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Synthesis and Properties of Carbamoyl Derivatives of Photolabile Benzoins[§]

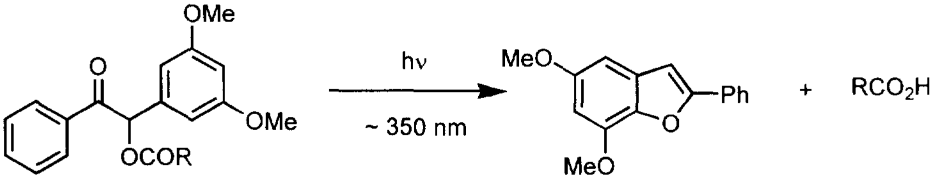
George Papageorgiou and John E.T. Corrie*

National Institute for Medical Research, The Ridgeway, Mill Hill, London NW7 1AA, U.K.

Abstract: Carbamoyl derivatives of photolabile benzoins, particularly of 3',5'-dimethoxybenzoin, are readily prepared via the mixed *p*-nitrophenyl carbonate of the benzoin. The method is most suitable for secondary amines, since many primary amines exist in varying proportions as the cyclic hydroxyoxazolidinone tautomer. In alkaline solution (0.2 M NaOH) the carbamates of unsymmetrical benzoins are readily equilibrated. Flash photolysis of 3',5'-dimethoxybenzoin carbamates generates the carbamate anion in a fast heterolytic process and liberation of the amine is controlled by the rate of decarboxylation. © 1997 Elsevier Science Ltd. All rights reserved.

INTRODUCTION

In recent years there has been considerable interest in photolabile derivatives of benzoins, and in particular of 3',5'-dimethoxybenzoin. In 1971 Sheehan *et al.*[1] showed that esters of the latter compound undergo efficient and very clean photolysis (Scheme 1) under near-UV illumination. The reawakening of interest in these compounds was initiated by a brief study of phosphate esters by Baldwin and co-workers[2] and has continued in work by our group on phosphate[3] and triphosphate[4] esters, by Pirrung and co-workers on phosphate[5a] and carbonate esters[5b] and in recent communications by Cameron *et al.*[6] and by Pirrung and Huang[7] on carbamate esters. Related studies by Givens[8] and by Pratt[9] used derivatives of the parent benzoin (i.e. lacking methoxy substituents), although the photochemistry of these compounds produces a more complex product mixture.



Scheme 1

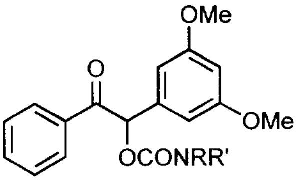
[§] Dedicated to the memory of Professor A. J. Birch, F. R. S.

Our interest in benzoin carbamates was prompted by our continuing involvement in development and application of photolabile precursors of biologically active compounds[10] and at the outset was principally directed towards derivatives of neuroexcitatory amino acids. Cameron *et al.*[6] prepared the derivatives **1** and **2** of piperidine and cyclohexylamine respectively while Pirrung and Huang[7] described derivatives of several secondary amines, including proline *t*-butyl ester. For reasons detailed below, it now appears that derivatives of this type are unlikely to be useful as photocleavable amino acid precursors in biological systems. However the results are of interest in a more general sense and specific areas addressed include the propensity for involvement of the benzoin carbonyl group, both in synthetic intermediates and in the carbamate products, the unexpectedly facile positional isomerisation of benzoin carbamates, and the determination of the decarboxylation rate of a typical carbamate anion. The latter experiment was facilitated by the rapid generation of the carbamate anion upon photolysis of its 3',5'-dimethoxybenzoin ester.

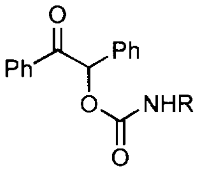
Parts of this work were carried out prior to the communications published by the Cameron[6] and Pirrung[7] groups. Our results complement theirs and are presented in a broadly chronological sequence, with appropriate cross-references to highlight areas of interest.

RESULTS AND DISCUSSION

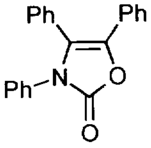
The complexities of the benzoin carbamate system became apparent during our initial experiments, which sought to reproduce an early report[11] on preparation of the aniline derivative **3a** by heating a mixture of benzoin and phenyl isocyanate. In several trials and despite rigorous exclusion of water the product, obtained in poor yield, was consistently contaminated with variable amounts of *N*,*N'*-diphenylurea, as had been reported previously.[11] The result implied some hydrolysis of phenyl isocyanate to aniline and the source of the water was traced to the co-formation of a third product, 3,4,5-triphenyl-4-oxazolin-2-one **4**, *via* cyclisation of the carbamate **3a** and dehydration of the resulting 4-hydroxyoxazolidinone. In an attempt to avoid this complication, benzoin ethylene ketal was cleanly converted to its carbamate **5** but the oxazolinone **4** was the only detectable product upon acid-catalysed cleavage of the ketal. Milder hydrolysis conditions using bis(acetonitrile)palladium(II) chloride[12] (3 days, aq. acetone, room temp.) did not cleave the ketal. In retrospect, these results could have been predicted from previous results of other workers[13,14] but they served at an early stage to alert us to the facile ring-chain isomerism inherent in these α-keto carbamates. The factors which control the preferred position of this isomerism are evidently subtle. Saettone[13] prepared phenacyl carbanilate by heating phenacyl alcohol and phenyl isocyanate similarly to our benzoin experiment described above and obtained only the open-chain form, which was cyclised and dehydrated on treatment with hot acetic acid. Similarly Church *et al.*[15] prepared several phenacyloxycarbonyl derivatives of primary amines, principally amino acids, and reported no complications of cyclisation, while the cyclohexylamine derivative **1** was evidently also in the open-chain form.[6] However Pirrung and Huang[7] noted that the *N*-*n*-butyl carbamate of 3',5'-dimethoxybenzoin existed entirely as the cyclic form, and Sheehan and Guziec[14] found only the cyclic tautomer for a number of primary amine carbamates of benzoin itself. We comment below on the effects of structure on the preferred position of the isomerism.



1 R, R' = $(CH_2)_5$
2 R = H, R' = cyclohexyl



3a R = Ph
3b R = $CHEt_2$



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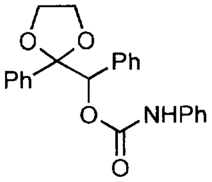

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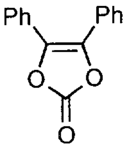

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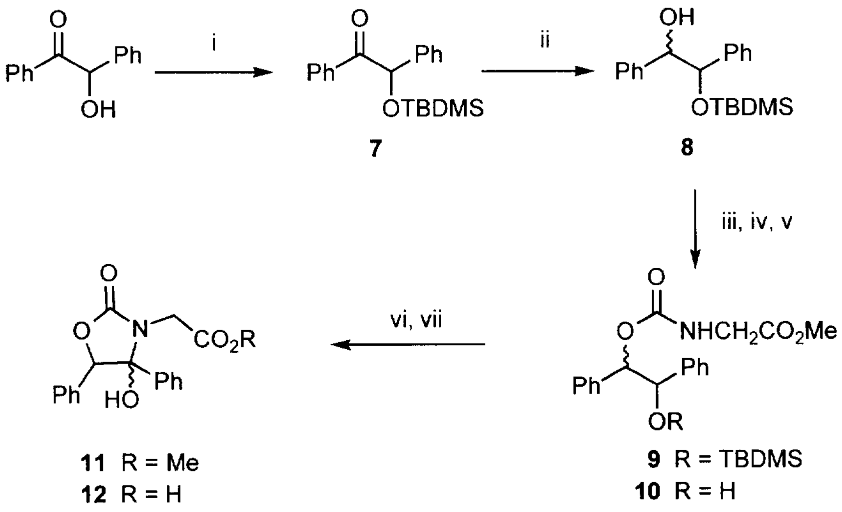
With these preliminary experiments and their implications in mind, we turned to approaches which appeared more likely to achieve our principal goals. Treatment of benzoin with *N,N'*-carbonyldiimidazole (CDI) and 4-dimethylaminopyridine (DMAP) in THF under reflux gave a high yield of the cyclic carbonate **6**, which upon treatment with 3-aminopentane was slowly converted to the carbamate **3b**. Formation of the cyclic carbonate **6** implies that the substitution pattern of an unsymmetrically-substituted benzoin would become scrambled and we return to this matter below. In order to avoid the possibility of scrambling, we explored a route which involved a monoprotected hydrobenzoin (Scheme 2).

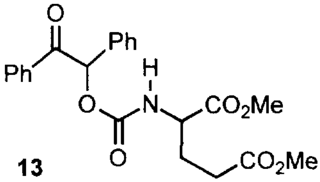


Scheme 2

Reagents: (i) TBDMS-imidazole; (ii) $NaBH_4$-MeOH; (iii) CDI-DMAP; (iv) methyl glycinate.HCl-NMM; (v) TBAF-THF; (vi) $(COCl)_2$-DMSO; (vii) NaOH-aq. MeOH

For simplicity the route was investigated with unsubstituted benzoin, which as its TBDMS ether **7** was reduced with $NaBH_4$ to the monoprotected hydrobenzoin **8**, obtained as a mixture of diastereoisomers. Activation of the free hydroxyl group with CDI–DMAP followed by treatment with glycine methyl ester gave a diastereomeric mixture of carbamates **9**. Removal of the TBDMS group and Swern oxidation[16] of the alcohol **10** cleanly gave the hydroxyoxazolidinone **11**, i.e. a product in which the preferred position of the ring-chain tautomerism was entirely as the cyclic form. Alkaline hydrolysis of the ester gave the salt of the free acid **12**, which was examined by UV spectroscopy at pH values between 6 and 8. There was no indication of the presence of the open-chain tautomer. This result was consistent with the findings of Sheehan and Guziec,[14] and since formation of the cyclic tautomer eliminates the long-wavelength chromophore which is necessary for the photocleavage reaction shown in Scheme 1, we abandoned work on these compounds until our interest was revived by the recent communications from other groups.[6,7]

We first re-considered the ring-chain isomerism, in the hope that an α-amino acid other than glycine might show a greater proportion of the open-chain form. Based on the report by Cameron *et al.*,[6] benzoin was converted to its mixed *p*-nitrophenyl carbonate[†] and subsequently treated with dimethyl glutamate. The crude reaction product showed multiple components by TLC, and although ^1H NMR spectroscopy of isolated fractions indicated that there was a proportion of the open-chain carbamate **13** present (2 singlets at δ 6.83 and 6.85 corresponding to the benzoin methine proton in two diastereoisomers), other singlets in the range δ 5.3-5.75 were consistent with the presence of the cyclic tautomer **14**, again in diastereoisomeric forms. Reference data from pure compounds described elsewhere in this paper were used to support these assignments. The ratio of the two forms was ~1:1 but could not be determined more accurately because of the multiple diastereomeric and rotameric forms of the two components.



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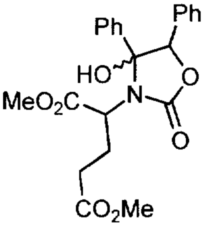

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We did not pursue this investigation by hydrolysis of the ester groups, but were nevertheless left with a strong indication that all benzoin carbamates derived from primary α-amino acids would be vulnerable to tautomerisation into the photochemically inert cyclic form and we therefore directed further investigations to carbamates derived from secondary amines. However it is of interest to summarise the empirical observations of our work and that of other groups on the ring-chain equilibrium of benzoin carbamates derived from primary amines. Evidently steric crowding in the *N*-substituent favours the open form as seen for compounds

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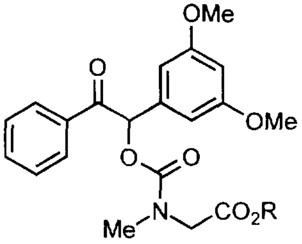
[†] Although not acknowledged by Cameron *et al.*[6] we note that *p*-nitrophenyl carbonates have been used for many years as intermediates for carbamate synthesis (e.g. ref. 17).

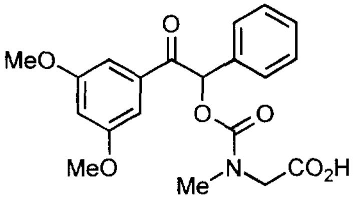
2[6] and **3b**. Conversely for a small substituent, as in the glycine derivative **11** and the *n*-butyl compound described by Pirrung and Huang,[7] the equilibrium is entirely towards the cyclic form. For intermediate-sized substituents as in the glutamate derivative described above and aniline derivative **3a**, the equilibrium is more finely balanced, and may be solvent-dependent. As reported above, we obtained a mixture of tautomers from a reaction sequence performed in THF but Sheehan and Guziec,[14] who made similar derivatives in DMF solution, appear to have obtained only the cyclic form.

As a suitable secondary amine related to compounds of potential biological interest such as *N*-methyl-D-aspartic acid, we chose initially to work with sarcosine, and using the chemistry described by Cameron *et al.*[6] readily obtained the carbamate **15a** in excellent yield. In common with all other carbamate derivatives described here where the nitrogen bears two different substituents, the ^{1}H NMR spectrum was complicated by the presence of two rotamers which did not interconvert on the NMR time scale. This property is evident in the spectra reported in the Experimental section. Upon mild alkaline hydrolysis of the ethyl ester **15a**, we were surprised to observe two components in the reaction products. When these compounds were separated by reverse phase HPLC, their UV spectra indicated that they contained the chromophores[3a] of the isomeric 3,5- and 3',5'-dimethoxybenzoins and ^{1}H NMR spectroscopy confirmed them to be the isomeric carbamates **16** and **17**. To probe the generality of this unexpected isomerisation, we prepared the piperidine carbamate **1** previously described by Cameron *et al.*,[6] and its isomer **18** by an identical reaction sequence starting with 3,5-dimethoxybenzoin. For each compound, the spectral data gave definitive confirmation of the expected structure and homogeneity, although in the crude reaction mixtures it was difficult to be certain of absolute structural homogeneity because of the presence of a small amount of the benzil **19**. ^{1}H NMR signals from the substituted aromatic ring of the latter compound (an authentic sample of which was prepared by MnO_2 oxidation of 3,5-dimethoxybenzoin) appeared very close to the position of the corresponding protons of **18**. The adventitious formation of traces of benzils under these conditions has been noted previously (J.F. Cameron, personal communication) and was also encountered by us during synthesis of 3,3',5,5'-tetramethoxybenzoin.[3a] When compound **1** was treated with 0.2 M NaOH in 10% aqueous methanol for 3 h at room temperature, i.e. the same conditions used for hydrolysis of the ester group of compound **15a**, it was cleanly equilibrated to a 1:1 mixture of the isomeric carbamates **1** and **18**. In this case the two compounds were not separable but could be identified by characteristic signals in the ^{1}H NMR spectrum (see Experimental section).

To enable more ready access to the desired sarcosine derivative **16** as a single entity, we used *t*-butyl sarcosinate to prepare the *t*-butyl ester **15b**. When this compound was deprotected by TFA treatment, it gave the free acid **16** with no trace of its isomer **17**. With isomer **16** readily available, we examined its equilibration with **17** under different conditions. In 0.2 M NaOH it was completely equilibrated within 30 min (room temp.), while at pH 11 the formation of **17** was just detectable after 24 h. At pH 8 the structural integrity of **16** was fully preserved.



15a R = Et
15b R = ^{t}Bu
16 R = H



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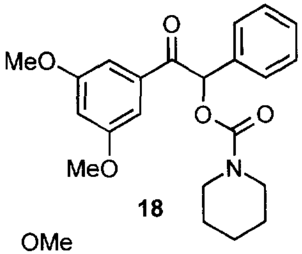

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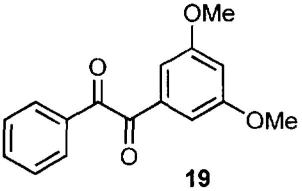

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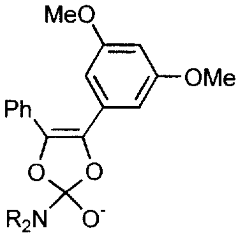
The easy isomerisation of benzoin carbamates is of interest both for practical reasons and in mechanistic terms. At the practical level it is important since the isomerised compounds are likely to have altered photochemical properties. Although quantum yields for photolysis of 3,5-dimethoxybenzoin derivatives have not been investigated, we have previously shown that 3,3',5,5'-tetramethoxybenzoin phosphate photolysed approx. 4-fold less efficiently than the corresponding 3',5'-dimethoxybenzoin phosphate and gave transient spectroscopic signals following flash photolysis which suggested the presence of long-lived ($t_{1/2}$ ~2 ms) intermediates which were not seen for the 3',5'-dimethoxy compound.[3a] Thus both the efficiency and rate of product formation are likely to be different for 3,5-dimethoxy compounds such as **17** and **18** than the corresponding parameters for their 3',5'-dimethoxy isomers.

From the mechanistic viewpoint, carbamoyl groups are known readily to undergo equilibration under basic conditions between suitably disposed hydroxyl groups for a variety of carbohydrate examples.[18] The rate has been measured for equilibration between the 2'- and 3'-OH groups of a ribonucleotide ($t_{1/2}$ 44 and 0.3 h at pH 7.1 and 9.4 respectively, room temp.).[19] The obvious mechanism for interconversion of the benzoin carbamates discussed above involves the enediol intermediate **20**, in which the relationship of the two aromatic rings to the rest of the molecule has become scrambled. It has long been recognised that unsymmetrical benzoins are susceptible to equilibration, either as the free alcohols under mildly basic conditions[20] or during esterification.[20,21] However, while **20** seems a reasonable intermediate and is consistent with the formation of the cyclic carbonate **6** already described, it contrasts with results for hydrolysis of benzoin[3a] and acetoin dialkyl phosphates.[22] In these compounds reaction via enediol derivatives was specifically excluded and the reaction pathway was shown to involve initial addition of base to the carbonyl group, in agreement with the proposed mechanism for accelerated hydrolysis of esters of α-keto-alcohols.[23] It is noteworthy that for the carbamate derivatives there was no evidence of hydrolysis under the alkaline conditions used to achieve full equilibration, i.e. ≤1 h at room temp., although oxidative degradation was evident after long (~24 h) incubation in the presence of oxygen. It remains an intriguing question why the ionised hydroxyl produced by base addition to the benzoin carbonyl group should be apparently unable to attack the carbamate carbonyl and lead to hydrolysis, while the same oxygen, as its enolate anion, is evidently capable of efficiently performing the same attack to generate the intermediate **20**.



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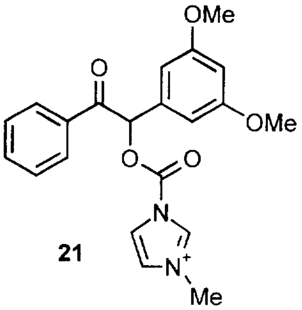

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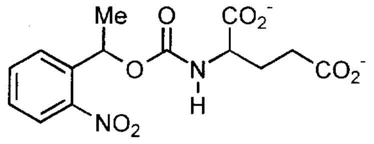

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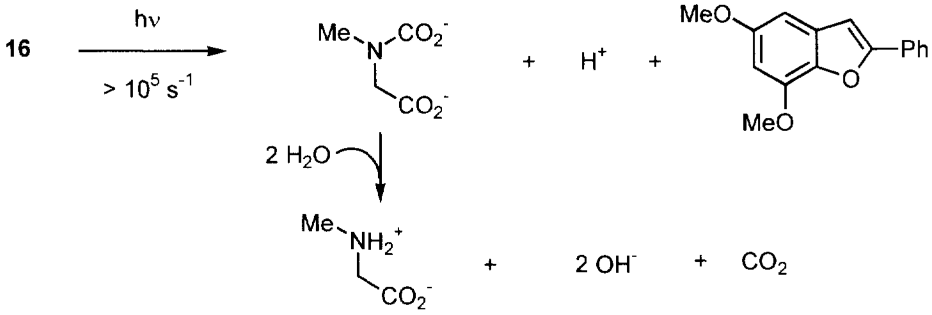
In the context of the potential for structural isomerism highlighted above, it is relevant briefly to review the structural fidelity of the activated intermediates used to synthesise the carbamates. We have described above that the CDI–DMAP combination leads exclusively to the cyclic carbonate **6**, and preliminary experiments using diphosgene gave similar results (data not shown). Church *et al.*,[15] reported a similar result upon treatment of phenacyl alcohol with phosgene. Pirrung and Bradley[5b] described the use of mono-*N*-methyl-CDI triflate in nitromethane to activate 3',5'-dimethoxybenzoin and reported that the intermediate **21** was stable even at reflux temperature. Treatment of **21** with amines was reported to give single carbamate products.[7] *p*-Nitrophenyl chloroformate–DMAP under our conditions (THF, room temp.) evidently gives a stable mixed carbonate and a single carbamate product.[7] Since the chloroformate is commercially available and relatively stable, it appears to be the reagent of choice for this transformation.

In the final part of this study, we examined the decarboxylation rate of the carbamate ion which is the initial product formed after photolytic cleavage of the protecting group. Knowledge of this parameter is essential to evaluate the potential use of these derivatives to study fast biological processes since it equates to the rate of liberation of the amine, i.e. the bioeffector species. Previous studies[24,25] of carbamate decarboxylation were mostly conducted over a limited range of high pH values in order to slow the reaction rate to a readily measurable range. In the present case, the carbamate anion can be photogenerated at any pH on a sub-microsecond time scale and the changes in pH as protons are taken up by the liberated amine can be followed by time-resolved absorption spectrophotometry in solutions containing appropriate indicators. This technique was previously used in a study of the photoliberation of glutamate from the 1-(2-nitrophenyl)ethyl derivative **22**. In that case photocleavage of the nitrophenylethyl group rather than the subsequent decarboxylation was rate-limiting.[26] Scheme 3 shows, at pH values above the pK for protonation of the carbamate anion, that the initial photocleavage is accompanied by rapid generation of one proton, followed by uptake of two protons as the carbamate anion loses CO_2. Laser flash photolysis of carbamate **16** was performed at 21 °C in solutions ranging from pH 4 - 8 and full details of these results will be described elsewhere. Figure 1 shows the data obtained at pH 7.0 and illustrates the "instantaneous" acidification followed by basification in a first order exponential process ($t_{1/2}$ ~4.5 ms), the rate of which corresponds to the rate of liberation of the amine from its carbamate anion. Note that hydration of the liberated CO_2 takes place much more slowly[27] and is not visible on this time scale. These results are consistent with heterolytic cleavage upon photolysis and contrast with the homolytic cleavage of carbamates derived from fluorenone oxime studied by Scaiano and co-workers[28] where decarboxylation of the initially formed carbamoyloxy radical takes place extremely rapidly. As such they cast doubt on mechanistic proposals by Cameron *et al.*[6] for benzoin carbamates and by Givens *et al.*[8a] for benzoin phosphates, which suggest an initial bond homolysis, followed by single electron transfer. Experiments which probe the photolysis of 3',5'-dimethoxybenzoin derivatives in more detail will be reported elsewhere.[29]



Scheme 3

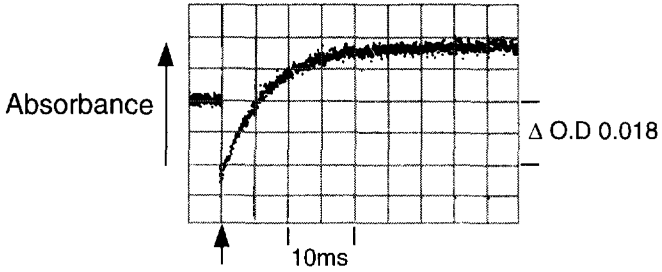


Figure 1 Time resolved absorption change at 615 nm following laser flash photolysis of carbamate **16** at pH 7.0, 21 °C in a solution containing Bromothymol Blue indicator. The arrow on the time axis marks the laser flash.

The amine release rate, which is limited by the rate of decarboxylation reported here, is probably too slow to enable these photolabile carbamates to be used as effective reagents for rapid release of neuroactive amino acids, where a half-time ≤ 1 ms would generally be required. Furthermore it indicates that other photolabile carbamates, which might be applied to primary amino acids without the complications of tautomerism involving the benzoin carbonyl group seen in the present series, would also release the amine too slowly upon photolysis. New approaches will need to be developed to enable the full potential of the flash photolysis technique to be realised in the study of synaptic transmission. Nevertheless, the reagents described here may have other applications in biology, for example to study responses to rapid alkalinisation, and we intend to pursue studies in this area.

ACKNOWLEDGEMENTS

We are grateful to Dr D. R. Trentham for the flash photolysis data and to Dr K. J. Welham for the high resolution mass spectra. We thank the MRC Biomedical NMR Centre for access to facilities. This work was supported by the Medical Research Council under the Neurosciences Approach to Human Health Initiative.

EXPERIMENTAL

Microanalyses were carried out by MEDAC Ltd., Brunel University, Uxbridge. NMR spectra were determined on JEOL FX90Q or Bruker AM400 instruments, for solutions in $CDCl_3$ and referenced to tetramethylsilane unless otherwise specified. *J* Values are given in Hz. For those cabamates where rotamers are present, all NMR signals are reported but the presence of the additional signals due to the rotamers is noted only once for each compound in the assignment data. High resolution FAB mass spectra were run on a VG ZAB-SE instrument. Merck 9385 silica gel was used for flash chromatography. Light petroleum was the fraction boiling at 40-60 °C. Organic extracts were dried over Na_2SO_4 and solvents were evaporated under reduced pressure. HPLC was performed using equipment from Millipore-Waters, with UV detection at 254 nm. Buffer solutions were prepared from $NaH_2PO_4.2H_2O$ at the specified molarities in water and adjusted to the required pH value with 2 M NaOH.

2-Phenyl-2-[α-(N-phenylcarbonyloxy)benzyl]-1,3-dioxolane **5**

A mixture of benzoin ethylene ketal[30] (1.00 g, 3.9 mmol) and phenyl isocyanate (1.3 ml, 12 mmol) was heated at 100 °C under nitrogen for 30 min. After cooling to room temp. the solid was washed with cold light petroleum and dissolved in EtOAc. The solution was filtered and evaporated, and the residue was recrystallised from cyclohexane to give the *title compound* as white needles (1.33 g, 92%), m.p. 128-129 °C

(Found: C, 73.72; H, 5.63; N, 3.74. $C_{23}H_{21}NO_4$ requires C, 73.58; H, 5.64; N, 3.73%); ν_{max}/cm^{-1} (Nujol) 3400, 1720, 1605, 1600, 1530, 1445, 1220, 1090, 1070, 1025 and 700; δ_H (90 MHz) 6.92-7.44 (15 H, m, Ph), 6.71 (1 H, s, NH), 6.06 (1 H, s, PhC*H*), and 3.84 (4 H, s, OCH_2CH_2O).

A sample of the carbamate **5** (188 mg, 0.5 mmol) was dissolved in acetone (12.5 ml) and treated with 2 M aq. HCl (12.5 ml). The solution was heated under reflux for 16 h and the solvent was evaporated. The residue was washed with ether (3 × 10 ml) and the combined organic phases were washed with water, dried and evaporated. The residue was recrystallised from ethanol to give 3,4,5-triphenyl-4-oxazolin-2-one **4** (134 mg, 85%), m.p. 217-219 °C (lit.[31] 215-217 °C).

4,5-Diphenyl-1,3-dioxol-2-one **6**

A solution of benzoin (1.06 g, 5 mmol) in dry THF (20 ml) was treated with DMAP (0.61 g, 5 mmol) and CDI (3.25 g, 20 mmol). The solution was heated under reflux for 3 h, then cooled, diluted with ether and washed with water. The organic phase was washed with 2 M HCl and saturated $NaHCO_3$, dried and evaporated to leave a viscous oil which crystallised on standing. Recrystallisation from ethanol gave the carbonate **6** as white prisms (0.95 g, 80%), m.p. 75-76 °C, (lit.[14] 75-76 °C).

1,2-Diphenyl-2-oxoethyl N-3-Pentylcarbamate **3b**

A solution of the cyclic carbonate **6** (23.8 mg, 1 mmol) in dry THF (10 ml) was treated with DMAP (183 mg, 1.5 mmol) and 3-aminopentane (179 μl, 1.5 mmol). The solution was stirred under nitrogen at room temp. for 16 h, diluted with ether, washed with 1 M HCl and water, dried and evaporated to a viscous oil (256 mg). Flash chromatography [EtOAc–light petroleum (1:9)] gave recovered cyclic carbonate (124 mg, 52%) followed by the *carbamate* **3b** (117 mg, 36%) as white crystals, m.p. 81-82 °C (from ether–light petroleum). (Found: C, 73.68; H, 7.17; N, 4.30. $C_{20}H_{23}NO_3$ requires C, 73.82; H, 7.12, N, 4.30%); λ_{max}/nm (MeOH) 247 (ε/M^{-1}cm^{-1} 12 500); ν_{max}/cm^{-1} (Nujol) 3320, 1690, 1600, 1290, 1225, 995, 960 and 695; δ_H (400 MHz) 7.80-8.00 [2 H, m, Ph(2) 2- and 6-H], 7.12-7.56 (8 H, m, Ar-H), 6.85 (1 H, s, ArC*H*), 4.91 and 5.01 (1 H, 2 × br s, NH, rotamers), 3.20-3.66 (1 H, m, NCH), 1.32-1.57 (4 H, m, NCHCH_2), and 0.88 and 0.93 (6 H, 2 × t, *J* 7.4, CH_2CH_3).

Benzoin TBDMS Ether **7**

A solution of benzoin (2.17 g, 10 mmol) in dry DMF (25 ml) was treated with imidazole (1.70 g, 25 mmol), followed by a solution of *t*-butyldimethylsilyl chloride (2.26 g, 15 mmol) in DMF (15 ml). The solution was stirred at room temp. for 22 h, diluted with ether (50 ml) and washed with water (50 ml). The organic phase was washed with 0.5 M HCl and water, dried and evaporated to a viscous oil (3.55 g). Flash chromatography [EtOAc–light petroleum (1:9)] gave the *title compound* as a colourless oil (3.04 g, 93%); ν_{max}/cm^{-1} (film) 3170, 2850, 2830, 1680, 1600, 1450, 1225, 1120, 1070, 865, 835, 780 and 695; δ_H (90 MHz)

7.88-8.04 [2 H, m, Ph(2) 2- and 6-H], 7.14-7.58 (8 H, m, Ar-H), 5.60 (1 H, s, ArC*H*), 0.88 (9 H, s, CMe_3), and 0.08 (6 H, s, $SiMe_2$); (m/z) 327 ($M^{\cdot}$, 8%), 311(16), 269(52), 221(100), 195(36), 167(30), M^+ measured 327.1770. $C_{20}H_{26}O_2Si$ + H requires 327.1780.

Hydrobenzoin Mono-TBDMS Ether **8**

A solution of the TBDMS ether **7** (2.96 g, 9.1 mmol) in methanol (50 ml) was cooled in an ice bath and treated under nitrogen with sodium borohydride pellets (1.89 g, 50 mmol). The solution was allowed to warm to room temp. and stirred for 4 h, then evaporated and the residue was dissolved in water (50 ml) and extracted with ether (3 × 50ml). The combined organic phases were washed with brine, dried and evaporated to give the *title compound*, a colourless viscous oil (2.73 g, 92%) as a ~1:2 mixture of diastereoisomers, which was used in the next step without purification; ν_{max}/cm^{-1} (film) 2985, 2855, 1500, 1255, 1070, 885, 835, 780, and 700; δ_H (90 MHz) 6.76-7.12 (10 H, m, Ar-H), 4.44 and 4.34 (2 H, 2 × s, ArC*H*), 0.88 and 0.76 (9 H, 2 × s, CMe_3) and -0.26 and -0.30 (6 H, 2 × s, $SiMe_2$); (m/z) 329 ($M^{\cdot}$, 3%), 311(64), 271(24), 221(100), 197(41), M^+ measured 329.1930. $C_{20}H_{28}O_2Si$ + H requires 329.1937.

2-(t-Butyldimethylsilyloxy)-1,2-diphenylethyl N-(Methoxycarbonyl)methylcarbamate **9**

A solution of the hydrobenzoin **8** (852 mg, 2.6 mmol) in dry acetonitrile (30 ml) was treated with DMAP (367 mg, 3 mmol) and CDI (1.69 g, 10.4 mmol). The solution was stirred under nitrogen at room temp. for 3 h, then treated with glycine methyl ester hydrochloride (1.88 g, 15 mmol) and *N*-methylmorpholine (NMM) (2.2 ml, 20 mmol). The solution was then heated under reflux for a further 20 h, cooled and evaporated. The residue was dissolved in ether, washed with 1 M HCl, saturated $NaHCO_3$ and brine, dried and evaporated to give a viscous oil (1.27 g). Flash chromatography [EtOAc–light petroleum (1:4)] gave a diastereomeric mixture of the *title compound* as a colourless viscous oil (1.08 g, 94%); ν_{max}/cm^{-1} (film) 3260, 2940, 2860, 1720, 1510, 1250, 1205, 900, 840, 780, 700; δ_H (90 MHz) 6.88-7.28 (10 H, m, Ar-H), 5.58-5.84 (1 H, m, PhC*H*OCO), 5.12-5.44 (1 H, m, NH), 4.76-5.00 (1 H, m, PhC*H*OSi), 3.78-4.18 (2 H, m NHC*H*$_2$), 3.72 and 3.68 (3 H, 2 × s, CO_2Me), 0.84 and 0.78 (9 H, 2 × s, CMe_3) and -0.18 and -0.25 (6 H, 2 × s, $SiMe_2$); (m/z) 466 (M^+, 12.5%), 311(100), 253(8.5), 221(73), 190(24), M^- measured 466.2020. $C_{24}H_{33}O_5NSi$ + H requires 466.2026.

1,2-Diphenyl-2-hydroxyethyl N-(Methoxycarbonyl)methylcarbamate **10**

A solution of the silyl ether **9** (0.96 g, 2.17 mmol) in dry THF (20 ml) was treated with 1 M tetrabutylammonium fluoride in THF (3 ml) and stirred at room temp. for 1.5 h, then evaporated and the residue dissolved in water (50 ml) and washed with ether (3 × 50 ml). The combined organic phases were washed with 10% $NaHCO_3$, dried and evaporated to give the *title compound* as a viscous oil (0.66 g, 93%) which was used in the next step without further purification; ν_{max}/cm^{-1} ($CHCl_3$) 3420, 1725, 1505, 1445, 1370, and 695; δ_H (90 MHz) 6.96-7.36 (10 H, m, Ar-H), 5.89 and 5.77 (1 H, 2 × d, *J* 5.4 and 7.6 respectively, PhC*H*OCO), 5.24-5.56 (1 H, m, NH), 5.06 and 4.89 (1 H, 2 × d, *J* 5.4 and 7.6 respectively, PhC*H*OH), 3.84-3.98 (2 H, m, NCH_2), 3.72 and 3.71 (3 H, 2 × s, CO_2Me); (m/z) 330(M^+, 7%), 221(17.5), 197(60), 186(52), 134(100), M^+ measured 330.1350; $C_{18}H_{19}NO_5$ requires 330.1341.

4,5-Diphenyl-4-hydroxy-3-(methoxycarbonylmethyl)oxazolidin-2-one **11**

A solution of oxalyl chloride (0.49 ml, 5.1 mmol) in dry dichloromethane (5 ml) was cooled to -78 °C in a flask protected by a drying tube and treated dropwise with a solution of DMSO (0.73 ml, 10.3 mmol) in dichloromethane (5 ml). The mixture was stirred at -78 °C for 10 min and a solution of the alcohol **10** (1.54 g, 4.7 mmol) in dichloromethane (25 ml) was added dropwise over 5 min. The mixture was stirred at -78 °C for 30 min, then treated with triethylamine (3.5 ml, 25 mmol). After 10 min. the cold bath was removed and the reaction mixture was allowed to warm to room temp. over 3 h. Water (30 ml) was added and the aqueous phase was extracted with dichloromethane (3 × 30 ml). The combined organic phases were washed with dilute HCl, water, saturated $NaHCO_3$ and brine, dried and evaporated. The residue was triturated with ether to give a white solid which was recrystallised from EtOAc to give the *title compound* as white crystals (1.16 g, 75%), m.p. 140-141 °C. (Found: C, 66.06; H, 5.27, N, 4.17. $C_{18}H_{17}NO_5$ requires C, 66.05; H, 5.23, N, 4.28%); λ_{max}/nm (EtOH) 251 (ε/$M^{-1}cm^{-1}$ 650) and 257 (660); ν_{max}/cm^{-1} (Nujol) 3380, 1760, 1740, 1215, 1175, 1005, 960, and 705; δ_H (400 MHz) 7.19-7.50 (10 H, m, Ar-H), 5.55 (1 H, s, PhC*H*), 4.31 and 3.59 (2 H, 2 × d, *J* 18 Hz, NCH_2), 4.16 (1 H, s, OH), and 3.75 (3 H, s, CO_2Me).

This compound (65 mg) was treated with 0.2 M NaOH in 10% aq. MeOH (2.2 ml) for 3 h at room temp. and the solution was diluted into solutions of 0.1 M phosphate or Tris buffers as appropriate at pH values in the range 6-8. The UV spectra of these solutions were consistent with the presence of the cyclic tautomer only.

General Procedure for Preparation of Carbamates Using p-Nitrophenyl Chloroformate

A solution of a benzoin (1.5 mmol) in dry THF (40 ml) was treated with DMAP (244 mg, 2 mmol) and *p*-nitrophenyl chloroformate (333 mg, 1.65 mmol). The solution was stirred at room temp. under nitrogen for 3 h and treated with a secondary amine (2 mmol). In the case of an amine hydrochloride, *N*-methylmorpholine (275 µl, 2.5 mmol) was also added. The mixture was stirred at room temp. for 20 h, diluted with ether and washed with saturated aq. K_2CO_3 until the aqueous washes became colourless. The organic layer was washed with 1 M HCl and water, dried and evaporated. The product was isolated by flash chromatography. In cases where TLC indicated that the starting benzoin and the product carbamate had similar chromatographic mobility, the crude product was dissolved in dichloromethane and treated with succinic anhydride (2 mmol) and DMAP (2.5 mmol) and stirred at room temp. for 16 h. The solution was then evaporated and flash chromatographed directly.

1-(3,5-Dimethoxyphenyl)-2-oxo-2-phenylethyl N-(Ethoxycarbonyl)methyl-N-methylcarbamate **15a**

Prepared from 3',5'-dimethoxybenzoin and sarcosine ethyl ester hydrochloride according to the general procedure. The crude product was flash chromatographed [EtOAc–light petroleum (3:7)] and recrystallised from EtOAc–light petroleum to give the *title compound* as white crystals (497 mg, 80%), m.p. 113 °C (Found: C, 63.61; H, 6.07; N 3.33. $C_{22}H_{25}NO_7$ requires C, 63.67; N, 6.11; N, 3.37%); ν_{max}/cm^{-1} (Nujol) 1750, 1690, 1600, 1215, 1145, 835, and 690; δ_H 90 (MHz) 7.82-8.02 [2 H, m, Ar(2) 2- and 6-H], 7.24-7.52 [3 H, m, Ar(2)-H], 6.72 (1 H, s, Ar*CH*), 6.61 and 6.55 [2 H, 2 × d, *J* 2.2, Ar(1) 2- and 6-H, rotamers], 6.39 and 6.37 (1 H, 2 × t, Ar(1) 4-H], 3.84-4.40 (4 H, m, CH_2CH_3 and NCH_2), 3.74 (6 H, s, OMe), 3.10 and 3.07 (3 H, 2 × s, NMe) and 1.25 and 1.22 (3 H, 2 × t, CH_2CH_3).

Hydrolysis of Carbamate **15a**

A solution of the carbamate **15a** (100 mg, 0.24 mmol) in methanol (5 ml) was treated with 2 M aq. NaOH (0.56 ml) and the solution was stirred for 3 h at room temp. The solution was evaporated and the residue was dissolved in water and adjusted to pH 7.06 with 1 M HCl, then washed with ether which had been prewashed with 1 M NaOH to remove coloured impurities. Analytical reverse phase HPLC [Merck RP8 Lichrosphere RP8 column (Cat. No. 50832), mobile phase 25 mM Na phosphate, pH 5.5–acetonitrile (76:24 v/v), flow rate 1.5 ml/min] showed two components, with t_R 11.2 and 14.2 min. The mixture was separated by preparative reverse phase HPLC [Waters 7.8 × 300 mm column filled with Waters C_{18} Bulk Packing Material (Cat. No. 20594), mobile phase 25 mM Na phosphate (pH 5.5)–acetonitrile (5:1 v/v), flow rate 1.5 ml/min]. Fractions were analysed by reverse phase HPLC as described above and pure fractions were combined. The combined fractions containing the individual components were each desalted by reloading onto the preparative HPLC column in 10 mM Na phosphate, pH 6.0. The column was first eluted with pure water until the conductivity of the eluate dropped to that of water, then with water–acetonitrile (2:1) which eluted the organic compound free of contaminating buffer salts.

The first-eluted product from the initial preparative HPLC was *1-(3,5-dimethoxyphenyl)-2-oxo-2-phenylethyl N-carboxymethyl-N-methylcarbamate* **16** as its sodium salt; λ_{max}/nm [H_2O–MeCN (2:1)] 249; δ_H (400 MHz, D_2O, acetone ref.) 7.97-8.01 [2 H, m, Ar(2) 2- and 6-H], 7.62-7.66 [1 H, m, Ar(2) 4-H], 7.45-7.51 [2 H, m, Ar(2), 3- and 5-H], 6.87 and 6.81 (1 H, 2 × s, Ar*CH*, rotamers), 6.71 and 6.65 [2 H, 2 × d, *J* 2.2, Ar(1) 2- and 6-H], 6.51 and 6.48 [1 H, 2 × t, Ar(1) 4-H], 4.12 and 3.92 (1 H, 2 × d, *J* 17.5, half of NCH_2), 3.76 and 3.70 (1 H, 2 × d, half of NCH_2), 3.74 and 3.72 (6 H, 2 × s, OMe) and 3.02 and 2.92 (3 H, 2 × s, NMe).

The second-eluted product was the isomeric *2-(3,5-dimethoxyphenyl)-2-oxo-1-phenylethyl N-carboxymethyl-N-methylcarbamate* **17** as its sodium salt; λ_{max}/nm [H_2O–MeCN (2:1)] 268 and 320; δ_H (400 MHz, D_2O, acetone ref.) 7.34-7.49 [5 H, m, Ar(1)-H], 7.10 and 7.09 [2 H, 2 × d, *J* 2.3, Ar(2) 2- and 6-H, rotamers], 6.88 and 6.83 (1 H, 2 × s, Ar*CH*), 6.67 and 6.66 [1 H, 2 × t, Ar(2) 4-H], 4.11 and 3.92 (1 H, 2 × d, *J*

17.5, half of NCH_2), 3.74 and 3.71 (1 H, 2 × d, half of NCH_2), 3.72 and 3.71 (6 H, s, OMe) and 3.00 and 2.91 (3 H, s, NMe).

With the individual isomers available as standards, the ratio of the two products present in the original mixture could be estimated as 1:1 from the heights of the peaks in the HPLC trace and the relative absorbance at 254 nm.

1-(3,5-Dimethoxyphenyl)-2-oxo-2-phenylethyl N-(t-Butoxycarbonyl)methyl-N-methylcarbamate **15b**

Prepared from 3',5'-dimethoxybenzoin and *t*-butyl sarcosinate[32] as described for compound **15a**. The *product* was recrystallised from light petroleum (83% yield), m.p. 99-100 °C. (Found: C, 65.17; H, 6.71; N, 3.13. $C_{24}H_{29}NO_7$ requires C, 65.00; H, 6.59; N, 3.16%); ν_{max}/cm^{-1} (Nujol) 1730, 1690, 1605, 1190, 1155, 1065, and 825; δ_H (400 MHz) 7.95 [2 H, d, *J* 7.9, Ar(2) 2- and 6-H], 7.50 [1 H, t, *J* 7.9, Ar(2) 4-H], 7.39 [2 H, t, Ar(2) 3- and 5-H], 6.73 and 6.71 (1 H, 2 × s, ArC*H*, rotamers), 6.62 and 6.56 [2 H, 2 × d, *J* 2.2, Ar(1) 2- and 6-H], 6.40 and 6.38 [1 H, 2 × t, Ar(1) 4-H], 4.19 and 4.12 (1 H, 2 × d, *J* 17.5, half of NCH_2), 3.77 and 3.71 (1 H, 2 × d, half of NCH_2), 3.75 and 3.74 (6 H, 2 × s, OMe), 3.09 and 3.00 (3 H, 2 × s, NMe), and 1.50 and 1.45 (9 H, 2 × s, CMe_3).

1-(3,5-Dimethoxyphenyl)-2-oxo-2-phenylethyl N-Pentamethylenecarbamate **1**

Prepared from 3',5'-dimethoxybenzoin and piperidine according to the general procedure. The reaction product was flash chromatographed [EtOAc–light petroleum (3:7)] to give the *title compound* (88%) which was recrystallised from ether as white needles, m.p. 125.5-126.5 °C, (J.F. Cameron, personal communication, m.p. 124-125 °C) (Found: C, 68.83; H, 6.51; N, 3.59. $C_{22}H_{25}NO_5$ requires C, 68.91; H, 6.57; N, 3.65%); ν_{max}/cm^{-1} (Nujol) 1680, 1610, 1595, 1275, 1060, 940, and 730; δ_H (90 MHz) 7.84-8.04 [2 H, m, Ar(2) 2- and 6-H], 7.24-7.56 [3 H, m, Ar(2)-H], 6.72 (1 H, s, ArC*H*), 6.61 [2 H, d, *J* 2.2, Ar(1) 2- and 6-H], 6.39 [1 H, t, Ar(1) 4-H], 3.74 (6 H, s, OMe), 3.28-3.50 (4 H, m, NCH_2), and 1.32-1.76 (6 H, m, CH_2).

2-(3,3-Dimethoxyphenyl)-2-oxo-1-phenylethyl N-Pentamethylenecarbamate **18**

3,5-Dimethoxybenzoin[3a] and piperidine were reacted according to the general procedure to give the *title compound* (58%) as white crystals, m.p. 68 °C (from ether–light petroleum). (Found: C, 69.00; H, 6.57; N, 3.59. $C_{22}H_{25}NO_5$ requires C, 68.91; H, 6.57; N, 3.65%); ν_{max}/cm^{-1} (Nujol) 1700, 1595, 1245, 1205, 1160, 1065, 900, and 780; δ_H (90 MHz) 7.22-7.56 [5 H, m, Ar(1)-H], 7.09 [2 H, d, *J* 2.2, Ar(2) 2- and 6-H], 6.74 (1 H, s, ArC*H*), 6.57, [1 H, t, Ar(2) 4-H], 3.76 (6 H, s, OMe), 3.30-3.60 (4 H, m, NCH_2), and 1.36-1.76 (6 H, m, CH_2).

1-(3,5-Dimethoxyphenyl)-2-phenylethane-1,2-dione **19**

A solution of 3,5-dimethoxybenzoin (272 mg, 1 mmol) in chloroform (10 ml) was treated with activated MnO_2 (1 g; Merck Type 805958) and the mixture was stirred at room temp. for 3 days. The solid was filtered and washed with more chloroform and the filtrate was evaporated. The residue was flash chromatographed [EtOAc–light petroleum (1:4)] to give unreacted 3,5-dimethoxybenzoin (37 mg, 14%), preceded by the desired product as a yellow viscous oil which was triturated with light petroleum and recrystallised from the same solvent to give the *title compound* as a pale yellow solid (130 mg, 48%), m.p. 62-63 °C. (Found: C, 70.95; H, 5.16. $C_{16}H_{14}O_4$ requires C, 71.10; H, 5.22); ν_{max}/cm^{-1} (Nujol) 1685, 1660, 1595, 1305, 1210, 1170, 855, 775, and 670; δ_H (90 MHz) 7.84-8.04 [2 H, m, Ar(2) 2- and 6-H], 7.36-7.68 [3 H, m, Ar(2)-H], 7.08 [2 H, d, *J* 2.3, Ar(1) 2- and 6-H], 6.72 [1 H, t, Ar(1) 4-H], and 3.01 (6 H, s, OMe).

Flash Photolysis of Carbamate ***16***

The kinetics of photolysis were measured in an absorption spectrophotometer linked to a Candela dye laser (320 nm).[33] The absorption changes of the Bromothymol Blue indicator were measured at 615 nm. Solutions for photolysis contained the carbamate **16** (1 mM), 150 mM KCl, 1 mM sodium phosphate buffer and Bromothymol Blue to give an optical density of 0.8 in the 4 mm path length cell. The composite solution was adjusted to pH 7.0.

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