A Thesis entitled

SYNTHESIS AND REACTIONS OF BENZOYL-1,4-BENZOQUINONES: AN APPROACH TO ANTHRACYCLINONES.

Presented by

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The Author graduated from the National University of Malaysia with B.Sc. in Chemistry in June 1975 and obtaining his M.Sc. from The University of Manchester in October 1978. In October 1983 the Author came to the Department of Chemistry, University of Manchester, and since then has been engaged in research with Dr. J. Malcolm Bruce. The results of it are embodied in this Thesis.

No portion of the work in the Thesis has been submitted in support of any application for any other degree.

To my parents.

Acknowledgements.

I should like to thank my supervisor, Dr. J. Malcolm Bruce for his help, advice, and encouragement throughout my period of research, without which this Thesis would not have been completed. Thanks are also due to the following.

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Abstract.

The first Chapter gives a brief outline of the importance of, and synthetical approaches to anthracyclines, together with an introduction of the Subject on which this Thesis is based, and a specification of the objectives of the present work.

Chapter 2 describes several attempts to synthesise 2'-formyl-2,5-dimethoxybenzophenone, an intermediate for the synthesis of (2-formylbenzoyl)-1,4-benzoquinone, in a pure state.

Chapter 3 describes the synthesis of [2-(1,3-dioxolan-2-yl)-benzoyl]-1,4-benzoquinone and its Diels-Alder adduct with *trans*-penta-1,3-diene. [1,5] Aroyl migration in this adduct, followed by acid treatment, is shown to lead to a tetracyclic compound, involving a dehydration reaction which may occour rapidly during the cyclisation. Cyclisation of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone under acid conditions is also described. Mechanisms of the cyclisation reactions are discussed.

Chapter 4 describes other approaches to [2-(1,3-dioxolan-2-yl)-benzoyl]-1,4-benzoquinone, *via* 2,5-bis[(trimethylsilyl)oxy]benzophenone. Approaches to 4a,5,6,6a-tetrahydro-4a-(2-carboxybenzoyl)-5-methyl-1,4-naphthoquinone are discussed in Chapter 5.

Finally, the experimental details of the work are described in Chapter 6.

Abbreviations.

The following abbreviations are used in this Thesis.

CAN : Ceric ammonium nitrate $Ce(NH_4)_2(NO_3)_6$.

DBN : 1,5-Diazabicyclo[4,3,0]non-5-ene.

DBU : 1,8-Diazabicyclo[5,4,0]undec-7-ene.

DCC : Dicyclohexyl carbodiimide.

DDQ : 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.

DMF : Dimethylformamide.

DMAP : 4-Dimethylaminopyridine.

DiBAL-H : Di-isobutylaluminium hydride.

MOM : Methoxymethoxy ($-OCH_2OMe$).

MEM : Methoxyethoxy [$-OCH_2OMe(CEt)$].

THF : Tetrahydrofuran.

TMS : Trimethylsilyl ($-SiMe_3$).

PPTS : Pyridinium p-toluenesulfonate.

TSOH : Toluene-p-sulfonic acid.

THP : Tetrahydro-2H-pyran-2-yl ().

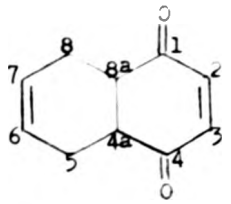
TBDMS : Tert-butyldimethylsilyl ($-SiMe_2Bu^t$).

TFAA : Trifluoroacetic anhydride.

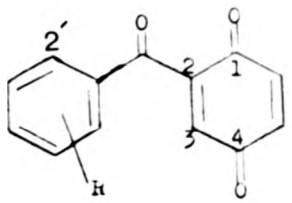
NBS : N-Bromosuccinimide.

Note on Nomenclature.

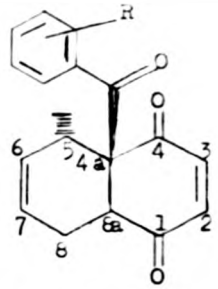
The name, according to I.U.P.A.C. rules, of the mono-adduct of butadiene and 1,4-benzoquinone is 4a,5,8,8a-tetrahydro-1,4-napnthoquinone. The systematic numbering is shown below.



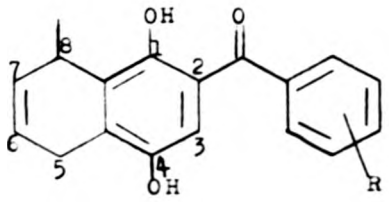
The names and numbering systems used in this Thesis, which are in accordance with I.U.P.A.C. practice, are as follows.



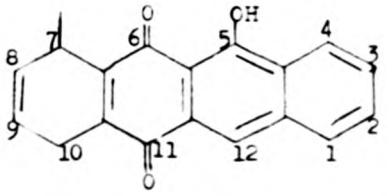
2-Aroyl-1,4-benzoquinone.



4a,5,8,8a-Tetrahydro-4aβ-aroyl-5α-methyl-1,4-napnthoquinone.

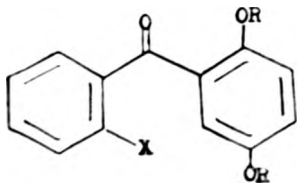


5,8-Dihydro-1,4-dihydroxy-2-aroyl-6-methylnaphthalene.



5-Hydroxy-7-methyl-7,10-dihydronaphthacene-6,11-dione.

Alternative names are used for the following



—X	R = Me
$-CO_2Me$	Methyl 2-(2,5-Dimethoxybenzoyl)benzoate.
$-CO_2H$	2-(2,5-Dimethoxybenzoyl)benzoic Acid.
$-COCl$	2-(2,5-Dimethoxybenzoyl)benzoyl Chloride.
$-CON$⬡	2-(2,5-Dimethoxybenzoyl)benzpiperidide.
$-CHO$	2-(2,5-Dimethoxybenzoyl)benzaldehyde.
$-CH$⬡(O,O)	2-(2,5-Dimethoxybenzoyl)-1,3-dioxolane.

Similar naming systems apply for R = $SiMe_3$ and R = MOM.

Note.

Throughout this thesis, all Diels-Alder adducts and products derived from them are racemic; only one enantiomer is shown.

Contents.

Chapter 1:

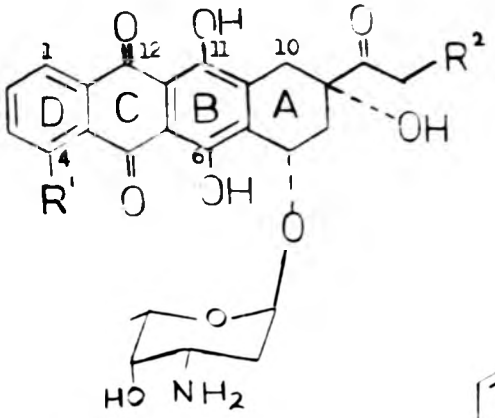
Introduction.

1.1. Anthracyclines; Importance and Synthetical Approaches.

During the past decade, the anthracycline antibiotics such as daunomycin (1) and adriamycin (2) have emerged as the most effective drugs for the treatment of a broad spectrum of human cancers.[1] However, these drugs display various side effects, the most serious being the cumulative dose-dependent cardiotoxicity.[2] In consequence, there has been a continued interest in the total synthesis of these antibiotics, including the analogue, 4-demethoxy-daunomycin (3) which has now assumed considerable clinical importance as it is found to be 5-10 times more effective than daunomycin (1) or adriamycin (2).[3]

It was noted that the anthraquinone system is an important structural feature of all anthracyclines.[4a] A wide range of oxygenated substitution patterns appears to be compatible with biological activity, although the existence of a direct contribution of the substitution pattern to the antitumour activity has not yet been established.[1a] It has been suggested that the hydroquinone-type ring B might also take part in the redox reactions, leading to radical species responsible of the toxicity of the antitumour anthracyclines.[4b] In the past few years, aclacinomycin A (4), an example of an 11-deoxyanthracycline, has been isolated and shown to possess good tumour-inhibitory properties, and importantly, to exhibit much lower cardiotoxicity.[5]

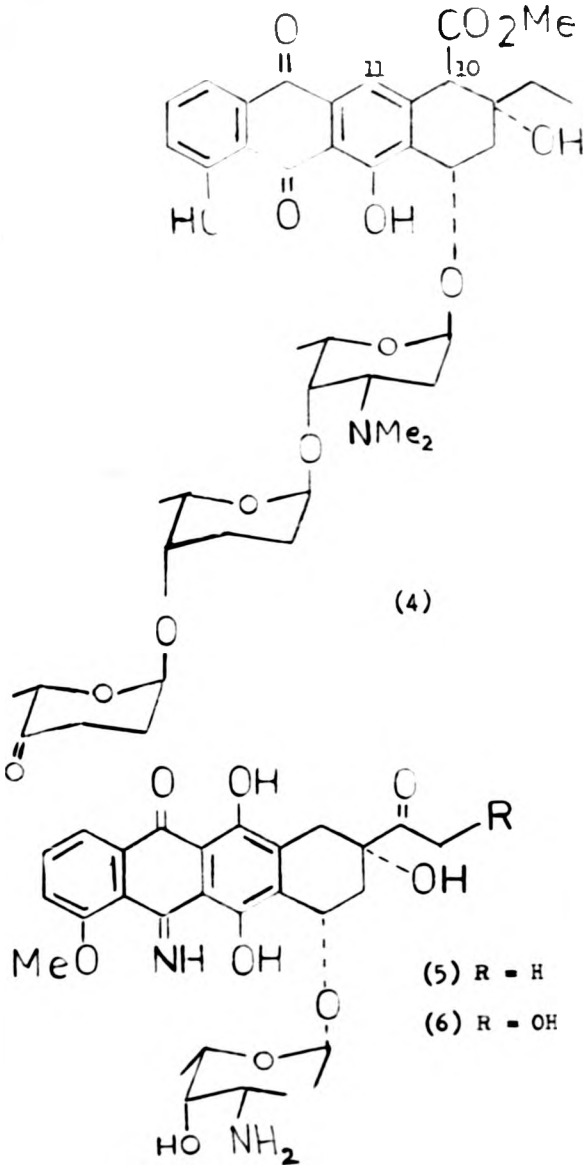
Acton *et al.*,[6,7] then reported that the 5-imino derivatives (5) and (6) of daunomycin and adriamycin retain the anti-tumour activity, and are significantly less toxic than their clinically important parents (1) and (2).



(1) R^1 = OMe, R^2 = H

(2) R^1 = OMe, R^2 = OH

(3) R^1 = H, R^2 = H

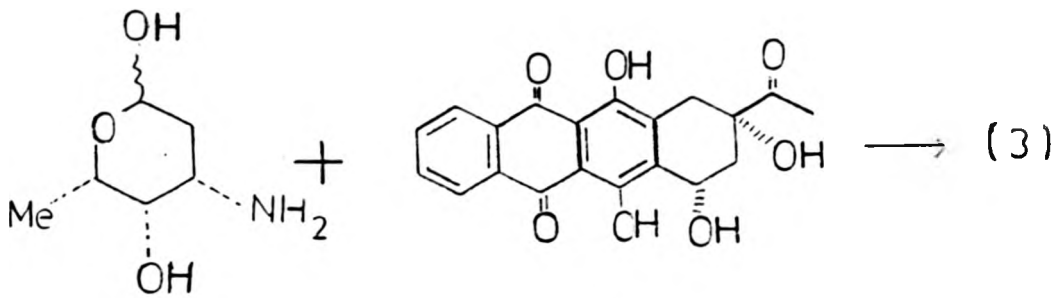


(4)

(5) R = H

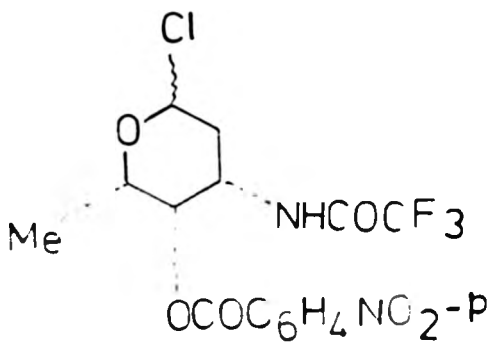
(6) R = OH

To date, all syntheses of anthracyclines have relied upon the glycosidation of a sugar with an aglycone, the anthracyclinone. Although this strategy has obvious flexibility, it is not without its problems. For example,[8] 4-demethoxydaunomycin (3) is prepared from L-daunosamine (7a) and 4-demethoxydaunomycinone (8d) (Scheme 1). To effect the coupling, it is necessary to protect and activate the sugar [e.g. by conversion into the chloro-compound (7b)[9]]. After the glycosidation step, the protecting groups are removed and the anthracycline (3) is isolated as its hydrochloride.



(7a) (8d) (3)

Scheme 1.

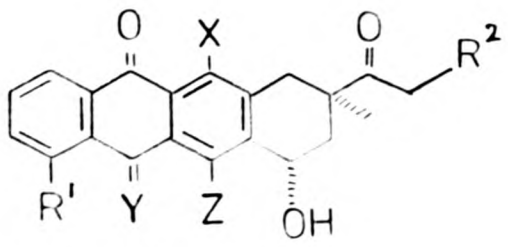


(7b)

During the last ten years, the field of anthracyclinone synthesis has developed rapidly. Among notable achievements were the synthesis of daunomycinone (8a),[10] 11-deoxydaunomycinone (6b),[11a-b] carminomycinone (6c),[11c-d] 4-demetnoxydaunomycinone (6d),[12] 5-iminodaunomycinone (6e),[13] 5-iminoadriamycinone (8f),[13] heteroanthracyclinones such as 4-demethoxyxanthodaunomycinone (9),[14] and aklavinone (10),[15] the aglycone of aclacinomycin A (4).

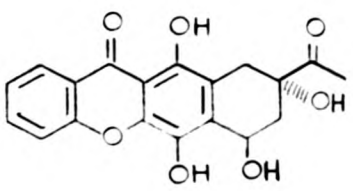
The very early synthesis of anthracyclinones were non-regioselective, e.g. a 1:1 mixture of daunomycinone (8a) and isodaunomycinone (11) was formed.[16] It turned out that regioselectivity is a key to any effective synthesis of the aglycones. Therefore, several synthetic strategies have been applied, the most important being based on the Friedel-Crafts reaction,[16,17] (eq. 1), the Fries type reaction,[17a,18] (eq. 2), the Marschalk reaction,[19] (eq. 3) and the Diels-Alder reaction,[10,20] (eq. 4) (Scheme 2), details of which are beyond the scope of the present brief survey. Recently, the development of tetracycline synthesis has been reviewed,[10,21] and recent aspects of anthracyclinone synthesis have been collected.[22] Interestingly, several regiospecific syntheses of anthracyclinones using organometallic reagents have been developed by many groups.[23] (Scheme 3).

One of the best solutions to the regiospecific synthesis of anthracyclinones may have been developed by Gesson and his Colleagues,[11b] who reported an elegant two-step preparation of an 11-deoxyanthracyclinone precursor via a Diels-Alder route, in 60% yield (Scheme 4). The cycloaddition reaction between commercially available juglone (12) and a trimethylsilylketene acetal synthon (13) proceeded rapidly at 0-20° in various solvents (CH_2Cl_2, THF, or benzene), to give after



(8)

	R'	R^2	X	Y	Z
(a)	OMe	H	OH	O	OH
(b)	OMe	OH	H	O	OH
(c)	OH	H	OH	O	OH
(d)	H	H	OH	O	OH
(e)	OMe	H	OH	NH	OH
(f)	OMe	OH	OH	NH	OH



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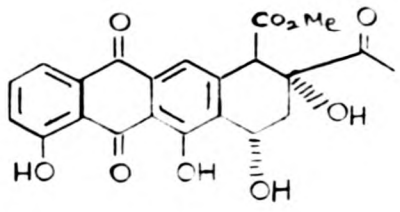
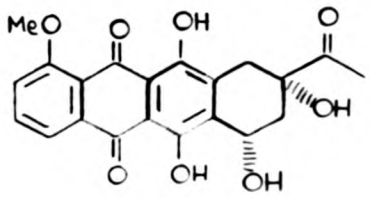
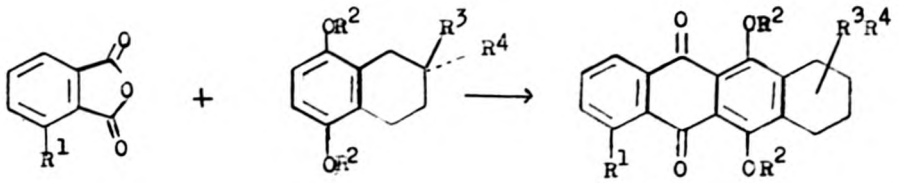


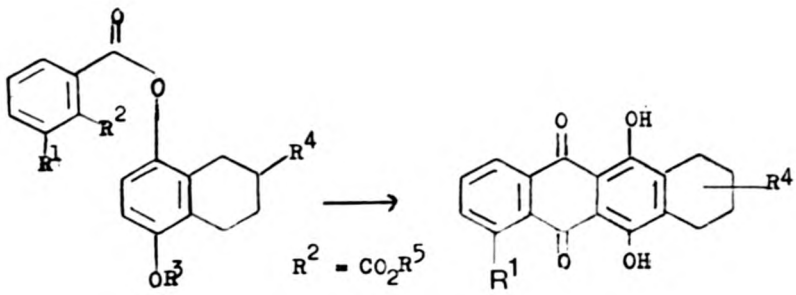
(10)



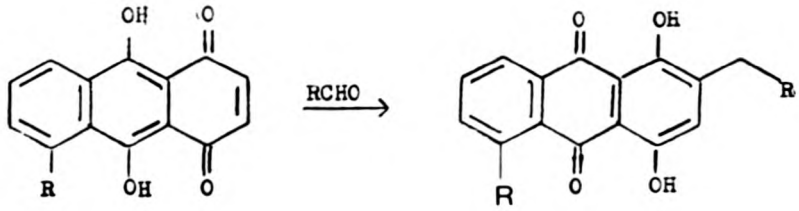
(11)



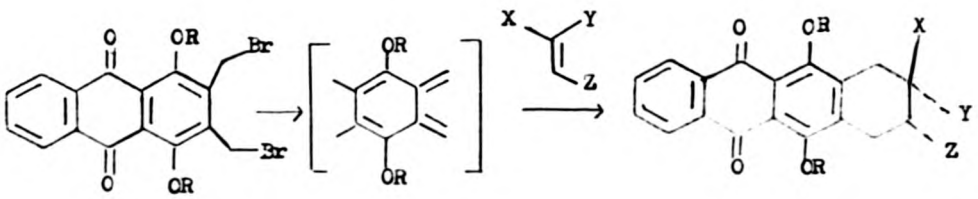
(eq. 1)



(eq. 2)

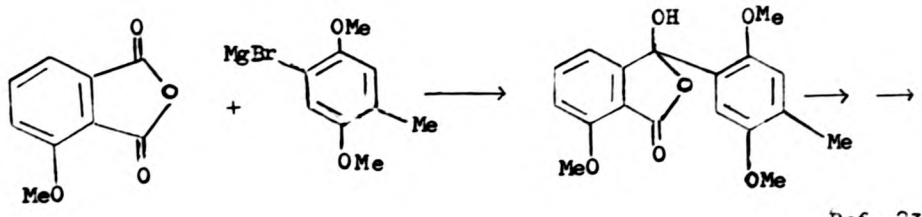


(eq. 3)

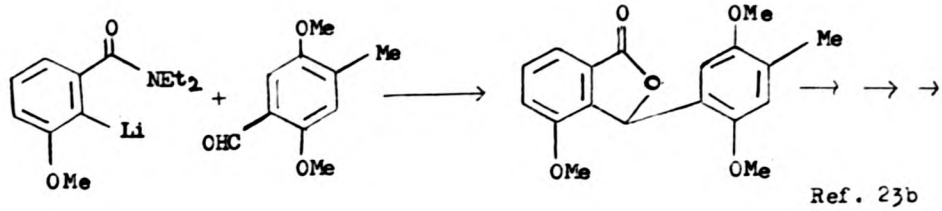


(eq. 4)

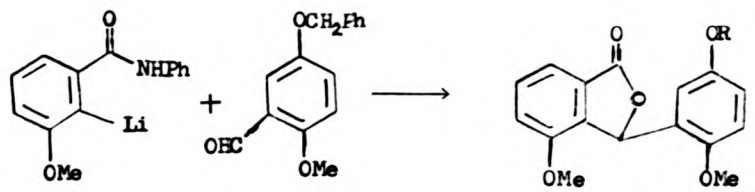
Scheme 2.



Ref. 23a

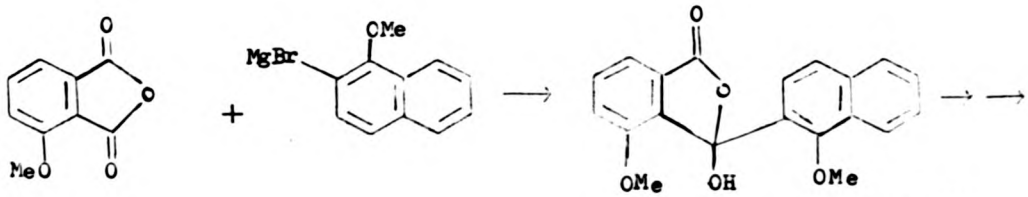


Ref. 23b



Ref. 23c

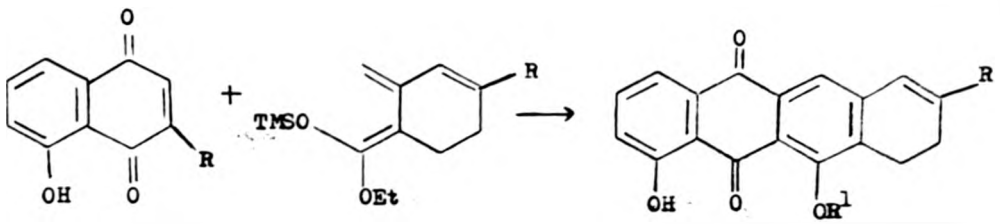
R = CH_2Ph, H



Ref. 23d

Scheme 3.

work-up under air (oxidation of the intermediate hydroquinone) a 1:4 mixture of phenol (14a) and of the corresponding ether (14b) which was then treated with aluminium chloride in refluxing dichloromethane overnight. Extraction and rapid column chromatography over SiO_2 gave the product (14a).



(12) (13) (14)

(a) R = H R = Me, Et (a) R = Me, Et; R^1 = H

(b) R = Cl (b) R = Me, Et; R^1 = Et

Scheme 4

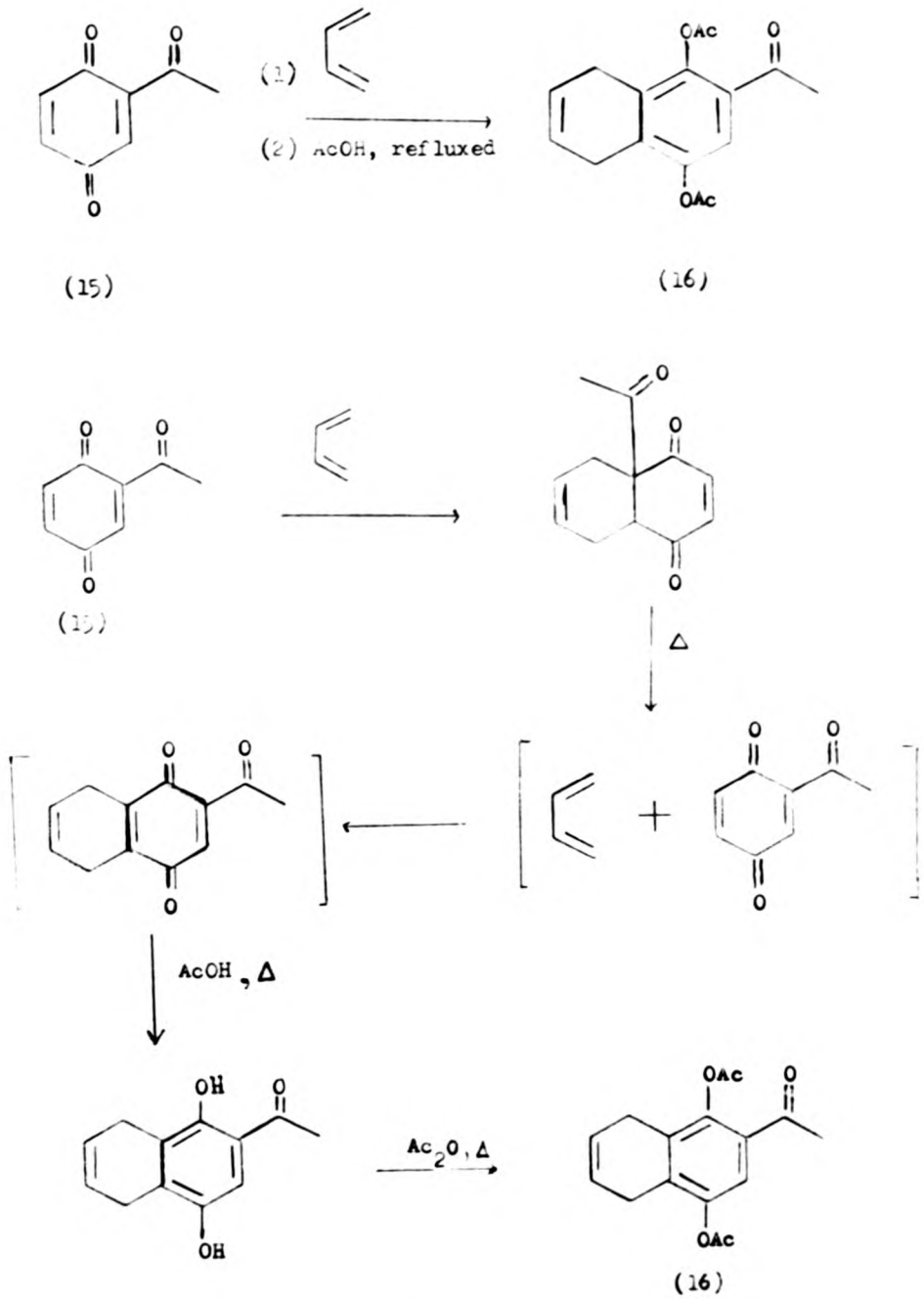
In these laboratories, one aim of work begun some twelve years ago and still in progress is an attempt to develop another efficient regiospecific synthesis of anthracyclinones.

1.2. Objectives of The Present Work.

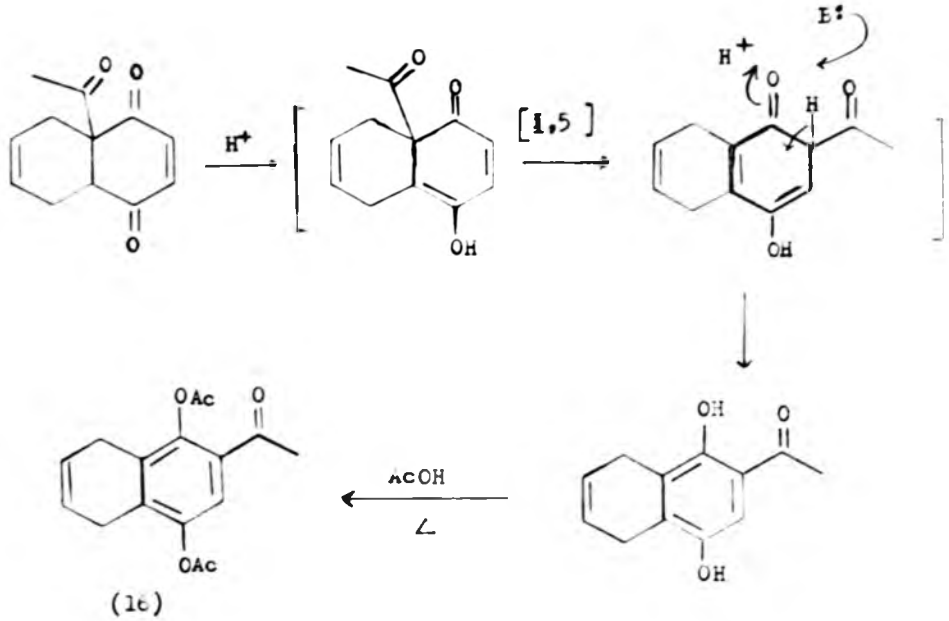
In 1967 Cort and Rodriguez[24] observed that treatment of 2-acetyl-1,4-benzoquinone (15) with buta-1,3-diene followed by boiling the product with acetic anhydride, afforded 2-acetyl-1,4-diacetoxy-5,8-dihydronaphthalene (16). This result was explained[25] at the time by a retro-diene reaction, under thermodynamic control, leading to re-addition of the diene component across the 5,6-double bond of the resulting quinone, and enol-acetylation. (Scheme 5).

Studies in these laboratories have shown[26] that the above isomerisation of the Diels-Alder adduct of buta-1,3-diene and acetyl-1,4-benzoquinone does not involve the retrodiene-recombination route, but that it occurs by [1,5] acetyl migration, (Scheme 6), and have confirmed an observation earlier reported by Cooper and Sammes,[27] (later published[28]) that the direction of the migration depends on the nature of the substituents, and that migration competes with deacetylation. Thus migration in the adduct (17) in the presence of pyridine in refluxing xylene gave 6-acetyl-1,4-naphthoquinone (18) (Scheme 7).

Studies of migration[29] of aroyl groups in Diels-Alder adducts of benzoyl-1,4-benzoquinones have shown that they behave in a similar manner to acetyl groups. Addition of trans-penta-1,3-diene to substituted benzoyl-1,4-benzoquinones affords the corresponding adducts (19) in good yield. Subsequent [1,5] migration of the benzoyl groups in the enols (20) under basic conditions at 35° was particularly facile, producing the benzoylhydroquinones (21) (Scheme 8).

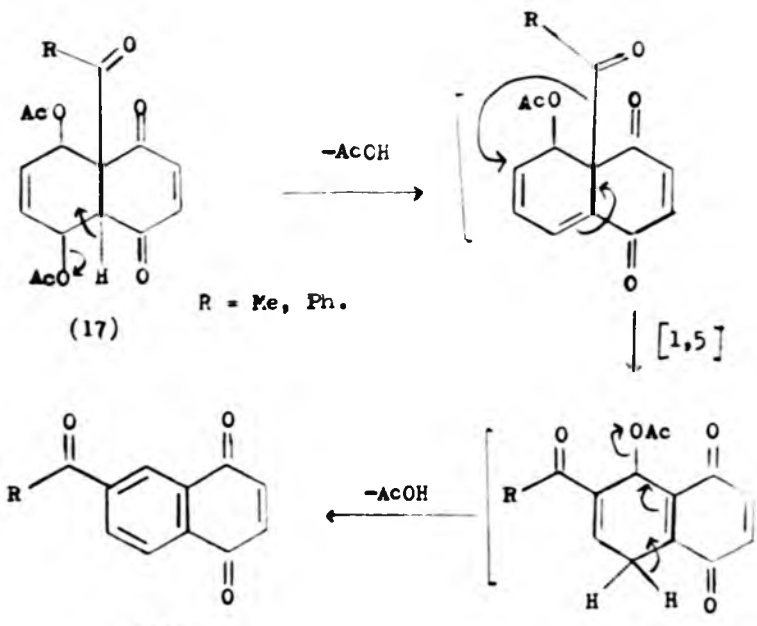


Scheme 5.



(1c)

Scheme 6.



(17)

(18)

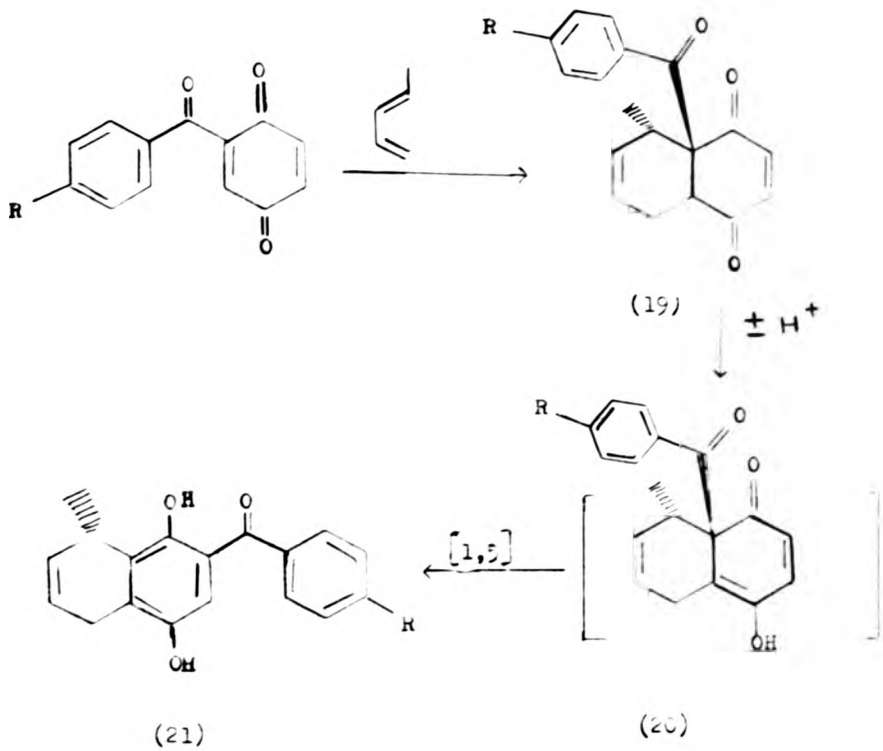
Scheme 7.

Examination of the effects of the substituents, R, on the base-induced migration revealed that, although these rearrangements occur smoothly for R=H, Me, Br, OH, and OMe, the regiospecificity, which is central to the synthesis, is lost under some conditions; although the products are still aroylhydroquinones, (21) and (22). This was thought to be due to the competition of an initial [1,2] shift with the [1,5] shift (Scheme 9), and was particularly important for $R=NO_2$.

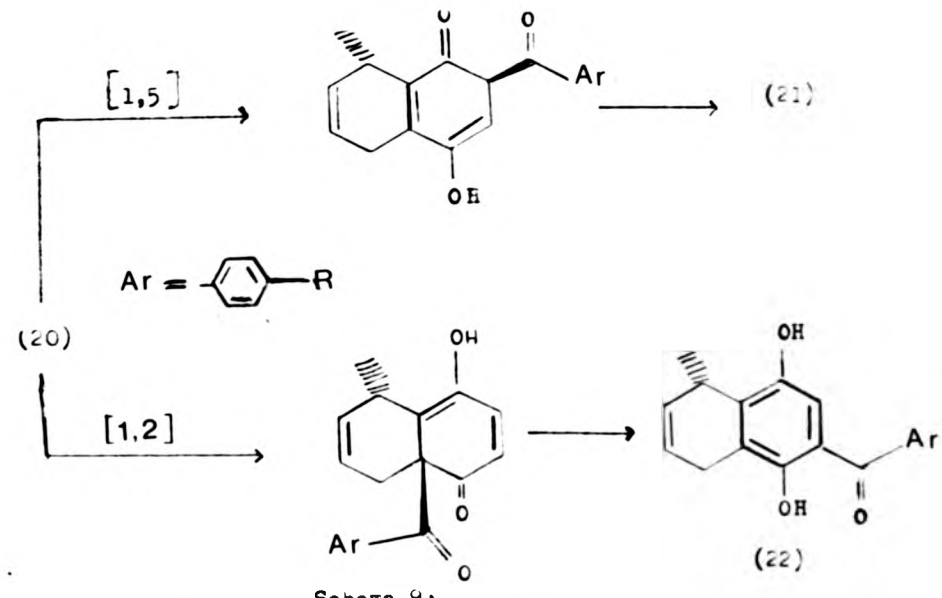
Similar [1,5] benzoyl migrations have previously been reported by Jones et al.[30] in the indenes (23), but at much higher temperatures.

Retrosynthetic analysis of the aglycones (24) suggests that the benzoyl-1,4-benzoquinone adducts such as (25) may serve as useful syntnetical intermediates, since the subsequent [1,5] benzoyl migration would lead to the aroyl hydroquinones (26) which, when R^1 or R^2=C, contain the array of ring carbon atoms and much of the key oxygenation pattern of the aglycones (24).

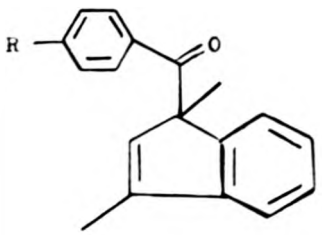
The feasibility of this synthetic approach was demonstrated by earlier observations from our laboratories. Based on the above methodology, Pardasani[31] explored the strategy towards generation of tetracyclic compounds by preparing adducts (28) from cycloaddition of acyclic dienes to ortho-substituted benzoyl-1,4-benzoquinones (27). Base-induced [1,5] aroyl migration in (28) gave the hydroquinones (29) which were then cyclised by the action of boron tribromide at 0° to give the desired products (30) (Scheme 10). The easy cyclisation of compound (29) with boron tribromide was explained in terms of the boron tribromide generating a stable six-membered pseudo-β-naphthol chelate, essentially planar because of the small



Scheme 8.



Scheme 9.



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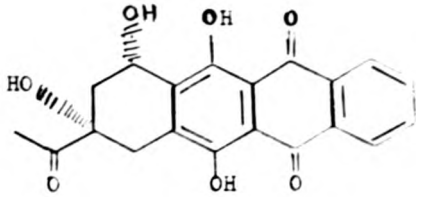
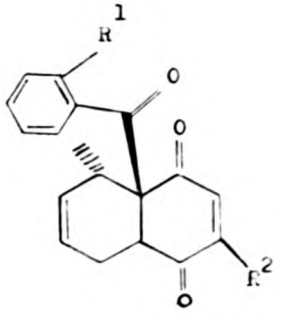
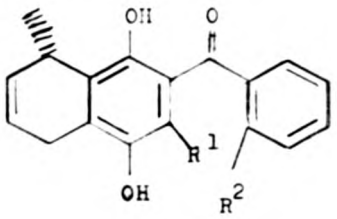


(24)

R = H, SO_2Me, OMe



(25)



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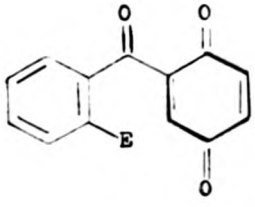
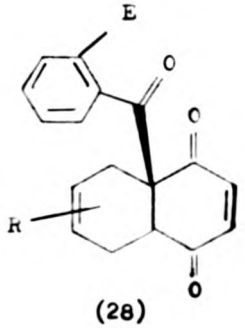


(27) E = CO_2Me



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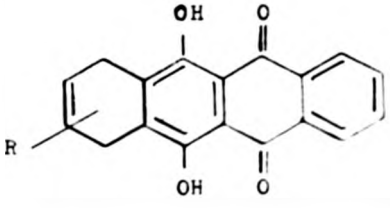

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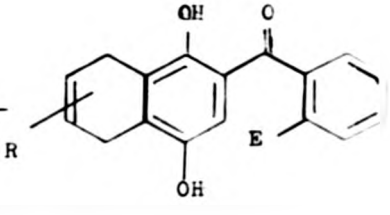
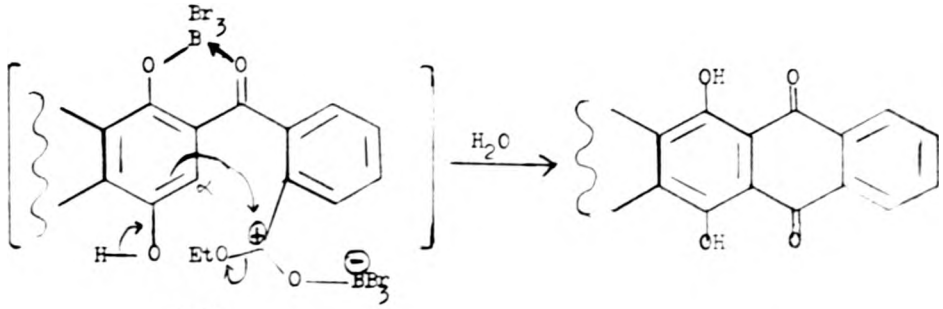


(29)

Scheme 10.

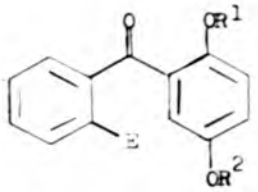
size of boron, making the α-position more nucleophilic for facile and low energy position-selective cyclisation. (Scheme 11)



(29) (30)

Scheme 11.

Syntheses based on this approach has suffered from many problems, among them the difficulties encountered in selective demethylation of compound (31) to 2,5-dihydroxy-2'-methoxycarbonylbenzophenone (32), which was the subject of earlier unsuccessful attempts.[32a] Treatment of compound (31) with 1.5 mol boron tribromide in dichloromethane at 0° produced mono-demethylated ketone (33), which on treatment with more boron tribromide (2.0 to 3.0 mol) resulted in the formation of the cyclised product, quinizarin (34). Eventually it was discovered that treatment of compound (31) with 2 mol of powdered anhydrous aluminium chloride in dichloromethane at 20° followed by addition of 2 mol of boron tribromide and work-up with 5% hydrochloric acid gave the required dihydroxy compound (32) in good yield.

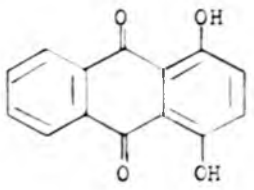


E = CO_2Me

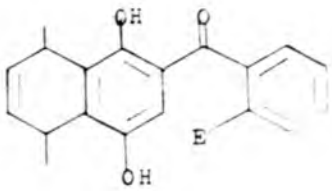
(31) $R^1 = R^2 = OMe$

(32) $R^1 = R^2 = H$

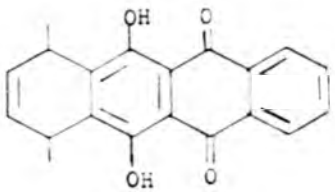
(33) $R^1 = H$; $R^2 = OMe$



(34)



(35)



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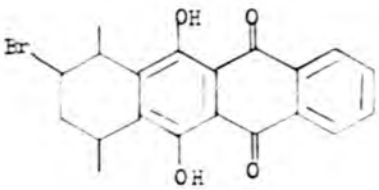
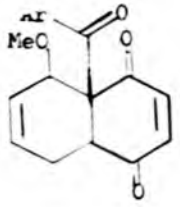


(37)



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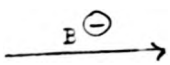
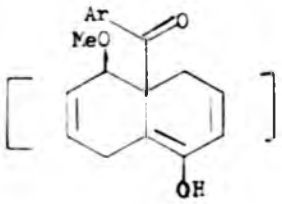
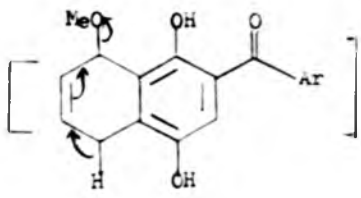
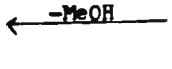
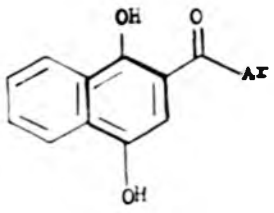








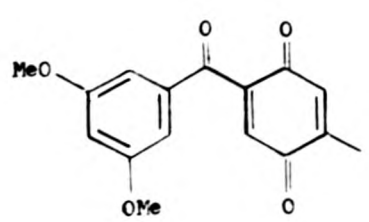


(39)

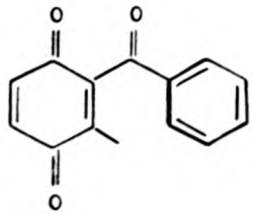
Scheme 12.

Furthermore, the cyclisation step (Scheme 10) was unclean; the required compound was always accompanied by byproducts resulting from addition of bromine and hydrogen bromide to the olefinic double bond. Thus, treatment of the rearrangement product (35), for example, with 4 mol of boron tribromide, produced a mixture of the desired product (36) and the bromo-compound (37) in the ratio 6:1 respectively. The author also showed that in the process of [1,5] aroyl migration in the 1-methoxy-buta-1,3-diene adduct (38) in pyridine, the methoxy group was lost to give the aroylnaphthohydroquinone (39). This was explained by hydrogen abstraction in the presence of base, resulting in elimination of methanol (Scheme 12).

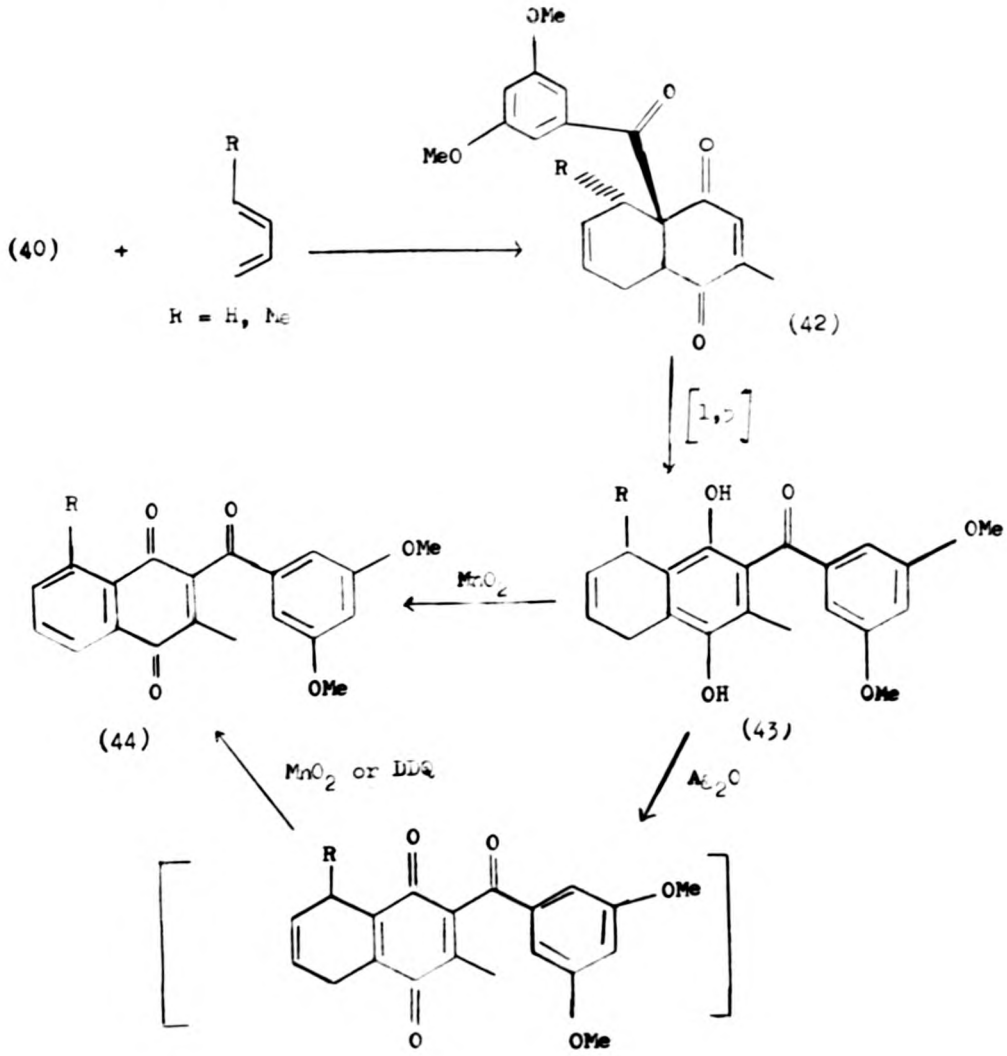
Due to these problems observed by Pardasani,[31] as described above, two years later Ahmed[33] synthesised the quinones (40) and (41). Addition of dienes to the quinone (40) gave the desired adduct (42) in good yield. Base-induced [1,5] aroyl migration of the adduct (42) gave benzoylhydroquinone (43) which was oxidised to the quinone (44) (Scheme 13). Although this strategy ensured overall regiospecificity in the course of [1,5] aroyl migration [because the intermediate (45) can only aromatise <u>via</u> a prior [1,2] shift,[32b] ultimately yielding only the required compound (43); (Scheme 14)], the final step, the cyclisation of the oxidation product (44) to the desired tetracycle (47) <u>via</u> the <u>ortho</u>-quinone methide (46) was unsuccessful (Scheme 15). Treatment of the naphthoquinone (44) with DBN[34] in benzene at room temperature under nitrogen for 24 h. gave the unchanged naphthoquinone (44), whilst at reflux temperature the product was a yellow semi-solid from which no cyclisation product such as (47) was isolated. Treatment of naphthoquinone (44) with 18-crown-6 and potassium fluoride[35] also failed[33] to give the desired product (47).



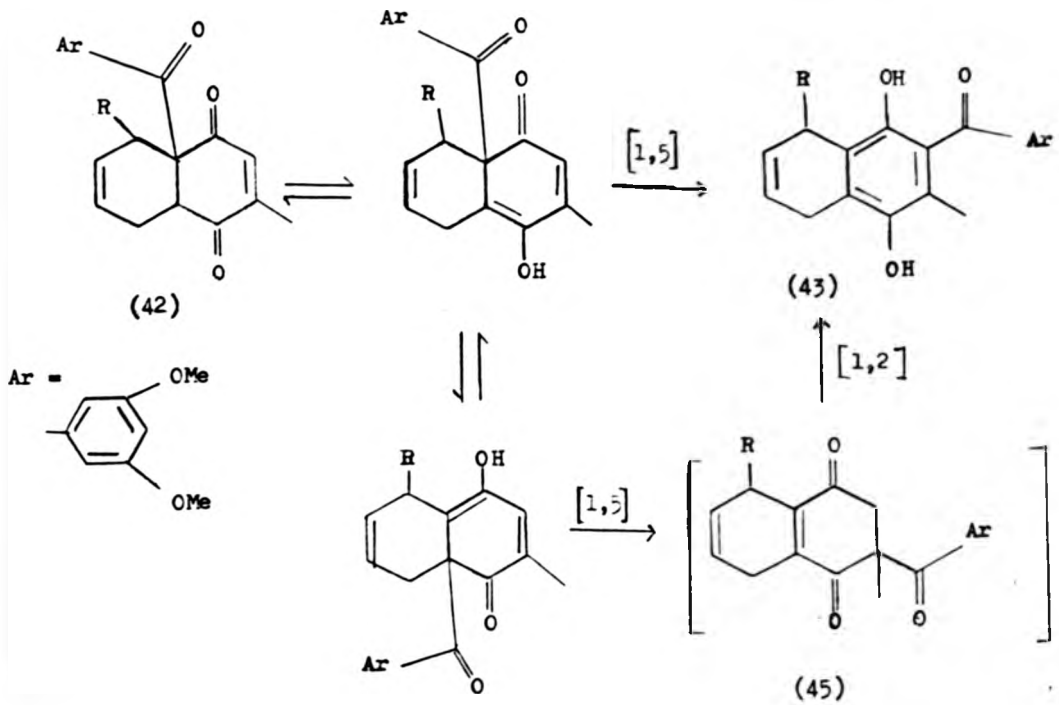
(40)



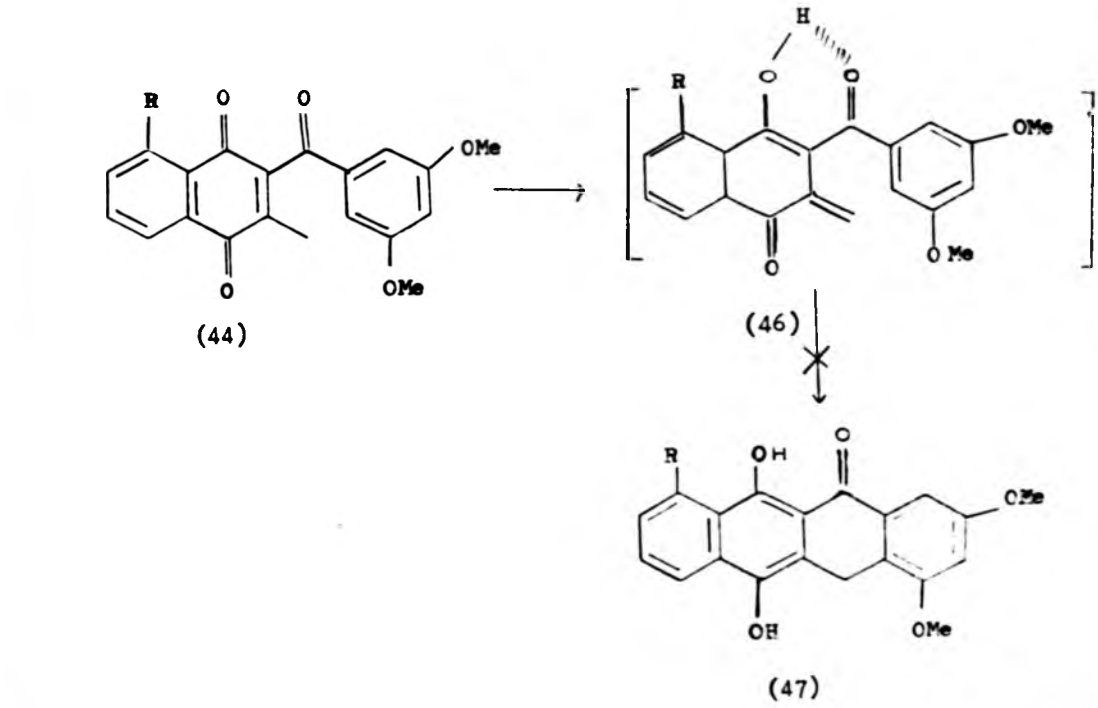
(41)



Scheme 13.



Scheme 14.

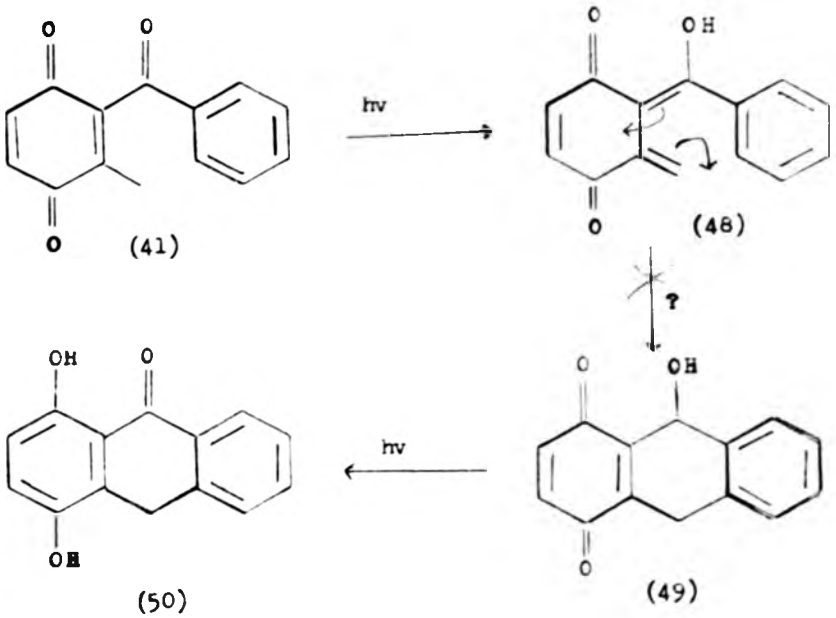


Scheme 15.

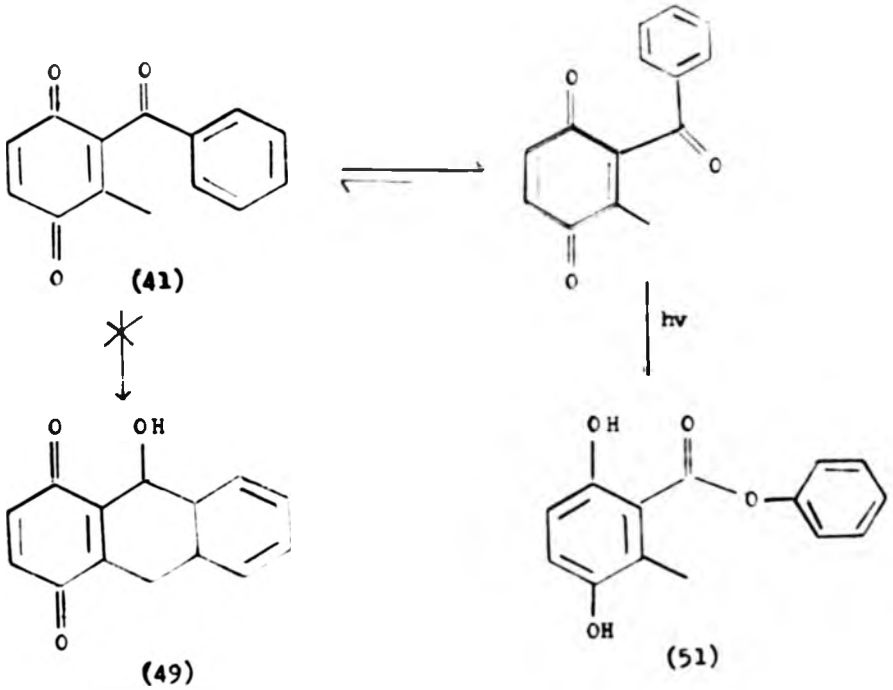
In this connection, photolysis of quinone (41), analogous to the naphthoquinone (44), was studied in detail.[33] The author was attempting to observe an intramolecular cyclisation of the photo-generated dienol intermediate (48) hoping to obtain the desired products (49) or (50) (Scheme 16). However, irradiation of the quinone (41) with visible light or with ultraviolet light in various solvents gave no cyclisation products such as (49) or (50), but the ester (51) was isolated in high yield. The ester (51) may be formed by the addition of acetic acid (used as solvent) or water to the benzoyl carbonyl group of the quinone (41) to generate a hemi-acetal or hydrate from which a diradical zwitterion (as 52) can be formed on excitation,[36] thus allowing a [1,2] phenyl shift to occur, producing another intermediate zwitterion (53) in which the cation is strongly stabilised. Loss of an acetyl cation or a proton followed by protonation of the phenolate would then give the phenyl gentisate (51) as the final product (Scheme 17).

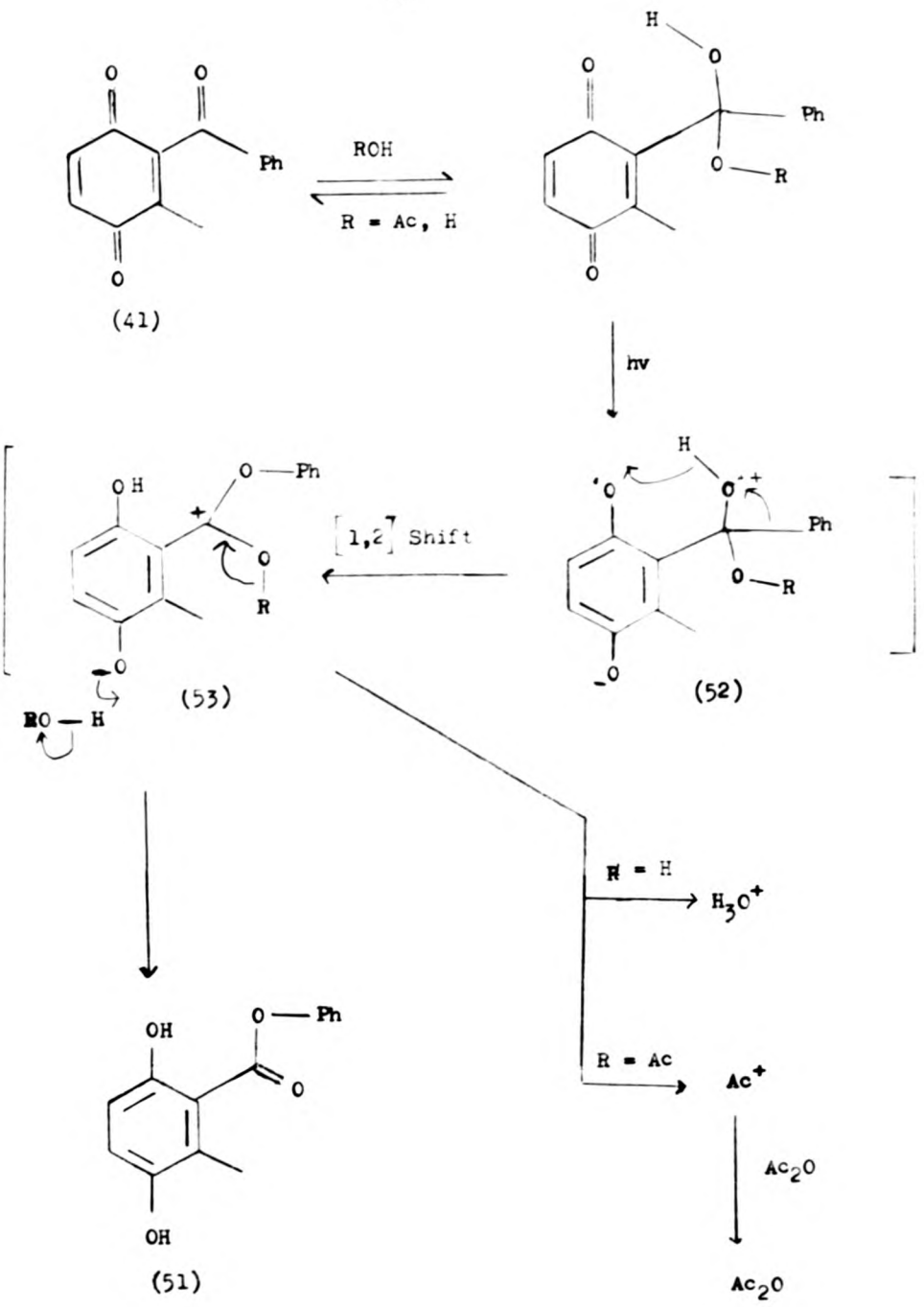
Likewise, irradiation of quinone (54) in acetic acid was observed[31] to give xanthone (55) and ester (56) in 35% and 16% yield respectively; there was no cyclisation product such as (57) (Scheme 18), although Sammes and Wallace[37] reported that the cyclisation of chromone (58) [analogous to quinone (54)] into the tetracycle (59) did occur, via photoenolisation (Scheme 19).

Interestingly, treatment of the quinone (41) with various bases also failed[33] to give the desired cyclised product (50) (Scheme 20). Refluxing of quinone (41) with pyridine gave 28% of its hydroquinone, but the product was mainly uncharged quinone (41). In contrast, reaction of quinone (41) with nitrogen-purged DBN[38] at room temperature, and with NBS,[39] in the presence of dibenzoyl peroxide gave the hydroxy-methyl-1,4-benzoquinone (62) and the bromomethyl-1,4-benzoquinone (63),

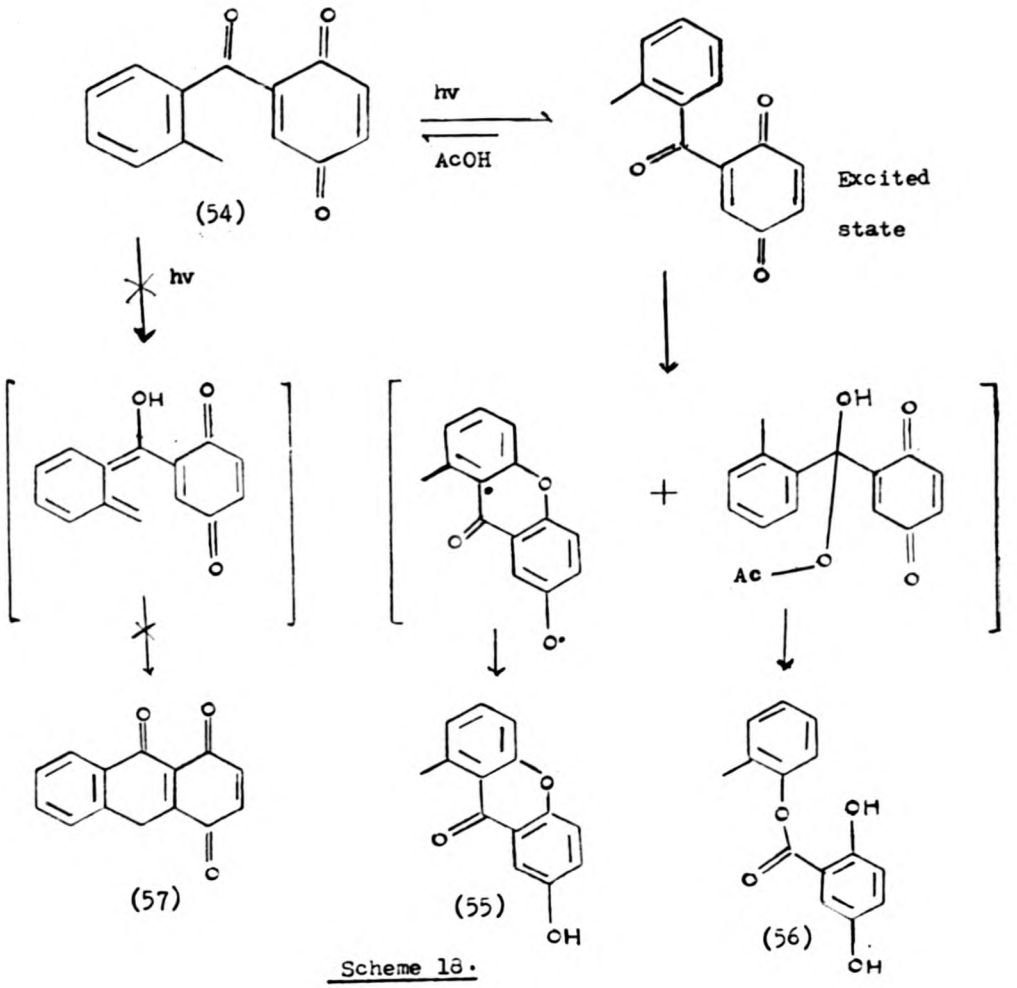


Scheme 16.

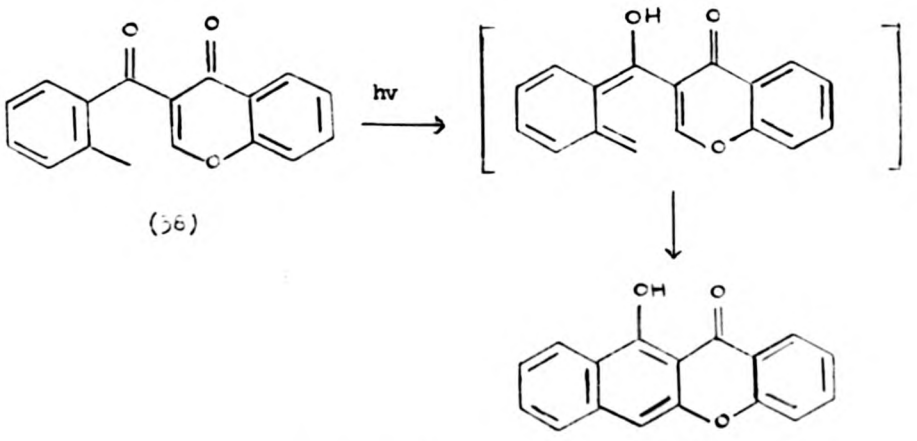




Scheme 17.



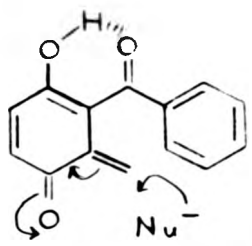
Scheme 18.



Scheme 19.

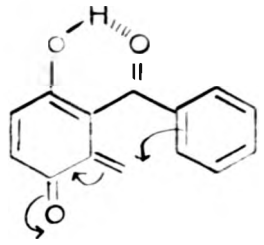
respectively, Similarly, reaction of quinone (41) with acetic anhydride and sodium acetate at 130° gave the tetra-acetate (64) in 24% yield. These results may have arisen from reaction of the quinone methide (60; Scheme 20) with water, bromide, and acetate, respectively, present in the system.

The author[33] then noted that despite the probable formation of the ortho-quinone methide intermediate (60), as indicated by the isolation of the compounds (62), (63), and (64), (Scheme 21), no intramolecular cyclisation, as hoped for, via the nearby phenyl ring and the methylene carbon, was observed. Seemingly, the intermolecular attack of the anion needs less energy than that for cyclisation, and hence predominates.



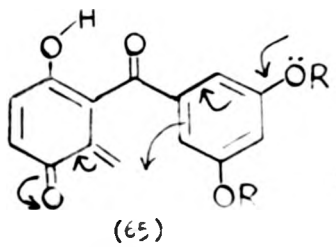
$Nu^- = OH^-, Br^-, AC^-$

Low energy



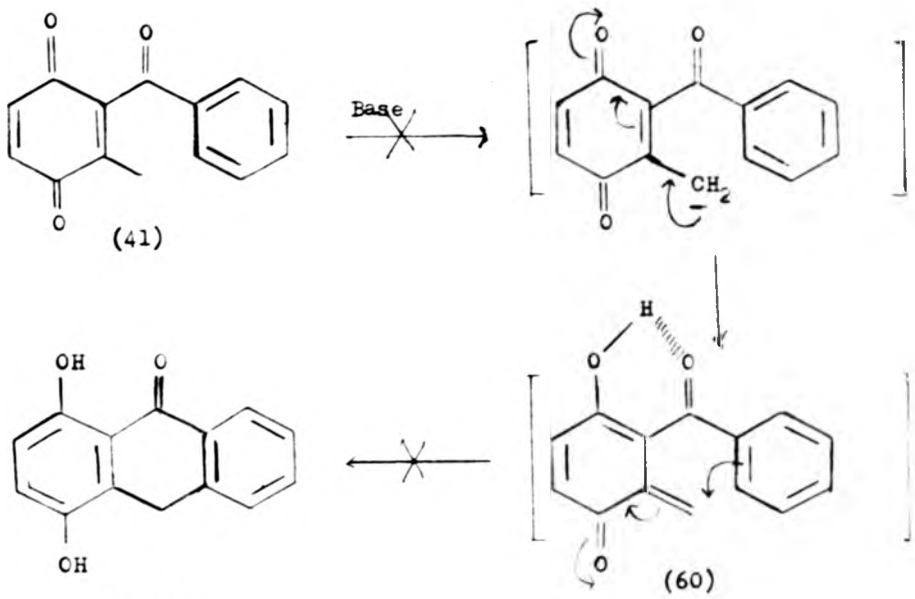
High energy

Therefore, it was argued that introducing electron-donating substituents in the benzoyl ring of the quinone (41), as (65), might assist the intramolecular cyclisation by making the benzoyl residue more nucleophilic. However, attempts to synthesise quinones such as (65) were unsuccesful.[33]

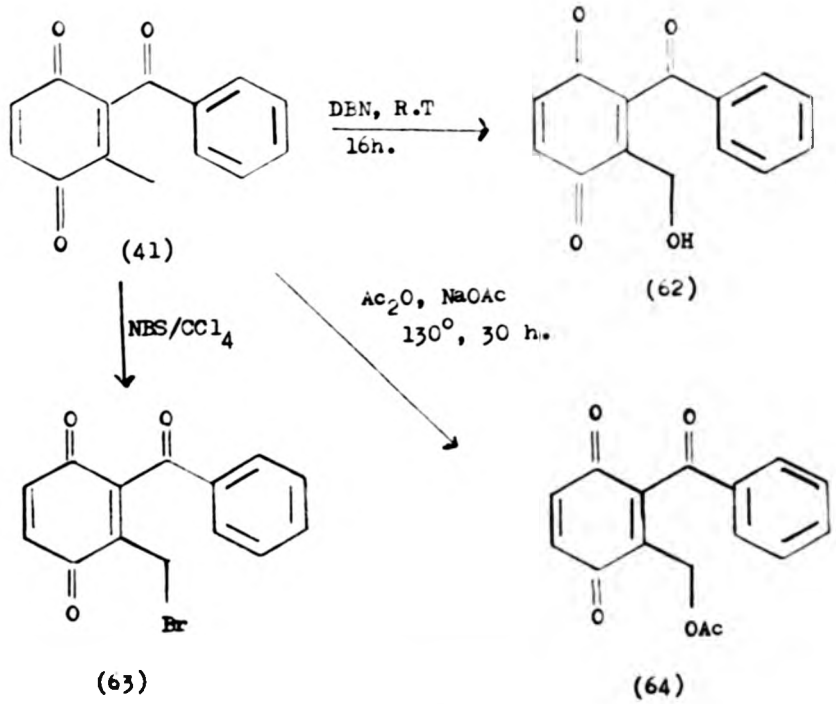


R = Me, H.

(65)



Scheme 20.



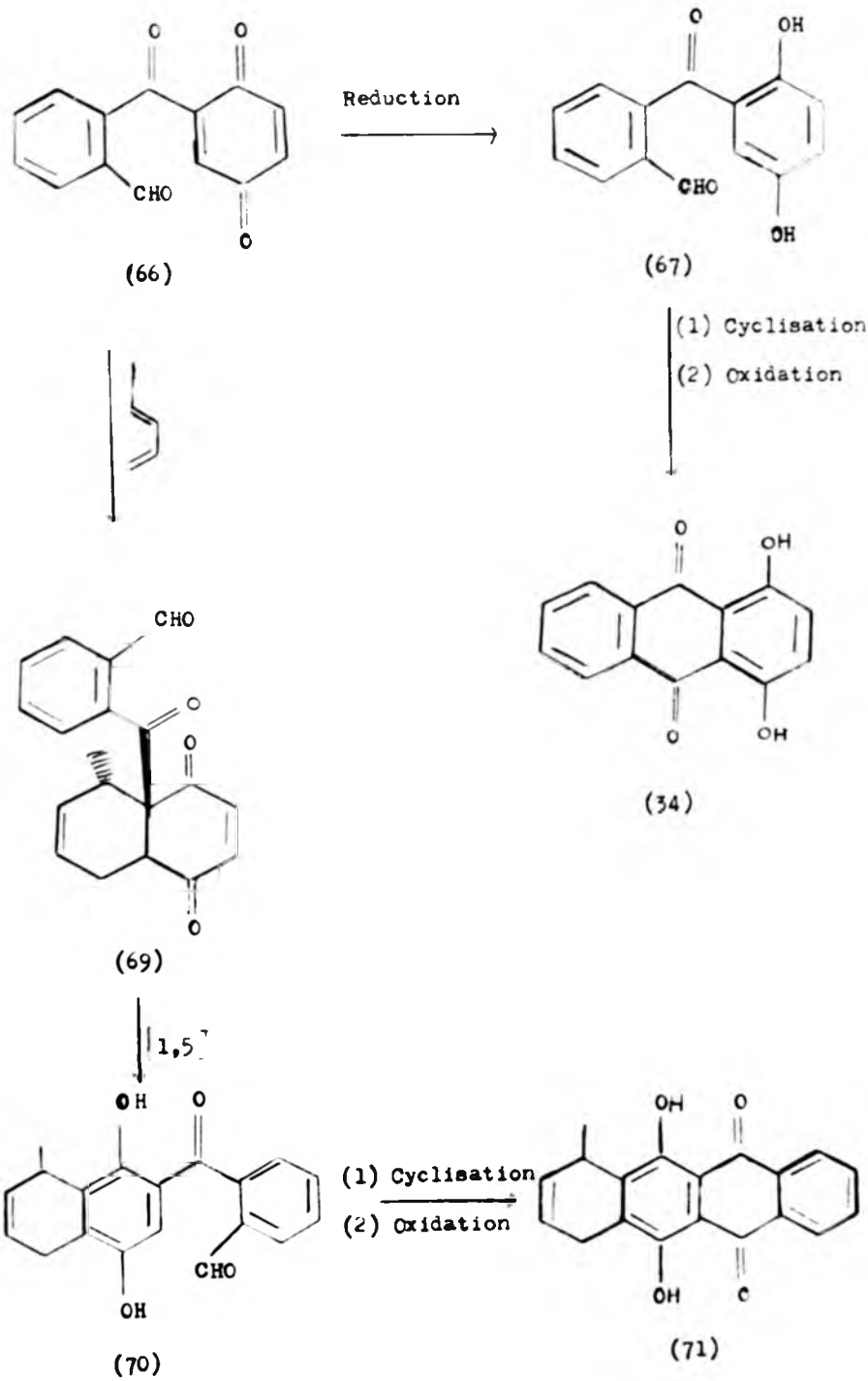
Scheme 21.

In the light of the aspects described in this section, we thought that a compound such as (66), having a formyl group at position 2', could overcome the problems left by earlier[31,33] observations from our laboratory. Such an ortho-formyl substituted benzoylbenzoquinone was particularly worth examining with a view to subsequent cyclisation. Reduction of quinone (66) should give the hydroquinone (67) which would be expected to cyclise to quinizarin (34). On the other hand, addition of trans-penta-1,3-diene to quinone (66) should give the adduct (69), which on treatment with pyridine or pyridine-methanol[31] should give the rearranged product (70). Compound (70), in which the relative positions of the substituents in the extreme rings are defined, is analogous to hydroquinone (67), and should cyclise to give the tetracyclic compound (71) (Scheme 22). The cyclisation step is expected to occur under milder conditions than those used by Pardasani;[31] mildly acidic or basic conditions, or even a neutral medium, may be sufficient (Scheme 23).

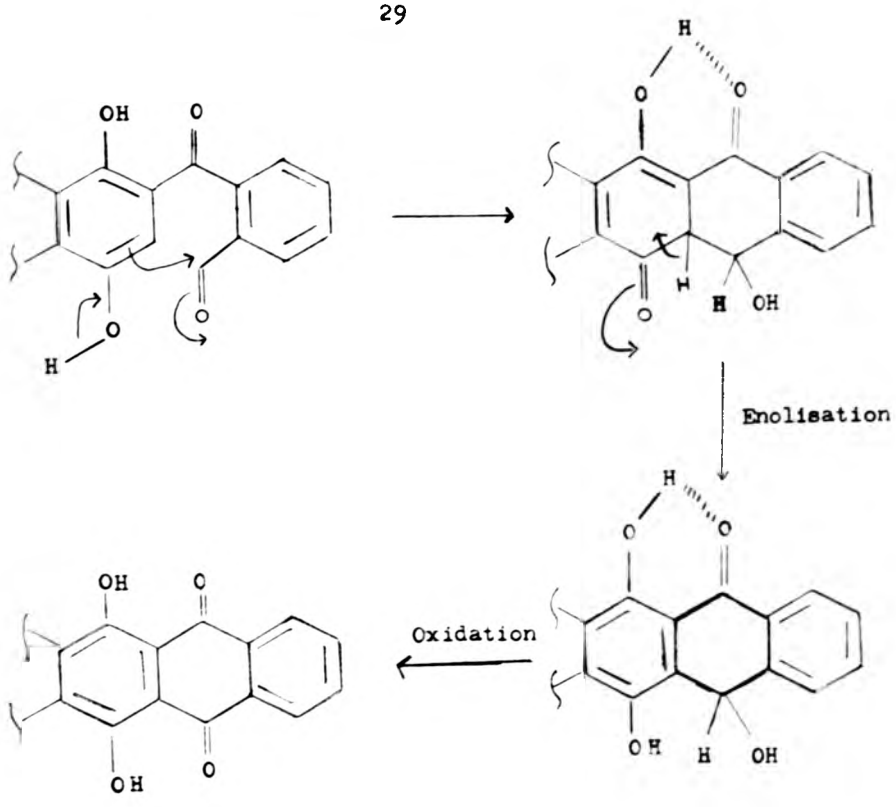
However, as will be described later, attempts to synthesise ketone (72), an intermediate for quinone (66), in a pure state, were unsuccessful. Therefore it was of interest to synthesise quinone (73) from which the desired quinone (66) could be generated. This was the basis of part of the work described in this Thesis. Furthermore, the formyl group could in principle be generated at a later stage, e.g. from the adduct (74), before the isomerisation (Scheme 24), or after the [1,5] shift.

As a minor objective, it was also of interest to attempt to synthesise the adduct (77b) since this compound may also serve as an intermediate for tetracyclic compound (71). The adduct(77b) might be obtainable from the quinones (75) or (76) (Scheme 25).

These aspects are described in the following Chapters.

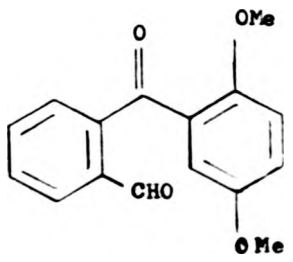

Reduction
(66)
(67)
(1) Cyclisation
(2) Oxidation
(34)
(69)
1,5
(70)
(1) Cyclisation
(2) Oxidation
(71)

Scheme 22.

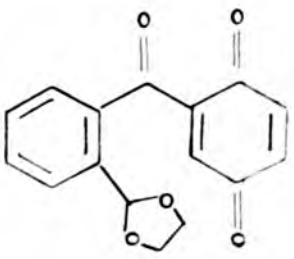


(71)

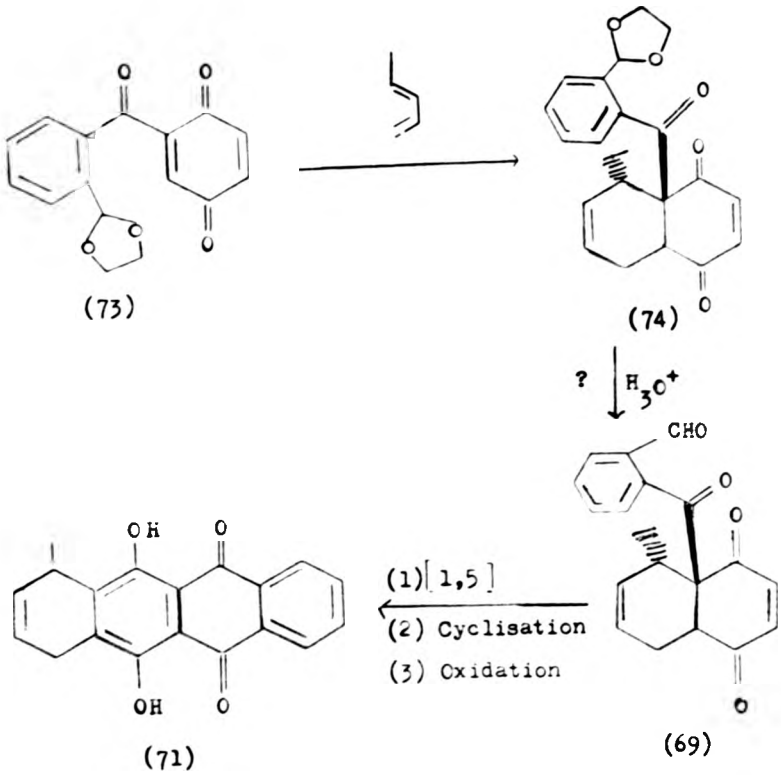
Scheme 23.



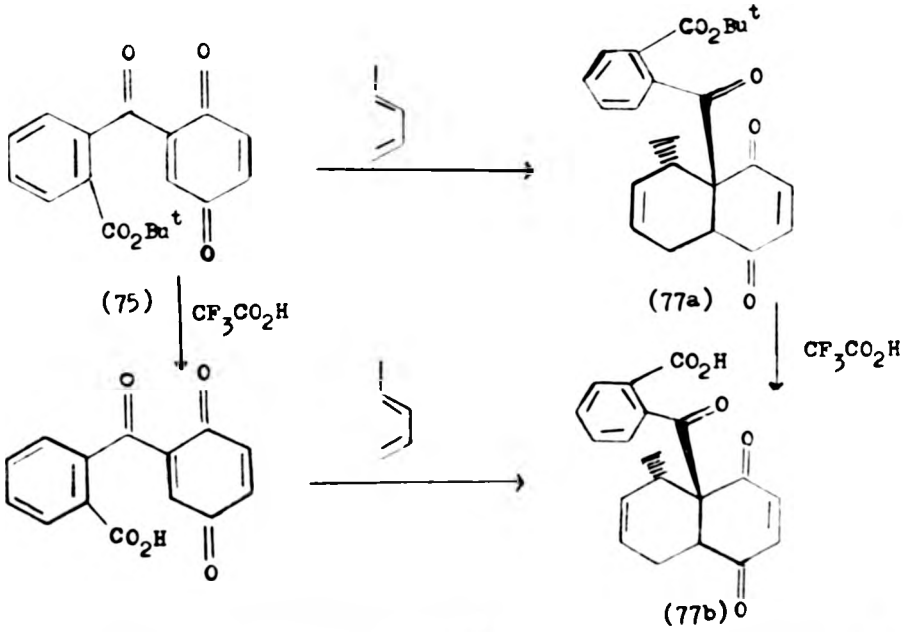
(72)



(73)



Scheme 24.



Scheme 25.

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Chapter 2.

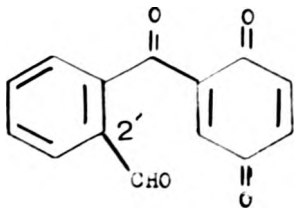
Attempted Synthesis of (2-Formylbenzoyl)-1,4-benzoquinone.

2.1. Attempted Synthesis of 2'-Formyl-2,5-dimethoxybenzophenone.

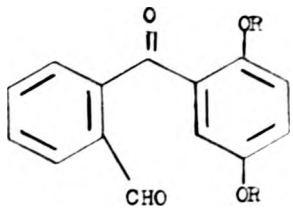
As mentioned in section 1.2, it was of interest to synthesise 2'-formylbenzoyl-1,4-benzoquinone (66), since addition of trans-penta-1,3-diene to it should give the desired angular aroyl adduct (69). 1,5-Aroyl migration in this adduct followed by cyclisation (expected to occur under mild conditions), should give the desired tetracyclic compound (71) (Scheme 22; Section 1.2). The quinone (66) could in principle be prepared by oxidation of 2'-formylbenzoyl-1,4-hydroquinone (67) which in turn could be obtained from its dimethyl ether (72) by the use of an appropriate demethylating agent, as in any general synthesis of 1,4-benzoquinones.[1a] Therefore, various approaches towards the synthesis of the desired aldehyde (72) were investigated.

The shortest way to the aldehyde (72) could be by the reduction of ester (31), since it is known that aldehydes can be obtained from esters by using appropriate reducing agents. Therefore 2'-methoxycarbonyl-2,5-dimethoxybenzophenone (31) was prepared, as described in the literature,[1c] by reaction of 1,4-dimethoxybenzene (78) with 2-chloroformylbenzoate (77) in the presence of aluminium chloride, in about 60% yield. Subsequently, the ester (31) was obtained by refluxing the acid chloride (79) with methanol (Scheme 26).

Reduction of ester (31) was attempted using di-isobutyl-aluminium hydride, DIBAL-H,[1b] since this reagent was reported to be more selective than lithium aluminium hydride, $LiAlH_4$ in reducing lactones, ester, amides, and nitriles to aldehydes. It was found[2] that at low temperature (about -70°), equimolar amounts of DIBAL-H reduced, in high yields, various esters of aliphatic and aromatic

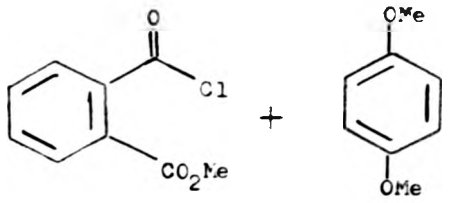


(66)

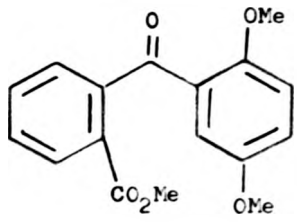


(67); R = H

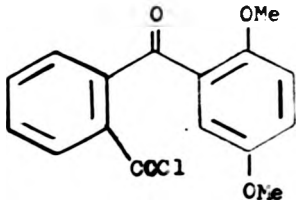
(72); R = Me



(77) (78)

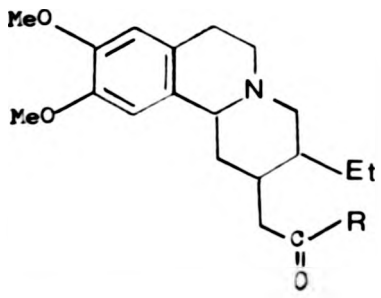


(31)



(79)

Scheme 26



(80); R = OEt

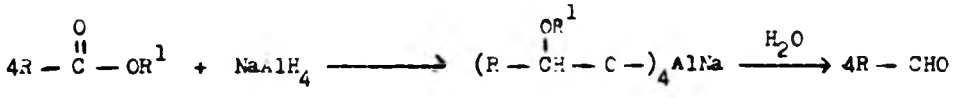
(81); R = H

acids to aldehydes, according to the following equation.

Szantay et al.[3] reported that the ester (60) gave the corresponding aldehyde (61) in 85% yield under these conditions.

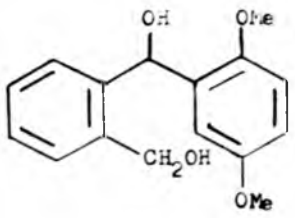
However, reduction of the ester (31) with DIBAL-H in toluene at -70° for 2 h. failed to give the desired aldehyde (72). The product isolated from this reduction was a yellowish oil, the p.m.r. spectrum of which in d-chloroform did not show a signal due to a formyl group. Repeating the reduction, initially at -70°, and then at room temperature gave the same result.

Reduction was then repeated using $LiAlH_4$, since it was reported[4] that $NaAlH_4$ in THF at room temperature reduced esters to aldehydes in generally good yield, although aromatic aldehydes were obtained in lower yields than aliphatic. The reduction was suggested to proceed according to the following scheme.

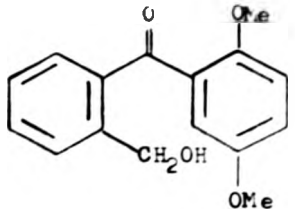


In the same publication it was noted that $LiAlH_4$ in THF or in a mixture of THF and pyridine (instead of ether) in some cases gave aldehydes in fair yield; reduction of ethyl laurinate using $LiAlH_4$ in THF at -75° for example, gave laurinic aldehyde in 45% yield.

However reduction of the ester (31) in THF at -70° and decomposition of the reaction product with water gave an oil, the mass spectrum of which suggested that the product may have contained the diol (82) (m/z 274), and the ketone (83) (m/z 272). The presence of the



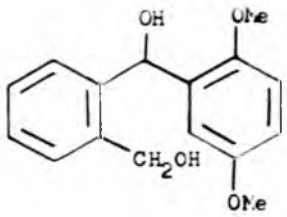
(62)



(63)

(31)

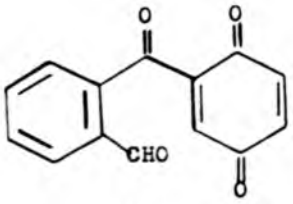
$LiAlH_4$



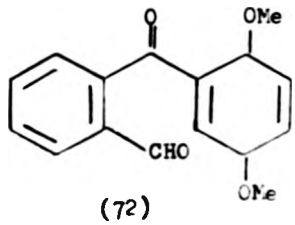
(62)

CAN
(?)

Oxidation



(66)



(72)

Scheme 27

diol (62) may be due to over-reduction of the ester (31).

Since one-step reduction of the ester (31) failed to give desired aldehyde (72), the reactions shown in Scheme 27 were then tried. The desired aldehyde (72) could in principle be obtained by oxidation of the diol (62), since several reagents for selective oxidation of primary or secondary alcohols to aldehydes or ketones, respectively, are known.[5]

The desired diol (62) was prepared by reduction of ester (31) with $LiAlH_4$ in ether-THF at room temperature, in 93% yield, as a white solid, m.p. 60-62°. The structure was confirmed by its elemental analysis, mass and p.m.r. spectra.

Oxidation of the diol (62) was then tried using several reagents. It was initially oxidised using four mol of CAN in aqueous acetonitrile at room temperature. This reagent is known[6] to demethylate several substituted 1,4-dimethoxybenzenes to the corresponding quinones, and at the same time to oxidise alcohols[7] to carbonyl compounds. However, this reagent failed to give the expected aldehyde (72) or even the required quinone (66). The p.m.r. spectrum of the total product did not show a signal due to a formyl group, although the spectrum showed that all the methoxy groups in the starting diol (62) had been completely removed. The mass spectrum of the total product showed a molecular ion at m/z 242, but not one at 240 for the required quinone (66). The product, however, may have contained the cyclised compound (84), or an isomer of it, since its mass spectrum showed a peak at m/z 226, as required for $M^{\cdot+}$ of (84).

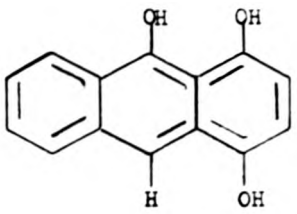
Oxidation was then tried using sodium bromate, $NaBrO_3$, catalysed by CAN (0.1 mol) in aqueous acetonitrile at refluxing temperature. It was reported[8] that the combination CAN-$NaBrO_3$ selectively oxidises

secondary alcohols to ketones in the presence of primary ones, in high yield. No mechanism for the oxidation was given. However, oxidation of the diol (82) using this oxidant failed to give the desired aldehyde (72). The product isolated was a yellowish oil, the p.m.r. spectrum of which in d-chloroform did not show a signal due to a formyl group. A similar reaction at refluxing temperature may have given a trace of the required aldehyde (72), since its p.m.r. spectrum in d-chloroform showed a singlet at δ 10.10, although the rest of the resonances were too complex to be identified in terms of the required product. The mass spectrum of the total product showed $M^{\cdot+}$ 270 for the required aldehyde.

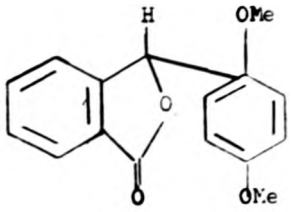
Recently, Aizpurua and Palomo reported[9] that the combination of chromium trioxide-trimethylsilyl chloride, CrO_3-Me_3SiCl (1:1), in dichloromethane or acetonitrile at room temperature is an efficient system for the oxidation of alcohols to the corresponding carbonyl compounds. It was suggested that the reaction proceeds *via* a trimethylsilyl chlorochromate intermediate, as the oxidising species, as shown in the following equation.

$$CrO_3 + Me_3Si - Cl \longrightarrow Me_3SiO - \overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{Cr}} - Cl$$

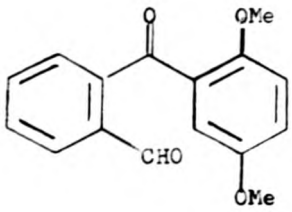
Oxidation of the diol (82) was then tried using CrO_3-Me_3SiCl in dichloromethane at -20 to -30°. The product isolated from this reaction was a mixture of the required aldehyde (72) and the lactone (85). Column chromatography on silica gel using dichloromethane as eluent allowed isolation of the aldehyde (72) in small quantities (*ca.* 16% from the total product). The major fraction was a mixture of the aldehyde (72) and the lactone (85) in the ratio 1:3, respectively.



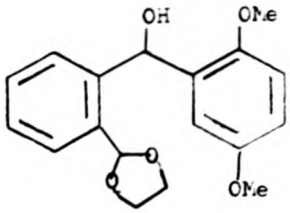
(84)



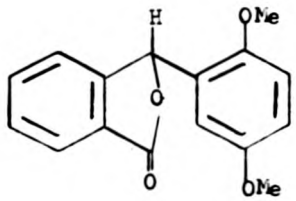
(85)



(72)

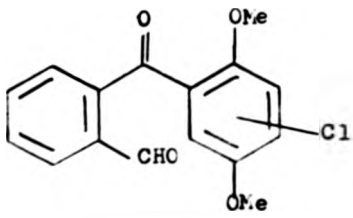


(86)



(85)

Scheme 28



(87)

Several attempts to improve the isolated yield of the aldehyde failed.

The p.m.r. spectrum of the required aldehyde (72) in d-chloroform showed singlets at δ 3.46 and 3.60, and at 10.18 due to two methoxy and one formyl group, respectively. The rest of protons gave multiplets at δ 6.60-6.30. Its mass spectrum showed the molecular ion at m/z 270 with fragments at 239, 211 and 165.

The p.m.r. spectrum of lactone (85) in d-chloroform showed singlets at 3.67 and 3.66 due to two methoxy groups, with the rest of the protons giving multiplets in the aromatic region. It had a molecular ion at m/z 270 as required.

Aldehyde (72) was then prepared [but still as a mixture with lactone (85)] from oxidation of alconol (86) followed by acid hydrolysis. Similarly lactone (85) was prepared by acid hydrolysis of acetal (86) followed by air oxidation during work-up (Scheme 28). The synthesis of alconol (86) will be described in Chapter 3.

Oxidation of the diol (82) using the combination CrO_3-Me_3SiCl was then repeated at 0°, and at room temperature, in the hope that at such temperatures it might gave more aldehyde (72) than lactone (85). Suprisingly, the product isolated after column chromatography on silica gel using dichlorometnane as eluent was a mixture of the desired aldehyde (72) and the chloro-aldehyde (87) in the ratio 3:1 respectively. The structure of the chloro-aldehyde (87) was supported by its p.m.r. and mass spectra. The p.m.r. spectrum of the total product showed singlets at δ 3.62, 3.82, and 10.52 due to the two methoxy groups and the formyl group of chloro-compound (87); the rest of the resonances were in the aromatic region. The mass spectrum of the total product showed molecular ions at m/z 306 and 304 in the ratio 1:3 respectively; with fragments at 291, 269, 275, 273, 201 and 199. The pattern of the fragments established

that the chlorine is attached to position 2', 4', or 6' of the dimethoxyphenyl group, and not at the 3', 4', 5' or 6' position, as shown in Figure 1; the corresponding fragmentation pattern for the parent compound (72) is shown in Figure 1a. Formation of the chloro-aldehyde (87) may result from electrophilic chlorination in the reaction mixture, since a slight excess of trimethylsilyl chloride was used in the above oxidation.

This result suggested that there was still some hope of obtaining the desired aldehyde (72) as the only product. Therefore, oxidation of alcohol (82) was repeated using the chromium trioxide-pyridine complex, $CrO_3.2C_5H_5N$, in dichloromethane at room temperature as described by Ratcliffe and Rodehorst.[10] However, the product isolated from this oxidation was still a mixture of the aldehyde (72) and the lactone (85) in the ratio 1:1; although the p.m.r. spectrum of the total product in d-chloroform showed that it was much cleaner than that obtained from the previous oxidation.

Several experiments were then performed in order to optimise formation of the aldehyde (72), either by carrying out the reaction at -5 to 5°, or by using more oxidant at room temperature. However, all attempts failed to give the aldehyde (72) as a single product; mixtures with lactone (85) in the ratio 1:1 were always obtained. Several attempts were also made to isolate the aldehyde (72) by column chromatography or by washing the mixture with 10% sodium hydrogen sulfite, but all gave mixtures which contained more lactone (85) then the desired aldehyde (72). After the above mixtures had been kept in air at room temperature for 76 days, their p.m.r. spectra in d-chloroform no longer showed a formyl peak.

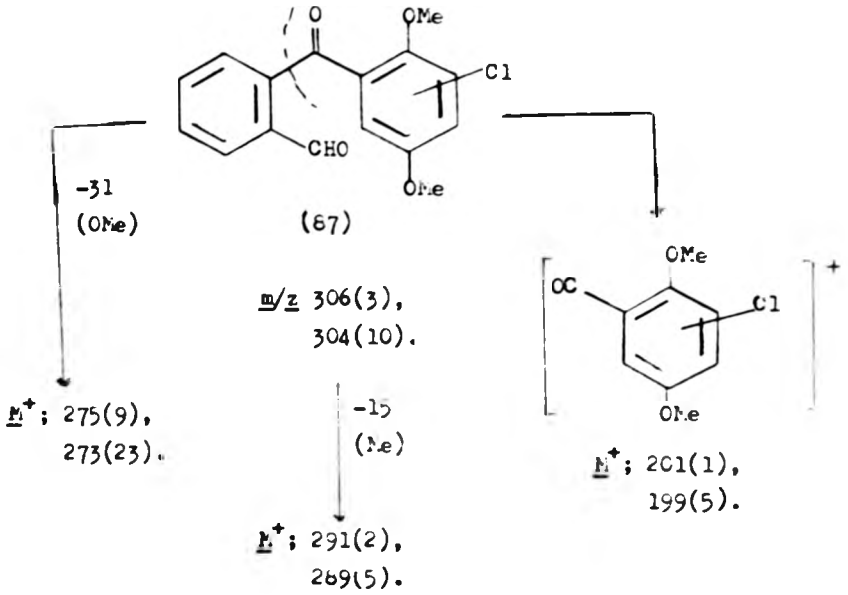


Figure 1.

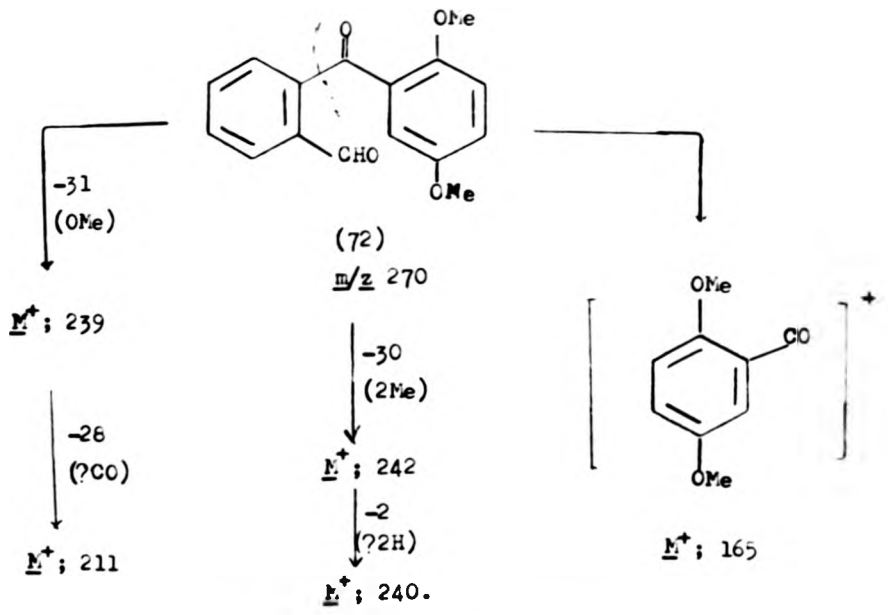


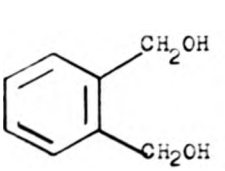
Figure 1d.

It is of importance to note here that oxidation of phthalyl alcohol (88) by the chromium trioxide-pyridine complex was reported to give a high yield of phthalide (89a) and it was postulated that phthalide was obtained by the oxidation of hemiacetal (89b).[11] Recently,[12] oxidation of diols (90), analogous to diol (82), using the same oxidant, was reported to give the lactones (91) in over 80% yield (Scheme 29). Similarly, oxidation of diol (92) using manganese dioxide was reported to give lactone (93), as shown in Scheme 30.[13]

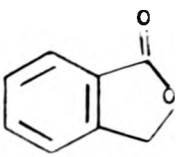
Interestingly, it was reported recently[14] that bispyridinesilver permanganate, $AgPy_2MnO_4$, or dinitratocerium (IV) chromate dihydrate, $[Ce(NO_3)_2]CrO_4.2H_2O$, oxidised phthalyl alcohol (88) into ortho-phthalaldehyde (94) in high yield,[14] while bis(2,2'-bipyridyl)copper(II) permanganate, $(Py_2)_2CuMnO_4$, BBCP, oxidised the diol (86) into the mono-aldehyde (95)[15] in quantitative yield (Scheme 31). Therefore, any of these oxidising reagents, may be very useful, since oxidation of the diol (82) may give the desired aldehyde (72) or alcohol (83), respectively, without cyclisation (Scheme 32). However, in our hands, all of these oxidants oxidised phthalyl alcohol (88) into the cyclic compound, phthalide (89a), as the only isolated product. Correspondingly, oxidation of the diol (82) using BBCP gave the lactone (85) in over 80% yield (Scheme 33).

Some of the oxidation products which have just been discussed are summarised in Scheme 34.

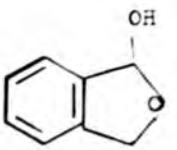
It was observed by earlier workers[16] in this laboratories that oxidation of diol (82) using manganese dioxide, selenium dioxide, pyridinium dichromate, and pyridinium chlorochromate, all gave a mixture which contained the required aldehyde (72), but attempts to isolate this in a pure state, were unsuccessful.



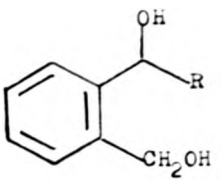
(88)



(89a)



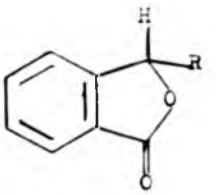
(89b)



(90)

$CrO_3/Py/CH_2Cl_2$

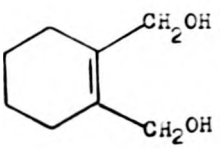
85%



(91)

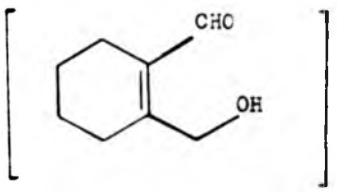
R = $i\text{-}C_3H_7$,
$(CH_2)_4CH$,
$(CH_2)_6CH$

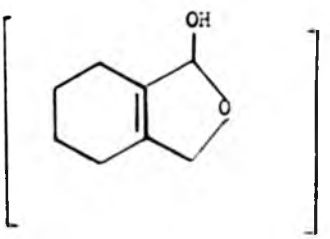
Scheme 29 -

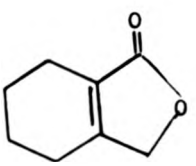


(92)

MnO_2

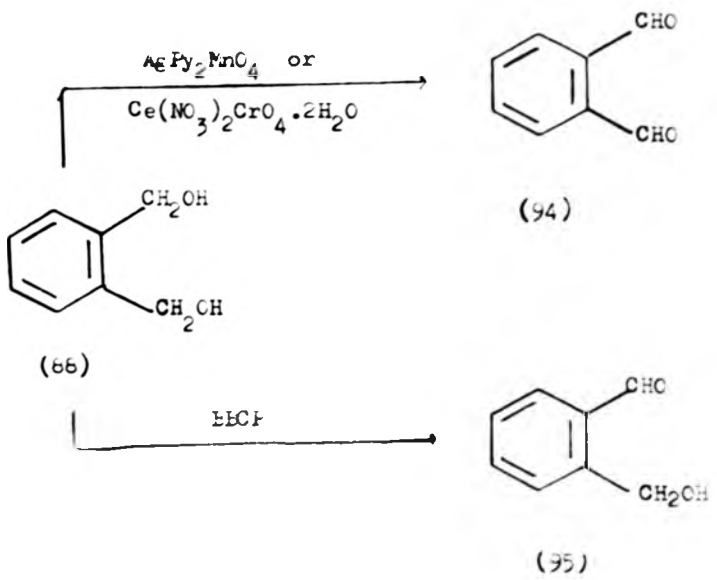






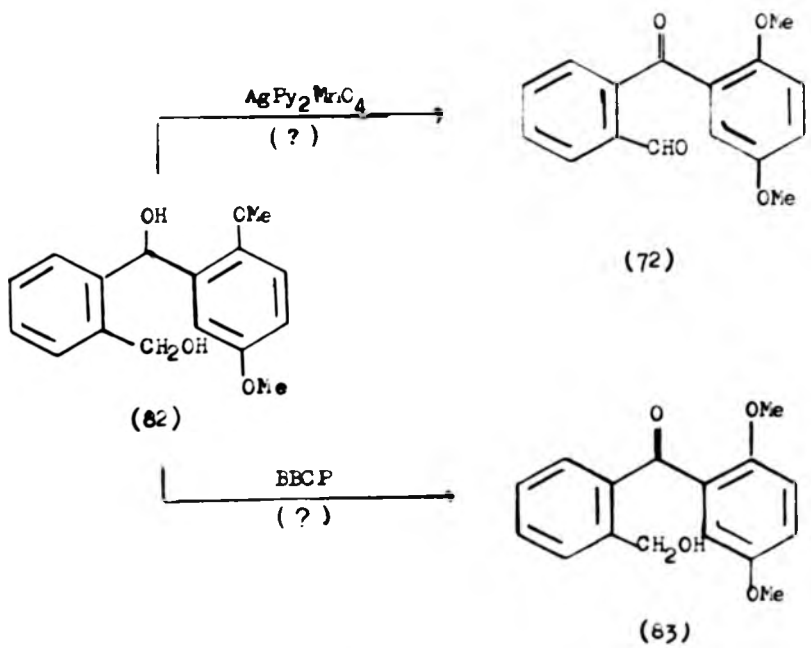
(93)

Scheme 30 .



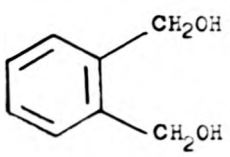
(66) (94) (95)

Scheme 31.

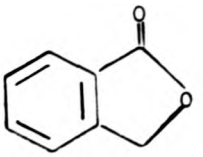


(82) (72) (83)

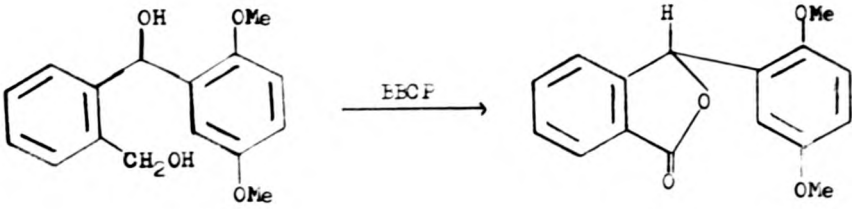
Scheme 32.



(88)

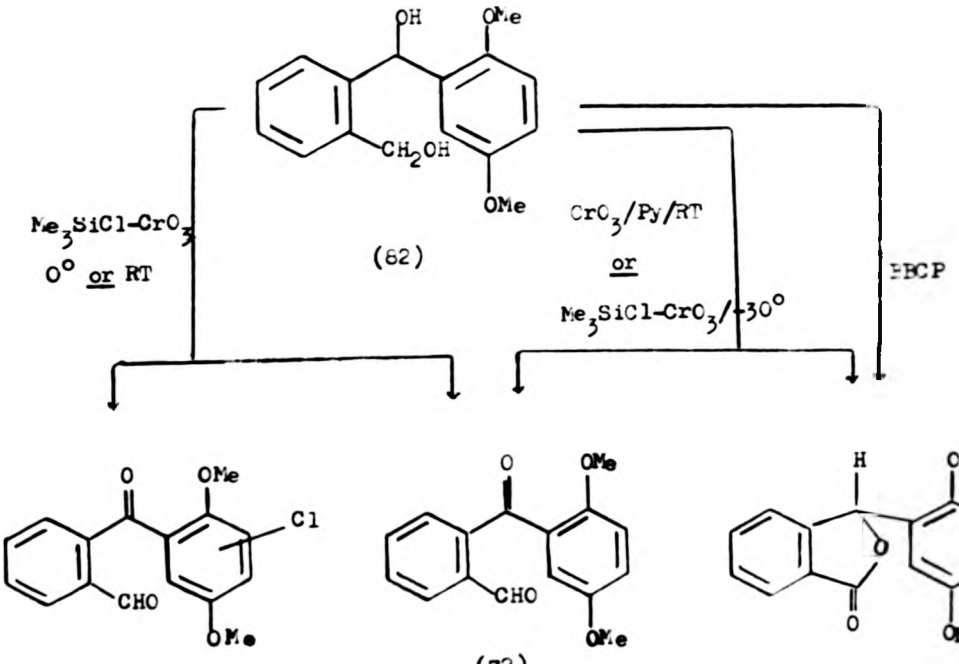


(89a)



(82) (85)

Scheme 33 .



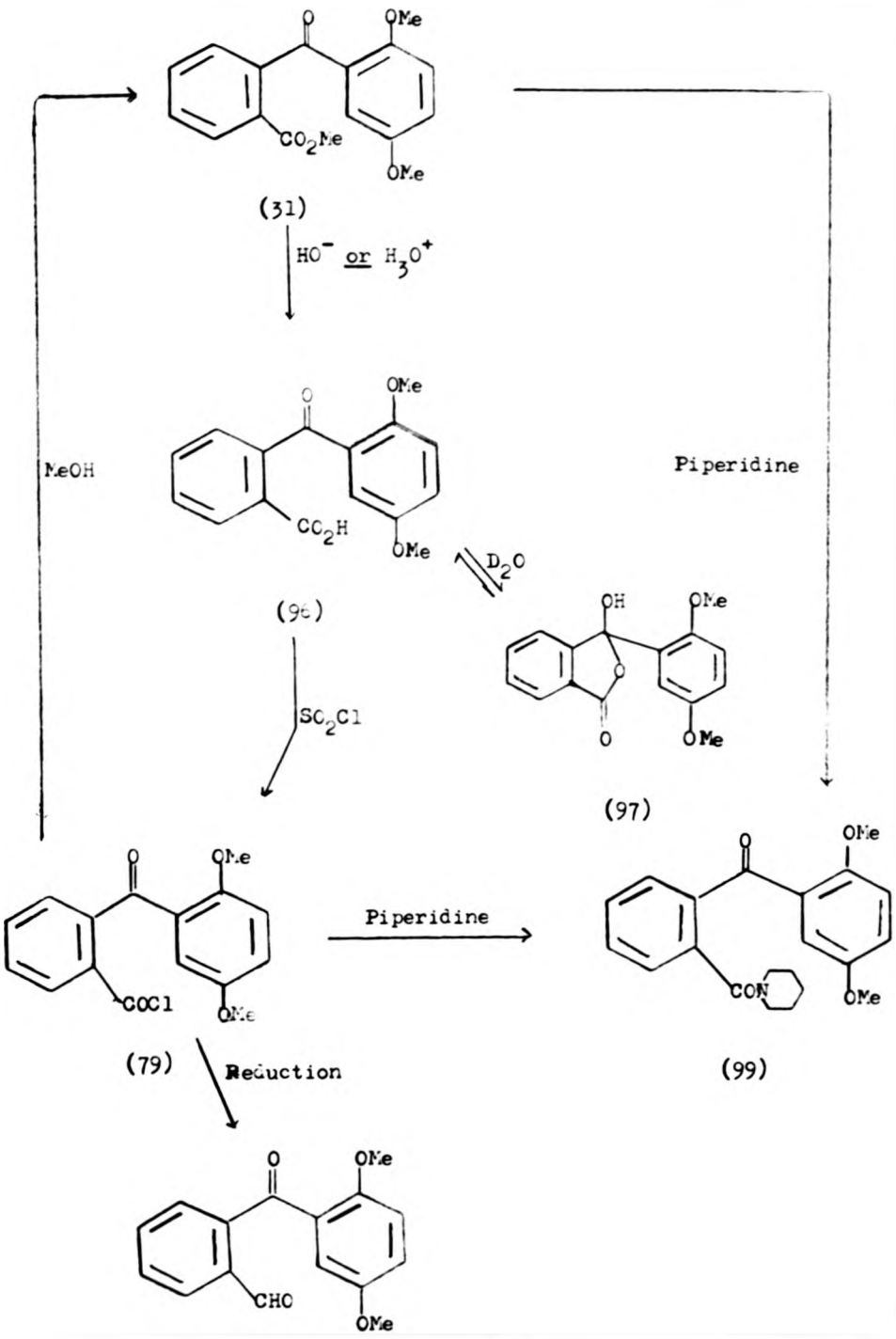
(87) (72) (85)

Scheme 34 .

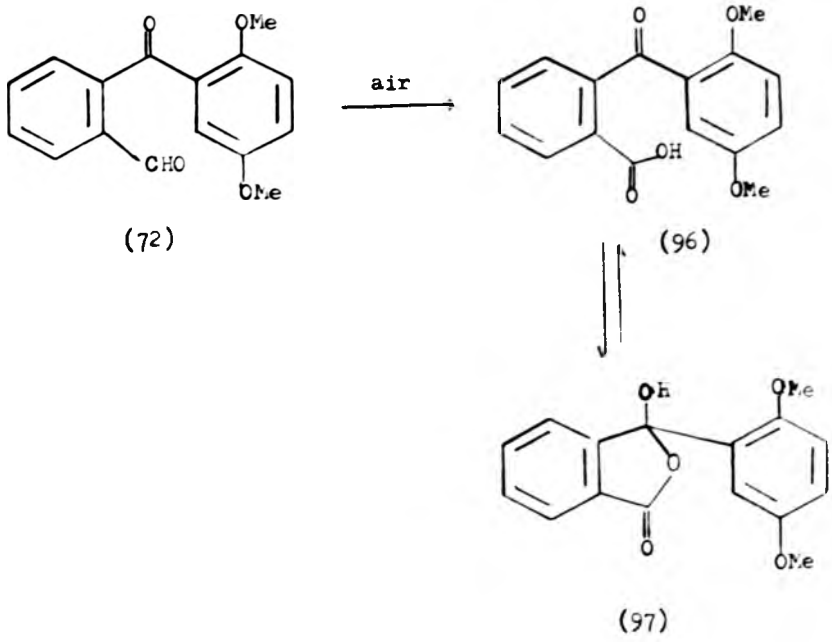
Since oxidation of the diol (82) failed to give the required aldehyde (72) as a single product, Scheme 35 was then tried.

It is known that aldehydes can be obtained from acid chlorides by various reduction methods.[17] The ester (31) was then hydrolysed to the carboxylic acid (96) by refluxing with 10% sodium hydroxide or 10% sulfuric acid overnight; refluxing with 10% sodium hydroxide for 3 h. gave mainly uncharged ester (31). The carboxylic acid (96) was isolated as a pale yellow solid, m.p. 159-161°. The structure was confirmed by its elemental analysis, mass and p.m.r. spectra, although it was difficult to assign the proton H-3' and the hydroxy group in its p.m.r. spectrum since addition of D_2O gave a p.m.r. spectrum suggesting the presence of a mixture of carboxylic acid (96) and lactone (97) in the ratio 3:2 respectively. This observation may confirm results obtained by earlier workers,[16] that the aldehyde (72) is oxidised by air to the carboxylic acid (96) which then lactonises to the cyclic hemiacetal (97) (Scheme 36), similarly to the aldehyde (95), which was reported[18] to be in equilibrium with the hemiacetal (69b) in basic solution (Scheme 37).

The carboxylic acid (96) was then refluxed with thionyl chloride for 2½ h., to give the desired acid chloride (79) in over 80% yield, as a pale yellow oil (Scheme 35). The acid chloride (79) was unstable, gradually hydrolysing to the carboxylic acid (96) on standing in air at room temperature, and therefore a good elemental analysis was not obtained. The acid chloride (79) showed molecular ions at m/z 306 and 304 as expected, and an important fragment at m/z 269 for $(M - Cl)^+$. On refluxing with methanol, the acid chloride (79) gave ester (31) as the only product; on treatment with one mol of piperidine in pyridine it gave amide (99) in 55% yield. The amide (99) could also be prepared,


OMe
CO2Me
OMe
(31)
HO⁻ or H3O+
MeOH
Piperidine
CO2H
D2O
(96)
SOCl2
OH
O
(97)
COCl
(79)
Piperidine
CON
(99)
Reduction
CHO
(72)

Scheme 35.



(72) (96) (97)

Scheme 36.

(95) (89b)

Scheme 37.

in 98% yield, by refluxing the ester (31) with an excess of piperidine.

Having prepared the required acid chloride (79), several reductions were then tried in attempts to prepare the aldehyde (72) as a single product. It is important to note that since the acid chloride (79) was unstable, it was freshly prepared before use in the reduction reactions.

The reduction was initially tried using bis(triphenylphosphine)-copper(I) tetranydroborate, $(Ph_3P)_2CuBH_4$, since it was reported[18] that acid chlorides in the presence of two mol of triphenylphosphine, at room temperature, are reduced to aldehydes in good yield by $(Ph_3P)_2CuBH_4$, and that acetone is a suitable solvent for this reaction. Reduction in other solvents gave lower yields. Under such conditions, other functional groups such as ketones, epoxides, esters, cyanides, imines, alkenes, and alkynes are unaffected.

Likewise, Sorrell and Pearlman reported[19] that $(Ph_3P)_2CuBH_4$ is capable of reducing acid chlorides to alcohols if a solvent other than acetone is used. For example, benzoyl chloride in chloroform solution is reduced partially to benzyl alcohol, although benzaldehyde itself is apparently inert. Addition of two mol of triphenylphosphine is necessary since one binds to the copper byproduct and the other traps liberated BH_3 as shown in the following equation.

$$(Ph_3P)_2CuBH_4 + RCOCl \xrightarrow[\text{acetone, } 25^\circ]{2Ph_3P} (Ph_3P)_3CuCl + RCHO + Ph_3PBH_3$$

However, reduction of acid chloride (79) with $(Ph_3P)_2CuBH_4$ in the presence of triphenylphosphine in acetone, at room temperature, gave a white solid and an oil, the p.m.r. spectrum in d-chloroform not showing a signal due to a formyl group. The product may have

contained the acid chloride (79) together with the carboxylic acid (96) which is in equilibrium with the lactone (97), since its p.m.r. spectrum showed singlets at δ 3.48, 3.55, 3.68, 3.73, 3.80 and 3.85 due to six methoxy groups, with the rest of the resonances in the aromatic region. Similar reactions without triphenylphosphine, either in acetone or in d-chloroform, gave the same result.

Reduction was then carried out using lithium tri-tert-butoxy-aluminium hydride, $(^tBuO)_3LiAlH$ at -70° in diglyme; this reagent[20] was reported to reduce acid chlorides, ketones and aldehydes, but not to react with esters and nitriles. However, reduction of acid chloride (79) with one mol of $(^tBuO)_3LiAlH$, after decomposition with water, gave carboxylic acid (96) as the only product. Similar reactions at 0° and at room temperature gave the same result. It seems that $(^tBuO)_3LiAlH$ did not react with acid chloride (79), since decomposition of the reaction mixture with water gave the carboxylic acid (96). In this connection, reduction of 4-nitrobenzoyl chloride with $(^tBuO)_3LiAlH$ at -70° was tried as a model reaction, and it gave the desired 4-nitrobenzaldehyde in 69% yield.

The above observations suggested that the acid chloride (79) may be difficult to react with bulky reducing agents. Brown and Rao,[20] reported that ortho substituted aromatic acid chlorides tend to give lower yields of aldehydes following reduction with $(^tBuO)_3LiAlH$.

It is known[21] that catalytic hydrogenation of acid chlorides (the Rosenmund reaction) is an established synthetic route to aldehydes. Therefore reduction of acid chloride (79) was attempted by catalytic hydrogenation, using 10% palladium-barium sulfate as the catalyst in refluxing toluene.[22] However, this reduction again failed to give the required aldehyde (72). The product obtained was a pale yellow oil,

the p.m.r. spectrum of which in d-chloroform did not show a signal due to a formyl group. This product was not further examined.

Recently, Babler and Invergo[23] reported that sodium borohydride, $NaBH_4$, in a mixture of DMF-THF at -70°, and quenching with a mixture of propionic acid-dilute hydrochloride acid-ethyl vinyl ether (to avoid over reduction) was capable of converting acid chlorides to aldehydes in high yield with minimal alcohol formation. Using this procedure the authors reduced 2-chlorobenzoyl chloride, lauroyl chloride, and 10-undecanyl chloride to the corresponding aldehydes in 93, 81, and 60% yield, respectively. We repeated one of their reactions, and succeeded in reducing 2-chlorobenzoyl chloride to 2-chlorobenzaldehyde together with 2-chlorobenzyl alcohol in the ratio 6:1 (total product, 61%), in accord with the results reported by Babler and Invergo.[23]

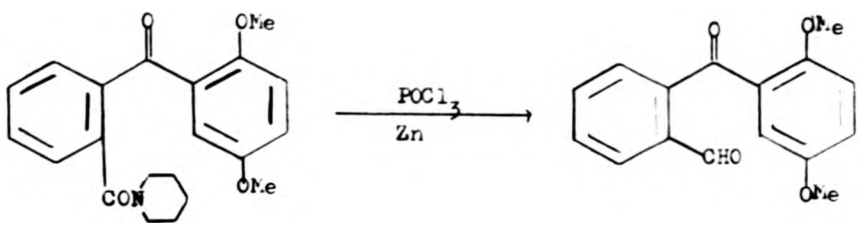
However, when the $NaBH_4$ reduction was tried with the acid chloride (79), it failed to give the desired aldehyde (72). The product isolated may have been the acid (96) in equilibrium with lactone (97) since its p.m.r. spectrum in d-chloroform showed singlets at δ 3.44, 3.50, 3.77 and 3.79, possibly due to four methoxy groups, with the rest of the resonances in the aromatic region. A similar reaction and decomposition of the product with water gave the acid (96) and lactone (97).

The reason for the failure of the reduction of the acid chloride (79) could be due to steric hindrance; similarly, the ester (31) was only slowly hydrolysed to the acid (96).

Since oxidation of diol (62) failed to give the desired aldehyde (72) as a single product, and furthermore because the required aldehyde (72) was unobtainable by reduction of the acid chloride (79), it was of interest to attempt to prepare the required aldehyde (72) by reduction

of Vilsmeier complexes of amide (99) (Scheme 38). It was mentioned earlier that the amide (99) was readily prepared either by refluxing the ester (31) with piperidine or by treatment of acid chloride (79) with piperidine in pyridine. The structure was confirmed by elemental analysis, mass and p.m.r. spectra. It mass spectrum showed the molecular ion at m/z 353, with important fragments at 269 (M-piperidyl)$^+$ and 64 (piperidyl$^+$).

However, scheme 36 was not tried, since reduction of Vilsmeier complexes of N-2-chlorobenzoylpiperidine (Section 4.2) as a model for the reduction, failed to give the corresponding aldehyde.

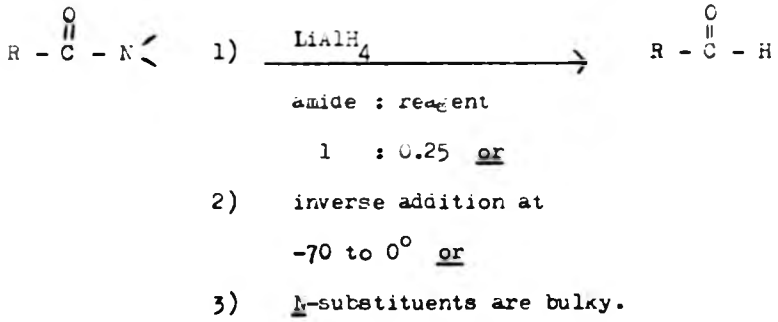


(99) (72)

Scheme 38.

2.2. Attempted Reduction of N-2-Chlorobenzoylpiperidine to 2-Chlorobenzaldehyde.

It is known that reduction of amides to aldehydes is a less common reaction since the amine formation competes. Furthermore amides, in general, are fairly resistant to reduction and only more potent reagents such as alkali metal hydrides, sodium in liquid ammonia (Birch reduction), and electrolysis are effective.[24] Aldehyde formation is particularly prevalent when the N-substituents are bulky, or if deficient amounts (less than 0.5 mol) of reductant (such as $LiAlH_4$) are used at low temperature (-70 to 0°), or if the hydride is added to the amide (inverse addition) instead of vice versa as in the usual method of reduction.



The best reagents for preparing aldehydes from amides reported in the literature are tris(ethoxy)-and bis(ethoxy)-lithium-aluminium hydride,[25] $(EtO)_3LiAlH$ and $(EtO)_2LiAlH_2$, respectively. These reagents reduce unhindered tert-amides to aldehydes in 60-90% yield.

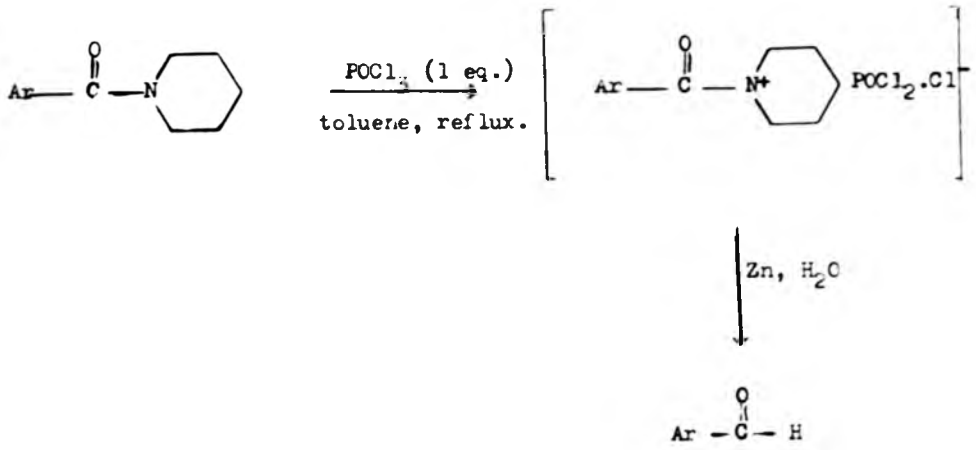
Interestingly, Rahman and Basha[26] reported that reaction of Vilsmeier complexes of tertiary aromatic amides with zinc affords the corresponding aldehydes in high yield; no experiments details were

given (Scheme 39). These authors reported that they reduced the Vilsmeier complex of N-2-chlorobenzoyl piperidine (100) to 2-chlorobenzaldehyde (101) in 95% yield. We then attempted to repeat some of their works, since this reduction method could be useful for reduction of Vilsmeier complexes of amide (99) to the required aldehyde (72) (Scheme 38).

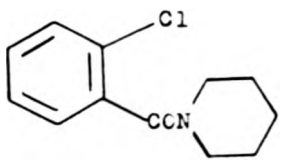
The required amide (100) was prepared by treatment of 2-chlorobenzoyl chloride with piperidine at 0°, in 84% yield, as a colourless oil. The amide (100) was then treated with one mol of phosphorus oxychloride in refluxing toluene for ½ h. After being cooled to room temperature, the mixture was then treated with zinc dust and worked up in an aqueous medium as described by Rahman and Basha[26] to give a pale yellow oil, the p.m.r. spectrum of which in d-chloroform showed only starting material, with no evidence for a formyl group. Repeating the reactions for longer refluxing times (1½ h., 4 h., and 48 h.), either in benzene or toluene, and treating the products with either zinc dust or anhydrous tin(II) chloride and work-up as before gave similar results.

The reason for the failure of the above reduction may be that the Vilsmeier complex (102) may not be formed. Therefore, amide (100) was refluxed with an excess of phosphorus oxychloride (5 mol) overnight, and the excess of phosphorus oxychloride was then removed to leave a light-brown oil, the p.m.r. spectrum of which in d-chloroform showed that it was different from the amide (100). The product was not further characterised, but it was assumed to be the required Vilsmeier complex (102).

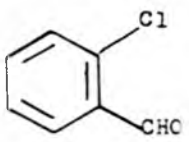
The complex (102) was then refluxed in toluene in the presence of actived zinc.[27] However, after work-up in an aqueous medium it gave amide (100) as the isolated product. A similar result was obtained when the complex was treated with zinc dust and then decomposed with 10%



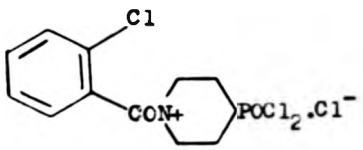
Scheme 39.



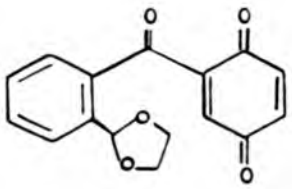
(100)



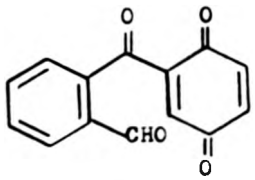
(101)



(102)



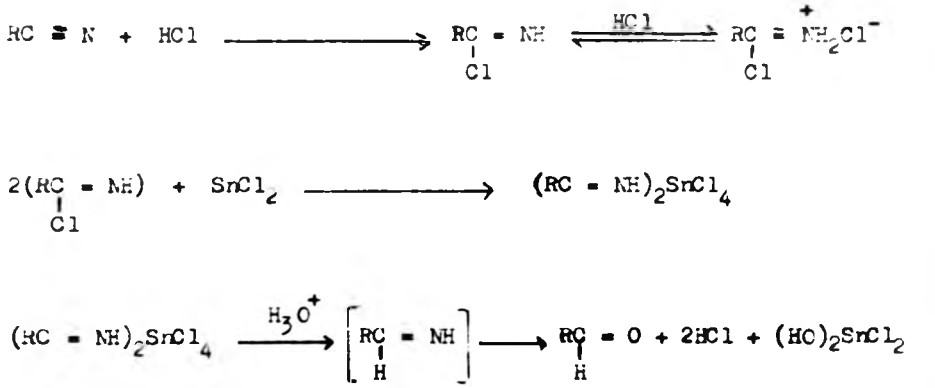
(66)



(73)

hydrochloric acid.

Because the above attempted reduction of the model compound (100) failed to give 2-chlorobenzaldenyde (101), the complex (102) was then reduced using a modification of the Stephen reduction. The Stephen reduction[28] orignally involved conversion of a nitrile through the imino-chloride to an aldenyde. The most suitable reducing agent is annydrous tin(II) chloride dissolved in etner saturated witn hydrogen cnloride.



Therefore the complex (102) was refluxed in THF and toluene in the presence of tin(II) chloride, and then decomposed by refluxing with 5% hydrochloric acid. After work-up, the reaction may have given a complex, which showed a molecular ion at m/z 316, but the desired aldehyde was not observed from its p.m.r. spectrum in d-chloroform. When the reaction was repeated, but refluxing in THF-dioxane, it gave N-2-chlorobenzoyl-piperidine (100). Similarly, the later compound was isolated when the reaction was repeated in ether at room temperature, and decomposition was with hydrogen chloride gas.

The best result was obtained when the complex (102) in toluene was stirred at room temperature in the presence of tin(II) chloride, and the mixture decomposed with 5% hydrochloride acid. Under these conditions, a

trace of the desired aldehyde (101) was detected by its p.m.r. spectrum in d-chloroform (singlet at δ 10.47). However several attempts to improve the production of the aldehyde by repeating the reaction, either in refluxing toluene or in ether gave the same result. In contrast, a similar reaction in pyridine at room temperature overnight gave N-2-chlorobenzoyl-piperidine (100) as the only product.

After spending several weeks studying this model reduction, we felt that it was not worthwhile to study the reactions of the Vilsmeier complex of amide (99). Thus the first objective (Scheme 38) was not tried. Therefore a new route to quinone (73), analogous to the desired quinone (66), was then investigated (Chapter 3).

2.3. References for Chapter 2.

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Chapter 3.

Syntnesis and Reactions of [2-(1,3-Dioxolan-2-yl)benzoyl]-1,4-benzoquinone.

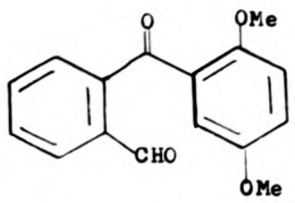
3.1. **Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-lithium with Substituted Benzaldehydes.**

As mentioned in Chapter 2, several attempts to synthesise aldehyde (72), a precursor for the desired quinone (66), in a pure state were unsuccessful. Furthermore, the quinone (66) was expected to be relatively unstable, and subsequently this was found to be so (Section 3.2). Therefore it was of interest to synthesise quinone (73) in which the formyl group in quinone (66) is protected as a 1,3-dioxolan-2-yl group. The required quinone (66), and the adduct (69) could then, in principle, be generated by hydrolysis of the acetal.

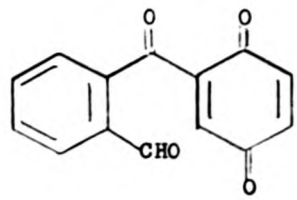
It is known[1] that irradiation of α-hydroxybenzyl-1,4-benzoquinone (104) in benzene affords acylquinol (105), and that photolysis of quinone (106)[2] under neutral, acid, or basic conditions gives low yields of photocyclisation product (107). Therefore it was hoped that the required quinone (73) could be prepared by irradiation of the α-hydroxybenzyl-1,4-benzoquinone (112) followed by oxidation; the quinone (112) could be prepared from phenol (111) by oxidation[3] with potassium nitrosodisulfonate, $[(KSO_3)_2N - O^{\cdot}$, Fremy's salt$]$. Thus Scheme 40 was first attempted.

1,3-Dioxolane (108) was reported in the literature,[4] prepared by reaction of 2-bromobenzaldehyde with ethylene glycol catalysed by toluene-p-sulfonic acid. However, for the present work it was prepared by reacting 2-bromobenzaldehyde with 2-methoxy-1,3-dioxolane[5] in refluxing toluene, and was obtained as a colourless liquid in about 80% yield.

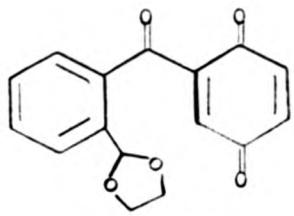
The dioxolane (108) in ether at -70° was then treated with n-butyllithium in hexane, followed by a solution of 3-methoxybenzaldehyde (109a) in ether. Decomposition with water and the usual work-up afforded a yellowish oil shown by its p.m.r. spectrum to contain mainly starting



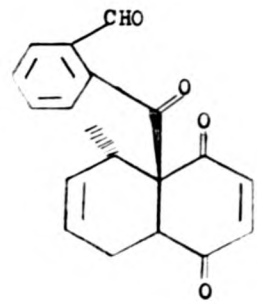
(72)



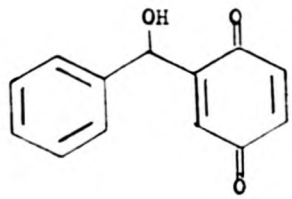
(66)



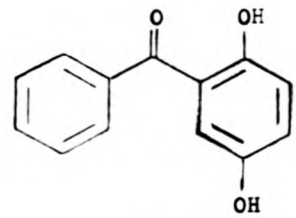
(73)



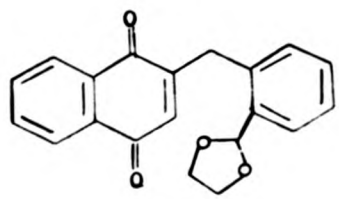
(69)



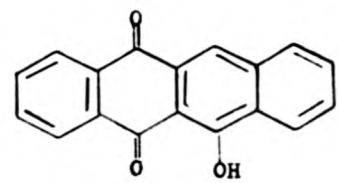
(104)



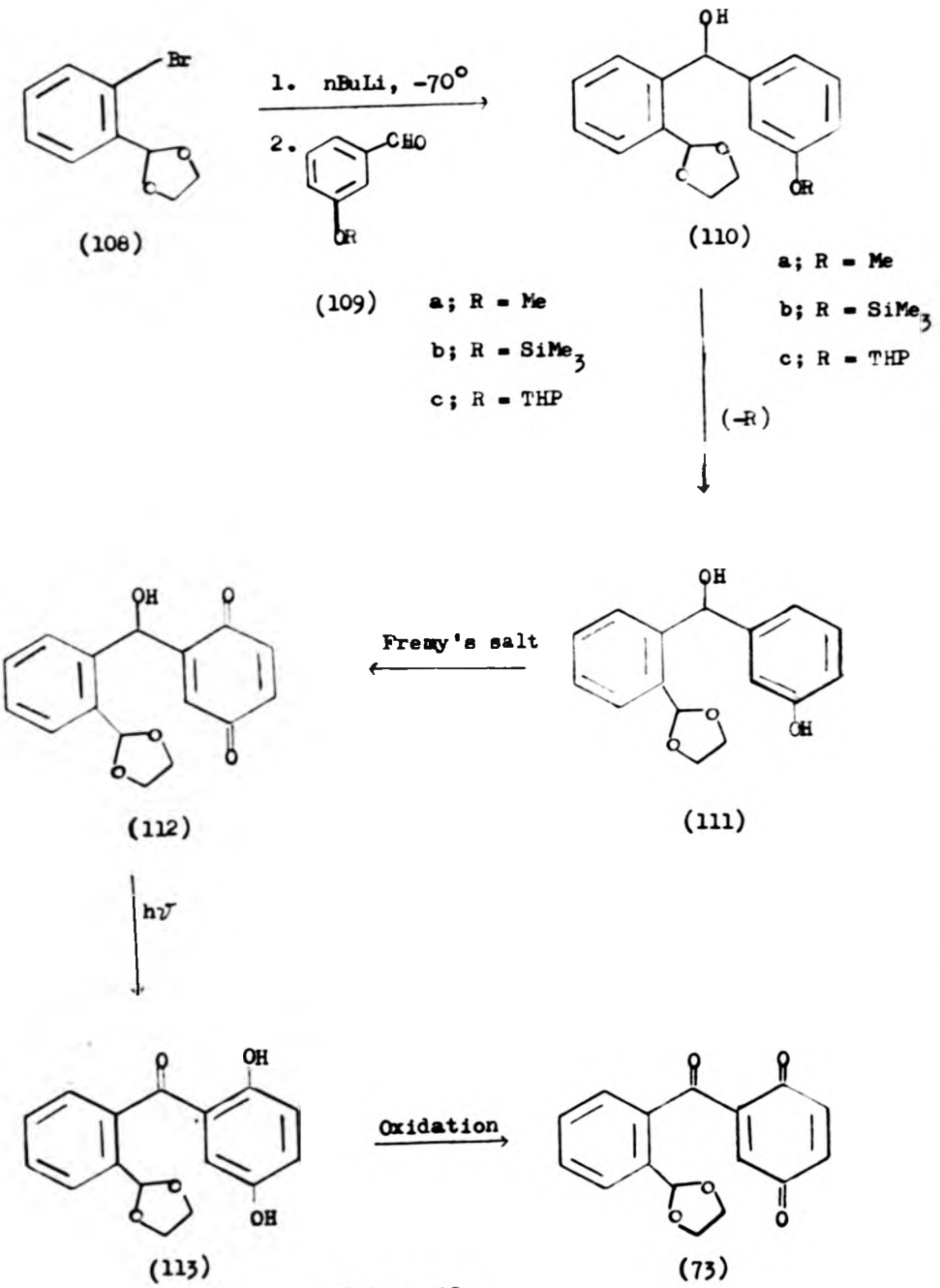
(105)



(106)



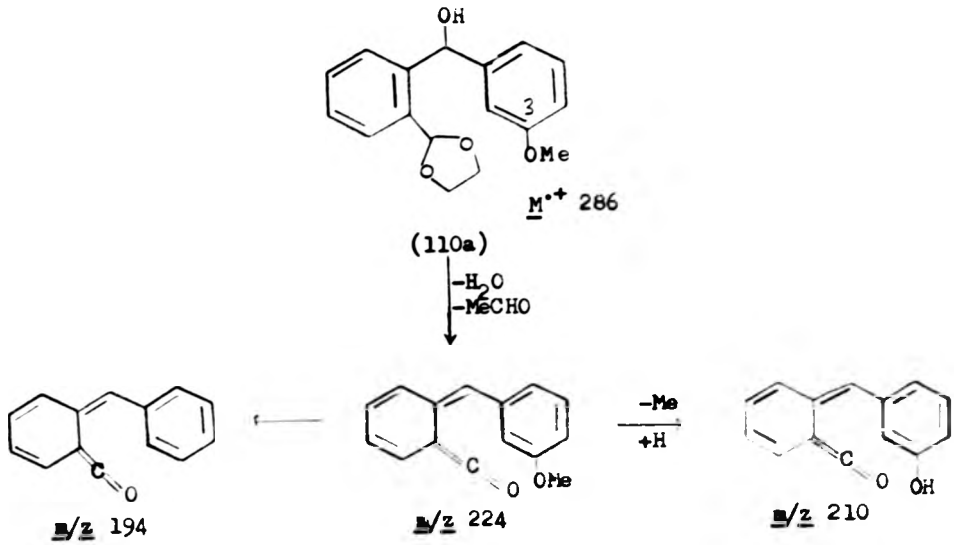
(107)


Br
1. nBuLi, -70°
2.
CHO
OR
OH
OR
(108)
(109) a; R = Me
b; R = SiMe3
c; R = THP
(110)
a; R = Me
b; R = SiMe3
c; R = THP
(-R)
OH
O
O
Fremy's salt
OH
OH
(112)
(111)
hν
O
OH
OH
Oxidation
O
O
O
(113)
(73)

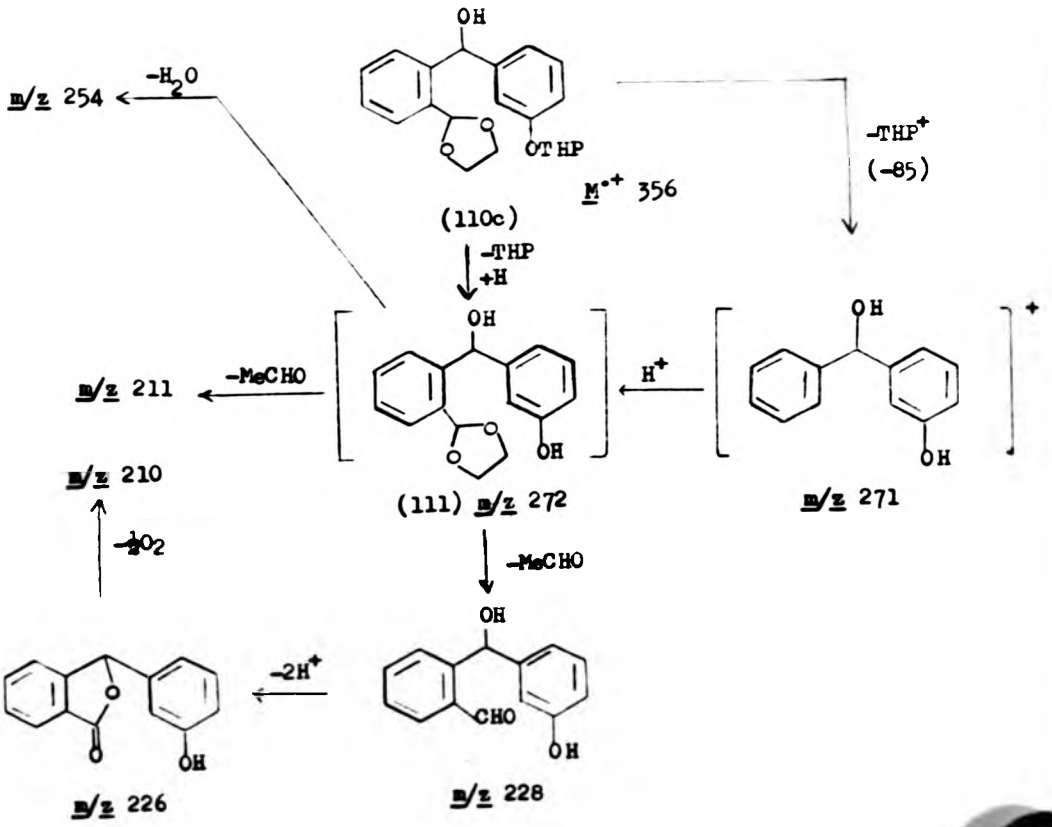
Scheme 40.

aldehyde (109a). It was difficult to assign the acetal group for the required alconol (110a), and furthermore the resonances in the aromatic region were too big to be assigned to the eight protons of the desired alconol (110a) alone. However, the mass spectrum of the total product suggested that the isolated material may have contained the coupled product (110a) since it showed the required molecular ion at m/z 266 with fragments at 224, 210, 194 and 181 (Scheme 41). No attempt was made to optimise the production of alcohol (110a) since it was expected that cleavage of the methoxy group at the 3-position in alcohol (110a) will be difficult in the presence of the dioxolan group at the 2'-position. However the above result suggested that if a labile protecting group, R, in aldehyde (109) could be used, than the desired phenol (111) could be obtained.

Thus the above coupling was repeated but using aldehyde (109b) instead of aldehyde (109a) (the former being prepared by silylation of 3-hydroxybenzaldehyde with trimethylsilyl chloride and pyridine[6]) to give a colourless oil. Its p.m.r. spectrum showed a trimethylsilyl group at δ 0.07, but resonances due to -OCHO and -OCH- groups of the required alcohol (110b) were not observed. The product also showed a singlet at δ 9.86 due to the formyl group of the starting aldehyde (109b), and the rest of the resonances were multiplets at δ 5.60-7.50. Its mass spectrum did not show a molecular ion at m/z 344 as required for alcohol (110b). Dissolving of the product in methanol gave a colourless oil the p.m.r. spectrum of which did not show a trimethylsilyl group, but it was too complex to be assigned to the desired benzyl alcohol (111).



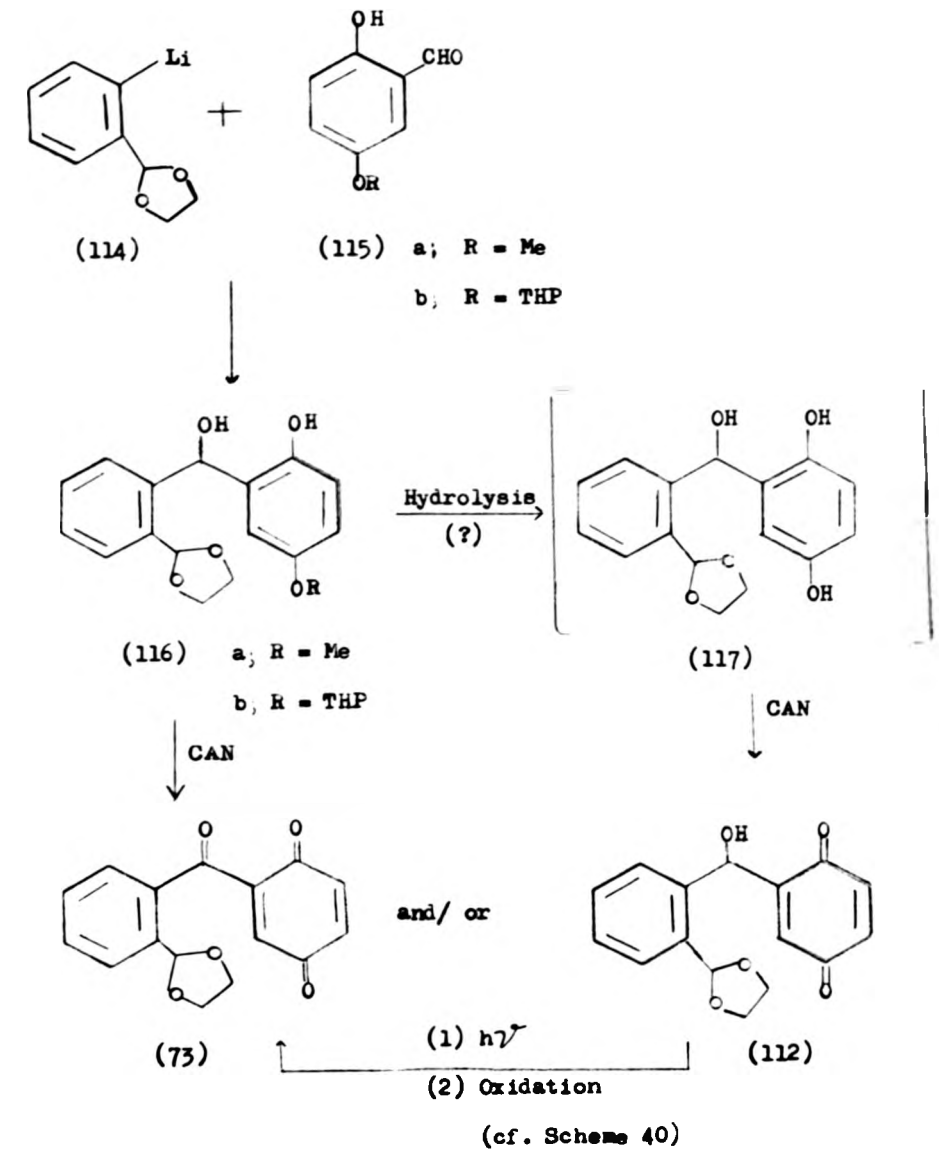
Scheme 41.



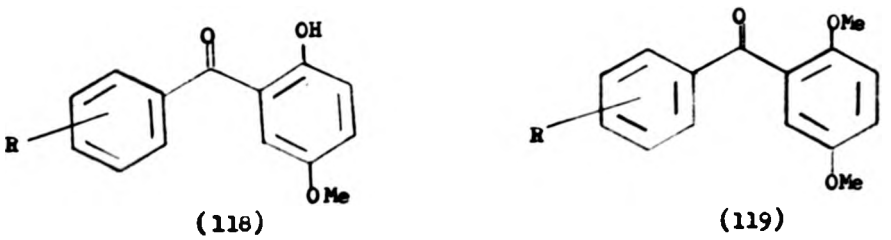
Scheme 42.

Having a problem with the silyl group, aldehyde (109c) was then prepared by treatment of 3-hydroxybenzaldehyde with 2,3-dihydropyran in the presence of pyridinium p-toluenesulfonate[7] and the above coupling reaction was then repeated. The product was a pale yellow oil its p.m.r. spectrum in d-chloroform showed that it may have contained the required product (110c), together with starting aldehyde (109c) as shown by a singlet at δ 9.86. The presence of the desired product (110c) was supported by the mass spectrum of the total product which showed fragments at m/z 272(1), 271(1), 254(6), 226(1), 227(4), 226(3), 211(22), 210(95), 85(100), accounted for as shown in Scheme 42. Removal of tetrahydro-2H-pyran-2-yl group in the mass spectrometer was expected. Therefore the total product was dissolved in methanol and treated with pyridinium p-toluenesulfonate in order to obtain the required phenol (111). The product from this hydrolysis was a colourless oil: its p.m.r. spectrum in d-chloroform was not clean, and showed the starting aldehyde (109c). Therefore the product was not further examined.

Since the Scheme 40 failed to give the required alcohol (111) cleanly, Scheme 43 was then tried. Reacting 2 mol of phenyl-litnium (114) (generated by the reaction of dioxolane (106) with n-butyl-lithium, as before) with phenolic aldehyde (115) was expected to give alcohol (116) from which the desired quinone (112) could be generated, either after removal of the protecting group R in (116) followed by CAN oxidation of hydroquinone (117), or by the reaction of CAN directly on the alcohol (116). It was found[5] that demethylation-oxidation of monomethyl ether (118) with CAN to the corresponding 1,4-benzoquinone occurred much more rapidly than for the dimethyl ether (119). Hydroquinone (117) was expected to be unstable.


Li
OH
CHO
OR
(114)
(115) a; R = Me
b; R = THP
OH OH
OR
Hydrolysis
(?)
OH OH
OH
(116) a; R = Me
b; R = THP
(117)
CAN
CAN
O O
and/ or
OH O
(73)
(1) hν
(2) Oxidation
(112)
(cf. Scheme 40)

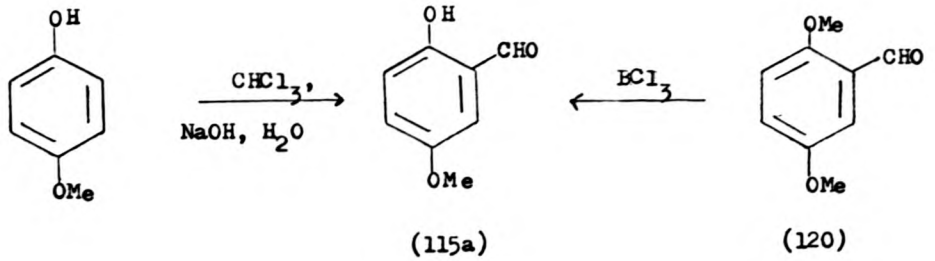
Scheme 43.


R
O
OH
OMe
(118)
R
O
OMe
OMe
(119)

The coupling reaction of phenyl-lithium (114) with aldehyde (115a) was then tried. Aldehyde (115a) was left to the author from earlier work;[31] it was prepared by Reimer-Tiemann formylation of hydroquinone mono-methyl ether, but it could also be prepared from 2,5-dimethoxybenzaldehyde (120) by treatment with boron trichloride[9a] (Scheme 44).

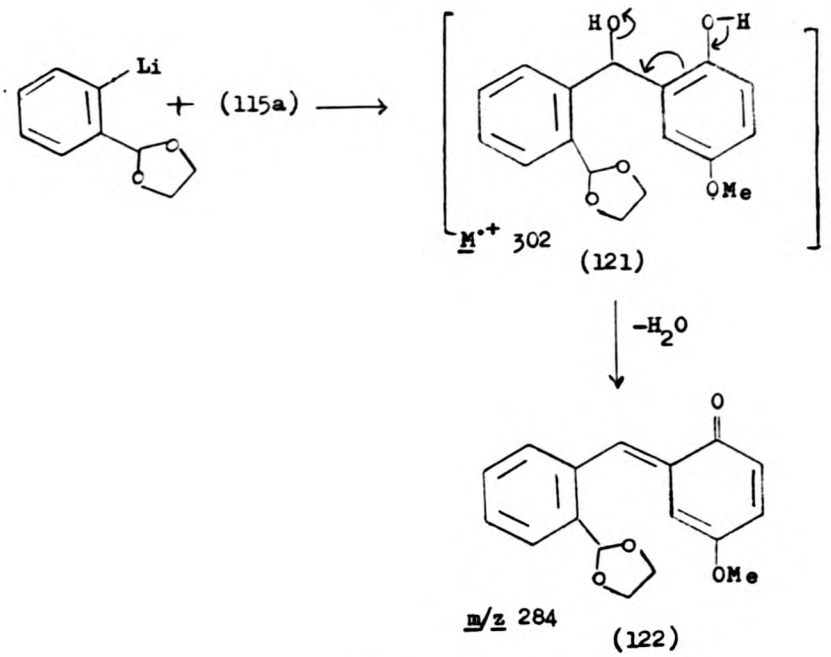
However, the product isolated from the above aryl-lithium coupling, after decomposition with 5% acetic acid, was a yellowish oil: its p.m.r. spectrum in d-chloroform showed that it may have contained desired alcohol (116a) together with starting aldehyde (115a). The presence of (116a) in the crude mixture was supported by its mass spectrum, which showed the molecular ion at m/z 302. However, its p.m.r. spectrum in d-chloroform was not clean, and the resonances due to the α-hydrogen [-CH(OH)-] group, expected to be a doublet [cf. compound (86), page 78]; at about δ 6.40-6.50 were not observed. Interestingly, a fragment at m/z 264 was observed in its mass spectrum, suggesting that an elimination reaction [as (121)] may have occurred in the mass spectrometer to give (122) (Scheme 45). Such eliminations are usual for systems such as (123) to give quinone methide-derived products.[9b]

Since the above coupling reaction did not give (116a) cleanly, the reaction was then repeated using phenolic aldehyde (115b). Compound (115b) was obtained by treatment of 2,5-dihydroxybenzaldehyde (124) with 2,3-dihydropyran, as for the preparation of aldehyde (109c), in 75% yield. However, the product obtained from the aryl-lithium coupling reaction, after decomposition with 5% acetic acid, was too complex to be identified as the desired compound (116b). The mass spectrum of the total product did not show a molecular ion at m/z 372 as required for compound (116b), or even fragments at m/z 288 $(M - THP + H)^+$ [structure 117] or 242 $(M - THP - MeCHO + H)^+$ [structure 125]; but it did show a fragment at 226

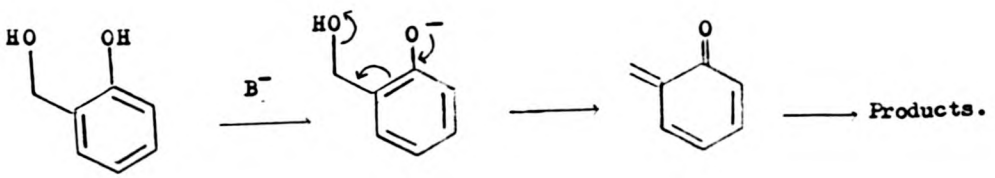


(115a) (120)

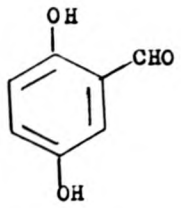
Scheme 44.



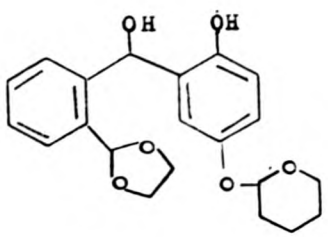
Scheme 45.



(123)

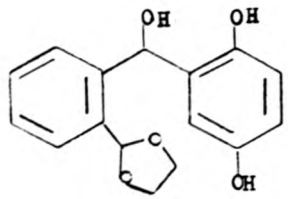


(124)

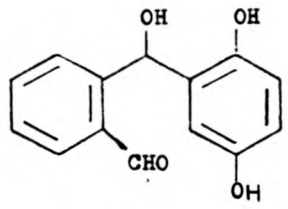


$\underline{M}^{\cdot+}$ 372

(116b)

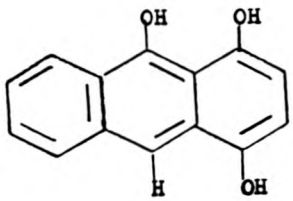


$\underline{m/z}$ 288 (117)



$\underline{m/z}$ 242

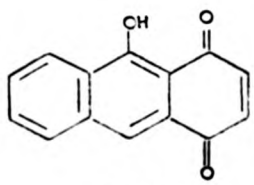
(125)



m/z 226

(84)

Scheme 46.

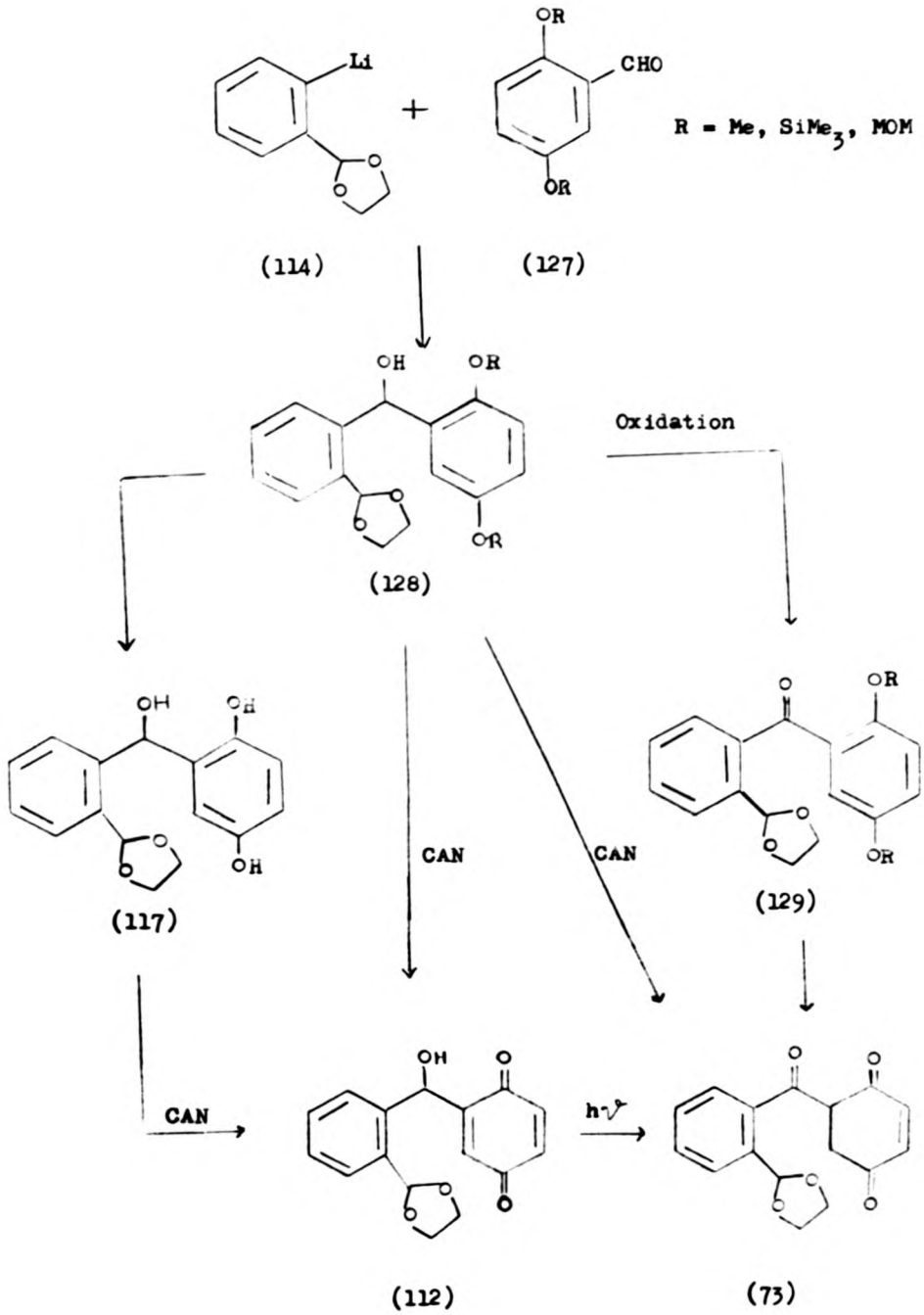


(134)

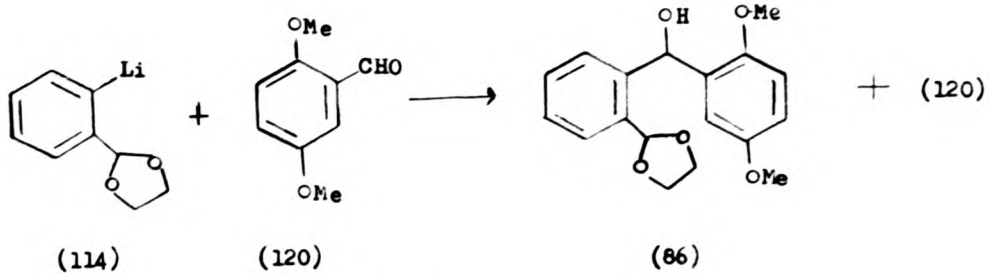
which may have been due to the cyclised product (84) (Scheme 46). Those observations suggested that the desired compound (116b), in contact with acetic acid during work-up could be easily hydrolysed to phenol (117) which gradually decomposed [due to the acidic phenolic group present in (117)] to give the final cyclisation product (84). Compound (84) would be expected to oxidise in air to give quinone (134) [(see page 100, Scheme 59)] as reported in the literature;[36] for analogous tetracyclic systems derived from daunomycin. However, a molecular ion at m/z 224 for compound (134) was not observed in the mass spectrum of the above mixture.

To complete the series of reactions between the phenyl-lithium (114) and substituted benzaldehydes, Scheme 47 was then investigated. It was hoped that reaction of aryl-lithium (114) with benzaldehydes having the general structure (127) would give benzyl alcohols (128) which on various transformations should give the desired quinone (73). The protecting group R in the starting aldehyde (127) could be chosen according mainly to its lability compared to that of the acetal group present in (128) or (129), thus leading to the quinones (112) or (73), respectively. Protective groups such as Me, $SiMe_3$, and CH_2OMe were particularly worth examining, and the preparation of ketones having the general structure (129) was of particular interest since the carbonyl group in them would stabilise the acetal towards acidic hydrolysis, and hence facilitate the preparation of the desired quinone (73).

The coupling reaction in Scheme 47 was initially tried using 2,5-dimethoxybenzaldehyde (120) at -70° in ether, since this aldehyde is readily available. Decomposition of the reaction mixture with water and the usual work-up gave a colourless oil: its p.m.r. spectrum in d-chloroform showed that it contained the desired benzyl alcohol (86) and starting aldehyde (120) in the ratio 1:1, respectively (Scheme 48).

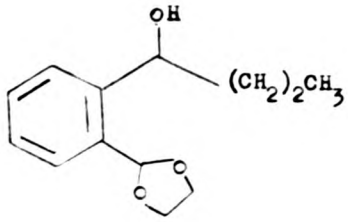

Li
OR
CHO
OR
R = Me, SiMe3, MOM
(114)
(127)
OH
OR
OR
(128)
Oxidation
OH
OH
OH
(117)
CAN
CAN
OR
OR
(129)
CAN
OH
O
h-v
O
O
O
(112)
(73)

Scheme 47.

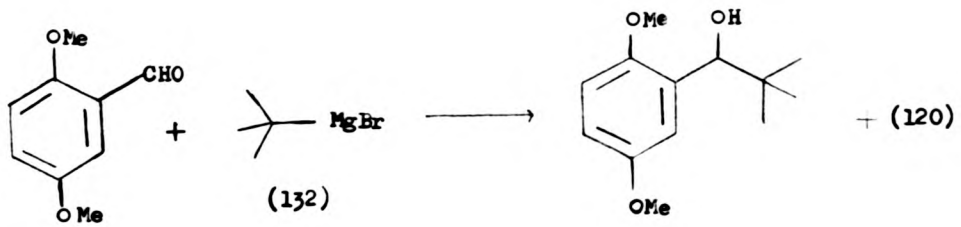


(114) (120) (86)

Scheme 48.

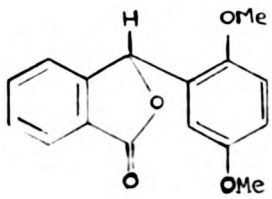


(131)



(120) (132) (133)

Scheme 49.



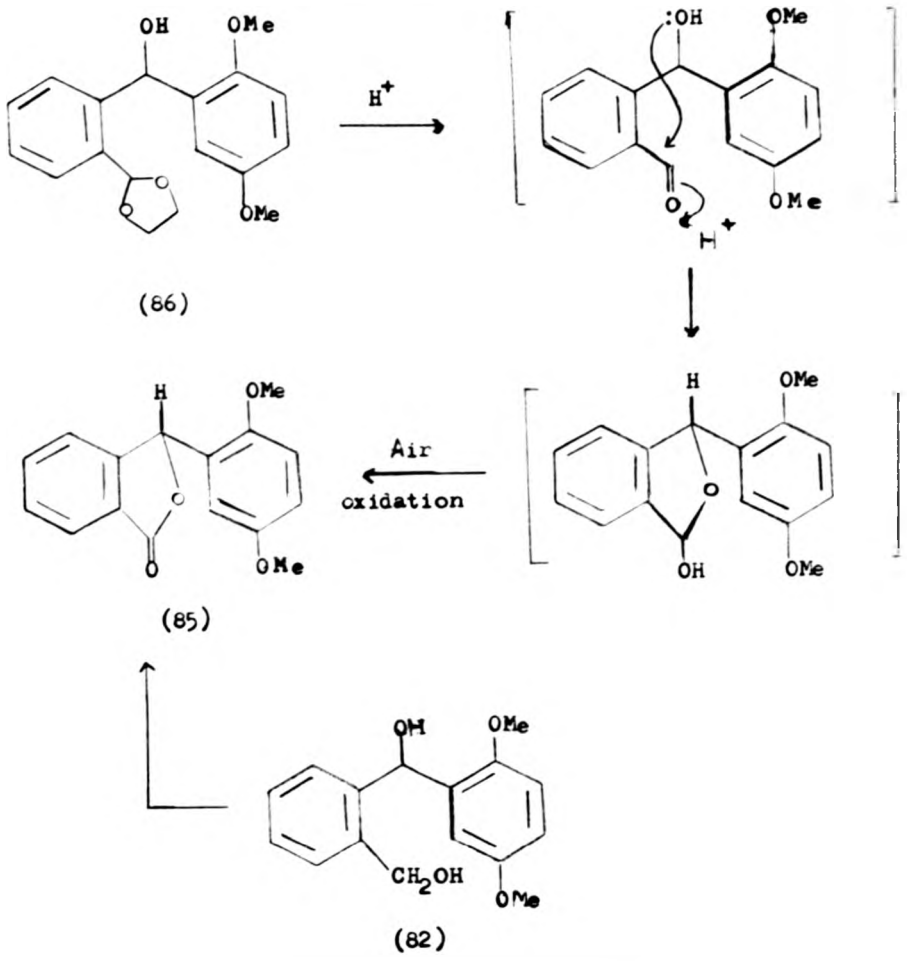
(85)

Repeating the reaction at -30° gave only starting aldehyde (120); so did reaction at -70° in THF. On the other hand, using a larger excess of n-butyl-lithium to generate the phenyl-lithium (114), also gave alcohol (131) as a byproduct.

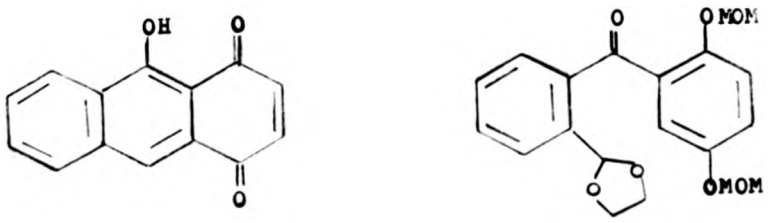
Monitoring the above coupling reaction at -70° showed that the ratio (ca. 1:1) of benzyl alcohol (86) and starting aldehyde (120) remained unchanged after ca. 20 min. following addition of aldehyde (120). (See Table in Experimental). In this connection, it was observed[10] in our laboratories that coupling of aldehyde (120) with Grignard regent (132) was never complete, even when a ten times excess of Grignard reagent (132) was used: a mixture with starting aldehyde (120) was always obtained (Scheme 49).

Therefore it was decided to isolate the benzyl alcohol (86) in a pure state. Small scale (mg) column chromatography using 1:1 hexane-ether as eluent afforded pure (86) in ca. 37% yield; starting aldehyde (120) and benzaldehyde ethylene acetal were also isolated. However, purification on a larger (g) scale failed to give pure product (86); the material isolated was always a mixture of (86) and the lactone (85), together with starting aldehyde (120). Formation of lactone (85) could be due to cleavage of the acetal in (86) followed by air oxidation and cyclisation during the work-up (Scheme 50).

The structure of benzyl alcohol (86) was confirmed by its elemental analysis, p.m.r. and mass spectra. Its p.m.r. spectrum in d-chloroform showed singlets δ at 3.60 and 3.74 due to two methoxy groups, a multiplet at 4.00–4.20 due to the acetal group, a singlet at 6.20 due to the -OCHO- group, a doublet J 2.5 at 6.40 due to -CH-, and the rest of the resonances in the aromatic region.



Scheme 50.

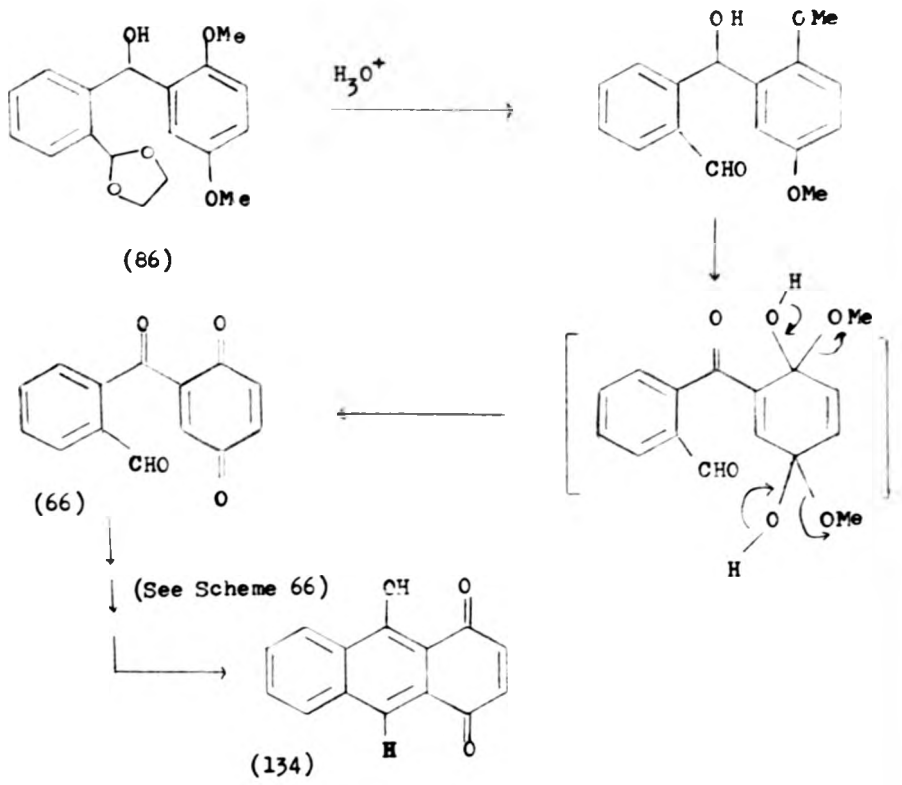


(134) (135)

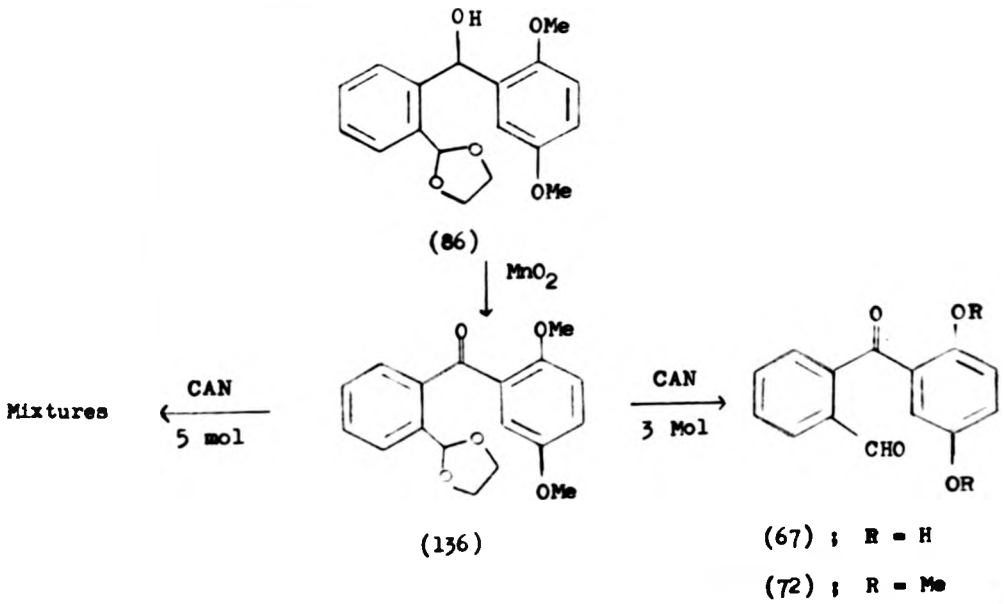
The mode of formation of lactone (85) was confirmed by treatment of the above mixture [(86) and lactone (85)] with 15% hydrochloric acid in THF followed by air oxidation: the lactone was produced quantitatively. Similarly, lactone (85) was obtained by oxidation of diol (82) as mentioned in Section 2.1, Scheme 33.

Having isolated benzyl alcohol (86), although only on a small scale, it was of interest to investigate some of its reactions, in an attempt to obtain the desired quinones (73) and (112) (Scheme 47). Thus benzyl alcohol (86) was treated with 5 mol of CAN in aqueous acetonitrile, giving a red-brown oil. Its p.m.r. spectrum in d-chloroform was not clean, and it was difficult to be assign peaks to the quinones (73) and/or (112) alone. Its mass spectrum, however, showed a molecular ion at m/z 284, which suggested that the product may have contained the benzoylquinone (73). Extraction with hot pentane gave a red powder, subsequently identified as anthraquinone (134) which was identical (m.p. and p.m.r. spectra) with the authentic sample prepared from benzophenone (135) (Section 3.2, Scheme 59). Presumably the formation of anthraquinone (134) proceeds via a mechanism such as that outlined in Scheme 51, since it was found that on standing at room temperature for 5 days, the crude quinone (66) gave anthraquinone (134) (see Section 3.2, Scheme 66).

Since the above reaction failed to give either of the desired quinones (73) and (112), benzyl alcohol (86) was then oxidised to the benzophenone (136) by the used of actived manganese dioxide,[11] in over 80% yield (Scheme 52). The Structure of benzophenone (136) was confirmed by its elemental analysis, p.m.r. and mass spectra. Its p.m.r. spectrum showed singlets at δ 3.52 and 3.75 due to two methoxy groups, multiplets at 4.08 due to the acetal group, a singlet at 6.20 due to



Scheme 51.



Scheme 52.

the -OCHO- group, with the rest of the protons in the aromatic region. Its mass spectrum showed the molecular ion at m/z 314 with a fragment at m/z 270 (M - MeCHO) as expected.

Several reactions were then tried in attempts to isolate the benzoylquinone (73). Thus benzophenone (136) was treated with 5 mol of CAN in aqueous acetonitrile, giving a red-brown oil, the p.m.r. spectrum of which in d-chloroform showed multiplets at δ 3.20-4.60 and 6.30-8.50, and two small singlets at 9.82 and 11.30. The spectrum was difficult to be assign to the desired quinone (73), although the mass spectrum of the product showed a molecular ion at m/z 284, as required.

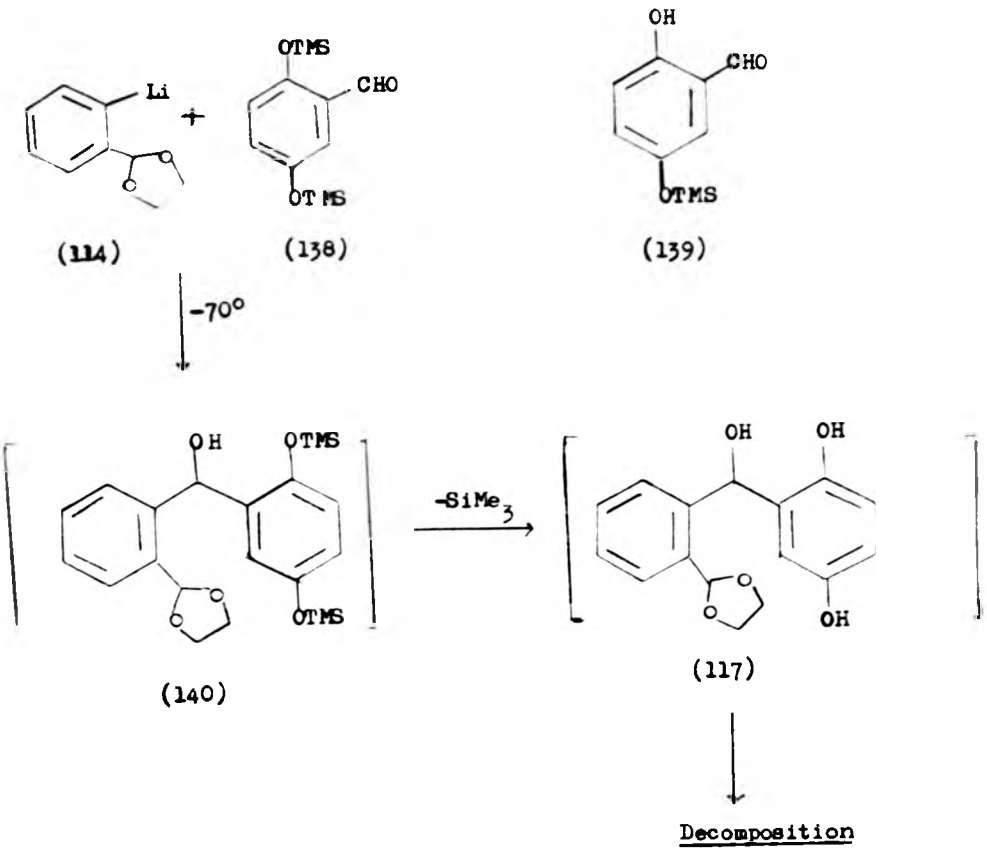
Treatment of benzophenone (136) with only 3 mol of CAN, in contrast, gave a mixture of hydroquinone (67) and benzophenone (72) in a 1:1 ratio. The p.m.r. spectrum of the total product in d-chloroform showed singlets at δ 3.56 and 3.76 due to two methoxy groups of benzophenone (72), singlets at δ 11.34 due to the hydroxy group at the 2-position of hydroquinone (67), two singlets at δ 9.95 and 9.85 due to two formyl groups, and the rest of the proton resonances in the aromatic region. Formation of hydroquinone (67) and benzophenone (72) was not suprising since it is known that aqueous CAN is acidic, and that it is a demethylating agent.[12a]

The mass spectrum of the total product showed m/z 242 and 240, consistent with the cyclisation of (67) to a dihydroquinizarin (156) (m/z 242), (see page 105), and its subsequent oxidation to quinizarin (34) (m/z 240). The reactions of benzophenone (136) with CAN, therefore, were not further examined. In this connection, it is interesting that dethioacetalisation with CAN in aqueous acetonitrile at room temperature was reported,[12b] to give the parent carbonyl compounds in good yield.

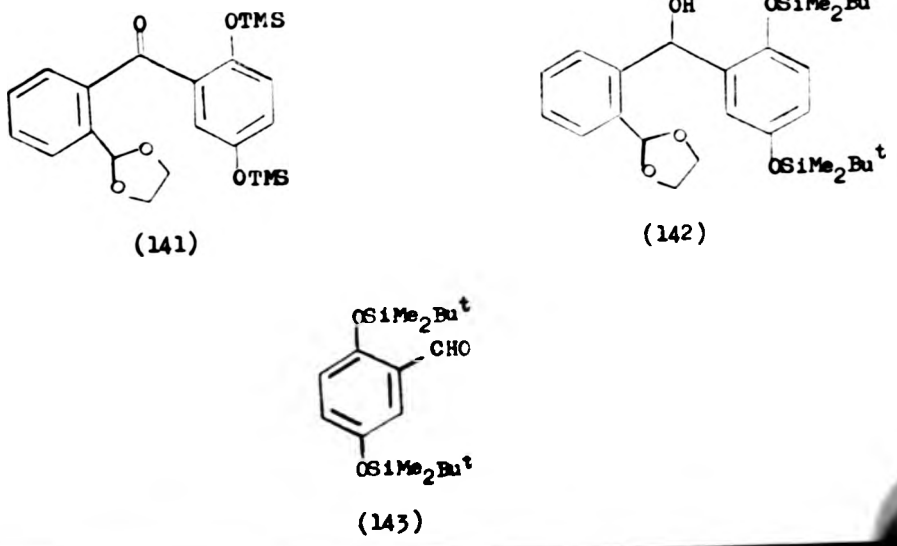
Isolation of benzophenone (136), however, suggested that if benzophenones (129) (Scheme 47) could be prepared, where R is more easily removed than the acetal group; it should be possible to obtain the desired quinone (73). Therefore benzaldehyde (138) was prepared by treatment of 2,5-dihydroxybenzaldehyde (124) with hexamethyldisilazane in the presence of imidazole,[13] in 64% yield. Preparation using trimethylsilyl chloride/pyridine in ether gave a mixture of the desired aldehyde (138) and mono-silylated aldehyde (139).

Coupling of the phenyl-lithuim (114) with benzaldehyde (138) was then carried out as shown in Scheme 53. After usual work-up the reaction gave the desired alcohol (140) as a brown oil in over 70% yield. The product was unstable: it gradually changed to a greenish gum even at the time of removal of the solvent. Its solutions in ether or dichloromethane either at room temperature or at 0° or under nitrogen were also unstable. Therefore it was not possible to obtain a good elemental analysis; only mass measurement was recorded. The instability of the alcohol (140) may be due to the fact that the trimethylsilyl groups are easily removed leaving hydroquinone (117), in which the acidic phenolic hydroxy groups accelerate the decomposition process (Scheme 53).

Having difficulties in handling the benzyl alcohol (140), the freshly prepared material was dissolved in ether and immediately treated with active manganese dioxide,[11] hoping to isolate benzophenone (141) in which the carbonyl group would stabilise the acetal function. The mixture was then either refluxed or stirred at room temperature overnight. However, the product isolated from both oxidation conditions was the starting material (140): suprisingly no sign of oxidation product (141) was detected even in the mass spectrum of the total product. Oxidation using 1:2 chromium trioxide-pyridine complex (6 mol),


Li
OTMS
CHO
OTMS
OH
CHO
OTMS
(114)
(138)
(139)
-70°
OH
OTMS
OTMS
-SiMe3
OH
OH
OH
(140)
(117)
Decomposition

Scheme 53.


O
OTMS
OTMS
(141)
OH
OSiMe2But
OSiMe2But
(142)
OSiMe2But
CHO
OSiMe2But
(143)

in dichloromethane,[14] still gave the starting benzyl alcohol (140), although its mass spectrum now showed a molecular ion at m/z 430, possibly due to the desired benzophenone (141).

Oxidation using B.D.H. precipitated manganese dioxide in ether with shaking at room temperature overnight gave a brownish oil, the p.m.r. spectrum of which in d-chloroform showed the absence of the trimethylsilyl groups. Its mass spectrum showed a molecular ion at m/z 286 which suggested that the product may have contained phenol (117). This product however was not further examined.

Having failed in the oxidation of benzyl alcohol (140), a different route towards the preparation of the desired benzophenone (141) was then tried. This will be discussed in Chapter 4.

At one stage it was of interest to prepare benzyl alcohol (142) by coupling the phenyl-lithium (114) with the benzaldehyde (143), since it was reported[15] that the tert-butyldimethylsilyl protecting group is more stable then trimethylsilyl itself. However, attempts to prepare the protected aldehyde (143) in a pure state from the corresponding phenolic aldehyde (124) failed. Purification either by sublimation of the crude product, or by column chromatography through polyamide, or by washing with water or saturated sodium hydrogen carbonate gave starting aldehyde (124).

Several further reactions were then tried in attempts to obtain the hydroquinone (117) from which, by successive oxidation, irradiation, and oxidation the required quinone (112) may be obtained (Scheme 43). Therefore, freshly prepared alcohol (140) was dissolved in methanol and the solution was stirred at room temperature for 3 h. As expected the product isolated from this reaction did not show a signal due to a trimethylsilyl group; however, the signal due to the acetal group was not

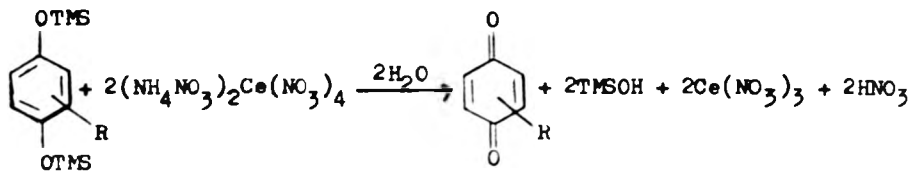
clean, and therefore the product was not further examined, although, its mass spectrum did show a molecular ion at m/z 284. In this connection removal of trimethylsilyl groups by treatment with methanol has been reported in the literature.[16]

It is known[17] that fluoride ion is a good nucleophile to remove trimethylsilyl groups to give the corresponding alcohols. Hence the freshly prepared alcohol (140) in methanol was treated with potassium fluoride, hoping to isolate hydroquinone (117). The product isolated was colourless oil. Its p.m.r. spectrum showed a singlet at δ 4.05 due to an acetal group, a broad singlet at δ4.20–4.75 due to two hydroxy groups, singlets at 5.85 and 6.15 due to a -OCHO- and -OCH- groups, respectively, and at 6.60 due to two aromatic protons, multiplets at 7.10–7.60 due to five aromatic protons and a singlet at 8.00 due to one hydroxy group. The spectrum suggested that the product may have contained the desired hydroquinone (117). Unfortunately the reaction was unreproducible: an attempted repetition gave a brownish oil for which the p.m.r. spectrum did not show signals due to -OCHO- and -CHO- groups.

It seemed that it was not possible to isolate hydroquinone (117), and therefore several attempts were made to prepare the desired quinone (112) without isolation of hydroquinone (117). Thus the freshly prepared alcohol (140) was treated with 4 mol of CAN in aqueous acetonitrile to give an orange sticky oil for which the p.m.r. spectrum in d-chloroform showed only two sets of aromatic protons at δ 6.65–6.90 and 7.30–7.60 in the ratio of about 1:1. Its mass spectrum showed a molecular ion at m/z 240, with fragments at 224, 197, 185, 152, 138, 137, 106 and 105. This product was not further examined. A similar reaction in a two phase mixture (dichloromethane-water) gave an orange oil for which the p.m.r. spectrum in d-chloroform was unclean, although the mass spectrum showed

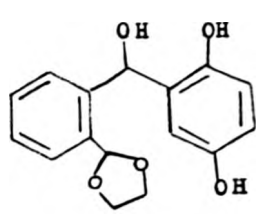
the required molecular ion at m/z 286, possibly due to the desired quinone (112).

The reaction with CAN in aqueous acetonitrile may proceed because of the presence of nitric acid in the mixture.

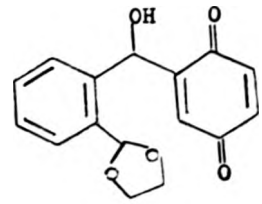


Therefore removal of nitric acid should protect the acetal group. It is known that nitric acid is absorbed by Fuller's earth.[18] Thus removal of the trimethylsilyl group was repeated using a combination of potassium fluoride and CAN in the presence of Fuller's earth. The product isolated was a brown oil for which the p.m.r. and mass spectra suggested that the desired quinone may have been present. However, attempted purification of the product, either by solvent extraction, sublimation or column chromatography showed further decomposition of the acetal group. The reactions of benzyl alcohol (140) discussed above are summarised in Scheme 54.

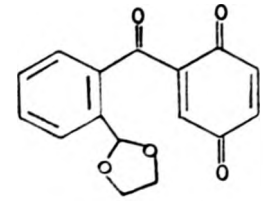
To date, it seemed that the desired quinone (112) would not be stable, and therefore a new route to the quinone (73) was investigated. This is described in Section 3.2.



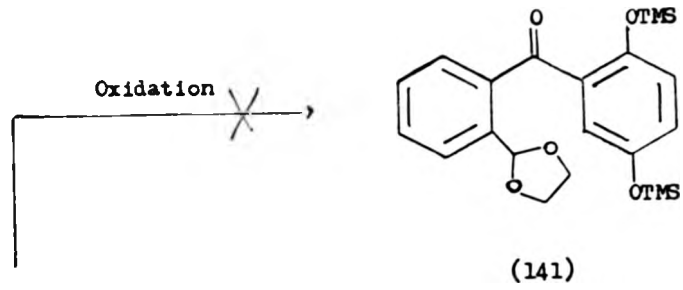
(117)



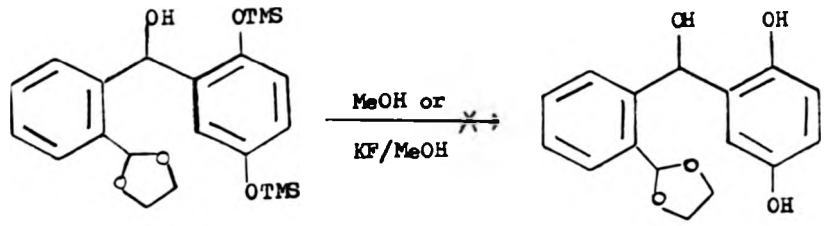
(112)



(73)

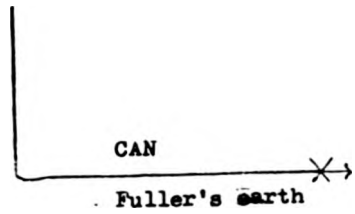


(141)



(140)

(117)



(112)

Some decomposition

Scheme 54.

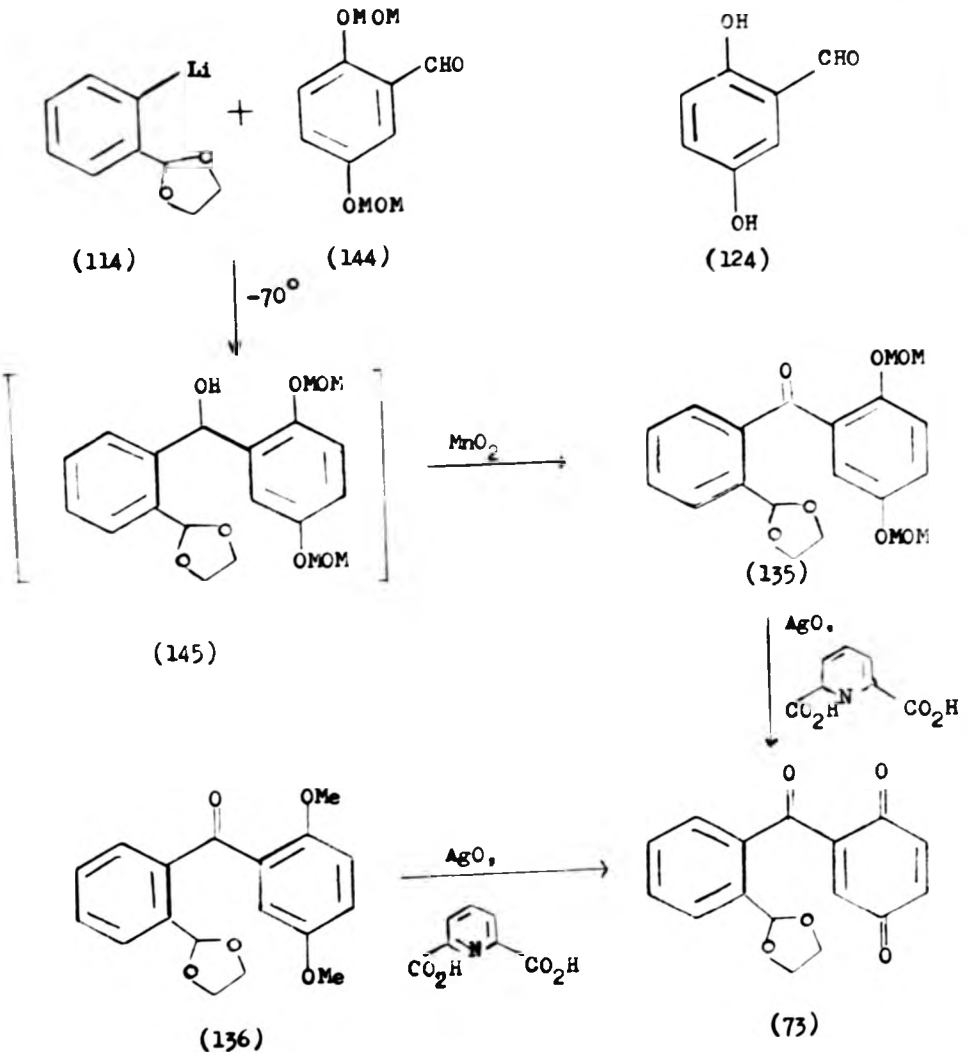
3.2. Synthesis of [2-(1,3-Dioxolan-2-yl)benzoyl]-1,4-benzoquinone and Some Reactions of 2'-(1,3-Dioxolan-2-yl)-2,5-bis(methoxymethoxy)-benzophenone.

The first successful synthesis of the quinone (73) is shown in Scheme 55. Coupling of phenyl-lithium (114) with bis(methoxymethoxy)-ether (144) followed by oxidation of the crude mixture (145) gave the desired benzophenone (135) in 63% yield. Treatment of benzophenone (135) with argentic oxide in the presence of pyridine-2,6-dicarboxylic acid[19] in aqueous acetonitrile gave the desired quinone (73) in 76% yield. Similarly the quinone (73) could be prepared from benzophenone (136) in 69% yield.

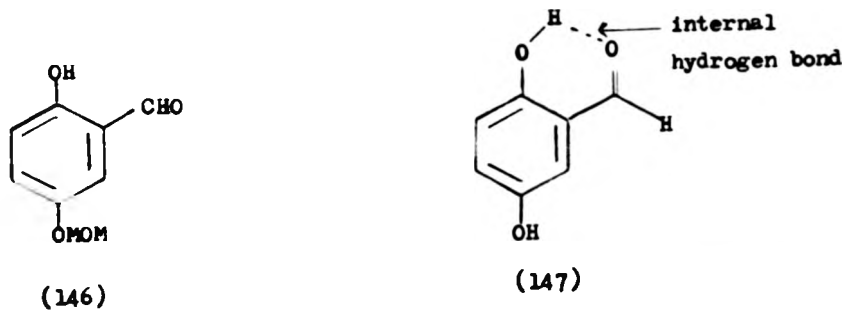
The structures of benzaldehyde (144) and benzophenone (135) were confirmed by their elemental analyses, and p.m.r. and mass spectra.

The p.m.r. spectrum of aldehyde (144) in d-chloroform showed singlets at δ 3.46 and 3.50 due to two methoxy groups, singlets at 5.16 and 5.26 due to the $-OCH_2$ groups, a doublet J 9.5, at 7.02 due to H-3, a double-doublet, J_1 9.5, J_2 3, at 7.26 due to H-4, a doublet J 3, at 7.52 due to H-6 and a singlet at 0.28 due to the formyl group. It showed the required molecular ion at m/z 262.

The 300 MHz p.m.r. spectrum of benzophenone (135) in d-chloroform showed singlets at δ 3.24 and 3.48 due to two methoxy groups, a multiplet at 4.02 due to the acetal group, singlets at 4.90 and 5.16 due to two $-OCH_2$ groups, a singlet at 6.26 due to the -OCHO- group, a doublet, J 9, at 7.14 due to H-3, a double-doublet, J_1 8, J_2 3, at 7.22 due to H-4, a doublet, J 3, at 7.32 due to H-6, a multiplet at 7.42 due H-4' + H-3', collapsed to a singlet on irradiation at 7.56, a multiplet at 7.56 due to H-5' and a doublet, J 8, at 7.80 due to H-6'. Its mass spectrum showed


OMOM
CHO
Li
OMOM
OH
CHO
OH
(114)
(144)
(124)
-70°
OH
OMOM
OMOM
MnO2
O
OMOM
OMOM
(135)
(145)
AgO,
CO2H
N
CO2H
O
O
OMe
OMe
AgO,
CO2H
N
CO2H
O
O
O
(136)
(73)

Scheme 55.


OH
CHO
OMOM
(146)
H
O
O
internal
hydrogen bond
H
OH
(147)

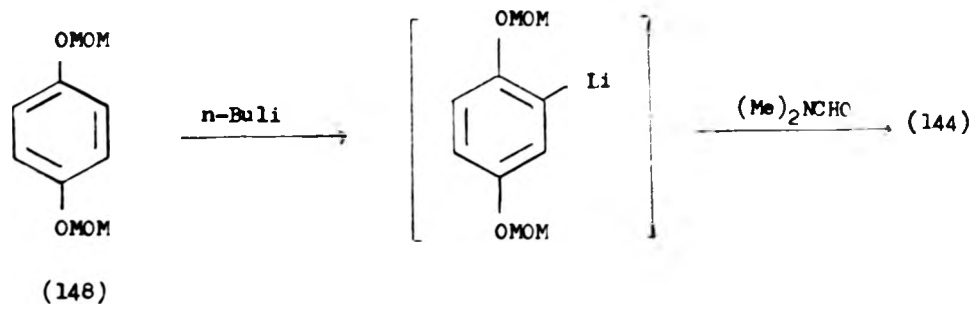
the molecular ion at m/z 374 (33%) with the MOM group lost in preference to the acetal group.

The structure of the desired quinone (73) was then confirmed by its p.m.r. and mass spectra. Its p.m.r. spectrum in d-chloroform showed singlets at δ 3.96 and 6.22 due to acetal and -OCHO- groups, respectively, a multiplet at 6.82-6.84 due to H-3 + H-5 + H-6, a multiplet at 7.42 due to H-5' + H-3', which changed to a doublet, J 3, on irradiation at 7.40, a doublet of triplets, J_1 8, J_2 4, at 7.60 due to H-4' which changed to a double-doublet, J_1 8, J_2 3, on irradiation at 7.42, and a doublet, J 8, at 7.65 due to H-6' which collapsed to a singlet on irradiation at 7.60. Its mass spectrum showed a molecular ion at m/z 286 probably due to its hydroquinone (formed on the probe of the mass spectrometer), and the required molecular ion at m/z 284 with fragments due to loss of the acetal group, as expected.

Interestingly, the main problem associated with the above synthesis was the preparation of starting aldehyde (144). Initial attempts to methoxymethylate aldehyde (124) using a 1:1 mixture of methyl acetate-methoxymethyl chloride[20] in dichloromethane in the presence of triethylamine either at room temperature or refluxing temperature gave only 5% of desired aldehyde (144): the major product being mono-methoxymethyl ether (146). Similar reactions using pyridine as the base in either dichloromethane, tetrahydrofuran or ether failed to give the desired aldehyde (144): the product isolated was starting material (124). Attempted methoxymethylation of aldehyde (124) by the use of powdered 4A molecular sieves to absorb hydrogen chloride (cf. ref. 21) again gave the mono-methoxymethylation product (146). The difficulty in preparation of (144) may be due to internal hydrogen bonding [as (147)] in the starting material (124).

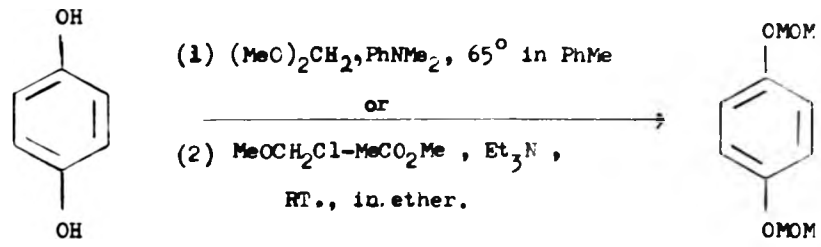
Therefore, at one stage it was of interest to prepare the desired aldehyde (144) via lithiation of bis(methoxymethoxy)benzene (148), followed by formylation (Scheme 56) since the aryl-lithium has been reported,[22] and bis(methoxymethoxy)benzene (148) is known;[23a] the latter was prepared by heating hydroquinone in ether with methoxymethyl chloride and dimethylaniline, in about 60-65% yield. In our hands, compound (148) was more easily prepared by treatment of hydroquinone with a 1:1 mixture of methyl acetate-methoxymethyl chloride[20] in the presence of triethylamine at room temperature, in ether, in about 60% yield (Scheme 57). Therefore the mono-methoxymethylation product (146) which was isolated previously was treated with a 1:1 methyl acetate-methoxymethyl chloride,[20] in the same manner as used for the preparation of (148) just described: this afforded the required bis(methoxymethoxy)benzaldehyde (144) in 60% yield. Hence, treatment of 2,5-dihydroxybenzaldehyde (124) with 2-3 mol of methyl acetate-methoxymethyl chloride in the presence of triethylamine in ether (instead of dichloromethane as before) was then tried: it gave the desired methoxymethoxy ether (144) in about 57% yield. The latter route reduces to one step the preparation of (144) from the available aldehyde (124) (Scheme 58). This procedure is clean and simple, and illustrates the importance of correct choice of solvent.

To the best of our knowledge, the above method for preparation of methoxymethoxy ethers has not been reported in the literature. Therefore it was of interest, to use the method for the preparation of other methoxymethoxy ethers, particularly from substrates having internally hydrogen bonded hydroxy groups similar to that in aldehyde (124). Models of general structures (149) and (150) were used. The progress of reaction was easily followed by observing the formation of triethylammonium chloride which separated during the reaction as shown below.



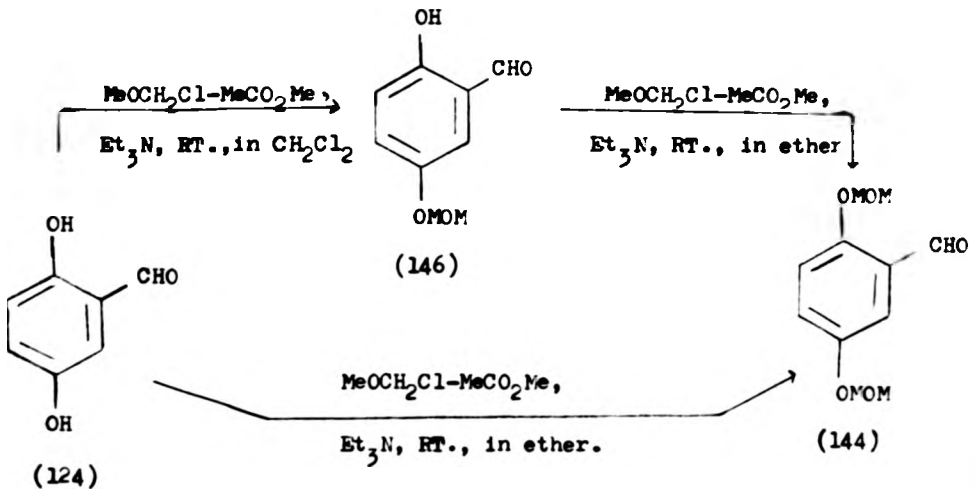
(148)

Scheme 56

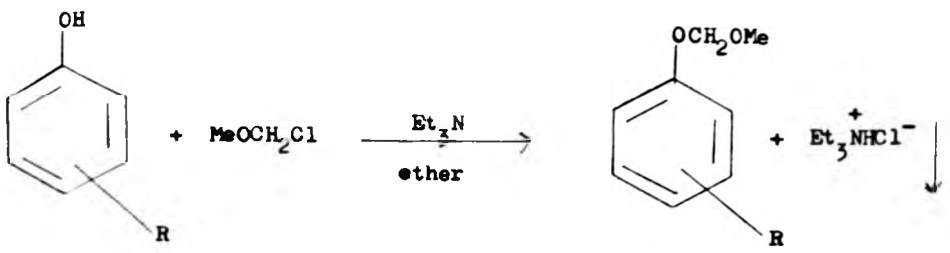


(148)

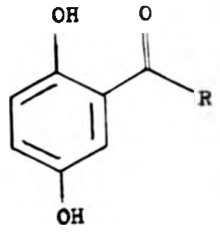
Scheme 57



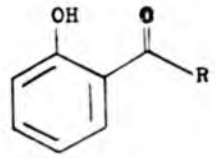
Scheme 58



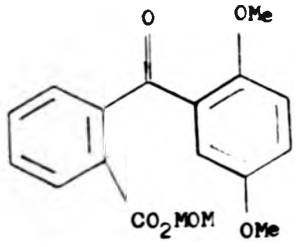
All the methoxymethoxy ethers which were prepared are summarised in Tables 1 and 2. These show that the substrates without the internal hydrogen bond gave 60-81% of the corresponding methoxymethoxy ethers ['a' and 'b' (Table 1) and 'a' (Table 2)]. The methoxymethoxy ester (151) was also prepared from the corresponding acid (96) in 83% yield. As shown in Table 1, it is worth noting that for the trisubstituted benzenes (149), the yield of bis(methoxymethoxy) ether decreases in the following order: R = H, Ph, OMe, and OMOM. This order may reflect the inductive and mesomeric effects of the substituent R on the strength of the internal hydrogen bond. Similar effects could also account for the yields of methoxymethoxy ethers from disubstituted benzenes (150) (Table 2). As expected, the preparation of mono(methoxymethoxy) ethers of trisubstituted benzenes (149) was much easier than that of the bis-ethers, and therefore the mono(methoxymethoxy) ethers of some tri-substituted benzenes (149) were isolated in high yield [entries 'h' and 'i' (Table 1)]. In contrast, it was difficult to prepare the bis(methoxy-methoxy) ether of 2,5-dihydroxyacetophenone (149, R = OMe): only its mono(methoxymethoxy) ether was obtained, in 10% yield. (Entry 'j', Table 1). The low yield of this ether may be due to the low solubility of methyl 2,5-dihydroxybenzoate in ether.



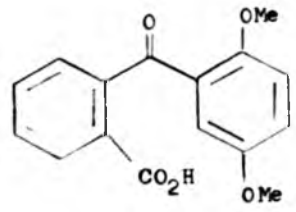
(149)



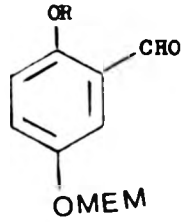
(150)



(151)



(96)



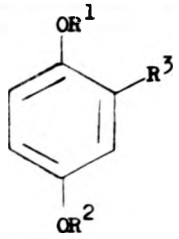
(152)

a; R = CH.Me .OEt

b; R = H

Table 1.

MOM Ethers of Some 1,2,4-Trisubstituted Benzenes.[a]



		Yield/%[b]	bp.°/mmHg
(a)	$R^1 = R^2 = MOM$, $R^3 = H$	61	76-80 /0.1[d]
(b)	$R^1 = R^2 = MOM$, $R^3 = OMe$	76	80-86/0.1
(c)	$R^1 = R^2 = MOM$, $R^3 = CHO$	57	56-60/0.05
(d)	$R^1 = R^2 = MOM$, $R^3 = CO_2H$	-	100-104/0.5
(e)	$R^1 = R^2 = MOM$, $R^3 = COPh$	23	96-100/0.1
(f)	$R^1 = R^2 = MOM$, $R^3 = CO_2Me$	18	Not determined
(g)	$R^1 = R^2 = MOM$, $R^3 = CO_2MOM$	17	Not determined
(h)	$R^1 = OH$, $R^2 = MOM$, $R^3 = CHO$	80[c]	50-56/0.1
(i)	$R^1 = OH$, $R^2 = MOM$, $R^3 = CO_2H$	82	Hydrolysed on distillation
(j)	$R^1 = OH$, $R^2 = MOM$, $R^3 = COMe$	10	Not determined

Notes:

(a) Prepared from the corresponding hydroxy compounds. Except for entry c, yields were not optimised.

(b) Except for entry d, all % are for isolated products. For d, the product was always a mixture with entry g.

(c) The compound was prepared in refluxing dichloromethane using powdered 4A molecular sieves.

(d) Lit.,[23] b.p. 136-137°/0.5 mmHg.

Table 2.

MOM Ethers of Some 1,2-Disubstituted Benzenes.[a]

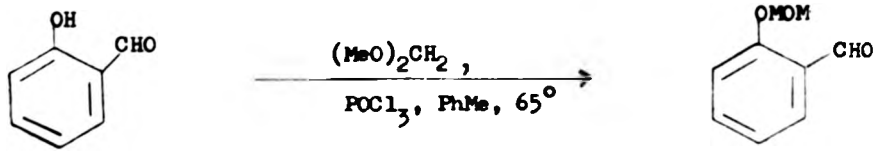
	Isolated Yield/%	b.p.°/mmHg
(a) R^1 = Br; R^2 = OMOM	81	60-64/0.1
(b) R^1 = OMOM; R^2 = H	75[c]	60-66/0.1
(c) R^1 = OMOM; R^2 = OH	82	60-64/0.1[b]
(d) R^1 = OMOM; R^2 = OMe	10	Not determined
(e) R^1 = OMOM; R^2 = OMOM	10	Not determined
(f) R^1 = OMOM; R^2 = Me	16	Not determined

Notes:

(a) Prepared from the corresponding hydroxy compounds. Yields were not optimised.

(b) Ref.,[24] white solid, m.p. 63-64°.

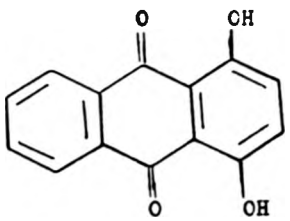
(c) This compound is known;[25] prepared by treatment of the corresponding aldehyde with methylal and phosphorus oxychloride in toluene at 65°, in 90% yield.



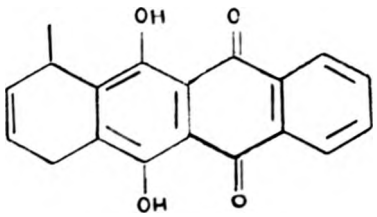
It is worth noting that the bis(methoxyethoxy) ether (152a) was also prepared, by the reaction of 2,5-dihydroxybenzaldehyde (124) with ethoxyethene in the presence of pyridinium p-toluenesulfonate in dichloromethane at room temperature for 15.5 h. as a yellowish oil in 76% yield. Preparation using ethoxyethane in the presence of concentrated hydrochloric acid,[23b] gave starting aldehyde (124). Compound (152a) was not very stable and sublimation on larger scale (>0.5 g), give mono(methoxyethoxy) ether (152b). Attempts to prepare the methoxyethoxy ether of 2-hydroxybenzaldehyde (150, R = H) using the above method failed: the reaction mixture rapidly changed to red-brown, and p.m.r. spectroscopy showed the absence of a formyl proton. Therefore, the preparation of other (methoxyethoxy) ethers corresponding to the methoxymethoxy ethers shown in Tables 1 and 2 was not attempted.

Having prepared benzophenone (135) as described above (See Scheme 55), it was of interest to examine some of its reactions, with a view to cyclisation to generate compounds such as (34), as models for the formation of tetracyclic compound (71). The results are summarised in Scheme 59.

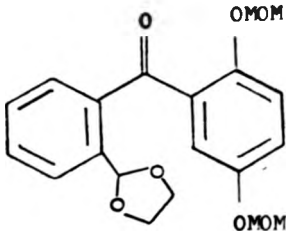
Benzophenone (135) was firstly treated with argentic oxide and nitric acid in THF[26] for 8 min. This reagent was reported[26] to oxidise 2,5-dimethoxytoluene to the corresponding benzoquinone in 41% yield. However, the product isolated from this reaction was a mixture which may have contained the starting material (135) and 2'-formyl-2,5-bis(methoxymethoxy)benzophenone (153) (in $CDCl_3$, singlets at δ 3.10, 3.14, 3.40, 3.41, 4.73, 4.75, 5.02, 5.04, and 10.05).



(34)



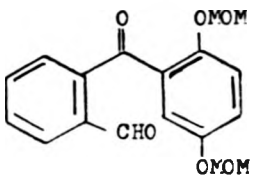
(71)



(135)

AgO / HNO_3 → Complex mixture; may have contained (135) and (153).

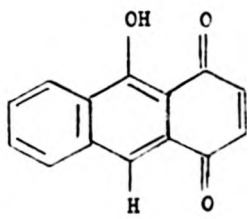
HIO_4/DMF or CAN/MeCN/H_2O →



(153)

CAN(excess) / CH_2Cl_2/H_2O → No reaction.

HCl/THF/RT or $TiCl_4/CH_2Cl_2/0°$ →



(134)

Scheme 59

Treatment of (135) with 4M periodic acid in DMF for 2½ h. and extraction of the product with ether gave a brownish liquid which was identified as aldehyde (153). Compound (153) had a molecular ion at m/z 330 and its 220 MHz p.m.r. spectrum in d-chloroform showed singlets at δ 3.20 and 3.50 due to two methoxy groups, singlets at 4.85 and 5.18 due to two OCH_2 groups, a doublet, J 9, at 7.12 due to H-3, a double-doublet, J_1 9, J_2 3.3, at 7.20 due to H-4 which collapsed to a doublet, J 8, on irradiation at 7.40, a doublet J 3.3, at 7.40, due to H-6, changed to a singlet on irradiation at 7.20, a multiplet at 7.52 due to H-3', multiplets at 7.62 due to H-4' + H-5', a multiplet at 8.02 due to H-8', changed to a singlet on irradiation at 7.62, and a singlet at 10.26 due to a formyl group. The p.m.r. spectrum is showed in Figure 2.

Grieco et al.[27] used 70% pechloric acid in dichloromethane at 0° to generate a carbonyl group from an ethylene acetal.

Compound (153) was also isolated from treatment of (135) with 4 mol of CAN in aqueous acetonitrile for 2 h. However, treatment of (135) with 8 mol of CAN in a two phase dichloromethane-water system and shaking at room temperature for 24 h. gave starting material (135).

Treatment of (135) with 6M hydrochloric[28] acid in THF at room temperature for 24 h. gave a red precipitate of 9-hydroxy-1,4-anthraquinone in 75% yield. It melted at 198-199° with decomposition to a black tar (lit.,[29] 200° decomp.). Its mass and 300 MHz p.m.r. spectra are shown in Figures 3 and 3a, respectively. Similarly, compound (134) was isolated from the treatment of (135) with titanium tetrachloride in dichloromethane[30] after 3 min. reaction time.

It was our expectation that acid treatment of (135) could give quinizarin (34) via cyclisation of (67) followed by aerial oxidation (Scheme 60). However, formation of (134) on treatment of benzophenone

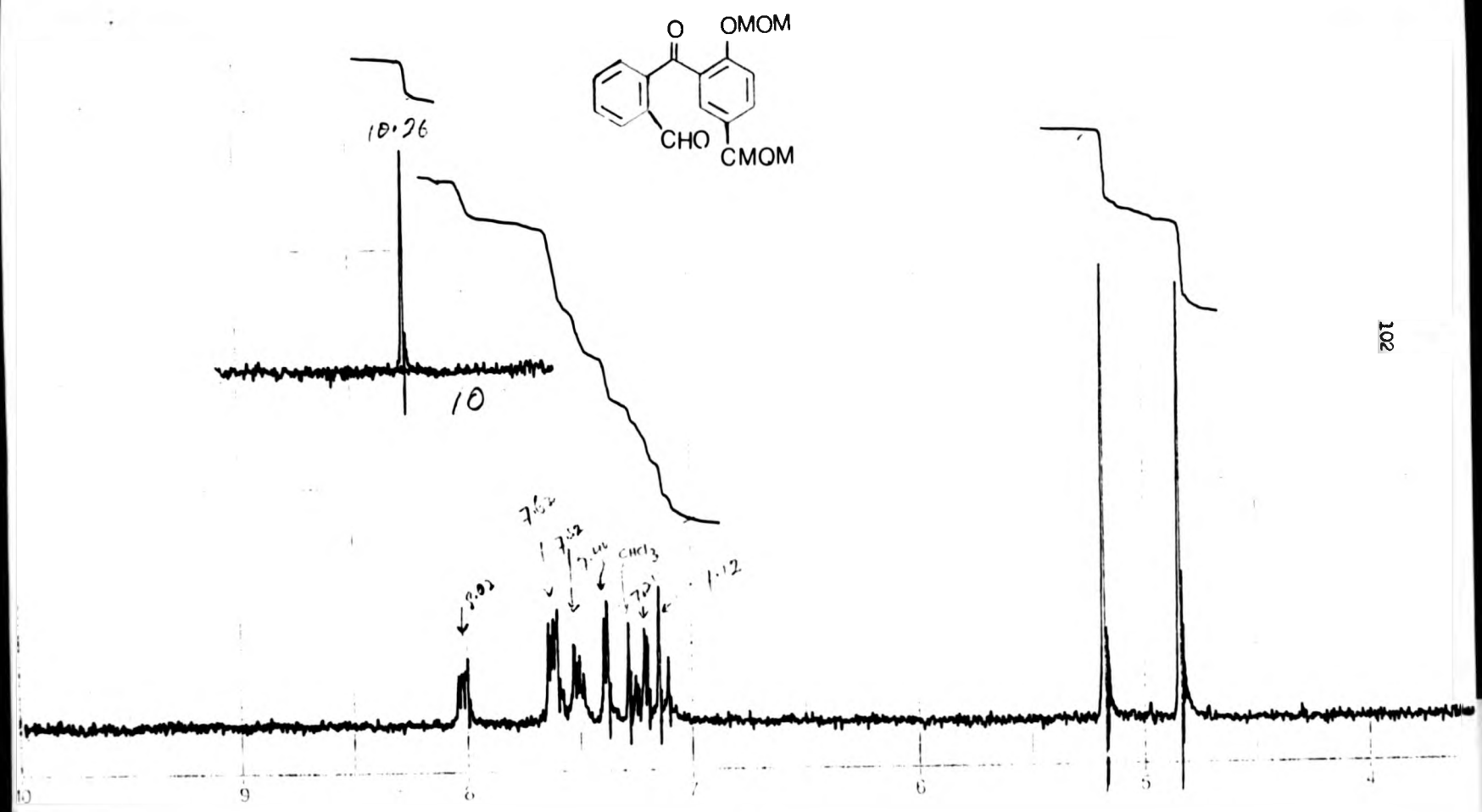


Figure 2.

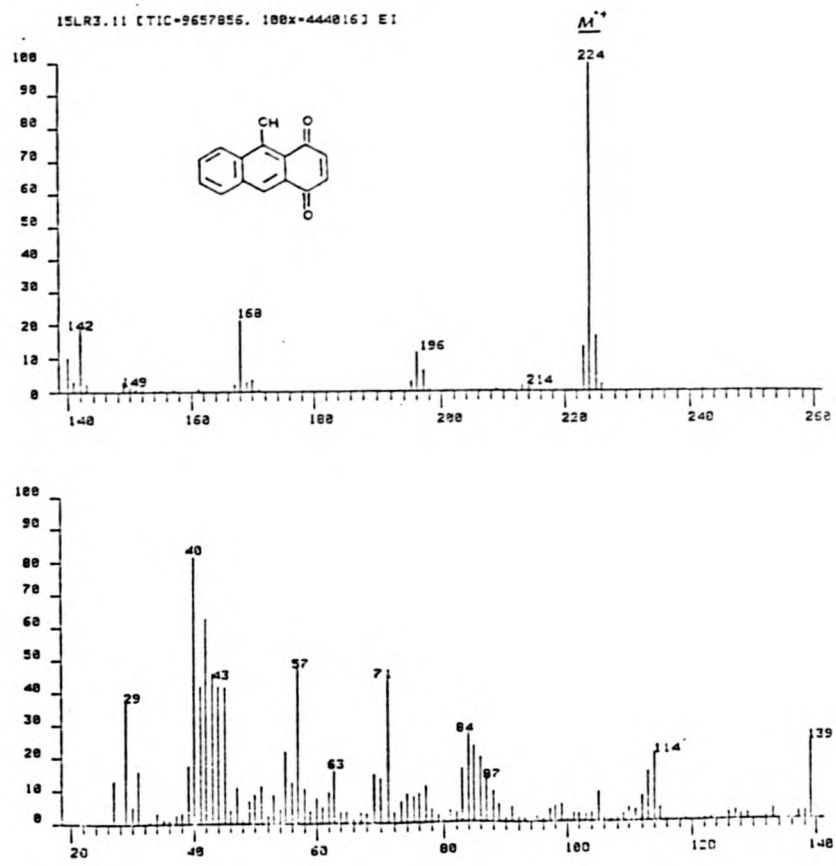

15LR3.11 [TIC=9657856, 100%=4440161] EI
M+·
224
CH
O
O
142
168
196
149
214
100
90
80
70
60
50
40
30
20
10
0
140
160
180
200
220
240
260
40
29
43
57
71
84
63
87
114
139
20
40
60
80
100
120
140

Figure 3.

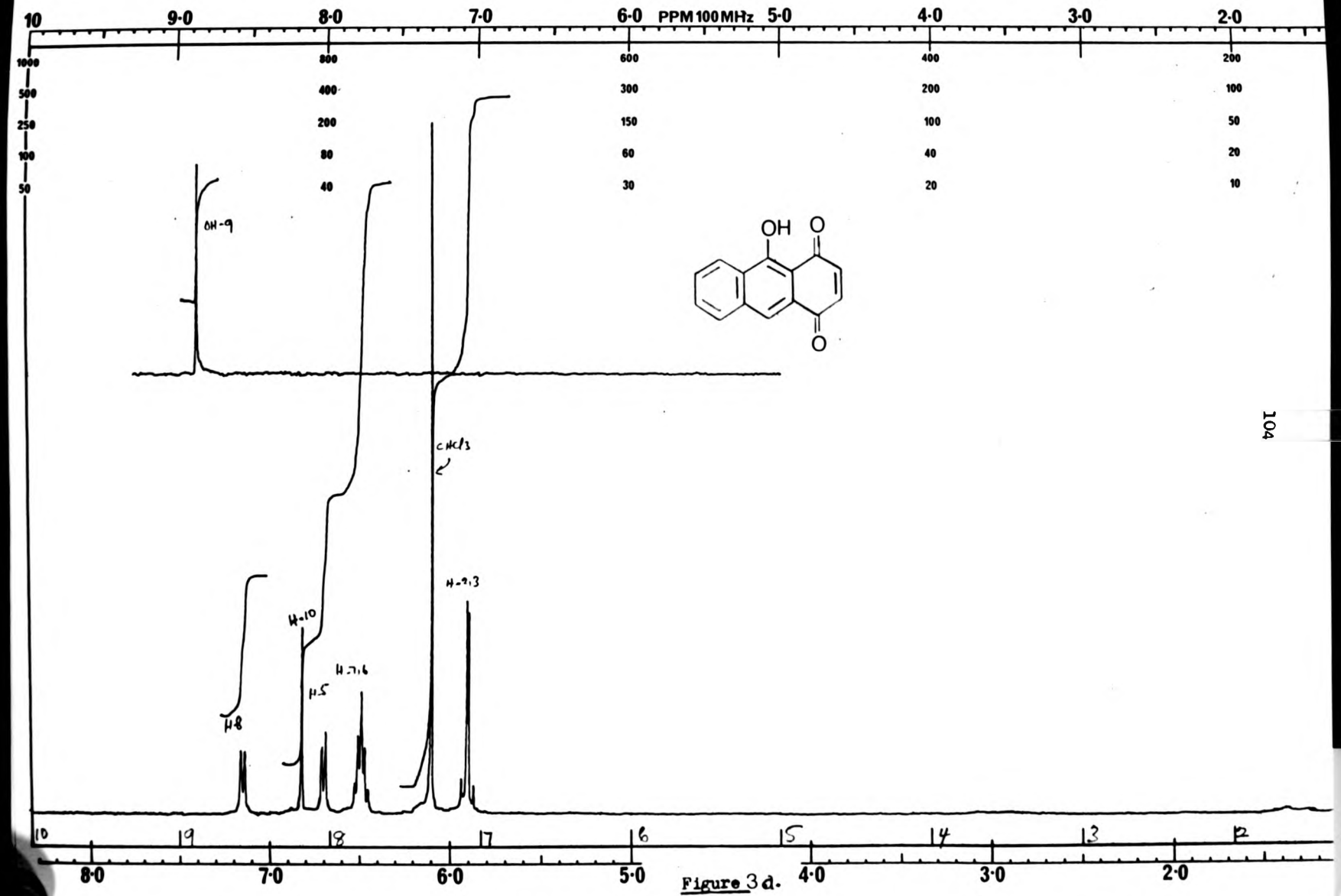
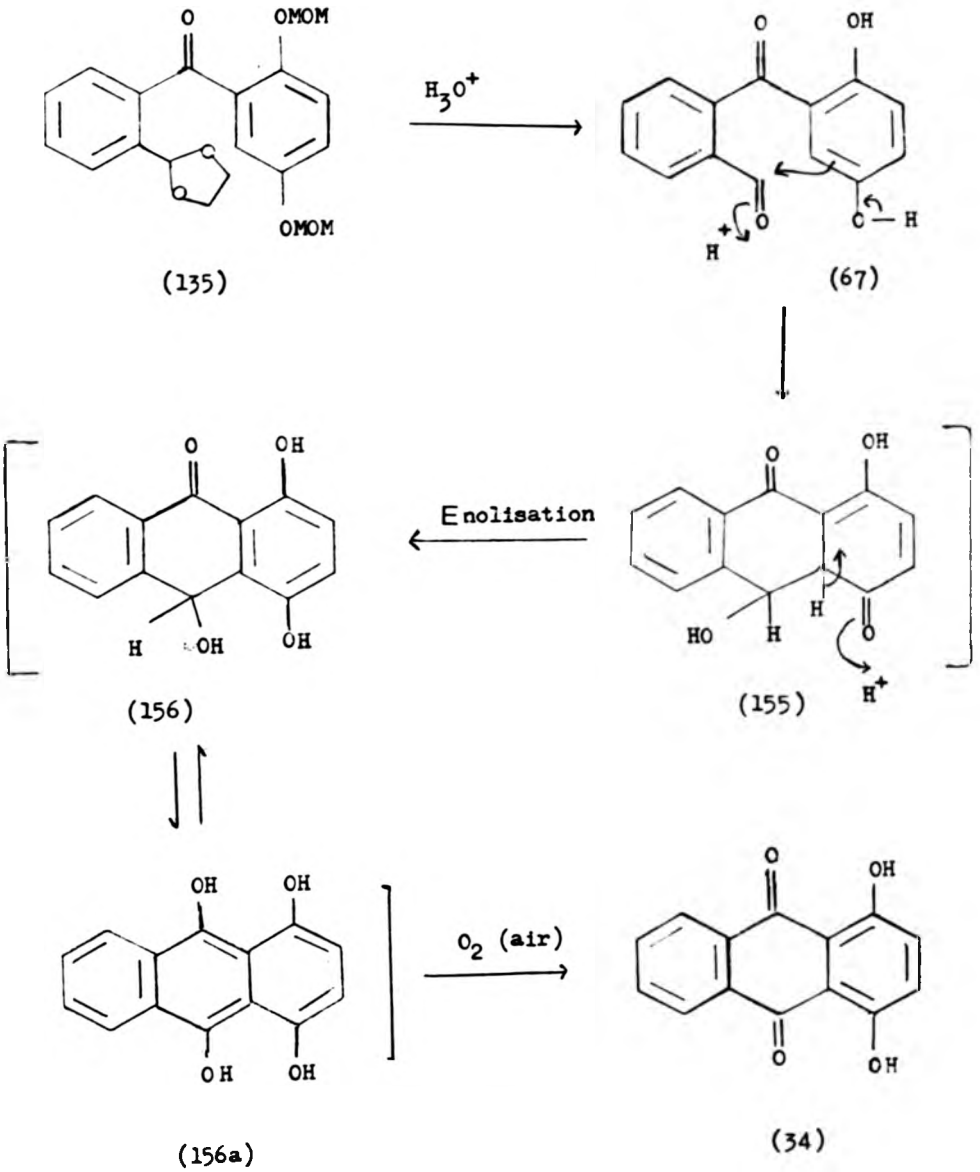

10
9·0
8·0
7·0
6·0
PPM 100 MHz
5·0
4·0
3·0
2·0
OH
O
O
OH-9
CHCl3
H-10
H-8
H-5
H-7,6
H-9,3

Figure 3 d.


O
OMOM
OMOM
H_3O^+
O
OH
H
O
C — H
(135)
(67)
O
OH
H
OH
OH
Enolisation
O
OH
HO
H
H
O
H^+
(156)
(155)
OH
OH
OH
OH
O_2 (air)
O
OH
O
OH
(156a)
(34)

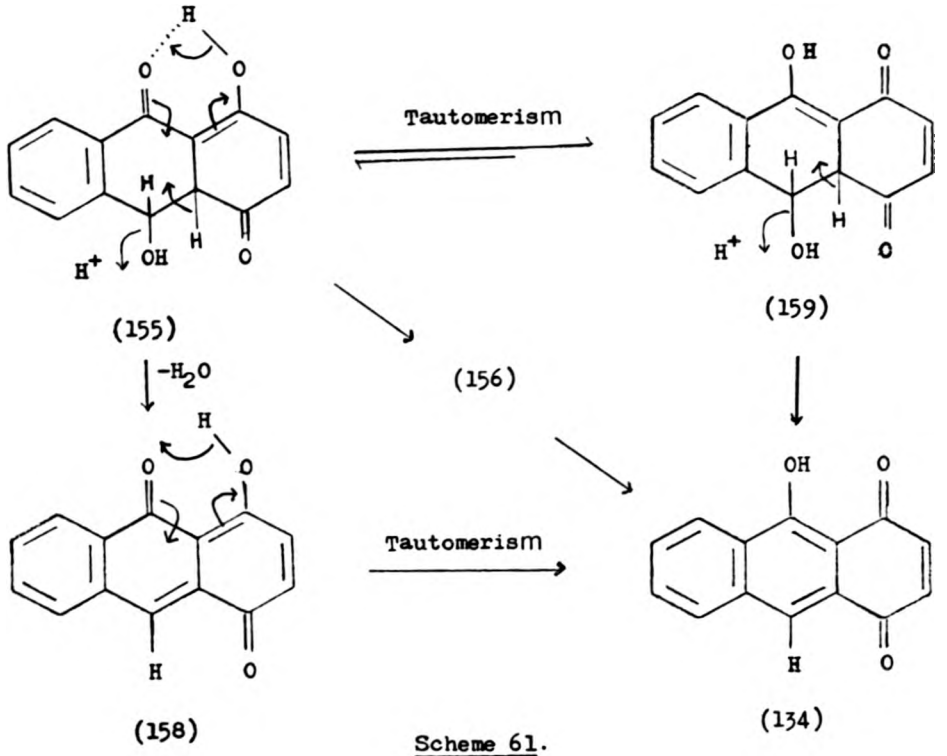
Scheme 60

(135) with hydrochloric acid presumably proceeds *via* the mechanism outlined in Scheme 61. Intermediate (155) could dehydrate to give (158) which could then tautomerise to give the final product (134). On the other hand, intermediate (155) could tautomerise to give (159) which then dehydrates to the same product (134). A similar explanation could also account for the transformation of benzophenone (135) into anthraquinone (134) by treatment with titanium tetrachloride (Scheme 62). Treatment of hydroquinone (160) with iron(III) chloride[29] was reported to give anthraquinone (134) (Scheme 63).

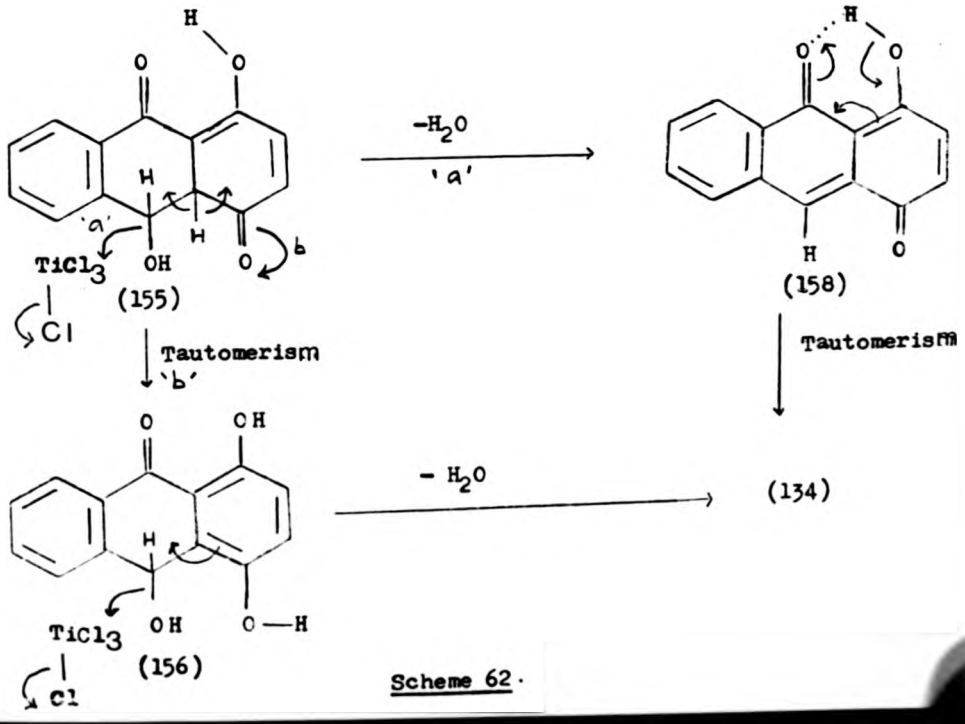
Isolation of compound (134) prompted us to prepare hydroquinone (113) which on acid treatment could give quinizarin (34) or 9-hydroxy-1,4-anthraquinone (134). The required hydroquinone (113) was obtained by reduction of benzoquinone (73) with zinc dust in acetic acid at room temperature, in 87% yield. Under such conditions, one might expect to obtain tricyclic compound (34) and/or (134), but yet hydroquinone (113) was isolated.

Compound (113) had a molecular ion at *m/z* 286 (36%), which easily lost C_2H_4O, presumably giving the aldehyde (67) cation radical which then cyclised [as (Scheme 60)] to give products with *m/z* 240 and 224 respectively; that with *m/z* 224 possibly being due to tricyclic compound (134).

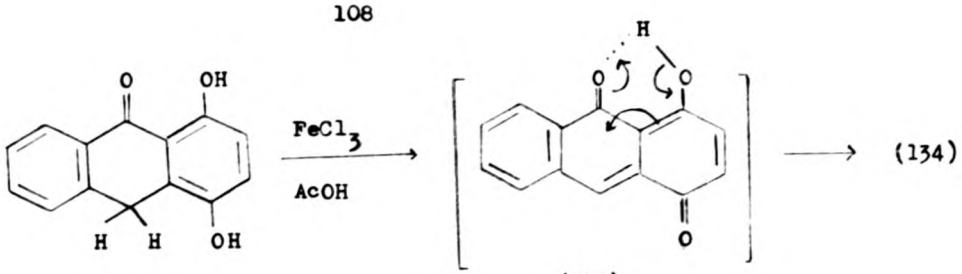
Treatment of (113) with 10% hydrochloric acid in THF for 24 h. gave, as expected, a mixture of the 1,4-anthraquinone (134) and quinizarin (34) in the ratio of about 3:1, respectively (Scheme 64). These results give further support to the mechanism suggested in Scheme 61. In this case, dehydration-tautomerisation of (155) (Scheme 61) competes with enolisation–oxidation (Scheme 60) to give the final products (134) and (34), respectively.



Scheme 61.

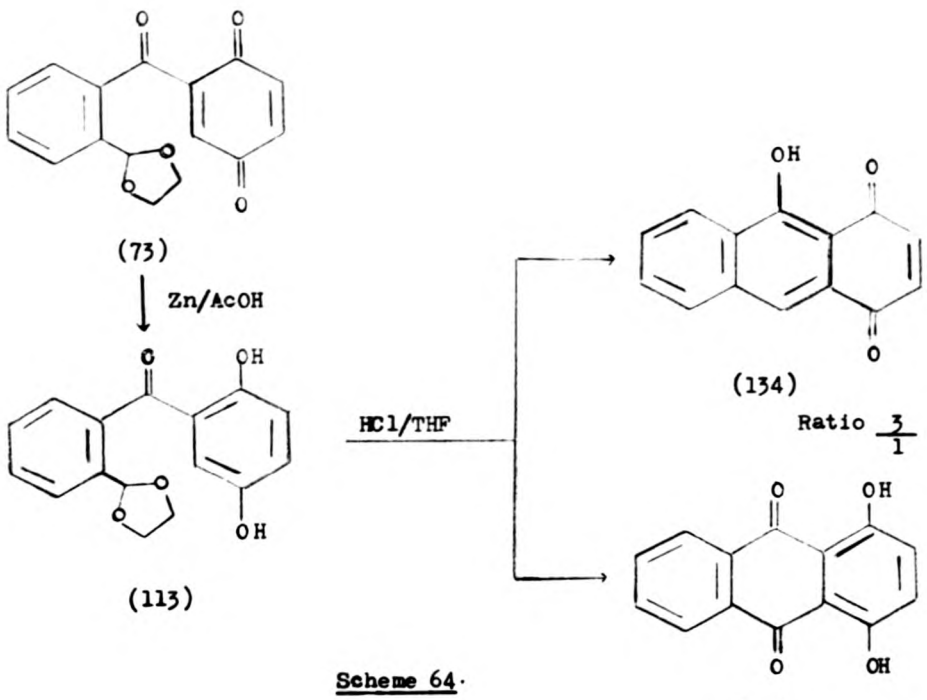


Scheme 62.

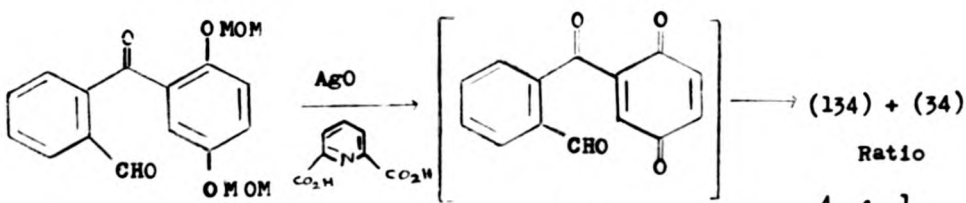


(160) (158)

Scheme 63.



Scheme 64.



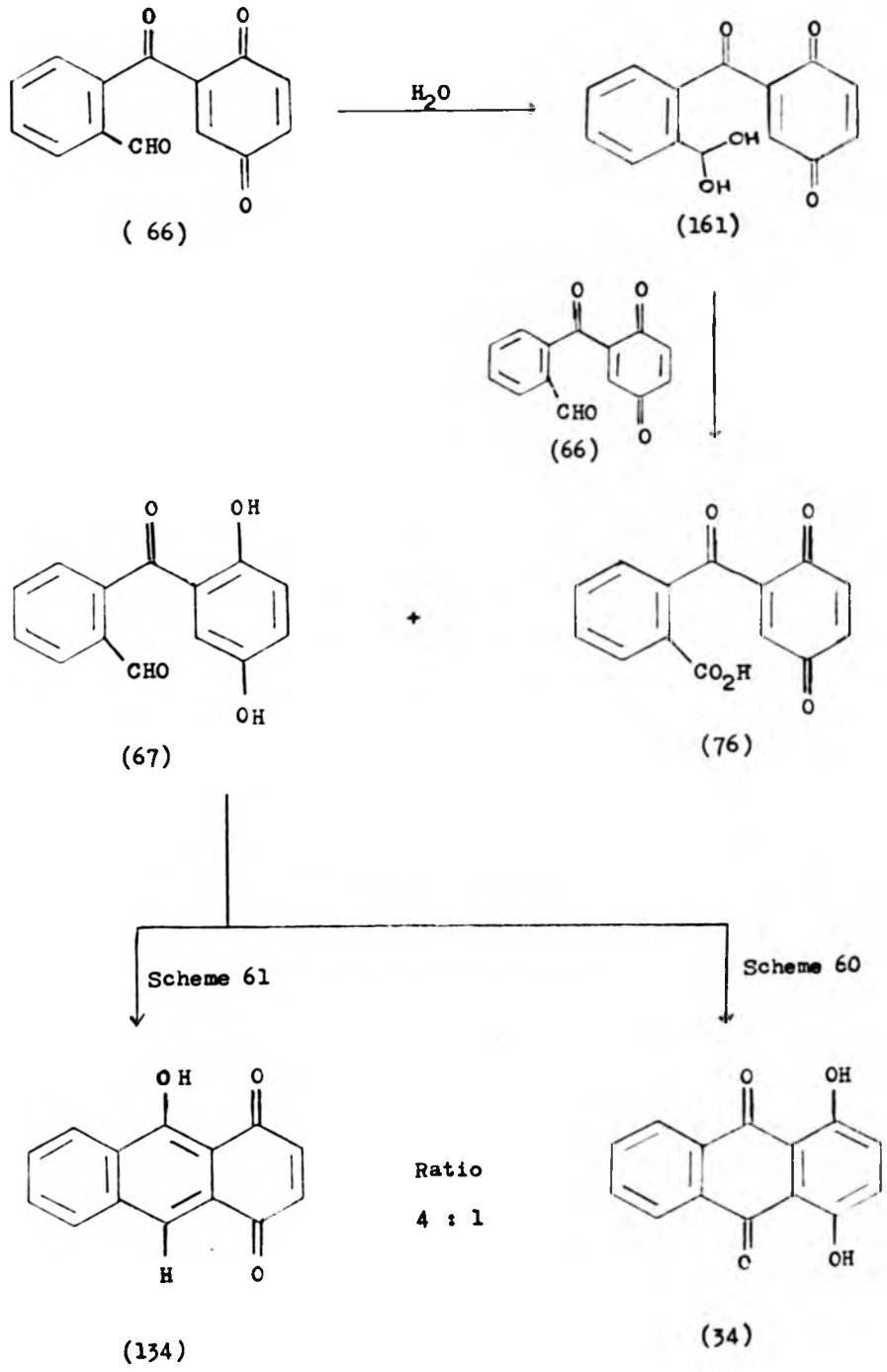
(153) (66)

Scheme 65.

As mentioned earlier in this Section, the reaction of benzophenone (135) with periodic acid in DMF give aldehyde (153) (Scheme 59). Therefore it was of interest to prepare quinone (66) [one of the required compounds (Chapter 2)] by treatment of aldehyde (153) with argentic oxide in the presence of pyridine-2,6-dicarboxylic acid, as for the preparation of quinone (73) shown in Scheme 55. The crude product obtained from this reaction may have contained the desired quinone (66) since its p.m.r. spectrum in d-chloroform showed multiplets in the aromatic region, broad singlets at δ 6.70 and 6.90, and a singlet at 9.98 due to a formyl group. The crude product had a molecular ion at m/z 240. The product was not very stable: its solution in dichloromethane on standing at room temperature overnight changed from red to dark brown. Furthermore, leaving the crude product in the dark at room temperature, followed by extraction with cold hexane gave a mixture of anthraquinone (134) and quinizarin (34) in the ratio 4:1 respectively, (total yield 40%)(Scheme 65).

Formation of (134) and (34) from quinone (66) could be explained by the mechanism shown in Scheme 66. Thus the quinone (66) could react with water to give hydrate (161) which then reduces quinone (66) to hydroquinone (67): which following cyclisation and tautomerisation-dehydration gives the anthraquinone (134) (Scheme 61) in competition; with the cyclisation-oxidation route (Scheme 60) to give quinizarin (34). The former route seems to be preferable to the latter, giving a mixture of (134) and (34) in the ratio 4:1 respectively. The reduction of quinone (66) to (67) could account for the fact that the total of (134) and (34) obtained from the mixture was only a 40% yield (the route shown in Scheme 66 predicts a maximum of 50%).

Formation of cyclic product (134) on treatment of (135) with acid (Scheme 59) prompted us to extend this work to the generation of tetracyclic compounds, a basic structure of anthracyclinones. The results are described in Section 3.3.



(66) (161) (66) (67) (76) (134) (34)

Scheme 66.

3.3. Synthesis and Reactions of 4a,5,8,8a-Tetrahydro-4a-[2-(1,3-dioxolan-2-yl)benzoyl]-5-methyl-1,4-naphthoquinone.

It was stated earlier in this Thesis (Section 1.2) that it was of interest to generate tetracyclic compounds such as (71) via Diels-Alder addition followed by [1,5] aroyl rearrangement and cyclisation. Therefore Scheme 67 was examined.

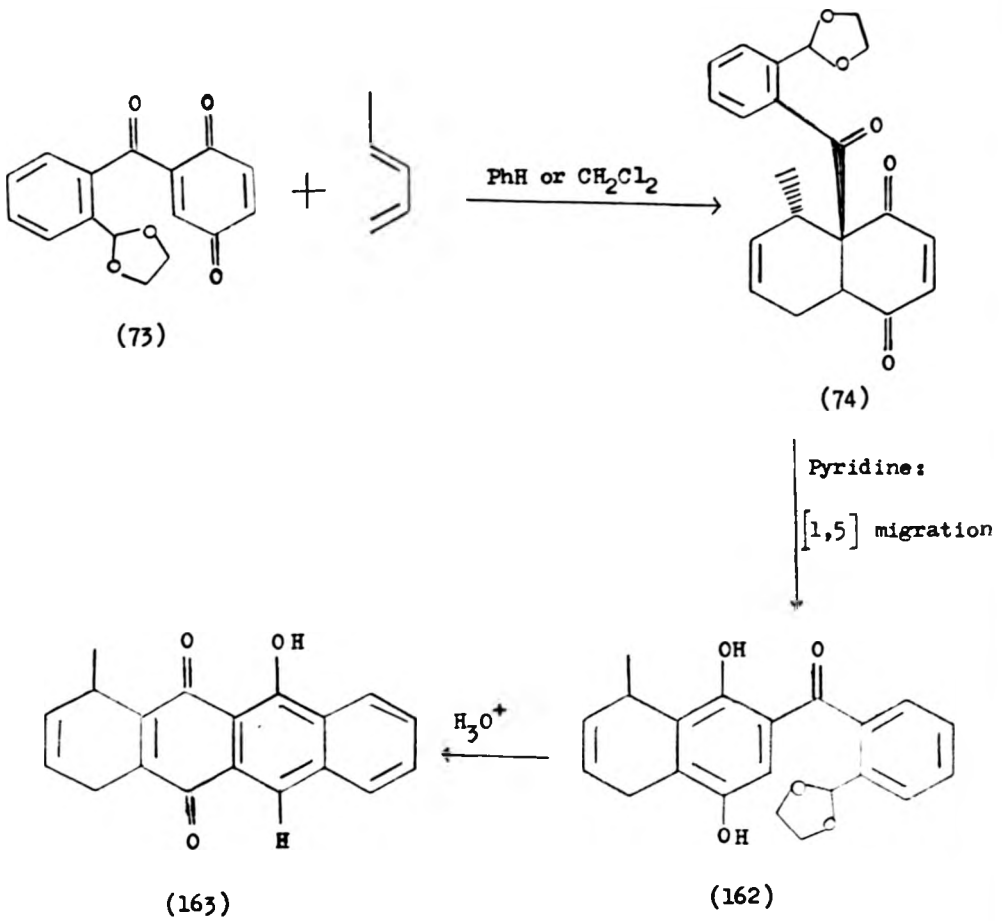
Benzoquinone (73) was treated with trans-penta-1,3-diene in benzene or dichloromethane at room temperature for 20 h. to afford the desired adduct (74) as a pale yellow oil in 92% yield.

Treatment of adduct (74) with d_5-pyridine[31] and monitoring of the progress of reaction by p.m.r. spectroscopy at room temperature showed that the rearrangement was complete in 21 h. Removal of the solvent afforded the desired isomer (162) in 94% yield.

Interestingly, when a solution of the adduct (74) was kept in dichloroform overnight, the compound isomerised to the aroylhydroquinone (162), possibly due to the presence of acid (DCl) which catalysed the enolisation necessary for the [1,5] aroyl shift. This is the first time that such a rearrangement has been observed under these conditions; a basic medium is usually required.

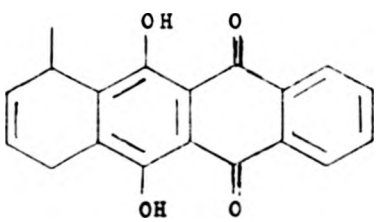
Finally. the cyclisation was achieved by treatment of rearrangement product (162) with either 10% hydrochloric acid in THF,[28] toluene-p-sulfonic acid in acetone,[32] trifluoroacetic acid in dichloromethane,[33] oxalic acid in DMF or trifluoroacetic anhydride[34] in dichloromethane: all gave tetracyclic compound (163) in 57-73% yield. The cyclisation reactions were carried out at room temperature, overnight.

All compounds (74), (162), and (163) showed satisfactory i.r., p.m.r. and mass spectral data. In particular, the p.m.r. and mass spectra of the cyclised product (163) are shown in Figures 4 and 5, respectively.



(73) (74) (163) (162)

Scheme 67



(71)

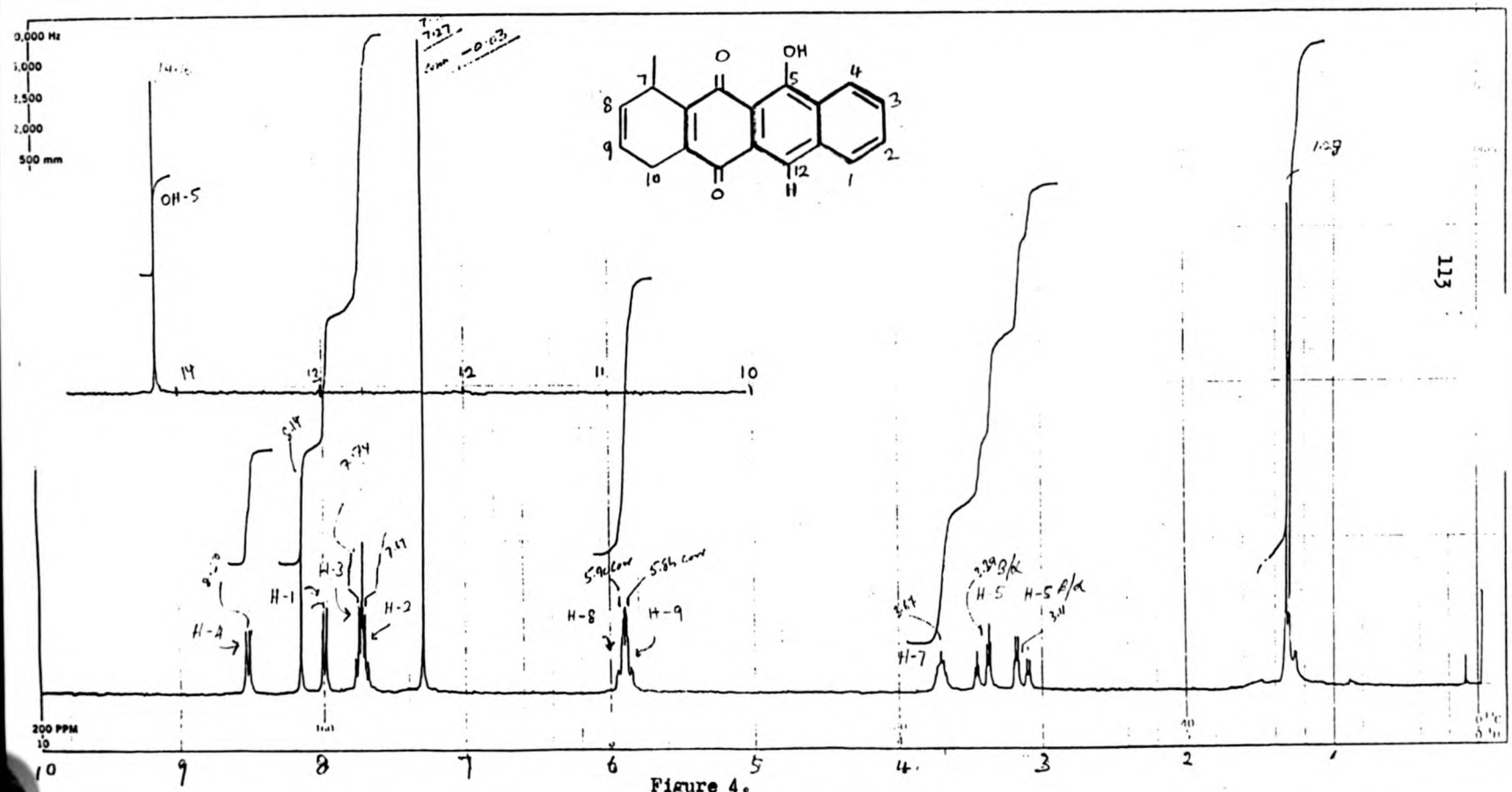


Figure 4.

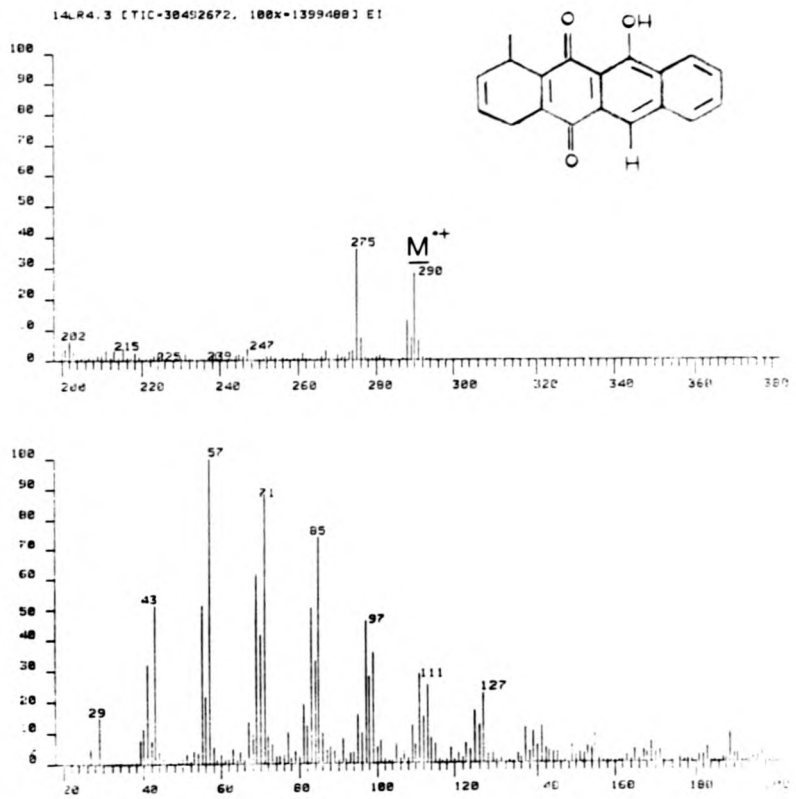
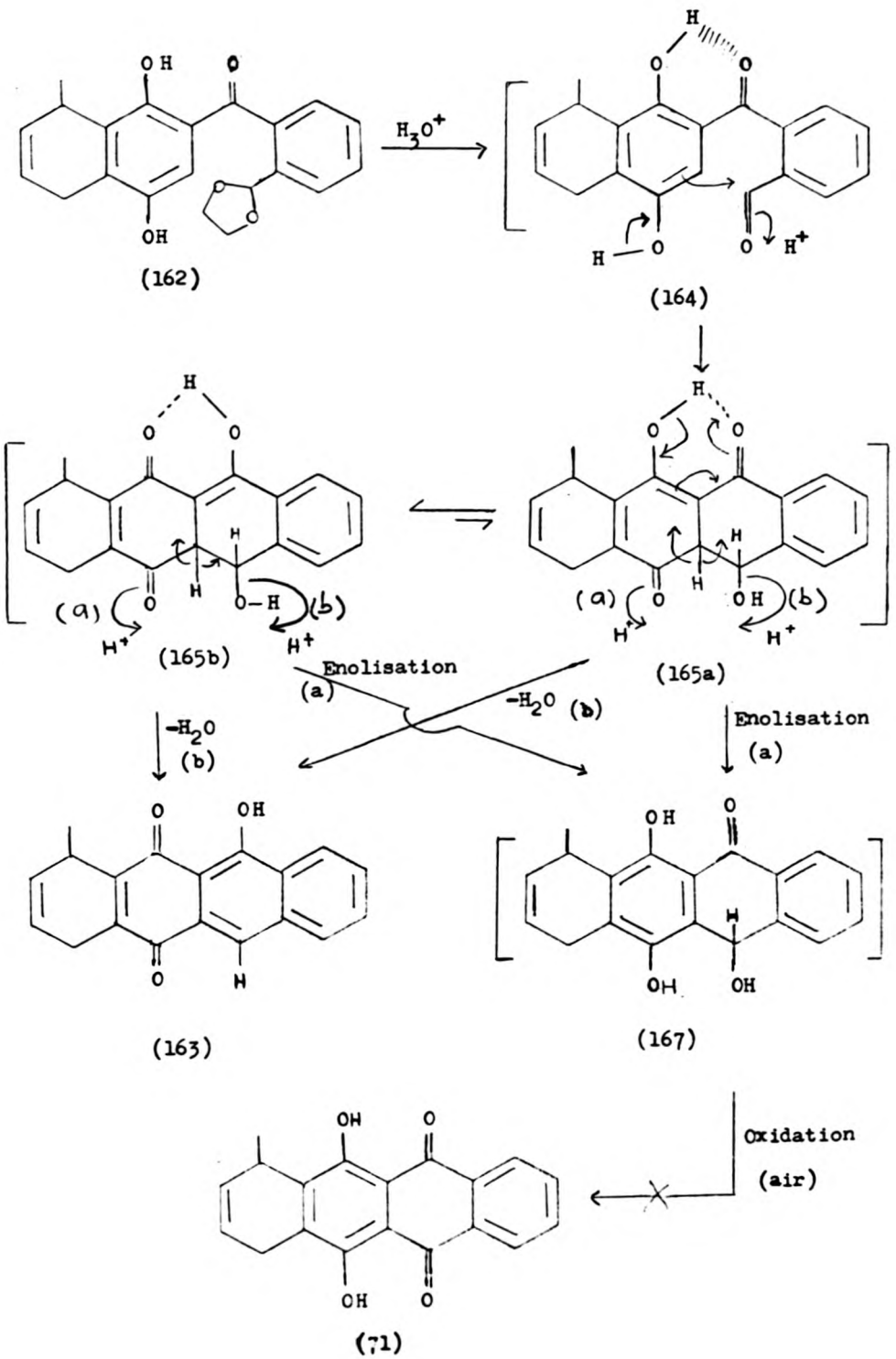

14LR4.3 [TIC=38452672, 100%=1399488] EI
O
OH
O
H
275
M++
290
282
215
225
239
247
57
71
85
43
97
111
127
29

Figure 5.

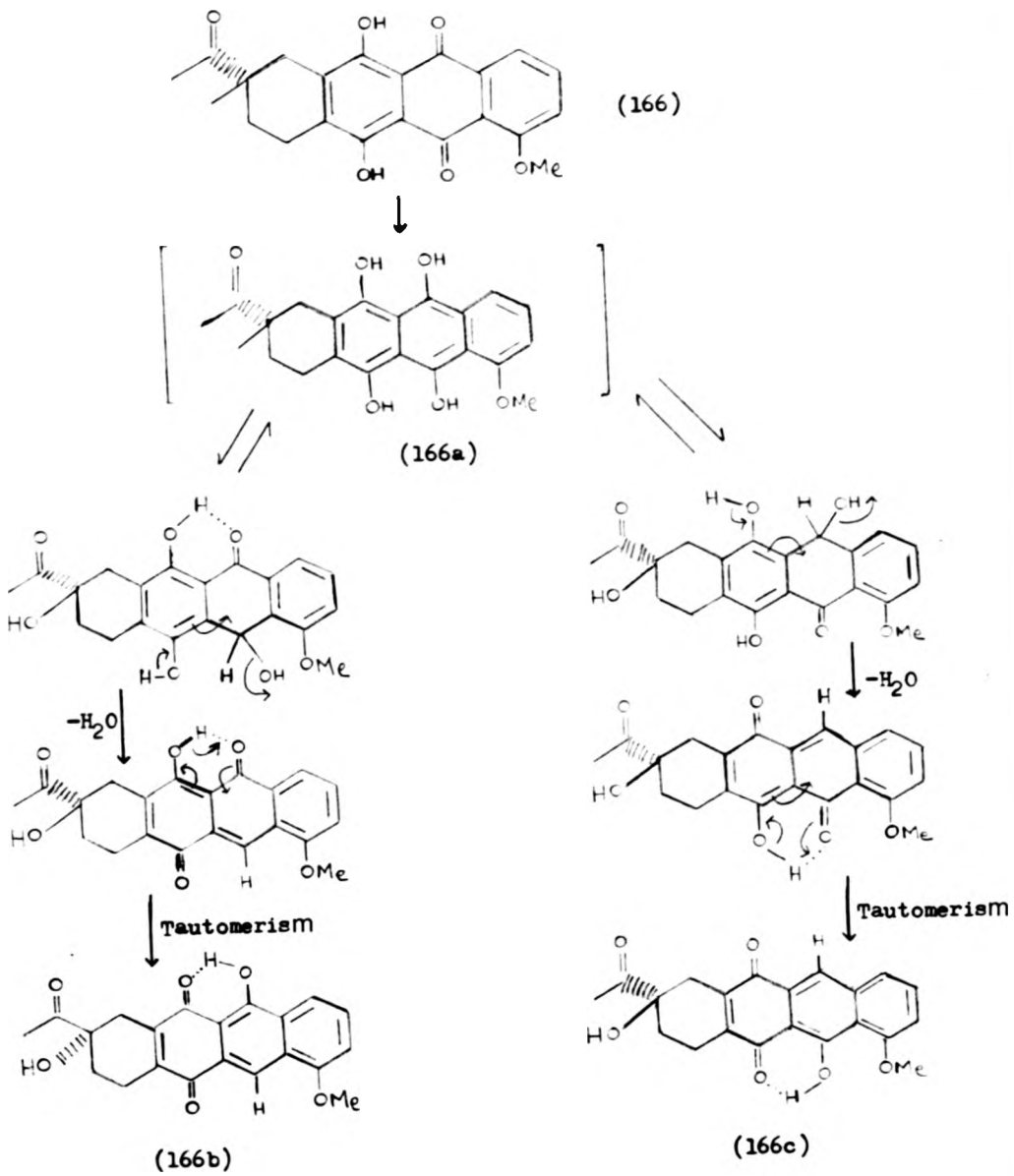
Formation of tetracyclic compound (163) could be explained by the mechanism outlined in Scheme 68, similar to Schemes 60 and 61. Rearrangement product (162) on contact with acid should give aldehyde (164). One might expect that this aldehyde would immediately cyclise to give intermediate (165a) which then either dehydrates to give (163) or tautomerises followed by oxidation to give the final product (71). The former process leading to final product (163) seems to be preferred since internal hydrogen bonding (Structure 165b) favours dehydration rather then enolisation. Note that, the internally hydrogen bonded OH group in structure (164) could prevent Hayashi-type rearrangement[35] during cyclisation.

Some important points should be noted in connection with the structure of compound (163). It has just been reported[36] that reduction of anthracyclinone (166) with dithionite in anaerobic buffered aqueous methanol at pH 7.4 gives (166a) (Scheme 68a). This compound is unstable, easily losing water to give (166b) and (166c)(Scheme 68a). Compound (166b) showed ($CDCl_3$) singlets at δ 13.77 due to the internally hydrogen bonded hydroxy group, and at 8.50 due to the aromatic proton H-12, which is deshielded by both the 11-carbonyl and the 1-methoxy groups. In contrast, compound (166c), an isomer of (166b), showed singlets at δ 15.11 and 8.01 due to the internally hydrogen bonded hydroxy group and the aromatic proton H-5, respectively, the latter being deshielded only by the 6-carbonyl group. Our compound (163) showed singlets at δ 14.16 and 8.14 due to the internally hydrogen bonded hydroxy group and the aromatic proton H-12, respectively.

The position of resonances due to internally hydrogen bonded hydroxy groups is very sensitive to the effects of substituents, even those at considerable distances from the hydrogen bond, and therefore direct comparison of these resonances for compounds (163), (166b), and (166c)


H3O+
(162)
(164)
(a)
(b)
H+
(165b)
(165a)
Enolisation
(a)
-H2O (b)
-H2O
(b)
Enolisation
(a)
(163)
(167)
Oxidation
(air)
(71)

Scheme 68.



Scheme 68a.

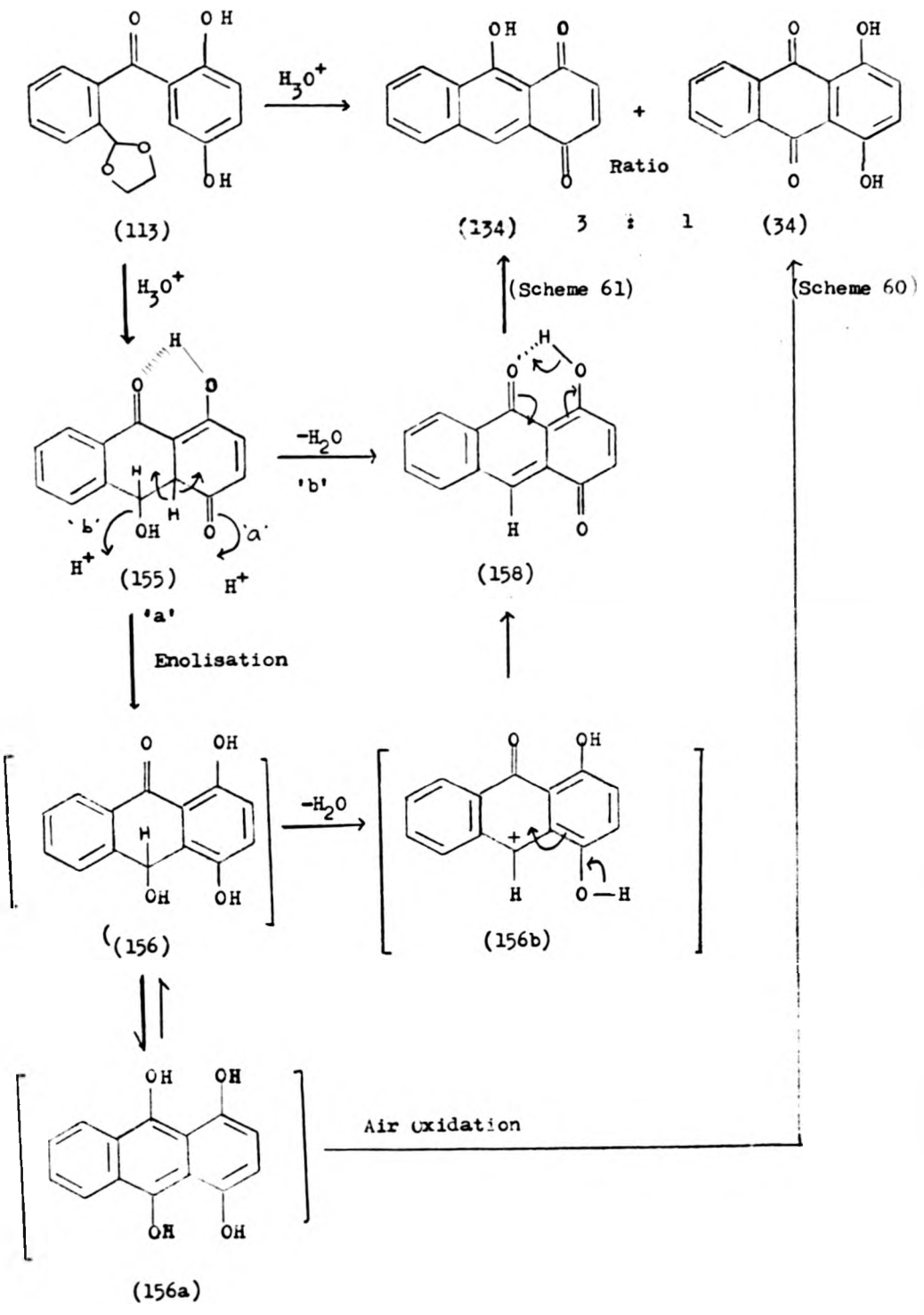
(163) (163a)

may not be structurally meaningful. However, such complications do not arise for simple aromatic proton resonances, and the similarity of the chemical shifts for H-12 of compound (163)(δ8.14) and for the comparable H-5 of compound (166c)(δ8.01) supports the assignment of the 1,4-anthraquinone structure to each series.

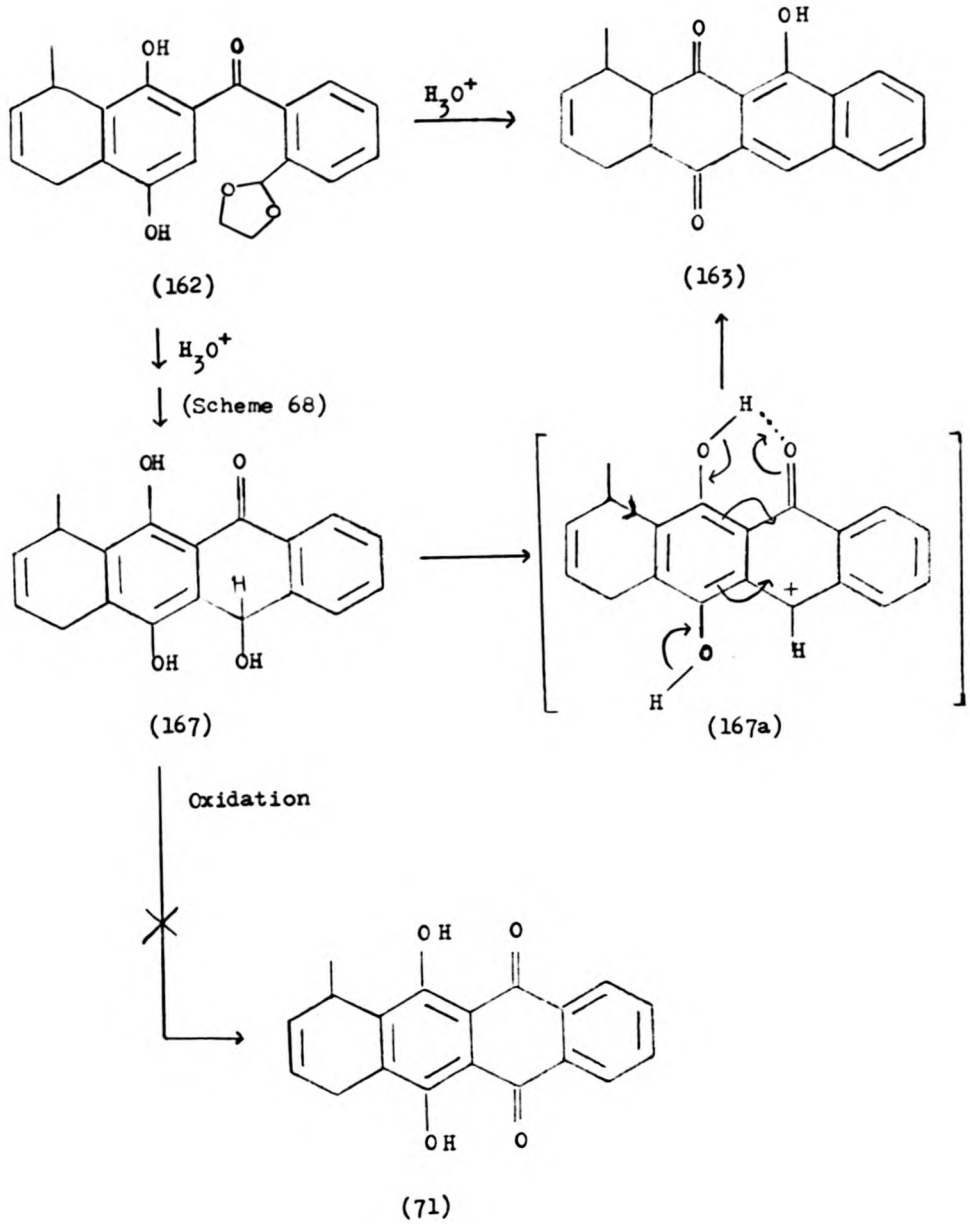
As shown in Scheme 68a, the formation of the two isomers (166b) and (166c) is a consequence of the ability of the anthrahydroquinone (166a) to tautomerise in two ways: 9,10-anthrahydroquinone-10-hydroxy-9-anthrone tautomerism occurs particularly under basic conditions. In contrast, formation of compound (163) as shown in Scheme 68 involves acidic conditions, and therefore analogous tautomerism in (165a) and (165b), which could lead to the formation of the isomer (163a) of compound (163), is considered to be unlikely. Further if this loss of regiochemistry had occurred, a mixture of (163) and (163a) would have been expected: only a single product was obtained.

It was mentioned earlier (Section 3.2; Scheme 64) that treatment of hydroquinone (113) with acid gave a mixture of 9-hydroxy-1,4-anthraquinone (134) and quinizarin (34) in the ratio of about 3:1, respectively. In contrast, treatment of the rearrangement product (162), a formyl analogue of (113), under the same conditions gave only the tetracyclic compound (163), analogous to (134), but no quinizarin analogue (71) was detected (Section 3.3; Scheme 68). These observations suggested that carbocation intermediates, such as structures (156b) and (167a) respectively, may participate in the cyclisations (Schemes 69 and 69a).

As shown in Scheme 61, the intermediate (155) could dehydrate giving (158) which tautomerises to give 9-hydroxy-1,4-anthraquinone (134). This intermediate (155) could also enolise to afford (156), oxidation in air then giving quinizarin (34) (Scheme 60). On the other hand one could expect that the intermediate (156) in the presence of acid could give the carbocation intermediate (156b) which then deprotonates to (158) giving the final product (134) (Scheme 69). The carbocation (156b) may not be very


(113)
(134)
Ratio 3 : 1
(34)
(Scheme 61)
(Scheme 60)
(155)
(158)
Enolisation
(156)
(156b)
Air oxidation
(156a)

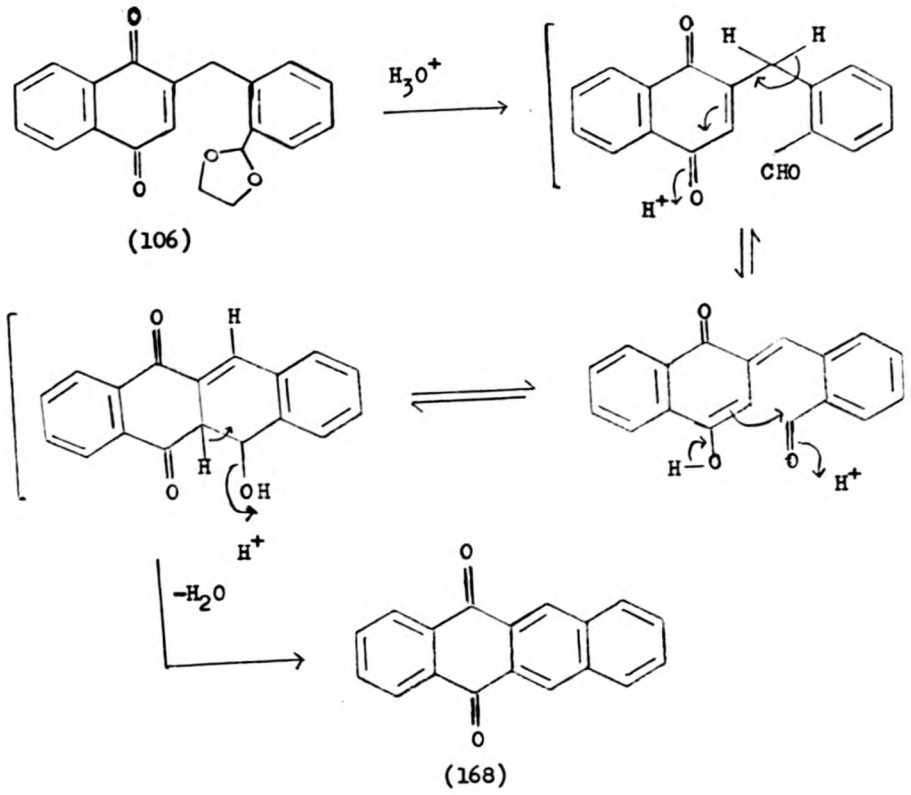
Scheme 69


OH
O
OH
H_3O^+
O
OH
O
(162)
(163)
H_3O^+
(Scheme 68)
OH
O
H
OH
OH
(167)
H
O
O
+
O
H
H
(167a)
Oxidation
OH
O
OH
O
(71)

Scheme 69a.

stable, and may be formed relatively slowly, therefore allowing some of the oxanthrone (156) to be oxidise to quinizarin (34), giving the final product of cyclisation of (113) as a mixture of the 1,4-anthraquinone (134) and quinizarin (34). Similarly, structure (167) (Scheme 68), analogous to the oxanthrone (156) (Scheme 60), could also dehydrate to give the corresponding carbocation (167a) which then deprotonates to give the final product (163) (Scheme 69a). Carbocation (167a) (Scheme 69a) should be more stabilised then carbocation (156b) (Scheme 69) due to the electron releasing effect of the alicyclic system. This carbocation should give the tetracyclic compound (163) after deprotonation and isomerisation. The greater stabilisation of (167a) may ensure that its formation from the oxanthrone (167) is fast relative to oxidation of (167) to the quinizarin (71), and therefore the hydroxyanthraquinone (163) becomes the only significant product formed from the acidic cyclisation of (162).

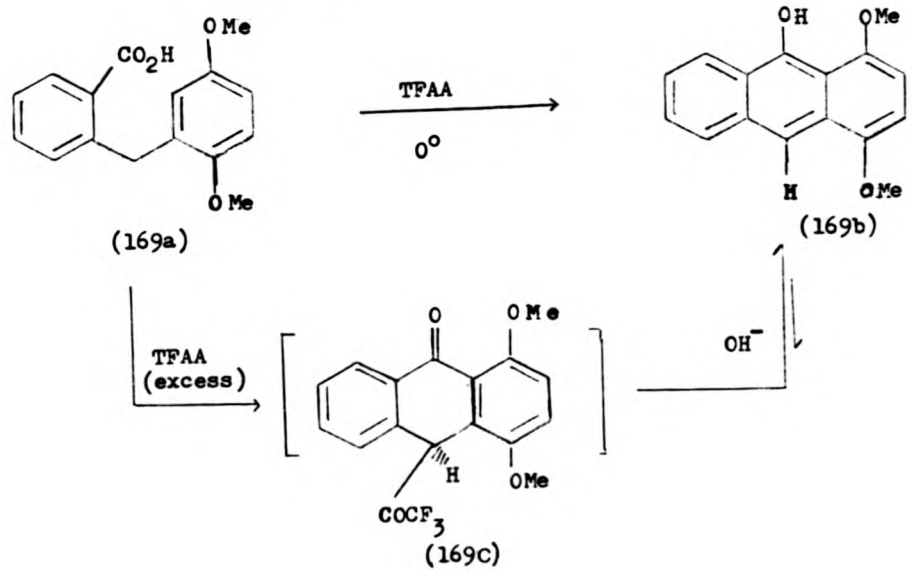
Interestingly, treatment of naphthoquinone (106) with acid was reported[2] to give tetracyclic compound (168), suggested to be via the mechanism shown in Scheme 70. Likewise, treatment of the diphenylmethane-carboxylic acid (169a)[34] with trifluoroacetic anhydride in dichloro-methane at 0° was reported to give cyclic product (169b); no Hayashi-type rearrangement was observed. If the reaction time for the cyclisation was increased or a large amount of trifluoroacetic anhydride was employed, the reaction gave the trifluoroacetyl anthracenone (169c) as a major product. Compound (169c) is an air-sensitive oil, reverts quantitatively to (169b) in hydroxylic solvents (Scheme 70a). This may account for the fact that reaction of the rearranged product (162) with trifluoroacetic anhydride initially gave a pale yellow oil which changed to brownish after a few days, then affording tetracyclic compound (163).



(106)

(168)

Scheme 70



(169a)

(169b)

(169c)

Scheme 70a

Since treatment of rearranged product (162) with acid, as described above, gave tetracycle (163) (Scheme 68) which lacked oxygen at C-12, several experiments were performed in attempts to retain the oxygen atom at C-12, as required for an anthracyclinone.

Compound (162) was therefore treated with mild acids such as pyridinium p-toluenesulfonate in acetone,[32] and glacial acetic acid in dichloromethane. However the product isolated from these experiments was starting material (162). Surprisingly, treatment of (162) with 10% sulfuric acid in a two phase ether-water system gave the same result. In contrast, treatment of (162) with CAN in aqueous acetonitrile gave a complex mixture, although the total product showed m/z 306, possibly due to the desired tetracyclic (71).

Cyclisation was then repeated using trifluoroacetic acid at 0° for only ½ h.; however the product was still tetracycle (163). It seems that the dehydration process (Scheme 68) may be very easy. Therefore it was of interest to attempt to trap the intermediate (165a)/(165b) as a chelate by using a boron compound (cf. the use of benzeneboronic acid[37]). Hence the cyclisation was repeated using trifluoroacetic acid in the presence of an excess of boron acetate in dichloromethane at room temperature for 6 h. However the product isolated still contained mainly tetracyclic compound (163) together with unidentified material which showed singlets at δ 9.82 and 14.90, and multiplets at 7.60. The total product showed a molecular ion at m/z 306 (< 1) which suggested that it may have contained the required compound (71) (Scheme 68).

Another possibility for introduction of oxygen at C-12 would be oxidation of (163) itself. Tetracycle (163) was therefore treated with chromium trioxide in glacial acetic acid.[37] However, the product obtained was a colourless oil, which showed m/z at 410 (< 1). This product was too

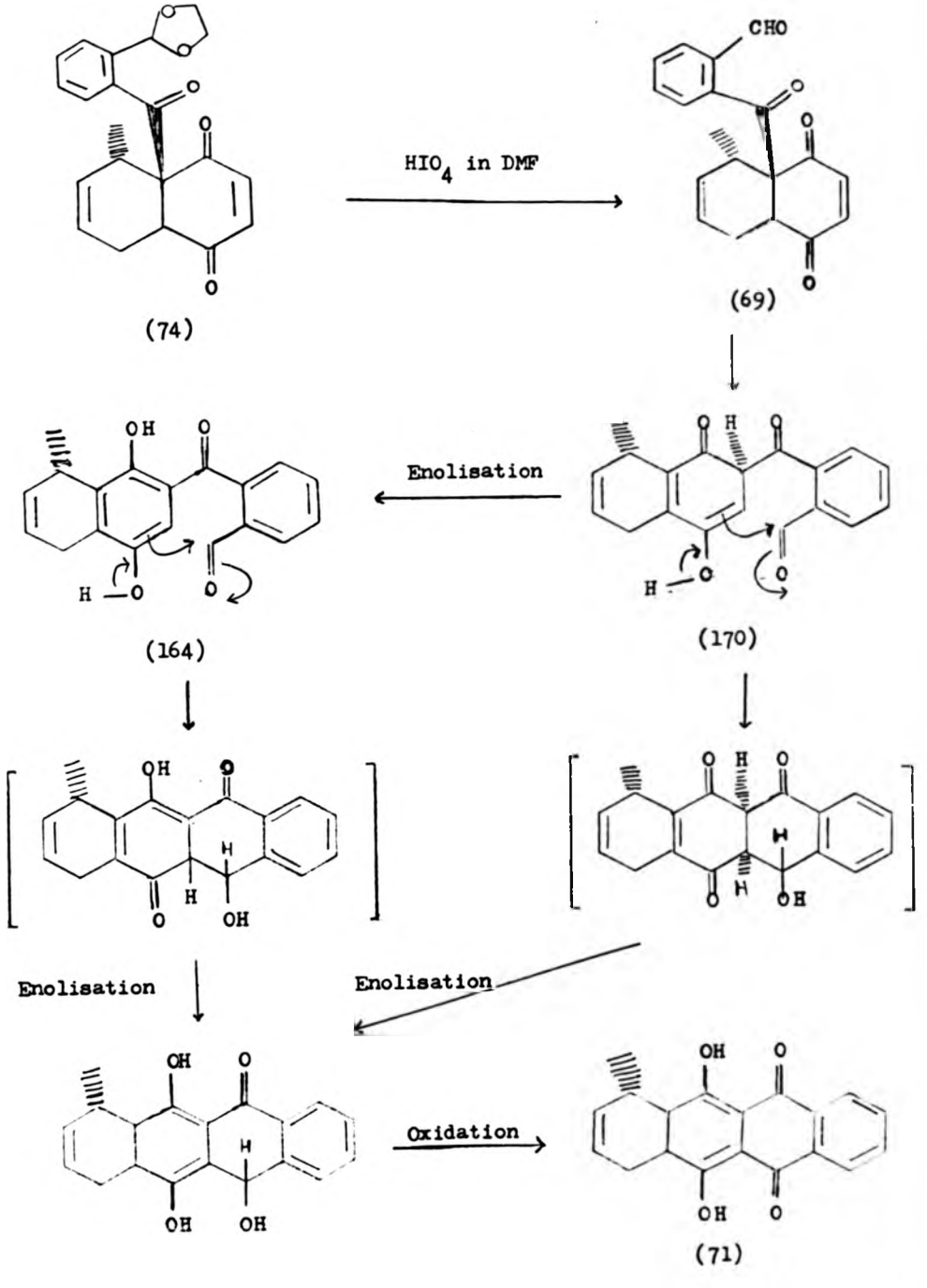
small in quantity for identification. Furthermore, the desired product (71) is expected to be red.

Oxidation of (163) was then tried using lead tetraacetate[38] in acetic acid at room temperature overnight. After work-up and purification by column chromatography on silica gel using 1:1 hexane-ether as eluent an orange oil was obtained which was not identified. Its p.m.r. spectrum in d-chloroform showed multiplets in the methyl region which were too big for six protons, multiplets at δ 3.50-3.98, 7.80-8.00, and 8.36-8.50, quartets at 4.80-5.06 and 5.20-5.26, and singlets at 7.32 and 12.96.

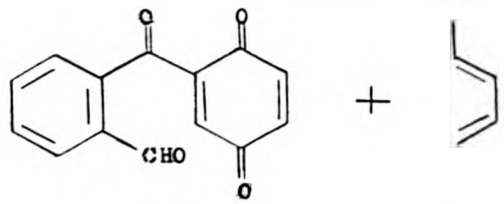
The next experiments were to examine other routes to tetracycle (71), as shown in Scheme 71. Our target was to prepare adduct (69), which under mildly basic conditions should isomerise and cyclise to give the desired compound (71). The cyclisation could occur either immediately after [1,5] aroyl migration, or after enolisation of the migration product (170) (Scheme 71). Dehydration may not occur in the absence of acid.

Adduct (69) could be prepared in two ways: either by acidic cleavage of acetal adduct (74) (Scheme 71) or by addition of trans-penta-1,3-diene to quinone (66) (Scheme 72). However, the latter route was not tried, since it was mentioned earlier that the quinone (66) was not very stable. Furthermore, the former route gave the desired adduct (69) in good yield.

The required adduct (69) was obtained by treatment of adduct (74) with periodic acid in DMF, in 88% yield. It had the molecular ion at m/z 308 as required, and its structure was confirmed by its p.m.r. spectrum. Treatment of adduct (74) with periodic acid in THF also gave the desired adduct (69), but in a very crude state. Surprisingly,


CHO
HIO_4 in DMF
(74)
(69)
Enolisation
(164)
(170)
Enolisation
Enolisation
Oxidation
(71)

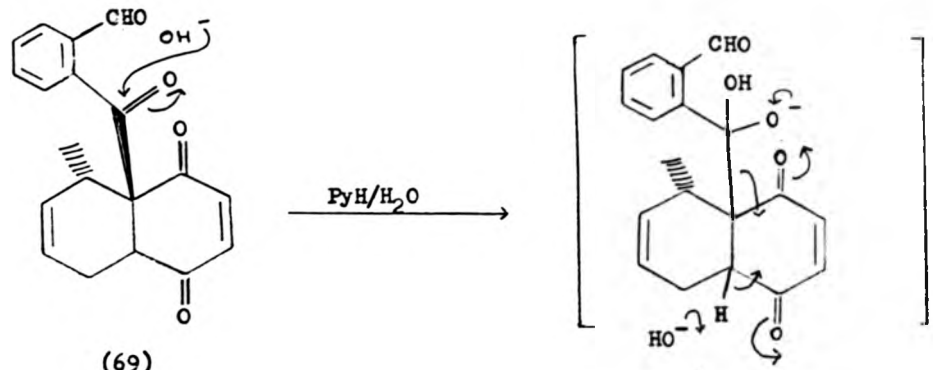
Scheme 71



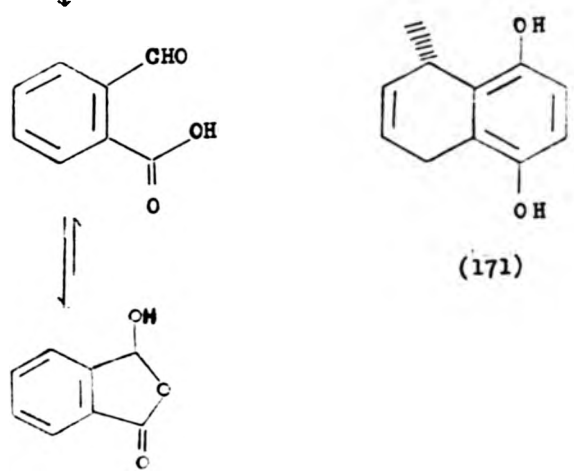
(66)

(69)

Scheme 72.



(69)



(171)

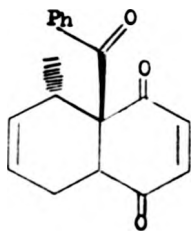
(172)

Scheme 73

treatment of adduct (74) with two phase 5% sulfuric acid–dichloromethane gave starting material. However, treatment of adduct (74) with 5% sulfuric acid in refluxing methanol gave a brown sticky oil which may have contained cyclised product (163; m/z 290) and traces of anthraquinone (134; m/z 224).

Adduct (69) was then dissolved in d_5-pyridine[31] and the progress of reaction was followed by p.m.r. spectroscopy at room temperature; it was complete after 24 h. Removal of the solvent gave a brown oil, the p.m.r. spectrum of which was too complex to be completely identified. No signal due to an internally hydrogen-bonded hydroxy group of the desired product (71) (Scheme 71) was observed. Similar reactions in 1:1 pyridine–methanol gave the same result.

These observations suggested that under such reaction conditions, [1,5] aroyl migration could compete with nucleophilic attack on the aroyl group, leading to hydroquinone (171) and lactone (172) (Scheme 73). However no direct evidence for such a mechanism was observed since the mass and p.m.r. spectra of the total product did not show clearly the presence of (171) and (172). However, such a cleavage reaction has been observed by earlier workers in our laboratories during benzoyl migration in adduct (173).[39]



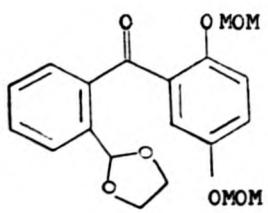
(173)

Suggestions For Further Studies.

It was mentioned in this Thesis that treatment of ketone (135) with hydrochloric acid gave cyclised product (134) (Scheme 59). It was reported[40] that anthraquinone (134) undergoes regiospecific cycloadition with isoprene, when the reaction was conducted in the presence of boron triacetate. Therefore, the basic result shown in Scheme 59 may be capable of extension to the synthesis of some anthracyclinones as shown in Scheme 74. Interestingly, regiospecific cycloaddition of 2-alkoxybutadienes to quinone of the form (173) was recently reported[41] to afford tetracyclic ketones (174).

It was found (Scheme 68) that rearranged product (162) cyclised smoothly to give tetracycle (163). This product is lacking an oxygen atom at C-12. Therefore, further work should be concerned with overcoming this problem. Time limitation prevented more than a preliminary investigation of this problem during the present work.

It is hoped that a study of these reactions will be undertaken shortly.



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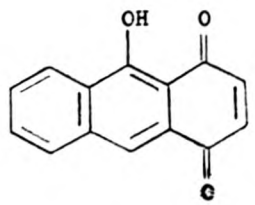
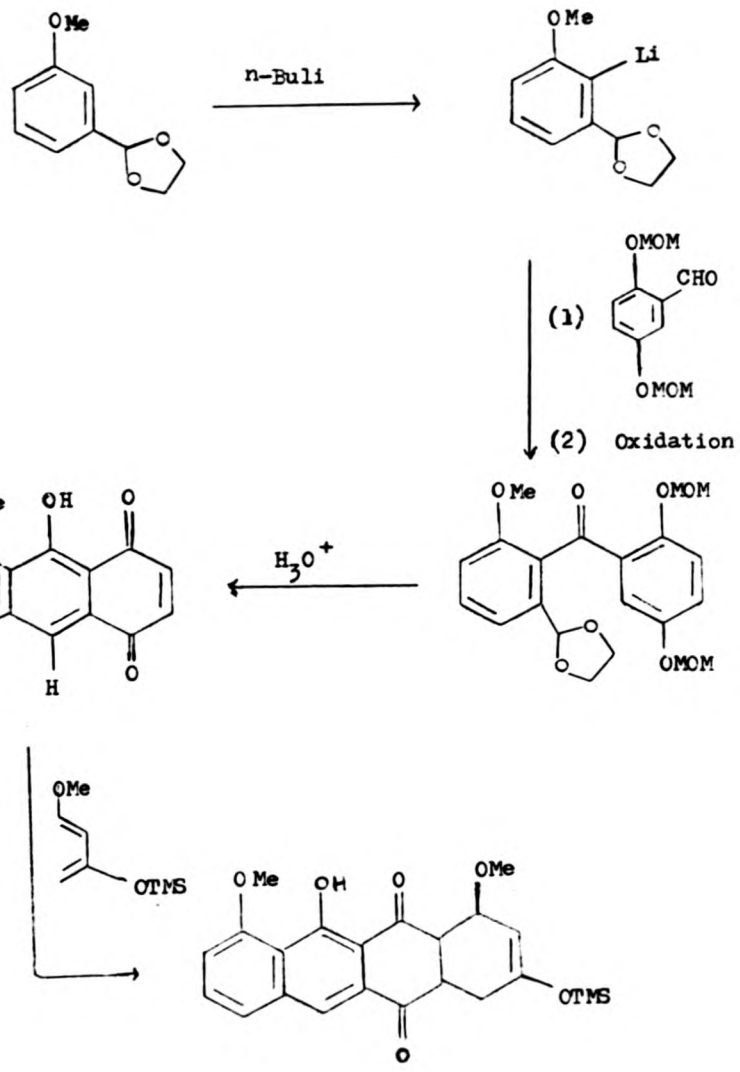
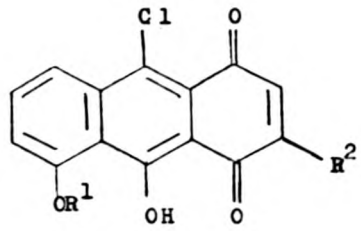


(134)



Scheme 74.



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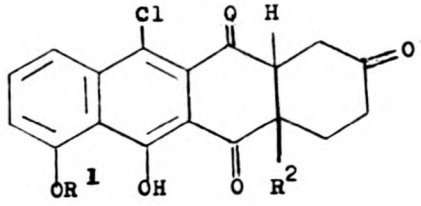

(174)

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Chapter 4

Other Approaches to [2-(1,3-Dioxolan-2-yl)benzoyl]-1,4-benzoquinone.

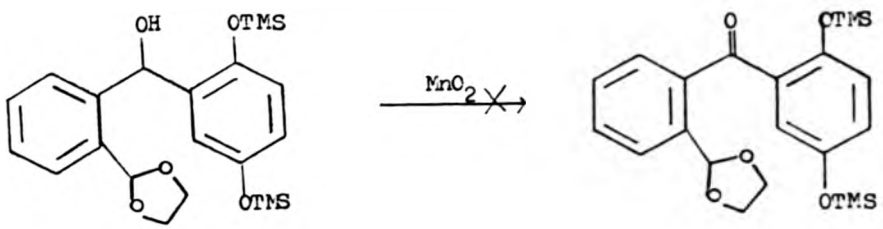
4.1 Attempted Synthesis of 2'-(1,3-Dioxolan-2-yl)-2,5-bis [(trimethylsilyl)oxy] benzophenone.

It was mentioned in section 3.1 that attempts to prepare the title compound (141) *via* oxidation of alcohol (140) were unsuccessful; the former compound might under appropriate conditions give the desired quinone (73) (Scheme 74a). Thus, at one stage, it was of interest to synthesise the ketone (141), and the route shown in Scheme 75 was attempted.

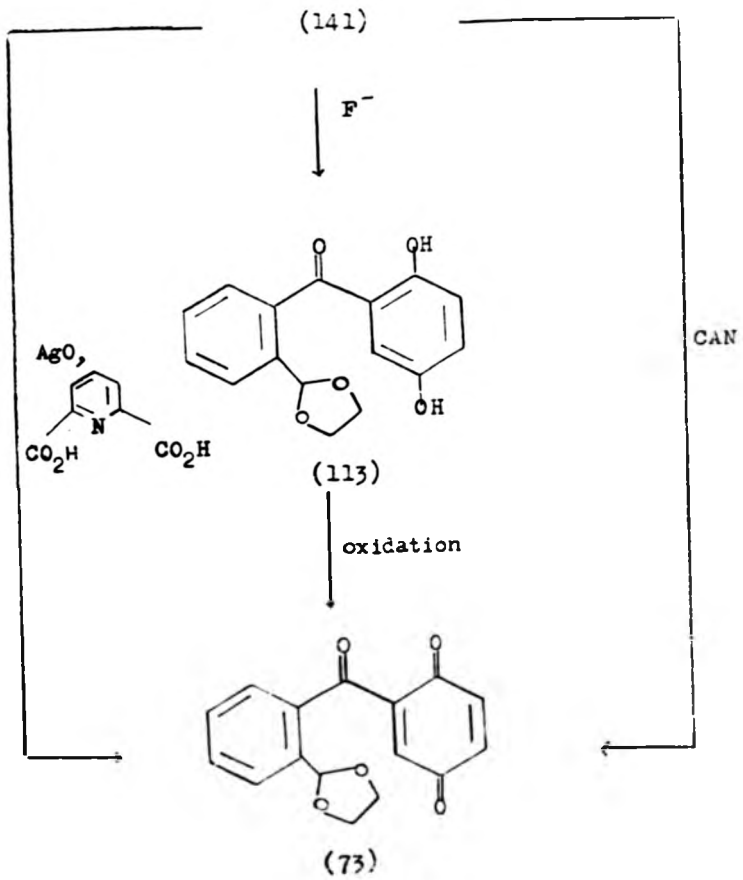
It was reported[1] that *N*-methoxy-*N*-methylamides couple in good yields with Grignard and organolithium reagents in THF to produce ketones. The conversion may proceed through a very stable metal-chelated intermediate (Scheme 76). Therefore the coupling of (178) with the phenyl-lithium (114), was expected to give the desired benzophenone (141) (Scheme 75).

Treatment of gentisic acid with acetic anhydride in the presence of sulphuric acid at 60° gave the desired gentisic acid diacetate (175) in 75 % yield. Reaction of its acid chloride [formed *in situ* by treatment of the diacetate (175) with oxalyl chloride] with *N*,*O*-dimethylhydroxylamine hydrochloride in dichloromethane at room temperature gave the desired diacetate (176) in 79% yield as a colourless sticky oil. Its structure was confirmed by elemental analysis, mass and p.m.r spectra. Its mass spectrum [$CI(NH_3)$] showed that diacetate (176) easily lost ketene and two methyl groups. Suprisingly, it was stable to acid, since it was unchanged on treatment with 2N hydrochloric acid in acetone at room temperature overnight.

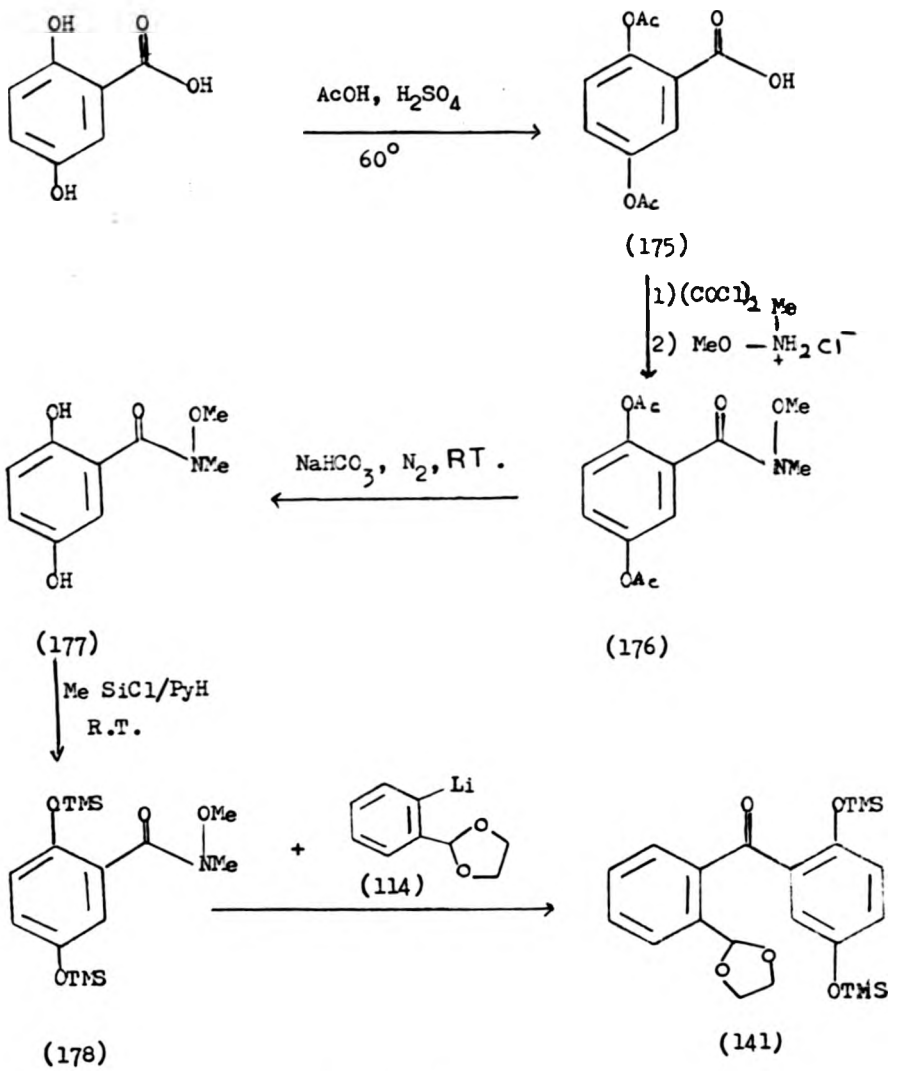
Treatment of diacetate (176) with saturated sodium hydrogen carbonate[2] under nitrogen gave the desired hydroquinone (177). Its structure was confirmed by its mass and p.m.r. spectra. Its mass spectrum (EI) showed that hydroquinone (177) easily lost [CO.(NMe).OMe] to give the base peak. However, it was difficult to obtain a good elemental



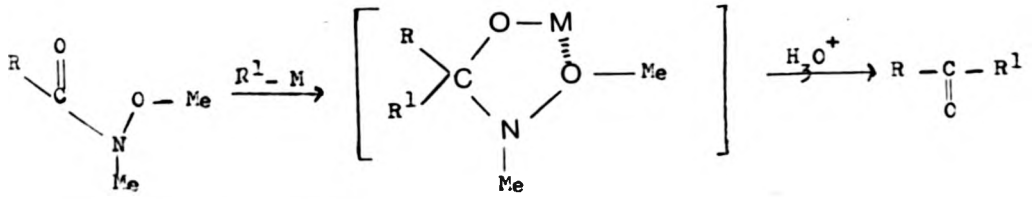
(140) (141)



Scheme 74a.



Scheme 75.

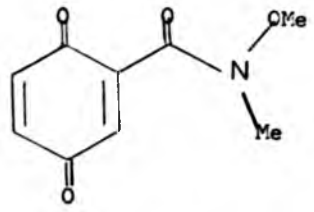


Scheme 76.

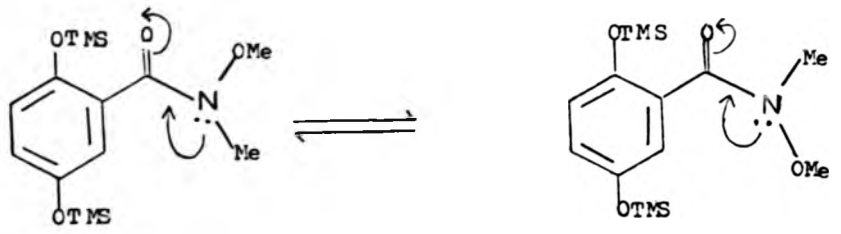
analysis: the nitrogen value was always low, although several attempts were made using freshly distilled material. Hydroquinone (177) was easily oxidised to quinone (179) by treatment with silver oxide in dichloromethane.

Treatment of hydroquinone (177) with trimethylsilyl chloride in the presence of pyridine at room temperature gave the desired silyl ether (178) in good yield, as a colourless liquid. Silyl ether (178) may exist as two isomers [structures (180) and (181)], since its p.m.r. spectrum in d-chloroform showed four singlets at δ 3.23, 3.34, 3.58, and 3.60, possibly due to two methyl and two methoxy groups, respectively. Again, it was not possible to obtain a good elemental analysis for silyl ether (178) since the compound was very sensitive to moisture and attempts to distil it (bulb-to-bulb) lead to the formation of the starting hydroquinone (177). Therefore, the freshly prepared silyl ether (178) was immediately used in the next step: the coupling reaction in Scheme 75.

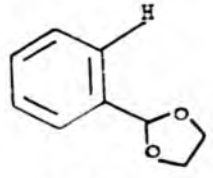
However, the coupling reaction failed to give the desired compound (141). Reaction of silyl ether (178) with lithium compound (114) either at -70°, or at room temperature, in the presence or absence of tetramethylethylenediamine failed to give the desired coupling product (141). The product isolated from the organic fraction was the acetal (182) which would have been formed from decomposition of unreacted aryl-lithium (114) with water. In one of the reactions [in the absence of tetramethylethylenediamine, at room temperature], ether extraction from the aqueous fraction following acidification with 5% sulphuric acid gave hydroquinone (177), probably formed by hydrolysis of unreacted silyl ether (178). The above results suggested that the amide group in the silyl ester (178) was possibly not sufficiently reactive to couple with the lithium compound (114).



(179)



(180) (181)

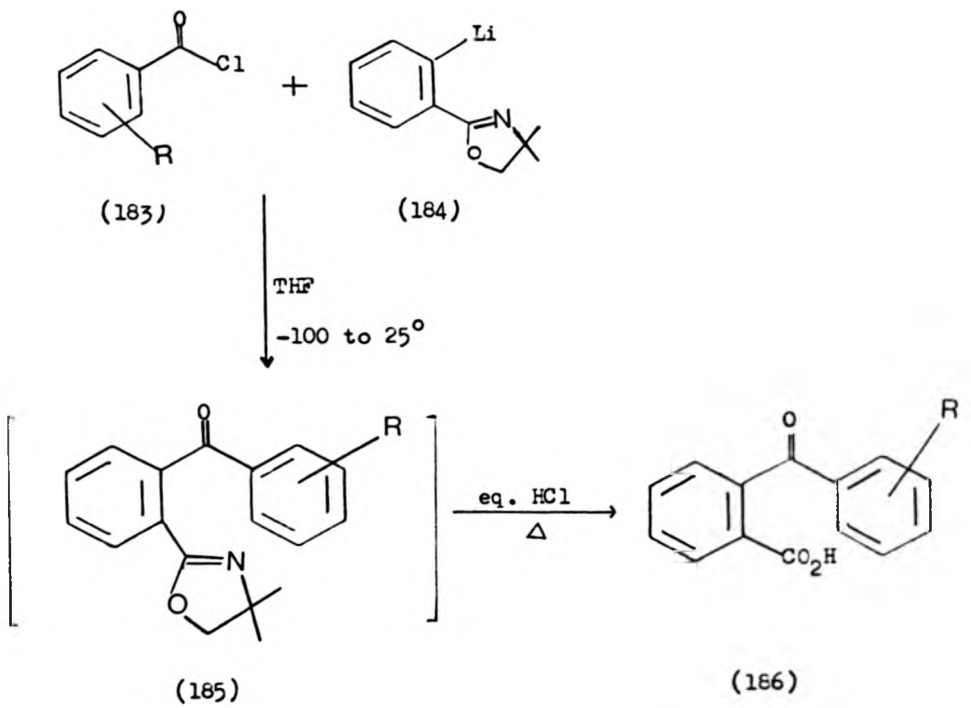


(182)

It was reported[3] that acid chlorides (183) condensed with (2-lithioaryl)oxazoline (184) in THF at -100° to room temperature to give phenyloxazolines (185), which after acidic hydrolysis gave, 2-benzoyl-benzoic acid (186) in a good yield (Scheme 77). Furthermore, condensation of acid chloride (187) with aryl-lithium (188) at -78° in ether,[4] was found to give the desired ketone (189) in 35% yield (Scheme 78).

Therefore, it was of interest to attempt to prepare the desired ketone (141) by the route shown in Scheme 79. Unfortunately, attempts to prepare the necessary acid chloride (190) ended in failure. Treatment of silyl ether (191) with oxalyl chloride in the presence of dimethylformamide either in dichloromethane or without solvent, at 0°, failed to give the desired acid chloride (190); the product isolated was gentisic acid. The reaction in each case was very exothermic and the solid gentisic acid was formed instantly after the addition of oxalyl chloride. This result suggested that the desired acid chloride (190) was unstable and easily hydrolysed.

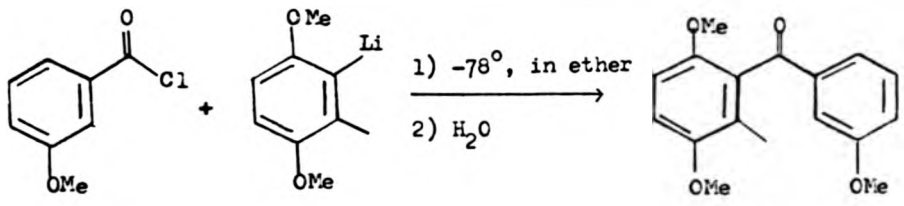
In this connection, Häusher and Schmidt[5] reported that treatment of trimethylsilyl pyruvate (192) with oxalyl chloride in the presence of dimethylformamide without solvent gave the acid chloride (193). Likewise Wissner and Grudzinskas[6] reported that treatment of tert-butyldimethylsilyl ether (194) with oxalyl chloride-dimethylformamide in dichloromethane gave, after treatment of the resulting acid chloride with ethanol-pyridine, the ethyl ester (195) in 90% yield. The author[6] suggested that the mechanism for the above transformation could involve addition of dimethylforminium chloride (196) to the carboxyl group of the silyl ester to give intermediate (197) which undergoes fragmentation to generate the acid chloride (Scheme 80).



(183) (184)

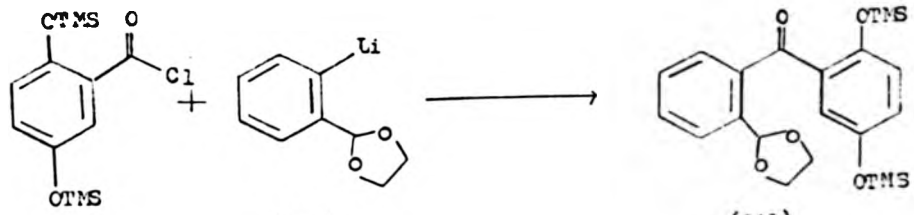
(185) (186)

Scheme 77.



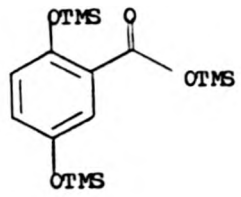
(187) (188) (189)

Scheme 78.

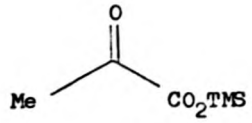


(190) (114) (141)

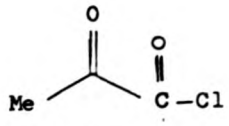
Scheme 79.



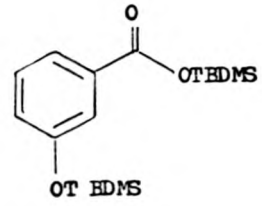
(191)



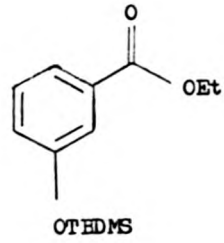
(192)



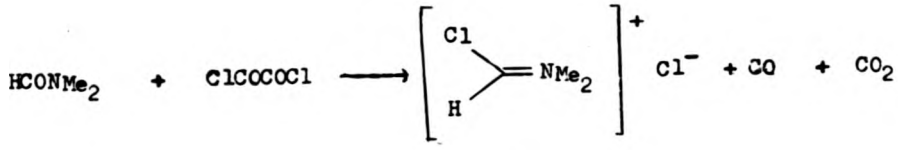
(193)



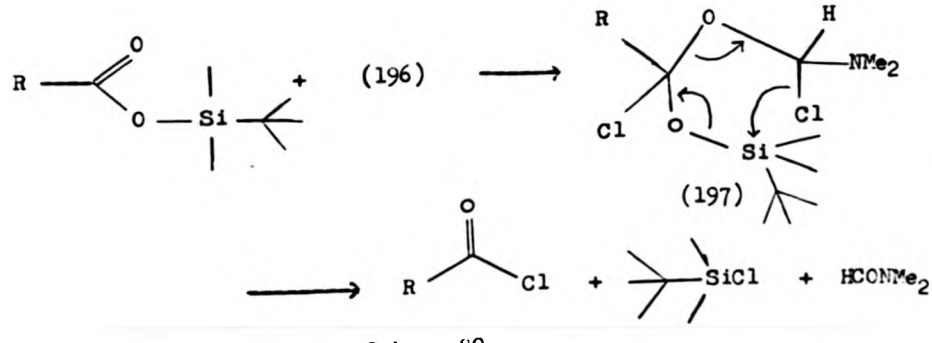
(194)



(195)



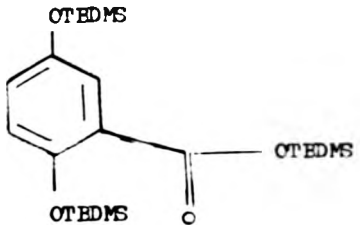
(196)



Scheme 80.

Interestingly, an attempt to prepare silyl ether (198) in a pure state by treatment of gentisic acid with tert-butyldimethylsilyl chloride in the presence of pyridine failed. The product isolated gradually changed to a white solid on standing at room temperature [probably gentisic acid]. On sublimation, the product decomposed to gentisic acid. It seem that the tert-butyldimethylsilyl ether (198) was unstable, although it is known that the tert-butyldimethylsilyl ethers are normally more stable than the trimethylsilyl ones.[7a]

Thus, due to these difficulties in the preparation of compound (141), we were unable to attempt the proposed Scheme 74a and the successful route to quinone (73) remained as shown in Scheme 55 of Section 3.2.



(198)

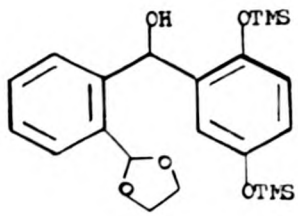
4.2 Desilylation of 2,5-Bis[(trimethylsilyl)oxy]toluene.

In connection with the difficulties encountered in handling the silyl etner (140) as mentioned in Section 3.1 (Scheme 53), several experiments on tne desilylation of silyl ether (199) were performed, as models for obtaining the required quinone (112), particularly under nonacidic conditions.

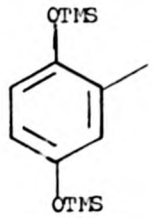
The silane compound (199) was easily prepared from tne hydroquinone (200) by treatment with trimetnylsilyl chloride in the presence of pyridine, in 72% yield as a colourless liquid. However, Miller et. al.,[7b] prepared compound (199) by treatment of hydroquinone (200) with trimethylsilyl chloride in the presence of hexamethyldisilazane, in 94% yield.

Desilylation of (199) was initially tried using tetrabutylammonium fluoride[6] in ether. Tne reaction gave a violet solid. Its p.m.r. spectrum in d-cnloroform showed tnat the product contained predominantly tne required hydroquinone (200). A similar reaction in THF, however, gave the starting material (199).

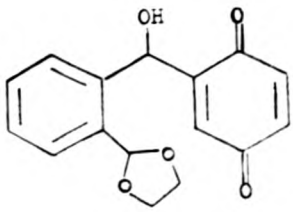
Desilylation using potassium fluoride[9] in methanol gave a better result: compound (200) was isolated in 86% yield, as a white solid. Longer reaction time, and reactions in other homogeneous solvents such as acetonitrile-water or THF-water, gave the same result. However, attempted desilylation using potassium fluoride in a two-phase ether-water system gave starting material. Formation of hydroquinone (200) from silane (199) in the presence of fluoride ion could proceed as shown in (201); desilylation by the use of potassium fluoride possibly proceded by the overall route shown in Scheme 61.



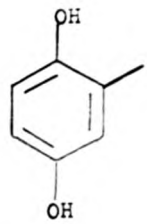
(140)



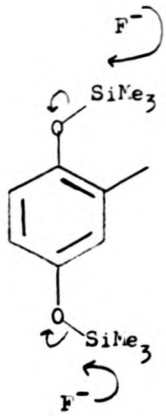
(199)



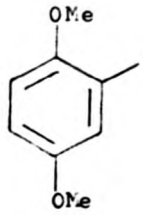
(112)



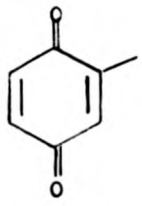
(200)



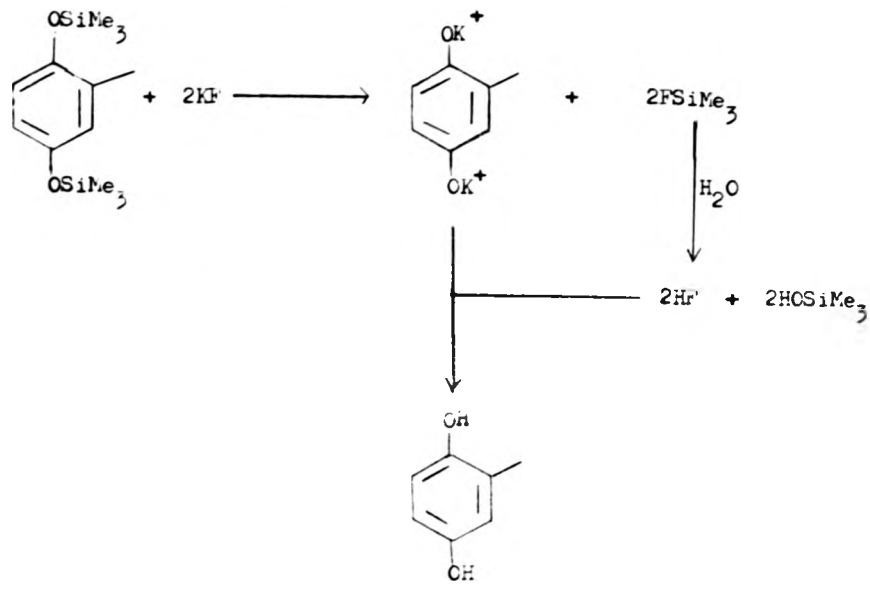
(201)



(202)



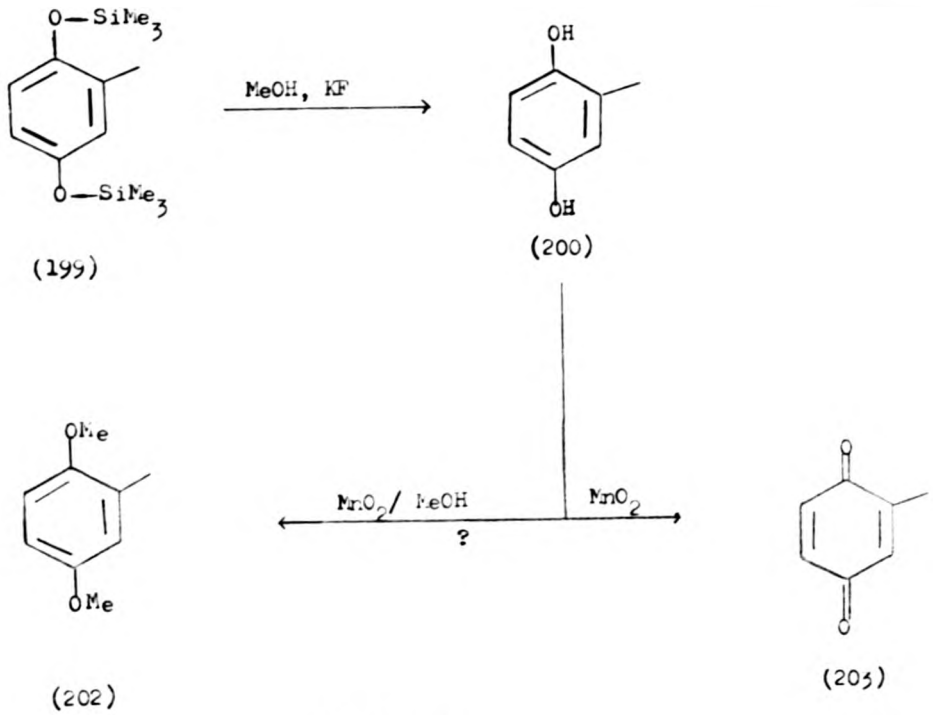
(203)



Scheme 81.

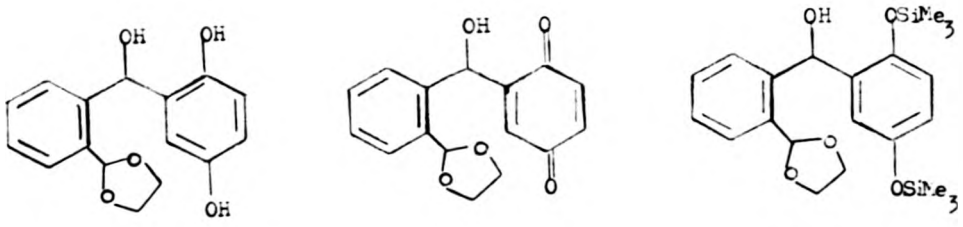
Similar desilylation using potassium fluoride in methanol in the presence of B.D.H. precipitated manganese dioxide gave a mixture: the mass spectrum of which showed fragments at m/z 152 [probably due to 2,5-dimethoxytoluene (202)], m/z 122 [probably due to methyl-1,4-benzoquinone (203)], and m/z 124 [probably due to dihydroxytoluene (200)]. The presence of (202) could be due to oxidative attack of methanol on the hydroxytoluene (200) which was formed in the reaction; oxidation of (200) would give (203) (Scheme 82).

As mentioned in Section 3.1, however, desilylation of (140) using potassium fluoride in methanol gave the required hydroquinone (117), but the reaction was not reproducible, and therefore a direct conversion of silane (140) to the quinone (112) was required. Hence, a direct method for conversion of silane (199) into quinone (203) was then sought, as a model for preparation of quinone (112) from silane (140).

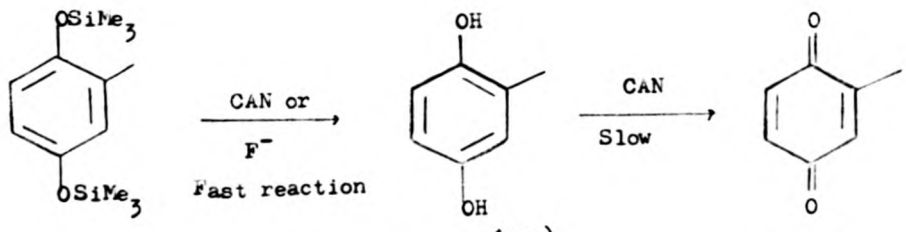


(199) (200) (202) (203)

Scheme 62.



(117) (112) (140)



(199) (200) (203)

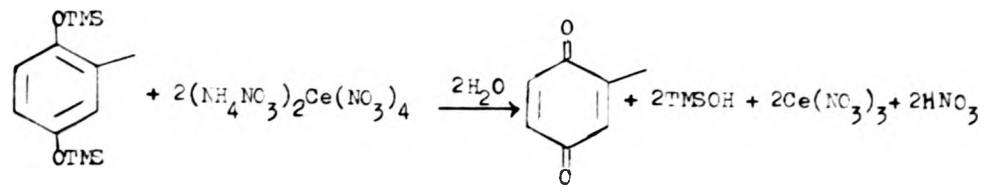
Scheme 63.

Thus compound (199) was treated with 5 mol of CAN in aqueous acetonitrile at room temperature for 2 h., giving the required quinone (203) in 74% yield. However these conditions were too acidic for use with the dioxolanyl-silane (140), and therefore two-phase dichloromethane-water systems were then tried. This latter procedure gave quinone (203) from silane (199), again in 74% yield, but it did not give quinone (112) from silane (140) in a pure state.

Interestingly, desilylation of (199) using 2 mol of CAN in dichloromethane-water (instead of 5 mol of CAN) gave a mixture of silane (199), hydroquinone (202), and quinone (203) in the ratio 3:3:1 respectively. A similar reaction in aqueous acetonitrile, using 2 mol of CAN, in the presence of Fuller's earth (as a proton trap) gave the same mixture, but in the ratio 2:3:1, respectively; the ratio changed to 4:3:1 when 4 mol of CAN was used. On the other hand, reaction in the presence of 2 mol of sodium acetate gave a mixture of hydroquinone (202) and quinone (203) in the ratio 1:1, respectively. As expected, reaction in the presence of an excess of sodium acetate gave only starting material (199). It thus seems that the desilylation of compound (199) with CAN requires acidic conditions.

Desilylation was then tried by the use of potassium fluoride followed by CAN. In this reaction, the quinone (203) was isolated in 65% yield. It seems that formation of quinone (203) from silane (199) in the presence of CAN follows the route shown in Scheme 83.

Our interest was then to reduce the acidity of the reaction conditions, resulting from nitric acid produced from CAN according to the following equation.

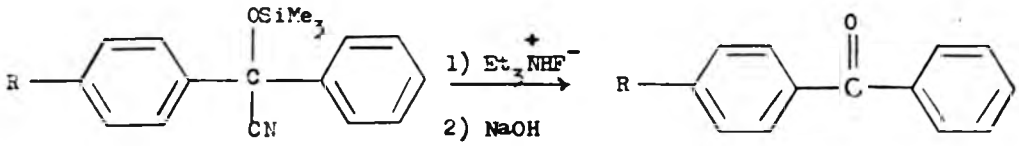


Therefore a solution of silane (199) in methanol was treated with potassium fluoride, and, after 5 min., Fuller's earth was added followed by portionwise addition of CAN in aqueous acetonitrile. In this way, the reaction gave quinone (203) in 75% yield. The advantage of using Fuller's earth is that it absorbs nitric acid without otherwise interfering with the reaction.

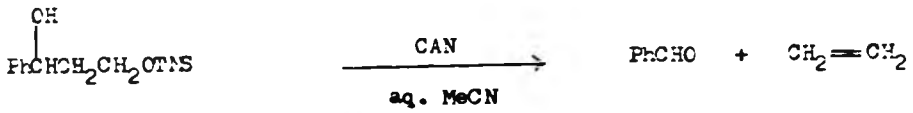
However, as mentioned in Section 3.1, this latter procedure still failed to give the desired quinone (112) from silane (140) in a pure state: in all cases, some decomposition of acetal group in quinone (140) was observed.

It is worth noting here that the desilylation of silane (199) as discussed in this Section; provides an alternative route to 1,4-benzoquinones, provided that they are stable to acidic media. To the best of our knowledge, the direct preparation of 1,4-benzoquinones from hydroquinone bis-silyl ethers by the use of CAN has not been reported in the literature.

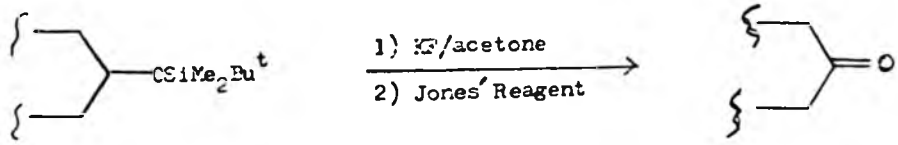
In this connection Miller et al.,[7b] reported that pyridinium dichromate oxidised bis(trimethylsilyl) ethers in dichloromethane to the corresponding 1,4-benzoquinones in 60-90% yield. Similarly, removal of silyl groups followed by elimination was reported[10] to give ketones (eq. 5), and desilylation followed by fragmentation was reported[11] to give aldehydes (eq.6). A direct conversion of silyl ethers into carbonyl compounds by Jones' reagent was also reported[12] in literature. (eq.7).


OSiMe3
R
C
CN
1) Et3NHF−
2) NaOH
O
R
C

(eq.5)


OH
PhCHCH2CH2OTMS
CAN
aq. MeCN
PhCHO + CH2=CH2

(eq.6)


CSiMe2But
1) KF/acetone
2) Jones' Reagent
O

(eq.7)

4.3 References for Chapter 4.

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Chapter 5.

Attempted Synthesis of 4a,5,8,8a-Tetrahydro-4a-(2-carboxybenzoyl)-5-methyl-1,4-naphthoquinone.

5.1. Attempted Synthesis of 2'-(tert-Butoxycarbonyl)-2,5-dimethoxybenzophenone.

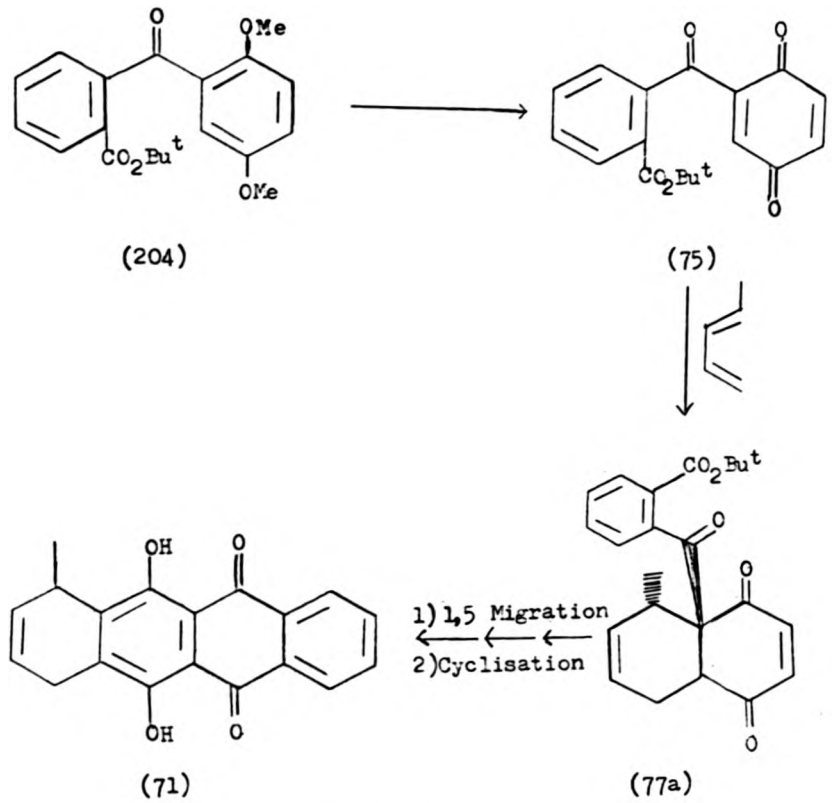
As mentioned in Section 1.2, it was of interest to synthesise the adduct (77a) in which [1,5] aroyl migration followed by cyclisation could lead to tetracyclic compound (71). The cyclisation of carboxylic acids or ester groups to give anthraquinones and eventually anthracyclinones has previously been reported by many workers.[1a-b] The desired adduct (77a) could in principle be prepared from quinone (75), by addition of trans-penta-1,3-diene. Based on the general procedure, the quinone (75) might be synthesised from the benzophenone (204) (Scheme 84). This compound was unknown, and had to be synthesised. Clearly, the starting material required for the synthesis of (204) was the acid chloride (79) or the carboxylic acid (96); both (79) and (96) were known (see Section 2.1)

It was reported[1] that reaction of acid chlorides with lithium tert-butoxide (prepared *in situ* by the reaction of n-butyl-lithium with tert-butyl alcohol) gave tert-butyl esters in good yield, as follows.

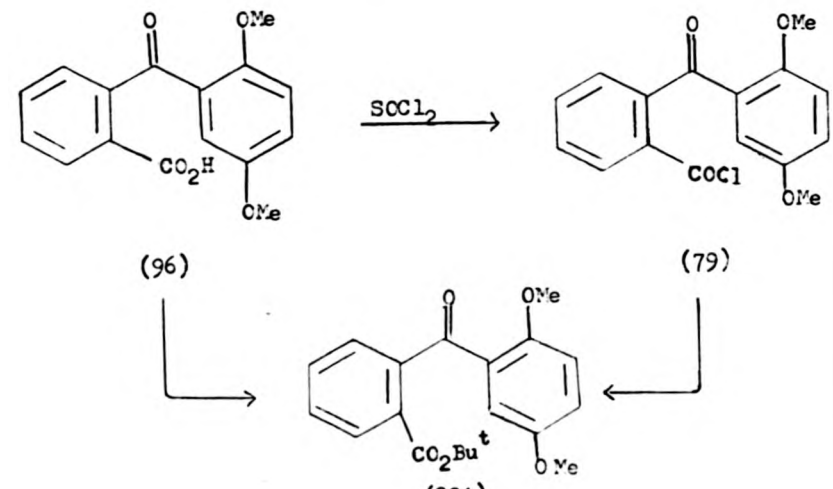
$$tBuOH \xrightarrow{n\text{-}BuLi} tBuOLi + nC_4H_{10}$$

$$R\text{-}COCl + tBuOLi \longrightarrow R\text{-}CO_2Bu^t + LiCl.$$

Therefore, freshly prepared acid chloride (96) was treated with lithium tert-butoxide at room temperature. However, this procedure probably gave the n-butyl ester (205) since the p.m.r. spectrum of the product in d-chloroform showed a broad multiplet at δ 0.60-1.60 due to an n-propyl group, singlets at 3.44 and 3.78 due to methoxy groups,



Scheme 84.



Scheme 85.

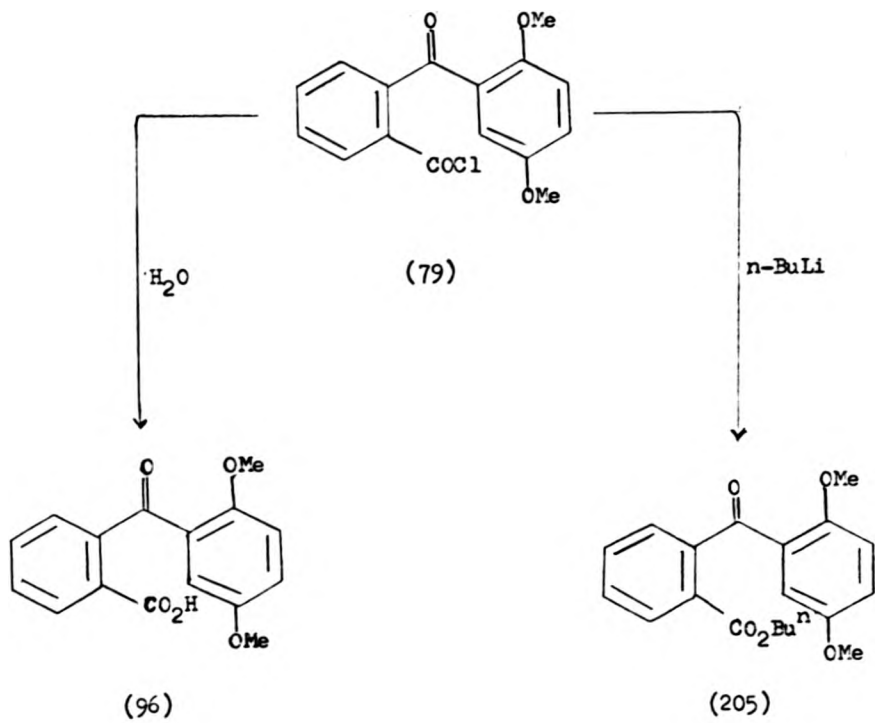
and a triplet J 6, at 4.05 due to an OCH_2 group, together with signals due to the acid (96). The presence of ester (205) was supported by its mass spectrum, which showed molecular ions at m/z 342 ($M^{\cdot+}$) and 286 ($M - C_4H_8$).

Formation of ester (205) could be due to the attack of n-butyllithium on acid chloride (79); on the other hand, formation of acid (96) could be due to hydrolysis of unreacted acid chloride (79) (Scheme 66).

Freshly prepared acid chloride (79) was then treated with an excess of neat tert-butyl alcohol, since this procedure was reported to give tert-butyl esters in reasonable yield.[2] After refluxing for 21 h., the excess of alcohol was removed, leaving a yellowish oil which solidified at room temperature. Its p.m.r. spectrum suggested that the product may have contained some of the desired ester (204) (singlets at δ 1.25, 3.42, and 3.75 due to a tert-butyl group and two methoxy groups, respectively), together with, probably, lactone (97). Its mass spectrum showed the required molecular ion at m/z 342.

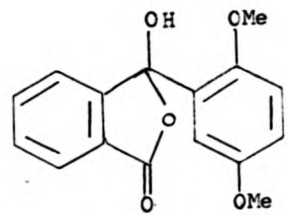
The normal way of preparing tert-butyl esters would be by treatment of an acid chloride with tert-butyl alcohol in the presence of a base.[3] Thus, acid chloride (79) was reacted with tert-butyl alcohol in pyridine at room temperature. Following dilute acid work-up, only the carboxylic acid (96) was obtained. This suggested that acid chloride (79) may or may not have reacted with tert-butyl alcohol; possibly the required ester (204) was hydrolysed during work-up.

Reaction of acid chloride (79) with tert-butyl alcohol in the presence of potassium tert-butoxide at room temperature was then tried, since this method was also reported[4] to give tert-butyl esters. However, this method, gave the same result as the reaction of the acid chloride (79)



(96) (205)

Scheme 86.



(97)

with tert-butyl alcohol alone. Repeating the reaction at refluxing temperature, however, gave a yellowish oil, which may have contained the desired ester (204). Its p.m.r. spectrum in d-chloroform showed a singlet at δ1.33 due to a tert-butyl group, singlets at 3.46 and 3.80 due to two methoxy groups, with the rest of the proton resonances in the aromatic region. Its mass spectrum showed the molecular ion 342 (100, $M^{\cdot+}$). Attempts to improve the yield by the use of 18-crown-6 were unsuccessful. The only product isolated was the carboxylic acid (96).

It is known that treatment of carboxylic acids with tert-butyl alcohol containing dicyclonexyl carbodi-imide and 4-dimethylaminopyridine gives tert-butyl esters in good yield. However, reaction of carboxylic acid (96) with this reagent system gave a mixture: the p.m.r. spectrum of which in d-chloroform was complex, and did not show evidence for the desired ester (204).

The fact that it was difficult to prepare ester (204), either from the acid chloride (79) or the carboxylic acid (96) may be due to steric hindrance; it was previously found (Section 2.1) that it was difficult to reduce acid chloride (79) to the corresponding aldehyde.

5.2. Attempted Syntneeis of 2'-Carboxy-1,4-benzoquinone.

Since several attempts to syntnesis tert-butyl ester (204) were unsuccessful, a direct route to quinone (76) from the carboxylic acid (96) was tnen tried.

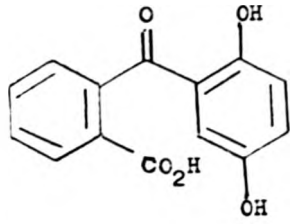
Carboxylic acid (96) was initially treated with CAN in aqueous acetonitrile at room temperature for 1 h., giving an orange oil whose p.m.r. spectrum in d-cnloroform showed a singlet at δ6.66 with the rest of the signals being multiplets in the aromatic region. Its mass spectrum snowed m/z 256, which suggested that the product may have contained hydroquinone (206). A similar reaction in a two phase dichlorometnane-water system gave starting material (96).

Reaction of (96) with trimethylsilyl chloride-sodium iodide[6] in acetonitrile again gave starting material, altnough this reagent was found to give hydroquinone (207) from the corresponding ether (208).[8]

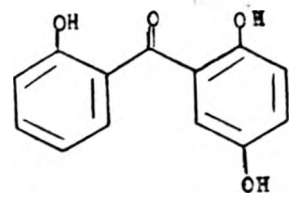
Treatment of carboxylic acid (96) with hydrobromic acid was then carried out. The product obtained was quinizarin (34) in 92% yield. Formation of quinizarin (34) could proceed by internal Friedel-Crafts acylation followed by demethylation, or by demetnylation followed by cyclisation as snown in Scheme 66a.

Finally, carboxylic acid (96) was treated with argentic oxide-pyridine-2,6-dicarboxylic acid,[7] giving an orange liquid, the p.m.r. spectrum of which in d-chloroform showed only multiplets in the aromatic region and a singlet at δ6.70. The 300 MHz p.m.r. spectrum of freshly prepared material measured immediately showed extensive decomposition. It seems tnat tne desired quinone (76) is probably unstable at room temperature.

To date, we have been unable to obtain either quinone (75) or (76). Therefore Scheme 64 has not been examined.



(206)



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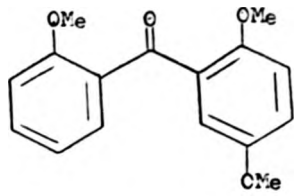
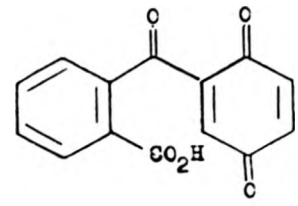
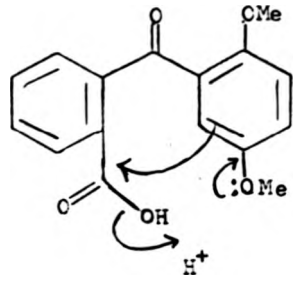


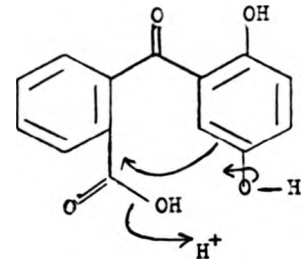
(208)



(76)

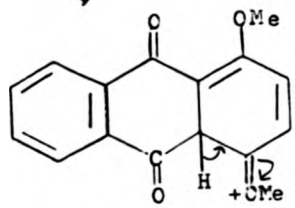


Demethylation

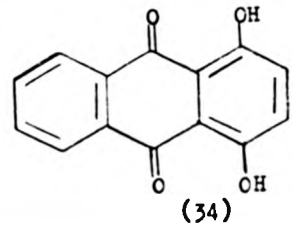


(96)

Cyclisation

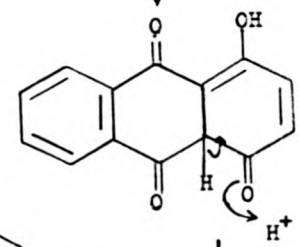


Demethylation



(34)

Cyclisation



Scheme 86 a.

5.3. References for Chapter 5.

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Chapter 6.

Experimental.

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Materials and Methods

Melting points (m.p.) were recorded on a Kofler block and are uncorrected. Temperatures are throughout in °C.

Infrared spectra (i.r.) were recorded on either Perkin-Elmer FT-IR 1710 or Pye Unicam SP3-200 spectrophotometers as Nujol mulls, liquid films, or solutions as stated. Absorption positions are quoted in cm^{-1}. Intensities are expressed by s, m, w, and sh to indicated strong, medium, weak, and shoulder respectively; a prefix b indicates broadening of the signal.

Proton magnetic resonance spectra (p.m.r.) were measured on a Perkin-Elmer R12B instrument at 60 MHz, a Brüker WP80 instrument at 80 MHz, a Perkin-Elmer R32 instrument at 90 MHz, a Perkin-Elmer R34 instrument at 220 MHz, and a Varian SC300 instrument at 300 MHz as stated. Multiplicities of peaks are denoted by s, d, t, q, dd, dt, dq, and m indicating singlet, doublet, triplet, quartet, double doublet, double triplet, double quartet, and multiplet respectively; a prefix b indicates broadening of the signal. Coupling costants (J) are in Hz. Resonances assigned to hydroxyl groups were removed by addition of D_2O.

Mass spectra (m.s.) were recorded on a Kratos MS30 instrument coupled to a DS55 data system for low resolution electron impact (EI) work and accurate mass measurements, and on a Kratos MS25 instrument coupled to a DS55 data system for EI and chemical ionization (CI;NH_3) work. The relative abundances (% of base peak) of fragments are quoted in parentheses after m/z values.

Microanalyses were carried out by the departmental staff.

Thin layer chromatography (t.l.c.) was carried out on silica gel [MFC 75-100 nm (100-200)] coated plates. Visualization was achieved by ultraviolet fluorescence at 254 or 297 nm.

Column chromatography was carried out using silica gel MFC 60-120 mesh or Woelm polyamide.

Evaporation of organic solvents was carried out under reduced pressure using a Büchi rotary evaporator.

Sublimations were carried out using Büchi ovens.

Reaction solvents[1]

Diethyl ether was dried by standing over lithium aluminium hydride for 24 h., and then distilling from fresh litnium aluminium hydride.

Tetranydrofuran (THF) was dried by standing over potassium hydroxide pellets for 24 h., and then refluxing and distilling from sodium wire in the presence of benzophenone under a nitrogen atmosphere.

Dichloromethane was dried by standing over calcium hydride for 24 h., and then refluxing and distilling from fresh calcium hydride.

Benzene was dried by azeotropic distillation and then kept over 4A molecular sieves.

Toluene was dried by standing over calcium hydride for 24 h., and then refluxing and distilling from sodium.

Acetonitrile and methanol were dried by shaking with 4A molecular sieves and then refluxing and distilling from calcium hydride.

Pyridine was dried by refluxing with potassium hydroxide followed by fractional distillation.

Acetone was dried by standing over 4A molecular sieves.

Cyclohexane, hexane, pentane, and light petroleum (30–40°, 40–60°, and 60–80°) were distilled prior to use. Acetic anhydride was also distilled before use.

Reaction temperatures of -70° were obtained by use of a dry ice–methanol cooling bath; temperatures between 0° and 10° were obtained by use of ice–water cooling baths; and elevated temperatures were obtained by use of sand, steam, or oil baths.

Methyl Hydrogen Phthalate.

Phthalic anhydride (Note 1) (25.73 g, 0.66 mole) and dry methanol (16 ml) were refluxed for 2 h. The excess of methanol was distilled off, finally azeotropically with dry benzene (2 x 12 ml) to ensure complete removal of unreacted methanol whose presence impeded crystallisation of the product. The residue was diluted with a mixture of benzene (60 ml) and hexane (60 ml), at which point crystallisation commenced. After standing overnight in the refrigerator, methyl hydrogen phthalate was collected, washed with hexane, and dried, giving a white crystalline solid (25.3 g, 61%), m.p. 81-82° (lit.,[2] m.p. 81-82°). It had δ (60 MHz, $CDCl_3$), 3.90 (s, Me), 7.24-8.12 (m, ArH_4), 11.06 (s, OH).

Note 1. Phthalic anhydride (m.p. 131.5°) was purified by extracting with cold chloroform, filtering from phthalic acid, and evaporating the chloroform.

Methyl 2-Chloroformylbenzoate.

A mixture of methyl hydrogen phthalate (13.6 g, 0.076 mole) and freshly distilled thionyl chloride (40 ml) was refluxed for exactly[3] one hour using an oil-bath at 100°. The excess of thionyl chloride was removed, finally under reduced pressure, azeotropically with freshly distilled toluene (3 x 15 ml) to leave the desired product as colourless liquid (15.0 g, 99%). It had δ (60 MHz, $CDCl_3$) 3.93 (s, Me), 7.52-8.07 (m, ArH_4).

2'-Methoxycarbonyl-2,5-dimethoxybenzophenone.

(a) From Methyl 2-Chloroformylbenzoate.

Freshly prepared methyl 2-chloroformylbenzoate (15.0 g, 0.076 mole)

in dichloromethane (30 ml) was added to a stirred mixture of 1,4-dimethoxybenzene (10.4 g, 0.075 mole) and anhydrous granulated aluminium chloride (20.1 g, 0.15 mole) in dry methylene chloride (140 ml) at 0° during the course of $\frac{3}{4}$ h. The red-brown mixture was stirred at 0° for an additional of 3 h. and then at room temperature overnight. The mixture was then treated dropwise with cold 5% hydrochloric acid (100 ml), and the organic layer separated. The aqueous layer was extracted with dichloromethane (2 x 15 ml) and the combined extracts were washed with saturated aqueous sodium hydrogen carbonate (4 x 40 ml), water (3 x 40 ml) and dried (Na_2SO_4). Evaporation of the solvent gave a yellow solid (20.0 g). Its p.m.r. spectrum in d-chloroform showed the desired product together with some unreacted 2,5-dimethoxybenzene. The product was purified by washing with cold ether to remove 1,4-dimethoxybenzene, leaving pale yellow crystals (15.0 g, 56%), m.p. 62-63° (lit.,[2] 63-65°). It had δ(60 MHz, $CDCl_3$) 3.46 (s, OMe), 3.65 (s, CO_2Me), 3.80 (s, OMe), 6.76-6.80 (m, ArH_3), and m/z 300(100, $M^{\cdot+}$), 269 [10, $(M-OMe)^+$], 165 { 92, [$(OMe)_2C_6H_3CO$]$^+$ }, 163 { 100, [$(CO_2Me)C_4H_4CO$]$^+$ }.

(b) From 2'-Chlorocarbonyl-2,5-dimethoxybenzophenone. (p. 186)

Freshly prepared 2'-chlorocarbonyl-2-5-dimethoxybenzophenone (33 mg, 0.11 mmole) was refluxed in dry methanol (5 ml) for 17 h. Removal of the solvent gave the desired ester as a pale yellow oil (32.0 mg, 99%) which solidified on standing overnight at room temperature. Sublimation at 110-114°/ 0.05 mmHg followed by washing with cold ether gave the pure product as a white solid. It was identical (m.p. mixture m.p., and p.m.r.) with the authentic ester prepared as described under (a).

Some Reductions of 2'-Metnoxycarbonyl-2,5-dimethoxybenzophenone.

(a) Using DIBAL-H .

To a solution of the ester (45 mg, 0.15 mmole) in toluene (10 ml) at -70° under a nitrogen atmosphere was added 1.0 M DIBAL-H in hexane (0.3 ml, 42.6 mg, 0.3 mmole). After stirring the mixture at the above temperature for an additional 2 h., saturated sodium hydrogen sulfite (5 ml) was added and the mixture was warmed up to room temperature. The organic layer was separated, and extracted with saturated sodium hydrogen sulfite (3 x 10 ml). The combined aqueous layers were basified with 10% sodium hydroxide to pH ~8-9 (with cooling). The product was extracted with ether (4 x 15 ml), and the extracts were washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave a yellowish oil (15 mg). Its p.m.r. spectrum in d-chloroform showed multiple signals in the methoxy and aromatic regions; no signal due to the formyl group was observed.

Note:

A similar reaction initially at -70° for 2 h., then at room temperature overnight, gave the same result.

(b) Using $LiAlH_4$ at -70°.

To a stirred solution of $LiAlH_4$ (7.6 mg, 0.2 mmole) in THF (5 ml) at -70° under a nitrogen atmosphere was added the ester (60 mg, 0.2 mmole) in THF (5 ml) all at once. After stirring at the above temperature for an additional 2 h., the mixture was poured into ice-water (15 ml). The product was extracted with ether (4 x 10 ml), and the extracts were washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave a white oil (57 mg). Its p.m.r. spectrum in d-chloroform showed singlets at δ 3.67, 3.69, 3.70 and 3.83 due

to four methoxy groups, and multiplets at δ 6.20–6.20 due to aromatic protons. No signal due to a formyl group was observed. Its mass spectrum showed molecular ions at m/z 274(12) and 272(38) with fragments at 270(100), 256(15), 255(26), 254(14), 241(24), 240(53), 225(58), 211(26), 165(37), suggesting that the product may have contained α (2-hydroxymethyl) phenyl-2,5-dimethoxybenzyl alcohol (m/z 274), and 2'-hydroxymethyl-2,5-dimethoxybenzophenone (m/z 272).

(c) Using $LiAlH_4$ at room temperature: Preparation of α -(2-Hydroxymethyl-phenyl)-2,5-dimethoxybenzyl Alcohol.

To a stirred mixture of $LiAlH_4$ (760 mg, 20 mmole) in ether (60 ml) and THF (15 ml) at room temperature was added a solution of 2'-methoxycarbonyl-2,5-dimethoxybenzophenone (1.06 g, 3.6 mmole) in ether (60 ml) over a period of ½ h. After stirring for an additional 3 h., the excess of $LiAlH_4$ was destroyed by addition dropwise of ice-cold water (20 ml) followed after 1 h. by addition of 5% sulfuric acid (30 ml) until it gave a colourless solution. The ether layer was then separated and the aqueous layer extracted with ether (4 x 15 ml). The combined ether solution were washed with water (3 x 20 ml) and dried (Na_2SO_4). Removal of the solvent gave a white solid (915 mg, 93%), m.p. 79–83°. The required benzyl alcohol was purified by recrystallisation from 1:1 hexane-toluene. It then had m.p. 80–82° (Found: C, 69.6; H, 6.9. $C_{6}H_{12}O_4$ requires C, 70.1; H, 6.6%). It had δ (200 MHz, $CDCl_3$) 2.90–4.00 (b , 2 x OH), 3.75 (s, 2 x OMe), 4.65 and 4.76 (d and d, each J 12.5, CH_2), 6.30 (s, CH), 6.85 (s, ArH_3), 7.10–7.53 (m, ArH_4); m/z 274 (20, $M^{\cdot+}$), 225 [100, $(M - CO\text{-}OMe)^+$] ; and ν_{max} (Nujol) 3100–3400s cm^{-1}.

2'-Formyl-2,5-dimethoxybenzophenone.

(a) From Oxidation of α-(2-Hydroxymethylphenyl)-2,5-dimethoxybenzyl alcohol.

(1) Using aqueous CAN.

A solution of α-(2-hydroxymethylphenyl)-2,5-dimethoxybenzyl alcohol (27.4 mg, 0.1 mmole) in acetonitrile (2 ml) and water (1 ml) was treated with solid CAN (219 mg, 0.4 mmole) and the resulting yellow solution was stirred at room temperature for 4 h. The product was then extracted with dichloromethane (4 x 15 ml), and the combined extracts were washed with saturated sodium hydrogen carbonate (2 x 10 ml), brine (2 x 10 ml), water (2 x 10 ml), and dried ($MgSO_4$). Removal of the solvent gave a brownish oil (11.0 mg). It had δ (60 MHz, $CDCl_3$) 4.85 (bs, 1H), 5.47 (bs, < 1H), 6.07 (bs, 1H), 6.72 (s, 1H), 6.97 (m, 1H), 7.30 (bs, ArH_4), 7.50-8.00 (bs, 1H), 10.12 (s, < 1H); and m/z 242(2), 228(10), 226(34), 208(8), 197(75), 144(43), 119(100), 105(28), 91(96). The product was not further examined.

(2) Using aqueous CAN in the present of Sodium Bromate.

To a suspension of sodium bromate (66.4 mg, $NaBrO_3$, 10 mmole) in 3:7 aqueous acetonitrile (5 ml) was added α-(2-hydroxymethylphenyl)-2,5-dimetnoxybenzyl alcohol (30.0 mg, 0.11 mmole) and CAN (24 mg, 0.04 mmole). The reaction mixture was then refluxed for 46 h. The resulting yellow suspension was diluted with etner (20 ml), and the organic layer was separated, washed with saturated sodium hydrogen carbonate (2 x 5 ml), brine (2 x 5 ml), and dried (Na_2SO_4). Removal of the solvent gave a yellowish oil (20.5 mg). Its p.m.r. spectrum in d-chloroform showed only two sets of protons: a singlet at δ 5.34, and multiplets at δ 7.40-8.20 in the intensity ratio 1:3; no signal due to a formyl group was

observed. It had m/z 334(4), 303(4), 256(43), 241(9), 225(50), 165(16), 134(31), 119(81), 105(100), 91(65), 77(56).

Note:

A similar reaction, after being refluxing overnight, gave a mixture which may have contained 2-formyl-2,5-dimethoxybenzophenone (singlet at δ 10.10 for formyl H). The product isolated from this reaction was too complex to be identified, but showed a molecular ion at 496(3) with fragments at 462(2), 451(4), 334(4), 303(9), 270(1), 256(10), 119(100), 116(56), 91(87).

(3) Using Trimethylchlorosilane-Chromium Trioxide.

(i) Oxidation at -20° to -30°.

A mixture of chromium trioxide (30.0 mg, 0.30 mmole) and trimethylchlorosilane (0.045 ml, 0.35 mmole) was stirred at room temperature to form an homogeneous orange-red solution which was diluted with dichloromethane (3 ml). The solution was then cooled to -20° to -30° (methanol-CO_2). To this solution was added α-(2-hydroxymethylphenyl-2,5-dimethoxybenzyl alcohol (41.0 mg, 0.15 mmole) and the resulting dark brown mixture was stirred at above temperature for about 3.5 h. Moist silica gel was then added to give a paste, and the mixture was chromatographed through silica gel using dichloromethane as eluent to give three fractions.

The first fraction was a pale yellow oil (10.0 mg). Its p.m.r. spectrum in d-chloroform showed singlets at δ 3.40, 3.48, 3.66, 3.72, 3.80, and 3.89 probably due to six methoxy groups; a broad singlet at δ 5.28 possibly due to a methylene group; multiplets at δ 6.20-6.40 due to aromatic protons, and a singlet at δ 10.18 assigned to a formyl

group. Thus this product may have contained the desired aldehyde (i.e. δ 3.46 and 3.60 due to two methoxy groups and δ 10.16 due to the formyl group)* and 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone (δ 3.66 and 3.84 due to two methoxy groups)* in the ratio about 1:3 together with other compounds as suggested by the broad singlet at δ 5.28. Its mass spectrum showed m/z 286(12), 272(<1), 270(14), 256(97), 255(35), 241(4), 239(14), 227(43), 225(100), 211(17), 210(13), 209(15), 165(60), 119(56).

The second fraction was a pale yellow oil (3.4 mg). Its p.m.r. spectrum in d-chloroform showed singlets at δ 3.46 and 3.80 due to two methoxy groups; a multiplet at δ 6.50-6.40 due to seven aromatic protons, and a singlet at δ 10.16 due to a formyl group, suggesting that it may be the desired aldehyde. It had m/z 286(<1), 270(41), 255(11), 242(11), 240(16), 239(100), 225(11), 211(24), 186(20), 165(21).

The third fraction was a pale yellow oil (5.0 mg). Its p.m.r. spectrum in d-chloroform showed broad multiplets in the methoxy and aromatic regions, and no signal due to a formyl group. This fraction was not further investigated.

(ii) Oxidation at 0°.

The above oxidation was repeated but the reaction temperature was controlled at 0° (ice-salt bath) for 3 h. and the mixture then worked up as in (i) to give the following results.

The first fraction was a colourless oil (14 mg). Its p.m.r. spectrum in d-chloroform showed singlets at δ 3.46, 3.62, 3.78, and 3.82 due to four methoxy groups; multiplets at δ 6.60-6.30 due to

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* All aromatic protons were at δ 6.20 - 6.40.

aromatic protons, and singlets at δ 10.20 and 10.52 due to two formyl groups. It is suggested that the product probably contained the desired aldehyde (δ at 3.46 and 3.78 due to two methoxy groups and δ 10.20 due to the formyl group)*, together with 3,4 or 6-chloro-2'-formyl-2,5-dimethoxybenzophenone (δ at 3.62 and 3.82 due to two methoxy groups, and singlet at δ 10.52 due to formyl group)* in the ratio about 3:1. This product had m/z 306(1), 304(3), 291(1), 289(2), 270(28), 256(11), 255(11), 240(19), 239(100), 225(14), 211(23), 196(7), 165(17). The peaks at 306 and 304 suggested the presence of 2,4 or 6-chloro-2'-formyl-2,5-dimethoxybenzophenone.

The second fraction was as a pale yellow oil (3.9 mg). Its p.m.r. spectrum in d-chloroform showed two broad multiplets in the methoxy and aromatic regions. No signal due to a formyl group was observed. This product was not further examined.

(iii) Oxidation at Room Temperature.

The above oxidation was again repeated but the mixture was left stirring at room temperature for 4 h. The total product was separated on a silica gel column using dichloromethane as eluent to give a yellowish oil (16.4 mg). Its p.m.r. spectrum in d-chloroform was similar to that of the product in the first fraction of the oxidation at 0°. Its mass spectrum also showed m/z 306(3), 304(10), 291(2), 289(5), 275(9), 273(23), 201(<1) and 199(5), suggesting the presence of 2,4 or 6-chloro-2'-formyl-2,5-dimethoxybenzophenone together with the desired aldehyde; [i.e. m/z at 270(38), 239(100), 211(26), 165(16)].

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* All aromatic protons were at δ 6.60-8.30.

The product isolated from this oxidation was then distilled (bulb-to-bulb at 114-120°/0.05 mmHg) to give a pale yellow oil. Its p.m.r. spectrum in d-chloroform showed that it was unchanged except that the singlet at δ 10.52 was absent. However its mass spectrum remained similar to that of the undistilled product.

This product was not further examined.

(4) Using Chromium Trioxide-Pyridine.

Chromium trioxide was stored in a vacuum desiccator over phosphorus pentoxide prior to use.

Chromium trioxide (120 mg, 1.2 mmole) was added to a magnetically stirred solution of pyridine (190 mg, 2.4 mmole) in dry dichloromethane (4 ml) and the deep burgundy solution was stirred for 15 min. at room temperature. At the end of this period a solution of the diol (27.4 mg, 0.1 mmole) in dichloromethane (1.0 ml) was added in one portion: tarry black deposit separated immediately. After stirring for an additional hour, ether (5 ml) was added and the precipitate was filtered off. The filtrate was washed with aqueous 10% sodium chloride (2 x 5 ml), water (2 x 5 ml) and dried ($MgSO_4$). Removal of the solvent gave a pale yellow oil (19 mg). Its p.m.r. spectrum in d-chloroform showed four singlets at δ 3.67, 3.61, 3.66, and 3.50, in the ratio 1:1:1:1 (due to four methoxy groups); multiplets at δ 6.60-6.20 (due to about fourteen aromatic protons and one methine proton), and a singlet at δ 10.18 (probably may due to one formyl group). The spectrum suggested that the product may have contained the desired aldehyde together with 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone in the ratio 1:1. Its mass spectrum showed m/z 287(36), 286(61), and fragments at 277(65), 270(100), 269(47), 255(32), 240(22), 239(74), 212(21), 211(67), 210(12), 183(26), 165(67), 139(37).

Note:

Similar reaction conditions gave 2,5-dimethoxybenzophenone in 72% yield from α-phenyl-2,5-dimethoxybenzyl alcohol.

Attempts to optimise formation of the aldehyde.

Several experiments were tried in attempts to optimise the yield of the aldehyde in the above oxidation reaction. Its progress was monitored by removal of small samples of the reaction mixture at intervals of ½ h., 1 h., 2 h., 3 h., and overnight. Each sample was worked up as described above, and its p.m.r. spectrum was recorded. However, all samples gave the same p.m.r. spectrum as that described in previous experiment. After 1 h., the product contained slightly more desired aldehyde (δ at 3.50, 3.80 due to two methoxy groups, and δ at 10.10 due to the formyl group)* than 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone (δ at 3.66 and 3.88 due to two methoxy groups)*; ratio 10:9 respectively.

Similar results were obtained when the reaction was performed at - 5 to 5°. Oxidation using more oxidant (24 mol), at room temperature for $\frac{3}{4}$ h. gave a more complicated mixture, its p.m.r. spectrum in d-chloroform showing six methoxy groups at δ 3.56, 3.48, 3.65, 3.76, 3.78, and 3.85.

Attempts to Isolate the Aldehyde.

(a) The room temperature oxidation was again repeated, and the total product isolated (19 mg) was separated using a silica gel column and 1:1 ether-hexane as eluent. The first fraction was a pale yellow oil (10.5 mg). Its p.m.r. spectrum in d-chloroform still showed the presence of a mixture, which contained more

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* All aromatic protons were at δ 6.80-8.20.

1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone then the desired aldehyde (ratio 5:1). Its mass spectrum showed molecular ions at 266 and 270.

The second fraction was a pale yellow oil (2.1 mg) which had m/z 266 and 270.

(b) The oxidation was again repeated. The total product (20 mg) was dissolved in ether (5 ml) and washed with aqueous 10% sodium hydrogen sulfite (3 x 5 ml). The aqueous layer was neutralised with aqueous 10% sodium hydrogen carbonate, extracted with ether, and the extract was washed with water and dried (Na_2SO_4). Removal of the solvent gave a pale yellow oil (6.2 mg), the p.m.r. spectrum of which in d-chloroform showed it to be mainly 1,3-dihydro-3-(2,5-dimetnoxyphenyl)isobenzofuranone.

Removal of the solvent from the first ether solution gave a yellowish oil (6.6 mg), its p.m.r. spectrum in d-chloroform showing a mixture of 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone and the desired aldehyde.

Notes:

(a) Treatment of the mixtures of aldehyde and lactone with 2,4-dinitrophenylhydrazine reagent gave a red precipitate, mostly melting at 210 -214°, which had m/z 439(2), 438(2), 437(3), 270(6), 254(11), 239(11), 224(8), 167(19), 155(17).

(b) The ratio of 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone and the desired aldehyde was unchanged on treatment of the mixture with 10% hydrochloric acid and with 10% sodium hydroxide overnight at room temperature.

(c) After the above mixtures had stood at room temperature for 76 days their p.m.r. spectrum in d-chloroform no longer showed formyl peak.

(b) From Hydrolysis of 2'-(1,3-Dioxolan-2-yl)-2,5-dimethoxybenzophenone. (p. 229).

To a solution of 2'-(1,3-dioxolan-2-yl)-2,5-dimethoxybenzophenone (13 mg, 0.04 mmole) in ether (4 ml) was added 5% hydrochloric acid (4 ml) and the two phase system was shaken at room temperature for 3 h. The organic layer was then separated and washed with water (4 ml) and dried (Na_2SO_4). Removal of the solvent gave a pale yellow liquid (10 mg, 98%). Its p.m.r. spectrum in d-chloroform (60 MHz) showed it to be a mixture of the desired aldehyde (singlets at δ 3.45 and 3.76 due to too methoxy groups, and a singlet at 10.10 due to the formyl group) * and probably 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone (singlets at δ 3.65 and 3.83 due to two methoxy groups)* in the ratio of about 3:1 respectively.

Column chromatography, using silica gel with ether as the eluent; still gave a mixture, probably of these two compounds, but with further 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone formed during the process.

1,3-Dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone.

(a) From Hydrolysis of α-[2-(1,3-Dioxolan-2-yl)phenyl]-2,5-dimethoxybenzyl Alcohol. (p. 222).

A solution of the alcohol (31.6 mg, 0.1 mmole in THF (4 ml) and 15% hydrochloric acid (4 ml) was stirred at room temperature for 36 h. The mixture was then diluted with water (10 ml). The product was extracted with ether (3 x 10 ml), and the extracts were washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the

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* All aromatic protons gave multiplets at δ 6.50-8.00.

solvent gave a pale yellow liquid (25 mg, 93%) which was then distilled (bulb-to-bulb) at 84-90°/ 0.05 mmHg. (lit.,[4] m.p. 80°). (Found: $\underline{M}^{\cdot+}$, 270.0892. Calc. for $C_{16}H_{14}O_4$: $\underline{M}$, 270.0892). It had δ (220 MHz, $CDCl_3$), 3.67 (s, OMe), 3.68 (s, OMe), 6.64 (d, $\underline{J}$ 3, H-3), 6.84 (bs, H-4' + H-6'), 6.92 (d, $\underline{J}$ 7.5, H-3'), 7.40-7.70 (m, H-4 + H-5 + H-6), 7.94 (d, $\underline{J}$ 7, H-7); and $\underline{m/z}$ 270 (100, $\underline{M}^{\cdot+}$), 255 [17, $(\underline{M} - Me)^+$], 239 [84, $(\underline{M} - OMe)^+$], 211 [54, $(\underline{M} - OMe - CO)^+$], 165 [37, $(MeO)_2C_6H_3CO^+$], 105 (15, $PhCO^+$).

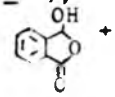
(b) From Oxidation of α-(2-Hydroxymethylphenyl)-2,5-dimethoxybenzyl alcohol.

To a stirred solution of the alcohol (31.6 mg, 0.1 mmole) in dichloromethane (5 ml) was added bis(2,2'-bipyridyl)copper(II) permanganate (446.5 mg, 0.1 mmole). The mixture was refluxed for 3 h., and the solid was then filtered with suction and washed with dichloromethane (3 x 10 ml). The filtrates were combined and evaporated to give the title compound (24 mg, 89%). It was identical (p.m.r. and m.s.) with the product isolated from the foregoing experiment.

2'-Hydroxycarbonyl-2,5-dimethoxybenzophenone.

(a) By Base Hydrolysis.

2'-Methoxycarbonyl-2,5-dimethoxybenzophenone (2.10 g, 7.0 mmole) in 10% sodium hydroxide (160 ml) was refluxed for 24 h. (Note 1). The yellow solution was then cooled to room temperature and acidified with 10% hydrochloric acid. The precipitate was then filtered, washed with water and dried to give the desired product as pale yellow crystals (1.98 g, 99%). It was purified by crystallisation from toluene or water, or by sublimation at 140-146° /0.05 mmHg to give the pure product as a pale yellow solid, m.p. 159-161° (Found: C, 66.8; H, 4.9. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9 %). It had δ (300 MHz, $CDCl_3$)

3.56 (bs, OMe), 3.72 (s, OMe), 6.86 (d, J 9, H-3), 6.96 (d, J 9, H-4) 7.42 (bs, H-6), 7.56 (dd, J_1 7.5, J_2 7.5, H-5'), 7.64 (dd, J_1 7.5, J_2 7.5, H-4'), 7.96 (d, J 7.5, H-6') (Note 2); m/z 287 (15, $M^{\cdot+}$ + 1), 286 (81, $M^{\cdot+}$), 211 [47, $(M - CO_2 - OMe)^+$], 165 {100, $[(OMe)_2C_6H_3CO]^+$}, 149 (66, ), 122 (19, $PhCO_2H$); and ν_{max} (Nujol) 1720s cm^{-1}.

Note 1. A similar reaction, refluxed for 3 h. and worked up as in the above procedure, gave mainly starting material together with a little of the desired acid.

Note 2. The protons H-3' and OH of the acid were not assigned. Addition of D_2O gave a 300 MHz p.m.r. spectrum which showed a mixture of the title compounds (singlets at δ 3.44 and 3.80 due to two methoxy groups) in the ratio 3:2, respectively. The aromatic protons resonance were too complex for identification.

Its 75 MHz ^{13}C spectrum showed 15 lines, instead of the expected 16 lines. It showed sharp lines at 55.76, 56.40, 113.92, 114.59, 127.02, 127.60 and 153.35, and broader lines at 121.13, 126.57, 129.0, 129.8, 132.6, 145.0, 170.5 and 195.6. The presence of broad lines suggested that there is a mobile equilibrium between the desired acid and 1,3-dihydro-3-hydroxy-3-(2,5-dimethoxyphenyl)isobenzofuranone. Its 20 MHz ^{13}C spectrum showed sharper lines than that at 75 MHz also indicating such a mobile equilibrium.

(b) By Acid Hydrolysis.

A mixture of 2'-methoxycarbonyl-2,5-dimethoxybenzophenone (210 mg, 0.70 mmole) in a mixture of 1,4-dioxane (8 ml) and 10% sulfuric acid (20 ml) was refluxed for 24 h. The yellow solution was then cooled to room temperature and the resulting precipitate was collected by filtration, washed with water and dried to give

the desired product (130 mg, 65%) which sublimed at 140-144°/0.05 mmHg as a pale yellow solid. It was identical (m.p., mixture m.p., i.r., and p.m.r.) with the product obtained by hydrolysis in basic media as described above.

2'-Chlorocarbonyl-2,5-dimethoxybenzophenone.

A mixture of 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone (130 mg, 0.45 mmole) and freshly distilled thionyl chloride (4 ml) was refluxed for 2.5 h. The excess of thionyl chloride was removed under reduced pressure and the residue was dried at 0.05 mmHg to leave the desired product as a pale yellow oil (115.5 mg, 83%) (Found: $\underline{M}^{\cdot+}$, 304.0510 and 306.0477. $C_{16}H_{13}C_4Cl$ requires $\underline{M}$, 304.0522 and 306.0473). It had δ (200 MHz, $CDCl_3$) 3.56 (s, OMe), 3.82 (s, OMe), 6.82 (d, $\underline{J}$ 9, H-3), 6.95 (dd, $\underline{J}_1$ 9, $\underline{J}_2$ 3, H-4), 7.58 (d, $\underline{J}$ 3 H-6), 7.60- 7.72 (m, H-4' + H-5' + H-6'), 7.92 (d, $\underline{J}$ 8, H-3'); $\underline{m/z}$ 306 (3, $\underline{M}^{\cdot+}$), 304 (9, $\underline{M}^{\cdot+}$), 269 {100, $[C_6H_3(OMe)_2CO.\ C_6H_4CO]^+$}, 239 {19, $[C_6H_4(OMe)CO.\ C_6H_4CO]^+$}, 211 {21, $[C_6H_4(OMe)CO.\ C_6H_5]^+$}; and ν_{max} (film) 1760s cm^{-1}, together with a broad absorbance at 2600-3700 cm^{-1} suggesting partial hydrolysis.

Note:

A similar reaction gave 2-chlorobenzoyl chloride in 83% yield from 2-chlorobenzoic acid. It had b.p. (bulb-to-bulb) 80-84°/0.05 mmHg (lit.,[5] b.p. 235-238°) and δ(60 MHz, $CDCl_3$) 6.96-7.68 (m, ArH_3), 7.88-8.28 (m, ArH).

Some Reductions of 2'-Chlorocarbonyl-2,5-dimethoxybenzophenone.

(a) Using bis(triphenylphosphine)copper(I) Tetrahydroborate, $(Ph_3P)_2CuBH_4$.

Solid bis(triphenylphosphine)copper(I) tetrahydroborate (60.3 mg, 0.1 mmole) was added to a stirred solution of freshly prepared 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (30.5 mg, 0.1 mmole) and triphenylphosphine (52.4 mg, 0.1 mmole) in acetone (2.5 ml). The mixture was stirred overnight and the precipitate was then removed by filtration. The filter cake was washed with acetone, and the solvents removed from the combined filtrates; the residue was extracted with ether (4 x 5 ml) and dried ($MgSO_4$). Removal of the solvent gave a white solid and an oil (total 41.3 mg). The n.m.r. spectrum in d-chloroform of the total product showed singlets at δ 3.48, 3.55, 3.66, 3.73, 3.80 and 3.85 due to six methoxy groups, with the rest of the protons in the aromatic region; a signal due to a formyl group was not observed. The spectrum suggested that the product may have contained unreacted acid chloride (δ 3.55 and 3.80) and its carboxylic acid (in equilibrium with 1,3-dihydro-3-hydroxy-3-(2,5-dimethoxyphenyl)isobenzofuranone, δ 3.48, 3.66, 3.73 and 3.85). The product was not further investigated.

Notes:

(a) A similar reaction without triphenylphosphine gave the same result.

(b) A similar reaction in d-chloroform without triphenylphosphine gave the starting material.

(b) Using Litnium tri-tert-Butoxyaluminium Hydride. $(t\text{-}BuO)_3LiAlH$.

To a stirred solution of freshly prepared acid chloride (32 mg, 0.11 mmole) in diglyme (1 ml) at -70° (dry ice-methanol) was added a cooled solution of litnium tri-tert-butoxyaluminium hydride (30 mg, 0.11 mmole) in diglyme (1 ml) over 5 min. After stirring at the above

temperature for a further $1\frac{1}{4}$ h., the reaction mixture was allowed to warm to room temperature, and then poured onto crushed-ice. The product was extracted with ether (3 x 15 ml), washed with water (2 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow solid (31 mg). It was identical (m.p., mixture m.p., and p.m.r. spectrum) with authentic 2-hydroxycarbonyl-2',5-dimethoxybenzophenone.

Notes:

(a) Similar reactions at 0° for 2h., or at room temperature overnight followed by decomposition with ice-water and 2 M hydrochloric acid gave the same results.

(b) A similar reduction at -70° gave 4-nitrobenzaldehyde in 69% yield from 4-nitrobenzoyl chloride. The product had m.p. 102-103° (lit.,[6] m.p. 104-105).

(c) Using Catalytic Hydrogenation in the Presence of Palladium-Barium Sulfate.

A solution of freshly prepared 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (35 mg, 0.12 mmole) in dry toluene (2 ml) was placed in the hydrogenation flask together with 10% palladium-barium sulfate (15 mg). The hydrogenation was carried out at the boiling point of toluene with stirring for about 3.5 h. The reaction mixture was then cooled to room temperature, and the catalyst was removed by filtration. Evaporation of the solvent left a pale yellow oil (27 mg). Its p.m.r. spectrum in d-chloroform did not show a signal due to a formyl group, but showed major singlets at δ 3.35 and 3.54 possibly due to two methoxy groups, together with singlets at δ 3.35, 3.56, 3.70, and 3.80 possibly due to four methoxy groups. The rest of the resonances were in the aromatic regions. The product was not further characterised.

(d) Using $NaBH_4$, in DMF-THF.

To a stirred solution of freshly prepared 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (40 mg, 0.13 mmole) in THF (1.2 ml) and DMF (0.4 ml) at approximately -70° (dry ice-methanol) under a nitrogen atmosphere was added dropwise (ca. 5 min.) a solution of $NaBH_4$ (4.4 mg, 1.2 mmole) in DMF (1.0 ml). Immediately ethyl vinyl ether (0.8 ml), followed in rapid succession by the reaction mixture, was added to a flask containing a well-stirred mixture of propionic acid (0.8 ml) and 2 M aqueous hydrochloric acid (0.6 ml). In order to minimise the time of contact between ethyl vinyl ether and this acidic mixture, ether (15 ml) was then introduced into the flask and stirring was continued for several minutes until hydrogen evolution had ceased. The organic layer was then separated, washed with aqueous 15% sodium chloride (2 x 5 ml), 1 M sodium hydroxide (2 x 5 ml), saturated brine (2 x 5 ml), and water (2 x 10 ml), and dried ($MgSO_4$). Removal of the solvent gave a yellowish oil (44.5 mg). Its p.m.r. spectrum in d-chloroform showed singlets at δ 3.44, 3.50, 3.77 and 3.79 possibly due to four methoxy groups, while the rest of the resonances were in the aromatic region. A signal due to a formyl group was not observed. The product was not further examined.

Notes:

(a) Similar reactions at -70° , followed by room temperature either for ½ h. or overnight gave mainly 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone together with unidentified products.

(b) A similar reaction at -70° , and decomposition with water gave a colourless oil, its p.m.r. spectrum in d-chloroform showing mainly 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone in equilibrium with 1,3-dihydro-3-hydroxy-3-(2,5-dimethoxyphenyl)isobenzofuranone, together with an unidentified product showing a singlet at δ 3.44. The rest of

resonances were in the aromatic region. Its mass spectrum showed m/z at 300(3), 286(21), 271(40), 270(100), 255(10), 239(35), 225(10), 211(33), 165(35). The product was not further examined.

(c) Similar reduction of 2-chlorobenzoyl chloride at -70° , and decomposition of the reaction mixture with propionic acid - hydrochloric acid as in the above experiment, gave 2-chlorobenzaldehyde and 2-chlorobenzoyl alcohol in ratio 6:1, respectively (total yield 61%).

2'-N-Piperidylcarbonyl-2,5-dimethoxybenzophenone.

(a) From 2'-Methoxycarbonyl-2,5-dimethoxybenzophenone.

A mixture of the ester (110 mg, 0.37 mmole) and freshly distilled piperidine (4 ml, 0.04 mole) was refluxed for 26 h. to give a yellowish solution. The excess of piperidine was removed (rotary evaporator) and the residue was dried under vacuum to leave a yellow oil (162 mg, 96%) which was then distilled at 160-166°/0.05 mmHg to give the required product as a light brown oil (Found: C, 71.3; H, 6.7; N, 4.2. $C_{21}H_{23}O_4N$ requires C, 71.4; H 6.7; N, 4.0%). It had δ (220 MHz, $CDCl_3$) 1.30-1.70 (m, 3 x CH_2), 3.20 (s, 2H), 6.62 (s, OMe), 6.90 (s, OMe), 3.30-3.90 (bs, 2H), 6.60-7.10 (m, ArH_3), 7.20-7.60 (m, ArH_4); m/z 353 (6, $M^{\cdot+}$), 269 {27, $[C_6H_3(OMe)_2CO.\ C_6H_4CO]^+$}, 239 {53, $[C_6H_4(OMe)CO.\ C_6H_4CO]^+$}, 211 {20, $[C_6H_4(OMe)CO.\ C_6H_5]^+$}, 165 {8, $[C_6H_3(OMe)_2CO]^+$}, 84 (100, $C_5H_{10}N^+$); and ν_{max} (film) 2220s, 1750s cm^{-1}.

(b) From 2'-Chlorocarbonyl-2,5-dimethoxybenzophenone.

A solution of piperidine (Note 1) (0.55 ml, 5.6 mmole) in pyridine (1.5 ml) was treated with acid chloride (60 mg, 0.20 mmole) in pyridine (1 ml) at 0° , The mixture was stirred at this temperature for about 15 min., then poured into cold water (3 ml), acidified to pH 1 with 10% hydrochloric acid, extracted with ether (3 x 10 ml), washed with water (2 x 10 ml)

and dried (Na_2SO_4). Removal of the solvent gave the desired product (36.4 mg, 55%) as a very pale yellow oil. Its p.m.r. spectrum was identical with that of the product obtained from the foregoing reaction.

Note 1: Preparation of N-2-Chlorobenzoylpiperidine

A similar reaction of 2-chlorobenzoyl chloride with piperidine at 0° for 20 min. and work-up as for the above experiment gave 2-chlorobenzoylpiperidine as a colourless oil in 84% yield, which was distilled (bulb-to-bulb) at 120-124°/0.1 mmHg (lit.,[7] b.p. 100-105°). It had δ (60 MHz, $CDCl_3$) 1.04 (bs, 3 x CH_2), 3.16 (bs, CH_2), 3.72 (bs, CH_2), 7.26 (m, ArH_4) and m/z 224 (29, $M^{\cdot+}$), 222 (83, $M^{\cdot+}$), 186 (26, Cl. $C_6H_4CONC_5H_{10}^+$), 141 (32, Cl. $C_6H_4CO^+$). 139 (100, Cl. $C_6H_4CO^+$), 113 (6, $C_6H_4Cl^+$), 111 (25, $C_6H_4Cl^+$), 84 (8, $C_5H_{10}N^+$).

Attempted Reduction of N-2-Chlorobenzoylpiperidine to 2-Chlorobenzaldehyde.

From its Vilsmeier Complex formed in Situ.

A mixture of the amide (112.5 mg, 0.5 mmole) and freshly distilled phosphorus oxychloride (76.5 mg, 0.5 mmole) in toluene (5 ml) was refluxed for ½ h. The mixture was then cooled to room temperature and treated with zinc dust (163.5 mg, 2.5 mmole). After stirring at room temperature for ½ h. the solid was filtered off. Removal of the solvent from the filtrate left a pale yellow oil which was diluted with water (15 ml), extracted with (3 x 5 ml), and the extracts were washed with water (3 x 5 ml) and dried (Na_2SO_4). Removal of the solvent gave a pale yellow oil (102 mg) shown by its p.m.r. spectrum in d-chloroform to be starting material.

Note:

Similar reactions for longer refluxing times (e.g. 1½ h., 4 h., and 48 h.) either in benzene or toluene and treating of the mixtures with either zinc dust or anhydrous tin(II) chloride followed by worked-up as in the above experiment, gave the same results.

Isolation of the Vilsmeier Complex.

A mixture of N-2-chlorobenzoylpiperidine (112.5 mg, 0.45 ml, 0.5 mmole) and phosphorus oxychloride (2 ml, 2.2 mmole) was refluxed overnight. The excess of phosphorus oxychloride was then removed to leave a light-brownish oil (110 mg, 80%). It had δ (60 MHz, $CDCl_3$) 1.30 (bd, J 16, 6H), 3.16 (s, H), 3.75 (s, H), 4.12 (s, H), 4.30-5.00 (bs, H), 7.33 (s, ArH_3), 7.62 (m, ArH).

From its Vilsmeier Complex.

(a) Using Activated Zinc / Zinc dust.

A solution of the Vilsmeier Complex (50 mg, 0.13 mmole) in toluene (5 ml) was treated with actived zinc (Note 1) (150 mg, 2.3 mmole) and the resulting mixture was refluxed with stirring for about 1 h. After cooling to room temperature, the solid was filtered. Removal of the solvent from the filtrate left a pale yellow oil. Water (10 ml) was added to this oil and the mixture was heated on a steam bath for about 10 min. The product was extracted with ether (3 x 10 ml), washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave a greenish oil (30 mg). Its p.m.r. and mass spectra showed it to be N-2-chlorobenzoylpiperidine.

Note:

A similar reaction in which the complex was treated with zinc dust and then heated at 90° overnight followed by decomposition with 10% hydrochloric acid gave the same result.

Note 1. Preparation of actived zinc. Zinc dust (3 g) was treated with 5% hydrochloric acid (5 ml) and the resulting suspension was stirred at room temperature for 5 min. The solid was then filtered and washed with water until the filtrate was free from acid, and then with acetone. The reagent was kept in a desiccator prior to use.

(b) Using Tin(II) Chloride.

(1) A solution of the Vilsmeier Complex (120 mg, 0.3 mmole) in THF (5 ml) was treated with anhydrous tin(II) chloride (508 mg, 2.7 mmole) and the solution was then refluxed for about 4 h. After being cooled to room temperature, the resulting pink solution was treated with 5% hydrochloric acid (10 ml), and then refluxed for 24 h. After cooling, the product was extracted with ether (4 x 15 ml), washed with water (2 x 20 ml) and dried (Na_2SO_4). Removal of the solvent gave a brownish oil (155.3 mg), the p.m.r. spectrum of which in d-chloroform did not show any sign of the desired product; it may have been a THF-complex since its p.m.r. spectrum showed a broad singlet at δ 1.70, multiplets at 3.10-4.00, a broad signal at 4.00-4.60 and multiplets at 7.35 in the ratio of about 5:4:1:1, respectively. Its mass spectrum showed m/z 316(2), 314(3), 225(16), 223(42), 222(100), 186(9), 139(38), 111(11), 91(19), 71(14). The product was not further studied.

Notes:

(a) A similar reaction in refluxing toluene overnight and decomposition of the product in refluxing 5% hydrochloric acid for 4 h. gave the same result.

(b) A similar reaction in a refluxing mixture of THF and dioxane, followed by decomposition with either cold or refluxing 5% hydrochloric acid gave only N-2-chlorobenzoylpiperidine. A similar result was obtained when the reaction was repeated in ether at room temperature followed by decomposition with hydrogen chloride gas.

(c) A similar reaction in THF either at room temperature overnight (followed by decomposition with cooled 5% hydrochloric acid) or at reflux for 2 h. (followed by decomposition with refluxing 10% hydrochloric acid) may have given a trace of the desired aldehyde (as shown by its p.m.r. spectrum in d-chloroform: a singlet at δ 10.47).

(2) A solution of the Vilsmeier Complex (65 mg, 0.17 mmole) in toluene (5 ml) was treated with tin(II) chloride (305 mg, 1.6 mmole). After stirring the reaction mixture at room temperature for 72 h. it was then treated with 10% hydrochloric acid (10 ml) and stirring was continued for an additional 1 h. The product was extracted with ether (3 x 15 ml), washed with water (2 x 20 ml) and dried (Na_2SO_4). Removal of the solvent gave a light brown oil (34 mg). It p.m.r. spectrum in d-chloroform showed that it may have contained a trace of the desired aldehyde (δ at δ 10.45) together with N-2-chlorobenzoylpiperidine as the major component.

Notes:

(a) Similar reactions either in refluxing toluene (for 3 h.) or ether in the presence of a few drops of DMF (overnight) and work-up as in the foregoing description gave the same results.

(b) A similar reaction in pyridine at room temperature overnight gave N-2-chlorobenzoylpiperidine as the only product.

2,5-Dimethoxydiphenylmethanol.

To a stirred solution of 2,5-dimethoxybenzophenone (1.1 g) in 95% ethanol (20 ml) was added sodium borohydride (1.9 g). After stirring for 48 h. at room temperature, the mixture was diluted with water (20 ml), extracted with ether (4 x 15 ml), and the combined extracts were washed with water (2 x 15 ml), and dried (Na_2SO_4). Removal of the solvent gave a colourless oil (1.0 g, 91%) which was then distilled (bulb-to-bulb) at 110°/0.1 mmHg (lit.,[8] 163.5°/0.02 mmHg). (Found: C, 73.5; H, 6.7. Calc. for $C_{15}H_{16}O_3$: C, 73.6; H, 6.6%). It had δ (60 MHz, $CDCl_3$) 3.01 (d, J 6, OH), 3.71 (s, 2 x OMe), 6.01 (d, J 6, -CH-, changed to a singlet on addition of D_2O), 6.80 (s, ArH_3), 7.32 (s, ArH_5), m/z 224 (60, $M^{\cdot+}$), 227 [100, $(M - OH)^+$], 213 [10, $(M - OMe)^+$], 105 (20, $ArCO^+$), 91 (11, $ArCH_2^+$), 77 (8, Ar^+), and ν_{max} (film) 3410s cm^{-1}.

Note:

A similar mixture, after being stirred at room temperature for 10 h., still gave a product containing the starting material as shown by its p.m.r. spectrum.

2,5-Dimethoxybenzophenone.

This compound,[9] was recrystallised from hexane as white crystals, m.p. 48–49° (lit.,[10] m.p. 51°). It had δ (60 MHz, $CDCl_3$), 3.61 (s, OMe), 3.74 (s, OMe), 6.91 (s, ArH_3), 7.46 (s, ArH_3), 7.63 (m, ArH_2); m/z 243 [16, $(M + 1)^+$], 242 (100, $M^{\cdot+}$), 211 [3, $(M - OMe)^+$], 165 (65, $Me_2C_6H_3CO^+$), 105 (48, $PhCO^+$), 77 (69, Ph^+).

Phthalide.

An authentic sample of phthalide had ν_{max} (Nujol) 1740s cm^{-1}.

α-Hydroxybenzyl-1,4-benzoquinone.

(a) From 3-Hydroxydiphenylmethanol.

(1) Reaction in Methanol.

To a stirred solution of potassium dihydrogen orthophosphate (1.12 g) in water (120 ml) was added a solution of 3-hydroxydiphenylmethanol (500 mg) in methanol (30 ml) followed by Fremy's salt (2 g). After stirring for 5 h., the product was extracted with ether (5 x 20 ml), washed with water (2 x 20 ml), and dried (Na_2SO_4). Removal of the solvent gave the desired product (346 mg, 70%) as a brown oil. It had δ ($CDCl_3$), 60 MHz) 3.03 (d, J 4, OH), 7.32 (b, α-H, changed to singlet by addition D_2O), 6.66-6.85 (m, H-3 + H-4 + H-5), 7.20 (m, ArH_5), identical with that reported.[11]

The quinone was obtained in 53% yield when 3.5 equivalents of sodium acetate was used, instead of potassium dihydrogen orthophosphate.

(2) Reaction in two phases.

Using dichloromethane (3 ml) to dissolved the phenol (50 mg, 0.25 mmole) and water (3 ml) to dissolved the Fremy's salt (200 mg, 0.75 mmole) and sodium acetate (71.6 mg, 0.86 mmole) and shaking at room temperature for 4½ h. gave after work-up (34 mg, 69%) of the desired quinone.

(b) From 2,5-Dimethoxydiphenylmethanol.

To a stirred solution of 2,5-dimethoxydiphenylmethanol (76.8 mg, 0.31 mmole) in aqueous acetonitrile (H_2O : CH_3CN 3:7; 3 ml) was added slowly a solution of CAN (822 mg, 1.5 mmole) in aqueous acetonitrile (H_2O : CH_3CN 3:7 ; 3 ml) over 5 min. The colourless solution immediately changed to dark brown. The flask was then covered with aluminium foil.

After being stirred for 5 h., the mixture was diluted with water (10 ml), extracted with dicnloromethane (3 x 5 ml), and the combined extracts washed with brine (1 x 5 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product as a brown oil (44 mg, 65%). Its p.m.r. spectrum in d-chloroform was identical to that described above .

Protection of Phenolic Hydroxy with the Trimethylsilyl (TMS) Group: A General Procedure.

To a stirred solution of the hydroxy compound (1.0 mmole) in ether (5 ml) under nitrogen was added trimethylsilyl chloride (1.2 mmole) (Note 1) and pyridine (1.4 mmole) (Note 2). The mixture was then stirred at room temperature for an additional 3-20 h. (Note 3). The white precipitate was then filtered. Removal of the solvent from the filtrate gave a pale yellow oil which was then distilled or extracted with pentane to give the desired product.

Note 1. 1.2 Equivalents of trimethylsilyl chloride were used for each hydroxy group present in the compound.

Note 2. 1.4 Equivalents of pyridine were used for each hydroxy group present in the compound.

Note 3. The reaction occurred rapidly, and normally ended within 3-4 h., leaving the reaction overnight gave the same results.

2,5-Bis[(trimethylsilyl)oxy]toluene.

2,5-Dihydroxytoluene (1.24 g, 10 mmole) after the above procedure and distillation (bulb-to-bulb) at 68-74°/ 0.05 mmHg, gave the pure title product as a colourless liquid (1.93 g, 72%) (lit.,[12] b.p. 158°/0.2 mmHg) (Found: C, 58.2; H, 9.2. Calc. for $C_{13}H_{24}O_2Si_2$: C, 58.2; H, 9.0%). It had δ (60 MHz, $CDCl_3$) 0.25 (s, 2 x $SiMe_3$), 2.12 (s, Me), 6.40-6.70 (bs, ArH_3); m/z CI(NH_3) 286 [16, $(M + 18)^+$], 269 [100, $(M + 1)^+$], 90, (38, Me_3SiOH^+), m/z 268 (100, $M^{\cdot+}$), 253 [92, $(M - Me)^+$], 223 [10, $(M - Me_3)^+$], 179 [14, $(M - OSiMe_3)^+$]; and ν_{max} (film) 1500s, 1410s, cm^{-1}.

3-[(Trimethylsilyl)oxy]benzaldehyde.

3-Hydroxybenzaldehyde (1.22 g, 10 mmole) gave after the above procedure the title compound, which distilled (bulb-to-bulb) at 60-64°/0.05 mmHg as a colourless liquid (1.53 g, 79%) (Found: C, 61.9; H, 7.3. $C_{10}H_{14}O_2Si$ requires C, 61.9; H, 7.2%). It had δ (220 MHz, $CDCl_3$) 0.29 (s, $SiMe_3$), 7.12 (ddd, J_1 7.6, J_2 4.5, J_3 1.7, H-4), 7.36 (dt, J_1 4.5, J_2 1.7, H-2, changed to a doublet, J 1.7 on irradiation at 7.12), 7.45 (d, J 7.8, H-5), 7.50 (dt, J_1 7.8, J_2 1.5, H-2 + H-6; changed to a double-doublet on irradiation at 7.12); m/z 194 (43, $M^{\cdot+}$), 179 [72, $(M - Me)^+$], 122 [100, $(M - SiMe_3 + H)^+$], 121 [87, $(M - SiMe_3)^+$], 9.82 (s, CHO); and ν_{max} (film) 1690s, 1590s, 1460s, 1440s cm^{-1}.

2,5-Bis[(trimethylsilyl)oxy]benzaldehyde.

Hexamethyldisiliazane (7 ml, 32 mmole) and imidazole (15 mg, 0.23 mmole) were added to a stirred solution of 2,5-dihydroxybenzaldehyde (500 mg, 3.6 mmole) in tetrahydrofuran (20 ml) under nitrogen. After stirring at room temperature overnight the solvent was removed under vacuum to give a brownish oil which was distilled (bulb-to-bulb) at 96-104°/0.05 mmHg to give the desired product as a yellowish liquid (645 mg, 64%) (Found: C, 55.4; H, 7.9. $C_{13}H_{22}O_3Si_2$ requires C, 55.3; H, 7.8%).

It had δ (220 MHz, $CDCl_3$) 0.26 (s, $SiMe_3$), 0.30 (s, $SiMe_3$), 5.90 (d, J 8.5, H-3), 6.35 (d, J 3, H-6), 6.70 (dd, J_1 8.5, J_2 3, H-5), 9.60 (s, CHO); m/z CI(NH_3) 283 [67, $(M + 1)^+$], 267 [13, $(M - Me)^+$], 211 [100, $(M - SiMe_3 + 2H)^+$], 210 [42, $(M - SiMe_3 + H)^+$], 195 [15, $(M - SiMe_3 - Me + H)^+$], 90 (23, Me_3SiOH^+); m/z EI 282 (5, $M^{\cdot+}$), 267 [78 $(M - Me)^+$], 210 [100, $(M - SiMe_3 + H)^+$], 195 [86, $(M - SiMe_3 + H)^+$], 167(38); and ν_{max} (film) 1685s, 1490s, 1420m, 1390s cm^{-1}.

Note:

Reaction using trimethylsilyl chloride and pyridine in ether gave a ca. 1:1 mixture of the title product together with 2-hydroxy-5-[(trimethylsilyl)oxy]benzaldehyde [singlets at δ 0.26 ($SiMe_3$), 10.20 (CHO), and 10.50 (OH) and the rest of protons at δ 6.60-7.20].

2-[(Trimethylsilyl)oxy]-5-methoxymethoxybenzaldehyde.

2-Hydroxy-5-methoxymethoxybenzaldehyde (p. 205) (182 mg, 1 mmole) gave, after the above procedure, the desired product as a colourless liquid. Pentane extraction afforded the pure material (214 mg, 84%) (Found: $M^{\cdot+}$ 254.0978. $C_{12}H_{18}O_4Si$ requires M 254.0974). It had δ (220 MHz, $CDCl_3$) 0.30 (s, $SiMe_3$), 3.44 (s, OMe), 5.09 (s, OCH_2), 6.75 (d, J 9, H-3), 7.12 (dd, J_1 9, J_2 3, H-4), 7.40 (d, J 3, H-6); m/z 254 (36, $M^{\cdot+}$), 239 [58, $(M - Me)^+$], 209 [(19, $(M - MOM)^+$], 182 [59, $(M - SiMe_3 + H)^+$]; and ν_{max} (film) 1660s, 1595m, 1430m, 1395m cm^{-1}.

Trimethylsilyl 2,5-Bis[(trimethylsilyl)oxy]benzoate.

2,5-Dihydroxybenzoic acid (308 mg, 0.2 mmole) gave, after the above procedure, the title compound as a colourless liquid. (555 mg, 74%) which distilled (bulb-to-bulb) at 76-80°/0.1 mmHg (Found: C, 52.4; H, 7.9. $C_{16}H_{30}O_4Si_3$ requires C, 51.9; H, 8.1%). It had δ (220 MHz, $CDCl_3$)

0.25 (s, 2 x $SiMe_3$), 0.40 (s, $SiMe_3$), 6.85 (d, J 9, H-3), 6.98 (dd, J_1 9, J_2 3, H-4), 7.25 (d, J 3, H-6); m/z CI(NH_3) 371 [37, $(M + 1)^+$], 355 [26, $(M + 1 - Me)^+$], 299 [100, $(M - SiMe_3)^+$]; and ν_{max} (CH_2Cl_2) 1655s cm^{-1}.

Note:

Treatment of the silyl ester with oxalyl chloride-DMF at 0° under nitrogen either in THF or without solvent, gave 2,5-dihydroxybenzoic acid.

Protection of Phenolic Hydroxy with the Tetrahydropyranyl (THP) Group.

3-[(Tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde.[13]

To a stirred solution of 3-hydroxybenzaldehyde (1.2 g, 10 mmole) in dichloromethane (60 ml) was added pyridinium p-toluenesulfonate (Note 1) (0.25 g, 1 mmole) and 2,3-dihydropyran (1.26 g, 15 mmole). After stirring at room temperature for 5 h. the solution was diluted with ether, washed once with half-saturated brine to remove the catalyst, and dried (Na_2SO_4). Evaporation the solvent gave a pale yellow oil (1.6 g, 76%) which was purified by column chromatography on silica gel using 3:1 petroleum ether (b.p. 40-60°) - ether as eluent, to give two fractions.

The first fraction was the desired product as a pale yellow oil (1.35 g, 68%) (Found: C, 69.6; H, 6.9. $C_{10}H_{14}C_3$ requires C, 69.9, H, 6.8%). It had δ (60 MHz, $CDCl_3$), 1.40-2.10 (bs, 3 x CH_2), 3.30-4.10 (m, OCH_2), 5.35 (bs, O-CH-O), 7.10-7.50 (m, ArH_4), 9.79 (s, CHO); m/z 206 (0.4, $M^{\cdot+}$), 85 (100, THP^+); and ν_{max} (film) 1700s cm^{-1}.

Small scale sublimation at 60-62°/0.01 mmHg gave the desired product as a colourless liquid; on a larger scale, the compound decomposed.

The second fraction was isolated as a white solid (190 mg, 9%). It was identical (m.p., mixed m.p., and p.m.r. spectrum) with authentic 3-hydroxybenzaldehyde.

Note 1. Preparation of Pyridinium p-Toluenesulfonate (PPTS). p-Toluenesulfonic acid monohydrate (2.8 g, 15 mmole) was added to pyridine (6 ml, 75 mmole) with stirring at room temperature (slightly exothermic). After stirring for an additional ½ h., at the above temperature, the excess of pyridine was removed with a rotary evaporator on a water bath at 60° to afford slightly hygroscopic colourless crystals, which were recrystallised from acetone to give the pure product as white crystals (3.2 g, 86%), m.p. 116° (lit.,[14] 120°).

2-Hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde.

A similar reaction using 2,5-dihydroxybenzaldehyde (1.38 g, 10 mmole), pyridinium p-toluenesulfonate (0.25 g, 1 mmole), and 2,3-dihydropyran (1.26 g, 15 mmole in dichloromethane (50 ml), stirring of the solution at room temperature for 36 h.; and work-up as above afforded the desired product as a greenish oil (1.66 g, 75%). It was purified either by filtration through silica gel using 3:1 ether-hexane as eluent, or by distillation at 60–66°/0.05 mmHg (Found: C, 64.8; H, 6.4. $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.3%). It had δ (220 MHz, $CDCl_3$) 1.30–2.00 (m, 3 x CH_2), 3.55 (m, H-6', α/β), 3.82 (m, H-6', β/α), 5.26 (s, H-2'), 6.84 (d, J 9.6, H-3), 7.19 (s, H-4 + H-6), 9.73 (s, CHO), 10.60 (s, OH); m/z 222 (4, $M^{\cdot+}$), 205 [2, $(M - OH)^+$], 136 [74, $(M - THP)^+$], 85 (100, THP^+); and ν_{max} (film) 3000–3600b, 1690s, 1620s cm^{-1}.

Protection of Hydroxy with tert-Butyldimethylsilyl Chloride.

1,1-(Dimethylethyl)dimethylsilyl 2,5-{bis-[(1,1-dimethylethyl)dimethylsilyl]oxy}benzoate.

In a 25 ml 2-necked flask, swept with dry nitrogen and equipped with a magnetic stirrer, was placed 2,5-dihydroxybenzoic acid (38.5 mg, 0.025 mmole) in ether (5 ml). t-Butyldimethylsilyl chloride (226 mg, 0.15 mmole) and pyridine (160 mg, 0.20 mmole) were then added and the mixture was stirred at room temperature under a nitrogen atmosphere overnight. The precipitate was then filtered. Removal of the solvent from the filtrate gave the desired product, in a crude state as a pale yellow oil (97 mg, 78%) which changed gradually to a white solid on standing in the air at room temperature and even in the p.m.r. tube in d-chloroform solution during recording of the p.m.r. spectrum. It had δ (60 MHz, $CDCl_3$) 0.10 (s, 2 x $SiMe_2$), 0.33 (s, $SiMe_2$), 0.90 (s, 2 x Bu^t), 0.92 (s, Bu^t), 6.61 (d, J 9, H-3), 7.00 (dd, J_1 9, J_2 3, H-4), 7.21 (d, J 3, H-3) together with impurities as shown by multiplets at δ 7.30-8.60. The product was not further examined.

Note:

(a) Sublimation at 80-86°/0.1 mmHg gave a white solid. It was identical (m.p. mixture m.p.) with 2,5-dihydroxybenzoic acid.

(b) Similar reactions using imidazole as the base (instead of pyridine) in DMF (instead of ether) failed to give the desired compound.

2,5-{Bis-[(1,1-dimethylethyl)dimethylsilyl]oxy}benzaldehyde.

To a stirred solution of tert-butyldimethylsilyl chloride (332 mg, 0.22 mmole) in dry THF (15 ml) was added imidazole (150 mg, 0.22 mmole). To the resulting cloudy mixture was then added 2,5-dihydroxybenzaldehyde (138 mg, 0.1 mmole) and the mixture was stirred at room temperature overnight under a nitrogen atmosphere. The white precipitate was filtered. Removal of the solvent from the filtrate gave, probably, the desired product as a pale yellow liquid (285 mg, 78%). It had δ (60 MHz, $CDCl_3$) 0.18 (s, 2 x $SiMe_2$), 0.94 (s, 2 x Bu^t), 6.80 (d, J 9, H-3), 6.95 (s, H-6), 7.0 (d, J 9, H-4); and m/z CI(NH_3) 367 (2, $M^{\cdot+}$), 254 [49, $(M - 2 \times Bu^t)^+$], 195 [53, $(M - 2 \times Bu^t - SiMe_2 + H)^+$], 138 [61, $(M - 2 \times SiMe_2Bu^t)^{\cdot+}$]. The smell of the product indicated that it contained some t-butyldimethylsilyl chloride.

Note:

A similar reaction in ether using pyridine as the base gave a ca. 2:3 mixture of the desired product and 2,5-dihydroxybenzaldehyde.

Attempted purification of the product.

(a) The product was insoluble in pentane: pentane extraction gave nothing, as shown by the absence of a p.m.r. spectrum of the extract in d-chloroform.

(b) Dissolving the product in d-chloroform followed either by column chromatography through polyamide or washing of the chloroform solution with water gave some hydrolysis product, 2,5-dihydroxybenzaldehyde. A similar result was obtained when its solution in ether was washed with saturated sodium hydrogen carbonate.

(c) Sublimation at 54-60°/0.1 mmHg gave 2,5-dihydroxybenzaldehyde as the only product.

Methoxymethylation of Phenolic Hydroxy Group: A General Procedure.

To a stirred solution of the hydroxy compound (e.g. hydroxybenzene, hydroxyaldehyde, hydroxyketone, hydroxycarboxylic acid, or carboxylic acid, 1.0 mmole) in ether (5 ml) (Note 1) under a nitrogen atmosphere was added methoxymethyl chloride (as a 1:1 mixture with methyl acetate, 1.5 mmole) (Note 2) and triethylamine (2.0 mmole) (Note 3). The reaction mixture was stirred at room temperature for about 24 h. and the white precipitate was then filtered. Removal of the solvent usually gave as the methoxymethyl ether as a liquid which was purified either by washing with aqueous 5% sodium hydroxide or distillation.

Note 1. 5 ml of ether was used as the solvent for every 1.0 mmole of the hydroxy compound, except for those hydroxy compounds which were not very soluble in ether when more ether was used.

Note 2. Unless otherwise stated, 1.5 mmole of methoxymethyl chloride was used for each hydroxy group present in the starting material.

Note 3. 2.0 mmole of triethylamine was used for every 1.5 mmole of methoxymethyl chloride used in the reaction mixture. Excess of amine was necessary to keep the reaction mixture basic throughout.

2,5-Bis(methoxymethoxy)benzaldehyde.

2,5-Dihydroxybenzaldehyde (1.38 g, 10 mmole) gave after the above procedure the title compound (1.28 g, 57%) as a yellowish oil which distilled at 56-60°/ 0.05 mmHg to afford a pale yellow liquid (Found: C, 58.6; H, 6.3%. $M^{\cdot+}$, 226.0841. $C_{11}H_{14}O_5$ requires C, 58.4; H, 6.2%. M, 226.0847. It had δ (300 MHz, $CDCl_3$) 3.46 (s, OMe), 3.50 (s, OMe), 5.16 (s, OCH_2), 5.26 (s, OCH_2), 7.02 (d; J 9.5, H-3), 7.26 (dd; J_1 9.5, J_2 3, H-4), 7.52 (d, J 3, H-6), 0.28 (s, CHO); m/z ~~226~~ 262 (42, $M^{\cdot+}$), 195 [29, $(M - OMe)^+$], 180 [37, $(M - MeCMe)^+$]; and ν_{max} (film) 1680s, 1490m, and 1385m cm^{-1}.

Note:

(a) A similar reaction using dichloromethane either at room or refluxing temperature gave only 5% of the title compound. 2-Hydroxy-5-methoxymethoxybenzaldehyde (p. 205) was isolated in 60% yield after extraction with 5% sodium hydroxide followed by acidification with 5% acetic acid. Treatment of 2-hydroxy-5-methoxymethoxybenzaldehyde (182 mg, 0.1 mmole) under the condition of the general procedure gave the title compound in 60% yield.

(b) Similar reactions using pyridine as the base in either dichloromethane, tetrahydrofuran or ether, failed to give the title compound.

2-Hydroxy-5-methoxymethoxybenzaldehyde.

A solution of 2,5-dihydroxybenzaldehyde (2.07 g, 15 mmole) and methoxymethyl chloride (8.0 ml of 1:1 mixture with methyl acetate, 42 mmole) in dichloromethane (30 ml) was refluxed for 24 h. under a nitrogen atmosphere using a Soxhlet containing powdered 4A molecular sieves (20 g). After being cooled to room temperature and washed with aqueous 5% sodium hydroxyde (3 x 20 ml), the aqueous solution was neutralised (to pH about 7) with aqueous 5% acetic acid, extracted with ether

(4 x 50 ml), and dried (Na_2SO_4). Removal of the solvent gave the desired product as a light brown oil (2.17 g, 80%). It distilled at 50-56°/0.1 mmHg as a pale yellow liquid (Found: C, 59.6; H, 5.7. $C_9H_{10}O_4$ requires C, 59.3; H, 5.5%. $\underline{M}^{\cdot+}$ 182.0581. $C_9H_{10}O_4$ requires $\underline{M}$ 182.0579). It had δ (220 MHz, $CDCl_3$) 3.43 (s, OMe), 5.12 (s, OCH_2), 6.92 (d, $\underline{J}$ 9, H-3), 7.22 (m, H-4 + H-6), 9.79 (s, CHO), 10.65 (s, OH); $\underline{m/z}$ 182 [52, $\underline{M}^{\cdot+}$], 152 [30, $(\underline{M} - OMe + H)^+$], 137 [18, $(\underline{M} - MOM)^+$]; and ν_{max} (film) 3100-3600b, 1660s cm^{-1}.

2-Methoxy-1,4-bis(methoxymethoxy)benzene.

2-Methoxy-1,4-dihydroxybenzene (140 mg, 1 mmole) gave after the above procedure a colourless liquid (177 mg, 76%) which was purified by distillation (bulb-to-bulb) at 80-86°/0.1 mmHg to give the pure product. (Found: C, 57.6; H, 7.2. $C_{11}H_{16}O_5$ requires C, 57.9; H, 7.0%). It had δ (220 MHz, $CDCl_3$) 3.46 (s, OMe), 3.50 (s, OMe), 3.85 (s, OMe), 5.12 (s, OCH_2), 5.14 (s, OCH_2), 6.55 (dd, $\underline{J}_1$ 8.8, $\underline{J}_2$ 2.8, H-5), 6.65 (d, $\underline{J}$ 2.8, H-3), 7.05 (d, $\underline{J}$ 8.8, H-6); $\underline{m/z}$ 228 (70, $\underline{M}^{\cdot+}$), 198 [22, $(M - 2 \times Me)^+$], 183 [28, $(\underline{M} - MOM)^+$], 166 [16, $(\underline{M} - OMOM + H)^+$], 153 [17, $(\underline{M} - OMOM - Me + H)^+$]; and ν_{max} (film) 1511m, 1153m, 1009m cm^{-1}.

2-Hydroxy-5-methoxymethoxybenzoic Acid.

2,5-Dihydroxybenzoic acid (154 mg, 1 mmole) gave after the above procedure the title product as a sticky pale yellow oil (163 mg, 82%) (Note 1) together with trace of 2,5-bismethoxymethoxybenzoic acid (Note 2). The mixture was neutralised with 5% acetic acid, and ether extraction then gave the title compound as a white solid, m.p. 104-106° (Found: C, 54.5; H, 5.6%. $\underline{M}^{\cdot+}$, 198.0530. $C_9H_{10}O_5$ requires C, 54.5; H, 5.6%. $\underline{M}$, 198.0528. It had δ (220 MHz, $CDCl_3$) 3.50 (s, OMe), 5.16 (s, OCH_2), 6.96 (d, $\underline{J}$ 8, H-3), 7.25 (dd, $\underline{J}_1$ 8, $\underline{J}_2$ 3, H-4), 7.60 (d, $\underline{J}$ 3, H-6), 10.10 (bs, 2 x OH); $\underline{m/z}$ 199 [21, $(\underline{M} + 1)^{\cdot+}$], 198 (67, $\underline{M}^{\cdot+}$),

180 [50, $(M - H_2O)^+$], 150 [62, $(M - H_2O - OCH_2)^+$]; and ν_{max} (Nujol) 3100-3600b, 1682s, 1618s, 1489m cm^{-1}.

Note 1. The title product not stable on sublimation; it decomposed to 2,5-dihydroxybenzoic acid.

Note 2. The compound was isolated on distillation (bulb-to-bulb) at 100-104°/0.5 mmHg as a colourless liquid (15 mg, 6%). (Found: $M^{\cdot+}$, 242.0794. $C_{11}H_{14}O_6$ requires M,242.0790). It had δ (220 MHz, $CDCl_3$) 3.52 (s, OMe), 3.69 (s, OMe), 5.15 (s, OCH_2), 5.52 (s, OCH_2), 6.94 d, J 8, H-3), 7.25 (dd, J_1 8, J_2 3, H-4), 7.58 (d, J 3, H-6); m/z 242(28, $M^{\cdot+}$), 198 [15, $(M - OCH_2OMe + H)^+$], 180 [29, $(M - OMOM - H_2O + H)^+$]; and ν_{max} ($CDCl_3$) 2900bs, 1683s, 1489m cm^{-1}.

Methoxymethoxy 2,5-Bis(methoxymethoxy)benzoate.

2,5-Dihydroxybenzoic acid (154 mg,1.0 mmole) gave after the above procedure a colourless liquid (223 mg, 78%), its p.m.r. spectrum in d_6-benzene (220 MHz) showing it to be a mixture of the title compound [singlets at δ 3.12, 3.20 and 3.22 (due to three methoxy groups), at 4.78, 4.92 and 5.30 (due to three methylene groups)]*, and 2,5-bismethoxymethoxybenzoic acid (Note 1); [singlets at δ 3.05 and 3.12 (due to two methoxy groups), at 4.76 and 5.08 (due to two methylene groups), and at 10.80 (due to one hydroxy group)]* in the ratio 2:1 respectively. Washing of the product mixture with aqueous 5% sodium hydroxide afforded the title compound as a colourless liquid (50 mg, 17%) (Found: C, 54.1, H, 6.4%. $M^{\cdot+}$ 286.1045. $C_{13}H_{18}O_4$ requires C, 54.5, H, 6.3% . M,286.1052). It had δ (60 MHz, $CDCl_3$) 3.47 (s, OMe),

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* The rest of protons were in the aromatic region.

3.52 (s, OMe), 3.54 (s, OMe), 5.02 (s, OCH_2), 5.17 (s, OCH_2), 5.42 (s, CH_2), 7.08 (s, ArH), 7.10 (s, ArH), 7.42 (d, J 2, H-6); m/z 286(51, $M^{\cdot+}$), 225 [41, $(M - OMOM)^+$], 180 [59, $(M - OMOM - MOM)^+$], 150 [12, $(M - OMOM - MOM - Me)^+$]; and ν_{max} (film) 1736s, 1498s cm^{-1}.

Note 1. Several attempts to prepare 2,5-bismethoxymethoxybenzoic acid as a single product failed. Mixtures with methoxymethoxy 2,5-bis(methoxymethoxy)benzoate were always obtained, although less then two equivalents of methoxymethyl chloride were used.

Note 2. Neutralisation of the aqueous solution with aqueous 5% acetic acid followed by ether extraction afforded 2-hydroxy-5-methoxymethoxybenzoic acid.

Methyl 2,5-Bis(methoxymethoxy)benzoate.

Methyl 2,5-dihydroxybenzoate (168 mg, 1 mmole) gave after the above procedure a colourless liquid (120 mg). Its n.m.r. spectrum in d-chloroform showed the product to be a mixture of the title compound together with methyl 2-hydroxy-5-methoxymethoxybenzoate [showing singlets at δ 3.42 (OMe), 3.88 (CO_2Me), 5.02 (OCH_2), with the rest of protons in the aromatic region], in the ratio about 1:3, respectively. The total product was dissolved in chloroform (5 ml), washed with aqueous 5% sodium hydroxide (2 x 5 ml) and dried (Na_2SO_4). Removal of the solvent gave the title compound as a colourless liquid (45 mg, 18%) (Found: $M^{\cdot+}$ 256.0947. $C_{13}H_{16}O_6$ requires M 256.0952). It had δ (300 MHz, $CDCl_3$) 3.48 (s, OMe), 3.52 (s, OMe), 3.90 (s, CO_2Me), 5.16 (s, OCH_2), 5.20 (s, OCH_2); m/z 256(53, $M^{\cdot+}$), 225 [59, $(M - OMe)^+$], 180 [80, $(M - OMe - MOM)^+$], 150 [25, $(M - OMe - MOM - 2 \times Me)^+$]; and ν_{max} (film) 1720s, 1490m cm^{-1}.

2,5-Bis(methoxymethoxy)benzophenone.

2,5-Dihydroxybenzophenone (160 mg, 0.75 mmole) gave after the above procedure a colourless liquid (117.5 mg, 52%). The p.m.r. spectrum of which in d-chloroform (60 MHz) showed a mixture of the title compound and 2-hydroxy-5-methoxymethoxybenzophenone (singlets at 3.37 and 4.97 due to methoxy and methylene protons, respectively; the rest of protons were in the aromatic region) in the ratio 10:9, respectively. Work-up was as in the foregoing procedure, and afforded the title compound (53 mg, 23%) which was distilled (bulb-to-bulb) at 96-100°/ 0.1 mmHg to give the pure product as a pale yellow liquid (Found: C, 66.1; H, 6.0. $C_{17}H_{18}O_5$ requires C, 67.6; H, 6.0%). It had δ (220 MHz, $CDCl_3$) 3.28 (s, OMe), 3.46 (s, CH_2), 4.96 (s, OCH_2), 5.13 (s, OCH_2), 7.06 (m, H-4'), 7.04 (s, H-3' or 5'), 7.05 (s, H-5' or 3'), 7.44 (m, H-3 + H-4), 7.53 (m, H-6), 7.66 (dd, J_1 7, J_2 2, H-3' + H-6'); m/z 303 [12, $(M + 1)^{\cdot+}$], 302(49, $M^{\cdot+}$), 272 [21, $(M - 2 \times Me)^+$], 242 [12, $(M - OMOM + H)^+$], 227 [25, $(M - OMOM - Me + H)^+$], 105(43, $COPh^+$); and ν_{max} (film) 1669s, 1597m, 1493s cm^{-1}.

2-Hydroxy-5-methoxymethoxyacetophenone.

2,5-Dihydroxyacetophenone (304 mg, 2 mmole) gave after the above procedure a mixture of a yellowish solid and an oil (345 mg). Its p.m.r. spectrum in d_6-acetone showed a mixture of the title compound together with unchanged 2,5-dihydroxyacetophenone in about 2:1 ratio. Removal of the solvent and extraction of the residue with cold d-chloroform gave the title compound (39 mg, 10%) as a pale yellow oil (Found: $M^{\cdot+}$, 196.0731. $C_{10}H_{12}O_4$ requires M, 196.0736). It had δ (300 MHz, $CDCl_3$) 2.62 (s, COMe), 3.50 (s, OMe), 5.12 (s, OCH_2), 6.88 (d, J 9, H-3), 7.80 (dd, J_1 9, J_2 3, H-4), 7.42 (d, J 3, H-6), 11.92 (s, OH); m/z 196(6, $M^{\cdot+}$), 166 [3, $(M - 2 \times Me)^+$],

152 [3, $(M - MOM + H)^+$], 151 [3, $(M - MOM)^+$], 137 [5, $(M - MOM)^+$]; and ν_{max} ($CDCl_3$), 3150b, 1640s cm^{-1}.

1,4-Bis(methoxymethoxy)benzene.

1,4-Dihydroxybenzene (1.1 g, 10 mmole) gave after the above procedure the title compound (1.2 g, 61%) as a pale yellow liquid which distilled at 76-80°/0.1 mmHg to gave a colourless liquid (lit.,[15] b.p. 136-137°/5 mmHg). (Found: $M^{\cdot+}$, 198.0892. Calc. for $C_{10}H_{14}O_4$; M, 198.0895). It had δ (60 MHz, $CDCl_3$) 3.42 (s, 2 x OMe), 5.04 (s, 2 x OCH_2), 6.92 (s, ArH_4); m/z 198(15, $M^{\cdot+}$), 167 [6, $(M - OMe)^+$], 138 [16, $(M - OMOM - H)^+$]; and ν_{max} (film) 1500s cm^{-1}.

Note:

Preparation using phosphorus pentoxide and methylal in chloroform[16], gave the title compound in about 30% yield. This procedure involved a large amount of base during neutralisation in the work-up.

2-Methoxymethoxybenzaldehyde.

2-Hydroxybenzaldehyde (244 mg, 2 mmole) gave after the above procedure the title compound (250 mg, 75%) as a colourless liquid. It distilled at 60-66°/0.1 mmHg (Found: C, 65.3; H, 6.1%. $M^{\cdot+}$, 166.0660. $C_9H_{10}O_3$ requires C, 65.1; H, 6.0%. M, 166.0629). It had δ (220 MHz, $CDCl_3$) 3.45 (s, OMe), 5.22 (s, OCH_2), 7.02 (t, J 8.3, H-5 changed to a doublet on irradiation at 7.76), 7.16 (d, J 8.3, H-3), 7.48 (td, J_1 8.3, J_2 2.2, H-4; changed to a triplet on irradiation at 7.76), 7.76 (dd, J_1 8.3, J_2 2.2, H-6), 10.42 (s, CHO); m/z 166(6, $M^{\cdot+}$), 135 [7, $(M, OMe)^+$], 121 [11, $(M - MOM)^+$], 105 [2, $(M - MOM)^+$]; and ν_{max} (film) 1690s, 1600s cm^{-1}.

Methoxymethoxy 2-Bromobenzoate.

2-Bromobenzoic acid (201 mg, 1 mmole) gave after the above procedure the title compound (198 mg, 81%) as a colourless liquid. It distilled at 60-64°/0.1 mmHg (Found: C, 44.2; H, 3.7; Br, 32.4. $C_9H_9O_3Br$ requires C, 44.1; H, 3.7; Br, 32.7%). It had δ (220 MHz, $CDCl_3$) 3.50 (s, OMe), 5.42 (s, OCH_2), 7.29 (m, H-3 + H-5), 7.60 (m, H-4), 7.80 (m, H-6); m/z 246(25, $M^{\cdot+}$), 244(24, $M^{\cdot+}$), 201 [11, $(M - MOM)^+$], 199 [10, $(M - MOM)^+$], 186(78), 185(65), 184(82), 183(64); and ν_{max} (film) 1740s cm^{-1}.

2-Methoxymethoxybenzoic Acid.

To a stirred solution of 2-hydroxybenzoic acid (207 mg, 1.5 mmole) in ether (5 ml) under nitrogen was added methoxymethoxy chloride (0.4 ml of 1:1 mixture with methyl acetate, 2 mmole) and triethylamine (26 mg, 3 mmole). After stirring the mixture at room temperature overnight and working up as the above procedure, it gave a colourless liquid (229 mg, 82%), which was distilled (bulb-to-bulb) at 60-64°/0.1 mmHg (lit.,[17] m.p. 63-64°) (Found: C, 59.5; H, 5.9. Calc. for $C_9H_{10}O_4$: C, 59.3; H, 5.5%). It had δ (220 MHz, $CDCl_3$) 3.56, (s, OMe), 5.51 (s, OCH_2), 6.90 (t, J 8.3, H-5), 7.00 (d, J 8.3, H-3), 7.48 (td, J_1 8.3, J_2 2.2, H-4), 7.93 (td, J_1 8.3, J_2 2.2, H-6), 8.66 (s, CHO); m/z 182 (33, $M^{\cdot+}$), 152 [21, $(M - 2 \times Me)^+$], 120 [51, $(M - MOM - H_2O)^+$]; and ν_{max} (film) 3210-3004b, 1680s, 1615s, 1486m, 1304m, 1155m, 1057m cm^{-1}.

Methoxymethoxy 2-Methoxymethoxybenzoate.

To a solution of 2-hydroxybenzoic acid (276 mg, 2 mmole) in ether (5 ml) under nitrogen was added methoxymethyl chloride (0.8 ml of 1:1 mixture with methyl acetate, 4.2 mmole), and triethylamine (1.0 ml, 7.2 mmole). The mixture was left stirring at room temperature overnight. The white precipitate was then filtered. Removal of the solvent gave a colourless liquid (320 mg). Its p.m.r. spectrum in d-chloroform showed, mainly 2-methoxymethoxybenzoic acid; together with the desired ester in the ratio 6:1, respectively by integration of OMe groups.

The product was then dissolved in chloroform (5 ml) and washed with 10% sodium hydroxide (2 x 5 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product as a pale yellow oil (45 mg, 10%) (Found: C, 59.0: H, 6.4%. $M^{\cdot+}$ 226.0836. $C_{11}H_{14}O_5$ requires M 226.0841). It had δ (220 MHz, $CDCl_3$) 3.35 (s, OMe), 3.39 (s, OMe), 5.10 (s, CH_2), 5.30 (s, CH_2), 6.92 (dt, J_1 7.5, J_2 2.2, H-5), 7.09 (d, J 7.8, H-3), 7.32 (td, J_1 7.8, J_2 2.2, H-4), 7.70 (dd, J_1 7.8, J_2 2.2, H-6); m/z 226(1, $M^{\cdot+}$), 181[2, $(M - OMe)^+$], 165[7, $(M - MOM)^+$], 120[21, $(M - MOM - OCH_2)^+$]; and ν^{film}_{max} 1734s, 1602s, 1486s cm^{-1}.

Note:

Neutralisation of the aqueous portion with 10% acetic acid gave 2-hydroxybenzoic acid. A similar result was obtained when the aqueous portion was acidified with 5% sulfuric acid. When carbon dioxide was bubbled through the aqueous portion, it gave 2-methoxymethoxybenzoic acid as a pale yellow oil.

Methyl 2-Methoxymethoxybenzoate.

Methyl 2-hydroxybenzoate (304 mg, 1 mmole) gave after the above procedure a colourless liquid (170 mg, 54%) the p.m.r. spectrum of which in d-chloroform showed it to be a mixture of starting material and the desired product in the ratio 3:1, respectively by integration of the CO_2Me and OMe resonances. The product was then dissolved in chloroform (10 ml) and the solution was washed with aqueous 5% sodium hydroxide (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product as a colourless liquid (39 mg, 10%) (Found: C, 61.2; H, 6.4. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.1%). It had δ (220 MHz, $CDCl_3$) 3.54 (s, OMe), 3.90 (s, CO_2Me), 5.28 (s, OCH_2), 7.08 (dt, J_1 8.9, J_2 2, H-5), 7.20 (d, J 8.9, H-3), 7.46 (td, J_1 8.9, J_2 2, H-4), 7.80 (dd, J_1 8.9, J_2 2, H-6); m/z 196(37, $M^{\cdot+}$), 181[6, $(M - Me)^+$], 165[69, $(M - OMe)^+$], 135[33, $(M - MOM)^+$], 120[31, $(M - MOM - OMe)^+$]; and ν_{max} (film) 1731s, 1255m cm^{-1}.

2-Methoxymethoxyacetophenone.

2-Hydroxyacetophenone (372 mg, 2 mmole) gave after the above procedure a colourless liquid (317 mg, 64%), the p.m.r. spectrum of which in d-chloroform showed it to be a mixture of the starting material and the desired product in the ratio 4:1, respectively by integration of the OMe and COMe resonances. Work-up was as in the foregoing procedure afforded the title compound as a colourless liquid (77 mg, 16%) (Found: C, 66.5; H, 6.7%. $M^{\cdot+}$ 180.0792. $C_{10}H_{12}O_3$ requires C, 66.7; H, 6.7%. M 180.0786). It had δ (220 MHz, $CDCl_3$) 2.62 (s, COMe), 3.50 (s, OMe), 5.28 (s, OCH_2), 7.05 (td, J_1 9, J_2 3, H-5), 7.18 (d, J 9, H-3), 7.45 (td, J_1 9, J_2 2, H-4), 7.72 (dd, J_1 9, J_2 2, H-6); m/z 180(24, $M^{\cdot+}$), 156[100, $(M - 24)^+$], 135[22, $(M - MOM)^+$]; and ν_{max} (film) 1677s, 1598m, 1483m, 1454m cm^{-1}.

2'-(Methoxymethoxy)carbonyl-2,5-dimethoxybenzophenone.

2'-Hydroxycarbonyl-2,5-dimethoxybenzophenone (50 mg, 0.17 mmole) gave after the above procedure the title compound (48 mg, 83%) as a pale yellow liquid which was distilled (bulb-to-bulb) at 100-105°/0.1 mmHg (Found: $M^{\cdot+}$, 330.1103. $C_{18}H_{18}O_6$ requires M,330.1116). It had δ (220 MHz, $CDCl_3$) 3.35 (s, OMe), 3.48 (s, OMe), 3.62 (s, OMe), 5.26 (s, OCH_2), 6.85 (d, J 8.9, H-3), 7.08 (dd, J_1 8.9, J_2 3.3, H-4), changed to a doublet J 8.9 on irradiation at 7.42), 7.32 (dd, J_1 7.8, J_2 2.2, H-3'), 7.42 (d, J 3.3, H-6), 7.52 (td, J_1 7.8, J_2 2.2, H-5'), 7.58 (dt, J_1 7.8, J_2 2.2, H-4', changed to a triplet on irradiation at 8.01), 8.01 (dd, J_1 7.8, J_2 2.2, H-6'); m/z 330(73, $M^{\cdot+}$), 285[5, $(M - MOM + H)^+$], 165[30, $2,5\text{-}(MeO)_2C_6H_3CO^+$]; and ν_{max} (film) 1658s, 1727s cm^{-1}.

2,5-Bis(1-ethoxyethoxy)benzaldehyde.

To a stirred solution of 2,5-dihydroxybenzaldehyde (552 mg, 4 mmole) in dichloromethane (40 ml) was added ethoxyethene (1.6 ml, 16.6 mmole) and pyridinium p-toluenesulfonate (125 mg, 0.5 mmole). The solution was then stirred at room temperature for 15.5 h., washed with 10% sodium hydroxide (2 x 20 ml), then with saturated sodium chloride (1 x 20 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product as a yellowish oil (850 mg, 76%). Small scale distillation (bulb-to-bulb) (110 mg) at 70-74°/0.5 mmHg gave the pure product as a pale yellow oil (100 mg) (Found: C, 63.6; H, 7.8. $C_{15}H_{22}O_5$ requires C, 64.0; H, 8.2%). It had δ (220 MHz, $CDCl_3$) 1.18 (t, J 7.2, 2 x Me of the Et groups), 1.45 (d, J 5.5, Me), 1.50 (d, J 5.5, Me), 3.56 (qq, J_1 11, J_2 9, CH_2), 3.26 (qq, J_1 11, J_2 9, CH_2), 5.32 (q, J 5.5, CH), 5.41 (q, J 5.5, CH), 7.12 (d, J 8.9, H-3), 7.18 (dd, J_1 8.9, J_2 3.3, H-4), 7.42 (d, J 3.3, H-6), 10.43 (s, CHO); m/z 282(3, $M^{\cdot+}$), 237[9, $(M - OEt)^+$], 210[27, $(M - MEM + H)^+$],

165 [60, $(M - MEM - OEt)^+$], 138 [60, $(M - 2MEM + 2H)^+$]; and ν_{max} (film) 1690s, 1610m, 1480m, 1380m cm^{-1}.

Note:

Reaction using 2,5-dihydroxybenzaldehyde and ethoxyethene in the presence of concentrated hydrochloric acid[18] gave starting aldehyde.

2-Hydroxy-5-(1-ethoxyethoxy)benzaldehyde.

On distillation (bulb-to-bulb) of 2,5-bis(1-ethoxyethoxybenzaldehyde (800 mg, 2.8 mmole) at 76-80°/0.5 mmHg, the above compound was obtained as a greenish liquid (465 mg, 78%) (Found: C, 62.9; H, 7.0. $C_{11}H_{14}O_4$ requires C, 62.9; H, 6.7%). It had δ (220 MHz, $CDCl_3$) 1.20 (t, J 7, Me of Et group), 1.45 (d, J 5.5, Me), 3.58 (dq, J_1 17, J_2 7, OCH), 3.76 (dq, J_1 17, J_2 7, OCH), 5.30 (q, J 5.5, CH), 6.82 (d, J 8.5, H-3), 7.21 (bs, H-6), 7.25 (d, J 8.5, H-4), 9.80 (s, CHO), 10.68 (bs, OH); m/z 210 (6, M^+), 165 [17, $(M - OEt)^+$], 138 [71, $(M - MEM + H)^+$]; and ν_{max} (film) 2930-2977b, 1663s cm^{-1}.

2-(2-Bromophenyl)-1,3-dioxolane.

A mixture of 2-bromobenzaldehyde (10.0 g, 0.4 mole) 2-methoxy-1,3-dioxolane (9.0 g, 0.6 mole) and toluene-p-sulfonic acid 3.0 g. 9.0 mmole) in dry toluene (160 ml) was refluxed for 36 h., using a Dean-Stark apparatus. The resulting pale yellow solution was then cooled to room temperature. Triethyl amine (2.0 g) was then added and after stirring for 10 min. the reaction mixture was poured into water (100 ml). The organic layer was separated, washed with water (3 x 50 ml) and dried (Na_2SO_4). Removal of the solvent gave a pale yellow oil (9.8 g, 81%) which was distilled (bulb-to-bulb) at 98-104°/0.5 mmHg to give the pure product as a colourless oil

(8.0 g, 68%) (lit.,[19] 102-106°/0.5 mmHg) (Found: C, 47.0; H, 4.0. Calc. for $C_9H_9O_2Br$: C, 47.2; H, 3.9%). It had δ (60 MHz, $CDCl_3$) 4.02 (b, OCH_2CH_2O), 6.02 (s, OCHO), 7.00-7.70 (m, ArH_4); m/z 330 (240, $M^{\cdot+}$), 228 (26, $M^{\cdot+}$), 229 [58, $(M - 1)^+$], 227 [60, $(M - 1)^+$], 185 [30, $(M - MeCHO)^+$], 183 [30, $(M - MeCHO)^+$], 149 [30, $(M - Br)^+$], 73 (100, $-\overset{O}{\underset{O}{CH}}$); and ν_{max} (film) 1690s, 755s cm^{-1}.

Note:

A similar reaction of benzaldehyde (1.06 g, 0.1 mole) and 2-methoxy-1,3-dioxolane (15.7 g, 0.15 mole) in the presence of p-toluenesulphonic acid (300 mg, 2.9 mmole) with work-up as in the foregoing procedure afforded benzaldehyde ethylene acetal (11.7 g, 78%). It had δ (60 MHz, $CDCl_3$) 3.90 (s, OCH_2CH_2O), 5.86 (s, OCHO), 7.25-7.40 (m, ArH_5).

Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-lithium with Substituted Benzaldehyde: A General Procedure.

To a solution of 2-(2-bromophenyl)-1,3-dioxolane (1.0 mmole) in ether at -70° under nitrogen was added 15% n-butyl-lithium in hexane (1.2 mmole) and the resulting yellow solution was stirred at -70° for 1 h. The aldehyde (Note 1) in ether was added portion-wise and after stirring for an additional 2 h. at the above temperature the mixture was decomposed by water or mild acid as follows.

(i) Decomposition with water.

The cold reaction solution was poured into water and the organic layer separated, washed with water, and dried (Na_2SO_4). Removal of the solvent always gave a colourless oil.

(ii) Decomposition by mild acid.

The cold solution was treated with either aqueous 5% acetic acid or solid pyridinium p-toluenesulfonate until it was about neutral (pH 7-8). Usual work-up then normally gave a colourless oil.

Note 1. In most of the coupling reactions, less then 1.0 equivalent of aldehyde was used: the quantity is stated for the individual experiments.

Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-lithium with 3-Methoxybenzaldehyde: An Attempt to Prepare α-[2-(1,3-Dioxolan-2-yl)phenyl]-3-methoxybenzyl Alcohol.

A solution of 2-(2-bromophenyl)-1,3-dioxolane (230 mg, 1.0 mmole) in ether (15 ml), 15% n-butyl-lithium in hexane (0.55 ml, 1.2 mmole), and 3-methoxybenzaldehyde (122.5 mg, 0.9 mmole) in ether (5 ml) gave, after decomposition with water and work-up as in the general procedure, a yellowish oil (224 mg). Its p.m.r. spectrum in d-chloroform showed a singlet at δ 3.73 possibly due to the methoxy group of the desired product, a singlet at 3.81 due to the methoxy group of starting aldehyde, a singlet at 4.05 possibly due to the acetal group of the desired product and starting aldehyde, singlets at 5.77, 5.72, 6.05 and 6.25 which may be due to -OCH- and -OCHO- groups, respectively, a singlet at 6.15 possibly due to a hydroxy group of the desired product (removed by D_2O), a singlet at 9.92 due to the formyl group of the starting aldehyde, and a multiplet at 6.80-7.60 which was too big for eight aromatic protons. Its mass spectrum showed a molecular ion at 286 (4, $M^{\cdot+}$) and fragments at

225 [100, (M - OH - MeCHO)$^+$], 224 [99, (M - H_2O - MeCHO)$^+$], 210 [10, (M - HO - MeCHO - Me)$^+$], 194 [14, (M - OH - MeCHO - OMe)$^+$], 181 [46, (M - OH - $HCOCH_2CH_2O$ - Me)$^+$], 165 [36, (M - OH - $HCOCH_2CH_2O$-OMe)$^+$], 135 (21, 3 - $MeOC_6H_3CO^+$), 105 (32, $PhCO^+$), 77 (78, Ph^+). The spectrum suggested that the product may have contained the desired alcohol together with the starting aldehyde.

Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-lithium with 3-[(Trimethylsilyl)oxy]benzaldehyde: An Attempt to Prepare α-[2-(1,3-Dioxolan-2-yl)phenyl]-3-bis[(trimethylsilyl)oxy]benzyl Alcohol.

The above coupling reaction was repeated, using a solution of 3-[(trimethylsilyl)oxy]benzaldehyde (194 mg, 0.1 mmole) in ether (5 ml), instead of 3-methoxybenzaldehyde. Work-up as in the foregoing procedure, afforded a colourless oil (218 mg). Its p.m.r. spectrum in d-chloroform showed a singlet at δ 0.07 due to a trimethylsilyl group, singlets at 3.79 and 4.01 possibly due to acetal groups, and a singlet at 9.86 due to the formyl group of the starting aldehyde. The rest of signals were multiplets at δ 5.80-7.50, and were not assigned. Its mass spectrum showed a molecular ion at 614(1), and fragments at 420(2), 402(10), 226(5), 211(22), 210(39), 185(20), 165(20), 194(8), 121(26), 105(14). The spectrum suggested that the product may have contained the desired alcohol (which may not be thermally stable) together with unreacted aldehyde.

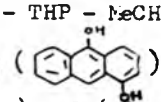
Note:

Dissolving the above product mixture in dry methanol and stirring the solution at room temperature for 3.5 h. followed by removal of the solvent gave a colourless oil. Its p.m.r. spectrum in d-chloroform did not show the trimethylsilyl group, and the rest of the signals were

too complicated to be assigned to the desired alcohol, although its CI mass spectrum showed the required quasimolecular ion; m/z (EI) 227 [4, $(M - CH_3CHO - H)^+$] and m/e (CI, NH_3) 273 [3, $(M + 1)^+$] which suggested that the hydrolysis product may have contained the desired alconol: α-[2-(1,3-Dioxolan-2-ylphenyl)]-3-hydroxybenzyl Alcohol. The product was not further examined.

Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-lithium with 3-[(Tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde: An Attempt to Prepare α-[2-(1,3-Dioxolan-2-yl)phenyl]-3-[(tetrahydro-2H-pyran-2-yl)oxy]benzyl Alcohol.

To a solution of 2-(1,3-dioxolan-2-yl)phenyl-lithium [prepared from 0.50 ml (1.20 mmole) of 15% n-butyl-lithium in hexane and 230 mg (1.0 mmole) of 2-(2-bromophenyl)-1,3-dioxolane in ether (15 ml), as described in the above experiment , was added 3-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde (138.8 mg, 0.50 mmole) in ether (5 ml), under nitrogen. After decomposition with water and work-up as in the general procedure, a pale yellow oil (273.5 mg) was obtained. Its p.m.r. spectrum in d-chloroform showed a broad singlet at δ 1.20-2.10 possibly due to six methylene protons, a broad singlet at 3.50-3.60 possibly due to two methylene protons α- to oxygen of a tetrahydropyranyl group, a singlet at 3.95 perhaps due to four protons of an acetal group, singlets at 5.75 and 5.95 possibly due to protons of -OCHO- and -CHO- groups, respectively, a multiplet at δ 6.90-7.60 due to eight aromatic protons, and a singlet at 9.88 due to the formyl group of the starting aldehyde. Its mass spectrum showed fragments at 272 [1, $(M - THP + H)^+$], 271 [1, $(M - THP)^+$],

254 [6, ($\underline{M}$ - THP - H_2O + H)$^+$], 228 [1, (M - THP - MeCHO + H)$^+$], 227 [4, (M - THP - MeCHO)$^+$], 226 [3, (M - THP - MeCHO - H)$^+$], 211 [22, (M - THP - MeCHO -HO)$^+$], 210 [95, ] and 85 (100, THP$^+$). Other fragments at $\underline{m/z}$ 122(4), 121(4), 105(13), 104(4) were also observed. The above spectra suggested that the product may have contained the desired product together with starting aldehyde.

Hydrolysis of The Above Product Mixture with Pyridinium p-Toluenesulfonate (PPTS).

A mixture of the above product (35.6 mg) and pyridinium p-toluenesulfonate (3.0 mg) in ethanol (3 ml) was stirred at room temperature for 4 h. The solvent was then removed and water (5 ml) was added to the residue. Ether extraction afforded a colourless oil (24.6 mg). Its p.m.r. spectrum in d-chloroform showed multiplets at δ 1.01-1.80 and 3.50-4.00, a singlet at 4.05 possibly due to an acetal group, a doublet, $J \simeq 5$, at 5.75 possibly due to an -OCH- proton, a singlet at δ 6.05 possibly due to -OCHO- protons, and a singlet at 10.80 due to the formyl group of the starting aldehyde. The rest of the protons showed multiplets at δ 7.20-7.70 but the integration was too big for eight aromatic protons. Its mass spectrum showed fragments at 275 [3, ($\underline{M}$ + 3)$^+$?], 273 [3, ($\underline{M}$ + 1)$^+$], 255 [6, ($\underline{M}$ - HO)$^+$], 227(11), 211(100), 210(55). The material was not further examined.

Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-litnium with 2-Hydroxy-5-methoxybenzaldehyde: An Attempt to Prepare α-[2 -(1,3-Dioxolan-2-yl)phenyl]-2-hydroxy-5-methoxybenzyl Alcohol.

2-(2-bromophenyl)-1,3-dioxolane (460 mg, 2.0 mmole) in ether (15 ml), 15% n-butyl-lithium in hexane (1.10 ml, 2.4 mmole) and 2-hydroxy-5-methoxybenzaldehyde (136 mg, 0.9 mmole) gave, after decomposition with 5% acetic acid and work-up as in the general procedure, a yellowish oil (225 mg). Its p.m.r. spectrum in d-chloroform showed singlets at δ 3.60, 3.66, 3.73 which may be due to methoxy groups, a singlet at 4.03 due to an acetal group, singlets at 5.73 and 5.98 which may be due to two protons of -CCHC- groups, and a singlet at 10.65 possibly due to the formyl group of the starting aldehyde; the rest of the protons were in the aromatic region. Its mass spectrum showed the molecular ion at 302(1), and fragments at 300(1), 286(1), 285(4), 284(7), 269(6), 255(3), 240(91), 225(14), 211(100), 197(16), 181(10), 168(12), 152(12), 141(11), 115(15), 105(16). The above spectra suggested that the product may have contained the desired product together with the starting material. The product was not further investigated.

Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-lithium with 2-Hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde: An Attempt to Prepare α-[2-(1,3-Dioxolan-2-yl)phenyl]-2-hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]benzyl Alcohol.

2-(2-Bromophenyl)-1,3-dioxalane (460 mg, 1.0 mmole) in ether (15 ml), 15% n-butyl-litnium in hexane (1.10 ml, 2.4 mmole), and 2-hydroxy-5-[(tetrahydro-2H-pyran-2-yl)oxy]benzaldehyde (200 mg, 0.91 mmole) after decomposition with 5% acetic acid and work-up as in the general procedure gave a yellowish oil (290 mg). Its p.m.r. spectrum in d-chloroform was too complex to be due to the desired product, and showed a broad singlet at δ 1.62, singlets at 3.70, 4.02, 5.76, 9.62, and 9.75. The rest of the protons gave multiplets in the aromatic region. Its mass spectrum showed a molecular ion at 226(14), and fragments at 107(20), 165(23), 155(13), 149(30), 107(13), 105(22), 91(44), 85(67), 73(35). The product was not further examined.

α-[2-(1,3-Dioxolan-2-yl)phenyl]-2,5-dimethoxybenzyl Alcohol.

A solution of 2-(2-bromophenyl)-1,3-dioxolane (1.40 g, 6.0 mmole) in ether (Note 1) (65 ml), 15% n-butyl-litnium in hexane (3.10 ml, 6.9 mmole) (Note 2), and 2,5-dimetnoxybenzaldehyde (0.66 g, 5.4 mmole) in ether (10 ml) gave, after decomposition with water and work-up as in the general procedure a colourless oil (1.73 g, 90%). Its p.m.r. spectrum in d-chloroform (60 MHz) showed it to be a mixture of the title compound (Note 3) (singlets at δ 3.56 and 3.73 due to two metnoxy groups, singlets at 6.20 and 6.35 due to -OCHO- and -CHO- groups, respectively) and the starting aldehyde (Note 2), (singlets at δ 3.75

and 3.80 due to two methoxy groups and a singlet at 10.30 due to the formyl group) in about 1:1 ratio, respectively.

Note 1. Similar reaction in THF gave more starting material.

Note 2. Using a large excess (100%) of 15% n-butyl-lithium in hexane gave 1-(2,5-dimethoxyphenyl)-butan-1-ol; isolated as the second fraction from flask column chromatography, as a colourless oil, b.p. 70-76°/0.01 mmHg. It had δ (60 MHz, $CDCl_3$) 0.95 (bm, Me), 1.20-2.20 [bm, $(CH_2)_3$], 3.75 (s, OMe), 3.79 (s, OMe), 4.50-5.00 (bm, CH), 6.80 (s, ArH_2), 6.90 (m, ArH); and m/z 224 (9, $M^{\cdot+}$), 206 [4, $(M - H_2O)^+$], 185(11), 167(53), 149(34). The product was not studied in further detail.

Note 3. The rest of the signals were multiplets in the aromatic region (δ 6.50-7.60).

Isolation of The Product.

The above crude product (300 mg) (Note 4), was purified using flash column chromatography on silica gel (rinsed with 5% triethylamine in ether before use) using 1:1 ether-hexane as eluent.

The first fraction was a pale yellow oil which probably contained benzaldehyde ethylene acetal. It had the same Rf on t.l.c. as an authentic sample. This fraction was not further examined.

The second fraction was a pale yellow oil (140 mg). Its p.m.r. spectrum in d-chloroform showed that it was 2,5-dimethoxybenzaldehyde.

The third fraction was the desired product as a colourless oil (110 mg, 37%) (Found: C, 66.4; H, 6.1%. $M^{\cdot+}$, 316.1296. $C_{10}H_{20}O_5$ requires C, 66.4; H, 6.3%. M, 316.1311). It had δ (300 MHz, $CDCl_3$) 3.60 (s, OMe), 3.74 (s, OMe), 4.00-4.24 (m, OCH_2CH_2O), 6.20 (s, -OCHO-),

6.40 (d, J 2.5, -CH-; changed to a singlet on addition of D_2O), 6.76 (s, H-3 + H-4), 7.12 (s, H-6), 7.20 (m, H-6'), 7.26-7.32 (m, H-4' + H-5'), 7.62 (t, J 4, H-3'), 7.10-7.40 (bs, OH); m/z 316 (19, $M^{\cdot+}$), 254 [87, $(M - CH_3CHO - H_2O)^{\cdot+}$], 239 [33, $(M - MeCHO - H_2O - Me)^{+}$], 223 [41, $(M - MeCHO - H_2O - Me - OMe)^{+}$], 133 (100, )$^{+}$; and ν_{max} (CH_2Cl_2) 3700b, 1700s cm^{-1}.

Note 4. Purification on a gram scale failed to give the pure product: a mixture with 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone was always isolated.

Monitoring of The Above Coupling Reaction.

The above reaction was repeated using a smaller scale: 0.2 mmole of 2-(2-bromophenyl)-1,3-dioxolane 0.23 mmole of 15% n-butyl-lithium in hexane, and 0.18 mmole of 2,5-dimethoxybenzaldehyde. When the addition of 2,5-dimethoxybenzaldehyde was completed, 2 ml samples of the reaction mixture were removed, using a syringe, at intervals of 5, 10, 15, 20, 25, 30, 60, 120, 150, and 240 min. Each sample was then immediately decomposed with water (2 ml) and worked up as in the previous experiment. The product isolated, usually a colourless oil, was analysed using p.m.r. spectroscopy (60 MHz) in d-chloroform, All the samples showed that they still contained 2,5-dimethoxybenzaldehyde. The followings ratios of unreacted aldehyde, the desired product, and 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone were obtained; estimated by comparison of the integration at δ 10.30 (starting aldehyde), 6.20 (desired product), and 3.67 (methoxy group, for 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone).

Time (min)	Starting aldehyde	Desired product	Lactone *
5	1	2	-
10	1	3	-
15	1	1.5	-
20	1	1	-
25	1	-	1
30	1	1	-
60	1	1	-
120	1	1	-
240	1	1	-

Lactone * is 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzophenone.

Notes:

(a) Formation of 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzofuranone may be due to hydrolysis of the acetal group in the desired product followed by oxidation, since the product changed in to 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzophenone when it was left at room temperature for several days. One reaction which was left at room temperature overnight, gave mostly a mixture of 2,5-dimethoxybenzaldehyde and 1,3-dihydro-3-(2,5-dimethoxyphenyl)isobenzophenone.

(b) Monitoring showed that the above coupling reaction at -30° gave only 2,5-dimethoxybenzaldehyde, as shown by its p.m.r. spectrum in d-chloroform.

α-[2-(1,3-Dioxolan-2-yl)phenyl]-2,5-bis[(trimethylsilyl)oxy]benzyl Alcohol.

A solution of 2-(2-bromophenyl)-1,3-dioxolane (230 mg, 1.0 mmole) in ether (15 ml), 15% n-butyl-lithium in hexane (0.54 ml, 1.2 mmole) and 2,5-bis[(trimethylsilyl)oxy]benzaldehyde (254 mg, 0.9 mmole) gave after decomposition with water and work-up as in the general procedure a light brown oil (284 mg, 73%) (Note 1) (Found: $M^{\cdot+}$, 432.1782. $C_{22}H_{32}Si_2O_5$ requires M, 432.1788). It had δ (60 MHz, $CDCl_3$) 0.43 (s, $SiMe_3$), 0.65 (s, $SiMe_3$), 4.45 (s, OCH_2CH_2O), 6.47 (s, CH), 6.64 (s, CH), 6.97 (s, ArH_2), 7.35–8.00 (m, ArH_5 + OH); m/z 432 (4, $M^{\cdot+}$), 370 [11, $(M - Me_3 - OH)^{\cdot+}$], 342 [6, $(M - SiMe_3 - HO)^{\cdot+}$], 298 [42, $(M - SiMe_3 - OH - MeCHO)^{\cdot+}$], 269 [29, $(M - SiMe_3 - OH - Me_3 - MeCHO)^{+}$], 226 [18, $(M - 2 \times SiMe_3 - MeCHO - OH + 2H)^{+}$], 197{26, [$(M - 2 \times SiMe_3 - HCOCH_2CH_2O - OH + H)^{+}$]}, 178(16), 133(23); and ν_{max} (film) 3000-3600b, 1500s, 1640s cm^{-1}.

Note 1. The product was unstable: it changed to a greenish gum even at the time of removal of the solvent. Similarly, its solutions in ether or dichloromethane either at room temperature or at 0° or under a nitrogen atmosphere were unstable.

2'-(1,3-Dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone.

2-(2-bromophenyl)-1,3-dioxolane (600 mg, 0.26 mmole) in ether (30 ml), 15% n-butyl-litnium in hexane (1.46 ml, 0.32 mmole), and 2,5-bis(methoxymethoxy)benzaldehyde (590 mg, 0.26 mmole) in ether (5 ml) gave after decomposition with water and work-up as in the general procedure, the benzyl alcohol as a colourless oil (790 mg, 80%)). The product was dissolved in ether (100 ml) and treated with activated manganese dioxide[20] (3.9 g). After stirring the reaction mixture at room temperature for 20 h. the oxidant was filtered off. Removal of the solvent gave the desired ketone as a pale yellow oil (700 mg, 71% from bromo-acetal). The product was purified using a silica gel column (which was run with 5% triethylamine in ether before use) and 1:1 hexane-ether as eluent, and was collected as the third fraction (Note 1): as a colourless oil in 63% yield (from the bromo-acetal) (Found: C, 64.5; H, 6.0%. $M^{\cdot+}$, 374.1367. $C_{20}H_{22}O_7$ requires C, 64.2; H, 5.9%. M, 374.1365). It had δ (300 MHz, $CDCl_3$) 3.24 (s, OMe), 3.48 (s, OMe), 4.02 (m, OCH_2CH_2O), 4.90 (s, OCH_2), 5.16 (s, OCH_2), 6.26 (s, OCHO), 7.14 (d, J 9, H-3), 7.22 (dd, J_1 8, J_2 3, H-4), 7.32 (d, J 3, H-6), 7.42 (m, H-4' + H-3', collapsed to a singlet on irradiation at 7.56), 7.56 (m, H-5'), 7.80 (d, J 8, H-6'); m/z 374 (33, $M^{\cdot+}$), 329 [42, $(M - MOM)^+$], 283 [24, $(M - 2 \times MOM)^{\cdot+}$], 241 [55, $(M - MeCHO - 2 \times MOM + 2H)^{\cdot+}$], 224(56); and ν_{max} (film) 1660s cm^{-1}.

Note 1. On t.l.c., the crude oxidation product showed three spots. On separation with a silica gel column as described above, the first fraction was isolated as a yellowish oil which was not identified. The second fraction was isolated as a pale yellow oil which may have contained 1-(2,5-bismethoxymethoxy)phenylpentan-1-one (Found: $M^{\cdot+}$, 282.1467). Its p.m.r. spectrum in d-chloroform showed two methoxy

groups at δ 3.30 and 3.34, two methylene protons at δ 5.05 and 5.60, aromatic protons at δ 6.80-7.50 and the rest of the protons as broad multiplets at δ 0.50-1.50, 2.30-3.10 and 3.80-4.20. It had m/z 282 (27, $M^{\cdot+}$), 251 [10, $(M - OMe)^+$], 221 [14, $(M - OMOM)^+$], 149(56). This product was not studied in further detail.

Reaction of α-[2-(1,3-Dioxolan-2-yl)phenyl]-2,5-dimethoxybenzyl Alcohol with CAN.

To a stirred solution of the alcohol (23 mg, 0.07 mmole) in acetonitrile (3 ml) and water (1 ml) was added CAN (199.5 mg, 0.35 mmole) in acetonitrile (5 ml) and water (2 ml) dropwise. The mixture was then stirred at room temperature for 2.5 h. Usual work-up gave a red-brown oil (13 mg). Its p.m.r. spectrum in d-chloroform (60 MHz) showed a broad singlet at δ 3.52, and singlets at 6.05, 6.68, and 9.90. The rest of the signals were multiplets of the aromatic region; however, the spectrum was not clean. Its mass spectrum showed a molecular ion at 284 (< 1, $M^{\cdot+}$), with fragments at 242(6), 241(7), 240(6), 226(18), 225(18), 224(42), 214(27), 197(42), 105(76), 77(64), suggesting that the product may have contained [2-(1,3-dioxolan-2-yl)benzoyl]-1,4-benzoquinone (m/z 284).

Note:

Extraction of the product with hot pentane, and removal of the pentane from the extract gave a red powder, subsequently identified as 9-hydroxy-1,4-anthraquinone (see p. 237).

2'-(1,3-Dioxolan-2-yl)-2,5-dimethoxybenzophenone.

To a stirred solution of α-[2-(1,3-dioxolan-2-yl)phenyl]-2,5-dimethoxybenzyl alcohol (42 mg, 0.13 mmole) in ether (5 ml) was added, active manganese dioxide[20] (150 mg). The mixture was then stirred at room temperature overnight and filtered through Celite. Solvent evaporation from the filtrate gave a colourless oil (34 mg, 82%) which was sublimed at 110-114°/0.01 mmHg (Found: $M^{\cdot+}$, 314.1154. $C_{18}H_{18}O_5$ requires M, 314.1154). It had δ (300 MHz, $CDCl_3$), 3.52 (s, OMe), 3.75 (s, OMe), 4.08 (m, OCH_2CH_2O), 6.20 (s, -OCHO), 6.70 (d, J 9.2, H-3), 7.06 (dd, J_1 9.2, J_2 3, H-4), 7.16 (d, J 3, H-6), 7.84 (dd, J_1 7.7, J_2 2, H-3' + H-5'), 7.50 (dd, J_1 7.7, J_2 2, H-4'), 7.75 (d, J 7.7, H-6); m/z 319 (19, $M^{\cdot+}$), 286 [65, $(M - CO)^{\cdot+}$], 270 [23, $(M - MeCHO)^{\cdot+}$], 239 [53, $(M - MeCHO - OMe - CO)^{\cdot+}$], 210 [40, $(M - MeCHO - OMe - CHO)^{\cdot+}$]; and ν_{max} (film) 1750s, 1640m cm^{-1}.

Reactions of 2'-(1,3-Dioxolan-2-yl)-2,5-dimethoxybenzophenone with CAN.

To a stirred solution of the ketone (31.4 mg, 0.1 mmole) in acetonitrile (7 ml) and water (3 ml) was added CAN (274 mg, 0.5 mmole) in acetonitrile (3 ml) and water (1 ml) and the resulting brownish solution was stirred at room temperature for 2½ h. Water (10 ml) was then added, and the product was extracted with dichloromethane (4 x 15 ml), washed with water (2 x 15 ml) and dried (Na_2SO_4). Removal of the solvent gave a red-brown oil (23 mg). Its p.m.r. spectrum in deuterochloroform showed multiplets at δ 3.20-4.60 and 6.30-8.50, and two small singlets at 9.62 and 11.30. Its mass spectrum showed the molecular ion at 284 (1, $M^{\cdot+}$), and fragments at 240 [4, $(M - CH_3CHO)^{\cdot+}$], 224 {23, $[M - (CH_2O)_2]^{\cdot+}$}, which suggested that the product may have contained [2-(1,3-dioxolan-2-yl)benzoyl]-1,4-benzoquinone (m/z 284).

Note:

A similar reaction using less CAN (3 mol instead of 5 mol) and work-up as in the above experiment, gave a red brown oil (25 mg). Its p.m.r. spectrum in d-chloroform showed that the product was a mixture of 2'formyl-2,5-dimethoxybenzophenone (singlets at δ 3.46 and 3.7o due to two methoxy group)* and 2'-formyl-2,5-dihydroxy-benzophenone (singlet at δ 11.34 due to the hydroxy group at the 2-position) * in a 1:1 ratio. Its mass spectrum showed the corresponding molecular ions at 270 (1, $M^{\cdot+}$) and 242 [1, $(M + 2)^{+}$], and a peak at 240 (3, $M^{\cdot+}$ of the quinone).

Oxidation of α-[2-(1,3-Dioxolan-2-yl)phenyl]-2,5-bis[(trimethylsilyl)-oxy]benzyl Alcohol: An Attempt to Prepare 2'-(1,3-dioxolan-2-yl)-2,5-[bis(trimethylsilyl)oxy]benzophenone.

To a solution of α-[2-(1,3-dioxolan-2-yl)phenyl]-2,5-bis[(trimethylsilyl)oxy]benzyl alcohol (43.2 mg, 0.1 mmole) in ether (5 ml) was added activated manganese dioxide[20] (100 mg, 1.15 mmole). After stirring and refluxing the reaction mixture for 2.5 h., the solid was filtered off. Removal of the solvent gave a dark brown oil (40 mg). Its p.m.r. spectrum in d-chloroform showed that it was the starting material.

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* All aromatic protons were at δ 6.20-8.40. Protons due to formyl groups were as singlets at δ 9.95 and 9.65.

It mass spectrum showed a molecular ion at 432 due to the alcohol, but no molecular ion at 430 due to the desired ketone, although its i.r. spectrum showed a small signal at ν_{max} (film) 1650w cm^{-1}.

Notes:

(a) Similar oxidations at room temperature for 4.5 h., and overnight gave the same result.

(b) Similar oxidation at room temperature using B.D.H. precipitated manganese dioxide in ether and shaking the reaction mixture at room temperature overnight, after the usual work-up, gave a brownish oil, the p.m.r. spectrum of which in d-chloroform showed the absence of the trimethylsilyl group. Its mass spectrum showed a molecular ion at 286(3), and fragments at 240(7), 226(39), 208(69), 197(41), 185(19), 152(42), 126(32). The product was not further examined.

(c) Oxidation using 1:2 chromium trioxide-pyridine (6 equivalents) in dichloromethane,[21] for 40 min. after the usual work-up gave a brownish oil the p.m.r. spectrum of which in d-chloroform still showed the starting alcohol, although its mass spectrum showed a molecular ion at 430(1) possibly due to the desired ketone.

Some Reactions of α-[2-(1,3-Dioxolan-2-yl)phenyl]-2,5-bis[(trimethylsilyl)oxy]benzyl Alcohol.

(a) With Methanol.

A solution of freshly prepared α-[2-(1,3-dioxolan-2-yl)phenyl]-2,5-bis[(trimethylsilyl)oxy]benzyl alcohol (108 mg, 0.25 mmole) in methanol (5 ml) was stirred at room temperature for 3 h. Removal of the solvent gave a brownish oil (90.5 mg). Its p.m.r. spectrum in d-chloroform contained two set of aromatic protons at δ 6.20-6.80 and

δ 6.80-7.30 in the ratio of about 1:1; a signal due to a trimethylsilyl group was not observed. However the signal due to dioxolane group was not clean. The mass spectrum of the product showed a molecular ion at 284(1) with major fragments at 240(4), 226(27), 178(100), 149(56), and 123(61).

(b) With Potassium Fluoride.

A solution of α-[2-(dioxolan-2-yl)phenyl]-2,5-bis[(trimethylsilyl)oxy]benzyl alcohol (100 mg, 0.23 mmole) in methanol (5 ml) was treated with solid potassium fluoride (26.9 mg, 0.46 mmole) all at once. After stirring at room temperature for 15 min. water (5 ml) was then added, and the product was extracted with ether (3 x 15 ml), washed with water (2 x 15 ml) and dried (Na_2SO_4). Removal of the solvent gave a colourless oil (52.5 mg). Its p.m.r. spectrum in d-chloroform showed a singlet at δ 4.05 (due to a 1,3-dioxolanyl group), a broad singlet at 4.20-4.75 (due to two hydroxy groups), singlets at 5.85 and 6.15 (due to -OCHO- and -CCH- groups, respectively), and at 6.60 (due to two aromatic protons), multiplets at 7.10-7.60 (due to five aromatic protons), and a singlet at 8.00 (due to one hydroxy group). Its mass spectrum showed a molecular ion at 226(14) with major fragments at 208(8), 197(23), 152(14), 126(12), 115(13), 105(10), and 77(26). The above p.m.r. and mass spectra suggested that the product may have contained the desired alcohol which was unstable on the probe of the mass spectrometer. The reaction was unreproducible since a repeated reaction gave a brownish oil for which the p.m.r. spectrum did not show signals due to -OCHO- and -CHO- groups.

(c) With CAN.

To a solution of freshly prepared α-[2-(1,3-dioxolan-2-yl)-phenyl]-2,5-bis[(trimethylsilyl)oxy]benzyl alcohol (108 mg, 0.25 mmole) in 7:3 acetonitrile-water (5 ml) was added CAN (548 mg, 1.0 mmole) in 7:3 acetonitrile-water (5 ml). After stirring the mixture at room temperature for 2 h. the product was diluted with water (10 ml), extracted with ether (3 x 10 ml), washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave an orange sticky oil (60 mg). Its p.m.r. spectrum in d-chloroform showed only two sets of aromatic protons, at δ 6.65-6.90 and 7.30-7.60 in the ratio of about 1:1, and its mass spectrum showed a molecular ion at 240(5) with fragments at 224(18), 197(12), 185(11), 152(29), 138(56), 137(60), 106(55), and 105(100). The product was not further examined.

Note.

Similar reactions in dichloromethane-water, and shaking the two phase mixture at room temperature for 25 min. gave an orange oil. The mass spectrum of the product showed a molecular ion at 286(3) with fragments at 270(3), 240(19), 226(74), 225(56), 224(61), 208(48), 197(100), 152(60), and 137(70) which suggested that the total product may have contained the desired α-hydroxy-2-[(1,3-dioxolan-2-yl)benzyl]-1,4-benzoquinone. The product was not further examined; since its p.m.r. spectrum in d-chloroform was not clean.

(d) With Potassium Fluoride and CAN in the Presence of Fuller's Earth.

A solution of α-[2-(1,3-dioxolan-2-yl)phenyl]-2,5-bis[(trimethylsilyl)oxy]benzyl alcohol (430 mg, 0.1 mmole) in methanol (20 ml) was treated with solid potassium fluoride (116 mg, 0.2 mmole) and Fuller's earth (2.5 g). After stirring for 10 min. a solution of CAN (1.10 g, 2.0 mmole) in water (15 ml) was added dropwise. When the addition was completed (ca. 20 mi.), the product was extracted with ether (4 x 20 ml), washed with water (2 x 20 ml), and dried (Na_2SO_4). Removal of the solvent gave a brownish oil (190 mg). Its p.m.r. spectrum in d-chloroform showed a singlet at 3.90 (due to some of the original 1,3-dioxolane group), a singlet at 6.00 (due to an -OCHO- group), a broad singlet at 6.15 (possibly due to an -OCH- group), a singlet at 6.50 (due to H-5 and H-6), a multiplet at 6.78 (due to H-3), and the rest of protons at δ 7.00-7.50. Its mass spectrum showed a molecular ion at 286(1) and fragments at 270(3), 242(3), 240(11), 226(7), 224(32), 208(52), 197(100), 152(45), 126(28), and 115(24). The above p.m.r. and mass spectra suggested that the product may have contained α-hydroxy-[2-(1,3-dioxolan-2-yl)benzyl]-1,4-benzoquinone (m/z 286).

Attempted Purification of the Product.

(a) Extraction the crude mixture with hot cyclohexane gave a deep red oil, the p.m.r. spectrum of which did not show signals due to -OCH- or -OCHO- groups.

(b) Sublimation at 70-74°/0.1 mmHg gave a brown oil, the p.m.r. spectrum of which showed only two sets of protons, as multiplets,

at δ 6.68 and at 7.10-7.40, in the ratio about 1:1. This product was not further examined.

(c) Column chromatography through polyamide using dichloromethane as eluent gave a light brown oil, the p.m.r. spectrum of which in d-chloroform showed further decomposition of the dioxolane group.

Reaction of 2'-(1,3-Dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone with Argentic Oxide and Nitric Acid.

To a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone (30 mg, 0.08 mmole) in THF (5 ml) was added argentic oxide (40 mg, 32 mmole) and 6N nitric acid (0.05 ml). After 8 min. the mixture was diluted with chloroform (15 ml) and water (5 ml) and stirring was continued for an additional 10 min. The organic layer was separated, washed with water (1 x 10 ml) and dried (Na_2SO_4). Evaporation of the solvent gave a brownish oil together with a solid (28 mg). Its p.m.r. spectrum in d-chloroform was complex. It may have contained the starting material and 2'-formyl-2,5-bis-(methoxymethoxy)benzophenone (due to singlets at δ 3.10, 3.14, 3.40, 3.41, 4.73, 4.75, 5.02, 5.04, and 10.05) together with other compounds. The crude product showed a molecular ion at 374(1) and fragments at 330(4), 285(4), 255(4), 253(4), 241(7), 240(6), 224(17). It was not further investigated.

2'-Formyl-2,5-bis(methoxymethoxy)benzophenone:

(a) Aqueous 4M periodic acid (1.5 ml, 1.37 g, 5.9 mole) was added to a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone (20 mg, 0.054 mmole) in dimethylformamide (5 ml), and the resulting yellow solution was stirred at room temperature for 24 h. Water (10 ml) was then added and the product was extracted with ether (3 x 10 ml), washed with water (10 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product as a brownish liquid (15 mg, 90%), which was purified by filtration through silica gel using ether as eluent. It had δ (220 MHz, $CDCl_3$) 3.20 (s, OMe), 3.50 (s, OMe'), 4.85 (s, OCH_2), 5.16 (s, OCH_2), 7.12 (d, J 9, H-3), 7.20 (dd, J_1 9, J_2 3.5, H-4; changed to a doublet, J 6, on irradiation at 7.40), 7.41 (d, J 3.5, H-6; changed to a singlet on irradiation at 7.20), 7.52 (m, H-3'), 7.62 (m, H-4' + H-5'), 8.02 (m, H-6'; changed to a singlet on irradiation at 7.62) 10.26 (s, CHO); m/z 330 (11, $M^{+\cdot}$), 286 [13, $(M - MOM)^+$], 255 [11, $(M - OMe - MOM - H)^+$], 253 [14, $(M - MOM - OMe + 2H)^+$], 241 [8, $(M - 2 \times MOM + H)^+$]; and ν_{max} (film) 1770s, 1640s cm^{-1}.

(b) To a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone (25 mg, 0.067 mmole) in 7:3 aqueous acetonitrile (5 ml) was added CAN (26.4 mg, 0.27 mmole). After stirring the mixture at room temperature for 2 h., water (10 ml) was added, and the product was extracted with ether (3 x 10 ml), washed with water (1 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product (15 ml, 66%). It had a p.m.r. spectrum identical with that of the product isolated from the reaction described in (a).

2'-Formyl-2,5-bis(methoxymethoxy)benzophenone:

(a) Aqueous 4M periodic acid (1.5 ml, 1.35 g, 5.9 mole) was added to a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone (20 mg, 0.054 mmole) in dimethylformamide (5 ml), and the resulting yellow solution was stirred at room temperature for 2½ h. Water (10 ml) was then added and the product was extracted with ether (3 x 10 ml), washed with water (10 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product as a brownish liquid (15 mg, 90%), which was purified by filtration through silica gel using ether as eluent. It had δ (220 MHz, $CDCl_3$) 3.20 (s, OMe), 3.50 (s, OMe), 4.85 (s, OCH_2), 5.18 (s, OCH_2), 7.12 (d, J 9, H-3), 7.20 (dd, J_1 9, J_2 3.3, H-4; changed to a doublet, J 6, on irradiation at 7.40), 7.40 (d, J 3.3, H-6; changed to a singlet on irradiation at 7.20), 7.52 (m, H-3'), 7.62 (m, H-4' + H-5'), 8.02 (m, H-8'; changed to a singlet on irradiation at 7.62) 10.26 (s, CHO); m/z 330 (11, $M^{\cdot+}$), 285 [13, $(M - MOM)^+$], 255 [10, $(M - OMe - MOM - H)^+$], 253 [14, $(M - MOM - OMe + 2H)^+$], 241 [8, $(M - 2 \times MOM + H)^+$]; and ν_{max} (film) 1770s, 1640s cm^{-1}.

(b) To a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzopnenone (25 mg, 0.067 mmole) in 7:3 aqueous acetonitrile (5 ml) was added CAN (26.4 mg, 0.27 mmole). After stirring the mixture at room temperature for 2 h., water (10 ml) was added, and the product was extracted with ether (3 x 10 ml), washed with water (1 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product (15 ml, 68%). It had a p.m.r. spectrum identical with that of the product isolated from the reaction described in (a).

Note:

Reaction with 8 mol of CAN in a two phase dichloromethane–water system and shaking at room temperature for 24 h., after the usual work-up, gave starting material.

9-Hydroxy-1,4-anthraquinone.

(a) From 2'-(1,3-Dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone.

(1) A solution of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)-benzophenone (15 mg, 0.04 mmole) in THF (4 ml) and 6M hydrochloric acid (3 ml) was stirred at room temperature for 24 h. The red precipitate was then filtered, washed with cold pentane and dried to give the title compound (7.6 mg, 75%), m.p. 198–199° with decomposition to a black tar (lit.,[22] m.p. 200°, decomp.) (Found: $M^{\cdot+}$, 224.0476. Calc. for $C_{14}H_8O_3$ M, 224.0473). It had δ (300 MHz, $CDCl_3$) 7.04 (d, J 9, H-3/2), 7.08 (d, J 9, H-2/3), 7.76(dt, J_1 8, J_2 3.3, H-6; changed to a doublet on irradiation at 8.04), 7.80 (dt, J_1 8, J_2 2, H-7; changed to a doublet on irradiation at 8.58), 8.04 (dd, J_1 8, J_2 2, H-5; changed to a doublet J 2 on irradiation 7.80), 8.18 (s, H-10), 8.58 (dd, J_1 8, J_2 2, H-8; changed to a singlet on irradiation at 7.80), 13.88 (s, OH-9); m/z 224 (100, $M^{\cdot+}$), 196 [44, $(M - 28)^+$], 168 [62, $(M - 56)^+$], 142 [56, $(M - 82)^+$], 140 [33, $(M - 3 \times 28)^+$], 139 [68, $(M - 85)^+$]; and ν_{max}^{c} (film) 3100–3600b, 1660w, 1635w cm^{-1}.

Note:

A similar reaction for 2½ h. gave a brownish semi-solid (15 mg, 90%), which on washing with cold ether left the title compound as red needles (7.5 mg, 45%). Removal of the solvent from the mother liquor

gave a red semi-solid (7.0 mg) with a very complex p.m.r. spectrum in d-chloroform, but showing singlets at δ 9.94 and 11.42 possibly due to a formyl and a hydroxy group respectively.

(2) To a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5- bis(methoxy-methoxybenzophenone (30 mg, 0.06 mmole) in dichlorometnane (5 ml) at 0° was added titanium tetrachloride (0.05 ml, 89.4 mg, 4.7 mmole). After 3 min., water (10 ml) was then added and the product was extracted with dichlorometnane (2 x 15 ml), washed with saturated aqueous sodium hydrogen carbonate (2 x 5 ml), and dried (Na_2SO_4). Removal of the solvent gave the title compound (15.2 mg, 85%). It was identical (m.p., mixture m.p., p.m.r., and m.s. spectra) with the product obtained from the foregoing reaction.

(b) From 2'-(1,3-Dioxolan-2-yl)-2,5-dihydroxybenzophenone. (p. 240).

To a stirred solution of the dihydroxybenzophenone (12 mg, 0.04 mmole) in THF (1 ml) was added 10% hydrochloric acid (3 ml). The resulting red solution was stirred at room temperature for 24 h. and the red precipitate was then collected by filtration to give a red powder (6 mg, 65%). Its p.m.r. spectrum (300 MHz) in d-chloroform showed the product contained mainly the desired anthraquinone together with 1,4-dihydroxy-9,10-anthraquinone (quinizarin) in the ratio 3 : 1 respectively.

[2-(1,3-Dioxolan-2-yl)benzoyl]-1,4-benzoquinone.

(a) From 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone.

To a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5-bis(methoxymethoxy)benzophenone (170 mg, 0.45 mmole) in a mixture of acetonitrile (7 ml) and water (3 ml) containing suspended pyridine-2,6-dicarboxylic acid (380 mg, 2.27 mmole), argentic oxide (282 mg, 2.27 mmole) was added in small portions with efficient stirring and cooling in an ice-water bath. When the addition was complete (30 min.) the mixture was filtered through Celite and the solid was washed with dichloromethane until the filtrate become colourless. The organic extracts was washed with water (2 x 15 ml), and dried (Na_2SO_4). Removal of the solvent gave a brownish oil (100 mg, 76%) which was then purified by passage through a polyamide column using benzene as eluent, to give the desired product as an orange liquid. [Found: ($\underline{M}^{\cdot+}$ + 2), 286.0835; $\underline{M}^{\cdot+}$, 284.0666. $C_{16}H_{12}O_5$ requires ($\underline{M}$ + 2), 286.0841; $\underline{M}$, 284.0685). It had δ (300 MHz, $CDCl_3$) 3.96 (s, OCH_2CH_2O), 6.22 (s, OCHO), 6.82-6.84 (m, H-3 + H-5 + H-6), 7.42 (m, H-5' + H-3'; changed to a doublet, $\underline{J}$ 3, on irradiation at 7.40), 7.60 (dt, $\underline{J}_1$ 8, $\underline{J}_2$ 3, H-4'; changed to a double-doublet $\underline{J}_1$ 8, $\underline{J}_2$ 3, on irradiation at 7.42), 7.65 (d, $\underline{J}$ 8, H-6'; changed to a singlet on irradiation at 7.60); $\underline{m/z}$ 286 25, $(\underline{M} + 2)^+$, 284 (10, $\underline{M}^{\cdot+}$), 240 [52, $(\underline{M} - MeCHO)^{\cdot+}$], 224 {46, $[\underline{M} - (CH_2O)_2]^{\cdot+}$}, 197 {74, $[\underline{M} - (CH_2O)_2 - CO + H]^{\cdot+}$}; and $\tilde{\nu}_{max}$ (film) 1660s cm^{-1}.

(b) From 2'-(1,3-Dioxolan-2-yl)-2,5-dimethoxybenzophenone.

To a stirred solution of 2'-(1,3-dioxolan-2-yl)-2,5-dimethoxy-benzophenone (31.4 mg, 0.1 mmole) in a mixture of acetonitrile (3 ml) and water (1 ml) containing suspended pyridine-2,6-dicarboxylic acid (83.7 mg, 0.5 mmole), argentic oxide (62.1 mg, 0.5 mmole) was added in small portions with efficient stirring and cooling in on ice-water bath. When the addition was complete (20 min.) the mixture was filtered through Celite and the solid was washed with dichloromethane until the filtrate became colourless. The organic extracts was washed with water (2 x 15 ml), and dried (Na_2SO_4). Removal of the solvent gave a brownish oil (19.6 mg, 69%) of the desired quinone. It was identical (p.m.r. and m.s.) with the product obtained as described under (a) above.

2'-(1,3-Dioxolan-2-yl)-2,5-dihydroxybenzophenone.

To a stirred solution of 2'- (1,3-dioxolan-2-yl)benzoyl -1,4-benzoquinone (15 mg, 0.052 mmole) in acetic acid (3 ml) was added zinc dust (30 mg, 0.46 mmole). The mixture was stirred at room temperature overnight and the solid was then filtered and rinsed with dichloromethane (4 x 5 ml). The filtrate was washed with water (2 x 5 ml) and dried (Na_2SO_4). Removal of the solvent gave the desired product as a sticky orange liquid (13 mg, 67%) (Found: $M^{\cdot+}$, 286.0851. $C_{15}H_{12}O_5$ requires M, 286.0841). It had δ (300 MHz, $CDCl_3$) 3.87 (s, OCH_2CH_2O), 5.95 (s, OCHO), 6.70 (d, J 3, H-6), 6.95 (d, J 9, H-3), 7.07 (dd, J_1 9, J_2 3, H-4), 7.33 (dd, J_1 7.5, J_2 3, H-3'), 7.50 (dt, J_1 7.5, J_2 2, H-5'), 3.55 (dt, J_1 7.5, J_2 2, H-4'), 7.90 (dd, J_1 7.5, J_2 2, H-6'), 11.63 (s, CH-2), 7.40-8.00 (bs, CH-5); m/z 286 (36, $M^{\cdot+}$), 240 [44, $(M - MeCHO + 2H)^{\cdot+}$], 224 [56, $(M - MeCHO + H_2O)^{\cdot+}$], 197 (100); and ν_{max} (film) 3000-3600b, 1660s, 1586s cm^{-1}.

Note:

The product may also have contained a trace of 9-hydroxy-1,4-anthraquinone, indicated by a singlet at δ 13.88.

Preparation of Crude 2'-Formylbenzoyl-1,4-benzoquinone.

To a stirred solution of 2'-formyl-2,5-bis(methoxymethoxy)-benzophenone (36 mg, 0.11 mmole) in a mixture of acetonitrile (7 ml) and water (3 ml) containing suspended pyridine-2,6-dicarboxylic acid (91.1 mg, 0.55 mmole), argentic oxide (676 mg, 0.55 mmole) was added in small portion, whilst efficiently stirring and cooling in an ice-water bath as described for the above experiment. Usual work-up gave a brownish sticky oil (19 mg, 73%). Its p.m.r. spectrum in d-chloroform showed multiplets in the aromatic region, broad singlets at δ 6.70 and 6.90, and a singlet at δ 9.98 due to a formyl group. It had m/z 240 (20, $M^{\cdot+}$), 224 [38, $(M - 16)^{\cdot+}$], The product was not further examined.

Notes:

(a) On standing overnight at room temperature a solution of the product in dichloromethane changed from red to dark brown.

(b) Removal of the d-chloroform, leaving of the residue at room temperature in darkness for 5 days, and then extraction with cold hexane gave a mixture of 9-hydroxy-1,4-anthraquinone and 1,4-dihydroxy-9,10-anthraquinone in the ratio 4:1, respectively. (Total product, 40%).

4a-[2-(1,3-Dioxolan-2-yl)benzoyl]-5-methyl-4a,5,8,8a-tetrahydro-1,4-naphthoquinone.

A solution of [2-(1,3-dioxolan-2-yl)benzoyl]-1,4-benzoquinone (100 mg, 0.35 mmole) and trans-penta-1,3-diene (47 mg, 69 mmole) in benzene or dichloromethane (5 ml) was left at room temperature for 20 h. Evaporation of the solvent afforded a brownish sticky oil which was purified by polyamide column chromatography using benzene as eluent to give the desired product as a pale yellow oil (113 mg, 92%) (Found: $M^{\cdot+}$, 352.1311. $C_{21}H_{20}O_5$ requires M, 352.1311). It had δ (300 MHz, $CDCl_3$) 0.92 (d, J 8, 8-Me; changed to a doublet on irradiation at 3.34), 1.98 (dm, J_1 20, H-8 α/β), 2.74 (dm, J_1 20, H-8 β/α), 3.34 (bs, H-5), 3.75 (dd, J_1 8, J_2 2.5, H-8a), 3.86-4.16 (m, OCH_2CH_2O), 5.60 (dm, J_1 12, H-7; changed to a doublet, J 12, on irradiation at 3.75), 5.70 (dm, J_1 12, H-6; changed to a doublet, J 12, on irradiation at 3.34), 5.77 (s, H-2'α), 6.76 (d, J 10, H-3/2), 6.86 (d, J 10, H-2/3), 7.44 (d, J 4.5, H-3'; changed to a singlet on irradiation at 7.54), 7.54 (m, H-4' + H-5'; changed to a doublet, J 7.5, on irradiation at 7.44 and a quartet, J 7.5, on irradiation at 7.76, 7.70 (d, J 7.5, H-6'); m/z 352 (1, $M^{\cdot+}$), 284 {5, $[M - Me(CH)_3CH_2]^{\cdot+}$}, 240 {5, $[M - Me(CH)_3CH_2 - MeCHO]^{\cdot+}$}, 224 {6, $[M - Me(CH)_3CH_2 - OCH_2CH_2O]^{\cdot+}$}, 177 (100, o-o-$CO.C_6H_4$-  $^+$), 133 (73, o-$CO.C_6H_4CO^+$), 105 (20, $PhCO^+$); and ν_{max} (film) 1973s, 1998s cm^{-1}.

Note:

Removal of the d-chloroform from the crude product, and extraction of the residue with hot hexane gave the title compound. However when the product was left at room temperature overnight, it gave a pale yellow oil. Its p.m.r. spectrum in d-chloroform indicated that it was mainly the rearrangement product 5,8-dihydro-2-[2-(1,3-dioxolan-2-yl)benzoyl]-6-methyl-1,4-dihydroxynaphthalene.

5,8-Dihydro-2-[2-(1,3-dioxolan-2-yl)benzoyl]-8-methyl-1,4-dihydroxy-naphthalene.

4a-[2-(1,3-dioxolan-2-yl)benzoyl]-5-methyl-4a,5,8,8a-tetrahydro-1,4-naphthaquinone (32 mg, 0.09 mmole) was dissolved in d_5-pyridine (0.4 ml) and the progress of reaction was followed by p.m.r. spectroscopy at room temperature. It showed the rearrangement completed after 21 h. After 36 h. the solvent was removed to give a brownish oil (30 mg, 94%). The product was purified by polyamide column chromatography using benzene as eluent (Found: $M^{\cdot+}$, 352.1304. $C_{21}H_{20}O_5$ requires M, 352.1311). It had δ (300 MHz, $CDCl_3$) 1.68 (d, J 7, 6-Me; changed to a doublet on irradiation at 3.80), 3.22 (ddt, J_1 23, J_2 8, J_3 2, H-5α/β; changed to a doublet J 23, on irradiation at 3.80), 3.40 (ddt, J_1 23, J_2 8, J_3 2, H-5β/α; changed to a double-doublet J_1 23, J_2 8, on irradiation at 3.80), 3.80 (bs, H-8), 3.92 (s, OCH_2CH_2O), 5.80 (ddd, J_1 10, J_2 4, J_3 2, H-6; changed to a doublet J 10, on irradiation at 3.40, and to a double-doublet J_1 10, J_2 4, on irradiation at 3.22), 5.96 (s, H-2'α), 6.00 (bs, H-7; changed to a doublet J 10 on irradiation at 3.80 and to a double-doublet J_1 10, J_2 4, on irradiation at 3.22), 6.50 (s, H-3), 7.36 (dd, J_1 7.5, J_2 1.5, H-3'; changed to a doublet J 7.5, on irradiation at 7.56), 7.48 (td, J_1 7.5, J_2 1.5, H-4'; changed to a triplet J 7.5, on irradiation at 7.72), 7.56 (td, J_1 7.5, J_2 1.5, H-5'; changed to a triplet J 7.5, on irradiation at 7.36), 7.72 (dd, J_1 7.0, J_2 1.5, H-6'; changed to a doublet J 1.5, on irradiation at 7.56, and to a doublet J 7.0, on irradiation at 7.48), 7.44-7.62 (b, OH-4), 12.20 (s, OH-1); m/z 352 (40, $M^{\cdot+}$), 307 [29, $(M - MeCHO + H)^+$], 290 [41, $(M - MeCHO + H_2O)^+$], 275 [56, $(M - MeCHO - H_2O - Me)^+$]; and ν_{max} (film) 3200-3420bs, 1620s, 1560s cm^{-1}.

Cyclisation of 5,6-Dihydro-2-[2-(1,3-dioxolan-2-yl)benzoyl]-8-methyl-1,4-dihydroxynaphthalene: Preparation of 5-Hydroxy-7-methyl-7,10-dihydronaphthacene-6,11-dione.

(a) Using Hydrochloric Acid.

The rearrangement product from the foregoing reaction (12 mg, 0.34 mmole) was dissolved in THF (2 ml) and 10% hydrochloric acid (4 ml) was added. The resulting brownish solution was stirred at room temperature for 20 h. The precipitate was then filtered and washed with cold pentane to give the title compound as an orange powder (6.7 mg, 68%), m.p. 156-158° (Found: $M^{\cdot+}$, 290.0932. $C_{19}H_{14}O_3$ requires M, 290.0943). It had δ (300 MHz, $CDCl_3$) 1.28 (d, J 6, Me-7; changed to a singlet on irradiation at 3.67), 3.11 (ddt, J_1 24, J_2 4, J_3 2, H-10β; changed to a doublet, J 6, on irradiation at 3.67; some fine structure removed on irradiation at 5.88), 3.39 (dt, J_1 24, J_2 4, H-10α; changed to a double-doublet, J_1 6, J_2 1.5, on irradiation at 3.67), 3.67 (m, H-7; changed to a quartet on irradiation at 5.88), 5.86 (dq, J_1 9, J_2 2, H-6; changed to a doublet of triplet, J_1 6, J_2 2, on irradiation at 3.67 and to a double-doublet, J_1 7, J_2 3, on irradiation at 3.11), 5.90 (dq, J_1 9, J_2 2, H-9; changed to a doublet of triplet, J 9, on irradiation at 3.99, and to a double-doublet, J_1 9, J_2 2, on irradiation at 3.11), 7.67 (td, J_1 9.5, J_2 1.5, H-2; changed to a double-doublet, J_1 9, J_2 4, on irradiation at 8.50), 7.74 (td, J_1 9.5, J_2 1.5, H-3; changed to a doublet, J 9.5, on irradiation at 8.50), 7.96 (dd, J_1 8, J_2 2, H-1 changed to a doublet, J 2, on irradiation at 7.74 and 7.67), 8.14 (s, H-12), 8.50 (dd, J_1 8, J_2 2, H-4; changed to a singlet on irradiation at 7.74), 14.16 (s, OH-5); m/z 290 (28, $M^{\cdot+}$), 275 [36, $(M - Me)^+$]; and ν_{max} (Nujol) 3000-3400b, 1653s, 1620s cm^{-1}.

Note:

A similar reaction using aqueous 10% sulfuric acid in ether, and shaking at room temperature for 3 h. gave starting material.

(b) Using Toluene-p-sulfonic Acid.

To the rearranged product (14 mg, 0.39 mmole) in acetone (3 ml) under nitrogen was added toluene-p-sulfonic acid (22.6 mg, 0.12 mmole). After stirring the solution at room temperature overnight, water (5 ml) was added. The product was then extracted with dichloromethane (3 x 10 ml), washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave an orange semi-solid (8.4 mg, 73%). Its p.m.r. spectrum in d-chloroform (300 MHz) showed that it contained mainly the title compound.

Note:

A similar reaction using pyridinium toluene-p-sulfonate (PPTS) instead of toluene-p-sulfonic acid gave starting material.

(c) Using Trifluoroacetic Acid.

To the rearranged product (14 mg, 0.39 mmole) in dichloromethane (3 ml) at 0° (ice-water bath) was added trifluoroacetic acid (0.5 ml). The violet coloured solution was then stirred at room temperature overnight. The mixture was then diluted with water (10 ml), and the product was extracted with dichloromethane (3 x 15 ml) washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave the title compound as an orange semi-solid (6.5 mg, 57%).

Notes:

(a) A similar reaction at 0° for ½ h., and work-up as in the above experiments gave the same result.

(b) A similar reaction using glacial acetic acid instead of trifluoroacetic acid gave starting material.

(d) Using Oxalic Acid.

The rearranged product (14 mg, 0.39 mmole) in dimethylformamide (DMF) (3 ml) was treated with aqueous 10% oxalic acid (5 ml) and the resulting orange solution was stirred at room temperature overnight. The product was extracted with dichloromethane (4 x 15 ml), washed with water (2 x 15 ml), and dried (Na_2SO_4). Removal of the solvent gave an orange semi-solid, which was then extracted with toluene to give the title compound as an orange powder (7.5 mg, 65%).

(e) Using Trifluoroacetic Anhydride.

To a stirred solution of the rearranged product (14 mg, 0.39 mmole) in dichloromethane (3 ml) was added trifluoroacetic anhydride (0.5 ml). The mixture was stirred at room temperature overnight. The excess of trifluoroacetic anhydride was then removed *in vacuo*, leaving a pale yellow oil (10 mg), which changed to brownish after a few days at room temperature. The brown product was then purified by polyamide column chromatography using 1:1 ether-hexane as eluent to give the title compound as an orange powder (7 mg, 61%).

(f) Attempted Cyclisation Using CAN.

A solution of the rearranged product (17.6 mg, 0.05 mmole) in acetonitrile (3 ml) and water (1 ml) was treated with ceric ammonium nitrate (82.2 mg, 0.15 mmole) in acetonitrile (3 ml) and water (2 ml). The mixture was stirred at room temperature for 2½ h. Ether extraction (3 x 15 ml), washing with water (2 x 20 ml), drying (Na_2SO_4), and removal of the solvent gave a pale yellow oil (11 mg). Its p.m.r. spectrum in d-chloroform was too complex for assignment. Its mass spectrum showed *m/z* 306(7), 290(20), 275(24), 261(9), 249(11), 247(13), 174(56), 149(40), 143(64), 119(46), 105(98), 91(64), 77(100).

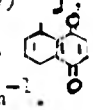
(g) Using Trifluoroacetic Acid-Boric Acetate.

To a solution of the rearranged product (14 mg, 0.39 mmole) in dichloromethane (4 ml) was added boric acetate (Note 1) (400 mg, 6.5 mmole). To the resulting pale yellow solution was added trifluoroacetic acid (0.02 ml, 29 mg, 0.26 mmole). After stirring the mixture at room temperature for 6 h., the solvent was removed. To the residue was then added cold ether (20 ml), and the solid was then filtered off. The ether solution was washed with water (2 x 15 ml) and dried (Na_2SO_4). Removal of the solvent gave a brownish semi solid (10.5 mg). Its p.m.r. spectrum in d-chloroform showed that it contained mainly the title compound, together with an unidentified product (singlets at δ 9.82 and 14.90, and a multiplet at 7.60). It mass spectrum showed a molecular ion at 306(<1), with fragments at 290(11), 288(15), 275(14), 189(4), 149(3), 133(7), 105(5). The product was not further examined.

Note 1. Boric acetate was prepared by boiling boric oxide in acetic anhydride for 15 min. The solvent was then removed, giving a white solid which was freshly used in the reaction.

Some Reactions of 4a-[2-(1,3-dioxolan-2-yl)benzoyl]-5-methyl-4a,5,8,8a-tetrahydro-1,4-naphthoquinone.

(a) With Periodic Acid: Preparation of 4a-(2-Formylbenzoyl)-5-methyl-4a,5,8,8a-tetrahydro-1,4-naphthoquinone.

The above adduct (14 mg, 0.039 mmole) was dissolved in DMF (4 ml) and 2M periodic acid (2 ml) was added. The mixture was stirred at room temperature for 2½ h. The resulting yellow solution was then diluted with water (5 ml) and the product was extracted with ether (2 x 5 ml), washed with water (2 x 5ml) and dried (Na_2SO_4). Removal of the solvent gave a pale yellow oil (11 mg, 88%), crude title compound. The product was extracted with ether and passed through a polyamide column to give the desired product as a pale yellow oil (Found: $M^{\cdot+}$, 308.1056. $C_{19}H_{16}O_4$ requires M, 308.1049). It had δ (300 MHz, $CDCl_3$) 0.88 (d, J 6, Me-5), 2.05 (dd, J_1 20, J_2 10, H-8α/β), 3.03 (dm, J_1 20, H-8β/α), 3.25 (bs, H-5), 4.00 (d, J 10, H-8a), 5.65 (m, H-6 + H-7), 6.79 (d, J 10, H-3/4), 6.95 (d, J 10, H-4/3), 7.61 (dd, J_1 8, J_2 2, H-4'/5'), 7.63 (dd, J_1 8, J_2 2, H-5'/4'), 7.75 (dd, J_1 8, J_2 2, H-3'), 7.97 (dd, J_1 8, J_2 2, H-6'), 9.80 (s, CHO); m/z 308 (4, $M^{\cdot+}$), 290 [5, $(M - H_2O)^{\cdot+}$], 275 [4, $(M - H_2O - Me)^+$], 240 {10, $[M - Me(CH)_3CH_2]^{\cdot+}$}, 175 (36, ), 133 (100, $o\text{-}CCC_6H_4CHO^+$); and ν_{max} (film) 1772s, 1695s cm^{-1}.

Note:

A similar reaction in THF, after work-up as in the above experiment, gave the desired product in a very crude state.

(b) With 5% Sulfuric Acid, Using Dichloromethane as Solvent.

Treatment of the adduct (12 mg, 0.34 mmole) in dichloromethane (3 ml) with aqueous 5% sulfuric acid and shaking the two phase mixture at room temperature for 2 h. gave, after the usual work-up, starting material (10.2 mg, 80% recovery).

(c) With 5% Sulfuric Acid in Refluxing Methanol.

To a solution of the adduct (24 mg, 0.68 mmole) in methanol (5 ml) was added 5% sulfuric acid (5 ml). The resulting pale yellow solution was then refluxed for 2½ h. The product was extracted with ether (3 x 15 ml), washed with water (2 x 15 ml) and dried (Na_2SO_4). Removal of the solvent gave a brown sticky oil (18 mg). Its p.m.r. spectrum showed singlets at δ 3.62 and 6.32, whilst the rest of the resonances were in the aromatic region. The product may have contained traces of 9-hydroxy-1,4-anthraquinone (signals at δ 7.08 and 13.84). Its mass spectrum showed m/z 354(<1), 308(2), 290(4), 275(5), 240(6), 224(20), 196(12), 163(12), 133(83), Ether extraction from the above crude mixture gave the same spectrum.

Reaction of 4a-(2-Formylbenzoyl)-5-methyl-4a,5,8,8a-tetrahydro-1,4-naphthaquinone with Pyridine.

The naphthaquinone (8 mg, 0.02 mmole) was dissolved in d_5-pyridine and the progress of reaction was followed by p.m.r. spectroscopy at room temperature; it was completed after 24 h. The solvent was then removed to give a brown oil (8 mg). Its p.m.r. spectrum in d-chloroform (300 MHz) was too complex to be completely identified; however it showed doublets at δ 0.86 and 0.96, each

J_1 19, J_2 2.5, possibly due to two methylene protons, and singlets at 5.64 and 6.88; the rest of the signals were not assigned. No signal due to an internally hydrogen-bonded OH was observed. Its mass spectrum showed a molecular ion at 308(Cl) with fragments at 290(1), 240(1), 224(1), 208(2), 175(6), 133(10), 105(12), 86(63), 84(100). The product may have contained at least two compounds.

Ether extraction of the above mixture gave a pale yellow oil, its p.m.r. spectrum of which in d-chloroform was simpler, but still difficult to interpret. Its mass spectrum CI(NH_3) showed a quasimolecular ion at 342(5) with fragments at 326(26), 309(36), 291(11), 241(44), 195(9), 168(17), 151(25), 133(17), 105(21). The product was not further examined.

Note:

A similar reaction in 1:1 pyridine-methanol gave the same result.

Some Oxidations of 5-Hydroxy-7-methyl-7,10-dihydronaphthacene-6,10-dione.

(a) Using Chromium Trioxide-Acetic Acid.

A solution of the dihydronaphthacene (4.5 mg, 0.017 mmole) in glacial acetic acid (1 ml) was treated with chromium trioxide (15 mg, 1.7 mmole). The mixture was stirred at room temperature for 3 h. and then diluted with water (5 ml). The product was extracted with ether (3 x 5 ml), washed with water (10 ml) and dried (Na_2SO_4). Removal of the solvent gave a colourless oil (1.6 mg). Its mass spectrum showed m/z 410(< 1), 379(1), 365(2), 351(2), 337(3), 323(3), 309(4), 295(5), 283(5), 281(6), 267(6), 253(7). The product was not identified.

(b) Using Lead Tetra-acetate.

A solution of the dihydronaphthacene (3.5 mg, 0.01 mmole) in dichloromethane (0.5 ml) and acetic acid (0.5 ml) was treated with lead tetra-acetate (10.7 mg, 0.02 mmole) at room temperature, and the mixture was left overnight. The mixture was diluted with water (5 ml), and the product was extracted with dichloromethane (3 x 5 ml), washed with brine (10 ml) and dried (Na_2SO_4). Removal of the solvent gave a pale yellow oil (3.0 mg) which changed to brownish after a few days at room temperature. The brown product was then purified by column chromatography through silica gel using 1:1 hexane–ether as eluent. The first fraction was isolated as an orange liquid (2.1 mg). Its p.m.r. spectrum in deuterochloroform showed multiplets in the aromatic region which were too big for six protons, multiplets at δ 3.50–3.96, 7.80–8.00 and 8.36–8.50, quartets at 4.80–5.06 and 5.20–5.26, and singlets at 7.32 and 12.96. The product was not further examined.

The column was then washed with dichloromethane, giving a brownish oil; its p.m.r. spectrum was uninformative.

2,5-Diacetoxybenzoic Acid.

To a stirred solution of gentisic acid (7.5 g, 5 mmole) in acetic anhydride (12 ml) was added concentrated sulphuric acid (10 drops) and the reaction mixture then heated for 1 h. at 70°. The solution was then cooled, water (100 ml) added, and the suspension shaken vigorously for several minutes. The product was allowed to crystallise at 0° and collected by filtration to afford white crystals (9.0 g, 76%), m.p. 120-121° (lit.,[22] m.p. 116-119°). It had δ (60 MHz, $CDCl_3$) 2.30 (s, OAc), 7.10 (d, J 9, H-3), 7.40 (dd, J_1 9, J_2 3, H-4), 7.90 (d, J 3, H-6); and m/z CI(NH_3) 332 [100, $(M + 18)^+$], 290 [15, $(M + 18 - CH_2CO)^+$], 221 {42, $[C_6H_3CO(OAc)_2]^+$}.

2,5-Diacetoxy-N-methoxy-N-methylbenzamide.

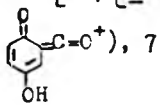
To a stirred solution of gentisic acid diacetate (3.2 g, 15 mmole) in dichloromethane (40 ml), was added oxalyl chloride (2.1 g, 16 mmole), and DMF (15 drops). Effervescence occurred and the reaction was allowed to continue for about 40 min. To this solution was then added N,O-dimethylhydroxylamine hydrochloride (1.6 g, 16 mmole) followed by pyridine (2.52 g, 2.6 ml, 32 mmole). The mixture was stirred at room temperature for 1½ h. Brine solution (40 ml) was then added and the organic layer separated. The aqueous layer was extracted with a 1:1 mixture of ether and dichloromethane (4 x 20 ml). The combined extracts were washed with brine (1 x 30 ml) and dried. Removal of the solvent gave the desired product (2.24 g, 78%) as a sticky colourless oil which was then distilled (bulb-to-bulb) at 76-78°/0.1 mmHg. (Found: C, 55.6; H, 5.6; N, 4.9. $C_{13}H_{15}NO_6$ requires C, 55.5; H, 5.4; N, 5.0%). It had δ (60 MHz, $CDCl_3$) 2.20 (s, Ac), 2.50 (s, Ac), 3.24 (s, Me), 3.47 (s, Me), 7.21 (bs, ArH_3);

m/z CI(NH_3) 299 [9, $(M + 18)^+$], 282 [100, $(M + 1)^+$], 252 [18, $(M + 1 - 2Me)^+$], 210 [79, $(M + 1 - CH_2{=}C{=}O - 2Me)^+$]; and ν_{max} (film) 1640s, 1760s cm^{-1}.

2,5-Dihydroxy-N-methoxy-N-methylbenzamide.

To a stirred solution of the foregoing diacetate (160 mg, 0.57 mmole) in methanol (10 ml), under nitrogen at room temperature was added saturated sodium hydrogen carbonate (6 ml). After stirring for 2 h. the mixture was acidified with 10% hydrochloric acid, extracted with ethyl acetate (4 x 20 ml), and dried (Na_2SO_4). Evaporation of the solvent gave a brownish oil (73 mg, 66%) of the desired product which was purified by distillation (bulb-to-bulb) at 74-80°/0.1 mmHg. (Found: C, 54.6; H, 5.8; N, 6.4. $C_9H_{11}NO_4$ requires C, 54.8; H, 5.6; N, 7.1%). Elemental analysis always showed a low nitrogen content. The above data were obtained at the third attempt using freshly distilled material (which had $M^{\cdot+}$, 197.0690. $C_9H_{11}NO_4$ requires M, 197.0688). It had δ (300 MHz, $CDCl_3$) 3.40 (s, NMe), 3.64 (s, OMe), 6.80-7.10 (b, HO-5), 6.92 (d, J 9, H-3), 6.98 (dd, J_1 9, J_2 3, H-4), 7.50 (d, J 3, H-6), 13.30-13.40 (b, HO-2), 197 (8, $M^{\cdot+}$), 168 [6, $(M - NMe)^{\cdot+}$], 167 [17, $(M - OMe + 1)^+$], 137 [100, $(M - CO.NMe.OMe)^+$]; and ν_{max} (CH_2Cl_2) 3680-3560b, 1575s cm^{-1}.

2,5-Bis[(trimethylsilyl)oxy]-*N*-methoxy-*N*-methylbenzamide.

To a stirred solution of 2,5-dihydroxy-*N*-methoxy-*N*-methylbenzamide (19.7 mg, 0.1 mmole) in ether (5 ml) under nitrogen was added trimethylsilyl chloride (43.2 mg, 0.4 mmole) and then pyridine (47.4 mg, 0.6 mmole), and the mixture was stirred at room temperature for 2½ h. The solid was then filtered off. Removal of the solvent from the filtrate gave a pale yellow oil (30.5 mg, 89%). Pentane extraction gave the desired product as a colourless oil (Found: $M^{\cdot+}$, 341.1485. $C_{15}H_{27}NO_4Si_2$ requires *M*, 341.1479). It had δ (60 MHz, $CDCl_3$) 0.23 (s, 2 x $SiMe_3$), 3.23 (s, Me), 3.34 (s, Me), 3.58 (s, OMe), 3.60 (s, OMe), 6.60–6.80 (m, ArH_3); *m/z* 341 (1, $M^{\cdot+}$), 296 [67, $(M - Me_3)^+$], 281 {61, $[M - NMe(OMe)]^+$}, 208 {66, $[M - NMe(OMe) - SiMe_3]^{\cdot+}$}, 136 (13, ), 73 (100, $SiMe_3^+$); and ν_{max} ($CDCl_3$) 1605m, 1480s cm^{-1}.

Notes:

(a) The product was very unstable: it gradually hydrolysed to the starting material either on sublimation or during work-up. Because of this, a better p.m.r. spectrum was not obtained even from the freshly prepared material. Therefore the product freshly obtained from the pentane extraction was used in the coupling reaction without further purification.

(b) Treatment of trimethylsilyl 2,5-bis[(trimethylsilyl)oxy]benzoate with oxalyl chloride followed by *N*,*O*-dimethylhydroxylamine hydrochloride at 0° under nitrogen in dichloromethane or THF failed to give the title compound. The product obtained was 2,5-dihydroxybenzoic acid.

Reaction of 2-(1,3-Dioxolan-2-yl)phenyl-lithium with 2,5-Bis[(trimethylsilyl)oxy]-*N*-methoxy-*N*-methylbenzamide.

To a solution of 2-(2-bromophenyl)-1,3-dioxolane (86.3 mg, 0.38 mmole) in ether (15 ml), at -70° under nitrogen was added 15% n-butyllithium in hexane (0.28 ml, 0.40 mmole) and the resulting yellow solution was stirred at -70° for 1 h. Then freshly prepared 2,5-bis[(trimethylsilyl)oxy]-*N*-methoxy-*N*-methylbenzamide (136 mg, 0.40 mmole) in ether (5 ml) was added portionwise and after stirring the mixture for an additional 2 h. at the above temperature, it was decomposed with water (15 ml). The organic layer was then separated, washed with water (15 ml) and dried (Na_2SO_4). Removal of the solvent gave a greenish oil (59 mg). Its p.m.r. spectrum in d-chloroform showed that it was benzaldehyde ethylene acetal.

Notes:

(a) A similar reaction at room temperature gave the same result. A similar result also obtained when the reaction was repeated in the presence of tetramethylethanediamine either at 0° or at room temperature.

(b) In one of the reactions, at room temperature without tetramethylethanediamine, the aqueous layer was neutralised with 10% acetic acid. Ether extraction from this aquecus medium gave 2,5-dihydroxy-*N*-methoxy-*N*-methylbenzamide.

N-Methoxy-N-methylaminocarbonyl-1,4-benzoquinone.

A mixture of 2,5-dihydroxy-N-methoxy-N-methylbenzamide (20 mg, 0.1 mmole), silver oxide (60 mg, 0·3 mmole), and anhydrous sodium sulphate (150 mg) in dry dichloromethane (5 ml), was shaken for 5 h. in a flask covered with aluminium foil, at room temperature. The suspension was then filtered through Celite, and washed with dichloromethane until the washings had no colour. Solvent evaporation gave an orange sticky oil (16 mg, 81%), which was sublimed at 60–68°/0.1 mmHg (Found: $M^{\cdot+}$, 195.0532. $C_9H_9O_4N$ requires M, 195.0534). It had δ (220 MHz, $CDCl_3$) 3.32 (s, NMe), 3.51 (s, OMe), 6.85 (s, H-3 + H-4 + H-6); m/z 195 (32, $M^{\cdot+}$), 135 [72, $(M^{\cdot+} - NMe.OMe)^+$], 107 [92, $(M - CO.NMe.OMe)^+$]; and ν_{max} (film) 1664s cm^{-1}.

Desilylation of 2,5-Bis[(trimethylsilyl)oxy]toluene.

(a) Using Tetrabutylammonium Fluoride.

To a stirred solution of 2,5-bis[(trimethylsilyl)oxy]toluene (100 mg, 0.37 mmole) in ether (15 ml) under nitrogen was added 1.0M tetrabutylammonium fluoride (329 mg, 1.5 mmole) in THF (1.5 ml) and the solution was stirred at room temperature overnight, washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave a violet solid (36.4 mg, 80%) which was identified as predominantly 2,5-dihydroxytoluene.

Note:

A similar reaction in THF followed by decomposition with water and extraction of the product in ether gave the starting material.

(b) Using Potassium Fluoride.

To a stirred solution of 2,5-bis[(trimethylsilyl)oxy]toluene (100 mg, 0.37 mmole) in methanol (5 ml) was added solid potassium fluoride (43.4 mg, 0.75 mmole) and the mixture was stirred at room temperature for 10-15 min. Water (10 ml) was then added and the product was extracted with ether (4 x 10 ml), washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave 2,5-dihydroxytoluene (41 mg, 86%) as a white solid.

Notes:

(a) Longer reaction times (e.g. 3 h.), and reactions in solvents such as acetonitrile-water or THF-water gave the same result. However reaction in ether-water (shaken) gave the starting material.

(b) A similar reaction in methanol in the presence of B.D.H. precipitated manganese dioxide gave a dark brownish solid; its mass spectrum showed m/z 272(<1), 154(4), 152(32), 149(27), 124(19), 122(19), 105(12), 84(10), and 69(100). Its p.m.r. spectrum was not clean, although no signal due to a trimethylsilyl group was observed. The product may have contained 2,5-dimethoxytoluene (m/z 152), methyl-1,4-benzoquinone (m/z 122) and dihydroxytoluene (m/z 124).

(c) Using CAN.

To a stirred solution of the silyl ether (134 mg, 0.5 mmole) in acetonitrile (3.5 ml) and water (1.5 ml) was added dropwise a solution of CAN (1.37 g, 2.5 mmole) in acetonitrile (7 ml) and water (3 ml) and the mixture was stirred at room temperature for 2 h. The product was extracted with ether (4 x 15 ml), washed with water (2 x 15 ml) and dried (Na_2SO_4). Removal of the solvent gave 2-methyl-1,4-benzoquinone as a yellow solid (44 mg, 74%) identical (m.p., mixture m.p., and p.m.r. spectra) with an aunthentic sample.

Notes:

(a) Similar reactions in two phase solvent systems such as ether-water and dichloromethane-water with shaking at room temperature for 2 h. gave, after the usual work-up, the same results.

(b) In contrast, a similar reaction in dichloromethane-water, but using only 2 mol of CAN instead of 5 mol gave, after work-up, a mixture of starting material, 2,5-dihydroxytoluene, and 2-methyl-1,4-benzoquinone in the ratio 3:3:1, respectively, as shown by the p.m.r. spectrum of the total product in d-chloroform.

(c) A similar reaction in dichloromethane-water in the presence of 2 mol of sodium acetate gave, after work-up, a mixture of 2,5-dihydroxy-toluene and 2-methyl-1,4-benzoquinone in about 1:1 ratio. A similar reaction in ether-water in the presence of an excess of sodium acetate (i.e. until the pH of the aqueous phase was about 6 at the beginning of the reaction) gave, after the usual work-up, the starting material.

(d) A similar reaction in aqueous acetonitrile in the presence of Fuller's earth (1.0 g) gave a mixture of starting material, 2,5-dihydroxytoluene, and 2-methyl-1,4-benzoquinone in the ratio 2:3:1,

respectively. The product contained these three compounds, in the ratio 4:3:1, respectively, when 4 mol of CAN was used.

(d) Using Potassium Fluoride and CAN.

To a stirred solution of the silyl ether (100 mg, 0.37 mmole) in methanol (10 ml) was added all at once solid potassium fluoride (110 mg, 1.9 mmole). Stirring was continued for 5 min., after which a solution of CAN (406 mg, 1.5 mmole) in water (3 ml) was added dropwise during 5 min., and the solution was then stirred for an additional ½ h. The product was extracted with ether (3 x 10 ml) washed with water (2 x 15 ml) and dried (Na_2SO_4). Removal of the solvent gave 2-methyl-1,4-benzoquinone (29.5 mg, 65%).

Notes:

(a) A similar reaction stopped after 10 min. gave a mixture of 2,5-dihydroxytoluene and 2-methyl-1,4-benzoquinone in the ratio 7:12, respectively.

(b) A similar reaction in the presence of Fuller's earth gave 2-methyl-1,4-benzoquinone in about 75% yield.

Attempted Preparation of 2'-(tert-butoxycarbonyl)-2,5-dimethoxy - benzophenone.

(a) From 2'-Chlorocarbonyl-2,5-dimethoxybenzophenone.

(1) Using tert-Butyl Alcohol and n-Butyl-lithium.

A solution of tert-butyl alcohol (7.4 mg, 0.1 mmole) in ether (2 ml) at room temperature under nitrogen was treated with 1.6M n-butyl-lithium in hexane (0.06 ml, 0.1 mmole). The resulting turbid mixture was stirred for 20 min. after which freshly prepared 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (30.6 mg, 0.1 mmole) in ether (1.0 ml) was added. After stirring the mixture at room temperature overnight, it was diluted with ether (15 ml), washed with brine (1 x 10 ml), and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow oil (15.6 mg). Its p.m.r. spectrum in d-chloroform showed that the product may have contained 2'-(n-butoxycarbonyl)-2,5-dimethoxybenzophenone [multiplet at δ 0.60-1.60 (due to n-propyl group), singlets at 3.44 and 3.78 (due to two methoxy groups) and triplet at 4.05, J 6, due to $-OCH_2$ group]* and 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone [singlets at 3.54 and 3.78 (due to two methoxy groups)]*. Its mass spectrum showed molecular ions at 342(37) and 286(40) with major fragments at 269(17), 255(8), 239(29), 225(11), 211(48), 105(77) and 149(58).

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* The rest of protons were multiplets at δ 6.70-8.10.

(2) Using tert-Butyl Alcohol alone.

A solution of freshly prepared 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (46.0 mg, 0.15 mmole) in tert-butyl alcohol (2 ml, 1.57g, 21.2 mole) was refluxed for 21 h. The solution was then cooled to room temperature. Removal of the alcohol, left a yellowish oil (46.0 mg, 100%) which solidified at room temperature m.p. 153-158°. Its p.m.r. spectrum in d-chloroform showed that it may have contained some of the desired product [singlet at δ 1.25, (too small for nine protons of tert-butyl group), singlets at δ 3.42 and 3.75 (due to two methoxy groups), and multiplets at δ 6.80-8.10 (too big for seven aromatic protons) together with, probably, the lactone of 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone, Its mass spectrum showed a molecular ion at 342(8) with fragments at 287(21), 286(96), 269(27), 239(29), 225(11), 211(73), 183(19), 165(100) and 149(57). The product was not further identified.

(3) Using tert-Butyl Alcohol in the presence of Pyridine.

A solution of tert-butyl alcohol (150 mg, 20.3 mmole) in pyridine (1.5 ml, 1.47 g, 18.5 mmole) was treated with 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (46.0 mg, 0.15 mmole) in d-chloroform (ethanol-free) (0.3 ml). The resulting light pink solution was stirred at room temperature for 2 h. and then poured into water (10 ml) and neutralised with 5% hydrochloric acid (pH 6-7). The product was extracted with ether (4 x 15 ml) washed with water (2 x 10 ml) and dried ($MgSO_4$). Evaporation of the solvent gave a pale yellow oil (18 mg). It was identical (p.m.r. spectrum) with 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone.

Note:

A similar reaction, but stirring the solution at room temperature overnight and then refluxing for 2 h. gave the same result.

(4) Using tert-Butyl Alcohol in the presence of Potassium tert-Butoxide.

A solution of freshly prepared 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (35.0 mg, 0.11 mmole), in tert-butyl alcohol (2.0 ml, 2.12 mmole) was treated with potassium tert-butoxide (25 mg, 0.22 mmole). The resulting colloidal mixture was then stirred at 35° overnight, diluted with water (10 ml), and the product was extracted with ether (3 x 15 ml), washed with water (3 x 15 ml) and dried ($MgSO_4$). Removal of the solvent gave a yellowish oil (24.5 mg). Its p.m.r. spectrum in d-chloroform was similar to that obtained from the reaction using tert-butyl alcohol alone.

Note:

A similar reaction at refluxing temperature for 5½ h., and work-up as in the foregoing procedure, gave a yellowish oil (11.5 mg, 29%), which was then distilled at 104-110°/0.5 mmHg to give a pale yellow oil. It had δ (60 MHz, $CDCl_3$) 1.33 (s, Bu^t), 3.46 (s, OMe), 3.80 (s, OMe), 6.70-7.00 (m, ArH_2), 7.25-7.60 (m, ArH_3), 7.70-7.90 (m, ArH_2); and m/z 343 [22, $(M + 1)^+$], 342 (100, $M^{\cdot+}$), 286 [42, $(M - Me_2C{=}CH_2)^{\cdot+}$], 269 [43, $(M - Me_2C{=}CH_2 - HO)^+$], 239 [46, $(M - Me_2C{=}CH_2 - CH - 2Me)^+$], 211 [69, $(M - Me_2C{=}CH_2 - CH - 2Me - CO)^+$], 165 [95, $(MeO)_2C_6H_3{\cdot}CO^+$]. The spectra suggested that the reaction may have given some of the desired product.

(5) Using tert-Butyl Alcohol in the presence of Potassium tert-Butoxide and 18-crown-6.

To a solution of freshly prepared 2'-chlorocarbonyl-2,5-dimethoxybenzophenone (30.6 mg, 0.1 mmole) in tert-butyl alcohol (2.0 ml, 21.2 mmole) was added potassium t-butoxide (11.2 mg, 0.1 mmole) and 18-crown-6 (6 mg, 0.02 mmole). The resulting greenish mixture was refluxed overnight. After cooling to room temperature, the mixture was diluted with water (15 ml), and the product was extracted with ether (4 x 15 ml), washed with water (3 x 15 ml) and dried ($MgSO_4$). Removal of the solvent gave a pale yellow oil (30.6 mg) of 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone.

(b) From 2'-Hydroxycarbonyl-2,5-dimethoxybenzophenone: Using tert-Butyl Alcohol-DCC-DMAP.

To a solution of 2'-hydroxycarbonyl-2,5-dimethoxybenzophenone (28.6 mg, 0.1 mmole) in dichloromethane (5 ml) were obtained DMAP (1.2 mg, 0.01 mmole) and tert-butyl alcohol (7.4 mg, 0.1 mmole). The solution was cooled to 0° and DCC (20.6 mg, 0.3 mmole) was added. The mixture was then stirred at room temperature overnight, and the white precipitate was filtered off. Removal of the solvent from the filtrate gave a mixture of a white solid and an oil (20.0 mg). Its p.m.r. spectrum in d-chloroform was complex, and did not show evidence for the desired product. It was not further examined.

Some Reactions of 2'-Hydroxycarbonyl-2,5-dimethoxybenzophenone.

(a) With CAN.

To a stirred solution of the carboxylic acid (28.6 mg, 0.1 mmole) in acetonitrile (3 ml) and water (1 ml) was added dropwise a solution of CAN (164 mg, 0.3 mmole) in acetonitrile (3 ml) and water (1 ml). The resulting pale yellow solution was stirred at room temperature for 1 h. Usual work-up gave an orange oil (20 mg). Its p.m.r. spectrum in d-chloroform showed a singlet at δ 6.68 with the rest of the resonances as multiplets in the aromatic region. Its mass spectrum showed m/z 258(32), 241(25), 240(100), 212(42), 184(28), 149(30), 128(19), 104(31). These spectra suggested that the product may have contained 2'-hydroxycarbonyl-2,5-dihydroxybenzophenone (m/z 258).

On sublimation at 136-140°/mmHg, it gave a pale yellow powder, but the p.m.r. spectrum of this in d-chloroform was still very complex.

Note:

A similar reaction in a two phase dichloromethane-water solution using 5 mol of CAN and shaking at room temperature for 3 h. gave the starting material.

(b) **With Trimethylsilyl Chloride-Sodium Iodide.**

To a stirred solution of the carboxylic acid (28.6 mg, 0.1 mmole) and sodium iodide (30 mg, 0.2 mmole), in acetonitrile (5 ml) under nitrogen, was added trimethylsilyl chloride (21.8 mg, 0.2 mmole). The mixture was stirred at room temperature overnight. The product was extracted with dichloromethane (3 x 10 ml), washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave the starting material.

(c) With Hydrobromic Acid.

A mixture of the carboxylic acid (28.6 mg, 0.1 mmole) and aqueous 48% hydrobromic acid (3 ml) was refluxed for 1½ h. After cooling, the product was extracted with ether (5 x 5 ml), washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave a red-brown solid (22 mg, 92%). It had m.p. 190-192° (lit.,[23] 194° It had δ (60 MHz, $CDCl_3$) 7.70-8.00 (m, H-6 + H-7), 8.10-8.50 (m, H-5 + H-8), 7.78 (s, 2 x OH) identified as 1,4-dihydroxy-9,10-anthraquinone.

(d) With Argentic Oxide-Pyridine-2,6-dicarboxylic Acid: **An Attempt to Prepare** 2'-Hydroxycarbonylbenzoyl-1,4-benzoquinone.

To a stirred solution of 2'-carboxy-2,5-dimethoxybenzophenone (28.6 mg, 0.1 mmole) in a mixture of acetonitrile (7 ml) and water (3 ml) containing suspended pyridine-2,6-dicarboxylic acid (74.5 mg, 0.45 mmole), was added argentic oxide (56.0 mg, 0.45 mmole) in small portion with efficient stirring and cooling in an ice-water bath. When the addition was complete (30 min.), the mixture was filtered through Celite and the solid was washed with dichloromethane until the filtrate became colourless. The organic layer was separated and

washed with water (2 x 10 ml) and dried (Na_2SO_4). Removal of the solvent gave an orange liquid (20 mg, 78%). Its p.m.r. spectrum in d-chloroform (60 MHz) showed only multiplets in the aromatic region and a singlet at δ 6.70. Its mass spectrum showed m/z 286(2) (Note 1), 256 (10, $M^{\cdot+}$), 199(5), 173(12), 104(100). The product gradually changed to a dark brown oil. After being left overnight at room temperature, its p.m.r. spectrum in d-chloroform showed that the singlet at δ 6.70 was no longer present (Note 2).

Note 1. The molecular ion at m/z 286 may be due to trace of the unchanged carboxylic acid or its lactone.

Note 2. The 300 MHz p.m.r. spectrum of freshly prepared material measured immediately showed extensive decomposition.

6.1. References for Chapter 6.

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