Synthetic, Mechanistic and Photochemical Studies of Phosphate Esters of Substituted Benzoins

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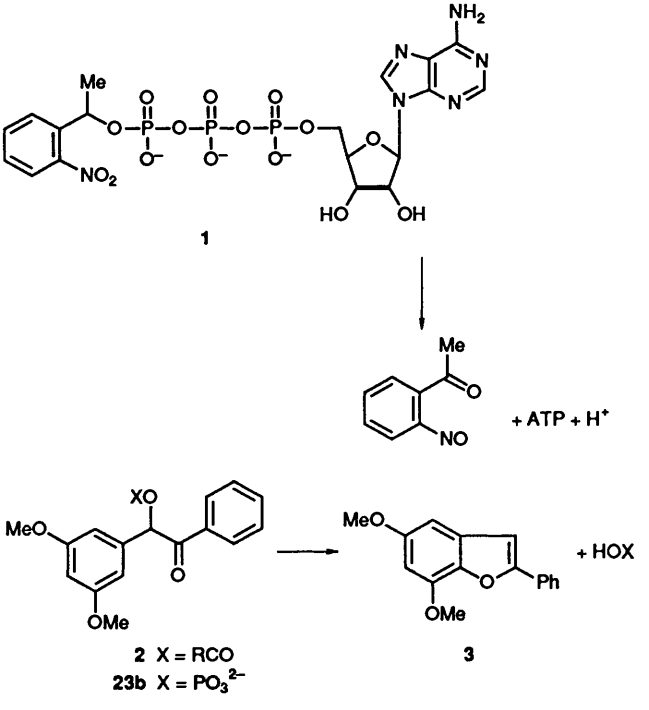
Synthesis of the phosphate esters of several benzoins, variously substituted with methoxy groups in one or both aromatic rings, proceeds *via* the corresponding cyclic ethylene ketals. These are phosphitylated with bis-(2-cyanoethyl) diisopropylphosphoramidite and the phosphites are oxidised to phosphates. Cleavage of the 2-cyanoethyl groups with methanolic alkali, followed by acid-catalysed hydrolysis of the ethylene ketal, yields the required phosphate monoesters. Application of the same reaction sequence to benzoin itself, not protected as the cyclic ketal, leads to at least three products, the phosphate monoester **5**, the phosphate diester **7** and a substance not containing phosphorus, which appeared to be the ketal **8**. The likely origin of these three products is discussed. The potential of these phosphate esters and their derivatives for study of rapid biochemical processes by fast photochemical cleavage of the benzoin group was examined. Best results were obtained with 3′,5′-dimethoxybenzoin phosphate **23b**, where a single pulse of 347 nm light (100 mJ in 50 ns) resulted in 10% conversion into products, with a first-order rate constant $>10^5\ s^{-1}$.

Biologically inert photocleavable derivatives of effector or reporter species have been widely exploited in modern biological research. The technique involves the addition of the so-called 'caged' compound to a biological preparation such as a muscle fibre or tissue slice, which is then left for a period of time to allow uniform diffusion of the photocleavable reagent. Irradiation with a pulse of near-UV light then causes rapid photocleavage of the protecting group with a concomitant rapid change in concentration of the effector species, and enables the study of rapid processes without diffusion artefacts. The photochemically labile groups used in most of these studies are based on the 2-nitrobenzyl moiety, as exemplified in Scheme 1 by the P^3-1-(2-nitrophenyl)ethyl ester of adenosine triphosphate (**1**, 'caged' ATP).[1] Despite the widespread use of the 2-nitrobenzyl group and substituted variants, its photochemical properties are not ideal and application of the 'caged' compound technique would be enhanced by the availability of a wider range of photolabile groups sensitive to light in the 300–360 nm wavelength region. A recent report by Baldwin *et al.*[2] described photorelease of inorganic phosphate from, *inter alia*, phosphate esters of benzoins within this wavelength range, deriving from earlier work by Sheehan *et al.*,[3a,b] on benzoins as photolabile protecting groups for carboxylic acids. The photochemical cleavage of benzoin dialkyl phosphates has also been reported previously.[3c]†

The reports by both Baldwin and Sheehan consider these photolabile protecting groups in the conventional sense, *i.e.* the important features are conditions and yield of photolysis. Sheehan *et al.*[3b] studied the photolysis mechanism, with particular reference to the lifetime of the excited state and noted that the reaction was complete within 1 μs. For the study of rapid biological processes the relevant information is the rate and extent of product release following a brief (<1 ms) light pulse. To obtain these data we have re-examined the synthesis of benzoin phosphates, with particular attention to the 3′,5′-dimethoxy compound **23b** since Sheehan *et al.*[3b] found for the corresponding carboxylic esters **2** that this specific pattern of methoxy substitution gave rise to near-quantitative photolysis. Baldwin *et al.*[2] concluded for benzoin phosphates that the unsubstituted compound **5** was useful in view of its easier synthesis. However, the reported properties[2] of 3′,5′-dimethoxybenzoin phosphate **23b** led us to question its purity and structural integrity (*vide infra*). To clarify this position, we have established an independent, unambiguous synthesis of unsymmetrical benzoin phosphates. During this work we encountered some novel observations which are relevant to the long-standing interest[4–6] in the role of carbonyl participation during the hydrolysis of 2-oxoalkyl dialkyl phosphates.



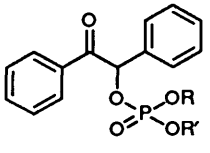
Scheme 1

Although phosphotriesters **4** arising from the reaction between trialkyl phosphites and benzil are well known (see ref. 7 for an extensive bibliography), the corresponding monoester **5** is almost unknown, being briefly described only in a report by

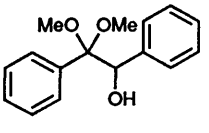
† For the sake of brevity, phosphate esters of benzoins are referred to in the discussion as benzoin phosphates, with primed numerals used to locate substituents on the aromatic ring not in conjugation with the carbonyl group. Formal IUPAC nomenclature is used in the Experimental section.

Burgada,[8] who observed it as a product of the acid-catalysed hydrolysis of 2,2,2-tris(dimethylamino)-2,2-dihydro-4,5-diphenyl-1,3,2-dioxaphosphole, which was itself prepared by reaction of tris(dimethylamino)phosphine with benzil. The regiospecificity of these reactions with an unsymmetrical benzil would be uncertain, particularly in the 3,5-dimethoxy case where there are no strong resonance interactions which might otherwise control the direction of product formation. Phosphorylation of benzoins of defined structure is a more satisfactory route, although even here the possibilities must be considered for isomerisation of an unsymmetrical benzoin *via* enediol intermediates to its more stable isomer, as is known to happen for benzoin carboxylate esters.[9]

In order to minimise the possibility of side reactions, we wished to use mild phosphorylation conditions and chose to examine phosphitylation with a phosphoramidite, followed by oxidation to a phosphate.[10] When we treated benzoin with bis-(2-cyanoethyl) diisopropylphosphoramidite under catalysis by 1*H*-tetrazole and treated the reaction mixture directly with 3-chloroperbenzoic acid (MCPBA), the phosphotriester **6** was readily obtained. However, when this compound was exposed to warm methanolic sodium hydroxide to effect a one-pot cleavage of both 2-cyanoethyl groups, two water-soluble products were obtained in the ratio 1:2.5, together with a small proportion of a neutral, ether-soluble material. The charged compounds were readily separable by anion-exchange chromatography, with elution positions which suggested that at pH 7 the minor product was a monoanion while the major product was a dianion. NMR and mass spectroscopy showed that the latter compound was the salt of the expected phosphate **5** while the minor product was the salt of the mixed phosphodiester **7**. The structure of the ether-soluble product was not established unequivocally, but from its spectral properties and ready hydrolysis to benzoin on treatment with dilute mineral acid it seemed likely to be benzoin dimethyl acetal **8**. Formation of this compound has been previously reported[4] from sodium methoxide treatment of benzoin diethyl phosphate **4** (R,R′ = Et).



4 R, R′ = alkyl
5 R, R′ = H or cation
6 R, R′ = CH_2CH_2CN
7 R = H, R′ = Me



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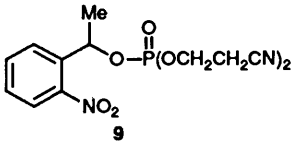

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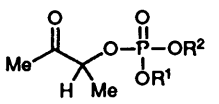
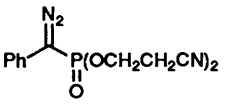
Formation of the monomethyl ester **7** requires the presence of the neighbouring carbonyl group, since no such product could be detected when the bis-(2-cyanoethyl) phosphate[11] **9**, which lacks this group, was treated with alkali under identical conditions (see Experimental section). As mentioned above, the hydrolysis mechanism of dialkyl phosphate esters of 2-keto alcohols has been studied over many years, dating from the observation in 1962 by Ramirez[5] that the rate of base-catalysed hydrolysis of acetoin dimethyl phosphate **10** was at least 10^6-times greater than that of trimethyl phosphate. A recent paper by Kluger and Taylor[6] summarises the work of various groups and provides a detailed mechanistic interpretation. In dilute base (pH ~10) the sole hydrolysis products of acetoin diethyl phosphate **11** are acetoin and diethyl phosphate, but as the hydroxide concentration is increased a second set of products, ethanol and acetoin ethyl phosphate **12**, begins to appear and



10 $R^1 = R^2 = Me$
11 $R^1 = R^2 = Et$
12 $R^1 = H$, $R^2 = Et$



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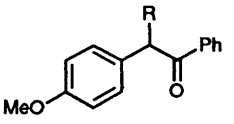
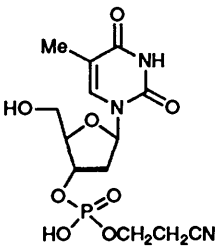


15 R = OH
16 R = $OP(O)(OCH_2CH_2CN)_2$
17 R = $OP(O)(OMe)O^-$
18 R = OPO_3^{2-}

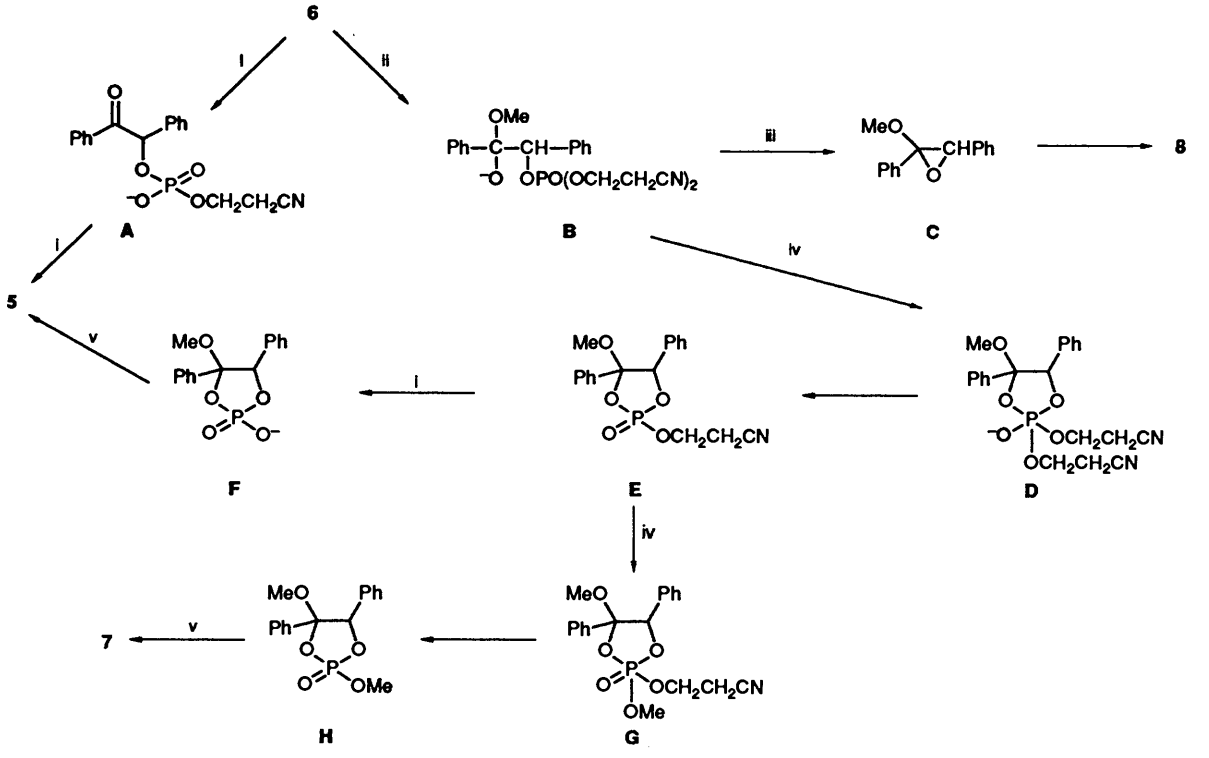


14

reaches approximately 10% of the product distribution in 4 mol dm^{-3} alkali.[6]

However, our work differs from previous studies since the two 2-cyanoethyl groups present in the phosphotriester **6** are intrinsically labile *via* a β-elimination pathway. The mechanistic outline proposed in Scheme 2 represents a reasonable hypothesis to explain the observed product distribution. Initial β-elimination from the triester **6** leading to the diester **A** would suppress pathways involving nucleophilic attack on the now charged phosphate, which should proceed directly to the fully deprotected phosphate **5**. Alternatively, addition of methoxide to the carbonyl of triester **6**, leading to intermediate **B**, then opens two pathways, one being displacement of bis-(2-cyanoethyl) hydrogen phosphate by the internal alkoxide ion to give the methoxyoxirane **C** and subsequently benzoin dimethyl ketal **8**. As already noted, a pathway of this type has been suggested previously.[4] The other possible fate for intermediate **B** is conversion into the phosphorane **D** and expulsion of 2-cyanoethoxide to form the cyclic triester **E**. Intermediates analogous to **D** have been proposed by Ramirez[5] and by Kluger and Taylor,[6] who in addition postulated the type **E** intermediate to explain formation of acetoin monoethyl phosphate **12**. β-Elimination of a 2-cyanoethyl group from phosphorane **D** is improbable considering the lack of stabilisation of the phosphorane as a putative leaving group, but is possible for the cyclic triester **E**. Alternatively, ligand exchange on **E**, a process known to occur easily for at least some cyclic phosphotriesters,[12] could proceed *via* phosphorane **G** to the triester **H**, thus incorporating the methyl group which appears in the diester **7**. Intermediates **F** and **H** may be stable in alkaline methanol and collapse to the acyclic phosphates **5** and **7** only during aqueous work-up.

Kinetic data from the literature demonstrate the potential for competing mechanistic pathways in the alkaline hydrolysis of the triester **6**. The second-order rate constant for hydrolysis at 25 °C of acetoin diethyl phosphate **11** was reported by Witzel *et al.*[4] as 81.6 dm^3 mol^{-1} s^{-1}, while Kluger and Taylor[6] reported a value of 48 dm^3 mol^{-1} s^{-1} under similar conditions. Without reporting an exact number, Witzel *et al.* state that the hydrolysis of benzoin diethyl phosphate is retarded by an order of magnitude compared with that of the acetoin analogue. For the sake of argument, one can propose an approximate value of 6 dm^3 mol^{-1} s^{-1}. β-Elimination of a 2-cyanoethyl group from a phosphotriester, a reaction widely used in oligonucleotide synthesis, is very rapid,[13] although we have been unable to find a report of quantitative kinetic data in an exact model compound. However, Goldstein *et al.*[14] have reported data for sequential elimination of the two 2-cyanoethyl groups from the phosphonate **13**. At 25 °C the second-order rate constant for alkaline hydrolysis was 11.4 dm^3 mol^{-1} s^{-1} for cleavage of the first 2-cyanoethyl group. The cleavage rate found for the second 2-

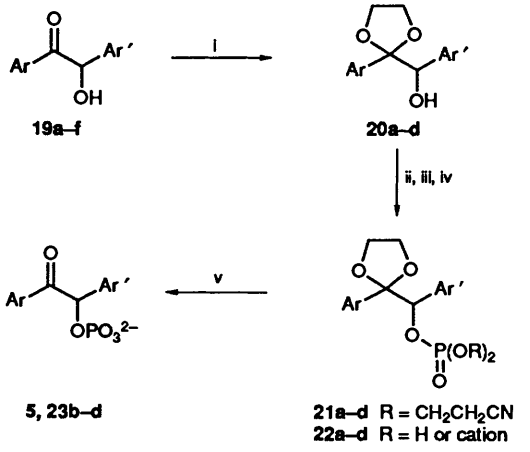


Scheme 2 *Reagents and reactions:* i, β-elimination; ii, carbonyl addition; iii, attack on C; iv, attack on P; v, water

cyanoethyl group was comparable to the data reported by Tener[15] for the diester thymidine 3′-(2-cyanoethyl hydrogen phosphate) **14** and hence suggests that the bis-(2-cyanoethyl) phosphonate is a reasonable kinetic model for a bis-(2-cyanoethyl) phosphate such as **6**. Hence the likely rate constants for pathways in Scheme 2 which lead to an initial partitioning into intermediates **A** and **B** provide support for the operation of the two competing pathways.

We have performed an experiment which confirmed the positional integrity, implicit in Scheme 2, of the two aromatic rings. When 4′-methoxybenzoin **15** was subjected to phosphorylation and methanolic alkali treatment exactly as for benzoin itself, the intermediate triester **16** and the two derived products **17** and **18** were each obtained with at least 97% retention of the initial substitution pattern, as established by UV and NMR spectral comparisons with the isomeric 4-methoxybenzoin **19f** (see Experimental section). Since the benzoin **15** is particularly susceptible to isomerisation in order to bring the methoxy substituent into conjugation with the carbonyl group,[9] this result constitutes a stringent test for the absence of any enediol-type intermediate which would be required for isomerisation. Without appropriate kinetic measurements further speculation on the mechanism is not warranted, not least because under the conditions we have used (0.1 mol dm^{-3} sodium hydroxide in anhydrous methanol) the predominant nucleophilic species is methoxide ion, which may itself influence relative rates.

By this stage it was evident that our goal of an efficient, unambiguous synthesis of unsymmetrical benzoin phosphates was unlikely to be achieved by direct reactions on the benzoins, and it seemed probable that ketalisation of the carbonyl group would eliminate the side reactions encountered above. Formation of acyclic dialkyl ketals of benzoin involves treatment of desyl chloride with sodium alkoxide, a reaction in which the timing of the alkoxide addition is apparently critical.[16] However, the cyclic ethylene ketal **20a** can be conveniently prepared from benzoin itself by the normal acid-catalysed procedure,[17] and the subsequent reactions shown in Scheme 3 then proceeded smoothly. Thus phosphitylation with bis-(2-cyanoethyl) diisopropylphosphoramidite followed by oxidation with MCPBA[10] and treatment with sodium hydroxide in warm methanol gave the phosphate **21a**. Acid-catalysed hydrolysis of the ketal was very slow at room temperature but proceeded smoothly under reflux to give benzoin phosphate **5** in 54% overall yield from the ketal **20a**, after isolation as the barium salt. Subsequent preparations using ion-exchange chromatography for isolation of products gave higher yields (see Experimental section). By-products such as the diester **7** were not formed.



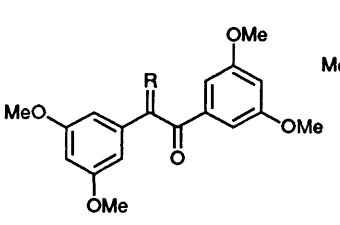
a: Ar = Ar′ = Ph; **b**: Ar = Ph, Ar′ = 3,5-$(MeO)_2C_6H_3$; **c**: Ar = 3,5-$(MeO)_2C_6H_3$, Ar′ = Ph; **d**: Ar = Ar′ = 3,5-$(MeO)_2C_6H_3$; **e**: Ar = 4-MeC_6H_4, Ar′ = 3,5-$(MeO)_2C_6H_3$; **f**: Ar = 4-$MeOC_6H_4$, Ar′ = Ph

Scheme 3 *Reagents:* i, $HOCH_2CH_2OH$-TsOH; ii, $Pr^i_2NP(OCH_2CH_2CN)_2$-1*H*-tetrazole; iii, MCPBA; iv, NaOH–MeOH; v, aq. HCl

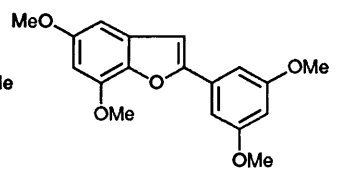
With the successful development of this reaction sequence, we were able to prepare the phosphates **23b–d** shown in Scheme 3. The substituted benzoins were prepared either (**15**, **19b**) by addition of an aryl Grignard reagent to the trimethylsilyl (TMS) ether of an aromatic cyanohydrin[18] or (**19c–f**) by

metallation of a cyanohydrin TMS ether and addition to a benzaldehyde,[19] with appropriate substitution patterns as required in each case. In our hands preparation of 3′,5′-dimethoxybenzoin **19b** by addition of phenylmagnesium bromide to the unprotected cyanohydrin[3b] was inefficient, and a poor yield for an alternative synthesis *via* a metallated 1,3-dithiane has also been reported.[20] The symmetrical tetramethoxybenzoin **19d** could, in principle, be prepared by a classical benzoin condensation, but 3,5-dimethoxybenzaldehyde has been found not to undergo this reaction.[21] Unexpectedly, the synthesis used here also yielded a small amount of the corresponding 3,3′,5,5′-tetramethoxybenzil **24**, presumably *via* aerial oxidation at some stage of the synthesis. No benzil products were isolated from reaction mixtures which yielded the other benzoins, and the precise origin of compound **24** remains unexplained.

With unambiguous syntheses of unsymmetrical benzoin phosphates in hand, we gave further consideration to the properties reported by Baldwin *et al.*[2] for the phosphate **23b**. Their published data, which appeared inconsistent, include the quoted maximum extinction coefficient in the UV spectrum of the unpurified free acid (log ε 5.6) which is at least 20-fold greater than expected from the data of Sheehan *et al.*[3b] The ^{1}H NMR spectrum of the triethylammonium salt, after fractionation by anion-exchange chromatography is reported as showing two methoxy resonances (δ 3.62 and 3.80) which is unlikely in view of the symmetrical substitution of methoxy groups on the aromatic ring. In addition, the upfield aromatic signals, expected to be those arising from the protons on the dioxygenated ring, are reported as singlets (δ 6.50 and 6.58) which is inconsistent with the expected coupling pattern for a 1,3,5-trisubstituted aromatic ring, and the methine proton (geminal to the phosphate) is reported as a singlet, inconsistent with an expected[22] 8–10 Hz coupling to the adjacent phosphorus. Although our proposal could not fully reconcile these data, we speculated that the two methoxy resonances reported in the ^{1}H NMR spectrum of compound **23b** might have arisen from the presence of an equivalent amount of the isomeric phosphate **23c**; the propensity of benzoins for such isomerisation has already been noted above. However, when authentic samples of the two phosphates **23b** and **23c** were prepared by the route shown in Scheme 3, the aromatic regions of their ^{1}H NMR spectra showed the expected differences, but the methoxy signals in the individual spectra differed by only 0.04 ppm and were not resolved (at least in the 90 MHz spectrum) when the two compounds were mixed in equal proportions. We have therefore failed to identify the contaminant(s) in the material reported by Baldwin *et al.* and have not pursued the question.



24 R = O
25 R = H, OAc



26

Flash photolysis of the phosphate **23b** was encouraging. As shown in Scheme 1, photolysis of the 3′,5′-dimethoxybenzoin derivatives **2** and **23b** produces the benzofuran **3**, with a large increase in absorbance around 315 nm[3b] by which the reaction kinetics can be monitored using a time-resolved spectrometer.[23] The absorbance change in response to a 50 ns pulse of 347 nm light from a frequency-doubled ruby laser is shown in Fig. 1(*a*) and occurred within the time resolution of the spectrometer. Thus the rate constant, k, of formation of benzofuran **3** and hence of inorganic phosphate appears to be at least 10^5 s^{-1}, although some caution is needed in case the observed spectral change is due to an immediate precursor of the benzofuran [see results in Fig. 1(*b*)]. We have reported preliminary data[24] which show that the corresponding P^3-3′,5′-dimethoxybenzoin ester of ATP also photolyses with $k > 10^5$ s^{-1}. For comparison, 1-(2-nitrophenyl)ethyl dihydrogen phosphate photolyses under identical conditions with $k = 8 \times 10^4$ s^{-1}, and when the same photolabile group esterifies the terminal phosphate of ATP (*i.e.*, 'caged' ATP **1**) the photolysis rate constant[23] (depending on magnesium concentration) is in the range 100–300 s^{-1}. The 3′,5′-dimethoxybenzoin derivatives therefore photolyse significantly faster than those esterified with the 1-(2-nitrophenyl)ethyl group.

The extent of conversion in equimolar mixtures of compounds **23b** and **1** at pH 7.4 following a single pulse of 347 nm light was 10 and 30.2% respectively (see Experimental section for conditions). When allowance is made for the lower absorption of compound **23b** (ε_{347} 170 dm^3 mol^{-1} cm^{-1}) compared with that of 1-(2-nitrophenyl)ethyl compounds such as **1** (ε_{347} 660 dm^3 mol^{-1} cm^{-1}), the benzoin phosphate **23b** was converted 1.24-fold more efficiently than was compound **1**. If we assume that no multiple excitation of individual molecules occurred,[25] comparison with the known[23] product quantum yield, Q_P, of 0.63 for 'caged' ATP **1** gives $Q_P = 0.78$ for the phosphate **23b**. This compares with the value of $Q_P = 0.64$ for the dimethoxybenzoin acetate **2** (X = Ac) determined in benzene by Sheehan *et al.*[3b] using actinometry.

In an attempt to manipulate the extinction coefficient and possibly to increase the extent of conversion, we have examined two other substituted benzoins, Our first attempt used a 4-methyl substituent (compound **19e**) since this causes a 10–12 nm bathochromic shift in the π–π* transition.[26] Although the absorption spectrum of compound **19e** showed this effect as expected, the long-wavelength (n–π*) transition appeared to be largely unaffected as judged from the measured spectrum, with the extinction coefficient at 347 nm actually showing a slight fall to 140 dm^3 mol^{-1} cm^{-1}. Further elaboration of the benzoin **19e** to the corresponding phosphate was not pursued. The tetramethoxybenzoin **19d**, was apparently more promising since it had ε_{347} 1000 dm^3 mol^{-1} cm^{-1}. This compound was first converted into its acetate **25** which photolysed smoothly in toluene under continuous irradiation to give the predicted[3b] benzofuran **26** in high yield. The benzoin **19d** was therefore converted into the phosphate **23d**, but pulse photolysis of the latter compound gave approximately four-fold less conversion than did that of the dimethoxy compound **23b** under identical conditions. Furthermore, when the kinetics of formation of the benzofuran **26** were monitored using time-resolved spectrophotometry as described above for the phosphate **23b**, the initial rapid increase in absorbance at 317 nm was followed by a transient decrease at 600 s^{-1} [Fig. 1(*b*)]. We have not analysed this biphasic signal further, but it has interesting implications for the photolysis mechanism. In the light of these results, we abandoned further efforts to improve the conversion by manipulation of the substitution pattern.

Since Baldwin *et al.*[2] reported that the unsubstituted benzoin phosphate **5** was a suitable protecting group, we made a preliminary examination of its photolysis. Under continuous irradiation conditions the benzoin chromophore gradually diminished and a new absorption band appeared at shorter wavelength (226 nm) with an extended tail to longer wavelength. However, within this tail there was no evidence of absorption which could be associated with formation[3a] of the unsubstituted 2-phenylbenzofuran.[27] Sheehan and Wilson[3a] have described the complex product mixture obtained on photolysis of benzoin acetate. Unlike the 3′,5′-dimethoxybenzoin phosphate **23b**, the unsubstituted compound **5** therefore shows no convenient spectroscopic signal by which to monitor its photolysis.

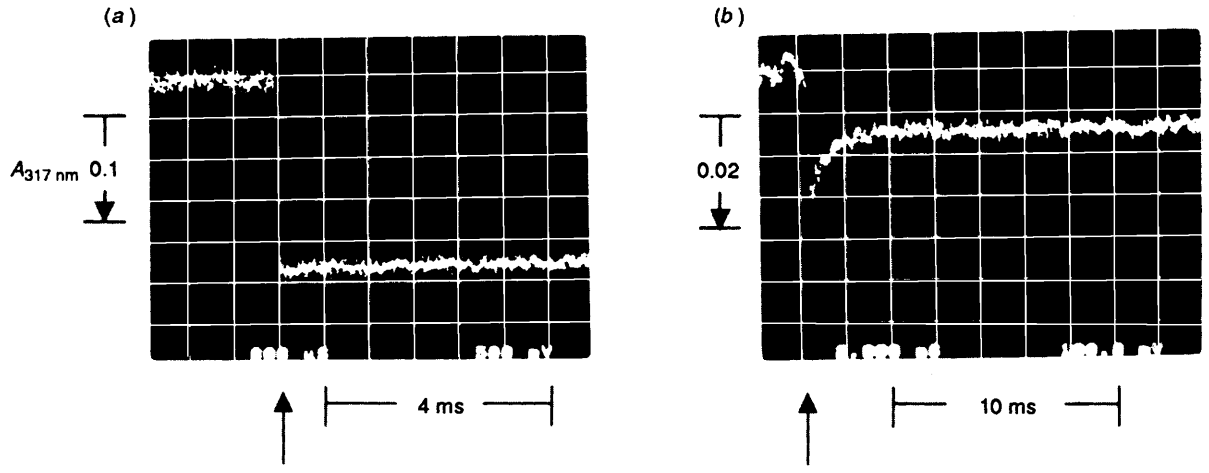


Fig. 1 Spectrophotometric records at 317 nm of the photolysis of 3′,5′-dimethoxybenzoin phosphate **23b**, and of 3,3′,5,5′-tetramethoxybenzoin phosphate **23d**. In (*a*) the solution at 20 °C contained 1 mmol dm^{-3} **23b**, and 100 mmol dm^{-3} piperazine-*N*,*N*′-bis(ethane-2-sulfonic acid) (PIPES) adjusted to pH 7.1 with KOH. In (*b*) the solution at 20 °C contained 0.4 mmol dm^{-3} **23d** and 150 mmol dm^{-3} PIPES adjusted to pH 6.7 with KOH. Arrows indicate the time of the 347 nm laser pulse. The perturbation to the record in (*b*) prior to the laser pulse is due to the laser-pumping flash.

Since we now have available a satisfactory synthesis of 3′,5′-dimethoxybenzoin, and the photolysis properties of its derived phosphate are so readily monitored by spectroscopy, we chose not to pursue examination of the unsubstituted phosphate **5**.

We examined photolysis of the dimethoxy phosphate **23b** at 320 nm by using a tunable dye laser, since the extinction coefficient rises steeply as the wavelength shortens and is 620 $dm^3\ mol^{-1}\ cm^{-1}$ at 320 nm. Despite this increase, the extent of photolysis of phosphate **23b** was approximately 3-fold lower at the shorter wavelength, which we assume is caused by decreased excitation of the n–π* transition. Thus the optimal conditions we have found are to use the 3′,5′-dimethoxybenzoin derivative and to photolyse at 347 nm. However, it is possible to compensate for the lower extent of photolysis [relative to 1-(2-nitrophenyl)ethyl compounds] by using increased concentrations of phosphate **23b** (see Experimental section). The 3.9-fold lower extinction coefficient of the benzoin permits the use of a correspondingly higher initial concentration than of a 1-(2-nitrophenyl)ethyl compound for the same attenuation of light across the irradiation path. We are pursuing the use of these compounds in studies of muscle physiology.

Experimental

Analyses were carried out by Butterworth Laboratories, Teddington, Middlesex and by the Chemical Analysis Centre, The University, Canterbury, Kent. ^1H NMR spectra at 90 MHz and ^{31}P NMR spectra at 36.2 MHz were determined on a JEOL FX90Q spectrometer, using tetramethylsilane or acetone as internal standard for ^1H spectra in $CDCl_3$ or D_2O respectively. ^{31}P spectra were referenced to 85% H_3PO_4. *J*-Values are given in Hz. Negative ion FAB mass spectra were run on a VG 70-250SE instrument for samples in a glycerol matrix. For water-soluble phosphate salts, which were not isolated in an anhydrous state, quantitation was by UV absorption, taking the extinction coefficient to be the same as for the parent benzoin when determined in EtOH–water (1:9). Merck 9385 silica gel was used for flash chromatography. Ion-exchange chromatography was performed on a column of DEAE-cellulose (2.5 × 40 cm). Triethylammonium hydrogen carbonate (TEAB) buffer for elution was prepared by bubbling CO_2 into an ice-cold 1 mol dm^{-3} solution of triethylamine in water until the pH stabilised at ~7.4. Pooled column fractions were evaporated at ~1 mmHg and freed from buffer salts by repeated evaporation with methanol. For NMR spectroscopy, triethylammonium salts were converted into sodium salts by treatment with Dowex 50 (Na form). Analytical HPLC was performed on a Whatman Partisphere SAX column (Cat. No. 4621-0505), with mobile-phase flow rates at 1.5 cm^3/min and UV detection at 254 nm. Mobile-phase buffers were prepared from solutions of ammonium dihydrogen phosphate at the molarities noted in the text and adjusted to the pH-values specified by addition of either 1 mol dm^{-3} hydrochloric acid or conc. aq. ammonia as required. Light petroleum was the fraction boiling in the range 40–60 °C. Bis-(2-cyanoethyl) diisopropylphosphoramidite was prepared as described previously.[10] The frequency-doubled ruby laser and time-resolved spectrophotometer for flash photolysis were as previously described.[23]

Bis-(2-cyanoethyl) 2-Oxo-1,2-diphenylethyl Phosphate **6** *and its Reaction with Methanolic Alkali.*—A solution of benzoin **19a** (424 mg, 2 mmol) and bis-(2-cyanoethyl) diisopropylphosphoramidite (677 mg, 2.5 mmol) in dry tetrahydrofuran (THF) (15 cm^3) was stirred under nitrogen and treated with 1*H*-tetrazole (314 mg, 4.5 mmol). After 1.5 h at room temp. the mixture was cooled in an ice-bath and treated dropwise during 5 min with a solution of MCPBA (61% peracid; 940 mg, 3.3 mmol) in CH_2Cl_2 (10 cm^3). The solution was stirred for 1 h at 4 °C then diluted with diethyl ether and washed successively with 10% aq. $Na_2S_2O_5$, 1 mol dm^{-3} aq. HCl, 10% aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography with ethyl acetate–light petroleum (3:1) to give the triester **6** as a pale gum (515 mg, 65%); $\delta_H(CDCl_3)$ 7.84–7.95 (2 H, m, ArH), 7.36–7.60 (8 H, m, ArH), 6.71 (1 H, d, $J_{H,P}$ 7.0, PhC*H*), 4.10 and 4.42 (4 H, 2 m, 2 × OCH_2) and 2.57 and 2.85 (4 H, 2 t, *J* 6.8, 2 × CH_2CN); $\delta_P(CDCl_3)$ −3.36 (sextet).

The total material (1.29 mmol) was dissolved in 0.1 mol dm^{-3} NaOH in dry MeOH (48 cm^3) and kept at 50 °C for 0.75 h, then concentrated under reduced pressure to ~10 cm^3, diluted with water, and adjusted to pH 7 with dil. HCl. The mixture was partitioned with diethyl ether and the ethereal phase was washed with water, dried (Na_2SO_4) and evaporated to give a pale oil (52 mg) with spectral properties compatible with the ketal **8**; λ_{max}(EtOH)/nm 250; $\delta_H(CDCl_3)$ 6.83–7.23 (10 H, m, ArH), 5.07 (1 H, s, ArC*H*), 3.47 (3 H, s, OMe) and 3.23 (3 H, s, OMe).

This material was dissolved in MeOH (7 cm^3)–2 mol dm^{-3} aq. HCl (2 cm^3) and kept for 2 h at room temp. TLC showed one major product, which co-chromatographed with authentic benzoin. Quantitative UV analysis at λ 247 nm indicated the

benzoin recovery [λ_{max}(EtOH)/nm (ε/dm^3 mol^{-1} cm^{-1} 12 500)] as 0.20 mmol (16%).

The total aqueous phase from the reaction mixture was quantitated by UV analysis at 250 nm {λ_{max}[water–EtOH (9:1)]/nm 250 (ε/dm^3 mol^{-1} cm^{-1} 11 960)} and gave a 'benzoin phosphate' recovery of 0.845 mmol. A portion of the aqueous phase was fractionated by ion-exchange chromatography, using a linear gradient formed from 10 and 200 mmol dm^{-3} TEAB (each 1000 cm^3) to give a less polar and more polar fraction which eluted at ~75 and 125 mmol dm^{-3} TEAB respectively. The more polar fraction was processed as described to give the *2-oxo-1,2-diphenylethyl phosphate* **5** as the triethylammonium salt (Found: M$^-$, 291. $C_{14}H_{11}O_5P$ + H requires *M*, 291); $\delta_H(D_2O)$ 7.88–8.08 (2 H, m, ArH), 7.28–7.60 (8 H, m, ArH) and 6.65 (1 H, d, $J_{H,P}$ 8.8, ArC*H*). The less polar fraction co-eluted with chloride and was desalted by percolation through a column of Sephadex LH20 (2.5 × 40 cm) in water. Conductivity and absorbance measurements, showed that the chloride eluted prior to the product, which was concentrated and treated with Dowex 50 (Na form) to give *methyl 2-oxo-1,2-diphenylethyl hydrogen phosphate* **7** as the sodium salt (Found: M$^-$, 305. $C_{15}H_{14}O_5P$ requires *M*, 305); $\delta_H(D_2O)$ 7.88–8.04 (2 H, m, ArH), 7.32–7.60 (8 H, m, ArH), 6.58 (1 H, d, $J_{H,P}$ 8.4, ArC*H*) and 3.39 (3 H, d, $J_{H,P}$ 11.0 OMe); δ_P 0.67 (overlapping d/q).

With authentic pure samples of the monoester **5** and diester **7** in hand, the relative yields in the unfractionated mixture were determined by quantitative HPLC [0.3 mol dm^{-3} aq. ammonium phosphate (pH 4) plus 10% MeOH (v/v)]. Retention times for the mono- and diester were 3.3 and 1.7 min, respectively, and the product ratio was 2.5:1, corresponding to yields of 47 and 19%, respectively. With the benzoin recovered from the organic phase, the total product recovery based on the triester **6** was 82%.

Bis-(2-cyanoethyl) 1-(4-Methoxyphenyl)-2-oxo-2-phenylethyl Phosphate **16** *and its Reaction with Methanolic Alkali.*—2-Hydroxy-2-(4-methoxyphenyl)-1-phenylethanone (484 mg, 2 mmol) was subjected to phosphitylation and oxidation exactly as above and the crude reaction mixture was purified by flash chromatography in ethyl acetate–light petroleum (3:1) to give the title product **16** as a viscous oil (626 mg, 73%), $\delta_H(CDCl_3)$ 7.81–7.95 [2 H, m, Ar(2) 2- and 6-H], 7.43–7.57 [3 H, m, Ar(2)-H], 7.32 [2 H, d, J_o 8.8, Ar(1) 2- and 6-H], 6.89 [2 H, d, Ar(1) 3- and 5-H], 6.68 (1 H, d, $J_{H,P}$ 7.1, ArC*H*), 4.11 and 4.40 (4 H, 2 m, 2 × OCH_2), 3.77 (3 H, s, OMe) and 2.60 and 2.85 (4 H, 2 t, *J* 6.8, 2 × CH_2CN).

This material (605 mg, 1.41 mmol) was dissolved in 0.1 mol dm^{-3} NaOH in dry MeOH (52 cm^3), kept at 50 °C for 0.75 h then worked up as above. The ether-soluble product was not examined, but a portion of the water-soluble material was fractionated by a combination of ion exchange and Sephadex LH 20 chromatography as above to give 1-(4-methoxyphenyl)-2-oxo-2-phenylethyl methyl hydrogen phosphate **17** as the sodium salt, λ_{max}(water)/nm 224 and 249; $\delta_H(D_2O)$ 7.81–7.93 [2 H, m, Ar(2) 2- and 6-H], 7.21–7.47 (5 H, m, ArH), 6.68 [2 H, d, J_o 8.8, Ar(1) 3- and 5-H], 6.55 (1 H, d, $J_{H,P}$ 8.8, ArC*H*), 3.51 (3 H, s, ArO*Me*) and 3.38 (3 H, d, $J_{H,P}$ 11.0, POMe), together with 1-(4-methoxyphenyl)-2-oxo-2-phenylethyl dihydrogen phosphate **18** as the sodium salt, λ_{max}(water)/nm 224 and 249; $\delta_H(D_2O)$ 7.89–8.05 [2 H, m, Ar(2) 2- and 6-H], 7.27–7.56 (5 H, m, ArH), 6.77 [2 H, d, J_o 8.8, Ar(1) 3- and 5-H], 6.57 (1 H, d, $J_{H,P}$ 9.3, ArC*H*) and 3.60 (3 H, s, ArO*Me*). The isolated ratio of the monoester **18** and diester **17** was 3.1:1, and the overall yield of the two products was 74%. The spectra of 2-hydroxy-2-(4-methoxyphenyl)-1-phenylethanone **15** and its isomer **19f** are given below for comparison.

Reaction of Bis-(2-cyanoethyl) 1-(2-Nitrophenyl)ethyl Phosphate **9** *with Methanolic Alkali.*—1-(2-Nitrophenyl)ethanol was phosphitylated and oxidised as previously described.[11] The crude product was purified by flash chromatography [EtOAc–light petroleum (85:15)] to give the phosphotriester **9** (210 mg, 0.6 mmol), which was dissolved in 0.1 mol dm^{-3} methanolic NaOH (19 cm^3) and heated at 50 °C for 0.5 h. The solution was cooled, concentrated to a small volume under reduced pressure, diluted with water, and extracted with diethyl ether. The aqueous layer was analysed by quantitative UV spectroscopy at 265 nm and showed 98% recovery of the nitrophenyl chromophore. Analytical HPLC (mobile phase 0.25 mol dm^{-3} aq. ammonium phosphate, pH 4.3) showed a single peak, t_R 3.2 min, which co-eluted with authentic[11] 1-(2-nitrophenyl)ethyl dihydrogen phosphate.

2-Oxo-1,2-diphenylethyl Dihydrogen Phosphate **5** via *the Dioxolane* **20a**.—A solution of 2-(α-hydroxybenzyl)-2-phenyl-1,3-dioxolane **20a** [512 mg, 2 mmol; m.p. 149–150 °C (lit.,[17] 146–146.8 °C)] and bis-(2-cyanoethyl) diisopropylphosphoramidite (800 mg, 3 mmol) in dry THF (15 cm^3) was treated with 1*H*-tetrazole (314 mg, 4.5 mmol) and stirred under nitrogen at room temp. for 1 h, then cooled in an ice-bath and treated dropwise with a solution of MCPBA (61% peracid; 940 mg, 3.3 mmol) in CH_2Cl_2 (10 cm^3). After 1 h at 0 °C the solution was diluted with diethyl ether, washed successively with 10% aq. $Na_2S_2O_5$, 1 mol dm^{-3} citric acid, 10% aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated to leave the crude bis-(2-cyanoethyl) phosphate **21a** as a gum (900 mg); $\delta_H(CDCl_3)$ 7.11–7.34 (10 H, m, ArH), 5.49 (1 H, d, $J_{H,P}$ 9.1, ArC*H*), 3.60–4.14 (8 H, m, 4 × OCH_2) and 2.40 and 2.46 (4 H, 2 t overlapping, *J* 6.5, 2 × CH_2CN).

The crude material was dissolved in 0.1 mol dm^{-3} NaOH in dry MeOH (40 cm^3), kept at 50 °C for 0.5 h, and evaporated under reduced pressure. The residue was partitioned between diethyl ether and water (each 80 cm^3) and the aqueous layer which contained compound **22a** was adjusted to pH 7 with 2 mol dm^{-3} hydrochloric acid, then was treated with one-hundredth of its volume of conc. hydrochloric acid (0.83 cm^3) and heated under reflux for 1 h. The cooled solution was neutralised with 1 mol dm^{-3} aq. NaOH, concentrated under reduced pressure to ~30 cm^3, and treated with 2 mol dm^{-3} $Ba(OAc)_2$, followed by EtOH (30 cm^3). After storage at 4 °C for several hours, the precipitate was filtered off and washed successively with 50% aq. EtOH, EtOH, and diethyl ether and then dried *in vacuo* to give 2-oxo-1,2-diphenylethyl dihydrogen phosphate **5** as its barium salt (460 mg, 54%). A portion of the barium salt was converted into the soluble sodium salt by suspension in water and treatment with Dowex 50 (Na form). The ^{1}H NMR spectrum and HPLC retention time were identical with those of authentic benzoin phosphate **5** described above. In later preparations of substituted benzoin phosphates, the products were isolated by ion-exchange chromatography (see below) since the barium salts were difficult to filter off.

2-(3,5-Dimethoxyphenyl)-2-hydroxy-1-phenylethanone **19b**.—A solution of 3,5-dimethoxybenzaldehyde (7.96 g, 48 mmol) and zinc iodide (20 mg) in dry benzene (30 cm^3) was treated dropwise during 5 min with a solution of trimethylsilyl cyanide (5 g, 50.5 mmol) in dry benzene (20 cm^3) and stirred for 1.5 h at room temp., then evaporated under reduced pressure. The residue was distilled to give α-(3,5-dimethoxyphenyl)-α-(trimethylsiloxy)acetonitrile (11.85 g, 93%) as a pale oil, b.p. 110–120 °C (0.04 mmHg); $\delta_H(CDCl_3)$ 6.63 (2 H, d, J_m 2.2, Ar 2- and 6-H), 6.47 (1 H, t, Ar 4-H), 5.44 (1 H, s, ArC*H*), 3.79 (6 H, s, OMe) and 0.23 (9 H, s, $SiMe_3$).

A solution of this compound (16.68 g, 62.9 mmol) in dry diethyl ether (60 cm^3) was added dropwise to a solution of phenylmagnesium bromide [prepared from magnesium (1.81 g) and bromobenzene (11.91 g, 75.8 mmol) in dry diethyl ether (40 cm^3)] and the mixture was stirred for 1 h at room temp., then

poured over a mixture of ice and NH_4Cl. The ethereal phase was separated and the aqueous phase was extracted with EtAOc. The combined organic layers were washed successively with water and brine, dried (Na_2SO_4) and evaporated, and the residue was dissolved in a mixture of MeOH (110 cm^3) and 2 mol dm^{-3} hydrochloric acid (35 cm^3). The solution was heated under reflux for 2 h, concentrated under reduced pressure, diluted with water, and extracted with EtOAc, which was then washed with water, dried (Na_2SO_4) and evaporated. The residue was crystallised on trituration with a little methanol and gave the product **19b** (8.60 g, 46%), after crystallisation from EtOAc–light petroleum, m.p. 109–110 °C (lit.,[3b] 110–111.5 °C); λ_{max}[EtOH–water (1:9)]/nm 250 (ε/dm^3 mol^{-1} cm^{-1} 12 500); $\delta_H(CDCl_3)$ 7.88–8.02 [2 H, m, Ar(1) 2- and 6-H], 7.27–7.58 [3 H, m, Ar(1)-H], 6.48 (2 H, d, J_m 2.2, Ar(2) 2- and 6-H], 6.31 [1 H, t, Ar(2) 4-H], 5.84 (s, 1 H, ArC*H*) and 3.72 (6 H, s, OMe).

2-*Hydroxy*-1-(4-*methoxyphenyl*)-2-*phenylethanone* **19f**.—This compound was prepared analogously to the benzoin **19b** by reaction of 4-methoxyphenylmagnesium bromide with α-(trimethylsiloxy)phenylacetonitrile[28] and was crystallised as needles from EtOAc–light petroleum, m.p. 105–106 °C (lit.,[29] 106.5–107 °C); λ_{max}(EtOH)/nm 281 (ε/dm ^{3} mol^{-1} cm^{-1} 16 200); λ_{max}[EtOH–water (1:9)]/nm 285 (ε/dm^3 mol^{-1} cm^{-1} 15 000); $\delta_H(CDCl_3)$ 7.90 [2 H, d, J_o 9.2, Ar(1)- 3- and 5-H], 7.32 (5 H, br s, ArH), 6.85 [2 H, d, Ar(1) 2- and 6-H], 5.88 (1 H, s, ArC*H*) and 3.80 (3 H, s, OMe).

1-(3,5-*Dimethoxyphenyl*)-2-*hydroxy*-2-*phenylethanone* **19c**.—1.6 mol dm^{-3} Butyllithium in hexane (20 cm^3, 32 mmol) was added dropwise under nitrogen to a solution of redistilled diisopropylamine (3.22 g, 32.2 mmol) in dry 1,2-dimethoxyethane (DME; 30 cm^3) at −78 °C, with the temperature kept below −60 °C. The solution was stirred at −78 °C for 15 min, then treated dropwise during 5 min with a solution of α-(3,5-dimethoxyphenyl)-α-(trimethylsiloxy)acetonitrile (7.68 g, 29 mmol) in dry DME (12 cm^3). After 30 min at −78 °C, a solution of benzaldehyde (3.06 g) in dry DME (12 cm^3) was added during 5 min, and the solution was allowed to warm to room temp. during 4 h. Saturated aq. NH_4Cl (60 cm^3) was added, and the mixture was stirred for 10 min and extracted with diethyl ether. The ethereal phase was washed with saturated aq. NH_4Cl and evaporated under reduced pressure. The residue was dissolved in a mixture of 1,4-dioxane (60 cm^3), methanol (40 cm^3) and 2 mol dm^{-3} hydrochloric acid (50 cm^3) and stirred overnight at room temp., then diluted with brine and extracted with diethyl ether. The extract was washed successively with 1 mol dm^{-3} NaOH and brine, dried (Na_2SO_4) and evaporated. Trituration of the residue in methanol gave a solid, which was crystallised from benzene–light petroleum to afford the *ketol* **19c** as prisms (5.10 g, 65%), m.p. 92–93 °C (Found: C, 70.6; H, 5.8. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%); λ_{max}(EtOH)/nm 267 and 321 (ε/dm^3 mol^{-1} cm^{-1} 7000 and 2400); λ_{max}[EtOH–water (1:9)]/nm 267 and 315 (ε/dm^3 mol^{-1} cm^{-1} 6200 and 1840); $\delta_H(CDCl_3)$ 7.30 (5 H, br s, ArH), 7.02 [2 H, d, J_m 2.2, Ar(1) 2- and 6-H], 6.57 [1 H, t, Ar(1) 4-H], 5.88 (1 H, s, ArC*H*) and 3.74 (6 H, s, OMe).

1,2-*Bis*-(3,5-*dimethoxyphenyl*)-2-*hydroxyethanone* **19d** *and* 1,2-*Bis*-(3,5-*dimethoxyphenyl*)*ethanedione* **24**.—α-(3,5-Dimethoxyphenyl)-α-(trimethylsiloxy)acetonitrile (11.85 g, 44.7 mmol) was lithiated as described above for the preparation of ketol **19c** and allowed to react with 3,5-dimethoxybenzaldehyde (7.43 g, 44.7 mmol). After work-up as described above, the crude reaction product was triturated in MeOH to give a yellow solid (0.8 g), which was filtered off, and the filtrate then spontaneously deposited a large mass of material, which was recrystallised from MeOH, then from CH_2Cl_2–diisopropyl ether to give the *ketol* **19d** as prisms (8.83 g, 59%), m.p. 102–103 °C (Found: C, 64.9; H, 6.1. $C_{18}H_{20}O_6$ requires C, 65.0; H, 6.1%); λ_{max}(EtOH)/nm 268 and 316 (ε/dm^3 mol^{-1} cm^{-1} 8100 and 2300); λ_{max}[EtOH–water (1:9)]/nm 269 and 316 (ε/dm^3 mol^{-1} cm^{-1} 8000 and 2400); $\delta_H(CDCl_3)$ 7.05 [2 H, d, J_m 2.2, Ar(1) 2- and 6-H], 6.60 [1 H, t, Ar(1) 4-H], 6.47 [2 H, d, J_m 2.2, Ar(2) 2- and 6-H], 6.36 [1 H, t, Ar(2) 4-H], 5.79 (1 H, d, $J_{H,OH}$ 6.1, ArC*H*), 4.45 (1 H, d, OH), 3.76 (6 H, s, OMe) and 3.73 (6 H, s, OMe).

The yellow solid which had separated out initially was purified from traces of the ketol **19d** by flash chromatography [CH_2Cl_2–light petroleum (1:1)] to give the *diketone* **24** as bright yellow laths (from EtOAc–light petroleum), m.p. 172 °C (Found: C, 65.4; H, 5.5. $C_{18}H_{18}O_6$ requires C, 65.4; H, 5.5%); λ_{max}(EtOH)/nm 276, 326 and 370sh (ε/dm^3 mol^{-1} cm^{-1} 10 600, 3600 and 2400); $\delta_H(CDCl_3)$ 7.07 (4 H, d, J_m 2.2, Ar 2- and 6-H), 6.73 (2 H, t, Ar 4-H) and 3.82 (12 H, s, OMe).

2-(3,5-*Dimethoxyphenyl*)-2-*hydroxy*-1-(4-*methylphenyl*)*ethanone* **19e**.—α-(4-Methylphenyl)-α-(trimethylsiloxy)acetonitrile[30] was lithiated and the carbanion was treated with 3,5-dimethoxybenzaldehyde in an analogous manner to that described above. The reaction mixture was worked up in the same way to afford the *ketol* **19e** as prisms from EtAOc–light petroleum, m.p. 95–96 °C (Found: C, 71.4; H, 6.2. $C_{17}H_{18}O_4$ requires C, 71.3; H, 6.3%); λ_{max}(EtOH)/nm 257 (ε/dm^3 mol^{-1} cm^{-1} 16 100); $\delta_H(CDCl_3)$ 7.81 [2 H, d, J_o 7.9, Ar(1) 2- and 6-H], 7.12 [2 H, d, Ar(1) 3- and 5-H], 6.48 [2 H, d, J_m 2.2, Ar(2) 2- and 6-H], 6.31 [1 H, t, Ar(2) 4-H], 3.66 (6 H, s, OMe) and 2.28 (3 H, s, Me).

2-*Hydroxy*-2-(4-*methoxyphenyl*)-1-*phenylethanone* **15**.—This compound was prepared similarly to ketol **19b** by reaction between lithiated α-(trimethylsiloxy)phenylacetonitrile and 4-methoxybenzaldehyde. The ketol **15** formed needles from EtOAc–light petroleum, m.p. 87–88 °C (lit.,[3b] 90–91 °C); λ_{max}(EtOH)/nm 227 and 245 (ε/dm^3 mol^{-1} cm^{-1} 14 100 and 12 900); λ_{max}[EtOH–water (1:9)]/nm 226 and 250 (ε/dm^3 mol^{-1} cm^{-1} 11 800 and 12 300); $\delta_H(CDCl_3)$ 7.84–8.00 [2 H, m, Ar(1) 2- and 6-H], 7.34–7.56 [3 H, m, Ar(1)-H], 7.27 (2 H, d, J_o 8.8, Ar(2) 2- and 6-H], 6.83 [2 H, d, Ar(2) 3- and 5-H], 5.91 (1 H, d, $J_{H,OH}$ 5.7, ArC*H*), 4.48 (1 H, d, OH) and 3.74 (3 H, s, OMe).

2-(α-*Hydroxy*-3,5-*dimethoxybenzyl*)-2-*phenyl*-1,3-*dioxolane* **20b**.—A solution of the ketol **19b** (3.21 g), ethylene glycol (1.63 g) and toluene-*p*-sulfonic acid (75 mg) in dry benzene (75 cm^3) was heated under reflux in a Dean–Stark apparatus for 16 h, then cooled, washed successively with aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The residue was crystallised from benzene–light petroleum to give the *dioxolane* **20b** as fine needles (2.82 g, 70%), m.p. 122–124 °C. An analytical sample had m.p. 124–125 °C (Found: C, 68.0; H, 6.5. $C_{18}H_{20}O_5$ requires C, 68.3; H, 6.4%); $\delta_H(CDCl_3)$ 7.25 (5 H, br s, ArH), 6.22–6.34 (3 H, m, ArH), 4.82 (1 H, s, ArC*H*), 3.70–4.15 (4 H, m, OCH_2) and 3.63 (6 H, s, OMe).

2-(3,5-*Dimethoxyphenyl*)-2-(α-*hydroxybenzyl*)-1,3-*dioxolane* **20c** *and* 2-(3,5-*Dimethoxyphenyl*)-2-(α-*hydroxy*-3,5-*dimethoxybenzyl*)-1,3-*dioxolane* **20d**.—These compounds were prepared as for the dioxolane **20b** above, but in each case the ketalisation reaction, as described, did not go to completion and TLC [EtOAc–light petroleum (30:70)] showed that the ketals were contaminated by the starting benzoins. Flash chromatography in the same solvent gave the pure compounds. The *dimethoxy dioxolane* **20c** was crystallised from diethyl ether–light petroleum in fine rosettes, m.p. 78–79 °C (Found: C, 68.3; H, 6.35. $C_{18}H_{20}O_5$ requires C, 68.3; H, 6.4%); $\delta_H(CDCl_3)$ 7.19 (5 H, br s, ArH), 6.35 (3 H, br s, ArH), 4.85 (1 H, s, ArC*H*), 3.72–4.09 (4 H, m, OCH_2) and 3.64 (6 H, s, OMe). The *tetramethoxy dioxolane*

20d was crystallised from benzene–light petroleum as needles, m.p. 88–89 °C (Found: C, 63.6; H, 6.4. $C_{20}H_{24}O_7$ requires C, 63.8; H, 6.4%); $\delta_H(CDCl_3)$ 6.34–6.43 (6 H, m, ArH), 4.79 (1 H, s, ArC*H*), 3.81–4.08 (4 H, m, OCH_2) and 3.67 (12 H, s, OMe).

1,2-*Bis*-(3,5-*dimethoxyphenyl*)-2-*oxoethyl Acetate* **25**.—Reaction of the ketol **19d** with acetic anhydride–pyridine gave the *acetate* **25** as rods from CH_2Cl_2–MeOH, m.p. 108 °C (Found: C, 63.95; H, 5.85. $C_{20}H_{22}O_7$ requires C, 64.2; H, 5.9%); $\delta_H(CDCl_3)$ 7.07 [2 H, d, J_m 2.2, Ar(2) 2- and 6-H], 6.68 (1 H s, ArC*H*), 6.57–6.62 [3 H, m, Ar(1) 2- and 6-H and Ar(2) 4-H], 6.41 [1 H, t, J_m 2.2, Ar(1) 4-H], 3.77 (6 H, s, OMe), 3.76 (6 H, s, OMe) and 2.21 (3 H, s, OAc).

2-(3,5-*Dimethoxyphenyl*)-5,7-*dimethoxybenzofuran* **26**.—A solution of the acetate **25** (0.10 g) in toluene (30 cm^3) was irradiated under nitrogen in a Pyrex flask with a 150 W xenon arc lamp, until TLC showed complete consumption of the starting material (2 h) and one major product, together with traces of polar impurities. The solvent was evaporated off and the residue was purified by flash chromatography [EtOAc–light petroleum (15:85)] to give the *benzofuran* **26** as crystals (76 mg, 90%). Recrystallisation from MeOH gave plates, m.p. 110–111 °C (Found: C, 68.9; H, 5.7. $C_{18}H_{18}O_5$ requires C, 68.8; H, 5.8%); λ_{max}(EtOH)/nm 286sh, 300 and 319sh (ε/dm^3 mol^{-1} cm^{-1} 23 500, 28 200 and 18 500); $\delta_H(CDCl_3)$ 7.00 (2 H, d, J_m 2.6, Ar 2- and 6-H), 6.91 (1 H, s, 3-H), 6.60 and 6.44 (2 H, 2 d, $J_{4,6}$ 2.2, 4- and 6-H), 6.45 (1 H, t, Ar 4-H), 4.00 (3 H, s, 7-OMe), 3.85 (6 H, s, OMe) and 3.83 (3 H, s, 5-OMe).

1-(3,5-*Dimethoxyphenyl*)-2-*oxo*-2-*phenylethyl Dihydrogen Phosphate* **23b**.—1*H*-Tetrazole (314 mg, 4.5 mmol) was added to a solution of the dioxolane **20b** (632 mg, 2 mmol) and bis-(2-cyanoethyl) diisopropylphosphoramidite (800 mg, 3 mmol) in dry THF (15 cm^3) and the solution was stirred under nitrogen at room temp. for 1.5 h, then cooled in an ice-bath. A solution of MCPBA (61% peracid; 940 mg, 3.3 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise and the solution was stirred at 4 °C for 1 h, then diluted with diethyl ether and washed successively with 10% aq. $Na_2S_2O_5$, 1 mol dm^{-3} aq. HCl, saturated aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography [EtOAc–light petroleum (3:1)] to give the bis-(2-cyanoethyl) phosphate **21b** as a pale gum (1.0 g, 94%), which solidified on storage. Although not essential, the flash chromatograph purification of this and other bis-(2-cyanoethyl) phosphates was advantageous. Its omission sometimes led to incomplete reaction in the next step, apparently because of the presence of impurities which consumed part of the available alkali.

The pure triester was dissolved in a solution of 0.1 mol dm^{-3} NaOH in dry MeOH (45 cm^3) and the mixture was kept at 50 °C for 0.5 h, then evaporated, and the residue was partitioned between diethyl ether and water (each 80 cm^3). The aqueous layer, which contained the phosphate **22b**, was adjusted to pH 7 with 1 mol dm^{-3} hydrochloric acid, then treated with conc. hydrochloric acid (0.80 cm^3) and heated under reflux for 1 h. The solution was cooled and neutralised with 1 mol dm^{-3} aq. NaOH. Quantitative UV analysis at 250 nm indicated a recovery of the 3′,5′-dimethoxybenzoin chromophore of 1.61 mmol (85% from the triester). The solution was diluted to ~1800 cm^3 (conductivity <800 μmho) and purified in two batches by ion-exchange chromatography, using a linear gradient of 10–250 mmol dm^{-3} TEAB (each 1000 cm^3). The major fraction began to elute at ~125 mmol dm^{-3} TEAB and was freed from buffer salts as described to give the *product* **23b** as its triethylammonium salt (1.37 mmol, 68% overall from the dioxolane **20b**) (Found: M^-, 351. $C_{16}H_{15}O_7P$ + H requires *M*, 351); $\delta_H(D_2O)$ 7.93–8.05 [2 H, m, Ar(2) 2- and 6-H], 7.36–7.60 [3 H, m, Ar(2)-H], 6.71 [2 H, d, J_m 2.1, Ar(1) 2- and 6-H], 6.50 (1 H, d, $J_{H,P}$ 8.8, ArC*H*), 6.36 [1 H, t, Ar(1) 4-H] and 3.70 (6 H, s, OMe).

2-(3,5-*Dimethoxyphenyl*)-2-*oxo*-1-*phenylethyl Dihydrogen Phosphate* **23c** *and* 1,2-*Bis*-(3,5-*dimethoxyphenyl*)-2-*oxoethyl Dihydrogen Phosphate* **23d**.—These compounds were prepared from the respective dioxolanes exactly as described above for the phosphate **23b**. For *phosphate* **23c** (Found: M^-, 351. $C_{16}H_{15}O_7P$ + H requires *M*, 351); $\delta_H(D_2O)$ 7.25–7.58 [5 H, m, Ar(1)-H], 7.08 [2 H, d, J_m 2.2, Ar(2) 2- and 6-H], 6.58 (1 H, d, $J_{H,P}$ 9.4, ArC*H*), 6.51 [1 H, t, Ar(2) 4-H] and 3.66 (6 H, s, OMe). For *phosphate* **23d** (Found: M^-, 411. $C_{18}H_{19}O_9P$ + H requires *M*, 411); $\delta_H(D_2O)$ 7.12 [2 H, d, J_m 1.8, Ar(2) 2- and 6-H], 6.70 [2 H, d, J_m 1.8, Ar(1) 2- and 6-H], 6.47 (1 H, d, $J_{H,P}$ 9.2, ArC*H*), 6.28 [1 H, t, Ar(2) 4-H], 6.18 [1 H, t, Ar(1) 4-H] and 3.60 (12 H, br s, OMe).

Extent of Photolysis of Phosphates **23b** *and* **23d**.—Aliquots (30 mm^3) of a solution of 'caged' ATP **1** and phosphate **23b** (each 0.44 mmol dm^{-3}) in 25 mmol dm^{-3} 3-(1-morpholino)-propane-1-sulfonic acid (pH 7) containing 2 mmol dm^{-3} 1,4-dithiothreitol were irradiated in a 1 mm path-length cell with a single 50 ns pulse of 347 nm light from the frequency-doubled ruby laser, which delivered 80–110 mJ of 347 nm irradiation. Each sample was analysed by HPLC [mobile phase 0.125 mol dm^{-3} aq. ammonium phosphate (pH 5.9) plus 15% MeOH (v/v)]. The phosphate **23b** and 'caged' ATP **1** had retention times of 3.2 and 6.2 min, respectively, and the extent of conversion for the two compounds (mean of 3 determinations) was 10.0 and 30.2% respectively. The extent of conversion per photon absorbed was thus 1.24-fold greater for compound **23b**. In a separate series of experiments a more concentrated solution (8.66 mmol dm^{-3}) of the phosphate **23b** in the same solvent showed 11.5% photolysis. The tetramethoxybenzoin phosphate **23d** (8.92 mmol dm^{-3}) gave 3.7% conversion when photolysed under the same conditions.

Photolysis Kinetics of Phosphates **23b** *and* **23d**.—The kinetics were analysed in an absorption spectrophotometer in which light from a xenon arc lamp was passed horizontally through a monochromator set to 317 nm and the sample in a 4 mm path-length cuvette, then through a 317 nm interference filter and a second monochromator. The photolysis was initiated by a 50 ns 347 nm laser pulse (see above) that illuminated the optical cell orthogonally to the detection light beam. Other details of the spectrophotometer were as previously described.[23]

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