Translated from *Uspekhi Khimii*, **43**, 2045-2087 (1974) U.D.C. 547.241 : 547.316.3; 547.451

Aminoalkyl Organophosphorus Compounds

K.A.Petrov, V.A.Chauzov, and T.S.Erokhina

Data on the methods of preparation of aminoalkyl compounds of phosphorus (by transformation of functional groups and by aminoalkylation of tervalent phosphorus compounds) and their physical and chemical properties are presented and the practical applications of substances of this type are briefly described.
The bibliography includes 528 references.

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I. INTRODUCTION

Aminoalkyl organophosphorus compounds are used as complex-forming agents with chelating properties, extractants, herbicides, insecticides, wetting agents, pharmaceutical preparations, ion exchangers, etc. A number of novel methods have now been proposed for their synthesis. However, there are no reviews dealing with compounds of this class either in Soviet or foreign literature. These considerations and also the potential practical and theoretical value of these compounds led to the publication of this review.

II. METHODS OF SYNTHESIS

A wide variety of numerous methods of synthesis have been proposed for amino-substituted organophosphorus compounds, some of which are simple and can be used to prepare such compounds in large amounts. The methods of synthesis can be usefully divided into two groups in terms of the starting materials and the mode of introduction of the amino-group. The first group includes methods analogous to those used for the introduction of the amino-group into any organic compounds. They are based on the transformation of various functional groups in organophosphorus compounds into amino-groups, these reactions are classified as amination of organophosphorus compounds without the formation of new phosphorus–carbon bonds.

The second group includes methods specific to organophosphorus compounds, leading to the formation of phosphorus–carbon bonds. These are classified as aminoalkylation of phosphorus compounds with formation of phosphorus–carbon bonds.

1. Amination of Organophosphorus Compounds without the Formation of New Phosphorus–Carbon bonds

The method of conversion of carboxy- and carbonyl groups into the amino-group (the Curtius, Hofmann, Lossen, and Beckmann reactions) has been frequently used to synthesise amino-substituted organophosphorus compounds. By treating phosphonocarboxylic acid esters in succession with hydrazine and nitrous acid, one obtains azides, which are converted into aminophosphonic acids after the Curtius rearrangement, alcoholysis, and hydrolysis [1,2]:

$$\begin{aligned} &R{-}\underset{\underset{COOEt}{|}}{CH}{-}P(O)(OEt)_2 \xrightarrow{N_2H_4} R{-}\underset{\underset{CONHNH_2}{|}}{CH}{-}P(O)(OEt)_2 \xrightarrow{HNO_2} \\ &\rightarrow R{-}\underset{\underset{CON_3}{|}}{CH}{-}P(O)(OEt)_2 \xrightarrow{H_2O,H^+} R{-}\underset{\underset{NCO}{|}}{CH}{-}P(O)(OEt)_2 \xrightarrow{EtOH} \\ &\rightarrow R{-}\underset{\underset{NHCOOEt}{|}}{CH}{-}P(O)(OEt)_2 \xrightarrow{HCl,H_2O} R{-}\underset{\underset{NH_2}{|}}{CH}{-}PO_3H_2 , \end{aligned} \quad (1)$$

where R = H, Me, $PhCH_2$, or $Me(CH_2)_n$ and n = 9–15. The yields of the desired products in this procedure are 31–83%. [1-4]

The Schmidt rearrangement, which is of a similar type, has been used to synthesise ω-aminodecylphosphonic acid [5]:

$$HO_2C(CH_2)_{10}PO_3H_2 \xrightarrow{HN_3} H_2N(CH_2)_{10}PO_3H_2 + CO_2 + N_2 . \quad (2)$$

The synthesis of diethyl α-aminobenzylphosphonate by the Hofmann degradation of α-(*OO*-diethylphosphono)phenylacetamide has been described [6]:

$$\underset{\underset{CONH_2}{|}}{PhCHP(O)(OEt)_2} \xrightarrow{NaBrO} \underset{\underset{NH_2}{|}}{PhCHP(O)(OEt)_2} . \quad (3)$$

This method is applicable also to the synthesis of β-aminoalkylphosphonates and phosphonic acids [7,8]. For example, 2-aminoethylphosphonic acid has been obtained by this method in 71% yield.

NN'-Bisdiphenylphosphinylmethylurea and *N*-diphenylphosphinylmethylurethane were obtained by the Lossen reaction, which has a mechanism similar to those described above, in 20 and 29% yields respectively [9]:

$$\begin{aligned} &Ph_2P(O)CH_2C(O)NHOH \xrightarrow{(EtO)_3CH} Ph_2P(O)CH_2NCO \rightarrow \\ &\xrightarrow{EtOH,H_2O} [Ph_2P(O)CH_2NH]_2CO + Ph_2P(O)CH_2NHCOOEt . \end{aligned} \quad (4)$$

The Beckmann rearrangement has been used to synthesise *N*-acyl-αα-dimethyl-β-aminoethyldiphenylphosphine oxides [10,11]:

$$R{-}\underset{\underset{NOH}{\diagdown}}{C}{-}CH_2CMeP(O)Ph_2 \xrightarrow{\text{polyphosphoric acid or } PCl_5} R{-}CONHCH_2CMe_2P(O)Ph_2 , \quad (5)$$

where R = Me, or $Ph_2P(O)CMe_2CH_2$.

Other methods of synthesis of the substances under consideration are based on the reduction of nitrogen-containing organic compounds of phosphorus. Thus α-aminobenzylphosphonic acid has been obtained[12,13] in yields up to 50% by the reduction of the *p*-nitrophenylhydrazone of diethyl benzoylphosphonate with sodium sulphide or, better, with aluminium amalgam and subsequent hydrolysis:

$$p\text{-}NO_2C_6H_4NH-N=\underset{\underset{Ph}{|}}{C}-P(O)(OEt)_2 \xrightarrow[2)\ HCl,H_2O]{1)\ Na_2S\ or\ Al/Hg} H_2NCHPO_3H_2 \cdot \quad (6)$$
$$\qquad\qquad\qquad

have been introduced into the reaction with potassium phthalimide in dimethylformamide:



$$\longrightarrow (H_2NCH_2)_nP(O)Ph_{3-n}\ . \qquad (13)$$

(n = 2, 3; X = Cl; n = 1, X = OTs)

The corresponding phthalimidomethylphosphine oxides, which are formed in 46–81% yields, can be readily converted by treatment with hydrazine into aminomethylphosphine oxides in 70–95%.

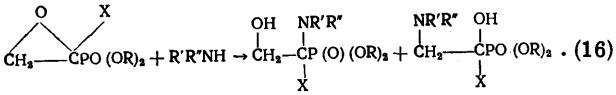
Phosphonoethylation of the sodium derivative of diethyl β-acetamidomalonate led after hydrolysis to γ-amino-γ-carboxypropylphosphonic acid in 46% yield [1]:

$$BrCH_2CH_2P(O)(OEt)_2 + Na^+C^-(COOEt)_2NHCOMe \rightarrow$$
$$\rightarrow (EtO)_2P(O)CH_2CH_2C(NHCOMe)(COOEt)_2 \xrightarrow{H^+,H_2O} H_2O_3PCH_2CH_2CH(CO_2H)NH_2\ . \qquad (14)$$

The addition of amines to vinylphosphonates constitutes a specific method for the synthesis of β-aminoalkylphosphonates [57,61,63,74–79]. Thus the corresponding diethyl β-aminoethylphosphonates have been obtained in 53–83% yields by the reaction of diethyl vinylphosphonate with a number of amines in the presence of sodium ethoxide as the catalyst or in its absence on heating [74,76]:

$$CH_2{=}CH{-}P(O)(OEt)_2 \xrightarrow{HNR_2} R_2NCH_2CH_2P(O)(OEt)_2\ , \qquad (15)$$

where R = H or Me and $R_2 = (CH_2)_2$ or $(CH_2)_5$. The esters of vinylphosphonothioic acid [80], the amides of vinylphosphonic and vinylphosphonothioic acids [81], acid esters of vinylphosphonous acid, vinylphosphonites [82], vinylphosphinates, vinylphosphines [82–84], vinylphosphine oxides [83–86], and trialkyl(aryl)vinylphosphonium salts [87–89] have also been used in this reaction. In all cases, the amino-group adds to the β-carbon atom of the vinyl group and an increase of the electron-donating properties of the substituents at the phosphorous atom significantly reduces the rate of reaction. The addition of lithium amides to diphenylvinyl- and diphenylallyl-phosphines, 1-phenylphosphorin-3-ene and 3,4-dimethyl-1-phenyl-3-phospholene also leads after hydrolysis to β-aminoalkylphosphines [90]. Epoxyethylphosphonates and the corresponding diphosphonates readily react with amines to form mixtures of 1-amino-2-hydroxy- and 2-amino-1-hydroxy-isomers [91,92]:



(X=H, P(O)(OR)$_2$)

Phosphonates with an active methylene group readily add to azomethines in the presence of acid or basic catalysts with formation of β-aminoalkylphosphonates [93–98]. The yields obtained by this method [93,94], which resembles the first stage of the addition of olefins to the P–O group, amount to 32–88%:

$$RCH_2P(O)(OR')_2 + PhCH{=}NAr \xrightarrow{H_2NNa} ArNHCH(Ph)CH(R)P(O)(OR')_2\ . \qquad (17)$$

(R=Ph, COOEt CN; R'=Et, *i*-Pr; Ar=Ph, C_6H_4Cl-*p*,*m*, C_6H_4OMe-*p*, *m*)

Diphenylbenzylphosphine oxide reacts similarly with Schiff bases [99]. Alkylation of benzylphosphonate carbanions with dialkyl-2-chloroethylamines yielded the corresponding α-(γ'-aminopropyl)-α-phenylphosphonates [100]:

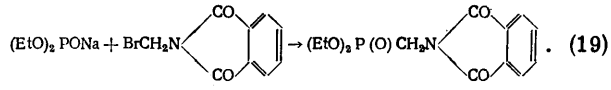
$$PhCH_2P(O)(OEt)_2 \xrightarrow[2.\ R_2N(CH_2)_2Cl]{1.\ NaNH_2} PhCH(C_2H_4NR_2)P(O)(OEt)_2\ . \qquad (18)$$

2. Aminoalkylation of Phosphorus Compounds with Formation of Phosphorus–Carbon Bonds

A common feature of this group of methods for the formation of aminoalkyl organophosphorus compounds is the employment of phosphorus(III) compounds, including tautomeric P–H acids, as one of the reactants. The mechanisms of these reactions probably resemble those of Michaelis–Becker and Arbuzov reactions and the addition of phosphorus(III) compounds to systems with multiple bonds, which are widely used in phosphorus chemistry.

The Michaelis–Becker and Arbuzov Reactions

The reactions of dialkyl phosphites and sodium or potassium phosphites with ω-halogenoalkylamines and the corresponding amides proceed via the usual Michaelis–Becker mechanism and lead to the corresponding ω-aminoalkylphosphonates [5,55,101–105]. Thus diethyl phthalimidomethylphosphonate was obtained in 40% yield by the reaction of sodium diethyl phosphite with *N*-bromomethylphthalimide [101]:

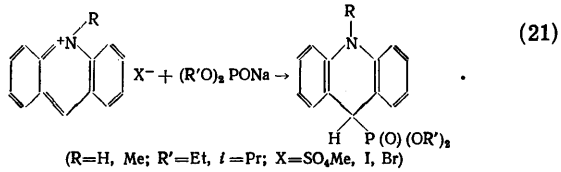


The more reactive α-chloroalkylamines can react directly with dialkyl phosphites to form the hydrochlorides of aminophosphonates in 47–95% yields [102,106]:

$$R_2NCH(R')Cl + (R''O)_2PHO \rightarrow R_2NCH(R)P(O)(OR'')_2 \cdot HCl\ , \qquad (20)$$

where $R_2 = (CH_2)_4$ or $(CH_2)_5$, R' = H, Et, i-Pr, or $CONC_5H_{10}$, and R'' = Me or Et.

The reaction of diaryl phosphites with diphenylbromoethyl isocyanate in the presence of triethylamine led to the formation of diaryl isocyanatodiphenylmethylphosphonates [107] in 32–88% yields. Sodium dialkyl phosphites readily react with acridinium salts to form dihydroacridylphosphonate esters [108] (yield 63–68%):



(R=H, Me; R'=Et, *i*=Pr; X=SO_4Me, I, Br)

The reaction of lithium, potassium, sodium, and magnesium phosphides with ω-chloroalkylamines has been proposed as a general method for the synthesis of ω-aminoalkylphosphines [109–116]. 2-Diethylaminoethyldialkyl(phenyl)phosphines have been obtained in this way in 40–65% yields [110]:

$$Et_2NCH_2CH_2Br + MPR_2 \rightarrow Et_2NCH_2CH_2PR_2\ \cdot$$
$$(M=Li, K;\ R=Et, Ph, C_6H_{11}\text{-cyclo.}) \qquad (22)$$

The Arbuzov reaction is widely used for the synthesis of aminoalkyl organophosphorus compounds. Triethyl phosphite readily reacts with *N*-chloromethylpiperidine to form piperidinomethylphosphonate in 52% yield [117]:

$$(EtO)_3P + ClCH_2NC_5H_{10} \rightarrow (EtO)_2P(O)CH_2NC_5H_{10} + EtCl\ . \qquad (23)$$

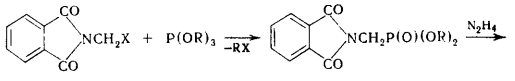
Aminoalkylation of neutral phosphites by halogenoalkyl amines has been used successfully to synthesise aminoalkylphosphonates with various functional groups [103,104,106,118–123]: aminomethyltriphosphonates were obtained in

71–77% yield by the reaction of trichloromethylamines with triethyl phosphite in chloroform at −40°C:[121]

$$3\,(EtO)_3P + R_2NCCl_3 \xrightarrow{CHCl_3,\,-40^\circ} [(EtO)_2P(O)]_3CNR_2 + 3\,EtCl \qquad (24)$$

where R = Me and $R_2 = (CH_2)_5$.

The reaction of *N*-halogenomethylphthalimides with trialkyl phosphites gave rise to the formation of phthalimidomethylphosphonates in 82–94% yields [55,124–128]. Treatment of the latter with hydrazine leads to aminomethylphosphonates:



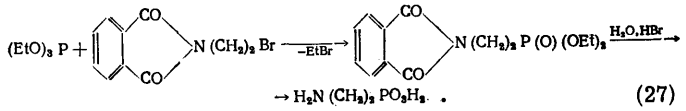
$$\longrightarrow H_2NCH_2P(O)(OR)_2\,. \qquad (25)$$

(X = Cl, Br; R = Me, Et)

When dialkyl phosphonites and alkyl phosphinites are used instead of trialkyl phosphites, the products are aminoalkylphosphinic acids and aminoalkylphosphine oxides [129–131]. The reactions of chloromethyl isocyanate with trialkyl phosphites and alkyl phosphinites takes place similarly. Isocyanatomethylphosphonates and isocyanatomethylphosphine oxides were obtained by this procedure in 7–40% yields [132]:

$$R_2P(OR') + ClCH_2NCO \rightarrow R_2P(O)CH_2NCO + R'Cl\,. \qquad (26)$$
(R=OR', Pr)

Dialkyl phosphorochloridites and phosphorofluoridites and alkyl phosphorodichloridites and phosphorodifluoridites also react with chloromethyl isocyanate [133–135]. When di- and tri-chloromethyl isocyanates instead of chloromethyl isocyanate are used in the reaction with phosphites, products phosphorylated to different extents are obtained, depending on the ratio and reactivities of the reactants [135–138]. The method has been used also to synthesise ω-aminoalkylphosphonates [12,55,105,139–141]: 2-aminoethylphosphonic acid has been synthesised in 50% yield by the reaction of *N*-(2-bromoethyl)phthalimide with triethyl phosphite and subsequent hydrolysis [12]:

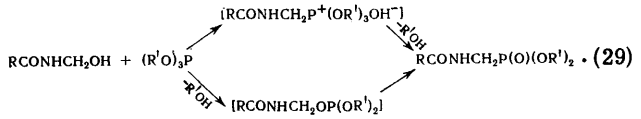


$$\rightarrow H_2N(CH_2)_2PO_3H_2\,. \qquad (27)$$

Apart from halogenoalkylamines and the corresponding amides, *N*-trimethylammoniummethylformamide [142], *N*-acetoxymethylamides [143], and the corresponding amines [144] have also been introduced into this reaction. Trialkyl phosphites [142,143], triphenyl phosphite, and phosphorous hexaethyltriamide [144] have been used as the phosphorus-containing components. In the reactions with triphenyl phosphite and phosphorous hexaethyltriamide the desired products were isolated in 54 and 73% yields respectively:

$$PX_3 + MeCOOCH_2NEt_2 \rightarrow [X_3P^+CH_2NEtMeCOO^-] \rightleftarrows [X_3P^+CH_2NEt_2(OCOMe)\,X^-] \rightarrow$$
$$\rightarrow X_3P(O)CH_2NEt_2 + MeCOX\,. \qquad (28)$$
(X=OPh, NEt_2)

N-Hydroxymethylamides are also capable of aminoalkylating trialkyl phosphites at 100–160°C with a 30–59% yield of the desired products [145,146]. It is suggested that under these conditions the phosphite is either alkylated directly or there is a preliminary transesterification and a subsequent Arbuzov rearrangement [145]:



(R = Me, Ph; R' = Me, Et, Pr, Bu)

A mixture of an amide and paraformaldehyde can be introduced into the reaction instead of *N*-hydroxymethylamides [147]. Aminophosphonates have been obtained under the same conditions from secondary amines, aldehydes, and trialkyl phosphites in 21–94% yields [147–150]:

$$RR'NH + R''CHO + (R'''O)_3P \rightarrow RR'NCH(R'')P(O)(OR''')_2 + R'''OH\,, \qquad (30)$$

where R and R' = Me or Et, $RR' = (CH_2)_5$, R'' = H or Ph, and R''' = Et, Pr, or Bu.

In the presence of acetic acid at 100–160°C trialkyl phosphites are capable of being aminomethylated by aminoacetals of formaldehyde and by diethylaminoacetonitrile [151,152]:

$$(RO)_3P + R'R''NCH_2X \xrightarrow{MeCOOH} R'R''NCH_2P(O)(OEt)_2 + MeCOOEt + HX\,. \qquad (31)$$
(X=CN, OR; R=Me, Et, Pr, Bu; R', R''=Me, Et, Ph)

The yields of aminophosphonates are 50–65%. The authors believe [151,153] that the role of acetic acid reduces either to an increase of the polarity of the medium, which promotes the ionisation of the aminoalkylating agent, or to transesterification of the latter and a subsequent reaction of type (28).

N-Aminomethyl- and *N*-alkoxymethyl-amides of carboxylic acids are also capable of reacting under these conditions with trialkyl phosphites to form carbamoylmethylphosphonates in 52–85% yields [153,154].

N-Aminomethylamides of carboxylic acids containing a hydrogen atom at the amide nitrogen atom readily react with trialkyl phosphites also in the absence of acetic acid, forming acetamidomethylphosphonates [154] (50–70%); a secondary amine and an alcohol have been isolated as side products:

$$RCONHCH_2NR'_2 + P(OR'')_3 \rightarrow RCONHCH_2P(O)(OR'')_2 + HNR'_2 + R''OH + R''NR'_2\,, \qquad (32)$$

where R = Me, Ph, or $CH_2{=}C(CH_3)-$, R' = Me or Et, and R'' = Et or Bu.

The authors suggest that this is caused by acid catalysis due to the imidine form (I).

In the presence of acid agents, trialkyl phosphites are capable of being aminoalkylated by Schiff bases [155,156]. Thus trialkyl phosphites react with benzylideneaniline in the presence of phenol at 100–130°C, giving rise to 20–30% yields of aminophosphonates [155]:

$$(RO)_3P + ArN{=}CHPh \xrightarrow{PhOH} (RO)_2P(O)CH(Ph)NHAr + PhOR\,. \qquad (33)$$
(Ar=Ph, C_6H_4Me-*p*; C_6H_4Cl-*m*; R=Et, Pr).

When aminoacetals are treated with PCl_3, aminoalkylphosphonates are also formed ultimately [157,158]. It is suggested that the reaction proceeds via the formation of α-chloromethylamine and a phosphite [157]:

$$3\,R'_2NCH_2OR + PCl_3 \rightarrow 3\,R'_2NCH_2Cl + P(OR)_3\,, \qquad (34)$$
$$P(OR)_3 + R'_2NCH_2Cl \rightarrow R'_2NCH_2P(O)(OR)_2 + RCl\,,$$

where R = Et, R' = Et, and $R'_2 = (CH_2)_5$.

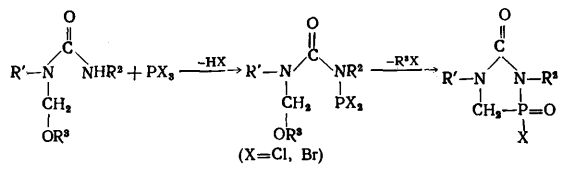
The occurrence of the first stage was demonstrated by the isolation of α-chloromethylamines [117]. Phosphorochloridites [119,159] and chlorophosphines react similarly with aminoacetals [160]. An analogous mechanism probably

operates in the reactions of diaminals and aminoacetals of formaldehyde with mixed anhydrides of diethylphosphorus acid on the one hand and acetic, benzoic, and diethylphosphoric acids on the other and with tetraethyl pyrophosphite [161]:

$$(EtO)_2POY + R_2NCH_2X \rightarrow X(EtO)P(O)CH_2NR_2 + YOEt\ , \qquad (35)$$

where Y = COMe, COPh, $P(OEt)_2$, or $P(O)(OEt)_2$, X = OBu, NMe_2, or NEt_2, R = Me, and $R_2 = (CH_2)_5$. The yields of aminophosphonates in these reactions amount to 43–65%.

1,3-Dialkyl-4-halogeno-2,4-dioxo-1,3,4-diazaphospholans have been obtained in 40–86% yields by the reaction of phosphorus trihalides with *NN'*-dialkylalkoxyalkylureas [162]:



(X=Cl, Br) . (36)

The reaction of *N*-hydroxymethylamides with phosphorus trichloride, which probably proceeds via the formation of the corresponding phosphorochloridite and its rearrangement, leads to amidomethylphosphonic acids after hydrolysis [101,163–167] (yields 20–34%):

$$RCON(R')CH_2OH + PCl_3 \rightarrow [RCON(R')CH_2OPCl_2] \rightarrow$$

$$\rightarrow [RCON(R')CH_2P(O)Cl_2] \xrightarrow{H_2O} RCON(R')CH_2PO_3H_2\ , \qquad (37)$$

where R = Me, $Me(CH_2)n$ (n = 10–16), or β-pyridyl and R' = H, alkyl, or aryl.

The reaction of diethyl phosphorochloridite and chlorodiphenylphosphine with *N*-hydroxymethylamidine, which is similar to those already discussed, leads to amidomethylphosphonates and amidomethylphosphine oxides in yields up to 80% [37,145]:

$$R_2PCl + HOCH_2NHCOR' \xrightarrow{NEt_3} R_2P(O)CH_2NHCOR'\ . \qquad (38)$$

(R=OEt, Ph; R'=Me, Ph)

The reaction of dialkyl phosphorochloridites with 4-(*NN*-diethylamino)but-2-yn-1-ol in the presence of bases proceeds with isomerisation and the formation of dialkyl-(α-*NN*-diethylaminomethyl)allenylphosphonates [168,169]:

$$(RO)_2PCl + HOCH_2C\equiv CCH_2NEt_2 \xrightarrow[-NR_3\cdot HCl]{NR_3} [(RO)_2POCH_2C\equiv CCH_2NEt_2] \rightarrow$$

$$\rightarrow CH_2=C=CP(O)(OR)_2\ . \qquad (39)$$

$$\quad\quad CH_2NEt_2$$

(R=Et, Pr)

The α-aminoalkylation of tertiary phosphines, leading to α-aminoalkylphosphonium salts, can be carried out only when effective α-aminoalkylating agents, such as α-halogenoalkylamines and the corresponding amides [102,170–173] and ureas [174,175], are used:

$$R_2NCH(R')X + R''_3P \rightarrow R_2NCH(R')P^+R''_3X^-\ . \qquad (40)$$

The yields of the α-aminoalkylphosphonium salts are 40–98%.

Reactions of Dialkyl Phosphites and Their Analogues with Amines and Carbonyl Compounds

In 1952 Kabachnik and Medved' [176] and Fields [177] proposed independently a new general method for the synthesis of α-aminophosphonates by the reaction of dialkyl phosphites and aldehydes or ketones† with ammonia (Kabachnik and Medved') and amines (Fields):

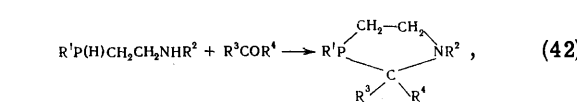
$$(RO)_2PHO + HN\langle + \rangle C=O \rightarrow (RO)_2P(O)\overset{|}{\underset{|}{C}}-N< + H_2O\ . \qquad (41)$$

Aminophosphonates are obtained after only brief heating of the reactants in solvents (water, alcohol) or in their absence. The yields of aminophosphonates vary within wide limits and depend on the structures of the initial reactants. The desired products are isolated from the reaction mixture by distillation in the form of hydrochlorides or picrates.

By varying the amines, aldehydes, ketones, and the phosphorus-containing component, it is possible to obtain by this method a wide variety of α-aminoalkyl phosphorus-containing compounds. The following amines (or ammonia) were introduced into the reaction: ammonia [176,178–189]‡, aliphatic primary and secondary amines [86,177,180,187,190–202], aromatic and heterocyclic amines [177,203–207], alkylenediamines and alkylenepolyamines [78,208–213], and hydroxyalkylamines [214–221].

$$(EtO)_2PHO + CH_2O + NH_3 \rightarrow [(EtO)_2P(O)CH_2]_2NH + [(EtO)_2P(O)CH_2]_3N\ .$$

Aziridine [57] and carboxamides [147] could not be made to undergo this reaction. Formaldehyde [86,214][114? (Ed. of Translation)] [177,180,187,190–193,195–197,199–204,209,211,218,219,221] as a 40% aqueous solution or paraformaldehyde, aliphatic and alicyclic aldehydes and ketones [78,177,178,180,181,183,186,188,194,199,206–208,210–213], and aromatic and heterocyclic aldehydes and ketones [176,178,179,183,185,189,190,205,210] have been used as the carbonyl components. Apart from dialkyl or diaryl phosphites [78,176–179,181–184,187–189,194,198,199,203,204,208–214,216–222], other compounds with a phosphorus-hydrogen bond readily enter into the reaction: dialkyl phosphorothioites [186,189], monoalkyl phosphonites [211], dialkyl(aryl)-phosphine oxides [86,180,196,200], dialkylphosphine sulphides [192], hypophosphorus acid [185,193,205–207,223–227]§, and phosphines [71,115,190,195,201,228]. In all cases the reaction proceeds via mechanism (41), i.e. with formation of a product resulting from the substitution of a hydrogen atom at the phosphorus atom by an α-aminoalkyl residue. 2-Aminoethylphosphines with hydrogen atoms at nitrogen and phosphorus readily react with carbonyl compounds to form intramolecular aminoalkylation products—1,3-azaphospholidines [114,115,229,230] (yields 47–91%):



(42)

where R^1 = H, Et, Bu, or Ph, R^2 = H or Et, R^3 and R^4 = H, Me, Et, or Ph, and $R^3R^4 = (CH_2)m$ (m = 4–6) or

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†Kabachnik and Medved' studied this reaction in relation to ketones somewhat later [178].

‡When ammonia, a primary amine, and a sterically unhindered aldehyde are used, products substituted to different extents at the nitrogen atom are obtained, depending on the reactant ratio and the reaction conditions [182,187,209,220].

§The aminoalkylation of hypophosphorous acid with a mixture of an amine and an aldehyde leads to mono- and bis-aminoalkylation products—aminoalkylphosphonic and di(aminoalkyl)phosphinic acids respectively [193,206,223]:

$$H_3PO_2 + CH_2O + R_2NH \rightarrow R_2NCH_2P(O)(H)OH \xrightarrow{R_2NH+CH_2O} (R_2NCH_2)_2POOH\ .$$

R=Me, Et; $R_2 = (CH_2)_5$, $(CH_2)_2O(CH_2)_2$; $R_2N{=}N(CH_2CH_2)_2N$.

$(CH_2)_2O(CH_2)_2$. *o*-Aminophenylphosphines[231], 3-aminopropylphenyl(butyl)phosphine[232-234], and 4-aminobutylphenylphosphines[233] react similarly with aldehydes and ketones.

Compounds containing a phosphorus–phosphorus bond are readily aminoalkylated under these conditions with formation (among other products) of mixtures of organophosphorus compounds with different degrees of aminoalkylation and oxidation of the phosphorus atom[191,197,202,235-238]. Thus the reaction of tetraphenyldiphosphine with formaldehyde and diethylamine yields diethylaminomethyldiphenylphosphine and phosphine oxide together with other products[235,236]:

$$Ph_2P{-}PPh_2 + CH_2O + HNEt_2 \xrightarrow{H_2O} Ph_2PCH_2NEt_2 + Ph_2P(O)CH_2NEt_2 + \\ + Ph_2PH + Ph_2PHO . \quad (43)$$

An even more complex mixture of products is formed in the aminoalkylation of white phosphorus[191,202,236]:

$$P_4 + CH_2O + HNR_2 \xrightarrow{H_2O} R_2NCH_2PO_2H_2 + (R_2NCH_2)_2PO_2N + (R_2NCH_2)_3PO + \\ + (R_2NCH_2)_2PH + (R_2NCH_2)_3P + (HOCH_2)_2PO_2H + HOCH_2PO_2H_2 , \quad (44)$$

where R = Me, Et, Bu, or cyclo-C_6H_{21} and R_2 = $(CH_2)_4$, $(CH_2)_5$, or $(CH_2)_2O(CH_2)_2$.

Depending on the reactant ratio and the type of amine employed, the main product (trisdialkylaminomethylphosphine oxide) is obtained in yields up to 47%.[191,236] It is believed that the dialkylhydroxymethylamine, formed from formaldehyde and a secondary amine, initially cleaves the phosphorus–phosphorus bond and then aminoalkylates the dissociation products[202,236]:

$$R_2NH + CH_2O \longrightarrow R_2NCH_2OH ,$$

$$Ph_2P{-}PPh_2 + R_2NCH_2OH \longrightarrow \begin{matrix} Ph_2P{-}PPh_2 \\ | \quad\quad | \\ R_2NCH_2{-}O{-}H \end{matrix} \longrightarrow$$

$$\longrightarrow Ph_2POCH_2NR_2 + Ph_2PH , \quad (45)$$

$$Ph_2POCH_2NR_2 \xrightarrow{+H_2O} Ph_2PHO + HOCH_2NR_2 ,$$

$$Ph_2PHO + HOCH_2NR_2 \longrightarrow Ph_2P(O)CH_2NR_2 ,$$

$$Ph_2PH + HOCH_2NR_2 \longrightarrow Ph_2PCH_2NR_2 .$$

The aminoalkylation of phosphorus acid must be considered in connection with the practical importance of aminoalkylphosphonic acids formed by this method in high yields in a single stage and readily isolated from the reaction mixture[239]:

$$H_3PO_3 + H{-}N\!\!<\!\!\!> + CH_2O \xrightarrow{H^+} H_2O_3PCH_2N\!\!<\!\!\!> + H_2O . \quad (46)$$

A significant difference between the method for the aminoalkylation of phosphorous acid and those discussed above is that a satisfactory reaction is achieved only in strongly acid media (pH 1–3). The reaction is carried out with heating to 120–150°C in the course of 1–2 h and goes a most to completion. The yields of the products of exhaustive phosphonomethylation amount to 49–96% when primary amines and polyamines are used[239]. Ammonia (in the form of ammonium salts)[239-241], primary amines[239,242-245], ethanolamine[239,246], glycine[239,247], diethanolamine[239,246], iminodiacetic acid[239,247], alkylenediamines[239,248], polyethyleneimines[245], and other amines[78,250-254] were used in the reaction. Apart from formaldehyde (in the form of the 40% solution), other aldehydes and ketones can be made to react[242-244,250-253,255,256]. A promising method for the aminomethylation of phosphorous acid is its reaction at 100–160°C with aminopolyacetic acids[257-259]. For example, nitrilotri(methylphosphonic) acid was obtained in 93% yield by heating phosphorous acid with nitrilotriacetic acid[259]:

$$N(CH_2COOH)_3 + H_3PO_3 \xrightarrow{160^\circ} N(CH_2PO_3H_2)_3 . \quad (47)$$

In the presence of phosphorus trichloride, the reaction proceeds under milder conditions.

Two views have been expressed about the mechanism of reaction (41), which in many respects resembles the Mannich reaction[260]. One of these is based on a study of the reactions of diethyl phosphite with benzaldehyde and ammonia: it is suggested that in the first stage the dialkylphosphite adds to the carbonyl compound [reaction (48a)] under the influence of the catalyst (ammonia) and then the hydroxy-group in the α-hydroxyalkylphosphonate is substituted by the amino-group[179,180] [reaction (48b)].

$$(RO)_2PHO + R'R''CO \xrightarrow{NH_3} (RO)_2P(O)CR'R''OH , \quad (48a)$$

$$(RO)_2P(O)CR'R''OH + NH_3 \rightarrow (RO)_2P(O)CR'R''NH_2 + H_2O . \quad (48b)$$

This hypothesis was put forward because the main product of the reaction of diethyl phosphite with ammonia and benzaldehyde in the cold is α-hydroxybenzylphosphonate $(EtO)_2P(O)CH(Ph)OH$; the formation of α-aminobenzylphosphonate $(EtO)_2P(O)CH(Ph)NH_2$ is observed only on heating the reaction mixture[179]. Stage (48a) constitutes the addition of dialkyl phosphites to carbonyl compounds in the presence of a base (in the present case ammonia), which has been thoroughly investigated[261]. The possibility of the second stage—the nucleophilic substitution of the hydroxy-group by the amino-group—has been demonstrated by the formation of α-aminobenzylphosphonate on heating α-hydroxybenzylphosphonate with an alcoholic solution of ammonia[179].

The second view is based on the reaction of dialkyl phosphites with formaldehyde and secondary amines; it is suggested that the first stage involves the addition of the amine to formaldehyde with formation of hydroxymethylamine [reaction (49a)] and the subsequent interaction of the latter with the dialkyl phosphite, leading to the dialkylaminomethylphosphonate[177] [reaction (49b)]:

$$R_2NH + CH_2O \rightleftarrows R_2NCH_2OH , \quad (49a)$$

$$(R'O)_2PHO + R_2NCH_2OH \rightarrow (R'O)_2P(O)CH_2NR_2 + H_2O . \quad (49b)$$

This hypothesis arose in view of the absence of the exchange of the hydroxy-group for the dialkylamino-group on heating diethyl hydroxymethylphosphonate with diethylamine[177]. The possibility of stage (49b) was demonstrated by the formation of aminophosphonates in high yields on reaction of dialkyl phosphites with bisaminals and aminoacetals of formaldehyde[177,198]:

$$R_2NCH_2X + (EtO)_2PHO \rightarrow R_2NCH_2P(O)(OEt)_2 + HX . \quad (50)$$
$$(R=Et, i\text{-}Pr, Bu;\ X=OMe, NR_2)$$

Thus on the basis of this mechanism the reaction can probably be regarded as a process of the Michaelis–Becker type in which the amine catalyses the formation of a highly nucleophilic dialkyl phosphite anion and the dissociation of α-hydroxyalkylamines at the C–O bond leads to a stable carbonium–immonium ion[262-264]:

$$R_2N{-}CH_2OH \rightleftarrows [R_2N{-}CH_2^+ \longleftrightarrow R_2N^+{=}CH_2] + OH^- , \quad (51)$$

$$(R'O)_2P(O)H \overset{B}{\rightleftarrows} [(R'O)_2PO]^- + BH^+ ,$$

$$[(R'O)_2PO]^- + R_2N^+{=}CH_2 \rightarrow (R'O)_2P(O)CH_2NR_2 .$$

There are at present no data for the mechanism of the reactions of phosphorous acid with formaldehyde and

amines [reaction (46)] in a highly acid medium. One can only suppose that in this case the aminoalkylating species is the carbonium-immonium ion and the object of electrophilic attack is phosphorous acid [containing phosphorus(III)], the reversible formation of which is promoted by the high acidity of the medium.

In conclusion one should note that, despite the conflict between mechanisms (48) and (49) although there is evidence in support of each), the proposed versions of reaction (41)—amination of the α-hydroxyalkyl organophosphorus compounds [reaction (48)] and aminoalkylation of organophosphorus compounds with a phosphorus–hydrogen bond by aminoacetals and bisaminals [reaction (50)]—are of preparative value. The first version—the amination of α-hydroxyalkylorganophosphorus compounds¶—has been investigated mainly for hydroxymethyl derivatives of phosphines and for hydroxymethylphosphonium salts. The value of this method is due to the availability of such compounds, which obviates the necessity for the employment of the relatively inconvenient phosphines: heating of hydroxymethylphosphines with diethylamine in a sealed tube at 150–160°C for 8 h leads to diethylaminoethylphosphines in 57–88% yields [265]:

$$Pr_nP(CH_2OH)_{3-n} + (3-n)\,Et_2NH \rightarrow Pr_nP(CH_2NEt_2)_{3-n} + (3-n)\,H_2O\,. \quad (52)$$

When tri(hydroxymethyl)phosphine is treated with aniline under the conditions of azeotropic distillation of water, tri-(*N*-phenylaminomethyl)phosphine is formed in 81% yield [266]:

$$P(CH_2OH)_3 + 3\,PhNH_2 \rightarrow P(CH_2NHPh)_3 + 3\,H_2O\,. \quad (53)$$

Acetoxymethylphosphines can be used in the reaction instead of hydroxymethylphosphines. In this case the reaction is carried out in an aqueous or aqueous alcoholic medium in the presence of potassium hydroxide and involves the preliminary hydrolysis of the acetoxymethylphosphines to the corresponding hydroxymethylphosphines [267,268]. An advantage of this method compared with those described above is the ease of the purification of the initial acetoxymethylphosphines, which has a significant influence on the purity of the desired products [267]. The use of hydroxymethylphosphonium salts instead of hydroxymethylphosphines leads to aminomethylphosphines [269,270]. This method is used also to synthesise aminomethylphosphine oxides: diethylaminomethyldiphenylphosphine oxide was obtained in a quantitative yield by heating hydroxymethyldiphenylphosphine oxide with diethylamine [271]:

$$Ph_2P(O)CH_2OH + HNEt_2 \rightarrow Ph_2P(O)CH_2NEt_2 + H_2O\,. \quad (54)$$

There are patent data concerning the condensation of hydroxymethylphosphonium salts and tri(hydroxymethyl)-phosphine oxide with amines to form high-molecular-weight compounds [272–274].

The second version of reaction (41) (aminoalkylation of compounds with a phosphorus–hydrogen bond by bisamials and aminoacetals) has also found applications in the synthesis of a wide variety of aminoalkyl derivatives of phosphorus. The high yields of the desired substances, the absence from the reaction mixture of water which is difficult to remove, and the possibility of employing aminals with different functional groups make this synthetic procedure extremely useful and in many cases the only one possible. Aminophosphonoacetate esters have been obtained in yields of 73–82% from the aminoacetals of glyoxylic acid esters [106]:

$$R_2NCHCOOMe + (EtO)_2PHO \rightarrow (EtO)_2P(O)CHCOOMe + MeOH\,. \quad (55)$$
(OMe; NR₂)

(R=Me; R₂= (CH₂)₅)

The reaction of the dimethylacetal of dimethylformamide with diethyl phosphite leads to a 62% yield of aminomethylenediphosphonate [275,276]:

$$Me_2NCH(OMe)_2 + 2\,(EtO)_2PHO \rightarrow [(EtO)_2P(O)]_2CHNMe_2 + 2\,MeOH\,. \quad (56)$$

Cyclic bisaminals and aminoacetals readily react with dialkyl phosphites, forming aminophosphonates containing amino- and hydroxyalkyl substituents at the nitrogen atom [277–280]:

$$(EtO)_2PHO + \underset{\diagdown\,N\,\diagup}{\overset{CH_2-X}{|\quad|}}{}_{CH_2\quad CHR} \rightarrow (EtO)_2P(O)CH(R)N(R')CH_2CH_2XH\,. \quad (57)$$
(R′)

(R=H, Me; R′=H, CH_2CH_2OH; X=O, NH)

Aminoalkylphosphonamides were obtained by this method from phosphoramidites in 35–79% yields [281–283]:

$$(R_2N)_2PHO + (R'_2N)_2CHR'' \xrightarrow{Na} (R_2N)_2P(O)CH(R'')NR'_2 + R'_2NH\,. \quad (58)$$
(R=Me, Et, Bu; R₂= (CH₂)₅; R′=Me, Et; R″=H, Ph)

Apart from dialkyl phosphites and phosphorodiamidites, hypophosphite esters [284,285], dialkyl(aryl)phosphine oxides [180,286], alkylphosphonous and phosphonothious acids [287], and phosphines [265] react readily with bisaminals and aminoacetals.

The Addition of Compounds with a Phosphorus–hydrogen Bond to Multiple Carbon–nitrogen and Carbon–carbon Bonds

Dialkyl phosphites readily add to aromatic Schiff bases, forming α-aminoalkylphosphonates in 67–91% yields [288,289]:

$$(RO)_2PHO + ArHC{=}NAr' \rightarrow (RO)_2P(O)CH(Ar)-NHAr'\,. \quad (59)$$

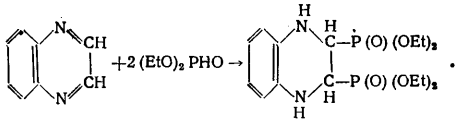
The reaction proceeds slowly even when the reactants are mixed in the cold in the absence of a solvent and is rapid in the presence of catalytic amounts of alkali metal alkoxides [288,289] or acids (HCl, $SnCl_2$) [290–293] in alcohol. When carefully purified reactants are used, the desired products can be obtained in nearly quantitative yields by the reaction without a solvent and without heating [294].

The above method of synthesis is of undoubted interest, although its applications are limited to the formation of *N*-monosubstituted α-aminoalkyl derivatives of phosphorus. Its usefulness is primarily due to the ready availability of the aromatic Schiff bases and the high yields of the desired products.

Under the conditions described above, dialkyl phosphites readily add not only to Schiff bases obtained from aromatic amines, aldehydes, and ketones [288–299] but also to those synthesised from aromatic amines and heterocyclic aldehydes [300–303], from heterocyclic amines and aromatic aldehydes [304,305], from aliphatic amines and diamines and aromatic aldehydes [306–311], and from aliphatic amines and aldehydes [310,312–314]. Certain heterocyclic compounds containing multiple carbon–nitrogen bonds are capable of combining with dialkyl phosphites to form phosphorus-containing heterocycles [315,316]. For example,

¶ This method is probably not general, since in many cases the corresponding α-aminoalkyl compounds could not be obtained by treating hydroxyalkyl organophosphorus derivatives with amines [177,185,196].

the addition of two dialkyl phosphite molecules to quinoxaline in sodium ethoxide leads to 1,4-dihydro-2,3-bis-(diethoxyphosphinyl)quinoxaline in 77% yield[315]:



(60)

Imines containing functional groups at the nitrogen and carbon atoms also readily combine with dialkyl phosphites, forming α-aminoalkyl phosphonates with different functional groups in 23–84% yields[317–320]†:

$$PhN{=}CXY + (RO)_2PHO \rightarrow PhNHC(X)(Y)P(O)(OR)_2 , \quad (61)$$

where X = H, P(O)(OEt)$_2$ or P(O)Ph$_2$ and Y = P(O)(OEt)$_2$ or P(O)Ph$_2$.

The synthesis of optically active α-aminobenzylphosphonic acid by the addition of diethyl phosphite to the Schiff base derived from benzaldehyde and α-phenylethylamine enantiomers has been described. The reaction proceeds with asymmetric induction; subsequent hydrolysis and hydrogenolysis of the addition product resulted in the formation of the enantiomers of α-aminobenzylphosphonic acid[322]‡:

$$PhCHO + PhC^*H(Me)NH_2 \rightarrow \underset{(II)}{PhCH{=}NC^*H(Me)Ph} \xrightarrow{(EtO)_2PHO} \rightarrow (EtO)_2P(O)C^*HPhNHC^*HMePh \xrightarrow{HCl,\ H_2O} H_2O_3PC^*HPhNHC^*HMePh \xrightarrow{H_2,\ Pd/C} \rightarrow H_2O_3PC^*HPhNH_2 . \quad (62)$$

$[\alpha]_D = -18{,}1°$ [from (+) - II];
$[\alpha] = +18{,}1°$ [from (−) - II].

Apart from dialkyl phosphites, other organophosphorus compounds with a phosphorus–hydrogen bond readily add to azomethines: diaryl phosphites[291,324–326]; monoalkyl phosphites[327], dialkyl phosphorothioites[328–332], phosphorodiamidites[281], hypophosphorous acid[205,206,227,333–336], alkylphosphonites[337], dialkyl(aryl)phosphine oxides[180,318,320] and sulphides[338,339], dialkyl(aryl)phosphines[318,340], and triphenylphosphine hydrobromide[318]. Instead of diaryl phosphites, the more readily available triaryl phosphites can be introduced into the reaction in the presence of water and hydrochloric acid[341]. The imides of α-aminoalkylphosphonates have been synthesised in 36–95% yields by the addition of the anilides and phenylhydrazides of dialkylphosphorous acids to Schiff bases[342–345]:

$$(EtO)_2PNHX + PhCH{=}NC_6H_4R \rightarrow (EtO)_2P(=NX)CH(Ph)NHC_6H_4R . \quad (63)$$
(R=H, Me, NO$_2$; X=C$_6$H$_4$R, NHC$_6$H$_4$R)

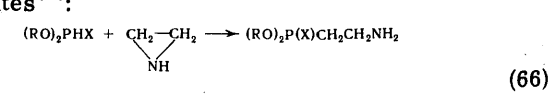
α-Aminoalkyl organophosphorus compounds are formed also following the addition of compounds with a phosphorus–hydrogen bond to enamines[346–348]; for example, the reaction of diphenylphosphine oxide with 2-dialkylaminovinyldiphenylphosphine oxides resulted in the formation of tetraphenyldialkylaminoethylenediphosphine dioxides in 67–75% yield[347]:

$$Ph_2P(O)CH{=}CHNR_2 + Ph_2PHO \rightarrow Ph_2P(O)CH_2CH(NR_2)P(O)Ph_2 . \quad (64)$$
(R=Me, Et)

It is noteworthy that the mode of addition to 1-acetamidoacrylic acid is determined by the presence of an electron-accepting substituent and leads after hydrolysis to β-amino-β-carboxyethylphosphonic acid in 50% yield[1]:

$$CH_2{=}\underset{NHCOMe}{C}{-}COOH + P(OMe)_3 \rightarrow CH_2{=}\underset{NHCOMe}{C}COOMe + (MeO)_2PHO \rightarrow \rightarrow (MeO)_2P(O)CH_2{-}\underset{NHCOMe}{CH}COOMe \xrightarrow{HCl,\ H_2O} H_2O_3PCH_2\underset{NH_2}{CH}COOH . \quad (65)$$

The addition of dialkyl phosphites and phosphorothioites to aziridine has been proposed as a method for the synthesis of 2-aminoethylphosphonates and 2-aminoethylphosphonothioates[349]:



(66)

(X = O, S; R = Et, Pr, *i*-Pr, Bu)

Phosphine[350,351], alkyl(phenyl)phosphines[232,234,352–355], and dialkylphosphines[350] add to allylamines in the presence of radical catalysts contrary to the Markovnikov rule with formation of 3-aminopropylphosphines.

Several studies have been made on the mechanism of the addition of compounds with a phosphorus–hydrogen bond to Schiff bases. The following mechanism has been proposed for reaction (59) catalysed by alkoxides[289]:

$$(RO)_2PHO + RONa \rightleftarrows (RO)_2PONa + ROH , \quad (67)$$
$$(RO)_2PONa + R'R''C{=}NR''' \rightarrow (RO)_2P(O)C(R')(R'')N(Na)R''' ,$$
$$(RO)_2P(O)C(R')(R'')N(Na)R''' + (RO)_2PHO \rightarrow (RO)_2P(O)C(R')(R'')NHR''' + (RO)_2P(O)Na .$$
etc.

Recently this mechanism was confirmed by kinetic investigations[356]. The catalytic effect of acids in reaction (59) has been explained both by the enhancement of the electrophilicity of the Schiff base and by an increase of the dialkyl phosphite content in the reactive symmetrical [with phosphorus(III)] form[357].

The employment of an equimolar mixture of the amine and the carbonyl compound instead of the complete Schiff base[291,319,324,325], i.e. the reaction carried out under conditions analogous to those described in the preceding section, constitutes a modification of the process discussed above. This evidently shows that the methods are related: one cannot rule out the possibility of the occurrence of reactions of type (41) employing primary amines and ammonia, via a stage involving the formation of an azomethine and their subsequent course in accordance with Eqn. (59).

Synthesis of α-Aminoalkylphosphorus Derivatives by the Reaction of Phosphoramidites with Carbonyl Compounds

The full ester-amides and triamides of phosphorus(III) acids react with carbonyl compounds to form α-aminoalkylphosphorus derivatives in many instances. Such a reaction was investigated for the first time§ in relation to dialkyl *NN*-dialkylphosphoramidites, aldehydes[361], and ketones[362]. In such cases the desired products are formed in 9–53% yields[361–364]:

$$(RO)_2PNR'_2 + R''(R'')CO \rightarrow (RO)_2P(O)C(R'')(R'')NR'_2 , \quad (68)$$

where R = Pr, Bu, or Pe, (RO$_2$) = C$_2$H$_4$O$_2$, R′ = Me or Et, R″ = H, Me, or Et, R‴ = H, Et, Pr, C$_6$H$_{13}$, or Ph, and R″R‴ = (CH$_2$)$_4$ or (CH$_2$)$_5$.

†Subsequently it was concluded on the basis of spectroscopic data that the reverse order of addition obtains for X, Y = P(O)(OEt)$_2$ and P(O)Ph$_2$ [Eqn. (61)].[321]

‡Diethyl α-aminobenzylphosphonate was resolved into its enantiomers by the fractional crystallisation of its salt with dibenzoyltartaric acid[323].

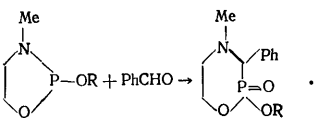
§The formation of an adduct in the reaction of *o*-phenylene *N*-phenylphosphoramidite with benzaldehyde was described as early as 1959.[358,359] Later it was shown that the proposed structure of the adduct is incorrect and that the reaction product is an aminophosphonate[360].

It has been shown that reaction (68) probably does not involve the preliminary hydrolysis of the initial phosphoramidite by traces of water to the dialkyl phosphite and the amine with subsequent interaction via mechanism (41).[361] Dialkyl *N*-arylphosphoramidites[360,365], propyl *NN*-diethylphenylphosphonamidite[366,367], phosphorous triamides[364], and diphenylphosphinamidous acids[365,368] react similarly with aldehydes. Acid alkylphosphoramidites can also react with aldehydes and ketones to form the acid esters of phosphonamidic acids[369] (45–65%):

$$(RO)(R'_2N)PHO + R''(R''')CO \rightarrow HO(RO)P(O)C(R'')(R''')NR'_2, \qquad (69)$$

where R = Me, Et, Pr, or Bu, R′ = Me or Et, R″ = H or Me, R‴ = Me or Ph, and R″R‴ = $(CH_2)_5$.

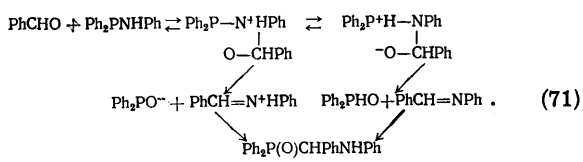
The reaction of benzaldehyde with 2-alkoxy-3-methyl-1,3,2-oxazaphospholans takes place with ring expansion and leads to 2-alkoxy-2-oxo-3-phenyl-4-methyl-1,4,2-oxazaphosphorinanes[370]:



(70)

It is noteworthy that the formation of aminophosphonates in reactions of phosphorus(III) amides and carbonyl compounds is by no means observed in all cases and frequently other processes take place[371]. This factor and also the relatively low availability of the initial amines reduce the practical value of this method.

Several hypotheses have been put forward concerning the mechanism of reaction (68). Some workers suggest a preliminary nucleophilic attack by the phosphorus atom on the carbonyl carbon atom with a subsequent series of rearrangements[360,361], while others believe, on the basis of experimental data, that nucleophilic attack by the nitrogen atom (analogous to that in the Wittig and PO–olefin addition reactions) is most likely with a subsequent rearrangement of the adduct in accordance with mechanism (71) to an aminoalkyl compound[365]:



(71)

The catalytic effect of amine hydrochlorides in reactions of type (68) can also be accounted for[364] within the framework of a mechanism analogous to mechanism (71).

Synthesis of Aminoalkyldiphosphonic Acids by the Reaction of Phosphorus(III) Trihalides with Nitriles

When nitriles are heated with phosphorus trihalides in the presence of organic and inorganic oxygen-containing acids with subsequent hydrolysis of the reaction mixture, aminoalkyldiphosphonic acids are formed[372–375]:

$$R{-}CN + P(Hal)_3 \xrightarrow[2.H_2O]{1.t^\circ} (H_2O_3P)_2C(R)NH_2. \qquad (72)$$

The desired products were obtained in yields of 28 and 51% respectively by the reaction of phosphorus tribromide with acetonitrile (R = Me) and benzonitrile (R = Ph)[374]. If instead of being hydrolysed, the reaction mixture is subjected to alcoholysis, acid esters are formed[372,373]. The reaction of cyanomethylated polystyrene copolymers with phosphorus trihalides and phosphorous acid in the presence of carboxylic acids leads after hydrolysis to phosphorus-containing complex-forming ion-exchange resins[376]. The reactions with phosphorous acid of the adducts of HCl or HBr and nitriles $[(H_2N{-}CRHal)^+Hal^-]$ or the products of the interaction of PCl_5, $COCl_2$, $(COCl)_2$, etc. with carboxamides $[(RR''N{=}CRHal)^+Hal^-]$ are modifications of the method under consideration. These also lead to aminoalkyldiphosphonic acids (4–78%); in the latter case nitrogen-substituted aminoalkyldiphosphonic acids are produced[377]. Formamides react directly with PCl_3 to form aminomethyldiphosphonic acids, which are or are not substituted at the nitrogen atom[378,379].

III. PHYSICAL AND CHEMICAL PROPERTIES

PHYSICAL PROPERTIES

The first members of the series of aminomethylphosphonates $[RR'NCH_2PO(OR'')_2$, R,R′ = H, Me, or Et and R″ = Me or Et) are soluble in water[177]; their salts (hydrochlorides, hydrobromides, and picrates) are much more soluble in water and are sparingly soluble in organic solvents (alcohol and ether). The latter properties are frequently used for their isolation and purification. Aminophosphinates and phosphine oxides are oily liquids or solids which dissolve in organic solvents and are sparingly soluble in water; they are isolated from the reaction mixture by distillation, crystallisation, or in the form of salts.

Acid esters of aminophosphonic acids and aminophosphonic and aminophosphinic acids are to some extent soluble in water and much less so in organic solvents. The surfactant properties of these compounds have been investigated[2,380]. Infrared spectroscopic and NMR data for many substances of this class have been published[3,124,201,267,320,363,381–385].

CHEMICAL PROPERTIES

The chemical properties of aminoalkyl organophosphorus compounds are determined by the presence in their molecules of the phosphorus-containing residue, the amino-group, and the methylene or methylidyne groups linked directly to nitrogen and phosphorus atoms. In many reactions these groups behave in the same way as in the corresponding compounds with a single heteroatom, exhibiting in a few instances certain chemical properties due to the mutual influence resulting from the close proximity of the nitrogen- and phosphorus-containing fragments.

Reactions Involving the Organophosphorus Fragment

One of the most important reactions involving the organophosphorus fragment is hydrolysis of α-aminoalkylphosphonic acid esters to the free acids on heating the esters with hydrochloric acid at 100–140°C for several hours:

$$H_2NC(R)(R')P(O)(OR'')_2 \xrightarrow{HCl,H_2O} H_2NC(R)(R')PO_3H_2. \qquad (73)$$

Aminoalkylphosphonic acids[178,179,181] are obtained in 35–85% yields. The hydrolysis of *N*-mono- and *N*-disubstituted α-aminoalkylphosphonates[187,203,210,386] and the analogous phosphinates[310,387], β- and γ-aminoalkylphosphonates[17,20], and ω-trialkylammoniumalkylphosphonates[388]

proceeds similarly. α-Aminoalkylphosphonothionates are converted into aminoalkylphosphonic acids under these conditions[186]. To remove hydrogen chloride from the hydrochlorides of aminoalkylphosphonic acids, the latter are treated in some cases with silver oxide and then with hydrogen sulphide[208] or epoxyalkanes[1,208].

The method described above has been used to eliminate both alkyl groups from dialkylaminoalkylphosphonates. The method involving the thermal decomposition of the hydrochlorides and hydrobromides of aminoalkylphosphonates until the complete elimination of the alkyl halide has proved convenient for the removal of only one alkyl group, i.e. for the preparation of the acid ester[389-391]. Thus acid esters were obtained in 78–97% yields by heating the hydrochlorides and hydrobromides of dialkylaminomethylphosphonates[389]:

$$R_2NCH_2PO(OR')_2 \cdot HX \rightarrow R_2NCH_2PO(OR')(OH) + RX. \quad (74)$$
(X=Cl, Br; R=Me, Et; R'=Et, Bu)

This method proved to be unsuitable for aminophosphonates containing aromatic substituents at the nitrogen atom and at the α-carbon atom owing to their complete cleavage in an acid medium. Such aminophosphonates are hydrolysed in an alkaline medium[299,392,393], since under these conditions both the esters themselves and their hydrolysis products are fairly stable[297]. The hydrolysis is usually carried out in an aqueous or alcoholic solution of alkali; the acid is isolated from the resulting salt by acidification[392,393]. It is noteworthy that in the alkaline hydrolysis of alkyl esters it is possible to obtain only the acid esters[299,392]. Phenyl esters, which are completely hydrolysed under severe conditions in an alkaline medium, are used for the synthesis of the free acids[393]:

$$ArNHCH(Ar')P(O)(OR)_2 \xrightarrow{KOH} \begin{cases} \xrightarrow{R=Alk} ArNHCH(Ar')P(O)(OR)OH \\ \xrightarrow{R=Ph} ArNHCH(Ar')PO_3H_2 \end{cases}. \quad (75)$$
(Ar=Ph, *m*, *p*-C_6H_4Me; Ar'=Ph, *p*-$C_6H_4CHMe_2$)

Acid esters and acids are obtained in 63–92% yields. This method is also suitable for the synthesis of acid esters of *N*-alkylaminoalkylphosphonic acids[392]. The resulting ω-aminoalkylphosphonic acids have three dissociation constants corresponding to the protonation of the phosphonate anion in the titration with an acid (pK_1), the second dissociation of the phosphonate group (pK_2), and the dissociation of the betaine proton in the titration with alkali (pK_3):[394]

$$\begin{aligned} &H_3N^+(CH_2)_nPO_3^-H + H^+ \rightleftarrows H_3N^+(CH_2)_nPO_3H_2 \quad pK_1, \\ &H_3N^+(CH_2)_nPO_3^-H \rightleftarrows H_3N^+(CH_2)_nPO_3^{2-} + H^+ \quad pK_2, \\ &H_3N^+(CH_2)_nPO_3^{2-} \rightleftarrows H_3N(CH_2)_nPO_3^{2-} + H^+ \quad pK_3. \end{aligned} \quad (76)$$
(n=1, 2, 4, 5, 10)

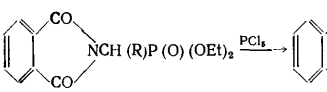
For the compounds under consideration, the above dissociation constants are $pK_1 = 2.35–2.6$, $pK_2 = 5.9–8.0$, and $pK_3 = 10.8–11.25$.[394] For comparison, we may quote the first and second dissociation constants of alkylphosphonic acids: $pK_1 = 2.35–2.6$ and $pK_2 = 7.1–8.25$ for $Me(CH_2)_{n-1}PO_3H_2$ (n = 1, 2, 6, or 12). Owing to the high pK_3 values of such acids, due to the high basicity of the amino-residue, they are titrated as mono-basic acids in the presence of indicators[395]. γ-Anilinopropylphosphonic acid also has the betaine structure, but, owing to the low basicity of the nitrogen atom, it is titrated as a dibasic acid [$pK_1 = 2.10$, $pK_3 = 4.25$, and $pK_2 = 7.15$ for $PhNH_2^+(CH_2)_3PO_3^-H$].[394] The same observations have been made also for the acid esters of aminophosphonic acids: whereas the acid esters of dialkylaminomethylphosphonic acids are neutral in an aqueous medium[389,392], the acid esters of *N*-arylaminophosphonic acids behave as acids themselves[392]. Owing to this difference, the former acid esters do not form stable salts with many metals[392]. The acid properties of polyaminopolyalkylphosphonic acids and mixed polyaminopolyalkylphosphonic and polyacetic acids are characterised by a large set of dissociation constants whose values are determined both by the nature of the dissociating functional groups and by their mutual influence¶.

Other reactions involving the phosphorus atom have been well investigated. Thus aminophosphonic acids are esterified by expoxyalkanes[397] and orthoformates[123].

Phenyl *N*-arylaminobenzylphosphonates are readily transesterified by alcohols in the presence of alkoxides[393]:

$$ArNHCH(Ar')PO(OPh)_2 \xrightarrow[-PhONa]{ROH,\ RONa} ArNHCH(Ar')PO(OR)_2. \quad (77)$$
Ar=Ph, *m*, *p*-C_6H_4Me, *p*-C_6H_4Cl, *p*-$C_6H_4CHMe_2$; Ar'=Ph, *p*-C_6H_4Me; R=Me, Pr, Bu.

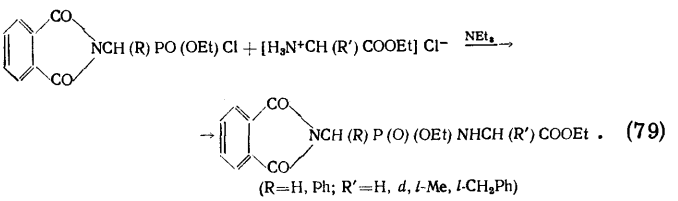
Treatment of diethyl ω-dialkylaminomethyl(ethyl)phosphonates with phenyl-lithium leads to ω-dialkylaminomethyl(ethyl)diphenylphosphine oxides[398]. Phthalimidobenzyl(methyl)phosphonates are quantitatively converted into ester-acid chlorides by reaction with phosphorus pentachloride[128,399]:



(78)

(R=H, Ph)

The resulting acid chlorides were used to synthesise peptides containing aminoalkylphosphonic acid moieties in 70–88% yields[128,399]:

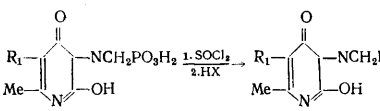


(79)

(R=H, Ph; R'=H, *d*, *l*-Me, *l*-CH_2Ph)

β-Phthalimidoethylphosphonyl chloride, obtained by treating the corresponding acid with thionyl chloride or its diethyl ester with phosphorus pentachloride, has been used to synthesise lipids and kephalins containing aminoethylphosphonic acid residues[400,401].

The conversion of pyrimidinylmethylphosphonic acids into the dimethyl and dibutyl esters and *NN'*-diphenyldiamide in 29–50% yields by successive treatment with thionyl chloride, methyl or butyl alcohol, and aniline has been described[54,402]:



(80)

(R1=H, Br; X=OMe, OBu, NHPh)

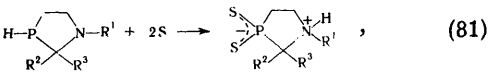
Treatment of *N*-substituted α-aminobenzylphosphonates with thionyl chloride and then with *p*-nitrophenol and triethylamine is accompanied by the cleavage of the phosphorus–carbon bond and leads to di(nitrophenyl)phosphate[403]. Phosphorus pentachloride completely cleaves nitrilotri(methylphosphonic)acid to tri(chloromethyl)amine and phosphoryl chloride; the hexaethyl ester is cleaved similarly[123].

¶Detailed data on their acid dissociations are quoted in the review of Kabachnik et al.[396]

Like other phosphines, ω-aminoalkylphosphines are converted into the corresponding sulphides and oxides on treatment with sulphur or hydrogen peroxide [24,110,111,114,230,234,265,267,340,352,353,355].

Phosphinic and phosphinodithioic acids are formed under these conditions from di-(β-aminoethyl)phosphines and β-aminoethylphenylphosphines [114,115].

1,3-Azaphospholidines containing a hydrogen atom at the phosphorus atom are converted into inner salts of phosphinodithioic acids in 71–81% yields by treatment with sulphur in benzene [230]:



(81)

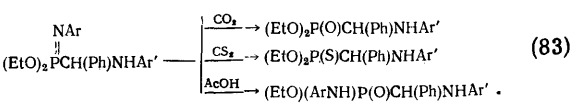
where R^1 = H or Et, R^2 = H, R^3 = Ph, and R^2R^3 = $(CH_2)_5$.

The oxidation of *NNN'N'*-ethylenediaminetetra(methylenephosphonous) acid with mercury(II) chloride to the phosphonic acid has been proposed as a method of synthesising the latter in an analytically pure form [404].

The alkylation of β-diethylaminoethyldialkyl(aryl)phosphines by ethyl iodide involves the phosphorus atom and results in the formation of aminophosphonium salts in 74–87% yields [110]:

$$Et_2NCH_2CH_2PR_2 + EtI \rightarrow [Et_2NCH_2CH_2P^+(R_2)\,Et]\,I^- . \quad (82)$$
(R=Et, Ph, cyclo-C_6H_{11})

Aminoalkylphosphonimidates readily exchange the imino-residue for oxygen and sulphur on treatment with carbon dioxide and carbon disulphide; treatment with acids leads to ester-amides [343]:



(83)

Reactions Involving the Nitrogen Atom

The amino-group of aminoalkyl phosphorus derivatives enters into many of its characteristic reactions. *N*-Alkyl-substituted and unsubstituted aminoalkyl organophosphorus compounds form stable salts with acids. In contrast to alkylation, the protonation of aminoalkylphosphines also takes place at the nitrogen atom [23,231]. The alkylation of the nitrogen atom is of preparative interest. Thus, on reaction with dimethyl sulphate (DMS) in an alkaline medium and subsequent acidification, *NN*-di(carboxymethyl)aminomethylphosphonic acid is converted into its *N*-methylbetaine [26]:

$$H_2O_3PCH_2N(CH_2COOH)_2 \xrightarrow[2.\ H^+]{1.\ NaOH,\ Me_2SO_4} HO_3^-PCH_2N^+Me(CH_2COOH)_2 . \quad (84)$$

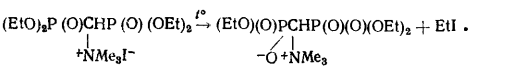
Depending on the methylating agent, aminoalkylphosphonic acid containing an unsubstituted amino-group are converted into dimethylaminoalkylphosphonic acids (formaldehyde and formic acid) or into fully methylated derivatives—betaines (DMS in an alkaline medium or methyl iodide in methanol) [395,405]. It has been suggested that polyaminoalkylpolyphosphonic and polyaminoalkylpolyphosphonicpolyacetic acids be obtained by alkylating aminoalkylphosphonic acids with alkylene dihalides and chloroacetic acid in an alkaline medium [48,406–410].

The full esters of dialkylaminoalkylphosphonic acid are readily alkylated by alkyl halides and DMS even at room temperature in inert solvents (dioxane, ether) or in the absence of a solvent on heating with formation of salts of trialkylammoniumalkylphosphonates [63,75,411–414].

Thus alkylation of diethyl ω-dimethylaminoalkylphosphonates with methyl iodide in ether at 0°C leads to the corresponding methiodides in 61–81% yields [388]:

$$Me_2N(CH_2)_nP(O)(OEt)_2 \xrightarrow{MeI} Me_3N^+(CH_2)_nP(O)(OEt)_2I^- . \quad (85)$$

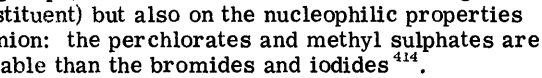
A characteristic feature of these compounds is their tendency to undergo dealkylation to the betaines—slowly at room temperature and rapidly on heating [411,414,415]. For example, when trimethylammoniummethylenediphosphonate is refluxed for 3 h in benzene, the betaine is formed in 97% yield [411]:



(86)

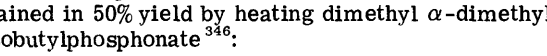
It has been noted that the tendency towards betaine formation depends not only on the type of substituent in the alkoxy-group (increases with decrease of the length of the substituent) but also on the nucleophilic properties of the anion: the perchlorates and methyl sulphates are more stable than the bromides and iodides [414].

A simple method for the synthesis of such betaines is the coupled *N*-alkylation and *O*-dealkylation of aminophosphonates occurring when these are heated [346,415]: a betaine was obtained in 50% yield by heating dimethyl α-dimethylaminoisobutylphosphonate [346]:



(87)

Toluene-*p*-sulphonic acid is used as a catalyst for this process [415]. The *N*-dealkylation of aminoalkyl phosphorus derivatives has been less thoroughly investigated. *N*-Benzylaminoalkylphosphonic and the analogous phosphinic acids are readily dealkylated [310] by hydrogenolysis in glacial acetic acids over a palladium catalyst at a temperature as low as 20°C, the yields being 92–98%:



(88)

When the iodide of diethyl triethylammoniummethylphosphonate is heated with triethylphosphite, the latter is alkylated and an ethyl group is removed from the nitrogen atom [416]. The ethyl esters of *N*-t-butylaminomethylphosphonic and *N*-t-butyliminodi(methylphosphonic) acids are hydrolysed and cleaved by hydrochloric acid to aminomethylphosphonic and iminodi(methylphosphonic) acids respectively [312,314].

Aminoalkyl organophosphorus compounds, both unsubstituted and mono-substituted at the nitrogen atom, are readily acylated. Thus, on heating with acetic anhydride, aminomethylphosphonic acid is converted into acetamidomethylphosphonic acid in 57% yield [417]:

$$H_2NCH_2PO_3H_2 + (MeCO)_2O \rightarrow MeCONHCH_2PO_3H_2 . \quad (89)$$

Fusion of this acid with phthalic anhydride leads to phthalimidomethylphosphonic acid [417]. In this case the chlorides of chloroacetic, benzoic, and *p*-nitrobenzoic acids are also effective acylating agents in an alkaline medium [417,418]. The full esters of aminoalkylphosphonic and aminoalkylphosphonothioic acids are smoothly acylated by acetic anhydride [417,418], acyl chlorides in the presence of pyridine and by the Schotten–Baumann reaction [329,418,419], aryl isocyanates [420], keten [421], mixed anhydrides of aminocarboxylic and carbonic acids [422,423], phthalimidoacetic acid in the presence of dicyclohexylcarbodi-imide [399], and phosgene [424]. The acylation of aminoalkylphosphinates and phosphine oxide has also been described [72,387].

Phosphonic acids containing a tertiary nitrogen atom can be converted by treatment with hydrogen peroxide in alkaline or neutral aqueous and aqueous alcoholic media

into the *N*-oxides of aminophosphonic acids and into their salts[425-432]; for example, the oxidation of nitrilotri(methylphosphonic) acid with hydrogen peroxide leads to the *N*-oxide in 49% yield[425]:

$$N[CH_2PO_3H_2)_3 \xrightarrow{H_2O_2} ON(CH_2PO_3H_2)_3 . \quad (90)$$

The oxidation of *NN*-disubstituted aminomethylphosphine oxides takes place similarly[86,433]. The oxidation of aminoalkylphosphonic acids and their esters, containing a primary amino-group, with sodium hypochlorite leads to azodi(alkylphosphonic) acids and their esters[434]:

$$2\,(RO)_2P(O)\,C(R')(R'')\,NH_2 \xrightarrow{NaOCl} (RO)_2P(O)\,C(R')(R'')N{=}NC(R')(R'')P(O)(OR)_2 . \quad (91)$$
(R=H, Alk)

The diazotisation of aminoalkyl organophosphorus compounds with a primary amino-group is of considerable preparative interest. The reaction with α-aminoalkylphosphonic acids proceeds with evolution of nitrogen and the formation of α-hydroxyalkylphosphonic acids[28,183,387]:

$$H_2O_3PCH(R)\,NH_2 \xrightarrow[(R=H,\ Ph)]{HNO_2,\ \text{nitrogen oxides}} H_2O_3PCH(R)\,OH + N_2 . \quad (92)$$

Aminomethylphosphonate esters are converted into diazomethylphosphonates in 46–64% yields on diazotisation with sodium nitrite in aqueous acetic acid[125-127]:

$$(RO)_2P(O)\,CH_2NH_2 \xrightarrow[(R=Me,\ Et)]{HNO_2} (RO)_2P(O)\,CHN_2 . \quad (93)$$

α-Diazoalkylphosphine oxides were obtained similarly in 45–90% yields by the diazotisation of α-aminoalkylphosphine oxides[18,36,127]:

$$R_2P(O)\,CH(R')\,NH_2 \xrightarrow[(R=Ph,\ CH_2Ph,\ R'=H;\ R=Ph,\ R'=Ph)]{HNO_2} R_2P(O)\,C(R')\,N_2 . \quad (94)$$

The possibility of such diazotisation of aminophosphonates and phosphine oxides is probably due to their high α-C—H acidity and the considerable stability of the resulting α-diazoalkyl derivatives of organophosphorus compounds: comparison of the thermal stabilities of α-diazoalkyl organophosphorus compounds with those of the carbonyl analogues showed that the former are just as stable and in some cases even more stable than the latter[435].

The diazotisation of β-amino-αα-dimethylethyldiphenylphosphine oxide takes place with deamination and is accompanied by the isomerisation of the intermediate carbonium ion, to a large extent owing to the migration of the diphenylphosphinyl group[10]:

$$Ph_2P(O)CMe_2CH_2NH_2 \xrightarrow[\text{or } C_5H_{11}ONO]{NaNO_2,\ H_2SO_4} [Ph_2P(O)CMe_2CH_2^+] \longrightarrow$$
$$\longrightarrow Ph_2P(O)CH_2{-}C(Me){=}CH_2\ (25\%) + Ph_2P(O)CH{=}CMe_2\ (8\%) +$$
$$+ Ph_2P(O)CH_2CMe_2OH\ (38.8\%) + Ph_2P(O)CMe_2CH_2OH\ (6.8\%) +$$
$$+ Ph_2P(O)C(Me)\begin{matrix}CH_2\\ \diagdown\\ \diagup\\ CH_2\end{matrix}\ (14.7\%) . \quad (95)$$

The primary amino-group in aminomethylphosphonates and aminomethylphosphine oxides is converted in the usual way into the isonitrile group in 72–80% yield[142,436]:

$$R_2P(O)\,CH_2NHCHO \xrightarrow[NEt_3]{COCl_2} R_2P(O)\,CH_2N{=}C . \quad (96)$$
(R=Ph, CH_2Ph, OEt)

Reactions Involving the α-Carbon Atom

These reactions are usually accompanied by the dissociation of carbon–nitrogen and phosphorus–carbon bonds or the elimination of an α-hydrogen atom and the formation of phosphorylated nitrogen yields.

When the carbon–nitrogen bond in aminoalkyl derivatives of organophosphorus compounds is broken, the amino-group is substituted by other organic residues. For example, heating of tri(dimethylaminomethyl)phosphine with aniline leads to tri(anilinomethyl)phosphine in 45% yield[266]:

$$(Me_2NCH_2)_3P + 3\,H_2NPh \xrightarrow[-3Me_2NH]{} (PhNHCH_2)_3P . \quad (97)$$

The substitution of the diethylamino-group in *NN*-diethylaminomethylphosphines by the diphenylphosphine residue has been suggested[190] as a method for the synthesis of compounds with a P–C–P bond system (yields 31–100%):

$$Ph_nP[CH_2NEt_2]_{3-n} + m\,HPPh_2 \xrightarrow[Et_2NH]{} Ph_nP[CH_2NEt_2]_{3-n-m}[CH_2PPh_2]_m . \quad (98)$$
$(n=0-2,\ m=1-3)$

The formation of a cyclic product in 76% yield on dehydrochlorination of tetra(anilinomethyl)phosphonium chloride with triethylamine probably proceeds via a mechanism involving the cleavage of the P–C and C–N bonds[266]:

$$(PhNHCH_2)_4P^+Cl \xrightarrow[-Et_3N\cdot HCl]{Et_3N} \left[\begin{matrix}PhNCH_2 & & CH_2NHPh\\ & \diagdown\ \diagup^{+} & \\ & P & \\ & \diagup\ \diagdown & \\ PhNHCH_2 & & CH_2NHPh\end{matrix}\right] \longrightarrow$$
$$\longrightarrow \left[\begin{matrix}PhNCH_2 & & CH_2NHPh\\ & \diagdown & \\ & CH_2{-}P & \\ & & \\ PhN: & \longrightarrow & CH_2{-}NHPh\\ H & & \end{matrix}\right] \longrightarrow \begin{matrix}Ph\\ |\\ N{-}CH_2\\ \diagdown\\ CH_2\\ \diagup\\ N{-}CH_2\\ |\\ Ph\end{matrix}\!\!\!

Immoniumphosphonates were synthesised by treating aminoacetals of formylphosphonic acid esters with thionyl chloride[103]:

$$(RO)_2P(O)CH\langle^{OMe}_{NMe_2} \xrightarrow{SOCl_2} (RO)_2P(O)CH{=}N^+Me_2Cl^- + SO_2 + MeCl \quad (104)$$

(R=Me, Et)

The products are very reactive with respect to compounds with a mobile hydrogen atom[122]:

$$(EtO)_2P(O)CH{=}N^+Me_2Cl^- + RH \xrightarrow[-NEt_3\cdot HCl]{NEt_3} (EtO)_2P(O)CH(R)NMe_2 \quad (105)$$

(R=R'S, R'_2N, R' O, $R'_2P(O)$, $(MeCO)_2CH$, $ArCOCH_3$)

The chemical and thermal instability of certain aminoalkyl organophosphorus compounds is due to the lability of their phosphorus–carbon bond. The lability is manifested most clearly in α-aminoalkylphosphonium salts[170–173]: *NN*-disubstituted aminomethyltriphenylphosphonium halides are unstable even at room temperature and are fully hydrolysed by water[173]:

$$Ph_3P^+CH_2NR_2X^- \overset{t^\circ}{\rightleftarrows} Ph_3P + CH_2{=}N^+R_2X^- \xrightarrow{H_2O} Ph_3P + CH_2O + H_2NR_2X \quad (106)$$

X=Cl, Br; R=Me; $R_2=(CH_2)_5$, $(CH_2)_2O(CH_2)_2$

The replacement of the phenyl groups at the phosphorus atom by alkyl groups[171,173] (i.e. an increase of the basicity of the initial phosphine) and a decrease of the stability of the carbonium-immonium ion by the introduction of acyl groups at the nitrogen atom[172] appreciably stabilise such compounds, but they too decompose in an alkaline medium or under the influence of powerful nucleophilic agents (MeONa, NEt_3, MeLi, t-BuOK) with formation of trialkyl(aryl)phosphines[171–173]. The introduction of substituents stabilising the positive charge (for example, the *p*-dimethylaminophenyl group) at the α-carbon atoms reduces sharply the thermal and hydrolytic stability of α-aminoalkylphosphonium salts[170]. An ethynyl group at the phosphorus atom is cleaved[438]:

$$Bu_2PC{\equiv}CH + HOCH_2NEt_2 \rightarrow [Bu_2\overset{+}{P}(C{\equiv}CH)CH_2NEt_2]OH^- \rightarrow Bu_2P(O)CH_2NEt_2 + C_2H_2 . \quad (107)$$

The stability of the carbonium-immonium ion formed determines also the lability of the carbon–carbon bond in β-aminoalkylphosphonium salts[89]:

$$[Ph_2PC(Ph){=}CH_2]Br^- + HNC_5H_{10} \rightleftarrows [Ph_2\overset{+}{P}CH(Ph)CH_2NC_5H_{10}]Br^- \rightarrow$$
$$\rightarrow Ph_3P{=}CHPh + [CH_2{=}\overset{+}{N}C_5H_{10}]Br^- . \quad (108)$$

On heating (distillation), certain α-aminoalkylphosphonates undergo partial cleavage of the phosphorus–carbon bond with formation of enamines and dialkyl phosphites[102,363]:

$$R_2NCHP(O)(OR''')_2 \xrightarrow{t^\circ} R_2NCH{=}CR'R'' + (R'''O)_2PHO , \quad (109)$$

(R'R'' on CHR'R'')

where $R_2=(CH_2)_4$, R'R'' = Me, and R''' = Et or $R_2=(CH_2)_5$, R' = H, R'' = Me, and R''' = Me.

Aminophosphonates containing aromatic groups at the nitrogen and α-carbon atoms are relatively stable in an alkaline medium[297], but, when treated with acetic or hydrochloric acid at 40–60°C, they are fully decomposed into an amine, aldehyde, alcohol, and phosphorus acid[291,439]:

$$ArNHCH(Ar')P(O)(OR)_2 \xrightarrow{HCl \text{ or } MeCOOH} ArNH_2 + Ar'CHO + H_3PO_3 + 2\,ROH \quad (110)$$

β-Aminoalkylphosphonates, which are intermediates in the PO–olefin addition reaction (17), undergo a further conversion into an olefin and a phosphoramidate in the presence of bases[94] or acids[98]:

$$PhCHP(O)(OEt)_2 \quad (CHPh, NHPh) \xrightarrow[-NH_3]{NaNH_2} PhCH + PhN(Na)P(O)(OEt)_2 . \quad (111)$$

(PhCH: HCPh)

Like α-aminocarboxylic acids, aminomethylphosphonic acid is cleaved by ninhydrin with formation of a blue dye and a mixture of phosphates[440].

The phosphonate carbanions obtained from aminophosphonates readily enter into the PO–olefin addition reaction[275,319,441]. For example, phosphorylated enamines were obtained in 60–75% yields by treating dimethylaminoethylenediphosphonates with sodium hydride in dioxane and then with aldehydes (ketones do not enter into this reaction)[275]:

$$[(EtO)_2P(O)]_2CHNMe_2 \xrightarrow[2.RCHO]{1.NaH} (EtO)_2PO_2Na + RCH{=}CP(O)(OEt)_2 , \quad (112)$$

(NMe$_2$ on CP)

where R = Ph, *p*-$C_6H_4NO_2$, PhCH=CH, or 3,4-(OCH_2O)Ph. When nitroso-compounds are introduced into this reaction instead of aldehydes, amidines are formed in 45–97% yields[319,324,441]:

$$(PhO)_2P(O)CH(NHR'')R \xrightarrow[2.\ R'NO]{1.NaH \text{ or } KOH} (PhO)_2PO_2Na + R'N{=}C(R)NHR'' .$$

(R=Ph, *p*-$C_6H_4NO_2$; R' = Ph, *o*-C_6H_4Me; R''=Ph, *p*-$C_6H_4NO_2$, *o*-C_6H_4Me, *p*-C_6H_4OMe) (113)

Phosphorylated nitrogen ylides have been obtained by the reaction of α-ammoniumalkylphosphonates with bases[414,442]:

$$(RO)_2P(O)CH(R')N^+R''_3X^- \xrightarrow[-B\cdot HX]{B} (RO)_2P(O)C^-(R')N^+R''_3 . \quad (114)$$

In this case, where R' is a group capable of stabilising the negative charge [COR', COOR', $PO(OR')_2$], the formation of the ylide is observed even on treatment with potassium carbonate[414,442], whereas stronger bases (sodium hydride or dimsyl sodium) are needed when R' = H.[443] The chemical properties of these compounds have been little investigated: only alkylation with methyl iodide leading to a *C*-methylated ammoniumalkylphosphonate[414] and PO–olefin addition on treating *N*-diphenylphosphinylmethylpyridinium salts with aromatic aldehydes in the presence of diethylamine[444] have been described. The carbanions obtained by the reaction of diethylphosphinylmethyl isocyanide with butyl-lithium also react with carbonyl compounds to form vinyl isocyanides[142] (68–84%).

IV. APPLICATIONS OF AMINOALKYL ORGANOPHOSPHORUS COMPOUNDS

Owing to their ready availability and their chemical properties, compounds of this class can find extensive applications in various branches of science and engineering. Much interest is shown at present in the employment of aminoalkylphosphonic acids as effective complexones with electron-donating functions of the nitrogen atoms and the oxygen atoms in the phosphoryl groups, which are capable of forming chelate rings and of assuming various conformations depending on the configurations of the metal ions being chelated. Numerous publications have been devoted to this problem and have been described exhaustively in the review of Kabachnik et al.[396] Here only some data on the employment of these compounds as complexones are quoted.

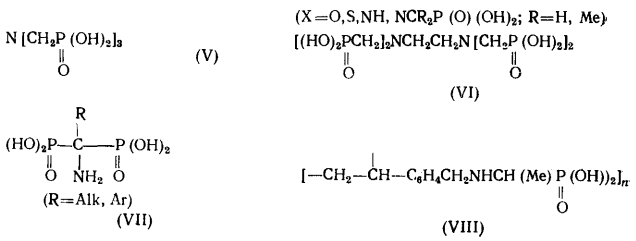
Polyaminoalkylpolyphosphonic acids [for example (III)–(VI)], which are analogous of polyaminoalkylpolyacetic acids, are capable of effective complex formation with many metal ions:

$$(HO)_2P(R)CNH(CH_2)_nNHC(R)P(OH)_2$$

(n=2 – 5; R=H, Me) (III)

$$(HO)_2P(R)CNHCH_2CH_2XCH_2CH_2NHC(R)P(OH)_2$$

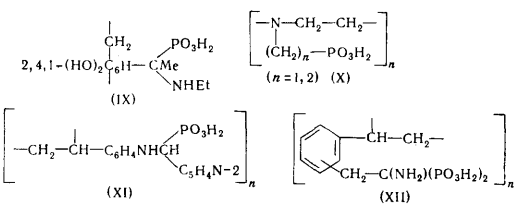
(IV)



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

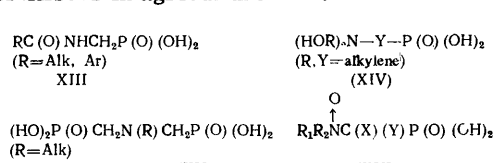
However, owing to their stereochemical characteristics and the high electron-donating capacity of the phosphonate group, they form relatively unstable complexes with alkaline earth metal ions, while their complex-forming capacity with respect to transition metal, lanthanide, and beryllium ions is very high [78,104,375,396,445-450]. An important feature of organophosphorus complexones is the formation of very stable "acid" or "hydrogen" complexes at low pH in which the metal is not coordinated to the nitrogen atom owing to the protonation of the latter [396]. This property is of undoubted interest in studies with readily hydrolysable salts. For these reasons, certain organophosphorus complexones [for example (III) and (VI)] can be used for the extraction of valuable elements and for the separation of lanthanides and actinides within their respective groups [448-452].

The high complex-forming capacity of these compounds is used also in the ion-exchange resins (VIII)-(XII) containing aminophosphonic acid residues [50,79,249,376,453-459]. For example, ion exchangers of the type (VIII)-(XI) effectively extract Cu^{2+} ions from an acetate buffer (capacity 1.1-1.4 mequiv. of Cu^{2+} per gram of resin) [453,459]:



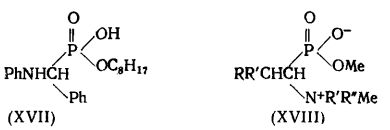
(IX) (X) (XI) (XII)

Aminophosphonic acids can also find application in most cases where it is necessary to bind metal ions giving rise to undesirable effects. It has been suggested that they be used for water softening and to prevent the formation of scale [375,460] [compounds of type (V) and (VII)], as antioxidants [compounds (XIII)] [167] and as corrosion inhibitors [461], for the removal of rust and for the etching of aluminium alloys [compounds (VII) and (XIV)], [53,462] for the passivation of metals [253] [compounds (V), (VI) and (XV)], and as metal deactivating additives to lubricating oils [compounds (XIII)]. [45,167] The effective dispersing and deflocculating properties of salts (Li, Na, K, NH_4) of aminophosphonic acids [240,244,253] permit their employment for the formation of oil gels [164] [compounds (XIII)], as components of a boring solution [compound (V)], [182] for the prevention of ice formation in water-containing hydrocarbon fuels [compounds (XV)], [242] and in detergent compositions [45,240,243] [compounds (V) and (XV)]. Their manganese, copper, zinc, etc. salts can be used as microfertilisers in agriculture [53,373].



(XIII) (XIV) (XV) (XVI)

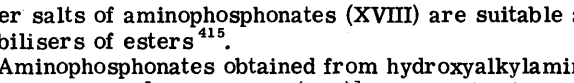
Aminophosphonic acid *N*-oxides [of the type of compound (XVI)] and their salts have been suggested as complexones [425,428,431], stabilisers of peroxide compounds, antioxidants for oils and soaps, water softening agents, metal corrosion inhibitors, and metal passivators [428-432]. In view of its ability to form complexes soluble in ligroin with a number of metal atoms, mono-octyl anilinobenzylphosphonate (XVII) has been proposed as an effective extractant at the interface between organic and aqueous phases [385,463-465].



(XVII) (XVIII)

Inner salts of aminophosphonates (XVIII) are suitable as stabilisers of esters [415].

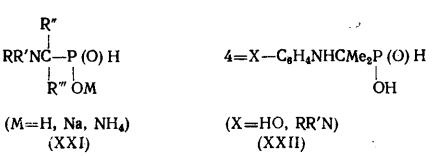
Aminophosphonates obtained from hydroxyalkylamines and polyamines [for example (XIX)] and also the hydroxyalkyl esters of aminophosphonic acids [for example (XX)], which contain hydroxy- and amino-groups, have been suggested as fire-resistant polyhydroxy-components in the manufacture of polyurethanes [213,215,218-220,277,279,280,397,466,467].



(XIX) (XX)

Their non-combustibility and thermal and chemical stability permit the employment of certain aminophosphonates as hydraulic liquids, heat exchangers, lubricators, and plasticisers [146,194,466,468]. These compounds can also be used as surfactants, emulsifying agents [194,222], and extractants [469].

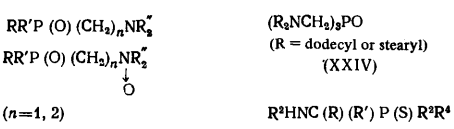
Aminoalkylphosphonous acids and their salts of the general type (XXI) have been suggested as surfactants, antioxidants, and complex-forming agents [33,205,206,223].



(XXI) (XXII)

Compounds of the general type (XXII) have been patented as photographic developers which are stable in air, readily soluble, and free from allergic effects [225].

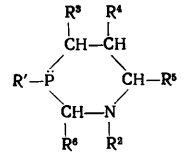
Aminoalkylphosphine oxides and *N*-oxides of type (XXIII) are promising extractants suitable for the extraction of uranium and for the separation of lanthanides and actinides within their respective groups [86,286,433,470]:



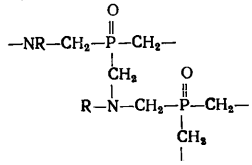
(XXIII) (XXIV) (XXV)

Tri(aminomethyl)phosphine oxides (XXIV) have been proposed as additives which reduce the static electric charge of synthetic fibres and impart fire resistance to them [237]. Aminoalkylphosphine sulphides (XXV) are suitable as lubricating materials and additives to oil [338].

Aminoalkylphosphines of the general type (XXVI) can be employed to modify carbonyl catalysts in oxo synthesis[471].

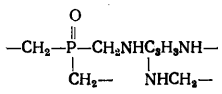


(XXVI)

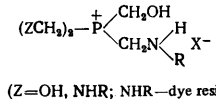


(XXVII)

Products obtained by the condensation of tetra(hydroxymethyl)phosphonium halides, tri(hydroxymethyl)phosphine and the corresponding phosphine oxide with nitrogen-containing compounds (primary amines, ammonia, urea, guanidine, melamine, etc.) of type (XXVII) and (XXVIII) are thermostable non-combustible resins suitable for impregnating veneers, wool, textiles, etc.[272-274,472-477].



(XXVIII)

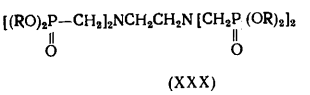


(Z=OH, NHR; NHR—dye residue

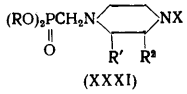
(XXIX)

When the aim was to make fabrics non-combustible, best results were obtained by condensation directly on the fibre[478]. Dyes with amino-groups give rise to wear-resistant colours on cellulose fibres on treatment with tetra(hydroxymethyl)phosphonium halides (XXIX).[479] Certain polyamides based on di(aminoalkyl)phosphine oxides and phosphinic acids have the self-quenching property and exhibit an enhanced adhesion to metals[355,480-482].

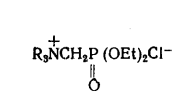
The biological activity of aminoalkyl organophosphorus compounds has been comparatively little studied. It has been established that 2-aminoethylphosphonic acid and some of its derivatives enter into the composition of the proteins and polysaccharides of some marine animals and lower organisms[483-488]. Many aminoalkyl organophosphorus compounds exhibit a low toxicity to warm-blooded animals[489]. Their much higher toxicity to plants and insects permits the employment of some of them [for example (V), (XVI), (XXI), (XXX)–(XXV)] as insecticides, fungicides, antiparasite agents, herbicides, growth regulators, and defoliants[33,194,203,209,431,490-492]. The chelate complexes formed by aminoalkylphosphonic acids with iron(III) ions are suitable for the protection of plants from chlorosis[52,59]. The low toxicity of aminoalkylphosphonous acids (XXI) and ammoniumalkylphosphonates (XXXII) to warm-blooded animals permits their use as antibacterial agents[58,205,224,334-336]. It has been suggested that salts of aminophosphonic acids of the type (V) and (XIII) be used to improve the contrast of X-ray photographs[493] and to increase the concentration of 5-hydroxytetracycline in blood[494]; their salts with microelements are suitable for the introduction of the latter into the organism[165]. The high complex-forming capacity of polyaminoalkylpolyphosphonic acids [for example (III), (IV), and (VI)] with respect to beryllium and certain heavy elements gives rise to the possibility of using them for the effective treatment of intoxications caused by the presence of these metals in the organism[396].



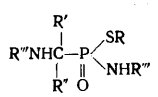
(XXX)



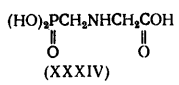
(XXXI)



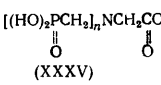
(XXXII)



(XXXIII)



(XXXIV)



(XXXV)

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After the review had been sent to the editors, a number of publications dealing with methods for the synthesis and properties of aminoalkyl organophosphorus compounds appeared.

β-Dialkoxyphosphinylethyl isocyanate was obtained by the Curtius rearrangement of the azide of β-dialkoxyphosphinylpropionic acid[495].

A number of α-aminophosphonic acids were synthesised by the Hofmann degradation of the amides of α-diethoxyphosphinylcarboxylic acids[496,497].

α-Aminophosphonates, tri-(γ-aminopropyl)phosphine, and the corresponding phosphine oxide were obtained by reducing the oximes of α-ketophosphonates[498], tri-(β-cyanoethyl)phosphine, and the corresponding phosphine oxide[499].

1-Alkyl-4-alkoxy-4-oxo-1,4-azaphosphorinanes and silicon-containing β-aminoethylphosphonic acid esters have been synthesised by the addition of primary amines and silicon-containing amines to divinylphosphinic[500] and vinylphosphonic[501] acid esters.

The interaction of alkali metal derivatives of benzyl phosphonates and phosphine oxides with β- and γ-chloramines led to the formation of a number of phosphorus analogues of methadone and their analgesic activity was studied[502].

The synthesis of dialkylphosphinobis(dimethylamino)methanes by the reaction of *NNN'N'*-tetramethylformamidinium chloride with lithium dialkyl phosphites and their disproportionation to bis(dialkylphosphino)dimethylaminomethane and tris(dimethylamino)methane have been described[503].

The condensation of trialkyl(aryl) phosphites with thiourea and urea has been suggested as a general method of synthesising α-ureidophosphonates[504].

Methods have been patented for the synthesis of nitrilotri(ethylenephosphonic) acid by the reaction of sodium and potassium dialkyl phosphites with tri-(2-chloroethyl)amine[505] and for the synthesis of ureidomethylphosphonyl halides by the reaction of phosphorus trihalides with alkoxymethylureas[506]. They have been suggested as fire resistant agents.

New polydentate *PN*-ligands have been obtained by the reaction of *N*-substituted ethylenediamines with diphenylphosphine and formaldehyde and their properties have been investigated[507].

The phosphonomethylation of silicon-containing[508,509] and heterocyclic[510] amines and glycine[511] with phosphorous acid and formaldehyde in hydrochloric acid has been described. The compounds thus obtained have been suggested as inhibitors of corrosion and scale formation and as complex-forming agents.

Dialkyl 1-(*N*-acylamino)-2,2,2-trichloroethylphosphonate esters have been obtained by treating *N*-1,2,2,2-tetrachloroethylbenzamide and *N*-acetyltrichloroacetaldimine with trialkyl phosphites and dimethyl phosphite[512,513].

It has been shown that magnesium derivatives of phosphorodiamidites readily add to Schiff bases[514];

N-allyl- and *N*-pyridyl-aminophosphonates have been synthesised by the reaction of dialkyl phosphites with Schiff bases [515,516]. A new method has been proposed for the synthesis of α-aminobenzylphosphonates by heating benzaldazines with an excess of diethyl phosphite in the presence of sodium diethyl phosphite—in the course of the reaction two molecules of diethyl phosphite add to the C=N bonds with subsequent reduction of the resulting 1,2-bis(diethoxyphosphinylbenzyl)hydrazine [517].

The kinetics and mode of the reactions of dialkyl(phenyl) phosphites with Schiff bases have been discussed [518,519].

The chromatographic determination of many aminophosphinic acids has been described [520,521], and it is suggested that they be identified with the aid of crystalline *N*-di- and *N*-tri-nitrophenyl derivatives [522]; the infrared and ^{1}H NMR spectra of certain aminoalkyldiphosphonic acids have been investigated [523,524].

It has been shown that the deamination of 2-amino-1-hydroxy-1-phenylethylphosphonic acid involves appreciable rearrangement with formation of phenylacylphosphonic acid [525].

Ion-exchange resins based on chloromethylated styrene-divinylbenzene copolymers containing β-aminoethylphosphonic [526] and (−)-α-aminobenzylphosphonic [527] acid groups have been synthesised and investigated; the synthesis and polymerisation of *N*-methacryloyl-β-aminoethylphosphonic acid has been described [528].

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