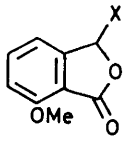
Photochemical Transformations of Methoxyphthalaldehydic Esters: Synthesis of Methyl 6-Methoxyphthalaldehydate from the 3-Methoxy-isomer

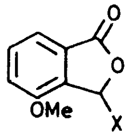
By Michael E. Jung* and Roberto B. Blum
(*Department of Chemistry, University of California, Los Angeles, California* 90024)

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

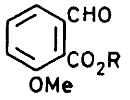
Recently several groups,[1–4] especially those of Hauser[1] and Johnson,[2] have reported approaches to the total synthesis of the anthracycline antitumour antibiotics and other anthraquinone natural products, all beginning with 4-(or 7-)methoxy 3-substituted phthalides. For example, the 3-phenylsulphonyl-7-methoxyphthalide (**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.



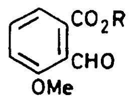
(1)
a; X = SO_2Ph
b; X = OH
c; X = OMe



(2)
a; X = SO_2Ph
b; X = OH
c; X = OMe
d; X = Br



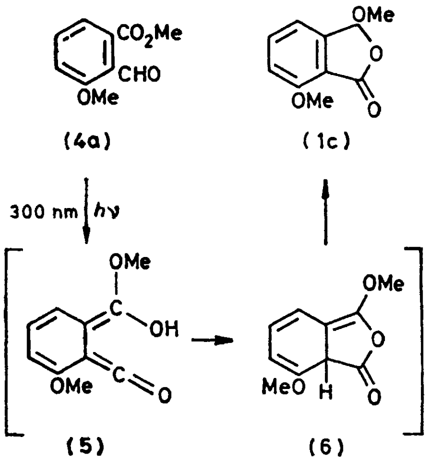
(3)
a; R = Me
b; R = H



(4)
a; R = Me
b; R = H

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 (K_2CO_3; MeI; acetone) to give methyl 6-methoxyphthalaldehydate (**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

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† 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 process[8] 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] However, 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.