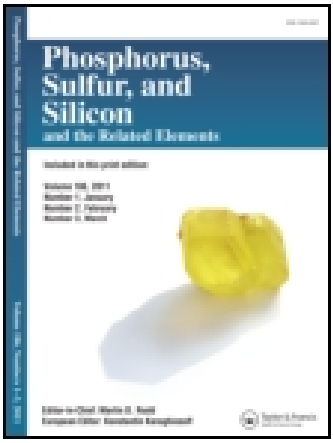

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THE FORMATION OF α-AMINO AND α-HYDROXY-ALKANEPHOSPHONIC ACIDS IN THE REACTIONS OF PHOSPHITE ESTERS WITH ALDEHYDES AND ALKYL CARBAMATES

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THE FORMATION OF α-AMINO- AND α-HYDROXY-ALKANEPHOSPHONIC ACIDS IN THE REACTIONS OF PHOSPHITE ESTERS WITH ALDEHYDES AND ALKYL CARBAMATES

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The preparation of α-aminoalkanephosphonic acids from triphenyl phosphite, an aldehyde, and ethyl or benzyl carbamate in glacial acetic acid, followed by hydrolysis, is accompanied by the formation of the corresponding α-hydroxyphosphonic acid. Reaction in toluene, using boron trifluoride-etherate as catalyst, affords an alternative preparative procedure but does not prevent the formation of α-hydroxyphosphonic acid. ^{31}P nmr reveals the presence of numerous intermediates. The reactions are discussed.

Keywords: Aminophosphonic acids; hydroxyphosphonic acids; ^{31}P NMR spectroscopy

INTRODUCTION

A convenient one-pot method for the preparation of α-aminoalkanephosphonic acids (**7**), described originally by Oleksyszyn and Tyka,[1] consists in heating together a mixture of triphenyl phosphite, an aliphatic aldehyde (**1**), and ethyl (or benzyl) carbamate (**2**) in glacial acetic acid, followed by hydrolysis *in situ*. An intermediate phosphonate (**6**, $R^1 = Me$, $R^2 = PhCH_2$) has been isolated at the stage before hydrolysis is carried out[2] and it is reasonable to assume that it may be formed (Scheme 1) by

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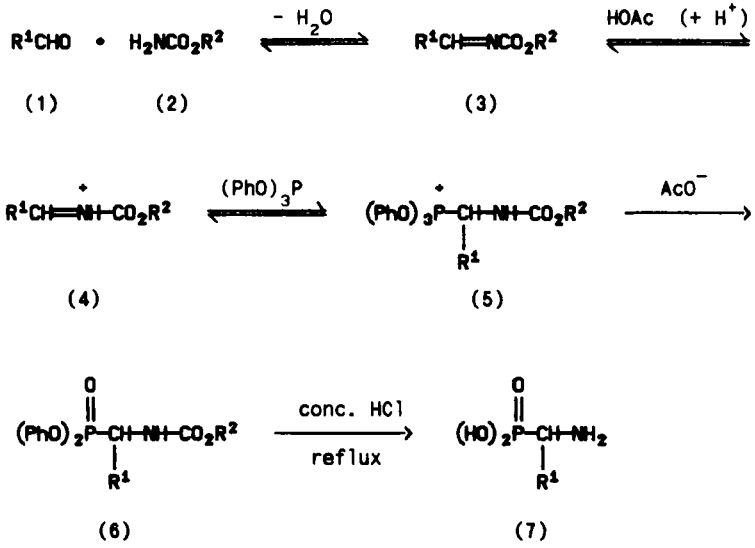
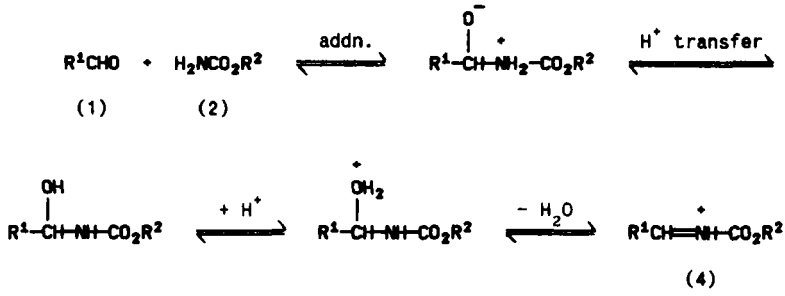
the acid-catalyzed addition of phosphite to an initially-formed imine (**3**), followed by monodearylation of the quasiphosphonium species (**5**). *N*-Alkoxycarbonylimines (**3**) are not, however, stable and have not been isolated or identified. It is, of course, possible that the protonated species (**4**) becomes available directly from the aldehyde-carbamate interaction (Scheme 2) and that the free imine is not itself involved. Other possibilities also exist and the detailed mechanism of reaction has yet to be established.



SCHEME 1

In any event we found that α-aminoalkanephosphonic acids (**7**) are readily obtained in a high state of purity by this procedure, after work-up and recrystallization,[3] although the yields were only moderate and it appeared likely that one or more side reactions were leading to the formation of other products. To investigate this possibility we have used ^{31}P nmr to monitor the reactions which occur with various reactant combinations of triphenyl phosphite, ethanal or propanal (used as typical aldehydes), and either ethyl or benzyl carbamate,[1] and we discuss the reactions involved. The effect of using triethyl phosphite in place of triphenyl phosphite is also reported.



SCHEME 2

RESULTS AND DISCUSSION

Reaction products obtained by heating mixtures of triphenyl phosphite, ethanal or propanal, and ethyl or benzyl carbamate, in glacial acetic acid (one hour, under reflux),[1] were examined by ^{31}P nmr spectroscopy.[4] In each case, the major products gave rise to several partially overlapping signals in the region 17 – 19 ppm (Table I). A peak in this region is expected for the intermediate (**6**, R^1= Me, R^2 = $PhCH_2$; δ_P 18.2 ppm)[2] and other intermediates are also clearly present. After complete hydrolysis of the products, however, by boiling with concentrated hydrochloric acid (11 hours), only two nmr signals were observed, one in the region δ_P 16 – 17 and the other at δ_P 24 – 25 ppm (Table II), which are assigned to the α-amino- (**7**) and α-hydroxyphosphonic acids (**8**) in the approximate molar ratio of 3:1, respectively. In some cases an additional signal at *ca.* δ_P 5 – 6 ppm (d, J_{PH} 670 Hz) was assigned to phosphorous acid,[5] produced by hydrolysis of residual triphenyl phosphite. ^{31}P nmr chemical shifts for α-aminophosphonic acids are pH-dependent,[3] but we found those for the α-hydroxyphosphonic acids to remain fairly constant (δ_P 24–26 ppm) in the presence of an excess of acid. Assignments for the various products were confirmed by comparison with authentic samples, under comparable conditions. The α-hydroxyphosphonic acid and other by-products (including phenol) are readily separated from the α-aminophosphonic acid, which forms a salt with hydrochloric acid, by extraction with toluene in the normal work-up procedure.

TABLE I ^{31}P nmr data for the phosphorus-containing products obtained by the interaction under reflux of triphenyl phosphite with ethanal or propanal, and ethyl or benzyl carbamate, in glacial acetic acid

R^1 in R^1CHO	R^2 in R^2OCONH_2	Products, δ_P/ppm (mol %)[a]
Me	Et	18.8 (73), 19.4 (27)
Et	Et	17.3 (11), 18.0 (67), 18.8 (22)
Me	$PhCH_2$	18.7 (74), 19.3 (26)
Et	$PhCH_2$	17.1 (9), 17.9 (72), 18.9 (19)

a. Approximate compositions calculated from relative peak intensities.

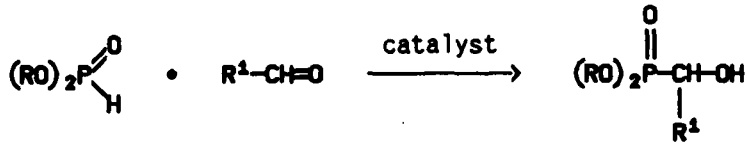
TABLE II ^{31}P nmr data for α-amino- (**7**) and α-hydroxyalkanephosphonic acid (**8**) in the total hydrolysis products obtained after the interaction of triphenyl phosphite with ethanal and ethyl carbmate, or propanal and benzyl carbamate, in glacial acetic acid

R^1 in R^1CHO	R^2 in R^2OCONH_2	δ_P/ppm (mol %)[a]	
		7	*8*
Me	Et	16.8 (72)	24.6 (28)
Et	$PhCH_2$	16.2 (75)	24.1 (25)

a. Approximate compositions calculated from relative peak intensities.

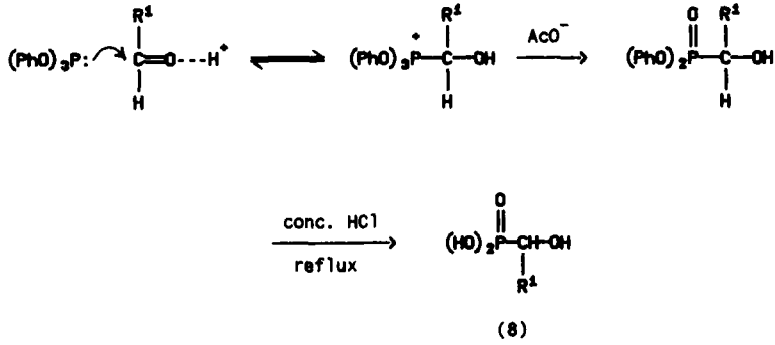
It has long been recognized that α-hydroxyphosphonates may be formed together with α-aminophosphonates in the Kabachnik-Fields reaction (i.e. the interaction of a dialkyl phosphite, carbonyl compound, and ammonia or amine).[6–8] In such cases, the α-hydroxyphosphonate is formed by direct addition of the dialkyl phosphite to the carbonyl compound (Scheme 3, R = alkyl), a reaction that is catalyzed by amine[9] and is analogous to the metal ion- or alumina-cataylzed reactions used for the preparation of α-hydroxyphosphonates.[10,11] The mechanisms of α-aminophosphonate and α-hydroxyphosphonate formation in the Kabachnik-Fields reaction have been studied.[12,13]

The formation of α-hydroxyphosphonic acids in the triphenyl phosphite-aldehyde-carbamate systems may similarly result from the direct interaction of triphenyl phosphite with the aldehyde. Nucleophilic attack of the phosphite on the carbonyl group of the aldehyde in these cases is presumably catalysed by the acidic medium (Scheme 4). This type of reac-



SCHEME 3

tion can compete with the formation of imine (**3**) (or protonated imine **4**), which is required for the formation of aminophosphonate (Scheme 1), depending on the equilibria involved. It is of interest in this context to note that the first method reported for the preparation of α-hydroxyphosphonic acids was by the interaction of phosphorus trichloride with aldehydes in acetic acid, followed by hydrolysis,[14,15] although the mechanism of interaction between the aldehyde and phosphorus(III) reagent is not necessarily the same in this case.



SCHEME 4

To obtain further information on the triphenyl phosphite-aldehyde-carbamate system we monitored the reactions of various combinations of triphenyl phosphite, propanal, and benzyl carbamate in acetic acid (Table III) and found that triphenyl phosphite undergoes dearylation at 80–85 °C to give diphenyl phosphite (δ_P 6.9 ppm, J_{PH} 720 Hz) and monophe-

nyl phosphite (δ_P 3.7 ppm, J_{PH} 570 Hz), on the basis of data obtained for an authentic sample of diphenyl phosphite and literature nmr data for both esters.[5] These esters might also be expected to undergo addition to the carbonyl compound under acid conditions, giving α-hydroxyphosphonate by a reaction (Scheme 3, R = Ph and/or H) which is similar to the metal ion- or alumina-catalysed reaction of dialkyl phosphites with aldehydes and ketones.[10,11] We found no evidence for direct interaction between triphenyl phosphite and the carbamate reagent **(2)** under the conditions used, the only identifiable products being di- and mono-phenyl phosphite (Table III).

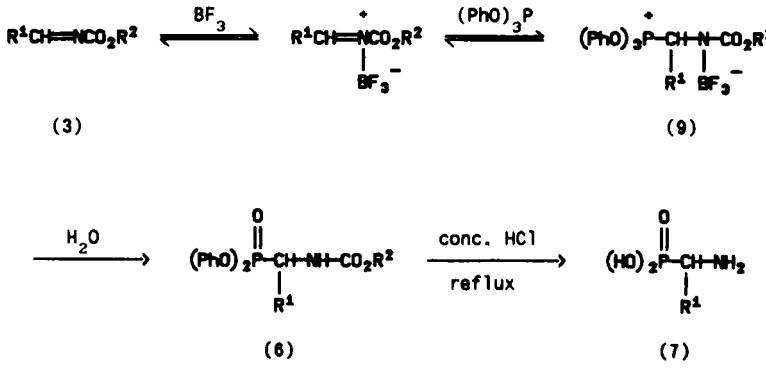
TABLE III ^{31}P nmr data for products derived from various reactant combinations of triphenyl phosphite, propanal, and benzyl carbamate, in glacial acetic acid

Reactants	*temp/°C*[a]	*Products, δ_P/ppm (mol%)*[b]
$(PhO)_3P$ (only)	RT	127.1
$(PhO)_3P$ (only)	80 – 85	6.9 (56),[c] 3.7 (43)[d]
$(PhO)_3P$ + EtCHO	RT	127.6 (67), 22.0 (8), 15.4 (25)
$(PhO)_3P$ + EtCHO	80 – 85	25.1 (13), 21.6 (26), 17.0 (28), 13.0 (9), 6.9 (14), 3.9 (10)
$(PhO)_3P$ + $PhCH_2OCONH_2$	80 – 85	6.9 (41).[c] 4.1 (59)[d]
$(PhO)_3P$ + $PhCH_2OCONH_2$ + EtCHO	RT	127.0 (67), 22.0 (19), 15.0 (14)
$(PhO)_3P$ + $PhCH_2OCONH_2$ + EtCHO	80 – 85	129.9 (6), 127.7 (30), 18.8 (22), 17.9 (25), 12.4 (8), −10.0 (4), −18.0 (5)[e]

a. Reaction time 1 h.
b. Approximate compositions calculated from relative peak intensities.
c. Diphenyl phosphile, J_{PH} 720 Hz.[5]
d. Monophenyl phosphite, J_{PH} 570 Hz.[5]
e. Hydrolysis of this product using concentrated hydrochloric acid (8 h under reflux) gave an aqueous solution of phosphorus-containing products consisting of α-hydroxypropanephosphonic acid (8, R = Et, δ_P 25.3, 23 mol%), α-aminopropanephosphonic acid (7, R = Et, δ_P 17.4, 51 mol %) and phosphorous acid (δ_P 6.4, J_{PH} 670 Hz)[5] (26 mol %), only.

Triphenyl phosphite underwent no reaction with propanal alone, but in acetic acid two products (δ_P 22.0 and 15.4) were slowly formed. On heating, four compounds were obtained (δ_P 25.1, 21.6, 17.0 and 13.0), in addition to di- and mono-phenyl phosphite (Table III). The identity of each of these components has not been established but it seems likely that they include various derivatives of α-hydroxypropanephosphonic acid, e.g. the

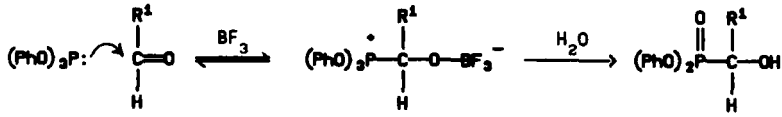
di- or mono-phenyl esters, and possibly *O*-acetyl derivatives, all of which give α-hydroxypropanephosphonic acid on hydrolysis. The simplicity of the total hydrolysis products in typical reaction mixtures (Table II) adds support to this view. In addition we found that a solution of α-hydroxypropanephosphonic acid (**8**, R^1 = Et) in acetic acid gave rise, after heating, to two nmr signals (δ_P 26.0 and 21.3) suggesting that acetylation had occurred.



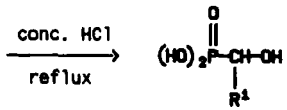
SCHEME 5

In an attempt to avoid the formation of α-hydroxyphosphonic acid and to increase the yield of α-aminophosphonic acid in preparations using the triphenyl phosphite-aldehyde-carbamate procedure,[1] we replaced acetic acid with anhydrous toluene as the reaction medium and employed boron trifluoride-etherate as catalyst. Although this proved to be a good alternative method, giving over 60% yield of α-aminopropanephosphonic acid (**7**, R^1 = Et) when benzyl carbamate was used in the reaction, the formation of α-hydroxypropanephosphonic acid (**8**, R^1 = Et) and other unidentified by-products still occurred. It seems likely that boron trifluoride may act as a Lewis acid catalyst for the nucleophilic attack of triphenyl phosphite on the imine (Scheme 5) and also on the aldehyde (Scheme 6), and that hydrolysis of the intermediate complexes (**9** and **10**) then gives the α-amino- and α-hydroxy-phosphonic acids, respectively. The ^{31}P nmr spectrum of the total reaction products before the hydrolysis stage (Table IV) included a peak at δ_P 36.3, which is in the region associated with

triphenoxyphosphonium ions,[16] although the other main peaks are more in the region expected for phosphonates. Triphenoxyphosphonium species, however, are very readily hydrolysed and the role of adventitious moisture in the removal of one phenoxy group cannot be excluded. In addition, the imine-forming reaction itself generates a molecule of water which could remain closely associated with the α-aminophosphonate complex (**9**) in a solvent cage.



(10)



(8)

SCHEME 6

In spite of the relative complexity of the initial reaction products (Table IV), complete hydrolysis gave only the α-amino- (7) and α-hydroxyphosphonic acids (8) (apart from phosphorous acid, if the phosphite had been used in excess) and it seems likely, therefore, that the initial products are all closely related derivatives.

It is of interest that the use of triethyl phosphite instead of triphenyl phosphite gave α-hydroxypropanephosphonic acid (8, R^1 = Et) (17%) as the only crystalline product that could be isolated from the reaction with propanal and benzyl carbamate in acetic acid. Although the same reactants in toluene/boron trifluoride-etherate gave α-aminopropanephosphonic acid (7, R^1 = Et) the yield was low (21%) and α-hydroxypropanephosphonic acid (8, R^1 = Et) was also formed. The formation of ammonium chloride in these cases during work-up indicated that a significant amount of benzyl carbamate remained after the usual reaction time (1 h) and that the overall reactions were considerably slower than those using triphenyl

phosphite. This is an interesting observation which suggests that the nucleophilicity of phosphorus is not a controlling factor in these reactions. The leaving ability of phenoxy may, however, be important in the conversion of **5** to **6** in acetic acid (Scheme 1), or of **9** to **6** in the presence of a molecule of water (Scheme 5), thus driving the whole reaction over to the formation of phosphonate (**6**). Similarly, the leaving ability of chloride ion is no doubt an important factor in the use of phosphorus trichloride in acetic acid for the preparation of α-hydroxyphosphonates,[5,6] and α-aminophosphonates.[17]

TABLE IV ^{31}P nmr data for the phosphorus-containing products obtained by the interaction of triphenyl phosphite with propanal and benzyl carbamate in the presence of boron trifluoride-etherate in toluene

Reaction time (h)[a]	*Products, δ_P/ppm (mol %)*[b]
1	1.4 (3), 7.4 (5), 12.7 (7), 15.8 (3), 17.7 (50), 18.5 (14), 22.1 (8), 22.6 (6), 36.4 (3)
5	0.5 (18), 1.3 (6), 8.4 (2), 12.8 (5), 14.2 (4), 17.7 (53), 21.9 (3), 22.4 (2), 36.3 (7)[c]

a. Reaction temperature 85–90 °C.
b. Approximate compositions calculated from relative peak intensities.
c. Hydrolysis of this product using concentrated hydrochloric acid (8 h under reflux) gave an aqueous solution of phosphorus-containing products consisting of α-hydroxypropanephosphonic acid (8, R = Et, δ_P 24.0, 27 mol%), α-aminopropanephosphonic acid (7, R = Et, δ_P 16.0, 61 mol %) and phosphorous acid (δ_P 4.6, 12 mol %), only. The residual oil showed weak nmr peaks at δ_P 12.4, 17.4, 18.4, 26.7, 29.7, and 63.3 ppm.

It is likely that α-hydroxy- and α-amino-alkanephosphonic acids are formed concurrently in many related preparative systems based on the combined use of phosphorus(III) reagents, aldehydes or ketones, and amino derivatives.[18–21] The relative proportions of each product may be expected to depend on the equilibrium concentration of the intermediate imine that is formed and on the individual rates of the competing reactions between the phosphorus reagent and the imine or carbonyl compound.[22]

EXPERIMENTAL

Phosphite esters, aldehydes, carbamates, solvents, and other standard reagents were obtained from Aldrich. Toluene was dried over sodium wire.

Authentic samples of α-aminoethanephosphonic acid,[3] α-aminopropanephosphonic acid[3] and diphenyl α-(*N*-benzyloxycarbonyl)aminoethanephosphonic acid, m.p. 116 – 121°C (lit.[2] m.p. 115 – 117°C), δ_P 18.2 ($CDCl_3$), were prepared as described. α-Hydroxypropanephosphonic acid was isolated in the course of the present work (see below).

Nmr Spectroscopy

Spectra were recorded on a Bruker WP80 instrument operating at 80 MHz (^1H, with TMS as internal standard) or 32 MHz (^{31}P, with 85% phosphoric acid as external standard).

Nmr studies of the interaction between triphenyl phosphite, ethanal or propanal, and ethyl or benzyl carbamate in glacial acetic acid

(a) Triphenyl phosphite (0.08 mol), ethyl or benzyl carbamate (0.08 mol), and the aldehyde (0.12 mol), in glacial acetic acid (17.2 ml), were heated under reflux (1 h). The total products were examined by ^{31}P nmr ($CDCl_3$) (Table I).

(b) After identical experiments, the products were heated under reflux (11 h) with concentrated hydrochloric acid (86 ml) and the aqueous products were examined by ^{31}P nmr (D_2O) (Table II).

(c) Various combinations of the above reactants, in equimolar quantities (0.05 mol), were dissolved in glacial acetic acid (10 ml) and the mixtures were heated at 80 – 85 °C (1 h). Examination of the total products by ^{31}P nmr ($CDCl_3$) gave the results shown in Table III.

Reaction of triphenyl phosphite, propanal and benzyl carbamate in the presence of boron trifluoride-etherate

(a) Preparative procedure

Triphenyl phosphite (26.7 g, 0.086 mol), benzyl carbamate (13.0 g, 0.086 mol), and propanal (5.0 g, 0.086 mol) were dissolved in sodium-dried toluene (80 ml) and boron trifluoride-etherate (2.5 ml) in toluene (50 ml) was added dropwise with stirring at room temperature (15 min). The mixture was heated under reflux at 85 – 90 °C (5 h), after which toluene was removed under reduced pressure to leave a pale yellow

oil. Concentrated hydrochloric acid (120 ml) was added and the mixture was heated under reflux (105 °C/8 h). Phenol and other by-products were removed by extraction with toluene (3 × 20 ml) and the aqueous layer was evaporated *in vacuo* to give a yellowish oil which was then dissolved in methanol (15 ml). The solution was warmed slightly under reflux and propylene oxide (10 ml) was added to give a white precipitate which was filtered off, washed with acetone (15 ml), and dried *in vacuo* at 60 °C to give the crude product (7.88 g, 65.8%), m.p. 259–260 °C (lit.[23] m.p. 264–266 °C). Recrystallization from water/ethanol gave white crystalline α-aminopropanephosphonic acid (**7**, R^1= Et) (6.83 g, 57.1%), m.p. 261–262 °C; δ_H (D_2O) 1.11 (3H, t, CH_3, $^3J_{HCCH}$ 6.0 Hz), 1.39–2.20 (2H, m, CH_2), 2.85–3.40 (1H, m, CH).

(b) Nmr studies

During identical experiments to the above, ^{31}P nmr spectra were recorded for (i) the oil remaining after the intial reaction (1 h or 5 h) and subsequent removal of toluene and (ii) the total hydrolysis product after heating with concentrated hydrochloric acid. Results are shown in Table IV.

Reaction of triphenyl phosphite, propanal and ethyl carbamate in the presence of boron trifluoride-etherate

A similar preparation to the above, in which benzyl carbamate was replaced by ethyl carbamate (7.60 g, 0.086 mol) gave an initial crude product (5.06 g, 42.3%), m.p. 256–258 °C, which, after recrystallization from water/ethanol, gave α-aminopropanephosphonic acid (**7**, R^1 = Et) (4.39 g, 36.7%), m.p. 259–260 °C, δ_H (D_2O) 1.12 (3H, t, CH_3, $^3J_{HCCH}$ 6.1 Hz), 1.38–2.20 (2H, m, CH_2), 2.84–3.39 (1H, m, CH).

Reaction of triethyl phosphite, propanal and benzyl carbamate in glacial acetic acid

Triethyl phosphite (3.81 g, 0.023 mol), benzyl carbamate (3.47 g, 0.023 mol), and propanal (1.45 g, 0.025 mol) were heated under reflux (1.5 h) in glacial acetic acid (5 ml). Concentrated hydrochloric acid (20 ml) was added, and the mixture was then heated under reflux (6 h), cooled, and extracted with toluene (2 × 10 ml). Concentration of the aque-

ous phase by rotary evaporation gave a yellow oil which was treated with methanol (10 ml) to give ammonium chloride (0.74 g, 60%), sublm. > 180 °C, (IR), which was filtered off. Addition of propylene oxide to the filtrate gave an oil which was recrystallized from water/ethanol to give α-hydroxypropanephosphonic acid (**8**, R^1= Et) (0.54 g, 17.0%), m.p. 162–163 °C (lit.[24] m.p. 165 °C) (Found: C, 25.4; H, 6.2. Calc. for $C_3H_9O_4P$: C, 25.7: H, 6.4%); δ_H (D_2O) 1.20 (3H, t, CH_3, $^3J_{HCCH}$ 6.2 Hz), 1.45 – 2.25 (2H, m, CH_2), 2.85 – 3.45 (1H, m, CH); δ_P 23.9.

Reaction of triethyl phosphite, propanal and benzyl carbamate in the presence of boron trifluoride-etherate

Boron trifluoride-etherate (0.5 ml) in toluene (5 ml) was added dropwise (20 min) to a mixture of triethyl phosphite (3.81 g, 0.023 mol), benzyl carbamate (3.47 g, 0.023 mol), and propanal (1.45 g, 0.025 mol) in toluene (25 ml). The mixture was heated under reflux (5h), after which volatile materials were removed on a rotary evaporator to leave a yellow oil (δ_P 28.1, 25.3, 6.3) which was then heated under reflux (8 h) with concentrated hydrochloric acid (125 ml). Extraction with dichloromethane (2 × 10 ml) and ether (2 × 10 ml) left an aqueous phase which was boiled with charcoal, concentrated *in vacuo*, and treated with methanol to give ammonium chloride (0.32 g, 26%), sublm. > 185 °C, (IR), which was filtered off. Addition of propylene oxide to the filtrate gave a semi-solid, which was recrystallized from methanol and washed with acetone to give α-aminopropanephosphonic acid (**7**, R^1 = Et) (0.52 g, 20.8%), m.p. 249–250 °C, (Found: C, 24.3; H, 7.1; N, 9.4. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H. 7.2; N, 10.1%), δ_P 16.3, contaminated with a trace of α-hydroxypropanephosphonic acid, (**8**, R^1 = Et), δ_P 23.9. The filtrate contained α-hydroxypropanephosphonic acid, (**8**, R^1 = Et), δ_P 24.1, as the major component.

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4. In certain experiments (Tables I and II) a 50% excess of aldehyde was used in order to compensate for probable loss of this volatile reactant from the reaction system under reflux. The results using equimolar quantities of all reagents are given in Table III and show the presence in the final product of unreacted phosphite (δ_P 127.7) and also a second P(III) derivative (δ_P 129.9), which may possibly be an acetyl phosphite. Small amounts of the oxidation products triphenyl phosphate (δ_P −18.0) and diphenyl phosphate (δ_P −10.0) were also detected.
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