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The Phosphorus Analogues of Aminocarboxylic Acids

V.P.Kukhar' and V.A.Solodenko

The review is devoted to aminophosphonic, aminophosphinic, and aminophosphonous acids and their derivatives. The interest in these compounds is in many respects because some of them have been detected in Nature and have an appreciable bioactivity. The review deals with the methods of synthesis of aminophosphonic, aminophosphinic, and aminophosphonous acids and with the properties of these compounds, attention being specially concentrated on the phosphorus analogues of natural α-aminocarboxylic acids.
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I. INTRODUCTION

β-Aminoethylphosphonic acid (ciliatine)—the first natural product with a P–C bond—was isolated from natural sources in 1959.[1] Subsequently other natural aminophosphonic, aminophosphinic, and aminophosphonous acids and their derivatives were discovered.[2-10] The appreciable bioactivity of these compounds stimulated interest in the study of their chemistry and bioreactions. The phosphorus analogues of natural aminocarboxylic acids have attracted special attention. These compounds belong to the class of aminoalkyl organophosphorus compounds, whose chemistry has been considered in a number of reviews.[11-13] At the same time, the presence in their structure of the free amino-group, frequently in combination with other functional groups (hydroxy-, mercapto-, etc.), imposes definite limitations on the choice of methods and frequently requires special approaches to their synthesis. Stereochemical aspects are also important.

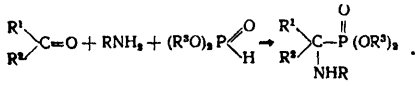
The chemistry of α-aminophosphonic acids has been examined in a review[14] published in 1975, but during the intervening period has been significantly supplemented by new results. A later review[15] on the chemistry of aminophosphinic acids is extremely concise.

This review deals with the methods of synthesis of aminophosphonic, aminophosphinic, and aminophosphonous acids (APA) and their properties. Attention is concentrated on the phosphorus analogues of natural α-aminocarboxylic acids.

II. METHODS OF SYNTHESIS OF AMINOPHOSPHONIC, AMINOPHOSPHINIC, AND AMINOPHOSPHONOUS ACIDS

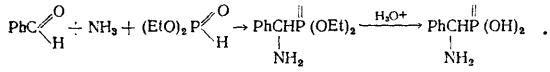
1. Amino- and Amido-alkylation of Hydrophosphoryl Compounds; the Kabachnik–Fields Reaction

At the beginning of the 1950's, Kabachnik and co-workers[16-21] and independently the American investigator Fields[22] showed that the interaction of ammmonia (or an amine), a carbonyl compound, and a dialkyl phosphite leads to the formation of α-aminophosphonic acid esters (the Kabachnik–Fields reaction):



It has been suggested that the reaction mechanism involves the initial formation of an α-hydroxyalkylphosphonic acid ester with the subsequent replacement of the hydroxy-group by the amino-group.[23] Another view on the mechanism of this reaction has been described in a monograph,[24] where the reaction is treated as aminoalkylation of a hydrophosphoryl compound (HPC) by an electrophilic intermediate formed form the carbonyl compound and the amine.

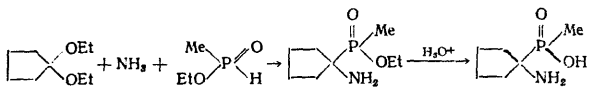
The range of compounds which can be involved in this process is extremely large.[23,24] We shall deal only with studies where the synthesis of α-APA† with an unsubstituted amino-group has been described. The most convenient method for the synthesis of these compounds uses ammonia as the amino-component.[16-21,25] When benzaldehyde, an alcoholic ammonia solution, and diethyl phosphite are heated in a sealed tube at 100 °C, diethyl α-aminobenzylphosphonate is formed, its hydrolysis leading to free α-aminobenzylphosphonic acid:[16,18]



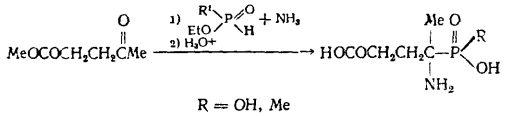
Phosphonic analogues of alanine (Ala^P) and phenylalanine (Phe^P) have been obtained by this method.[26] The yields of α-aminophosphonic acid esters synthesised in this way do not usually exceed 45%. Diethyl α-aminoethylphosphonate has been obtained in 76% yield by a somewhat modified method (stirring of a mixture of acetaldehyde–ammonia, diethyl phosphite, and ammonia in a sealed tube at room temperature).[27] The use of acid esters of phosphonous acids makes it possible to obtain derivatives of α-aminophosphinic acid.[20] The phosphonic and phosphinic analogues of cycloleucine were obtained in this way, starting from the diethylketal of cyclopentanone

†The APA which are analogues of natural aminocarboxylic acids are designated by the generally accepted three letter abbreviations with the superscript P. For the phosphorus analogues of aspartic and glutamic acids, the additional subscripts α, β, and γ, denoting the position of the phosphorus-containing group, are introduced. For the phosphine analogues, a superscript indicating the position of the substituent at the phosphorus atom is added.

and diethyl phosphite or ethyl methylphosphonite respectively:[28]



The α-phosphonic and α-phosphinic analogues of α-methylglutamic acid has been synthesised analogously by the aminoalkylation of diethyl phosphite and ethyl methylphosphonite:[29]

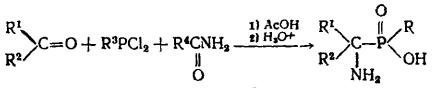


R = OH, Me

Overall, the Kabachnik–Fields reaction is a convenient general method for synthesis of α-aminophosphonic and α-aminophosphinic acids; the important advantages of the method are a single-stage process and the availability of the starting compounds.

The aminoalkylation of HPC has been extended to tervalent phosphorus acids—hypophosphorus, phosphorous, and phosphonous acids, which made it possible to obtain directly free α-aminophosphonous,[30,31] α-aminophosphonic,[32] and α-aminophosphinic,[33,34] acids. However, this approach has not found extensive application in the synthesis of α-APA with a free amino-group because it is restricted almost exclusively to the aminoethylation reaction. The report[35] of the synthesis of a series of α-(*N*-benzylamino)alkylphosphonic acids by the aminoalkylation of phosphorous acid was subsequently judged to be erroneous.[36] It is noteworthy that the aminoalkylation of phosphorous acid is used extremely widely for the synthesis of APA derivatives with valuable complex-forming properties.[12,13]

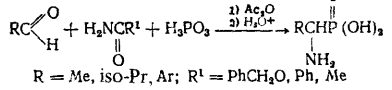
The reaction involving the amidoalkylation of tervalent phosphorus halides has found very extensive application in the synthesis of α-APA. When a carbonyl compound, phosphorus trichloride [or an alkyl(aryl)dichlorophosphine], and a compound containing the amide group interact in acetic acid, an intermediate is formed, whose hydrolysis leads to the formation of α-aminophosphonic or α-aminophosphinic acid in 40–60% yield:[37]



R^3 = Cl, Alk, Ar; R^4 = EtO, $PhCH_2O$;
R = OH, Alk, Ar

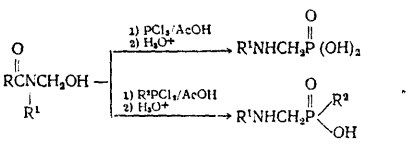
The use of acetals instead of carbonyl compounds and of carboxylic acid amides (acetamide, benzamide) instead of carbamates lowers the yield of α-APA. It is of course not permissible to employ amines and ammonia in this reaction.[37] The process can be carried out successfully also in trimethylacetic acid.[38] Aminomethylphosphonic acid (Gly^P) [39] as well as the phosphonic and phosphinic analogues of cycloleucine,[28] proline,[40] serine,[41] α-methylaspartic, α-methylpyroglutamic, glutamic, and pyroglutamic acids,[42] and ornithine[43] have been obtained by this method. The use of *N*-alkylbenzylcarbamates as the amide components makes it possible to synthesise α-(*N*-alkylamino)alkylphosphonic and the corresponding phosphinic acids.[44] The attempts to employ *NN'*-dialkylbenzylcarbamates in the reaction were unsuccessful.[44]

The amidoalkylation of phosphorous acid in acetic anhydride has been used to obtain phosphonic analogues of alanine, valine, and also other α-aminophosphonic acids (yields from 10 to 75%):[45]



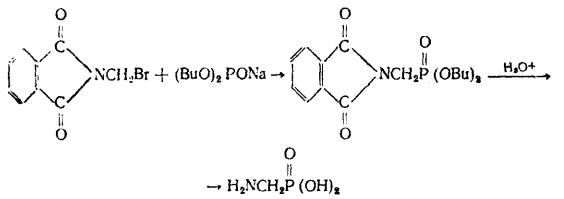
R = Me, iso-Pr, Ar; R^1 = $PhCH_2O$, Ph, Me

The interaction of *N*-hydroxymethylamides with phosphorus trichloride or alkyl(aryl)dichlorophosphines in acetic acid leads to the formation of aminomethylphosphonic or aminomethylphosphinic acid, including *N*-alkylated derivatives, in 25–80% yield:[46–48]



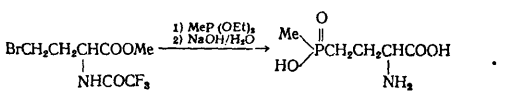
2. The Arbuzov and Michaelis–Becker Reaction

The Arbuzov and Michaelis–Becker reactions have been of fundamental importance for the chemistry of organophosphorus compounds and historically were the first methods of synthesis of aminomethylphosphonic acid—the phosphonic analogue of glycine (Gly^P):[26,49]

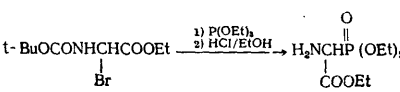


The use of dialkyl phosphonites makes it possible to obtain aminophosphinic acids.[50] The use of the Arbuzov and Michaelis–Becker reactions for the synthesis of β-, γ-, and ω-APA has been described.[49,51–55]

For example, the Arbuzov reaction has been the key stage in the first synthesis of phosphinothricin—a phosphinic analogue of glutamic acid ($Glu^{\gamma-PMe}$):[9]



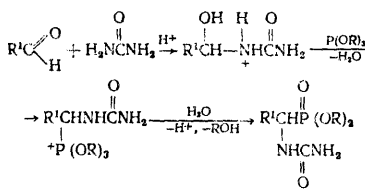
Diethyl α-ethoxycarbonylaminomethylphosphonate—an important intermediate in the synthesis of cephalosporin—has been obtained by the reaction of the ethyl ester α-bromo-*N*-t-butoxycarbonylglycine with triethyl phosphite:[56,57]



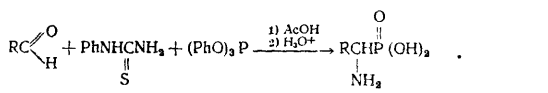
The phosphonic analogues of alanine containing from one to three chlorine atoms[58] or fluorine atoms[59] at the β-carbon atom have been obtained by the Arbuzov reaction.[59] The long duration and relatively severe reaction conditions can be regarded as disadvantages of the Arbuzov reaction as a method of synthesis of APA. In certain cases this method does not yield satisfactory results. Thus the phosphinic analogue of alanine (Ala^{P-Ph}) has been obtained by the Arbuzov reaction in only 5% yield.[50]

The Arbuzov reaction in its classical form is used for the synthesis of α-APA as a rule only in order to obtain aminomethylphosphonic and aminomethylphosphinic acids and their

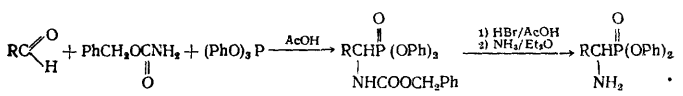
derivatives. On the other hand, the non-classical variants of the Arbuzov reaction, where electrophiles other than alkyl halides are introduced into the reaction with tervalent phosphorus acid esters, have found extremely extensive applications in the synthesis of phosphonic and phosphinic analogues of α-aminocarboxylic acids. Thus it has been found that, on heating with aldehydes and ureas, phosphites and phosphonites give rise to esters of α-ureidophosphonic and the corresponding phosphinic acids. Mono- and di-substituted ureas produce only monophosphonates, while unsubstituted urea gives rise to a mixture of mono- and di-phosphonates. Instead of urea, thiourea may be employed. The reaction is facilitated in the presence of acid catalysts. The following process mechanism has been discussed:[60]



This process is the basis of a series of methods of synthesis of α-APA and their derivatives. Thus, when an aldehyde, *N*-phenylthiourea, and triphenyl phosphite are heated in acetic acid, the diphenyl esters of α-thioureidoalkylphosphonic acid esters are formed and their hydrolysis leads to the free α-aminoalkylphosphonic acids:

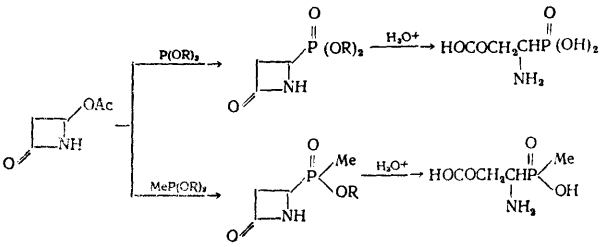


A series of α-APA, including the phosphonic analogues of alanine, valine, phenylalanine,[61] methionine,[62,63] cysteine, and cystine,[64] have been obtained by this method. Instead of *N*-phenylthiourea, unsubstituted thiourea,[61] *N*-(α-phenylethyl)thiourea,[61] and ethyl- or benzyl-carbamates[65] can be used in the reaction. The *N*-benzyloxycarbonyl derivatives of α-APA formed when benzylcarbamate is used are smoothly converted into the diphenyl esters of α-aminophosphonic acids on treatment with hydrogen bromide in glacial acetic acid, which constitutes a convenient method of synthesis of these compounds:[66]

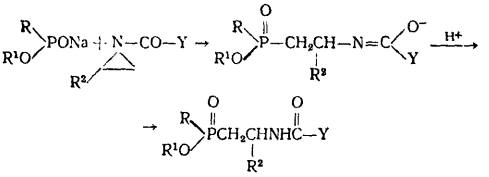


The phosphonic analogues of valine and phenylglycine have been obtained by the hydrolysis of α-ureidoalkylphosphonates, formed on heating a mixture of *N*-phenylurea, triethyl phosphite, and the corresponding aldehyde in toluene in the presence of boron trifluoride etherate.[67] When an *N*-monosubstituted urea, obtained from the optically active α-phenylethylamine, is used in this reaction, asymmetric induction is observed and the optically active α-aminophosphonic acid is formed (but the enantiomeric excess is small).[68]

4-Acetoxyazetidin-2-ones readily react with phosphites and phosphonites to form 2-oxoazetidin-4-ylphosphonates and the corresponding phosphinates; the acid hydrolysis of the resulting compounds affords the phosphonic and phosphinic analogues of aspartic acid (Asp$^{\alpha-P}$ and Asp$^{\alpha-P-Me}$):[69-71]



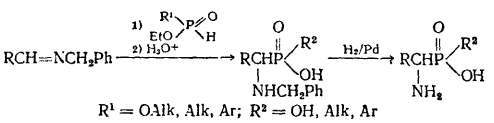
The esters of tervalent phosphorus acids enter into the Arbuzov and Michaelis–Becker reactions with *N*-acyl- or *N*-sulphonyl-aziridines to form derivatives of α-aminoethylphosphonic and the corresponding phosphinic acid:[72-74]



On interaction with phosphites, *N*-(trimethylammoniamethyl)-formamide gives rise to esters of *N*-formylaminomethylphosphonic acid.[75] The reaction of diethyl methylphosphonite proceeds analogously.[15]

3. The Addition of Hydrophosphoryl Compounds to Carbon–Nitrogen and Carbon–Carbon Multiple Bonds

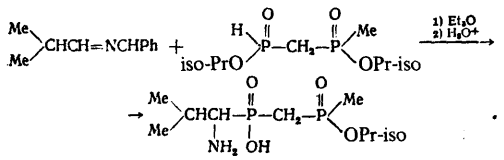
The addition of HPC to the carbon–nitrogen double bond is an important general method for the formation of the P–C–N bond system.[11,13,24] The addition of HPC to Schiff bases, choosing a substituent at the nitrogen atom which can be removed with formation of a free amino-group, is most often employed for the synthesis of α-APA. Many α-aminophosphonic and α-aminophosphinic acids, for example, have been obtained by the addition of acid phosphites and phosphonites to aldimines based on benzylamine, since the *N*-benzyl group is readily removed by hydrogenolysis in the presence of the palladium catalyst:[76,77]



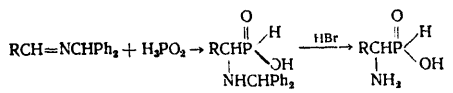
The *N*-α-phenylethyl group is also removed by catalytic hydrogenolysis.[78-80] The addition of dialkyl phosphites to aldimines, obtained from the optically active α-phenylethylamine, is accompanied by appreciable asymmetric induction, which has been used for the asymmetric synthesis of α-aminophosphonic acids.[78,79,81] The highest degree of asymmetric induction (up to 80% optical purity) has been observed in acid catalysis (HCl, AcOH); with increase of temperature, the stereoselectivity of the addition diminishes appreciably. Diethyl phosphite can be replaced in this reaction successfully by tris(trimethylsilyl) phosphite.[80]

Together with dialkyl phosphites, mono-,[82] bis-,[82] and tris-(trimethylsilyl) phosphites[80] also add to Schiff bases. The silyl esters of α-aminophosphonic acids formed are readily hydrolysed under neutral conditions (on heating with water or alcohol) to the free acids, which facilitates the isolation of the latter.

The addition of acid esters of methylenediphosphonic acids to Schiff bases has been described:[83]



Phosphorous acid usually reduces Schiff bases to secondary amines and products of addition to the C=N bonds can be obtained in satisfactory yields only in isolated instances.[84] In contrast to phosphorous acid, hypophosphorous acid adds fairly smoothly to Schiff bases with formation of *N*-substituted α-aminophosphonous acids.[85] Many α-aminophosphonous acids, including the phosphonous analogues of all the most important natural α-aminocarboxylic acids, have been obtained in this way:[86–89]



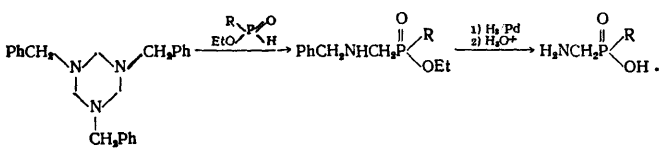
Catalytic hydrogenolysis is unsuitable in this instance for the removal of the protecting group owing to the poisoning of the catalyst by the hydrophosphoryl compound and for this reason azomethines with the *N*-diphenylmethyl substituent, which is readily removed in an acid medium, are employed.

The addition of dialkyl phosphites to azomethines with the acid-removable *N*-diphenylmethyl substituent has been used to synthesise phosphonic analogues of alanine, valine, phenylalanine, and cycloleucine;[90] mono- and di-aminodiphosphonic acids, including the diphosphonic analogues of aspartic and glutamic acids, have been synthesised in this manner.[91]

The application of other *N*-protecting groups, removable by acid hydrolysis, for the synthesis of α-APA has been described, namely the t-butyl,[92] 1-phenylcyclopentyl,[93,94] and αα-disubstituted benzyl[95] groups.

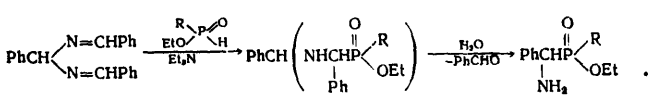
The addition of HPC to azomethines has been used widely in the synthesis of various α-APA, in particular potential bacteriostatic compounds,[96] analogues of morphactins (plant growth regulators),[97–100] phosphorus analogues of penicillamine,[101] and spin-labelled compounds.[102]

Hexahydrotriazines react with acid phosphites and phosphonites to form esters of *N*-substituted α-aminophosphonic and the corresponding phosphinic acids:[15,33,92,103]



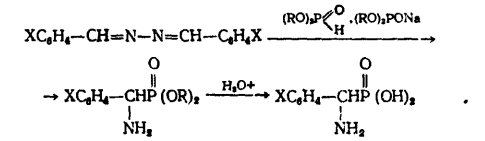
Phosphinic analogues of glycine (Gly^{P-R}) (R = Me or Et)[15] as well as the phosphonic analogue of proline[104] have been obtained by this method. The latter compound has also been synthesised by the addition of diphenyl phosphite to monomeric 1-pyrroline.[77] Aminomethylphosphonous acid (Gly^{P-H}) has been synthesised by adding hypophosphorous acid to 1,3,5-tris(diphenylmethyl)hexahydrotriazine in 10% yield.[88]

Hydrobenzamide combines with two equivalents of dialkyl phosphite or a monoester of phenylphosphonous acid to form phosphorus-containing aminals, the controlled hydrolysis of which affords the esters of α-aminobenzylphosphonic and the corresponding phosphinic acids:[105,106]

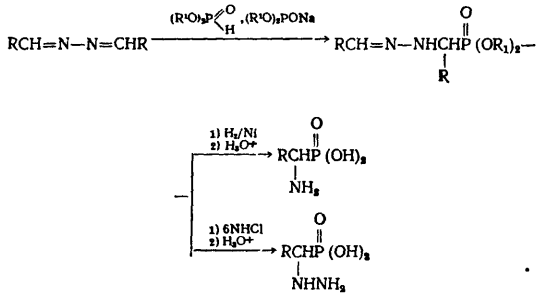


NN'-Dialkylidene-1,2-diaminoalkanes, formed from ammonia and aliphatic aldehydes, behave similarly, which has been used to obtain the esters of certain α-aminophosphonic acids, including the dialkyl esters of the phosphonic analogues of valine.[107]

α-Aminophosphonic acid can be obtained also from aldazines by adding HPC to the C=N bond with subsequent reductive cleavage of the nitrogen–nitrogen bond. Aromatic aldazines combine with two equivalents of dialkyl phosphite and the resulting adducts are reduced with an excess of sodium dialkyl phosphite to esters of α-aminobenzylphosphonic acids:[108–110]



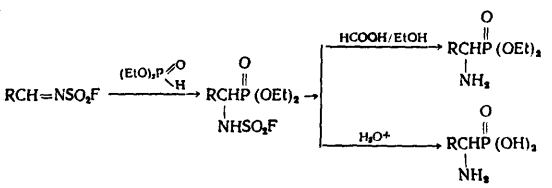
This method has also been used to obtain a series of α-aminobenzylphosphinic acids.[111] Aliphatic aldazines react with dialkyl phosphites to form only monoadducts, from which α-hydrazinophosphonic acids can be obtained by acid hydrolysis[112] or α-aminophosphonic acids can be produced by hydrogenation on Raney nickel:[112,113]



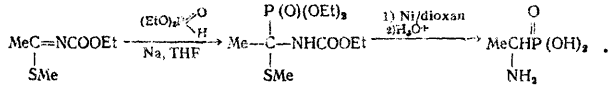
Acid phosphonites interact similarly with aliphatic aldazines, which makes it possible to obtain α-aminophosphinic acids.[114] This method has been used to obtain phosphonic and phosphinic analogues of alanine, valine, and leucine. The phosphonic and phosphinic analogues of cycloleucine have been synthesised analogously by adding one mole of diethyl phosphite or ethyl methylphosphonite respectively to the ketazine based on cyclopentanone.[28]

HPC can also be added to a series of other compounds with a C=N bond, which has been employed to synthesise α-APA. For example, benziminoethyl ether combines with two equivalents of dialkyl phosphite to form the ester of the N-phosphorylated α-aminobenzylphosphonic acid.[115] It has been suggested that iminoesters are intermediates in the reaction of orthoformate, a primary amine, and a dialkyl phosphite (or a monoalkyl phosphonite), which results in the formation of aminomethylenebis(phosphonates) or aminomethylenebis(phosphinates).[15,116]

Dialkyl phosphites add to *N*-acylimines to form the esters of *N*-acylated α-aminophosphonic acids.[117,118] Hydrolysis of these compounds leads to α-aminophosphonic acids; it is sometimes possible to remove selectively the *N*-acyl group with formation of esters of α-aminophosphonic acid:[119]

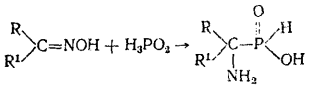


N-Acyliminothioesters are capable of reacting with dialkyl phosphites analogously to *N*-acylimines. The reductive elimination of alkylthio-groups from the adducts and subsequent hydrolysis lead to α-aminophosphonic acids:[120]



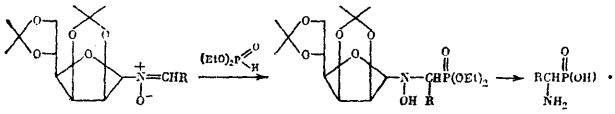
This method has been used to synthesise the enantiomers of the phosphonic analogue of phenylalanine.[121]

Under the conditions of alkaline catalysis, oximes combine with two equivalents of dialkyl phosphite to form *N*-phosphorylated α-aminophosphonates as a result of the postulated aminophosphonate–amidophosphate [phosphoramidate?] rearrangement.[122] The addition of hypophosphorous acid to oximes, which leads to the formation of α-aminophosphonous acids, is of considerable interest. The phosphonous analogues of alanine, valine, and glutamic acid ($Glu^{\alpha-P-H}$) have been obtained by this method:[123]



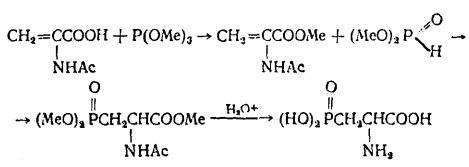
The mechanism of this reaction has not been elucidated.

The addition of dialkyl phosphites to *N*-glycosylnitrones has been used for the asymmetric synthesis of dextrorotatory phosphonic analogues of serine, valine, and alanine:[124]

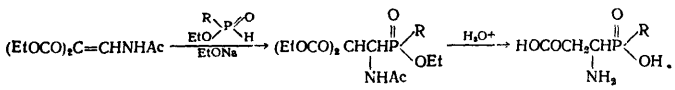


Dialkyl phosphites[125] and phosphorous acid[126,127] add to nitriles with formation of aminomethylenediphosphonic acids or their esters. Under the conditions of base catalysis, dialkyl phosphites react with arylisonitriles to form *N*-arylaminomethylenediphosphonates.[128]

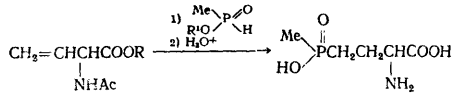
The ability of HPC to undergo Michael addition to activated carbon–carbon double bonds has also been used to synthesise α-, β-, and γ-APA. The phosphonic analogue of aspartic acid $Asp^{\beta-P}$, where the β-carboxy-group has been replaced by the phosphono-group, has been obtained by the interaction of α-acetamidoacrylic acid with phosphite:[129]



The addition of esters of methyl- and ethyl-phosphonous acids to α-acetamidoacrylic acid proceeds with formation of the corresponding phosphonic analogue of aspartic acid ($Asp^{\beta-P-Me}$ and $Asp^{\beta-P-Et}$).[130] The phosphonic and phosphinic analogues of aspartic acids, in which the phosphono- or phosphino-group replaces the α-carboxy-group, have been obtained by the addition of dialkyl phosphites or acid phosphonites to acetamidomethylenemalonate with subsequent hydrolysis and decarboxylation of the adducts:[130,131]

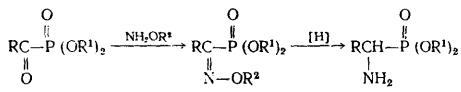


The esterification of the carboxy-groups in these compounds with subsequent ammonolysis leads to the formation of the phosphonic and phosphinic analogues of asparagine.[130,131] The phosphonic and phosphinic analogues of α-methylaspartic acid have been obtained by adding the corresponding HPC to β-aminocrotonate.[29] The same approach has been used to obtain the phosphinic analogue of glutamic acid—phosphinothricin ($Glu^{\gamma-P-Me}$):[15]



4. Amination of α-Oxophosphonates (The Oxime Method)

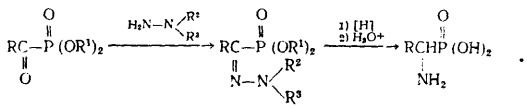
A number of methods of synthesis of α-aminophosphonic and α-aminophosphinic acids are based on the use of α-oxoalkylphosphonates and the corresponding phosphinates, which are converted into oximes and then reduced (the oxime method):



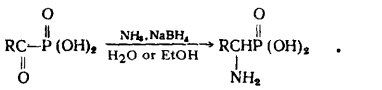
The oxime group can be reduced by a wide variety of reductants. Thus α-aminobenzylphosphonic acid and its derivatives[132] and also the phosphonic analogue of dihydroxyphenylalanine (DOPA) [133] have been obtained by the reduction of the corresponding oximes with aluminium amalgam. Diborane has also been used as the reductant;[134] the phosphonic analogues of alanine, valine, leucine, and isoleucine have been obtained in this way. The oximes can be reduced by hydrogenation on Raney nickel,[135,136] which has been used in the synthesis of the phosphonic analogues of tryptophan.[136]

In the reduction of oximes with zinc in formic acid, the amino-group formed is partly formylated; to achieve deformylation, the reaction mixture is treated with hydrogen chloride in methanol.[137] The esters of phosphonic analogues of alanine, valine, leucine, phenylalanine, glutamic acid, and methionine,[137] as well as the phosphonic analogue of cysteine[138] have been synthesised by this procedure. The reduction of oximes with zinc in formic acid has also been employed for the synthesis of α-aminophosphonic acids.[42]

α-Oxophosphonates can be converted into hydrazones, whose reduction with aluminium amalgam[139] or zinc in a mixture of acetic and trifluoroacetic acids[140] as well as catalytic hydrogenation[139,140] lead to α-aminophosphonates:



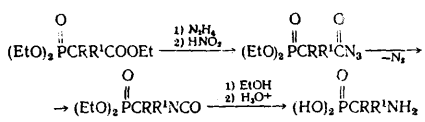
The single-stage method for the direct conversion of α-oxophosphonic acids into α-aminophosphonic acids on treatment with ammonia and sodium tetrahydroborate[141] is undoubtedly attractive:



The phosphonic analogues of alanine, valine, leucine, phenylalanine, and glutamic acid ($Glu^{\alpha-P}$) have been obtained in this way. Instead of ammonia, primary amines can be used in the reaction. It is of interest that the mono- and di-esters of α-oxophosphonic acids do not enter into this reaction. The use of NaB^3H_4 makes it possible to obtain tritium-labelled α-aminophosphonic acids.[142]

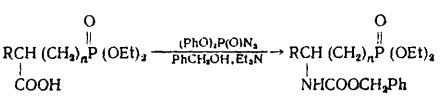
5. Synthesis of Aminophosphonic Acids using the Curtius and Hofmann Rearrangements

One of the most frequently employed methods of synthesis of α-APA is that from the esters of α-phosphonocarboxylic acids, whose key stage is the Curtius rearrangement of the corresponding phosphonocarboxylic acid azides. The general scheme of this multistage synthesis, which is usually carried out as a "single flask" process, i.e. without the isolation of intermediates, is presented below:[129,143]



The phosphonic analogues of glycine, alanine, phenylalanine, valine, α-methylalanine, tyrosine, lysine, ornithine, etc. have been obtained by this procedure.[129,143–145] The method has also been used to synthesise α-aminoethylphosphonic acid (ciliatine) and γ-aminopropylphosphonic acid (the phosphine analogue of γ-aminobutyric acid [146]). The broad limits of its applicability, in particular the possibility of synthesising α-, β-, γ-, and ω-APA as well as αω-diaminophosphonic acids must be regarded as advantages of the methods. Its disadvantage is its multistage nature, which is frequently the reason for the moderate overall yields of the aminophosphonic acids.

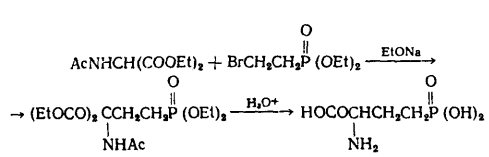
If the rearrangement of the phosphonocarboxylic acid azides is carried out in the presence of alcohols, it is possible to isolate the corresponding carbamates derived from the aminophosphonic acids, which has been used to synthesise *N*-benzyloxycarbonyl derivatives of α- and β-aminophosphonates:[147]



The Hofmann degradation of phosphonocarboxylic acid amides can also be used to synthesise aminophosphonic acids. This method has been used successfully to obtain β-aminoethylphosphonic acid[148] and its derivatives.[149,150] On the other hand, there are contradictory literature data concerning the possibility of using the Hofmann degradation for the synthesis of α-aminophosphonic acids. The successful preparation by this method of a series of α-aminophosphonic acids, including the phosphonic analogues of α-alanine, has been reported.[151] However, it has been shown that, depending on the structure, the phosphonoacetamides $(EtO_2)P(O)CHRC(O).NH_2$ either undergo the Hofmann rearrangement with formation of α-APA (for R = Et or Ph) or are brominated at the α-carbon atom (for R = Me or $PhCH_2$). The phosphonic analogue of α-alanine could not be obtained by this method.[152]

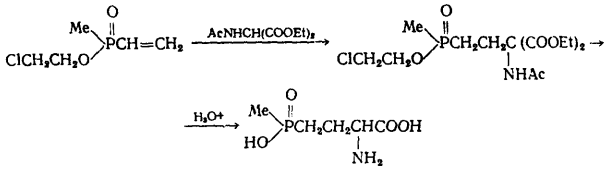
6. Syntheses Using Acetamidomalonic Ester and Vinylphosphonates or Vinylphosphinates

In one of the first specific syntheses of phosphonic analogues of natural aminoacids, the alkylation of acetamidomalonic ester with β-bromoethylphosphonate was used to obtain the analogue of glutamic acid ($Glu^{\gamma-P}$):[153]

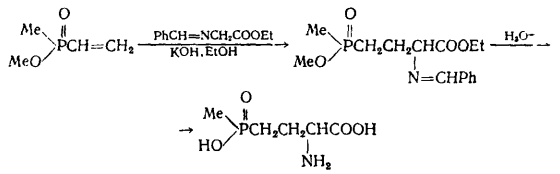


The introduction of β-bromoethylphosphonates into this reaction entailed the formation of phosphinic analogues of glutamic acid ($Glu^{\gamma-P-R}$, R = Me, Et, or Ph).[154,155]

Aminophosphonic and aminophosphinic acids can probably be obtained from the acetamidomalonic ester also via the mechanism involving addition to the corresponding vinyl compounds of phosphorus, as has been achieved in the synthesis of phosphinothricin ($Glu^{\gamma-P-Me}$):[156]

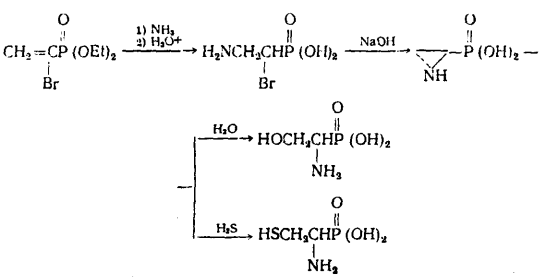


The same method has been used to obtain phosphinic analogues of glutamic acids containing various substituents at the phosphorus atom, including functional groups [$Glu^{\gamma-P-R}$, where R = CH_2COOMe, CH_2COOH, $CH_2CH_2CH(NH_2)COOH$, $CH_2C_6H_4Br$-p, or $PhCH_2$].[115] Certain Schiff bases also undergo Michael addition to methylvinylphosphinate, which has been used successfully to synthesise phosphinothricin:[157]



The addition of chiral Schiff bases to vinylphosphonates and vinylphosphinates has been used for the asymmetric synthesis of α-amino-γ-phosphonobutyric acid [(+)-$Glu^{\gamma-P}$] and (+)-phosphinothricin [(+)-$Glu^{\gamma-P-Me}$], as well as their (−)-enantiomers.[158]

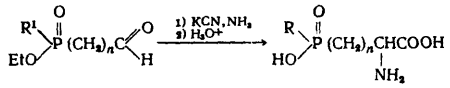
Ammonia adds to α-bromovinylphosphonate with formation of β-amino-α-bromoethylphosphonic acid, which cyclises in an alkaline medium to aziridinylphosphonic acid. The opening of the aziridine ring in this acid by treatment with water or hydrogen sulphide leads to the formation of the phosphonic analogues of serine[159,160] and cysteine[138] respectively:



7. Other Methods of Synthesis of Aminophosphonic, Aminophosphinic, and Aminophosphonous Acids

The traditional methodology for the synthesis of aminocarboxylic acids has also been applied to the synthesis of APA. For example, the phosphonic and phosphinic analogues of aspartic and glutamic acids ($Asp^{\beta-P}$ and $Glu^{\gamma-P}$) have been

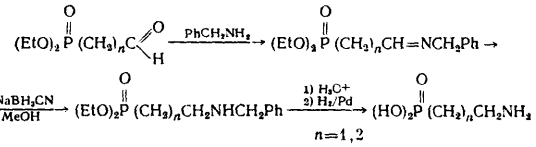
synthesised from β- and γ-oxophosphonates and the corresponding phosphinates using the Strecker reaction:[161,162]



R = OH, Me, Et; $n = 1, 2$

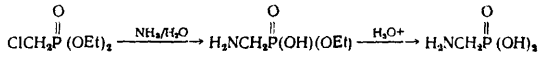
The phosphonic and phosphinic analogues of α-methylaspartic and α-methylglutamic acids can be obtained in the same way.[29] The use of (-)-α-phenylethylamine in the Strecker synthesis makes it possible to obtain phosphonic analogues of aspartic and glutamic acids enriched in the (+)-enantiomers.[163]

β- and γ-Aminophosphonic acids have been synthesised by condensing benzylamines with β- and γ-oxophosphonates with subsequent reduction of the resulting azomethines with sodium cyanohydroborate and the removal of the P-ester and N-benzyl groups by acid hydrolysis and hydrogenation over a palladium catalyst respectively:[164]

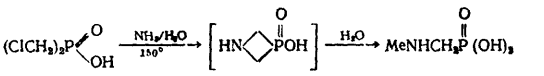


$n = 1, 2$

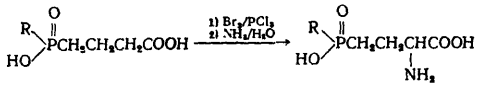
α-Aminophosphonic acids can also be synthesised by the direct substitution of the halogen atoms in α-halogenoalkylphosphonic acids or their derivatives by the amino-group. However, this method is not used frequently, possibly because the substitution by the amino-group in chloromethylphosphonate on treatment with ammonia proceeds under extremely severe conditions and aminomethylphosphonic acid is formed in a moderate yield (20–48%):[165,166]



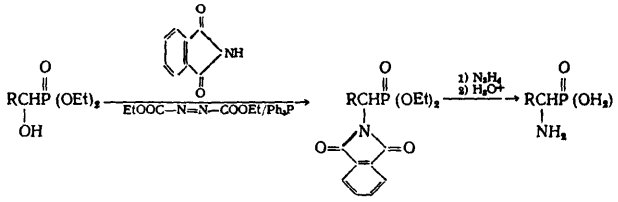
Aminomethylphosphonous acid has been obtained analogously by the reaction of chloromethylphosphonous acid with ammonia.[167] The interaction of ammonia and amines with di(chloromethyl)phosphinic acid has been investigated in a number of studies.[168–171] The products of the reaction of this acid with aqueous ammonia proved to be *N*-methylaminomethylphosphonic acid, which has been explained by the initial formation of the azaphosphetidine oxide ring, which is cleaved by water at the P–C bond:[168]



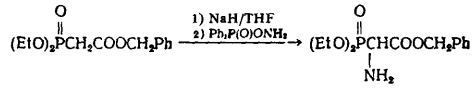
On reaction with di(chloromethyl)phosphinic acid, benzylamine gives rise to di(benzylaminomethyl)phosphinic acid, the catalytic hydrogenolysis of which affords di(aminomethyl)phosphinic acid.[168] The substitution of a halogen atom by the amino-group has been used in the synthesis of phosphonic and phosphinic analogues of glutamic acid ($Glu^{\gamma-P}$ and $Glu^{\gamma-P-Me}$):[172]



α-Aminoalkylphosphonic acids can be obtained from the readily available α-hydroxyphosphonic acids, which are formed from carbonyl compounds and HPC. The substitution of the hydroxy-group by the amino-group is achieved by means of the Mitsunobu reaction between the α-hydroxyphosphonate and phthalimide in the presence of triphenylphosphine and diethyl azodicarboxylate and subsequent removal of the phthalimide group by the standard treatment with hydrazine:[173]

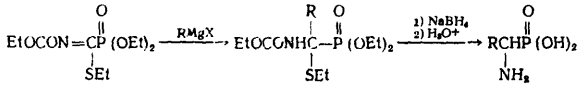


The amino-group can be introduced directly into the α-position in the molecules of phosphonoacetates, which produce stabilised carbanions, by treatment with reagents such as *O*-(mesitylenesulphonyl)hydroxylamine [174] and *O*-(diphenylphosphinoyl)hydroxylamine.[175] The α-aminophosphonoacetates formed are important intermediates in the synthesis of cephalosporins:

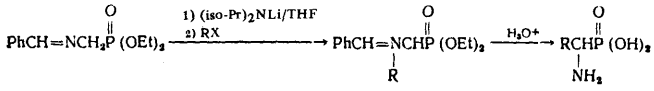


Treatment with trifluoromethanesulphonyl azide results in the introduction in the α-position of phosphonoacetates of the azido-group, whose reduction by catalytic hydrogenation affords α-aminophosphonoacetates.[176]

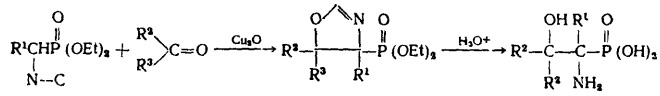
Approaches based on the modification of the P–C–N bond system already formed can also be used in the synthesis of α-aminophosphonic acids. Thus the reaction of a Grignard reagent with α-(*N*-ethoxycarbonylimino)-α-(ethylthio)methylphosphonate leads to the formation of an adduct, which is converted into an α-aminoalkylphosphonic acid after the reductive elimination of the ethylthio-group and hydrolysis.[177] The phosphonic analogues of alanine, valine, and phenylalanine have been synthesised in this way:



The aldimine obtained from aminomethylphosphonate can be alkylated by halogenoalkanes; the hydrolysis of the resulting compounds leads to the α-aminophosphonic acids Ala^{P}, Phe^{P}, and $As\text{-}^{\alpha-P}$:[178]

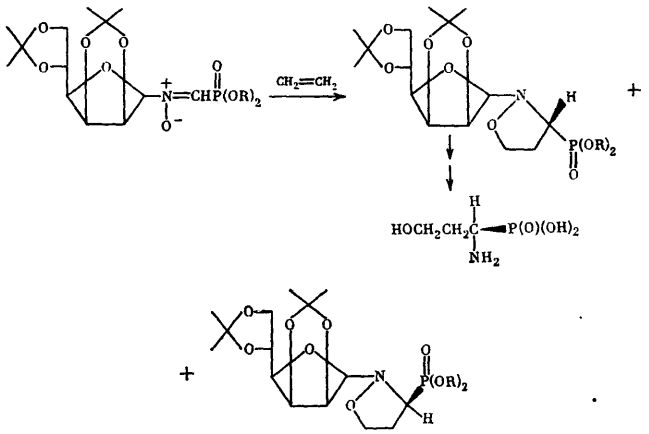


The oxazoline method of synthesis of α-aminoacids has been applied to the synthesis of the phosphonic analogues of derivatives of serine, the oxazolinylphosphonates necessary for this purpose being formed as a result of the addition of carbonyl compounds to isocyanomethylphosphonates:[179]

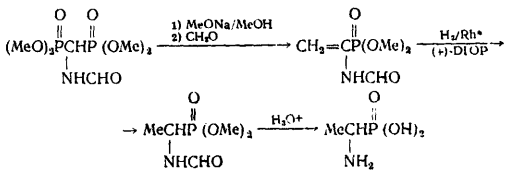


The cycloaddition of ethylene to *C*-dialkoxy-*N*-glycosylphosphonoylnitrones, which proceeds with appreciable stereoselectivity, has been used to synthesise laevorotatory phosphonic analogues of homoserine, aspartic acid, and

asparagine:[180]



α-(*N*-Formylamino)vinylphosphonate, obtained by the Horner–Wittig reaction from *N*-formylaminomethylenediphosphonate and paraformaldehyde, gives rise to α-(*N*-formylamino)ethylphosphonate as a result of hydrogenation on a complex rhodium catalyst (Rh*) in the presence of the chiral ligand (+)-2,3-dihydroxy-2,3-*O*-isopropylidene-1,4-bis-(diphenylphosphino)butane (DIOP). Hydrolysis of the product leads to the optically active (-)-α-aminoethylphosphonic acid (with an enantiomeric excess of 76%):[181]

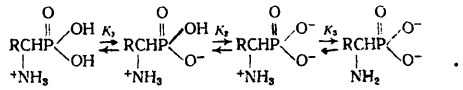


Many aminophosphonic acids have been obtained by modifying particular functional groups present in the phosphonates. For example, the phosphonic analogue of arginine has been obtained from the phosphonic analogue of ornithine by converting the δ-amino-group into the guanidino-group.[182] Derivatives of β-aminoethylphosphonic acid have been obtained by reducing the nitro-group in β-nitroethylphosphonates[183,184] and the nitrile group in phosphonoacetonitriles.[185] Catalytic hydrogenation of α-hydroxy-β-nitroethylphosphonates has been used to obtain derivatives of β-amino-α-hydroxyethylphosphonic acid.[186,187] This acid is also formed on ammonolysis of oxiranylphosphonates.[188]

As can be seen from the foregoing, there is at present a fairly wide set of methods of synthesis of APA based both on the specific properties of individual phosphorus-containing reagents and on the application of the "standard" methodology for the synthesis of aminocarboxylic acids. Phosphorus analogues of many natural α-aminocarboxylic acids have been obtained by these methods. However, one should note that α-APA containing additional functional groups (analogues of serine, threonine, lysine, etc.) are still difficult to obtain and the phosphorus analogues of certain important natural aminoacids have not been described hitherto. The problem of the asymmetric synthesis of α-APA also remains urgent and requires new solutions.

III. THE PROPERTIES OF AMINOPHOSPHONIC, AMINOPHOSPHINIC, AND AMINOPHOSPHONOUS ACIDS

Aminophosphonic, aminophosphinic, and aminophosphonous acids are white high-melting crystalline substances, soluble in water and sparingly soluble in ethanol and other organic solvents. On recrystallisation from aqueous solvents, some of them are isolated as hydrates.[51,189] The potentiometric titration curves for aminophosphonic acids have three breaks corresponding to the three ionisation constants of these compounds:[129,190]



The ionisation constants and isoelectric points of valine and its phosphonic and phosphonous analogues are presented in Table 1.

Table 1. The ionisation constants and isoelectric points of valine and its phosphorus analogues.[88]

Acid	pK_1	pK_2	pK_3	pI
$Me_2CHCH(NH_2)COOH$	2.28	9.36	—	5.82
$Me_2CHCH(NH_2)P(O)(OH)_2$	1.23	5.68	10.46	3.46
$Me_2CHCH(NH_2)P(O)(H)OH$	1.19	7.79	—	4.49

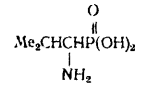
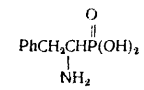
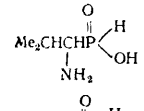
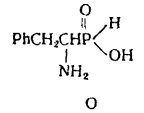
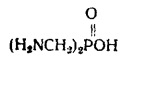
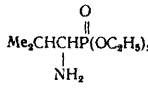
The ionisation constants of α-aminophosphonic acids in water[143,190] indicate the greater acidity of the phosphonic acid group in these compounds compared with the corresponding phosphonic acids themselves,[191] which is due to the influence of the amino-group. As was to be expected, aminophosphonic, aminophosphinic, and aminophosphonous acids have a zwitter-ionic structure, which has been confirmed by the NMR study of their aqueous solutions[88,192] and an X-ray diffraction study of crystalline specimens.[189]

Like aminocarboxylic acids, α-aminophosphonic acids are able to form complexes with many metal cations, in particular with Ni^{2+} and Cu^{2+}.[193] In their chelating capacity, α-aminophosphonic acids are close to aminocarboxylic acids and, with increase of the number of phosphono-groups in the molecule, the complex-forming capacity also increases, polyaminopolyalkylphosphonic acids being effective complexones.[194,195] Aminomethylphosphonic acid reacts with the Co^{2+} ion to form the compound $[Co(H_2NCH_2PO_3H_2)_2.2H_2O]H_2O$, which crystallises in the monoclinic system and is a coordination polymer produced as a result of the formation of -O–P–O bridge bonds between the cobalt atoms.[196]

The IR spectra of the APA and their esters have characteristic absorption bands due to the P=O (1150–1250 cm^{-1}), P–O–C (1040–1060, 1165 cm^{-1}), and P–O^- (1000–1100 cm^{-1}) groups.[88,197] The IR spectra of aminophosphonous acids also contain the absorption band due to the P–H group (2300 to 2400 cm^{-1}).[88] The amino-group in free APA is protonated, as a result of which the IR spectrum exhibits broad absorption bands due to the $^+NH_3$ group (2000–3200 cm^{-1}, 1560 to 1600 cm^{-1}), which usually overlap in the region of approximately 3000 cm^{-1} with the absorption due to the stretching vibrations of the C–H and O–H bonds.[37,198] The IR spectra of APA esters show absorption bands due to the NH_2 group (3280–3380 cm^{-1}, 1500–1620 cm^{-1}).[66]

The ^{31}P NMR chemical shifts for certain APA and their esters are presented in Table 2. The table shows that these chemical shifts depend on the pH of the medium, which can be explained by the formation of protonated forms of these compounds in an acid medium and the deprotonated forms in an alkaline medium.[33,88,168,199]

Table 2. The chemical shifts and spin–spin coupling constants for the ^{31}P NMR spectra of certain aminophosphonic, aminophosphinic, and aminophosphonous acids.

Compound	$\delta(^{31}P)$*, p.p.m. (solvent)	Refs.
	+21.0 (2N KOH) +16.36 (85% H_3PO_4)	[61] [134]
	+21.2 (2N KOH)	[177]
	+18.6, J_{P-H} 540 Hz (D_2O) +31.2, J_{P-H} 501 Hz (NaOD)	[88] [88]
	+19.2, J_{P-H} 543 Hz (D_2O) +31.7, J_{P-H} 513 Hz (NaOD) +24.8, J_{P-H} 574 Hz (DCl)	[88] [88] [88]
	+29.77 (D_2O) +40.6 (NaOH) +20.36 (HCl)	[168] [168] [168]
	+28.36 (CH_2Cl_2) +19.7 (AcOH)	[140] [140]

*δ > 0 when the signal is in a low field relative to the external standard—85% H_3PO_4.

α-Aminophosphonic, α-aminophosphinic, and α-aminophosphonous acids contain a chiral centre—the α-carbon atom—and exist in the form of two enantiomers. Almost all the methods of synthesis examined above lead to racemic mixtures with the exception of the instances of asymmetric synthesis where one of the enantiomers predominates in the product.[68,78–81,124,158,163,180,181] In order to obtain optically active α-APA, mixtures of diastereoisomers, formed on treatment of the racemate with an optically reactive reagent, are separated by repeated recrystallisation. The reagent of this kind most often employed is dibenzoyl-L-(+)-tartaric acid, which forms mixtures of diastereoisomeric salts on reaction with esters of α-aminophosphonic and the corresponding phosphinic acids. The (-)-diethyl ester of α-aminobenzylphosphonic acid with an optical purity in excess of 97%,[106,200] the (+)- and (-)-diethyl esters of the phosphonic analogue of phenylalanine, formed on hydrolysis of the enantiomeric Phe^P,[189] other optically active α-aminophosphonates,[25,201] and also the (+)-ethyl ester of α-aminobenzylphenylphosphinic acid[202] have been obtained in this way. On reaction with the diphenyl esters of α-aminophosphonic acids, the anhydride of dibenzoyl-L-(+)-tartaric acid gives rise to mixtures of diastereoisomeric amides (or imides), which afford optically active α-aminophosphonic acids after separation and hydrolysis. The enantiomers of the phosphonic analogues of alanine, valine, leucine, phenylalanine, phenylglycine,[203,204] and serine[41] have been synthesised by this procedure. The monoalkyl esters of *N*-acylated α-aminobenzylphosphonic acid have been separated into their enantiomers via the diastereoisomeric salts with *R*-(+)- and *S*-(-)-α-phenylethylamines [205] and (-)-ephedrine.[206] The (+)- and (-)-α-phenylethylamines have also been used to obtain optically active α-aminophosphonous acids.[88]

The acylation of the amino-group in racemic α-aminophosphonates by derivatives of optically active α-aminocarboxylic acids gives rise to diastereoisomeric phosphonodipeptides, which can be separated by chromatography on ion-exchange resins[200,207] or silica gel;[208] a method based on the separation by column chromatography for unprotected or fully protected phosphonodipeptides with subsequent acid hydrolysis of the resulting diastereoisomers has been proposed for the synthesis of optically active α-aminophosphonic acids.[203] The possibility of the enzymic separation of *N*-acyl derivatives of α-aminophosphonic acids has also been reported.[209]

The absolute configuration of certain optically active α-aminophosphonic acids has been determined by X-ray diffraction. The *S*-configuration of the chiral centre has been observed for (-)-Val^P and (-)-α-aminobenzylphosphonic acid;[78,79] (+)-Phe^P also has the *S*-configuration and the bond lengths and angles do not differ significantly from the usual values and are close to the analogous parameters of phenylalanine derivatives;[189] (+)-Ala^P likewise has the *S*-configuration.[210]

Comparative analysis of the NMR data and of the specific rotations of the glycosidic precursors made it possible to attribute the *R*-configuration to the laevorotatory enantiomers of the phosphonic analogues of homoserine, asparagine, and aspartic acid [(-)-$Asp^{\alpha-P}$].[180] From the chromatographic behaviour of diastereoisomeric phosphonodipeptides containing the *N*-terminal L-Phe residue and the P-terminal Leu^P, Met^P, and Phe^P residues, the *R*-configuration was also attributed to the laevorotatory enantiomers of these α-aminophosphonic acids.[208] The absolute configurations of a series of optically active α-aminophosphonic acids, namely *S*-(+)-Ser^P, *S*-(+)-aziridinylphosphonic acid, *S*-(+)-α-amino-β-chloroethylphosphonic acid, R-(-)-Phe^P, and R-(-)-Tyr^P, have been established by means of chemical correlation with α-aminophosphonic acids having known configurations.[201] The laevorotatory enantiomer of the phosphonous analogue of alanine has the *R*-configuration, because it is oxidised to R-(-)-Ala^P.[88]

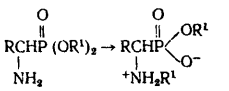
The asymmetric esters of α-aminophosphonic acids contain two asymmetric centres, C_α and P, and exist in the form of diastereoisomers which are clearly distinguishable by the NMR spectra.[206,211,212] Mixtures of diastereoisomers are formed similarly in the case of α-aminophosphinic acid esters. It has been established by X-ray diffraction that the asymmetric centres of the (+)-isomer of ethyl α-aminobenzylphenylphosphinate have the absolute *R*(C_α), *S*(P)-configuration.[202]

1. Reactions of the Amino-group in Aminophosphonic, Aminophosphinic, and Aminophosphonous Acids

α-Aminophosphonic acids are protonated at the amino-group in acid media, but it is not possible to isolate the salts, in particular the hydrochlorides, in a pure state, since the ratio α-APA/HCl is greater than unity.[146] After prolonged heating of the hydrochlorides of aminophosphonic acids, hydrogen chloride is fully eliminated with formation of free aminophosphonic acids, which can be accounted for by the appreciable

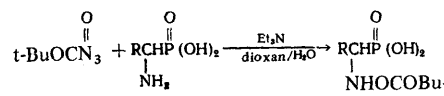
acidity of the phosphono-group.[18,129] α-Aminophosphonic acid esters form hydrochlorides,[103,197] picrates,[197] and acid oxalates[136,137,175] with characteristic melting points, which are used for their isolation, purification, and identification. Racemic α-aminophosphonates and the corresponding phosphinates react with optically active acids to form diastereoisomeric salts, which are used for their resolution into enantiomers.[25,106,189,200,201]

α-Aminophosphonic acids and their esters are alkylated at the amino-group on treatment with methyl iodide or dimethyl sulphate; exhaustive alkylation of α-APA leads to the formation of "phosphonobetaines".[213–215] The full esters of α-aminophosphonic acids are gradually converted into the monoesters even at room temperature:



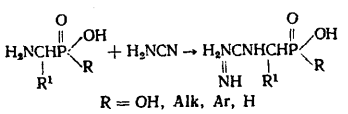
The rate of this process depends on the nature of the group R^1 and diminishes in the sequence Me > Et > n-Pr > iso-Pr.[107] The *N*-arylation of α-aminophosphonic acids by 1-nitro-9-phenoxyacridine has been described.[216]

On interaction with an excess of acetic anhydride, α-aminophosphonic acid esters give rise to *N*-acetyl derivatives, while their reaction with benzoyl chloride or tosyl chloride in the presence of pyridine affords *N*-benzoyl and *N*-tosyl derivatives respectively.[217,218] *N*-Benzyloxycarbonyl derivatives of α-aminophosphonic acid esters have been obtained by the Schotten–Baumann acylation,[219] by reaction with *N*-(*O*-benzyloxycarbonyl) hydroxysuccinimide,[206] and by acylation with benzyloxycarbonyl chloride in chloroform in the presence of triethylamine.[220,221] On heating with acetic anhydride, the free α-aminophosphonic acids produce *N*-acetyl derivatives;[115,217] *N*-chloroacetyl,[215] *N*-benzoyl,[129,143,217] *N*-tosyl,[222] and *N*-benzyloxycarbonyl derivatives[222–224] of α-APA have been obtained by the Schotten–Baumann acylation with the corresponding acid chlorides in aqueous alkaline media. α-Aminophosphonic acids are formylated by 100% formic acid in acetic anhydride and are converted into *N*-trifluoroacetyl derivatives on interaction with trifluoroacetic acid anhydride.[141] On fusion with phthalic anhydride, *N*-phthaloyl derivatives of α-aminophosphonic acids are formed.[215,222] The interaction of α-aminophosphonic acids with t-butoxycarbonyl azide in aqueous dioxan in the presence of triethylamine leads to the formation of *N*-t-butoxycarbonyl derivatives:[225]

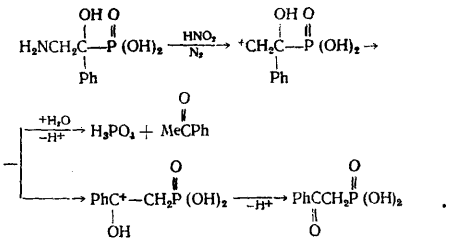


The amino-group in α-aminophosphonic acids[226] and their esters[227] condenses with aldehydes to form the corresponding aldimines.

On interaction with cyanamide, α-aminophosphonic, α-aminophosphinic and α-aminophosphonous acids give rise to α-guanidinophosphonic,[228] α-guanidinophosphinic,[229] and α-guanidinophosphonous[228] acids:



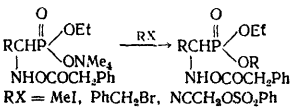
α-Guanidinophosphonic acids have also been synthesised by the reaction of α-aminophosphonic acids with *S*-ethylisothiourea.[230] α-Aminoalkylphosphonates can be oxidised to the corresponding α-nitroalkylphosphonates.[231] The diazotisation of aminophosphonic and aminophosphinic acids leads to the formation of carbonium ions, which fragment or rearrange depending on their structure:[51,198,232]



Like aminocarboxylic acids, α-APA produce a characteristic purple-violet colour on interaction with ninhydrin, which is used for their detection.[15,88,129,233]

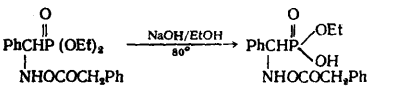
2. Reactions of the Phosphorus-containing Fragments of Aminophosphonic, Aminophosphinic, and Aminophosphonous Acids

The di- and mono-esters of α-aminophosphinic acids can be obtained by the esterification of the phosphono-group in *N*-protected α-aminophosphonic acids. The dimethyl esters are formed when *N*-acylated *N*-aminophosphonic acids are treated with diazomethane.[222,225] The interaction of diazomethane with the monoesters of *N*-acylaminophosphonic acids affords asymmetric esters.[205,211,222,234,235] Diazoethane[205] and diphenyldiazomethane[236,237] interact with *N*-acylated α-aminophosphonic acids and their monoesters like diazomethane. In the presence of [tritiated? (Ed.of Translation)] ultra-heavy water, diazoethane esterifies the monoethyl esters of *N*-benzyloxycarbonylaminophosphonic acids with formation of tritium-labelled diethyl esters.[238] Ethyl orthoformate is used to introduce the ethyl group in the synthesis of diethyl and asymmetric alkyl ethyl esters.[206,211,224,234] Asymmetric ethyl methyl, benzyl ethyl, and cyanomethyl ethyl esters have been obtained by the reaction of the tetramethylammonium salts of the monoethyl esters of *N*-acylated α-aminophosphonic acids with corresponding alkylating agents:[239]



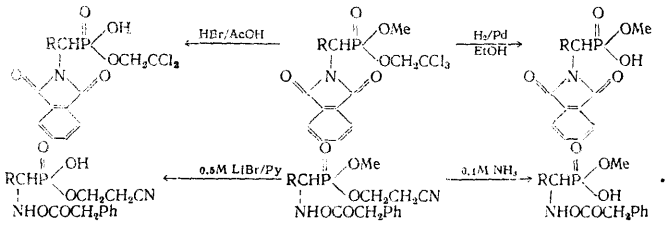
N-Acylated α-aminophosphonic acids give rise to monoesters on esterification with hydroxy-compounds in the presence of pyridine in trichloroacetonitrile[211,234,235,240,241] and on condensation with alcohols in the presence of dicyclohexylcarbodiimide (DCC).[141,242]

Another approach to the synthesis of the monoesters of α-aminophosphonic acids involves the partial hydrolysis of the diesters. When the diethyl ester of the phosphono-analogue of phenylalanine was heated with 80% acetic acid, the monoethyl ester was obtained in 10% yield.[141] The alkaline hydrolysis of *N*-acylated dialkyl aminophosphonates proceeds more successfully:[221,243]



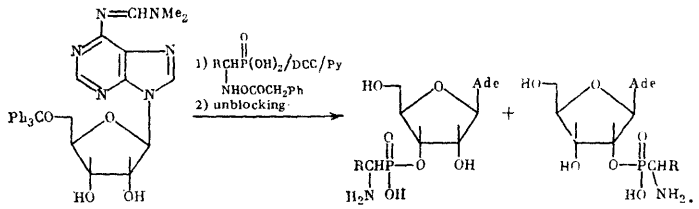
In many instances, the monoesters of *N*-acylated α-aminophosphonic acids can be obtained by the non-hydrolytic cleavage of the diesters by treating the latter with reagents such as boron tribromide in methylene chloride, lithium

bromide in pyridine, sodium thiophenoxide in ethanol, or a 45% solution of HBr in glacial acetic acid.[244] The monoesters of *N*-acylated α-aminophosphonic acid are also formed when the ester groups in asymmetric diesters are removed selectively:[206,211,234,235]



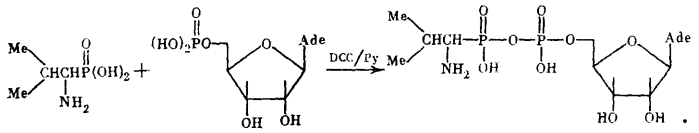
The monoethyl ester of the phosphonic analogue of valine has been obtained by heating the hydrochloride of its diethyl ester.[141] The monoethyl ester of *N*-phthaloylaminomethylphosphonic acid is formed on hydrolysis of the corresponding chlorophosphonate obtained on treatment of the diethyl ester with phorphorus pentachloride.[243]

α-Aminophosphonic acids have been made to react with nucleosides and nucleotides. The *N*-benzyloxycarbonyl derivatives of Ala^P and Phe^P (in the form of pyridinium salts) condense with the free 2'- or 3'-hydroxy-groups of *N*-dimethylaminomethylene-5'-*O*-trityladenosine in the presence of DCC. After the removel of the protecting groups and chromatographic purification on DEAE-cellulose, adenosine derivatives phosphorylated in the 2'- and 3'-position by the corresponding α-aminophosphonic acids were obtained in 20–38% yield:[245]



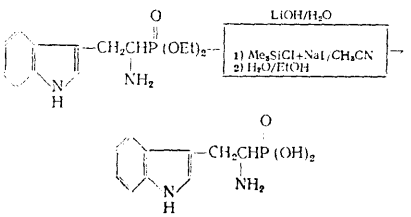
R = Me, $PhCH_2$; Ade = 9-adeninyl.

N-Benzyloxycarbonyl-Ala^P interacts with 2',3'-*O*-isopropylideneuridine or the corresponding adenosine derivative in the presence of mesitylenesulphonyltriazole as the condensing agent with formation of the corresponding 5'-*O*-(α-aminoethylphosphonoyl) ribonucleosides in 40–50% yield.[246] When 2,4,6-triisopropylbenzenesulphonyl chloride is used as the condensing agent, the yield of the phosphorylated ribonucleosides is low; only traces of the target product are formed in the presence of DCC.[246] Val^P condenses with adenosine monophosphate (AMP) in the presence of DCC to form a mixed anhydride (in 20% yield):[142]



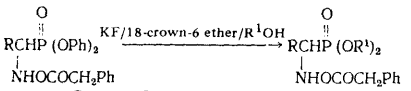
The mixed anhydrides of AMP with Phe^P and Met^P were obtained analogously (in yields of 17–24%).[247] In the condensation of the trioctylammonium salts of AMP with the imidazolides of α-aminophosphonic acids, the yield of the corresponding mixed anhydrides is somewhat higher (26–35%). The highest yields of the mixed anhydrides (50–62%) were attained in the reaction of *N*-protected α-aminophosphonic acids with AMP imidazolides.[247] In the condensation of AMP with the monoethyl ester of the phosphonic analogue of valine, the phosphono-group of the latter was activated by treatment with phosgene; the yield of the condensation products was 45%.[247] The chemical and enzymic syntheses of the mixed anhydride of β-aminoethyl phosphonic acid and cytidine 5'-phosphate have also been described.[248]

The esters of α-aminophosphonic and the corresponding phosphinic acids are converted into the free acids usually by hydrolysis in acid media. The rate of hydrolysis depends on the nature of the *O*-alkyl (*O*-aryl) groups split off (for example, in acid hydrolysis the *C*-isopropyl groups are eliminated much more readily than the *O*-ethyl groups[109]) and the character of the acid employed (the rate of hydrolysis falls in the sequence HI > HBr > HCl [143]). In those cases where the aminophosphonate is unstable in an acid medium, the hydrolysis is carried out with alkalies[136] or the compound is *O*-dealkylated by treatment with halogenosilanes in acetonitrile:[136,159]

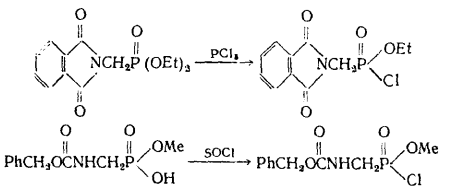


Phenyl,[249] benzyl,[250] diphenylmethyl,[236,237] and trichloroethyl[211] P-ester groups can be removed by catalytic hydrogenolysis. The diphenylmethyl group is eliminated also on refluxing with ethanol or on treatment with trifluoroacetic acid at room temperature.[237] The *p*-methylbenzyl group is eliinated by treatment with 98% formic acid.[251] *OO*-Disilylaminophosphonates are converted into free aminophosphonic acids after prolonged heating with alcohols or a water–alcohol mixture.[80,82] The diethyl esters of *N*-alkylaminophosphonic acids, which are extremely resistant to hydrolysis by aqueous solutions of acids and bases, have been converted into the free acids by treatment with dry hydrogen chloride at an elevated temperature.[197,152]

The diphenyl esters of *N*-acylated α-aminophosphonic acids can be converted into the dialkyl esters by transesterification in the fluoride–crown ether–alcohol system:[204,253]

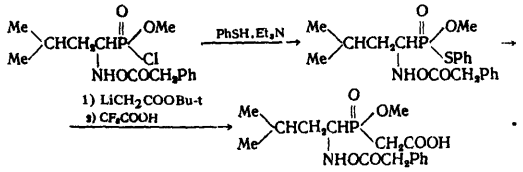


The *N*-protecting groups and peptide bonds are not involved in such transesterification, which makes it possible to employ this process for the modification of phosphonopeptides.[249] *N*-Protected aminophosphonates can be converted into the corresponding aminophosphonochloridates by treatment with phosphorus pentachloride[243,250,254] or thionyl chloride:[220,221]

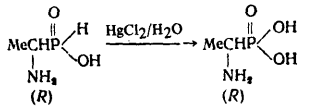


These phosphonochloridates interact readily with nucleophiles and are used for the synthesis of phosphonopeptides and other derivatives of aminophosphonic acids. For example, the α-aminophosphonic acid Leu^P has been converted into

the α-aminophosphinic acid with a carboxymethyl substituent at the phosphorus atom ($Leu^{P}-CH_2COOH$) in accordance with the following scheme:[255]

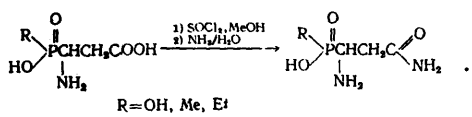


α-Aminophosphonous acids are oxidised with mercury(II) chloride or bromine water to the corresponding α-aminophosphonic acids with retention of the configuration of the chiral α-carbon atom:[86,88,123]



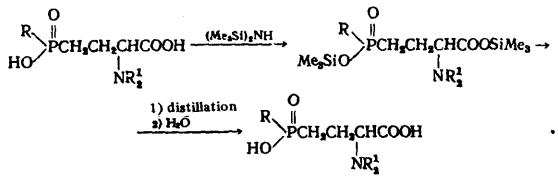
3. Reactions of Other Groups Present in Aminophosphonic and Aminophosphinic Acids

The carboxy-group in carboxylated aminophosphonic and aminophosphinic acids can be esterified without involving the phosphorus-containing fragment.[33,42,199] Such esterification of the carboxy-group in $Asp^{\alpha-P}$ with subsequent ammonolysis has been used to obtain the phosphonic and phosphinic analogues of asparagine:[130,131]

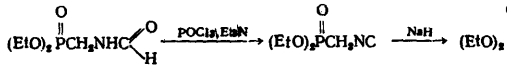


R=OH, Me, Et

In the presence of diazabicycloundecene and alkyl halides or diazomethane the carboxy- and phosphono-groups in carboxylated aminophosphonic acid are esterified simultaneously.[163] When aminophosphonic and aminophosphonic acids are heated with an excess of hexamethyldisilanzane, the trimethylsilyl derivatives are formed.[100] A method has been proposed for the purification of APA, consisting in their silylation with subsequent distillation and removal of silyl groups by hydrolysis or alcoholysis:[15,256]

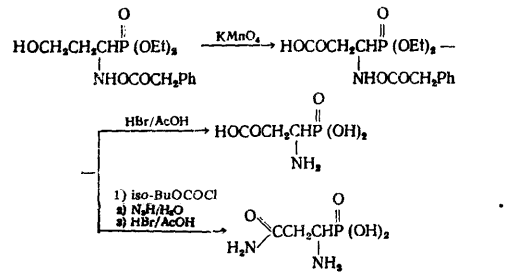


On treatment with phosphoryl chloride, *N*-formamidomethylphosphonates are converted into isocyanomethylphosphonates containing the readily metallated methylene group:[75]

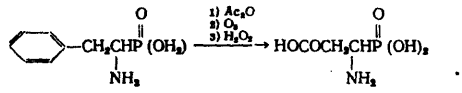


The interaction of the resulting anion with electrophiles leads to the heterocyclic P–C–N systems: the esters of oxazolylphosphonic acids (reactions with acid chlorides and carbonyl compounds) and the ester of mercaptothiazolylphosphonic acid (reaction with carbon disulphide).[75,257,258] Analogous reactions have been described for *N*-formamidomethylphosphinates.[15]

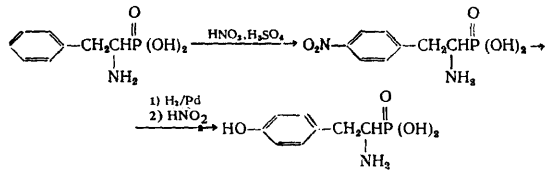
On treatment with a mixture of acetic and hydrobromic acids, the phosphonic analogues of serine and isoserine give rise to the *O*-acetyl derivatives without affecting the amino-group.[159] The oxidation of the β-hydroxymethylene fragment of the phosphonic analogue of homoserine has been used to synthesise the phosphonic analogues of asparagine (Asn^{P}) and aspartic acid ($Asp^{\alpha-P}$):[180]



The ozonolysis of the phosphonic analogue of phenylalanine followed by oxidative treatment results in the decomposition of the benzene ring and the formation of the phosphonic analogue of aspartic acid ($Asp^{\alpha-P}$):[201]



The phosphonic analogue of phenylalanine has been converted into the phosphonic analogue of tyrosine via the following scheme:[201]



Since these reactions do not involve the chiral centre, they have been used to determine the absolute configurations of the optically active aminophosphonic acids $Asp^{\alpha-P}$, $Asn^{\alpha-P}$, Phe^{P}, and Tyr^{P}.[180,201]

As can be seen from the foregoing, the chemistry of APA constitutes at the present time an independent chapter in the chemistry of organophosphorus compounds with its own tasks and approaches to their solution. Both traditional methods of synthesis of OPC and the "phosphorus" versions of the classical methods of synthesis of aminocarboxylic acids are widely used in the chemistry of APA. The advances in the chemistry of APA have made available a wide range of phosphorus analogues of natural aminoacids, although many problems, for example the synthesis of polyfunctional and optically active APA, have still not had optimal solutions.

A characteristic feature of this field of HPC is that it adjoins closely bio-organic chemistry and biochemistry. This is related not only to the structural similarity of the aminoacids and APA but also to the existence of natural APA, which confirms their definite biological role. The development of research into the field of APA has already led to the creation of highly active herbicides (glyphosphate, phosphinothricin) and promising medicinal drugs (the antibiotic alaphosphin).

Presumably further studies in the field of APA will involve primarily the development of methods of synthesis of APA and the complex analogues of the most important biologically active natural products containing APA fragments. Secondly, they will involve the wide-scale employment of

these compounds in bio-organic research and, finally, they will be associated with the search for new substances of practical use in medicine and agriculture.

REFERENCES

1. M.Horiguchi and M.Kandatsu, Nature, 1959, **184**, 901.
2. J.S.Kittredge and E.Roberts, Science, 1969, **164**, 37.
3. E.D.Korn, D.G.Deaborn, H.M.Fales, and E.A.Sokolowski, J.Biol.Chem., 1973, **248**, 2257.
4. B.K.Park, A.Hirota, and H.Sakai, Agricul.Biol. Chem., 1976, **40**, 1905.
5. L.D.Quin, in "Topics in Phosphorus Chemistry", Vol.4 (edited by M.Grayson and E.J.Griffith), Wiley Intersci., New York, 1967, p.23.
6. J.S.Kittredge and R.R.Hughes, Biochemistry, 1964, **3**, 991.
7. T.Kamiya, K.Hemmi, H.Takeno, and M.Hashimoto, Tetrahedron Lett., 1980, **21**, 95.
8. R.L.Hilderbrand, J.Curley-Joseph, H.Lubansky, and T.O.Henderson, in "Topics in Phosphorus Chemistry", Vol.11 (edited by M.Grayson and E.J.Griffith), Wiley Intersci., New York, 1983, p.297.
9. E.Bayer, K.H.Gugel, H.Hägele, H.Hagenmaier, S.Jessipow, W.A.König, and T.Zähler, Helv.Chim. Acta, 1972, **55**, 224.
10. H.Seto, T.Sasaki, S.Imai, T.Tsuruoka, H.Ogawa, A.Satoh, S.Inouye, T.Niida, and N.Otake, J.Antibiotics, 1983, **36**, 96.
11. A.N.Pudovik, I.V.Gur'yanova, and E.A.Ishmaeva, "Reaktsii i Metody Issledovaniya Organicheskikh Soedinenii" (Reactions and Methods for the Investigation of Organic Compounds), Izd.Khimiya, Moscow, 1968, Book 19, 848 pp.
12. K.A.Petrov, V.A.Chauzov, and T.E.Erokhina, Uspekhi Khim., 1974, **43**, 2045 [Russ.Chem.Rev., 1974(11)].
13. D.Redmore, in "Topics in Phosphorus Chemistry", Vol.8 (edited by M.Grayson and E.J.Griffith), Wiley Intersci., New York, 1976, p.515.
14. K.Prajer and J.Rachon, Z.Chem., 1975, **15**, 209.
15. L.Maier, Phosphorus Sulfur, 1983, **14**, 295.
16. M.I.Kabachnik and T.Ya.Medved', Dokl.Akad. Nauk SSSR, 1952, **83**, 689.
17. T.Ya.Medved' and M.I.Kabachnik, Dokl.Akad. Nauk SSSR, 1952, **84**, 717.
18. M.I.Kabachnik and T.Ya.Medved', Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 1953, 868.
19. M.I.Kabachnik and T.Ya.Medved', Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 1954, 314.
20. M.I.Kabachnik and T.Ya.Medved', Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 1954, 1024.
21. T.Ya.Medved' and M.I.Kabachnik, Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 1957, 1357.
22. E.K.Fields, J.Amer.Chem.Soc., 1952, **74**, 1528.
23. M.I.Kabachnik, T.Ya.Medved', N.M.Dyatlova, O.G.Arkhipova, and M.V.Rudomino, Uspekhi Khim., 1968, **37**, 1161 [Russ.Chem.Rev., 1968(7)].
24. E.E.Nifant'ev, "Khimiya Gidrofosforil'nykh Soedinenii" (The Chemistry of Hydrophosphoryl Compounds), Izd.Nauka, Moscow, 1983, 263 pp.
25. Yu.P.Belov, V.A.Davankov, and S.V.Rogozhin, Izv.Akad.Nauk SSSR, Ser.Khim., 1977, 1596.
26. M.E.Chalmers and G.M.Kosolapoff, J.Amer.Chem. Soc., 1953, **75**, 5278.
27. T.Kametani, S.Suzuki, K.Kigasawa, M.Hiiragi, K.Wakisaka, H.Sugi, K.Tanigawa, K.Fukawa, O.Irino, O.Saita, and S.Yamabe, Heterocycles, 1982, **18**, 295.
28. J.Oleksyszyn, M.Soroka, and J.Rachon, Chimia, 1978, **32**, 253.
29. E.Gruszecka, M.Soroka, and P.Mastalerz, Polish J.Chem., 1979, **53**, 2327.
30. H.Schimdt, Chem.Ber., 1948, **81**, 477.
31. L.Maier, Helv.Chim.Acta, 1967, **50**, 1742.
32. K.Moedritzer and R.R.Irani, J.Org.Chem., 1966, **31**, 1603.
33. L.Maier, Phosphorus Sulfur, 1981, **11**, 139.
34. L.Maier, Phosphorus Sulfur, 1981, **11**, 149.
35. W.Szczepaniak and J.Siepak, Roczn.Chem., 1973, **47**, 929.
36. D.Redmore, J.Org.Chem., 1978, **43**, 996.
37. J.Oleksyszyn, R.Tyka, and P.Mastalerz, Synthesis, 1978, 479.
38. E.W.Petrillo, D.C.Karanewsky, E.R.Spitzmiller, and M.E.Duggan, Phosphorus Sulfur, 1983, **11**, 149.
39. US P.2328358 (1943); Chem.Abs., 1944, **38**, 754.
40. W.Subotkowski, R.Tyka, and P.Mastalerz, Polish J.Chem., 1980, **54**, 503.
41. B.Lejczak, P.Kafarski, M.Soroka, and P.Mastalerz, Synthesis, 1984, 577.
42. J.Oleksyszyn, E.Gruszecka, P.Kafarski, and P.Mastalerz, Monatsh.Chem., 1982, **113**, 59.
43. G.Sosnovsky, J.Lukszo, E.Gravela, and M.Zuretti, J.Medicin.Chem., 1985, **28**, 1350.
44. J.Oleksyszyn, Synthesis, 1980, 722.
45. J.Oleksyszyn and E.Gruszecka, Tetrahedron Lett., 1981, **22**, 3537.
46. US P.2304156 (1942); Chem.Abs., 1943, **37**, 3261.
47. Polish P.117780 (1982); Chem.Abs., 1983, **99**, 70992.
48. R.Tyka and G.Hagele, Synthesis, 1984, 218.
49. V.Chavane, Bull.Soc.chim.France, 1948, 774.
50. I.C.Popoff, L.K.Huber, B.P.Block, P.D.Morton, and R.P.Riordan, J.Org.Chem., 1963, **28**. 2829.
51. P.Mastalerz and G.Richtarski, Roczn.Chem., 1971, **45**, 763.
52. D.J.Collins, P.F.Drygala, and J.M.Swan, Tetrahedron Lett., 1982, **23**, 1117.
53. J.A.Miles, R.C.Grabiak, and M.T.Beeny, J.Org. Chem., 1981, **46**, 3486.
54. G.M.Kosolapoff, J.Amer.Chem.Soc., 1947, **69**, 2112.
55. D.Brigot, N.Collignon, and P.Savignac, Tetrahedron, 1979, **35**, 1345.
56. U.Schmidt, A.Lieberknecht, U.Schanbacher, T.Beuttler, and J.Wild, Angew.Chem., 1982, **94**, 797.
57. R.Kober and W.Steglich, Annalen, 1983, 599.
58. Y.Vo Quang, D.Carniato, L.Quang, and F.LeGoffic, Synthesis, 1985, 62.
59. G.A.Flynn, D.W.Beight, E.H.W.Bohme, and B.W.Metcalf, Tetrahedron Lett., 1985, **26**, 285.
60. G.H.Birum, J.Org.Chem., 1974, **39**, 209.
61. Z.H.Kudzin and W.J.Stec, Synthesis, 1978, 469.
62. Z.H.Kudzin and W.Stec, Synthesis, 1980, 1032.
63. C.C.Tam, K.L.Mattocks, and M.Tischer, Synthesis, 1982, 188.
64. Z.H.Kudzin, Synthesis, 1981, 643.
65. J.Oleksyszyn and R.Tyka, Tetrahedron Letters, 1977, 2823.
66. J.Oleksyszyn, L.Subotkowska, and P.Mastalerz, Synthesis, 1979, 985.

67. J.W.Huber and M.Middlebrooks, Synthesis, 1977, 883.
68. J.W.Huber and W.F.Gilmore, Tetrahedron Lett., 1979, 3049.
69. K.Clauss, D.Grimm, and G.Prossel, Annalen, 1974, 539.
70. M.M.Campbell and N.Carruthers, Chem.Comm., 1980, 730.
71. M.M.Campbell, N.I.Carruthers, and S.J.Mickel, Tetrahedron, 1982, **38**, 2513.
72. H.Stamm and G.Gerster, Tetrahedron Lett., 1980, **21**, 1623.
73. H.Stamm, G.Gerster, and T.Baumann, Chem.Ber., 1983, **116**, 2936.
74. M.E.Duggan and D.C.Karanewsky, Tetrahedron Lett., 1983, **24**, 2935.
75. U.Schöllkopf and R.Schroeder, Tetrahedron Lett., 1973, 633.
76. R.Tyka, Tetrahedron Lett., 1970, 677.
77. K.Issleib, K.-P.Dopfer, and A.Balszuweit, Z.Chem., 1982, **22**, 215.
78. I.Glowiak, W.Sawka-Dobrowolska, J.Kowalik, P.Mastalerz, M.Soroka, and J.Zon, Tetrahedron Lett., 1977, 3965.
79. I.Glowiak, W.Sawka-Dobrowolska, J.Kowalik, R.P.Mastalerz, M.Soroka, and J.Zon, Symposium, "Khimiya i Primenenie Fosfororganicheskikh Soedinenii" (Chemistry and Applications of Organophosphorus Compounds), Izd.Naukova Dumka, Kiev, 1981, p.306.
80. J.Zon, Polish J.Chem., 1981, **55**, 643.
81. W.F.Gilmore and H.A.McBride, J.Amer.Chem.Soc., 1972, **94**, 4361.
82. K.Issleib, A.Balszuweit, H.-J.Richter, and W.Tonk, Z.Chem., 1983, **23**, 434.
83. N.B.Tarusova, Z.S.Novikova, A.A.Prishchenko, G.M.Yaklovleva, and R.M.Khomutov, Izv.Akad. Nauk SSSR, Ser.Khim., 1982, 402.
84. D.Redmore, J.Org.Chem., 1978, **43**, 992.
85. W.M.Linfield, E.Jungermann, and A.J.Guttmann, J.Org.Chem., 1961, **26**, 4088.
86. E.K.Baylis, C.D.Campbell, J.D.Dingwall, and W.Pickles, in "ACS Symposium Series No.17 (edited by L.D.Quin and J.Verkade), Amer.Chem.Soc., Washington, 1981, p.183.
87. B.P.1542938 (1979).
88. E.K.Baylis, C.D.Campbell, and J.G.Dingwall, J.Chem.Soc., Perkin Trans.I, 1984, 2845.
89. J.G.Dingwall, in "Third International Conference on Chemistry and Biotechnology of Biologically Active Natural Products", Sofia, 1985, Vol.2, p.87.
90. K.Issleib, K.-P.Dopfer, and A.Balszuweit, Z.Naturforsch., 1981, **36b**, 1392.
91. K.Issleib, K.-P.Dopfer, and A.Balszuweit, Phosphorus Sulfur, 1983, **14**, 171.
92. K.Moedritzer, Synth.Inorg.Met.Org.Chem., 1972, **2**, 317.
93. J.Lukszo and R.Tyka, Polish J.Chem., 1978, **52**, 321.
94. J.Lukszo and R.Tyka, Polish J.Chem., 1978, **52**, 959.
95. J.Lukszo and R.Tyka, Synthesis, 1977, 239.
96. J.Zon and P.Mastalerz, Roczn.Chem., 1976, **50**, 1403.
97. J.S.Wieczorek and R.Gancarz, Roczn.Chem., 1976, **50**, 2171.
98. R.Gancarz and J.S.Wieczorek, J.prakt.Chem., 1980, **322**, 213.
99. R.Gancarz, P.Kafarski, B.Lejczak, P.Mastalerz, J.S.Wieczorek, E.Przybylka, and W.Czerwinski, Phosphorus Sulfur, 1983, **18**, 373.
100. J.S.Wieczorek, B.Boduszek, and R.Gancarz, J.prakt.Chem., 1984, **326**, 349.
101. K.Drauz, H.G.Koban, J.Martens, and J.Schwarze, Annalen, 1985, 448.
102. R.Skowronski, Z.H.Kudzin, and J.Skolimowski, Phosphorus Sulfur, 1983, **18**, 411.
103. R.W.Ratcliffe and B.G.Christensen, Tetrahedron Lett., 1973, 4645.
104. E.W.Petrillo and E.R.Spitzmiller, Tetrahedron Lett., 1979, 4929.
105. N.Kreutzkamp and G.Cordes, Annalen, 1959, **623**, 103.
106. S.V.Rogozhin, V.A.Davankov, and Yu.P.Belov, Izv.Akad.Nauk SSSR, Ser.Khim., 1973, 955.
107. K.Issleib, K.-P.Dopfer, and A.Balszuweit, Z.anorg. Chem., 1978, **444**, 249.
108. J.Rachon and C.Wasielewski, Z.Chem., 1973, **13**, 254.
109. J.Rachon and C.Wasielewski, Roczn.Chem., 1975, **49**, 397.
110. J.Rachon and C.Wasielewski, Tetrahedron Lett., 1978, 1609.
111. C.Wasielewski, K.Antczak, and J.Rachon, Z.Chem., 1979, **19**, 253.
112. J.Rachon and C.Wasielewski, Roczn.Chem., 1976, **50**, 477.
113. M.Hoffmann, C.Wasielewski, and J.Rachon, Chimia, 1976, **30**, 187.
114. C.Wasielewski, K.Antczak, and J.Rachon, Pol.J. Chem., 1978, **52**, 1315.
115. A.N.Pudovik, M.G.Zimin, I.V.Konovalova, V.M.Pozhidaev, and L.I.Vinogradov, Zhur.Obshch. Khim., 1975, **45**, 30.
116. L.Maier, Phosphorus Sulfur, 1981, **11**, 311.
117. B.S.Drach, A.D.Sinitsa, and A.V.Kirsanov, Zhur.Obshch.Khim., 1969, **39**, 2192.
118. M.M.Sidky, M.F.Zayed, K.Praefcke, W.Wong-ng, and S.C.Nyburg, Phosphorus Sulfur, 1982, **13**, 319.
119. H.Hoffmann and H.Forster, Monatsch.Chem., 1968, **99**, 380.
120. A.Kotynski and W.J.Stec, Polish J.Chem., 1978, **52**, 659.
121. A.K.Kotynski and W.J.Stec, J.Chem.Res.S, 1978, 41.
122. M.G.Zimin, A.R.Burilov, and A.N.Pudovik, Zhur. Obshch.Khim., 1980, **50**, 751.
123. R.M.Khomutov and T.I.Osipova, Izv.Akad.Nauk SSSR, Ser.Khim., 1978, 1951.
124. R.Huber, A.Knierzinger, J.-P.Obrecht, and A.Vasella, Helv.Chim.Acta, 1985, **68**, 1730.
125. V.V.Orlovskii and B.A.Vovsi, Zhur.Obshch.Khim., 1976, **46**, 297.
126. BRD P.2754821 (1979).
127. US P.4239695 (1980).
128. A.N.Pudovik, V.I.Nikitina, M.G.Zimin, and N.M.Vostretsova, Zhur.Obshch.Khim., 1975, **45**, 1450.
129. J.R.Chambers and A.F.Isbell, J.Org.Chem., 1964, **29**, 832.
130. M.Soroka and P.Mastalerz, Roczn.Chem., 1976, **50**, 661.
131. M.Soroka and P.Mastalerz, Roczn.Chem., 1974, **48**, 1119.
132. K.D.Berlin, N.K.Roy, and E.T.Gaudy, J.Org. Chem., 1968, **33**, 3090.

133. M.J.Stringer, J.A.Stock, and L.M.Cobb, Chem.-Biol.Interactions, 1974, **9**, 411.
134. K.D.Berlin, N.K.Roy, R.T.Claunch, and D.Bude, J.Amer.Chem.Soc., 1968, **90**, 4494.
135. S.Asano, T.Kitahara, T.Ogawa, and M.Matsui, Agric.Biol.Chem., 1973, **37**, 1193.
136. W.Subotkowski, J.Kowalik, R.Tyka, and P.Mastalerz, Polish J.Chem., 1981, **55**, 853.
137. J.Kowalik, L.Kupczyk-Subotkowska, and P.Mastalerz, Synthesis, 1981, 57.
138. J.Kowalik, J.Zygmunt, and P.Mastalerz, Pol.J.Chem., 1981, **55**, 713.
139. G.M.Kosolapoff, J.Amer.Chem.Soc., 1948, **70**, 1283.
140. Z.H.Kudzin and A.Kotynski, Synthesis, 1980, 1028.
141. R.M.Khomutov, T.I.Osipova, Yu.N.Zhukova, and I.A.Gandurina, Izv.Akad.Nauk SSSR, Ser.Khim., 1979, 2118.
142. R.M.Khomutov and T.I.Osipova, Izv.Akad.Nauk SSSR, Ser.Khim., 1979, 1110.
143. J.P.Berry, A.F.Isbell, and G.E.Hunt, J.Org.Chem., 1972, **37**, 4396.
144. A.Merijanian, Dissertation Abstr., 1964, **25**, 2196; Chem.Abs., 1965, **62**, 6510.
145. M.Shin-Yu, Dissertation Abstr., 1966, **26**, 6374; Chem.Abs., 1966, **65**, 8954.
146. A.F.Isbell, J.P.Berry, and L.W.Tansey, J.Org. Chem., 1972, **37**, 4399.
147. J.Zon, Pol.J.Chem., 1979, **53**, 541.
148. J.Finkelstein, J.Amer.Chem.Soc., 1946, **68**, 2397.
149. J.Barycki, P.Mastalerz, and M.Soroka, Tetrahedron Lett., 1970, 3147.
150. J.Barycki, P.Mastalerz, H.Ratajczak, and M.Soroka, Roczn.Chem., 1971, **45**, 557.
151. J.Rachon, C.Wasielewski, and A.Sobczak, Z.Chem., 1974, **14**, 152.
152. M.Soroka and P.Mastalerz, Tetrahedron Lett., 1973, 5201.
153. P.Mastalerz, Acta Biochim.Polon., 1957, **4**, 19.
154. Y.Ogawa, H.Yoshida, S.Inoue, and T.Niida, Meiji Seika Kenkyu Nempo, 1973, 49; Chem.Abs., 1974, **81**, 37788.
155. P.Mastalerz, Roczn.Chem., 1959, **33**, 985.
156. H.Gross and T.Gnauk, J.prakt.Chem., 1976, **318**, 157.
157. N.Minowa, S.Fukatsu, T.Niida, M.Takada, and K.Sato, Tetrahedron Lett., 1983, **24**, 2391.
158. N.Minowa, M.Hirayama, and S.Fukatsu, Tetrahedron Lett., 1984, **25**, 1147.
159. J.Zygmunt and P.Mastalerz, Polish J.Chem., 1978, **52**, 2271.
160. J.Zygmunt and P.Mastalerz, Polish J.Chem., 1981, **55**, 411.
161. E.Gruszecka, P.Mastalerz, and M.Soroka, Roczn. Chem., 1975, **49**, 2127.
162. E.Gruszecka, P.Mastalerz, and M.Soroka, Polish J.Chem., 1979, **53**, 937.
163. J.M.Villanaeva, N.Collignon, A.Guy, and P.Savignac, Tetrahedron, 1983, **39**, 1293.
164. G.Fabre, N.Collignon, and P.Savignac, Canad.J. Chem., 1981, **59**, 2864.
165. M.I.Kabachnik and T.Ya.Medved', Izv.Akad.Nauk SSSR, Otd.Khim., Nauk, 1950, 635.
166. M.I.Kabachnik and T.Ya.Medved', Izv.Akad.Nauk SSSR, Otd.Khim., Nauk, 1951, 95.
167. US P.3160632 (1964); Chem.Abs., 1965, **62**, 4053.
168. L.Maier, J.Organomet.Chem., 1979, **178**, 157.
169. T.A.Zyablikova, I.M.Magdeev, and I.M.Shermergorn, Izv.Akad.Nauk SSSR, Ser.Khim., 1969, 694.
170. M.K.Il'ina and I.M.Shermergorn, Izv.Akad.Nauk SSSR, Ser.Khim., 1967, 1346.
171. M.K.Il'ina and I.M.Shermergorn, Izv.Akad.Nauk SSSR, Ser.Khim., 1968, 1860.
172. C.Wasielewski and K.Antczak, Synthesis, 1981, 540.
173. P.G.Baraldi, M.Guarneri, F.Moroder, G.P.Pollini, and D.Simoni, Synthesis, 1982, 653.
174. D.I.C.Scopes, A.F.Kluge, and J.A.Edwards, J.Org. Chem., 1977, **42**, 376.
175. E.W.Colvin, G.W.Kirby, and A.C.Wilson, Tetrahedron Lett., 1982, **23**, 3835.
176. G.H.Hakimelahi and G.Just, Synth.Comm., 1980, **10**, 429.
177. W.J.Stec and K.Lesiak, J.Org.Chem., 1976, **41**, 3757.
178. A.Dehnel and G.Lavielle, Bull.Soc.chim.France, 1978, 95.
179. U.Schöllkopf and T.Wintel, Synthesis, 1984, 1033.
180. A.Vasella and R.Voeffray, Helv.Chim.Acta, 1982, **65**, 1953.
181. U.Schollkopf, I.Hoppe, and A.Thiele, Annalen, 1985, 555.
182. A.-M.Lacoste, A.Cassaigne, and E.Neuzil, Compt. rend.D, 1972, **275**, 3009.
183. T.A.Mastryukova, V.N.Lazareva, and V.V.Perekalin, Izv.Akad.Nauk SSSR, Ser.Khim., 1972, 1164.
184. H.Paulsen and W.Creve, Chem.Ber., 1973, **106**, 2114.
185. J.Blanchard, N.Collignon, P.Savignac, and H.Normant, Tetrahedron, 1976, **32**, 455.
186. G.M.Baranov, T.A.Mastryukova, V.V.Perekalin, M.V.Ponomarenko, and M.I.Kabachnik, Izv.Akad. Nauk SSSR, Ser.Khim., 1969, 179.
187. A.V.Serdyukova, G.M.Baranov, and V.V.Perekalin, Zhur.Obshch.Khim., 1978, **48**, 522.
188. J.Zygmunt, U.Waliowiak, and P.Mastalerz, Polish J.Chem., 1980, **54**, 233.
189. J.Kowalik, W.Sawka-Dobrowolska, and T.Glowiak, J.Chem.Soc., Chem.Comm., 1984, 446.
190. M.Wozniak, J.Nicole, and G.Trodot, Bull.Soc.chim. France, 1972, 4452.
191. M.I.Kabachnik, in "Khimiya i Premenenie Fosfor-organicheskikh Soedinenii" (The Chemistry and Applications of Organophosphorus Compounds), Izd.Akad.Nauk SSSR, Moscow, 1962, p.24.
192. L.Maijs and O.Lukevics, Izv.Akad.Nauk Latv.SSSR, Ser.Khim., 1973, 443.
193. D.Giron-Forest and G.Thomas, Bull.Soc.chim. France, 1972, 390.
194. N.M.Dyatlova, V.Ya.Temkina, and I.D.Kolpakova, "Kompleksony" (Complexones), Izd.Khimiya, Moscow, 1970, 417 pp.
195. K.B.Yatsimirskii (Editor), "Biologicehskie Aspekty Koordinatsionnoi Khimii" (Biological Aspects of Coordination Chemistry), Izd.Naukova Dumka, Kiev, 1979, 268 pp.
196. A.Antonow and B.Jezowska-Trzebiatowska, Polish J.Chem., 1978, **52**, 1313.
197. Yu.P.Belov, V.A.Davankov, and S.V.Rogozhin, Izv.Akad.Nauk SSSR, Ser.Khim., 1977, 1861.
198. G.Richtarski, M.Soroka, P.Mastalerz, and H.Starzemska, Roczn.Chem., 1975, **49**, 2001.
199. L.Maier and M.J.Smith, Phosphorus Sulfur, 1980, **8**, 67.
200. Yu.P.Belov, V.A.Davankov, V.A.Tsyryapkin, and S.V.Rogozhin, Izv.Akad.Nauk SSSR, Ser.Khim., 1975, 1619.
201. J.Kowalik, J.Zygmunt, and P.Mastalerz, Phosphorus Sulfur, 1983, **18**, 1983.

202. Yu.P.Belov, G.B.Rakhnovich, V.A.Davankov, N.N.Godovikov, G.G.Aleksandrov, and Yu.G.Struchkov, Izv.Akad.Nauk SSSR, Ser.Khim., 1980, 1125.
203. B.Lejczak, L.Kupczyk-Subotkowska, P.Kafarski, P.Mastalerz, and J.Szewczyk, Phosphorus Sulfur, 1983, **18**, 484.
204. P.Kafarski, B.Lejczak, and J.Szewczyk, Canad.J. Chem., 1983, **61**, 2425.
205. M.Hoffmann, Polish J.Chem., 1978, **52**, 851.
206. J.Szewczyk and M.Hoffmann, Phosphorus Sulfur, 1983, **16**, 325.
207. P.Kafarski, B.Lejczak, P.Mastalerz, J.Szewczyk, and C.Wasielewski, Canad.J.Chem., 1982, **60**, 3081.
208. L.Kupczyk-Subotkowska and P.Mastalerz, Int.J. Peptide Protein Res., 1983, **21**, 485.
209. J.Telegdi, F.Kraiczovits, and L.Otvos, Phosphorus Sulfur, 1983, **18**, 412.
210. F.R.Atherton, M.J.Hall, C.H.Hassall, R.W.Lambert, and P.S.Ringrose, Antimicrob.Agents Chemother., 1979, **15**, 677.
211. J.Szewczyk and C.Wasielewski, Polish J.Chem., 1981, **55**, 1985.
212. J.Szewczyk, Phosphorus Sulfur, 1983, **16**, 365.
213. T.Ya.Medved' and M.I.Kabachnik, Izv.Akad.Nauk SSSR. Otd.Khim.Nauk, 1955, 1048.
214. T.Ya.Medved' and M.I.Kabachnik, Izv.Akad.Nauk SSSR. Otd.Khim.Nauk, 1951, 620.
215. M.I.Kabachnik and T.Ya.Medved', Izd.Akad.Nauk SSSR, Otd.Khim.Nauk, 1953, 1126.
216. B.Wysocka-Skrzela, Polish J Chem., 1982, **56**, 1573.
217. T.Ya.Medved' and M.I.Kabachnik, Izv.Akad.Nauk SSSR, Otd.Khim.Nauk, 1955, 1043.
218. D.Seyferth, R.S.Marmor, and D.Hilbert, J.Org. Chem., 1971, **36**, 1379.
219. K.T.Poroshin and V.K.Burichenko, Dokl.Akad.Nauk SSSR, 1964, **156**, 386.
220. N.E.Jacobsen and P.A.Bartlett, in "ACS Symposium Series No.171 (edited by L.D.Quin and J.Verkade), Amer.Chem.Soc., Washington, 1981, p.221.
221. N.E.Jacobsen and P.A.Bartlett, J.Amer.Chem.Soc., 1981, **103**, 654.
222. M.Hoffmann and C.Wasielewski, Roczn.Chem., 1976, **50**, 139.
223. W.F.Gilmore and H.A.McBride, J.Pharm.Sci., 1974, **63**, 1087.
224. J.W.Huber, W.F.Gilmore, and L.W.Robertson, J.Med.Chem., 1975, **18**, 106.
225. M.Hoffman, Pol.J.Chem., 1979, **53**, 1153.
226. W.Dzczepaniak and J.Siepak, Pol.J.Chem., 1978, **52**, 721.
227. A.Dehnel, J.P.Finet, and G.Lavielle, Synthesis, 1977, 474.
228. G.L.Rowley, A.L.Greenleaf, and G.L.Kenyon, J.Amer.Chem.Soc., 1971, **93**, 5542.
229. J.Oleksyszyn, R.Tyka, and P.Mastalerz, Polish J. Chem., 1979, **53**, 1347.
230. J.Oleksyszyn, R.Tyka, and P.Mastalerz, Synthesis, 1977, 571.
231. K.A.Petrov, V.A.Chauzov, N.N.Bogdanov, and I.V.Pastukhova, Zhur.Obshch.Khim., 1976, **46**, 1246.
232. G.Richtarski and P.Mastalerz, Tetrahedron Lett., 1973, 4069.
233. S.G.Warren, J.Chem.Soc.C, 1966, 1349.
234. C.Wasielwski and J.Szewczyk, Polish J.Chem., 1978, **52**, 1097.
235. J.Szewczyk, J.Rachon, and C.Wasielewski, Polish J. Chem., 1982, **56**, 477.
236. M.Hoffmann, Polish J.Chem., 1979, **53**, 2639.
237. M.Hoffmann, Polish J.Chem., 1981, **55**, 1695.
238. A.Arendt, M.Hoffmann, A.Kolodziejczyk, A.Sobczak, and C.Wasielewski, Polish J.Chem., 1978, **52**, 1601.
239. J.Rachon and M.Hoffmann, Polish J.Chem., 1978, **52**, 1103.
240. C.Wasielewski, M.Hoffmann, and E.Witkowska, Roczn.Chem., 1975, **49**, 1795.
241. C.Wasielewski, M.Hoffmann, E.Witkowska, and J.Rachon, Roczn.Chem., 1976, **50**, 1613.
242. W.F.Gilmore and H.A.McBride, J.Pharm.Sci., 1974, **63**, 965.
243. K.Yamauchi, M.Kinoshita, and M.Imoto, Bull.Chem. Soc.Japan, 1972, **45**, 2528.
244. C.Wasielewski, A.Sobczak, and J.Szewczyk, Roczn. Chem., 1976, **50**, 1795.
245. J.Zemlicka and S.Chladek, Coll.Czech.Chem.Comm., 1969, **34**, 1007.
246. K.Lesiak, W.Stec, and W.Zielinski, Polish J.Chem., 1979, **53**, 327.
247. R.M.Khomutov, T.I.Osipova, A.I.Biryukov, and B.Kh.Ishmuratov, Bioorg.Khim., 1979, **5**, 56.
248. C.R.Liang and H.Rosenberg, Biochim.Biophys.Acta, 1966, **125**, 548.
249. B.Lejczak, P.Kafarski, and J.Szewczyk, Synthesis, 1982, 412.
250. K.Yamauchi, S.Ohtsuki, and M.Kinoshita, J.Org. Chem., 1984, **49**, 1158.
251. J.Lukszo, J.Kowalik, and P.Mastalerz, Chem.Lett., 1978, 1103.
252. Yu.P.Belov, V.A.Davankov, and S.V.Rogozhin, Izv.Akad.Nauk SSSR, Ser.Khim., 1977, 1856.
253. J.Szewczyk, B.Lejczak, and P.Kafarski, Synthesis, 1982, 409.
254. K.Yamauchi, M.Kinoshita, and M.Imoto, Bull.Chem. Soc.Japan, 1972, **45**, 2531.
255. P.A.Bartlett and W.B.Kezer, J.Amer.Chem.Soc., 1984, **106**, 4282.
256. L.Maier, G.Rist, and P.J.Lea, Phosphorus Sulfur, 1983, **18**, 349.
257. J.Rachon and U.Schöllkopf, Annalen, 1981, 1693.
258. J.Rachon and U.Schöllkopf, Annalen, 1981, 1186.

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