

Photochemical Transformations of Methoxyphthalaldehydic Esters: Synthesis of Methyl 6-Methoxyphthalaldehyde from the 3-Methoxy-isomer

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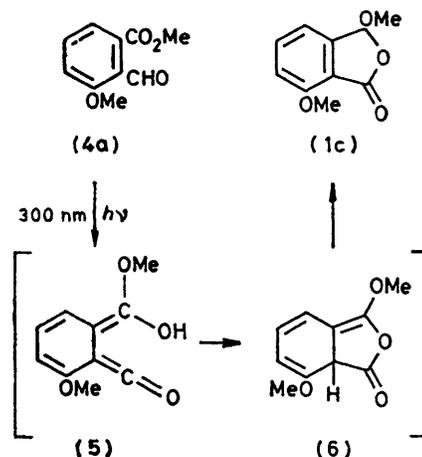
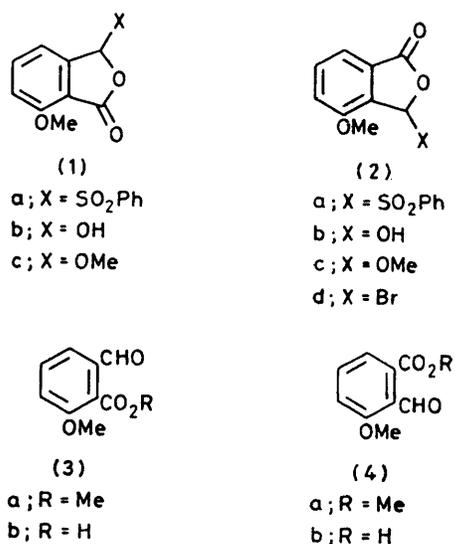
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Summary Irradiation of the 3-methoxyphthalaldehyde (4a) in methanol gives an excellent yield of the methoxyphthalide (1c) which can be converted into the 6-methoxyphthalaldehyde (3a) in excellent yield, thus effecting an 'isomerization' of the original phthalaldehyde.

RECENTLY several groups,¹⁻⁴ especially those of Hauser¹ and Johnson,² have reported approaches to the total synthesis of the anthracycline antitumour antibiotics and other anthraquinone natural products, all beginning with 4-(or 7-)methoxy 3-substituted phthalides. For example, the 3-phenylsulphonyl-7-methoxyphthalide (1a)^{1a} and the 3-bromo-4-methoxyphthalide (2d)² are both starting materials for syntheses of the anthracycline antitumour agents while the synthesis of the chartreusin aglycone begins with the isomeric 3-phenylsulphonyl-4-methoxyphthalide (2a).^{1b} These compounds are simple derivatives of the corresponding methoxyphthalaldehydic acids, (1b) and (2b),† and are generally prepared from these simpler materials. While the acid (2b)/(4b) is readily available from the inexpensive naphthalene-1,5-diol,⁵ the isomeric acid (1b)/(3b) is generally prepared in several steps from crotonaldehyde.^{1a,6} We report here the efficient preparation of the methoxyphthalaldehydic acid (1b) from the isomeric acid (2b), in which a photochemically promoted internal oxidation-reduction serves as the key step.

Oxidation of 1,5-dimethoxynaphthalene produced the 3-methoxyphthalaldehydic acid mixture (2b) and (4b),⁵ which was esterified to give (4a) by alkylation with potassium carbonate and methyl iodide.⁷ Irradiation of a methanolic solution of (4a) (300 nm; Rayonette) at room temperature under nitrogen for 14 h produced in quantitative yield a ca. 6:1 (by n.m.r.) mixture of the two isomeric dimethoxyphthalides (1c) and (2c). Chromatography afforded the pure 3,7-dimethoxyphthalide (1c) in 82% isolated yield. Basic hydrolysis (2% aq. NaOH; reflux; 90 min) furnished a quantitative yield of the crystalline acid (1b)/(3b) which could be esterified (K₂CO₃; MeI; acetone) to give methyl 6-methoxyphthalaldehyde (3a) in 96% isolated yield. Thus the 'isomerization' of the 3-methoxy-compound (4a) into the 6-methoxy-isomer (3a) proceeds in three steps in 78% yield.

The structure of the photo-product (1b)/(3b)‡ was established by comparison of its methylation product (3a) with an authentic sample prepared by a different route.⁶ Free-radical bromination of methyl 2-acetoxy-6-methylbenzoate produced the dibromomethyl compound which was hydrolysed directly to give 3,7-dihydroxyphthalide in 57% yield. Methylation of both the phenol and the carboxylic acid functionalities was accomplished by treatment with excess of potassium carbonate and methyl iodide to give (3a) in 93–96% yield. The two esters, prepared by different routes, were shown to be identical by 200 MHz ¹H n.m.r., i.r. and u.v.§ spectroscopy and t.l.c. in several solvents.



SCHEME

† These compounds exist as an equilibrium between the pseudoacid forms (1b) and (2b) and the phthalaldehydic acid forms (3b) and (4b), generally favouring the cyclized isomers.

‡ Since the m.p.s of the two acids (3b) and (4b) are very similar (J. Blair, J. J. Brown, and G. T. Newbold, *J. Chem. Soc.*, 1955, 708), it was decided to secure other evidence of the structural integrity of (3b), namely comparison with an authentic sample.

§ The u.v. spectra were measured in cyclohexane-methylene dichloride [50:50 for (3a); 95:5 for (4a)]; (3a): λ_{max} 310 (ϵ 3050), 248 (6440), and 226 nm (10,160); (4a): λ_{max} 310 (3940), 248 (4640), and 224 nm (7160).

A possible mechanism for the formation of (1c) from (4a) is given in the Scheme. Irradiation of the ester could effect a photoenolization process⁸ with the formation of the bis-keten monohemiacetal (5). Internal trapping of the keten by the hydroxy-group of the hemiacetal could give a lactone which could then aromatize *via* thermal enolization to give the phthalide (1c). This mechanism is similar in its general outline to that proposed by Pinhey for the formation of phthalide from photolysis of *o*-phthalaldehyde.⁹

The intermolecular trapping of the proposed monohemiacetal (5) in a Diels–Alder reaction with naphthoquinone or other good dienophiles could provide a useful approach to the anthracycline antitumour agents.¹⁰ How-

ever, irradiation of a solution of (4a) in cyclohexane–methylene dichloride in the presence of several dienophiles (maleic anhydride, naphthoquinone, juglone, methyl acrylate) gave the desired adducts in only very poor (*ca.* 5%) yields. Thus this absence of trapping casts some doubt on the mechanism presented above and therefore this approach to the anthracyclines has been abandoned.

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¹ (a) F. M. Hauser and R. P. Rhee, *J. Org. Chem.*, 1978, **43**, 178; *ibid.*, 1980, **45**, 3061; *J. Am. Chem. Soc.*, 1980, **101**, 1628; (b) F. M. Hauser and D. W. Combs, *J. Org. Chem.*, 1980, **45**, 4071.

² K. S. Kim, E. Vanotti, A. Suarato, and F. Johnson, *J. Am. Chem. Soc.*, 1979, **101**, 2483; K. S. Kim, M. W. Spatz, and F. Johnson, *Tetrahedron Lett.*, 1979, 331.

³ One of the earliest approaches of this sort is due to Eugster: C. H. Eugster and W. Treub, *Helv. Chim. Acta*, 1972, **55**, 969; C. H. Eugster and A. Brain, *ibid.*, p. 974.

⁴ Similar compounds with less functionality have also been employed, for example, 4-methoxyphthalide: P. G. Sammes and D. J. Dodsworth, *J. Chem. Soc., Chem. Commun.*, 1979, 33; N. J. P. Broom and P. G. Sammes, *ibid.*, 1978, 162; and 3-cyanophthalide: G. Kraus and H. Sugimoto, *Tetrahedron Lett.*, 1978, 2263.

⁵ C. A. Naylor, Jr., and J. H. Gardner, *J. Am. Chem. Soc.*, 1931, **53**, 4109.

⁶ F. Bohlmann and K. Prezewowsky, *Chem. Ber.*, 1964, **97**, 1176.

⁷ C. Brown and M. V. Sargent, *J. Chem. Soc. C*, 1969, 1818.

⁸ For an excellent recent review, see: P. G. Sammes, *Tetrahedron*, 1976, **32**, 405.

⁹ K. F. Cohen, J. T. Pinhey, and R. J. Smith, *Tetrahedron Lett.*, 1968, 4729.

¹⁰ For a similar photochemical approach see: M. E. Jung and J. A. Lowe, *J. Org. Chem.*, 1977, **42**, 2371.