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β-Aminophosphonates and β-aminophosphinates, synthesis, and properties

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ABSTRACT. **Methods of obtaining β-aminophosphonates and β-aminophosphinates, their physical and chemical properties and also the practical application of these substances are reviewed.**

The bibliography contains 98 references.

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I. Introduction

β-Aminoethylphosphonic acid (AEP) was isolated for the first time in 1959 from a living organism (molluscs) by Horiguchi and Kondatsu[1] who named it ciliatine. Other authors later isolated AEP and derivatives of it from other natural sources.[2–4] AEP is a component of cell membranes and protects them from degradation of cellular structure. There is currently a hypothesis that AEP is a vitamin or equates to one.[5] It has been established that AEP and its derivatives possess high biological activity.[6,7]

The chemistry of aminophosphonates and aminophosphinates has been discussed in several reviews but these are mainly devoted to α-aminomethylphosphonates[6–10] or the biochemistry of these substances.[11,12]

Preparative methods, chemical and physical properties, and the practical use of β-aminophosphonates and β-aminophosphinates are considered in the present review.

II. Methods of preparation

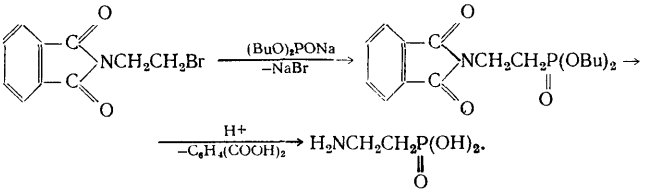
1. The Michaelis–Becker reaction

The method consists of the reaction of β-substituted ethyl halides with the sodium or potassium salt of a dialkyl phosphorous acid (Michaelis–Becker reagent).[13–22] The reaction is carried out in acid or other inert solvent.

AEP was synthesised for the first time by the Michaelis–Becker reaction in 1946.[13] On reacting the Michaelis–Becker reagent with the ethyl ester of β-bromopropionic acid a phosphonocarboxylic acid triester is formed. It was converted into the amide then AEP was obtained by a Hofmann rearrangement.

$$BrCH_2CH_2COOEt \xrightarrow[-NaBr]{(EtO)_2PONa} (EtO)_2P(O)CH_2CH_2COOEt \xrightarrow{NH_3} (EtO)_2P(O)CH_2CH_2CONH_2 \xrightarrow[2)\ H^+]{1)\ NaOBr} (HO)_2P(O)CH_2CH_2NH_2.$$

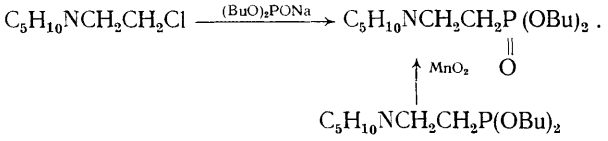
Soon afterwards AEP was synthesised by the reaction of sodium dibutyl phosphite with bromoethylphthalimide and subsequent hydrolysis with hydrobromic acid.[14]



When using β-bromoethylamine hydrobromide in place of the phthalimide the yield of AEP fell sharply probably as a result of the poor solubility of the initial hydrobromide in inert solvent.[15]

The Michaelis–Becker method is useful for introducing a phosphono group into a molecule of a compound in which there is a chlorine atom in the β position to an amino group.[16–19]

M I Kabachnik and collaborators[16] synthesised the dibutyl ester of a β-piperidino substituted phosphonate. This same compound was formed on oxidation of β-piperidinoethylphosphinic acid diester with manganese dioxide.



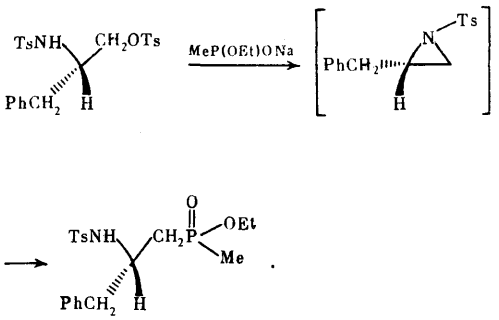
N-Alkyl- and *N*-silylaminophosphonates were obtained by the reaction of the corresponding *N*-substituted β-chloroethylamines with a Michaelis–Becker reagent.[17,19]

$$R'R''NCH_2CH_2Cl \xrightarrow{(EtO)_2PONa} R'R''NCH_2CH_2P(O)(OEt)_2.$$

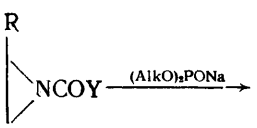
Maier has synthesised 'tris-AEP'.[18]

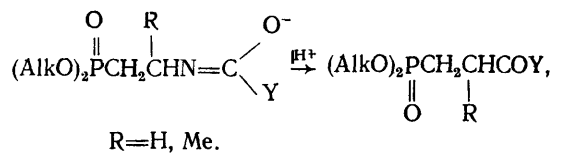
$$N(CH_2CH_2Cl)_3 \xrightarrow{(EtO)_2POK} N[CH_2CH_2P(O)(OEt)_2]_3 \xrightarrow{H^+} N[CH_2CH_2P(O)(OH)_2]_3.$$

A method[21] has been developed for obtaining optically active *N*-substituted β-aminoethylphosphonic acid and -phosphinic acids. An ester is formed by reacting an *N*-tosylaminotosylate with an excess of Michaelis–Becker reagent in tetrahydrofuran solution at room temperature and is converted into the acid by hydrolysis with 48% HBr.

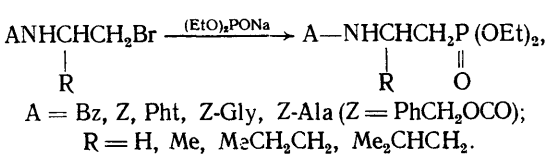


The reaction proceeds through an *N*-tosylaziridine intermediate. Aminophosphonates were obtained with high diastereoselectivity in relation to the chiral centre at phosphorus. *N*-Acyl substituted diesters of aminophosphonic acid were synthesised from *N*-acyl- or *N*-sulphonylaziridines and a Michaelis–Becker reagent.[22]





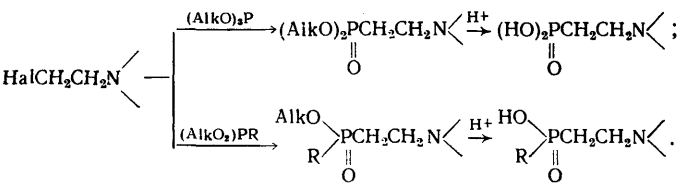
The Michaelis–Becker reaction is used for obtaining phosphonate analogues of aminoacids and peptides.[23]



Phthaloylglycine, benzoylglycine, carbobenzoxydipeptides, carbobenzoxyaminoacids, etc. were used as starting materials. The method has great importance since it affords the preparation of various phosphonic analogues of biologically active aminoacids containing functional groups and asymmetric centres and also of polyphosphonopeptides.[23]

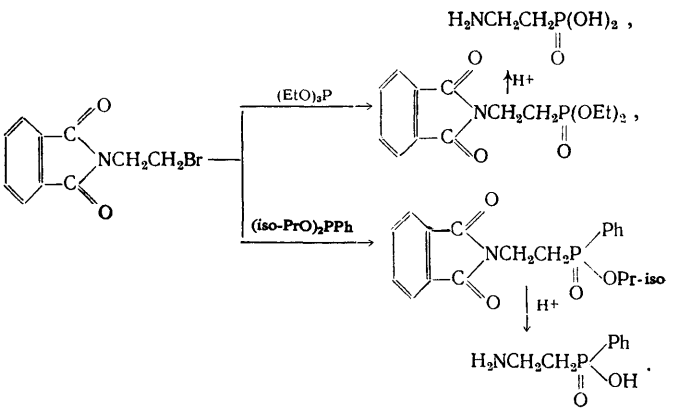
2. The Arbuzov reaction

The method comprises the introduction of an alkylphosphonic group with the aid of a trialkyl phosphite or dialkylaryl phosphonite into a molecule of *N*-substituted amine with the formation of a phosphorus–carbon bond and subsequent hydrolysis of the ester groups.[24–29]

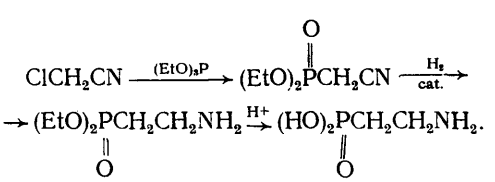


β-Aminoethylphosphonic acid was obtained by the Arbuzov reaction by heating β-bromoethylphthalimide with triethyl phosphite at 160 °C and subsequent hydrolysis of the ester groups.[25]

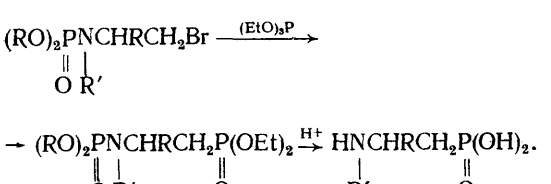
The reaction with *O,O*-diisopropyl phenylphosphonite proceeds in a similar manner, whereby β-aminoethylphenylphosphinic acid is obtained in good yield.[26]



An aminophosphonate is formed by reacting chloroacetonitrile with triethyl phosphite and subsequent reduction of the nitrile group. This compound is converted into AEP by hydrolysis of the ester group.[11]

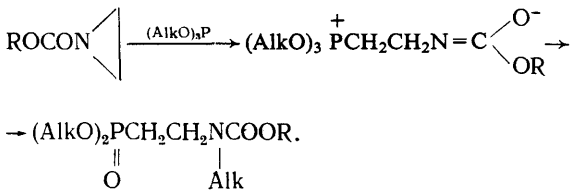


N-Substituted aminophosphonates containing substituents at the α- and β-carbon atoms have been obtained by the Arbuzov reaction.[27,28] *N*-Phosphorylated diesters are formed by reacting the β-bromoethylamide of a dialkyl phosphate with triethyl phosphite at 150–160 °C. Subsequent hydrolysis with hydrochloric acid leads to fission of the ester groups and the nitrogen–phosphorus bond forming β-aminoethylphosphonic acids.



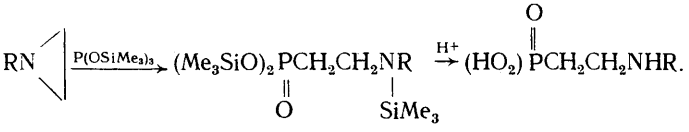
A non-classical variant of the Arbuzov reaction has been used to obtain *N*-acylated aminophosphonates.[24] *N*-Acylaziridines in place of alkyl halides were reacted with esters of trivalent phosphorus

acids. It was suggested that the reaction proceeds through a zwitterionic intermediate.



The hydrobromide of aminoethylphosphonic acid was isolated after further hydrolysis with hydrobromic acid.

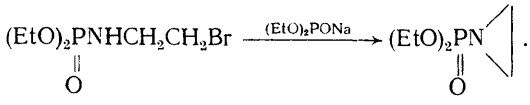
N-Acylaziridines react with *tris*-(trimethylsilyl) phosphite in a similar manner.[30]



Drawbacks of the method of obtaining aminophosphonates by the Arbuzov reaction are the time taken for the process and the forcing conditions of carrying out the reaction.

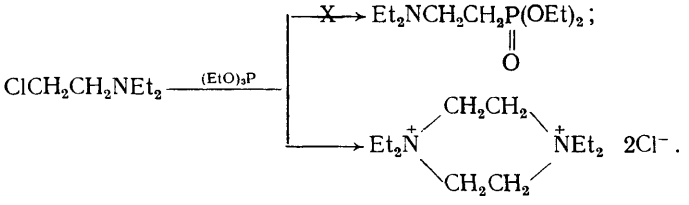
It should be mentioned that in certain cases it is possible to obtain an aminophosphonate (-phosphinate) only by the Arbuzov or Michaelis–Becker reactions.

An *N*-phosphorylated aziridine is formed by interacting the β-bromoethylamide of a diethyl phosphate with a Michaelis–Becker reagent.[28]



In this case the Arbuzov reaction is used to obtain the β-aminophosphonate.

The dimer of the initial amine is obtained on reacting β-chloroethyldiethylamine with triethyl phosphite.[17]



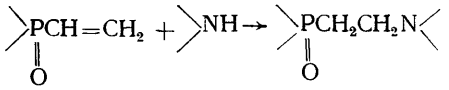
The reaction with *tris*-(β-chloroethyl)amine proceeds in a similar manner.[18]

The Michaelis–Becker and Arbuzov reactions do not have broad scope and are strictly specific methods for obtaining particular aminophosphonates and -phosphinates.

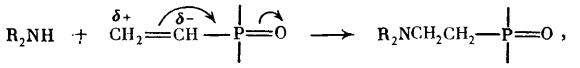
3. Addition to an unsaturated system

a) Addition of amines to a multiple carbon–carbon bond in phosphonates

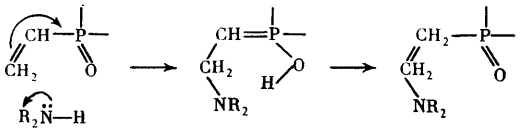
Addition of amines at a multiple carbon–carbon bond in phosphonates has been studied in fair detail.[16,31–48] In all cases addition occurs according to the inverse Markovnikov rule, i.e. the amino group is added to the β-carbon atom of the vinyl group.[32]



Kabachnik and collaborators[16,32] have interpreted the addition to the β-position by a shift of electrons under the influence of the electron-accepting group:



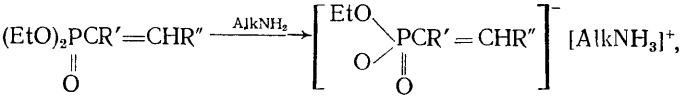
or by the formation of a transition complex.



The addition of amines to a diethyl vinylphosphonate has been studied.[35,36] The reaction proceeds most readily with secondary amines and with more difficulty with primary amines and ammonia.[35,36,38] Dimethylamine adds to diethyl vinylphosphonate without a catalyst at 20 °C.[13] Piperidine reacts similarly.[16,32,35] The reaction of vinylphosphonates with secondary amines usually proceeds with an equimolar ratio of reactants without a solvent or with a 10–15% excess of amine or in aqueous solution.[31,35,39]

Primary amines react only in the presence of a catalyst, such as an alkali metal alkoxide, in an excess of amine on heating.[19,35,38,40]

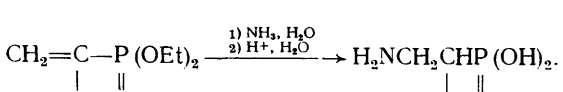
It should be mentioned that the action of alkylamines on a vinylphosphonate containing substituents at the α- or β-carbon atom leads to dealkylation of the initial phosphonate and the formation of an alkylammonium salt of the ethyl vinylphosphonate.[19]



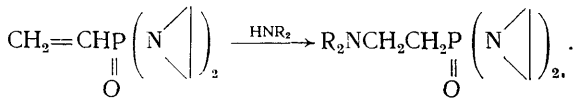
R′, R″ = Me, Ph.

The more basic aliphatic amines react more readily and give aminophosphonates in high yield. Diethyl vinylphosphonate reacts with butylamine in the presence of catalytic amounts of sodium ethoxide at 80–90 °C.[19,40] Diethyl vinylphosphonate reacts with aniline on heating on a water bath. The yield of diethyl *N*-phenylaminophosphonate was low due to the formation of a larger quantity of byproducts.[35,36] Sterically hindered amines [Me_3CNH_2, $(Me_3Si)_2NH$] did not add to vinylphosphonate in the presence of catalytic amounts of sodium ethoxide even on extended boiling (15–20 h) because of the spatial obstacles.[19]

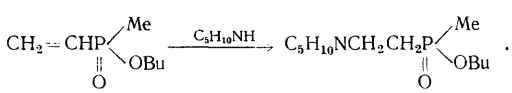
An aminoethylphosphonate with a free amino group was obtained in high yield by reacting a vinylphosphonate with ammonia in alcoholic solution in the presence of catalytic amounts of sodium methoxide.[35,36] α-Bromovinylphosphonate reacts with a concentrated aqueous solution of ammonia on heating for 10 min at 50–60 °C and subsequent hydrolysis of the ester groups with hydrochloric acid.[41,42]



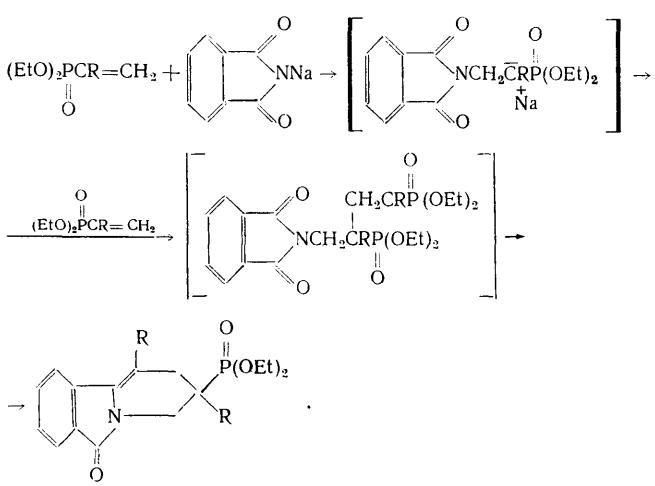
The rate of addition depends not only on the nature of the amine but also on the nature of the substituent at the phosphorus atom. An increase in electron-donating properties for the substituent at phosphorus significantly reduces the reaction rate.[43] This is caused by the different polarity of the multiple bond in imides and esters of vinylphosphonic acid. Vinylphosphonic acid diamides react with ethylenimine, diethylamine, piperidine and morpholine at 20 °C for 1.5–2 d or at 40–50 °C for 4–5 h. Allylamine and dibenzylamine add in the presence of catalytic amounts of sodium ethoxide.



Reaction of the butyl ester of methylvinylphosphonic acid with piperidine continued for 4 days at 20 °C and led to an almost quantitative yield of *N*-substituted phosphonate.[32]



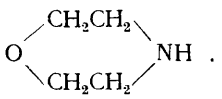
α-Substituted vinylphosphonates are synthons for preparing AEP and its derivatives.[49]



Various heterocyclic compounds were obtained by this method by treating vinylphosphonates with such imides as maleimide, succinimide and glutarimide.[49]

Reactions of vinylenediphosphonic acid with primary and secondary aliphatic and cyclic amines have been investigated. These were carried out in water or other highly polar media (H_2O–EtOH, AcOH) at 100–120 °C.[44–46]

$CH_2{=}C(PO_3H_2)_2 \xrightarrow{R'R''NH} R'R''NCH_2CH(PO_3H_2)_2$,
$R'R''NH$ = $MeNH_2$, $EtNH_2$, $(HOCH_2)_3CNH_2$, $HOCH_2CH_2NH_2$, $C_5H_{11}NH_2$, $C_7H_{15}NH_2$, $C_9H_{19}NH_2$, Et_2NH, $(HOCH_2CH_2)_2NH$, $(CH_2)_5NH$,



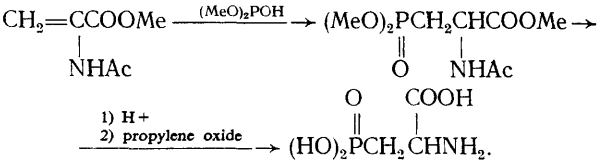
Usually a 2–6 fold molar excess of amine was used especially in the case of primary amines to suppress further reaction of products with the initial acid.

Investigation by TLC of the dependence of reaction rate on the pH of the medium showed the existence of an optimum region of pH values which was 7–9 for ethylamine, diethylamine and piperidine. At lower and higher pH values the reaction rate was sharply reduced. It was assumed that the optimum pH value must be lower than the pK_a of the nucleophile.[44–46] As was to be expected the sterically hindered *tris*-hydroxymethylaminomethane proved to be the least active. In difference to the indicated amines morpholine added at a high rate to the acid in the pH range 2–8.

b) Addition of dialkyl phosphites to unsaturated nitrogen-containing compounds

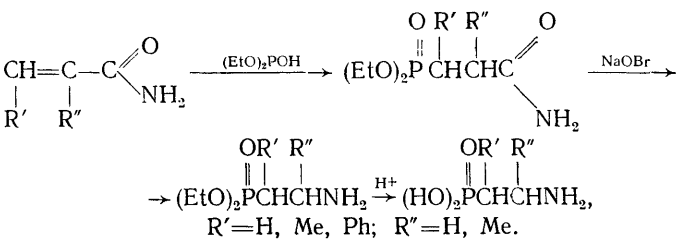
The addition of dialkyl phosphites to unsaturated compounds containing a carboxyl or carbonyl group has been described. The products were converted into amino compounds (by Hofmann, Curtius or Beckmann reactions).[11,50–52]

The ability of dimethyl phosphite to add to an activated carbon–carbon double bond has been demonstrated.[50] The phosphonic analogue of aspartic acid, where the β-carboxyl group is replaced by a phosphonate group, was obtained by the interaction of the methyl ester of *N*-acyl-α-aminoacrylic acid with dimethyl phosphite and subsequent hydrolysis.



Soroka and collaborators[53] improved this method by using esters of methyl- or ethylphosphonic acids in place of dimethyl phosphite. As a result the corresponding phosphinic analogues of aspartic acid were formed.

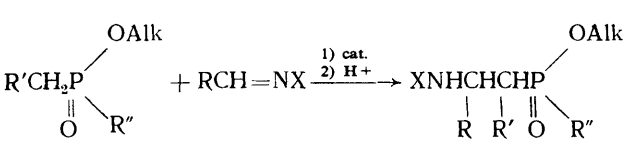
Carbamoyl phosphonates were formed on reacting amides of unsaturated acids with diethyl phosphite in the presence of catalytic amounts of EtONa. AEP or its analogues were obtained after several conversions and hydrolysis.[51,52]



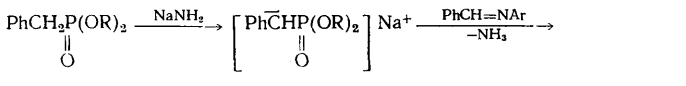
This reaction enabled AEP analogues to be obtained with various substituents on the α- and β-carbon atoms.[51]

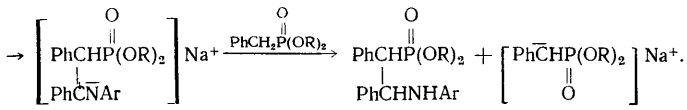
c) Addition of phosphonates at multiple carbon–nitrogen bonds

Aminophosphonates were obtained from Schiff's bases and phosphonates with an active methylene group in the presence of acidic or basic catalysts.[54–59]

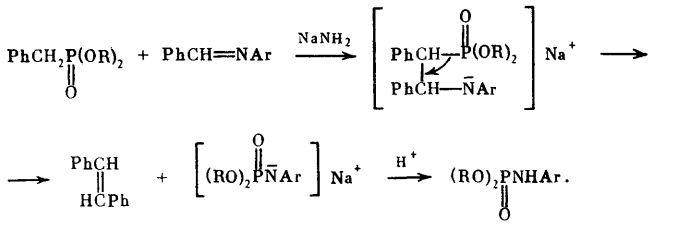


The reactions were investigated in the presence or absence of catalysts ($AlCl_3$, $NaNH_2$, $LiNH_2$) in ether and liquid ammonia at various temperatures. The influence was studied of the position of the substituent in the phenyl nucleus located on the nitrogen atom of the Schiff's base on the rate and route of the reaction. Optimum conditions were established for forming aminophosphonates. The following reaction mechanism was proposed.





The reaction did not proceed without a catalyst. In the presence of an excess of catalyst breakdown of the intermediate probably occurs and olefins are formed.

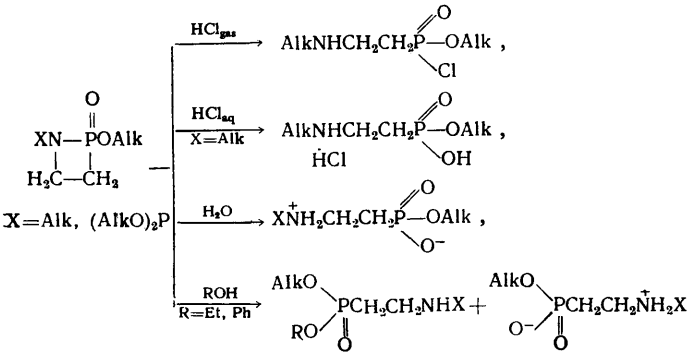


Chlorine in the *meta*-position of a benzene ring on the nitrogen atom increases the yield of aminophosphonate by 5–10%. The influence of electron-donating substituents varies depending on the position in the benzene ring. A methyl substituent in the *ortho*-position increases the yield of aminophosphonate, in the *para*- and *meta*-positions it aids dephosphorylation and the formation of olefins. The aminophosphonate is formed in 52–88% yield on reacting equimolar quantities of phosphonate and azomethine in the presence of catalytic amounts of sodium amide at 10–15 °C in ether.[54]

This method is very important since it affords the possibility of obtaining 1,2-substituted *N*-aryl-, *N*-carboxyl- and *N*-acylamino-phosphonates which are difficult to obtain by other routes.

4. Decomposition of 1,2-azaphosphetidines

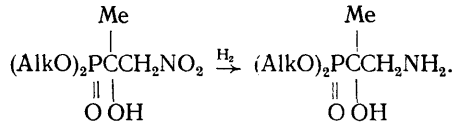
Monoesters of *N*-substituted aminoethylphosphonates are readily formed in almost quantitative yield by the action of hydrogen chloride, water or hydrochloric acid on 1,2-azaphosphetidines.[60–63] Diesters of aminophosphonates, together with the monoester, are formed on reaction with alcohol or phenol. Yields of mono- and diesters were not high because of the formation of reaction byproducts.



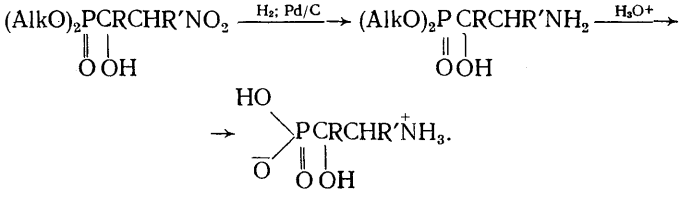
5. Reductive amination

a) Reduction of nitro compounds

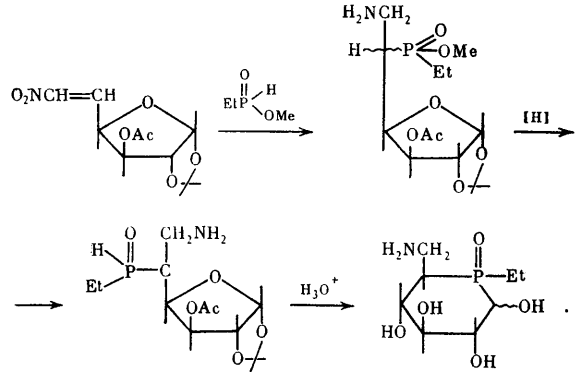
Aminophosphonates have been obtained by the reduction of nitro groups in phosphonates in the presence of Raney nickel catalyst.[64–67]



The hydrogenation of α-hydroxy-β-nitroalkylphosphonates over a neutral 5% palladium on carbon catalyst proved to be more successful. Aminophosphonates were obtained in high yield. They gave AEP analogues on hydrolysis with hydrochloric acid (1 : 1).[64–66,68,69]

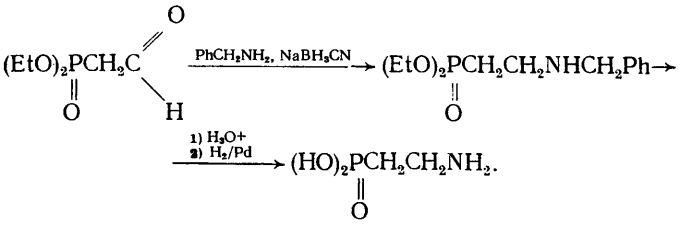


Japanese authors[70] have carried out hydrophosphorylation of a carbohydrate nitrovinyl derivative with the methyl ester of ethylphosphonic acid then reduction of the nitro and phosphono groups in the adduct obtained with the aim of taking off protecting groups. An original cyclisation reaction occurred.

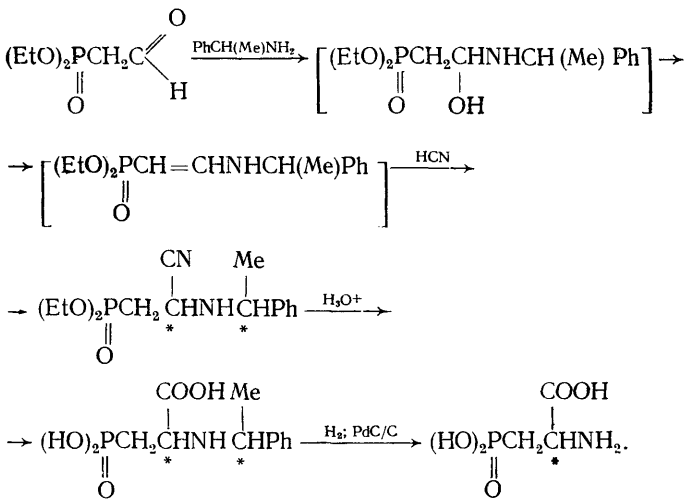


b) Reduction of azomethines

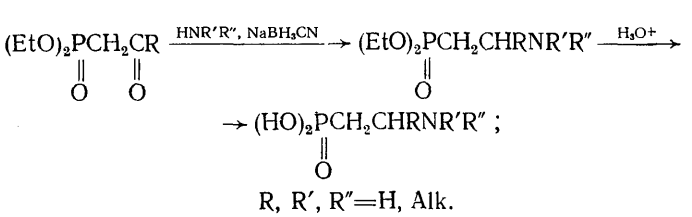
N-Benzylaminophosphonates are formed on condensing phosphonaldehydes with benzylamine in the presence of sodium cyanoborohydride.[71] Hydrogenolysis in the presence of palladium catalyst was used to remove the protecting *N*-benzyl and obtain a free amino group.



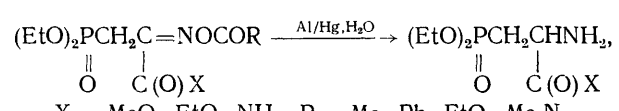
Phosphonaldehydes react with $S(-)$α-methylbenzylamine in the presence of HCN with the formation of optically active *N*-substituted aminophosphonates with an enantiomeric excess of 50%. Removal of the α-methylbenzylamino group by hydrogenolysis in the presence of a 10% palladium on carbon catalyst, followed by hydrolysis of the ester groups at the P atom with hydrochloric acid to obtain β-phosphonylalanine, occurred without epimerisation.[72]



Ketophosphonates,[73,74] like phosphonoaldehydes[71] also condense readily with amines in the presence of sodium cyanoborohydride. The reaction takes place in methanol at 20 °C and aminophosphonates are formed in high yield. β-Aminoethylphosphonic acids, either mono-*N*-substituted or containing a free amino group were obtained by hydrolysis of the ester groups at the P atom.[73]



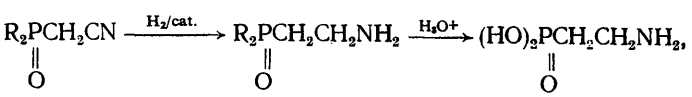
An interesting method of obtaining β-phosphonylalanine by reduction of *O*-acylated oximes with aluminium amalgam has been proposed.[75]



This method is convenient for the synthesis of various β-phosphorylated derivatives of α-aminopropionic acid.[75]

c) Reduction of the nitrile group

Aminoethylphosphonates are formed on reducing phosphonacetonitriles.[76–79]

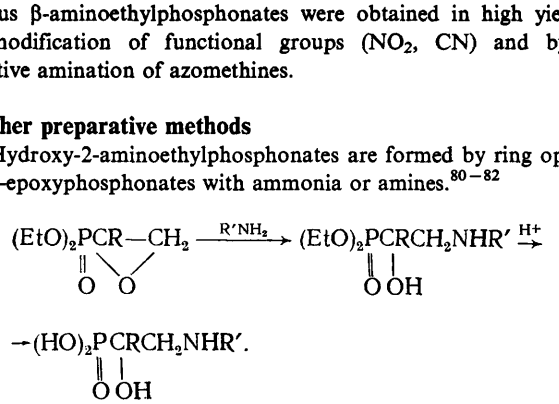


Hydrogenation was carried out in alcoholic ammonia solution in the presence of Rh/Al_2O_3 catalyst[76] and other additives preventing polymerisation at the increased pressure of 3–4 atm.[78] Dimethyl amido- and diethyl cyanomethylphosphonates were readily hydrogenated in the presence of Raney nickel catalyst and on hydrolysis gave AEP.[77–79] Palladium (10%) on carbon was also used as catalyst for the reduction of the CN group in diethyl cyanomethylphosphonate.[79]

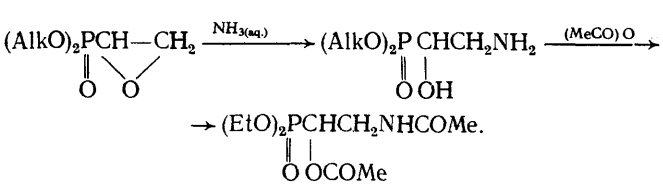
Thus β-aminoethylphosphonates were obtained in high yield by the modification of functional groups (NO_2, CN) and by the reductive amination of azomethines.

6. Other preparative methods

1-Hydroxy-2-aminoethylphosphonates are formed by ring opening of 1,2-epoxyphosphonates with ammonia or amines.[80–82]



The interaction of dialkyl 1,2-epoxyethylphosphonates with ammonia and with aniline has been investigated.[81] It was established that the reaction proceeded more readily with ammonia. With an excess of aqueous ammonia at 20 °C a distillable substance was obtained which was identified by conversion into the acetyl derivative.

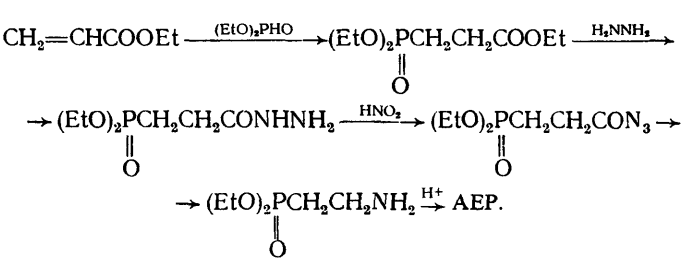


With aniline reaction occurred at 120–125 °C and took 24 h.

A method has been patented for obtaining *N*-substituted aminodiphosphonates by the action of ammonia, arylamines and dialkylamines on 2,2-diphosphonyloxirane.[82]



A method has been proposed for obtaining AEP by a scheme comprising addition of diethyl phosphite to an unsaturated compound, several transformations and subsequent hydrolysis of the resulting diethyl β-aminoethylphosphonate.[11]



Aminophosphonates are formed in high yield on reacting diethyl β-bromoethylphosphonate with diethylamine or dibutylamine.

The reaction was effected by boiling with an excess of amine in aqueous solution.[83]

$$(EtO)_2PCH_2CH_2Br \xrightarrow[H_2O]{Et_2NH} (EtO)_2PCH_2CH_2NEt_2.$$

Reaction with aziridine was carried out in a similar manner in aqueous solution in the presence of triethylamine.[84]

$$(EtO)_2PCH_2CH_2Br \xrightarrow[Et_3N]{HN} (EtO)_2PCH_2CH_2N.$$

Synthesis of a carbamate of β-aminophosphonic acid has been effected starting from the diester of β-phosphonocarboxylic acid. This was converted into the azide which was then subjected to a Curtius rearrangement to give the carbamate.[85]

$$(EtO)_2PCH_2CH_2COOH \xrightarrow[PhCH_2OH,\ Et_3N]{(PhO)_2PON_3} \rightarrow (EtO)_2PCH_2CH_2NHC(O)OCH_2Ph.$$

This reaction has been used to obtain *N*-substituted urethanes and ureas.[86]

$$(AlkO)_2PCH_2CH_2NCO \xrightarrow{Alk'OH} (AlkO)_2PCH_2CH_2NHCOOAlk',$$
$$(AlkO)_2PCH_2CH_2NCO \xrightarrow{ArNH_2} (AlkO)_2PCH_2CH_2NHCONHAr.$$

This phosphonic and phosphinic analogues of aspartic acid have been obtained using the Strecker reaction.[87,88]

$$R(EtO)P(O)CH_2CHO \xrightarrow[2)\ H_3O^+]{1)\ NaCN,\ RNH_2\cdot HCl} R(HO)P(O)CH_2CHNHR\cdot COOH.$$

β-Aminoethylphenylphosphinic acid was formed on oxidation of a phosphine with hydrogen peroxide.[89]

$$PhP(H)CH_2CH_2NH_2 \xrightarrow{2H_2O_2} PhP(OH)CH_2CH_2NH_2.$$

Diesters of 2-benzylimidazolylmethylphosphonic acid were synthesised by reacting *C*-phosphorylated imidates with *o*-phenylenediamine.[90]

$$(RO)_2PCH_2C(=NH\cdot HCl)OR' \xrightarrow[-R'OH,\ -NH_4Cl]{-NH_2,\ -NH_2} \text{benzimidazole-}CH_2P(O)(OR)_2.$$

A method has been suggested for obtaining optically active β-aminophosphonates and -phosphinates.[21,91]

III. Properties

1. Physical properties

β-Aminoethylphosphonic and -phosphinic acids are colourless, high melting, crystalline substances, soluble in water, less well in ethanol, nitromethanol and other polar solvents. The potentiometric titration curve for the amino acids has three discontinuities corresponding to the three ionisation constants of these compounds.[12] As for other aminophosphonic acids, they have a zwitterionic structure.[8] Polymorphism is a characteristic of AEP, two crystalline forms of it are known, an α form of rhombic plates and a β of needles, which is more stable.[11,12,79] The melting point is near 280 °C, however depending on the form the melting point may vary up to 20 °C.[12]

The diesters of *N*-alkylaminoethylphosphonic acids are colourless liquids, distillable in vacuum. The diesters of 1-hydroxy-2-aminoethyl phosphonic acids are thick viscous liquids, decomposing on distillation in vacuum.

There are broad absorption bands in the infra-red spectra of 1-hydroxy-2-aminoethylphosphonic acids in the 2700–3400 cm^{-1} region characteristic of the zwitterionic $PO^-\ldots NH_3^+$ with strong hydrogen bonds.[66] The zwitterionic structure is also confirmed by the presence of bands at 1620–1660 and 1520 cm^{-1} characteristic of NH and NH_3^+ deformation vibrations. The absorption frequency of the phosphoryl group is lowered to 1120–1150 cm^{-1}. An absorption band in the region of 3260 cm^{-1} is characteristic of OH group vibrations.

A significant low frequency shift was observed in the IR spectra of the mono ester of aminophosphonic acid[61] for the stretching vibrations of the N–H group in the 2750–2400 cm^{-1} region in comparison with the IR spectrum of the diester [ν(NH) 3280 cm^{-1}], where it was overlapped by the bands of C–H stretching vibrations,[61] which is characteristic for quaternary ammonium bases. The splitting of P=O group stretching vibrations in the 1230–1190 cm^{-1} region indicates the formation of associates.

A specific absorption for the amino group of AEP esters was detected in the 3500–3300 cm^{-1} region.[75]

The ^1H and ^{31}P NMR spectra have been studied in detail.[19,21–24,28,41,49,61,62,67,71–75,77,80,81,85,87,88,91,92]

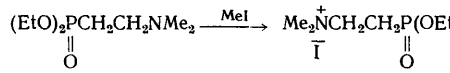
2. Chemical properties

a) Interaction with electrophilic reagents

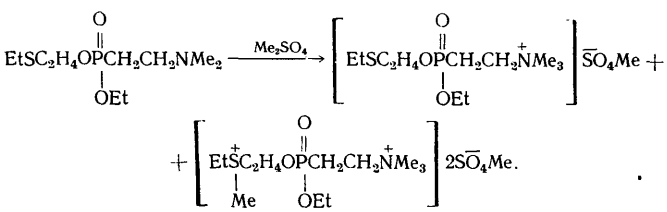
The diesters of *N*-monosubstituted aminophosphonates display the properties of proton-containing nucleophiles. They are readily phosphorylated by dialkyl chlorophosphites in the presence of triethylamine, are alkylated by alkyl halides, and add to isocyanates and *N*-oxides.[19,28,61,75]

$$(EtO)_2PCH_2CH_2NHR \xrightarrow[Et_3N]{(AlkO)_2PCl} (AlkO)_2PN(R)CH_2CH_2P(O)(OEt)_2,$$
$$(EtO)_2PCH_2CH_2NHR \xrightarrow[Et_3N]{(AlkO)_2POCl} (AlkO)_2PN(R)CH_2CH_2P(O)(OEt)_2,$$
$$(EtO)_2PCH_2CH_2NHR \xrightarrow[R=H,\ Alk]{R'NCO} R'NHCON(R)CH_2CH_2P(O)(OEt)_2,$$
$$(EtO)_2PCH_2CH_2NHR \xrightarrow{ArC\equiv N\rightarrow O} ArCN(R)(NOH)CH_2CH_2P(O)(OEt)_2,$$
$$(EtO)_2PCH_2CH_2NHR \xrightarrow[R=P(O)(OAlk)_2]{AlkHal} RN(Alk)CH_2CH_2P(O)(OEt)_2.$$

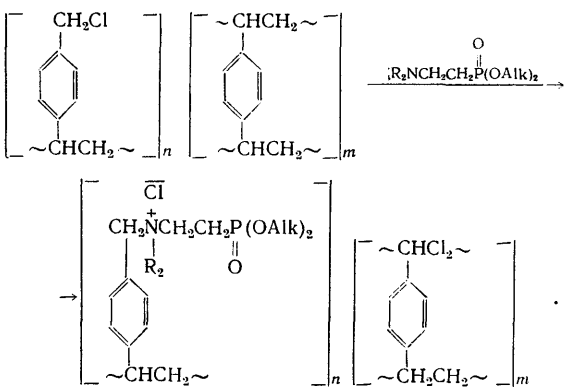
N-Disubstituted aminophosphonates are also readily alkylated by methyl iodide or dimethyl sulphate with the formation of salts, viz. the iodides or methosulphates of the corresponding aminophosphonates.[31,33,93]



On reacting *O*-ethyl-*O*-(β-ethylmercaptoethyl)-β-dimethylaminophosphonate with dimethyl sulphate the *N*-methyl methosulphate and *N*,*S*-dimethyl dimethosulphate were formed in the ratio 1 : 2.[33]



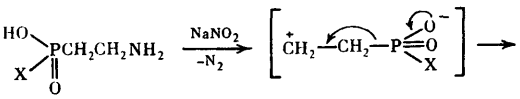
N-Disubstituted aminophosphonates react with the chloromethylated copolymer of styrene with divinylbenzene in a similar manner.[94] The reaction is usually carried out in a medium of the aminophosphonate at 90 °C in a nitrogen atmosphere.



b) Diazotisation

The diazotisation of aminophosphonates and -phosphinates has been studied.[26,69,95] It was established that the reaction proceeded through a carbocation intermediate and, depending on the structure, may go by two routes: rearrangement with migration of the phosphono group to a carbon atom with reduced electron density[95] or decomposition (fragmentation) with the formation of unsaturated compounds and inorganic phosphate.[26,69]

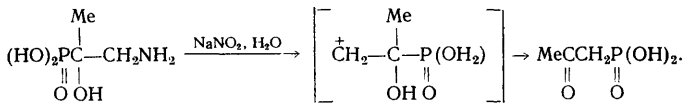
Diazotisation of aminophosphonates and -phosphinates containing an OH-group on the phosphorus atom is usually accompanied by fragmentation with the formation of olefins (in 70–80% yield), inorganic phosphate, vinylphosphonic acids and other contaminants.[26] The reaction was carried out with sodium nitrite in aqueous solution at 100 °C.



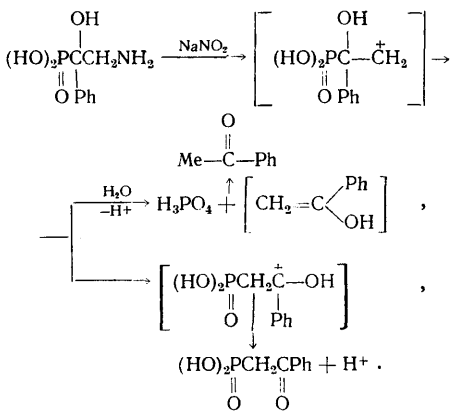
→ $CH_2=CH_2$ + inorganic phosphate,

X = OH, Ph.

When two substituents (methyl and OH-group) are present on the α-carbon atom a rearrangement occurs with migration of the phosphonic fragment and formation of 2-ketopropanephosphonic acid.[80]

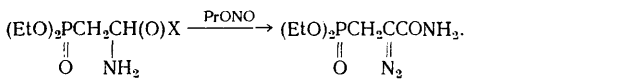


If the substituents on the α-carbon atom are OH and Ph then mainly (80%) rearrangement and only insignificant (7%) fragmentation occurs.[69]



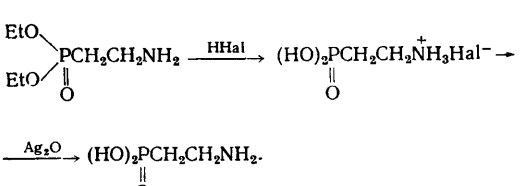
The reaction takes place at room temperature.

A diazo compound is formed on diazotising aminophosphonate with propyl nitrite in the presence of catalytic amounts of acetic acid.[75]

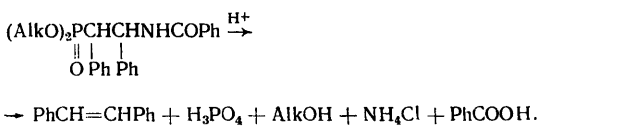


c) Hydrolysis

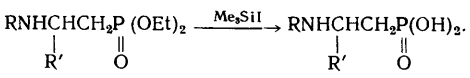
Conversion of esters of β-aminoethylphosphonic acids into the free acids is usually effected by hydrolysis in acid medium. Hal^- is removed using silver oxide,[26] propylene oxide, butylene oxide,[23,40,50] sodium hydroxide,[61] or aniline[66,68] or an aqueous solution of the aminophosphonate hydrochloride is passed through a column of Dowex 50W-X2 (H-form) ion exchange resin.[41,53,75]



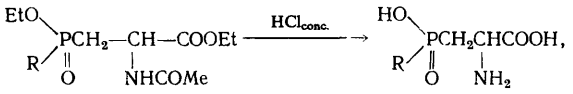
Exceptions are diesters of 1,2-diphenyl-substituted aminophosphonates which are decomposed on boiling in 20% HCl with the formation of olefin.[58]



Esters of aminophosphonic acids are converted into acids by the action of trimethylsilyl iodide[23] or trimethylsilyl bromide.[92]



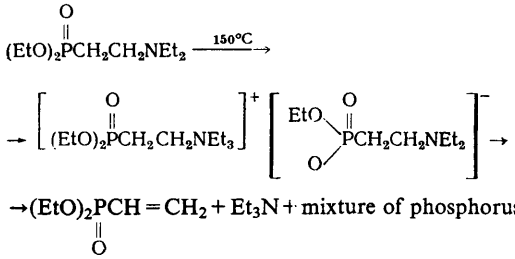
An *N*-acetyl group on an aminophosphonate may be converted into a free amino group by boiling with an excess of HCl for 10–12 h.[53]

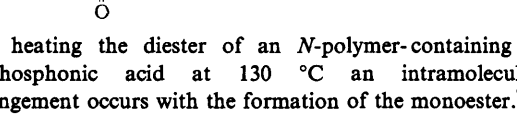


R = Me, Et, EtO.

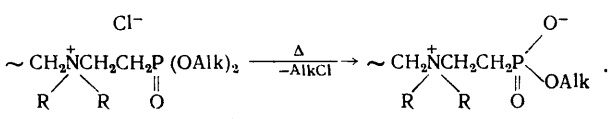
d) Stability

Diesters of 1-hydroxy-2-aminoethylphosphonic acid have low stability,[66,68] are decomposed on distillation[81] and were isolated as picrates which are then used for their purification and identification.[66,68] In contrast the diesters of β-aminoethylphosphonic acid are stable under normal conditions. On heating at 150 °C for 34 h they are decomposed with the formation of diethyl vinylphosphonate, triethylamine and a mixture of oxyacids of phosphorus.[17] It was proposed that an intermolecular reaction occurred with the formation of an intermediate salt which decomposed and gave diethyl vinylphosphonate. The presence of triethylamine was explained by an intramolecular alkylation.



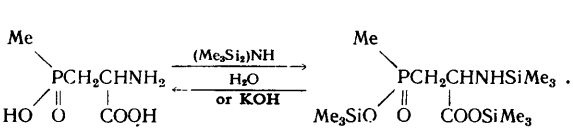


On heating the diester of an *N*-polymer-containing β-aminoethylphosphonic acid at 130 °C an intramolecular ionic rearrangement occurs with the formation of the monoester.[94]



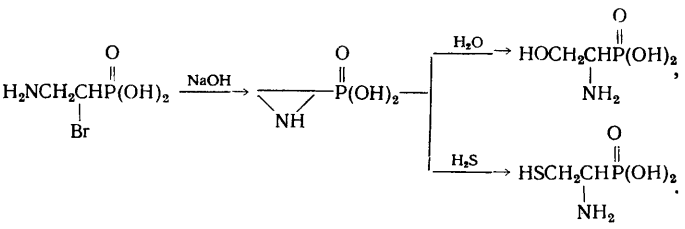
e) Other reactions

On reacting an aminoethylmethylphosphinic acid with an excess of hexamethyldisilazane an *N*-silylated derivative is formed which on treatment with water or alcohol is converted once again into the initial acid.[9]



This method has been proposed for purifying such compounds.[9]

α-Bromo-β-aminoethylphosphonic acid is cyclised in an alkaline medium to aziridinephosphonic acid.[41,42] Fission of the aziridine ring by the action of water or hydrogen sulphide leads to the formation of the phosphonic analogues of serine and cysteine respectively.



It is possible in this way to go from β-aminophosphonic to α-aminophosphonic acids.

IV. Applications

Diesters of aminophosphonic acid possess bactericidal, fungicidal and also antipyretic action.[76,96]

β-Amino-substituted phosphonates and -phosphinates display high extraction properties.[6,7,48,91,94,98] Their important advantage is the combination of good selectivity with high extractive ability.

N-Substituted phosphonic acids have been proposed as extractants and for imparting fire-resistant properties to cellulose material.[82] They possess complexing ability, immunotropic activity and may find application as chelating complexants for multicharged ions, flotation agents, and pharmaceutical preparations.[44,46]

β-Phosphonylalanine displays antiblastic action.[88] The introduction of a CH_3 group in place of an OH at phosphorus sharply reduces the cytostatic activity.[88]

The synthesis of medicinal preparations based on β-aminophosphonic acids is promising.[5,23]

The material presented shows the promise of these compounds. It is possible to be confidant that these compounds will find wide application not only in laboratory practice, but also in medicine, agriculture and other branches of the national economy.

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