

Persulphate Oxidations. Part VII.¹ Oxidation of *o*-Benzyl- and *o*-Benzoyl-benzamides

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Persulphate oxidation of *o*-benzylbenzamide gave mainly 2,2'-bibenzyl- $\alpha\alpha'$ -diylidibenzamide, and smaller amounts of 3-phenylphthalide, 3-phenylphthalimidine, and related dimers. The initial oxidation occurs at the benzyl and not the amide group. Analogous products were obtained from the oxidation of *o*-benzylbenzoic acid. In both cases dimerisation at the benzylic position was suppressed by addition of copper(II) ions. Persulphate oxidation of *o*-benzoylbenzamide afforded phthalimide, fluorenone, and *o*-benzoylbenzoic acid.

WE have shown, in the preceding paper,¹ that amidyls can be generated by the oxidation of amides with persulphate, and in the favourable case of *o*-phenylbenzamide intramolecular cyclisation to phenanthridones then follows. This is analogous to the oxidative cyclisation of *o*-phenylbenzoic acid to dibenzo[*b,d*]pyran-6-one.² We have observed previously³ that persulphate oxidation of *o*-benzyl- and *o*-benzoylbenzoic

¹ Part VI, A. R. Forrester, A. S. Ingram, and R. H. Thomson, preceding paper.

acids leads to the formation, respectively, of 3-phenylphthalide and fluorenone, and it was of interest to compare the behaviour of the corresponding amides.

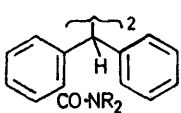
RESULTS

Persulphate oxidation of *o*-benzylbenzamide gave a complex mixture of products which were separated and

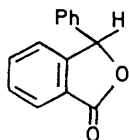
² P. M. Brown, J. Russell, R. H. Thomson, and A. G. Wylie, *J. Chem. Soc. (C)*, 1968, 842.

³ J. Russell and R. H. Thomson, *J. Chem. Soc.*, 1962, 3379.

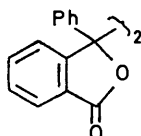
identified as the diamide (1; R = H), 3-phenylphthalide (2) and its dehydro-dimer (3),⁴ the unsymmetrical dimer (5), and trace amounts of 3-phenylphthalimidine (4)⁵ and fluorenone. The sparingly



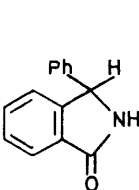
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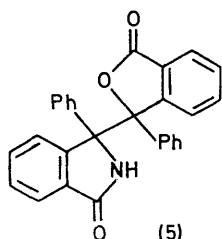
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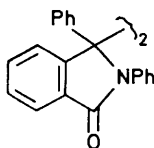
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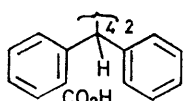
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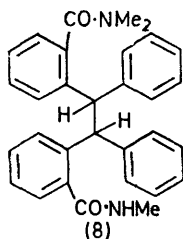
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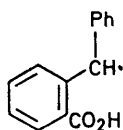
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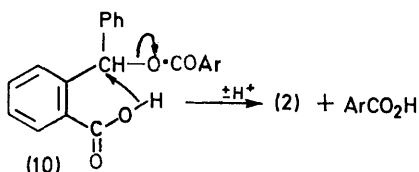
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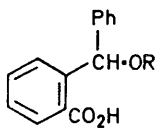
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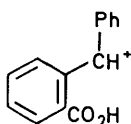
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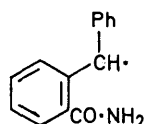
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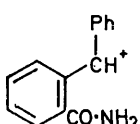
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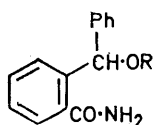
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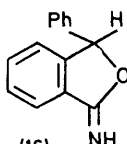
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(14)



(15)



(16)

and *meso*-forms: the n.m.r. spectrum showed two methine proton signals of different intensity. Cleavage of the central C-C bond gave rise to the base peak in the mass spectrum at *m/e* 210, other significant peaks resulting from loss of hydrogen (50%), ammonia (15%), and carbon monoxide (15%) from the monomeric fragment. This diamide was difficult to hydrolyse by normal methods; it resisted hot 8N-sodium hydroxide and concentrated sulphuric acid. It was finally converted into the diacid (7) by treatment with *n*-butyl nitrite and dry hydrogen chloride.⁶ When *o*-benzylbenzamide was oxidised in the presence of copper(II) ions formation of the diamide (1; R = H) was suppressed, the only products being 3-phenylphthalide and a trace of dimer (3).

The biphthalimidyl (3) was also obtained, in very low yield, by persulphate oxidations of 3-phenylphthalide (2) and of the diamide (1; R = H). Another minor oxidation product is regarded as the unsymmetrical dimer (5) (*M*, 417); it showed both lactone (1735 cm⁻¹) and lactam (1680 cm⁻¹) i.r. absorption and cleaved under electron bombardment predominantly at the central C-C bond to give fragments of *m/e* 208 (100%) and 209 (44%). The structure was confirmed by converting both compounds (3) and (5) into the same biphthalimidyl (6) by heating with aniline-anilinium chloride.

Oxidation of *NN*-dimethyl-*o*-benzylbenzamide also gave 3-phenylphthalide and a trace of dimer (3), the main products (*ca.* 30%) being a mixture of diamides of type (1). Fractional crystallisation of this dimeric material yielded the expected diamide (1; R = Me) [also prepared from the acid (7) with thionyl chloride and dimethylamine], and the *NNN'*-trimethyldiamide (8) was isolated from the mother liquors by chromatography. Demethylation of *N*-methylamides by persulphate is not unusual.¹

In view of the complexity of the products derived from the amide (1; R = H) we repeated the earlier work³ on the persulphate oxidation of *o*-benzylbenzoic acid. The neutral products were 3-phenylphthalide and the biphthalimidyl (3), and the acidic fraction also contained monomeric and dimeric products [the n.m.r. spectrum of the mixture showed both methylene (τ 4.72) and methine (τ 2.49) proton signals]. After methylation, repeated chromatography of the mixture afforded small amounts of the methyl esters of the starting material and the acid (7) (*meso*- and/or racemic), and an unresolved mixture of rotational stereoisomers of the diester. When this oxidation was repeated in the presence of copper(II) ions formation of the acid (7) was completely suppressed and only 3-phenylphthalide was isolated.

Persulphate oxidation of *o*-benzoylbenzamide yielded fluorenone (12%), phthalimide (21%), and *o*-benzoylbenzoic acid (26%). It was shown in a separate experiment that the amide is partly hydrolysed to the

soluble diamide (1; R = H), m.p. 316–317°, was the principal product (28%). Spectroscopically (u.v., i.r.) it was similar to the starting material, and was apparently a mixture of rotamers as well as (presumably) racemic

⁴ A. M. Creighton and L. M. Jackman, *J. Chem. Soc.*, 1960, 3138.

⁵ R. E. Rose, *J. Amer. Chem. Soc.*, 1911, **33**, 388.

⁶ N. Sperber, D. Papa, and E. Schwenk, *J. Amer. Chem. Soc.*, 1948, **70**, 3091.

acid by the acidic reaction medium, and its oxidation to fluorenone is known.³ According to the spectroscopic data of Flitsch⁷ and of Armarego and Sharma,⁸ *o*-benzoylbenzamide exists entirely in the cyclic tautomeric form (18) (3-hydroxy-3-phenylphthalimidine) in the solid state and in aprotic organic solvents. When prepared⁹ from *o*-benzoylbenzoic acid by reaction with thionyl chloride, followed by treatment with ammonia, this is the form normally obtained, and data for our product, m.p. 161—163°, $\nu_{\max.}$ (KBr) 1709 and 1665 cm^{-1} , $\nu_{\max.}$ (CHCl_3) 1720—1710 cm^{-1} , agree well with those of Armarego and Sharma.⁸ [This compound (18) has also been obtained¹⁰ by an independent route from 1-phenylisoquinoline.] However, by pyrolysis¹¹ of the ammonium salt of *o*-benzoylbenzoic acid, authentic *o*-benzoylbenzamide (17) can be obtained, m.p. 157—159°, $\nu_{\max.}$ (KBr) 1660 cm^{-1} , $\nu_{\max.}$ (CHCl_3) 1650 and 1620 cm^{-1} ; the i.r. spectrum of this material is distinct from that of (18). This compound was used in our oxidation experiments; presumably in aqueous solution structures (17) and (18) are in equilibrium.

DISCUSSION

The results from the oxidation of *o*-benzylbenzoic acid are in substantial agreement with previous work¹² on the decomposition of *o*-benzylbenzoyl peroxide in which the key intermediate is the radical (9) formed from the initial carboxyl radical by intramolecular hydrogen transfer. Dimerisation then leads to the diacid (7) and it was suggested^{3,12} that 3-phenylphthalide and *o*-benzylbenzoic acid were formed by disproportionation of the radical (9). However, this diphenylmethyl system (9) would not disproportionate readily; the formation of the products can be more reasonably explained in terms of induced decomposition of the peroxide by the radical (9) to give compound (10), which would collapse as shown to give 3-phenylphthalide and *o*-benzylbenzoic acid. In the persulphate oxidation of *o*-benzylbenzoic acid 3-phenylphthalide can be formed by a similar process in which the decomposition of persulphate ion is induced by the radical (9) to give either the sulphate (11; $\text{R} = \text{SO}_3^-$) or the cation (12), and hence structure (2) by cyclisation. The radical (9) is probably produced initially by attack on the benzylic position¹³ by sulphate radical ions, as benzyl groups are more easily oxidised than phenyl or carboxyl. The formation of the diacid (7) was completely suppressed when the oxidation of *o*-benzylbenzoic acid was carried out in the presence of copper(II) sulphate. This is fully consistent with the observations of Kochi and Gilliom¹⁴ and can be attributed to oxidation of the radical (9) either to the cation (12) by electron transfer or to the benzyl sulphate (11;

$\text{R} = \text{SO}_3^-$) by ligand transfer, followed by collapse to the lactone.¹⁵

In the absence of copper(II) ions a minor oxidation product was the biphthalidyl (3), presumably formed, stepwise, from the diacid (7), as for the monomer (2). The dimer (3) was obtained, in separate experiments, by persulphate oxidation of the acid (7) and also of the phthalide (2), although in very low yield, probably attributable to the low solubility of the substrates. The oxidation (2) \rightarrow (3) must involve hydrogen abstraction from the benzylic position by persulphate radical anions.

The oxidation of *o*-benzylbenzamide is similar to that of the benzyl acid insofar as the dimer (1; $\text{R} = \text{H}$) is the principal product, the intermediate radical (13) being formed by direct attack on the methylene group by sulphate radical anions and not by hydrogen transfer to an amidyl radical. The alternative process, intramolecular abstraction of a benzylic hydrogen atom by amidyls, has been observed with amidyls generated from *N*-halogeno-amides.¹⁵ This conclusion follows from the observation that oxidation of *NN*-dimethyl-*o*-benzylbenzamide gave approximately the same amount of dimeric material (1) as the parent amide, and is consistent with the relative difficulty experienced¹ in the persulphate oxidation of amide groups. As expected, no diamide (1; $\text{R} = \text{H}$) was formed when *o*-benzylbenzamide was oxidised in the presence of copper(II) sulphate, and 3-phenylphthalide was the main product.

In the absence of copper(II) ions a trace of 3-phenylphthalimidine (4) was obtained as well as the phthalide (2). This implies that the cation (14) [derived from the radical (13) as already described], and/or the sulphate (15; $\text{R} = \text{SO}_3^-$) or solvolysis product (15; $\text{R} = \text{H}$), cyclise both on nitrogen to give the phthalimidine (4) and on oxygen to form the imine (16) and hence the phthalide (2) after hydrolysis. It was established that *o*-benzylbenzamide is not hydrolysed detectably to the acid under the conditions of the oxidation reaction, so the phthalide (2) cannot be formed by that route. Of the other minor oxidation products the biphthalidyl (3) may be derived either from the phthalidyl (2) or from the amide (1; $\text{R} = \text{H}$), both of which gave (3) in small yield in separate experiments, and the lactam-lactone (5) is presumably formed by coupling of the benzylic radicals derived from (2) and the phthalimidine (4). It was also obtained by oxidation of an equimolar mixture of compounds (2) and (4), again in low yield because the oxidation was heterogeneous.

An unexpected product from the persulphate oxidation of *o*-benzoylbenzamide (17) was phthalimide (21%). However, as the amide (17) will be in equilibrium with its tautomer (18) (see before), its formation can be

⁷ W. Flitsch, *Chem. Ber.*, 1970, **103**, 3205.

⁸ W. L. F. Armarego and S. C. Sharma, *J. Chem. Soc. (C)*, 1970, 1600.

⁹ C. L. Hewett, L. J. Lermitt, H. T. Openshaw, A. R. Todd, A. H. Williams, and F. N. Woodward, *J. Chem. Soc.*, 1948, 292.

¹⁰ W. Davies, T. H. Ramsay, and E. R. Stove, *J. Chem. Soc.*, 1949, 2633.

¹¹ C. Graebe and F. Ullmann, *Annalen*, 1896, **291**, 8.

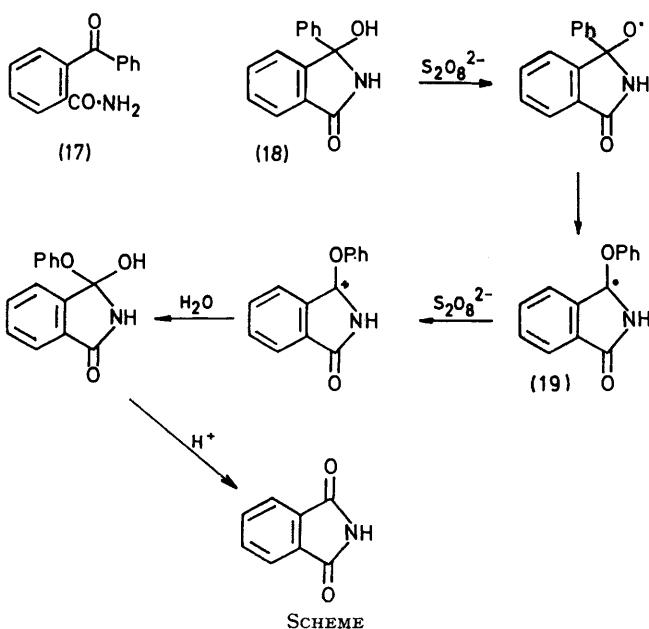
¹² F. D. Greene, G. R. van Norman, J. C. Cantrill, and R. D. Gilliom, *J. Org. Chem.*, 1960, **25**, 1790.

¹³ R. G. R. Bacon and J. R. Doggart, *J. Chem. Soc.*, 1960, 1332.

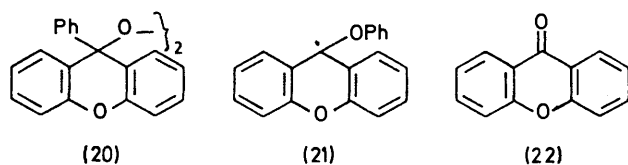
¹⁴ J. K. Kochi and R. D. Gilliom, *J. Amer. Chem. Soc.*, 1964, **86**, 5251.

¹⁵ A. L. J. Beckwith and J. E. Goodrich, *Austral. J. Chem.*, 1965, **18**, 747.

rationalised as shown in the Scheme, the key step being the 1,2-shift of a phenyl radical to form a more stable



tertiary benzylic radical (19). A similar shift occurs in the thermolysis¹⁶ of the peroxide (20), the initial



alkoxyl radical rearranging to (21) *en route* to the final product (22). This thermal rearrangement¹⁷ appears to be general for radicals of the type $Ar^1Ar^2Ar^3CO\cdot$. Support for the Scheme comes from the persulphate oxidation of 3-phenylphthalimidine (4), which also gave phthalimide, in low yield, together with 3-hydroxy-3-phenylphthalimidine (18).

EXPERIMENTAL

For general methods see Part V (p. 2842). Oxidations were carried out as described previously.¹

Oxidation of *o*-Benzylbenzamide.—(a) The amide (4.25 g) gave an ether-soluble fraction which was chromatographed (p.l.c., t.l.c.) on silica gel in dichloromethane to give 3-phenylphthalide (111 mg, 2.6%), 3,3'-diphenylbi-3-phthalidyl (3) [corresponds (i.r.) to compound B of ref. 4] (111 mg, 3%), 3-phenylphthalimidine, m.p. 217–218° (lit.⁵ 218–220°) (from aqueous methanol) (trace), fluorenone (trace), and 3-phenyl-3-(3-phenyl-3-phthalimidyl)phthalide (5), needles, m.p. 262–265° (from aqueous methanol) (53 mg, 1%) (Found: M , 417.1366. $C_{28}H_{19}NO_3$ requires M , 417.1365), λ_{max} (C_8H_{14}) 213, 220sh, 277, and 285 nm ($\log \epsilon$ 4.70, 4.66, 3.46, and 3.46), ν_{max} , 3160, 1735, and 1680 cm^{-1} . The ether-insoluble material crystallised from methanol to give 2,2'-bibenzyl- $\alpha\alpha'$ -diylidibenzamide (1; R =

H), plates, m.p. 316–317° (1.19 g, 28%) (Found: C, 80.2; H, 5.5; N, 6.3%; M , 420.1847. $C_{28}H_{24}N_2O_2$ requires C, 79.95; H, 5.8; N, 6.7%; M , 420.1838), ν_{max} , 3420, 3260, 3130, 1660, and 1615 cm^{-1} , τ [(CD_3)₂SO] 1.91–3.18 (22H, m, ArH, NH), and 3.73 and 3.92 (2H, unequal s, Ar_2CH).

The diamide was treated as follows: dry hydrogen chloride was bubbled through a solution of the amide (150 mg) in dioxan (25 ml) at 20° for 15 min, and freshly prepared *n*-butyl nitrite (1 ml) was added during 30 min. A deep red colour appeared and nitrogen was evolved. The solution was heated and stirred at 100° for 2 h further, cooled, and evaporated *in vacuo*. Extraction of the residue with aqueous 10% potassium hydroxide, and acidification, gave the diacid (7), needles, m.p. 280–285° (decomp.) (lit.⁸ 270–290°) (from aqueous methanol) (48 mg).

(b) Repeating the oxidation in the presence of copper(II) sulphate (3 mol. equiv.) gave neutral material which was separated (t.l.c.) into 3-phenylphthalide (27%), the dimer (3) (trace), and starting amide (24%).

Oxidation of the Diamide (1; R = H).—The neutral material was mainly starting diamide (91%), with 3,3'-diphenylbi-3-phthalidyl (3) (2%), and intractable products (15%).

Oxidation of *NN*-Dimethyl-*o*-benzylbenzamide.—The starting material, prepared from *o*-benzylbenzoyl chloride and dimethylamine, had m.p. 69–70° (from petroleum) (Found: C, 80.3; H, 7.0; N, 5.9. $C_{16}H_{17}NO$ requires C, 80.3; H, 7.2; N, 5.9%), ν_{max} , 1635 cm^{-1} , τ ($CDCl_3$) 1.00–1.50 (9H, m, ArH), 5.49 (2H, s, $ArCH_2Ar$), 6.47 (3H, s, NMe), and 7.20 (3H, s, NMe). The neutral material from the oxidation of the amide (3.0 g) was separated (p.l.c.) on silica gel in dichloromethane into 3-phenylphthalide (120 mg, 4%), the dimer (3) (trace), and a dimeric fraction (970 mg, 32%), evidently (n.m.r.) a mixture of partially demethylated products. Fractional crystallisation from aqueous methanol gave *tetra-N-methyl-2,2'-bibenzyl- $\alpha\alpha'$ -diylidibenzamide* (1; R = Me), prisms, m.p. 304–305° (580 mg, 19%) (Found: C, 80.7; H, 6.8; N, 5.8. $C_{32}H_{32}N_2O_2$ requires C, 80.6; H, 6.8; N, 5.9%), ν_{max} , 1625 cm^{-1} , τ 2.13–3.34 (18H, m, ArH), 4.86 (2H, s, Ar_2CH), and 7.13 and 8.27 (each 6H, s, NMe). Further chromatography (t.l.c.) of the mother liquors gave the *NNN'*-trimethyldiamide (8), prisms, m.p. 269–270° (from aqueous methanol) (80 mg, 3%) (Found: C, 80.2; H, 6.3. $C_{31}H_{30}N_2O_2$ requires C, 80.5; H, 6.5%), ν_{max} , 3330 and 1630 cm^{-1} , τ 0.70–1.88 (19H, m, ArH, NH), 4.60 (2H, s, Ar_2CH), 6.99 (3H, d, NMe), and 8.22br (6H, s, NMe₂).

The dimer (1; R = Me) was prepared from the diacid (7) (213 mg) by treatment with thionyl chloride (1.19 g) in dry benzene (25 ml) for 24 h. After removal of solvent the residual oil, in benzene (5 ml), was added, dropwise, to ice-cold aqueous dimethylamine (26% w/v; 20 ml). The precipitate had m.p. 304–305° (from aqueous methanol), not depressed by admixture with a specimen prepared by oxidation.

Oxidation of 3-Phenylphthalide.—The lactone (2.6 g) gave 3,3'-diphenylbi-3-phthalidyl (25 mg, 1%), starting compound (220 mg, 8%), and intractable material (1.70 g, 65%).

Oxidation of 3-Phenylphthalimidine.—From 400 mg of starting material, 112 mg (28%) was recovered together

¹⁶ A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 1945, 657.

¹⁷ M. S. Kharasch, A. C. Poshkus, A. Fono, and W. Nudenberg, *J. Org. Chem.*, 1951, 16, 1458.

with phthalimide (25 mg, 9%), and 3-hydroxy-3-phenylphthalimidine (18), needles, m.p. 164—165° (50 mg, 12%).

Oxidation of a Mixture of Compounds (2) and (4).—3-Phenylphthalide (420 mg) and 3-phenylphthalimidine (418 mg) in water (100 ml) were oxidised with persulphate (546 mg) in the usual way. Work-up of the small amount of neutral material yielded the dimer (5) (<1%) and a trace (t.l.c.) of phthalimide.

Oxidation of o-Benzoylbenzoic Acid.—(a) The neutral material from the acid (2.71 g) oxidation products yielded (p.l.c.) 3-phenylphthalide (420 mg, 15.5%) and 3,3'-diphenylbi-3-phthalidyl (3) (110 mg, 4%). The acid fraction (1.50 g) was methylated with methyl iodide-acetone-potassium carbonate, and the esters were chromatographed on silica gel in benzene to give methyl o-benzoylbenzoate (266 mg \equiv 9% starting acid), dimethyl 2,2'-bibenzyl- $\alpha\alpha'$ -diylidibenzoate⁸ (190 mg \equiv 6% starting acid), and an unresolved mixture (540 mg) of rotational isomers (n.m.r.) of the diester.

(b) Repeating the oxidation (on 2.13 g of acid) in the presence of copper(II) sulphate (5 mol. equiv.) gave 3-phenylphthalide (390 mg, 74%) and no dimer. The acidic fraction was entirely starting material.

Oxidation of 2,2'-Bibenzyl- $\alpha\alpha'$ -diylidibenzoic Acid.—The diacid (7) (530 mg), on oxidation with persulphate, afforded neutral material (90 mg) from which the biphtalidyl (3) (25 mg, 14%) was isolated by t.l.c. Starting material (350 mg) was recovered from the potassium hydrogen carbonate extracts.

Preparation of o-Benzoylbenzamide.—Ammonium o-benzoylbenzoate, prepared by dissolving the acid (22.5 g) in ammonia (250 ml; d 0.880) under reflux and evaporating the resulting solution to dryness, was heated at 160—170° for 15 min. The residue was extracted with ether (2 \times 150 ml) and the ethereal solution was washed with water, dried, and evaporated. Crystallisation of the residue from aqueous ethanol gave the amide, m.p. 157—159° (20 g, 90%), λ_{max} (cyclohexane) 209, 247sh, 283sh, and 293sh nm.

Oxidation of o-Benzoylbenzamide.—The neutral material from the amide (4.0 g) was separated on silica gel plates in chloroform-methanol (19 : 1) into fluorenone (400 mg, 12%) and phthalimide (520 mg, 21%). The acidic fraction yielded o-benzoylbenzoic acid (1.04 g, 26%).

Hydrolysis of o-Benzoylbenzamide.—The amide (300 mg) was heated under reflux for 2 h with an acidic solution prepared by decomposing potassium persulphate (485 mg) in boiling water (10 ml). The mixture was extracted with ether which was then shaken with a saturated potassium hydrogen carbonate solution. Acidification gave o-benzoylbenzoic acid (65 mg, 22%).

Attempted Hydrolysis of o-Benzoylbenzamide.—The amide (150 mg) was refluxed for 2 h in an acidic solution prepared by decomposing potassium persulphate (190 mg) in boiling water (5 ml). The amide was recovered quantitatively by extraction with ether.

2,2',3,3'-Tetraphenylbi-3-phthalimidyl (6).—3-Phenyl-3-(3-phenyl-3-phthalimidyl)phthalide (5) (30 mg), anilinium chloride (10 mg), and aniline (0.1 ml) were boiled under reflux for 12 h. The mixture was then extracted with benzene (20 ml); the extract was washed with water and 2N-hydrochloric acid, and dried (MgSO₄). Removal of the solvent and t.l.c. on silica gel in chloroform gave starting material (14 mg) and the desired *di-imide* which formed needles, m.p. 197—198° (sublim.) (from aqueous methanol) (7 mg) (Found: C, 84.2; H, 5.2; N, 4.9. C₄₀H₂₈N₂O₂ requires C, 84.5; H, 4.95; N, 4.9%), λ_{max} (C₆H₁₄) 216, 222sh, 277, and 285 nm (log ϵ 4.83, 4.80, 3.60, and 3.60), ν_{max} 1670 cm⁻¹. The same product (35 mg) was obtained in the same way from 3,3'-diphenylbi-3-phthalidyl (3) (150 mg) and anilinium chloride (150 mg) in aniline (1 ml).

We thank the S.R.C. Physico-Chemical Measurements Unit, Aldermaston, for the mass spectra. This work was supported by the United States Army through its European Research Office.

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