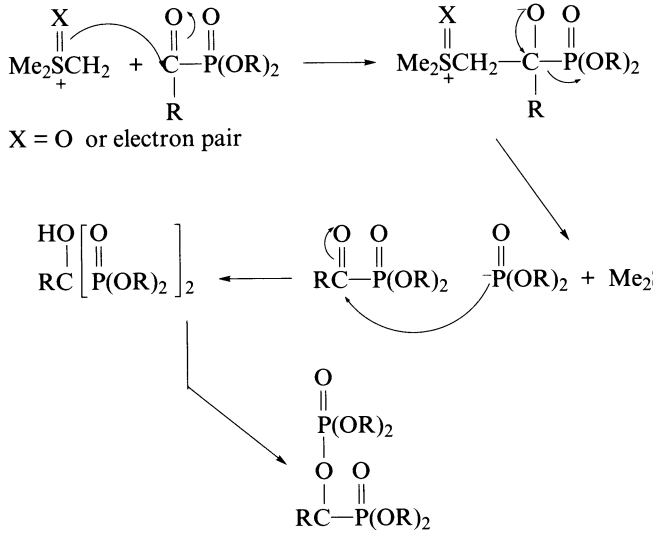
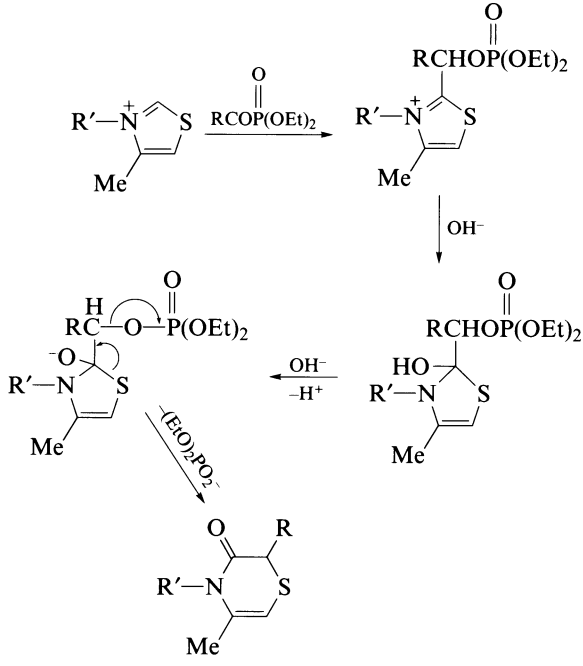


(68)

also Sections II. B. 6 and II. C. 3. c). This series of papers describes the reactions of thiazolium, thiadiazolium, oxazolium, oxadiazolium and imidazolium ylides. As an example, the reaction of a thiazolium ylide with an acylphosphonate yielding, after the elimination of diethyl phosphate, an oxodihydrothiazine derivative is shown in equation 69.

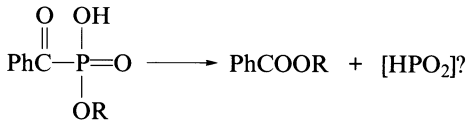
f. Hydrazoic acid. Study of the reaction of hydrazoic acid with a number of aroylphosphonates (Schmidt reaction) showed the formation of a number of products. Depending on the nature of the aryl group, both the migration of the aryl and the diethylphosphono groups to the electron-deficient nitrogen are seen. For example rearrangement of diethyl benzoylphosphonate yielded formanilide (53%), diethyl *N*-phenylcarbamoylphosphonate (9%), aniline (14%) and diethyl benzoylphosphoramidate (3%). The results obtained so far indicate no synthetic value for this reaction[112].



(69)

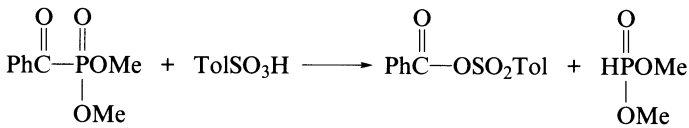
3. Fragmentation of acylphosphonates

a Thermal and acid-catalysed fragmentations. Benzoylphosphonic acid and methyl benzoylhydrogenphosphonate were reported to undergo fragmentation to benzoic acid and methyl benzoate, respectively[113]. Stoichiometry requires the formation of HPO_2 in these reactions; however, no direct evidence could be found for the formation of such low-coordination phosphorus species in these reactions (equation 70).



(70)

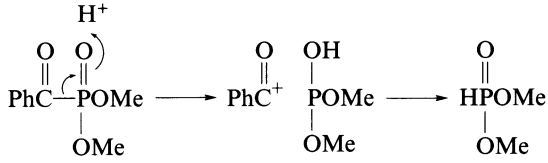
The reaction of dialkyl acylphosphonates with sulphonic acids was reported lead to sulphonic esters and acylphosphonic acids[114]. Reinvestigation of this reaction using ^{31}P NMR spectroscopy revealed that the reaction of equimolar amounts of dimethyl benzoylphosphonate and *p*-toluenesulphonic acid at room temperature gives dimethyl hydrogenphosphonate (equation 71). It was proposed that the by-product of this reaction, benzoic *p*-toluenesulphonic anhydride, reacts with the excess *p*-toluenesulphonic acid to yield *p*-toluenesulphonic anhydride and benzoic acid. Heating these two compounds with



(71)

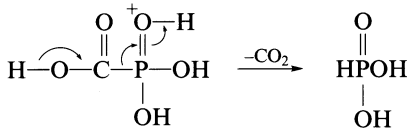
dimethyl phosphonate yielded methyl *p*-toluenesulphonate and methyl benzoate, respectively. A postulated by-product of these reactions is phosphenous acid (HPO_2).

Quantum mechanical calculations by the MNDO/H method that were carried out on dimethyl benzoylphosphonate and its protonation products showed that the preferred site of protonation of dimethyl benzoylphosphonate is the P=O oxygen, and that protonation at this site is followed by C—P bond breaking, with zero energy of activation, leading to dimethyl phosphite and benzolium cation (equation 72)[115].



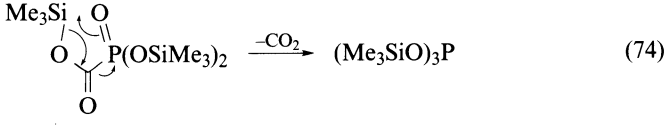
(72)

Phosphonoformic acid undergoes acid-catalysed decarboxylation to phosphorous acid under relatively drastic conditions (equation 73)[116].



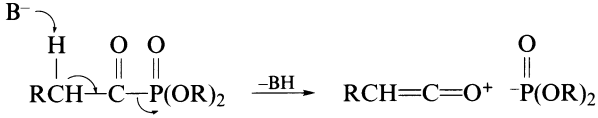
(73)

A similar reaction occurs much more readily with tris(trimethylsilyl) phosphonoformate, which undergoes spontaneous fragmentation to tris(trimethylsilyl) phosphite. A cyclic mechanism was proposed for this reaction (equation 74)[117]. This reaction was utilized in nucleoside chemistry for the preparation of nucleoside hydrogenphosphonates and related derivatives[117].



(74)

b. Base-catalysed fragmentations. Treatment of acylphosphonate diesters with anydrous base (e.g. butyllithium or sodium hydride) resulted in the formation of *gem*-bisphosphonates, $RC(OH)(PO_3R'_2)_2$[105,118]. This was interpreted as a unimolecular fragmentation of the acylphosphonate to form a ketene and dialkyl phosphite anion, which then adds to the carbonyl of a second molecule of dialkyl acylphosphonate (equation 75).

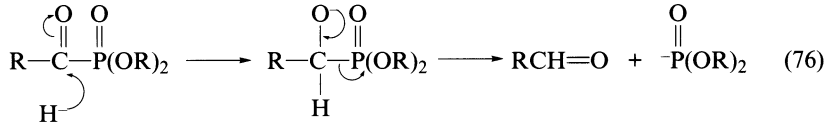


(75)

4. Reductions of acylphosphonates

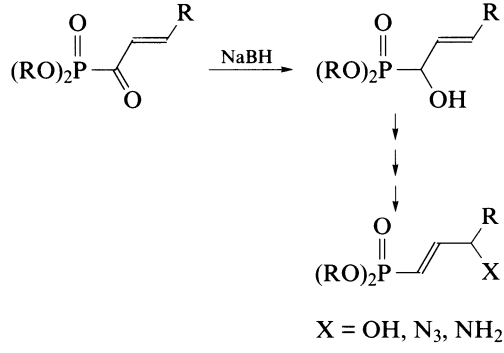
a. Reduction to hydroxyphosphonates. Dialkyl acylphosphonates have been reduced to α-hydroxyphosphonates by sodium borohydride[119], alumimium isopropoxide[96], activated zinc in acetic acid[96] and diborane in tetrahydrofuran[21]. The last method is

particularly convenient and gives pure products quantitatively. Treatment of diethyl benzoyl phosphonate with lithium triethylborodeuteride gave the corresponding α-deuterio-α-hydroxyphosphonate[120]. The same paper reports asymmetric reduction of the same acylphosphonate by an optically active borohydride derived from α-pinene and 9-BBN. Since α-hydroxyphosphonates hydrolyse easily to the corresponding carbonyl compounds (equation 76), this reaction has been suggested as a synthetic approach to aldehydes[119].



(76)

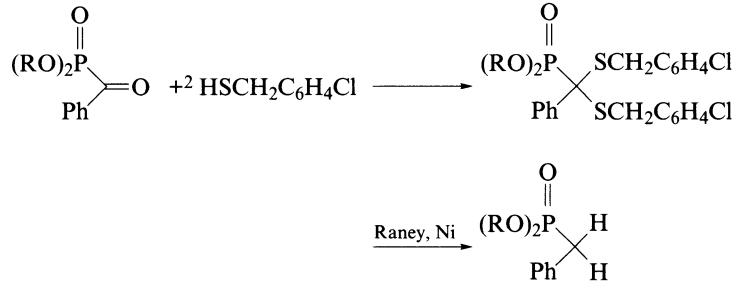
Reduction of the benzoylphosphonate anion and its monomethyl ester by sodium borohydride gave the corresponding α-hydroxyphosphonates[3]. Reduction of an α,β-unsaturated acylphosphonate by sodium borohydride under carefully controlled conditions (0–5 °C, pH 6–7) was one of the possible synthetic routes to the corresponding α-hydroxy α,γ-unsaturated phosphonates, which served as starting materials towards 3-aminoalk-1-enylphosphonic acids (equation 77)[121].



(77)

X = OH, N_3, NH_2

b. Reduction to alkylphosphonates. The keto group in dimethyl benzoylphosphonate could be reduced to methylene through conversion to di-*p*-chlorobenzyl thioketal and desulphurization of the latter by Raney nickel (equation 78)[96].



(78)

The thiocarbonyl group in *S*-methyl diisopropoxyphosphinyl methanedithioate was reduced to a methylene group, with cleavage of the S-Me bond, by sodium borohydride in refluxing MeCN (equation 79)[122].

$$(RO)_2P(O)C(O)SMe \xrightarrow{NaBH_4\text{–}MeCN} (RO)_2PCH_2SH(=S) \quad (79)$$

c. Reductive amination of acylphosphonates. Treatment of acylphosphonic acids in aqueous ammonia solution with sodium borohydride gave α-aminoalkylphosphonic acids (equation 80); see also pyridoxamine-induced transamination : in Section II. B. 6 and equation 45)[123]. Alternatively, the same reductive amination can also be carried out using dimethylamine–borane and ammonia[18].

$$RC(O)P(O)(OH)_2 \xrightarrow{NaBH_4\text{–aq. } NH_3} RC(H)(NH_2)P(O)(OH)_2 \quad (80)$$

5. Oxidations of acylphosphonates

The Baeyer–Villiger oxidation of dialkyl acylphosphonates was shown to provide a convenient entry to acylphosphates (equation 81)[124]. The reaction has been shown to constitute a migration of dialkoxyphosphonyl group to an electron-deficient oxygen[124].

$$RC(O)P(O)(OR)_2 \xrightarrow{H_2O_2 \text{ or } RCO_3H} RC(O)OP(O)(OR)_2 \quad (81)$$

6. Photochemical reactions of acylphosphonates

Irradiation of a series of dialkyl (methyl, ethyl, 2-propyl and 2-butyl) acetylphosphonates in benzene caused them to rearrannge to half esters of β-ketophosphonates (equation 82). High yields were obtained only with 2-propyl and 2-butyl esters, while dimethyl and diethyl esters gave such products only in low yields, in addition to dialkyl phenylphosphonates, resulting from reaction with the solvent. No results were reported from longer chain alkanoylphosphonates[125].

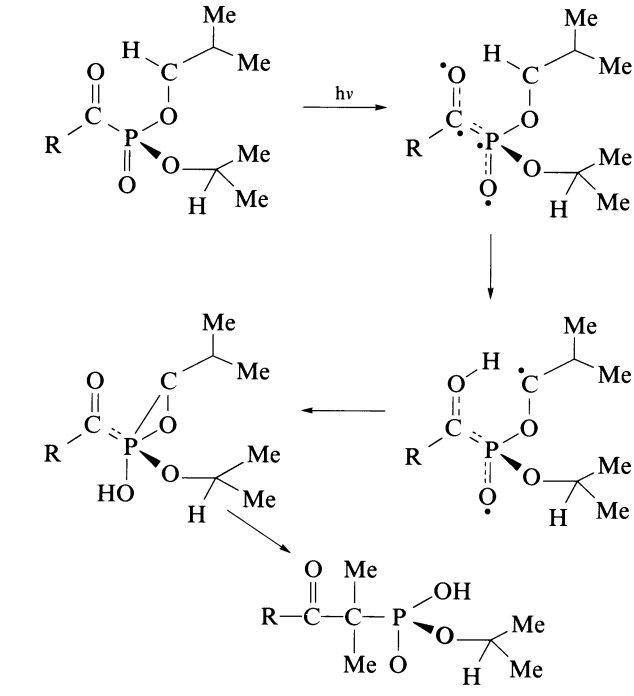
A different kind of reaction is observed in case of the photochemical and thermal reaction of an α-diazo-β-methoxycarbonyl acylphosphonate. The carbene formed after the loss of nitrogen rearranges to a ketene, by exclusive migration of the phosphoryl group (equation 83)[126].

7. Reactions of acylphosphonates with transition metals and complex formation

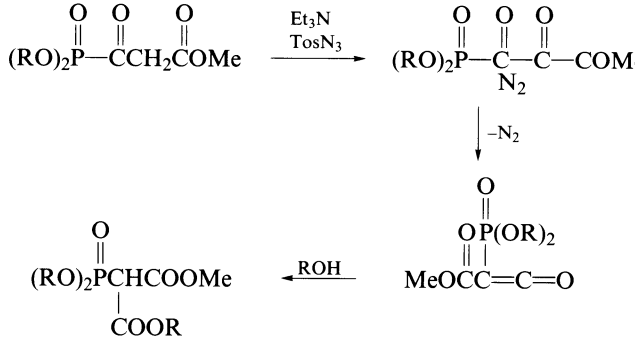
a. Palladium-catalysed decarbonylation. Aroyl- and alkanoylphosphonates undergo decarbonylation to aryl- and alkylphosphonates ($RCOPO_3R_2 \rightarrow RPO_3R_2$), respectively, in refluxing toluene in the presence of a catalytic amount of *cis*-$[(PdMe_2(PMePh_2)_2]$[127]. The yields of the arylphosphonates are much higher than those of the alkylphosphonates. A metathesis reaction:

$$RCOPO_3R_2 + R'COPO_3R'_2 \rightleftharpoons RCOPO_3R'_2 + R'COPO_3R_2$$

precedes the decarbonylation. More recently, the isolation of an intermediate of this reaction was reported[128]. In order to ascertain whether the isolated complex is indeed involved

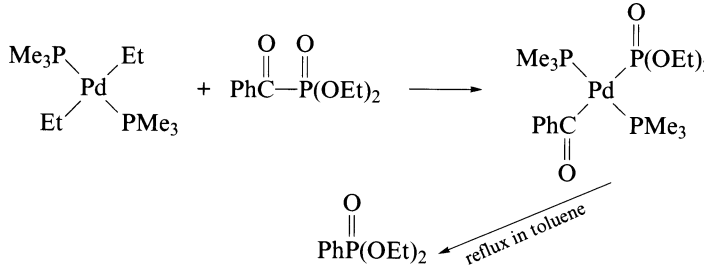


(82)



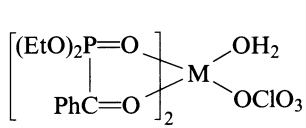
(83)

in the reaction, it was reacted with a five fold excess of diethyl benzoylphosphonate. This reaction gave the expected phenylphosphonate in 56% yield (equation 84).



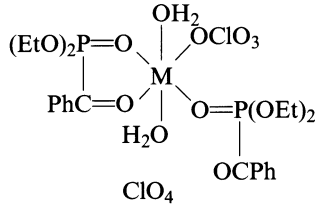
(84)

b. Transition metal complexes of acylphosphonates. Complexes (2:1) of diethyl benzoylphosphonate with metal perchlorates were synthesized and characterized by spectroscopic methods. In complexes of Fe, Co and Zn, both diethyl benzoylphosphonate molecules are bound in a bidentate manner, whereas in Mn and Ni complexes one benzoylphosphonate coordinates as bidentate, while the second ligand is unidentate (**26** and **27**)[129]. In contrast, diethyl acetylphosphonate is able, presumably because of lesser steric requirements, to form tridentate complexes with Mn, Fe, Co, Ni and Zn[130].



$(ClO_4)_n$

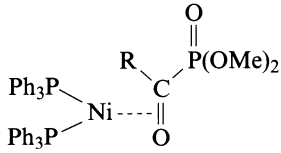
(26)



ClO_4

(27)

The reaction of both aromatic and aliphatic acylphosphonates with zerovalent nickel was shown to yield η^2-(CO)-type complexes (**28**)[131]. These complexes undergo exchange reaction of the acylphosphonate ligand in solution. Judging from the π-coordinating ability of acylphosphonates towards nickel (0), the electronegativity of the dimethyl phosphoryl group was estimated to be equal to that of the CF_3 group. This is in agreement with the results obtained from ^{17}O NMR spectral examination of acylphosphonates and rate and equilibrium data from hemiketal formation of acylphosphonates (see Sections II. A.3.b.iv. and II.C.2.a.i).



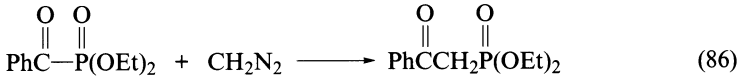
(28)

8. Other reactions involving the carbonyl group

a. Conversion of aroylphosphonates into benzylic α,α-difluorophosphonates. This conversion could be carried out using diethylaminosulphur trifluoride (DAST) (equation 85)[61].

(85)

b. Reactions of acylphosphonates with diazomethane. Diethyl benzoylphosphonate is converted by diazomethane into diethyl phenacylphosphonate (equation 86)[132]. In contrast, diethyl isobutyrylphosphonate was reported to yield an epoxyphosphonate as an additional product[133].



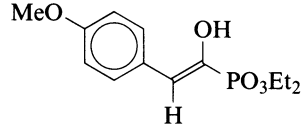
(86)

III. ENOLS, THIOENOLS AND ENAMINES RELATED TO ACYLPHOSPHONATES AND THEIR DERIVATIVES

A. Enols Derived from Acylphosphonates

1. Structure

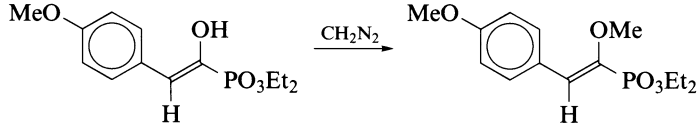
The proportion of enols in simple aliphatic acylphosphonates is too small to observe by ^{31}P NMR spectroscopy. Dialkyl arylacetylphosphonates exist as predominantly enol tautomers[58,133,134], which resonate at 13–16 ppm in the ^{31}P NMR spectrum (in one study the keto tautomer was found in the aqueous extract and showed a signal at $\delta^{31}P \approx -3$ ppm)[58]. The enol tautomer of diethyl *p*-anisylacetylphosphonate (**29**) has been shown by X-ray crystallography to possess the *E* structure[133]. The keto–enol tautomer ratios of a large number of dialkyl aryl- and pyridylacetylphosphonates have been determined by ^{1}H NMR[135]. The keto to enol ratio of dimethyl phenylacetylphosphonate was found to depend on the medium. Examination of the ^{31}P NMR spectrum of this compound in acetone showed a keto to enol ratio of 17:83, whereas in deuteriochloroform a ratio of 7:93 was found[136].



(**29**)

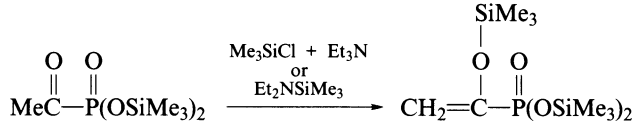
2. Formation and reactions

Diazomethane converts the enol derived from diethyl *p*-anisylacetylphosphonate (as other arylacetylphosphonates) into the corresponding methyl enol ether (equation 87).



(87)

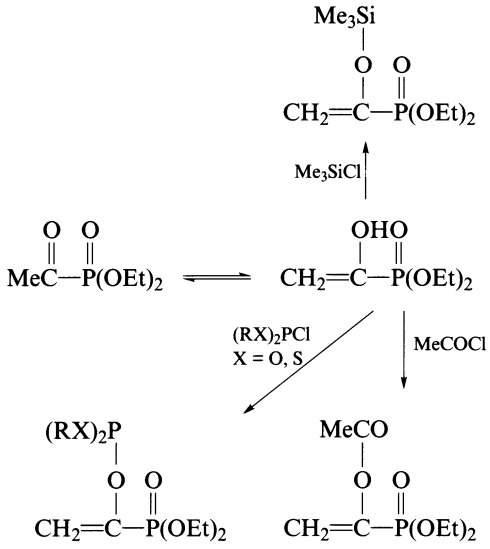
The synthesis of 1-bis(trimethylsilyl)phosphinyl-1-trimethylsilyloxyvinylphosphonate (**30**) was studied thoroughly, because this compound is a starting material to a diphosphorus analog of phosphoenol pyruvate (equation 88)[46]. It was found that bis(trimethylsilyl) acetylphosphonate can be silylated by using either chlorotrimethylsilane with triethylamine or *N*,*N*-diethyl-*N*-(trimethylsilyl)amine.



(**30**) (88)

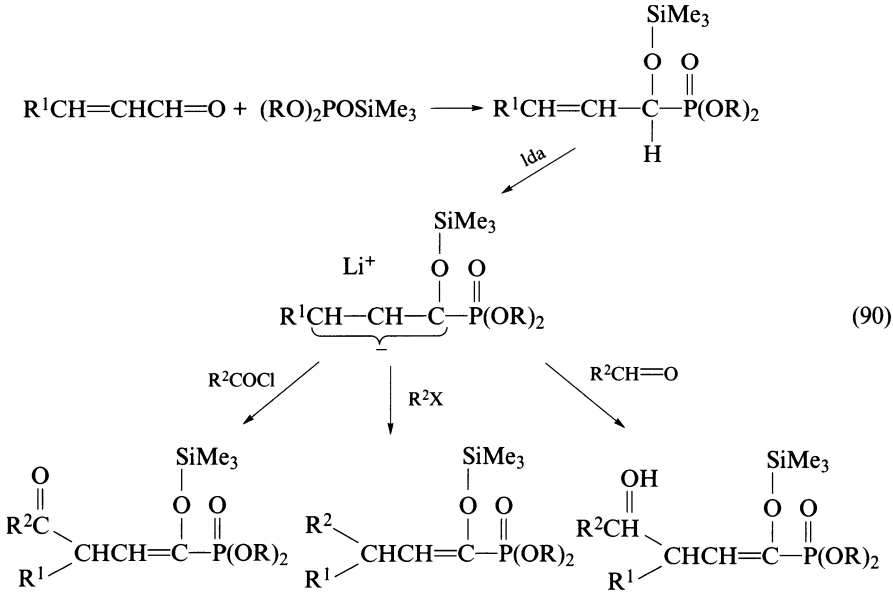
In another study chlorotrimethylsilane alone was reported to convert dimethyl acetylphosphonate into the trimethylsilyl enol ether[137]. This is a general type of reaction,

applicable to other electrophilic reagents, such as diethyl phosphochloridite (or its thio analogue) or acetyl chloride (see equation 89).



(89)

An indirect method for obtaining 1-dialkoxyphosphinyl-1-trimethylsilyoxyvinylphosphonates is through the addition of dialkyl trimethylsilyl phosphite to α,β-unsaturated aldehydes. When the initial β,γ-unsaturated phosphonates were treated with lithium diisopropylamide (lda) followed by an electrophile such as an alkyl halide, acyl halide or aldehyde, the corresponding γ-substituted silyl enol ethers resulted (equation 90)[138].

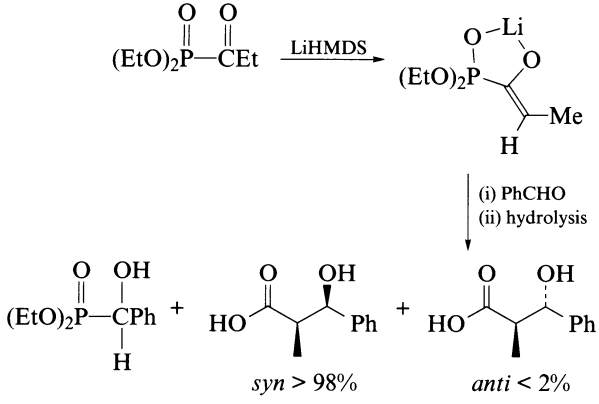


(90)

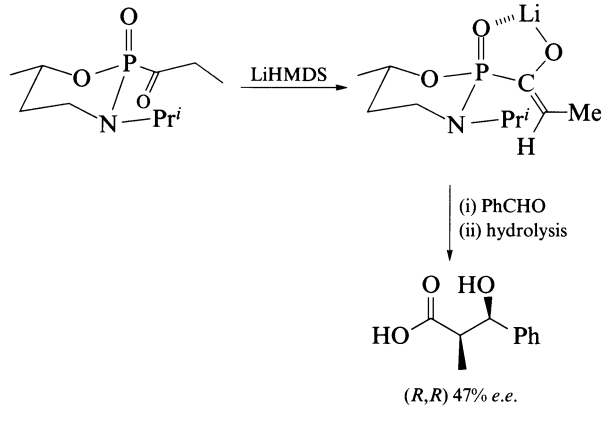
1-Acetoxyvinylphosphonates are formed as the main products (along with acylphosphonates as byproducts) in the reactions of dialkyl phosphite with acetic anhydride in MeCN, in the presence of chlorides of transition metals such as iron (II), iron (III) or cobalt. The same chlorides also catalyse the transformation of acylphosphonates into enol acetates by treatment with Ac_2O in MeCN[139].

When the preparation of alkali metal enolates derived from alkanoylphosphonates was attempted by treatment with strong anhydrous bases such as lithium diisopropylamide or sodium hydride, the formation of phosphate phosphonate-type products was observed. This was interpreted in terms of fragmentation of the enolate formed in the first step to ketene and dialkyl phosphite anion (equation 75), and addition of the latter to the carbonyl group of an unreacted acylphosphonate molecules to form a bisphosphonate. Such molecules are known to rearrange to phosphate phosphonates[105,118].

In contrast, reaction of diethyl propionylphosphonate with lithium bis-(trimethylsilyl)amide (LiHMDS) at –78 °C gave the expected enolate as evidenced by its highly diastereoselective condensation with benzaldehyde, leading to the formation of 3-hydroxy-2-methyl-3-phenylpropionic acid (equation 91)[140]. An attempt was made to develop this concept to enantioselective aldol condensation. However, condensation of a cyclic chiral propionylphosphonamidate (**31**), synthesized from (*S*)-*N*-isopropyl-4-aminobutan-2-ol, with benzaldehyde yielded 3-hydroxy-2-methyl-3-phenylpropionic acid in disappointingly low 47% *e.e.* (equation 92)[141].



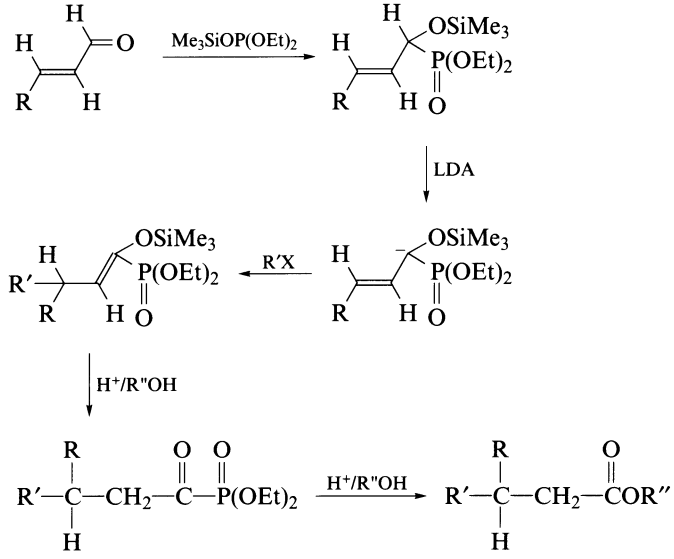
(91)



(92)

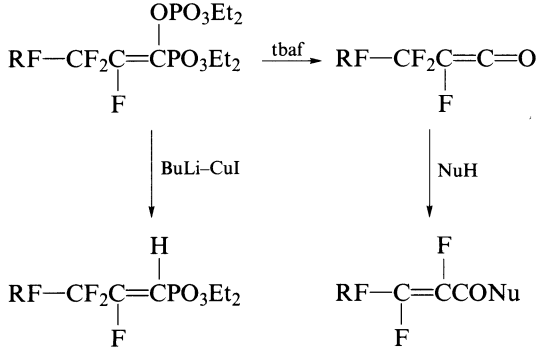
Silylated 3-amino-1-hydroxypropane-1,1-bisphosphonic acid was shown to rearrange thermally to a silyl enolate, which could be converted into the corresponding acylphosphonate (see equation 40)[14].

Reaction of α,β-unsaturated aldehydes with diethyl trimethylsilyl phosphite was used for the synthesis of chain-lengthened esters. Alkylation of the α-silyloxy-β,γ-unsaturated phosphonate with lithium diisopropylamide (lda) and an alkyl halide occurs at the γ-position with migration of the double bond to the α,β-position. The silyloxyenolate could isolated in this reaction. Acide-catalysed alcoholysis leads to the carboxylic ester through the acylphosphonate (equation 93)[142].



(93)

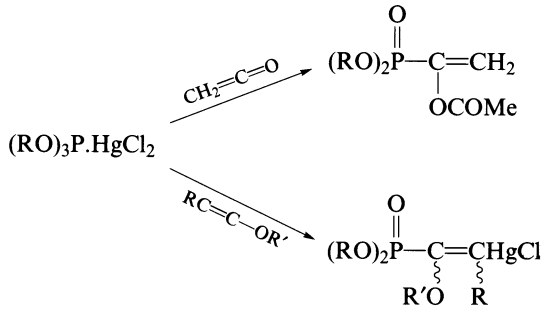
Enolphosphate phosphonates derived from perfluoroalkanoylphosphonates have a number of synthetic uses. Reactions of such compounds with nucleophiles such as amines or alcohols in the presence of catalytic amounts of tetrabutylammonium fluoride (tbaf) gave α,β-unsaturated perfluorocarboxylic acid derivatives, presumably via a ketene type intermediate (equation 94)[143]. When a primary amine was employed as the nucleophile α,β-unsaturated amides were formed, which could be converted into fluorinated pyrimidinones by treatment with urea. On the other hand, butylcopper(I) reagent reduces such



(94)

enolphosphate phosphonates to (*Z*)-1*H*-perfloro-1-alkenylphosphonates via a single electron-transfer mechanism[144].

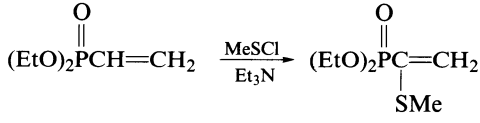
2-Mercurated 1-acyloxy or 1-alkoxy-vinylphosphonates have been synthesized by the reaction of trialkyl phosphite–mercury (II) chloride complexes with ketene[145] or alkynyl ethers[146], respectively (equation 95).



(95)

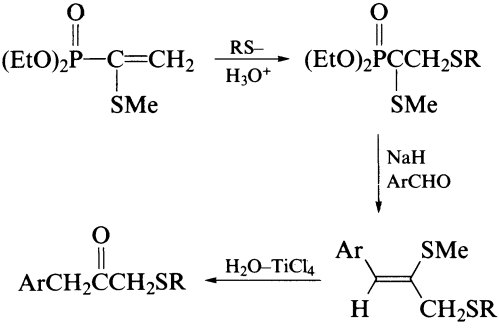
B. Enethiols Derived from Acylphosphonates

Diethyl 1-methylmercaptovinylphosphonate could be obtained by a number of methods[147]. The method shown in equation 96 is especially suitable for large-scale preparations[148].



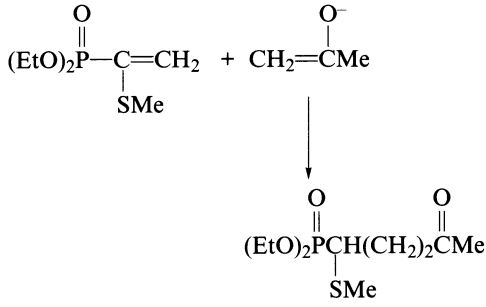
(96)

Enethiols are reactive molecules and therefore useful starting materials in syntheses. They are acyl anion equivalents and good Michael acceptors. Addition of a thiol to the double bond, followed by Horner–Wittig reaction and then hydrolysis, constitutes a regioselective synthesis of α-sulphenyl ketones (equation 97).



(97)

Carbon nucleophiles can also add to the double bond. For example, addition of the enolate derived from acetone leads to a δ-ketophosphonate, which can be viewed as a masked form of a 1,4-dicarbonyl compound (equation 98)[149].



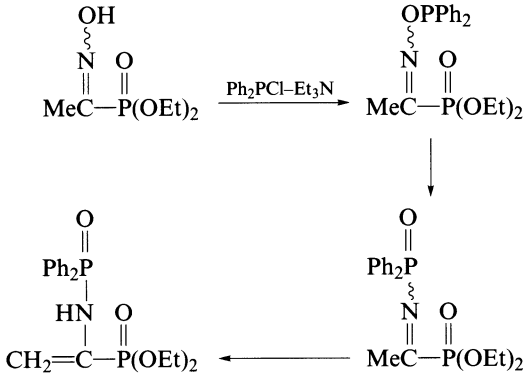
(98)

C. Enamines Derived from Acylphosphonates

1. Formation and synthesis

Enaminophosphonates were obtained by adding diethyl phosphite to ynamines[150] and in the dehydrogenation of α-aminophosphonates[151].

The enamine tautomer was obtained exclusively when a hydroxyiminophosphonate derived from acetylphosphonate was treated with chlorodiphenylphosphite (equation 99)[152]. The enamine was identified by X-ray crystallography and NMR spectroscopy, $\delta^{31}P$ = 12.4 and 18.7 ppm (J_{PP} = 29.3 Hz). Analogous compounds derived from non-enolizable acylphosphonates gave imines which showed J_{PP} = 60–90 Hz.

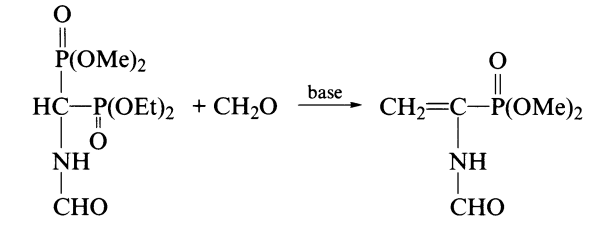


(99)

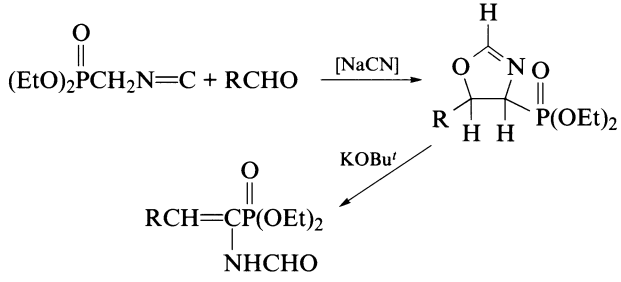
Enaminophosphonates were also synthesized by the Horner–Wittig reaction of *N*-substituted aminomethanebisphosphonates. The products were obtained as mixtures of *E*- and *Z*-isomers (equation 29)[58]. Analogously, the Horner–Wittig reaction of *N*-formamidomethylenebisphosphonate with formaldehyde leads to α-(*N*-formamido)-vinylphosphonate (equation 100)[153].

A number of synthesis entries to enamides have been reported. Reaction of an isocyanomethylphosphonate with a catalytic amount of cyanide gave an oxazoline, which was opened by potassium *tert*-butoxide to a formamidovinylphosphonate (equation 101)[154].

Another more general approach to enamides derived from an acetylphosphonate is based on 1,2-dichloroethyl isocyanate. This compound underwent Arbuzov reaction with methyl phosphorodichloridite to yield the 2-chloroethyl compound which, when treated

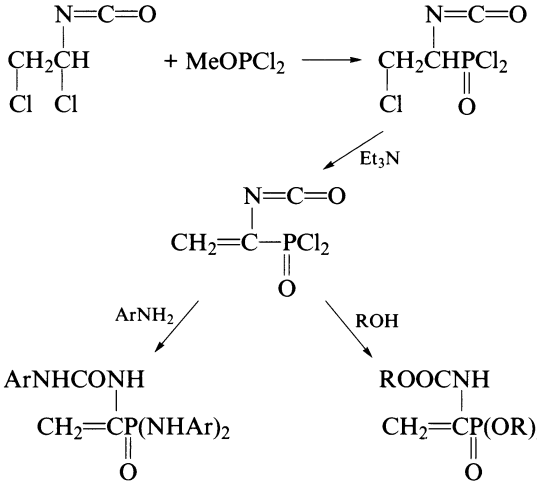


(100)



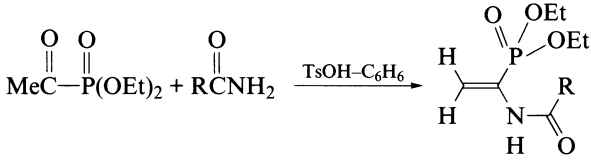
(101)

with Et_3N, lost HCl to give 1-dichlorophosphonyl isocyanate. The latter reacted with amines or alcohols simultaneously at the phosphorus and at the isocyanate functions to yield ureidophosphonediamidates and carbamoyl dialkyl phosphonates (equation 102)[155].



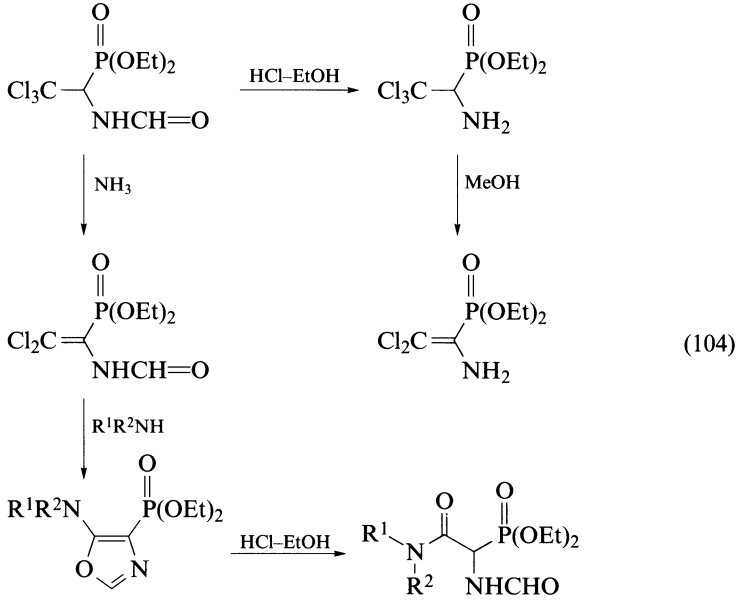
(102)

The simplest apparent approach to enamidophosphonates, albeit in modest yields, (12–20%) is the anhydrous acid-catalysed condensation of amides with diethyl acetylphosphonate (equation 103)[156].



(103)

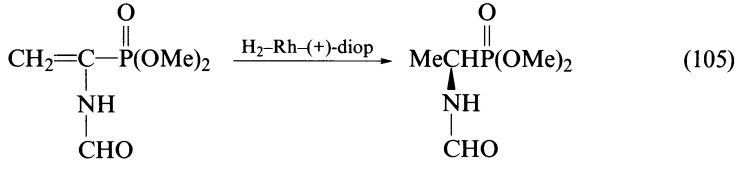
A special class of enamino and enamidophosphonates is available from 1,2,2,2-tetrachloroethylformamide (obtained from chloral and formamide) and triethyl phosphite. The resulting formamidophosphonate may be hydrolysed to the corresponding aminophosphonate. Base treatment of the amido and aminophosphonate leads to enamido- or enamino-phosphonates, respectively[157]. The former can be converted into oxazoles (or thiazoles[158]), which in turn can be converted into phosphonoglycine amides (equation 104)[159].



(104)

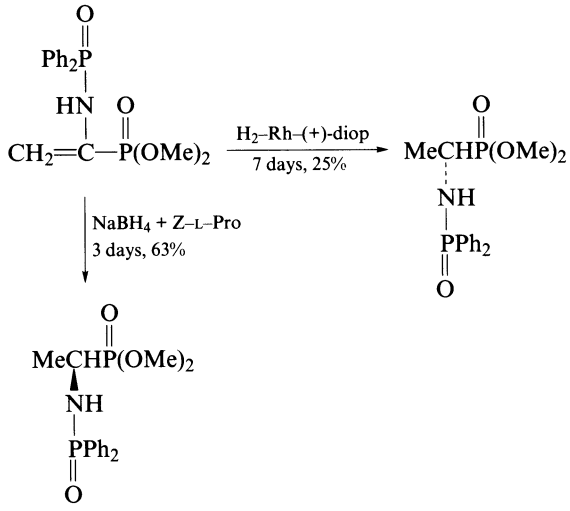
2. Reactions

α-Enamidophosphonates served as starting materials in attempted asymmetric syntheses of α-aminophosphonates. Thus, hydrogenation of α-(*N*-formamido)vinylphosphonate in the presence of the rhodium complex of (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1, 4-bis(diphenylphosphino)butane [(+)-diop] resulted in the formation of (*R*)-(–)-α-(*N*-formamido)ethylphosphonate in an enantiomeric excess of 76% (equation 105)[153].



(105)

In contrast, reduction of α-(*N*-diphenylphosphinylamino)vinylphosphonate in the presence of the same catalyst proceeded very slowly and gave the saturated product with a low enantiomeric excess (*e.e.* ≈ 3% of the *S*-isomer) (equation 106). Reduction of the same enamidophosphonate with $NaBH_4$ in the presence of *N*-benzyloxycarbonyl-L-proline gave the opposite aminophosphonate enantiomer[152] in a higher excess.



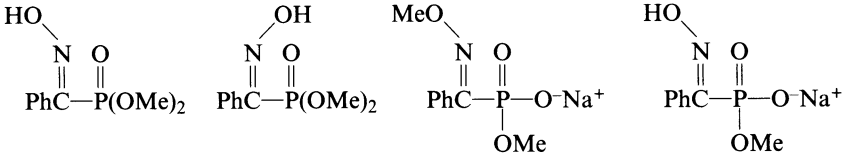
(106)

IV. IMINE DERIVATIVES OF ACYLPHOSPHONATES

A. Structure

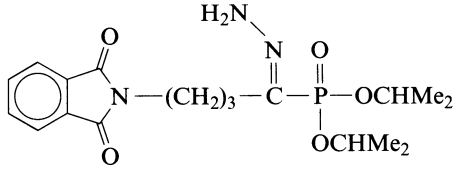
1. Crystallography

The structures of a number of hydroxyiminophosphonates were determined by single-crystal X-ray crystallography. These include dimethyl (*E*) and (*Z*)-α-hydroxyiminophosphonate (**32** and **33**), methyl sodium (*E*)-α-methoxyiminophosphonate (**34**)[160] and methyl sodium (*E*)-α-hydroxyiminophosphonate (**35**)[161]. The bond lengths, bond angles and torsion angles all fall within the reasonable range expected for similar compounds. The results indicate that there is steric crowding between the oxime OH group and the phosphorus oxygen atoms in the (*Z*)-isomer and between the oxime OH and the phenyl ring in the *E*-isomer. The crystal structures analyses reveal that there is a fair amount of conformational flexibility, which should be manifested in the solution structures of the molecules. There is no clear evidence as to the existence of intramolecular hydrogen bonds between the N—OH···O=P groups.

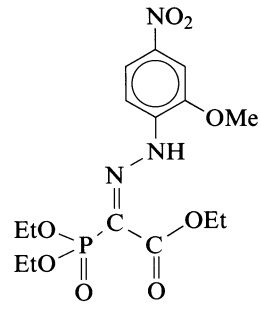


(*E*)-oxime (**32**) (*Z*)-oxime (**33**) (*E*)-oxime ether (**34**) (*E*)-oxime anion (**35**)

In the hydrazone series the structures of both diisopropyl 1-hydrazono-4-phthalimidobutyl-1-phosphonate (**36**)[162] and of the 2-methoxy-4-nitrophenylhydrazone derived from triethyl oxophosphonoacetate (**37**)[63], were found to be *E* by X-ray crystallography.



(36)



(37)

The separation of (*E*)- and (*Z*)-tosylhydrazones has been reported[33]. In a series of acylphosphonate phenylhydrazones, mixtures of geometrical isomers were observed and structures were assigned based on infrared data[52].

2. Theoretical

MNDO/H calculations were carried out on dimethyl (*E*) and (*Z*)-α-hydroxyiminophosphonates. These demonstrate the feasibility of forming intramolecular hydrogen bonds in (*Z*)-oximes, and their possible contribution to conformational preferences[160,161].

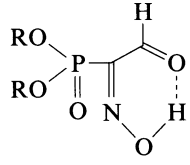
3. Spectroscopy

^{1}H NMR spectroscopy is not always useful as a diagnostic tool for revealing the presence of two isomers of oximes in a mixture of α-hydroxyiminobenzylphosphonates. However, in those cases in which two isomers are distinguishable, the P—O—Me proton signal of the *E*-isomer appeared at lower field, by approximately 0.05–0.08 ppm, than the corresponding signal of the *Z*-isomer[160]. In all cases examined, the (*E*)-oxime resonated at lower field than the (*Z*)-oxime in the ^{31}P NMR spectrum (see Table 4). This is consistent with the expected shielding effect of the phosphorus by the lone pairs of the oxime oxygen.

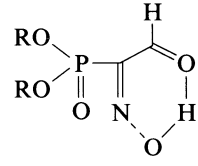
In addition to ^{31}P NMR measurements, ^{13}C NMR spectroscopy was also found to be a useful tool to assign steric structure in α-hydroxyiminophosphonates. The $^1J_{PC}$ coupling constants were found to be in range 150–160 Hz in (*Z*)-oximes, compared with 200–220 Hz (*E*)-oximes[164,165].

Geometrical isomerism in α-hydroxyiminophosphonamidates (established by X-ray crystallographically) was also correlated with their ^{31}P NMR spectra. *E*-isomers in this series have chemical shifts in the range 13–17 ppm[68].

The structures of some phosphorylated glyoxal oximes have been examined by NMR and IR spectroscopic methods[166]. These compounds may exist as two types of intramolecularly hydrogen-bonded species (**38**, **39**) or as intermolecularly hydrogen bonded molecules (not shown). It was concluded, on the basis of spectroscopic studies, that the *E*-form,

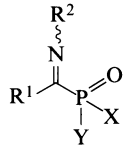


(**38**) (*E*)



(**39**) (*Z*)

TABLE 4. ^{31}P chemical shifts of some representative α-iminophosphonate derivatives



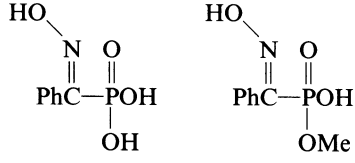
R^1	R^2	X	Y	δ(*E*) (ppm)	δ(*Z*) (ppm)	Solvent	Ref.
Me	OH	OMe	OMe	11.9	6.8	$CDCl_3$	158
Ph	OH	OMe	OMe	11.6	5.2	$CDCl_3$	160
Ph	OH	OEt	OEt	7.7	3.3	$CDCl_3$	160
Ph	OMe	OMe	OMe	10.1	5.7	$CDCl_3$	160
Ph	OH	OMe	NR_2[a]	13.7	9.1	$CDCl_3$	67
Ph	OH	OMe	NHtBu	12.8	–	$CDCl_3$	67
Ph	OH	OMe	ONa	6.4	1.8	D_2O	160
Ph	OMe	OMe	ONa	6.4	1.6	D_2O	160
Ph	NH_2	OMe	OLi	9.4	6.3	D_2O	160
FtPr[b]	NH_2	iPr	iPr	10.1	6.7	$CDCl_3$	160
Ph	Me	OMe	ONa	6.7[c]	–	D_2O	160
COOEt	H	OEt	OEt	2	–2	$CDCl_3$	163

[a] $R_2 = (CH_2CH_2)_2O$
[b] FtPr = 3-phthalimidopropyl.
[c] *E* stereochemistry not established.

in which there is an intramolecular hydrogen bond between the oxime OH and the aldehyde carbonyl, predominates in the equilibrium. Solvent and temperature have been shown to affect the position of the equilibrium.

4. Acidity

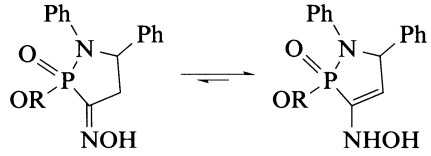
The pK_a values of dihydrogen (*E*)-α-hydroxyiminobenzylphosphonate (**40**) and of hydrogenmethyl (*E*)-α-hydroxyiminobenzylphosphonate (**41**) were determined by potentiometric titration and found to be $pK_{a_1} \approx 2.2$ and $pK_{a_2} \approx 6.1$ for the former and $pK_a \approx 2.1$ for the latter[167].



(**40**) (**41**)

5. Oxime–N-hydroxyenamine tautomerism

A series of α-hydroxyiminoazaphospholanes (**42**) prepared by addition of the dilithio-α-hydroxyiminophosphonates to benzalaniline have been shown to exist as the *N*-hydroxyenamines (**43**). The evidence for this structure is mainly based on ^{13}C and ^1H NMR



(42) (43)

spectral data[168]. Interestingly, the ^{31}P NMR chemical shifts and $^{1}J_{PC}$ coupling constants reported are also consistent with the oxime structure.

B. Synthesis

Three main synthetic approaches have been taken to α-iminophosphonates, as described below.

1. *Conversion of acylphosphonate carbonyl groups into imines*

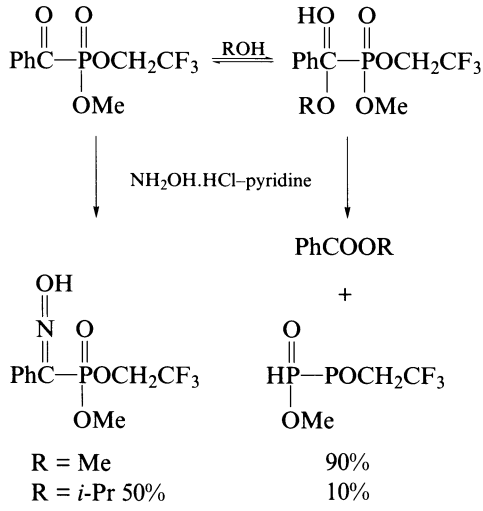
In contrast to most other nucleophiles (e.g. amines, alkoxides), hydroxylamine and hydrazine derivatives may also react with acylphosphonates as with ketones, and lead to the formation of imines, although these reactions are often accompanied with C—P bond cleavage. The extent of this side-reaction depends on the reagents, reaction conditions and/or the groups linked to the phosphorus.

a. Oximes

i. Dialkyl α-hydroxyiminophosphonates. Since the formation of oximes on treatment of dialkyl acylphosphonates with hydroxylamine was first reported[169], this is the most general method for this class of compounds. The reaction almost always leads to mixtures of *E*- and *Z*-isomers which can be observed by ^{31}P NMR spectroscopy. The reactions are usually carried out by reacting hydroxylamine hydrochloride with the dialkyl acylphosphonate in the presence of base (pyridine) in an alcohol as solvent. If the reaction with hydroxylamine is monitored by ^{31}P NMR spectroscopy, it is possible to observe the appearance of a transient signal at around 20 ppm, presumably due to the tetrahedral reaction intermediate. At the end of the reaction the extent of C—P bond cleavage (leading to an ester or to hydroxamic acid and dialkyl hydrogen phosphonate) can be estimated by ^{31}P NMR from the intensity of the signal belonging to the latter. This method was applied successfully to the synthesis of α-hydroxyiminophosphonates derived from protected amino acids[170], which were subsequently incorporated into short peptides[171].

In the case of acylphosphonates esterified by strongly electron-withdrawing alkoxy groups (OCH_2CF_3 or OCH_2CCl_3), such C—P bond cleavage was found to be predominant in methanol[67]. It was shown that the C—P bond cleavage results from base-catalyzed collapse of the hemiketal initially formed. Consequently, when hemiketal formation was supressed (by employing a sterically hindered alcohol as solvent) the yield of the oxime could be raised (equation 107)[67]. The synthesis of oximes from hydrolytically unstable acylphosphonates was further improved and simplified by carrying out the reaction in dichloromethane in a one-pot procedure[67].

Another type of complication was observed when hexafluoro-2-propyl methyl benzoylphosphonate was treated with hydroxylamine in propan-2-ol. Instead of the expected product, methyl 2-propyl α-hydroxyiminobenzylphosphonate was isolated, probably as a result of exchange of POR groups after the formation of the hexafluoro-2-propyl oxime[10].



(107)

Oxime ethers have been synthesized (as mixtures of *E*- and *Z*-isomers) similarly to oximes, by reacting acylphosphonates with the respective *O*-methyl-[160] or *O*-benzylhydroxylamines[165,172,173]. Alternatively, treatment of diethyl α-hydroxyiminophosphonates with benzyl bromide in the presence of sodium methoxide in boiling methanol gave pure (*E*)-*O*-benzylhydroxyiminophosphonates in good yields[165].

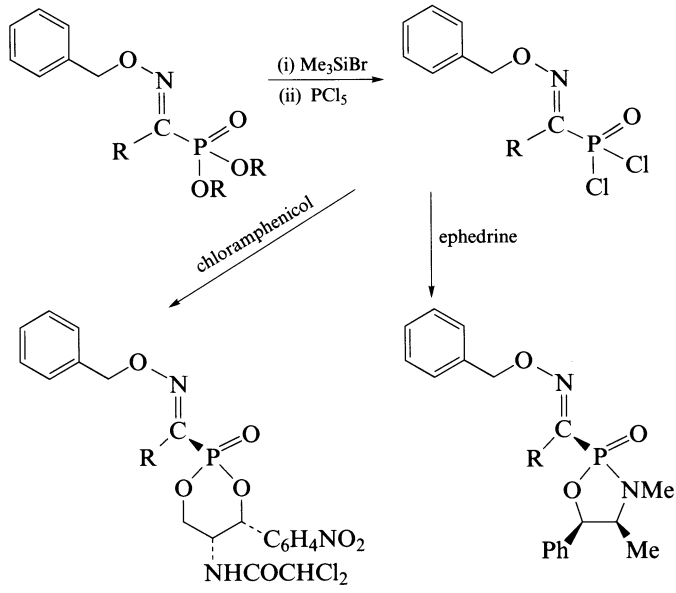
ii. Monoesters of α-hydroxyiminophosphonates. These can be obtained from the dialkyl α-hydroxyiminophosphonates, although in certain cases oximation of acylphosphonate salts or their monoesters was found to be preferable. Monodealkylation of dialkyl esters can be performed by sodium iodide or similar nucleophilic reagents. If basic nucleophiles such as amines or alkoxides are used, the dealkylation is usually preceded by $Z \rightarrow E$ isomerization. In contrast to the oximation of certain dialkyl acylphosphonates, which yielded predominantly (*Z*)-oximes, presumably owing to kinetic control, oximation of the corresponding acylphosphonate anions yielded (*E*)-isomers, presumably owing electrostatic repulsion of the N—OH and the P—O^- groups[67].

Methyl sodium (*Z*)-α-hydroxyiminobenzylphosphonate was separated from the *E*-isomers (**35**) by means of the cobalt (II) complex of the latter[161].

iii. α-Hydroxyiminophosphonic acids. α-Hydroxyiminophosphonic acid (**40**) was synthesized by bromotrimethylsilane-induced didemethylation of the corresponding dimethyl ester[174]. An experiment aimed at preparing α-methoxyiminobenzylphosphonic acid by the same method showed that this compound can exist in solution. On removal of the solvent, an exothermic decomposition led to benzonitrile and methyl dihydrogenphosphate[10].

iv. α-Oxyiminophosphonic dichlorides and oxyiminophosphonamidates. α-Benzyloxyiminoalkylphosphonic dichlorides were prepared by treatment of diethyl α-benzyloxyiminophosphonates with bromotrimethylsilane followed by phosphorus pentachloride. The dichlorides were converted into cyclic diesters by treatment with chloramphenicol or to cyclic ester amide by treatment with ephedrine (equation 108)[165].

α-Hydroxyiminophosphonamidates were obtained from acylphosphonamidates by treatment with hydroxylamine[68,69].



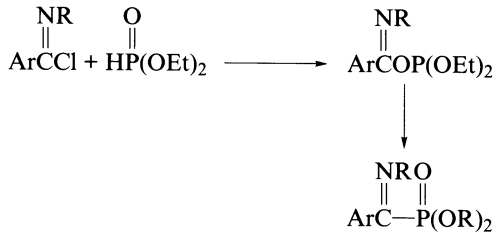
(108)

b. Hydrazones. There are several reports on the reactions of hydrazine derivatives with acylphosphonates. Phenylhydrazine[52], 2,4-dinitrophenyldrazine[4] and *p*-toluenesulphonylhydrazine[33,175,176] were reported to give mainly the corresponding hydrazones. In contrast, *N,N*-dimethylhydrazine was reported to give mixtures of *N,N*-dimethylhydrazones along with products of C—P bond cleavage, namely *N,N*-dimethylacylhydrazides[177]. A more recent paper reported the failure to obtain hydrazones in the reaction of dimethyl benzoylphosphonate with hydrazine or phenylhydrazine. Only the formation of benhydrazides was observed[162]. In contrast, no fission of the C—P bond can occur when hydrazine is reacted with methyl lithium benzoylphosphonate, since the ionized phosphoryl group cannot function as a leaving group. Monitoring the reaction of hydrazine with methyl lithium benzoylphosphonate by ^{31}P NMR spectroscopy showed the appearance of a transient signal at 16 ppm, probably due to the tetrahedral reaction intermediate. The reaction led to the formation of 65:35 mixture of *E*- and *Z*-isomers[162].

2. Phosphorylation of imine derivatives

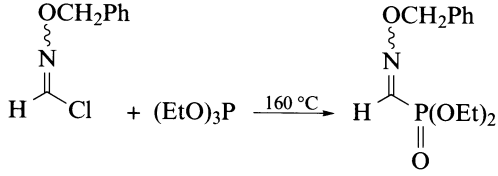
a. Imines. A series of aromatic imidoyl chlorides underwent the Arbuzov reaction with trialkyl phosphites to yield α-alkyliminobenzylphosphonates. Imidoyl chlorides were far less reactive than the corresponding acyl chlorides, therefore the reactions required high temperatures (120–160 °C) (equation 109)[178]. In contrast reaction of benzimidoyl chloride with diethyl hydrogen phosphite yielded benzimidoyl phosphite. This underwent thermal rearrangement to the isomeric phosphonate (equation 110)[179].

$$\underset{\|}{\overset{NR}{}}\!\!ArCCl + (RO)_3P \xrightarrow{120\text{–}160\ ^\circ C} \underset{\|\quad\|}{\overset{NR\quad O}{}}\!\!ArC{-}P(OR)_2 \qquad (109)$$



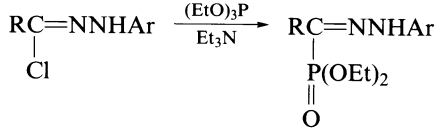
(110)

b. Oximes. Arbuzov reaction of *O*-benzylformhydroxamyl chloride was applied recently to the synthesis of diethyl benzyloxyiminomethylphosphonate (equation 111)[173].



(111)

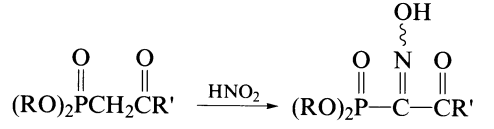
c. Hydrazones. The reaction of some acyl chloride phenylhydrazones with triethyl phosphite in the presence of triethylamine afforded the expected hydrazonophosphonates (equation 112)[180]. This reaction was interpreted in terms of nitrilimine formation in the first step, and its subsequent reaction with triethyl phosphite. However, since ethyl chloride formation was observed in the reaction, Arbuzov reaction of the hydrazonyl chloride cannot be excluded. Unfortunately, there is no report of an experiment without triethylamine.



(112)

3. Synthesis based on alkylphosphonates

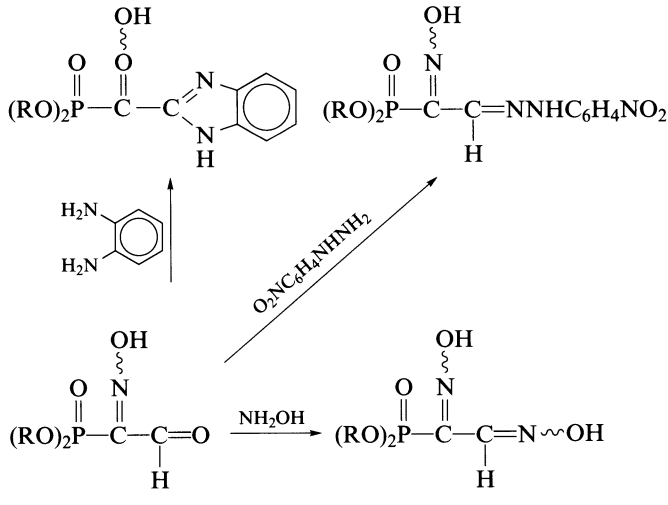
a. Oximes. Phosphorylacetaldehyde[181] and ketones[182] readily undergo nitrosation to afford the corresponding α-hydroxyimino-β-carbonyl phosphonates (equation 113). Such compounds have been reacted with carbonyl reagents such as *o*-phenylenediamine, *p*-nitrophenylhydrazine or hydroxylamine, to afford more complex α-hydroxyiminophosphonates (equation 114)[183].



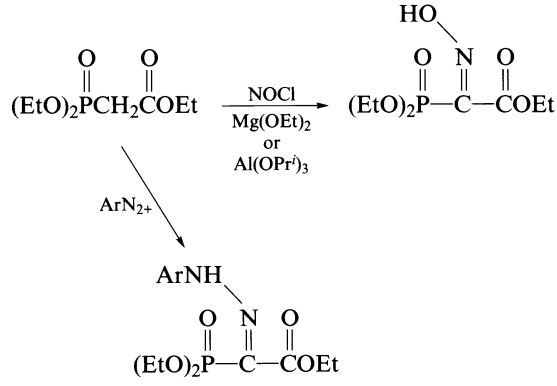
(113)

R' = H or Me

Further work showed that sodium or potassium derivatives of phosphonoacetic esters are not nitrosated by nitrous acid or by alkyl nitrites, but they can be converted into the corresponding oximes via their magnesium[163] or aluminum[184] derivatives (equation 115).

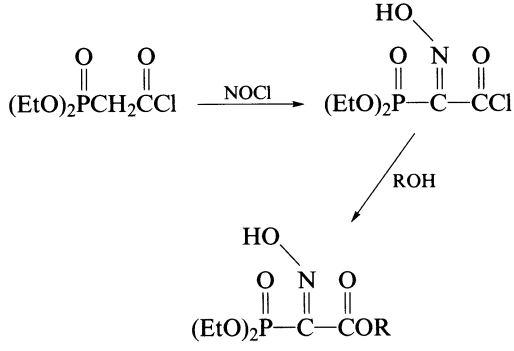


(114)



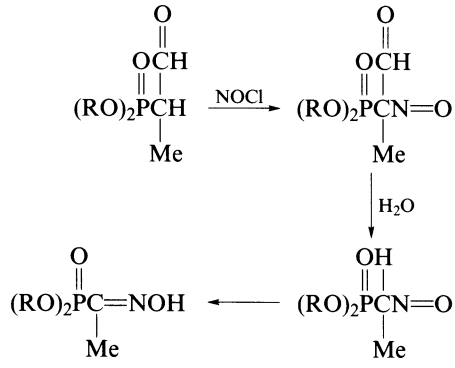
(115)

In contrast, diethoxyphosphinylacetyl chloride reacted with nitrosyl chloride without any catalyst and gave diethoxyphosphinyl hydroxyiminoacetyl chloride, which could be converted *in situ* into an ester by the addition of an alcohol (equation 116)[185].



(116)

An unusual reaction leading to an α-hydroxyiminophosphonate reported recently is based on 2-(diisopropoxyphosphinyl)propanal, which was nitrosated by nitrosyl chloride to give a nitrosoaldehyde. Hydrolysis of these compounds cleaved off the formyl group and led, through the nitroso tautomer, to the oxime (equation 117)[186].



(117)

b. Hydrazones. Reaction of triester of phosphonoacetate with aromatic diazonium salts gave hydrazonophosphonoacetates (e.g. **37**)[63].

C. Reactions

1. E–Z *Isomerization*

a. Oximes. From publications dealing with several series of α-hydroxyiminobenzylphosphonates, it appears that *E*-isomers are usually more stable than *Z*-isomers.

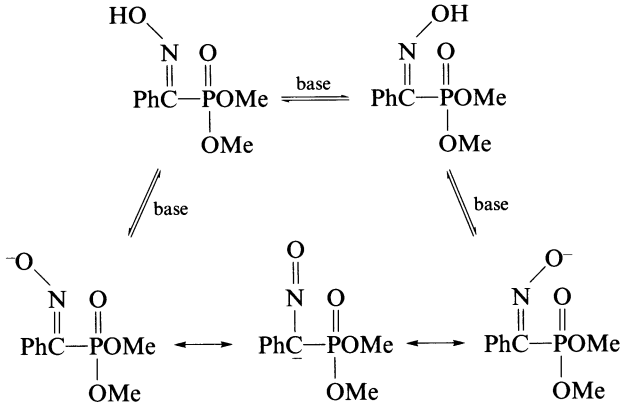
E–Z isomerizations are generally catalysed by heat, acid or base. Dimethyl (*E*)- and (*Z*)-α-hydroxyiminobenzylphosphonates were found to be in equilibrium at high temperature and under acidic or basic conditions[160]. The rate constants for acid-catalyzed $Z \rightarrow E$ conversions were determined for dimethyl α-hydroxyiminobenzylphosphonate and methyl α-hydroxyiminobenzylhydrogenphosphonate[187].

With regard the base-catalyzed $Z \rightarrow E$ isomerization, it was found that dimethyl α-hydroxyiminobenzylphosphonate isomerizes, presumably with involvement of the ionized oxime function in which the negative charge is delocalized on to the α-position relative to the phosphorus (equation 118)[160]. This assumption is supported by the observation that the analogous α-methoxyiminophosphonate, in which the ionization of the oxime is blocked, did not undergo $Z \rightarrow E$ isomerization under identical conditions[160]. Finally, methyl hydroxyiminobenzylphosphonate anion was resistant to attempted isomerizations under basic conditions. This was attributed to the lack of ability of the anionic phosphonate function to stabilize the negative charge at the adjacent α-position.

b. Hydrazones. Oxophosphonoacetate (*E*)-phenylhydrazone was reported to isomerize to the *Z*-isomer when heated in acetone solution[63].

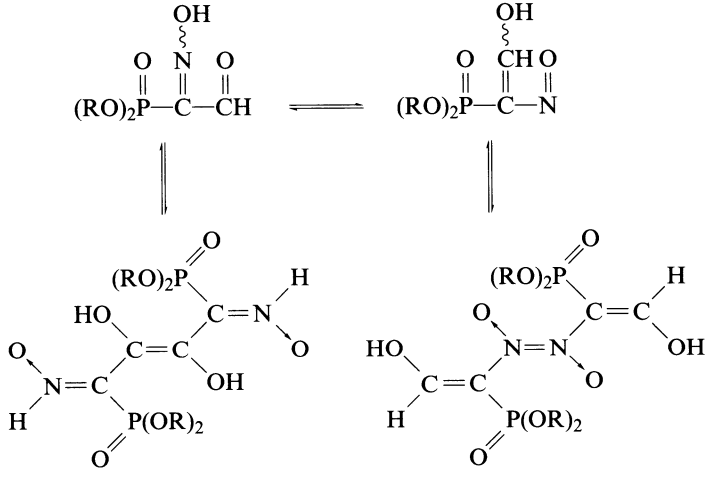
2. *Dimerization of glyoxal derivatives*

These compounds, obtained by nitrosation of diisopropyl phosphonoacetaldehydes, were found to exist as an equilibrium mixture containing (*E*)- and (*Z*)-oximes, and the



(118)

dimers, 1-(diisopropylphosphoryl)-1-nitrosoethen-2-ols and diisopropylphosphorylacetaldonitrones (equation 119)[188].



(119)

+ geometrical isomers

3. Reductions

a. Oximes

i. To aminophosphonates. Since phosphonate analogue of amino acids have been shown to possess biologically or economically important properties as pesticides, insecticides, herbicides, bactericides, enzyme inhibitors and receptor antagonists, considerable activity has been devoted to developing convenient methods for their synthesis. Among these, the reduction of α-hydroxyiminophosphonates to aminophosphonates has occupied a prominent place. Several reducing agents have been tested under different conditions. Initial attempts include the diborane reduction of α-methoxyiminophosphonates[169] and reduction of benzoylated oximes by aluminium amalgam[189].

Hydrogenation, using Raney nickel, was reported to give good yields, provided that it was conducted in ethanol under high pressure[135]. Previously, this method was reported to give low yields, in an undisclosed solvent[190].

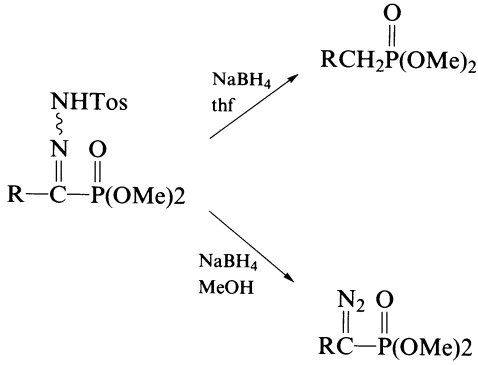
More recently reported reagents for this reduction include zinc in formic acid (yields of 40–70%)[191,192], Zn–Cu couple in aqueous ethanol (yield of 69%)[193] and $LiBH_4$–Me_3SiCl in dry thf (yields of 43–95%)[194].

ii. To hydroxyaminophosphonates. The reduction of a series of α-hydroxyiminoalkanephosphonates to hydroxyaminoalkanephosphonic acids in yields of 35–92% was reported by using borane–pyridine complex in ethanolic HCl solution[195]. Benzyloxyaminoalkanephosphonic acids could be obtained through the reduction of α-benzyloxyiminoalkanephosphonates by borane–pyridine or borane–triethylamine (in yields of 30–70%)[196], or more recently by triethylsilane-trifluoroacetic acid in 50–80% yield[173].

b. Hydrazones

i. To aminophosphonates. The reduction of *N,N*-dimethylhydrazonoalkanephosphonates by hydrogenation over Pd–C in acetic acid or by Zn in CH_3COOH–CF_3COOH was shown to be an additional, feasible approach to α-aminoalkanephosphonates[177].

ii. To alkylphosphonates. Sodium borohydride in thf reduces acylphosphonate tosylhydrazones to alkylphosphonates[197]. If the reaction is carried out in methanol, α-elimination leads to α-diazophosphonates being formed, which are not reduced further (equation 120).

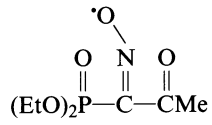


(120)

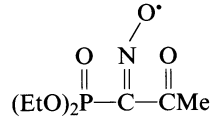
4. Oxidation

a. Oximes. Diisopropyl α-hydroxyiminophosphonates were oxidized to α-nitroalkanephosphonates by *m*-chloroperbenzoic acid in 65–70% yields[198].

Diethyl 1-hydroxyimino-2-oxopropanephosphonate was oxidized by lead dioxide or by electrochemical means to the corresponding nitroxide free radicals. These exist as stable (at least for weeks) *Z*- and *E*-isomers (**44** and **45**); the isomeric composition was found to depend on the solvent. EPR spectral data have been reported[182]. Similarly, aliphatic and aromatic α-hydroxyiminophosphonates were oxidized by AgO to stable (*E*)- and (*Z*)-nitroxide radicals[199]. The *E*-isomers were found to be the more stable of the two. The stereochemistries of the two isomers were established on the basis of hyperfine splitting of the EPR signals, due to ^{14}N, ^{31}P and ^{1}H nuclei.

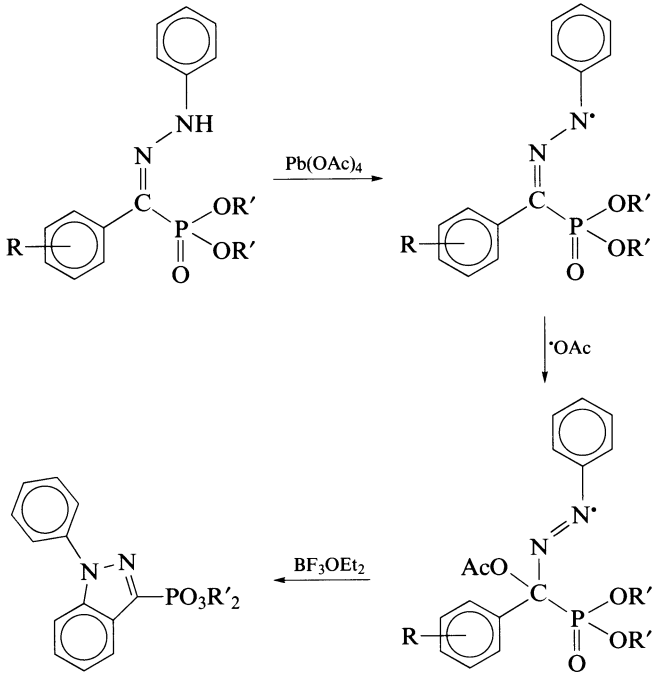


(44) (*Z*)



(45) (*E*)

b. Hydrazones. Oxidation of aroylphosphonate phenylhydrazones by $Pb(OAc)_4$ was reported to lead to azoacetates, which underwent cyclization to 1*H*-indazoles (equation 121)[52].



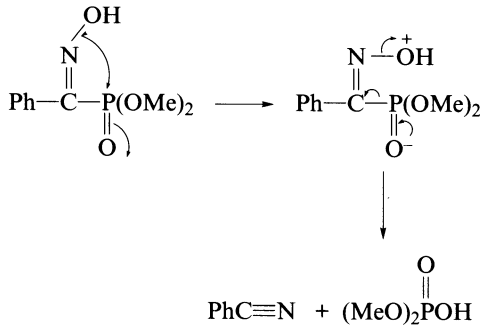
(121)

5. Fragmentation

a. Oximes

i. Thermal. Heating of α-hydroxyiminophosphonates may cause them to undergo fragmentation or rearrangement (see next section), depending on their stereochemistry, and the nature of substituents bound to phosphorus and to the nitrogen.

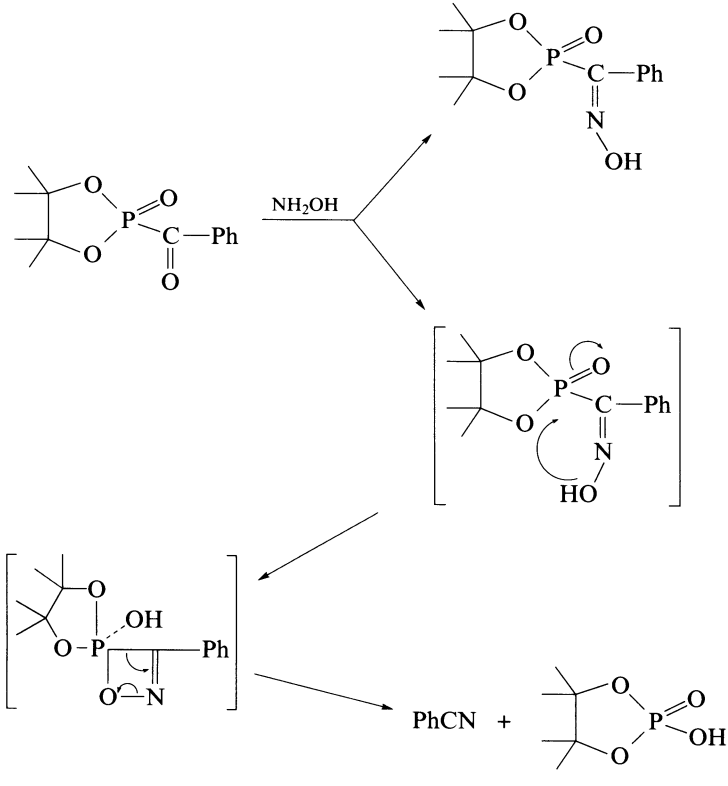
Dimethyl (*Z*)-α-hydroxyiminobenzylphosphonates undergo fragmentation to benzonitrile and dimethyl hydrogenphosphate[160]. A four-centred cyclic mechanism was suggested for this reaction (equation 122). The fragmentation of *O*-methyl oxime ethers required a much higher temperature and it was found to yield trimethyl phosphate, in addition to benzonitrile[160]. The rate and the ease of this reaction are influenced by the groups attached to the phosphorus. For example, in α-hydroxyiminobenzylphosphonate esterified with the



(122)

electron-withdrawing 2,2,2-trifluoroethyl groups this reaction is faster owing to the increased electrophilicity of the phosphorus[67].

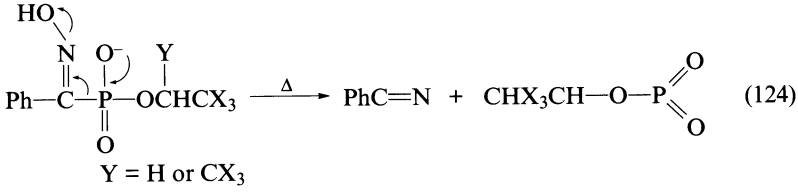
Tetrahedral phosphorus in a five-membered ring is highly strained. To relieve this strain, such compounds tend to expand the coordination of the phosphorus to five[106]. It was reasoned that if indeed the thermal fragmentation should proceed by the four-centred mechanism outlined above, it would proceed much more readily in a five-membered cyclic α-hydroxyiminophosphonate. To test this, a five-membered cyclic benzoylphosphonate was reacted with hydroxylamine[200]. This reaction yielded only the (*E*)-oxime along with a considerable amount of benzonitrile (equation 123). This result is consistent with the



(123)

assumption that of the two geometric oxime isomers, the (*E*)-oxime is stable whereas the (*Z*)-oxime is formed and undergoes facile cyclization to the spirophosphorane intermediate, which then fragments to products.

α-Hydroxyiminobenzylphodsphonate 2,2,2-trihaloethyl or 1,1,1,3,3,3-hexafluoro-2-propyl monoester monoanions undergo thermal fragmentation to benzonitrile and metaphosphate (equation 124)[201]. This reaction is specific to the *E*-isomer and its rate depends on the nature of the solvent. The fragmentation can be carried out in higher alcohols and aprotic solvents, but it does not take place in boiling water or methanol. In aprotic solvents the rate increases increasing solvent polarity. The lack of reaction in water was interpreted in terms of stabilization of the starting material by hydrogen-bond formation, whereas the rate enhancement by polar solvents was attributed to stabilization of the transition state and solvation of the departing OH^- group.

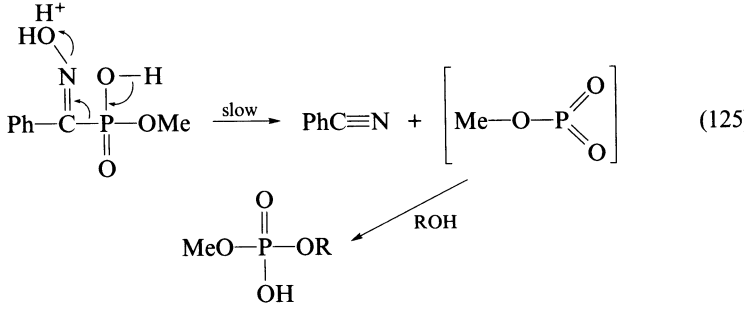


(124)

Attempted distillation of dipropyl 1-hydroxyimino-2-oxopropylphosphonate led to dipropyl cyanophosphonate (δ_{31P} = 20 ppm), together with other unidentified products of decomposition (δ_{31P} = 1.5 and 13 ppm)[182].

ii. Base-catalysed. (*Z*)-α-Hydroxyiminophosphonates, having an ionizable N—OH group, undergo base-catalysed fragmentation to a nitrile and phosphate. Since this reaction does not proceed with the related oxime ether, it is concluded that the mechanism involves a four-membered ring intermediate formed by an attack of the ionized oxygen on the phosphorus (similar to equation 122). This fragmentation occurs even in α-hydroxyiminophosphonate salts, demonstrating that even in the anionic form the phosphorus is susceptible to intramolecular nucleophilic attack[160].

iii. Acid catalysed fragmentation—formation of metaphosphates. An attempt to prepare methyl α-hydroxyiminobenzylhydrogenphosphonate by acidification of a methanolic solution of the corresponding sodium salt resulted in the formation of benzonitrile and dimethyl phosphate[202]. Further examination using a series of alcohols of varying steric requirements revealed that the rate of the reaction does not depend on the structure of the alcohol[187]. Consequently, the reaction was formulated as taking place in two steps (equation 125), the first step being a unimolecular, acid-catalysed dissociative formation of

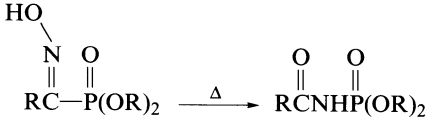


(125)

metaphosphate ester (or metaphosphoric acid, HPO_3[174]), and the second, fast step is its subsequent trapping by alcohol (or water) to form a phosphate ester (or acid). Consequently, oxyiminophosphonates have been recognized as convenient precursors of metaphosphates and novel reagents for the phosphorylation of hydroxy groups. Thus, when methylhydrogen α-hydroxyiminobenzylphosphonate was allowed to undergo fragmentation in the presence of a silica gel suspension in toluene, phosphorylation of silica gel resulted[203]. This result was interpreted as additional evidence for the intermediacy of metaphosphate in the reaction[203]. Benzyl α-hydroxyiminobenzylphosphonate esters were shown to be useful stable precursors from which the corresponding unstable α-hydroxyiminophosphonic acids can be obtained photochemically[7]. Other precursors for α-hydroxyiminophosphonic acids are 2-cyanoethyl and *p*-nitrophenethyl esters, from which the former can be obtained by base-catalysed elimination[204].

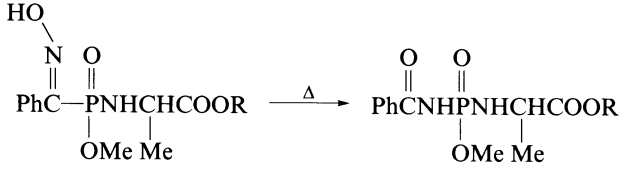
6. Beckmann rearrangement

In contrast to (*Z*)-α-hydroxyiminophosphonates, which undergo fragmentation on heating (see previous section), (*E*)-α-hydroxyiminophosphonates undergo Beckmann rearrangement to *N*-acylphosphoramidates (equation 126)[205]. The rate and the ease of this reaction depend greatly on the groups attached to the phosphorus. For example, methyl 2,2,2-trihaloethyl (*E*)-α-hydroxyiminobenzylphosphonate do not undergo Beckmann rearrangement at all[67]. Apparently, because of the electron-withdrawing effect of the trihaloethyl group, the migratory aptitude of the phosphorus moiety is greatly reduced relative to the rate of $E \rightleftharpoons Z$ isomerization. At the same time, the rate of the fragmentation (see previous section) is increased in these compounds because of the influence of the trihaloethyl group.



(126)

α-Hydroxyiminophosphonamidates rearrange, much more rapidly, to phosphordiamidates at relatively low temperature[68]. This reaction was applied to *N*-(α-hydroxyiminoalkylphosphonyl) amino acids. Beckmann rearrangement of these compounds yielded acylphosphordiamidates (equation 127), which represent a new type of peptide analogue.[69]

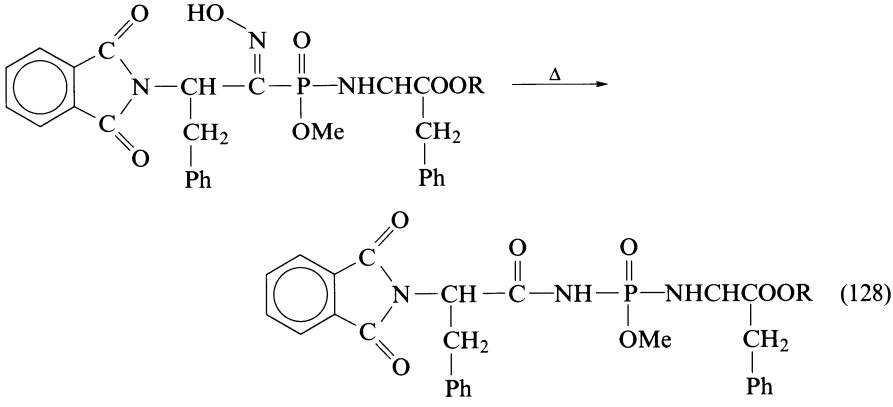


(127)

To demonstrate further the utility of this method for peptide analogue, it was applied to an α-hydroxyiminophosphonamidate derived from two molecules of phenylalanine (equation 128)[68].

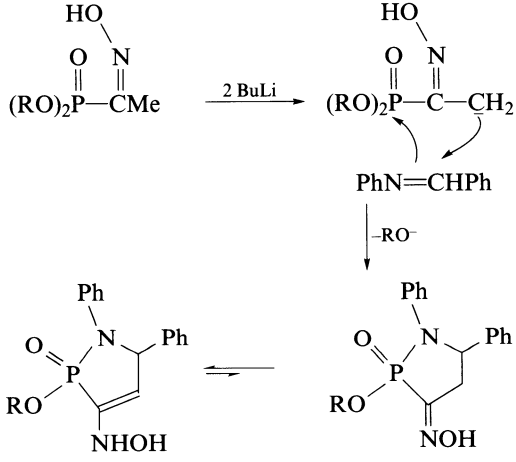
7. Addition to C=N bond

The examples in this section include reactions in which α-iminophosphonates may be involved in any capacity. The dianion derived from dialkyl α-hydroxyiminoethylphos-



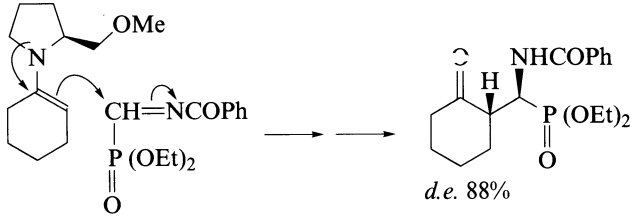
(128)

phonate adds to the C=N bond to benzalanil with the formation of an azaphospholene (equation 129)[168].



(129)

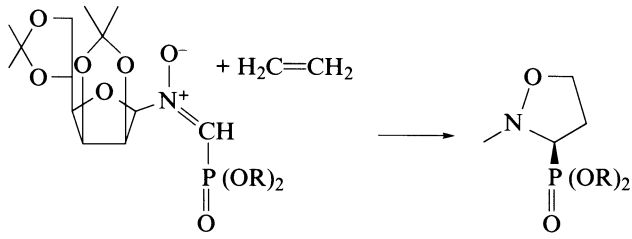
An α-acylimidophosphonate can serve as an acceptor of nucleophiles. Addition of a chiral enamine to benzoylimidophosphonate provides an entry to a phosphaamino acid in 88% diastereoisomeric excess as shown in equation 130[206].



(130)

Finally, 1,3-dipolar cycloaddition to an *N*-glycosyl *C*-dialkoxyphosphinyl nitrone should also be mentioned in this section. This reaction leads to preferential formation of

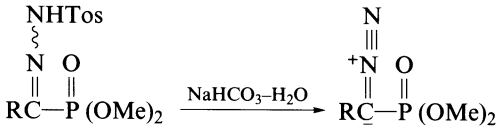
an (*R*)-5-oxaphosphaproline (equation 131), which can be converted into certain chiral phosphaamino acids (homoserine, aspartic acid)[207].



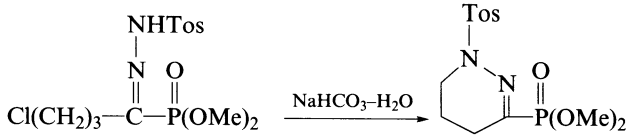
(131)

8. Bamford–Stevens reaction of tosylhydrazones

On treatment of series of α-tosylhydrazonophosphonates with aqueous sodium carbonate, they underwent facile Bamford–Stevens-type elimination to give the corresponding diazoalkanes (equation 132)[208], with the exception of the tosylhydrazone derived from 4-chlorobutyrylphosphonate, which underwent cyclization (equation 133)[33,176].



(132)



(133)

9. Complex formation

a. Oximes

i. Diesters. A dichlorobis(α-hydroxyiminophosphonate)cobalt (II) complex has been prepared from diethyl (*E*)-α-hydroxyimino-*p*-methoxybenzylphosphonate[209]. The cobalt atom has a coordination number of six and the complex has a distorted *cis*-octahedral structure. The two α-hydroxyiminophosphonate molecules are coordinated in a bidentate manner via the oxime nitrogens and the P=O oxygen atoms. The equatorial plane of the octahedron contains the cobalt, two oxygen and two chlorine atoms and the axial positions are occupied by the nitrogen atoms.

Diethyl (*E*)-α-hydroxyimino-*p*-methoxybenzylphosphonate also forms coordination compounds with copper (II) which were prepared using $CuCl_2$ and $CuBr_2$[210]. These have binuclear structures, with the two copper atoms having a coordination number of five. The complexes have square-pyramidal structures formed by two bridging halogen atoms, terminal halogens and the oxygens and nitrogens from the α-hydroxyiminophosphonate ligands. In the copper coordination polyhedron the nitrogen, oxygen and the two halogen atoms (bridging and terminal) form the base of the tetragonal pyramid and the apex is a bridging halogen atom.

Complexes of diethyl (*E*)-α-hydroxyimino-*p*-methoxybenzylphosphonate with cobalt (II), nickel (II) and copper (II) have been investigated by IR, electronic and NMR spectroscopy and by conductivity measurements. In all of these complexes the ligand is coordinated in a bidentate manner via the oxime nitrogens and the P=O oxygens[211].

ii. Monoester acids. Treatment of a mixture of *E*- and *Z*-isomers of sodium methyl α-hydroxyiminobenzylphosphonate with $CoCl_2 \cdot 6H_2O$ precipitated selectively the complex of the *E*-isomer, allowing isolation of the *Z*-isomer in a pure state[161]. Chemical analysis of the cobalt complex revealed that the complex contained two ligands per metal atom.

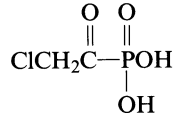
The *E*-isomer of sodium methyl α-hydroxyiminobenzylphosphonate reacts with $CuCl_2 \cdot 2H_2O$ and yields a pentacoordinate copper chelate, which contains two ligands and a water molecule. The X-ray structure of this complex revealed a mononuclear structure with a near trigonal-bipyramidal geometry where each ligand is bound as bidentate, through the oxime nitrogen and the phosphoryl oxygen. The *Z*-isomer did not react with copper (II) ion. In contrast, the formation of a copper (II) complex with sodium methyl (*Z*)-α-methoxyiminobenzylphosphonate was reported, in which the metal is coordinated to the P—O^- and N—O—Me oxygens[161].

In contrast to the copper complexes, calcium and cadmium complexes of the same ligand, prepared by reacting sodium methyl (*Z*)-α-hydroxyiminobenzylphosphonate with MCl_2, are polymeric species. Single-crystal X-ray diffraction studies revealed that the metals are seven-coordinated with distorted pentagonal-bipyramidal geometry, containing two bidentate and two mondentate ligands and one water molecule[212]. Each ligand molecule acts simultaneously in a bidentate chelating mode (through the oxime nitrogen and a phosphonate oxygen) and in bridging to another calcium atom via another phosphonate oxygen.

V. BIOLOGICAL ASPECTS OF ACYLPHOSPHONATES AND DERIVATIVES

A. Antibiotics

Fosfonochlorin, a new antibiotic isolated from soil samples in Japan, was identified as chloroacetylphosphonic acid (46)[213]. It is moderately active against some Gram-negative bacteria.

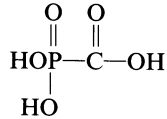


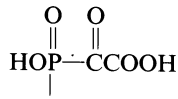
(46)

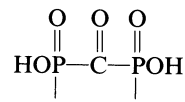
B. Antivirals

Phosphonoformic acid (Foscavir, Foscarnet, PFA) is an inhibitor of HIV-1 reverse transcriptase and is of clinical utility in acquired immunodeficiency syndrome (AIDS)[214]. Foscarnet acts by inhibiting viral-specific DNA polymerases[215]. It is useful in the treatment of severe cytomegalovirus retinitis in immunodepressed patients. More recently it has also been found effective against acyclovir-resistant herpes infections in AIDS patients[216]. Owing to its ionic character it is not absorbed when give orally. Attempts to prepare prodrugs of phosphonoformic acid met with no success, mainly because of the lability of the P—C bond in fully esterified derivatives[14,86]. A new approach to the design of prodrugs of phosphonoformic acid is based on the assumption that the mechanism responsible for the

transport of peptides across biological membranes can be utilized to transport non-peptide drugs if they are coupled with amino acids. Phosphonoformic acid was coupled with glycine through amide formation between the carboxy group of the former and the amino group of the latter. The resulting compound showed significantly improved bioavailabiity over PFA[217].

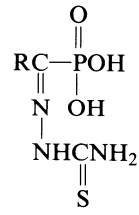

PFA


COPAA


COMBP

Other pyrophosphate analogues containing the α-ketophosphonic function that have been tested against the HIV-1 reverse transcriptase (RT) include oxophosphonacetic acid (COPAA) and oxomethanebisphosphonic acid (COMBP). These compounds have been found to be significantly less active against RT than PFA[218]. COMBP has also been shown to inhibit mammalian DNA polymerases selectively[219].

Some aromatic thiosemicarbazones are active against smallpox virus, while phosphonoformic acid (PFA) and phosphonoacetic acid (PAA) are active against herpes viruses. Consequently, some acylphosphonate thiosemicarbazones, (**47**), in which the two types of structural moieties appear together, were synthesized and tested for antiviral activity. However, no inhibitory activity was observed against herpes and/or pox viruses[220].



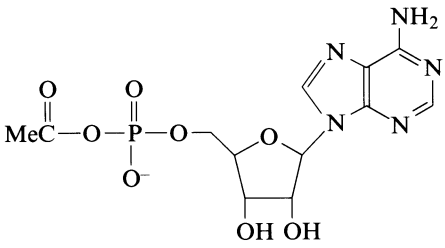
(**47**)

C. Enzyme inhibitors

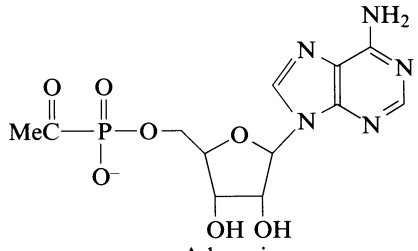
Phosphonates may be viewed as structural analogues of phosphate or carboxylates. They are chosen as inhibitors of enzymes which catalyse reactions of carboxylates or phosphates following the recognition that ionic interactions are an important component in enzymic specificity and thus a major factor in the design of inhibitors. They may be expected to interfere with enzymatic processes involving phosphates due to the substitution of the P—O—C bond by the hydrolytically stable P—C bond. On the other hand, the combination of the electrostatic similarity with the stereochemical difference between the tetrahedral phosphonic groups and the planar carboxy groups makes it likely that phosphonates can inhibit enzymes which catalyse reactions of carboxylic acids.

1. Acetyl CoA-synthase

Among a number of structural analogues of acetyladenylate (adenosine-5′-acetylphosphate), adenosine-5′-acetylphosphonate was synthesized and examined. It was found that, along with the other analogues, it inhibited the enzyme[221].



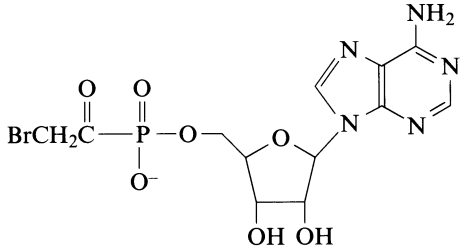
Adenosine
5′ -acetylphosphate



Adenosine
5′ -acetylphosphonate

2. Na,K-ATPase

The inhibition of ATPase with a series of ATP analogues has been studied. Among the compounds examined, adenosine-5′-bromoacetylphosphonate inhibited the enzyme at a fairly high rate, both in the presence and in the absence of ATP[222].

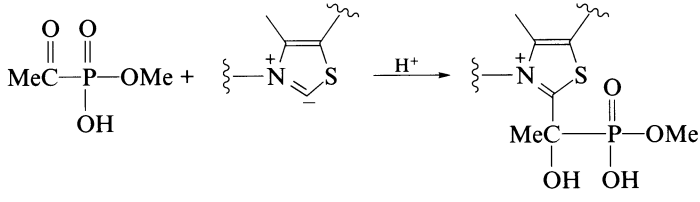


Adenosine
5′ -bromoacetylphosphonate

3. Pyruvate and lactate dehydrogenase

Pyruvate dehydrogenases (PDH) are multienzyme complexes responsible for the conversion of pyruvate of acetyl-CoA. The decarboxylation step requires thiamin pyrophosphate (TP). The mechanism involves ionization of thiamine to produce an yielde which adds to the carbonyl of pyruvate forming a covalent adduct. This adduct has properties which permit CO_2, to leave, an event that could not occur in pyruvic acid.

Methyl acetylphosphonate was designed as a pyruvate analogue in order to study the enzyme reaction mechanism[6]. When methyl acetylphosphonate was allowed to interact with thiamine pyrophosphate, an adduct which can be regarded as a 'reactive intermediate analogue' was formed (equation 134)[223]. Addition of this adduct to an enzyme lacking TP resulted in its regeneration. Methyl acetylphosphonate and acetylphosphonic acid

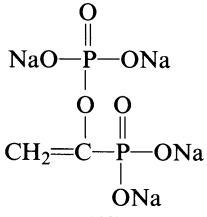


(134)

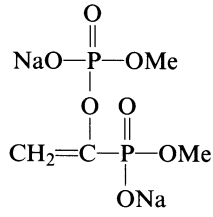
inhibit pyruvate dehydrogenase[17,18]. Both acylphosphonates are substrates for lactate dehydrogenase[18].

4. Phosphoenolpyruvate enzymes

Phosphoenol acetylphosphonate (**48**) and its dimethyl ester (**49**) were examined as potential inhibitors of three phosphoenopyruvate (PEP) enzymes[224]. Both compounds inhibited enolase and PEP carboxylase but they did not bind to pyruvate kinase. Neither compounds was a substrate for any of the enzymes.



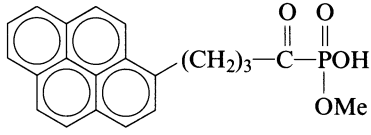
(**48**)



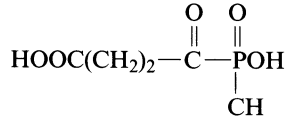
(**49**)

5. α-Ketoglutarate dehydrogenase (KGD)

By analogy with pyruvate dehydrogenase, the components of the KGD multienzyme complex catalyse the conversion of α-ketoglutarate, NAD^+ and CoA to CO_2, succinyl-CoA and NADH. The reaction is a thiamine-dependent decarboxylation. Consequently, α-ketophosphonic acids are logical candidates to inhibit such enzymes, as they can enter into the first step of the reaction, but the second step, dephosphorylation, cannot take place. Indeed, two acylphosphonates were reported to inhibit KGD. The first, methyl pyrenebutyrylphosphonate (PBMP), was found to be a competitive inhibitor of α-ketoglutarate[225]. Because of it fluorescent properties, PBMP could serve as a probe for fluorescence energy transfer measurements to estimate distances on the enzyme. Succinylphosphonate (SP) and its monomethyl ester were examined more recently[226]. SP was found to be the most powerful inhibitor of KGD, its monomethyl ester being much less effective. The inhibition of SP was 'strong enough' even at a 170-fold excess of α-ketoglutarate.



PEMP



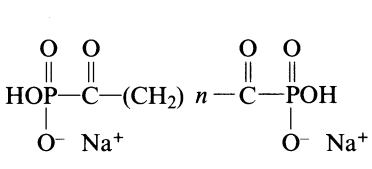
SP

6. Glyceraldehyde-3-phosphate dehydrogenase (GDP)

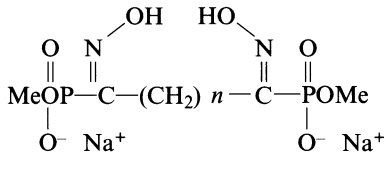
Chloroacetylphosphonic acid (see also Sections II.C.1 and V.A) and bromoacetylphosphonic acid have been designed to mimic structurally the nucleophilic attack of inorganic phosphate on the acyl enzyme. Both compounds were found to be effective thiol-blocking reagents and irreversible inhibitors of glyceraldehyde-3-phosphate dehydrogenase from a variety of sources[82]. Interestingly, monoionized haloacetylphosphonates were found to react with thiols at a rate faster by two orders of magnitude than phosphonate dianions.

D. Calcium Metabolism Regulators

Bisacylphosphonates[27] (**50**) and bishydroxyiminophosphonates[227] (**51**) were found to be the first examples of non-geminal bisphosphonates biologically active in calcium metabolism disorders such as pathological calcification and bone resorption[228]. These compounds showed less toxic side-effects and improved bioavailability than bisphosphonates approved for clinical use[229].



(**50**)



(**51**)

E. Antifungal activity

Twenty dimethyl and diethyl aliphatic acylphosphonates and the corresponding α-hydroxyiminophosphonate diesters were screened against five pathogenic fungi: *P. oryzae*, *H. oryzae*, *R. bataticola*, *A. alternate*, and *P. aphanidermatum*[230]. A few of the compounds were reported to possess significant activity. However, since it does not appear from the paper that the researchers were aware of the fact that acylphosphonate diesters hydrolyse rapidly, their concentration in the test medium (and the possible presence of fatty acids) is uncertain at best. In a later paper, the activity of dimethyl and diethyl mono-, di- and trichloroacetylphosphonate and their oximes were examined against the same fungi[231]. Diethyl trichloroacetylphosphonate exhibited 'promising fungicidal activity'. Again, there was no report of a control experiment using trichloroacetic acid.

VI. ACKNOWLEDGEMENTS

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CHAPTER 8

Gas-phase positive and negative ion chemistry of organophosphorus compounds via mass spectrometric techniques

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I. INTRODUCTION

A. Recent Developments in Mass Spectrometry

Mass spectrometry is currently undergoing a revolution with the development and application of new ionization methods, with constant improvements to instrumentation and with the coupling of a range of chromatographic techniques to mass spectrometers[1]. In particular, the past decade has seen the introduction of electrospray ionization (ESI)[2] and matrix-assisted laser desorption/ionization (MALDI)[3], two methods which have pushed back the frontiers of mass spectrometric analysis of high molecular mass compounds (M_r >20 000). Although most of the excitement over these two methods has been in the area of biological macromolecule analysis, ESI has also been a boon for the analysis of highly polar and ionic species, since this technique essentially involves transferring preformed ions from solution to the gas phase[4]. The types of ionization methods now available include electron impact (EI), chemical ionization (CI)[5a], fast atom bombardment (FAB, which is often used as a generic term to include liquid secondary ionization mass spectrometry)[6], plasma desorption[7], laser desorption[8], ESI[2] and MALDI[3]. A range of different types of instruments have proliferated, including various types of sector instruments, quadrupole instruments, hybrid instruments, ion traps, time-of-flight instruments and Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer[9]. Since many of the newer 'soft ionization' techniques produce pseudomolecular ions (e.g. protonated $[M + H]^+$ ions or deprotonated $[M - H]^-$ ions) with little or no fragmentation, some structural information is lost compared with the standard EI mass spectrum. With the introduction of tandem mass spectrometers, this problem is overcome by mass selecting the pseudomolecular ion and subjecting it to dissociation via: (i) collisions with a collision gas such as helium [this is known as collision-induced dissociation (CID) or collisional activation (CA)]; (ii) collisions with a surface (this is known as surface-induced dissociation or SID; or (iii) interaction with a laser[10].

B. Scope of the Review

With the rapid advances in mass spectrometry described above, any review of the mass spectrometry of organophosphorus compounds which solely lists the type of mass spectra which have been accumulated to date can only represent a 'snapshot' of the burgeoning literature. Clearly, the modern-day organophosphorus chemist has a range of alternatives for the mass spectrometric analysis of organophosphorus compounds, apart from the traditional EI mass spectrum. In no way do we mean to downplay the importance of these traditional mass spectra; indeed, many problems are still successfully solved using EI. However, several excellent reviews[11–16] have already been published on the fragmentation mechanisms in EI spectra of organophosphorus compounds and McLafferty's book has recently been updated[17]. Further, several databases of EI mass spectra are available for searching[18], the *Dictionary of Organophosphorus Compounds* contains references to many EI mass spectra of organophosphorus compounds[19] and the Royal Society of Chemistry's

TABLE 1. Gas-phase properties of HCP and HCP^+

Species	*IP* (eV)[a]		*PA* (kcal mol^{-1})[b]	
HCP	10.79 ± 0.01[c]		167 ± 2 experiment[d] 166.6 (*ab initio*)[e]	
	State	ν_1 (cm^{-1})	ν_2 (cm^{-1})	ν_3 (cm^{-1})
HCP^+[f]	$\tilde{X}^2\Pi_{3/2}$	3125.1	642	1147.1
	$^2\Pi_{1/2}$	3124.9		1159.9
	$\tilde{A}^2\Sigma^+$	2985.6	706	1275.4

[a] The ionization potential (*IP*) is defined by equation 1.
[b] The proton affinity (*PA*) is defined by equation 2.
[c] Ref. 22.
[d] Ref. 23.
[e] Carbon protonation, ref. 88.
[f] Vibrational frequencies of the phosphaethyne cation were inferred from its $\tilde{A}^2\Sigma^+ \rightarrow \tilde{X}^2\Pi_i$ emission spectrum, as described in ref. 24.

Organophosphorus Chemistry series regularly lists new mass spectra in the 'Physical Methods' chapter[20]. With this in mind, an approach which considers fundamental aspects of organophosphorus ions (i.e. structure and reactivity) in the gas phase has been adopted. The gas-phase structure and reactivity of ions can be probed via several different techniques[21], including thermochemical measurements, kinetic energy release of metastable ions, collisional activation mass spectrometry, neutralization reionization mass spectrometry and ion–molecule reactions. An example is the molecule HCP (Table 1): its ionization potential[22], proton affinity[23] and the IR and rotational spectroscopy of the HCP^+ ion[24] have all been determined in the gas phase. Another important tool for understanding the structure and reactivity of gas phase ions is *ab initio* molecular orbital theory. With advances in computational hardware and software, it is now possible to carry out high-level *ab initio* calculations on smaller systems. Indeed, the interplay between experiment and theory has fuelled many studies[25].

Fundamental studies of gas-phase ionic processes are also of interest in other areas, including combustion, the chemistry of the ionosphere, interstellar chemistry and chemical vapour deposition. Another important aspect of gas-phase studies is that they probe the *intrinsic* reactivity of ionic species in the absence of counter ions and solvent. Indeed, in cases where sufficient data are available, comparisons between solution- and gas-phase studies provide insights into solvent and counter ion effects[26].

The following topics will not be discussed in this review: photoelectron spectroscopy[27] and IR and rotational spectroscopy of ions[28]. Although ion mobility spectroscopy can provide useful insights into the structures of gas-phase ions and has also been used as an analytical tool, no further mention will be made of this technique[29]. In addition, the gas-phase ion chemistry and mass spectrometry of the following classes of compounds are beyond the scope of this review: metal compounds containing phosphorus ligands[30]; inorganic phosphorus compounds[12]; and pesticides[14,16] and phosphorus-containing biomolecules such as DNA and RNA[31].

II. THERMOCHEMISTRY AND KINETICS

A knowledge of the gas-phase thermochemistry of ions and neutrals is important in mass spectrometry. This is particularly true for those ionization techniques (such as CI) involving proton transfer reactions in the gas phase which result in the formation of pseudomol-

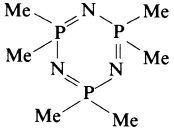
ecular ions (e.g. protonated $[M + H]^+$ ions or deprotonated $[M - H]^-$ ions). The mass spectra observed using these ionization techniques can change dramatically, depending on the thermochemistry of the ionization process (for example, highly exothermic proton transfer reactions often result in the formation of fragment ions)[5]. Fortunately, it is now often possible to estimate which particular ionizing conditions may be suitable for certain classes of compounds based on thousands of gas-phase thermochemical measurements which have been critically reviewed and compiled into a database[22]. Two important thermochemical quantities related to the formation of gas-phase positive ions are the ionization potential (defined in equation 1) and the proton affinity (defined in equation 2) of a neutral molecule. The important thermochemical quantity related to the formation of gas-phase negative ions derived from compounds with acidic protons is the gas-phase acidity (defined in equation 3). A listing of gas-phase ionization potential (*IP*), proton affinities (*PA*) and acidities ($\Delta H°_{acid}$) of some organophosphorus compounds are given in Tables 2, 3 and 4, respectively. Those readers interested in how such measurements are made are directed to the appropriate reviews[22,23].

$$M \xrightarrow{IP_a} M^+ + e \quad (1)$$

$$M + H^+ \xrightarrow{-PA} MH^+ \quad (2)$$

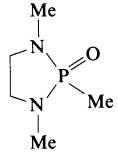
$$AH \xrightarrow{\Delta H°_{acid}} A^- + H^+ \quad (3)$$

TABLE 2. Selection of ionization potentials of some organophosphorus compounds[a]

Compound	*IP* (eV)[b]	Compound	*IP* (eV)[b]
$MePH_2$	9.12 ± 0.07	Me_3P	8.11 ± 0.05
$MePF_2$	9.8		
$MePCl_2$	9.5	$PhPMe_2$	7.58 ± 0.05
$MeCH_2PCl_2$	9.3	$Bu^n{}_3P$	7.5
Me_3CPH_2	8.9	Ph_2PMe	8.28 ± 0.05
Me_3CPF_2	9.2	Ph_3P	7.39 ± 0.03
Me_3CPCl_2	9.0	$MeCl_2PO$	10.91
$PhPH_2$	8.47 ± 0.01	Me_3PO	9.5
$PhP(OEt)_2$	8.2	CP	10.5 ± 0.5
	9.4 ± 0.1		9.0
Me_2PH	8.47 ± 0.07		8.35 ± 0.05
Me_2PF	8.8		
Me_2PCl	8.9		
Et_2PH	8.69		
$(Me_3C)_2PH$	7.9		
$(Me_3C)_2PF$	8.2		
$(Me_3C)_2PCl$	8.0		
Ph_2PH	7.8 ± 0.01		

[a] The *IP* is defined by equation 1.
[b] All values are taken from ref. 22.

TABLE 3. Proton affinities of some organophosphorus compounds[a]

Compound	*PA* (kcal mol^{-1})[b]	Compound	*PA* (kcal mol^{-1})[b]
PH_3	188.6	F_3PO	167.8
PF_3	166.5	Me_3PO	217.1
$MePH_2$	204.1	Et_3PO	222.6
Me_2PH	216.3	$Pr^n{}_3PO$[e]	224.5
Me_3P	227.1	$Pr^i{}_3PO$[e]	225.6
$PhPH_2$[c]	206.1	$(Me_2NCH_2)_3PO$	235
$C_6H_{11}PH_2$[c]	208.6	$Me(Me_2N)_2PO$[e]	224.5
$PhPMe_2$	229.6	$Me_2(Me_2N)PO$[e]	221.4
Et_3P	231.7		224.8
Ph_2PMe	230.3	$PhMe_2PO$	216
Ph_3P	230	Ph_2MePO	216
	191.4	$Ph_2(Me_2CH)PO$	216
	195.8	$Ph_2(Me_3C)PO$	216
		Ph_3PO	216
		Ph_3PS	216

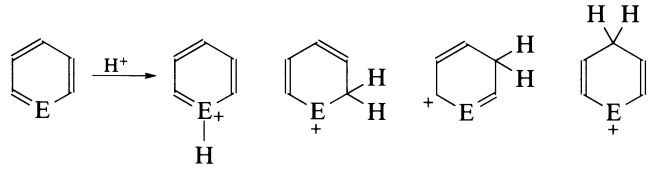
[a] Proton affinities are defined by equation 2.
[b] All values are taken from ref. 22 unless noted otherwise.
[c] Ref. 33b.
[d] Ref. 35.
[e] Calculated from the gas-phase basicities reported in ref. 36a.

TABLE 4. Gas-phase acidities[a]

Compound	$\Delta H°_{acid}$(kcal mol^{-1})[b]
PH_3	370.9 ± 2.0
$MePH_2$	364.4 – 371.5
$HP{=}PH$[c]	355.0 ± 3.0
$P(CH_3)_3$	384.0 ± 3.0
$(MeO)_2POH$[c]	357.0 ± 3.0
$(MeO)_2PNH_2$[c]	373.0 ± 3.0
	373.0 ± 3.0[d]
	332.0 ± 4.0[d]

[a] Gas-phase acidities are defined by equation 3.
[b] All values are taken from ref. 22 unless noted otherwise.
[c] Determined by the bracketting method.
[d] Ref. 72.

The effects of substituents on the proton affinities of a range of phosphines have been discussed and compared with analogous nitrogen systems in a review[33a]. As shown in Table 3, phosphines are moderate to strong bases in the gas phase. Interestingly, phosphirane is a considerably weaker base than dimethylphosphine in the gas-phase. This has been ascribed to unfavourable angle strain on the protonation of phosphirane[34]. Similar geometric arguments have been proposed to rationalize the low basicity of phosphabenzene[35]. This study also considered the sites of protonation of the Group 5 heterobenzenes: pyridine, phosphabenzene and arsabenzene. In theory, protonation could occur at the heteroatom to produce **1** or at either of the α-, β- or γ-carbons to give **2**, **3** or **4**.



(1) **(2)** **(3)** **(4)**

The sites of protonation were probed by forming the $[M + D]^+$ ion of each heterobenzene and then allowing them to react with a suitable base. Phosphabenzene only transferred D^+ (equation 4) whereas arsabenzene transferred both D^+ and H^+ in an approximately 1:1 ratio (equation 5). This indicates that phosphabenzene protonates at the phosphorus atom while arsabenzene protonates at carbon rather than at the arsenic atom.

$$[C_5H_5P + D]^+ + MeC(=O)Et \longrightarrow MeC(=\overset{+}{O}D)Et + C_5H_5P \quad (4)$$

$$[C_5H_5As + D]^+ + (CD_3CD_2)_2O \longrightarrow (CD_3CD_2)_2\overset{+}{O}D + C_6H_5As \quad (5a)$$

$$[C_5H_5As + D]^+ + (CD_3CD_2)_2O \longrightarrow (CD_3CD_2)_2\overset{+}{O}H + C_6H_4DAs \quad (5b)$$

The gas-phase protonation reactions of a number of phosphine oxides and phosphoramides have also been studied[36]. In these instances protonation occurs at oxygen to form stable quasiphosphonium ions. Oxygen protonation is thermodynamically favoured over nitrogen protonation for phosphoramides. It has been suggested that this is due to the fact that the quasiphosphonium ion thus formed can be stabilized via π back-donation to the d orbitals of phosphorus.

Much less work has been carried out on the gas-phase acidities of phosphorus compounds. Many of the acidities listed in Table 4 were determined by the bracketing method in which the conjugate base (R^-) of a phosphorus acid (RH) is allowed to react with a series of acids (AH) of known gas-phase acidity (equation 6). One of the difficulties of such measurements is that the structure of the neutral acid formed (RH) is unknown. This is especially problematic for ambident phosphorus anions such as $(MeO)_2PX^-$ (X = O and NH) where protonation could occur either at phosphorus to give $(MeO)_2HPX$ or at X to give the tautomer $(MeO)_2PXH$[37,38]. This is an area which would greatly benefit from high-level *ab initio* calculations on a model system such as H_2PO^-, since essentially nothing is known about the kinetic barriers associated with P versus X protonation in these ambident anions[39]. In favourable circumstances, hydrogen–deuterium exchange reactions can be used to determine the sites of protonation. For example, the ambident ion $HSiNH^-$ undergoes H–D exchange of the nitrogen H, indicative of nitrogen protonation to form $HSiNH_2$[40].

$$R^- + AH \longrightarrow RH + A^- \quad (6)$$

Nonetheless, gas-phase acidities are valuable since when they are combined with electron affinities (*EA*) of the radical related to the conjugate base, they can be used to determine bond dissociation energies (*BDE*)[41], as shown in equations 7–10. This is particularly useful for species whose *BDE* may not be directly measured via traditional techniques[41,42]. Unfortunately, little progress has been made in this area since there is also a dearth of data on gas-phase electron affinities of phosphorus species[42]. Berger and Brauman[42] have commented on how both the *EA* and *BDE* can influence the gas-phase acidity of a species.

$$RH \longrightarrow R^- + H^+ \qquad \Delta H°_{acid}(RH) \quad (7)$$

$$R^- \longrightarrow R^\bullet + e^- \qquad EA(R^\bullet) \quad (8)$$

$$H^+ + e^- \longrightarrow H^\bullet \qquad -IP(H^\bullet) \quad (9)$$

$$RH \longrightarrow R^\bullet + H^\bullet \qquad D(R—H) \quad (10)$$

Of course, the gas-phase thermochemistry of ions is not solely restricted to the measurement of the quantities described above; a wide range of other ion affinities have been measured, including methyl cation affinities, hydride affinities and halide affinities[22,32]. Further, such measurements can often be related to unknown neutral thermochemistry via the appropriate thermochemistry cycle. For example, the phosphorus–carbon 'double bond' strength (the sum of the σ and π bond contributions) in $HP{=}CH_2$ was recently estimated via mass spectrometric measurements to be 101 ± 7 kcal^{-1} (ref. 43).

Favourable thermochemistry for a particular gas-phase reaction does not guarantee that it will be kinetically viable. Although many gas-phase ion–molecule reactions are fast owing to the ion–dipole and ion–induced dipole attractive electrostatic potential, there can be significant barriers to certain reactions. Hence experimental kinetic data are important, especially for the modelling of atmospheric and interstellar processes. Those interested in the kinetics of gas-phase ion–molecule reactions involving phosphorus species are directed to a number of databases[44].

III. ION–MOLECULE REACTIONS

Apart from the proton transfer reactions discussed in Section II, phosphorus species undergo a range of other ion–molecule reactions in the gas phase. The types of instruments which have been used to study ion–molecule reactions of phosphorus species include ion cyclotron resonance (ICR) mass spectrometers and the related FT-ICR instruments, flowing afterglow (FA) instruments and their related selected-ion flow tubes (SIFT) and also more conventional instruments[9,45]. This section is divided into four topics: (A) positive ion–molecule reactions; (B) negative ion–molecule reactions; (C) neutralization–reionization reactions; and (D) phosphorus–carbon bond formation reactions.

A. Positive Ions

1. *Formation, structure and reactivity of $M^{+\bullet}$ ions*

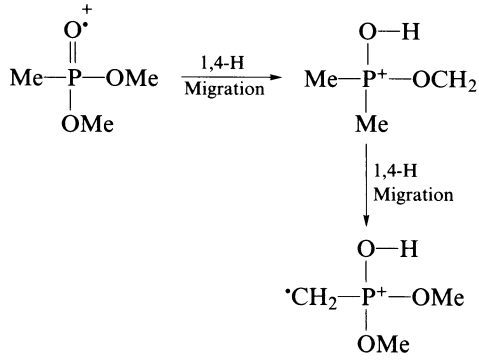
The formation and fragmentation of $M^{+\bullet}$ ions are ubiquitous processes in electron impact mass spectrometry. These radical cations are usually assumed to have similar bonding arrangements to their neutral precursors. A considerable amount of recent theoretical and experimental work indicates that this is not necessarily true. Indeed, radical cations

with the same connectivity as in their neutral precursors can be both thermodynamically and kinetically less stable than isomeric structures with spatially separated charge and radical sites[46]. In a theoretical paper, Yates *et al.*[47] introduced the term 'distonic ion' to describe ions with separated charge and radical sites and recognized that such species formally arise from the ionization of zwitterions or diradicals. Since then, there has been a dynamic interplay between theory and experiment and it is now widely recognized that distonic ions play an important role in mass spectrometry[46]. The isomeric phosphorus ions $MePH_2^{+\bullet}$ and $^{\bullet}CH_2PH_3^+$ have been subjected to a number of theoretical and experimental investigations[47,48]. One theoretical study mapped out many aspects of the $[C,H_5,P]^{+\bullet}$ potential energy surface[48a]. This study indicates that $MePH_2^{+\bullet}$ is 9.6 kcal mol^{-1} more stable than $^{\bullet}CH_2PH_3^+$ and that a considerable barrier (52.6 kcal mol^{-1}) prevents their isomerization. The highest level of theory carried out on this isomeric pair is the *G2'* theory which indicates that $CH_3PH_2^{+\bullet}$ is more stable than $^{\bullet}CH_2PH_3^+$ by 8.1 kcal mol^{-1} at 298 K[48b]. The early theoretical studies prompted an experimental investigation into structures of isomeric $[C,H_5,P]^{+\bullet}$ and $[C_2,H_7,P]^{+\bullet}$ ions via their collisional activation (CA) spectra[48c]. The $MePH_2^{+\bullet}$ ion formed via direct electron impact on $MePH_2$ yields a number of products ions in the CA spectrum, of which the reaction shown in equation 11 is diagnostic of the structure $MePH_2^{+\bullet}$. The CA spectrum of $^{\bullet}CH_2PH_3^+$, which is formed by dissociative ionization on hexylphosphine, is considerably different, yielding the ions $PH_3^{+\bullet}$ (equation 12a) and $CH_2^{+\bullet}$ (equation 12b), both of which provide evidence for the structure $^{\bullet}CH_2PH_3^+$. Similar evidence was presented for the isomeric ions $Me_2PH^{+\bullet}$, $EtPH_2^{+\bullet}$, $^{\bullet}CH_2CH_2PH_3^+$ and $Me^{\bullet}CHPH_3^+$.

$$MePH_2^{+\bullet} \longrightarrow Me^+ + PH_2 \qquad (11)$$

$$^{\bullet}CH_2PH_3^+ \longrightarrow CH_2 + PH_3^{+\bullet} \qquad (12a)$$

$$^{\bullet}CH_2PH_3^+ \longrightarrow CH_2^{+\bullet} + PH_3 \qquad (12b)$$



(13)

A case in which the distonic ion is considerably more stable than the conventional radical cation involves organophosphorus esters[49,50]. Deuterium labelling studies combined with CA mass spectra indicate that the $M^{+\bullet}$ of dimethyl methylphosphate undergoes the keto to enol isomerization reaction shown in equation 13 prior to dissociation[49].

Further evidence that isomerization of the $M^{+\bullet}$ ion occurs comes from a consideration of the ion–molecule reactions of the radical cation formed trimethyl phosphate[50]. This ion was allowed to react with trimethyl phosphite. If the $M^{+\bullet}$ of trimethyl phosphate had retained its original structure, electron transfer was expected (based on the differences of their *IP*s), since this reaction (equation 14a) is exothermic by 34 kcal mol^{-1}. No electron

transfer was observed. Instead, a facile proton transfer reaction to give protonated trimethyl phosphite was observed, consistent with the distonic structure shown in equation 14b, since protonated trimethyl phosphate readily undergoes a proton transfer reaction with $(MeO)_3P$ (equation 15). In contrast, the sulphur analog $(MeO)_3PS^{+\bullet}$ does not undergo rearrangement, but reacts via electron transfer (equation 16)

$$(MeO)_3P{=}O^{+\bullet} + (MeO)_3P \not\longrightarrow (MeO)_3P^{+\bullet} + (MeO)_3PO \qquad (14a)$$

$$\downarrow$$

$$(MeO)_2\overset{+}{P}(\cdot CH_2O)-OH + (MeO)_3P \longrightarrow (MeO)_3\overset{+}{P}H + (MeO)_2P(\cdot CH_2O)=O \qquad (14b)$$

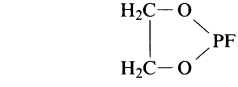
$$(MeO)_3\overset{+}{P}OH + (MeO)_3P \longrightarrow (MeO)_3\overset{+}{P}H + (MeO)_3PO \qquad (15)$$

$$(MeO)_3PS^{+\bullet} + (MeO)_3P \longrightarrow (MeO)_3P^{+\bullet} + (MeO)_3PS \qquad (16)$$

The proton transfer reaction shown in equation 14b represents a general class of reactions (equation 17) known as 'self CI' reactions in which a compound acts as its own CI reagent gas[32]. Such reactions can be observed in EI/CI sources of conventional mass spectrometers, and are important in ICR mass spectrometers[32]. The rates of formation of MH^+ ions from $M^{+\bullet}$ (equation 17) ions of organophosphorus species are shown in Table 5[51]. It should be pointed out that although the structures of the $M^{+\bullet}$ ions in these experiments were assumed to have the same connectivity as in the neutral precursors M, distonic ions may also be responsible for the proton-transfer reactions observed, based on the work of Kenttämaa and coworkers[46b,c].

$$M^{+\bullet} + M \longrightarrow MH^+ + \text{neutrals} \qquad (17)$$

TABLE 5. Rate constants for formation of the MH^+ ions from $M^{+\bullet} + M$

M	Rate constants (10^{-10} cm^3 molecule^{-1}s^{-1})
Me_2PPMe_2	<<0.1
Me_3P	0.1
Me_2PH	1.4
$MePH_2$	8.2
Me_2PF	1.8
$MePF_2$	0.33
$(MeO)_3P$	0.1
	0.54
	<0.1
Me_3PCH_2	2.1
Me_2NPF_2	1.0

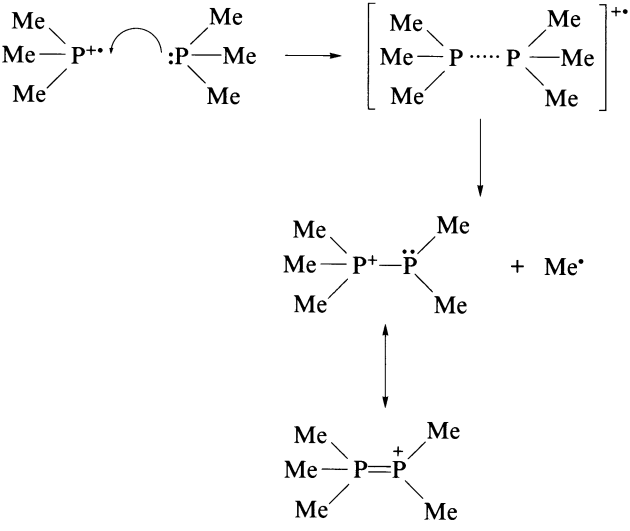
Wanczek[51] noted that protonated molecules are only formed in a considerable amount if the M species shown in equation 17 contain a P—H or a P—F bond. Deuterium labelling studies indicated that both P—H (equation 18a) and C—H (equation 18b) bond dissociations occurs for Me_2PH, where $k_{18a}/k_{18b} = 2.3$[51].

$$Me_2PD^{+\bullet} + Me_2PD \longrightarrow \begin{cases} Me_2PD_2^+ + Me_2P & (18a) \\ Me_2PDH^+ + MeDPCH_2 & (18b) \end{cases}$$

2. *Positive ion–molecule reactions of organophosphorus species*

The detection of phosphine in Jupiter's atmosphere[52] and the search for molecules containing phosphorus in interstellar clouds[53] have stimulated interest in the gas-phase positive ion–molecule chemistry of phosphorus and its compounds. The results of laboratory experiments using mass spectrometric techniques have been used to develop models of phosphorus chemistry in interstellar clouds[54].

a. Ion-molecule reactions of methylphosphines, tetramethyldiphosphine and methylfluorophosphines. Two different groups have studied positive ion–molecule reactions (including many kinetic measurements) of methylphosphines (Me_nPH_{3-n}, where n = 1, 2 and 3) using ICR mass spectrometers[55,56]. The molecular ion $M^{+\bullet}$ and fragment ions undergo a variety of ion–molecule reactions with neutral molecules M present in the cell. A total of 64 ion–molecule reactions were identified for methylphosphine[56a], 45 for dimethylphosphine[56a] and 60 for trimethylphosphine[56b]. The molecular ion undergoes two reactions for each of the methylphosphines: proton transfer (equation 17) and a condensation reaction with concomitant loss of a methyl radical to form a diphosphonium species ($R_3{}^+PPR_2$) as illustrated for Me_3P in Scheme 1.



SCHEME 1

The two most abundant fragment ions in the EI mass spectra of $MePH_2$ and Me_2PH are CH_2P^+ and $MeP^{+\bullet}$. Although several isomers are possible for ions with formulae $[C,H_2,P]^+$ and $[C,H_3P]^{+\bullet}$, *ab initio* calculations indicate that the thermodynamic stability orders of the isomers are $CH_2{=}P^+ > HCPH^+ > CPH_2^+$ and $MeP^{+\bullet} > CH_2PH^{+\bullet} > CHPH_2^{+\bullet} > CPH_3^{+\bullet}$[57]. CH_2P^+ reacts with $MePH_2$ via proton transfer (equation 19) and via condensation with loss of CH_4 (equation 20) and C_2H_4 (equation 21). CH_2P^+ reacts with Me_2PH in a similar fashion but also undergoes a hydride transfer reaction (equation 22). The reactions of $Me_3P^{+\bullet}$ with Me_3PH_2 include proton transfer (equation 23) and condensation with loss of the radicals CH_3 (equation 24) and PH_2 (equation 25). A similar series of reactions are observed between $MeP^{+\bullet}$ and Me_2PH.

$$CH_2P^+ + MePH_2 \xrightarrow{60\%} MePH_3^+ + HCP \quad (19)$$

$$CH_2P^+ + MePH_2 \xrightarrow{30\%} MeP_2^+ + CH_4 \quad (20)$$

$$CH_2P^+ + MePH_2 \xrightarrow{10\%} H_3P_2^+ + C_2H_4 \quad (21)$$

$$CH_2P^+ + Me_2PH \longrightarrow CH_2PH + Me_2P^+ \quad (22)$$

$$MeP^{+\bullet} + MePH_2 \xrightarrow{67\%} MePH_3^+ + CH_2P \quad (23)$$

$$MeP^{+\bullet} + MePH_2 \xrightarrow{27\%} C_2H_5P_2^+ + CH_3 \quad (24)$$

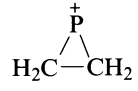
$$MeP^{+\bullet} + MePH_2 \xrightarrow{6\%} C_2H_6P^+ + PH_2 \quad (25)$$

The fragment ion $(CH_2)_2P^+$ is common to EI mass spectra of both Me_2PH and Me_3P[55,56]. A cyclic phosphiranyl structure has been proposed for this ion based on the P^+ transfer reactions observed with Me_2PH and Me_3P (equation 26)[56].

$$\begin{array}{l} CH_2 \\ | \quad \diagdown \\ CH_2 \quad P^+ \end{array} + Me_2PR \longrightarrow Me_2RP_2^+ + CH_2{=}CH_2 \quad (26)$$

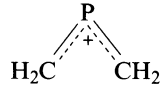
(R = H, Me)

Two separate *ab initio* studies have considered many aspects of the singlet and triplet $[C_2,H_4,P]^+$ potential energy surfaces[58a,b]. The stabilities of five isomers at the MP4(SDTQ)/6–31+G(d,p)//RHF/6–31 + G(d,p) level of theory (including zero-point energy corrections) are shown below (isomers **5**–**10**)[58a]. The phosphiranyl cation **5** is more stable than the phosphaallyl cation **6**, with a barrier to disrotatory ring opening of **5** to **6** of 11.2 kcal mol^{-1} (ref. 59a).



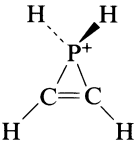
E_{rel} = 0.0 kcal mol^{-1}

(5)



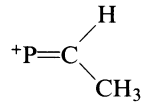
E_{rel} = + 9.9 kcal mol^{-1}

(6)



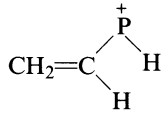
E_{rel} = –3.3 kcal mol^{-1}

(7)



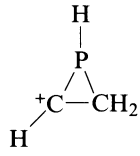
E_{rel} = –3.8 kcal mol^{-1}

(8)



E_{rel} = –4.6 kcal mol^{-1}

(9)

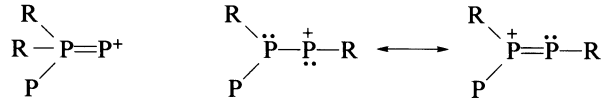


(10)

A number of other unimolecular reactions were investigated[57]. A 1,2-H shift of **5** yields an unstable phosphacyclopropyl cation (**10**) which spontaneously decomposes to **9** with an overall barrier of 18.4 kcal mol^{-1} (ref. 58a). The decomposition channel of **5** to yield P^+ and $CH_2{=}CH_2$ (equation 27) is predicted to be strongly endothermic in the ground state[58b]. Although the reactions shown in equations 20, 21, 24, 25 and 26 look deceptively straightforward, it should be pointed out that the structures of the ionic products remain uncertain. Thus, while it is interesting to speculate that the product of equation 20 is the methyldiphosphonium ion, $MeP{=}P^+$, other isomeric structures are clearly possible[59].

(27)

Indeed, when the deuterated phosphine Me_2PD is used, the complexity of many of the reactions are revealed. For example for the P^+ transfer reactions shown in equation 26, the ionic product contains no deuterium, instead it is lost in the neutral C_2H_3D[56a]. Further, it has been noted that the ionic products ($R_3P_2^+$) of reactions 24 and 26 could in principle have structure **11** or **12**[51,56a]. The latter structure requires a rearrangement reaction to take place. $R_3P_2^+$ ions are also formed in the gas-phase ion chemistry of Me_2PPMe_2 (equation 28) and its mixture with PH_3 (equations 29 and 30)[51,60]. The ion–molecule reactions shown in equations 31 and 32 are indicative of structure **12**[51,60].



(11) **(12a)** **(12b)**

The gas-phase ion chemistry of $MePF_2$, Me_2PF and their mixtures with Me_2NPF_2 have been studied in an ICR mass spectrometer[61]. The reactions of the molecular ions and also

$$Me_2PPMe_2 \xrightarrow{EI} Me_2PPMe^+ + Me^\bullet + e^- \quad (28)$$

$$PH^{+\bullet} + Me_2PPMe_2 \longrightarrow Me_2PPH^+ + Me_2P \quad (29)$$

$$PH_2^+ + Me_2PPMe_2 \longrightarrow Me_2PPH^+ + Me_2PH \quad (30)$$

$$Me_2PPMe^+ + PH_3 \longrightarrow Me_2PPH^+ + MePH_2 \quad (31)$$

$$Me_2PPH^+ + Me_2PPMe_2 \longrightarrow \begin{cases} Me_4P_3^+ + Me_2PH & (32a) \\ Me_4P_3H^{+\bullet} + Me_2P & (32b) \\ Me_3P_3H^+ + Me_3P & (32c) \end{cases}$$

the fragment ions PF_2^+, $MePF^+$ and Me_2P^+ were investigated. PF_2^+ reacts with $MePF_2$ via fluoride ion transfer (equation 33a) and electron transfer (equation 33b), while $MePF^+$ reacts via electron transfer (equation 34a), proton transfer (equation 34b) and addition (equation 34c). $MePF^+$ reacts with Me_2PF in an analogous fashion (cf equation 34a–c) with an additional fluoride transfer reaction (cf. equation 33a). Me_2P^+ is less reactive and only undergoes electron transfer (cf. equation 34a) and addition (cf. equation 34c). In addition, the fluoride ion transfer reactions 35 and 36 help establish the following orders of fluoride ion affinities: $PF_2^+ > MePF^+ > Me_2NPF^+ > Me_2P^+$.

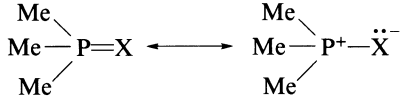
$$PF_2^+ + MePF_2 \longrightarrow \begin{cases} MePF^+ + PF_3 & (33a) \\ MePF_2^{+\bullet} + PF_2 & (33b) \end{cases}$$

$$MePF^+ + MePF_2 \longrightarrow \begin{cases} MePF_2^{+\bullet} + MePF & (34a) \\ MePF_2H^+ + CH_2{=}PF & (34b) \\ \text{Me(F)P—F—P(F)Me} & (34c) \end{cases}$$

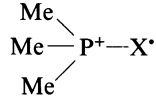
$$MePF^+ + Me_2NPF_2 \longrightarrow Me_2NPF^+ + MePF_2 \quad (35)$$

$$Me_2NPF^+ + Me_2PF \longrightarrow Me_2P^+ + Me_2NPF_2 \quad (36)$$

b. Ion–molecule reactions of Me_3PX (X = CH_2, NH, NMe and O). The gas-phase ion chemistry of isoelectronic trimethylphosphoranes Me_3PCH_2, Me_3PNH, Me_3PNCH_3 and Me_3PO have been studied using an ICR mass spectrometer[62]. The neutral species, which can be described by two resonance contributors (**13a** and **b**) of which the ionic structure **13b** is more important, loses an electron to form the distonic ion **14**.



(13a) **(13b)**



(14)

The unimolecular and bimolecular reactions of the distonic ions **14** and fragment ions of Me_3PX have been described in detail[62]. With the exception of Me_3PO, the $M^{+\bullet}$ ions are the most abundant ions in the mass spectra of Me_3PX. All the molecular ions dissociate via loss of a methyl radical to form intense signals of the fragment ions $Me_2PCH_2^+$, Me_2PNH^+, Me_2PNMe^+ and Me_2PO^+[62a]. The molecular ion and fragment ions of Me_3PCH_2 undergo 43 different reactions with the neutral parent molecules present in the cell, while the ions derived from Me_3PNH, ME_3PNMe and Me_3PO undergo 33,39 and 68 reactions respectively, with their parent neutrals. The distonic ions **14** have lost much of their ylide character, as dramatically illustrated by the fact that $Me_3PCH_2^{+\bullet}$ fails to undergo a Wittig reaction with acetone (equation 37)[62c]. Instead, only cations derived from acetone undergo Wittig reactions with neutral Me_3PCH_2 (equation 38 and 39).

$$Me_3PCH_2^{+\bullet} + Me_2C{=}O \not\longrightarrow \begin{cases} Me_3PO + Me_2C{=}CH_2^{+\bullet} & (37a) \\ Me_3PO^{+\bullet} + Me_2C{=}CH_2 & (37b) \end{cases}$$

$$Me_2C{=}O^{+\bullet} + Me_3PCH_2 \longrightarrow Me_3PO^{+\bullet} + Me_2C{=}CH_2 \quad (38)$$

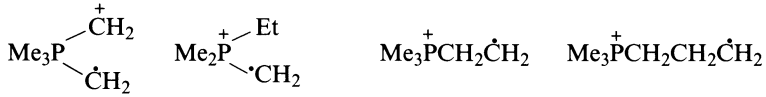
$$[MeCO]^+ + Me_3PCH_2 \longrightarrow \begin{cases} Me_3PO^{+\bullet} + MeC^{\bullet}{=}CH_2 & (39a) \\ Me_3POH^+ + CH_2{=}C{=}CH_2 & (39b) \end{cases}$$

The protonated molecules Me_3PXH^+ are among the most abundant product ions and are mainly formed by reactions of the molecular ions (equation 17)[62a]. The $Me_3PCH_2^{+\bullet}$ ion undergoes numerous reactions with Me_3PCH_2, of which the reactions shown in equation 40 are among the most important[62a]. Reaction 40a results in the formation of the resonance-stabilized symmetrical ion **15**, a species which has also been observed in solution[63]. Reactions 40b and 40c are evidence for CH_2 transfer from Me_3PCH_2. It has been suggested that the product of reaction 40b is the distonic ion **16**, which undergoes a rearrangement to form the ion **17** based solely upon the fact that the product ion undergoes a further methylene group transfer with Me_3PCH_2 (equation 41). In the light of Kenttämaa and coworker's work[64] on CH_2 transfer from ketene to distonic ions, another feasible structure of the product ion of reaction 40b is the β-distonic ion **18**, which could react further (equation 41) to yield the γ-distonic ion **19**.

$$Me_3PCH_2^{+\bullet} + Me_3PCH_2 \longrightarrow \begin{cases} Me_3PCHPMe_3^+ + CH_3 & (40a) \\ Me_3P(CH_2)_2^{+\bullet} + Me_3P & (40b) \\ Me_3P^{+\bullet} + [C_5, H_{13}, P] & (40c) \end{cases}$$

$$Me_3\overset{+}{P}CH{=}PMe_3 \longleftrightarrow Me_3P{=}C\overset{+}{H}PMe_3$$

(15)

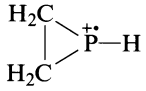


(16) **(17)** **(18)** **(19)**

$$Me_3P(CH_2)_2^{+\bullet} + Me_3PCH_2 \longrightarrow Me_3P(CH_2)_3^{+\bullet} + Me_3P \quad (41)$$

In contrast, the $Me_3PX^{+\bullet}$ ions (where X = NH, NMe and O) undergo fewer reactions with Me_3PX than the $Me_3PCH_2^{+\bullet}$ ion. In particular, they do not abstract X from neutral Me_3PX molecules. The protonated species Me_3PXH^+ are, however, much more reactive than the $Me_3PX^{+\bullet}$ ions and undergo a wide range of condensation reactions.

c. Reactions of three-membered ring ions: Phosphirane and thiirane. The mass spectrum and ion–molecule reactions of phosphirane and of mixtures of phosphirane with NH_3, NH_2D, NHD_2 and ND_3 have been studied with an ICR mass spectrometer[65]. It has been suggested that the $M^{+\bullet}$ ion of phosphirane retains its cyclic structure **20**, based on the fact that it undergoes PH^+ transfer reactions with ND_3 (equation 42) and the parent M (equation 43a). The authors postulated that the product formed in equation 43a rearranges from structure **21** to **22**. The parent ion also undergoes proton transfer (equation 43b) and two other reactions (equations 43c and 43d) with neutral parent molecules. The gas-phase ion chemistry of the HP_2^+ production (equation 43c) has been studied[66]. In contrast, the $M^{+\bullet}$ ion of phosphabenzene is less reactive in an ICR mass spectrometer and only undergoes the clustering reaction shown in equation 44[35]. It has been suggested that the thiirane molecular ion also retains its cyclic structure since it undergoes $S^{+\bullet}$ ion transfer to trimethylphosphine to give the distonic ion $Me_3PS^{+\bullet}$ (equation 45)[67]. This product ion abstracts an S atom from the parent neutral, probably to give a β-distonic ion (equation 46).



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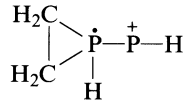

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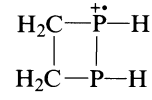

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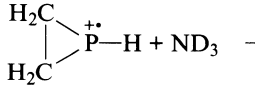

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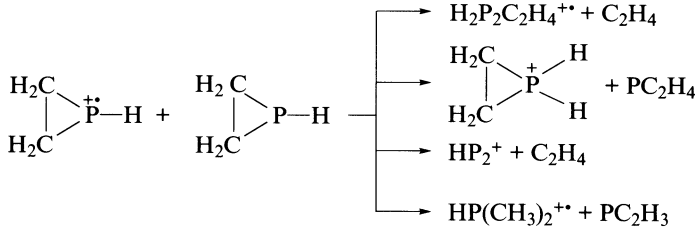
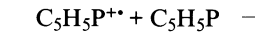


(43a)

(43b)

(43c)

(43d)



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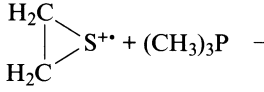

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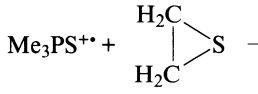


(46)

B. Negative Ions

The gas-phase anion-molecule reactions of organophosphorus and organosulphur species have been the subject of a previous review[68]. As noted in that review, the gas-phase anion chemistry of organophosphorus compounds represents a relatively unexplored area, especially when compared with positive ion studies. Only modest progress has been made since then.

1. Reactions of alkylphosphines

The $[M - H]^-$ ions of PH_3, $MePH_2$, $C_6H_{11}PH_2$, $PhPH_2$ and Me_3P can readily be prepared by deprotonation reactions using bases such as NH_2^-, HO^- or F^-[42,69,70]. For PH_3 and Me_3P, it is obvious that deprotonation will occur at phosphorus and carbon, respectively, to form the anions PH_2^- and $Me_2PCH_2^-$. These anions react differently: PH_2^- reacts with N_2O to give the products shown in equation 47 whereas $Me_2PCH_2^-$ reacts to give the diazo anion shown in equation 48[69,70b]. Further, $Me_2PCH_2^-$ undergoes up to eight H–D exchanges with D_2O[70b].

$$PH_2^- + N_2O \longrightarrow H_2PO^- + N_2 \quad (47a)$$

$$PH_2^- + N_2O \longrightarrow PN_2^- + H_2O \quad (47b)$$

$$Me_2PCH_2^- + N_2O \longrightarrow Me_2PCN_2^- + H_2O \quad (48)$$

For $MePH_2$, deprotonation could occur at either carbon or phosphorus. Ion–molecule reactions of the $[M - H]^-$ ion of $MePH_2$ with N_2O reveal that deprotonation by F^- occurs at phosphorus since a reaction similar to that for H_2P^- (equation 47a) is observed (equation 49)[42]. Although the deprotonation reactions of Me_2PH have not been studied, the Me_2P^- ion has been observed via Penning ionization Me_3P[70a]. Apart from proton transfer (equations 50a and 52a), trimethylphosphine also undergoes a range of other reactions with various anions including addition/elimination (equation 50b, 51a, 51b and 52d), S_N2 displacement at carbon (equation 50c) and adduct formation (equation 51c). The $O^{-\bullet}$ ion also undergoes H atom abstraction (equation 52b) and H_2^+ abstraction (equation 52c).

(49)

$$MeSCH_2^- + Me_3P \longrightarrow Me_2PCH_2^- + Me_2S \quad (50a)$$

$$MeSCH_2^- + Me_3P \longrightarrow Me_2P\bar{C}HSCH_3 + CH_4 \quad (50b)$$

$$MeSCH_2^- + Me_3P \longrightarrow Me_2P^- + MeSEt \quad (50c)$$

$$EtO^- + Me_3P \longrightarrow Me(EtO)PCH_2^- + CH_4 \quad (51a)$$

$$EtO^- + Me_3P \longrightarrow Me_2PO^- + CH_4 + C_2H_4 \quad (51b)$$

$$EtO^- + Me_3P \longrightarrow EtOPMe_3^- \quad (51c)$$

$$O^{-\bullet} + Me_3P \longrightarrow \begin{cases} Me_2PCH_2^- + HO & (52a) \\ HO^- + Me_2PCH_2 & (52b) \\ (C_3H_7P)^{-\bullet} + H_2O & (52c) \\ Me_2PO^- + CH_3 & (52d) \end{cases}$$

2. *Reactions of other organophosphorus species*

The gas-phase isotope exchange reaction between $^{37}Cl^-$ and $Me_2P^{35}Cl$ has been studied (equation 53) and a rapidly equilibrating pentacoordinate complex has been suggested as an intermediate to explain the fast rate[71]. The anion–molecule reactions of dimethyl methylphosphonate have been studied in detail using a flowing afterglow apparatus[72]. A wide range of anions of varying basicity and structure (e.g. localized heteroatomic bases such as HO^-, localized carbon bases such as $C_6H_5^-$ and delocalized carbon nucleophiles such as $PhCH_2^-$) were allowed to react with $(MeO)_2P(O)Me$. In general, proton transfer reactions (equation 54a) and S_N2 reactions at carbon (equation 54b and 55a) dominate although elimination of CH_2O (equation 54c) and addition/elimination reactions (equation 55b) are also observed.

$$^{37}Cl^- + Me_2P^{35}Cl \rightleftharpoons \left[\begin{array}{c} ^{37}Cl \\ | \\ Me \diagdown P^{:-} \\ Me \diagup {}^{35}Cl \end{array} \right] \rightleftharpoons {}^{35}Cl^- + Me_2P^{37}Cl \quad (53)$$

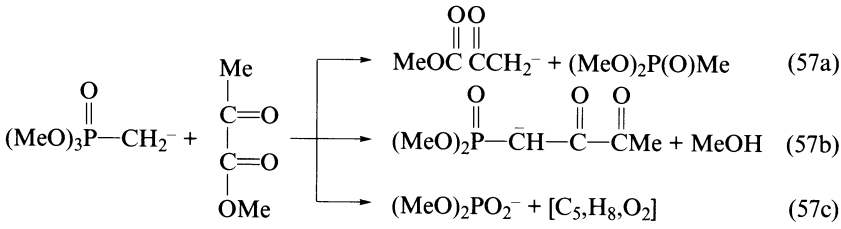
$$H_2N^- + (MeO)_2P(O)Me \longrightarrow \begin{cases} (MeO)_2P(O)CH_2^- + H_3N & (54a) \\ (Me_2O)(Me)PO_2^- + H_2NMe & (54b) \\ (MeO)(Me)PO^- + H_3N + CH_2O & (54c) \end{cases}$$

$$F^- + (MeO)_2P(O)Me \longrightarrow \begin{cases} (MeO)(Me)PO_2^- + MeF & (55a) \\ (MeO)(F)P(O)CH_2^- + MeOH & (55b) \end{cases}$$

The conjugate base of dimethyl methylphosphonate readily reacts with alcohols and carbonyl compounds in the gas phase. $(MeO)_2P(O)\ CH_2^-$ reacts with CD_3OH via three pathways, each of which proceed initially via proton transfer to form the ion–molecule complex $[CD_3O^- \cdot (MeO)_2P(O)Me]$, which subsequently undergoes S_N2 attack at carbon (equation 56a) or addition/elimination at phosphorus (equation 56b and c). $(MeO)_2\ P(O)CH_2^-$ reacts with methyl pyruvate via proton transfer (equation 57a), addition/elimination (equation 57b) and also via a Horner–Emmons–Wadsworth reaction (equation 57c). The latter reaction is the dominant one for benzaldehyde. Although a consideration of the reactions of phosphate esters were not a mandate for this review, it is

$$(MeO)_2P(O)CH_2^- + CD_3OH \longrightarrow \begin{cases} (MeO)(Me)PO_2^- + CD_3OMe & (56a) \\ (CD_3O)(Me)PO_2^- + MeOMe & (56b) \\ (CD_3O)(MeO)P(O)CH_2^- + MeOH & (56c) \end{cases}$$

worth mentioning that the use of ethyl dimethylphosphate as a substrate allows an evaluation of the intrinsic competition between elimination and substitution as a function of nucleophile structure[73].



(57a)

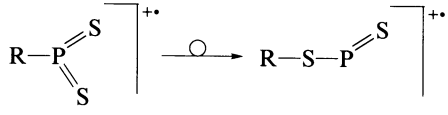
(57b)

(57c)

C. Neutralization–Reionization Reactions

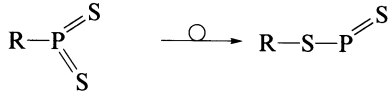
The technique known as neutralization–reionization mass spectrometry (NRMS) has proved to be a useful way of probing the structure and stabilities of neutral species by generating them from their corresponding ions[74]. This is an area where there has been a dynamic interplay between theory and experiment. For example, theoretical predictions led to the suggestion that NRMS would be a useful way of generating the ylide H_3PCH_2 by reduction of the corresponding distonic ion $H_3PCH_2^{+\bullet}$[47]. Years later this prediction was experimentally verified[75].

NRMS studies of phosphorus ions have been dominated by those dealing with phosphorus sulphides[76–81]. For example, it has been shown by a combination of CA and NRMS experiments that both ionic and neutral organo thioxophosphoranes isomerize to their corresponding organothio thioxophosphanes species in the gas phase (equations 58 and 59)[76]. Similar studies have considered the structures of radical cations of composition $[R_2HPS]^{+\bullet}$ where (R = Et and MeO) and $[C_2H_7PS]^{+\bullet}$[77]. The former ions have structures corresponding to tricoordinate phosphorus ($R_2PSH^{+\bullet}$) while the latter consists of a mixture of structures ($EtP(H)SH^{+\bullet}$ and $EtPSH_2^{+\bullet}$).



(58)

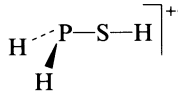
(R = Me, Ph)



(59)

(R = Me, Ph)

The gas-phase structures of the ions $[H,P,S]^{+\bullet}$, $[H_3,P,S]^{+\bullet}$ and $[H_3,P,S_2]^{+\bullet}$ and also their corresponding neutrals species have been investigated by CA and NRMS techniques[78–80]. Both HPS and HSP are stable in the gas phase. The former is synthesized via oxidation of $HPS^{-\bullet}$ anions while the latter are formed via reduction of $HSP^{+\bullet}$ cations[78]. Related investigations into the structures of $[H_3,P,S]^{+\bullet}$ and $[H_3,P,S_2]^{+\bullet}$ and their neutral species provide evidence for structures **23**–**27**[79,80].



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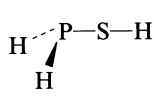

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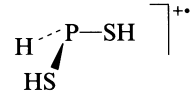

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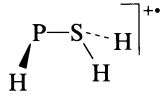

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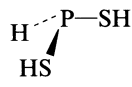


(27)

The structures of the cations and neutrals of the following P_xS_y species have been investigated via CA and NRMS experiments: PS, PS_2,PS_3,P_2S,P_2S_2,P_3S and P_3S_2[81].

D. Phosphorus–Carbon Bond Formation Reactions

There has been considerable interest in the synthesis of organophosphorus compounds with carbon–phosphorus bonds[82]. A range of such reactions also occur in the gas phase and are discussed in detail below.

1. Negative ion–molecule reactions

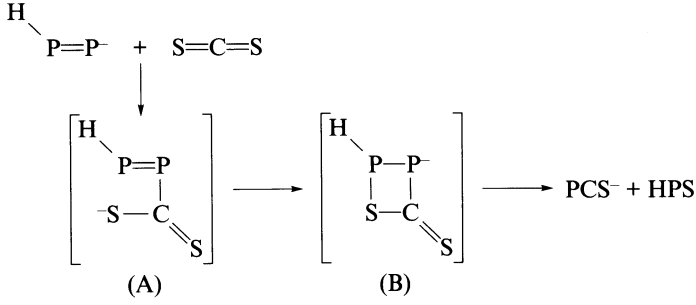
DePuy and coworkers[69] have studied the gas-phase ion-molecule reactions of the phosphide ion. A number of reactions were observed which result in phosphorus–carbon bond formation, including S_N2 reactions (equation 60), adduct formation (equation 61) and the formation of the low-valent ions PCO^- (equation 62) and PCS^- (equation 63). The latter ion is also formed in a reaction between $HP{=}P^-$ and CS_2, for which the mechanism shown in Scheme 2 has been proposed[66].

$$H_2P^- + MeX \xrightarrow[X = Cl, Br, I]{} H_2PMe + X^- \quad (60)$$

$$H_2P^- + CO_2 \longrightarrow H_2PCO_2^- \quad (61)$$

$$H_2P^- + COS \longrightarrow PCO^- + H_2S \quad (62)$$

$$H_2P^- + CS_2 \longrightarrow PCS^- + H_2S \quad (63)$$



SCHEME 2

The major product in the reaction of the allyl anion with trimethylphosphite involves nucleophilic attack at phosphorus with subsequent elimination of methanol (equation 64)[37]. A similar series of addition/elimination reactions between several carbanions and trimethylphosphine have been observed in a flowing afterglow reactor (equation 65)[70a]. In contrast, various carbanions react with trimethylphosphate via S_N2 displacement at carbon (equation 66)[83].

$$CH_2{=}CHCH_2^- + (MeO)_3P \longrightarrow (MeO)_2PCHCHCH_2^- + MeOH \quad (64)$$

$$RCH_2^- + Me_3P \longrightarrow Me_2PCHR^- + CH_4 \quad (65)$$
$$R = H_2CCH, HCC, MeS$$

$$CH_2{=}CHCH_2^- + (MeO)_3PO \longrightarrow (MeO)_2PO_2^- + CH_2{=}CHEt \quad (66)$$

The ambident phosphoryl anion $(MeO)_2PO^-$ is a weak nucleophile in the gas phase; further, the neutral products in its reactions with MeX (X = Cl, Br and I) remain uncertain[38]. Methyl transfer to PO would result in $(MeO)_2P(O)Me$ while methyl transfer to O would result in $(MeO)_3P$.

2. *Positive ion–molecule reactions*

The gas-phase reactions of PH_x^+ (x = 0,1,2) ions with methane have been studied by a number of groups[23,84–86]. These ions are reactive and undergo a series of insertion reactions to produce ions containing phosphorus carbon bonds (equation 67–69). The reaction between the methyl cation and phosphine also produces ions containing phosphorus–carbon bonds (equation 70)[84].

$$P^+ + CH_4 \longrightarrow PCH_2^+ + H_2 \quad (67)$$

$$HP^+ + CH_4 \longrightarrow PCH_4^+ + H \quad (68a)$$
$$HP^+ + CH_4 \longrightarrow PCH_3^+ + H_2 \quad (68b)$$

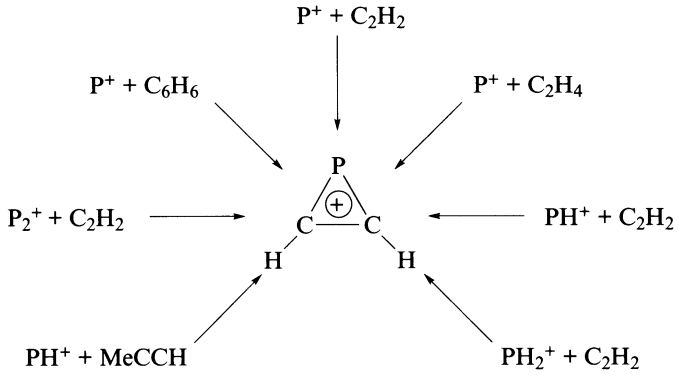
$$H_2P^+ + CH_4 \longrightarrow PCH_2^+ + H_2 \quad (69)$$

$$CH_3^+ + PH_3 \longrightarrow PCH_4^+ + H_2 \quad (70a)$$
$$CH_3^+ + PH_3 \longrightarrow PCH_2^+ + 2H_2 \quad (70b)$$

Of all of the product ions shown in equations 67–70, the only ones which have been characterized experimentally are PCH_2^+ and $PCH_3^{+\cdot}$ (see equations 19–25). In addition, PCH_2^+ was allowed to undergo proton transfer to several bases (equation 71)[23]. These studies suggest that PCH_2^+ is carbon-protonated PCH, in good agreement with a number of *ab initio* studies[87,88]. The structure of the $[P,C,H_4]^+$ ion remains uncertain and requires further experimental work.

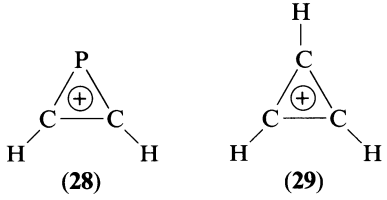
$$PCH_2^+ + B \longrightarrow PCH + BH^+ \quad (71)$$

A number of other interesting insertion reactions between several phosphorus-containing ions and various organic molecules which result in the formation of species containing P—C bonds have been studied[85,89,90]. A seemingly ubiquitous product observed when



SCHEME 3 Routes to the formation of $PC_2H_2^+$.

unsaturated organic molecules are allowed to react with a number of phosphorus-containing ions is $PC_2H_2^+$. This ion is also formed as a fragment ion in the EI mass spectra of Me_2PH and Me_3P[56a,b]. It reacts in a complex fashion with Me_2PH and Me_3P[56b]. The different synthetic pathways to this ion are outlined in Scheme 3. Smith and coworkers[23] have suggested that this ion is the cyclic ion **28**, which should exhibit a similar stability to that of the aromatic $C_3H_3^+$ ion **29**[91]. *Ab initio* calculations verify that the cyclic structure **28** is considerably more stable than other isomeric structure[92].



(28) **(29)**

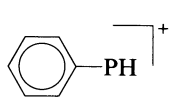
The ion P_2^+ reacts with C_2H_4 to produce P_2CH^+ (equation 72), which may have a related cyclic structure[89].

$$P_2^+ + CH_2{=}CH_2 \longrightarrow P_2CH^+ + CH_3 \quad (72)$$

$$P^+ + C_6H_5 \longrightarrow \begin{cases} C_6H_6^+ + P & (73a) \\ C_6H_5^+ + PH & (73b) \\ PC_4H_4^+ + C_2H_2 & (73c) \\ C_5H_5^+ + PCH & (73d) \\ PC_2H_2^+ + C_4H_4 & (73e) \\ C_3H_3^+ + PC_3H_3 & (73f) \end{cases}$$

Two groups have studied the reactions of P^+ with benzene using an ICR mass spectrometer[89,90]. Apart from charge exchange (equation 73a) and hydride transfer (equation 73b), many of the products involve the formation of phosphorus–carbon bonds via insertion reactions (equations 73c–f).

The nature of these insertion reactions has been probed by subjecting the $[P,C_6,H_6]^+$ adducts (formed by reacting P^+ with benzene in a chemical ionization source) to CA[90]. These experiments suggest that P^+ inserts into the C—H bond to give **30** and also into the C—C bond to give **31**.



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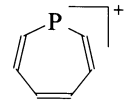


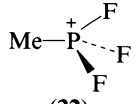
(31)

Phosphines (e.g. Me_3P and Me_2PPh) are readily alkylated in the gas phase to form the corresponding phosphonium ions (equation 74)[55,62,93]. The HPF_3^+ ion reacts with MeF to give $MePF_3^+$ (equation 75), which may have either of the structures **32** or **33**[94]. The $MePF_3^+$ product ion undergoes a Me^+ transfer with MeF (equation 76).

$$Me_3P + R^+ \longrightarrow Me_3PR_5 \quad R = Et, Me_2PCH_2 \tag{74}$$

$$HPF_3^+ + MeF \longrightarrow MePF_3^+ + HF \tag{75}$$

$$MePF_3^+ + MeF \longrightarrow Me_2F^+ + PF_3 \tag{76}$$



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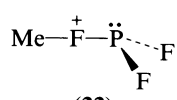

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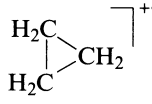
Finally, it should be noted that distonic ions can be synthesized via phosphorus–carbon bond-forming reactions (equations 77–79)[95–97].



$$+ PH_3 \longrightarrow H_3PCH_2^{+\bullet} + C_2H_4 \tag{77}$$

$$Me_2SCH_2^{+\bullet} + (MeO)_3P \longrightarrow (MeO)_3PCH_2^{+\bullet} + Me_2S \tag{78}$$

$$(MeO)_3\overset{+}{P}OCH_2\dot{C}H_2 + (MeO)_3P \longrightarrow (MeO)_3\overset{+}{P}CH_2\dot{C}H_2 + (MeO)_3PO \tag{79}$$

IV. MASS SPECTROMETRIC ANALYSIS OF ORGANOPHOSPHORUS SPECIES

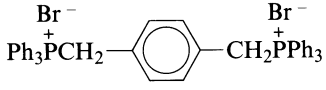
This section deals primarily with the mass spectrometric analysis of organophosphorus compounds via techniques other than traditional EI-MS. Newer ionization techniques have greatly expanded the realm of mass spectrometric analysis to include polar, thermally labile species[2,3,6–8], while tandem mass spectrometric techniques are now more routinely used to gain further structural information[10]. The most commonly used tandem mass

spectrometric technique is collisional activation, in which an ion is mass selected, accelerated and allowed to collide with a neutral gas (such as He). These collisions cause the ion to fragment into product ions which are analysed via a second stage of mass spectrometry. These fragment ions are often diagnostic of the structure of the original ion (e.g. equations 11 and 12). Those readers interested in the fundamental aspects of the actual collision process are referred to the appropriate reviews[10,98].

There are two general classes of fragmentation reactions observed in the CA-MS of even-electron ions: charge-initiated (sometimes called charge-mediated) fragmentation and charge-remote fragmentations. The mechanisms of charge initiated fragmentation reactions often involve the intermediacy of ion-neutral complexes[99,100]. Charge-remote fragmentations involve bond-cleavage reactions which take place at a site in the ion which is removed from the charge site and do not involve any significant intervention of the site of the charge[101,102].

A. Organophosphonium Salts

Organophosphonium salts are a general class of compounds which are difficult to analyse via conventional EI-MS[103]. Thus several reports have appeared in the literature which describe the use of alternative ionization methods to analyse this important class of compounds[104–108]. Early studies, which centered around the use of field desorption (FD), demonstrated that the intact phosphonium ion is often the most abundant ion[104]. A comparison was made between the use of FD and FAB as ionization methods for the analysis of the diphosphonium salt **34**[105]. FD produces high abundances of the intact phosphonium ions $[M - Br^-]^+$ and $[M - 2Br^-]^{2+}$, whereas these ions are only minor peaks in the FAB mass spectrum using glycerol as the matrix. Instead, the fragment ion **35** is the base peak in the FAB spectrum.



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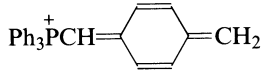

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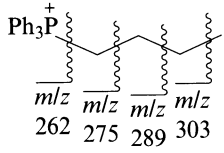
In a detailed study McCrery. *et al.*[106a] compared the use of FAB (using a glycerol matrix) and high energy CA in a tandem mass spectrometer with the use of LD coupled with CA in an FT-ICR system as a means of analysing alkyltriphenylphosphonium halides. Both ionization methods are equally useful in determining molecular masses of the phosphonium ions. However, only high-energy CA using the tandem mass spectrometer was able to distinguish between the isomeric butyltriphenylphosphonium ions **36**–**38**. The high-energy CA mass spectra of each of these ions contain both charge directed and charge remote fragmentations. Some of the fragmentations which lead to unambiguous identification are shown for these ions. In particular, the location of the methyl branch points is indicated by 'gaps' of 28 and 26 u in the CA mass spectra of **37** and **38**, respectively. Further McCrery



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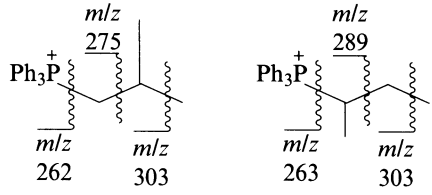
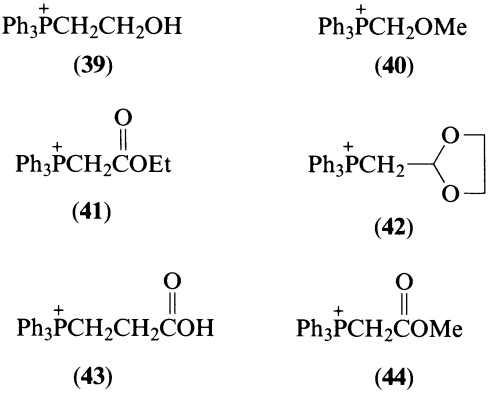


(37) (38)

et al.[106a] suggested that the ratio of the abundances of the product ions $Ph_3P^{+\cdot}$ (*m/z* 262) and Ph_3PH^+ (*m/z* 263) in the FAB and LD spectra of alkyltriphenylphosphonium ions provide information about the internal energy of the decomposing phosphonium ions.

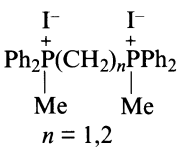
Several other groups have investigated the use of FAB-MS to analyse organophosphonium halides[106b–d]. Claereboudt *et al.*[106d] extended the studies of these species to include the FAB mass spectra of a series of mono- and bis-phosphonium halides derived from triphenylphosphine. Two different matrices were used to generate FAB Mass spectra: glycerol and 3-nitrobenzyl alcohol (3-NBA). The use of 3-NBA is recommended not only to avoid artifact ions but also to aid in the observation of dications derived from biphosphonium halides (which are observed in lower abundance or are completely absent when glycerol is used)[106d]. Williams *et al.*[106c] investigated one-electron reduction reactions of bisphosphonium dihalides by the FAB matrix. Further, the fragmentation reactions of phosphonium ions have been discussed in detail[106b]. Once again, high-energy CA was shown to be useful in distinguishing a series of isomers, including 39–40, 41–42 and 43–44[106b,d].



Claereboudt *et al.*[107c] also studied the same series of mono- and bis- phosphonium halides using LD mass spectrometry. They compared the LD mass spectra generated via direct analysis of the neat salts versus matrix-assisted LD mass spectrometry. The latter method was found to be superior for the following reasons: (i) increase in ion yield of preformed cations; (ii) reduction of artifact peaks (caused by thermal decomposition and other deleterious surface reactions); and (iii) much better reproducibility. Unlike the FAB mass spectra, no doubly charged cations were observed in the LD mass spectra of the biphosphonium halides.

More recently, ESI-MS has been used to analyse a series of mono- and poly-phosphonium halides[108]. Electrospray mass spectra of the cations can be obtained directly from dichloromethane–methanol solutions[108b]. The intact dications for the bisphosphonium

iodides **45** are observed, but for the trisphosphonium iodide **46**, the intact trication is not observed[108b]. Instead, the base peak is due to the formation of a fragment ion **47**. In some of the polyphosphines with free phosphine groups (**48**), higher mass ions (at 16 and 32 u higher than the molecular ion) were observed and were ascribed to oxidation of the free phosphine groups[108b]. The CA mass spectra of the electrosprayed ions show consistent modes of fragmentation, with the formation of alkene ions dominating[108b].



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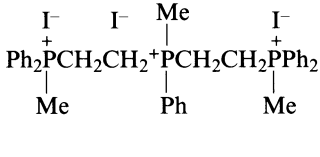

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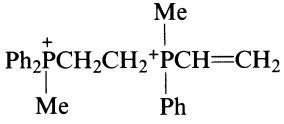

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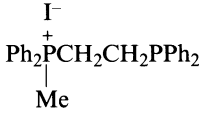
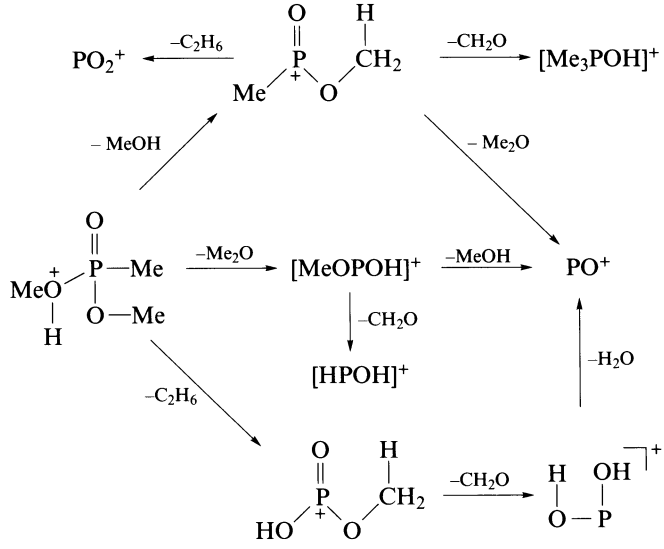


(48)

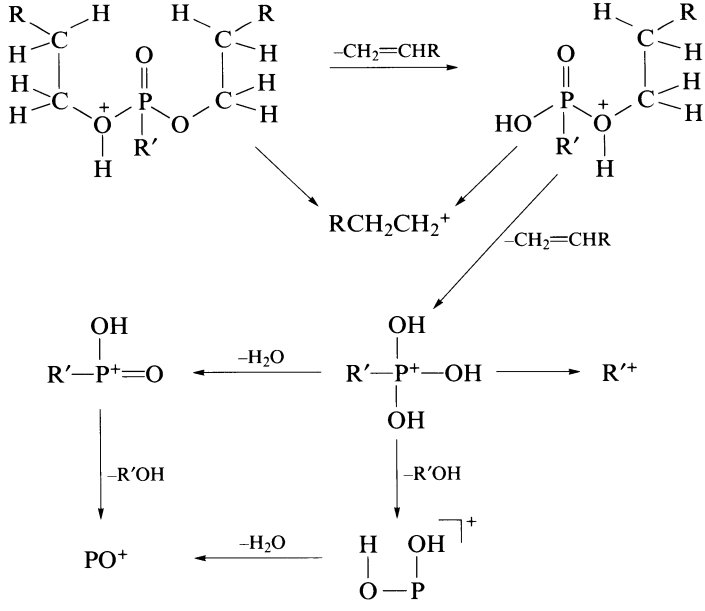
B. Organophosphorus Acids and Their Esters

Much of the mass spectrometric research on organophosphorus acids has focused on the EI mass spectra of their esters. More recently, the CA mass spectra of $[M + H]^+$ and $[M - H]^-$ ions derived from dialkyl alkylphosphonates have been measured[109,110]. The $[M + H]^+$ ions were generated via atmospheric pressure ionization (using either air or H_2O) and were subjected to CA using a triple quadrupole mass spectrometer[109]. In general, the fragment ions are produced via losses of one or a successive number of stable molecules rather than losses of radicals. The mechanisms of many of these fragmentation reactions were probed using the $[M + D]^+$ ion (formed from D_2O atmospheric pressure ionization). The three primary decomposition pathways for the $[M + H]^+$ ion of dimethyl methylphosphonate involve losses of MeOH, Me_2O and C_2H_6 (or $2CH_3$). The product ions formed undergo further fragmentation involving MeOH, Me_2O, CH_2O and C_2H_6 losses. The overall mechanistic pathways are summarized in Scheme 4[109a]. Similar fragmentation reactions are observed for higher homologues of dimethyl methylphosphonate, although when the alkoxy groups is ethyl or larger the fragmentation reactions are often dominated by McLafferty-type rearrangements (Scheme 5)[109b,c].

The $[M - H]^-$ ions derived from a series dialkyl alkylphosphonates and alkyl dimethylphosphinates were generated via chemical ionization using either NH_2^-, CD_3O^- or HO^- as the reagent ion. The mechanisms of the high-energy CA of these ions in a tandem mass spectrometer were determined by a combination of detailed deuterium labelling experiments together with product ion studies (using CA)[110]. The main fragmentation reactions of deprotonated dimethyl methylphosphonate proceed via losses of both radicals (equations 80a and b) as well as neutral molecules (equations 80c and d). Ions related to the metaphosphite (CH_2PO^- and PO_2^-) and metaphosphate (PO_3^-) ions are observed only as minor products. Deprotonated methyl dimethylphosphinate undergoes a similar series of losses (cf. equations 80a–d) in addition to the additional fragmentation reactions shown in equations 81a and b. The mechanisms for the loss of CH_2 (equations 80c) and CH_2O



SCHEME 4



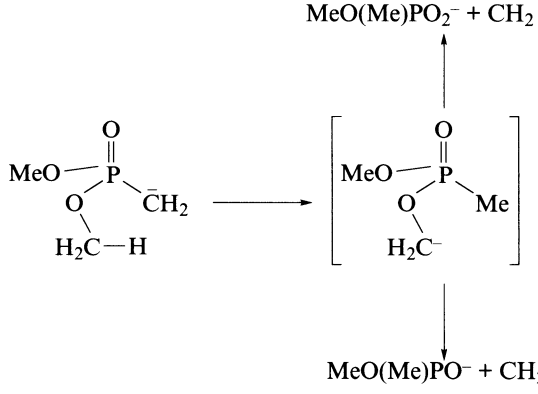
SCHEME 5

(equation 80d), which were investigated via a combination of deuterium labelling studies and CA-MS of the product ions, involve specific proton transfer to carbon as shown in Scheme 6. Isotope effects of 2.0 and 3.2 for the losses of CH_2 and CH_2O [as determined from the CA mass spectrum of $(MeO)(CD_3O)P(O)CH_2^-$] indicate that the proton-transfer step is rate determining. The dominant fragmentation reactions of deprotonated ethyl esters of dimethyl phosphinate and methyl phosphonate involves losses of MeCHO (equation 82a) and the elements of $[C_2,H_4]$. The latter loss occurs via two processes, as illustrated by deuterium labelling: elimination of $CH_2{=}CH_2$ (equation 82b) and elimination of MeCH (equation 82c), which is analogous to the loss of CH_2 (equation 80c). These reactions proceed via similar mechanisms to those shown in Scheme 6.

$$(MeO)_2P(O)CH_2^- \longrightarrow \begin{cases} (MeO)(CH_2O)P(O)CH_2^{-\bullet} + H & (80a) \\ (MeO)(CH_2)PO_2^{-\bullet} + CH_3 & (80b) \\ (MeO)(Me)PO_2^- + CH_2 & (80c) \\ (MeO)(Me)PO^- + CH_2O & (80d) \end{cases}$$

$$(MeO)(Me)P(O)CH_2^- \longrightarrow \begin{cases} (MeO)P(O)CH_2^{-\bullet} + CH_3 & (81a) \\ (CH_2)_2PO^- + MeOH & (81b) \end{cases}$$

$$(EtO)_2P(O)CH_2^- \longrightarrow \begin{cases} (EtO)(Me)PO^- + MeCHO & (82a) \\ (EtO)(Me)PO_2^- + CH_2{=}CH_2 & (82b) \\ (EtO)(Me)PO_2^- + MeCH & (82c) \end{cases}$$



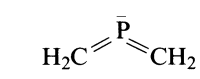
SCHEME 6

It is worth mentioning that the metaphosphate anion (PO_3^-) is readily observed in the negative ion mass spectra of many organophosphorus esters[111a]. Further, its ion–molecule reactions have been studied in a SIFT apparatus[111b]. Interestingly, the CA mass spectra of

a range of phosphorus-containing anions (e.g. equation 83) reveal the formation of families of negative ions based on the bis(methylene)metaphosphite anion [including $(CH_2)_2P^-$, CH_2PO^-, PO_2^-, POS^- and PS_2^-] and the tris(methylene)metaphosphate anion [including $(CH_2)_3P^-$, $(CH_2)_2PO^-$, $CH_2PO_2^-$, $(CH_2)_2PS^-$, $CH_2P(O)S^-$ and $CH_2PS_2^-$][112]. *Ab initio* calculations indicate that tris(methylene)metaphosphate anion is 'propeller shaped' with D_3 symmetry[112]. In a comparative study to the cationic system **5** and **6**, the phosphiranyl anion **50** and the bis(methylene)metaphosphite anion **49** have been studied via *ab initio* calculations[58b]. Both isomers have similar stabilities at the MP4(SDTQ)/6–31+G(d,p)//RHF/6–31+G(d,p) level of theory (including zero-point energy corrections) with a large calculated barrier to conrotatory ring opening of **50** to **49** of 33.7 kcal mol^{-1} (ref. 59a).

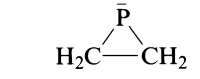
$$Me_2PCH_2^- \longrightarrow (CH_2)_3P^- + H_2 \quad (83a)$$

$$Me_2PCH_2^- \longrightarrow (CH_2)_2P^- + CH_4 \quad (83b)$$



E_{rel} = + 0.2 kcal mol^{-1}

(49)



E_{rel} = + 0.0 kcal mol^{-1}

(50)

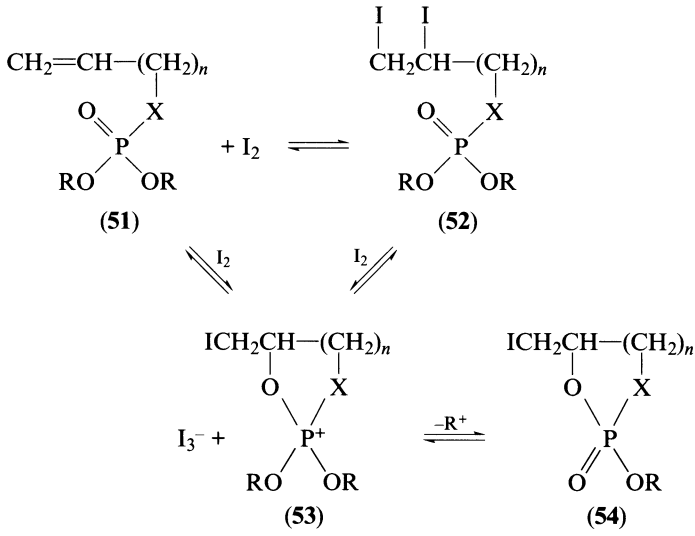
Finally the combination of ion-pair chromatography (using ammonium acetate or tetraalkylammonium salts) with thermospray mass spectrometry has been successfully applied to the analysis of a range of organophosphorus acids[113]. $[M + NH_4]^+$ ions are observed when ammonium acetate is used as the electrolyte, whereas clusters ions are observed using tetraalkylammonium salts.

C. Miscellaneous Intermediates of Solution Reactions of Organophosphorus Species

FAB-MS and ESI-MS have proved to be useful in the direct detection of intermediates formed in a number of solution reactions. As such, these techniques nicely complement ^{31}P NMR studies on the same systems. For example, the iodine-induced cyclization reaction of the unsaturated phosphoamidate **51a**, phosphonates **51b** and **c** and phosphate **51d** (illustrated in Scheme 7) was monitored by removing aliquots of the reaction mixture and analysing them via FAB-MS[114]. The FAB mass spectra revealed the presence of the reactant **51** (observed as an $[M + H]^+$ ion), the initial diiodo addition product **52** (observed as an $[M + H]^+$ ion) and the quasiphosphonium ion **53** (observed as the intact quasiphosphonium ion) and the iodolactone **54** (observed as an $[M + H]^+$ ion).

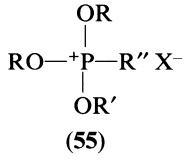
FAB-MS has also been used to identify quasiphosphonium halide intermediates (**55**) of the Arbuzov and Perkow reactions[115]. The quasiphosphonium ions fragment differently from conventional phosphonium ions under FAB conditions, preferring to undergo H transfer rearrangement with concomitant β cleavage (equation 84).

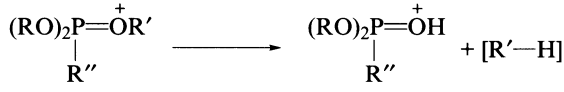
More recently, Wilson *et al.*[116a] have used ESI-MS to detect transient intermediates in the Wittig, Mitsunobu and Staudinger reactions directly from solution. Ionic intermediates were directly detected while zwitterionic intermediates were indirectly detected following acid quenching. The systems studied were those which had been previously investigated via ^{31}P NMR. This work demonstrated that the progress of these reactions can be



	X	*n*	R
51a	NH	1	Et
51b	CH_2	1	Et
51c	CH_2	2	Pr^n
51d	O	2	Et

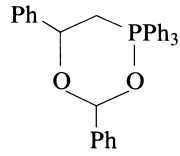
SCHEME 7





monitored over time by following the appearance and disappearance of peaks corresponding to the transient intermediates. Further, a new additional Wittig reaction product was detected, whose structure was proposed to be that of a cyclic acetal (**56**). The authors noted that this species may represent the previously unidentified product which gives rise to the extraneous ^{31}P NMR signals in the pentavalent phosphorus region of some Wittig reaction mixtures[116b].

Based on these few studies, the newer mass spectrometric techniques (particularly ESI-MS) hold great promise as a complimentary tool to ^{31}P NMR spectrometry in the direct analysis of solution reaction mixtures, without the need for product isolation. Such studies are particularly useful in unravelling mechanisms since transient species can be detected.



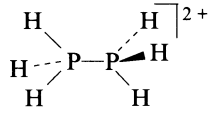
(56)

V. CONCLUSIONS

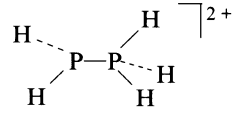
As noted in a previous review[68], there is a need for further experimental research on the electron affinities and acidities of organophosphorus species. Such data are especially valuable since they provide useful thermodynamic information on organophosphorus neutral species and radicals when used carefully in appropriate themochemical cycles (e.g. equations 7–10). The modelling of a range of gas-phase processes (such as combustion) involving organophosphorus species is currently hampered by a lack of such data.

Apart from some studies of the CA spectra of organophosphonium salts described in Section IV.A, there have been very few studies into the fundamental properties of multiply charged organophosphorus species in the gas phase. The doubly charged positive ion spectra of a range of organophosphorus compounds were investigated via a combination of experiment and theory[117]. The dications were allowed to undergo charge exchange reactions with methane as illustrated in equation 85. The observation of the intense product ion $POMe^{+\bullet}$ (equation 85) was explained by a diabatic curve-crossing model which predicts efficient electron transfer between the reactant and product potential energy curves at separation distances of between 4 and 5 Å. Further, based on *ab initio* calculations, Radom and coworkers[118,119] predict that the dications **57** and **58** should both be kinetically stable to dissociation to two singly charged cations. With the advent of electrospray ionization, further studies into the reactivities and properties of multiply charged organophosphorus species are anticipated and eagerly awaited.

$$[POMe]^{2+} + CH_4 \longrightarrow [POMe]^{+\bullet} + [CH_4]^{+\bullet} \qquad (85)$$



(57)



(58)

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CHAPTER 9

Biological activity of phosphonic and phosphinic acids

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I. INTRODUCTION

According to the nomenclature adopted by the American Chemical Society in the USA and the Royal Society of Chemistry in the UK, derivatives of tervalent phosphorus acids

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with one substituent linked to the P atom, $R^1P(OH)_2$ (**1**), are phosphonous acids and those with two substituents, $R^1R^2P(OH)$ (**2**) are phosphinous acids. For pentavalent P, compounds with one substituent, $R^1P(O)(OH)_2$ (**3**), are phosphonic acids and with two substituents, $R^1R^2P(O)(OH)$ (**4**), are phosphinic acids[1a]. The chemistry of these compounds was presented in detail over 30 years ago[1b] in a book which is still very useful. Additional information can be found in the *Encyclopedia of Chemical Technology*[2-4] and in *Organophosphates: Chemistry, Fate and Effects*[5].

Their numerous derivatives have pronounced physiological activity. They include not only the extremely poisonous warfare agents such as sarin $MeP(O)(OPr^i)F$, which is discussed in the next chapter, but also many compounds that have found use as in agriculture as insecticides, herbicides, chemical ripeners, etc., and important drugs, particularly in the treatment of osteoporosis, various viral infections and hypertension.

II. PHOSPHONIC ACIDS

A. Natural Occurrence and Metabolism

2-Aminoethylphosphonic acid (**3**, $R^1 = H_2NC_2H_4$)(AEP) was first isolated by Horiguchi and Kondatsu[6,7] from the ciliated protozoan *Tetrahymena pyriformis* (13% of the total P in the organism). Smith and O'Malley[8] found that the presence of this acid in growth medium increased the phosphonolipid content in this organism. It is present in the adult pulmonate snail *Heilosoma* sp. (29% of the total P), and in freshly laid eggs 98% of P occurs in the form of alkylphosphonates[9]. The same acid is the main P compound in locust haemolymph[10].

Bacteria are able to utilize various alkylphosphonates as sources of carbon, phosphorus and even nitrogen. *Pseudomonas putida* contains an enzyme system capable of cleaving the C—P bond[11]. Other organisms include *Pseudomonas fluorescens*, that was found to utilize diverse organophosphonates[12,13], *Rhodobacter capsulatus* ATCC 23782[14], *Enterobacter aerogenes* ATCC 15038[15] and *Escherichia coli*[16]. *Pseudomonas aeruginosa* A 237 can be grown in culture medium containing AEP as a source of P and C. A specific AEP-aminotransferase catalyses the formation of alanine and phosphonoacetaldehyde, which in turn is transformed into acetaldehyde and inorganic phosphate[17]. Evidence has been presented[18] for a 14 gene locus for phosphonate metabolism in *E. coli*. Many investigators have emphasized the importance of the metabolic reactions for removing alkylphosphonates from the natural environment. Reviews of the environmental degradation[19], detoxication by carboxylesterase[20] and metabolism of organophosphorus (OP) insecticides by flavin-containing monooxygenase have been published[21]. Publication No. 63 on *Environmental Health Criteria* published by the World Health Organization contains a wealth of information of chemical, analytical and physiological aspects of OP compounds, including phosphonates, with particular emphasis on their environmental effects[22].

B. Agricultural Applications

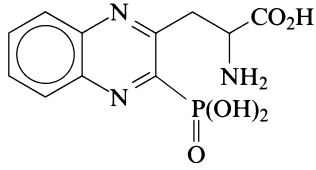
Although the majority of the well known phosphorus insecticides are derived from phosphoric acid, there are phosphonates, such as *O,O*-dimethyl (2,2,2-trichloro-1-hydroxyethyl)phosphonic acid, trichlorphon 5[$(MeO)_2P(O)(CHOHCCl_3)$], a compound with a relatively low mammalian toxicity[23].

Phosphonic acid itself controls downy mildew (*Peronospora parasitica*) in cauliflower curds, when applied twice before harvest (2.4 kg ha^{-1})[24]. Ethephon 3($R^1 = ClC_2H_4^-$) is a plant growth regulator and is used for ripening fruit crops[25]. Its LD_{50} in mice (orally) is 2850 mg kg^{-1}(ref. 26); accordingly, it has been discussed as a hazardous material[27]. Its alkyl and aryl esters have antifungal activity[28].

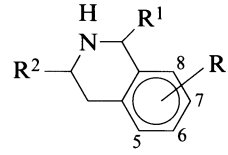
N-(Phosphonomethyl)glycine, $HOOCCH_2NHP(O)(OH)_2$ (**6**) (glyphosate), is a broad-spectrum, low-toxicity herbicide[29]. The related *N*,*N*-bis(phosphonomethyl)glycine, $HOOCCH_2H[P(O)(OH)_2]_2$ (**7**) (glyphosine), is a chemical ripener[30].

C. Biochemical and Physiological Activity

Various phosphonates have been reported as having antagonistic and inhibitory effects. The (phosphonoalkyl)(aminocarboxyalkyl)quinoxalines **8** have been prepared and patented as *N*-methyl-D-asparatate (NMDA) antagonists. The L-form inhibited NMDA-induced mortality in mice with $ED_{50} = 1.52$ mg kg^{-1} i.p.[31].

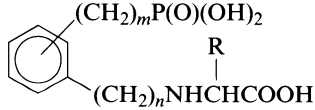


(**8**)



(**9**)

Phosphonoalkyl-substituted tetrahydroisoquinolines have been proposed as competitive antagonist models. Their structures were derived from an agonist pharmacophore model for NMDA. The most active was 1,2,3,4-tetrahydro-5-(2-phosphonoethyl)-3-isoquinolinecarboxylic acid (**9**, $R^1 = H$, $R^2 = COOH$, $R^3 = 5\text{-}CH_2CH_2PO_3H_2$)[32]. Less potent were *N*-(phosphonoalkyl)phenyl-(**10**) (*m* or $n = 1$, R = H) and *N*-(phosphonoalkyl)-α-amino acids (**11**)[33]. The subject has been reviewed[34].



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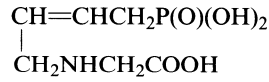
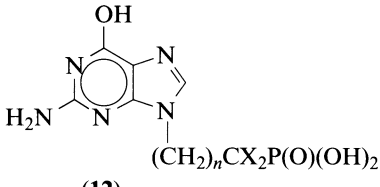


(**11**)

Several 9-(phosphonoalkyl)- and 9-(difluoroalkyl)-guanine derivatives (**12**, X = H or F) have been studied as potential inhibitors of guanylate kinase. The most pronounced effect was observed with $n = 5$[35]. Phenoxymethylene bisphosphonates (**13**, where R^1, R^2 and R^3 represent a variety of substituents) were prepared and found to act as inositol phosphatase inhibitors and antimanic agents; some inhibited the enzyme with $IC_{50} < 50$ μmol [36,37]. 4-(Phosphonomethylphenoxy)-1-carbamoylazetidine-2-ones (**14**) inhibited human leukocyte elastase; K_{obs} for **14** (R^1, R^2 = OEt = 1.2×10^{-6} mol^{-1} s^{-1} (ref. 38).



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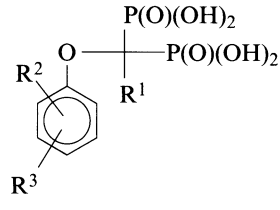

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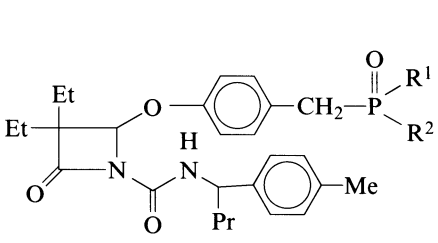

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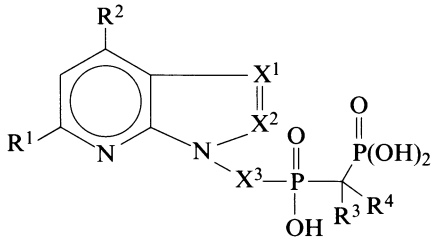
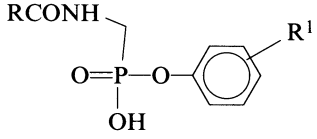
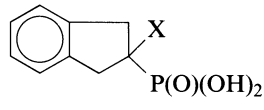


(15)

Purine-9-ylalkyl derivatives (**15**) containing both the phosphonic and phosphinic substituent inhibit purine nucleoside phosphorylase. Compound **15** [$R^1 = NH_2$, $R^2 = OH$, R^3, $R^4 = H$, $X^1 = N$, $X^2 = H$, $X^3 = CH_2$)$_3$] had $K_i = 0.0026$ μmol (ref. 39). The phosphonate monoesters **16** (R = Me, R^1 = *o*-, *m*- or *p*-NO_2) inhibit the class A β-lactamase, probably by phosphorylation of the active site of this enzyme[40]. When R = Ph they also inhibit class C β-lactamase of *Enterobacter cloacae* P99 and may led to new antibiotics. They should be useful as active titrants of the enzyme[41].

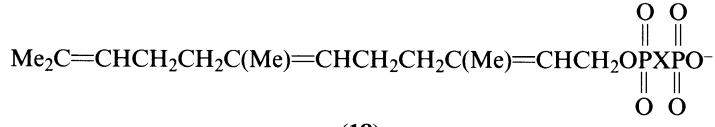


(16)



(17)

2-Aminoindan-2-phosphonic acid (**17**) has been found to be a strong inhibitor of the plant enzyme phenylalanine ammonia-lyase which blocks the synthesis of various phenylpropanoid compounds[42]. The isoprenoids (phosphinylmethyl)phosphonates **18** (X = CH_2), analogues of farnesyl pyrophosphate (**18**, X = O), act as inhibitors of squalene synthetase, which is involved in the biosynthesis of cholesterol[43]. Phosphonoformic acid (foscarnet) **19**, *n* = 0)[44] was found to inhibit the Na^+–P_i transport in opossum kidney cells although after prolonged exposure it increases this uptake[45]. It also affects the high-affinity Na^+-dependent phosphate transport processes in mouse renal brush-border membrane vesicles[46]. A series of α-halo[(phenylphosphinyl)methyl]phosphonates were studied as inhibitors of this transport, the most potent compound being α-fluoro[phenylphosphinyl)methyl]phosphonate [**20**, $(HO)_2P(O)CHFP(O)(Ph)OH$][47]. Long-chain phosphonate esters have been evaluated as enhancers of transdermal penetration of drugs. The



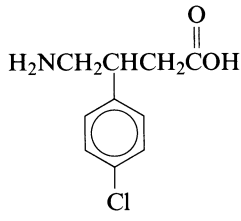
(18)

$HOOC(CH_2)_n(O)P(O)(OH)_2$

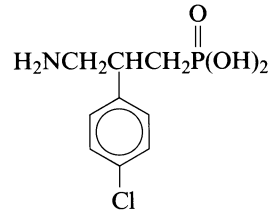
(19)

diethyl ester of hexadecylphosphonic acid (**3**, R = $C_{16}H_{33}$) raised the permeability coefficient of indomethacin about tenfold[48].

Much attention has been given recently to $GABA_B$ receptor and to its antagonists. A review on γ-aminobutyric acid (GABA) receptors was published in 1980[49], and more recently the pharmacology of $GABA_A$ receptor subtypes has been described[50]. Baclophen [β-(*p*-chlorophenyl)GABA, **21**] is a selective agonist for a population of GABA receptors. The phosphonate analogue of **21**, phaclophen (**22**), inhibits the effects of **21** and of GABA[51]; particularly potent are derivatives of phosphinic acid (see Section III. A).



(**21**)

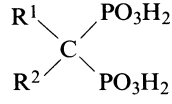


(**22**)

D. Pharmacological Activity

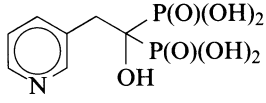
1. Osteoporosis

The bisphosphonates **23** inhibit bone resorption. They affect osteoclast metabolism through absorption on bone surfaces and their subsequent uptake and release[52,53]. The first such compounds reported were etidronate (**23**, R^1 = OH, R^2 = Me) and chlodronate (R^1, R^2 = Cl). Introduction of other groups yielded agents with higher potency that found clinical use, such as pamidronate [**23**, R^1 = OH, $R^2 = (CH_2)_2NH_2$]. Its pharmacological properties were investigated in various laboratory animals and no significant adverse effects were found[54], although it has been suggested that it should be avoided during pregnancy[55].

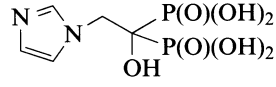


(**23**)

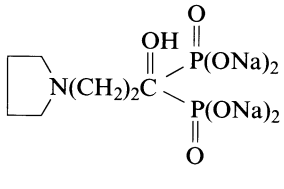
The effects of sex and age on the disposition of alendronate [**23**, R^1 = OH, $R^2 = (CH_2)_3NH_2$] were studied in rats. The uptake in old animals was lower than that in young animals by a factor of 2–3[56]. Alkylation of the amine enhanced further the activity as in dimethyl pamidronate [**23**, R^1 = OH, $R^2 = (CH_2)_2NMe_2$][57]. Heterocyclic derivatives containing a pyridine (**24**), imidazole (**25**) or pyrrolidine ring (**26**) were even more



(**24**)



(**25**)



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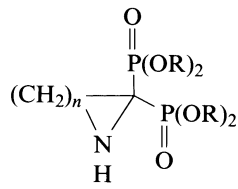


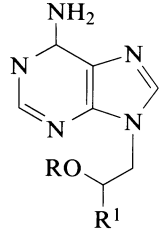
(27)

potent[58,59]. Azacycloalkane bisphosphonates (**27**, n = 7–16, R = H, C_{1-4} alkyl) were useful in the treatment of Ca^{2+} metabolism, osteoporosis, Paget's disease, urolithiasis, etc.[60]. The subject has been intensively pursued and many new compounds have been patented[61,62].

2. *Antiviral activity*

A substantial number of phosphonates have been prepared and tested against viral infections, including AIDS. Even relatively simple compounds such as the above-mentioned phosphonoformic acid (**19**, n = 0) and phosphonoacetic acid (**19**, n = 1) were reported as antivirals[44] and herpes virus inhibitors[63–65], active against acyclovirresistant herpes and cytomegalovirus retinitis in patients with AIDS[66,67]. The veterinary use has been mentioned[68].

Particularly active are derivatives of heterocyclic compounds. Their properties have been reviewed[69,70]. Thus, (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)-adenine (HPMPA) [**28**, R = —$CH_2P(O)(OH)_2$, R^1 = —CH_2OH] and -cytosine (HPMPC) [**29**, R = —$CH_2P(O)(OH)_2$] are highly selective inhibitors of herpes virus replication. 9-(2-Phosphonylmethoxyethyl)adenine (PME) [**28**, R = —$CH_2P(O)(OH)_2$, R^1 = H] has a marked activity against HIV-1, HIV-2 and other retroviruses[70]. The selective effect of the *S*-isomer of **29** against human cytomegalovirus replication has been reported[71].



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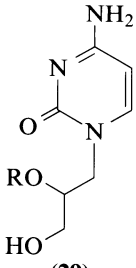
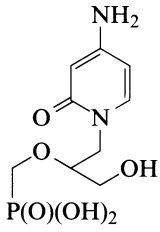


(29)

Compound **29** was found to be much more potent than ganciclovir against murine cytomegalovirus infections in immunodeficient mice[72] and in immunocompromised rats[73]. Martin and Hitchcock[74] tested 3-hydroxy-2-phosphonolmethoxypropylcytosine (**30**) and proposed this compound as an agent suitable for the parenteral treatment of severe herpes virus infections. A series of methyl derivatives of guanine (**31**) have been prepared and examined. Compound **31** (R = H or Me, R^1 = Me) demonstrated potent anti-HIV activity with ED_{50} values of 1.0 μmol[75]. From a plethora of other nucleotides, the adenine compound **32** has been reported to be very potent against Rauscher murine leukaemia virus (ID_{50} = 0.003 μmol) and against HIV (1.5 μmol)[76].



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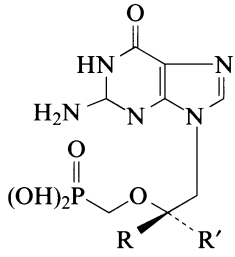

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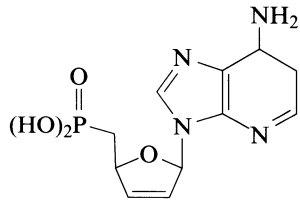

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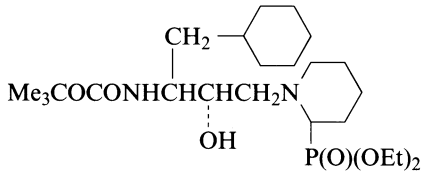
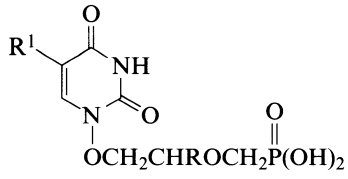


(33)

Pyrrolidinylphosphonate-containing peptides **33** have been patented as antivirals. They had $IC_{50}\ 10^{-6}$ mol (non-polar diastereoisomer) and $IC_{50}\ 10^{-7}$ mol (polar isomer) against HIV protease[77]. A number of 1-(phosphonomethoxyalkoxy)-thymine (**34**, R = CH_2OH, R^1 = Me) and -cytosine (**35**, R = CH_2OH) derivatives have been prepared, which are active against herpes, varicella-zoster and visna viruses at 19, 66 and 3 μg ml^{-1}, respectively[78].



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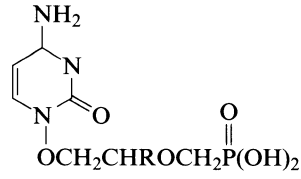
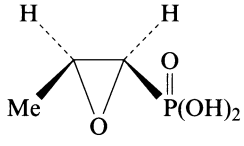


(35)

3. *Antibacterial activity*

(2*R*)-*cis*-(3-Methyloxiranyl)phosphonic acid (fosfomycin) (**36**) was isolated from *Streptomyces* strains and is used as an antibacterial[79]. Its biosynthetic pathway from phosphoenolpyruvic acid has been proposed[80].



(36)

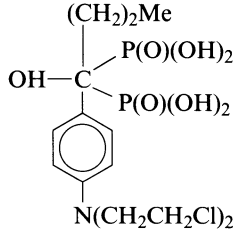
4. Anticancer agents

A derivative containing 2-chloroethylamino and nitroso groups, fotemustine (**37**)[81], is an antineoplastic, reported to be effective in cases of malignant melanoma[82]. Platinum complexes with phosphonocarboxylate ligands (**38**) of the general formula *cis*-M[PtA_2(PC)], (M = H or Na, A = ammonia or amine and the PC ligand = —$O_2C(CR^1R^2)_nPO_3$— with n = 0 or 1 and R^1, R^2 = phenyl or alkanoic acid substituents) were tested against sarcoma 180 ascites, L1210 leukaemia and M5076 reticulum cell sarcoma in mice. Several derivatives showed promising antitumour activity[83].

$$ClCH_2CH_2N(NO)C(O)NHCHMeP(O)(OEt)_2$$

(**37**)

A combination of 4-{4-[bis-(2-chloroethyl)amino]phenyl}-1-hydroxybutane-1,1-bisphosphonic acid (**39**) and aminotris(methylphosphonato)diamminoplatinum has shown good therapeutic activity against an osteosarcoma which metastasizes in the lung. In experiments with rats these compounds, with addition of the antimetastatic agent razoxane (**40**)[84]; displayed an enhanced anticancer activity[85].



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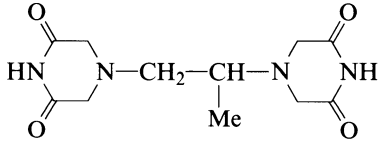
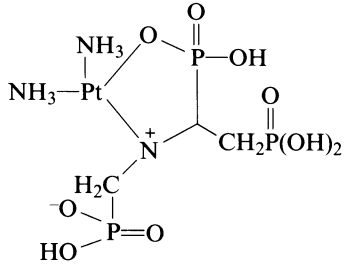


(**40**)



(**41**)

Related compounds such as the *cis*-Pt-linked phosphonate **41** showed high anticancer effects, as evidenced by a standstill of tumour growth after 3 weeks of therapy in intraosseously transplanted osteosarcoma in rats, and an increase in life span. Compound **41** at 0.346 and 0.6 mmol kg^{-1} total dose was very effective[86]. Aminoacyl diphosphonates have been prepared as neoplasm inhibitors. *N*-({4-[Bis(2-chloroethyl)amino]phenyl-alanyl}alanyl)-4-amino-1-hydroxybutane-1,1-diphosphonic acid hydrochloride (**42**) has been found to be active against murine leukaemia L-1210, ID_{50} 0.1 μg ml^{-1} (ref. 87).

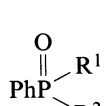
(42)

5. Other uses

Organic phosphonates have been added to dentifrices as calculus-inhibitory agents[88,89].

E. Sulphur-containing Derivatives

Phenylphosphono-thioates and -dithioates (**43**, R^1 = SPr, SBu; R^2 = $OC_6H_4NO_2$, SBu) have been found to enhance the activation of rat splenocytes by concanavalin A. Some of the compounds have a relatively low toxicity [the LD_{50} of **43**, (R^1, R^2 = SBu) was 173 mg kg^{-1}] and were found to support effectively lymphocyte growth *in vitro*[90]. Derivatives of sulphur-containing phosphonic acid are known to act as insecticides and acaricides, e.g. leptophos (**44**) [*O*-methyl-*O*-(4-bromo-2,5-dichlorophenyl) phenylphosphonothioate][91] and fonofos (**45**) [*O*-ethyl-*S*-phenyl (*RS*)-ethylphosphonodithioate][92].



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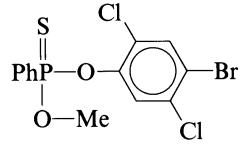

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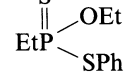
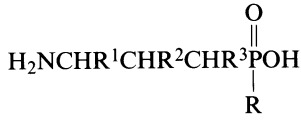


(45)

III. PHOSPHINIC ACIDS

A. Biochemical and Physiological Activity

Derivatives of phosphinic acids have been found to possess important physiological activity. As mentioned earlier, they act as antagonists to the $GABA_B$ receptor and to its antagonists. Particularly potent are derivatives of 3-aminopropylphosphinic acid (**46**), which interact with rat cortex $GABA_B$ receptors with IC_{50} about 10^{-7} mol[93]. One of these compounds, 3-aminopropyl(diethoxymethyl)phosphinic acid [**46**, R = $CH(OEt)_2$, R^1, R^2, R^3 = H; CGP 35348] has been intensively investigated. Several authors have described the antagonistic action of **46** to the antinociception induced by baclophen (**21**) in the spinal cord of the rat[94], and the potentiating effect of **21** on noradrenaline-induced stimulation of adenylate cyclase in rat cortex slices. It showed affinity only to the $GABA_B$ with IC_{50} 34 μmol and it is 10–30 times more potent than phaclophen (**22**)[95]. CGP 35348 had inhibitory effects on the reduction in [Ca^{2+}] in isolated melanotrophs of the rat[96], and it depressed excitatory postsynaptic potentials mediated by glutamate[97].



(46)

3-Aminopropyl(cyclohexylmethyl)phosphinic acid (**46**, R = $CH_2C_6H_{11}$, R^1, R^2, R^3 = H) has been patented as an antiepileptic. When given to epileptic rats (400 mg kg^{-1} i.p.) it eliminated spike and wave discharges after 20 min[98].

GABA receptor agonists have been proposed as drugs for the treatment of bladder instability without side-effects on the central nervous system. 3-Aminopropylphosphinic acid (**46**, R, R^1, R^2, R^3 = H) inhibited the contraction of urinary bladder smooth muscle strips of rabbit by 45% when compared with controls[99].

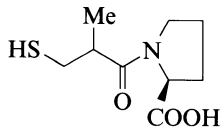
It has been suggested that the studies of receptor subtypes may open up the possibility of novel therapeutic strategies[100]. Aminoalkylphosphinates inhibit various bacterial enzymes. D-3-[(1-aminoethyl)phosphinyl]-2-heptylpropionic acid (**47**, R^1 = H, R^2 = C_7H_{15}) is a potent active site-directed inhibitor of D-alanine:D-alanine ligase of *Salmonella typhimurium*[101]. This compound and related dipeptide analogues, e.g. **47** (R^1 = Me, R^2 = SMe), were found to possess modest antibacterial activity[102]. Also, [(1*S*)-aminoethyl][(2*RS*)-2-carboxy-1-octyl]phosphinic acid (**47**, R^1 = H, R^2 = C_8H_{17}) was described as a classical slow-binding inhibitor of the *E. coli* ligase[103].

(**47**)

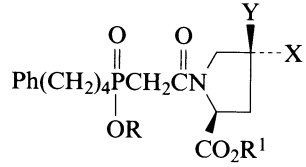
An azetidine compound, **14** (R^1 = Ph, R^2 = OEt), related to the earlier mentioned phosphonic derivative, inhibited the proteolytic function of human granulocyte elastase with $K_{obs} = 1.2 \times 10^{-6}$ l mol^{-1} s^{-1} (ref.104).

B. Pharmacological Activity

Following the introduction of captopril (**48**), an orally active angiotensin-converting enzyme inhibitor (ACE), many proline-containing analogues have been prepared for treatment of hypertension and congestive heart failure)[105]. One of the most active derivatives is fosinopril (**49**, R = $Me_2CHCHOC(O)Et$; R^1, Y = H; X = cyclohexyl), which, after oral administration, undergoes rapid hydrolysis to fosinoprilat (**49**, R, R^1, Y = H, X = cyclohexyl). Unlike other agents, fosinopril is cleared by the liver and kidney and well tolerated by patients with renal insufficiency[106,107].



(**48**)

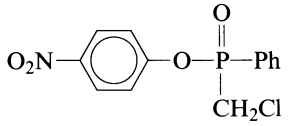


(**49**)

Phosphinic acid isosters of di-, tetra- and hexa-peptides, in which the —CONH— amide group has been replaced by —P(O)(OH)CHR, were found to act as powerful inhibitors of HIV protease. K_i ranged from 0.4 nmol to 26 μmol[108].

Various organophosphates induce delayed polyneuropathy (OPIDP), which is characterized by sensations in limbs, weakness and even paralysis[109–111]. Neuropathy target

esterase (NTE) is assumed to be the molecular target for OPIDP. Different compounds, including phosphinates, were found to protect against OPIDP when administered prior to OP[112]. Hens, which are very sensitive to intoxication, are used as test animals. Phosphinates, e.g. 4-nitrophenyl chloromethyl(phenyl) phosphinate (**50**), were considered as pretreatments drugs for nerve agents[113,114]. Sodium α-hydroxybenzylphosphinate (**51**) is mentioned as a nutrient[115].



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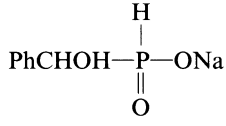
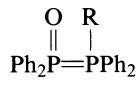


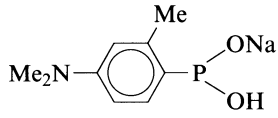
(**51**)

C. Other Phosphorus Derivatives

Phosphinamide derivatives were prepared mostly for agrochemical uses. Compound **52** (R = *p*-ClC_6H_4) showed 100% control of *Pseudospora cubenis* at 25 ppm without any harm to cucumber seedlings[116]. Derivatives of tervalent phosphorus are of minor biological importance. As an example of this group, the sodium salt of (4-dimethylamino-*o*-tolyl)phosphonous acid (**53**) has found use as a tonic[117].



(**52**)



(**53**)

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CHAPTER 10

The chemistry of organophosphorus chemical warfare agents

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I. INTRODUCTION

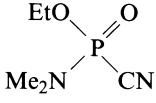
The 1914–18 war saw the first large-scale use (an estimated 125000 tons) of chemical weapons. Casualties numbered about 1.3 million, of which about 100000 were fatal[1]. The greatest number of casualties were caused by the vesicant sulphur mustard and the greatest number of lethalities by the industrial chemicals phosgene, diphosgene and chlorine. The organophosphorus nerve agents sarin and tabun were discovered in Germany in the period just before World War II (WWII). These and later compounds are 20–50 times more potent as lethal agents than phosgene and yet they were not used in WWII, almost certainly for fear of retaliation in kind. Only in the last decade has the use of nerve agents in armed conflict been substantiated[2–5]. Since their discovery, the nerve agents have been the subject of a considerable amount of chemical, biochemical and toxicological research, initially with the aim of producing more effective chemical warfare agents, but later with the goal of providing effective defensive measures such as detection, protection, decontamination and medical treatment. The study of organophosphorus nerve agents, and the related organophosphorus pesticides, has contributed significantly to our knowledge of the biochemistry of the cholinergic pathways in the nervous system.

This chapter will review the synthetic, analytical and toxicological chemistry of the organophosphorus nerve agents, together with their physicochemical and toxicological properties. Most of the discussion will concentrate on the 'traditional' organophosphorus chemical warfare agents, tabun, soman, sarin and VX. The last two sections deal with structure–activity relationships and the control of nerve agents and their analogues under the terms of the Chemical Weapons Convention. The coverage is highly selective and more detailed reviews are referred to in the text. Biochemical mechanisms, toxicology and medical treatment have been fully reviewed by Somani[6] and his collaborators. A full account of the physical and chemical properties of (all) CW agents is contained in a monogragh by Franke[7]. Much of the research on organophosphorus compounds as chemical warfare agents has been undertaken in, or on behalf of, defence establishments throughout the world and is recorded in reports that cannot easily be consulted. In this chapter, with very few exceptions, references have been restricted to those that are readily accessible in the scientific literature.

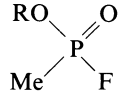
II. HISTORICAL DEVELOPMENT

During the 1930s, the need to increase crop yields and boost food production stimulated the development of new, cheap and selective synthetic pesticides as alternatives to naturally occurring materials such as nicotine, rotenone and pyrethrum. In Germany during

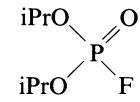
this period, Gerhard Schrader, an organic chemist employed in the laboratories of I. G. Farben, was involved in the synthesis and testing of new organophosphorus compounds as potential insecticides. In 1937, the efforts of Schrader resulted in the synthesis and patenting[8] of a highly toxic organophosphorus compound designated at the time as Le-100, *O*-ethyl *N*,*N*-dimethylphosphoramidocyanidate (**1**), later to be known as tabun or GA. The military potential of Le-100 was immediately recognized by the German Ordnance Department and the patent application was classified 'secret'. Shortly afterwards, in 1938, Schrader prepared Le-113, ethyl methylphosphonofluoridate (**2**), and T-144, isopropyl methylphosphonofluoridate (**3**), later known as sarin or GB. These compounds, especially sarin, were significantly more toxic than tabun. Pinacolyl methylphosphonofluoridate (**4**) (soman or GD), one of the most toxic of the phosphonofluoridates, was synthesized in 1944. These compounds comprised the group that later became known collectively as G-agents (US military designation) or more trivially as 'nerve gases' or 'nerve agents'. They were potent inhibitors of the enzyme acetylcholinesterase (AChE) with high mammalian toxicities by the inhalation route (and as such were too toxic for use as commercial insecticides). Tabun was manufactured and weaponised in large quantities (ca 12000 tons) in Germany during WWII and limited production of sarin had commenced in 1944. The G-agents were significantly more toxic than any chemicals available outside Germany at that time.



(**1**) tabun, GA



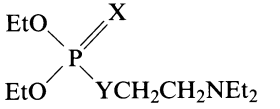
(**2**) R = Et, LE 113
(**3**) R = Pr^{i}, sarin, GB
(**4**) R = 1,2,2-trimethylpropyl, soman, GD



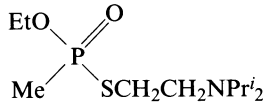
(**5**) DFP

In the UK (and later in the USA) during WWII, Saunders and his group at Cambridge, under the auspices of the Ministry of Supply, independently synthesized a large number of toxic (and non-toxic) organophosphorus compounds. An interesting account of the work carried out during this period has been published[9]. Their efforts were concentrated on the dialkyl phosphorofluoridates, of which the diisopropyl analogue **5** (DFP), synthesized in 1941[10], was one of the most toxic[11]; it was also easily synthesized. Following the end of WWII, as a result of samples recovered from German munition dumps and from the interrogation[8] of German scientists, the existence and structures of tabun, sarin and soman were established. The substantially greater toxicity of these compounds rendered DFP largely obsolete as a potential chemical warfare (CW) agent.

The period immediately after WWII saw, for the first time, the exploitation of organophosphorus compounds as pesticides. One such compound, Amiton (**6**)[12,13], proved to be too toxic for unrestricted commercial usage and was brought to the attention of the (then) Chemical Defence Experimental Establishment at Porton Down, UK. Amiton was reported to be highly toxic by intravenous administration, and, somewhat unusually, by the percutaneous route. Initial studies at Porton showed that the structure assigned to Amiton, mainly as a consequence of the method of synthesis[12], was incorrect, and that the compound has the 'thiolo' structure **6** (with a P—S bond) rather than the isomeric 'thiono' structure **7** (with a P=S bond). Systematic chemical modification of Amiton, of which the key feature was the introduction of a carbon–phosphorus bond into the molecule, produced a series of AChE inhibitors of low volatility that were several times more toxic than the G-agents. These nerve agents were known as V-agents; they were highly toxic by inhalation when dispersed as aerosols and, in contrast to G-agents, were almost as toxic when applied percutaneously to the skin. The best known compound from this series is *O*-ethyl *S*-(2-diisopropylaminoethyl) methylphosphonothiolate (**8**), code-named VX.

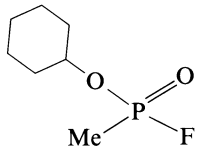


(6) X = O, Y = S, Amiton
(7) X = S, Y = O



(8) VX

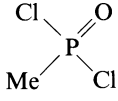
Tabun (GA), sarin (GB), soman (GD) and VX have emerged as the major nerve agents known to have been produced and weaponized and, together with sulphur mustard (a potent vesicant), have been the mainstay of chemical weapon arsenals throughout the world since the late 1950s. Following the 1990 Gulf War with Iraq, UN inspections revealed the production of a third member of the phosphonofluoridate series, cyclohexyl methylphosphonofluoridate (**9**)[14] previously designated as GF. DFP has achieved status as a research tool but is no longer realistically considered as a potential chemical warfare agent in countries with sophisticated chemical industries. However, it cannot be entirely discounted as a CW agent owing to its ease of synthesis from readily available starting materials. It is hoped that any further development of organophosphorus compounds as chemical warfare agents will be prevented by the Chemical Weapons Convention (signed in Paris in 1993). This represents the first attempt to limit the manufacture and use of chemical weapons that will be supported by on-site inspections by participating countries.



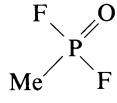
(9) GF

III. SYNTHESIS

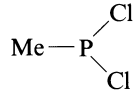
Tabun **1** [and DFP (**5**)] is the simplest of the nerve agents to synthesize owing to the absence of a phosphorus–carbon bond and, consequently, the ready commercial availability of suitable organophosphorus precursors. The synthesis of methylphosphonofluoridates and V-agents is made inherently more difficult by the absence of a large-scale commercial source of the key organophosphorus precursors, methylphosphonic dichloride, $MePOCl_2$ (**10**), methylphosphonic difluoride, $MePOF_2$ (**11**), and methylphosphonous dichloride, $MePCl_2$ (**12**). A number of practical methods are available for the synthesis of these compounds in the laboratory and are discussed below.



(10)



(11)



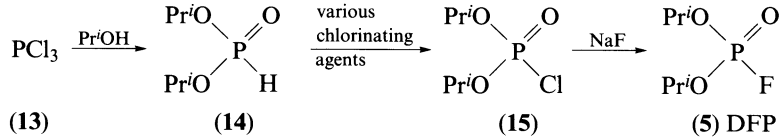
(12)

Procedures for the synthesis of tabun were developed in Germany[8] before and during WWII and have undergone little change since that time. In contrast, the development of methods for the plant-scale synthesis of methylphosphonofluoridates was the result of much research effort during the years following the war; V-agent syntheses were developed in the 1950s. Further impetus to modify and develop methods of nerve agent synthesis came during the 1960s with the development of the binary weapons system[15,16] for sarin and VX. The concept was formulated in response to political demands and environmental

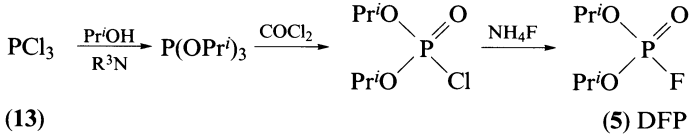
pressure groups to maintain and transport chemical weapon stockpiles in a safer and more secure manner. The concept of the binary weapon system required that the mixing and reaction of the nerve agent precursors took place in the chemical weapon munition during the time of flight. This in turn necessitated the development of new modifications to standard nerve agent syntheses using (relatively) non-toxic precursors that were capable of undergoing rapid reaction (within a few seconds) to afford toxic products in high yield. More recently, some novel procedures for the laboratory synthesis of phosphoro- and phosphono-fluoridates have been reported that make use of non-metallic oxyfluorides for P—F bond formation.

A. DFP

The synthesis of dimethyl and diethyl phosphorofluoridates, albeit in very low yield, was first described by Lange and Von Krunge[17] in 1932. DFP and other members of the series were intensively studied by Saunders and coworkers during WWII[9]. Whilst the methods employed for the synthesis of DFP (**5**) are broadly those that were developed at that time, some improvements have been reported by Ford-Moore *et al.*[18]. The first method (equation 1, Scheme 1)[19] uses the reaction between propan-2-ol and phosphorus trichloride (**13**), which in the absence of a tertiary base gives diisopropyl hydrogen phosphonite (**14**). The latter can be chlorinated by a variety of reagents to afford diisopropyl phosphorochloridate (**15**), which on heating with sodium fluoride gives DFP (**5**) in an overall yield of ca 70%. Chlorine is the preferred chlorinating agent for large-scale work when the three steps



(1)



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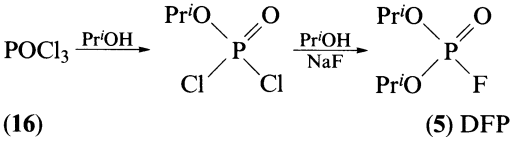

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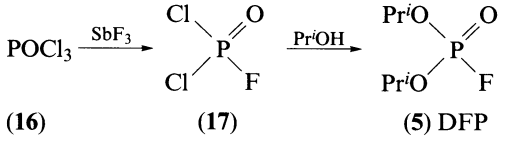


(4)

SCHEME 1. Some methods for the synthesis of DFP

can be condensed into a 'single-stage' synthesis[11,20,21] using carbon tetrachloride as solvent. For laboratory work, *N*-chlorosuccinimide[22] or sulphuryl chloride[23] are convenient chlorinating agents. Equations 2–4 show alternative procedures starting from **13** and phosphoryl chloride (**16**). Reaction 3 can also be carried out without the isolation of intermediates[18]. If **17** is available, equation 4 represents a very simple synthesis of phosphorofluoridates[9].

Some newer methods that have been used for the synthesis of DFP (and other organophosphorus fluoridates) are shown later in Scheme 6.

B. Tabun

Methods for the synthesis of tabun are shown in Scheme 2. Tabun is readily synthesized directly from **13** or **16**. The method[8] shown in equation 5, discovered by Schrader, was used in Germany during WWII and is still regarded as the method of choice for both small- and large-scale manufacture. The alternative synthetic procedures shown in equations 6–8 are also attributed to Schrader[8] and were disclosed to the Allied Forces shortly after WWII. Addition of **18**, prepared by boiling dimethylamine hydrochloride with $POCl_3$ to dry potassium cyanide in dry ethanol gives, after distillation, almost pure tabun. Saunders[24] independently reported the method based on the Arbusov reaction of diethyl *N*,*N*-dimethylaminophosphite with cyanogen iodide (equation 6).

$$POCl_3 \xrightarrow{Me_2NH \cdot HCl} Me_2NPOCl_2 \xrightarrow{NaCN\text{–}EtOH} \underset{\textbf{(1) tabun}}{\begin{matrix} EtO & & O \\ & \diagdown & \diagup \\ & P & \\ Me_2N & & CN \end{matrix}} \qquad (5)$$

(16) (18)

$$PCl_3 \xrightarrow{EtOH} (EtO)_2PCl \xrightarrow{Me_2NH} Me_2NP(OEt)_2 \xrightarrow[X=Cl,\,Br,\,I]{CNX} \mathbf{1} \qquad (6)$$

(13)

$$POCl_3 \xrightarrow{EtOH} EtOPOCl_2 \xrightarrow{Me_2NH} \begin{matrix} EtO & & O \\ & \diagdown & \diagup \\ & P & \\ Me_2N & & Cl \end{matrix} \xrightarrow{NaCN} \mathbf{1} \qquad (7)$$

(16)

$$POCl_3 \xrightarrow{Me_2NH \cdot HCl} Me_2NPOCl_2 \xrightarrow{NaCN} Me_2NPO(CN)_2 \xrightarrow{EtOH} \mathbf{1} \qquad (8)$$

(16) (18)

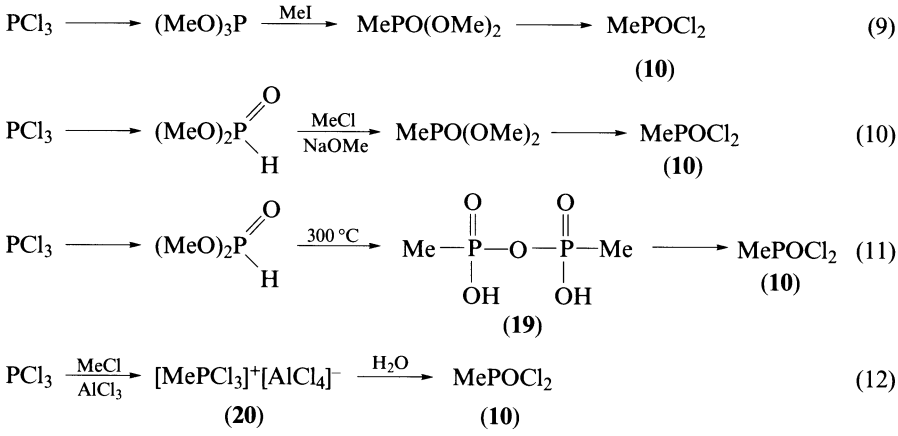
SCHEME 2. Some methods for the synthesis of tabun

C. Methylphosphonofluoridates

1. Precursors

Methylphosphonic dichloride (**10**) and methylphosphonic difluoride (**11**) are the most important precursors of methylphosphonofluoridates; **11** is invariably synthesized from **10**.

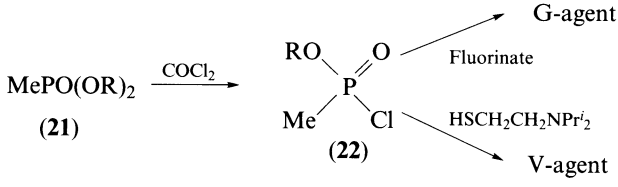
There are a number of methods available for the synthesis of **10**, of which the most important are shown in equations 9–12 in Scheme 3. Reaction of phosphorus trichloride



SCHEME 3. Some methods for the preparation of methylphosphonous dichloride

with methanol in the presence of tertiary base affords trimethyl phosphite; in the absence of base, dimethyl phosphite is obtained as a result of spontaneous demethylation promoted by hydrogen chloride liberated during the reaction. Arbusov[25] reaction with methyl iodide (equation 9) or Michaelis–Arbusov[25] reaction with methyl chloride and sodium methoxide (equation 10) affords dimethyl methylphosphonate, which can be chlorinated with phosphorus pentachloride or thionyl chloride to give **10**. The isolation of a pure product from these reactions is very difficult. Recent modifications to the reaction using thionyl chloride advocate the use of catalysts, such as dimethylformamide[26] or one of a wide variety of metal halides (including sodium chloride and calcium chloride)[27], which under carefully controlled conditions give excellent yields of a purer product. Alternatively, pyrolysis of dimethyl phosphite at 300 °C (equation 11) gives a pyro-acid **19**, which with PCl_5 gives methylphosphonic dichloride[7,8]. This method was developed and used for the large-scale production of **10** in Germany during WWII and has also been used in the USA. Finally, the method of Kinnear and Perren (equation 12)[28,29] is a useful large-scale procedure in which the reaction of phosphorus trichloride with methyl chloride in the presence of aluminum trichloride gives a complex **20**, which on decomposition with water gives **10**. A procedure for laboratory use has been described by Lindner *et al.*[30]. The Arbusov route (equation 9) is a useful laboratory procedure whilst reactions 10–12 have found plant-scale applications. Methylphosphonic difluoride (**11**) is synthesized directly from the dichloride **10** by treatment with hydrogen fluoride[31,32].

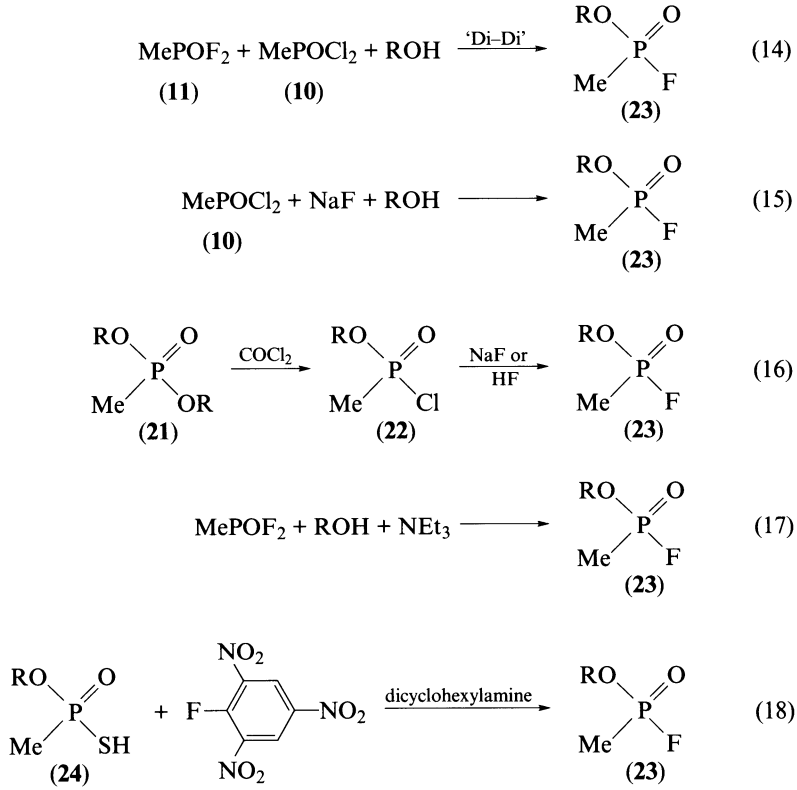
Alkyl methylphosphonochloridates (**22**) are also useful intermediates which can be synthesized by the reaction of a dialkyl methylphosphonate (**21**) (prepared as in reactions **9** and **10**) with phosgene (or chlorine or sulphuryl chloride). They can be used as precursors to phosphonofluoridates or, more rarely, to V agents, as shown in Scheme 4.



SCHEME 4

2. Classical methods of synthesis

Scheme 5 shows the most commonly used synthetic methods for making methylphosphonofluoridates. Equation 14 shows the best and most widely used method known trivially as the 'Di–Di' reaction[32,33]. The addition of an alcohol to an equimolar mixture of methylphosphonic dichloride (**10**) and methylphosphonic difluoride (**11**) results in a strongly exothermic reaction, which is usually moderated by the use of an inert solvent such as benzene or methylene chloride. The reaction is of general applicability and produces methylphosphonofluoridates (**23**) in good yield and high purity. The use of less reactive alcohols, such as pinacolyl alcohol and cyclohexanol, necessitates the use of higher temperatures and longer reaction times. The method is suitable for both laboratory and process-scale preparations and is the method of choice for the synthesis of sarin and soman. Plant-scale operations require specially lined equipment owing to the highly corrosive properties of hydrogen fluoride.



SCHEME 5

The second method (equation 15) uses methylphosphonic dichloride, an alcohol and an inorganic fluoride (sodium, potassium, ammonium, antimony, etc). Fluorination at phosphorus takes place *in situ*. This procedure was originally employed by Schrader[6] to prepare sarin using sodium fluoride as the fluorinating agent. Later, the method was adopted for pilot-plant production[7] of sarin in Germany towards the end of WWII. In practice, it is

considered that the process is more suited to small-scale work and in general the product is inferior in purity to that produced by the 'Di–Di' reaction. The procedure outlined in equation 16 is known as the 'phosgene method'[32] and uses the reaction of phosgene with a dialkyl methylphosphonate (**21**) to give the corresponding alkyl methylphosphonochloridate (**22**) that again can be readily converted (without purification if necessary) into the required phosphonofluoridate with sodium fluoride or hydrogen fluoride. The latter is preferred for pilot plant-scale operations. The importance of this method lies in the fact that it does not require methylphosphonic dichloride (**10**) as an intermediate. The G-agent produced is of high purity.

The chemistry illustrated in equation 17 was developed to meet the requirements of the binary weapons system. In the absence of base, the reaction of an alcohol with methylphosphonic difluoride (**11**) is slow and requires heating to drive to completion. In the presence of an amine, the reaction is extremely rapid and exothermic and proceeds in good yield. For the (US) binary munitions system for sarin, a mixture of propan-2-ol and isopropylamine are brought together with methylphosphonic difluoride when the separate canisters containing the reactants are ruptured as a result of the shock caused by firing the munition. The chemical reaction occurs within the time of flight of the munition[34].

The final method uses an entirely different approach. Treatment of an *O*-alkyl hydrogen methylphosphonothioic acid (**24**) with picryl fluoride in the presence of a tertiary base in acetone at room temperature results in the formation of the corresponding phosphonofluoridate (**23**)[35]. The method is useful for the synthesis of *O-tert*-butyl-substituted phosphonofluoridates that cannot be prepared by nucleophilic displacement methods using *tert*-butanol. It has also been employed for the synthesis of optically active phosphonofluoridates using resolved thio acid precursors (see below)[36].

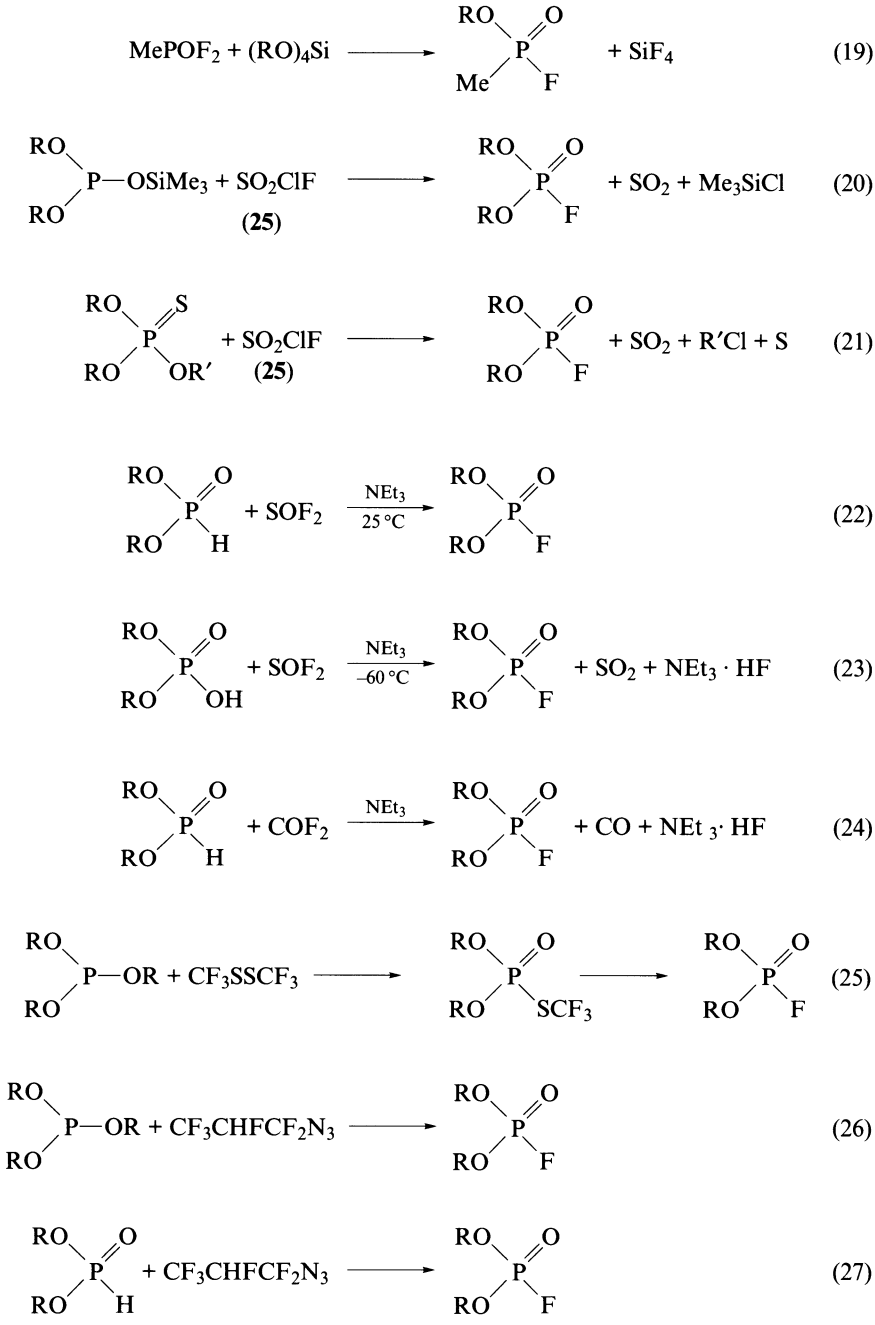
3. *New methods of synthesis*

Novel methods of phosphonofluoridate synthesis have resulted exclusively from the discovery of new methods for the formation of P—F bonds using non-metal fluorides and oxyfluorides as fluorinating agents rather than reliance on conventional methods that use halogen exchange (see above) of the intermediate phosphorus chloridate. Whilst some of these reagents are commercially available, their relative expense precludes their use in large-scale manufacture. However, they do provide simple laboratory methods of synthesis that provide nerve agents in good to excellent yields under mild reaction conditions. The methods are summarized in Scheme 6. In some instances, procedures have been studied using phosphorofluoridate analogues (e.g. DFP) only but are likely to be applicable to the synthesis of phosphonofluoridates.

The reaction of methylphosphonic difluoride (**11**) with a tetraalkoxysilane (alkyl= Me, Et, Pr^i) at room temperature (equation 19) gave the corresponding G-agent in good yield (>80%) and high purity (>97%) by simple vacuum distillation of the crude reaction mixture[37].

Michalski and coworkers[38] have shown that sulphuryl chloride fluoride (**25**) is a convenient reagent for preparing both simple phosphorofluoridates and more complex carbohydrate-substituted phosphorofluoridates for use in polynucleotide synthesis. Using phosphorus (III) trimethylsilyl esters (equation 20), products of very high purity are obtained in excellent yields under mild reaction conditions. Alternatively, phosphorus(V) thionophosphate or selenophosphate esters (equation 21) and **25** also give the corresponding phosphorofluoridates in high yields[39].

Occasionally, reactions with **25** show some loss of chemoselectivity and small amounts of phosphorus chloridates are observed; thionyl fluoride has been examined with a view to eliminating unwanted reactions. Although trialkyl phosphorus(III) esters give some of the



SCHEME 6. Non-classical methods of G-agent synthesis

required dialkyl phosphorofluoridate, the yields are low. However, the use of the dialkyl hydrogenphosphonite in the presence of triethylamine (equation 22) at room temperature gives the dialkyl phosphorofluoridate in good (R = Bu, 68%) to quantitative yield (R = Et, 100%)[40] and dialkyl phosphorus(V) acids give the corresponding fluoridate in essentially quantitative yield (equation 23)[41].

The reaction with carbonyl fluoride (equation 24) is similar, although yields are not as high[40]. Lopusinski[42] has advocated the use of bis(trifluoromethyl) disulphide and phosphorus(III) esters (equation 25) as a convenient reagent for synthesizing *S*-trifluoromethyl esters. The ester can be isolated or converted directly into the phosphorofluoridate by treatment with fluoride ion. Finally, Russian workers have reported the use of 2-hydroperfluoropropyl azide as a reagent that converts dialkyl[43] or trialkyl phosphites[44] into the corresponding fluorophosphate (equations 26 and 27, respectively). The azide is reported to be inexpensive, readily available and stable[45].

D. V-agents

1. Precursors

All reported procedures for the synthesis of V-agents depend on the availability of methylphosphonous dichloride (**12**) or, more rarely, ethylphosphonous dichloride ($EtPCl_2$) as intermediates. The most important synthetic routes to **12** are shown in Scheme 7. Using the method of Kinnear and Perren[28–30] (equation 28), complex **20**, prepared from phosphorus trichloride, methyl chloride and aluminum chloride, can be reduced with iron or aluminum and sodium chloride to give **12** in good yield. The method has been used on a pilot plant scale. An alternative process uses the reaction between aluminium and methyl chloride to give a mixture that consists mainly of methylaluminium dichloride and dimethylaluminium chloride (known as 'ASP', **26**). This mixture is used to methylate an excess of phosphorus trichloride (equation 29) via a further complex that is decomposed with sodium chloride. The process is suited to large-scale production methods and requires efficient fractionation of the crude product to separate the required methylphosphonous dichloride (b.p. 75 °C) from excess phosphorus trichloride (b.p. 83 °C).

The preparation of methylphosphonous dichloride by direct combination of methyl chloride and phosphorus trichloride (equation 30) has been described in a patent applica-

$$PCl_3 + MeCl \xrightarrow{AlCl_3} \underset{(\mathbf{20})}{[MePCl_3]^+[AlCl_4]^-} \xrightarrow{Al \text{ or } Fe} \underset{(\mathbf{12})}{MePCl_2} \qquad (28)$$

$$MeCl \xrightarrow{Al} \underset{(\mathbf{26})}{[MeAlCl_2 + Me_2AlCl_2]} \xrightarrow{PCl_3} [MePCl_2;\ AlCl_3 + (MePCl_2)_2;\ AlCl_3] \xrightarrow{NaCl} \underset{(\mathbf{12})}{MePCl_2} \qquad (29)$$

$$PCl_3 + CH_4 \xrightarrow{cat.} MePCl_2 \qquad (30)$$

$$PCl_3 + PbEt_4 \longrightarrow EtPCl_2 + EtCl + PbCl_2 \qquad (31)$$

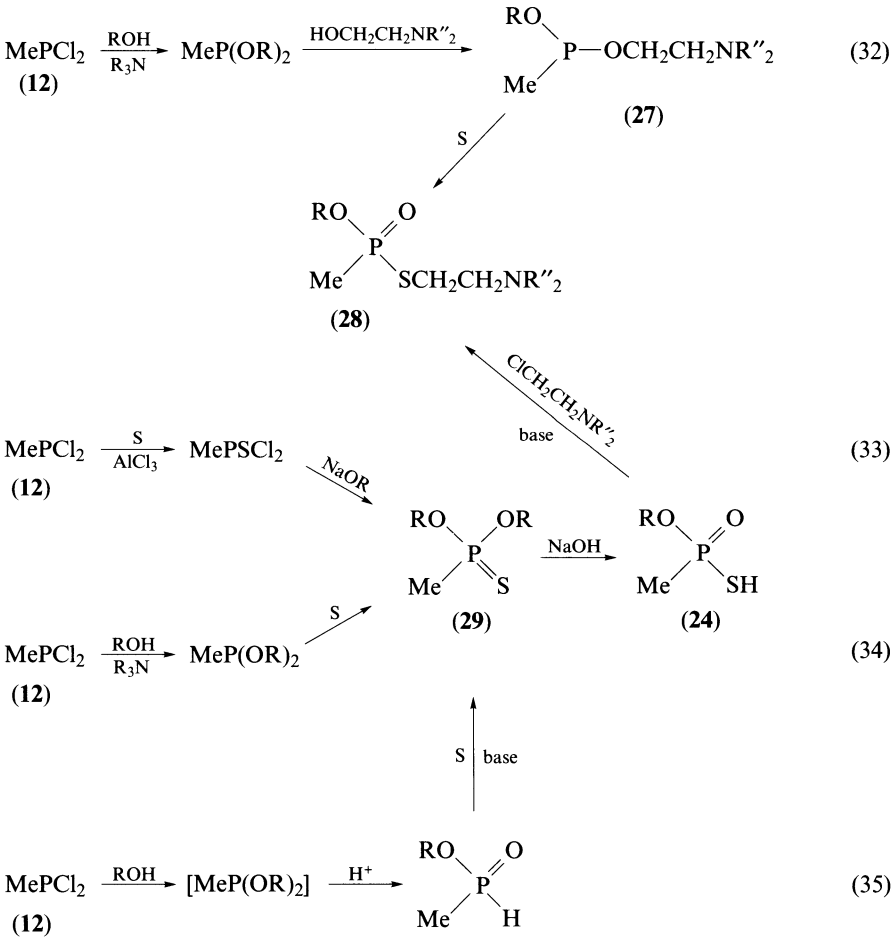
SCHEME 7

tion[46]. This method relies on the exposure of the reactants to high temperatures (ca 500 °C) in the presence of a catalyst using short contact times of a few seconds. Conversion rates are relatively low (a few percent) and even with recycling, careful separation of the product from excess phosphorus trichloride is required.

The final method (equation 31) shows the preparation of ethylphosphonous dichloride[47] from tetraethyl lead and an excess of phosphorus trichloride. The product can be isolated in high yield (89%) and is more easily separated from excess phosphorus trichloride than the methyl analogue because of the greater difference in b.p. (20 °C). The method is suited to both laboratory and plant production.

2. Methods of synthesis

The most important routes for V-agent synthesis are summarized in Scheme 8. The procedure shown in equation 32 is known as the transesterification method[48,49] and uses **12**



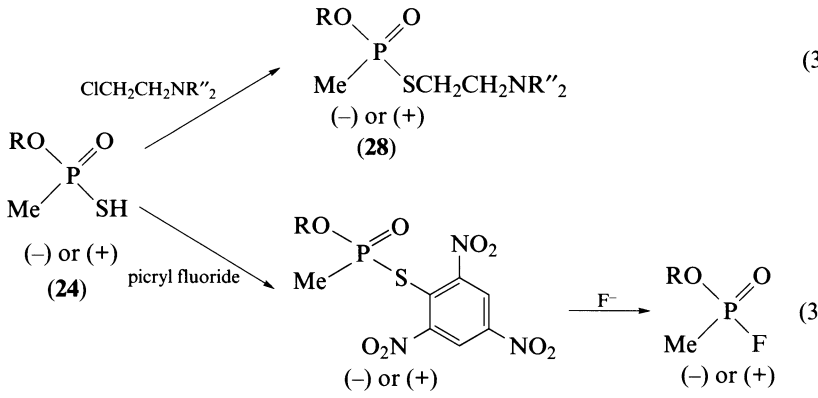
SCHEME 8. Some methods of V-agent synthesis

to prepare a dialkyl methylphosphonite. The phosphonite is transesterified by heating with an *N*,*N*-dialkylaminoethanol to give the V-agent precursor **27**. As a phosphorus(III) derivative, this readily adds elemental sulphur exothermically to give the thionate, which on heating can be isomerized via the thiono–thiolo rearrangement to the required V-agent **28**. Liquid dimethyl polysulphide [$MeS(S_n)SMe$] has been used[16] instead of solid sulphur. The procedure was developed and used for plant-scale production of VX (**28**, R = OEt, R″ = Pr^i) in the USA[48] and was also the subject of a British patent[49]. Technical-grade material is not distilled but is stabilized by the addition of 2% of diisopropylcarbodiimide. The chemistry shown in the final step also serves as the basis of the (US) binary weapon system for VX[15]. *O*-Ethyl *O*-(2-diisopropylaminoethyl) methylphosphonite (**27**, R = Et, R″ = Pr^i) is the immediate nerve agent precursor that is mixed and reacted with sulphur to give the thiono compound and then isomerized to VX during the time of flight of the chemical munition. Yields are good.

The procedures outlined in equations 33–35 differ only in the method of conversion of **12** into the key intermediate alkyl methylphosphonothioic acid (**24**). Equations 33 and 34 illustrate how the sequence of addition of the alcohol or sulphur to **12** can be varied to give the dialkyl methylphosphonothionate **29**, which in either case is hydrolysed to the thio acid **24**[50,51]. Alternatively, the addition of the alcohol to **12** can be carried out in the absence of base. Equation 35 shows that the dialkyl methylphosphonite is the primary product, which undergoes spontaneous acid-catalyzed *O*-dealkylation to the alkyl methylphosphonite, which on the addition of base and sulphur affords the thio acid **24** directly, omitting the need for a hydrolysis step. In each of these methods, subsequent alkylation of the thio acid **24** with an *N*,*N*-dialkylamino-2-chloroethane under basic conditions occurs exclusively on sulphur and gives the required V-agent in good yield. The alkylation can be carried out under either wholly aqueous conditions or in organic solvents (acetone or benzene is preferred). Aqueous conditions give better yields of purer products except for *N*,*N*-dimethylamino derivatives (R″ = Me), when dry benzene should be employed. In all these examples, VX is obtained when R = Et and R″ = Pr^i. Details of these methods are described in the patent literature[52–54].

E. Resolution

As a consequence of the asymmetrically substituted phosphorus atom, all G- and V-agents exhibit chirality about phosphorus. They are invariably prepared as a mixture of optical isomers during normal synthesis. If one of the substituent groups also possesses a chiral centre, for example the *O*-pinacolyl group in soman, then the nerve agent will have two chiral centres and therefore four possible stereoisomers. Early investigations[55–57] indicated that large differences (ca 10^3–10^4-fold) existed in the rates of inhibition of AChE by resolved enantiomers of nerve agents (see Section XII). These experiments demonstrated that pure optical forms were required if meaningful mechanistic biochemical and toxicological investigations were to be undertaken. As a result, methods have been developed to resolve tabun, sarin, soman, (especially) and VX into their optical isomers employing a variety of techniques. VX has been completely resolved using classical chemical methods. An alternative chemical approach was only partially successful with sarin (Scheme 9). More recent studies with sarin, soman, and, tabun, have relied on the stereoselectivity of enzyme systems towards one of the isomers that allow one isomer to be isolated at the expense of the other. Physicochemical methods have been developed that allow individual nerve agent enantiomers to be analysed and optical purities to determined (see Sections VI and VII). The isolation, analysis and toxicology of nerve agent stereoisomers have been reviewed by Benschop and De Jong[58].



SCHEME 9

1. Classical methods

a. V-agents. The resolution of *O*-ethyl hydrogen methylphosphonothioic acid (**24**, R = Et) by Aaron and Miller[59] in 1956, by fractional crystallization of its salts with the alkaloids quinine and brucine, paved the way for the synthesis of a number of chiral phosphorus compounds including the V-agents. Although the initial resolution procedure was tedious, condensation of the resolved thio acid **24** (sodium salt) with a 2-*N*,*N*-dialkylamino-2-chloroethane (equation 36) gave a facile preparation of the required V-agent **28** with retention of configuration at phosphorus (Scheme 9). The method was significantly improved in 1967 by Boter and Platenberg[60], who introduced the use of both enantiomers of (+)- and (–) α-phenylethylamine for the resolution of the thio acids. Inhibition experiments carried out with AChE using V-agent enantiomers prepared by this method indicated that optical purities approached 100%. The resolution of tetracoordinate phosphorus compounds and the determination of their enantiomeric purity have been reviewed by Hall and Inch[61].

b. G-agents. The resolution of thio acid **24** has also provided a route to G-agent enantiomers, albeit with less than 100% optical purity. Reaction of the thio acid sodium salt (**24**, R = Pr^i) with picryl fluoride gives sarin[57] by fluoride ion displacement of the intermediate *S*-(2,4,6-trinitrophenyl) ester (equation 37, Scheme 9). If it is assumed that the reaction with picryl fluoride occurs with retention of configuration at phosphorus whereas the subsequent nucleophilic substitution of 2,4,6-trinitrothiophenoxide by fluoride ion occurs with inversion of configuration, then the net stereochemical change at phosphorus is inversion. Unfortunately, the optical purity of the product is compromised, almost certainly, by fluoride ion exchange in the reaction mixture leading to partial racemization prior to isolation. The optical purities of different preparations of sarin varied from 54 to 76%. It is the only chemical method available for the preparation of optically enriched (+)-sarin.

2. Enzyme methods

a. Tabun. The incubation of (±)-tabun with α-chymotrypsin[62] results in the removal of the (+)-isomer from the incubation medium (by phosphonylation of the enzyme) and leaves the (–)-isomer in solution, which can be isolated with 98% enantromeric excess (*ee*).

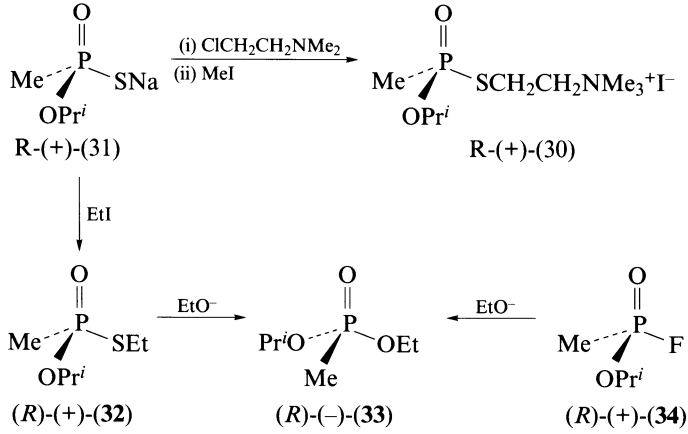
The (+)-isomer is obtained similarly by the use of a phosphorylphosphatase. The stereoselectivity of the hydrolysis of tabun enantiomers by phosphorylphosphatases is species dependent. It was observed that incubation with rat plasma was the only method that produced (+)-tabun with adequate optical purity (92–99% *ee*).

b. Sarin. Christen[56] first succeeded in isolating optically enriched (–)-sarin via the stereoselective hydrolysis of (±)-sarin with phosphorylphosphatases in rat plasma. This early work was improved upon by Benschop and De Jong[58], who obtained optically pure (–)-sarin by hydrolysis of the (+)-isomer in (±)-sarin by rabbit plasma. The same workers reported that there is no analogous method available for the preparation of the (+)-isomer. Enriched samples only (40–75% *ee*) are available from chemical synthesis (see equation 36) or via stereoselective phosphonylation of α-cyclodextrin[63] in aqueous solution at pH 9.

c. Soman. Soman exhibits asymmetry at both carbon and phosphorus and as a result, during normal synthesis, is invariably synthesized as a mixture of four stereoisomers. The separation of all four isomers has been described[64]. The use of the (+)- and (–)-enantiomers of pinacolyl alcohol (3,3-dimethylbutan-2-ol) allows the synthesis of C(+)P(±)- and C(–)P(±)-soman using conventional procedures. The separate incubation of each pair of isomers with α-chymotrypsin under optimum conditions results in the removal (by inhibition) of P(–) isomers from solution and allows the isolation of C(+)P(+)- and C(–)P(+)-soman with optical purities in excess of 99% in yields of 20–30%. Conversely, the incubation of C(+)P(±)- and C(–)P(±)-soman with phosphorylphosphatases in rabbit plasma for 1 min results in the selective hydrolysis of P(+)-soman isomers (exhibiting opposite stereoselectivity to the inhibition reaction) allowing the isolation of optically pure C(–)P(+) and C(+)P(–)-soman. Again yields are ca 20%.

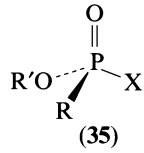
3. Absolute configuration

The absolute configurations at phosphorus of resolved organophosphorus nerve agent enantiomers and diastereoisomers have not been firmly established[58]. Some probable assignments have been made on the basis of an X-ray analysis[65] and some chemical correlations (Scheme 10). The X-ray analysis has shown that the dextrorotatory enantiomer of



SCHEME 10

the quaternized V-agent (+)-*O*-isopropyl *S*-[2-(trimethylamino)ethyl] methylphosphonothiolate (**30**) has the *R* configuration. Since the nerve agent **30** was prepared from the sodium salt of (+)-*O*-isopropyl hydrogen methylphosphonothioic acid (**31**) by alkylation (at sulphur) and quaternization (at nitrogen), using two reactions that are assumed to proceed with retention of configuration at phosphorus, then **31** should also have the *R* configuration. (*R*)-(+)-(**31**) may be chemically correlated with (+)-sarin (**34**), as shown in Scheme 10. Since alkylation at sulphur proceeds with retention of configuration, whereas the nucleophilic displacements of the thioethyl substituent (**32** → **33**) and of fluorine (**34** → **33**) by ethoxy probably proceed with inversion of configuration, it follows that the absolute configuration of (+)-sarin is probably *R*[58]. It has been proposed[58] that for a wide range of AChE inhibitors, when R′O is bulkier than *R*, the most active inhibitor has the absolute configuration **35**.



(**35**)

X = $SCH_2CH_2NPr^i_2$. R = Me, R′ = Et	VX
X = F, R = Me, R′ = Pr^i	sarin
X = F, R = Me, R′ = $CH(Me)C(Me)_3$	soman
X = CN, R = Me_2N, R′ = Et	tabun

IV. CHEMICAL AND PHYSICAL PROPERTIES

A. Physical Properties

1. General

Some physical data for DFP, tabun, sarin, soman, and VX are given in Table1.

The physical properties of a chemical warfare agent play an important part in defining the hazard presented by that agent[7]. The physical state (gas, liquid or solid) is important in determining the conditions and manner in which an agent would be used and dispersed.The vapour pressure gives an indication of both the vapour hazard and the persistency of the agent in the field. The solubility in water (and rate of hydrolysis) affects persistency in the environment, ease of decontamination and possible threat to water supplies. The viscosity affects the persistency, ability to penetrate surfaces and ease of decontamination. The

TABLE 1. Physical properties of organophosphorus nerve agents

Compound	M.p. (°C)	B.p. (°C/mm Hg)	Vapour pressure (mmHg) (20 °C)	Density (gml^{-1}) (20 °C)	Viscosity (cp) (20 °C)	Solubility in water (%) (20 °C)
DFP	–82	67–68/12	0.57	1.06	1.65	1.5
Tabun	–48	108/12	0.035	1.077	2.77	9.8
Sarin	–57	50/12	2.1	1.10	1.54	Miscible
Soman	–80	85/15	0.34	1.01		2.1
VX	~–39	97/0.005	0.0004	1.013	12.2	3

viscosity can be changed artificially by the addition of polymeric thickening agents such as poly(methyl methacrylate) (typically up to 5% by weight), a process most commonly performed with soman.

2. DFP

DFP is a colourless liquid with a slightly fruity odour. It is slightly soluble in water (1.5% to 20 °C) and generally soluble in organic solvents. It is liquid over an extremely wide temperature range (-82 to 183 °C) at atmospheric pressure.

3. Tabun

Pure tabun is a colourless liquid with a fruit-like odour. Technical-grade material is brown with a smell of bitter almonds (due to cyanide) and amines as a result of decomposition. It is very soluble in water, soluble in benzene, diethyl ether, alcohol, chloroform, etc., but poorly soluble in hydrocarbon solvents.

4. Sarin

Pure sarin is a colourless and odourless liquid. It is hygroscopic and miscible with water in all proportions and very soluble in most organic solvents. It is the most volatile of the commonly encountered organophosphorus nerve agents.

5. Soman

Pure soman is a colourless liquid, supposedly with a pineapple-like smell, and of intermediate volatility. It has limited solubility in water (1.5% at 20 °C) and high solubility in organic solvents.

6. VX

The pure material is a colourless, viscous, involatile liquid that has an extremely low vapour pressure. VX is hygroscopic and is moderately soluble in water.

B. Chemical Properties

1. General

The chemistry of the organophosphorus nerve agents has not been systematically investigated. Detailed studies have been confined to those reactions pertinent to their stabilization on storage, detection, behaviour in biological systems and decontamination. These include hydrolysis, reactions with nucleophiles other than water and the chemistry associated with oxidizing and chlorinating agents. Reactions in specifically designed decontamination systems are discussed in Section IV, and the chemistry specific to detection is discussed in Section IX.

The chemistry[7] of DFP, sarin and soman is essentially that of the P—F bond with initial bond breaking occurring invariably at that position by nucleophilic substitution of fluorine. This generally occurs under mild conditions with a wide variety of nucleophiles. The reaction with a nucleophilic serine hydroxyl group in AChE, with the displacement of

TABLE 2. Second-order rate coefficients for the hydrolysis of nerve agents with sodium hydroxide

Compound	k_2(OH)($mol^{-1}\ s^{-1}$)	T(°C)	Ref.	k_2(OH)($mol^{-1}\ s^{-1}$)	T(°C)	Ref.
DFP				0.83	25	7
Tabun	22	37	73	7.49	25	7
Sarin	71	37	73	25.8	25	7
Soman	30	37	73	10.0	25	74
VX				4.12×10^{-3}	22	75

fluoride, is the chemical basis of their toxic properties. Reactions involving the ester function occur only under more forcing conditions, for example extremes of pH or high temperatures.

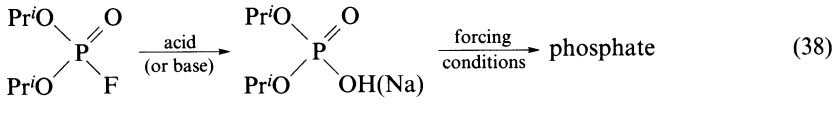
For tabun and VX, with different heteroatom substituents, the site of initial bond cleavage can vary depending on the reagents and reaction conditions, especially pH.

There is a considerable amount of published data available on the hydrolysis of tabun, its analogues and the organophosphorus fluoridates. However, the variation in experimental conditions under which the data were measured, and in some instances the contradictory nature of the data, make direct comparisons of rate data difficult. Some second-order rate coefficients for the basic hydrolysis of nerve agents are given in Table 2.

The following broad generalizations may be made with respect to basic hydrolysis (assuming comparable conditions). Phosphonofluoridates are hydrolysed much more rapidly than phosphorofluoridates. For phosphonofluoridates, the rate of hydrolysis decreases with increasing size of the alkoxy group. V-agent hydrolysis under basic conditions is ca 2–3 orders of magnitude slower than that of the corresponding fluoridate.

2. DFP

DFP is stable[9] and in the absence of moisture can be stored for considerable periods without decomposition. Hydrolysis[7,66] in neutral aqueous solution occurs slowly. The reaction is catalyzed by both acid and base. At pH>7, hydrolysis is proportional to the hydroxide ion concentration and at high pH is extremely rapid. The product is always diisopropyl phosphoric acid (equation 38), except under more forcing conditions which eventually produce phosphate (and propan-2-ol). The hydrolysis is strongly catalyzed by the addition of α-effect nucleophiles such as hypochlorite, peroxide, hydroxylamine, hydroxamic acid and their substituted derivatives[7,66]. Under basic conditions, such nucleophiles (HOX) are present as the anion and are responsible for the rapid initial displacement of fluoride ion from DFP to give intermediate **36** shown in equation 39. Displacement of OX by hydroxide ion regenerates the catalytic OX anion. The reaction with hydrogen



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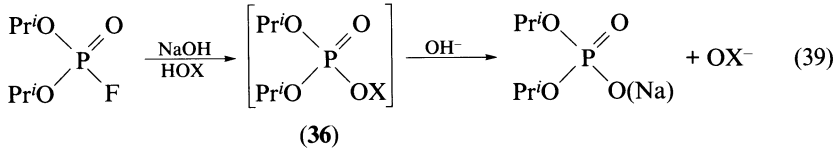


(39)

(36)

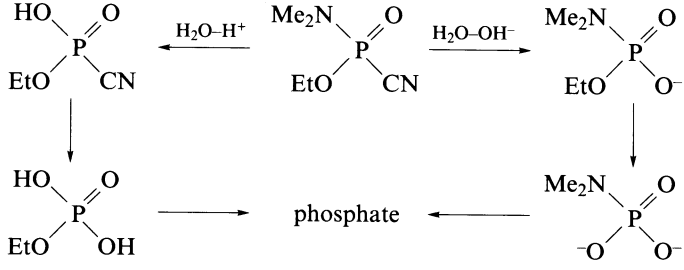
peroxide has also been examined under phase-transfer conditions[67]. Significant rate enhancements were observed.

In 1955, Warner–Jauregg *et al.*[68] showed that copper (II) chelates were particularly efficient catalysts of the hydrolysis of DFP. For example, a $CuSO_4$–dipyridyl (1:1) complex (0.0228 M in pH 7.6 buffer) reduced the half-life to 4.5 min from an uncatalysed half-life of >2500 min. This work was extended by Courtney *et al.*[69], who examined a series of chelating agents and various metal complexes as hydrolysis catalysts for DFP and sarin. Copper (II) catalysts as a group were shown to be the most effective.

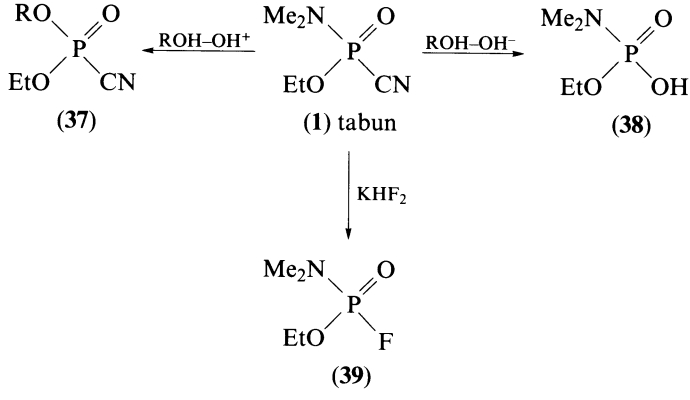
The reactions of DFP with primary amines, phenols and alcohols have been reported[7]. Basic conditions are required and products are as expected from a simple nucleophilic substitution reaction.

3. Tabun

The reaction of tabun with nucleophiles is more complex than that of the simple phosphorylfluoridates. The courses of such reactions are pH dependent and, according to the conditions, cleavage of either the P—N bond or the P—CN bond can predominate[66,70], as shown in Scheme 11. At low pH, in aqueous acid, protonation of the basic nitrogen atom leads to initial P—N cleavage with loss of dimethylamine, with further displacement of cyanide and ultimately the ethoxy group (under more forcing conditions). Under basic conditions, cyanide ion is displaced preferentially. At pH 7, the hydrolysis is slow and proceeds by non-selective multiple reaction pathways.



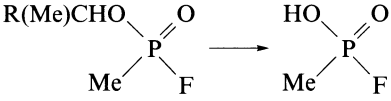
SCHEME 11. Hydrolysis of tabun



Similar pathways are followed by nucleophiles other than water. Alcoholysis of tabun under acid conditions results in cleavage of the P—N bond and substitution of the dimethylamino group by the alkoxy group to give **37**. Alcoholysis under basic conditions results initially in substitution of the cyanide group to give **38**. The cyano group may also be replaced by other nucleophilic anions, including fluoride ion to give the phosphorofluoridate **39**.

4. *Sarin and soman*

Simple methylphosphonofluoridates such as sarin, soman and GF are stable in the absence of water at ambient temperatures. On heating, they undergo acid catalyzed decomposition by *O*-dealkylation[71] with loss of the appropriate alkene at or near the boiling point (which precludes distillation at atmospheric pressure). The residue is mainly methylfluorophosphonic acid (**40**) and its disproportionation products, methylphosphonic difluoride (**11**) and methylphosphonic acid (equation 40). Thus, sarin loses propene on heating to temperatures in excess of 130 °C. For long-term storage, especially in metal containers, it is usual to add stabilizers. Typically, tertiary amines are used to neutralize traces of hydrogen fluoride and carbodiimide is added to remove any water or free phosphorus acids that may arise.



$$+ MePOF_2 + MePO(OH)_2 + RCH{=}CH_2 \quad (40)$$

(**40**) (**11**)

The chemistry of the phosphonofluoridates closely resembles that of DFP. In general, nucleophilic displacement reactions occur more readily, usually rationalized on the basis of enhanced electropositive character at phosphorus due to the lack of $p\pi$–$d\pi$ bonding in the PCH_3 group (however, it is of interest that a theoretical study[72] on a set of organophosphorus anticholinesterases, using CNDO/2 calculations, concluded that the rate dependence on charge is the reverse of that usually assumed, and is mainly dependent on the energy of the lowest unoccupied molecular orbital). The rate of hydrolysis of sarin is approximately 30 times that of DFP at pH 8–9 in aqueous solution at room temperature (see Table 2). At pH > 10, both sarin and soman are hydrolyzed to their corresponding acids in a few minutes. As with DFP, the hydrolysis of phosphonofluoridates is catalyzed by added nucleophiles (see also Section V). At pH> 8.4, rate enhancements of the order of 50-fold are observed in the presence of hydroperoxide anion[7].

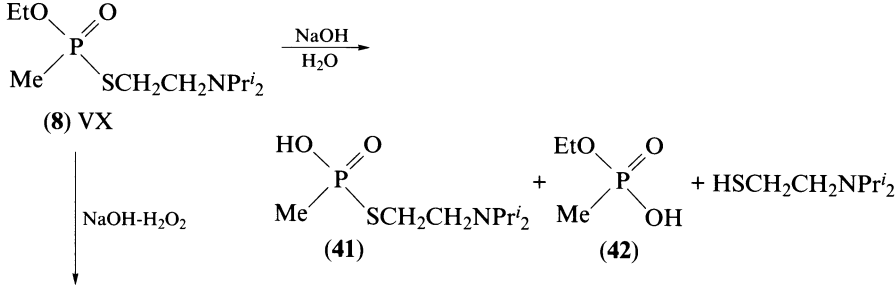
Reactions occur with a variety of nucleophiles under mild conditions. For oxygen nucleophiles, basic conditions or the presence of a tertiary base as a hydrogen fluoride acceptor are required. Some of this chemistry is the basis of the decontamination procedures that are discussed in Section V. The replacement of fluorine decreases or eliminates toxicity in most cases, but reactions with certain nucleophiles, such as those which introduce 4-nitrophenoxy, azide, oximino or methylphosphonate (to give the corresponding pyrophosphonate), produce products which retain substantial toxicity. Phosphonylated oximes derived from nerve agents are often significantly superior inhibitors of AChE *in vitro* than the parent nerve agent; rates of inhibition can be 10–100 times greater than for the parent nerve agent[73]. These phosphonylated oximes are prepared *in situ* from the corresponding nerve agent (or chloridate analogue) and the appropriate oxime. They are often unstable and difficult to purify[76].

The role of copper (II) and other ions in the catalysis of sarin (and DFP) hydrolysis has been investigated[68,69]. They have been shown to be potent catalysts either in solution or

when complexed with various diamines. Recent studies[77] have shown that a significant rate enhancement is observed when polymeric amine–copper (II) complexes are used as catalysts during the aqueous hydrolysis of soman (and DFP) at pH 7. This effect is inhibited by the presence of polymeric sorbents.

5. VX

For long-term storage, the stability of a V-agent is critically dependent on the absence of oxygen and water. The size of the alkyl group in the *N*,*N*-dialkylamino function is also important. *N*,*N*-Diisopropylamino derivatives are significantly more stable than the corresponding *N*,*N*-dimethyl or -diethyl analogues. This is evident during synthesis and storage, and probably reflects the effect of steric hindrance on the tendency of nitrogen to attack either phosphorus or the α-carbon atom adjacent to sulphur, either inter- or intramolecularly, as a primary mechanism of decomposition. This was an important factor in the selection VX as a CW agent rather than other analogues of comparable toxicity. The incidence of toxic pyrophosphonates as major degradation products in of VX samples has been demonstrated[76]. Under neutral conditions, VX hydrolyses very slowly via simultaneous cleavage of S—C, P—O and C—O bonds to form a series of products[79,80]. However, the course of V-agent decomposition is extremely complex[78] and a detailed discussion lies outside the scope of this chapter. The basic hydrolysis of VX differs from that of the organophosphorus fluoridates in that it does not result in detoxification. As a result of competition between P—O and P—S bond-breaking reaction pathways, hydrolysis gives products **41** and **42**, respectively, as shown in equation 41[79,80]. The existence of similar parallel hydrolysis pathways has been observed with other phosphonothiolate esters[81]. Product **41**, formed as a result of P—O cleavage, is still a highly toxic cholinesterase inhibitor (LD_{50} i.v. rabbits 0.017 mg kg^{-1} ref. 80). More recent studies[75] have demonstrated that the perhydrolysis (1% H_2O_2 in 0.1 M NaOH) of VX results in rapid detoxification in which P—S bond cleavage only occurs to give **42**; **41** is not observed.



(41)

Oxidative hydrolytic cleavage is brought about by a variety of other reagents, some of which constitute the basis of procedures used for decontamination. The chemistry is often complex depending on the reagents and reaction conditions. Some likely reaction pathways for the oxidation of VX under neutral conditions in aqueous solution, polar and non-polar organic solvents have been proposed by Yang *et al.*[81] based on a series of publications by Casida and coworkers. It is proposed that oxidation occurs at both nitrogen and sulphur but that *N*-oxide formation precedes oxidation at sulphur. These primary reactions lead to the fragmentation of VX via a series of solvent-dependent secondary reactions involving further oxidation and hydrolysis.

Some further examples of oxidation that are used in decontamination procedures are discussed below.

V. DECONTAMINATION

Procedures used to render bulk CW agents, equipment, personnel or any surface or object free from contamination by CW agents are referred to collectively as 'decontamination'. Protocols are available for applications ranging from small-scale laboratory decontamination under the supervision of trained scientific personnel to the battlefield decontamination of equipment and personnel where time and expertise are limited. Decontamination procedures are generally designed to cater for tabun, sarin, soman, VX and sulphur mustard. The decontamination of CW agents thickened with polymers presents additional problems owing to the inaccessibility of the agent, within the polymer matrix, to the applied reactive decontaminant. The chemistry of decontamination of the nerve agents (and sulphur mustard) has been comprehensively reviewed[81].

A. Laboratory Procedures

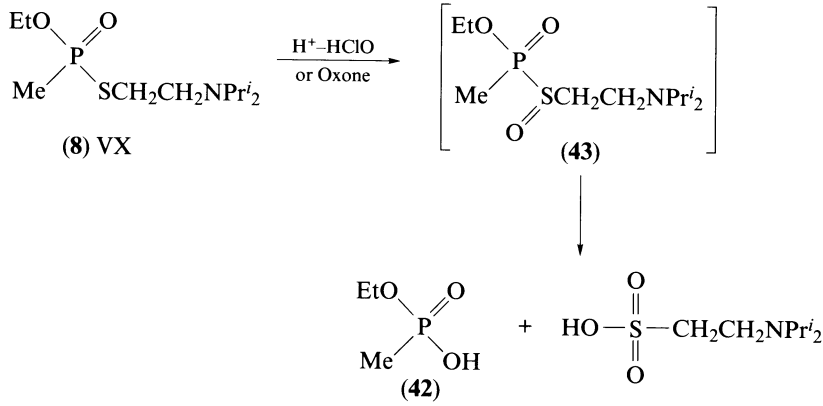
G-agents are readily decontaminated by basic hydrolysis in aqueous solution or in aqueous alcohol to improve solubility. At high pH, hydrolysis is virtually instantaneous. As discussed above, significantly enhanced rates of hydrolysis are observed in the presence of hypochlorite or peroxide ions.

Historically, bleach in its various guises (powder or solution) has found universal application in the decontamination of CW agents both in the field and in the laboratory. Bleach is inherently corrosive, inefficient at low temperatures and performs poorly against thickened agents. Whilst its basic role as a general-purpose decontaminant in the field has diminished, it is still an important fundamental component of many decontamination systems, and is still commonly used in solution in the laboratory for the decontamination of glassware and small quantities of chemical agents.

V-agents are less readily decontaminated than G-agents. Basic hydrolysis alone does not decontaminate VX (see above) owing to the formation of **41**, which is still highly toxic[80] (see equation 41); the *N*-oxide of VX is also very toxic. To effectively decontaminate VX, it is necessary to break the P—S bond.

At low pH, VX is more soluble in aqueous solution due to protonation of nitrogen; protonation also prevents oxidation at nitrogen. Under these conditions, 3 mol of hypochlorite per mole of V-agent are consumed in the decontamination procedure. Sulphur is readily oxidized to give sulphoxide **43** (the putative intermediate), which undergoes ready hydrolysis by cleavage of the P—S bond only as shown in Scheme 12. At high pH, the solubility of VX is much reduced; oxidation at nitrogen occurs prior to the oxidation of sulphur, which is the prerequisite for rapid hydrolytic P—S cleavage. Subsequent reactions are very complex with the evolution of chlorine and oxygen gas and the consumption of 10 mol of sodium hypochlorite. Although reaction pathways have not been elucidated, solutions are effectively decontaminated.

An aqueous solution of the commercial oxidizing agent Oxone[82] (consisting of $2KHSO_5$–K_2SO_4–$KHSO_4$ and whose active component is $KHSO_5$) has been recommended for the decontamination of VX[80,81] (superseding bleach in aqueous ethanol at high pH). The pH of the solution is 1.9, which enhances the solubility of VX through protonation of nitrogen. Oxidation at sulphur to putative intermediate **43** is rapid, as is the subsequent hydrolysis of the P—S bond. The nitrogen is protected from oxidation by protonation. The overall chemistry follows the same course as that of hypochlorite under acid conditions



SCHEME 12. Oxidation of VX with hypochlorite or Oxone under acidic conditions

(Scheme 12), again with the consumption of only 3 equiv. of oxidant for each equivalent of VX.

B. Field Procedures

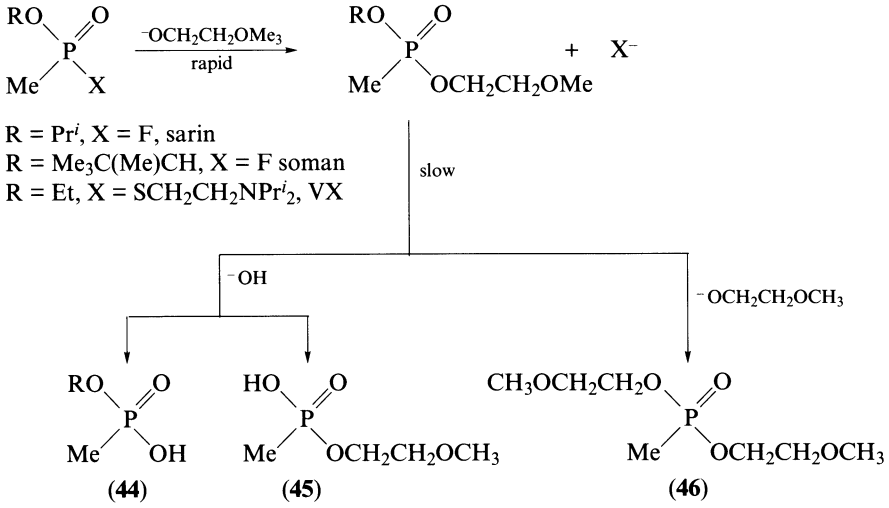
1. Chemical agent decontaminant (CAD)

Chemical agent decontaminant (CAD) is the standard UK CW agent decontaminant[83] and is prepared from sodium dichloroisocyanurate (FiClor, 85 g), sodium hydroxide (225 g) and boric acid (85 g) containing 1% sodium dodecyl sulphate (detergent) in water (9 litres). The activity of the solution is reduced by 50% after 1 h. The solution is freshly prepared from its individual solid components immediately prior to use and has a pH of 10.2. Like hypochlorite, FiClor is a source of electropositive chlorine. Although detailed studies into products and reaction mechanisms have not been carried out, it is likely that the decontamination of V- and G-agents by CAD follows a similar course to the reactions with hypochlorite under basic conditions.

CAD is not intended to be used for personal decontamination, in contrast to some kits developed in the USA. Protective clothing is used to prevent skin contamination from occurring. Sensitive items that require decontamination are treated with Fuller's Earth, the primary role of which is to act as a physical absorbent.

2. Decontamination solution 2 (DS2)

Decontamination solution 2 (DS2) was developed during the 1950s and adopted in 1960 to replace bleach as a general purpose ready-to-use reactive decontaminant[81]. It is the current US chemical agent decontaminant, has good long-term storage stability and a wide operating temperature range (–26 to 52 °C). The solution consists (by weight) of diethylenetriamine (70%), ethylene glycol monomethyl ether (EGM) (28%) and sodium hydroxide (2%). The reactive component has been shown to be the conjugate base of EGM, i.e. $MeOCH_2CH_2O^-$, anion, with a lesser contribution from hydroxide ion. The chemistry[81] of the decontamination reactions is shown in Scheme 13 and is simply a series of nucleophilic displacements occurring in a polar solvent medium. Compounds **44**, **45** and **46** are the major products. Although DS2 is a very effective decontaminant and is non-corrosive to

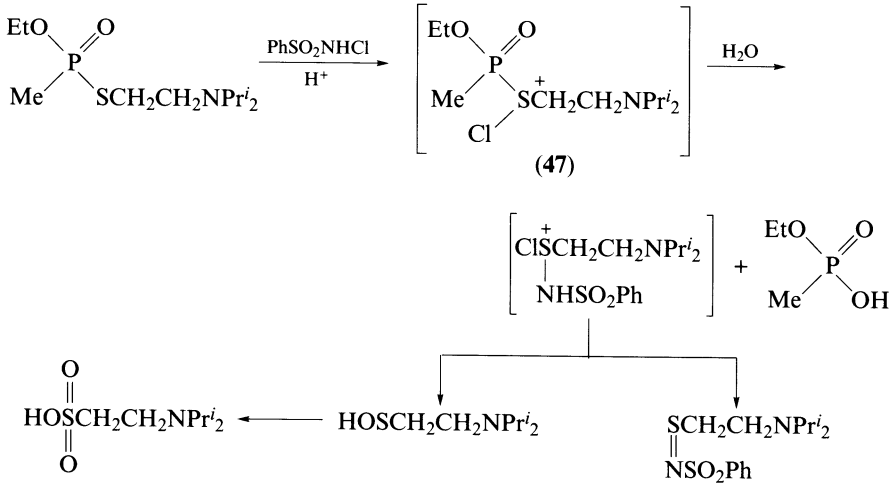


SCHEME 13. Reaction of sarin, soman and VX with DS2

most metal surfaces, it has some significant disadvantages. It can damage paints, plastics, rubber and leather and is also corrosive to skin. EGM has been shown to be teratogenic in rats. As a result, personnel handling DS2 are required to wear respirators with eye shields and chemically protective gloves to avoid skin contact. Exposure to air leads to degradation in performance as a result of absorption of water and carbon dioxide.

3. Skin and personal equipment

Skin decontamination requires the application of chemicals of minimum toxicity, used in a manner that ensures minimum skin damage but effective decontamination. Three personal decontamination kits have been developed in the USA[81]. The M258 kit was produced in 1974 and the M258A1 and M280 systems in the 1980s. The active components of these kits were contained in two sealed packets. Packet I contained a towelette prewetted with a decontamination solution of ethanol (72%), phenol (10%), sodium hydroxide (2%), ammonia (0.2%) and water (about 12%) (by weight). Packet II contained a towelette impregnated with chloramine-B ($PhSO_2NHCl$) and a sealed glass ampoule filled with a solution consisting of zinc chloride (5%), ethanol (45%) and water (50%) (by weight). The kit is used in the following way. The ampoule in packet II is broken and the towelette wetted with solution immediately prior to use. The two towelettes are used consecutively to wipe skin and any other contaminated personal items. Towelette I is effective against G-agents as a result of nucleophilic substitution of fluoride or cyanide by phenoxide, ethoxide or hydroxide. The procedure is effective against thickened soman but not VX as the reactions of VX with these reagents are very slow. Towelette II is designed to decontaminate VX (and sulphur mustard) by an oxidative mechanism. The primary processes leading to decontamination are shown in Scheme 14. Zinc chloride is present to maintain the pH on the acidic side of neutral (pH5–6) and to ensure that sulphur is the focal point of attack by the reactive decontaminant, chloramine B; **47** has been proposed as a probable intermediate which undergoes ready hydrolysis via P—S cleavage to effect decontamination of VX.



SCHEME 14. Reaction of VX with chloramine B in acidic solution

C. Current Developments

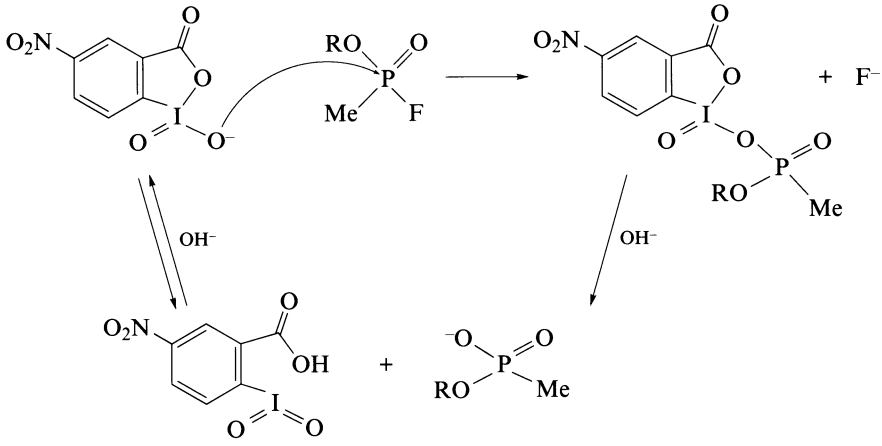
1. Decontamination media

Rapid dissolution of the CW agent in the decontamination medium is essential if complete and rapid decontamination is to be achieved. Although the non-aqueous medium of DS2 fulfils this requirement, including that of thickened agents, it is aggressive towards a number of surfaces, including skin. Conversely, CAD is a totally aqueous based system and, in spite of the detergent content, it does not easily dissolve the less polar chemical agents such as VX (and sulphur mustard) and performs poorly against thickened agents.

A compromise solution to these problems has been sought in the use of micelles and emulsions, both of which have been examined as potential liquid decontamination media. The best studied of a number of such systems are the German emulsion with the code name C8[81], a microemulsion system MCBD[81] (multi-purpose chemical, biological decontaminant) and the phase-transfer system by Ramsden *et al.*[84]. All of these systems use tetrachloroethane as the organic phase and active chlorine as the decontaminant.

The German emulsion contains (by weight) tetrachlorethane (15%), anionic surfactant (1%), calcium hypochlorite (8%) and water (76%). When sprayed on a surface, a thin, coherent film is formed that allows sufficient time for reaction with the agent to occur. It is non-corrosive, good for thickened agents and can penetrate into paint to react with embedded agent without damaging the paintwork.

The microemulsion of the MCBD system consists of (by weight) tetrachloroethane (7%), cetyltrimethylammonium chloride (28%), water (60%) and a small amount of tetrabutylammonium hydroxide as co-surfactant. The reactive decontaminants are FiClor (4%) and sodium 2-nitro-4-iodoxybenzoate (IBX, 0.1%) in sodium borate buffer. IBX is added as a nucleophilic catalyst for the hydrolysis of G-agents[85–87]. The borate buffer (pH10) is essential for the maintenance of the catalytic activity of the IBX (see above and Scheme 15). IBX has little catalytic effect on the hydrolysis of VX[81]. In the phase-transfer system, hypochlorite ion is transferred into the organic phase by the phase-transfer catalyst, tetrabutylammonium chloride.



SCHEME 15. Mechanism of IBX-catalysed hydrolysis of G-agents

All these systems allow chemical reactions leading to decontamination to occur in either the aqueous or organic phase or both, depending on the respective partition coefficients of the CW agents in the systems in use. This confers the degree of flexibility that is necessary to meet successfully the diverse requirements for the chemical detoxification of a disparate group of chemicals encountered in a variety of situations.

2. Decontamination reagents

The majority of systems still rely on the use of hypochlorite-based reactive decontaminants at high pH (ca 10). The underlying principles and chemistry of the decontamination reactions are very similar to those discussed previously, relying on catalytic nucleophilic substitution for G-agents and oxidative chlorination prior to hydrolysis for V-agents. Hypervalent iodides, for example, have been shown to function as catalysts of nerve agent hydrolysis and give good rate enhancements. The mechanism proposed for the catalytic action of IBX on the hydrolysis of G-agents[85–87] under basic conditions is shown in Scheme 15. The maintenance of high pH is essential for catalyst regeneration.

The use of a variety of per-acids has been examined by French workers and shown to be effective decontaminants of toxic organophosphorus compounds[88–91].

D. Future Trends

Incineration is a convenient method for the large scale destruction of bulk CW agents and is likely to continue to be used in the future.

The high profile of environmental considerations ensures that the development of non-corrosive decontamination systems with biodegradable components remains a high priority. The use of *N*-alkyl-2-pyrrolidones as the major organic biodegradable component of a hypochlorite-based liquid system has been shown to be effective in the decontamination of the major CW agents[81]. The use of strong base in *N*-ethyl-2-pyrrolidone has been shown to function in the same way as DS2[81].

The use of emulsions (see above) minimizes the amount of organic solvent in the decontaminating system and consequently the impact on the environment. Menger and Elrington[92] advocated the use of microemulsions as stable homogeneous systems for

carrying out oxidations and hydrolysis reactions. Enzymes have the potential to be part of a totally non-corrosive system.

Solid macroparticulate decontaminants have been examined in the form of modern sorbent materials (to parallel the role of Fuller's Earth) that absorb liquid agent tightly into micropores. The concept of active polymeric decontaminants and catalysts[77] has been examined. Iodosobenzoates have been covalently bonded to a number of polymeric materials. Titanium dioxide and nylon covalently supported iodosobenzoate reagents are reported[93] to be good catalysts for the hydrolysis of some toxic phosphates at pH 8 under heterogeneous conditions. Solid decontaminants of this type present the obvious advantages of ease of use, the creation of 'self-decontaminating' surfaces and the possibility of continuous recycling, e.g. for the decontamination of bulk water supplies. The bonding to nylon gives credence to the concept of 'self-decontaminating' materials in which the reactive decontaminant is incorporated into synthetic fabrics.

VI. SPECTROSCOPIC ANALYSIS

The organophosphorus nerve agents and their analogues have been well characterized by infrared (IR), nuclear magnetic resonance (NMR) and mass spectrometry (MS). In recent years, efforts have been made to compile comprehensive spectroscopic data bases in support of analysis required for verification of compliance with the Chemical Weapons Convention (see Section XIV). Compilations of spectroscopic data are included in the series of 'Blue Books' for the verification of chemical disarmament, published by the Ministry for Foreign Affairs of Finland[94–96]. These volumes address the application of spectroscopic and chromatographic techniques to verification analysis[97].

A. Infrared

Extensive correlations of IR absorption frequencies against functional groups, and substituents on phosphorus, have been made by Thomas[98,99] and Corbridge[100] for condensed phase spectra.

The most useful diagnostic bands for identification are the P=O stretching vibration and the P—F stretching vibration in phosphonofluoridates such as sarin, GF and soman. Each of the three types of nerve agent contain a P=O bond which is recognizable by a medium to strong band in the frequency range 1230–1290 cm^{-1}. The P—F bond gives a characteristic medium to strong band in the range 840–845 cm^{-1}. Assignment of the P—C stretching vibration is less certain because of its range (880–930 cm^{-1}) and the presence of other bands in the same region of the spectrum; the presence of a P—C bond may be deduced from the frequency of the P=O band[98,99]. P—N bonds in compounds such as tabun are also difficult to assign unequivocally. A P—S bond may be recognized as a single band between 520 and 540 cm^{-1} in the case of VX-type compounds containing a PMe group, or two bands in this region in the case of analogues containing a PEt substituent. Assignments of the important functional group frequencies in the classical nerve agents are shown in Table 3.

IR spectra provide functional group recognition in unknown compounds and serve as fingerprints for the confirmation of identification of known compounds. Over the past decade, Fourier transform IR (FTIR) spectrometry combined with gas chromatography has become a routine technique, applicable to the analysis of mixtures of volatile compounds[101]. It provides a useful and independent confirmatory technique to support the identification of nerve agents by GC–MS, particularly in the case of VX-type compounds where spectra obtained by GC–MS using electron impact ionization are dominated by low-mass fragmentation ions. Two types of GC interface, the light pipe and direct deposition,

TABLE 3. Stretching vibration frequencies (cm^{-1}) for the major bonds in nerve agents[a]

Compound	P=O	P—C	PO—C	P—F	Other
Sarin	1288	928, 1320	1016	844	
Soman	1288	920, 1320	1020	844	
GF	1280	928, 1320	1016	840	
Tabun	1276		1036		1008 (P—N), 2200 (CN)
VX	1232	884, 1300	1036		528 (P—S)

[a]Source: CBDE database.

have been applied to the analysis of nerve agents[97]. In the light pipe interface, spectra are recorded in the gas phase. With the direct deposition interface, compounds eluted from the gas chromatogrph are sequentially condensed on to a cooled, movable IR-transparent window. Spectra are recorded in the condensed phase and are comparable to conventional condensed-phase spectra for which an extensive database exists. Additional advantages of the direct deposition interface are greater sensitivity and, since the compounds are preserved on the window, the ability to scan retrospectively to increase resolution and signal-to-noise ratios. FTIR spectra are compared to reference spectra by the integral data system. Data can be manipulated by the computer to produce chromatograms of IR absorption at selected regions of the spectrum, e.g. P=O absorption. The light pipe method is less sensitive than GC–MS but the direct deposition method approaches the sensitivity of full scanning GC–MS in favourable cases where absorption is strong.

B. Ultraviolet Absorption

The P=O and P—F bonds are weak UV chromophores above 200 nm and UV absorption has been of little use in characterizing or detecting nerve agents. Sarin, soman, tabun and VX in cyclohexane solution give featureless, smooth, broad spectra between 350 and 200 nm with an implied maximum below 200 nm[102]. The strength of UV absorption was in the order VX > tabun >> soman > sarin.

C. Nuclear Magnetic Resonance

The organophosphorus nerve agents contain four nuclei, ^{1}H, ^{13}C, ^{19}F and ^{31}P, each with a spin of 1/2, which can be conveniently measured by routine NMR[94]. The relative sensitivities of these nuclei to NMR are ^{1}H (100) > ^{19}F (83) >> ^{31}P (6.6)> ^{13}C (1.6). ^{13}C and ^{31}P spectra are acquired under proton decoupled conditions for optimum signal-to-noise ratios. ^{31}P chemical shifts, measured relative to the frequency of 85% orthophosphoric acid, are generally much larger and have a wider range than ^{1}H chemical shifts. ^{31}P chemical shifts for nerve agents are shown in Table 4.

Electronegative substituents on phosphorus, such as fluorine, generally have a deshielding effect. The coupling constants between ^{31}P and ^{19}F are large and are useful in structural diagnosis. $^{1}J_{PF}$ of ca 1050 Hz is characteristic of a phosphonofluoridate-type nerve agent. P–H couplings (if concentrations allow their determination) may be useful for structural identification in simple first-order spectra such as tabun ($^{3}J_{PNCH}$ = 11.5 Hz), but are difficult to obtain in more complex molecules such as VX. ^{19}F NMR can be measured at higher sensitivity than ^{31}P NMR, and the chemical shifts in phosphonofluoridates (Table 4), measured from $CFCl_3$, are more sensitive to structural variations in the OR substituent in

TABLE 4. ^{31}P and ^{19}F chemical shifts (ppm) and P–F coupling constants (Hz)[a]

Compound	δ_P	δ_F	j_{P-F}
Sarin	28.25	56.89	1046
Soman	29.33	55.43	1048
	28.20	58.18	1047
GF	29.03	56.80	1047
Tabun	–9.68		
VX	54.58		

[a]Source: CBDE database.

comparison with ^{31}P NMR[103]. F–H couplings are less useful than P–F couplings because of the small absolute values ($^3J_{FPCH} \approx 4$–6 Hz) and problems of reliable determination, although the multiplicity is useful in indicating the number of hydrogens on the carbon adjacent to phosphorus.

Within the limits of their sensitivity, ^1H and ^{13}C NMR spectra provide a high level of structural information and unequivocal identification of nerve agents. ^{31}P and ^{19}F NMR are more indicative of type and may be useful for screening sample extracts for the presence of nerve agents as signal backgrounds are normally low. ^{31}P is particularly useful for the direct screening of aqueous extracts for hydrolysis products, which would otherwise require removal from the aqueous media and derivatisation for GC–MS analysis[97,104]. Both ^{31}P and ^{19}F NMR are useful for monitoring the progress of chemical reactions of nerve agents, especially hydrolysis and other reactions of importance in decontamination[80,105]. The major limitations of NMR in verification analysis are its comparatively low sensitivity and the lack of a suitable interface for coupling with a chromatographic technique.

NMR is the most useful technique for demonstrating and investigating the stereochemistry of organophosphorus compounds. Differentiation of stereoisomers is important for the study of chemical and biochemical reaction mechanisms[58]. Lanthanide shift reagents associate with the P=O bond of nerve agents; on addition of the chiral shift reagent tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium [Eu(fod)$_3$] to sarin, the protons in the two diastereotopic methyls of the isopropyl group, normally observable as a doublet, become non-equivalent on the NMR time-scale and are shifted downfield as a resolved pair of doublets[106]. Addition of the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium [Eu(hfc)$_3$] splits these signals further into four sets of doublets as the enantiomers are differentiated. The MeP hydrogens, normally observed as a doublet of doublets due to H—C—P and H—C—P—F coupling, are also observed as a quartet of doublets although the signals are broader. The four stereoisomers of soman were similarly resolved, the sharpest signal, and most useful for analytical purposes using ^1H NMR, being obtained for the Me_3C protons which appear as four well resolved singlets on addition of tris[3-(trifluoromethylhydroxymethylene)-camphorato]europium [Eu(tfc)$_3$][106]. In the ^{13}C spectrum the best resolution is observed for the MeP carbons which appear as an octet of doublets, as shown in Figure 1, due to C—P and C—P—F coupling, and the resolution of the four stereoisomers. The ^{19}F signal for soman in the presence of Eu(hfc)$_3$ or Eu(tfc)$_3$ appears as a quartet of doublets due to P—F coupling; the use of Eu(hfc)$_3$ in benzene gave the best resolution[107]. Chiral NMR resolution of tabun and VX was similarly demonstrated using Eu(tfc)$_3$ and Eu(hfc)$_3$, although the resolution was poor with VX[106].

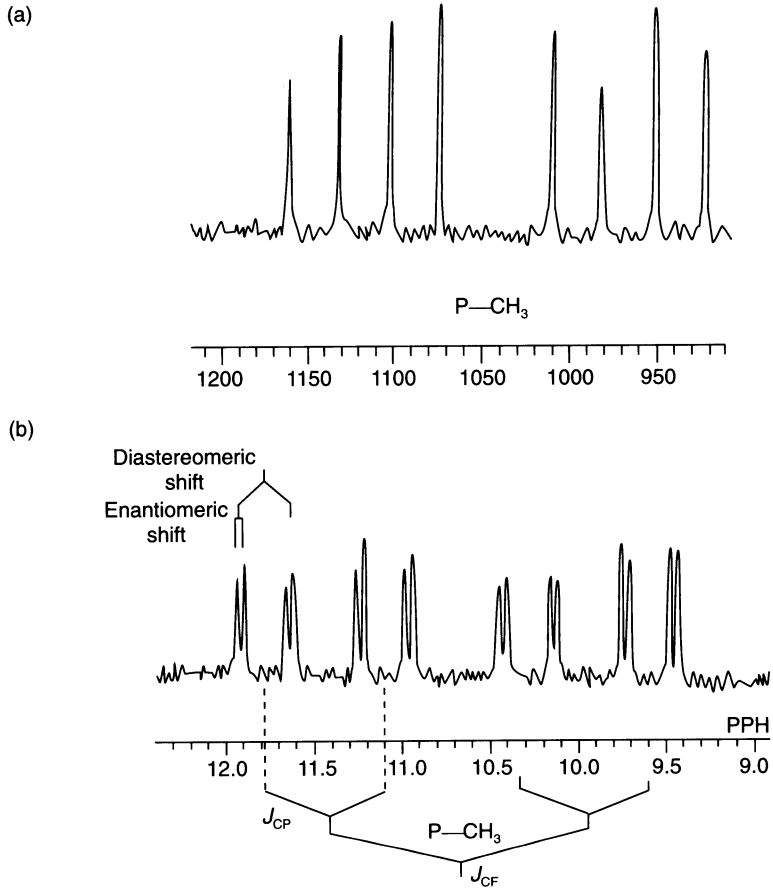
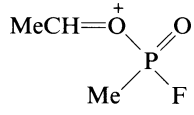


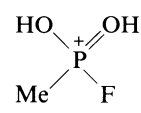
FIGURE 1. ^{13}C NMR (proton decoupled) spectra of soman (400 MHz, $CDCl_3$) showing signals for Me-P carbon (a) without added shift reagent and (b) after addition of $Eu(hfc)_3$

D. Mass Spectrometry

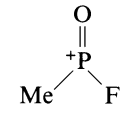
Under typical electron impact (EI) ionization conditions (i.e. electron energy of 70 eV), sarin, soman, GF and related methylphosphonofluoridates give a very weak (<0.5%) or no molecular ion[94]. The highest mass ion observed in the mass spectrum of sarin is *m/z* 125, $[M–CH_3]^+$, formed by cleavage of the C—C bond β to the alkoxy oxygen to form the relatively stable oxonium species **48**. A weak ion is observed at *m/z* 125 in soman, but an additional high-intensity ion is observed at *m/z* 126 due to elimination of the neutral species isobutene from the molecular ion[108]. Such side-chain fragmentations cannot easily occur with the cycloalkyl group in GF and no high-mass ions are observed other than a very weak molecular ion. A major ion common to all three compounds, and the base peak in sarin and GF, is *m/z* 99, which is attributed to fragmentation of the C—O bond accompanied by double hydrogen transfer to form **49**. This ion is particularly useful for selected ion



m/z 125
(48)



m/z 99
(49)



m/z 81
(50)

monitoring of methylphosphonofluoridates in trace analysis. Formal loss of water from **49** produces **50** at *m/z* 81, which is also common to soman and GF, although a much more intense ion is observed at *m/z* 82 with soman. The other major ions observed in the mass spectra of methylphosphonofluoridates are mostly derived from the alkoxy side-chains. Of the classical nerve agents, tabun is the only one which gives a moderately strong molecular ion under EI conditions at *m/z* 162. A high-mass ion is observed at *m/z* 133 resulting from C—O bond fission and an intense ion at *m/z* 70 whose structure ($C_4H_8N^+$)[101] is uncertain; the base peak, $[CH_2{=}NMe]^+$, is observed at *m/z* 43. The EI mass spectrum of VX is the least informative because of the stability of the ion $[CH_2{=}NiPr_2]^+$, formed by β-fission of the side-chain, which forms the base peak at *m/z* 114. Very weak high-mass ions are observed at *m/z* 252 (loss of Me) and 167 (loss of Pr^i_2N). The identification of VX based solely on the EI mass spectrum may therefore be erroneous. Unequivocal molecular mass information can be obtained on all of the nerve agents by using chemical ionization (CI), in which ionization occurs less energetically by proton (or ammonium ion) transfer during ion–molecule collisions with a preionized reagent gas. Methane CI gives moderately strong protonated molecular ions whilst providing a degree of structural information from a limited number of fragment ions[109], e.g. *m/z* 99 remains the base peak for sarin, soman, and GF. For this reason, methane CI is advantageous for selected ion monitoring of nerve agents (see below), where several high-mass ions can be monitored for greater specificity. Isobutane and ammonia CI are less energetic and give 100% MH^+ or MNH_4^+ ions with little fragmentation[110]. Typical mass spectra for the five nerve agents acquired using EI are shown in Table 5. Of the three major spectrometric techniques, mass spectrometry has found the widest application in the characterization and analysis of nerve agents owing to its overwhelming superiority in terms of sensitivity, the provision of specific structural information, including the molecular mass, and its routine combination with gas chromatography.

The power of full scanning capillary GC–MS as an analytical tool, using both EI and CI, is well illustrated by the identification of 30–50 impurities in aged munition samples of tabun and VX[78,111,112]. The combination of GC with MS has generally been the method of choice for detecting and confirming trace levels of nerve agents or their degradation products in various environmental and biological matrices. For detection or determination of nerve agents at nanogram levels, selected ion monitoring is employed[113,114], in which

TABLE 5. EI mass spectra of nerve agents[94]

Compound	*m/z* (% relative abundance)[a]
Sarin	125 (23), 99 (100), 81 (10), 47 (3), 43 (8), 42 (5), 41 (7), 39 (5)
Soman	126 (100), 99 (85), 83 (14), 82 (50), 69 (49), 57 (21), 43 (15), 41 (37)
GF	99 (100), 82 (6), 81 (6), 67 (20), 55 (5), 54 (14), 41 (8), 39 (6)
Tabun	162 (29), 133 (42), 117 (14), 106 (21), 70 (85), 44 (55), 43 (100), 42 (43)
VX	127 (13), 115 (8), 114 (100), 79 (8), 72 (21), 70 (9), 43 (7), 30 (8)

[a]Eight most abundant peaks.

structurally characteristic ions, preferably at high mass for greater selectivity, are monitored by rapid switching of the instrumental parameters. This mode of operation increases the sensitivity of detection by 2–3 orders of magnitude over full scanning GC–MS. Limits of detection and selectivity have been improved further by the use of tandem mass spectrometry (GC–MS–MS), in which structurally dependent fragmentations are monitored[115,116]. In the product ion (parent–daughter) mode of operation, the first mass spectrometer is tuned to transmit only a selected parent ion, usually a molecular or high-mass ion, which is then induced to fragment by collision with a gas; the product (daughter) ions are detected by the second mass spectrometer. By analogy with single-stage GC–MS, the second mass spectrometer can be operated in full scanning mode or monitoring specific product ions for optimum sensitivity (termed multiple or selected reaction monitoring). The benefits of using GC–MS–MS have been demonstrated in the analysis of picogram to nanogram quantities of GB in air in the presence of diesel fumes[115], and the detection of parts per 10^{12} of GB and VX in air using atmospheric pressure ionization and selected reaction monitoring[116]. GC–MS–MS is likely to find further application in the analysis of nerve agents and their degradation products in biological fluids and in investigations of allegations of use[114]. LC–MS, using a thermospray interface/ionization source, has been used for the determination of VX[117,118] and methylphosphonic acids[118,119] in aqueous media. Limits of detection are higher than can optimally be achieved using GC–MS, and thermospray mass spectra contain few fragment ions for identification. However, superior recoveries in comparison with GC–MS have been demonstrated for methylphosphonic acid spiked into soil[104]. LC–MS and LC–MS–MS are likely to find increasing use in the analysis of hydrolysis products as more laboratories become equipped with thermospray, ionspray or atmospheric pressure CI LC–MS interfaces.

VII. CHROMATOGRAPHIC ANALYSIS

Witkiewicz *et al.*[120] have comprehensively reviewed the application of chromatographic methods to the analysis of chemical warfare agents. A brief overview is presented below with the emphasis on applications in verification analysis and pharmacokinetic studies.

A. Thin-layer Chromatography (TLC)

TLC can be used as a screening procedure for the detection of nerve agents and their hydrolysis products but its use is not widespread owing to the superior resolution and sensitivity obtainable with GC. It does, however, offer the advantage of simplicity and cheapness, and can be easily adapted for use in a field laboratory. Most applications have used silica plates with moderately polar solvent mixtures as the mobile phase[120]. The mobility of VX on the acidic silica surface may be enhanced by the addition of a small amount of base, such as diethylamine, to the mobile phase. Various systems have been used for visualization[120], but for optimum sensitivity and selectivity the detection of intact agents is achieved biochemically. The developed plates are sprayed with reagent solutions of cholinesterase and a substrate, such as butyrylthiocholine, 2-naphthol acetate or indoxyl acetate, whose hydrolysis can be monitored by fluorescence, or colour change with the addition of a third reagent or indicator (see Section IX). Pesticides with anticholinesterase activity are also detected by these visualization reagents; a method using two-dimensional overpressurized TLC has been described in which the principal nerve agents were resolved from 22 pesticides with limits of detectability ranging from 1.3 pg for tabun to 48 ng for VX, with quantitation possible in the range 15 pg–100 ng[121].

B. Gas Chromatography (GC)

1. Intact agents

The use of modern bonded-phase fused-silica capillary columns, in combination with mass spectrometric or selective phosphorus detection, allows the resolution and detection of nerve agents down to trace levels (parts per 10^9 or pg injected) in complex matrices such as soil, paint or blood. The major nerve agents and their analogues are well resolved on relatively non-polar phases such as 5% diphenyl–95% dimethyl polysiloxane (SE-54, or similar commercial phases such as BP-5, DB-5 HP Ultra-2 and CP-Sil-8) and phases of intermediate polarity such as 14% cyanopropylphenyl–86% dimethyl polysiloxane (OV-1701, or similar commercial phases such as BP-10, DB-1701 and CP-Sil-19)[97,122]. Picogram injections of GB may give improved peak shapes on more polar columns such as poly(ethylene glycol) (Carbowax)[114], but these are not suitable for the general screening of nerve agents and other CW agents. Splitless injection is commonly employed for optimum sensitivity but on-column injection may be advantageous for VX (see below). For non-selective detection at moderate concentrations (ng injected), flame ionization detection (FID) can be used, but for most applications the more selective and sensitive nitrogen–phosphorus detection (NPD) or mass spectrometric detection are preferred. For example, soman was determined in serum down to levels of 40 pg ml^{-1} using GC–NPD[123]. Flame photometric detection (FPD) is also useful since it has enhanced sensitivity and selectivity for phosphorus- or sulphur-containing compounds, and is useful when simultaneous detection of sulphur mustard is required. For confirmation of identification, GC with FTIR or MS detection is employed.

The most problematic of the nerve agents for gas chromatography at trace levels is VX, which is prone to adsorption or thermal decomposition at active sites. Careful attention to conditions, and the use of on-column injection, have partially overcome these difficulties, but the detection limits for VX are still usually higher than for the other nerve agents. One solution has been to convert VX into the analogous phosphonofluoridate by reaction with silver fluoride[124,125]. This can be conveniently performed by reaction at room temperature with silver fluoride adsorbed on a solid support such as a felt pad[125] or polyethylene powder[124]. Limits of detection comparable to those achievable with G agents have been obtained using this procedure.

Near baseline resolution of the two diastereoisomers of soman can be obtained on non-polar columns under normal analysis conditions and complete resolution can be obtained on more polar columns such as poly(ethylene glycol)[123]. Chiral resolution of the four isomers of soman has been achieved on a chiral stationary phase consisting of L-valine-*tert*-butylamide bonded to a polysiloxane backbone (Chirasil Val)[126,127]. Only partial resolution of sarin was obtained using this phase and no resolution of tabun or VX was achieved. The enantiomers of tabun and sarin, but not VX, were resolved using the gas chromatographic equivalent of a chiral shift reagent[62,128]. Chiral complexation was achieved using a stationary phase consisting of 6% bis[(1*R*)-3-(heptafluorobutyryl)camphorate]nickel (II) in dimethylsiloxane.

2. Hydrolysis products

Nerve agent residues remaining in the natural environment are likely to undergo substantial hydrolysis in the period immediately following dissemination. In investigation of allegations of use it is therefore important to analyse for trace levels of hydrolysis products. The important hydrolysis products of sarin, soman and GF are the isopropyl, pinacolyl and cyclohexyl methylphosphonic acids, which are slowly hydrolysed further to methylphosphonic acid. VX is predominantly hydrolysed to ethyl methylphosphonic acid

and 2-(diisopropylamino)ethanethiol. In the environment, the former may be hydrolysed further to methylphosphonic acid whilst the latter is oxidized to bis[2-(diisopropylamino)ethyl] disulphide. None of the primary hydrolysis products which retain a P—C bond can be derived from commonly used pesticides, although methylphosphonic acid could conceivably arise from the hydrolysis of a flame retardant such as dimethyl methylphosphonate. Tabun hydrolysis products, which lack a P—C bond, are somewhat equivocal with regard to origin and less effort has been focused on methods for their detection.

The alkyl methylphosphonic acids are polar and involatile and must be derivatized before analysis by gas chromatography. The simplest derivatization involves conversion into the methyl esters using diazomethane[95,129], or trimethylphenylammonium hydroxide in the hot injection port[130]. However, the GC properties of the methyl esters, particularly dimethyl methylphosphonate, are not ideal and may give rise to poor peak shapes at low concentrations. Alternative derivatives are the trimethylsilyl[131,132] or *tert*-butyldimethylsilyl[114,133] esters. The latter are more stable than the trimethylsilyl esters and provide good high-mass ions for selected ion monitoring. An advantage of using silyl esters is that they can be used for the simultaneous detection of thiodiglycol, the hydrolysis product of sulphur mustard[114], which ranks with the nerve agents as one of the CW agents of most concern. The presence of calcium ions may seriously hinder the silylation of methylphosphonic acid, but this can be overcome by removal of the calcium ions by ion exchange[104] prior to derivatization. For optimum sensitivity, e.g. for the detection of hydrolysis products in urine and blood using selected ion monitoring, pentafluorobenzyl esters have been recommended, in combination with EI, positive ion CI or negative ion CI mass spectrometry[95,134], the last giving very high sensitivity. Bonded low-polarity mobile phases such as 5% diphenyl–95% dimethyl polysiloxane are generally used for separation.

C. Liquid Chromatography (LC)

1. *Intact agents*

Since the nerve agents are sufficiently volatile for GC analysis and are susceptible to hydrolysis, LC has found few applications in their analysis. A method has been described for the analysis of sarin, soman and tabun by C_{18} reversed-phase LC using gradient elution with methanol–water mixtures[135]. A post-column reactor system employing cholinesterase inhibition and the Ellman reagent was used for detection, giving limits of detection in the range 10–200 pg injected. Thermospray LC–MS using a C_{18} column has been used for the direct detection of VX in aqueous solutions, such as in river waters[117,118]. The method possessed moderate sensitivity, 200 pg injected using selected ion monitoring of the protonated molecular ion, which gave a limit of detection of 0.1 ng ml^{-1} after preconcentration of 50 ml water samples.

2. *Hydrolysis products*

LC is more useful for the direct analysis of hydrolysis products. A method using pre-column derivatization to *p*-bromophenacyl esters was described[136] to facilitate UV detection but the detection limits were poor (43–62 ng injected). Increased sensitivity was reported by pre-column derivatization to *p*-(9-anthroyloxy)phenacyl esters and using laser-induced fluorescence detection[137]. Direct detection of alkyl methylphosphonic acids by thermospray MS, using a C_{18} column and 0.1 M ammonium acetate as eluent, gave detection limits of around 1 ng injected using single ion monitoring, which extrapolated to 20 ng ml^{-1} in water using large injection volumes (50 μl)[119]. The most sensitive LC system

which has been reported[138,139] employs flame photometric detection, microcolumn (0.32 mm i.d.) reversed-phase or ion-exchange chromatography and the addition of hydrochloric acid or butanol as displacers to the mobile phase to give sharp compressed peaks. Detection limits in water were methylphosphonic acid 1 ppb, isopropyl methylphosphonic acid 10 ppb, and pinacolyl methyl phosphonic acid 20 ppb. LC detection of methylphosphonic acids is useful for screening purposes and for quantitation[104]. Capillary zone electrophoresis–MS using ionspray ionization in negative ion mode has recently shown promise for rapid separation and sensitive detection (10–30 pg injected) of methylphosphonic acids[140].

VIII. TRACE ANALYSIS OF NERVE AGENTS AND THEIR DEGRADATION PRODUCTS IN VERIFICATION

A major area of interest in chemical defence research over the past 10 years has been the development of methods for the analysis of chemical warfare agents and their degradation products in the environment[94–97]. The signing of the Chemical Weapons Convention (Section XIV) has added impetus to this work, with a requirement for analytical methodology to support verification of compliance, or non-compliance, with regard to destruction, production or use of chemical weapons. Less attention has been focused on the analysis of nerve agents or their degradation products in biological fluids.

A. General Strategies[97]

The trace analysis of environmental and biological samples can be conveniently divided into four components: sample preparation (extraction/clean-up), screening (preliminary identification), unequivocal identification and quantitation. In the context of CW agent verification, confirmation of identification is of much greater importance than quantitation. Careful attention is also being paid to sample collection, transportation, storage and documentation, and the need for scrupulous quality control in trace analysis[97]. The extraction of intact agents and hydrolysis products is usually performed separately as described below. Chromatographic techniques (GC or less commonly LC and TLC) are usually used for screening; LC and ^{31}P NMR are useful for screening aqueous extracts for the presence of hydrolysis products. For unequivocal identification at low concentrations in complex matrices, the combination of a chromatographic separation with a spectroscopic method, such as GC–MS, is required.

B. Sample Preparation

1. Intact nerve agents

The nerve agents are sufficiently lipophilic to be extracted from soil and other predominantly non-aqueous materials with organic solvents such as dichloromethane. Soil is a notoriously heterogeneous material and at concentrations below ca 1 ppm the recovery may be lowered substantially by binding to active sites and by hydrolysis. Experience with matrices such as soil, vegetation, rubber, plastic and paint, which are likely to be sampled in investigations of CW use, suggests that the intact agent is more likely to survive for prolonged periods in synthetic polymeric organic materials (where it is partially protected from moisture, microbes and oxidation) than in the natural environment[114]. Thermal desorption, directly into a gas chromatograph, is a useful technique for the recovery of the more volatile nerve agents from these materials[97]. Extraction of nerve agents from aqueous

solutions is conveniently achieved by solid-phase extraction on to bonded-silica reversed-phase C_{18} cartridges[141–143]. The addition of sodium chloride to the aqueous phase gave significantly improved recoveries[143]. High recoveries of tabun, sarin and soman were obtained by eluting the C_{18} cartridge with dichloromethane; VX was best eluted with acetone[143]. Liquid–liquid extraction of VX from a decontamination residue at pH 9 was found to be more efficient than solid-phase extraction[144]. A sensitive method for the analysis of soman in rat blood (buffered to pH 4.2) used solid-phase C_{18} extraction and elution with ethyl acetate[126]; recoveries were 45–61% at concentrations in the range 1–600 ng ml^{-1}. Alternatively, both sarin and soman were efficiently extracted from spiked human blood by liquid–liquid extraction with chloroform, after deproteination with perchloric acid and addition of saline to the supernatant[113]. Extraction of nerve agents from air has been achieved by absorption on polymers such as Tenax[145,146], XAD-2 resin[146] or Chromosorb 106[125], followed by thermal desorption into a gas chromatograph. The method gives good recoveries for tabun, sarin and soman but is poor for low concentrations of VX owing to adsorption on active sites.

2. Hydrolysis products

The methylphosphonic acids, with a pK_a around 2.5, are almost totally ionized at neutral pH, and accordingly have good solubility in polar solvents such as water and methanol, and poor solubility in dichloromethane. Extraction from soil can be achieved by tumbling or shaking with water[97,114] or aqueous methanol. In the case of methylphosphonic acid, recent experience has shown that co-extracted calcium ions may seriously interfere with the derivatization required for GC analysis, and removal of divalent metal cations by elution through a cation-exchange resin is recommended before concentration to dryness[97,104]. Isopropyl and pinacolyl methylphosphonic acids can be recovered from large volumes of aqueous solution by retention on aminopropyl anion-exchange cartridges[130]. The non-ionized forms of the alkyl methylphosphonic acids have sufficient hydrophobic character to allow them to be isolated from aqueous solution by retention on reversed-phase silica cartridges. Recovery from urine or plasma, acidified to pH 1, was achieved by retention on C_2 (pinacolyl and cyclohexyl) or C_{18} (isopropyl methylphosphonic acid) cartridges[134], followed by elution with methanol. Recoveries of pinacolyl and isopropyl methylphosphonic acid were 85% and 94%, respectively, from urine and 48% and 45% from blood. Retention on C_{18} may be enhanced by ion-pair formation with tetrabutylammonium hydroxide[119].

C. Screening Procedures

GC–NPD, GC–FPD or GC–MS (full scanning or selected ion monitoring) are most commonly employed for screening purposes. Absolute retention times, or relative retention times using an internal standard, are reliable for a tentative identification provided that frequent controls are run. Minimal variability can be achieved using retention index monitoring, where the retention time is related to those of a homologous series of internal standards. Straight-chain alkanes may be used[97,122] with non-selective detectors such as FID, but for use with GC–NPD, the M series of compounds $(CF_3)_2P(S)(CH_2)_nCH_3$ ($n = 2$, 3, 5, 7,..., 21) are used as standards[94]. Retention indices of analogues of tabun, sarin and VX have been compiled for SE-54 and OV-1701 capillary columns, using both types of standard[97], and factors affecting variability have been investigated[147]. As described above, ^{31}P NMR and LC are useful for the screening of hydrolysis products and avoiding the pitfalls of poor derivatization observed with methylphosphonic acid in the presence of calcium ions.

D. Unequivocal Identification

Criteria have been recommended for the unequivocal identification of chemical warfare agents[97]. Their application has been demonstrated in inter-laboratory comparison exercises[104]. With multi-component extracts the preferred method, where concentrations are sufficient, is full scanning GC–MS using EI and CI. Identification is therefore based on retention time, molecular mass (CI) and the fragmentation fingerprint provided by EI. Spectral comparison by GC–FTIR is recommended as an independent spectroscopic technique if concentrations allow. In sample extracts where concentrations of analyte, or resolution from extraneous material, are insufficient to obtain good-quality full-scan mass spectra, selected ion data may be used. At least three ions with relative intensity ratios within 15–20% of those of a standard have generally been accepted as proof of identification (together with retention time), but for increased confidence higher resolution selected ion monitoring (obtainable with double focusing magnetic sector instruments) or GC–MS–MS using multiple reaction monitoring have been recommended. It is also useful to repeat the analysis using GC columns of substantially different polarity. An example of such data is provided in the recent identification of sarin and its hydrolysis products in soil residues from a bomb crater[114] associated with an allegation of CW use.

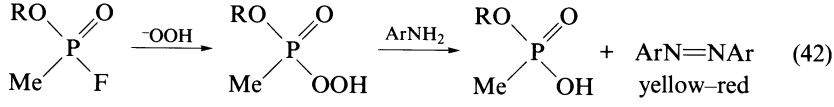
IX. GENERIC DETECTION OF NERVE AGENTS

A. Laboratory Detection

Simple, inexpensive, colorimetric-, fluorescence- or chemiluminescence-based detection systems[148] have proved useful for monitoring contamination in laboratories and storage facilities, for quantifying nerve agents in simple matrices and for monitoring reactions, for example in decontamination. Some of these methods have been combined with TLC and LC separations, as described in Section VII, for more demanding applications. Sensitive biochemical, toxicological or immunological methods may be of use in screening procedures for environmental investigations, although chromatographic methods are usually preferred.

1. Reactions based on an initial nucleophilic displacement at phosphorus

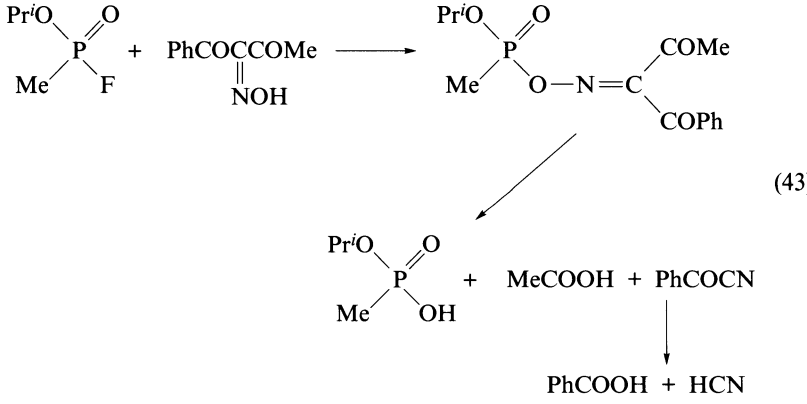
a. The peroxide–amine (Schönemann) reaction. One of the earliest chemical reactions to be exploited for the detection of nerve agents, first described by Schönemann[149] and reviewed by Poziomek and Crabtree[150], is the acceleration of the peroxide-induced oxidation of aromatic amines by an electrophilic organophosphorus compound. The reaction proceeds via a peroxyphosphonate intermediate[151], which then reacts rapidly with the amine. In the procedure reported by Schönemann, *o*-toluidine was used as the amine which forms a yellow–red diazine on oxidation. The chemistry is outlined in equation 42. Various modifications of the reaction have been reported; sodium perborate or sodium peroxodiphosphate are used as oxidant for greater stability. Increased sensitivity to colorimetric detection was obtained using substituted benzidines such as *o*-dianisidine[152]. Sensitivity was further increased by using indole[153] or luminol (5-amino-2, 3-dihydrophthalazine-1,



(42)

4-dione)[154] as substrates to form fluorescent and chemiluminescent oxidation products respectively. Limits of detection for sarin were 500 ng using *o*-dianisidine (red colour) or luminol (chemiluminescence) and 30 ng using indole (fluorescence)[154]. The reaction is enhanced by the presence of chloride ions. In a more recent modification of the luminol-based reaction, limits of detection were lowered to 500 pg for sarin and soman, 1 ng for tabun and 10 ng for VX[155], by the addition of chloride ions, and EDTA to supress background emission caused by catalysis by metal ion impurities; linear calibrations were obtained over three decades.

b. Reaction with oximes. α-Ketoaldoximes react rapidly with phosphonofluoridates under slightly basic conditions with displacement of fluorine[158–158]. The initial product, formed in the rate-controlling step, rapidly undergoes a Beckmann-type fragmentation with the liberation of cyanide ion[156]. The reaction of sarin with diisonitrosodiacetone can be observed directly with the formation of a magenta-coloured product, although the sensitivity (ca 1 μg) is low[159]. In the most widely used method, employing 1-phenylbutane-1,2,3-trione-2-oxime, the liberated cyanide is detected by addition of nitrobenzaldehyde-dinitrobenzene[160] or chloramine T–pyridine–pyrazole reagents[156], to produce coloured reaction products. The reaction of sarin with 1-phenylbutane-1,2,3-trione-2-oxime, shown simplistically in equation 43, is non-stoichiometric with regard to cyanide formation since the initial oxime-nerve agent adduct and cyanide ion may react further with oxime to produce 2 mol of cyanide[160,161]. Tabun may be detected by direct displacement of cyanide; VX can be detected indirectly after conversion into the corresponding phosphonofluoridate with silver fluoride or fluoroborate.



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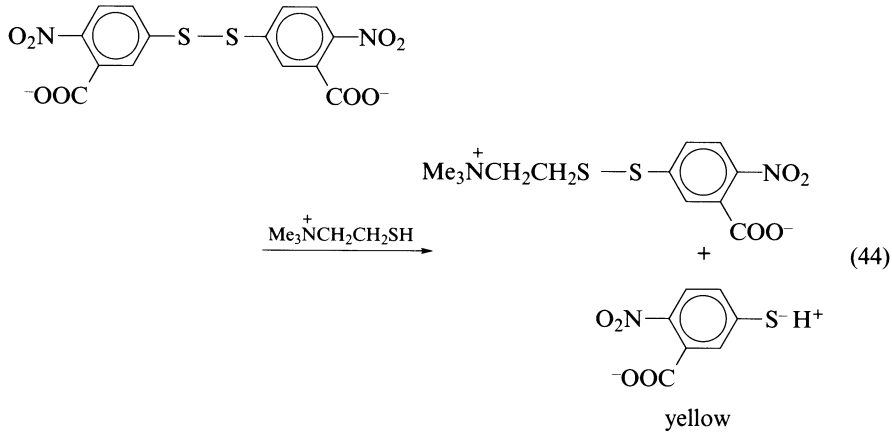
2. Inhibition of cholinesterase

The biochemical target for nerve agents is the enzyme AChE (see Section X); inhibitory concentrations are typically in the nanomolar to picomolar range and assays which measure this inhibition can be very sensitive. An advantage over the chemical methods described above is that enzymatic assays, using AChE or related esterases, are directly applicable and highly sensitive for VX. By suitable choice of substrate, enzymatic activity can be monitored colorimetrically[162,163], electrochemically[164], by fluorescence[165] or by chemiluminescence[166]. The simplest method is to monitor the change in pH on liberation of acetic or butyric acids from acetyl- or butyryl-choline, using a colorimetric pH indicator. Greater sensitivity is achieved using acetylthiocholine or butyrylthiocholine as

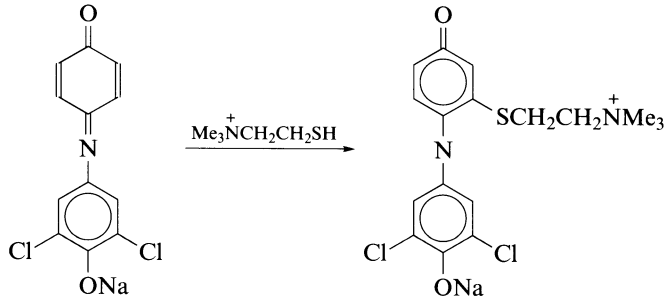
substrate and detection of the hydrolysis product thiocholine by a colorimetric redox reaction[162] or electrochemically[164]. In the commonly used Ellman method[162,167,168], the thiocholine is reacted with dithiobisnitrobenzoate to produce the yellow 2-nitro-5-thiobenzoate anion (equation 44). Sarin and VX were detectable in sea water at the parts



(44)

yellow

per 10^{12} level using this method, although a long incubation time (30 h) was employed[168]. Thiocholine can also be determined colorimetrically by addition to and decolorization of the blue indicator phenol-indo-2, 6-dichlorophenol (equation 45). Other substrates that have been used for measuring cholinesterase activity include indophenyl acetate[163] (blue–purple hydrolysis product) and indoxyl acetate[165] (fluorescent hydrolysis product, indoxyl). Inhibition of chymotrypsin has been used with 4-methylumbelliferyl 4′-trimethylammonium cinnamate as substrate, which releases the chemiluminescent 4-methylumbelliferone on hydrolysis[166].



(45)

blue yellow

3. Bioassay

Cell culture based bioassays are used in the agricultural field to screen for harmful contaminants such as mycotoxins. The chick embryo neuron culture system is very sensitive to the anticholinesterase activity of organophosphorus nerve agents, in a manner which parallels toxicities in animals; the sensitivity to sarin was around 100 pg[169]. The bioassay was used successfully to detect sarin at low ppm levels spiked into soil.

4. Immunoassay

An enzyme-linked immunoassay, using monoclonal antibodies linked to the enzyme peroxidase, was able to detect 2 ng of pure soman or a modest 180 ng ml^{-1} in human serum[170]. Little cross reactivity was observed with sarin and none with VX and tabun.

B. Battlefield Detection

Detectors for the battlefield need to be rugged, simple and sensitive to nerve agent at concentrations at or below the threshold for causing physiological effects[171]. They may be used as remote or point warning devices, or, as in most of the systems described below, for monitoring the presence of contamination. Sarin will be present primarily as a vapour on the battlefield; tabun, and soman may be present as vapour and liquid droplets (particularly if thickened); VX will be present primarily as liquid droplets. Liquid droplets of nerve agents and sulphur mustard can be tentatively detected simply by their ability to dissolve a dye, such as Orasol Navy Blue, impregnated on paper. Differentiation of nerve agent from sulphur mustard may be achieved by dissolution of the dye thiodiphenyl-4,4′-diazobissalicylic acid (Mordant Yellow 16), impregnated on paper. V-agent droplets can be differentiated from G-agents by deprotonation of the indicator ethyl bis(2,4-dinitrophenyl)acetate to give a blue colour. The latter two reagents have been incorporated into a three-way detector paper for differentiating sulphur mustard, G-agents and VX[171]. For vapour detection, equipment may be designed for intermittent or occasional point sampling, or for automatic operation over a limited period of time in the case of warning devices. The presence of nerve agent vapour can be monitored simply by drawing air over detector papers or pads impregnated with cholinesterase and treated, for example, with butyrylthiocholine substrate and phenol–indo-2,6-dichlorophenol indicator or 2,6-dichloroindophenyl acetate as substrate to give a direct colour change[172,173]. Other simple devices for monitoring vapour are glass tubes similar in mode of operation to Dräger tubes. The Schönemann reaction[157], oxime reaction[174] and cholinesterase inhibition have been adapted for this type of simple detection device. Typically, the reagents, e.g. benzidine and peroxide, or cholinesterase, butyrylcholine and indicator, are sealed separately in mini-ampoules inside small glass detector tubes containing silica as adsorbent. When usage is required, the mini-ampoules are broken to release their contents and the air to be sampled is drawn through the tube by means of a simple pumping device. Reaction takes place on the absorbent to produce a colour change.

Continuously operating devices, using chemistry similar to that described above, have been developed for use as warning detectors. For example, air is drawn across a moving tape, or a manually changeable pad, which is treated sequentially with the appropriate reagents and the reactions are monitored photocolorimetrically[175], by fluorescence[176] or electrochemically[171]. Examples of such systems in use by UK forces are the ship installed chemical system (SICS) and the nerve agent immobilized alarm and detector NAIAD[171]. SICS uses the nucleophilic reaction of 1-phenylbutane-1,2,3-trione-2-oxime with nerve agents at pH 8.5–9.5 as described above. The liberated cyanide is detected electrochemically at a silver anode and triggers an alarm when the potential generated exceeds a certain value. VX is detected only after conversion into the corresponding G-agent with silver fluoride. NAIAD uses the enzyme butyrylcholinesterase immobilized on Amberlite ion-exchange resin and incorporated into a paper pad. The pad is irrigated with a buffered solution of butyrylthiocholine methanesulphonate and the hydrolysis product thiocholine is monitored electrochemically, by oxidation to its disulphide at a graphite anode. The chemistry is illustrated in equation 46.

$$Me_3\overset{+}{N}CH_2CH_2S^- \longrightarrow Me_3\overset{+}{N}CH_2CH_2SSCH_2CH_2\overset{+}{N}Me_3 + 2e \qquad (46)$$

The most sophisticated detection systems, designed primarily for the monitoring of contamination by fully protected troops, operate on the physicochemical principal of ion mobility. The Chemical Agent Monitor (CAM)[171,177] is a hand-held point sampling device for detecting nerve agent and sulphur mustard vapours. Air is sampled through a heated membrane inlet (which excludes most of the water vapour) and is ionized at atmospheric pressure by β-rays from a ^{63}Ni foil. Reactant ions are formed by addition of nerve agent to water–air cluster ions and are separated on the basis of their mobilities through a drift tube under an applied electric field. Drift times and the amplitude of the current pulse generated at the detector are translated by microprocessors into bar readings on a liquid crystal display. Further developments of such monitors currently under investigation include the possibility of incorporating a miniaturized gas chromatograph at the inlet to increase selectivity[178].

Other physicochemical detection methods under active investigation are based on solid-state sensors, with selective surface coatings whose properties are modified on exposure to CW agents. These changes can be measured by techniques such as using piezoelectric crystals[179], surface acoustic wave devices or field effect transistors[172] and used as a basis for detection. IR and LIDAR (light detection and ranging) systems are being investigated for use in remote warning systems[180].

X. MECHANISM OF ACTION

Organophosphorus nerve agents act by inhibition of the enzyme acetylcholinesterase in the central and peripheral nervous systems. Acetylcholinesterase terminates the action of the neurotransmitter acetylcholine by hydrolysing it to choline and acetic acid. Inhibition of the enzyme produces an accumulation of acetylcholine which continues to stimulate the receptor. The enzymatic hydrolysis of acetylcholine is mediated via transfer of the acetyl group to a serine hydroxyl within the active site, a reaction which is promoted by partial proton transfer from the serine hydroxyl to the basic nitrogen atom of a proximal histidine imidazole group, which in turn is activated by hydrogen bonding to an aspartic acid carboxylate group (Figure 2)[181,182]. The acetylated enzyme undergoes rapid spontaneous hydrolysis (within microseconds) to regenerate the active site and acetic acid. Organophosphorus nerve agents react with the enzyme in a similar manner to phosphonylate or phosphorylate (phosphylate) the serine hydroxyl[181,183]. In contrast to the acetylated enzyme, the phosphylated enzyme regenerates extremely slowly (half-life hours to days) and is effectively irreversibly inhibited. The reactions are summarized in reactions 47 and 48 (E = enzyme). The organophosphorus compound initially forms a reversible complex with the enzyme, the kinetics of which are governed by the affinity of the inhibitor for the active site, measured as the dissociation equilibrium constant K_d:

$$K_d = k_{-1}/k_1$$

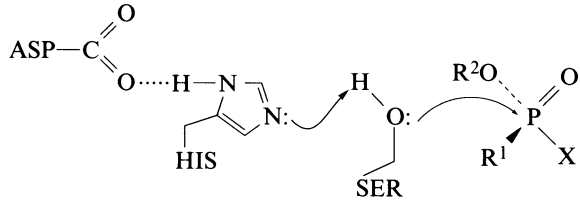


FIGURE 2. Phosphonylation of serine in AChE assisted by an imidazole residue

$$\text{E—OH + AcCH} \rightleftharpoons \text{E—OH} \cdot \text{AcCH} \longrightarrow \text{E—OAc + ChOH}$$

$$\longrightarrow \text{E—OH + AcOH} \quad (47)$$

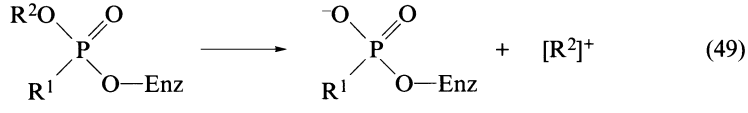
$$\text{E—OH + P—X} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{E—OH} \cdot \text{PX} \xrightarrow{k_p} \text{E—OP + HX}$$

$$\longrightarrow \text{E—OH + P—OH} \quad (48)$$

K_d is determined primarily by electrostatic, steric and hydrophobic factors[183,184]. An important feature is an anionic site on the enzyme which interacts with the positively charged quaternary nitrogen atom in acetylcholine, or the protonated tertiary nitrogen in VX. Steric/hydrophobic interactions adjacent to the serine-containing esteratic site are particularly important for phosphonofluoridates, and additional hydrophobic interaction close to the anionic site occurs with VX. A third hydrophobic region is postulated to be present beyond the anionic site from studies with a series of alkylsulphonium analogues of VX (see Section XII)[185]. A schematic representation of the active site, showing sites for coulombic and hydrophobic interactions, is shown in Figure 3[185]. Following complex formation, rapid covalent phosphylation occurs, the kinetics of which, measured as the phosphylation constant, k_p, are largely dependent on the strength of the P—X bond and pK_a of HX, although steric factors also contribute. The overall inhibitory potency is often expressed as the bimolecular rate constant k_i, which, under pseudo-first-order reaction conditions where the inhibitor is present at much higher concentration than the enzyme, is related to the dissociation and phosphylation rate constants by the equation.

$$k_i = k_p/k_d$$

An additional process which may occur on the phosphylated enzyme is a process termed ageing, which results in a covalently inhibited enzyme that is resistant to accelerated reactivation by therapeutic nucleophiles (see Section XII). Ageing results from PO—C bond cleavage in the alkoxy substituent as illustrated in equation 49 and occurs rapidly (within minutes) with phosphonofluoridates such as soman, whose highly branched alkoxy group produces a relatively stable secondary alkyl carbonium ion[186]. The dealkylation is



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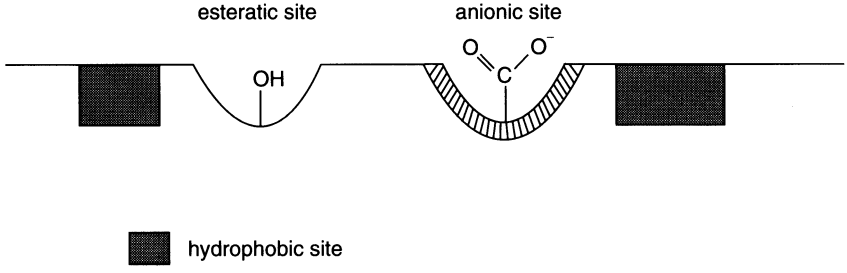


FIGURE 3. Schematic representation of the site of inhibition on AChE. Reproduced by permission of Waverly from Reference 185

postulated to be acid catalysed by the proximal protonated imidazole group with electrostatic stabilization of the developing positive charge by a glutamic acid carboxylate residue[187]. The development of a negative charge on the residual hemi-ester product of dealkylation makes the phosphorus atom resistant to interaction with nucleophiles. Qian and Kovach[187] have modelled the key active sites involved in the inhibition and ageing reactions.

XI. TOXICODYNAMICS

A. Acute Toxicity

The toxicodynamics of nerve agents have been comprehensively reviewed by Somani *et al.*[188] and by Dacre[189].

Table 6 shows the toxicities of the four classical nerve agents in guinea pigs together with estimates of human toxicity by the inhalation route. Estimates of human toxicity data have been extrapolated from animal data. Toxicity in rodents is ranked in the order guinea pig > rat > mouse. The guinea pig is the best rodent model for primates.

The most important route of intoxication for sarin, soman and tabun is by inhalation; cutaneous exposure may be significant with tabun and thickened soman. Owing to its extremely low vapour pressure, VX is primarily a cutaneous hazard [LD_{50}, percutaneous, rat = 0.012 mg kg^{-1} (ref. 192)], although it is extremely toxic by inhalation if disseminated as an aerosol. The much lower percutaneous toxicity of sarin [LD_{50}, percutaneous rat = 80 mg kg^{-1} (ref. 192)] reflects its volatility, since much of an applied cutaneous dose will evaporate. Overt symptoms of poisoning[188,193] can be divided into those which are mediated by excessive cholinergic stimulation of (a) parasympathetic nerve endings on glands and smooth muscles (muscarinic sites), (b) neuromuscular junctions and pre-ganglionic synapses (nicotinic sites) and (c) cholinergic synapses in the central nervous system. These are summarized in Table 7.

Death results from anoxia caused by a combination of central respiratory failure, bronchoconstriction, excessive bronchosecretion and paralysis of the diaphragm muscles. Signs of mild poisoning after inhalation are miosis with dimming of vision, tightness of the chest and nasal secretion; miosis does not occur with mild cutaneous exposure. Onset of symptoms is dose dependent and is more rapid after inhalation (seconds to minutes) than after cutaneous absorption (several minutes to more than 1 h.). The duration of effects may vary from a few hours with mild exposures to days or weeks in the case of severe exposure where survival has been achieved by therapy. Long-term neurotoxic effects have been observed in experimental animals[188].

TABLE 6. Acute toxicities of nerve agents in guinea pig and man (estimated)

Compound	LD_{50} (mg kg^{-1}) (s.c. guinea pig)[190]	LCt_{50} (mg min m^{-3})[a] [man (est.)][191]
Sarin	0.038	100
Soman	0.024	70
Tabun	0.120	150
VX	0.008	50[b]

[a] Product of vapour concentration and duration of exposure to kill 50% of exposed population.

[b] Aerosol droplets; Somani *et al.*[188] estimate 5–15 mg. min m^{-3}.

TABLE 7. Overt signs and symptoms of nerve agent poisoning

Site of action	Effects
Muscarinic:	
Glands	Salivation, excessive nasal, bronchial and gastrointestinal secretion sweating
Smooth muscles	Miosis, spasm of ciliary muscle of the eye, bronchoconstriction, bradycardia, abdominal cramps, diarrhoea, involuntary urination
Nicotinic:	
Neuromuscular junction	Weakness, twitching, fasciculations, cramps, paralysis
Sympathetic ganglia	Pallor, occasional raised blood pressure
CNS	Ataxia, confusion, loss of reflexes, slurred speech, convulsions, coma, respiratory failure

B. Metabolism and Toxicokinetics

Sarin and soman are metabolized by esterases to the corresponding alkylmethylphosphonic acids. Tabun is also hydrolysed in serum whilst VX may be a substrate for oxidases. The toxicokinetics of the stereoisomers of soman have been extensively studied by Benschop and coworkers[194,195] in rats, guinea pigs and marmosets. The relatively non-toxic P(+) isomers are rapidly eliminated by enzymatic hydrolysis and disappear within a few minutes from the blood stream. In contrast, significant levels of the toxic P(–) isomers remain in the bloodstream for 50–100 min at sub-lethal doses and are eliminated predominantly by binding to various proteins. Inter-species variation in toxicity is postulated to be inversely related to the availability of these additional binding sites. Aliesterases (non-specific carboxylesterase) appear to be important binding sites for detoxification[196]; Maxwell *et al.*[197] have shown a correlation between LD_{50} values and carboxylesterase activity in different species. An additional toxicokinetic factor with soman is the apparent existence of a depot which binds soman and then slowly releases it back into the bloodstream[188,198].

XII. THERAPY AND PRETREATMENT

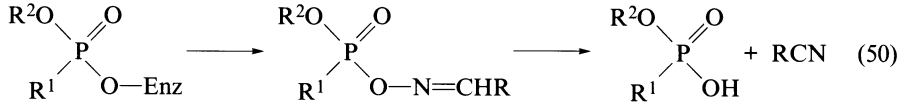
The objectives of drug treatment for nerve agent poisoning are primarily to ensure survival and, secondly, to enable the soldier to maintain a reasonable level of performance[199]. Ideally, with timely detection and the wearing of protective clothing and respirators, exposure should be minimal.

A. Therapy

Emergency administration of therapeutic drugs on the battlefield is performed by autoinjection, through the protective suit into the thigh muscles, and is aimed at ensuring survival until medical support is available. The major possibilities for immediate drug intervention following exposure are (a) blocking the access of the excess acetylcholine to the synaptic, glandular or neuromuscular receptor, (b) reactivation of the enzyme and (c) symptomatic treatment of convulsions to prevent brain damage.

The drug most commonly employed as a cholinergic antagonist is atropine, which acts at peripheral and central muscarinic sites. Other cholinergic antagonists which have been investigated include aprophen, benactyzine, scopolamine and trihexyphenidyl[200].

Reactivation of the inhibited enzyme is effected by a nucleophilic oxime, which also contains a cationic quaternary centre to promote coulombic interaction with the anionic site of the enzyme. Oxime reactivators act by nucleophilic reaction at the phosphorus atom to form a phosphylated oxime, with displacement of the regenerated enzyme[201,202] as illustrated by equation 50.



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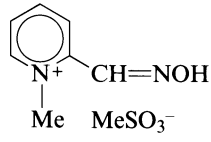
Some of the phosphonylated oximes are themselves very potent cholinesterase inhibitors, but are probably detoxified sufficiently rapidly to avoid significant reinhibition[73,203]. *N*-Methylpyridinium-2-aldoxime methanesulphonate (**51**) (pralidoxime, P2S), or the corresponding chloride salt (PAM Cl), and toxogonin (**52**) (obidoxime) are the major oximes in current use and are effective in reactivating cholinesterase inhibited by sarin and VX. They act synergistically with atropine to provide good protection against sarin and VX (LD_{50} doses are raised up to 20–40-fold in guinea pigs[199]) but not tabun, soman or GF. Studies *in vitro* have confirmed that no reactivation occurs with tabun or soman inhibited enzyme[204]. In the case of soman the enzyme rapidly ages (within minutes) by *O*-dealkylation to form a methylphosphonate hemi-ester, which is predominantly deprotonated at physiological pH and therefore resistant to nucleophilic reaction at phosphorus. Efforts to find oximes which are more effective against soman poisoning have continued, although complications arise from the considerable species variation in their response to oxime–nerve agent combinations. Hagedorn and coworkers[205] have synthesized and investigated a large number of bis-quaternary oximes related to toxogonin, of which two, codenamed HI-6 (**53**) and HLo-7 (**54**), are more effective against soman, GF and tabun poisoning in guinea pigs[206]. HI-6 was also shown to have some efficacy against soman and tabun in rhesus monkeys[207]. However, since aged soman-inhibited AChE is not reactivated, the beneficial effects of oxime treatment may be related to other mechanisms of action such as channel blocking activity. Initially there were formulation problems with these oximes owing to their instability in aqueous solution, but advances in wet–dry autoinjector design now enable lyophilized oxime to be dissolved on activation. The major site of action of the quaternary oximes is the neuromuscular junction; they do not penetrate the blood–brain barrier and are ineffective against the centrally mediated effects of nerve agents. A more detailed review of oxime therapy was given by Somani *et al*[188].



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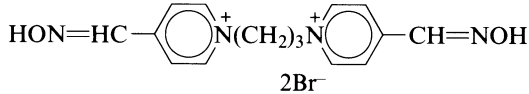

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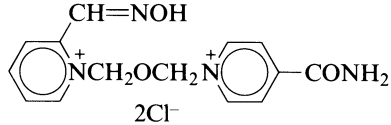

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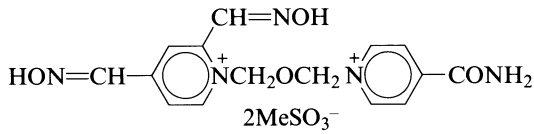

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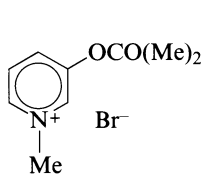
Diazepam, in tablet form, is used as an anticonvulsant drug for the treatment of convulsions, but as this requires temporary removal of respiratory protection, a water-soluble prodrug of diazepam, avizophone, has now been incorporated into the injector formulation in the UK[199].

B. Pretreatment

When the threat of exposure to nerve agents is anticipated, a more satisfactory approach to counteract poisoning is to prevent the phosphylation of the enzyme over a time period sufficient to allow the body to detoxify the nerve agent. Pyridostigmine (**55**), a high-affinity carbamate cholinesterase inhibitor, provides effective pretreatment for ensuring survival[199]. It reacts with the same biochemical target as a nerve agent, but acts by carbamoylating (rather than phosphylating) the serine hydroxyl. There is considerable redundancy in the amount of acetylcholinesterase available in the body and the carbamoylation of ca 20–30% with pyridostigmine can be tolerated without adverse effects. The carbamoylated enzyme undergoes spontaneous reactivation at a much slower rate than does acetylated enzyme but much faster than phosphylated enzyme. Provided atropine is administered following poisoning to counteract the combined inhibition by carbamate and nerve agent, considerable protection is afforded against the lethal effects of sarin, VX, soman and tabun. With combined pretreatment and therapy (administered i.m.), guinea pigs could be protected against 14 and 35 LD_{50} doses of soman and tabun, respectively[199]. Unfortunately, this combination of pretreatment and therapy does not prevent the severe centrally mediated incapacitation caused by high doses of nerve agents. As with quaternary oximes, pyridostigmine shows poor penetration of the blood–brain barrier; the non-quaternary and more lipophilic drug physostigmine (**56**) is currently under investigation as a more centrally active drug to overcome these deficiencies[188,199].



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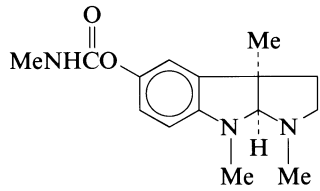


(56)

Additional possibilities for pretreatment are the administration of scavengers, such as exogenous cholinesterases or antibodies, which can remove the nerve agent before it reaches its physiological target[188]. To be effective, such scavengers would need to be administered prophylactically. The administration of monoclonal antibodies and exogenous cholinesterase has shown promise in experimental animals. For example, rhesus monkeys pretreated with purified foetal bovine serum acetylcholinesterase were protected against five LD_{50} doses of soman and showed no symptoms of toxicity[208]. However, both

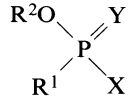
approaches involve stoichiometric interactions requiring the administration of relatively large amounts of exogenous proteinaceous material, which may pose immunological problems.

XIII. STRUCTURE–TOXICITY RELATIONSHIPS

Relatively few comprehensive structure–activity studies of organophosphorus nerve agents have been reported. Some of the data supplied below are extracted from quantitative correlations of structure against activity, where the original toxicological data have not been published. A knowledge of structure–toxicity relationships is implied in the Schedule A list of potential nerve agent analogues in the Annex to the Chemical Weapons Convention (see Section XIV). The aim of these lists is to minimize the possibility of circumventing the Convention simply by making structural analogues of the classical nerve agents from precursors that are not controlled. The following discussion will concentrate on those major classes of organophosphorus compounds that are too toxic to mammals to be considered for use as pesticides. Although toxicity should be quantified in terms of μmol kg^{-1} for rigorous structure–activity correlations, toxicity figures below are quoted in the more practical mg kg^{-1}, since relatively small differences in the molecular mass do not significantly effect the general structure–toxicity trends.

A. General Requirements

The general requirements for potent anticholinesterase activity and high mammalian toxicity are shown in **57**[209].



(57)

R^1 = alkyl, or dialkylamino
R^2 = alkyl, cycloalkyl, or hydrogen (in V series only), $(CH_2)_nN^+R_3$ (when X = F)
Y = O (rarely S)
X = F, CN, N_3, $S(CH_2)_2NR_2$, $S(CH_2)_2N^+R_3$, $S(CH_2)_2S^+R_2$

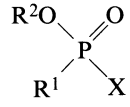
There are, in addition, a few compounds of moderate toxicity with choline- or thiocholine-type X groups, where R^1 may be alkoxy. The minimum structural requirement is the grouping —P(=Y)X, where X is a basic leaving group. The rate of phosphylation (k_p) of AChE, i.e. nucleophilic displacement of X^- by the serine hydroxyl, depends inversely on the strength of the P—X bond and the pK_a of the conjugate acid of the leaving group, HX[210]. Cyanide as leaving group is effective only in compounds possessing a dialkylamino substituent on phosphorus. Correlations of anticholinesterase activity with basic hydrolysis rates have been demonstrated in a limited number of closely related organophosphorus compounds where steric and other differences have been minimized[211]. If a compound is too reactive towards nucleophiles, then hydrolysis and reactions with non-specific nucleophiles will reduce the toxicity *in vivo*. Electrostatic, steric and hydrophobic factors play an important role in the formation of the initial enzyme–inhibitor complex and the overall rate of inhibition (k_i). Toxicity *in vivo* is not just a function of the ability of the compound to inhibit acetylcholinesterase, but is dependent on factors such as absorption,

distribution, metabolism (particularly by esterases) and hydrolytic stability. Effectiveness as a chemical warfare agent will also depend on physicochemical properties, stability under weaponization conditions and ease of production.

B. Tabun Analogues

In the simple series $ROP(O)CNNMe_2$, activity reaches a maximum where R is iso- or n-propyl[212]; LD_{50} values are shown in Table 8. Increasing the length of the alkyl substituent on nitrogen decreases toxicity, as does substitution of fluoride for cyanide as leaving group.

TABLE 8. Toxicity of tabun analogues

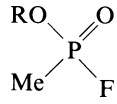


R^1	R^2	X	LD_{50} i.p. mouse (mg kg^{-1})[212]
Me_2N	Me	CN	1.9
Me_2N	Et	CN	0.6
Me_2N	Pr^i	CN	0.5
Et_2N	Et	CN	4.0
EtO	Et	CN	1.4
Me_2N	Et	F	2.5

C. Sarin and Soman Analogues

Phosphonofluoridates, such as sarin, are more potent inhibitors of AChE and more toxic than the analogous phosphorofluoridates, and this parallels differences in their alkaline hydrolysis rates. Comparative LD_{50} values (i.v. rabbit) for DFP and sarin were 0.45 and 0.017 mg kg^{-1} (ref. 213) respectively. Phosphinofluoridates are comparatively weak inhibitors of cholinesterase. As is generally the case in other series of cholinesterase inhibitors, the thiono analogues of phosphonofluoridates (i.e. containing a P=S bond) possess lower anticholinesterase activity, which is due in part, to their lower reactivity towards nucleophiles. Phosphonylation rate constants (k_p) for sarin and soman were 12–14-fold higher than those for their thiono counterparts[214]. In the case of thionosarin, the dissociation rate constant (K_d) is also adversely effected, resulting in a bimolecular inhibition rate constant (k_i) 50 times lower than that for sarin. This effect is postulated to result from adverse hydrophobic bonding associated with the P=S bond (it is particularly pronounced in pesticides such as paraoxon and parathion[214]). The effect on K_d is insignificant with thionosoman, whose overall bimolecular inhibition constant has been reported as 14 times[214] or 3 times[215] lower than that for soman, and it is one of the few thiono analogues which exhibits a moderate level of toxicity. Highest toxicity in the phosphonofluoridates is associated with compounds possessing a PMe substituent. A quantitative structure–activity study of homologous linear and branched-chain alkoxy substituents indicated a correlation with the shape of the substituent, particularly with mid-chain branching, maximum toxicity being associated with highly branched C_4–C_6 substituents[216]. LD_{50} values for rabbits are shown in Table 9. The data support the existence of a hydrophobic region close to the anionic site of the enzyme. Similar trends were observed with inhibition rate constants for AChE[217].

TABLE 9. Toxicities of alkyl methylphosphonofluoridates



R	LD_{50} i.v. rabbit[a] (mg kg^{-1})
CH_3—	0.042
CH_3CH_2—	0.045
$CH_3(CH_2)_2$—	0.025
$(CH_3)CH$— (sarin)	0.015
$CH_3(CH_2)$—	0.05
$CH_3CH_2CH(CH_3)$—	0.011
$(CH_3)_2CHCH_2$—	0.19
$CH_3(CH_2)_2CH(CH_3)$—	0.016
$CH_3CH(CH_3)CH(CH_3)$—	0.010
$CH_3C(CH_3)_2CH_2$—	0.012
$CH_3(CH_2)_5$—	0.145
$CH_3CH(CH_3)CH_2CH(CH_3)$—	0.018
$CH_3C(CH_3)_2CH(CH_3)$— (Soman)	0.010
Cyclohexyl-(GF)	0.018

[a] Calculated from data reported by Rohrbaugh *et al.*[216].

The potential for dealkylation of the alkoxy group on the phosphonylated enzyme (known as ageing) is also dependent on the degree of branching of the side-chain; this is related to the PO—R bond strength and the tendency towards the formation of a more stable secondary carbonium ion R^+.

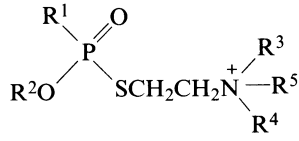
D. VX and Amiton Analogues

The discovery of Amiton, and shortly afterwards VX, followed the rationale that increased binding to the enzyme should accrue if the inhibitor contained a side-chain closely resembling the natural substrate acetylcholine. Phosphonothiolates, such as VX, are one to two orders of magnitude more toxic than the analogous phosphorothiolates such as Amiton[218] (Table 10). There is a large thiono effect in this series, the P=S compounds being considerably less toxic. In the VX series, analogues with PMe and PEt substituents are highly toxic. The effects of varying the alkoxy and dialkylamino substituents[219] are shown in Table 10.

Potent activity is retained with ethyl, propyl and butyl alkoxy substituents, and with methyl, ethyl (not shown), isopropyl and cycloalkyl substituents on the aminoethyl group. There are, therefore, many permutations which provide highly toxic compounds in this series. Analogous phosphonates and phosphates containing choline-type substituents are 1–3 orders of magnitude less toxic[218]. In the VX series, the products of hydrolysis where R^2 = H (resulting from P—O rather than P—S cleavage) have lower, but nevertheless potent, toxicity; the hydrolysis product from VX possessed an LD_{50} (i.v. rat) 0.017 mg kg^{-1} (ref. 78).

Introduction of a permanent charge on the nitrogen through quaternization, by analogy with acetylcholine, provides only a small increase in activity since at physiological pH the dialkylamino group is already predominantly protonated[218]. The contribution of a positive charge in the side-chain was more evident in a series of analogues with alkyl-

TABLE 10. Toxicity of VX and amiton analogues



R^1	R^2	R^3	R^4	R^5	Name	LD_{50} mice (mg kg^{-1})	
						i.p.[218]	s.c.[219]
EtO	Et	Me	Me			0.53	
EtO	Et	Me	Me	Me		0.14	
EtO	Et	Et	Et		Amiton	0.5	
Me	Et	Me	Me			0.05	
Me	Et	Me	Me	Me		0.026	
Me	Pr^i	Me	Me			0.27	
Me	Pr^i	Me	Me	Me		0.12	
					Sarin	0.45	
Me	Et	Pr^i	Pr^i		VX		0.022
Me	Pr^n	Pr^i	Pr^i				0.024
Me	Hex	Pr^i	Pr^i				0.110
Me	Et	Me	cyclo-Pen				0.022
Me	Et	Me	Cy				0.038

thioalkyl side-chains. In this series, conversion of a sulphide to a sulphonium species increased activity against cholinesterase by two orders of magnitude. Analogues with a side-chain $SCH_2CH_2S^+(Me)C_nH_{2n+1}$ (n = 1–10) showed potent anticholinesterase activity, which suggested that there is a second hydrophobic region beyond the anionic site on the receptor which can interact with alkyl groups substituted on sulphur up to C_{10}[185]. Both phosphoryl and phosphonyl analogues are highly toxic in this sulphonium series. The increase in toxicity of pesticides such as demeton-S-Me on storage has been attributed to the formation of a sulphonium species $(MeO)_2P(O)SCH_2CH_2S^+(Et)Me$ with an LD_{50} (i.v. rat) of 0.062 mg kg^{-1} (ref. 220).

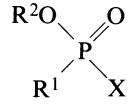
E. Other Choline and Thiocholine Esters

The substitution of choline side-chains for alkoxy into sarin and tabun also produces compounds with very high toxicity. A series of these compounds was first prepared by Tammelin[221,222]. In the choline series ($X = OCH_2CH_2N^+Me_3$), potent activity is observed only in the presence of fluoride as leaving group, as shown in Table 11.

These compounds induce very rapid inhibition of cholinesterase and are up to 100 times more potent as inhibitors *in vitro* than sarin, and up to 10 times more toxic depending on the route and species; in line with rapid rates of phosphylation, rates of alkaline hydrolysis are also 10–50 times that of sarin.

This series gives a good illustration of factors which influence toxicity other than affinity (K_d) and reactivity (k_p) with AChE. The phosphonylfluorocholines possess high affinity for the enzyme, are very reactive as electrophiles, but are presumably partially detoxified by rapid hydrolysis and reactions with other nucleophiles.

TABLE 11. Toxicity of choline esters



R^1	X	R^2	LD_{50} (mg kg^{-1})	
			i.p. mice[222]	i.m. rat[223]
Me	F	$CH_2CH_2N^+Me_3$	0.10	
Me	F	$CH(Me)CH_2N^+Me_3$	0.07	
Me	F	$CH_2CH_2CH_2N^+Me_3$	0.05	
Me	OEt	$CH_2CH_2N^+Me_3$	375	
Sarin			0.45	
Me_2N	F	$CH_2CH_2NMe_2$		0.017
Et_2N	F	$CH_2CH_2NMe_2$		0.035
Me_2N	F	$CH_2CH_2NEt_2$		0.092
Et_2N	F	CH_2CH_2NEt		0.261

In phosphono- and phosphoro-thiocholine compounds (Table 10), where the thiocholine moiety is the leaving group, the affinity for the enzyme is very high, phosphylation and alkaline hydrolysis rates are much slower, but toxicities *in vivo* are comparable to those of the fluorophosphonylcholines. Choline analogues in the tabun series also show high toxicity but have poor stability[223]. Despite the very high toxicity of this series of compounds, they have not been developed as CW agents, either because of their physical properties, e.g. the quaternary salts are solids, or because of inherent hydrolytic or thermodynamic instability, particularly in the case of the fluorocholine compounds.

F. Stereoselectivity

The first evidence for enantioselectivity in the reaction of organophosphorus compounds with AChE was reported by Michel[55], who noted a biphasic inhibition on incubation of AChE with racemic sarin. Shortly afterwards, Aaron *et al.*[224] reported enantioselective AChE inhibitory activity for the resolved isomers of *O*-ethyl *S*-(2-ethylthioethyl) ethylphosphonothionate. Subsequent isolation, or partial resolution, of the enantiomers of sarin, soman, tabun and VX has shown that there is a very large enantioselectivity for cholinesterase inhibition (k_i ratios 10^4–10^5) between the P(–) and P(+) isomers of sarin[57,225] and soman[64], shown in Table 12.

This large selectivity correlates with toxicity *in vivo* where the P(+) isomers are virtually non-toxic. There is little differentiation of the C(–) and C(+) isomers of soman. As discussed in Section XI, the enantioselective interaction of soman isomers with other esterases also effects toxicity *in vivo*. Tabun[62] and VX[60,226] show less enantioselectivity in their inhibition rate constants (k_i ratios 10–200) and toxicity.

XIV. CONTROL UNDER THE CHEMICAL WEAPONS CONVENTION

Attempts to outlaw the use of chemical weapons have been made for more than a century. The Brussels Declaration of 1874 prohibited the use of poisons and poisoned bullets during warfare, and signatories of the Hague Conventions of 1899 and 1907 additionally agreed

TABLE 12. Stereoselectivity in nerve agent AChE inhibition and acute toxicity (reprinted in part with permission from ref. 58 Copyright 1988 American Chemical Society).

Compound	k_i ($lmol^{-1}$ min^{-1})	LD_{50} mice ($mg\ kg^{-1}$)	
		s.c.	i.v.
P(–)-sarin[225]	1.4×10^7		0.041
P(+)-sarin	$<3 \times 10^3$		
P(–)C(+)-soman[64]	2.8×10^8	0.099	
P(–)C(–)-soman	1.8×10^8	0.038	
P(+)C(+)-soman	$<5 \times 10^3$	>5.0	
P(+)(C–)-soman	$<5 \times 10^3$	>2.0	
P(–)-tabun[62]	2.3×10^6		0.119
P(+)-tabun	3.7×10^5		0.837
P(+)-VX[58,226]	4×10^8		0.013
P(–)-VX	2×10^6		0.165

'to abstain from the use of projectiles, the object of which is the diffusion of asphyxiating or deleterious gases'. The nations that signed the Declaration included Britain, France, Germany, Italy, Russia and the USA, but this did not prevent the devastating use of a variety of chemical weapons (estimated as at least 125000 tons) during the 1914–18 war. After this war, fresh inititiatives were made, culminating in the 1925 Geneva Protocol which 'prohibited the use in war of asphyxiating, poisonous or other gases, and all analogous liquids, material or devices'; it also covered bacteriological methods of warfare. The protocol did not prohibit the manufacture and stockpiling of chemical weapons and clauses were introduced which permitted the use of chemical weapons in retaliation to first use by an aggressor. Forty-three countries had ratified the agreement by 1939. There were episodes of chemical warfare during this period, such as the use of mustard gas in the Italian invasion of Ethiopia, but surprisingly there was no large-scale use of chemical weapons during WWII, even though the nerve agents tabun and sarin had been developed in Germany. Since 1945, there have been numerous allegations of CW use in remote conflicts, such as in the Yemen (1961), SE Asia (1980–84), Afghanistan (1980–84) and Iraq–Iran (1984–88) and against Kurdish communities in Iraq (1987–88). The last two conflicts are the only ones where the use of nerve agents, tabun[3] and sarin[5] (and sulphur mustard), has been established. Amid growing concern for the number of nations acquiring chemical weapons, continued international efforts over the past 20 years have culminated in the signing, in January 1993 in Paris, of the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction, commonly referred to as the Chemical Weapons Convention (CWC)[227]. The Convention will enter into force after the 65th state has ratified the agreement, possibly during 1996.

The general Obligations under Article 1 of the Convention are that each State Party to the Convention undertakes never under any circumstances to:

- develop, produce, otherwise acquire, stockpile or retain chemical weapons or transfer directly or indirectly, chemical weapons to anyone;
- use chemical weapons, or engage in military preparations for doing so;
- assist, encourage or induce, in any way, anyone to engage in any activity prohibited by the Convention.

Each State Party undertakes to destroy, within 10 years of the Convention entering into force, its chemical weapons, any production facilities which have been used since 1946 to

manufacture chemical weapons in quantities exceeding 1 tonne per year, and any chemical weapons abandoned on the territory of another state party.

The radical departure of this Convention from previous agreements is that it not only prohibits the use of chemical weapons (under any circumstances), but also prohibits their production and stockpiling. Furthermore, procedures for ensuring compliance, including routine and challenge inspections of declared or suspected CW facilities, are included in the agreement.

In an Annex to the Convention is provided lists (Schedules) of chemicals whose manufacture and trade will be controlled under the terms of the Convention. Chemicals in Schedule 1 are known CW agents, their analogues and immediate precursors, and are effectively banned from production or industrial use. Schedule 2 chemicals have sufficient toxicity for potential CW use, or are precursors to such chemicals or to precursors included in Schedule 1; as with Schedule 1 compounds, they are not in large-scale commercial use. Schedule 3 chemicals have toxicities that might have some potential for CW use, or they could be used as precursors or raw materials. They are, however, produced in quantity for commercial purposes not prohibited under the CWC. With regard to the control of nerve agent production, the following phosphorus-containing chemicals are included in the Schedules (the nomenclature used is that of the official text of the CWC).

Schedule 1

Toxic chemicals

Alkyl (to C_{10}, including cycloalkyl), alkyl (Me, Et, Pr^n or Pr^i)-phosphonofluoridates

e.g. sarin: *O*-isopropyl methylphosphonofluoridate

soman: *O*-pinacolyl methylphosphonofluoridate

Alkyl (to C_{10}, including cycloalkyl), *N*,*N*-dialkyl (Me, Et, Pr^n or Pr^i) phosphoramidocyanidates

e.g. tabun: *O*-ethyl *N*,*N*-dimethylphosphoramidocyanidate

Alkyl (H or to C_{10}, including cycloalkyl) *S*-2-dialkyl (Me, Et, Pr^n or Pr^i)-aminoethyl alkyl (Me, Et, Pr^n or Pr^i) phosphonothiolates and corresponding alkylated or protonated salts

e.g. VX: *O*-ethyl *S*-2-diisopropylaminoethyl methyl phosphonothiolate

Precursors

Alkyl (Me, Et, Pr^n or Pr^i) phosphonyldifluorides

e.g. DF: methyl phosphonyldifluoride

O-Alkyl (H or to C_{10}, including cycloalkyl) *O*-2-dialkyl (Me, Et, Pr^n or Pr^i)-aminoethyl alkyl (Me, Et, Pr^n or Pr^i) phosphonites and corresponding alkylated or protonated salts

e.g. QL: *O*-ethyl *O*-2-diisopropylaminoethyl methyl phosphonite

Chlorosarin: *O*-isopropyl methylphosphonochloridate

Chlorosoman: *O*-pinacolyl methylphosphonochloridate

Schedule 2

Toxic chemicals

Amiton: *O*,*O*-diethyl *S*-[2-(diethylamino)ethyl] phosphorothiolate and correponding alkylated or protonated salts

Precursors

Chemicals, except those listed in Schedule 1, containing a phosphorus atom to which is bonded Me, Et, Pr^n or Pr^i group but not further carbon atoms

e.g. methylphosphonyl dichloride

dimethyl methylphosphonate

Exemption: fonofos: *O*-ethyl *S*-phenyl ethylphosphonothiolothionate

N,*N*-Dialkyl (Me, Et, Pr^n or Pr^i) phosphoramidic dihalides

Dialkyl (Me, Et, Pr^n or Pr^i) phosphoramidates

Schedule 3

Precursors

Phosphorus oxychloride, phosphorus trichloride, phosphorus pentachloride, trimethyl phosphite, triethyl phosphite, dimethyl phosphite, diethyl phosphite.

Comparison of the compounds in Schedules 1 and 2 with the general structure–activity trends discussed in Section XII shows that most of the highly toxic compounds and their analogues are included. The hope is that this Convention, supported by the availability of continually improving verification and defensive measures, will in the future prevent any production or use of CW agents.

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ADDENDUM

As hopes have risen that the CWC will prevent the production and proliferation of CW agents, a new and alarming development occurred in 1995. On 20 March 1995 during the Monday morning rush hour, terrorists released sarin into the Tokyo subway at several different locations, killing 10 people and causing more than 5000 casualties[228]. This was the first major incident involving terrorism and chemical weapons, and is a salutary reminder of the devastating consequencies of the use of crude chemical weapons against unprotected personnel. The sarin was alleged to have been manufactured at the headquarters of an extreme religious cult. Ton quantities of the precursor chemicals, sodium fluoride, phosphorus trichloride and isopropyl alcohol were subsequently discovered in a warehouse near the cult's headquarters, plus sodium cyanide (possibly for tabun production) and the solvent acetonitrile. The precise mode of production of the sarin, and its subsequent release into the subway, has yet to be disclosed. This alarming developement in the use of nerve agents serves to reinforce the need to control the trade of key precursor chemicals and the need to maintain our defence against such weapons.

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Author index

This author index is designed to enable the reader to locate an author's name and work with the aid of the reference numbers appearing in the text. The page numbers are printed in normal type in ascending numerical order, followed by the reference numbers in parentheses. The numbers in *italics* refer to the pages on which the references are actually listed.

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