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3,6-DIMETHOXYBENZOCYCLOBUTENONE: A VERSATILE QUINONE PRECURSOR

Manouchehr Azadi-Ardakani and Timothy W. Wallace*

Department of Chemistry and Applied Chemistry,
University of Salford, Salford M5 4WT.

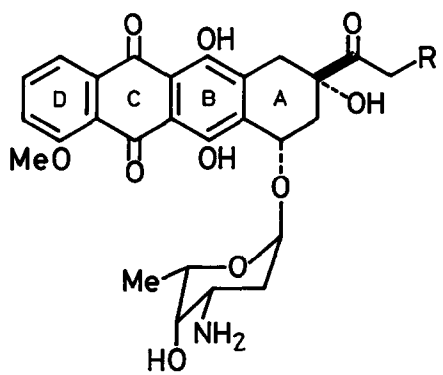
Summary: An improved route to the title compound is described and its potential as precursor to a variety of quinone derivatives, including analogues of the anthracycline antitumour agents, clearly illustrated by conversion to various 1,2,3,4-tetrahydro-5,8-dimethoxy-1-naphthols

The biological and physico-chemical properties of quinones make them important targets for organic synthesis. Our interest in this area, based on approaches to analogues of the anthracycline antitumour agents daunomycin (1) and adriamycin (2),[1] prompted us to seek an intermediate capable of serving as a common precursor to various quinones and derivatives, and we considered that 3,6-dimethoxybenzocyclobutenone (3) might be an appropriate choice because several combinations of the following synthetic transformations seem possible.

(a) Functionalisation at C-1, C-2, or C-5 *via* nucleophilic addition, homolytic bromination, or electrophilic substitution respectively.

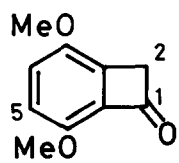
(b) Annelation of the aromatic ring *via* electrophilic substitution (*e.g.* phthaloylation) or an oxidative demethylation/Diels-Alder cycloaddition sequence.

(c) Thermal electrocyclic ring-opening of derived benzocyclobutenols and trapping of the resulting hydroxy-*o*-quinone dimethides with dienophiles.



1 R = H

2 R = OH



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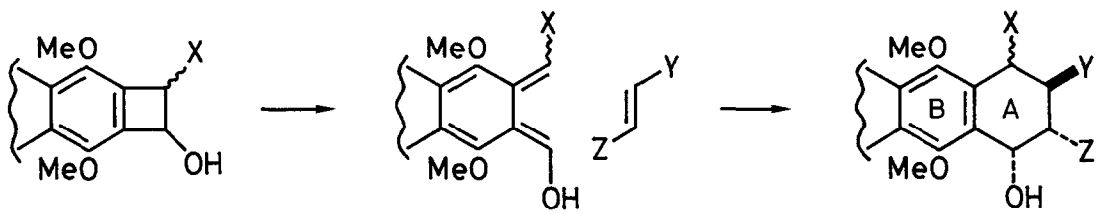
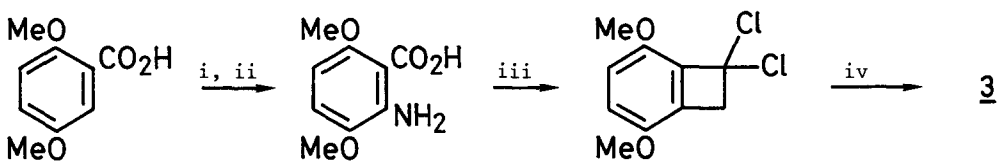
The latter reaction has particular relevance to anthracycline synthesis, since it offers a mild, flexible, and highly selective means of establishing an array of substituent groups around ring A of an aglycone (Scheme 1). Our priorities in the initial stages of this work were therefore to ensure that the proposed intermediate (3) is preparable without difficulty and that ring-opening and cycloaddition of the derived benzocyclobutenol proceeds efficiently and with a synthetically useful degree of selectivity.



SCHEME 1

Preparation of the ketone (3) was recently reported by McOmie and coworkers.[2] A crucial step was the (2 + 2) cycloaddition of 3,6-dimethoxybenzyne, generated *via* diazotisation of 2-amino-3,6-dimethoxybenzoic acid (4), to 1,1-dichloroethene, which gave the *gem*-dichloride (5) as an oil in 32% yield. We found this step troublesome, but the conditions described by Dürr and coworkers[3] for an analogous reaction proved both consistent and effective, giving dichloride (5) as a crystalline solid[4] in 80% yield after distillation, which is remarkable for this type of aryne cycloaddition.[5] Acid hydrolysis of dichloride (5) gave the ketone (3) quantitatively; it is therefore available from 2,5-dimethoxybenzoic acid[6] in four efficient steps, as shown in Scheme 2.



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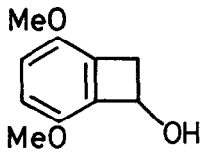
SCHEME 2 Reagents: i, HNO_3 (72%); ii, H_2/Pd-C (77%); iii, $C_5H_{11}ONO$, HCl, then $CH_2{=}CCl_2$, $ClCH_2CH_2Cl$, propylene oxide (80%); iv, aq.H^+ (100%).

We next turned our attention to ring-opening and cycloadditions of the benzocyclobutenol (6), prepared in 92% yield by reduction of (3) with sodium borohydride in ethanol.[4] Heating the alcohol (6) with acrylonitrile gave a 1:1 adduct, isolated by chromatography in 80% yield. Homogeneous by t.l.c. and ^{13}C-n.m.r. spectroscopy, it was assigned the *cis*-structure (7) on the basis of its ^1H-n.m.r. spectrum, which showed H-1 as a doublet, J = 4 Hz. Esters of acrylic acid also reacted regioselectively but gave mixtures of stereoisomers as shown in Table 1. Structures were again assigned on the basis of ^1H-n.m.r. signals due to H-1, which were consistently doublets, J = 3 - 4 Hz (*cis*) or 7 - 8 Hz (*trans*).



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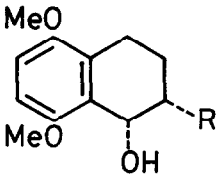
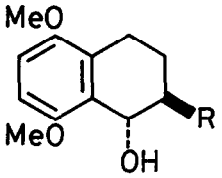
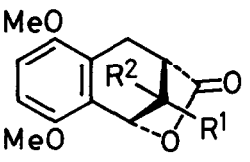


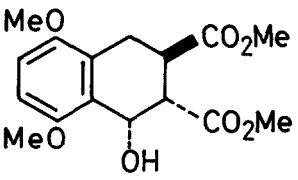
7 R = CN
8 R = CO_2Me
10 R = CO_2Et



9 R = CO_2Me
11 R = CO_2Et



12 R^1 = CO_2H R^2 = H
13 R^1 = CO_2Me R^2 = H
15 R^1 = H R^2 = CO_2Me



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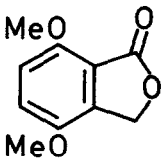

16

TABLE 1 THERMALLY-INDUCED CYCLOADDITIONS OF (6) TO DIENOPHILES[7]

DIENOPHILE	MOL. EQUIVALENT	PRODUCTS,[4] % YIELDS	
Acrylonitrile	10	(7) 80	
Methyl Acrylate	10	(8) 47	(9) 13
Ethyl Acrylate	1.1	(10) 23	(11) 54[8]
Maleic Anhydride	1.0	(12) 66[8]	
Dimethyl Fumarate	1.1	(14) 46	(15) 4

With maleic anhydride the product isolated was the acid lactone (12), characterised as the methyl ester (13) by spectral comparison with the analogue obtained from unsubstituted benzocyclobutenol.[9] With dimethyl fumarate the major product (14) was accompanied by some of the γ-lactone (15), formed presumably from the unobserved *exo*-adduct and suggesting that protection of the alcohol group in (6) might prove worthwhile for synthetic purposes. Other improvements would include the use of an inert atmosphere during cycloaddition, which should suppress the formation of the phthalide (16),[10] isolated in low yield from several reactions and in 36% yield by deliberately oxygenating a toluene solution of (6) under reflux in the absence of a dienophile.

Since little or none of the derived 2-methylbenzaldehyde was formed during the above cycloadditions, it can be assumed that the long reaction times compared to those of the parent benzocyclobutenol[9] (96 h *vs.* 5 h respectively) are a reflection of the retarding effect of the *peri*-substituents on the electrocyclic ring-opening process, in which the -OH

group prefers to undergo outward conrotation (*cf.* Scheme 1).[9,11] In the cycloaddition step the normal electronic preference for an *endo* transition state appears to be sensitive to the steric requirement of the dienophile (*cf.* acrylonitrile *vs.* methyl and ethyl acrylate). This might provide a simple means of controlling the stereochemistry of the product.

Since functionalised tetrahydro-1-naphthol derivatives have been widely sought and used in anthracycline synthesis,[12] the above short method for their preparation may prove valuable in such a context. However, a more direct approach to ring A analogues, implicit in Scheme 1 and recently shown to be feasible,[13] would involve annelation of (3) prior to cycloaddition to dienophiles. This and other aspects of the chemistry of 3,6-dimethoxybenzocyclobutenone are currently under investigation.

Acknowledgement: We thank the S.E.R.C. for a Postdoctoral Fellowship (to M. A.-A.).

REFERENCES AND NOTES

1 For a recent and comprehensive review of anthracycline chemistry, *cf.* F. Arcamone, 'Doxorubicin', Medicinal Chemistry, Vol. 17, Academic Press, New York, 1981.

2 O. Abou-Teim, R.B. Jansen, J.F.W. McOmie, and D.H. Perry, *J. Chem. Soc., Perkin Trans. 1*, 1980, 1841.

3 H. Dürr, H. Nickels, L.A. Pacala, and M. Jones, *J. Org. Chem.*, 1980, *45*, 973.

4 All compounds were characterised by spectroscopy and, excepting (10) and (11), by elemental analysis. M.p. data (°C): (5), 49-50 (petroleum); (6), 85-86 (ether-petroleum); (7), 143-145 (ethyl acetate-petroleum); (8), 111-113 (ethyl acetate-petroleum); (9), 91-92 (ether-petroleum); (12), 214-217 (dec.); (13), 164-167 (ethyl acetate-petroleum); (14), 152-154 (ethyl acetate-petroleum); (15), 117 (ethyl acetate-petroleum). N.m.r. data: (10), δ ($CDCl_3$) 5.37 (1H, d, J 3 Hz, H-1); (11), δ ($CDCl_3$) 5.33 (1H, d, J 8 Hz, H-1).

5 The efficiency of 3,6-dimethoxybenzyne in (4 + 2) cycloadditions has also been noted; *cf.* H. Heaney, J.H. Hollinshead, G.W. Kirby, S.V. Ley, R.P. Sharma, and K.W. Bentley, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1840.

6 Available from Lancaster Synthesis, catalogue number 3234.

7 Reaction conditions: The dienophile and (6) (1.0 mmol) were heated in toluene (20 ml) under reflux for 96 h. The products were isolated by medium pressure chromatography over silica gel except where otherwise stated. Yields refer to isolated material homogeneous by t.l.c.

8 Products (10) and (11) were obtained as a mixture, and the isomer ratio determined by resolution of an aliquot by h.p.l.c. Product (12) was isolated by filtration of the cooled reaction mixture.

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10 H. Inouye, *Pharmaceutical Bulletin*, 1954, *2*, 359.

11 M.J. Curry and I.D.R. Stevens, *J. Chem. Soc., Perkin Trans. 2*, 1980, 1391.

12 For examples, *cf.* reference 1, and J.S. Swenton, D.K. Anderson, D.K. Jackson, and L. Narasimhan, *J. Org. Chem.*, 1981, *46*, 4825; M.G. Dolson, B.L. Chenard, and J.S. Swenton, *J. Am. Chem. Soc.*, 1981, *103*, 5263; M.J. Broadhurst, C.H. Hassall, and G.J. Thomas, *J. Chem. Soc., Chem. Commun.*, 1982, 158; C.E. Coburn, D.K. Anderson, and J.S. Swenton, *ibid.*, 1982, 987.

13 Unsubstituted 2,3-quinone dimethides derived from 1,4-dimethoxy-9,10-anthraquinone undergo cycloaddition to dienophiles; *cf.* F.A.J. Kerdesky, R.J. Ardecky, M.V. Lakshmikantham and M.P. Cava, *J. Am. Chem. Soc.*, 1981, *103*, 1992, and R.J. Ardecky, D. Dominguez, and M.P. Cava, *J. Org. Chem.*, 1982, *47*, 409.

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