

Chemistry of Quinones. Part III.¹ Cleavage of the Methyl Ethers of some Naturally Occurring Hydroxyanthraquinones

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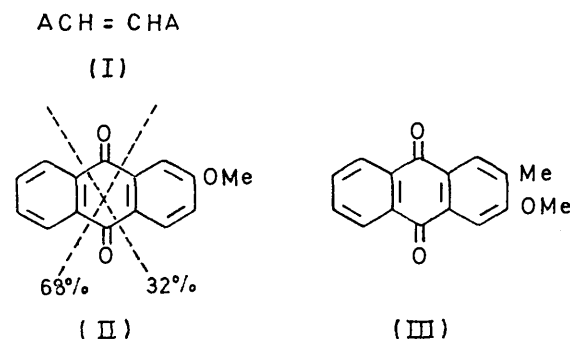
The action of the reagent formed by adding water (3 equiv.) to potassium t-butoxide (10 equiv.) in 1,2-dimethoxyethane on the methyl ethers of a range of naturally occurring mono-, di-, and tri-hydroxy- β -methylanthraquinones has been studied. All the substrates containing at least one α -methoxy-substituent were cleaved to give mixtures of benzoic acids and/or phthalic acids in 42–82% yield.

ANTHRAQUINONE and several methoxyanthraquinones are cleaved in high yield to give mixtures of benzoic acids and/or phthalic acids when treated with the reagent formed by adding water (3 equiv.) to potassium t-butoxide (10 equiv.) in 1,2-dimethoxyethane,² but 2-methylanthraquinone and some other alkyl derivatives are only cleaved in 1–2% yield under similar conditions.¹ The main reaction with the latter substrates is oxidation to give dehydro-dimers; 2-methylanthraquinone, for example, gives the ethylene derivative (I; A = anthraquinon-2-yl) in 84% yield. Many naturally occurring anthraquinones contain both hydroxy- and alkyl (commonly β -methyl) substituents³ and the main object of the present work was to determine whether the methyl ethers of such quinones, which might dimerise or cleave when treated with the butoxide–water reagent, could be cleaved satisfactorily. Such reactions would be useful in both structure elucidation and biosynthetic studies since relatively few methods are available for degrading anthraquinones.⁴

We have treated the methyl ethers of a range of mono-, di- and tri-hydroxy- β -methylanthraquinones with the butoxide–water reagent and determined the yields and compositions of the acid fractions. The results are summarised in the Table. The hydroxyquinones were converted into their methyl ethers before attempting cleavage because 1-hydroxy- and 1,4- and 1,5-dihydroxyanthraquinone are unaffected by the cleavage reagent under conditions that efficiently cleave the corresponding methoxyquinones.⁵

α -Methoxy-substituents are known to increase the rate of the cleavage reaction² but the effect of β -methoxy-substituents is less clear. Only one substrate with just β -methoxy-substituents, 2,6-dimethoxyanthraquinone,

one, has been studied previously and this cleaved less readily than anthraquinone, suggesting that β -methoxy-substituents decrease the rate of cleavage.² We have now treated 2-methoxyanthraquinone (II) with the cleavage reagent and the result obtained supports this conclusion: compound (II) was only cleaved in 31% yield under conditions that resulted in anthraquinone being cleaved in 60% yield. Cleavage occurred as shown



in formula (II). It was consequently not surprising that 3-methoxy-2-methylanthraquinone (III) reacted with the butoxide–water reagent in a manner analogous to that of 2-methylanthraquinone.¹ The major product (60%) was the ethylene derivative (I; A = 3-methoxyanthraquinon-2-yl) and the main component of the small acid fraction (4%) was benzoic acid; no methylmethoxybenzoic acids were detected.

Our results show that α -methoxy-substituents promote cleavage so strongly that cleavage is a major reaction even in the presence of β -methoxy- and β -methyl substituents.

³ R. H. Thomson, 'Naturally Occurring Quinones,' Academic Press, New York and London, 1971, ch. 5.

⁴ Ref. 3, p. 43.

⁵ D. G. Davies, P. Hodge, and P. Yates, unpublished results.

¹ Part II, D. G. Davies, P. Hodge, and P. Yates, *J.C.S. Perkin I*, 1973, 850.

² D. G. Davies and P. Hodge, *J. Chem. Soc. (C)*, 1971, 3158.

Cleavage of anthraquinones by butoxide-water reagent					
Substrate (II)	Wt. (mg) of substrate 9	Reaction time (h) ^a 2	Yield (%) of acids ^b 31 ^d	Acid(s) produced	Composition (%) of acid fraction ^c
(II)				Benzoic 3-Methoxybenzoic 4-Methoxybenzoic	50 16 34
(III)	21	2	4 ^e	Complex mixture of acids obtained: benzoic acid was the main component	
(IVa)	12	2	57	Benzoic 3-Methoxy-4-methylbenzoic	77 23
(IVb)	50	2	65	Benzoic 2-Methoxy-4-methylbenzoic 3-Methoxy-5-methylbenzoic	51 5 44
(V)	25	2	82 ^f	Phthalic	100
(VI)	10	4	42	3,4-Dimethoxybenzoic 3-Methoxy-4-methylbenzoic 4-Methoxy-3-methylbenzoic Two unidentified acids	54 2 38 each 3 ^g
(VII)	4	2	55	2,3-Dimethoxybenzoic 3,4-Dimethoxybenzoic 2-Methoxy-3-methylbenzoic 3-Methoxy-4-methylbenzoic	1 65 1 33
(VIIIa)	80	2	65 ^h	2,4-Dimethoxybenzoic 3,5-Dimethoxybenzoic 2-Methoxy-4-methylbenzoic 3-Methoxy-5-methylbenzoic	22 26 22 30
(VIIIb)	9	3	50	2,3-Dimethoxybenzoic 3,4-Dimethoxybenzoic 2-Methoxy-4-methylbenzoic 3-Methoxy-5-methylbenzoic	27 24 13 36
(IX)	144 140	2 0.5 ^f	98 ⁱ } 94 ^j }	3-Methoxybenzoic 2,5-Dimethoxybenzoic 3-Methoxyphthalic	27 23 50

^a Reactions carried out at reflux temperature (*ca.* 85°) unless indicated otherwise. ^b See Experimental section for method used to calculate the yields. ^c Determined by g.l.c. of the methylated acid fraction. ^d Similar results were obtained when the experiment was repeated. ^e 33% Starting material recovered. ^f 2,5-Dimethoxytoluene detected by g.l.c. ^g The unidentified esters were assumed to have the same molecular weight and response factor as methyl benzoate. ^h Starting material (14%) recovered. ⁱ 1,4-Dimethoxybenzene was isolated in 91% of the yield of 3-methoxyphthalic acid. ^j Reaction carried out at 20°.

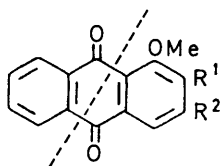
Thus 1-methoxy-2-methyl- and 1-methoxy-3-methyl-anthraquinone (IVa and b, respectively), 1,4-dimethoxy-2-methylanthraquinone (V), 1,2,6-trimethoxy-7-methyl-anthraquinone (VI), morindone trimethyl ether (VII), and frangula- and nataloe-emodin trimethyl ethers (VIIIa and b, respectively) were all cleaved in at least 42% yield when treated with the butoxide-water reagent. As the methyl ethers of most naturally occurring hydroxy-anthraquinones contain one or more α -methoxy-groups, the cleavage reaction should be widely applicable in this field.

The compositions of the acid fractions obtained are of interest because they indicate the principal directions of cleavage and these directions are not the same in every case. It would be expected that when cleavage occurred to give benzoic acids the yields of the two acids resulting from cleavage in one direction would, within experimental error, be equal, but this was not always so. The reason for the differences is not clear but in several instances it was the methyl-substituted benzoic acids that were deficient, and this suggests that in these cases oxidative dimerisation reactions,¹ either on the substrates themselves or the cleavage products, were reducing the yields of methyl-substituted acids. Despite the

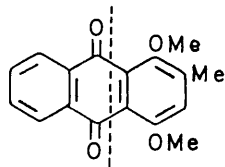
differences there is no doubt as to which were the principal directions of cleavage; these are indicated on the appropriate formulae. Comparison of the cleavage patterns found in this work with those of the methoxyquinones studied previously² indicates that when α -methoxy-substituents are present the pattern of cleavage is largely determined by the number and relative positions of these substituents. The patterns observed for anthraquinones with one α -methoxy-substituent and anthraquinones with two α -methoxy-substituents in a 1,4-, 1,5-, or 1,8-relationship are illustrated in formulae (IV), (V), (VII), and (VIII), respectively. No anthraquinone with three α -methoxy-substituents had previously been treated with the cleavage reagent so we investigated the behaviour of 1,4,5-trimethoxyanthraquinone (IX). Cleavage occurred so readily that the yield of acids was almost quantitative after 30 min at 20°. Analysis of the acid products indicated that cleavage occurred as shown in formula (IX).

As a degradative method, the cleavage reactions have several attractive features. First, all the carbon atoms present in the starting material can be recovered in relatively large fragments. Secondly, given the structures of the products (or most of them) and bearing in

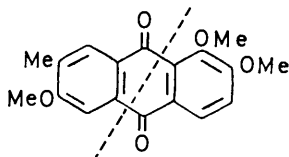
mind the cleavage of patterns (observed for the various types of α -methoxyanthraquinones, it is in many cases possible to deduce unambiguously the structure of the



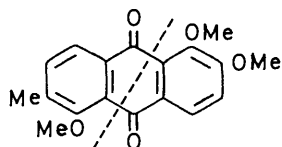
(IV) a; $R^1 = \text{Me}, R^2 = \text{H}$
b; $R^1 = \text{H}, R^2 = \text{Me}$



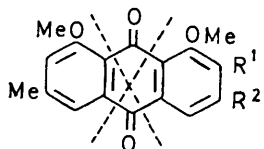
(V)



(VI)

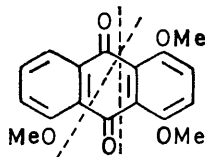


(VII)



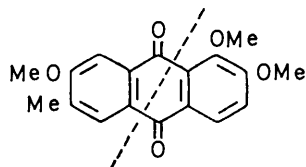
(VIII) a; $R^1 = \text{H}, R^2 = \text{OMe}$
b; $R^1 = \text{OMe}, R^2 = \text{H}$

quinone. Ambiguities that might arise, such as whether a quinone had one α -methoxy-substituent or had two in a 1,5-relationship could often be removed by consideration of the minor acid products. For example, cleavage

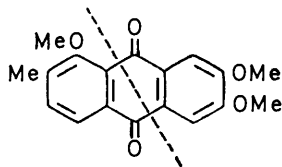


(IX)

of quinones (X) and (XI) (which have not been studied) would be expected to give the same *major* acid products as quinone (VII), but only structure (VII) can account



(X)



(XI)

for the formation of small amounts of 2,3-dimethoxybenzoic acid and 2-methoxy-3-methylbenzoic acid. Thirdly, since the products can be readily analysed by

g.l.c. the cleavages need only be carried out on a small scale. In the present work we carried out several cleavages on 4–12 mg samples of quinone. Finally, if, in connection with biosynthetic work, the substrate is labelled with ^{14}C , the amount of activity present in *each* carbonyl group can in most cases be readily determined.

EXPERIMENTAL

General procedures are as given before.^{2,6}

Substrates.—Most were already available in these laboratories. Others were donated by Professor R. H. Thomson and Dr. H. Anderson (both of University of Aberdeen), Professor L. H. Briggs (University of Auckland), and Dr. J. D. Bu'Lock (University of Manchester).

1,4-Dimethoxy-2-methylantraquinone (V), obtained by methylation (67%) of the corresponding dihydroxy-compound with potassium carbonate and dimethyl sulphate in acetone, crystallised from ether-petroleum (b.p. 40–60°) as yellow needles, m.p. 131–132°, ν_{max} (Nujol) 1667 cm^{-1} , δ (CDCl_3) 2.38br (3H, s, CMe), 3.85(s) and 3.97(s) (6H, two OMe), 7.12br (1H, s, H-3), and 7.5–8.3 p.p.m. (4H, complex m, H-5 to H-8) (Found: C, 72.0; H, 5.0. $\text{C}_{17}\text{H}_{14}\text{O}_4$ requires C, 72.3; H, 5.0%).

Cleavage Reactions.—Except where indicated otherwise the reactions were carried out as follows. If the amount of substrate used exceeded 25 mg the reagent was prepared by adding water (0.09 ml; added as a 10% solution in 1,2-dimethoxyethane) to a vigorously stirred mixture of potassium *t*-butoxide (2.00 g) and 1,2-dimethoxyethane (25 ml) at 20° under nitrogen. If the amount of quinone used was less than 25 mg the reagent was prepared on one-fifth of the above scale. The quinone was added to the reagent and the mixture was heated under reflux, the quantity of quinone used and the reaction time being as shown in the Table. At the end of the reaction period the mixture was cooled and added to saturated aqueous sodium chloride (five times the volume of the reaction solvent). The solution was acidified with hydrochloric acid and extracted with ethyl acetate (three times). The combined extracts were washed with water, dried, and evaporated to give the crude product. A sample of this was treated with diazomethane in ether and the methyl esters produced were analysed by g.l.c.⁶ The yield of acid products was determined by adding to another sample of the crude product a measured amount of a substituted benzoic acid (the methyl ester of which had a convenient retention time) as an internal standard. After methylation the product was analysed as before and the yield of each acid calculated. The cleavage yield quoted in the Table is in each case the sum of the yields for cleavages to benzoic acids and/or to phthalic acids, the former being taken as the combined yields of the benzoic acids derived from just one of the benzenoid rings of the quinone. When the combined yields of benzoic acids obtained from each of the benzenoid rings differed, the greater value was used.

In the reaction with 1,4-dimethoxy-2-methylantraquinone (V) a sample of the final reaction mixture was taken prior to work-up. G.l.c. analysis of this sample indicated that 2,5-dimethoxytoluene was present. The reactions with frangula emodin trimethyl ether (VIIIa) and 1,4,5-trimethoxyanthraquinone (IX) were carried out on a larger scale than the other reactions and the crude products were worked up^{2,6} to give base-insoluble and acid fractions.

⁶ D. G. Davies, M. Derenberg, and P. Hodge, *J. Chem. Soc. (C)*, 1971, 455.

Starting material (14%) was isolated from the base-insoluble fraction from the reaction of the emodin derivative, and quinol dimethyl ether (91% of the yield of 3-methoxyphthalic acid) from the base-insoluble fraction of the latter reaction. The cleavage yields were calculated from the weights of the acid fractions, on the assumption they had the compositions given in the Table.

Action of Butoxide-Water Reagent on 3-Methoxy-2-methylanthraquinone (III).—The quinone (21 mg) was treated with the reagent at reflux temperature for 2 h as described above. Addition of the cold mixture to saturated aqueous sodium chloride gave a precipitate. This was filtered off and the filtrate worked up to give base-insoluble and acid fractions. The precipitated solid was sublimed (360° at 0.5 mmHg) to give 1,2-bis-(3-methoxyanthraquinon-2-yl)ethylene (12 mg,

60%), yellow needles, m.p. >360°, m/e 500 (M^+ , 100%) (Found: C, 76.5; H, 3.8. $C_{32}H_{20}O_6$ requires C, 76.8; H, 4.0%). It was virtually insoluble in common organic solvents but dissolved in concentrated sulphuric acid to give a yellow solution with λ_{max} . 250, 300, 328, 400, and 470 nm (log ϵ 4.53, 4.75, 4.37, 4.24, and 4.17). The base-insoluble fraction (7 mg) was shown to be starting material (33%) by u.v. and t.l.c. analysis. The acid fraction was esterified. G.l.c. analysis of the ester mixture indicated that the main ester present was methyl benzoate and, by use of an internal standard, that the cleavage yield was 4%.

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