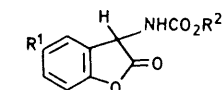


Synthesis and Chemiluminescent Reactions of Some 3-Alkoxy-carbamoylbenzo[*b*]furan-2(3*H*)-ones

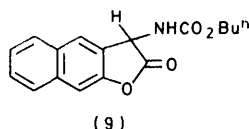
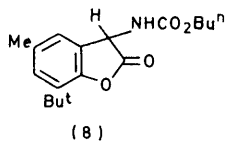
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The 3-alkoxy-carbamoylbenzo[*b*]furan-2(3*H*)-ones (1)–(9) have been synthesised, and were found to chemiluminesce in dipolar aprotic solvents in the presence of oxygen and a base. The end products of the chemiluminescent reactions are benzoxazinediones (23), and a mechanism for their formation and the light emission is proposed. A side-reaction gives dehydromers (22) which are slowly converted into the benzoxazinediones with weak chemiluminescence

McCAPRA¹ has made the generalisation that the juxtaposition of an auto-oxidisable CH group and an active ester or amide in a compound gives rise to chemiluminescence. The intensity of the luminescence is, however, variable, and the factors which govern it are not yet well established. We now report the synthesis of some 3-alkoxy-carbamoylbenzo[*b*]furan-2(3*H*)-ones [(1)–(9)]



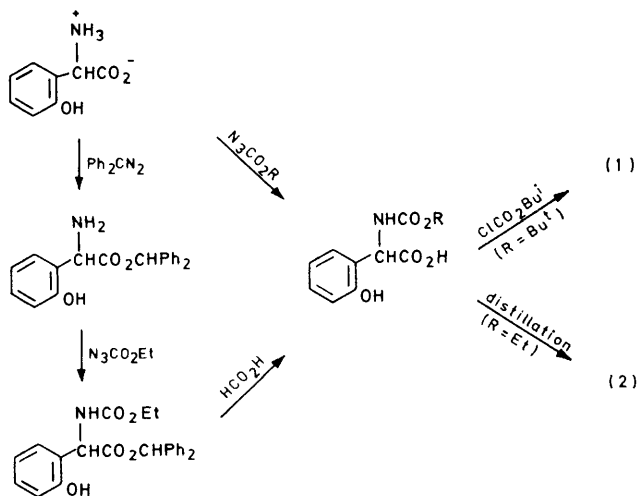
- (1) $R^1 = H, R^2 = Bu^t$
 (2) $R^1 = H, R^2 = Et$
 (3) $R^1 = Cl, R^2 = Bu^t$
 (4) $R^1 = Br, R^2 = Bu^t$
 (5) $R^1 = Me, R^2 = Bu^t$
 (6) $R^1 = [CH_2]_6Me, R^2 = Bu^t$
 (7) $R^1 = OMe, R^2 = Bu^t$



which under appropriate conditions undergo base-induced oxidation with the emission of light clearly visible in daylight.

RESULTS AND DISCUSSION

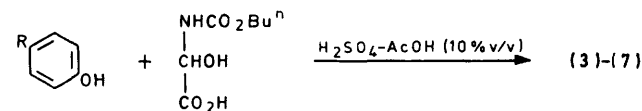
The benzofuranones were synthesised by two routes. The first, which was used for compounds (1) and (2), is summarised in Scheme 1. This route could presumably



SCHEME 1

be adapted to the synthesis of substituted analogues, but it is experimentally difficult, and the synthesis of the starting material, *o*-hydroxyphenylglycine, is itself laborious.² The alternative route, which is shown in Scheme 2, is an adaptation of the synthesis of 3-amido-benzofuranones reported by Ben-Ishai *et al.*³ α -Hydroxy-*N*-(*n*-butoxycarbonyl)glycine is readily prepared from *n*-butyl carbamate and glyoxylic acid, and although isolated yields were only modest this route is experimentally convenient. It was also adapted for the synthesis of the dialkyl derivative (8) and the naphthofuranone (9). Its main limitation is that it requires the *para*-position of the starting phenol to be blocked; both phenol and 3,5-dimethylphenol gave intractable mixtures of products arising from attack *para* as well as *ortho* to the hydroxy group, although in the latter case there is some evidence that the required compound was formed.

The 3-alkoxy-carbamoylbenzo[*b*]furan-2(3*H*)-ones [(1)–(9)] displayed chemiluminescence on base-induced oxidation. The conditions required were explored in



SCHEME 2

some detail for the chloro-compound (3). Dipolar aprotic solvents such as acetonitrile or dimethylformamide were best. Weak chemiluminescence was observed with potassium hydroxide in non-polar solvents (benzene, toluene, chlorobenzene) in the presence of dibenzo-18-crown-6, but none was detectable in water even with the aid of a phase-transfer catalyst (benzyltrimethylammonium hydroxide). In dimethylformamide a base with $pK_b < ca. 7.2$ was required for visible chemiluminescence: strong chemiluminescence was observed with the use of trimethylamine (pK_b 4.19) and stronger bases; no chemiluminescence was observed with papaverine (pK_b 7.50) and weaker bases; and very weak chemiluminescence was induced with imidazole (pK_b 7.05) and 2-aminopyridine (pK_b 7.18). For the above reactions the presence of air was essential. *t*-Butyl hydroperoxide or 94% hydrogen peroxide can function as sources of oxygen, but give only short-lived,

localised chemiluminescence, and dibenzoyl peroxide is ineffective.

In dimethylformamide, at room temperature under air in the presence of triethylamine, compound (3) emits violet light clearly visible in daylight for *ca.* 30 min, and then fading slowly but still detectable in a darkened room after 70 h. Under oxygen, in the presence of potassium *t*-butoxide, intense light emission occurs, but over a shorter period.

Although the colour of the visible light emitted varied somewhat from compound to compound, the emission spectra in each case showed a single broad peak, with its maximum near 425 nm and tailing into the visible region. Preliminary experiments indicated the possibility of modifying the colour of the emission by the addition of fluorescers. For example, in the presence of rubrene, base-induced oxidation of compound (3) gave a pale red light, and the emission spectrum showed an additional peak at λ_{max} 552 nm, corresponding to the fluorescence spectrum of rubrene (λ_{max} 560 nm).

The products from the reactions of the 3-carbamato-benzofurans (3) and (5) were investigated in detail. After extended reaction periods the major products were the corresponding benzoxazinediones (10) and (11) together with smaller amounts of the hydrolysis products (12) and (13) of the benzofuranones, which had already been characterised in the course of the preparation of the benzofuranones. The benzoxazinediones had properties corresponding to those reported in the literature,⁴ and (10) was synthesised independently from the 6-chlorosalicylamide and ethyl chloroformate.

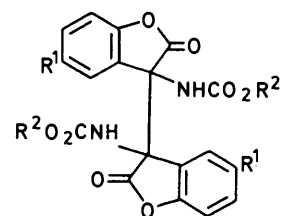


(10) R = Cl
(11) R = Me

(12) R = Cl
(13) R = Me

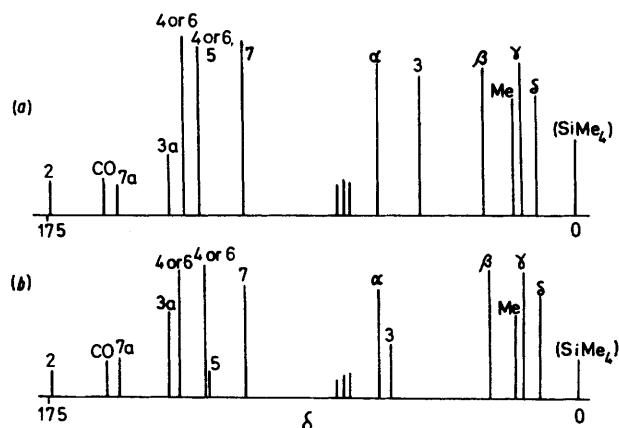
When the oxidations were carried out for shorter periods, additional products were observed and similar products were also obtained from compounds (1) and (2). In each case two isomers were formed, but one was unstable and was more or less rapidly transformed into its more stable isomer. To the stable isomers we ascribe the dimeric structures (14)–(17), on the basis of the following evidence. (i) Their i.r. spectra are very similar to those of the starting materials, showing in particular bands near 3 400 (NH stretch), 1 800 (lactone C=O stretch), and 1 720 cm^{-1} (carbamate C=O stretch). (ii) Their u.v. spectra are similar to those of the starting materials. (iii) Their mass spectra, under normal operating conditions, show ions at highest mass of one unit less than the molecular ions of the starting materials. In the case of compound (17), however, weak ions at *m/e* 307, 309, and 356 were also observed. The molecular weight of compound (14), determined by vapour osmometry, was consistent with a dimeric structure.

(iv) Their ¹H and ¹³C n.m.r. spectra resembled those of the starting materials but more detailed examination of the spectra of compounds (16) and (17) provided strong



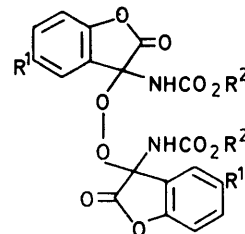
(14) R¹ = H, R² = Bu^t
(15) R¹ = H, R² = Et
(16) R¹ = Me, R² = Buⁿ
(17) R¹ = Cl, R² = Buⁿ

evidence for the structures proposed. The loss of the 3-H signal in the former was only apparent from the change in integrations. However, the ¹³C spectra were



The ¹H-decoupled ¹³C n.m.r. spectra of (a) the benzofuranone (5) and (b) its dehydromer (16)

more informative. The Figure shows the assignments made for the decoupled spectra of compounds (5) and (16). The chemical shift of the signal attributed to C-3 is at high field, and clearly corresponds to saturated carbon, in a similar location to that in the starting material rather than linked to oxygen as in the conceivable alternative structure (18). Furthermore, in the proton-



(18)

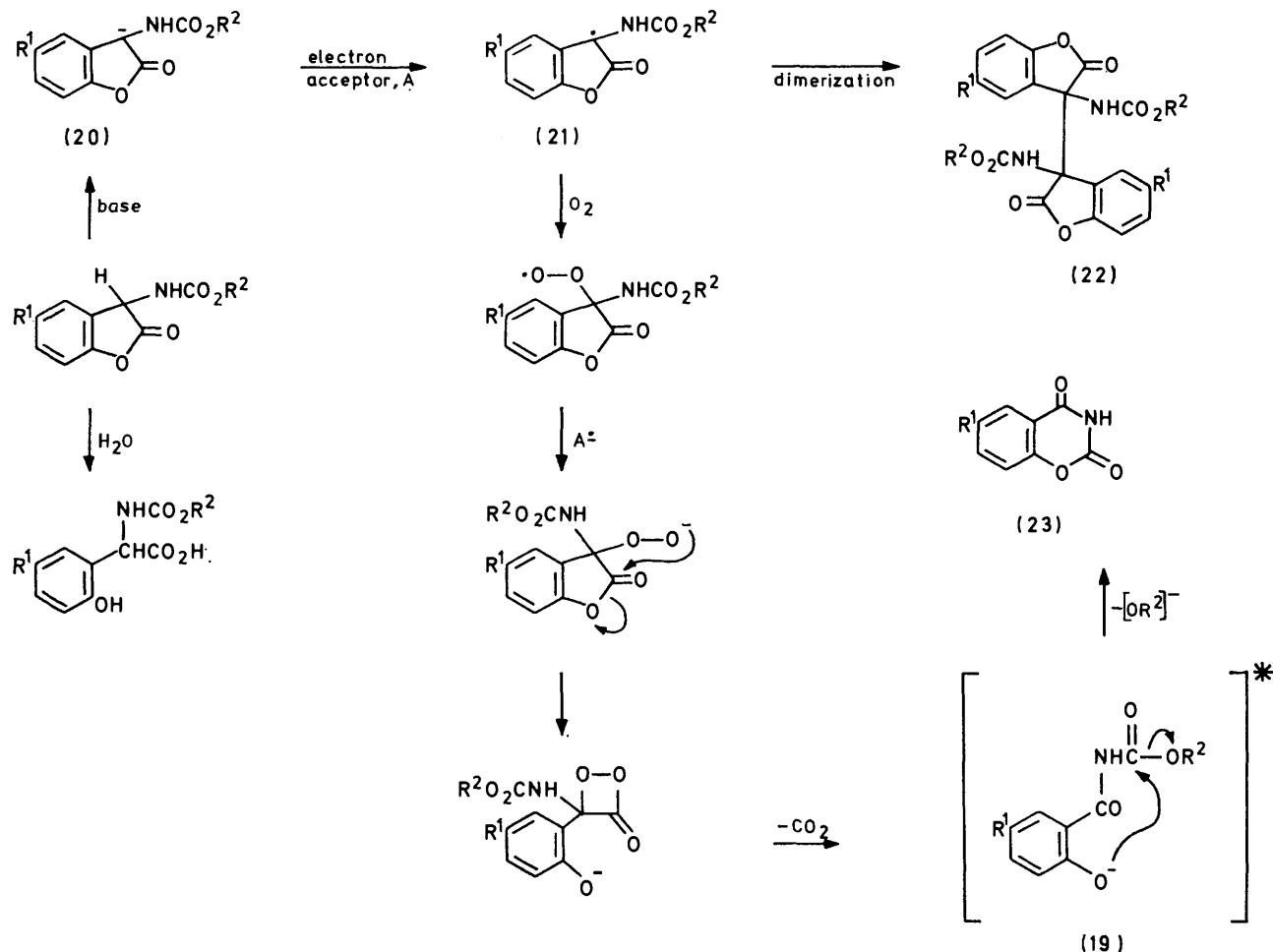
coupled spectrum this signal appears as a doublet in the spectrum of the starting material (5), but as a singlet in that of the product (16).

The less stable intermediates could only temporarily be freed from their more stable isomers. However, the spectra of both isomers were similar, and we believe that they are diastereoisomers. Attempts to build space-filling molecular models of the dimers revealed that the C-C bond joining the rings must be highly strained; dissociation of this bond could thus provide a route for their interconversion.

Further investigation is required to establish the mechanism of the chemiluminescence and for the form-

reaction between the carbanion and oxygen would be spin-forbidden, so that in this case the two-step pathway shown in Scheme 3 would be preferred; alternatively the sequence could be regarded as involving intersystem crossing within a carbanion-oxygen complex (*cf.* ref. 6).

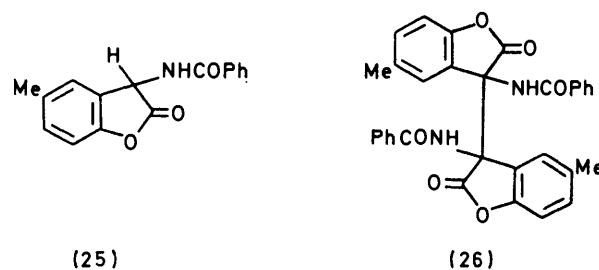
A comparison between the carbamates and the 3-benzamido-analogue (25) proved noteworthy. On treatment with triethylamine in acetonitrile, the amide (25) showed no visible chemiluminescence; the dehydromer



SCHEME 3

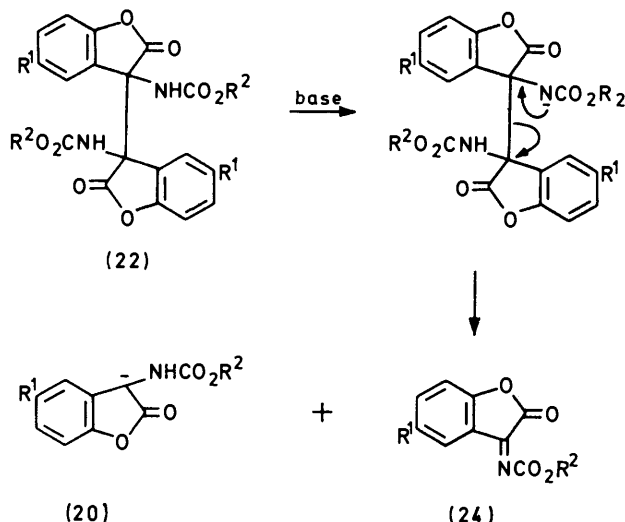
ation of the products. However, our preliminary observations allow us to postulate the routes shown in Scheme 3. The suggested mechanism of the chemiluminescence involves decomposition of a dioxetanone intermediate to give the photoexcited species (19) and is analogous to that for some other chemiluminescent systems.^{1,5} The key steps in the initiation of the reactions shown in Scheme 3 are deprotonation to form the carbanion (20) which then interacts with an electron acceptor to give the radical (21) and the radical anion, A^- . Various components of the reaction mixture could function as the electron acceptor, among them oxygen. It should be noted that a direct, one-step

(26) was isolated from the complex mixture of products, but not the benzoxazinedione (11). These observations suggest that a good leaving group is necessary both for



chemiluminescence and for the formation of the benzoxazinedione.

In Scheme 3, the formation of the dimers (22) is shown as a side-reaction, not on the direct pathway leading to chemiluminescence. However, solutions of the dimers do chemiluminesce, albeit weakly, under the reaction conditions, and are transformed into the oxazinediones (23). This could be because they dissociate to give low concentration of the radicals (21) but as the presence of base is necessary the carbanion (20) could be formed from them as exemplified in Scheme 4, and subsequently react as in Scheme 3. We have not obtained any evidence for the formation of compound (24), which might, however, be readily hydrolysed.



SCHEME 4

EXPERIMENTAL

U.v. spectra were recorded in methanol, i.r. spectra as Nujol mulls, and ¹H and ¹³C n.m.r. spectra in deuteriochloroform, unless otherwise stated. All compounds comprising chiral molecules were unresolved. The physical and spectral data for compounds (3)—(11) and (14)—(18) are deposited as Supplementary Publication No. SUP 22461 (5 pp).*

3-t-Butoxy- and 3-Ethoxy-carbamoyl-2,3-dihydrobenzo[b]furan-2(3H)-one (1) and (2).—(*o*-Hydroxyphenyl)glycine² (5.0 g, 0.03 mol) was dissolved in a mixture of water (45 ml) and triethylamine (12.6 ml). A solution of *t*-butyl azidoformate⁷ (5.1 ml, 0.036 mol) in dioxan (45 ml) was added slowly and the mixture was stirred overnight. The dioxan was evaporated off under reduced pressure, and the mixture was extracted with several portions of ether, acidified to pH 2.5, and extracted with several portions of ethyl acetate. The combined extracts were dried (MgSO₄) and evaporated, and the residual oil was triturated with light petroleum to give 2-*t*-butoxycarbamoyl-2-(*o*-hydroxyphenyl)acetic acid (5.5 g, 68%), m.p. 88—91 °C (from toluene—light petroleum); ν_{\max} 3 480, 3 360—3 140, 1 740, and 1 670 cm⁻¹; δ [(CD₃)₂SO] 9.0—8.6 (2 H, br, NH and OH, exchangeable), 7.3—6.7 (4 H, m, Ar-H), 5.5 (1 H, br, CH), and 1.4 (9 H, s, Bu^t); λ_{\max} (log ϵ) 274 (3.5) and 278 sh (3.4) nm.

* For details of Supplementary Publications, see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

The intermediate hydroxyacid (1.1 g, 4 mmol) was dissolved in a mixture of dry triethylamine (0.4 g, 4 mmol) and dry THF (20 ml) under nitrogen. The solution was maintained at -5 °C and stirred, as isobutyl chloroformate (0.56 g, 4 mmol) in THF (20 ml) was added dropwise during 30 min, and then for a further 10 min. Water (20 ml) was added, the THF was evaporated, and the solution filtered. The solid was repeatedly recrystallised from toluene to give 3-*t*-butoxycarbamoyl-2,3-dihydrobenzo[b]furan-2(3H)-one (1) (0.5 g, 49%), m.p. 147—149 °C; ν_{\max} 3 380, 1 840, and 1 680 cm⁻¹; λ_{\max} (log ϵ) 272 (3.1) and 278 sh (3.05) nm; δ 7.4—7.0 [5 H, (4 H after deuteration), m, Ar-H + NH], 5.1 (1 H, br, CH), 1.4 (9 H, s, Bu^t) (Found: C, 63.0; H, 6.2; N, 5.7%; M^+ , 249. C₁₃H₁₅NO₄ requires C, 62.6; H, 6.1; N, 5.6%; M , 249).

An analogous procedure, using ethyl azidoformate, gave 2-ethoxycarbamoyl-2-(*o*-hydroxyphenyl)acetic acid (3) as an oil; ν_{\max} 3 520—3 100, 1 780, and 1 660 cm⁻¹; δ [(CD₃)₂SO] 8.6 (s, exchangeable, CO₂H + OH), 7.3—6.6 (m, Ar-H), 6.3 (s, exchangeable, NH), 5.5 (s, CH), 4.0 (q, CH₂), and 0.9 (t, Me). The crude intermediate (8.0 g) was distilled (184—190 °C at 0.15 mmHg) in a Kugelrohr apparatus to give a yellow glass which solidified into a white powder. Redistillation, followed by chromatography (silica, ethyl acetate) and recrystallisation from toluene—light petroleum gave 3-ethoxycarbamoyl-2,3-dihydrobenzo[b]furan-2(3H)-one (2) (2.2 g, 29%), m.p. 141—143 °C; ν_{\max} 3 360, 1 835, and 1 690 cm⁻¹; λ_{\max} (log ϵ) 278 (3.06) and 272 (3.1) nm; δ 7.4—7.0 (m, 4 H, Ar-H), 6.5 (d, exchangeable, 1 H, NH), 5.1 (d, becomes s on deuteration, 1 H, CH), 4.05 (q, 2 H, CH₂), and 1.15 (t, 3 H, Me) (Found: C, 59.7; H, 5.05; N, 6.4%; M^+ , 221. C₁₁H₁₁NO₄ requires C, 59.7; H, 5.0; N, 6.3%; M , 221).

Benzofuranones from α -Hydroxy-*N*-(*n*-butoxycarbonyl)glycine.— α -Hydroxy-*N*-(*n*-butoxycarbonyl)glycine, from glyoxylic acid and *n*-butyl carbamate,^{3b} had m.p. 76—78 °C (lit.,^{3b} m.p. 76 °C). Some minor variations in procedure were employed for the various benzofuranones. Those for the 5-chloro-compound (3) were as follows. *p*-Chlorophenol (3.85 g, 0.03 mol), α -hydroxy-*N*-(*n*-butoxycarbonyl)glycine, and sulphuric acid—acetic acid (10% v/v, 250 ml) were stirred during 16 h. Water (400 ml) was added, and the resulting precipitate was filtered off, washed with water and light petroleum, and extracted with boiling benzene. The undissolved solid was *N*-(*n*-butoxycarbonyl)-(5-chloro-2-hydroxyphenyl)glycine (12) (1.8 g, 20%), m.p. 159—160 °C (from toluene—light petroleum); ν_{\max} 3 420, 3 200(br), 1 730, and 1 660 cm⁻¹; λ_{\max} 283 nm (log ϵ 3.3); δ [(CD₃)₂SO] 0.9 (t, 3 H, Me), 1.1—1.8 (m, 4 H, CH₂CH₂CH₂CH₃), 4.0 (t, 2 H, CH₂CH₂CH₂CH₃), 5.4 (d, s with D₂O, 1 H, CH), 6.6—7.9 (m, Ar-H, OH, NH, and CO₂H) (Found: C, 51.8; H, 5.5; N, 4.7. C₁₃H₁₆ClNO₅ requires C, 51.75; H, 5.3; N, 4.6%). The extract, on evaporation and chromatography (silica, ethyl acetate) gave 3-*n*-butoxycarbamoyl-5-chloro-2,3-dihydrobenzo[b]furan-2(3H)-one (3) (3.0 g, 35%), with the properties recorded in SUP 22461. An experiment in which the reagents were heated under reflux during 0.5 h gave the benzofuranone (50%). The properties of the other compounds, prepared by similar procedures, are also recorded in SUP 22461. In similar experiments, 4-hydroxybiphenyl and 3,5-dimethylphenol gave chemiluminescent materials with spectra appropriate to the benzofuranones, but pure samples were not obtained. The crude product from phenol gave faint chemiluminescence, but no identifiable compounds could be isolated.

Observation of Chemiluminescence.—For qualitative observation of chemiluminescence a few mg of the benzofuranone were dissolved in the solvent, and a drop of the base was added. The emission spectra were recorded in dimethylformamide, with triethylamine as the base, using an Aminco-Bowman spectrofluorimeter, and are recorded in Table 1.

TABLE 1

Emission spectra of 3-alkylcarbamoylbenzo[b]furan-2(3H)-ones

Compound	$\lambda_{\max.}/\text{nm}$	Compound	$\lambda_{\max.}/\text{nm}$
(2)	430	(7)	426
(3)	432	(8)	425
(4)	420	(9)	439
(5)	416	(10)	445
(6)	424		

Products of Base-induced Oxidation.—A typical procedure is described. 3-n-Butoxycarbamoyl-5-methyl-2,3-dihydrobenzo[b]furan-2(3H)-one (3.0 g, 11 mmol) was dissolved in acetonitrile (250 ml) and triethylamine (1.8 ml, 12 mmol) was added. After 16 h the solvent was removed under

in acetone (50 ml) until t.l.c. showed the absence of starting material. The solvent was evaporated off and dry column chromatography of the residue gave the dehydrodimer (16) (0.9 g, 45%) and the benzoxazinedione (11) (0.1 g, 7%).

(c) *With iodine and triethylamine.* A slight excess of 0.1M iodine in toluene was added dropwise to a stirred solution of the methylbenzofuranone (5) (1.3 g, 5 mmol) and triethylamine (0.55 g, 5 mmol) in toluene (50 ml). The solution was filtered, washed with water, dried, and evaporated. The residue was shown by t.l.c. to contain starting material and dehydrodimer (16); crystallisation gave the latter (0.5 g, 38%).

Base-induced Oxidation of 3-Benzamido-5-methyl-2,3-dihydrobenzo[b]furan-2(3H)-one (25).—The benzofuranone (3.0 g, 11 mmol), prepared as described by Ben-Ishai *et al.*,^{3a} was dissolved in acetonitrile (250 ml). Triethylamine (1.2 g, 12 mmol) was added. After 16 h the solvent was evaporated off under reduced pressure and the residue was chromatographed on silica. Toluene-ethyl acetate (9:1) eluted *bis*-(3-benzamido-5-methyl-2-oxo-2,3-dihydro-3H-benzofuran-3-yl) (26) (0.75 g, 25%), m.p. ca. 270 °C (decomp.)

TABLE 2

Products of base-induced oxidation of 3-carbamoylbenzofuranones

Starting material	Time of reaction/h	Products (yield %)		
		Dehydrodimer(s) ^a	Benzoxazinedione	Hydrolysis product
(1)	16	(14) (55 + 10)	<i>b</i>	<i>b</i>
(2)	16	(15) (50 + 10)	<i>b</i>	<i>b</i>
(3)	6	(17) (25)	(10) (14)	(12) (5)
	72	(17) (9)	(10) (48)	(12) (10)
(5)	16	(16) (25)	(11) (15)	(13) (12)
	62	(16) ^b	(11) (44)	(13) (19)

^a T.l.c. showed the initial products to be two-component mixtures; see text for discussion. ^b Not observed.

reduced pressure and the residue (yellow oil) was chromatographed on silica. Toluene-ethyl acetate (9:1) eluted *bis*-(3-n-butoxycarbamoyl-5-methyl-2-oxo-2,3-dihydrobenzo[b]furan-3-yl) (16) (1.3 g, 43%). Toluene-ethyl acetate (1:1) eluted 6-methyl-1,3-benzoxazine-2,4-dione (11) (0.3 g, 15%). Acetone eluted 2-n-butoxycarbamoyl-2-(2-hydroxy-5-methylphenyl)acetic acid (13) (0.4 g, 12%). The yields of the products obtained from other experiments are shown in Table 2; their properties are recorded in SUP 22461.

Isomerism of the Dehydrodimers, exemplified for the t-Butyl Compounds (14).—The crude product from the chemiluminescent reaction (overnight) of the benzofuranone (1) was chromatographed on a dry alumina column, using chloroform as eluant. Two isomeric compounds were obtained (properties in SUP 22461). The stable isomer was eluted less rapidly. Spectra of solutions of the less stable isomer in chloroform developed peaks corresponding to the stable isomer. The rate of isomerism did not decrease in the absence of oxygen.

Other Reactions of 3-Alkoxy-carbamoyl-2,3-dihydrobenzo[b]furan-2(3H)-ones.—(a) *With activated manganese dioxide.* A mixture of the chlorobenzofuranone (3) (2.0 g, 7.5 mmol), activated manganese dioxide (12 g), and dichloromethane (250 ml) was stirred for 16 h, filtered, and evaporated. Dry column chromatography of the residue (silica gel deactivated by 10% w/w water) gave the dehydrodimer (17) (0.8 g, 40%).

(b) *With potassium permanganate.* 1M-Potassium permanganate in acetone was added dropwise to a stirred solution of the methylbenzofuranone (5) (2.0 g, 7.5 mmol)

(from toluene-light petroleum); $\nu_{\max.}$ 3 400, 1 810, 1 790, and 1 670 cm^{-1} ; $\delta[(\text{CD}_3)_2\text{SO}]$ 2.25 (s, 3 H, Me), 6.7—8.0 (m, 8 H, Ar-H), and 8.85 (s, exchangeable, 1 H, NH); *m/e* 267 (Found: C, 72.45; H, 5.0; N, 5.1. $\text{C}_{32}\text{H}_{24}\text{N}_2\text{O}_6$ requires C, 72.2; H, 4.5; N, 5.3%).

Chemiluminescence of the Dehydrodimer (16).—Triethylamine (0.6 ml, 4 mmol) was added to a solution of the dehydrodimer (1.0 g, 1.9 mmol) in acetonitrile (50 ml). Weak chemiluminescence was observable in a darkened room. After 62 h the solvent was evaporated off. Extraction of the residue with chloroform afforded 6-methylbenzoxazine-2,4-dione (11) (0.25 g, 37%), m.p. 236—238 °C, and further extraction with 95% ethanol afforded starting material (0.1 g, 10%).

We thank the S.R.C. for C.A.S.E. Awards (to G. L. and R. A. W.) and for some of the ¹³C n.m.r. spectra.

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