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The Synthesis of 1-Aminobenzylphosphonic acids from Benzylidenediphenylmethylamines, for use as structural units in Antithrombotic tripeptides

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Abstract. Acid hydrolyses of *O,O*-dimethyl or *O,O*-diethyl 1-(diphenylmethylamino) benzylphosphonate intermediates **2**, formed from the addition at elevated temperature of dimethyl or diethyl phosphite to benzylidenediphenylmethylamines **1**, generates 1-aminobenzylphosphonic acids **3** in good yield.

The biological activity of 1-aminoalkanephosphonic acids, and their dialkyl ester derivatives, has been well established in a wide variety of instances[1]. Their negligible mammalian toxicity, and the fact that they bear a very close chemical resemblance to their corresponding aminocarboxylic acid analogues, makes them extremely important structural units in phosphonopeptides and other peptidomimetics. Although there are many classical methods for synthesising 1-aminophosphonic acids, these involve either long reaction times, expensive reagents, or the use of conditions which are amenable to aliphatic aminophosphonic acids rather than aromatic aminophosphonic acids[2].

Recent results have shown that following pre-incubation, free aminoalkanephosphonic acid derived tripeptides, based upon the fibrinogen-like sequence 'D-Phe-Pro-Arg', where the phosphorus residue replaces the charged P_1 Arg, inhibit thrombin in the micromolar range[3]. Preliminary molecular modelling analyses of the putative structure of the active site of thrombin, indicate that the

introduction of an aromatic substituent in the P_1 side chain of the tripeptide could maximise the hydrophobic interaction that occurs inside thrombin's specificity pocket. This could dramatically improve the inhibitory capacity of the tripeptides, making them useful, potent, anti-thrombotic agents. This was additional confirmation of the work carried out by Bode *et.al.*[4], Tapparelli *et.al.*[5] and Banner[6]. They showed through X-ray crystallographic analysis of thrombin-inhibitor complexes, that thrombin has an extremely hydrophobic specificity pocket that preferentially accomodates neutral hydrophobic moieties, rather than charged side chains, in that area of the enzyme. The fact that methods have been developed for esterifying 1-aminophosphonic acids[7], for which 1-aminobenzylphosphonic acids would be well suited, means that their chemical utility can be further extended to enhance the important specificity that these tripeptide derived inhibitors experience with thrombin.

$$RCHO + (C_6H_5)_2CHNH_2 \xrightarrow[CH_2Cl_2,\ 1h,\ RT]{K_2CO_3} RCH{=}NCH(C_6H_5)_2 \quad (1)$$

1

$$RCH{=}NCH(C_6H_5)_2 + (R'O)_2\overset{O}{\overset{\|}{P}}\text{-H} \xrightarrow[R' = Me \text{ or } Et]{130\text{-}140^\circ C,\ 0.5h} (R'O)_2\overset{O}{\overset{\|}{P}}\text{-CH(R)-NHCH}(C_6H_5)_2$$

2

$$\xrightarrow[(ii)\ \text{propene oxide, } 45\text{-}50^\circ C]{(i)\ HCl,\ \text{Reflux, } 3h} (HO)_2\overset{O}{\overset{\|}{P}}\text{-CH(R)-NH}_2 + (C_6H_5)_2CHCl \quad (2)$$

3

R = Aryl

Benzylidenediphenylmethylamines **1** (shown in the Scheme and listed in Table 1), were prepared in quantitative yield by a reaction involving the equimolar condensation of aromatic aldehyde and diphenylmethylamine in the presence of excess anhydrous potassium carbonate at room temperature, using dichloromethane as solvent. The products were isolated after 1 hour, as bright-yellow, low-melting point, crystalline solids. No further purification of these materials was necessary, as shown by the results of spectroscopic and elemental analyses. The structures of the

compounds were further authenticated using low resolution impact mass spectrometry. All the compounds (**1**) analysed in this way generated a molecular ion consistent with their structure. Their fragmentation patterns were further characterised by the production of the benzhydryl cation $(C_6H_5)_2CH^+$, usually the base peak, by the loss of the R-CH=N moiety from the molecular ion. In the proton N.M.R. spectrum for **1**, the low field imine hydrogen C<u>H</u>=N resonates between 8.30 and 8.50 ppm, and is a characteristic marker for their formation. This hydrogen is in the alpha position in the final product **3**. In the proton N.M.R. spectrum this signal appears as a doublet, moving significantly upfield, to resonate between 3.00 and 4.00 ppm. A brief summary of these observations is given in Table 1.

<u>Table 1</u> Benzylidenediphenylmethylamines $RCH{=}NCH(C_6H_5)_2$, synthesised for conversion to the corresponding 1-Aminobenzylphosphonic acids

Entry	R	M+, EIms:m/z(%)	δ C<u>H</u>=N/ppm ^{1}H N.M.R.	$(\dot{R}O)_2P(O)H$*
1	C_6H_5	271(43.9)	8.41	Me
2	2-HOC_6H_4	287(28.9)	8.46	Me
3	4-ClC_6H_4	305(6.1)	8.35	Me
4	4-BrC_6H_4	349(4.17)	8.34	Me
5	4-CNC_6H_4	296(3.34)	8.43	Me
6	4-$CH_3OC_6H_4$	301(16.9)	8.31	Et
7	4-$NO_2C_6H_4$	316(5.0)	8.46	Et
8	$C_6H_5CH_2$	285(2.2)	8.26	Et

*Dialkyl phosphite used in reaction 2

Acid hydrolysis of unisolable *O,O*-dialkyl 1-(diphenylmethylamino)benzylphosphonate intermediates **2**, formed by the nucleophilic addition of dialkyl phosphite to benzylidenediphenylmethylamines **1**, at 130 - 140°C, liberates 1-aminobenzylphosphonic acids as: nice-white, crystalline, high-melting point, water-soluble powders; following propene oxide treatment of the hydrochloride salt in methanol at 45 - 50°C. An analytically pure sample of the aminophosphonic acid was obtained if prior to propene oxide treatment, the hydrochloride salt precursor was diluted in water and concentrated under low pressure. These compounds give highly characteristic N.M.R. spectra, where in the ^{13}C(NaOD) N.M.R. spectra, the presence of the alpha carbon at approximately 55 ppm, with $^1J_{PC}$ in the region of 125 to 140 Hz, is very good confirmatory evidence for their formation. Additionally the FABMS profile of these compounds is exemplified by the $[M+H]^+$ fragment and a highly abundant species associated with the loss of H_3PO_3 via P-C cleavage. As shown in Table 2,

interesting P1 substituents may now be synthesised which if coupled to fibrinogen based peptides by modifications of classical methods[8], could generate a new series of phosphorus based tripeptides that would express important biological activity against thrombin. In the light of the information available that discusses the efficacy of free aminophosphonic acid derived peptides against thrombin, this method of synthesising 1-aminobenzylphosphonic acids could have crucial implications in the future.

Table 2 1-Aminobenzylphosphonic acids $(HO)_2P(O)CH(NH)_2R$ **3**, synthesised from acid hydrolyses of unisolable *O,O*-Dialkyl 1-(diphenylmethylamino)benzylphosphonates **2**

Entry	R	mol scale	yield(%)	FABMS:m/z(%) M+H	δ α C/ppm($^1J_{PC}$) ^{13}C N.M.R.(NaOD)*
1	C_6H_5	0.050	66	188(41.67)	55.40(127.34)
2	2-HOC_6H_4	0.050	33	204(10.56)	53.91(130.28)
3	4-ClC_6H_4	0.030	88	222(56.94)	55.07(128.61)
4	4-BrC_6H_4	0.050	96	267(5.56)	55.42(130.30)
5	4-CNC_6H_4	0.025	36	213(5.6)	55.43(126.60)
6	4-$CH_3OC_6H_4$	0.026	43	218(43.9)	55.62(132.59)
7	4-$NO_2C_6H_4$	0.041	68	233(39.7)	55.64(126.30)
8	$CH_2C_6H_4$	0.051	34	202(30.6)	52.83(139.19)

*It should be noted that chemical shifts and coupling constants for phosphonic acids are pH dependent and data given here are those for the anionic form, $^{=}O_2P(O)CH(NH_2)R$, where excess of NaOD is present.

Preparation of benzylidenediphenylmethylamine

Benzaldehyde (1.0 mol eq) dissolved in dichloromethane, was added with stirring to a solution of diphenylmethylamine (1.0 mol eq) also dissolved in dichloromethane, in the presence of anhydrous potassium carbonate (1.5 mol eq). When the addition had been completed, the mixture was stirred for an hour at room temperature. The desiccant was then filtered off, and the filtrate was concentrated under reduced pressure on a rotary evaporator to afford a viscous yellowish oil. Upon standing for 10 to 15 minutes at room temperature, the compound had become a bright yellowish solid. The product, benzylidenediphenylmethylamine was isolated in quantitative yield. (Found: C, 88.21; H, 6.44; N, 4.95. Calc. for $C_{20}H_{17}N$: C, 88.56; H, 6.27; N, 5.17%); ^{1}H(CDCl3): δ 5.59 (s,1H, NC<u>H</u>), 7.18-7.86 (m, 15H, aromatic region), 8.41 (s, 1H, C<u>H</u>=N); ^{13}C(CDCl3): δ 77.90 (s, N<u>C</u>H), 126.96-130.75 (aromatic <u>C</u>'s), 136.29 (s, <u>C</u>q of benzylidene ring), 143.87 (s, <u>C</u>q, of diphenyl rings), 160.78 (s, <u>C</u>H=N); EIms:m/z(%) 271 (M^+, 43.9), 194 ($[M-C_6H_5]^+$, 11.7), 167 ($[M-C_6H_5CH{=}N]^+$, 100). This method was used with the

appropriate aromatic aldehyde to synthesise the other substituted benzylidenediphenylmethylamines used in this present study. The analytical data for these compounds is shown below.

2-Hydroxybenzylidenediphenylmethylamine
(Found: C, 83.55; H, 5.96; N, 4.61. Calc. for $C_{20}H_{17}NO$: C, 83.62; H, 5.92; N, 4.88%); $^1H(CDCl_3)$: δ 5.61 (s, 1H, NCH), 6.89 (dd, 1H, H_5, $^3J_{HCCH}$ 7.58), 6.98 (d, 1H, H_6, $^3J_{HCCH}$ 8.13), 7.13-7.43 (m, 12H, C_6H_5x2 + H_3+H_4), 8.46 (s, 1H, CH=N); $^{13}C(CDCl_3)$: δ 76.82 (s, NCH), 117.01 (s, C_5 of benzylidene ring), 118.77 (s, C_6 of benzylidene ring), 126.88-128.68 (diphenyl rings), 131.67 (s, C_4 of benzylidene ring), 132.60 (s, C_3 of benzylidene ring), 142.53 (s, Cq of diphenyl rings), 161.03 (s, C_2 of benzylidene ring), 165.00 (s, CH=N); EIms:m/z(%) 287 (M^+, 28.9), 167 ([M - 2-$OHC_6H_4CH=N]^+$, 100).

4-Chlorobenzylidenediphenylmethylamine
(Found: C, 78.72; H, 5.08; N, 4.64. Calc. for $C_{20}H_{16}NCl$: C, 78.69; H, 5.25; N, 4.59%); $^1H(CDCl_3)$: δ 5.58 (s, 1H, NCH), 7.23 (d, 2H, H_2+H_6, $^3J_{HCCH}$ 7.20), 7.24-7.39 (m, 10H, C_6H_5x2), 7.75(d, 2H, H_3+H_5, $^3J_{HCCH}$ 8.42), 8.35 (s, 1H, CH=N); $^{13}C(CDCl_3)$: δ 77.84 (s, NCH), 127.05-130.87 (diphenyl rings), 134.73 (s, C_1 of benzylidene ring), 136.68 (s, C_4 of benzylidene ring), 143.66 (s, Cq of diphenyl rings), 159.42 (s, CH=N); EIms:m/z(%) 305 (M^+,6.1), 167 ([M - 4-$ClC_6H_4CH=N]^+$, 100).

4-Bromobenzylidenediphenylmethylamine
(Found: C, 68.51; H, 4.67; N, 3.93. Calc. for $C_{20}H_{16}NBr$: C, 68.57; H, 4.57; N, 4.00%); $^1H(CDCl_3)$: δ 5.58 (s, 1H, NCH), 7.16-7.42 (m, 10H, C_6H_5x2), 7.52 (d, 2H, H_2+H_6, $^3J_{HCCH}$ 8.47), 7.69 (d, 2H, H_3+H_5, $^3J_{HCCH}$ 8.38), 8.34 (s, 1H, CH=N); $^{13}C(CDCl_3)$: δ 77.85 (s, NCH), 125.16 (s, C_1 of benzylidene ring), 127.06-132.40 (diphenyl rings), 135.14 (s, C_4 of benzylidene ring), 143.62 (s, Cq of diphenyl rings), 159.53 (s, CH=N); EIms:m/z(%) 349 (M^+, 4.17), 272 ([M-$C_6H_5]^+$, 1.1), 167 ([M - 4-$BrC_6H_4CH=N]^+$, 100).

4-Cyanobenzylidenediphenylmethylamine
(Found: C, 84.78; H, 5.76; N, 9.11. Calc. for $C_{21}H_{16}N_2$: C, 85.14; H, 5.41; N, 9.46%); $^1H(CDCl_3)$: δ 5.64 (s, 1H, NCH), 7.22-7.40 (m, 10H, C_6H_5x2), 7.68 (d, 2H, H_2+H_6, $^3J_{HCCH}$ 8.34), 7.92 (d, 2H, H_3+H_5, $^3J_{HCCH}$, 8.32), 8.43 (s, 1H, CH=N); $^{13}C(CDCl_3)$: δ 78.00 (s, NCH), 113.98 (s, C_4-CN), 118.52 (s, C_4-CN), 140.00 (s, Cq of benzylidene), 143.23 (Cq of diphenyl rings), 158.94 (s, CH=N); EIms:m/z(%) 296 (M^+, 3.34), 167 ([M - 4-$CNC_6H_4CH=N]^+$, 100).

4-Methoxybenzylidenediphenylmethylamine
(Found: C, 83.74; H, 6.37; N, 4.49. Calc. for $C_{21}H_{19}NO$: C, 83.72; H, 6.31; N, 4.65%); $^1H(CDCl_3)$: δ 3.76 (s, 3H, OCH_3), 6.88 (d, 2H, H_2+H_6, $^3J_{HCCH}$ 8.85), 7.15-7.40 (m, 10H, C_6H5x2), 7.76 (d, 2H, H_3+H_5, $^3J_{HCCH}$ 8.75), 8.31 (s, 1H, CH=N); $^{13}C(CDCl_3)$: δ 55.25 (s,

$O\underline{C}H_3$), 77.76 (s, N$\underline{C}$H), 126.85-129.98 (diphenyl rings), 129.30 (s, $\underline{C}_1$ of aromatic ring), 144.11 (s, $\underline{C}q$ of diphenyl rings), 160.02 (s, $\underline{C}$H=N), 161.68 (s, $\underline{C}_4$ of benzylidene ring); EIms:m/z(%) 301 (M^+, 16.9), 224 ([M-C_6H_5]$^+$, 5.6), 167 ([M - 4-$CH_3OC_6H_4CH$=N]$^+$, 100).

4-Nitrobenzylidenediphenylmethylamine
(Found: C, 76.12; H, 4.92; N, 8.93. Calc. for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86%); ^{1}H($CDCl_3$): δ 5.65 (s, 1H, NC$\underline{H}$), 7.15-7.48 (m, 10H, $C_6\underline{H}_5$x2), 7.95 (d, 2H, $\underline{H}_2$+$\underline{H}_6$, $^3J_{HCCH}$ 8.73), 8.21 (d, 2H, $\underline{H}_3$+$\underline{H}_5$, $^3J_{HCCH}$ 8.74), 8.46 (s, 1H, C$\underline{H}$=N); ^{13}C($CDCl_3$): δ 78.09 (s, N$\underline{C}$H), 123.79-129.11 (diphenyl rings), 141.66 (s, $\underline{C}_1$ of benzylidene ring), 143.22 (s, $\underline{C}q$ of diphenyl rings), 149.09 (s, $\underline{C}_4$ of benzylidene ring), 158.60 (s, $\underline{C}$H=N); EIms:m/z(%) 316 (M^+, 5.00), 239 ([M-C_6H_5]$^+$, 4.2), 167 ([M - 4-$NO_2C_6H_4CH$=N]$^+$, 100).

Benzylmethylidenediphenylmethylamine
(Found: C, 88.13; H, 6.52; N, 5.06. Calc. for $C_{21}H_{19}N$: C, 88.42; H, 6.67; N, 4.91%); ^{1}H($CDCl_3$): δ 3.57-3.91 (m, 2H, $C\underline{H}_2$CH), 4.51 (dd, 1H, $CH_2C\underline{H}$, $^3J_{HCCH}$), 5.22 (s, 1H, NC$\underline{H}$), 7.07-8.23 (m, 15H, $C_6\underline{H}_5$x3), 8.26 (d, 1H, N=C$\underline{H}$, $^3J_{HCCH}$ 7.35); ^{13}C($CDCl_3$): δ 35.50 (s, $C_6H_5\underline{C}H_2$), 59.69 (s, N$\underline{C}$H), 125.00-128.02 (m, $\underline{C}_6H_5$x3), 163.75 (s, $\underline{C}$H=N); EIms:m/z(%) 285 (M^+, 2.20), 208 ([M-C6H5]$^+$, 5.60), 167 ([M - $C_6H_5CH_2CH$=N]$^+$, 100).

The General Preparation of 1-Aminobenzylphosphonic acids

Benzylidenediphenylmethylamine and dialkyl phosphite (1.1 mol eq.), were heated with stirring at 130-140°C for 30 minutes. No attempt was made to isolate and characterise the *O,O*-dialkyl 1-(diphenylmethylamino)benzylphosphonate intermediate which had formed as a viscous yellow-orange oil. Excess concentrated hydrochloric acid was added and the resultant solution was heated with stirring under reflux for 3 hours. Upon cooling, diphenylmethanechloride was extracted with toluene, and the aqueous layer was concentrated under reduced pressure on a rotary evaporator to afford a thick viscous oil. This material was dissolved in water, and concentrated for a second time under reduced pressure to afford a granular suspension in an oily residue. This material was dissolved in methanol and treated with propene oxide at 45-50°C, to liberate the benzylphosphonic acid as a white crystalline powder. The product was filtered off, washed with diethyl ether and dried under vacuum for 2 hours, before been subjected to various structural analyses. The above protocol was repeated with the various substituted benzylidenediphenylmethylamines to generate the required 1-aminobenzylphosphonic acid. The analytical data for these compounds is given in the following.

1-Aminobenzylphosphonic acid

(6.19g, 66%); m.p. 283-286°C; (Found: C, 45.03; H, 5.42; N, 7.38. $C_7H_{10}NO_3P$ requires: C, 44.92; H, 5.35; N, 7.49%); ^1H(NaOD): δ 3.79 (d, 1H, P-C<u>H</u>, $^2J_{PCH}$ 14.89), 7.02-7.08 (m, 5H, $C_6\underline{H}_5$); ^{13}C(NaOD): δ 55.40 (d, P-<u>C</u>H, $^1J_{PC}$ 127.34), 127.96 (2xs, $\underline{C}_3+\underline{C}_5$), 128.03 (s, $\underline{C}_4$), 128.88 (s, $\underline{C}_2+\underline{C}_6$), 136.55 (d, $\underline{C}_1$, $^2J_{PCC}$ 3.82); ^{31}P(NaOD): δ 11.63 (s); FABms(glycerol):m/z(%) 467 ([2M+H+G]$^+$, 1.39), 375 ([2M+H]$^+$, 9.72), 280 ([M+H+G]$^+$, 9.44), 198 ([M+H+G - H_3PO_3]$^+$, 7.78), 188 ([M+H]$^+$, 41.67), 106 ([M+H - H_3PO_3]$^+$, 89.72).

1-Amino-2'-hydroxybenzylphosphonic acid

(3.46g, 33%); m.p. 309-312°C; (Found: C, 41.53; H, 4.94; N, 7.09. $C_7H_{10}NO_4P$ requires: C, 41.38; H, 4.93; N, 6.90%); ^1H(NaOD): δ 3.90 (d, 1H, P-C<u>H</u>, $^2J_{PCH}$ 15.96), 6.77(d, 1H, $\underline{H}_6$, $^3J_{HCCH}$ 7.65), 6.84 (dd, 1H, $\underline{H}_5$, $^3J_{HCCH}$ 7.47), 7.10-7.13 (m, 2H, $\underline{H}_3+\underline{H}_4$); $^{13}C(CDCl_3)$: δ 53.91 (d, P-<u>C</u>H, $^1J_{PC}$ 130.28), 118.66 (d, <u>C</u>6, $^3J_{PCCC}$ 1.32), 121.03 (s, $\underline{C}_5$), 126.88 (d, $\underline{C}_1$, $^2J_{PCC}$ 2.83), 129.07 (s, $\underline{C}_4$), 130.18 (s, $\underline{C}_3$), 154.92 (d, <u>C</u>2, $^3J_{PCCC}$ 3.87); ^{31}P(NaOD): d 17.11 (s); FABms(glycerol):m/z(%) 296 ([M+H+G]$^+$, 5.00), 204 ([M+H]$^+$, 10.56), 122 ([M+H-H_3PO_3]$^+$, 16.67).

1-Amino-4'-chlorobenzylphosphonic acid

(5.84g, 88%); m.p. 269-272°C; (Found: C, 38.21; H, 4.33; N, 6.16. $C_7H_9NO_3PCl$ requires: C, 38.01; H, 4.07; N, 6.34%); ^1H(NaOD): δ 3.71 (d, P-C<u>H</u>, $^2J_{PCH}$ 15.39), 7.14 (s, 4H, $\underline{H}_2+\underline{H}_3+\underline{H}_5+\underline{H}_6$); ^{13}C(NaOD): δ 55.07 (d, P-<u>C</u>H, $^1J_{PC}$ 128.61), 128.47 (s, $\underline{C}_3+\underline{C}_5$), 129.42 (d, $\underline{C}_2+\underline{C}_6$, $^3J_{PCCC}$ 4.58), 132.28 (d, $\underline{C}_1$, $^2J_{PCC}$ 2.74), 138.29 (s, $\underline{C}_4$); ^{31}P(NaOD): δ 14.85 (s); FABms(glycerol):m/z(%) 535 ([2M+H+G]$^+$, 1.1), 443 ([2M+H]$^+$, 18.06), 361 ([2M+H-H_3PO_3]$^+$, 1.94), 314 ([M+H+G]$^+$, 7.5), 222 ([M+H]$^+$, 56.94), 140 ([M+H-H_3PO_3]$^+$, 100).

1-Amino-4'-bromobenzylphosphonic acid

(12.71g, 96%); m.p. 276-279°C; (Found: C, 31.61; H, 3.56; N, 5.17. $C_7H_9NO_3PBr$ requires: C, 31.58; H, 3.38; N, 5.26%); ^1H(NaOD): δ 3.57 (d, 1H, P-C<u>H</u>, $^2J_{PCH}$ 15.08), 7.09 (dd, 2H, $\underline{H}_2+\underline{H}_6$, $^3J_{HCCH}$ 8.48), 7.30 (d, 2H, $\underline{H}_3+\underline{H}_5$, $^3J_{HCCH}$ 8.38); ^{13}C(NaOD): δ 55.42 (d, P-<u>C</u>H, $^1J_{PC}$ 130.30), 119.54 (d, $\underline{C}_1$, $^2J_{PCC}$ 3.45), 129.78 (d, $\underline{C}_2+\underline{C}_6$, $^3J_{PCCC}$ 4.76), 131.13 (s, $\underline{C}_3+\underline{C}_5$), 141.59 (s, $\underline{C}_4$); ^{31}P(NaOD): δ 18.06 (s); FABms(glycerol):m/z(%) 535 ([2M+H]$^+$, 2.78), 451 ([2M+H-H_3PO_3]$^+$, 2.22), 359 ([M+H+G]$^+$, 10), 267 ([M+H]$^+$, 5.56), 185 ([M+H-H_3PO_3]$^+$, 100).

1-Amino-4'-cyanobenzylphosphonic acid

(1.88g, 36%); m.p. 266-268°C; (Found: C, 44.77; H, 4.48; N, 12.59. $C_8H_9N_2O_3P$ requires: C, 45.28; H, 4.25; N, 13.21%); ^1H(NaOD): δ 3.87 (d, P-C<u>H</u>, $^2J_{PCH}$ 15.35), 7.19 (d, 2H, $\underline{H}_3+\underline{H}_5$, $^3J_{HCCH}$ 6.99), 7.55 (d, 2H, $\underline{H}_2+\underline{H}_6$, $^3J_{HCCH}$ 8.24); ^{13}C(NaOD): d 55.43 (d, P-<u>C</u>H, $^1J_{PC}$ 126.60), 127.67 (d, $\underline{C}_2+\underline{C}_6$, $^3J_{PCCC}$ 4.27), 129.13 (s, $\underline{C}_3+\underline{C}_5$), 135.44 (s, $\underline{C}_1$), 140.96 (s, $\underline{C}_4$), 175.97 (s, <u>C</u>N); ^{31}P(NaOD): δ 12.69 (s); FABms(glycerol):m/z(%) 213 ([M+H]$^+$, 5.6), 131 ([M+H - H_3PO_3]+, 100).

1-Amino-4'-methoxybenzylphosphonic acid
(3.86g, 68%); m.p. 286-288°C; (Found: C, 44.26; H, 5.38; N, 6.19. $C_8H_{12}NO_4P$ requires: C, 44.24; H, 5.53; N, 6.19%); ^1H(NaOD): δ 3.66 (d, 1H, P-C<u>H</u>, $^2J_{PCH}$ 15.13), 3.74 (s, 3H, OC<u>H</u>$_3$), 6.87 (d, 2H, <u>H</u>$_3$+<u>H</u>$_5$, $^3J_{HCCH}$ 8.73); ^{13}C(NaOD): δ 55.62 (d, P-<u>C</u>H, $^1J_{PC}$ 132.59), 56.29 (s, O<u>C</u>H$_3$), 114.34 (s, <u>C</u>$_3$+<u>C</u>$_5$), 129.64 (d, <u>C</u>$_2$+<u>C</u>$_6$, $^3J_{PCCC}$ 4.91), 135.68 (s, <u>C</u>$_1$), 158.01 (s, <u>C</u>$_4$); ^{31}P(NaOD): δ 19.03 (s); FABms(glycerol):m/z(%) 435 ([2M+H]$^+$, 5.8), 310 ([M+H+G]$^+$, 20.8), 218 ([M+H]$^+$, 43.9), 136 ([M+H-H_3PO_3]$^+$, 100).

1-Amino-4'-nitrobenzylphosphonic acid
(4.13g, 43%); m.p. 236-239°C; (Found: C, 36.61; H, 4.21; N, 12.19. $C_7H_9N_2O_5P$ requires: C, 36.21; H, 3.88; N, 12.07%); ^1H(NaOD): δ 3.98 (d, 1H, P-C<u>H</u>, $^2J_{PCH}$ 17.35), 7.55-7.59 (dd, 2H, <u>H</u>$_2$+<u>H</u>$_6$, $^3J_{HCCH}$ 8.92), 8.19 (d, 2H, <u>H</u>$_2$+<u>H</u>$_6$, $^3J_{HCCH}$ 8.63); ^{13}C(NaOD): δ 56.64 (d, P-<u>C</u>H, $^1J_{PC}$ 126.30); 124.01 (s, <u>C</u>$_3$+<u>C</u>$_5$), 128.98 (d, <u>C</u>$_2$+<u>C</u>$_6$, $^3J_{PCCC}$ 4.03), 146 (s, <u>C</u>$_1$), 151.82 (s, <u>C</u>$_4$); ^{31}P(NaOD): δ 17.03 (s); FABms(glycerol):m/z(%) 325 ([M+H+G]$^+$, 27.8), 233 ([M+H]$^+$, 39.7), 151 ([M+H-H_3PO_3]$^+$, 47.8).

1-Amino-1-benzylmethanephosphonic acid
(3.52g, 34%); m.p. 272-274°C; (Found: C, 47.56; H, 5.96; N, 6.65. $C_8H_{12}NO_3P$ requires: C, 47.76; H, 5.97; N, 6.97%); ^1H(NaOD): δ 2.45-2.94 (m, 2H, P-CHC<u>H</u>$_2$), 3.19-3.28 (m, 1H, P-C<u>H</u>CH$_2$), 7.23-7.43 (m, 5H, C6<u>H</u>$_5$); ^{13}C(NaOD): δ 39.07 (s, P-CH<u>C</u>H$_2$), 52.83 (d, P-<u>C</u>H, $^1J_{PC}$ 139.19), 126.98 (s, <u>C</u>$_4$), 129.36 (s, <u>C</u>$_3$+<u>C</u>$_5$), 130.04 (s, <u>C</u>$_2$+<u>C</u>$_6$), 141.87 (d, <u>C</u>$_1$, $^3J_{PCCC}$ 15.35); ^{31}P(NaOD): δ 21.15 (s); FABms(glycerol):m/z(%) 405 ([2M+H]$^+$, 5.0), 295 ([M+H+G]$^+$, 20.1), 203 ([M+H]$^+$, 30.6), 121 ([M+H-H_3PO_3]$^+$, 100).

NB In the ^1H and ^{13}C N.M.R. spectra of the benzylidenediphenylmethylamines and 1-aminobenzylphosphonic acids the positions in the aromatic ring which are correspondingly designated 2 and 6, refer to the ortho sites of the ring; the positions designated 3 and 5, refer to the meta sites of the ring, and the position designated 4, refers to the para site of the ring. Position 1, is the point of attachment to rest of the molecule.

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REFERENCES

1. (a) Kafarski, P.; Lejczak, B.; Szewczyk, J., *Can. J. Chem.*; 1983, 2425-2430; (b) Diel, P. J.; Maier, L., *Phosphorus and Sulphur*, 1897, **29**, 201-209; (c) Dhawan, B.; Redmore, D., *Phosphorus and Sulphur*, 1987, **32**, 119-144; (d) Zecchini, G. P.; Paradisi, M. P.; Torrini, I.; Lucente, G., *Int. J. Peptide Protein Res.*, 1989, **34**, 33-36; (e) Oleksyszyn, J.; Powers, J. C., *Biochemistry*, 1991, **30**, 485-493; (f) Cameron, D. G.; Hudson, H. R.; Pianka, M., *Phosphorus, Sulphur and Silicon*, 1990, **51/52**, 391; (g) Kafarski, P.; Lejczak, B., *Phosphorus, Sulphur and Silicon*, 1991, **63**, 193-215.

2. (a) Tyka, R., *Tett Lett.*, 1970 (9), 677-680; (b) Petrov, K. A.; Chauzov, V. A.; Erokhina, T. S., *Uspekhi Khimii*, 1974, **43**, 2045-2087; *Eng Trans Russ. Chem. Rev.*, 1974, **43** (11), 984-1006; (c) Lukszo, J.; Tyka, R., *Synthesis*, 1977, 239-240; (d) Gancarz, R.; Wieczarek, J. S., *Synthesis*, 1977, 625; (e) Tyka, R.; Oleksyszn, J., *Tett. Lett.*, 1977, (32), 2823 - 2824; (f) Kudzin, Z. H.; Stec, W. J., *Synthesis*, 1978, 469-472; (g) Oleksyszn, J.; Tyka, R.; Mastalerz, P., *Synthesis*, 1978, 479-480; (h) Gandurina, I. A.; Zhukov, Y. N.; Osipova, T. I.; Khomutov, R. M., *USSR Patent*, 1979, **697519**; (i) Kudzin, Z. H.; Kotynski, A., *Synthesis*, 1980, 1028-1032; (j) Afarinkia, K.; Cadogan, J. I. G.; Rees, C. W., *Synlett.*, 1990, 415-416; (k) Corcoran, R. C.; Green, J. M., *Tett. Lett.*, 1990, **31** (47), 6827 - 6830; (l) Yuan, C.; Chen, S.; Wang, G., *Synthesis*, 1991, 490-493; (m) Genet, J. P.; Uziel, J.; Port, M.; Touzin, A. M.; Roland, S.; Thorimbert, S.; Taner, S., *Tett. Lett.*, 1992, **33** (1), 77-80; (n) Green, D.; Patel, G.; Elgendy, S.; Baban, J. A.; Claeson, G.; Kakkar, V. V.; Deadman, J., *Tett. Lett.*, 1993, **34** (43), 6917-6920.

3. Cheng, L.; Goodwin, C. A.; Scully, M. F.; Kakkar, V. V.; Claeson, G., *Tett. Lett.*, 1991, **32** (49), 7333-7336.

4. (a) Bode, W.; Turk, D.; Struzebecher, J., *Eur. J. Biochem*, 1990, **193**, 175-182; (b) Turk, D.; Sturzebecher, J.; Bode, W., *FEBS letters*, 1991, **287**, (1, 2), 133-138; (c) Bode, W.; Huber, R., *Eur. J. Biochem*, 1992, **204**, 433-451.

5. Tapparelli, C.; Metternich, R.; Ehrhardt, C.; Zurini, M.; Claeson, G.; Scully, M. F.; Stone, S. R., *J. Biol. Chem.*, 1993, **268** (7), 4734-4741.

6. Banner, D. W.; Hadvary, P., *J. Biol. Chem.*, 1991, **266** (30), 20085-20093.

7. (a) Sampson, N. S.; Bartlett, P. A., *J. Org. Chem.*, 1988, **53**, 4500-4503; (b) Kafarski, P.; Lejczak, B., *Synthesis*, 1988, 307-310; (c) Fastrez, J.; Jespers, L.; Lison, D.; Renard, M.; Sonveaux, E., *Tett. Lett.*, 1989, **30** (49), 6861-6864.

8. Atherton, F. R.; Hall, J. M.; Hassall, C. H.; Lambert, R. W.; Ringrose, P. S., *U. K. Patent*, **1577232**, 1980.

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