

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

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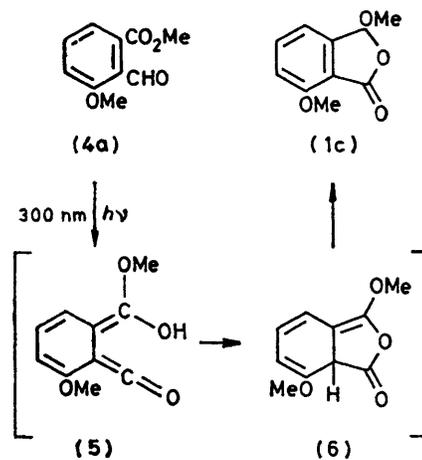
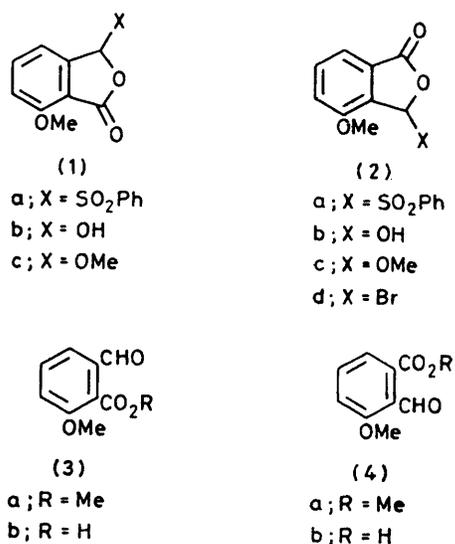
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**Summary** Irradiation of the 3-methoxyphthalaldehyde (4a) in methanol gives an excellent yield of the methoxyphthalide (1c) which can be converted into the 6-methoxyphthalaldehyde (3a) in excellent yield, thus effecting an 'isomerization' of the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

RECENTLY several groups,<sup>1-4</sup> especially those of Hauser<sup>1</sup> and Johnson,<sup>2</sup> 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)<sup>1a</sup> and the 3-bromo-4-methoxyphthalide (2d)<sup>2</sup> 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).<sup>1b</sup> 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,<sup>5</sup> the isomeric acid (1b)/(3b) is generally prepared in several steps from crotonaldehyde.<sup>1a,6</sup> 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),<sup>5</sup> which was esterified to give (4a) by alkylation with potassium carbonate and methyl iodide.<sup>7</sup> 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 (K<sub>2</sub>CO<sub>3</sub>; 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.<sup>6</sup> 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 <sup>1</sup>H 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):  $\lambda_{\text{max}}$  310 ( $\epsilon$  3050), 248 (6440), and 226 nm (10,160); (4a):  $\lambda_{\text{max}}$  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 process<sup>8</sup> 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.<sup>9</sup>

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.<sup>10</sup> 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.

We thank the National Institutes of Health for financial support. M. E. J. acknowledges a Camille and Henry Dreyfus Teacher-Scholar grant and an Alfred P. Sloan Foundation fellowship.

(Received, 27th May 1981; Com. 622.)

<sup>1</sup> (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.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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.

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

<sup>6</sup> F. Bohlmann and K. Prezewowsky, *Chem. Ber.*, 1964, **97**, 1176.

<sup>7</sup> C. Brown and M. V. Sargent, *J. Chem. Soc. C*, 1969, 1818.

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

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

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