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Preparation of 1-Aminoalkylphosphonic Acids and 2-Aminoalkylphosphonic Acids by Reductive Amination of Oxoalkylphosphonates

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Abstract: By reacting dialkyl 1-oxo- or 2-oxoalkylphosphonates with benzhydrylamine followed by reduction with triacetoxyborohydride and acid hydrolysis gave corresponding aminoalkylphosphonic acids with satisfactory yields. The use of benzylamine, α-methylbenzylamine and tritylamine was unsuccessful in the case of dialkyl 1-oxoalkylphosphonates whereas conversion of 2-oxoalkylphosphonates was also achieved although with lower yields.

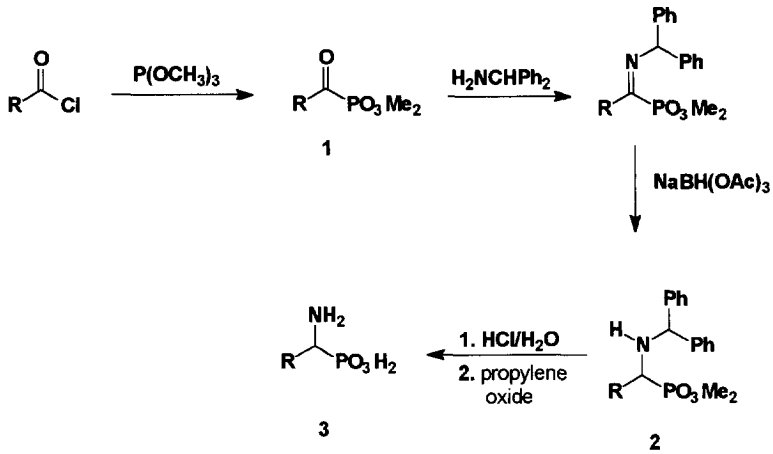
INTRODUCTION

Aminoalkylphosphonic acids were almost unknown compounds still in 1968 but today they are a subject of more than 5,000 papers. Their negligible mammalian toxicity, and the fact that they bear a very close chemical resemblance to amino acids makes them extremely important antimetabolites of amino acids. Thus, aminoalkylphosphonic acids have received a considerable attention after the demonstration of a wide variety of their biological activities, with the possible applications ranging from medicine to agriculture.[1] Consequently, considerable effort has been applied to the preparation of these compounds.[2] Although oxoalkylphosphonates are useful precursors for the synthesis of aminoalkylphosphonic acids their reductive amination was studied surprisingly scarcely. The only examples described so far consider the reduction of 1-oxoalkylphosphonic acids with borohydrides and catalytic hydrogenation of 2-oxo-4-(methyl)phosphinobutyric acid in the presence of ammonia,[3] electrochemical reduction of diethyl 2-oxoalkylphosphonates in the presence of ammonia,[4] and reduction of single examples of dialkyl 2-oxoalkyl- and 3-oxoalkylphosphonates with borohydrides in the presence of amines.[5] Such a reduction of dialkyl 1-oxoalkylphosphonates was unsuccessful since they undergo decomposition with the cleavage of phosphorus-to-carbon bond.[6]

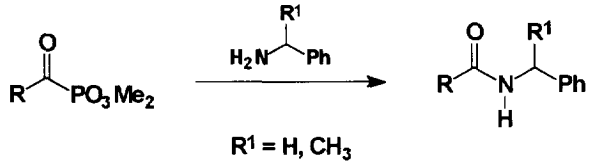
Continuing our studies on the methods for the synthesis of aminoalkylphosphonic acids we undertook the efforts to apply reductive amination for this purpose.

RESULTS AND DISCUSSION

Reaction of dimethyl 1-oxoalkylphosphonates (**1**) with benzhydrylamine and sodium triacetoxyborohydride (TABH) in aprotic media, followed by acid hydrolysis yielded 1-aminoalkylphosphonic acids (**3**) with moderate, although satisfactory yields (Table 1).



Reaction is practically non-dependent on the solvent used. Reductions carried out in THF, dichloromethane and chloroform gave similar yields. The addition of acetic acid (standardly used to promote the reduction step) resulted in small decrease of the reaction yields. The use of other amines was totally unsuccessful, although the results were strongly dependent on the type of the used amine. Thus, benzylamine and α-methylbenzylamine caused breakage of C-P bond and corresponding amides were obtained in quantitative yields:



Application of tritylamine gave neither the desired reaction nor C-P bond breakage and the starting 1-oxoalkylphosphonates were recovered in quantitative yields. In the case of this amine only dimethyl 1-oxoethylphosphonate (**1a**, R = CH_3) gave the desired 1-aminoethylphosphonic acid (**3a**) in 5% yield.

The advantage of reductive amination of 1-oxoalkylphosphonates lays also in the possibility of separation of all the intermediates of this reaction. Thus, 1-(N-benzhydrylamino)alkylphosphonates were easily separated from the reaction mixture in the form of oxalates. The selective removal of benzhydrylic group was achieved by catalytic hydrogenation.

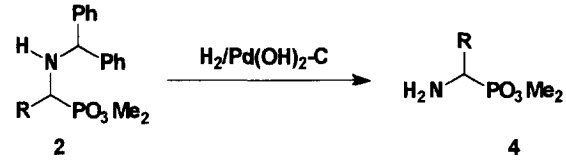


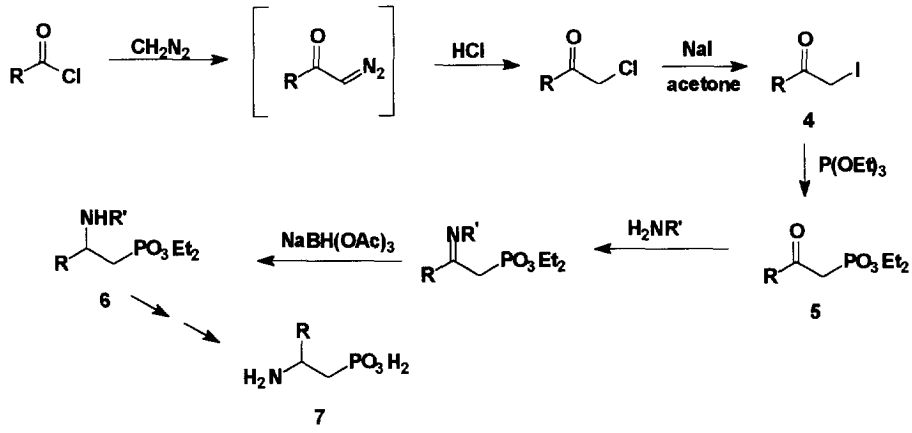
Table 1. 1-Aminoalkylphosphonic acids by reductive amination of dimethyl 1-oxoalkylphosphonates

Compound	R	Yield (%)	M.p. (dec., °C) [b]
3a	CH_3	60	251-253
3b	CH_3CH_2	50[a] 60	257-259
3c	$(CH_3)_2CHCH_2$	55	273-276
3d	$C_6H_5CH_2CH_2$	35	249-252
3e	2-FC_6H_4	30	245-247

[a] obtained from diethyl 1-oxoethylphosphonate

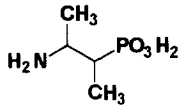
[b] melting points and spectral data are in a good agreement with literature data [7]

The same procedure was also used for the preparation of 2-aminoalkylphosphonic acids (**7**). Substrates for these reactions - diethyl 2-oxoalkylphosphonates (**5**) are readily available in reaction of 2-iodomethyl ketones (**4**) with triethyl phosphite. Preparation of iodomethylketones is the limiting step here. Hence, the synthesis of these known compounds was improved. The whole procedure is outlined in the Scheme given below and the yields of 2-aminoalkylphosphonic acids (in relation to 2-oxoalkylphosphonate) and 2-oxoalkylphosphonates (in relation to starting acid chlorides) are collected in Table 2.



As seen from Table 2 also in this case the best results were achieved if using benzhydrylamine. Also benzylamine yields the desired aminophosphonic acids in satisfactory yields. α-Methylbenzylamine gave the expected product but in significantly lower yields. The latter one was used on the premise that chiral amine might act as chiral discriminator and led to optically active aminophosphonic acids. Unfortunately no chiral discrimination was observed in this case. Quite surprisingly we were unable to remove benzhydryl moiety from diethyl 2-(benzhydrylamino)propylphosphonate (**6a**, R = CH_3) by refluxing in concentrated hydrochloric acid and stepwise procedure (hydrogenation followed by hydrolysis) had to be used in the case of this compound.

Table 2. 2-Aminoalkylphosphonic (7) acids from iodomethylketones (4)

Compound	R	Amine	M.p. (dec, °C)	Yield (%)	Oxophosphonate	
					Compound	Yield (%)
7a	CH_3	benzhydrylamine	250-253	65	5a	40[a]
7a	CH_3	benzylamine		55	5a	40[a]
7a	CH_3	α-methylbenzylamine		20	5a	40[a]
7b	CH_3CH_2	benzhydrylamine	232-235	60	5b	45
7c	$ClCH_2CH_2CH_2$	benzhydrylamine		60[b]	5c	25
7d	$(CH_3)_2CHCH_2$	benzhydrylamine		no reaction	5d	50
7e	C_6H_5	benzhydrylamine		no reaction	5e	40
7f	$C_6H_5CH_2$	benzhydrylamine		no reaction	5f	30
7g	$C_6H_5CH_2CH_2$	benzhydrylamine	292-297	50	5g	50
7h		benzhydrylamine		no reaction	5h	40[a]

[a] in relation to commercially available α-chloromethylketones

[b] yield given for isolated diethyl ester; hydrolysis of this ester yielded quite complicated mixture phosphorus compounds

Summing up, the reductive amination of oxoalkylphosphonates with benzhydrylamine is an alternative to the described methods for the synthesis of aminoalkylphosphonic acids, as well as their dialkyl esters.

EXPERIMENTAL

General. All the reagents were of analytical purity and were used without additional purification. Melting points were determined with Electrothermal IA9200 apparatus and were not corrected. ^1H, ^{13}C and ^{31}P NMR spectra were recorded on a Brucker DRX spectrometer. A Hewlett-Packard 5890 series II gas chromatograph with an electron impact (electron energy 70 eV) mass spectrum detector and capillary HP1 110/8/300 column was used for the determination of mass spectra of liquid samples, whereas Finnigan MAT 700 apparatus with an electron spray ionization was used for the determination of molecular masses of solid samples.

Preparation of Dimethyl 1-Oxoalkylphosphonates (1).[8] To the acyl chloride (0.28 mole) trialkylphosphite (0.25 mole) was added dropwise maintaining the temperature at -5° C. The mixture was then left overnight at room temperature and the volatile components of the reaction mixture were removed under reduced pressure. The crude products, obtained in 90-100% yield, were of satisfactory purity.

Preparation of Diethyl 2-Oxoalkylphosphonates (5). To the solution of 10 mmoles of acid chloride in 30 ml of diethyl ether, ethereal solution of diazomethane (obtained from 2.8 g of nitrosomethylurea[9]) was slowly added. The mixture was left for an hour at room temperature and conversion of diazoketone to α-chloromethylketone was accomplished by passing gaseous hydrogen chloride through the solution.[10] The solvent was evaporated *in vacuo* and the resulting oil was mixed with saturated aqueous solution of 15 mmoles of sodium iodide and methanol. The mixture was stirred for 24 h at room temperature, methanol was evaporated under reduced pressure and 20 ml of water was added. The iodomethylketone was extracted with two 30 ml portions of chloroform. The combined extracts were dried over magnesium sulphate. Evaporation of the solvent gave product of satisfactory purity.

To 5.5 mmoles of iodomethylketone 5 mmoles of triethyl phosphite were added dropwise maintaining temperature at -5° C. The mixture was left overnight at room temperature and the volatile components of the reaction were removed on rotary evaporator. The crude product was purified by means of column chromatography on silica gel using ethyl acetate as eluent.

***Diethyl 2-Oxopropylphosphonate* (5a), *2-Oxo-2-phenylethylphosphonate* (5e) and *1-Methyl-2-xopropylphosphonate* (5h).** Data for these compounds were identical with those described earlier.[11]

***Diethyl 2-Oxobutylphosphonate* (5b).**

^{1}H-n.m.r. (250 MHz, $CDCl_3$,TMS) δ_{ppm}: 1.10 [t, 3H, J = 7.3Hz, $CH_3CH_2C(O)$]; 1.36 (t-t, 6H, J = 7.3Hz, $POCH_2CH_3$); 2.66 [q, 2H, J = 7.3Hz, $CH_3CH_2C(O)$]; 3.10 (d, 2H, J_{PH}= 22.8Hz, CH_2P); 4.16 (q-q, 4H, J = J_{PH}= 7.3Hz, $POCH_2$); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 21.4. Mass spectrum (CI) *m/z* 209.15 ($C_8H_{17}O_4P$ + H^+ requires 209.09)

***Diethyl 2-Oxo-5-chloropentylphosphonate* (5c).**

^{1}H-n.m.r. (250 MHz, $CDCl_3$,TMS) δ_{ppm}: 1.39 (t-t, 6H, J = 7.1 Hz, $POCH_2CH_3$); 2.15-2.05 (m, 2H $CH_2CH_2CH_2$); 2.85 [t, 2H, J = 6.9Hz, $CH_2CH_2C(O)$]; 3.11 (d, 2H, J_{PH}=22.8Hz, CH_2P); 3.59 (t, 2H, J = 6.3Hz, $ClCH_2$); 4.15 (q-q, 4H, J = J= 7.1Hz, $POCH_2CH_3$); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 20.8. Mass spectrum (CI) *m/z* 257.05 ($C_9H_{18}ClO_4P$ + H^+ requires 257.07)

***Diethyl Methyl-2-oxobutylphosphonate* (5d).**

^{1}H-n.m.r. (250 MHz, $CDCl_3$,TMS) δ_{ppm}: 0.86 [d, 6H, J = 6.8Hz, $(CH_3)_2CH$]; 1.27 (t, 6H, J = 7.2Hz, $POCH_2CH_3$); 2.08 [oct, 1H, J = 6.8Hz, $(CH_3)_2CH$]; 2.43 (d, 2H, J = 6.8Hz, CH_2CH); 2.99 (d, 1H, J_{PH}= 22.9Hz, CH_2P), 3.9-4.2 (m, 4H, J= 7.2Hz, $POCH_2CH_3$); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 21.3. Mass spectrum (CI) *m/z* 237.17 ($C_{10}H_{21}O_4P$ + H^+ requires 237.13)

***Diethyl 2-Oxo-3-phenylpropylphosphonate* (5f).**

^{1}H-n.m.r. (250 MHz, $CDCl_3$,TMS) δ_{ppm}: 1.3 (t, 6H, J = 7.0 Hz, $POCH_2CH_3$); 3.06 (d, 2H, J_{PH}= 22.7Hz, CH_2P); 3.876 [s, 2H $CH_2C(O)$]; 4.14 (q-q, 4H, J_{PH}= J = 7.0Hz, $POCH_2CH_3$); 7.15-7.35 (m, 5H, C_6H_5); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 20.9. Mass spectrum (CI) *m/z* 271.15 ($C_{13}H_{19}O_4P$ + H^+ requires 271.11)

Diethyl 2-Oxo-4-phenylbutylphosphonate (5g).

^{1}H-n.m.r. (250 MHz, $CDCl_3$,TMS) δ_{ppm}: 1.29 (t, 6H, J = 7.2Hz, $POCH_2CH_3$); 2.8-3.0 [m, 4H, $CH_2CH_2C(O)$]; 3.05 (d, 2H, J_{PH}= 22.8Hz, CH_2P); 4.07 (q-q, 4H, J= J_{PH}= 7.2Hz, $POCH_2CH_3$); 7.15-7.35 (m, 5H, C_6H_5); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 21.1. Mass spectrum (CI) *m/z* 285.19 ($C_{14}H_{21}O_4P$ + H^+ requires 285.13)

Preparation of Oxalates of Dialkyl 2-(N-Benzhydrylamino)alkylphosphonates. Representative Examples. To the solution of 4 mmoles of oxoalkylphosphonate in 20 ml of 1,2-dichloroethane 4 mmoles of benzhydrylamine were added and left at room temperature for 1 h. Then 8 mmoles of triacetoxyborohydride were added and the mixture left overnight. Then the solution was washed with saturated disodium hydrogenphosphate, dried over anhydrous magnesium sulphate and the solvent was stripped off *in vacuo*. The obtained oil was purified by means of silica gel column chromatography using ethyl ether followed by 5% solution of methanol in ethyl ether as eluents. The oxalates were precipitated from anhydrous diethyl ether with ethereal solution of anhydrous oxalic acid.

Diethyl 2-(N-Benzhydrylamino)propylphosphonate Oxalate (6a).

Yield 60%; m.p.= 107-108° C; ^{1}H-n.m.r. (D_2O, HMDS) δ_{ppm}: 1.15 (t, 6H, J = 6.9Hz, $POCH_2CH_3$); 1.44 (d, 3H, J = 6.4Hz, CH_3CH); 2.1-2.45 (m, 2H, CH_2P); 3.4-3.55 (m, 1H $CHCH_2P$); 3.98 (q-q, J = J_{PH}= 6.8Hz, $POCH_2$); 5.66 (s, 1H, $CHPh_2$); 7.4-7.5 (m, 10H, 2 × C_6H_5); ^{31}P-n.m.r. (D_2O, H_3PO_4) δ_{ppm}: 28.8; Mass spectrum (ESI) *m/z* 362.1 ($C_{23}H_{32}NO_7P$ + H^+ minus oxalic acid requires 362.2).

Diethyl 2-(N-Benzhydrylamino)butylphosphonate Oxalate (6b).

Yield 55%; m.p.= 143-145° C; ^{1}H-n.m.r. (D_2O, HMDS) δ_{ppm}: 0.82 (t, 3H, J = 7.6Hz, CH_3CH_2CH); 1.10 (t-t, 6H, J = 7.1Hz, $POCH_2CH_3$); 1.65-1.9 (m, 2H, CH_3CH_2CH); 2.1-2.4 (m, 2H, CH_2P); 3.2-3.4 (m, 1H $CHCH_2P$); 3.95 (q-q, J = J_{PH}= 7.1Hz, $POCH_2$); 5.60 (s, 1H, $CHPh_2$); 7.25-7.4 (m, 10H, 2 × C_6H_5); ^{31}P-n.m.r. (D_2O, H_3PO_4) δ_{ppm}: 29.5; Mass spectrum (ESI) *m/z* 376.3 ($C_{23}H_{32}NO_7P$ + H^+ minus oxalic acid requires 376.2).

Preparation of Dialkyl 1- and 2-Aminoalkylphosphonates.[12] **Representative Examples.** 1 mmole of crude dialkyl (N-benzhydrylamino)alkylphosphonate was dissolved in 5 ml of anhydrous methanol and 0.05 g of 20% $Pd(OH)_2/C$ catalyst were added. The mixture was hydrogenated at ambient temperature for several hours. Then the catalyst was filtered off and the solvent removed under reduced pressure. Resulting oil was dissolved in 5 ml of 10% citric acid, diphenylmethane was removed by extraction with diethyl ether and the solution was alkalized by addition of potassium carbonate. Dialkyl aminoalkylphosphonate was extracted with ethyl acetate. Extract was dried over anhydrous magnesium sulphate. Removal of drying agent and solvent yielded crude products of satisfactory purity.

Diethyl 2-Aminopropylphosphonate.

^{1}H-n.m.r. ($CDCl_3$, TMS) δ_{ppm}: 1.17 and 1.20 (d, 1.5H each, J = 6.4Hz, CH_3CH); 1.35 (t-t, 6H, J = 7.0Hz, $POCH_2CH_3$); 1.69 (s, 2H NH_2); 1.75 - 1.9 (m, 2H, CH_2P); 3.3-3.5 (m, 1H, $CHCH_2P$); 4.05-4.2 (q-q, 4H, J

= J_{PH}= 7.0Hz, $POCH_2$); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 31.4; Mass spectrum (CI) *m/z* 196.15 $C_7H_{18}NO_3P + H^+$ requires 196.11)

Diethyl 2-Aminobutylphosphonate.

^{1}H-n.m.r. ($CDCl_3$, TMS) δ_{ppm}: 0.86 (t, 3H, J = 7.4Hz, CH_3CH_2CH); 1.26 (t-t, 6H, J = 7.0Hz, $POCH_2CH_3$); 1.39 (q-q, 2H, J = 7.4Hz, J = 7.6Hz, CH_3CH_2CH); 1.57 (s, 2H NH_2); 1.6-1.7 and 1.8-1.9 (m, 1H each, CH_2P); 3.0-3.1 (m, 1H, $CHCH_2P$); 4.0-4.1 (q-q, 4H, J = J_{PH} = 7.0Hz, $POCH_2$); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 32.2; Mass spectrum (CI) *m/z* 210.19 ($C_8H_{20}NO_3P + H^+$ requires 210.13)

Diethyl 2-Amino-5-chloropentylphosphonate.

^{1}H-n.m.r. ($CDCl_3$, TMS) δ_{ppm}: 1.26 (t, 6H, J = 7.1Hz, $POCH_2CH_3$); 1.30 - 1.40 (m, 1H, CH_2CH_aCH); 1.55 - 1.75 (m, 3H, CH_2CH_bCH and NH_2); 1.85-1.95 (m, 2H, CH_2P); 2.05 - 2.2 (m, 2H, $ClCH_2CH_2$); 2.75 - 2.85 and 3.2 - 3.35 (m 1H each, $ClCH_2CH_2$); 2.95 - 3.0 (m, 1H $CHCH_2P$); 4.0 - 4.15 (m, 4H, $POCH_2$); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ_{ppm}: 31.1; Mass spectrum (CI) *m/z* 258.19 ($C_9H_{21}ClNO_3P + H^+$ requires 258.10)

Dimethyl 1-Aminopropylphosphonate.

^{1}H-n.m.r. ($CDCl_3$, TMS) δ_{ppm}: 1.06 (t, 3H, J = 7.1Hz, CH_3CH_2CHP); 1.15 (s, 2H, NH_2); 1.65-2.05 (m, 2H, CH_2CHP); 2.9-3.05 (m, 1H, CHP); 3.80 (d, 6H, J_{PH}= 10.7Hz, $POCH_3$); ^{31}P-n.m.r. ($CDCl_3$, H_3PO_4) δ $_{ppm}$: 30.3; Mass spectrum (CI) *m/z* 196.08 ($C_7H_{17}NO_3P + H^+$ requires 196.11)

Preparation of Aminoalkylphosphonic Acids. An aminoalkylphosphonate or crude (N-benzhydrylamino)alkylphosphonate was dissolved in concentrated hydrochloric acid and refluxed for 4 h. After filtration the solvent was evaporated and the resulting dense oil was dissolved in methanol. Final product was precipitated by addition of propylene oxide and then of five-fold amount of acetone. Products were recrystallized from mixtures of water and methanol or water-methanol-acetone.

2-Aminopropylphosphonic Acid (7a).

M.p.= 250-253° C; ^{1}H-n.m.r. (D_2O, HMDS) δ_{ppm}: 1.35 (d, 3H, J = 6.5Hz, $CHCH_2P$); 1.87 (d-d, 2H J = 6.9Hz and J_{PH}= 7.7Hz, CHP): 3.55 - 3.6 (m, 1H, $CHCH_2P$); ^{31}P-n.m.r. (D_2O, H_3PO_4) δ_{ppm}: 19.9; Mass spectrum (ESI) *m/z* 140.0 ($C_3H_{11}NO_3P + H^+$ requires 140.06).

2-Aminobutylphosphonic Acid (7b).

M.p.= 172-174° C; ^{1}H-n.m.r. (D_2O, HMDS) δ_{ppm}: 0.93 (t, 3H, J = 7.4Hz, CH_3CH_2); 1.6-1.8 (m, 3H, one of CH_2P and CH_3CH_2CH); 1.9-2.05 (m, 1H, one of CH_2P); 3.3-3.45 (m, 1H, $CHCH_2P$); ^{31}P-n.m.r. (D_2O, H_3PO_4) δ_{ppm}: 20.6; Mass spectrum (ESI) *m/z* 154.0 ($C_4H_{12}NO_3P + H^+$ requires 154.06).

2-Amino-4-phenylbutylphosphonic Acid (7g).

M.p.= 292-297° C; ^{1}H-n.m.r. (D_2O, HMDS) δ_{ppm}: 1.85 - 2.25 (m, 4H, CH_2P, CH_2CH_2CH); 2.70 (t, 2H, J = 8.0Hz, $C_6H_5CH_2CH_2$); 3.7-3.8 (m, 21H, $CHCH_2P$); 7.26 (s, 5H C_6H_5); ^{31}P-n.m.r. (D_2O, H_3PO_4) δ_{ppm}: 20.4; Mass spectrum (ESI) *m/z* 286.1 ($C_4H_{12}NO_3P + H^+$ requires 286.16).

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