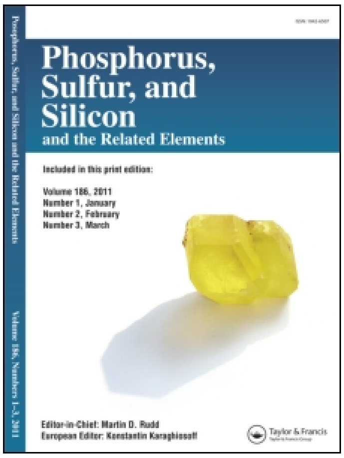

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

ADVANCES IN THE CHEMISTRY OF AMINOPHOSPHINIC ACIDS

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To cite this Article Mater, Ludwig(1983) 'ADVANCES IN THE CHEMISTRY OF AMINOPHOSPHINIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 14: 3, 295 — 322

To link to this Article: DOI: 10.1080/03086648308073262

URL: http://dx.doi.org/10.1080/03086648308073262

Phosphorus and Sulfur, 1983, Vol. 14, pp. 295–322
0308-664X/83/1403-0295/$18.50/0

ADVANCES IN THE CHEMISTRY OF AMINOPHOSPHINIC ACIDS*

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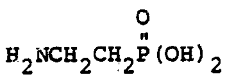
(*Received September 24, 1982*)

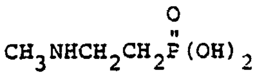
INTRODUCTION

Up to 1959, all the organic phosphorus compounds isolated from living things had been shown to have the carbon-containing portion of the molecule attached to either oxygen or, less commonly, to nitrogen on the phosphorus atom. It came therefore as a distinct surprise when Horiguchi and Kandatsu[29] announced the isolation of a compound having the carbon-to-phosphorus bond, viz. 2-aminoethylphosphonic acid, from ciliated protozoa. Since then several other phosphorus-carbon containing compounds have been detected in nature and isolated. Most of them contain nitrogen also, e.g.



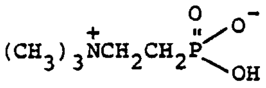
$H_2NCH_2CH_2\overset{O}{\overset{\|}{P}}(OH)_2$ Ref. 29

1



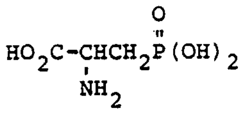
$CH_3NHCH_2CH_2\overset{O}{\overset{\|}{P}}(OH)_2$ Ref. 71a

2



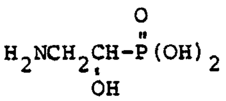
$(CH_3)_3\overset{+}{N}CH_2CH_2P(=O)(O^-)(OH)$ Ref. 33

3



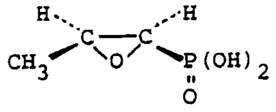
$HO_2C\underset{NH_2}{\underset{|}{C}}HCH_2\overset{O}{\overset{\|}{P}}(OH)_2$ Ref. 34

4



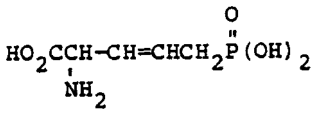
$H_2NCH_2\underset{OH}{\underset{|}{C}}H\text{-}\overset{O}{\overset{\|}{P}}(OH)_2$ Ref. 37

5



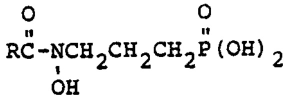
Ref. 25

6



$HO_2C\underset{NH_2}{\underset{|}{C}}H\text{-}CH{=}CHCH_2\overset{O}{\overset{\|}{P}}(OH)_2$ Ref. 68a

7



$R\overset{O}{\overset{\|}{C}}\text{-}\underset{OH}{\underset{|}{N}}CH_2CH_2CH_2\overset{O}{\overset{\|}{P}}(OH)_2$ Ref. 19

8 $R = H, CH_3$

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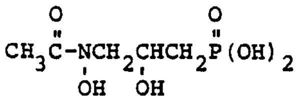
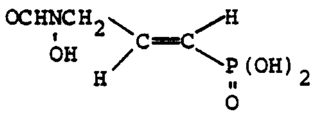
*Extended version of a lecture given at the "Colloque Phosphore" in Montpellier, September 22–24, 1982.



$CH_3\overset{O}{\overset{\|}{C}}-\underset{OH}{\underset{|}{N}}CH_2\underset{OH}{\underset{|}{C}}HCH_2\overset{O}{\overset{\|}{P}}(OH)_2$

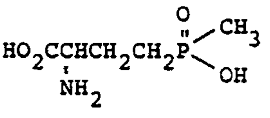
Ref. 20

9



Ref. 20

10



Refs. 2, 36

11

It is interesting to note that so far only one aminophosphinic acid **11** has been detected in nature and isolated from cultures of *Streptomyces viridochromogenes*[2] and *Streptomyces hydroscopicus*[36] as the tripeptide phosphinothricyl-L-alanyl-L-alanine.

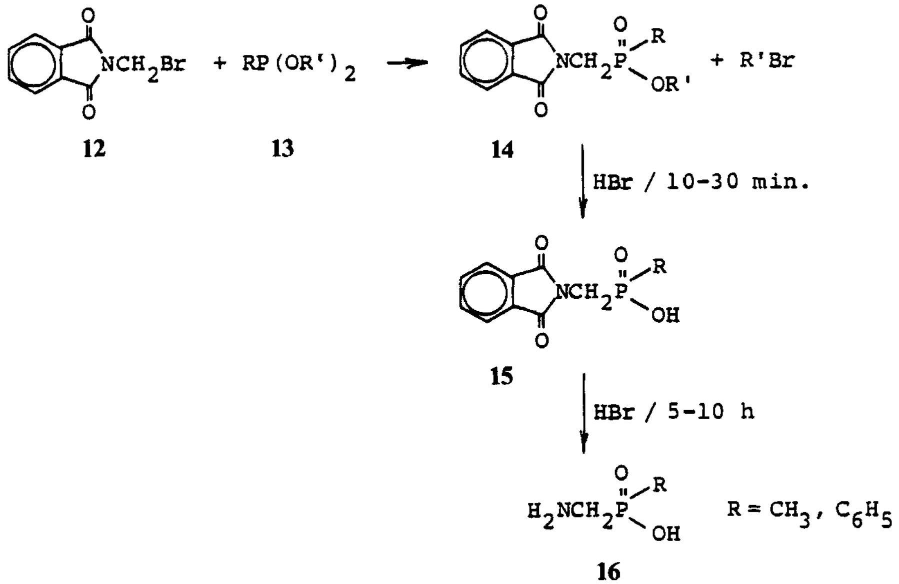
Since the chemistry of aminophosphonic[73] and aminophosphonous acids[3] has been reviewed recently, we shall limit our discussion to new aspects of aminophosphinic acid chemistry.

A. PREPARATION OF AMINOPHOSPHINIC ACIDS

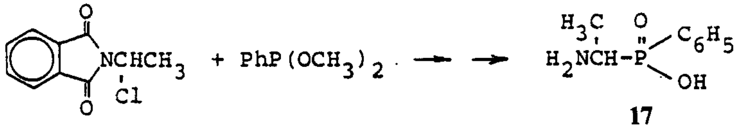
In general many of the methods which have been used for the preparation of aminophosphonic acids[73] are also suitable for the production of aminophosphinic acids.

1. Arbuzov and Michaelis Becker reactions

Reaction of N-bromomethyl-phthalimide **12** with phosphonites **13** gave the phosphinates **14** in high yields (66 to 94%),[69] but reaction of N-α-chloroethyl-phthalimide with dimethyl-phenylphosphonite proved less satisfactory. In this case only a 5% yield of the phosphinate **17** was obtained. On the other hand interaction of 2-bromoethylphthalimide and O,O-diisopropyl-phenylphosphonite at 160° followed by hydrolysis produced 2-aminoethyl-phenylphosphinic acid **18** in good yield.[50] Short treatment of the phthalimide derivatives **14** with HBr hydrolyzes only the ester group to give **15**, which can be isolated. Treatment with excess HBr for extended periods (5 to 10 h) produces the phosphinates **16**, **17**, and **18**. Reaction of o-N-phthalimidobenzyl bromide with dimethyl-phenylphosphonite yielded the phosphinate ester **18a** which upon hydrazinolysis and hydrolysis with HCl gave the aminophosphinic acid **18b**.[14] (α-Amino-2-tolyl)methylphosphinic acid **18c** was obtained from N-(*o*-iodobenzyl)acetamide and methylphosphonite followed by hydrolysis.[56]



12 13 14 15 16



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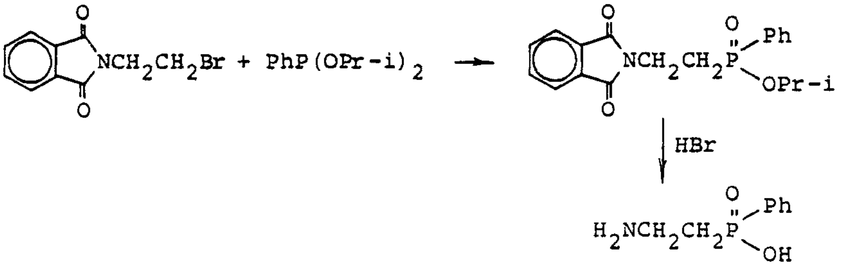

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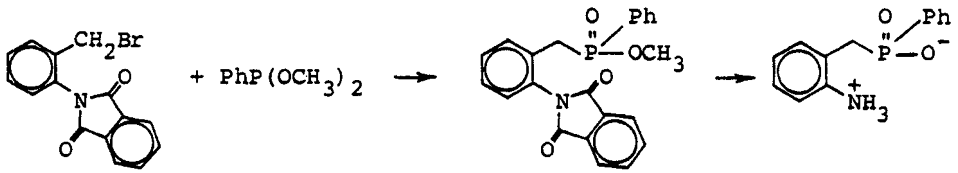
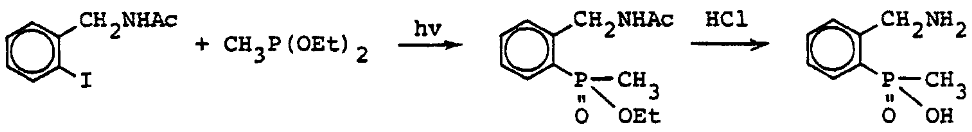
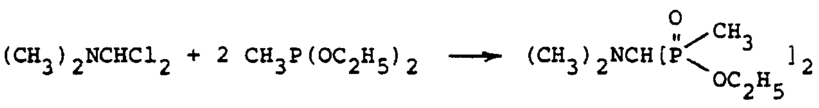


18a 18b



18c



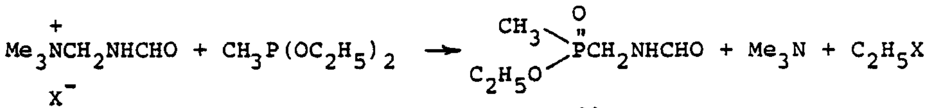
$$(CH_3)_2NCHCl_2 + 2\ CH_3P(OC_2H_5)_2 \longrightarrow (CH_3)_2NCH[P(O)(CH_3)(OC_2H_5)]_2$$

19

More recently the Arbuzov reaction has also been successfully used for the preparation of dimethylaminomethylene-bis(O-ethylmethylphosphinate) **19** according to Maier[45] (yield 60%).

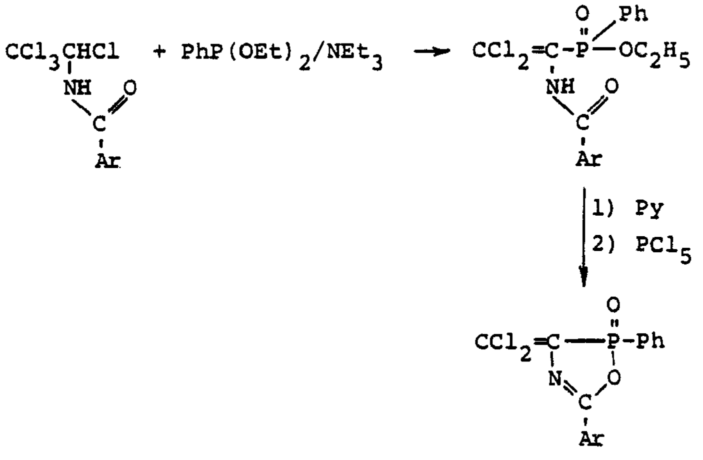
Trimethyl ammonium methylformamide not only undergoes attack by triethylphosphite[76] but also by O,O-diethyl-methylphosphonite to yield O-ethyl-formylaminomethyl-methylphosphinate **20** in 94% yield.[16]

Azlactones of N-acyl derivatives of α-aminophosphinic acids **21** have been obtained by an Arbuzov reaction.[15]



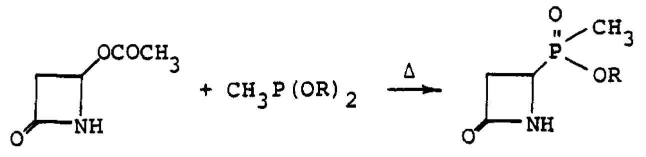
$$\overset{+}{Me_3N}CH_2NHCHO\ X^- + CH_3P(OC_2H_5)_2 \longrightarrow (CH_3)(C_2H_5O)P(O)CH_2NHCHO + Me_3N + C_2H_5X$$

20



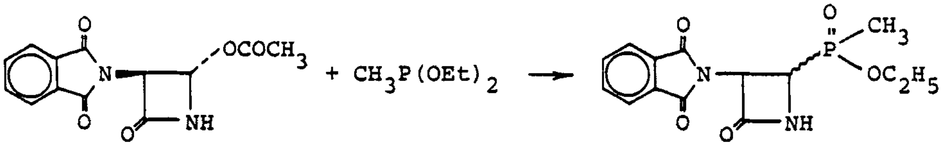
21

And finally 4-oxoazetidin-2-ylphosphinates[7] and -phosphonates[7,13] were obtained from the Arbuzov reaction of 4-acetoxyazetidin-2-one and 4α-acetoxy-3β-phthalimidoazetidin-2-one with phosphonites or phosphites. The phosphinates **22** and **23** were diastereomeric mixtures as shown by ^{13}C and ^{31}P NMR studies, whereas the



22 $R = C_2H_5$

23 $R = CH_2CCl_3$



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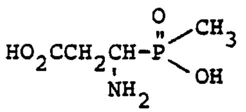

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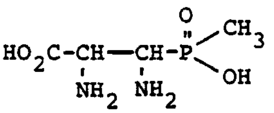

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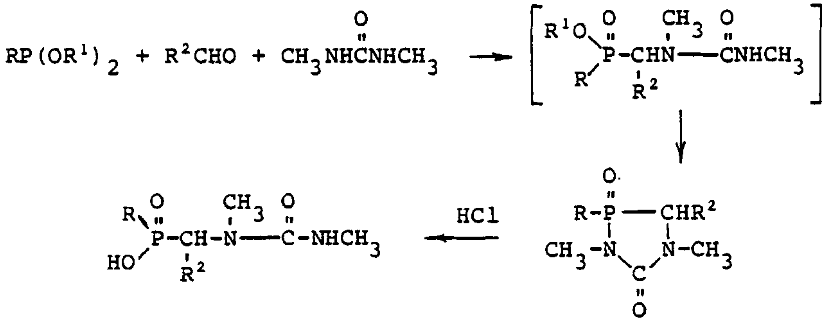


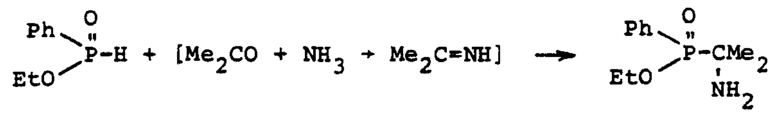
27

phosphinate **24** was obtained as a cis/trans mixture of products. Acid hydrolysis of the phosphinates **22**, **23** and **24** provided a new route to α-aminophosphinic analogs of aspartic acids, e.g. **25** and **26**.[7] Like phosphite, phosphonites also seem to undergo an Arbuzov type reaction when heated with 1,3-dimethyl urea to produce 1,4,2-diazaphospholidines (**27**)[6] which on hydrolysis give ureidophosphinic acids. Transesterification followed by isomerization and ring closure would produce the same products.

2. *Addition of a P—H group to Schiff's bases, enamines and hexahydrotriazines*

The addition of a P—H function to imines is a very general procedure for the formation of P—C—N systems (Ref. 73, p. 519 ff). Virtually any phosphorus moiety

28



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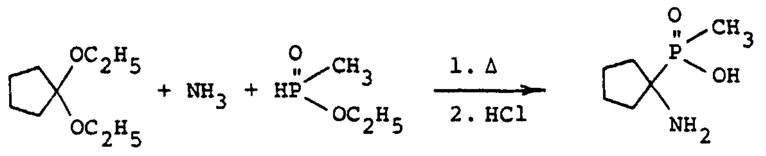

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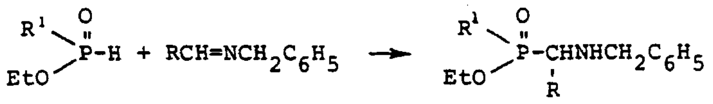
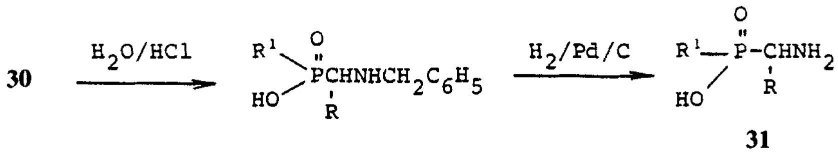


30

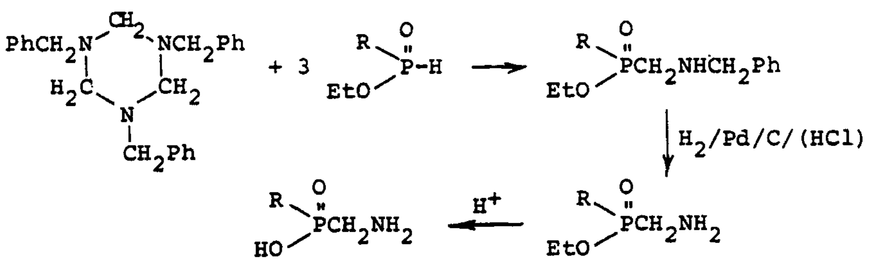
containing a P—H function can be utilized in this process, so that α-amino-phosphonates, -phosphinates, -phosphines, and -phosphine oxides can be prepared.

In an early study it was observed that O-ethyl phenylphosphonite added readily to benzylidene-phenylimine in the presence of an alkoxide as catalyst to give the phosphinate **28**.[71] The same phosphonite gave the α-aminophosphinate **29** when heated with acetone and ammonia in a sealed tube,[32] in low yield. Better yields of the aminophosphinic acid **34** were obtained when the cyclopentanone-diethylketal was heated with phosphonite and ammonia in an autoclave at 100–120°C.[65] α-Aminophosphinic acids were obtained more conveniently and in better yields by hydrogenolysis of an N-benzyl group,[82] e.g. **31**. This procedure is also suitable for



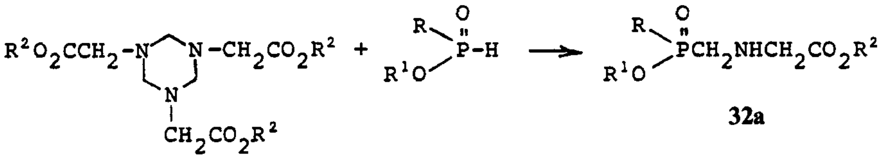
31

the preparation of α-aminomethylphosphinates **32**[46] and α-aminophosphonates,[72] if small amounts of HCl are added in the debenzylation step. The yields are high. (N-Glycinomethyl)-alkylphosphinates **32a** have been produced by the addition of phosphonites to substituted hexahydrotriazines.[43] When the group R is a 2-chloroethyl group, ring closure occurs with elimination of HCl and 1-ethoxycarbonylmethyl-1,3-azaphospholidin-3-ethoxy-3-oxide, **32b**, is formed.[44] The known

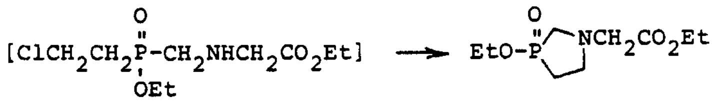


32 R = CH_3

R = C_2H_5



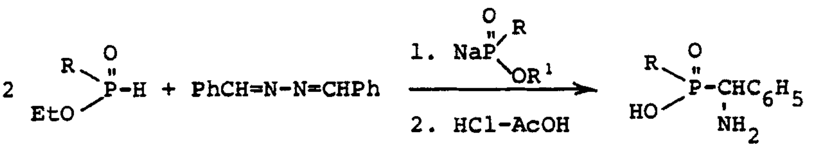
32a



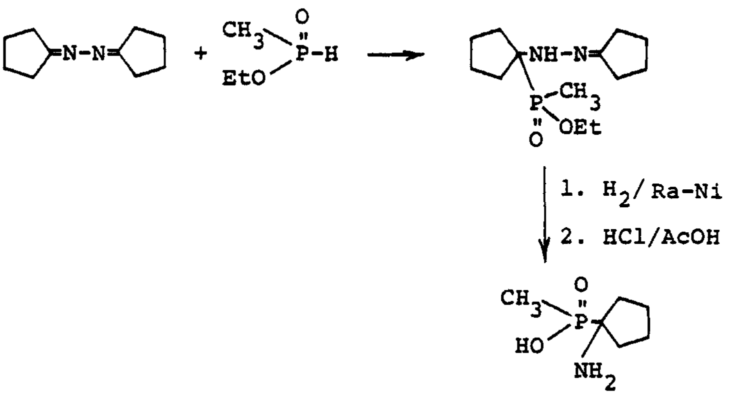
32b

addition of phosphites to aldehyde azine has recently been extended to include phosphonites.[86] The addition is catalyzed by sodium phosphonite. Excess phosphonite cleaves the N—N bond and produces α-aminophosphinates, **33**, directly. In other cases the monoaddition product could be hydrogenolyzed with Raney–Ni as a catalyst[65] to yield the phosphinyl analog of cycloleucine (**34**). The monoaddition product could be isolated in several cases.[59,86] Another route to α-aminophosphinic acids includes the addition of phosphonites to hydrobenzamide and subsequent decomposition with HCl (**35**).[4] At 100°C both diastereomeric racemic modifications are produced in equal concentrations. By lowering the temperature the ratio of diastereomers can be changed, however, and optical resolution by fractional crystallization of the tartrate salt has been achieved.[4]

A particularly simple procedure for the preparation of aminomethylene-bis(phosphonates)[60] and -bis(phosphinates)[45] involves heating a mixture consisting of a primary amine, an orthoformate and a sec. phosphite or a phosphonite, respectively,



33 R = CH_3, Et, Ph



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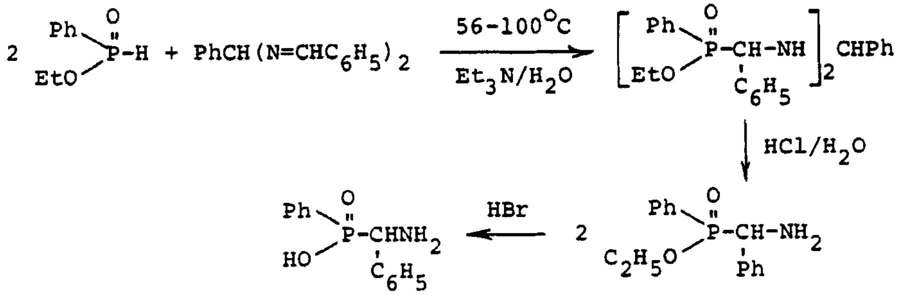
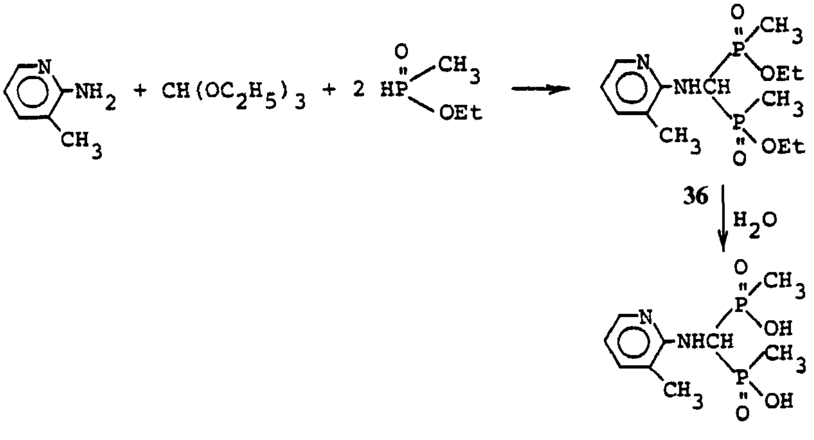


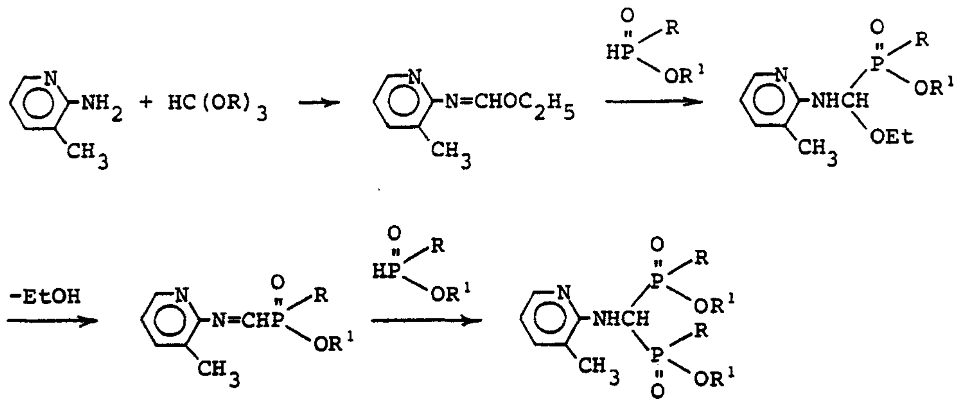
35

e.g. **36**. The bis(phosphinate) **36** hydrolyses easily in water and gives the corresponding bis(phosphinic acid) **37** in high yield.

Although the mechanism is not known it seems probable that as an intermediate an imino ether is formed to which stepwise two moles of a phosphonite are added.



37

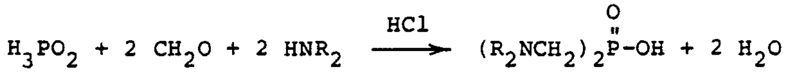


3. Mannich-type reaction of hypophosphorous and phosphonous acids

While the Mannich-type reaction of phosphorous acid has been investigated extensively (Refs. 57, 73 p. 527) that of hypophosphorous and phosphonous acids is much less known. In 1967 we observed[40] that hypophosphorous acid reacts with formaldehyde and secondary amines to give phosphonous, **38**, or phosphinic acids, **39**, depending on the conditions used. More recently this procedure has been extended by us to include functionally substituted secondary amines,[42] such as imino-diacetic acid or N-benzylglycine:

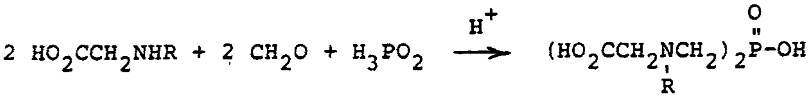
$$H_3PO_2 + CH_2O + HNR_2 \longrightarrow R_2NCH_2\overset{O}{\overset{\|}{P}}(H)OH + H_2O$$

38



$$H_3PO_2 + 2\ CH_2O + 2\ HNR_2 \xrightarrow{HCl} (R_2NCH_2)_2\overset{O}{\overset{\|}{P}}\text{-}OH + 2\ H_2O$$

39

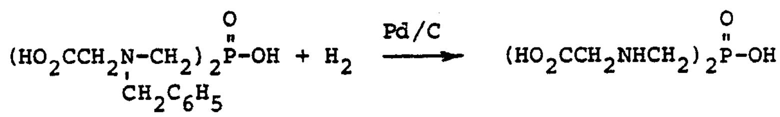


$$2\ HO_2CCH_2NHR + 2\ CH_2O + H_3PO_2 \xrightarrow{H^+} (HO_2CCH_2\underset{R}{N}CH_2)_2\overset{O}{\overset{\|}{P}}\text{-}OH$$

40 $R = CH_2CO_2H$

40a $R = CH_2C_6H_5$

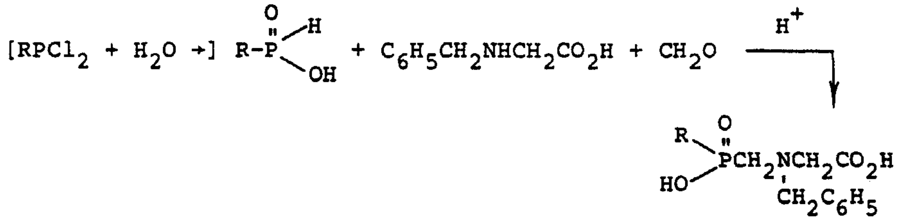
Attempts to oxidize **40** to bis(glycinomethyl)phosphinic acid, **41**, were not successful, but debenzylation of **40a** with H_2 in the presence of Pd/C as catalyst produced high yields of bis(glycinomethyl)phosphinic acid, **41**:



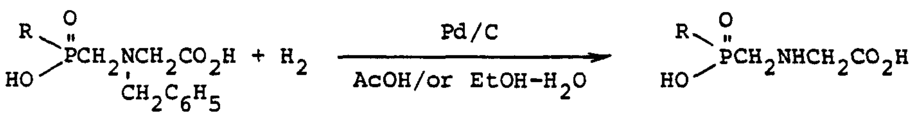
$$(HO_2CCH_2\underset{CH_2C_6H_5}{N}\text{-}CH_2)_2\overset{O}{\overset{\|}{P}}\text{-}OH + H_2 \xrightarrow{Pd/C} (HO_2CCH_2NHCH_2)_2\overset{O}{\overset{\|}{P}}\text{-}OH$$

41

The same procedure has also been successfully applied to the preparation of alkyl- and aryl(glycinomethyl)phosphinic acids **42** and **43**. Since alkyldihalophosphines hydrolyze in water to phosphonous acid, one can directly start with alkyldihalophosphines.[43] Debenzylation in acetic acid or in water/alcohol produces (glycinomethyl)alkyl- and aryl-phosphinic acid, **43**, in high yield. In the case of the trichloromethyl derivative excess hydrogen must be avoided, otherwise dechlorination occurs and the dichloromethyl derivative **43**, R = $CHCl_2$, is produced. Furthermore, the cyanomethyl group hydrolyses during the reaction, which leads to the

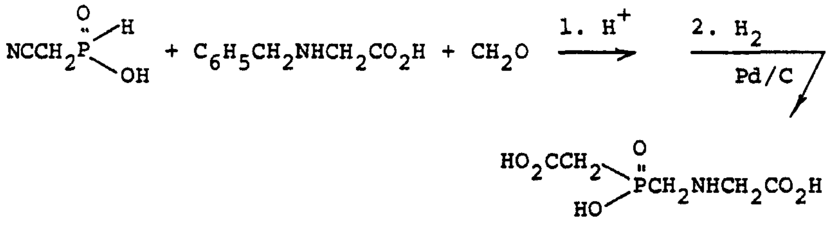


42



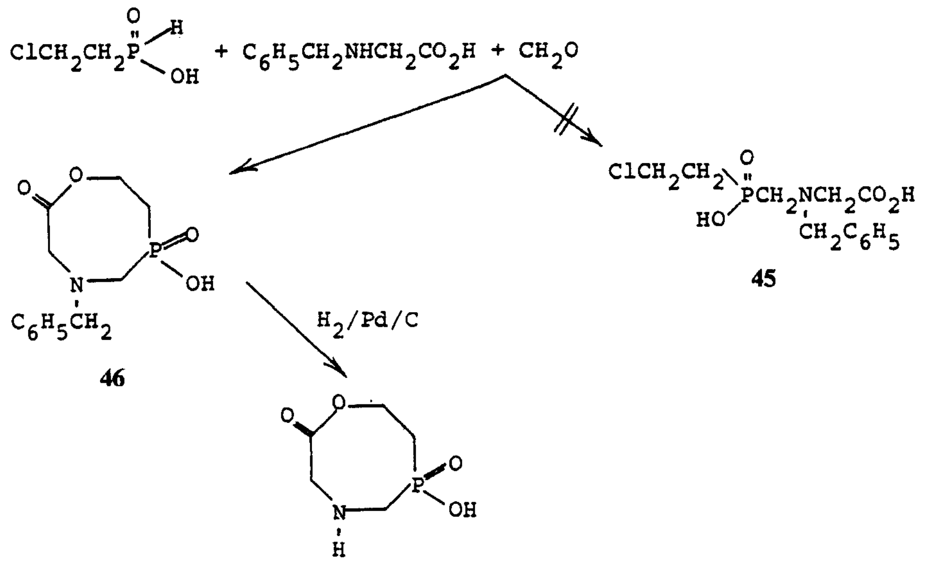
43

R = alkyl, $HOCH_2$, CCl_3, $CHCl_2$, CH_2Cl, Ph



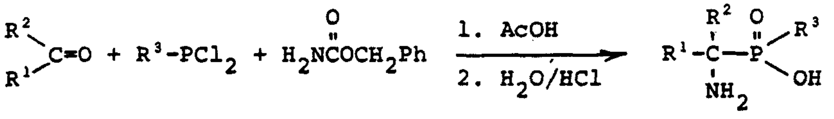
44

formation of a phosphinyl-substituted acetic acid derivative, **44**.[44] A further complication was observed when 2-chloroethylphosphonous acid was caused to react with N-benzylglycine and formaldehyde.[44] Instead of the expected (N-benzyl-N-hydroxycarbonylmethylaminomethyl)-2-chloroethylphosphinic acid **45**, an 8-membered ring lactone, 4-benzyl-1,4,6-oxazaphosphocane-2-oxo-6-hydroxy-6-oxide, **46**, formed by intramolecular esterification, was isolated in over 80% yield. On debenzylation the 8-membered ring lactone is preserved and 1,4,6-oxazaphosphocane-2-oxo-6-hydroxy-6-oxide, **47**, is formed in 75% yield.[44]

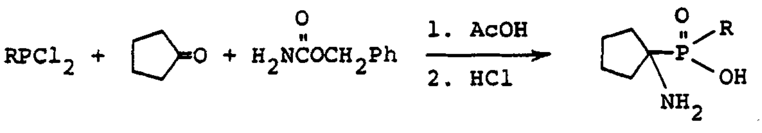


45 **46** **47**

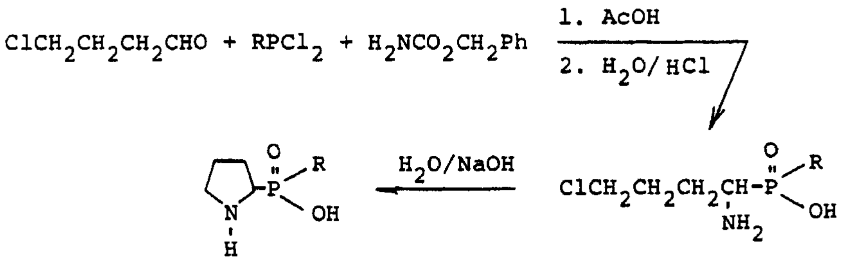
Related to the formation of aminomethylphosphonic acid from amides, formaldehyde, and PCl_3 in acetic acid[17] is the preparation of 1-aminoalkanephosphonic or -phosphinic acids, **48**, from phosphorus trichloride, alkyl- or aryldichlorphosphines, carbonyl compounds (aldehydes or ketones) and benzyl carbamate.[66] The yield is in the order of 40 to 60%. The reaction components may be varied widely. Thus the phosphonic and phosphinic analogs of cycloleucine **34**,[65] the phosphonic and phosphinic analogs of proline **49**[79] and the phosphonic and phosphinic analogs of α-methylaspartic **50**, α-methylpyroglutamic **51**, glutamic **52**, and pyroglutamic acids **53**, could also be obtained by this procedure.[64] Formation of the phosphinic analog of α-methylpyroglutamic acid **51** from ethyl levulinate was not expected because the analogous reaction with ethyl succinate semialdehyde produced, in moderate yields, the open-chain product **52** with only traces of the cyclic



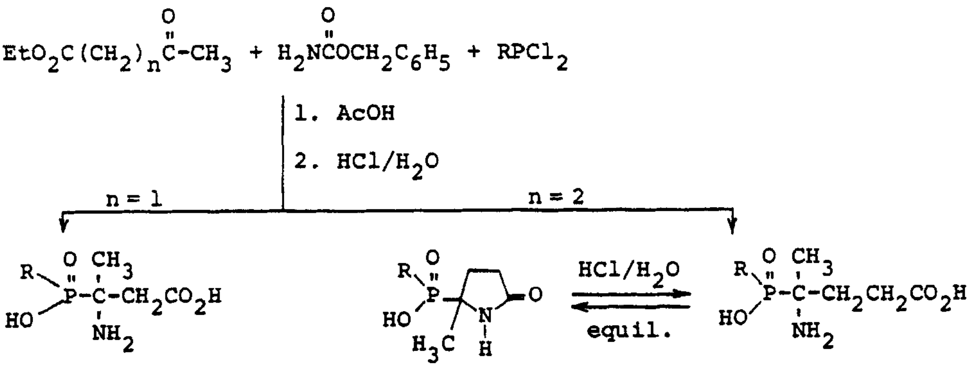
48 $R^3 = CH_3, C_2H_5, C_6H_5$, HO



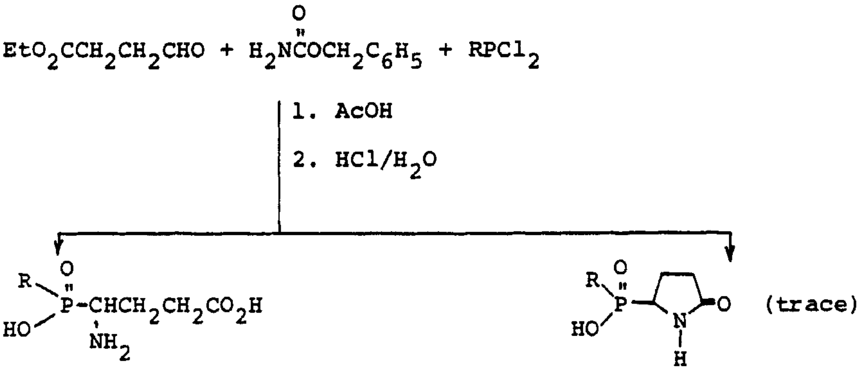
34 $R = CH_3, C_2H_5$, Ph



49 $R = CH_3, C_6H_5, OH$

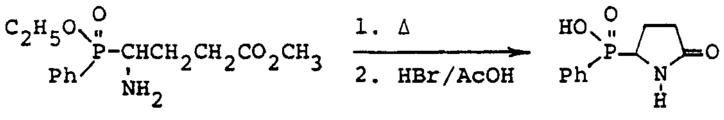


50 $R = CH_3$, Et, Ph, OH **51** $R = C_6H_5$, OH **51a**

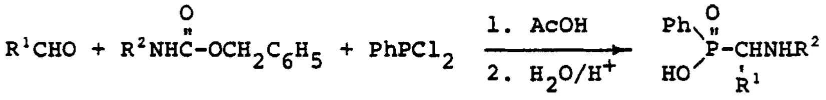


52 $R = C_6H_5$, OH **53** $R = C_6H_5$, OH

derivative **53**. However the cyclic derivative **53** could easily be prepared by cyclization of the ester **54**.[64] A further extension of the carbamate procedure consists in the use of N-alkylcarbamates, aldehydes, and phosphorus or phosphonous chlorides.[63] The yields of **55** are between 40 and 60%. Attempts to extend the scope of the reaction to include ketones and benzyl N,N-dialkylcarbamates were unsuccessful.[63]



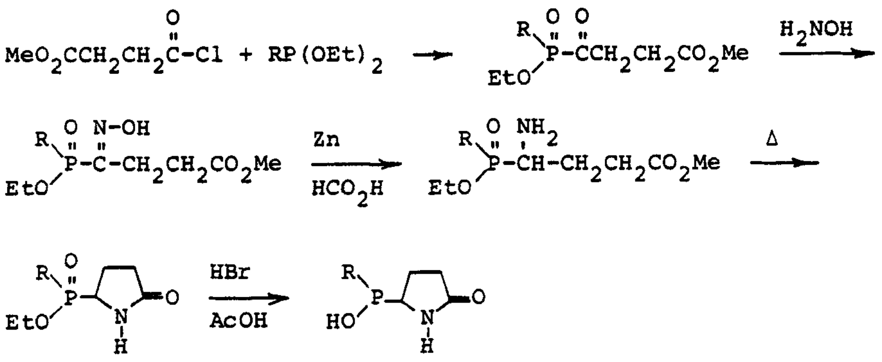
54 **53**



55

4. *The oxime procedure*

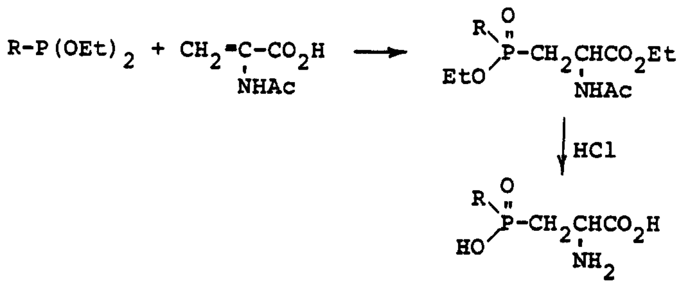
The oxime method for the preparation of α-aminophosphonates (Ref. 73 p. 538) has recently been successfully extended to include α-aminophosphinic acids such as **53**.[64] Instead of using aluminium amalgam, Raney nickel or diborane, respectively, as reducing agents, zinc in formic acid was successful in this case[38] and gave yields ranging from 40 to 68%.



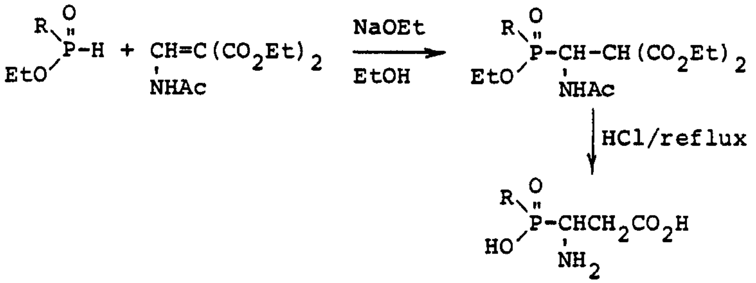
53 R = Ph, OH

5. *Miscellaneous methods*

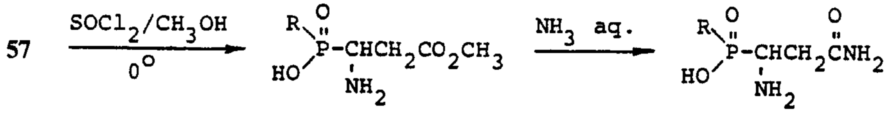
The synthesis of phosphonic and phosphinic analogs of aspartic acid **56** was accomplished by heating a mixture of acetaminoacrylic acid and phosphite[8] or phosphonite[78] respectively. Compound **57**, in which a phosphonic or phosphinic acid group replaces an α-carboxyl group of aspartic acid, has been obtained by addition of phosphite or phosphonites to diethyl acetaminomethylenemalonate followed by hydrolysis and decarboxylation of the adducts.[78] The analogs of asparagine **59** were obtained from **57** in a reaction sequence including esterification and ammonolysis of esters **58**.[78] A simple procedure for the preparation of 3-aminopropyl-alkylphosphinic acids involves heating a mixture of 2-oxo-1,2-oxaphospholanes with



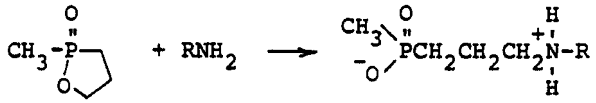
56 R = OH, CH_3, C_2H_5



57 R = OH, CH_3, C_2H_5



58 **59**



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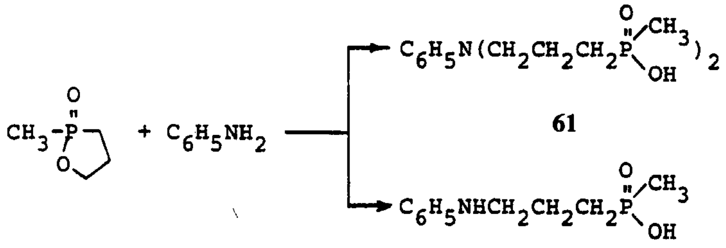
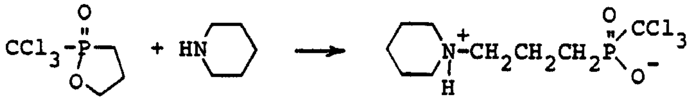
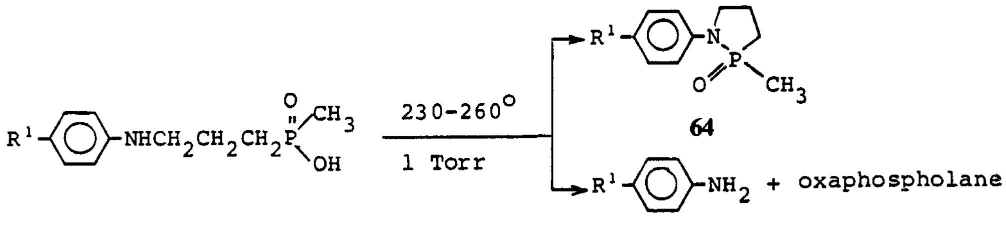


61 **62**



63

aliphatic[26] or aromatic amines.[35,80] Depending on the conditions used either **61** or **62** is obtained when the 2-oxo-1,2-oxaphospholane is heated with aniline or substituted anilines.[35] Compound **62** cyclizes with elimination of water when heated to 230–260° and yields the azaphospholane **64**; in addition starting material is also produced. The azaphospholanes are also formed when the thionophospholanes **64a** and **64b** are heated with anilines to 200°.[35] 2-Aminobenzylphenylphosphinic acid also underwent ring closure when heated to 200° to give 2,3-dihydro-1H-2-phenyl-1,2-benzazaphosphole-2-oxide **65**.[14] On the other hand the zwitterionic aminophosphinic acid **66** failed to undergo thermal cyclization to **67** at 200° in a vacuum.[56]



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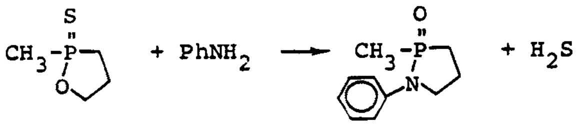
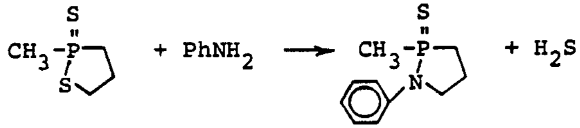
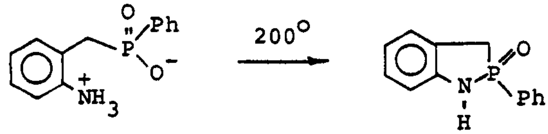


64a



64b



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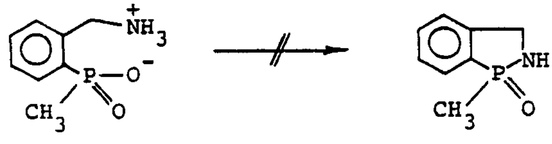
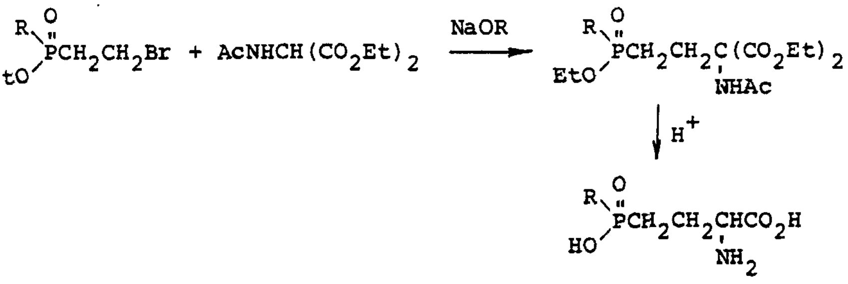


66 **67**

6. Synthesis of phosphinothricine and derivatives

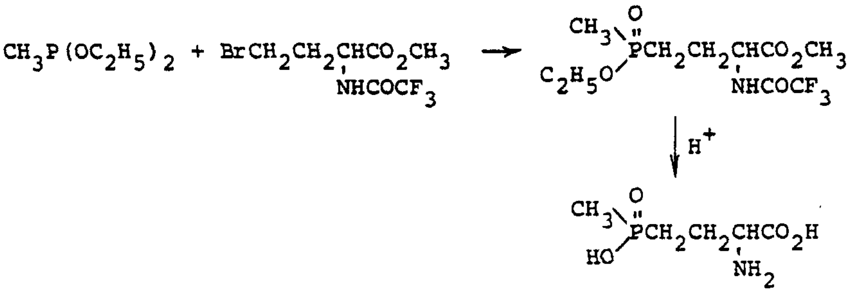
The synthesis of the ethyl and phenylphosphinic acid analogs of glutamic acid **68** was accomplished by condensation of diethyl acetaminomalonate with the corresponding phosphinates, followed by hydrolysis of the crude intermediate compounds according to:[49]



68 R = C_2H_5, C_6H_5

The phosphonic analog (**68**, R = OH) was synthesized in the same way starting from 2-bromoethylphosphonate.[8,47]

The first synthesis of phosphinothricine **69** was reported by Zaehner *et al.* using in the final step an Arbuzov reaction of a homoserine derivative followed by hydrolysis.[2] In another synthesis the acetaminomalonate procedure was used to prepare **69**.[68] Because of problems encountered in the preparation of 2-bromoethylmethylphosphinates, needed as a starting material, this method gave only a few per cent of **69**. A higher yield of phosphinothricine was obtained (35%) when O-2-chloroethyl methylvinylphosphinate was used as a starting material in the acetaminomalonate procedure.[21] Three other syntheses, all involving a Strecker reaction as the final step but differing in the preparation of the starting material (Arbuzov reaction[22] and addition reaction[23]) were also reported. Another variation consisted in the addition of a phosphonite half-ester to acetamino-but-3-ene-oate.[55] Finally phosphinothricine was also obtained by bromination of 4-methyl-phosphinylbutanoic acid followed by ammonolysis with aqueous ammonia solution.[85] We



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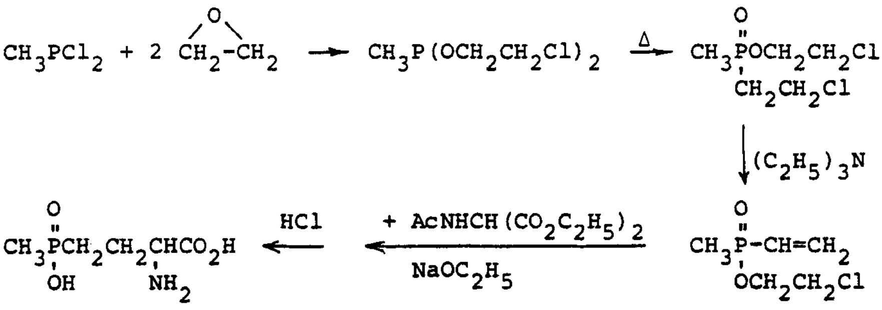

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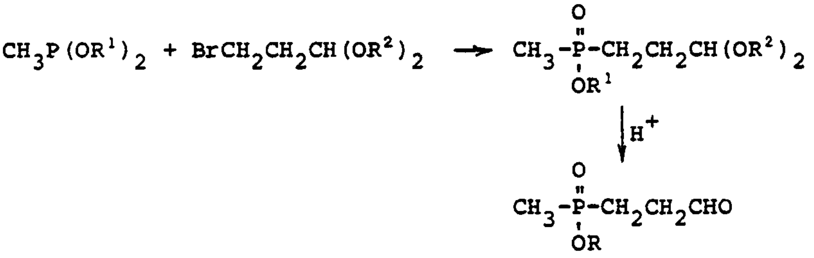
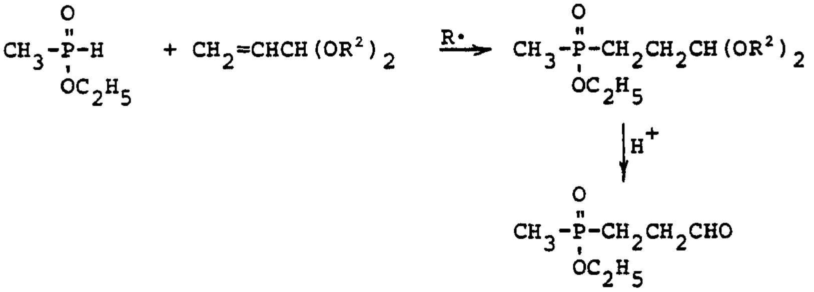
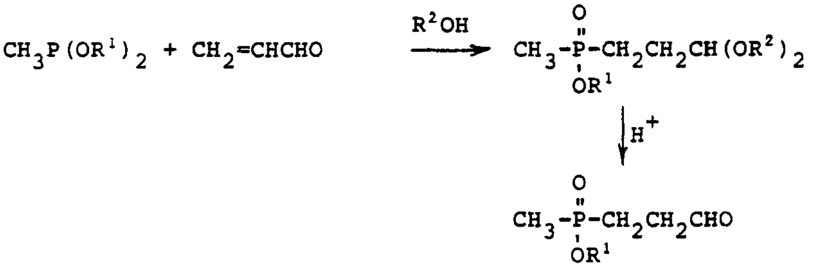


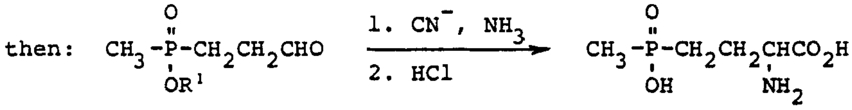
Ref. 22



Ref. 23



Ref. 52



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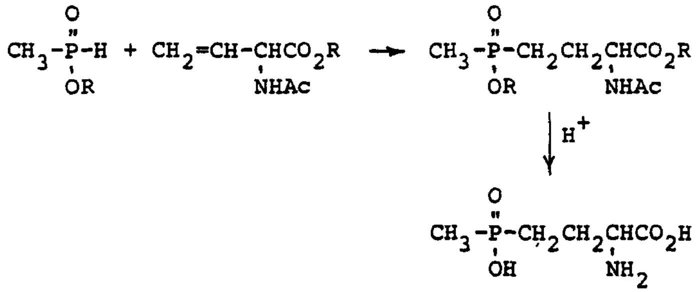
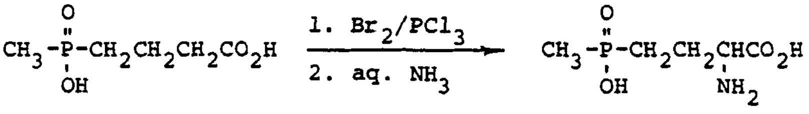


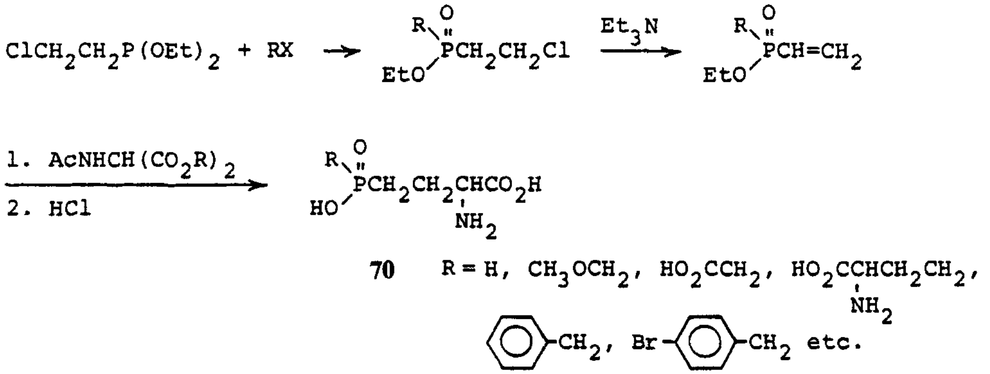
$$CH_3\text{-}\overset{O}{\underset{OR}{P}}\text{-}H + CH_2{=}CH\text{-}\underset{NHAc}{C}HCO_2R \rightarrow CH_3\text{-}\overset{O}{\underset{OR}{P}}\text{-}CH_2CH_2\underset{NHAc}{C}HCO_2R \xrightarrow{H^+} CH_3\text{-}\overset{O}{\underset{OH}{P}}\text{-}CH_2CH_2\underset{NH_2}{C}HCO_2H$$



$$CH_3\text{-}\overset{O}{\underset{OH}{P}}\text{-}CH_2CH_2CH_2CO_2H \xrightarrow[2.\ aq.\ NH_3]{1.\ Br_2/PCl_3} CH_3\text{-}\overset{O}{\underset{OH}{P}}\text{-}CH_2CH_2\underset{NH_2}{C}HCO_2H$$

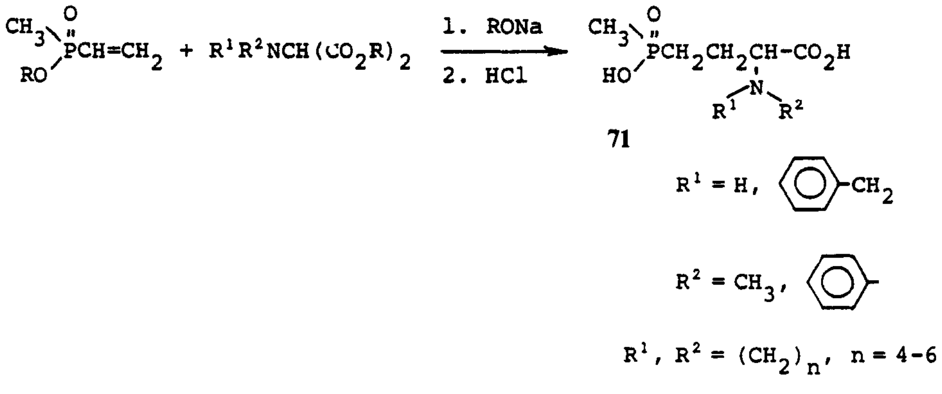
69

have recently found a general procedure for the preparation of phosphinothricine derivatives which have different alkyl groups attached to phosphorus or bear a substituent on the nitrogen.[46] Thus we observed that diethyl-2-chloroethylphosphonite undergoes a Michaelis-Arbuzov reaction with alkyl halides and yields 2-chloroethyl-substituted phosphinates which have been converted by the conventional acylaminomalonate procedure to phosphinothricine derivatives, **70**. Phosphinothricine derivatives, which bear substituents on the nitrogen **71**, have been obtained by the base catalyzed addition of substituted aminomalonates to methylvinylphosphinate followed by hydrolysis.[46] Phosphonic and phosphinic analogs of α-methylaspartic **72**, and α-methylglutamic acid **73** were prepared by a Strecker reaction,[24] and analogs of α-methylglutamic acid, in which an α-carboxylic group is replaced by phosphonic or phosphinic acid groups, **51a**, were obtained from methyl levulinate upon treatment with ammonia and diethyl phosphite or ethylmethylphosphonite, **51a**. Similarly the α-methylaspartic analogs **50** were obtained by addition of phosphite or phosphonite to ethyl 2-aminocrotonate.[24] As described previously, these compounds were also prepared by the benzylcarbamate procedure.



$$ClCH_2CH_2P(OEt)_2 + RX \rightarrow R(EtO)\overset{O}{P}CH_2CH_2Cl \xrightarrow{Et_3N} R(EtO)\overset{O}{P}CH{=}CH_2 \xrightarrow[2.\ HCl]{1.\ AcNHCH(CO_2R)_2} R(HO)\overset{O}{P}CH_2CH_2\underset{NH_2}{C}HCO_2H$$

70 R = H, CH_3OCH_2, HO_2CCH_2, $HO_2C\underset{NH_2}{C}HCH_2CH_2$, $C_6H_5CH_2$, $Br\text{-}C_6H_4\text{-}CH_2$ etc.



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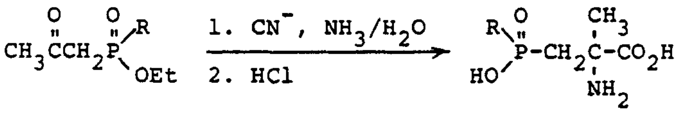
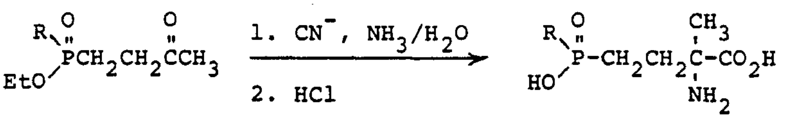
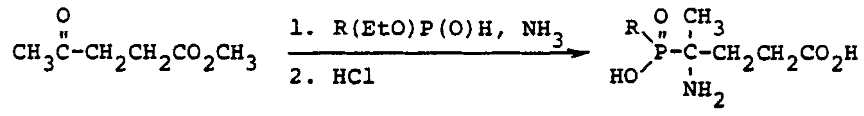


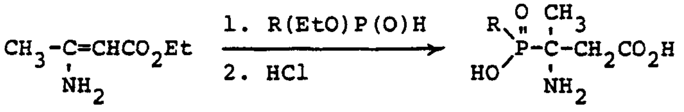
72 R = OH, CH_3



73



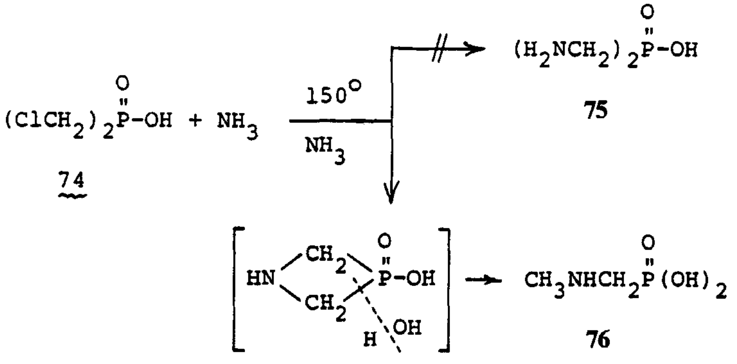
51a R = HO, CH_3



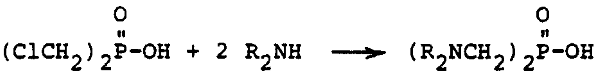
50

7. *Nucleophilic displacements on $P(C—X)_2$ systems*

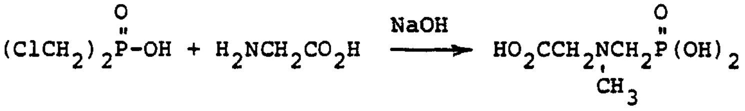
Attempts to prepare bis(aminomethyl)phosphinic acid **75** by interaction of bis(chloromethyl)phosphinic acid **74** with excess ammonia at 150°C in an autoclave were not successful. Instead methylaminomethylphosphonic acid, **76**, was produced.[41] Apparently ammonia forms with **74** initially a four-membered ring compound which is cleaved by water to give **75**. A similar mechanism must partially operate in the



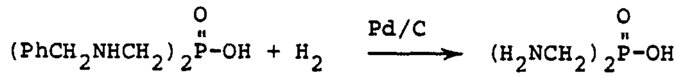
interaction of **74** with primary aliphatic amines because here also alkyl-methyl-amino-methylphosphonic acids are produced in addition to the expected bis(alkyl-aminomethyl)phosphinic acids.[41] With benzylamine[31,41] and secondary amines,[30] however, only bis(benzylaminomethyl)phosphinic acid and bis(disalkyl-aminomethyl)phosphinic acids are obtained, and with glycine only the N-methyl-substituted phosphonic acid is produced.[87] The unsubstituted



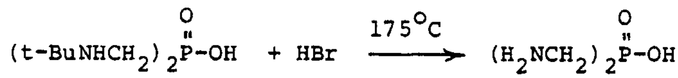
$$(ClCH_2)_2\overset{O}{\overset{\|}{P}}{-}OH + 2\ R_2NH \longrightarrow (R_2NCH_2)_2\overset{O}{\overset{\|}{P}}{-}OH$$



$$(ClCH_2)_2\overset{O}{\overset{\|}{P}}{-}OH + H_2NCH_2CO_2H \xrightarrow{NaOH} HO_2CCH_2\underset{CH_3}{N}CH_2\overset{O}{\overset{\|}{P}}(OH)_2$$



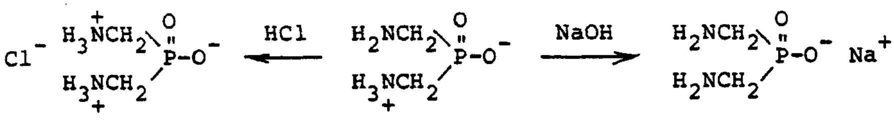
$$(PhCH_2NHCH_2)_2\overset{O}{\overset{\|}{P}}{-}OH + H_2 \xrightarrow{Pd/C} (H_2NCH_2)_2\overset{O}{\overset{\|}{P}}{-}OH$$



$$(t\text{-}BuNHCH_2)_2\overset{O}{\overset{\|}{P}}{-}OH + HBr \xrightarrow{175^\circ C} (H_2NCH_2)_2\overset{O}{\overset{\|}{P}}{-}OH$$

75

bis(aminomethyl)phosphinic acid has been obtained by debenzylation of bis(benzyl-aminomethyl)phosphinic acid with hydrogen using 5% Pd on carbon as catalyst, and also from bis(t-butylaminomethyl)phosphinic acid by isobutylene elimination with conc. HBr at 175°C in a sealed tube.[41] As expected, **75** has a betaine structure and forms an ammonium salt with HCl and a phosphinate with NaOH:



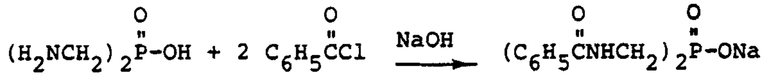
dec. 307° dec. 185-190° dec. 210°

^{31}P 20.36 ppm ^{31}P 29.77 ppm ^{31}P 40.6 ppm

The strong dependence of the ^{31}P-chemical shift on the pH has been observed with other aminoalkylphosphinic acids.[42-44]

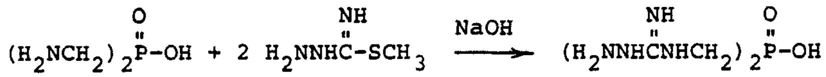
B. REACTIONS OF AMINOPHOSPHINIC ACIDS

Like other amino compounds, aminophosphinic acid can be acylated, **77**, and converted into aminoguanidino-, **78**,[41] and guanidino derivatives, **79**,[67,74] e.g.,



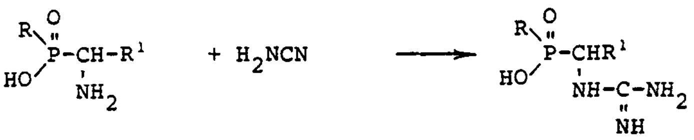
$$(H_2NCH_2)_2\overset{\overset{O}{\|}}{P}\text{-OH} + 2\ C_6H_5\overset{\overset{O}{\|}}{C}Cl \xrightarrow{NaOH} (C_6H_5\overset{\overset{O}{\|}}{C}NHCH_2)_2\overset{\overset{O}{\|}}{P}\text{-ONa}$$

77



$$(H_2NCH_2)_2\overset{\overset{O}{\|}}{P}\text{-OH} + 2\ H_2NNH\overset{\overset{NH}{\|}}{C}\text{-}SCH_3 \xrightarrow{NaOH} (H_2NNH\overset{\overset{NH}{\|}}{C}NHCH_2)_2\overset{\overset{O}{\|}}{P}\text{-OH}$$

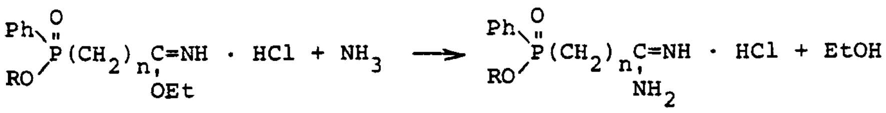
78



$$\underset{HO}{\overset{R}{}}\overset{\overset{O}{\|}}{P}\text{-}\underset{NH_2}{\underset{|}{CH}}\text{-}R^1 + H_2NCN \longrightarrow \underset{HO}{\overset{R}{}}\overset{\overset{O}{\|}}{P}\text{-}\underset{NH\text{-}\underset{\underset{NH}{\|}}{C}\text{-}NH_2}{\underset{|}{CHR^1}}$$

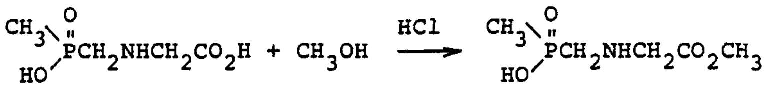
79

Amidinoalkylphosphinates **80** were obtained from the interaction of iminoalkylphosphinates and ammonia.[77] A carboxy group in phosphinic acid derivatives can be easily esterified, **81**, either with alcohol/HCl[42,43] or by treatment with SOCl$_2$/ROH/pyridine,[64] e.g. **82**. Phosphinyl-group containing peptides are ob-



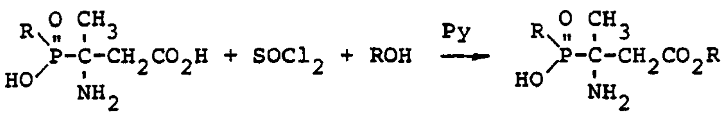
$$\underset{RO}{\overset{Ph}{}}\overset{\overset{O}{\|}}{P}(CH_2)_n\underset{OEt}{\underset{|}{C}}{=}NH \cdot HCl + NH_3 \longrightarrow \underset{RO}{\overset{Ph}{}}\overset{\overset{O}{\|}}{P}(CH_2)_n\underset{NH_2}{\underset{|}{C}}{=}NH \cdot HCl + EtOH$$

80



$$\underset{HO}{\overset{CH_3}{}}\overset{\overset{O}{\|}}{P}CH_2NHCH_2CO_2H + CH_3OH \xrightarrow{HCl} \underset{HO}{\overset{CH_3}{}}\overset{\overset{O}{\|}}{P}CH_2NHCH_2CO_2CH_3$$

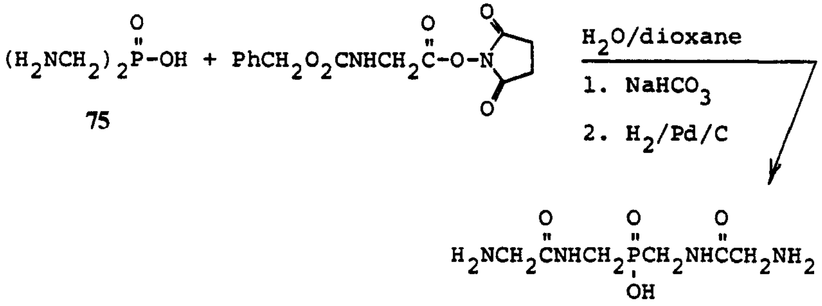
81



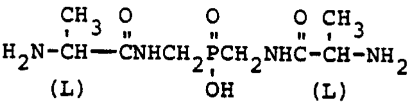
$$\underset{HO}{\overset{R}{}}\overset{\overset{O}{\|}}{P}\text{-}\underset{NH_2}{\underset{|}{\overset{\overset{CH_3}{|}}{C}}}\text{-}CH_2CO_2H + SOCl_2 + ROH \xrightarrow{Py} \underset{HO}{\overset{R}{}}\overset{\overset{O}{\|}}{P}\text{-}\underset{NH_2}{\underset{|}{\overset{\overset{CH_3}{|}}{C}}}\text{-}CH_2CO_2R$$

82

tained by methods also used in aminocarbonic acid chemistry,[83] e.g. **83**. Similarly prepared was **84**. The antibacterial agent (L-alanyl-aminomethyl)methylphosphinic acid, **85**, was obtained by a similar procedure:[28]

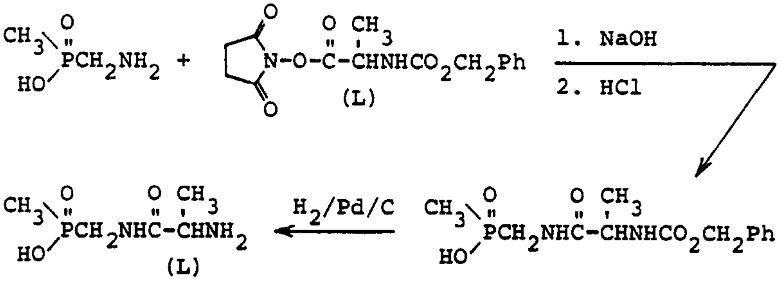


83 (dec. 150-155°)



$$H_2N-\underset{(L)}{\overset{CH_3}{CH}}-\overset{O}{\overset{\|}{C}}NHCH_2\underset{OH}{\overset{O}{\overset{\|}{P}}}CH_2NH\overset{O}{\overset{\|}{C}}-\underset{(L)}{\overset{CH_3}{CH}}-NH_2$$

84 ($[\alpha]_D$ 28° ± 1°)

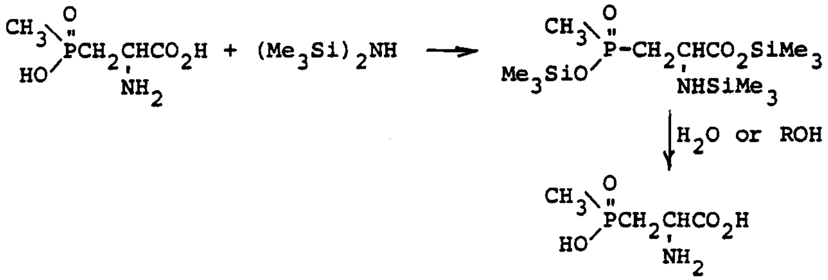


85

Interaction of **75** with excess hexamethyldisilazane under reflux leads to the formation of a distillable trisilyl derivative, **86**.[41] Other aminophosphonic and phosphinic acids react similarly, e.g.

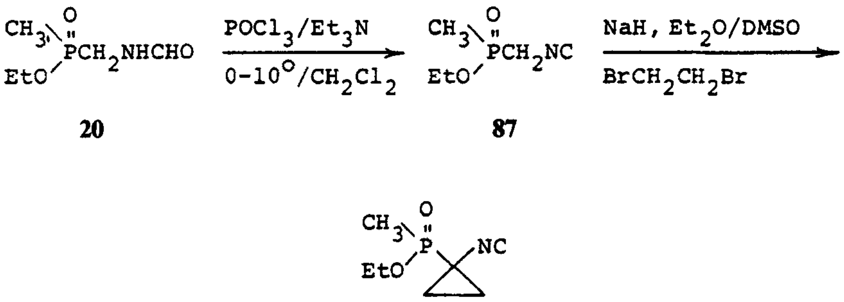
$$(H_2NCH_2)_2\overset{O}{\overset{\|}{P}}OH + [(CH_3)_3Si]_2NH \longrightarrow [(CH_3)_3SiNHCH_2]_2\overset{O}{\overset{\|}{P}}OSi(CH_3)_3$$

86



and therefore this method constitutes an effective purification procedure for this type of compound.[46]

Conversion of formylaminomethylphosphinate **20** to the corresponding isocyanide, **87**, with $POCl_3$ [16] is analogous to that used previously in the phosphonate series.[76] The isocyanide **87** could easily be alkylated, e.g. with 1,2-dibromoethane to

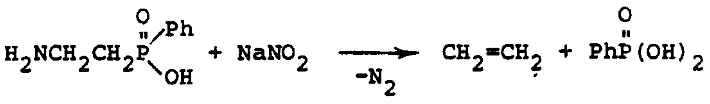


20

87

87a

give **87a**.[16] When 2-aminoethylphenylphosphinic acid, **88**, was treated with sodium nitrite and water and heated to 100°C, ethylene was obtained in 70–80% yield. Other fragmentation products were phenylphosphonic acid, and minor amounts of phenylvinylphosphinic acid and an unknown compound.[50] Like amino acids, aminophosphonic and -phosphinic acids react with ninhydrin to produce a purple anion[8] and metaphosphate or metaphosphonate, respectively.[84]



88

C. BIOLOGICAL ACTIVITY

The possibility of phosphorus analogs of amino acids acting as false substrates and so interfering with biological mechanisms has no doubt spurred investigation into their biological activity. Since the activity of aminophosphonic[73] and aminophosphonous acids[3] has been discussed previously, we shall describe here only that of aminophosphinic acids.

The first report of a biological activity of an aminophosphinic acid appeared in 1959. P. Mastalerz[48] showed that the ethylphosphinyl derivative of glutamic acid, **68**, $R = C_2H_5$, is a strong inhibitor of enzymatic glutamine synthesis; the same property is shared by the methyl-phosphinyl derivative,[2] while the phenylphosphinyl derivative **68**, $R = C_6H_5$, has only slight inhibitory properties.[48] The phosphinyl analog of asparagine, **59**, $R = CH_3$, C_2H_5, was not hydrolyzed by *E. coli* asparaginase.[78] Furthermore, none of the phosphinyl analogs of aspartic acid **56**, and **57**, shows any inhibition of substrate activity towards asparaginase from *Escherichia coli*, but some of them were found to inhibit the action of D-aspartic acid oxidase from rabbit kidneys.[78] Details have not been published yet. In a patent it has been claimed[51] that 2-amino-3-methylphosphinylpropionic acid **56**, $R = CH_3$, shows fungicidal activity.

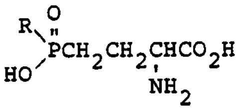
Preliminary results indicate[24] that introduction of an α-methyl group decreases the cytostatic activity of phosphonic and phosphinic analogs of aspartic and glutamic acid. Thus compound **72**, $R = CH_3$, and **89**, inhibited the growth of L1210 sl cells by 50% at concentrations of 100 μg/ccm, while in the case of the corresponding aminophosphonic acids without methyl groups a 50% inhibition was observed at 10 μg/ccm.[24]

Like aminophosphonic acid, **90**,[1,70] and glyphosate, **91**,[18,58] several of the aminophosphinic acids exhibit herbicidal and plant growth regulating properties, such as: **75**,[10] **41**,[11] **43**,[12] **92**, **93**, and others,[9] and in particular phosphinothricine as the NH_4 salt **69**,[27,75] which is being developed as a new contact herbicide for fruit and vine cultures. It works more slowly than paraquat, but hinders the reappearance of perennial weeds for a longer period. Good results have been achieved with about 1 kg a.i./ha for annuals, but perennials need higher doses.[39] Other derivatives of phosphinothricine, **68**, $R = C_2H_5$,[62] $R = PhCH_2$, CH_3OCH_2 etc.,[46] also show herbicidal properties. More recently it has been said that the herbicidal activity of the L-isomer of **69** is twice as high as that of the D,L-form.[54] It has been claimed that the tripeptide, phosphinothricyl-L-alanyl-L-alanine, **94**, also exhibits herbicidal properties.[53] This tripeptide is also active against gram-positive and gram-negative bacteria and against the fungi *Botrytis cinerea*,[2] sheath blight, and rice blast.[36] It was observed that the tripeptide **94** has 10,000 times greater antibacterial activity than the constituent amino acid **69**.[2] However, only **69** effectively inhibits *Escherichia coli* glutamine synthetase.[2] It has been suggested that the tripeptide, **94**, is more easily transported into the cell where it is hydrolyzed to **69**, which then inhibits the enzyme.[2]

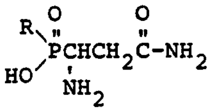
A recent Japanese patent claims the acaricidal properties of phosphinothricine **69**.[61] And finally (L-alanyl-aminomethyl)methylphosphinic acid, **85**, seems to have antibacterial activity similar to alafosfalin, **95**, which is a peptide mimetic and specifically inhibits bacterial cell wall synthesis.[28] Whereas for several of the phosphonic acids analogs of glycine, β-alanine, aspartic, and glutamic acids neuroactivity has been observed,[5] aminophosphinic acids seem not to have been investigated for this property.

Furthermore, while the 3-(N-acetyl-)- and, in particular, the 3-(N-formyl-N-hydroxyamino)propylphosphonic acids, **8**, $R = H$, CH_3, showed high activity against a variety of gram-negative bacteria including *Pseudomonas* species, the corresponding methylphosphinic acid derivatives **96**, R = H, CH_3, did not show any activity.[24a]

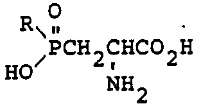
Biologically active aminophosphinic acid compounds:



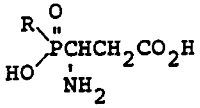
68 R = CH_3, C_2H_5, C_6H_5



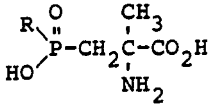
59 R = CH_3, C_2H_5



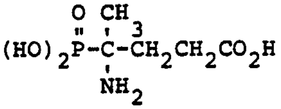
56 R = CH_3, C_2H_5



57 R = CH_3, C_2H_5

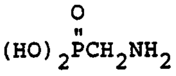


72 R = CH_3



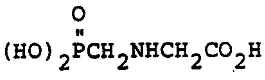
$(HO)_2\overset{O}{\overset{\|}{P}}-\underset{NH_2}{\overset{CH_3}{C}}-CH_2CH_2CO_2H$

89



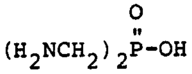
$(HO)_2\overset{O}{\overset{\|}{P}}CH_2NH_2$

90



$(HO)_2\overset{O}{\overset{\|}{P}}CH_2NHCH_2CO_2H$

91

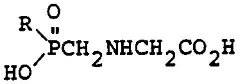


$(H_2NCH_2)_2\overset{O}{\overset{\|}{P}}-OH$

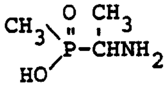
75

$(HO_2CCH_2NHCH_2)_2\overset{O}{\overset{\|}{P}}-OH$

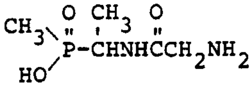
41 (and derivatives)



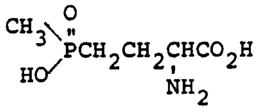
43 R = alkyl, $HOCH_2$, CCl_3



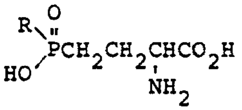
92



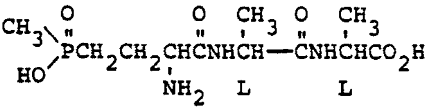
93



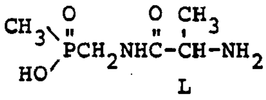
69



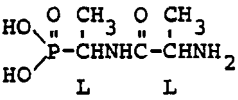
68 R = C_2H_5, CH_3OCH_2, $C_6H_5CH_2$



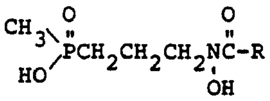
94



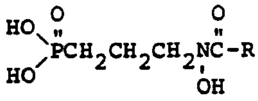
85



95



96 R = H, CH_3



8 R = H, CH_3

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