Synthesis and Bioactivation of Bis(aroyloxymethyl) and Mono(aroyloxymethyl) Esters of Benzylphosphonate and Phosphonoacetate

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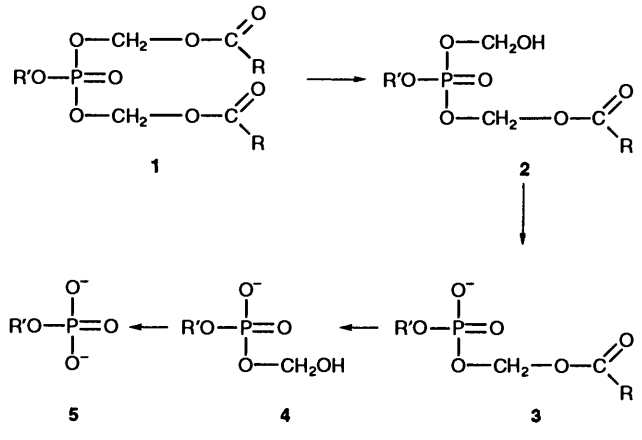
The bis(aroyloxymethyl) esters of benzylphosphonate **8** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) and methoxycarbonylmethylphosphonate **8** (X=MeO_2C, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) have been prepared by reaction of 2 equiv. of the appropriate aroyloxymethyl iodide with the disilver salt of either benzylphosphonate or methoxycarbonylmethylphosphonate. The cyclohexylammonium salts of the mono(aroyloxymethyl) esters of benzylphosphonate **12** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$, $M^+=C_6H_{11}NH_3^+$) were prepared by reaction of silver benzyl benzylphosphonate with the appropriate aroyloxymethyl iodide, with subsequent hydrogenolysis to remove the P-O-benzyl group. The bis(aroyloxymethyl) esters **8** (X=Ph or MeO_2C, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) and the mono(aroyloxymethyl) salts **12** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$, $M^+=C_6H_{11}NH_3^+$) were stable towards chemical hydrolysis at 37 °C at physiological pH. In the presence of porcine liver carboxyesterase, the bis(aroyloxymethyl) esters of benzylphosphonate **8** (X=Ph, Ar=Ph or 2-MeC_6H_4) degraded to the mono(aroyloxymethyl) esters **12** (X=Ph, Ar=Ph or 2-MeC_6H_4), which showed slow hydrolysis to benzylphosphonate. For the bis(aroyloxymethyl) esters of methoxycarbonylmethylphosphonate **8** (X=MeO_2C, Ar=Ph or 2-MeC_6H_4) there was competition between the esterase-catalysed hydrolyses of the aroyloxymethyl and methoxycarbonyl groups. For the triester **8** (X=MeO_2C, Ar=2,4,6-$Me_3C_6H_2$) cleavage of the methoxycarbonyl group was observed and hydrolysis of the sterically hindered 2,4,6-trimethylbenzoyl group (Ar=2,4,6-$Me_3C_6H_2$) was not detected for any compound.

Drugs that are charged at physiological pH typically have limited transport across biological membranes[1] such as the blood-brain barrier (BBB).[2] This is reflected in reduced bioavailability and therapeutic effectiveness in the brain. One approach to improving the transport properties of phosphates and phosphonates is to esterify the charged phospho groups ($-PO_3^{2-}$) to give the neutral phospho esters [$-P(O)(OR)_2$]. These derivatives, by virtue of their lipophilicity, should facilitate passive diffusion across physiological barriers. Ester groups could then be selected which would be susceptible to metabolism by host enzymes and thereby release the parent compound. The synthesis and bioactivation of the bis(acyloxymethyl) esters of benzyl and phenyl phosphate **1** (R'=Ph and Bn) have been reported.[3,4] In the presence of esterase, the hydroxymethyl intermediate **2** was formed, which then readily loses a molecule of formaldehyde to give the diester **3**. Repetition of this process gave the phosphate monoesters **5** *via* the hydroxymethyl intermediate **4**. The rate of chemical and esterase hydrolyses can be controlled by varying the acyl group R, and acetyl, isobutyryl and pivaloyl have been evaluated.[3,4] During the course of this study, bis(acyloxymethyl) esters have also been examined for the delivery of the 5'-monophosphate of dideoxyuridine,[5] phosphonoformate[6] and 9-(2-phosphonylmethoxyethyl)adenine.[7] Here, the aroyloxymethyl esters are investigated as an alternative to the acyloxymethyl substituent for biolabile protection of the phospho group. The scope for controlling the rate of degradation by steric and electronic means can then be explored by modification of the aryl ring with appropriate functional groups. Benzylphosphonate **6** (X=Ph) was used as a model compound and the diesters **8** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) and the corresponding monoesters **12** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) were prepared to investigate the effect of *ortho*-methyl substitution. This approach was then applied to the methyl ester of the antiviral phosphonoacetate[8] **6** (X=CO_2Me) with the synthesis and stability studies of the triesters **8** (X=CO_2Me, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$).



Results and Discussion

Adapting the method developed for the synthesis of the bis(acyloxymethyl) esters of phenyl and benzyl phosphate,[3,4] the bis(aroyloxymethyl) esters of benzylphosphonate **8** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) were prepared by treatment of disilver benzylphosphonate **6** (X=Ph, $M^+=Ag^+$) with the required aroyloxymethyl iodide[9,10] **7** (Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$). The triesters of phosphonoacetate **8** (X=CO_2Me, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) were similarly prepared by reaction of the disilver salt of methoxycarbonylmethylphosphonate **6** (X=CO_2Me, $M^+=Ag^+$) with 2 equiv. of the appropriate aroyloxymethyl iodide **7** in yields of around 40%.

The cyclohexylammonium salts of the mono(aroyloxy-

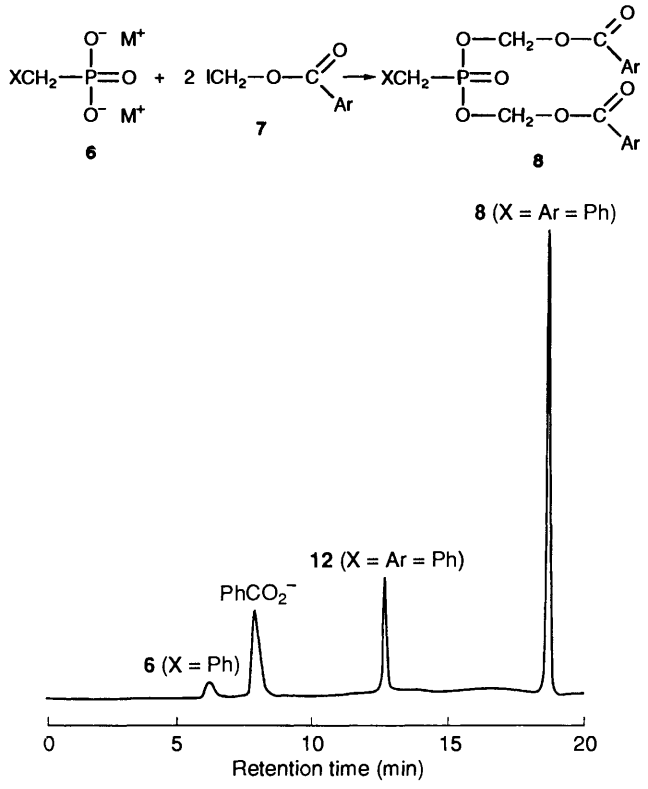
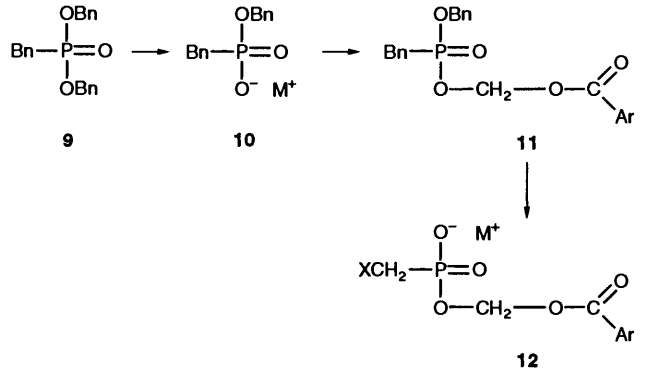


Fig. 1 High-performance liquid chromatogram of the possible degradation products from the hydrolysis of bis(benzoyloxymethyl) benzylphosphonate **8** (X=Ar=Ph)

methyl) esters **12** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$, M^+=$C_6H_{11}NH_3^+$) were prepared by adapting the method employed for the mono(acyloxymethyl) esters of phenyl and benzyl phosphate.[3,4] Dibenzyl benzylphosphonate **9**, prepared by reaction of disilver benzylphosphonate **6** (X=Ph, M^+=Ag^+) with 2 equiv. of benzyl bromide, was treated with 1 equiv. of sodium iodide[11] to give sodium benzyl benzylphosphonate **10** (M^+=Na^+) in 54% yield. The sodium salt was then treated with 1 equiv. of silver iodide in water to give the silver salt **10** (M^+=Ag^+) in 58% yield, and reaction with the appropriate aroyloxymethyl iodide **7** (Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) gave the mixed phosphonate esters **11** (Ar=Ph, 2-



MeC_6H_4 or 2,4,6-$Me_3C_6H_2$). Catalytic hydrogenation of **11** using 5% palladium on charcoal, followed by addition of 1 equiv. of cyclohexylamine and subsequent recrystallisation from ethyl acetate–hexane gave the required monoesters **12** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$, M^+=$C_6H_{11}NH_3^+$).

To evaluate the stability towards chemical hydrolysis, 2 mmol dm^{-3} solutions of the bis(aroyloxymethyl) esters of benzylphosphonate **8** {X=Ph; Ar=Ph [δ_P 28.5, δ_H includes 2.87 (2 H, d, J_{PH} 21.3) and 5.47 (4 H, d, J_{PH} 12.8)]; Ar=2-MeC_6H_4 [δ_P 28.1, δ_H includes 2.03 (6 H, br s), 2.86 (2 H, br d, J_{PH} 22) and 5.46 (4 H, br d, J_{PH} 12.2)]; Ar=2,4,6-$Me_3C_6H_2$ [δ_P 27.5, δ_H includes 1.78 (6 H, br s), 1.87 (12 H, br s), 2.94 (2 H, br d, J_{PH} 19.5) and 5.54 (4 H, br s)]} and 5 mmol dm^{-3} solutions of the cyclohexylammonium salts of mono(aroyloxymethyl) esters of benzylphosphonate **12** {X=Ph; M^+=$C_6H_{11}NH_3^+$; Ar=Ph [δ_P 23.2, δ_H includes 2.98 (2 H, d, J_{PH} 20.8) and 5.60 (2 H, d, J_{PH} 12.8)]; Ar=2-MeC_6H_4 [δ_P 23.1, δ_H includes 2.45 (3 H, s), 2.98 (2 H, d, J_{PH} 20.8) and 5.58 (2 H, d, J_{PH} 12.9)]; Ar=2,4,6-$Me_3C_6H_2$ [δ_P 22.8, δ_H includes 2.17 (6 H, s), 2.19 (3 H, s), 2.97 (2 H, d, J_{PH} 20.8) and 5.57 (2 H, d, J_{PH} 12.3)]} in potassium phosphate buffer (0.1 mol dm^{-3}, D_2O, pD 8.0)–CD_3CN (9 : 1, v/v) were monitored by ^1H and ^{31}P NMR spectroscopy at 37 °C. All of the aroyloxymethyl esters **8** and **12** were completely stable towards chemical hydrolysis over a period of at least 2 days. Some of the compounds hydrolysed in the presence of porcine liver carboxyesterase (PLCE): with 50 U, the diester **8** (X=Ar=Ph, 1 cm^3 of the 2 mmol dm^{-3} solution) was converted completely into the monoester **12** (X=Ar=Ph) after 15 min, and with 100 U, monoester **12** (X=Ar=Ph, 1 cm^3 of the 5 mmol dm^{-3} solution) degraded to benzylphosphonate [δ_P 20.8, δ_H includes 2.89 (2 H, d, J_{PH} 20.5)] with a half-life of 32 h. *ortho*-Methyl substitution was found to have a marked effect upon PLCE-catalysed hydrolysis: diester **8** (X=Ph, Ar=2,4,6-$Me_3C_6H_2$) or monoester **12** (X=Ph, Ar=2,4,6-$Me_3C_6H_2$) did not undergo hydrolysis in the presence of PLCE. This suggested that the 2,4,6-trimethylbenzoyl group is too hindered to be a substrate for PLCE. The compounds bearing one *ortho*-methyl group showed intermediate reactivity with PLCE: in the presence of 50 U, 70% of diester **8** (X=Ph, Ar=2-MeC_6H_4) was hydrolysed to the monoester **12** (X=Ph, Ar=2-MeC_6H_4) and 2-methylbenzoate [δ_H included 2.26 (s)] after 2.25 h, and in the presence of 100 U, monoester **12** (X=Ph, Ar=2-MeC_6H_4) gave 20% benzylphosphonate after 3 days. This result is in agreement with that reported for the rate of hydrolyses of benzoate esters of the dopamine agonist N-0437, for which the benzoyl ester had a half-life of 42 min and the 2-methylbenzoyl ester a half-life of 16 h.[12] In the presence of human plasma monoester **12** (X=Ar=Ph) was completely stable.

Analogous results were obtained by HPLC analysis. Fig. 1 shows the separation of prodrug **8** (X=Ar=Ph) from possible degradation products. The separation of benzylphosphonate (pK_a 2.30 and 7.55)[13] from benzoate (pK_a 4.12) was critically dependent upon pH, with an ion-pair mobile phase pH of 3.68 providing optimum separation. Rapid degradation of the prodrug **8** (X=Ar=Ph) was observed in the presence of 0.253 U of PLCE, together with the formation of benzoyloxymethyl benzylphosphonate **12** (X=Ar=Ph) and benzoate. Under these conditions, the monoanion **12** (X=Ar=Ph) was stable and no trace of benzylphosphonate was detected.

The triesters of phosphonoacetate **8** (X=MeO_2C, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$, 400 μg cm^{-3}) were incubated in a phosphate buffer (0.1 mol dm^{-3}, pH 7.4)–MeCN mixture (1 : 1, v/v) at 37 °C and the extent of hydrolysis for each was monitored by HPLC. The triesters were found to be hydrolytically stable over 24 h. The triesters **8** (X=MeO_2C, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$, 200 μg cm^{-3}) were then incubated with PLCE (37 U) and the reactions analysed by HPLC after 15 min (Fig. 2). The retention time of the benzoate product $ArCO_2^-$ (Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) was confirmed by analysis of standards. Without the availability of standards, peaks were assigned by analogy with the benzylphosphonate analogues and on lipophilicity for the aroyloxymethyl diesters **12** (X=MeO_2C, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) and the bis(aroyloxymethyl) diesters **8** (X=^-O_2C, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$). The diester **8** (X=^-O_2C, Ar=2,4,6-$Me_3C_6H_2$) was also isolated using a C-18 Bond-Elut

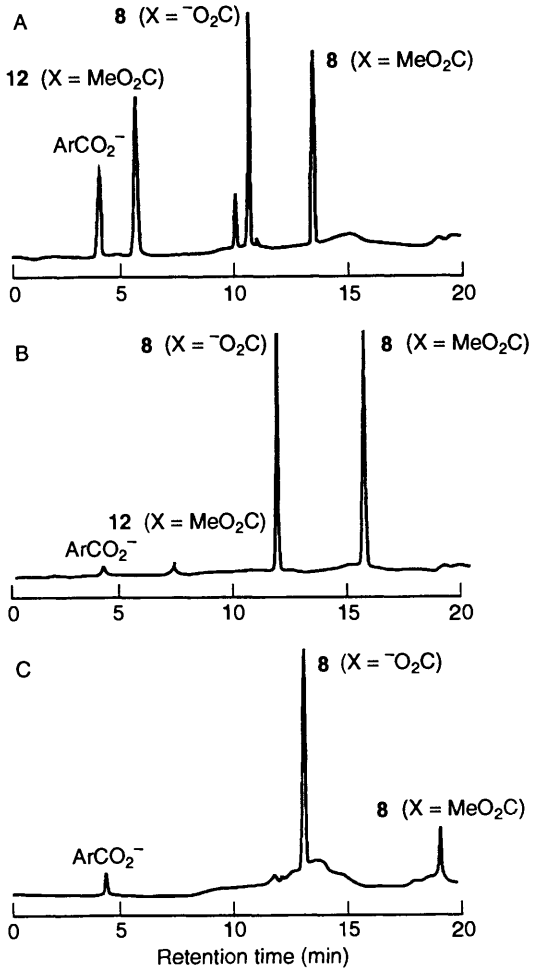
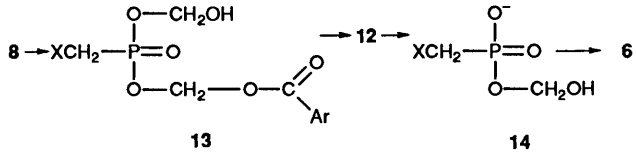


Fig. 2 High-performance liquid chromatograms obtained from the incubation of bis(aroyloxymethyl) esters of methoxycarbonylmethylphosphonate **8** (X=MeO_2C: A, Ar=Ph; B, Ar=2-MeC_6H_4; C, Ar=2,4,6-$Me_3C_6H_2$) with porcine liver carboxyesterase after 15 mins.

solid phase extraction column eluting with MeOH–H_2O (1:1, v/v) to give a pure compound with a retention time of 13.1 min by HPLC. A solution of diazomethane was added to the eluate after which HPLC gave a peak with a retention time of 19.2 min which co-eluted with the triester **8** (X=MeO_2C, Ar=2,4,6-$Me_3C_6H_2$). Incubation of the triester **8** (X=MeO_2C, Ar=Ph) with PLCE resulted in cleavage of either the benzoyloxymethyl or the methoxycarbonyl esters to give the diesters **12** (X=MeO_2C, Ar=Ph) and **8** (X=CO_2^-, Ar=Ph) respectively. Fig. 2 shows that *ortho*-methyl substitution on the aroyl group increases PLCE-catalysed hydrolysis of the methoxycarbonyl group, at the expense of cleavage of the aroyloxymethyl group, with the most hindered triester **8** (X=MeO_2C, Ar=2,4,6-$Me_3C_6H_2$) being degraded almost exclusively to the diester **8** (X=$^{-}O_2C$, Ar=2,4,6-$Me_3C_6H_2$). This supports the earlier result that the 2,4,6-trimethylbenzoyl group is not a substrate for PLCE, which therefore favours reaction at the methoxycarbonyl function. For each aroyl group, neither the diester **12** (X=MeO_2C) nor **8** (X=$^{-}O_2C$) showed further hydrolysis. Charged compounds are known to be poor substrates for esterases[14] and it is probable that the anionic charges on these diesters prevent them from being substrates for PLCE. Indeed, Srivastva and Farquhar[3,4] also experienced difficulties in the removal of the second acyloxymethyl group during the enzymatic hydrolysis of bis(acyloxymethyl) phenyl phosphates. In a separate study, Levy and Ocken[15] showed that the PLCE hydrolyses of carboxylate diesters, such as diethyl malonate, was restricted to the loss of one ester group. They suggested that this was due to like-charge repulsion between the monoanionic esters and the esterase, predicting the presence of negatively charged groups at or near the active site of the enzyme.

The triesters **8** (X=MeO_2C, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) were incubated with human plasma and the reactions were analysed by ion-pair reversed-phase HPLC. After 10 min, triester **8** (X=MeO_2C, Ar=Ph) was almost completely metabolised to benzoate and the diester **12** (X=MeO_2C, Ar=Ph). The introduction of *ortho*-methyl substituents into the benzoyl group of the triesters **8** (X=MeO_2C) increased their stability in plasma with the 2,4,6-trimethylbenzoyl analogue (Ar=2,4,6-$Me_3C_6H_2$) showing little reactivity after 10 min. In contrast to the PLCE incubations, the methoxycarbonyl function of the triester **8** (X=MeO_2C, Ar=2,4,6-$Me_3C_6H_2$) remained intact. A similar steric effect was observed by Srivastva and Farquhar[3,4] when the bis(acyloxymethyl) esters of phenyl phosphate were incubated with mouse plasma.

In summary, one aroyloxymethyl group is readily removed by incubation of the lipophilic diester of the benzylphosphonate **8** (X=Ar=Ph) with PLCE. This is thought to occur by way of the cascade effect with the initial formation of the hydroxymethyl intermediate **13** (X=Ph), which spontaneously loses a molecule of formaldehyde to give the phosphonate monoanion **12**



(X=Ar=Ph). The enzymatic removal of the second aroyloxymethyl group is impaired by the presence of an anionic charge on the substrate, but with high enzyme concentrations and long incubation times the diester **12** (X=Ar=Ph) gives benzylphosphonate *via* the hydroxymethyl intermediate **14** (X=Ph). *ortho*-Methyl substitution decreases the rate of esterase-catalysed hydrolyses: removal of the 2,4,6-trimethylbenzoyl group was not observed for any of the compounds studied. For the bis(aroyloxymethyl) esters of methoxycarbonylmethylphosphonate **8** (X=MeO_2C, Ar=Ph or 2-MeC_6H_4), cleavage of the aroyloxymethyl group competes with removal of the methoxycarbonyl ester. Therefore, unless a very slow release of parent drug is required, the aroyloxymethyl prodrug approach does not offer any apparent advantage over the acyloxymethyl[3-7] or 4-acyloxybenzyl[16,17] esters already described for several drugs containing the phospho group.

Experimental

Instrumentation, procedures and reagent suppliers were as previously described.[16] All *J* values are quoted in Hz.

Disilver Benzylphosphonate **6** (X=Ph, M^+=Ag^+).—Silver carbonate (11.21 g, 40.7 mmol) was added to a stirred solution of benzylphosphonic acid (3.50 g, 20.3 mmol) in water (500 cm^3). The reaction mixture was protected from light and stirred overnight at room temperature. The precipitate was filtered off, washed with water (3 × 50 cm^3) and dried *in vacuo* overnight to give the title compound as a grey powder (7.84 g, 100%).

Dibenzyl Benzylphosphonate **9**.—A solution of benzyl bromide (6.96 g, 40.7 mmol) in toluene (100 cm^3) was added dropwise over 30 min to a stirred suspension of disilver benzylphosphonate (7.84 g, 20.3 mmol) in toluene (200 cm^3). The mixture was protected from light and stirred at room temperature for 48 h. Filtration through Celite followed by

concentration of the filtrate under reduced pressure gave a yellow oil. Purification of this by flash column chromatography [ethyl acetate–light petroleum (1:1)] gave the title compound (R_f 0.35), 3.52 g (50%); $\delta_H(CDCl_3)$ 3.17 (2 H, d, J_{PH} 21.7, PhCH_2P), 4.91 (4 H, d, J_{PH} 8.4, OCH_2Ph) and 7.2–7.35 (15 H, m); δ_P 27.85 (s); δ_C 34.1 (d, J_{PC} 137.8, PhCH_2P), 67.7 (d, J_{PC} 6.7, OCH_2Ph), 127.1 (d, J_{PC} 3.7), 128.0 (s), 128.4 (s), 128.6 (s), 128.7 (s), 130.0 (d, J_{PC} 6.5), 131.3 (d, J_{PC} 9.0) and 136.4 (d, J_{PC} 5.9).

Sodium Benzyl Benzylphosphonate **10** (M^+=Na^+).—Sodium iodide (0.56 g, 3.77 mmol) was added to a stirred solution of dibenzyl benzylphosphonate (1.33 g, 3.77 mmol) in acetone (5 cm^3). After 12 h, the mixture was filtered and the precipitate washed with acetone. The filtrate was concentrated, after which more of the title compound was precipitated (0.57 g, 54%); $\delta_H(D_2O)$ 2.95 (2 H, d, J_{PH} 20.4, PhCH_2P), 4.70 (2 H, d, J_{PH} 8.3, OCH_2Ph) and 7.15–7.3 (10 H, m); δ_P 23.8 (s); δ_C 30.0 (d, J_{PC} 129.6, PhCH_2P), 69.1 (d, J_{PC} 5.6, OCH_2Ph), 128.8 (d, J_{PC} 3.5), 130.2 (s), 130.7 (s), 131.1 (d, J_{PC} 5.0), 131.25 (s), 132.2 (d, J_{PC} 6.1), 137.2 (d, J_{PC} 9.1) and 140.2 (d, J_{PC} 6.5).

Silver Benzyl Benzylphosphonate **10** (M^+=Ag^+).—Silver nitrate (0.34 g, 2.0 mmol) was added to a solution of sodium benzyl benzylphosphonate (0.57 g, 2.0 mmol) in water (10 cm^3). The mixture was protected from light and stirred overnight at room temperature. The precipitate which formed was filtered off, washed with water and dried *in vacuo* overnight to give the title compound as a white powder (0.43 g, 58%).

Benzoyloxymethyl Iodide[9] **7** (Ar=Ph).—Benzoyloxymethyl chloride[10] (10.0 g, 0.059 mol) and sodium iodide (10.7 g, 0.071 mol) were stirred in dry acetone (75 cm^3) for 24 h. The mixture was evaporated and diethyl ether was added to the residue. The resulting suspension was filtered and the filtrate washed with aqueous sodium thiosulfate (3 × 40 cm^3) and water (2 × 30 cm^3). The ethereal layer was dried ($MgSO_4$) and evaporated and flash column chromatography (EtOAc, R_f 0.7) of the residue gave the title compound as a brown semi-solid (11.3 g, 73%); ν_{max}(thin film)/cm^{-1} 1725 (C=O); $\delta_H(CDCl_3$; 60 MHz) 6.1 (2 H, s, CH_2I) 7.2–7.6 (3 H, m) and 7.85–8.15 (2 H, m).

The following compounds were prepared from sodium iodide and the appropriate aroyloxymethyl chloride[10] using a method similar to that described above:

2-*Methylbenzoyloxymethyl iodide*[9] **7** (Ar=2-MeC_6H_4). (60%); ν_{max}(thin film)/cm^{-1} 1730 (C=O); $\delta_H(CDCl_3)$ 2.65 (3 H, s, Me), 6.15 (2 H, s, CH_2I), 7.25–7.35 (2 H, m), 7.46 (1 H, td, J_{ortho} 7.4, J_{meta} 1.4) and 7.93 (1 H, dd, J_{ortho} 7.8, J_{meta} 1.5).

2,4,6-*Trimethylbenzoyloxymethyl iodide*[9] **7** (Ar=2,4,6-$Me_3C_6H_2$). (90%); ν_{max}(thin film)/cm^{-1} 1740 (C=O); $\delta_H(CDCl_3)$ 2.27 (3 H, s, 4-Me), 2.30 (6 H, s, 2- and 6-Me), 6.08 (2 H, s, CH_2I) and 6.83 (2 H, s).

Bis(benzoyloxymethyl) Benzylphosphonate **8** (X=Ar=Ph).—A solution of benzoyloxymethyl iodide (7.61 g, 29.05 mmol) in toluene (150 cm^3) was added dropwise over 30 min to a stirred suspension of disilver benzylphosphonate (5.57 g, 14.4 mmol) in toluene (150 cm^3). With protection from light the mixture was vigorously stirred for 20 h at room temperature. Filtration through Celite and concentration of the filtrate under reduced pressure gave a pale yellow oil. The title compound (R_f 0.3) was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (1:1), (4.56 g, 72%) (Found: C, 62.9; H, 5.1; P, 7.25. $C_{23}H_{21}O_7P$ requires C, 62.73; H, 4.80; P, 7.03%); ν_{max}(thin film)/cm^{-1} 1740 (C=O) and 1270 (P=O); $\delta_H(CDCl_3)$ 3.28 (2 H, d, J_{PH} 22.2, PhCH_2P), 5.84 (2 H, dd, J_{PH} 13.1, J_{gem} 5.5, OCH_AH_BO), 5.86 (2 H, dd, J_{PH} 13.5, J_{gem} 5.5, OCH_AH_BO), 7.1–7.3 (5 H, m, *Ph*CH_2P), 7.4–7.45 (4 H, m, 3-H and 5-H of PhC=O), 7.55–7.6 (2 H, m, 4-H of PhC=O) and 7.95–8.0 (4 H, m, 2-H and 6-H of PhC=O); δ_P 28.2 (s); δ_C 34.1 (d, J_{PC} 138.9, PhCH_2P), 81.7 (d, J_{PC} 6.7, OCH_2O), 127.1 (d, J_{PC} 3.5), 128.45 (s), 128.6 (d, J_{PC} 3.0), 129.7 (d, J_{PC} 8.0), 129.75 (d, J_{PC} 6.7), 130.0 (s), 133.7 (s) and 165.3 (s, C=O) (one aromatic C not observed or overlapping); *m/z* (FAB) observed accurate mass 441.110 (M + H^+). $C_{23}H_{22}O_7P$ requires 441.1097.

The following compounds were prepared from either disilver benzylphosphonate or disilver methoxycarbonylmethylphosphonate and the appropriate aroyloxymethyl iodide using a method similar to that described above:

Bis(2-methylbenzoyloxymethyl) benzylphosphonate **8** (X=Ph, Ar=2-MeC_6H_4). (41%) (Found: C, 63.8; H, 5.4; P, 7.6. $C_{25}H_{25}O_7P$ requires C, 64.10; H, 5.38; P, 6.61%); ν_{max}(thin film)/cm^{-1} 1740 (C=O) and 1250 (P=O); $\delta_H(CDCl_3)$ 2.58 (6 H, s, Me), 3.28 (2 H, d, J_{PH} 22.2, PhCH_2P), 5.815 (2 H, dd, J_{PH} 13.3, J_{gem} 5.5, OCH_AH_BO), 5.835 (2 H, dd, J_{PH} 13.3, J_{gem} 5.5, OCH_AH_BO), 7.1–7.3 (9 H, m, *Ph*CH_2P, 3-H and 5-H of ArC=O), 7.42 (2 H, td, J_{ortho} 7.4, J_{meta} 1.2, 4-H of ArC=O) and 7.88 (2 H, d, J_{ortho} 7.0, 6-H of ArC=O); δ_P 27.9 (s); δ_C 21.9 (s, Me), 34.2 (d, J_{PC} 138.6, PhCH_2P), 81.7 (d, J_{PC} 6.7, OCH_2O), 125.9 (s), 127.3 (d, J_{PC} 3.8), 127.7 (s), 128.7 (d, J_{PC} 3.2), 129.9 (d, J_{PC} 6.9), 130.0 (d, J_{PC} 9.4), 131.2 (s), 131.9 (s), 132.95 (s), 141.5 (s) and 165.4 (s, C=O); *m/z* (FAB) observed accurate mass 469.142 (M + H^+). $C_{25}H_{26}O_7P$ requires 469.1414.

Bis(2,4,6-trimethylbenzoyloxymethyl) benzylphosphonate **8** (X=Ph, Ar=2,4,6-$Me_3C_6H_2$). (70%) (Found: C, 66.7; H, 6.5; P. 6.5. $C_{29}H_{33}O_7P$ requires C, 66.40; H, 6.34; P, 5.90%); ν_{max}(thin film)/cm^{-1} 1745 (C=O) and 1255 (P=O); $\delta_H(CDCl_3)$ 2.27 (12 H, s, 2- and 6-Me), 2.29 (6 H, s, 4-Me), 3.32 (2 H, d, J_{PH} 27.7, PhCH_2P), 5.77 (2 H, dd, J_{PH} 13.1, J_{gem} 5.1, OCH_AH_BO), 5.82 (2 H, dd, J_{PH} 13.1, J_{gem} 5.1, OCH_AH_BO), 6.85 (4 H, s, ArC=O) and 7.30–7.25 (5 H, m, *Ph*CH_2P); δ_P 27.5 (s); δ_C 20.0 (s, 2- and 6-Me), 21.2 (s, 4-Me), 34.2 (d, J_{PC} 140.3, PhCH_2P), 81.9 (d, J_{PC} 6.4, OCH_2O), 127.4 (d, J_{PC} 3.8), 128.7 (s), 128.8 (s), 129.0 (s), 129.9 (d, J_{PC} 6.9), 130.0 (s), 135.9 (s), 140.1 (s) and 168.3 (s, C=O).

Bis(benzoyloxymethyl) methoxycarbonylmethylphosphonate **8** (X=CO_2Me, Ar=Ph). (EtOAc, R_f 0.56) (40%) (Elemental analysis not correct. Found: C, 52.3; H, 4.4. $C_{19}H_{19}O_9P$ requires C, 54.04; H, 4.53); ν_{max}(thin film)/cm^{-1} 1735 (C=O) and 1260 (P=O); $\delta_H(CDCl_3)$ 3.05 (2 H, d, J_{PH} 24.2, PCH_2), 3.52 (3 H, s, OMe), 5.89 (2 H, dd, J_{PH} 8.9, J_{gem} 5.3, OCH_AH_BO), 5.96 (2 H, dd, J_{PH} 8.8, J_{gem} 5.5, OCH_AH_BO), and 7.2–7.8 (10 H, m); δ_P 21.15 (s); δ_C 34.35 (d, J_{PC} 138.3, PCH_2), 52.5 (s, OMe), 82.2 (d, J_{PC} 6.0, OCH_2O), 128.1 (s), 129.8 (s), 133.8 (s), 164.7 (s, C=O) and 169.2 (s, C=O); *m/z* (FAB) 423 (M + H^+, 10%), 393 (15), 363 (100), 137 (15), 105 (100) and 77 (49). Observed accurate mass 423.0845 (M + H^+). $C_{19}H_{20}O_9P$ requires 423.0843.

Bis(2-methylbenzoyloxymethyl) methoxycarbonylmethylphosphonate **8** (X=CO_2Me, Ar=2-MeC_6H_4). (40%) (Found: C, 55.7; H, 5.2. $C_{21}H_{23}O_9P$ requires C, 56.01; H, 5.15%); ν_{max}(thin film)/cm^{-1} 1730 (C=O) and 1240 (P=O); $\delta_H(CDCl_3)$ 2.59 (6 H, s, 2-Me), 3.11 (2 H, d, J_{PH} 22.2, PCH_2), 3.61 (3 H, s, OMe), 5.89 (2 H, dd, J_{PH} 12.1, J_{gem} 5.9, OCH_AH_B) 5.96 (2 H, dd, J_{PH} 13.1, J_{gem} 5.2, OCH_AH_BO), 7.15–7.25 (4 H, m), 7.41 (2 H, t, J_{ortho} 7.5) and 7.95 (2 H, d, J_{ortho} 7.8); δ_P 20.05 (s); δ_C 21.8 (s, 2-Me), 34.6 (d, J_{PC} 149.2, PCH_2), 52.7 (s, OMe), 81.9 (d, J_{PC} 5.8, OCH_2O), 125.9 (s), 127.5 (s), 131.1 (s), 131.9 (s), 133.0 (s), 141.5 (s) and 165.2 (s, C=O) (other C=O not observed); *m/z* (FAB) 451 (M + H^+, 6%), 421 (23), 391 (100), 137 (25) and 119 (100). Observed accurate mass 451.1158 (M + H^+). $C_{21}H_{24}O_9P$ requires 451.1158.

Bis(2,4,6-trimethylbenzoyloxymethyl) methoxycarbonylmethylphosphonate **8** (X=CO_2Me, Ar=2,4,6-$Me_3C_6H_2$). (44%); ν_{max}(liquid film)/cm^{-1} 1740 (C=O) and 1250 (P=O); $\delta_H(CDCl_3)$ 2.25–2.3 (18 H, m, Me), 3.15 (2 H, d, J_{PH} 21.7, CH_2P), 3.76 (3 H, s, Me), 5.88 (2 H, dd, J_{PH} 12.0, J_{gem} 5.4, OCH_AH_BO), 5.93 (2 H, dd, J_{PH} 12.9, J_{gem} 5.1, OCH_AH_BO) and 6.83 (4 H, s); δ_P 19.8 (s); δ_C 19.9 (s, 2- and 6-Me), 21.1 (s, 4-Me), 34.4 (d, J_{PC} 140.6, PCH_2), 52.7 (s, OMe), 82.05 (d, J_{PC} 5.3, OCH_2O), 128.6 (s), 135.9 (s), 139.8 (s),

140.2 (s) and 168.2 (s, C=O) (other C=O not observed); *m/z* (FAB) 529 ($M + Na^+$, 79%), 447 (46) and 147 (100). Observed accurate mass 529.1603 ($M + Na^+$). $C_{25}H_{31}NaO_9P$ requires 529.1603.

Benzoyloxymethyl Benzyl Benzylphosphonate **11** (Ar=Ph).—A solution of benzoyloxymethyl iodide (1.1 g, 4.18 mmol) in toluene (50 cm^3) was added dropwise over 30 min to a stirred suspension of silver benzyl benzylphosphonate (1.55 g, 4.18 mmol). The mixture was protected from light and stirred for 20 h. Silver iodide was removed by filtration through Celite and the latter washed with toluene (3 × 10 cm^3). The combined filtrate and washings were evaporated under reduced pressure and the title compound was purified by flash column chromatography, eluting with ethyl acetate–light petroleum (1:1), R_f 0.3, (1.13 g, 73%); ν_{max}(thin film)/cm^{-1} 1740 (C=O) and 1270 (P=O); δ_H($CDCl_3$) 3.24 (2 H, d, J_{PH} 22.0, PhCH_2P), 5.01 (2 H, d, J_{PH} 8.35, POCH_2Ph), 5.75 (2 H, dd, J_{PH} 13.0, J_{gem} 7.8, OC$H_A$$H_B$O), 5.83 (2 H, dd, J_{PH} 13.0, J_{gem} 7.8, OCH$_A$$H_B$O), 7.15–7.25 (10 H, m, Ph), 7.43 (2 H, m, 3-H and 5-H of PhC=O), 7.62 (1 H, m, 4-H of PhC=O) and 8.0 (2 H, dd, J_{ortho} 7.3, J_{meta} 1.3, 2-H and 6-H of PhC=O); δ_P 28.1 (s); δ_C 34.1 (d, J_{PC} 138.2, PhCH$_2$P), 67.5 (d, J_{PC} 7.0, OCH$_2$Ph), 82.0 (d, J_{PC} 6.6, OCH$_2$O), 127.1 (d, J_{PC} 3.7), 127.8 (s), 127.9 (s), 128.35 (s), 128.5 (s), 128.6 (d, J_{PC} 3.1), 128.75 (s), 129.8 (d, J_{PC} 6.7), 130.0 (s), 130.4 (d, J_{PC} 9.6), 133.7 (s), 135.7 (d, J_{PC} 6.5) and 164.9 (s, C=O).

The following compounds were prepared from silver benzyl benzylphosphonate and the appropriate aroyloxymethyl iodide using a method similar to that described above:

2-Methylbenzoyloxymethyl benzyl benzylphosphonate **11** (Ar=2-MeC_6H_4). R_f 0.25 [ethyl acetate–light petroleum (2:3)], (61%); ν_{max}(thin film)/cm^{-1} 1735 (C=O) and 1250 (P=O); δ_H($CDCl_3$) 2.48 (3 H, s, Me), 3.13 (2 H, d, J_{PH} 22.0, PhCH_2P), 5.00 (2 H, d, J_{PH} 8.0, OCH_2Ph), 5.72 (1 H, dd, J_{PH} 13.1, J_{gem} 7.9, OC$H_A$$H_B$O), 5.81 (1 H, J_{PH} 13.2, J_{gem} 7.3, OCH$_A$$H_B$O), 7.2–7.3 (12 H, m, Ph and 3-H and 5-H of ArC=O), 7.4–7.45 (1 H, m, 4-H of ArC=O) and 7.85–7.9 (1 H, m, 6-H of ArC=O); δ_P 28.0 (s); δ_C 21.7 (s, Me), 33.9 (d, J_{PC} 138.0, PhCH$_2$P), 67.4 (d, J_{PC} 7.0, POCH$_2$Ph), 81.65 (d, J_{PC} 6.4, OCH$_2$O), 125.7 (s), 126.9 (d, J_{PC} 3.8), 127.6 (s), 127.65 (s), 127.75 (s), 128.2 (s), 128.3 (s), 128.4 (d, J_{PC} 3.2), 129.7 (d, J_{PC} 6.6), 130.4 (d, J_{PC} 9.4), 130.9 (s), 131.7 (s), 132.7 (s), 135.7 (d, J_{PC} 6.7) and 165.2 (s, C=O).

2,4,6-Trimethylbenzoyloxymethyl benzyl benzylphosphonate **11** (Ar=2,4,6-$Me_3C_6H_2$). R_f 0.3 [ethyl acetate–light petroleum (2:3)] (57%); ν_{max}(thin film)/cm^{-1} 1740 (C=O) and 1255 (P=O); δ_H($CDCl_3$) 2.26 (6 H, s, 2- and 6-Me), 2.28 (3 H, s, 4-Me), 3.23 (2 H, d, J_{PH} 26.5, PhCH_2P), 4.95 (1 H, dd, J_{gem} 11.8, J_{PH} 7.7, OC$H_A$$H_B$Ph), 5.02 (1 H, dd, J_{gem} 11.8, J_{PH} 8.2, OCH$_A$$H_B$Ph), 5.72 (1 H, dd, J_{PH} 13.8, J_{gem} 5.1, OC$H_A$$H_B$O), 5.77 (1 H, dd, J_{PH} 13.8, J_{gem} 5.1, OCH$_A$$H_B$O), 6.84 (2 H, s, ArC=O), 7.20–7.30 (10 H, m, Ph); δ_P 27.8 (s); δ_C 19.85 (s, 2- and 6-Me), 21.1 (s, 4-Me), 34.0 (d, J_{PC} 138.3, PhCH$_2$P), 67.6 (d, J_{PC} 6.9, OCH$_2$Ph), 81.9 (d, J_{PC} 6.4, OCH$_2$O), 127.7 (d, J_{PC} 3.8), 127.8 (s), 128.3 (s), 128.4 (s), 128.5 (s), 128.6 (s), 129.1 (s), 129.8 (d, J_{PC} 6.7), 130.4 (d, J_{PC} 9.4), 135.7 (s), 138.3 (s), 140.0 (s) and 168.3 (C=O).

Cyclohexylammonium Benzoyloxymethyl Benzylphosphonate **12** (X=Ar=Ph, M^+=$C_6H_{11}NH_3^+$).—Palladium on charcoal (5%; 100 mg) was added to a solution of benzoyloxymethyl benzyl benzylphosphonate (1.0 g, 2.71 mmol) in ethyl acetate (35 cm^3). The mixture was exposed to hydrogen at 30 psi for 3 h using a Parr hydrogenator. Charcoal was filtered off and the reaction vessel washed out with ethyl acetate (4 × 25 cm^3). The solution was reduced to a small volume (5 cm^3) and cyclohexylamine (0.27 g, 2.71 mmol) was added by syringe. The title compound was precipitated as colourless needles which were recrystallised from ethyl acetate–light petroleum (1:1) (0.7 g, 64%); m.p. 158–161 °C (Found: C, 61.8; H, 7.1; N, 3.45; P, 7.55. $C_{21}H_{28}NO_5P$ requires C, 62.21; H, 6.96; N, 3.45; P, 7.64%); ν_{max}($CHCl_3$)/cm^{-1} 1730 (C=O) and 1215 (P=O); δ_H($CDCl_3$) 1.0–1.2 (5 H, m, C_6H_{11}), 1.45–1.8 (5 H, m, C_6H_{11}), 2.55–2.75 (1 H, m, H_3N^+-C*H*), 3.06 (2 H, d, J_{PH} 20.5, PhCH_2P), 5.76 (2 H, d, J_{PH} 12.2, OCH$_2$O), 7.1–7.3 (5 H, m, *Ph*CH$_2$), 7.42 (2 H, td, J_{ortho} 6.6, J_{meta} 1.2, 3-H and 5-H of PhC=O), 7.56 (1 H, td, J_{ortho} 7.3, J_{meta} 1.3, 4-H of PhC=O), 8.04 (2 H, dd, J_{ortho} 8.2, J_{meta} 1.2, 2-H and 6-H of PhC=O) and 8.3 (3 H, br s, NH_3); δ_P 20.0 (s); δ_C 24.5 (s, C-3 and C-5 of C_6H_{11}), 24.8 (s, C-4 of C_6H_{11}), 30.8 (s, C-2 and C-6 of C_6H_{11}), 36.6 (d, J_{PC} 128.9, PhCH$_2$P), 49.7 (s, C-1 of C_6H_{11}), 83.5 (d, J_{PC} 5.0, OCH$_2$O), 125.7 (d, J_{PC} 2.3), 128.0 (d, J_{PC} 2.3), 128.4 (s), 129.6 (d, J_{PC} 6.3), 129.7 (s), 129.8 (s), 133.25 (s), 135.3 (d, J_{PC} 8.6) and 165.4 (s, C=O); *m/z* (FAB) observed accurate mass 406.1793 ($M + H^+$). $C_{21}H_{29}NO_5P$ requires 406.1783.

The following compounds were prepared from reaction of the appropriate aroyloxymethyl benzyl benzylphosphonate with hydrogen using a method similar to that described above:

Cyclohexylammonium 2-methylbenzoyloxymethyl benzylphosphonate **12** (X=Ph, Ar=2-MeC_6H_4, M^+=$C_6H_{11}NH_3^+$). (71%); m.p. 142–145 °C (Found: C, 62.6; H, 7.1; N, 3.3; P, 7.45. $C_{22}H_{30}NO_5P$ requires C, 62.90; H, 7.20; N, 3.33; P, 7.38%); ν_{max}($CHCl_3$)/cm^{-1} 1730 (C=O) and 1250 (P=O); δ_H($CDCl_3$) 1.0–1.2 (5 H, m, C_6H_{11}), 1.4–1.8 (5 H, m, C_6H_{11}), 2.60 (3 H, s, 2-Me), 2.6–2.75 (1 H, m, H_3N^+C*H*), 3.05 (2 H, d, J_{PH} 20.6, PhCH_2P), 5.75 (2 H, d, J_{PH} 12.0, POCH$_2$O), 7.05–7.3 (7 H, m, *Ph*CH$_2$P plus 3-H and 5-H of ArC=O), 7.40 (1 H, td, J_{ortho} 7.5, J_{meta} 1.4, 4-H of ArC=O) and 7.94 (1 H, dd, J_{ortho} 7.9, J_{meta} 1.3, 6-H of ArC=O); δ_P 20.0 (s); δ_C 21.8 (s, 2-Me), 24.5 (s, C-3 and C-5 of C_6H_{11}), 24.8 (s, C-4 of C_6H_{11}), 30.8 (s, C-2 and C-6 of C_6H_{11}), 36.5 (d, J_{PC} 129.0, PhCH$_2$P), 49.8 (s, C-1 of C_6H_{11}), 83.2 (d, J_{PC} 5.0, OCH$_2$O), 125.7 (d, J_{PC} 3.0), 125.75 (s), 127.95 (d, J_{PC} 2.5), 128.7 (s), 129.6 (d, J_{PC} 6.3), 130.85 (s), 131.75 (s), 132.35 (s), 135.4 (d, J_{PC} 8.6), 140.9 (s) and 166.0 (s, C=O); *m/z* (FAB) observed accurate mass 420.1970 ($M + H^+$). $C_{22}H_{31}NO_5P$ requires 420.1940.

Cyclohexylammonium 2,4,6-trimethylbenzoyloxymethyl benzylphosphonate **12** (X=Ph, Ar=2,4,6-$Me_3C_6H_2$, M^+=$C_6H_{11}NH_3^+$). (52%); m.p. 145–147 °C (Found: C, 64.1; H, 7.5; N, 3.15. $C_{24}H_{34}NO_5P$ requires C, 64.41; H, 7.66; N, 3.13%); ν_{max}($CHCl_3$)/cm^{-1} 1730 (C=O) and 1260 (P=O); δ_H($CDCl_3$) 1.0–1.2 (5 H, m, C_6H_{11}), 1.45–1.8 (5 H, m, C_6H_{11}), 2.27 (3 H, s, 4-Me), 2.29 (6 H, s, 2- and 6-Me), 2.55–2.7 (1 H, m, H_3N^+C*H*), 3.00 (2 H, d, J_{PH} 20.7, PhCH_2P), 5.75 (2 H, d, J_{PH} 11.9, OCH$_2$O), 6.83 (2 H, s, ArC=O) and 7.05–7.3 (5 H, m, *Ph*CH$_2$P); δ_P 20.1 (s); δ_C 19.9 (s, 2- and 6-Me), 21.1 (s, 4-Me), 24.5 (s, C-3 and C-5 of C_6H_{11}), 24.7 (s, C-4 of C_6H_{11}), 30.8 (s, C-2 and C-6 of C_6H_{11}), 36.65 (d, J_{PC} 127.3, PhCH$_2$P), 49.8 (s, C-1 of C_6H_{11}), 83.3 (d, J_{PC} 5.0, OCH$_2$O), 125.7 (d, J_{PC} 2.8), 128.0 (d, J_{PC} 2.3), 128.5 (s), 129.7 (d, J_{PC} 6.4), 130.1 (s), 135.3 (d, J_{PC} 8.9), 135.5 (s), 139.55 (s) and 169.0 (s, C=O); *m/z* (FAB) observed accurate mass 448.2218 ($M + H^+$). $C_{24}H_{35}NO_5P$ requires 448.2253.

Chemical, Plasma and PLCE-catalysed Hydrolyses of Bis(aroyloxymethyl) and Mono(aroyloxymethyl) Esters of Benzylphosphonate **8** *and* **12** (X=Ph, Ar=Ph, 2-MeC_6H_4 *and* 2,4,6-$Me_3C_6H_2$).—A solution of the diester **8** (2 μmol) or the monoester **12** (5 μ mol) in CD_3CN (0.1 cm^3) was added to potassium phosphate buffer (0.1 mol dm^{-3}; pD 8.0, D_2O; 0.9 cm^3) incubated at 37 °C. For the esterase-catalysed hydrolyses, a suspension of PLCE was added (0.02 cm^3, 50 U for the diesters; 0.04 cm^3, 100 U for the monoesters). The reactions were monitored by ^{31}P and ^1H NMR spectroscopy over several hours. For the reaction of monoester **12** (X=Ar=Ph) with plasma, human plasma (1 cm^3, supernatant derived from the centrifugation of human blood at 750 g for 10 min) was added to the above solution of the monoester, and the mixture was monitored by ^{31}P NMR spectroscopy over several hours.

Hydrolyses monitored by HPLC were performed in glass-

screw capped vials using a total incubation volume of 2 cm^3. Due to the poor solubility of bis(benzoyloxymethyl) benzylphosphonate **8** (X=Ar=Ph), a saturated solution was prepared from a 1 mmol dm^{-3} suspension of **8** (X=Ar=Ph) in phosphate buffer (0.1 mol dm^{-3}, pH 7.4)–acetonitrile (90:10 v/v, 37 °C). The suspension was sonicated for 2–3 min to facilitate dissolution and then centrifuged (1000 g, 10 min) to give a clear supernatant which was used for hydrolysis experiments. Enzyme hydrolyses were initiated by the addition of PLCE (0.253 U) in phosphate buffer (0.1 mol dm^{-3}, pH 7.4; 0.005 cm^3). Control and enzyme hydrolyses were incubated at 37 °C on a shaking water-bath. At the appropriate time, samples were removed (0.1 cm^3) and added to ice-cold acetonitrile (0.1 cm^3) and mixed on a vortex mixer. Samples were analysed by HPLC on a reversed-phase column (RP-C18, 25 cm × 4.2 mm) eluting with a convex gradient of acetonitrile–10 mmol dm^{-3} tetrabutylammonium hydroxide in water (pH 3.68), initial conditions 30:70 v/v; final conditions 90:10 v/v; gradient time 20 min; flow rate 1 cm^3 min^{-1}.

Chemical and Esterase-catalysed Hydrolyses of Bis(aroyloxymethyl) Esters of Methoxycarbonylmethylphosphonate **8** (X=Ph, Ar=Ph, 2-MeC_6H_4 *and* 2,4,6-$Me_3C_6H_2$).—Procedures were the same as described above with the following exceptions. A mixture of phosphate buffer (0.1 mol dm^{-3}, pH 7.4)–MeCN (90:10, v/v) was pre-incubated at 37 °C for 10 min. An acetonitrile solution of **8** (X=Ph, Ar=Ph, 2-MeC_6H_4 or 2,4,6-$Me_3C_6H_2$) was then added to give a final concentration of 0.5 mmol dm^{-3}. Enzyme hydrolyses were initiated by the addition of PLCE (37 U) in a shaking water-bath. Samples were then analysed by HPLC, eluting with a convex gradient of acetonitrile–10 mmol dm^{-3} tetrabutylammonium hydroxide in water; initial conditions, 35:65 (v/v); final conditions, 90:10 (v/v). Each reaction was performed in duplicate. The individual retention times for the triesters **8** were 13.2, 15.1 and 19.2 min for Ar=Ph, 2-MeC_6H_4 and 2,4,6-$Me_3C_6H_2$ respectively.

The bis(aroyloxymethyl) diester **8** (X=^-O_2C, Ar=2,4,6-$Me_3C_6H_2$) was isolated from the PLCE-catalysed hydrolysis of the triester **8** (X=MeO_2C, Ar=2,4,6-$Me_3C_6H_2$) using a C-18 Bond-Elut solid-phase extraction column eluting with MeOH–H_2O (1:1, v/v), to give a pure compound with a retention time of 13.1 min by HPLC. An ethereal solution of diazomethane was added to the eluate until a yellow colour persisted. The excess of diazomethane was removed by a stream of nitrogen to give a colourless solution, which by HPLC gave a peak with a retention time of 19.2 min which was co-eluted with the triester **8** (X=MeO_2C, Ar=2,4,6-$Me_3C_6H_2$).

Acknowledgements

We thank the MRC AIDS Directed Programme for a project grant, the SERC for a studentship (A. G. M.) and the Lister Institute for a fellowship (S. F.). We are grateful to the SERC mass spectrometry service at Swansea for mass spectral analyses.

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Paper 3/02850J
Received 19*th May* 1993
Accepted 14*th June* 1993