The Regiospecific Preparation of 1,4-Dioxygenated Anthraquinones: A New Route to Islandicin, Digitopurpone, and Madeirin

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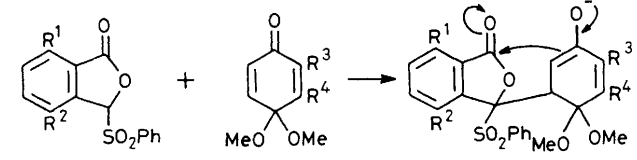
Summary A direct, versatile, one-step synthesis of anthraquinones which exhibits total regioselectivity (>99%) and involves the reaction of the anion of 4- or 7-methoxy-3-phenylsulphonylphthalides with variously substituted quinone monoacetals is reported.

RETROSYNTHETIC analysis of anthraquinones naturally suggests the use of phthalic anhydrides as bisacylating agents of benzenoid partners. In practice such reactions frequently lack regiocontrol if the two reagents are unsymmetrical[1,2] and are only useful where such control is not required.[3] Whilst modification of this synthetic strategy has led to alternative regiospecific routes to anthraquinones,[4] few of the reaction sequences afford the anthraquinone directly, and subsequent oxidation steps are usually unsatisfactory. The development of a reaction which is both regiospecific and capable of yielding an anthraquinone directly offers a marked improvement over existing methods. In considering this problem, we were mindful of the structural requirements of the clinically useful anthracyclines,[5,6] and concentrated our attention upon anthraquinones containing potential hydroxy-groups in the 1- and 4-positions. For reasons outlined elswehere,[7] we consider that oxo-bridged intermediates of the type (**8**) hold the key to a successful route to anthraquinones. We now report a new regiospecific, single-step reaction (Scheme 1) based upon this premise, and exploit it to synthesize the naturally occurring anthraquinones madeirin[8] (**15**), islandicin[9]† (**11**), and digitopurpone[10]† (**12**).

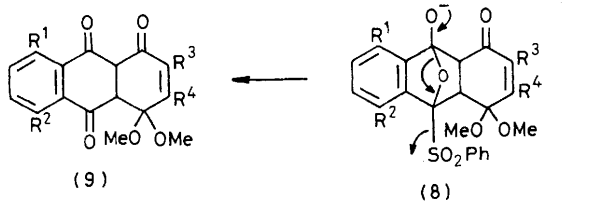
† These compounds were obtained by demethylating the ethers (**17** or **18**) and (**16** or **19**) with boron tribromide.

The process takes advantage of the Michael acceptor properties[11] of quinone monoacetals[12] to ensure regiocontrol, and the nucleophilic properties of phthalide anions[13] to initiate bond formation. The intermediate enolate anion (**7**), derived from the Michael adduct, undergoes subsequent ring closure[14] to form the bridged ether (**8**). The value of the phenylsulphonyl (or other)‡ leaving group in the nucleophile (**1**) is now apparent. Ring opening of the oxo-bridge in the ether (**8**), together with elimination of the phenylsulphonyl group, affords the triketone (**9**) which subsequently eliminates methanol to give the anthraquinones (**13**)—(**21**). All these processes occur under basic reaction conditions, but at different temperatures.§¶ A major feature of this reaction is its versatility with regard to regiochemical control. For example, the regiochemical requirements of islandicin (**11**) are met by treating either (**2**) with (**6**) to yield (**18**) or (**3**) with (**5**) to yield (**17**). The reversal of regiochemistry (in this case to that of digitopurpone), can therefore be achieved by suitable variation of substituents on either the phthalide or the dienone.

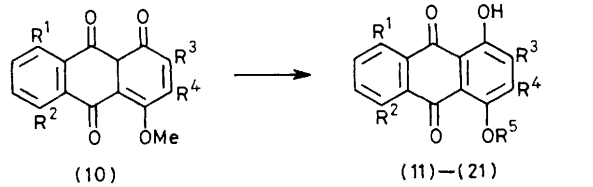


(1) $R^1 = R^2 = H$ (4) $R^3 = R^4 = H$
(2) $R^1 = H, R^2 = OMe$ (5) $R^3 = H, R^4 = Me$
(3) $R^1 = OMe, R^2 = H$ (6) $R^3 = Me, R^4 = H$

(7)



(9) (8)

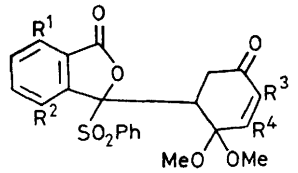


(10) (11)—(21)

R^1—R^5, for (**11**)—(**21**):

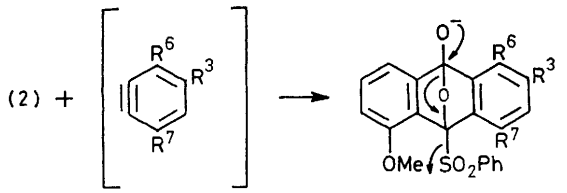
(**11**) $R^1 = R^4 = R^5 = H, R^2 = OH, R^3 = Me$
(**12**) $R^1 = R^3 = R^5 = H, R^2 = OH, R^4 = Me$
(**13**) $R^1 = R^2 = R^3 = R^4 = H, R^5 = Me$
(**14**) $R^1 = R^2 = R^3 = H, R^4 = R^5 = Me$
(**15**) $R^1 = R^2 = R^4 = H, R^3 = R^5 = Me$
(**16**) $R^1 = R^3 = H, R^2 = OMe, R^4 = R^5 = Me$
(**17**) $R^1 = OMe, R^2 = R^3 = H, R^4 = R^5 = Me$
(**18**) $R^1 = R^4 = H, R^2 = OMe, R^3 = R^5 = Me$
(**19**) $R^1 = OMe, R^2 = R^4 = H, R^3 = R^5 = Me$
(**20**) $R^1 = R^3 = R^4 = H, R^2 = OMe, R^5 = Me$
(**21**) $R^1 = OMe, R^2 = R^3 = R^4 = H, R^5 = Me$

SCHEME 1.



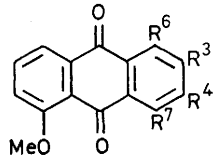
(22)

The following is an example of the reaction conditions. Addition of the phthalide (**3**) to 1·2 equiv. of lithium di-isopropylamide in tetrahydrofuran at −80 °C afforded the yellow anion which, when quenched with 1·2 equiv. of (**5**), gave a green–yellow solution. After stirring at −80 °C for 20 min the reaction mixture was allowed to warm to room temperature over 30 min. At about −20 °C the colour of the solution changed to brown and finally to a red–violet, indicating the formation of the anthraquinone phenolate anion. The solution was acidified at −10 °C, the solvent removed, and the product extracted into dichloromethane. The anthraquinone (**17**) was isolated either by direct crystallisation from methanol or by t.l.c. followed by crystallisation. Compounds prepared by this method are listed in the Table.



(23) $R^3 = R^7 = H, R^6 = OMe$ (regioselective) (26)
(24) $R^3 = Me, R^6 = R^7 = OMe$ (non-regioselective)
(25) $R^3 = Me, R^6 = OH, R^7 = OMe$

(no quinonoid product)



(27) $R^3 = R^4 = R^7 = H, R^6 = OMe$
(28) $R^3 = Me, R^4 = H, R^6 = R^7 = OMe$
(29) $R^3 = H, R^4 = Me, R^6 = R^7 = OMe$

SCHEME 2.

‡ Other leaving groups, such as phenylthiolate, can be used but the yields are lower.

§ The major by-products of these reactions appear to be the Michael adducts [*cf.* (**22**)]. These compounds are the intermediates which cyclise to yield the oxo-bridged compounds (**8**) and their presence in the reaction mixture supports the proposed mechanism.

¶ A similar reaction using a quinone rather than a quinone monoacetal failed to yield any anthraquinone. Presumably under the reaction conditions the intermediate Michael adduct exists as a less nucleophilic phenolate anion as observed by Treub and Eugster (W. Treub and C. H. Eugster, *Helv. Chim. Acta*, 1972, **55**, 969).

TABLE. Reaction of phthalide anions with quinone monoacetals.

Phthalide	Quinone monoacetal	Product	% Yield	M.p./°C
(**1**)	(**4**)	(**13**)	62	173—174[a,d]
(**1**)	(**5**)	(**14**)	54	174—176[a]
(**1**)	(**6**)	(**15**)	50	187—188[a,e]
(**2**)	(**5**)	(**16**)	40	172—174[a]
(**3**)	(**5**)	(**17**)	55	193—194[a]
(**2**)	(**6**)	(**18**)	50	164—165[a,b]
(**3**)	(**6**)	(**19**)	45	234—235[b,c]
(**2**)	(**4**)	(**20**)	40	176—178[a,f]
(**3**)	(**4**)	(**21**)	38	260—261

[a] From MeOH; [b] from $CHCl_3$–MeOH; [c] softens 150 °C; [d] Lit. m.p. 167—168 °C ('Dictionary of Organic Compounds,' 4th edn., eds. I. Heilbron, A. H. Cook, M. M. Bunbury, and D. H. Hey, Eyre and Spottiswoode, London, 1965); [e] Lit.[8] m.p. 188—189 °C; [f] Lit. m.p. 177—178 °C (J. E. Baldwin and K. W. Blair, *Tetrahedron Lett.*, 1978, 2559).

Our reaction finds some analogy with the route to anthraquinones recently reported by Sammes.[15] We have established[16] that this methodology can be extended by the use of phthalides (**1**)—(**3**) to yield an anthraquinone in one step (Scheme 2), again using the leaving ability of the phenylsulphonyl group to obtain the higher oxidation state. Furthermore, the reaction is regioselective if a monoalkoxybenzyne, is employed, *e.g.* (**23**) → (**27**), but we have been unable to observe any regiospecificity with dioxygenated species, *e.g.* (**24**) → (**28** + **29**). Contrary to expectation,[15] phenolic benzynes such as (**25**) yield no quinonoid products, and this underlines the value of the present procedure. Our methodology has been applied to the synthesis of anthracyclines and will be reported in due course.

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