STUDIES RELATED TO THE SYNTHESIS OF TETRACYCLINE

a thesis presented by

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in partial fulfilment of the requirements for the award of the degree of

DOCTOR OF PHILOSOPHY

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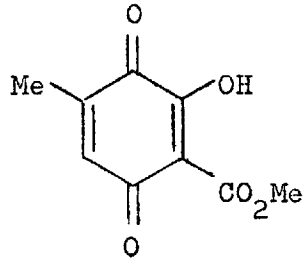
ABSTRACT

The first section of this thesis describes four aspects of tetracycline chemistry:

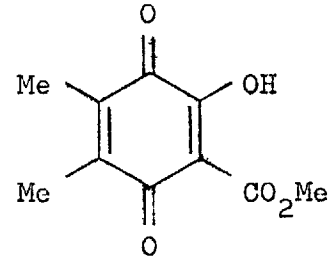
1. Some important reactions of tetracycline.
2. The biosynthesis of tetracyclines.
3. Some achievements in tetracycline synthesis.
4. A summary of the results obtained in these laboratories in the field of tetracycline synthesis.

A discussion of the author's work on this project is contained in the second section.

I. An examination of methods for the introduction of a 4-hydroxyl group onto aromatic ring A tetracycline precursors. The preparation of quinones A and B from resorcinols.

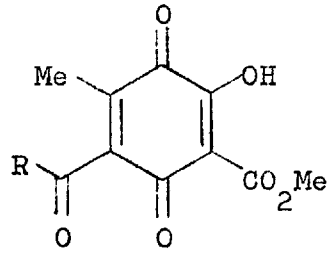


A



B

Attempts to hydrate quinones C and D to produce ring A in the correct oxidation level for tetracycline.



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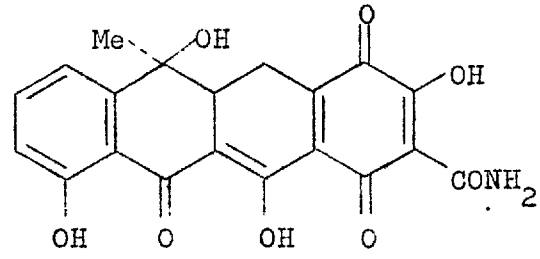
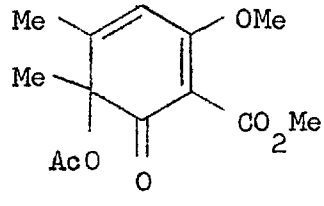


D

II. Preparation of the cyclohexadienone E from a protected orcinol derivative.



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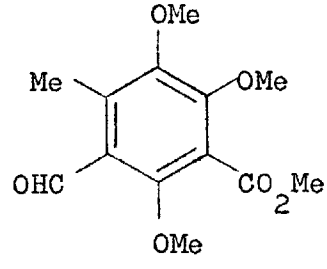
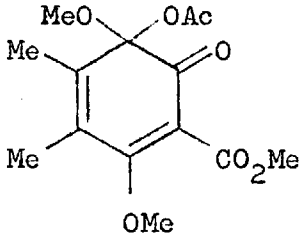


F

An investigation of the boron trichloride demethylation of the trimethoxyaldehyde F, and oxidation of the product with lead tetra-acetate to provide the quinone semiketal G.



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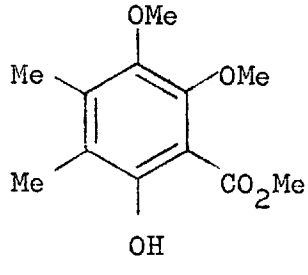

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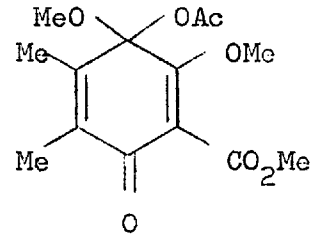
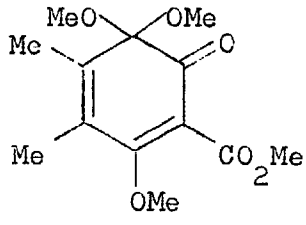
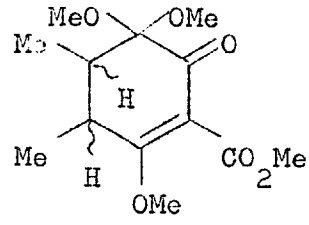


I

Preparation of the phenol H and its oxidation to the quinone semiketal I. Reduction of the semiketal J to K.

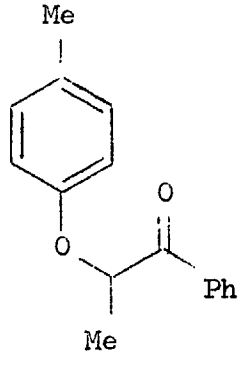


J



K

III. Attempts to finda method of o-hydroxylating phenols, including autoxidation of the ether L; pyrolysis of the phenanthrone M; rearrangement of the bromohydroperoxide N.



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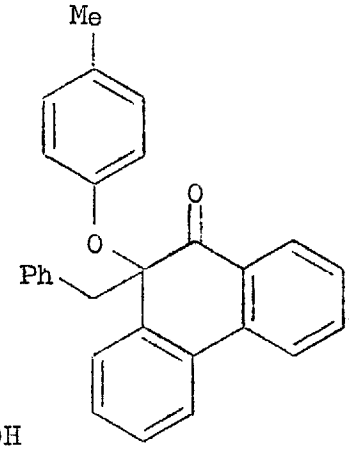

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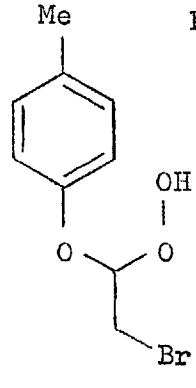

N

ACKNOWLEDGEMENTS

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I am indebted to the technical staff of the Chemistry Department for their assistance; in particular Mrs. I. Boston and Mr. K.I. Jones.

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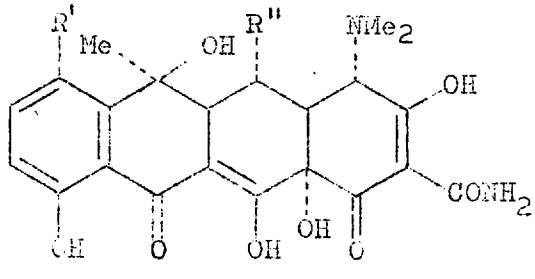
Whiffen Laboratory
July, 1968.

CONTENTS

INTRODUCTION

Since the discovery of aureomycin[1], or 7-chlorotetracycline (1), the tetracycline group of antibiotics has provided a challenge to the Organic chemist, both from the complexity of structure elucidation and from the difficulty of assembling the complex molecules synthetically.

Terramycin (2) was isolated shortly afterwards[2], and a comparison of the physical data and pharmacological properties[2,3] of the two antibiotics suggested a close similarity of structure. Chemical methods gave the structure of terramycin[4], and that of aureomycin[5] followed. At this time the structure of the parent compound, tetracycline (3), became apparent since it is obtained from aureomycin by hydrogenolysis[6]. Several more mould metabolites have now been isolated which are modifications of tetracycline[7,8,9,10].



	R	R
1	Cl	H
2	H	OH
3	H	H

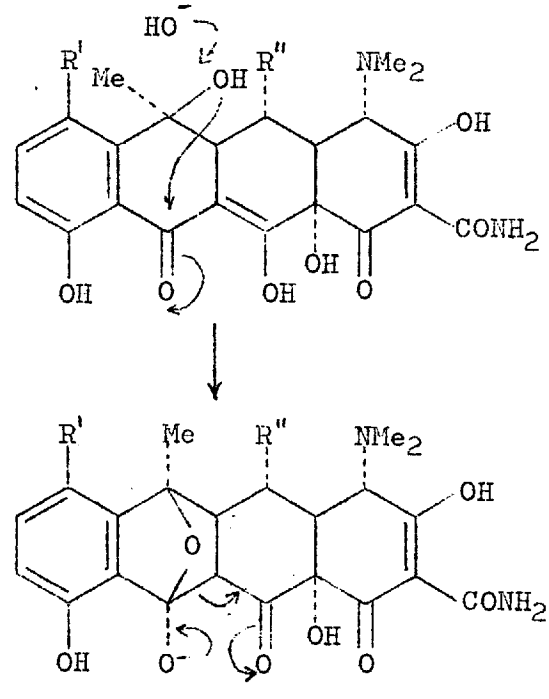
X-ray studies have confirmed the chemically assigned structures of terramycin[11] and aureomycin[12], and have established the relative configurations at the five common asymmetric centres. In the case

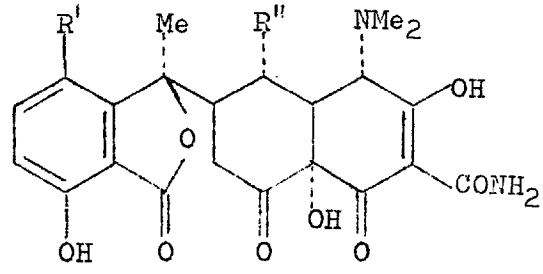
of terramycin the relative stereochemistry of the C-5 hydroxyl was deduced from the n.m.r. spectrum[13].

The chemistry of tetracyclines.

The chemistry of tetracyclines has been the subject of numerous reviews, the latest of these[14] covering the literature to 1965. Since this thesis is concerned with the synthesis of tetracycline, those aspects of the chemistry which must be taken into account in any synthesis will be surveyed.

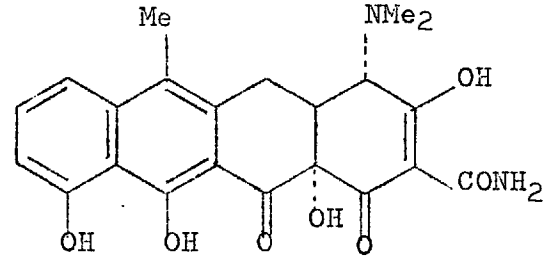
The oxygenation pattern of the tetracyclines renders them sensitive to both acid and base. Thus the conditions which may be used in the latter stages of a synthesis are restricted. The initial products formed in basic media are the iso-tetracyclines (4), produced in the manner indicated[15].





4

The effect of acid on tetracyclines is two-fold. First, the C-4 asymmetric centre epimerises in the pH range 2-6[16,17,18,19]. This transformation may be utilised in a synthesis since the change is controllable and both epimers can be isolated. Secondly, the benzylic hydroxyl at C-6 bears a <u>trans</u> relationship to the adjacent hydrogen and is, therefore, labile. As ring C in this dehydration product (5) becomes aromatic the reaction is facile.



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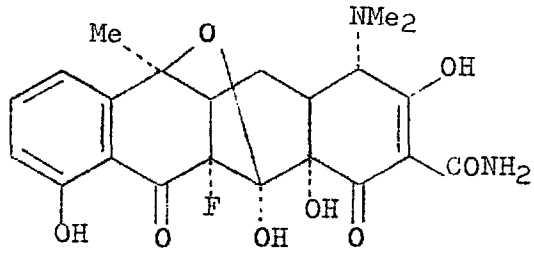
Although the C-6 hydroxyl group leads to the 5a,6-anhydrotetracyclines, it also leads to a series of hemiketals which could be very useful as synthetic intermediates.

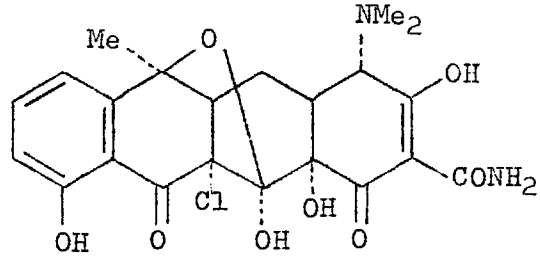
When tetracycline is treated with perchloryl fluoride in the presence of base[20,21,22] there is obtained a crystalline substance for which the 11a-fluoro-6,12-hemiketal structure (6) has been established.



6

This compound resists the dehydrating action of acids to the extent of surviving methanolic hydrogen chloride[22]. The antibiotic can be regenerated by hydrogenolysis under severe conditions[23], or by metallic reducing agents[24].

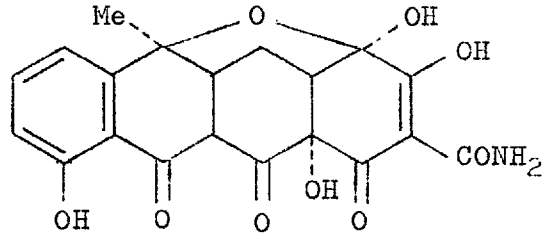
The reaction of amphoteric tetracycline in anhydrous glyme with N-chlorosuccinimide[22], affords the analogous 11a-chloro-6,12- hemiketal (7).



7

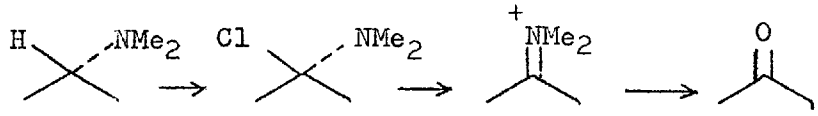
In this case, however, the compound is dissociated in solution, and the chlorine may be removed under mild conditions.

If tetracycline hydrochloride is treated with N-chlorosuccinimide in water, then 4-oxo-4-dedimethylaminotetracycline-4,6-hemiketal (8) is precipitated[25].

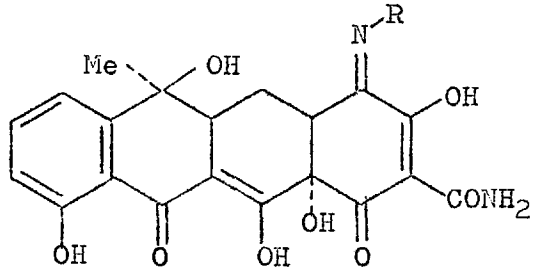


8

This structure has been confirmed by X-ray crystallography[26]. The 11a-chloro analogue may be obtained by the reaction of the 11a-chloro-6,12-hemiketal (7) with N-chlorosuccinimide in dilute hydrochloric acid[25]. The mechanism of this reaction has been suggested to be as follows[19].



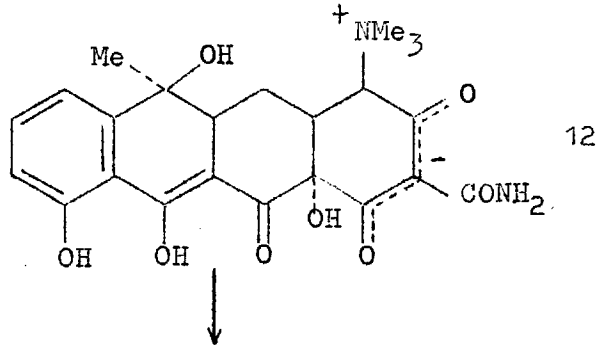
The significance of compound (8) is that it reacts with hydrazine or hydroxylamine to produce the hydrazone (9) and oxime (10) respectively.



	R
9	NH_2
10	Cl

Thus it could be a relay in a synthesis, and, furthermore, as it is relatively acid stable and as it forms a crystalline potassium salt it is a very suitable synthetic target.

A second class of tetracycline derivatives which is of synthetic interest and also of biosynthetic importance is the group of compounds now known as pretetramids[27]. 4-hydroxy-6-methylpretetramid (11) is prepared[29] by pyrolysis of tetracycline methyl betaine[28] in acetonitrile, followed by dehydration of the intermediate (13) with hydrogen iodide in phenol.



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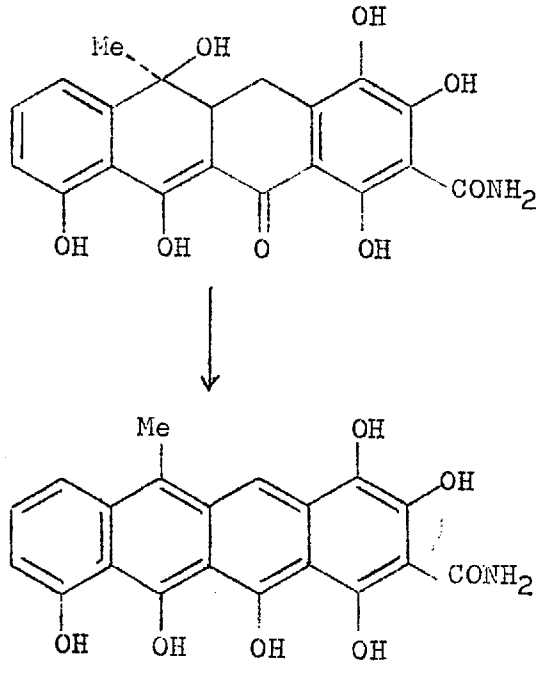
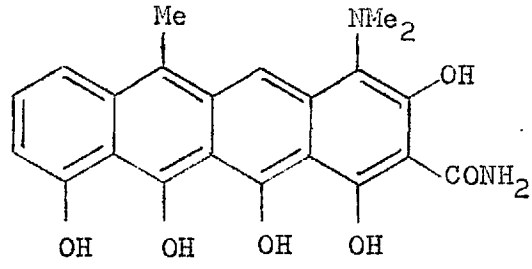


The suggested mechanism for this rearrangement is the loss of trimethylamine, ring-opening to a ketene and cyclisation to pretetramid. A similar mechanism has been formulated for the racemisations of usnic acid[30] and geodin[31].

The biosynthesis of tetracyclines.

Incorporation studies have indicated that tetracycline is derived from malonate units initiated by malonamyl coenzyme A[32]. This led to the suggestion that 6-methylpretetramid would be the precursor of 6-methylated tetracyclines. Experiments[33,34] have demonstrated this hypothesis, and have shown that terrarubein (14) is not a significant

intermediate.



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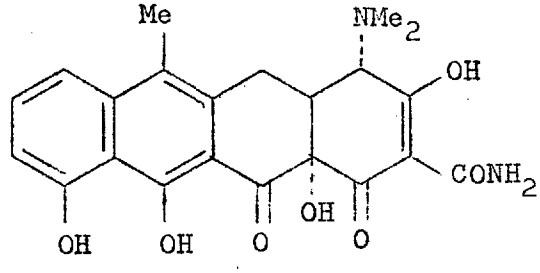
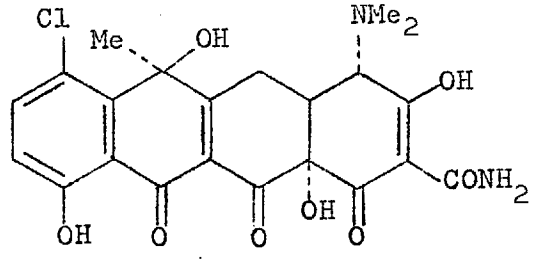
Evidence[35] has further pointed to 5a,6-anhydrotetracycline (15) as being an important precursor.



15

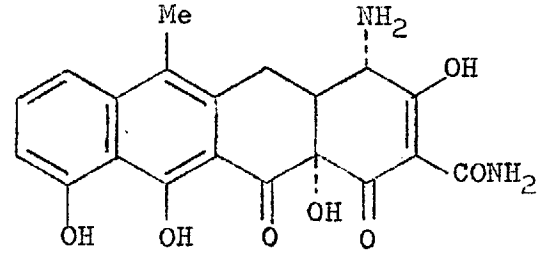
In the case of aureomycin the isolation[36], and proved precursor activity[37], of 7-chloro-5a,11a-dehydrotetracycline (16) indicates the next step in the biosynthesis.



16

Photo-oxygenation of 7-chloro-5a,6-anhydrotetracycline in the laboratory has given 7-chloro-5a,11a-dehydrotetracycline via the 6-hydroperoxide[38]. The subsequent reduction to aureomycin has also been achieved[36].

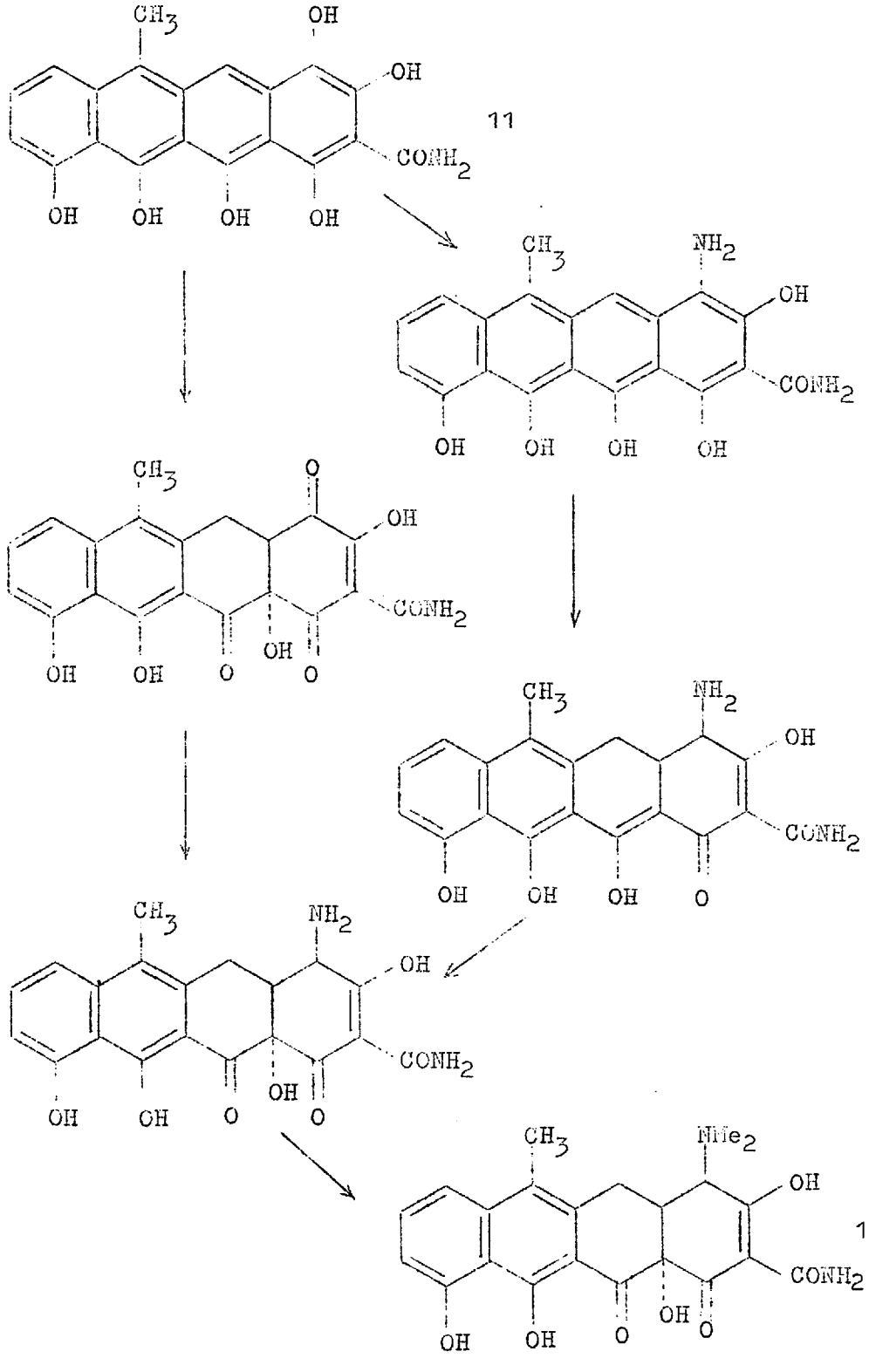
The conversion of pretetramid to 5a,6-anhydrotetracycline proceeds through N-demethyl-5a,6-anhydrotetracycline (17)[39].



17

The C-4 epimer has been isolated[40], and is not a tetracycline precursor. Evidence has not yet been advanced for the complete sequential conversion of 6-methyl-4-hydroxypretetramid to (17) although more conclusions may be drawn.

The presence of a 12a-hydroxyl group in the anhydro precursors is not necessary for C-6 hydroxylation. It cannot, however, be introduced at a later stage because 5a,6-anhydro-12a-desoxytetracycline leads to 12a-desoxytetracycline only. Thus 12a-hydroxylation precedes development of the 4-dimethylamino function but not necessarily 4-amination. Two possibilities now exist and these are indicated below.

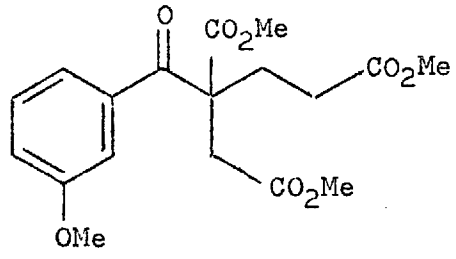

CH3
OH
OH
CONH2
OH OH OH OH
11
NH2
O
NMe2
15

The synthesis of tetracyclines.

The total synthesis of tetracyclines has been attempted by several schools and their work has been reviewed extensively[41]. Two successful syntheses will be reviewed here to demonstrate the approaches which have been used.

First, the synthesis due to Woodward[42]. The target of this work was 6-demethyl-6-deoxytetracycline, the simplest tetracycline derivative to retain antibiotic activity. The key-stone of the projected synthesis was the aromatic ring D, onto which rings C, B and A were to be attached successively.

Methyl m-methoxybenzoate was condensed, in dimethylformamide solution, with methyl acetate in the presence of sodium hydride, to provide methyl m-methoxybenzoylacetate. Without isolation, this material was treated with methyl chloroacetate to give dimethyl m-methoxybenzoylsuccinate. Michael condensation with methyl acrylate, using methanolic Triton B as catalyst resulted in formation of the keto-triester (18). Acid catalysed hydrolysis and decarboxylation, followed by catalytic hydrogenation under pressure, gave the adipic acid (19). It was now desired to form ring C by an internal cyclisation reaction, so the active p-site was blocked by treatment with chlorine in acetic acid. The desired cyclisation was now brought about with liquid hydrogen fluoride. Esterification provided the tetralone ester (20).



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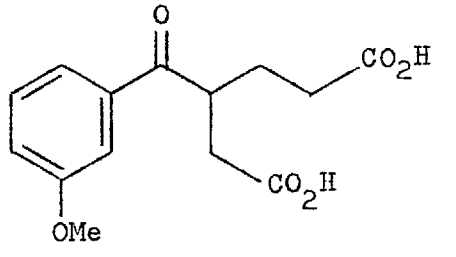

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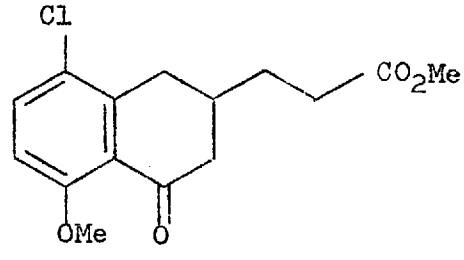
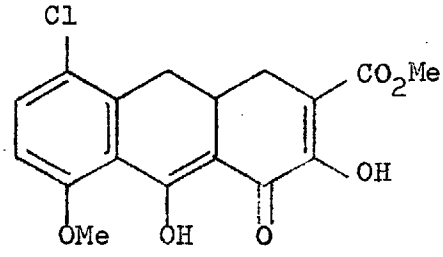


20

Formation of ring B by condensation with a 2-carbon unit now presented a problem for the conditions required could also bring about internal cyclisation of (20). However, condensation with

methyl oxalate in dimethyl formamide containing methanol gave the hydroanthracene (21) in 45% yield. Hydrolysis with hot hydrochloric and acetic acids provided the hydroanthracene ketone (22) in 75% yield.



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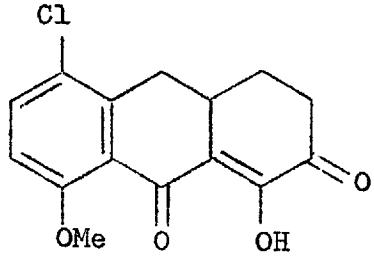
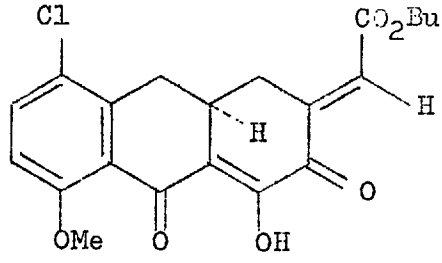


22

Reaction with n-butyl glyoxylate in boiling toluene, using magnesium methoxide as catalyst, produced the glyoxylidene derivative (23). Dissolving this in dimethylamine gave the base (24). This addition was found to be readily reversible. Although this complicated the synthesis practically, it did suggest that the substituent on the hydroanthracene was adopting the required equatorial disposition. The practical difficulty was overcome by reduction of the base with

sodium borohydride in situ. Thus the stable alcohol (25) could be isolated as the hydrochloride in a 60% over-all yield from (23).



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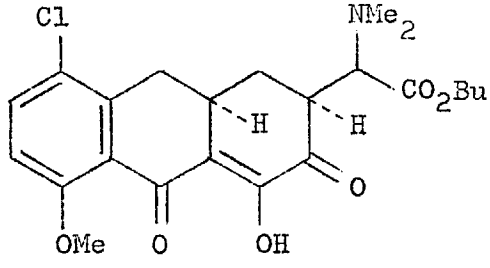

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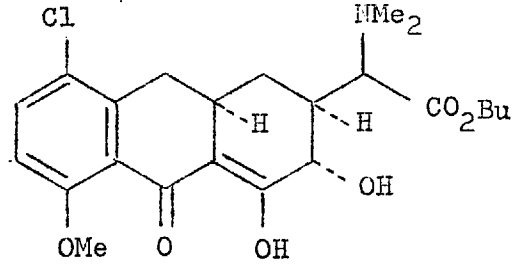
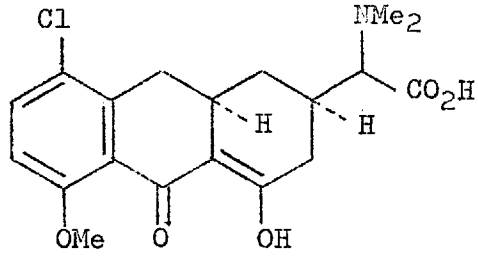


25

Lactonisation of (25) was brought about by refluxing the hydroxy ester in toluene containing a large amount of p-toluene-sulphonic acid. Treatment with zinc and formic acid readily gave the dimethylamino acid (26). Catalytic hydrogenation in the presence of triethylamine provided the chlorine-free acid (27).



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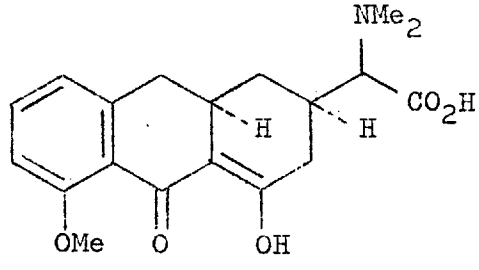
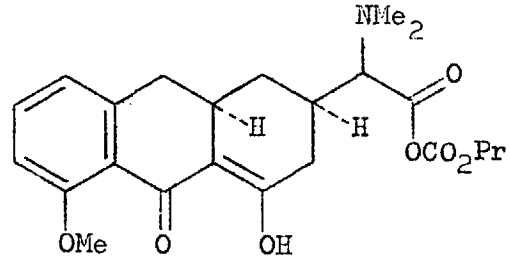


27

The construction of ring A was now carried out in three stages, the two intermediates being used without purification. Activation of the acid was obtained by preparation of the anhydride (28), the reaction with isopropyl chloroformate being catalysed by triethylamine. Reaction with the ethoxymagnesio derivative of ethyl N-t-butylmalonamate in the presence of sulphuric acid gave the acyl derivative (29).

Cyclisation to (30) was achieved by treatment with sodium hydride in dimethylformamide.



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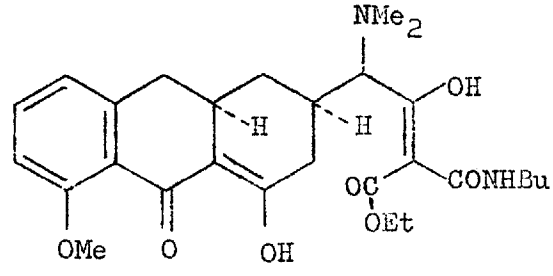

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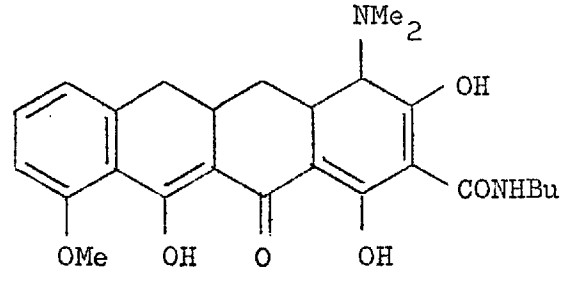
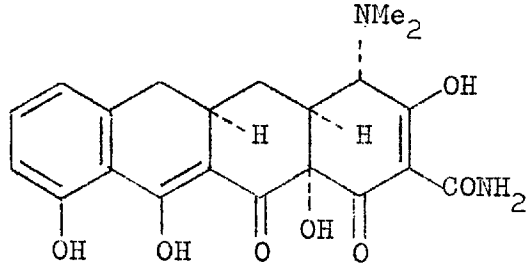


30

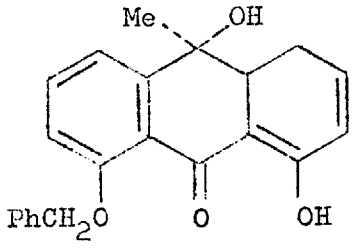
Treatment with hot aqueous hydrobromic acid cleaved the N-t-butyl and O-methoxyl groups and the dealkylated compound separated as a crystalline hydrobromide. It now remained to introduce the C-12a hydroxyl in the correct stereochemical sense, and to invert the C-4 dimethylamino group. Hydroxylation was achieved by means of oxygenation, in buffered methanol/dimethylformamide, in the presence of cerous ions. Treatment of the crude product with calcium chloride in a solution buffered to pH 8.5 resulted in a 25% overall conversion of (30) to racemic 6-demethyl-6-deoxytetracycline (31).



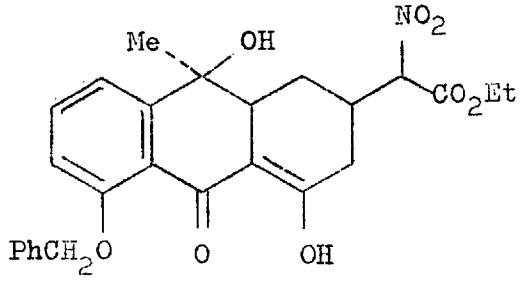
31

The second synthesis to be described is that due to Shemyakin[43]. In this case the 6-position was substituted and the work resulted in the first synthesis of a naturally occurring tetracycline.

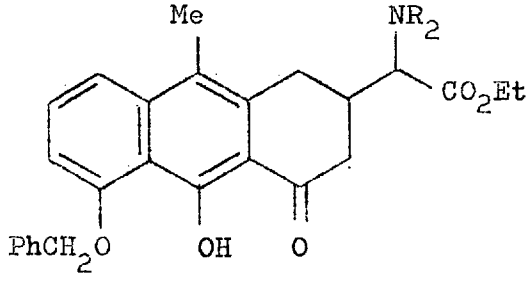
Condensation of the dienediolone (32), prepared from juglone[44], with the triethylammonium salt of ethyl nitroacetate, gave a mixture of the epimeric adducts (33). This mixture was dehydrated with methanolic hydrochloric acid at 80° to provide the nitro compound (34), which was reduced to the amine (35) with zinc dust in acetic acid.



32



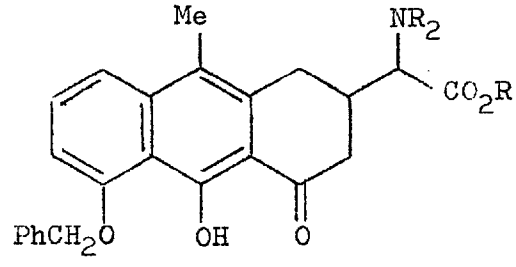
33



	R
34	O
35	H

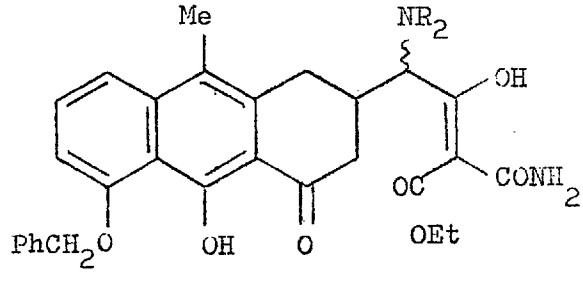
When the amine was methylated and the ester saponified, no condensation with ethyl ethoxymagnesium malonamate could be achieved. The amino ester was, therefore, acylated with carbethoxyphthalimide in

tetrahydrofuran to provide a phthaloyl derivative, which, after methylation with methyl iodide/silver oxide gave the ester (36). Saponification of the ester with dilute potassium hydroxide in aqueous tetrahydrofuran, followed by recyclisation of the phthalimido group by heating in diglyme at 140° provided the acid (37).

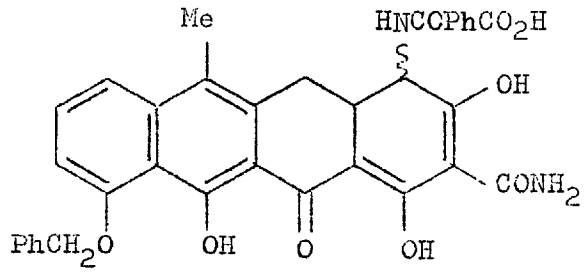


	R_2	R
36	Phthal	Me
37	Phthal	H

The malonamate (38) was obtained by conversion to the acid chloride with phosphorus pentachloride in dimethylformamide followed by treatment with ethyl ethoxymagnesium malonamate. Cyclisation to (39) was achieved with dimethylsulphoxide carbanion and hydrolysis with hydrogen bromide in acetic acid, and methylation with methyl iodide in tetrahydrofuran gave (±)-12a-deoxy-5a,6-anhydrotetracycline (40). This material was spectroscopically identical with the (-)-isomer obtained by degradation of tetracycline.



	R_2
38	Phthal



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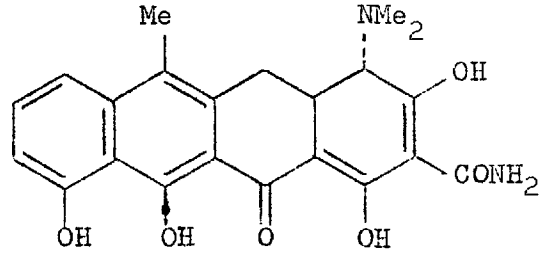


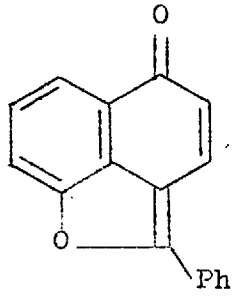
40

Since this compound had been 12a-hydroxylated[45], and the 5a,6-bond hydrated[46] by earlier workers this completed a synthesis of a naturally occurring tetracycline.

Synopsis of previous work

The Imperial College route for tetracycline synthesis[47] differs from those already in the literature in that a tetracyclic molecule is assembled in which ring A is aromatic, rather than the step-wise addition of a dihydro aromatic ring A onto a tricyclic molecule.

A CD ring system was prepared by condensing benzoic acid with 1,5-dihydroxynaphthalene in the presence of zinc chloride, to obtain the naphthofuran(41). Hydrogenation of this compound over Raney nickel gave the dihydro naphthofuran (42) which provides an excellent protected CD system.



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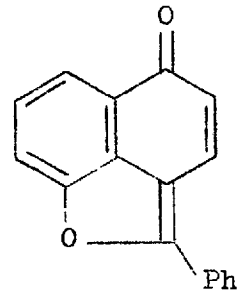
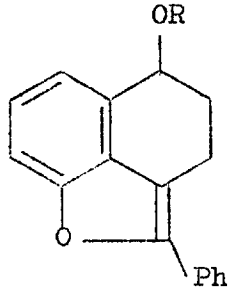
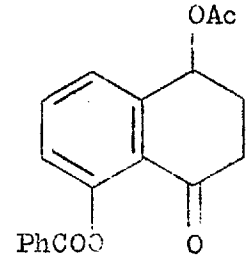


42

This was demonstrated by reduction to the alcohol (43), and ozonolysis of the derived acetate (44) to yield the tetralone (45). Similarly, treatment of the dihydro naphthofuran with methyl magnesium iodide produced the tertiary alcohol (46) which was ozonised to the tetralone (47).



	R
43	H
44	OAc



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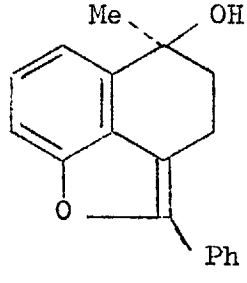
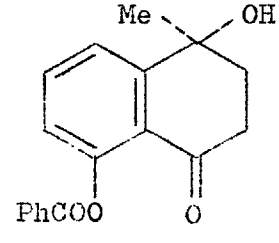
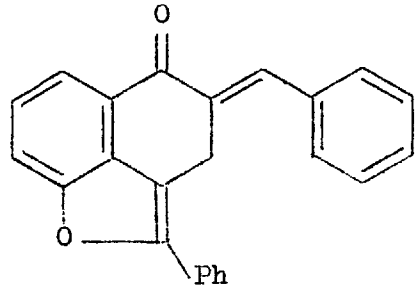


46



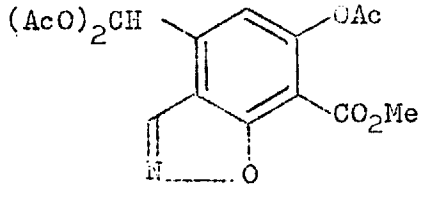
47

Condensation of the dihydro naphthofuran (42) with benzaldehyde in acetic acid containing sulphuric acid to give the benzylidene derivative (48) demonstrated the procedure for attaching ring A onto the CD system.

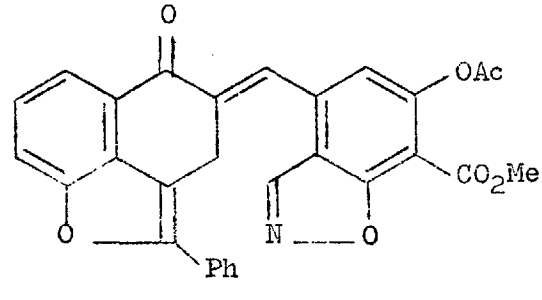


48

It was then necessary to synthesise a substituted benzaldehyde to form ring A. As it was decided to attach the eventual C-12 to ring A, a suitably protected carbonyl function had to be designed. This was achieved by preparation of the formyl diacetate (49) which was condensed with the dihydro naphthofuranto produce the benzylidene compound (50).

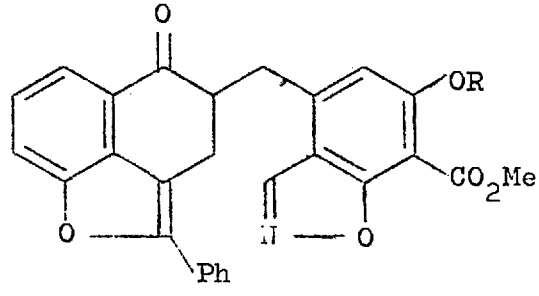


49

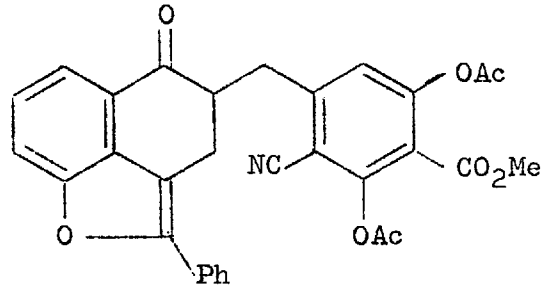


50

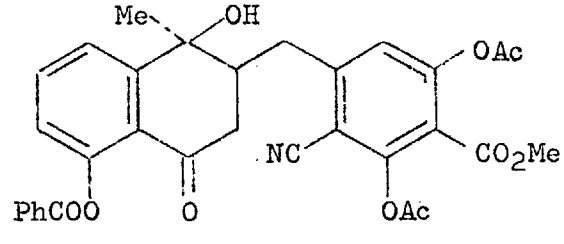
The exocyclic double bond was reduced with hydrogen iodide in acetic acid to the acetate (51) or the phenol (52). Both compounds were converted to the nitrile (53) by treatment with acetic anhydride and pyridine. Reaction of the nitrile with methyl magnesium iodide gave a tertiary alcohol which was ozonised to the tetralone (54). Treatment with a variety of basic catalysts failed to provide the expected cyclisation.



	R
51	Ac
52	H

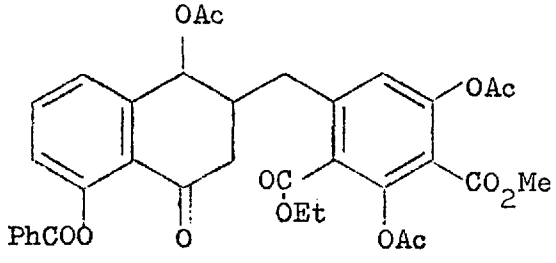


53



54

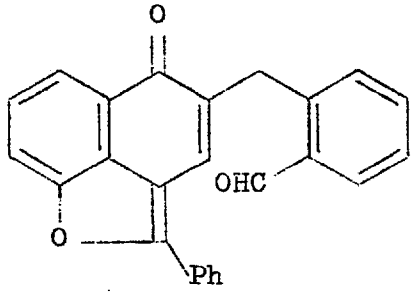
Having shown that cyclohexanone condensed with benzoic esters and not with benzonitrile when treated with sodium hydride, the carbomethoxy derivative (55) was synthesised. This was achieved by opening the isoxazole by hydrogenation and oxidation of the resulting aldehyde.



55

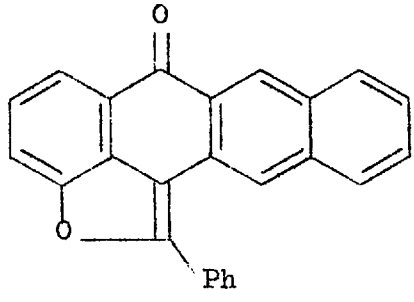
The tetralone failed to cyclise when treated with sodium hydride, this probably being due to the anion not being formed.

The failure to bring about ring B cyclisation meant that new methods had to be investigated. For this purpose, the model aldehyde (56) was prepared by base catalysed condensation of the dihydro naphthofuran with o-phthalaldehyde.

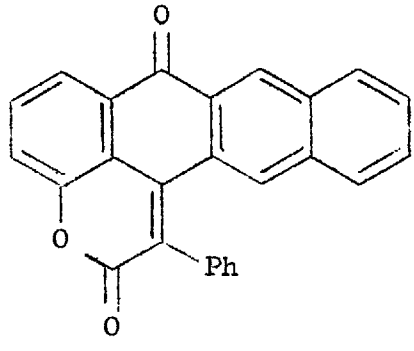


56

A reaction analogous to the benzoin condensation was attempted by treatment with sodium cyanide in refluxing ethanol, but the main products were the ketone (57) and the keto-lactone (58).

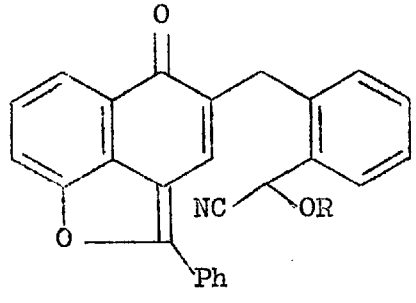


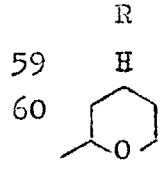
57

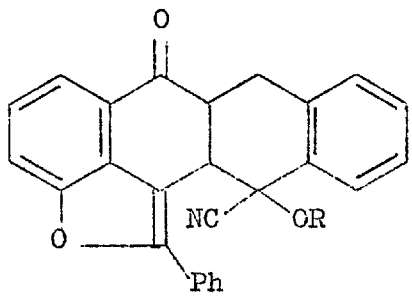


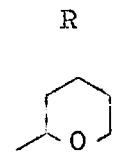
58

A successful cyclisation was achieved by conversion of the aldehyde (56) to the cyanohydrin (59), protection as the tetrahydro pyranyl ether (60), and treatment with potassium t-butoxide to yield the tetracyclic compound (61).





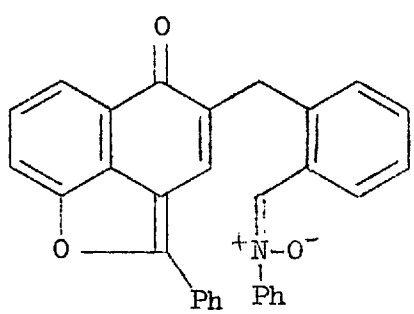




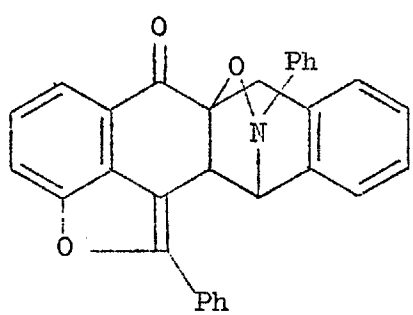
61

This reaction failed, however, when ring A was substituted. This failure has been attributed to either steric hindrance of the o-methoxyl group, or to destabilisation of the anion by the substituents on the aromatic ring.

An alternative method of cyclisation was found in the action of phenylhydroxylamine on the aldehyde (56). The intermediate nitrone (62) cyclised spontaneously to form the isoxazoline (63).



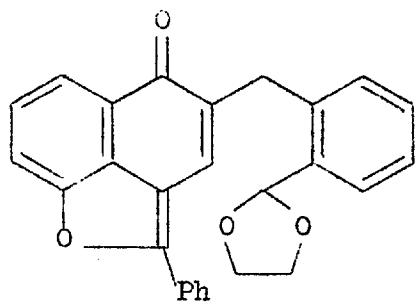
62



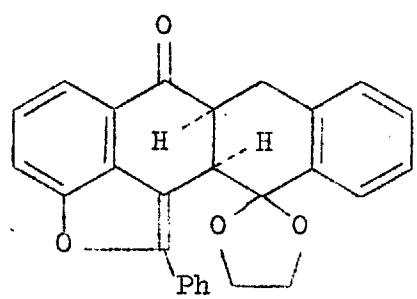
63

This reaction was also successful when ring A was substituted, but extensive study failed to provide a suitable method of regenerating the C-12 carbonyl function.

The problem of ring B cyclisation was finally overcome when the ethylene ketal (64) was photolysed in the presence of benzoyl peroxide to give (65). This process gives good yields when ring A is substituted, and the C-12 carbonyl function may be regenerated.



64



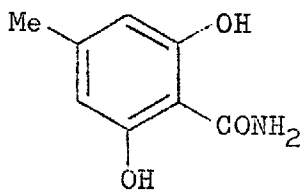
65

Now that a tetracyclic compound had been assembled there remained three major transformations:

1. Reduction of ring A to the dihydro aromatic level.
2. C-4 amination.

3. C-12a hydroxylation.

Catalytic reduction of substituted resorcinols had been investigated at an early stage. By this technique the amide (65) was easily converted to the β-diketone (67), but the tetracyclic compound (68) could not be so reduced.



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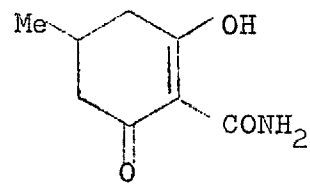
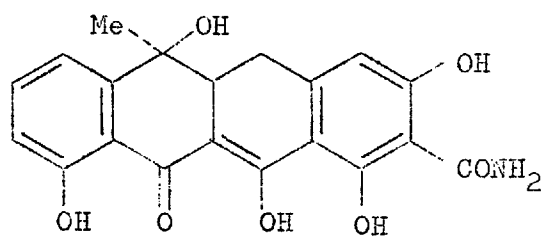
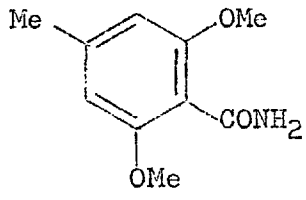


67

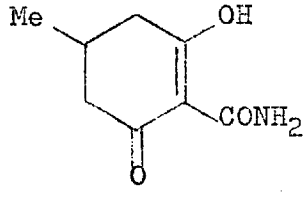


68

Birch reduction was investigated, and the β-diketone (69) was prepared by reduction of the dimethyl ether (70) followed by acid hydrolysis.

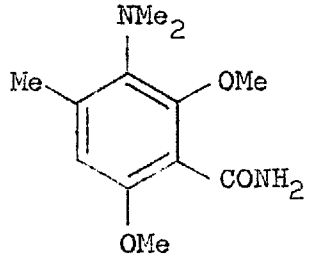


70



69

The more advanced model (71) was also subjected to metal-ammonia reduction but no useful product could be isolated. The amino group would, therefore, have to be introduced after reduction.



71 Me_2N-OTs 72

A series of experiments was carried out to study the possibility of inserting nitrogen into the double band of an enol ether. Nitrenes, nitrenium ions, and the novel hydroxylamine derivative (72) were all tried, but with no success. Moreover, it was found that dihydroresorcinol dimethyl ether underwent aromatisation in such a facile manner that a synthesis involving reduction of ring A would not be advisable.

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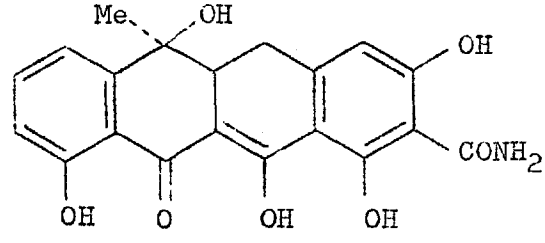
DISCUSSION

The initial objective of the studies undertaken in the Tetracycline group, before the work described in this thesis began, was the total synthesis of 4a,12a-anhydro-4-dedimethylaminotetracycline (1).



1

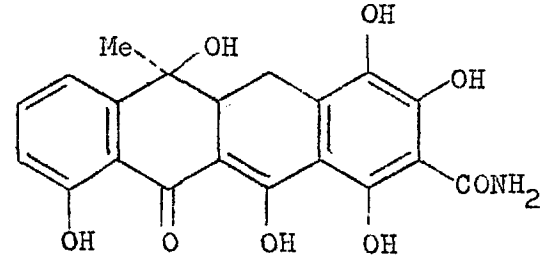
To complete a synthesis of tetracycline, this molecule would require:

a. Reduction of ring A.

b. C-4 amination

c. C-12a hydroxylation.

However, it had become apparent that the reduction of ring A after introduction of C-4 nitrogen, or amination after reduction of the aromatic ring would both be difficult transformations. The initial objective was, therefore, modified to 4a,12a-anhydro-4-hydroxy-4-dedimethylaminotetracycline (2).



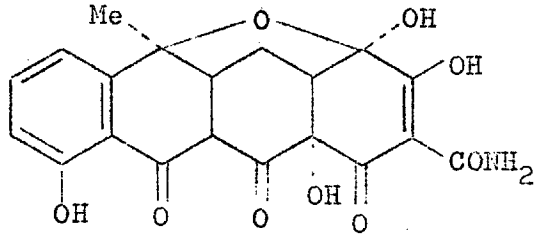
2

This offers several advantages:

a. It is easily obtained from tetracycline by pyrolysis of tetracycline methyl betaine[2].

b. It may be dehydrated to 4-hydroxy-6-methylpretetramid, a biosynthetic precursor of tetracyclines, and a compound of synthetic interest.

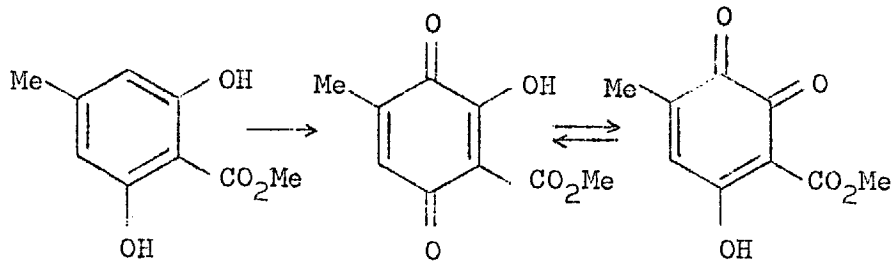
c. There is the possibility of oxidative hydroxylation and dearomatisation of ring A, and conversion to tetracycline via the tetracycloxide[3] (3).



3

Attention was, therefore, directed to the study of methods of introducing the 4-hydroxyl group into orcinol derived compounds.

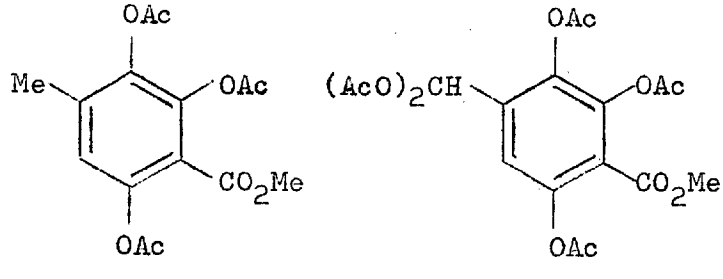
Methyl p-orsellinate (4) was prepared by carboxylation of orcinol followed by esterification[4]. Oxidation with Frémy's salt[5] in aqueous ethanol gave the orange crystalline hydroxyquinone (5) in 87% yield.



4 5

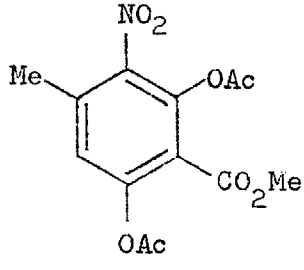
The n.m.r. spectrum of this compound showed 2 peaks for both the C-methyl and O-methyl signals. These collapsed to singlets when base was added to the solvent. This has been interpreted as showing that the quinone exists in both the <u>para</u> and <u>ortho</u> forms in chloroform solution.

Reduction to the triphenol was achieved either with sulphurous acid, zinc dust in acetic acid at 0^{0}, or by hydrogenation over palladium on barium sulphate. The phenol was not isolated, but was acetylated with acetic anhydride/pyridine to provide the stable triacetate (6) in over 90% yield.



6 7

Oxidation of the methyl group by the Thiele procedure [6] was successful, but the maximum yield achieved was 22%. T.l.c. indicated that the starting material was consumed after a 1 hr. reaction but work-up at this time gave no better yield. Thus further oxidation must occur readily. A similar result had been obtained earlier, when oxidation of the nitroacetate (8) gave only the acid (9)[7].



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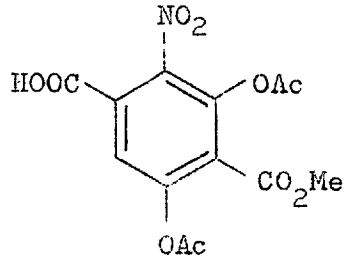
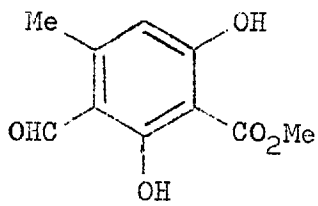


9

The Frémy's salt oxidation does, however, provide a high yield method of introducing a 4-hydroxyl, so the possibility of its use at a later stage in the synthesis was investigated.

The first model was methyl 2-formyl-p-orsellinate (10), obtained by the Gatterman formylation of methyl p-orsellinate[8]. When this was treated with excess Frémy's salt only a small amount of the aldehyde-ester was consumed. Altering the pH of the solution between 4.2 and 10 did not increase the amount of reaction. The product was isolated in an impure state and the mass spectrum showed a molecular ion at 212 m/e. This is in accordance with the product being the quinone (11), obtained by oxidative deformylation.



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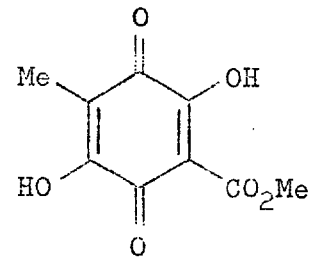
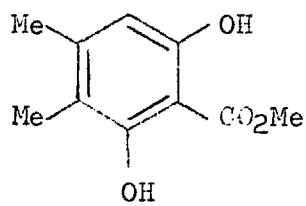


11

The fact that this reaction did not occur because of the electron withdrawing properties of the formyl substituent was demonstrated by hydrogenolysis to the dimethyl resorcinol[9] (12), and oxidation with Frémy's salt.



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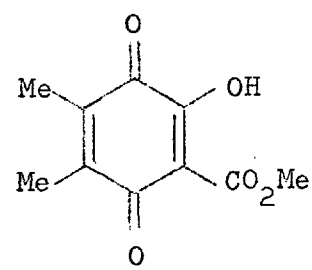
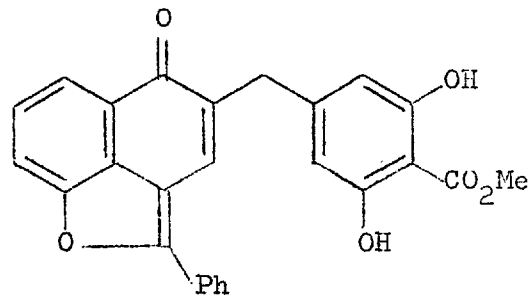


13

In this case the expected quinone (13) was formed in 95% yield in a reaction medium buffered with sodium acetate. The n.m.r. of this compound had singlets for the C-methyl and O-methyl resonances and thus exists in only the <u>para</u>-quinonoid form.

A third possibility exists for the introduction of the 4-hydroxyl by Frémy's salt oxidation. This is to use as substrate a tricyclic

compound with a dihydroxy ring A. As the bisphenol (14) was available[10], this was treated with Frémy's salt.

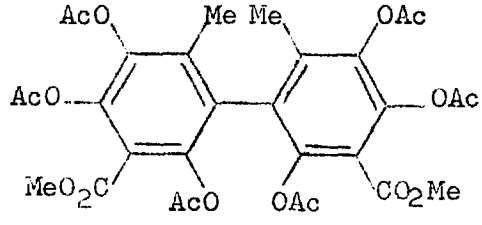


14

The difficulty that was encountered immediately was that the phenol (14) is insoluble in the media normally used for Frémy's salt oxidations. Aqueous dimethylformamide buffered to pH 6 with sodium acetate was used, but the substrate precipitated unchanged. Sufficient base was added to a dimethylformamide solution of the phenol to give the mono anion, and this was stirred with a solution of Frémy's salt at pH 10. An immediate reaction occurred and the reaction mixture was acidified and extracted. Reduction and acetylation at room temperature yielded a mixture with at least six components. The major product was separated by t.l.c. on silica gel. It had a melting point higher than 340^0, and the molecular ion could not be discerned in the mass spectrum. It was suggested that the product was probably dimeric, and to test this hypothesis, methyl p-orsellinate was oxidised with Frémy's salt in basic solution.

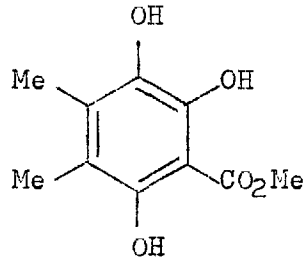
The product obtained from this reaction, after work-up by reduction and acetylation, showed the expected bands at 1778 and

and 1727 cm^{-1} in its infra-red spectrum. The Rf value on silica gel was identical with the triacetate (6). The n.m.r. spectrum, however, showed no signals due to aromatic protons. The molecular ion was at 582 m/e and the fragmentation pattern demonstrated the presence of 6 acetate and 2 carbomethoxy groups. Basic Frémy's salt oxidation, does, therefore, bring about dimerisation, and yields the biphenyl (15).



15

The dimethyl resorcinol (10) was also oxidised with basic Frémy's salt solution, and yielded, as an oil, the same quinone (11) as the acidic oxidation. This was confirmed by reduction to the triphenol (16) and acetylation to (17), the acetate being identical to that obtained from the characterised quinone (11).



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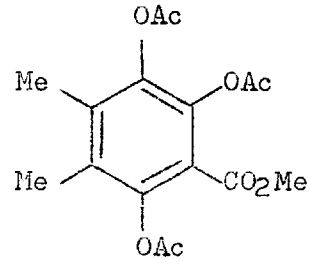


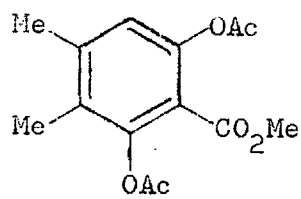
17

An advantage of the basic Frémy's salt oxidation is that it is faster than that carried out in neutral or acidic media. Thus it is to be preferred when the substrate has no sites available for dimerisation. One inherent disadvantage of Frémy's salt is that it requires aqueous solutions. In an attempt to overcome this, a synthesis of the aromatic analogue (18) was ventured.

$(PhSO_2)_2NO^{\cdot}$ 18

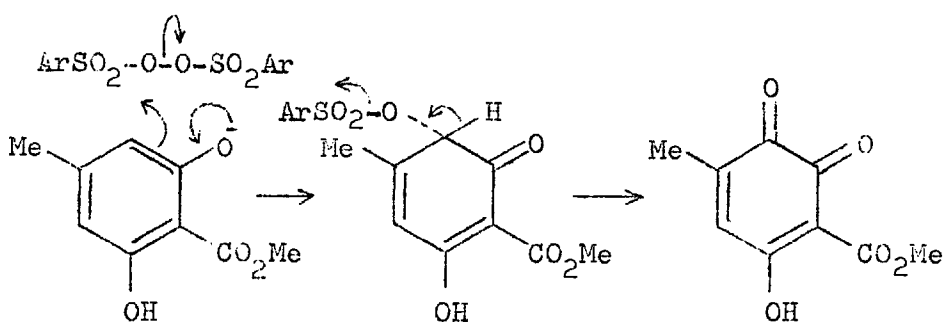
Benzenesulphinic acid was prepared by the zinc dust reduction of benzenesulphonyl chloride[11]. An aqueous solution of this was mixed with sodium nitrite and acidified, when N,N-dibenzenesulphonyl hydroxylamine was obtained as a crystalline solid[12]. Attempts to oxidise this with permanganate or chromic acid in aqueous systems, or with halogen or manganese dioxide in organic solvents, did not yield a stable radical.

An alternative mode of introduction of the 4-hydroxyl might be autoxidation in the presence of base. The dimethyl resorcinol (12) was dissolved in hexamethylphosphoramide, and was stirred with excess potassium t-butoxide in an atmosphere of oxygen. After 7 hr. t.l.c. indicated total consumption of the resorcinol, and the reaction was worked up by acidification, zinc dust reduction, and acetylation with acetic anhydride/pyridine. T.l.c. showed that the complex product did not contain either the triacetate (17) or the diacetate (19), obtained by acetylation of the dimethyl resorcinol (12).



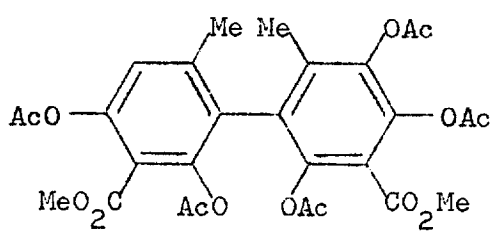
19

Another oxidative procedure investigated was the use of arylsulphonyl peroxides, the projected reaction path being shown below.



Tosyl peroxide was prepared by the action of basic hydrogen peroxide on tosyl chloride[13]. Iodometry indicated that the product contained 44% of the required peroxide. Reaction with methyl p-orsellinate and base did result, however, in the formation of a yellow compound, but this was too impure for characterisation.

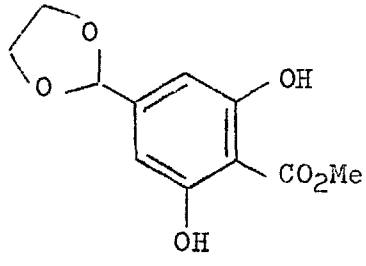
m-Nitrobenzenesulphonyl chloride, when reacted with basic hydrogen peroxide, gave a pure, crystalline peroxide[14]. When this peroxide was stirred with basic methyl p-orsellinate in a nitrogen atmosphere, a rapid reaction occurred. The product was isolated by acidification and extraction, reduced with zinc dust in acetic acid, and acetylated with acetic anhydride/pyridine. The colourless, crystalline product had absorptions at 1777, 1762 and 1724 cm^{-1} in the infra-red, indicating the presence of two types of aromatic acetate as well as the normal ester. The molecular ion was at 532 m/e and the fragmentation showed the loss of 5 acetate and 2 methyl ester functions. This evidence is in accordance with the product being the biphenyl (20).



20

Reaction of the peroxide with the dimethyl resorcinol (12) resulted in the formation, after reduction and acetylation, of the expected triacetate (17). The yield of quinene obtained from the peroxide reaction was not as high as that obtained from Frémy's salt so from a synthetic viewpoint the peroxide oxidation is not to be preferred.

The synthesis of a trihydroxy ring A is now achieved via a Frémy's salt oxidation of an orcinol derivative, before condensation to the CD moiety. The problem of the low yield Thiele oxidation is overcome by oxidation of the ethylene ketal (21)[10].

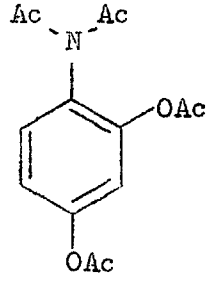


21

C-4 Amination

There is in the literature[15], a method of aminating 1,2,4-trihydroxybenzene in the 1-position. As this is equivalent to C-4 in tetracyclines; the reaction was investigated.

1,2,4-trihydroxybenzene was obtained by Thiele acetylation[16] of p-benzoquinone, followed by hydrolysis with methanolic hydrogen chloride. Stirring this with concentrated ammonia solution at room temperature resulted in the formation of a black tar. Acetylation with acetic anhydride/pyridine gave a product with three main components, separated by t.l.c. on silica gel. The compound obtained in highest yield was the N-diacetate (22) together with a smaller amount of the N-acetate (23) and a trace of the diphenylamine (24).



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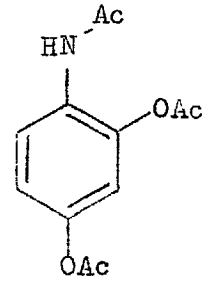

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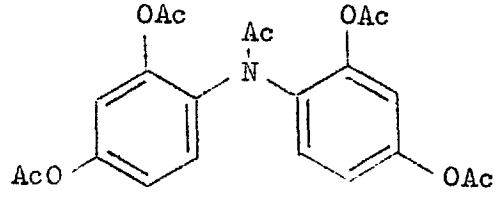
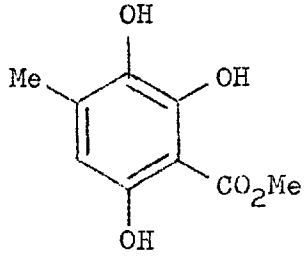


24

Attention was then turned to the reaction of ammonia with methyl 2,3,6-trihydroxy-4-methylbenzoate (25). The triphenol was dissolved in ethanol and the solution degassed with nitrogen. Ammonia gas was then passed through the solution for 30 min. Work-up by acidification and reductive acetylation gave a complex mixture with no product predominating. Methyl 2,3,6-trihydroxy-4,5-dimethylbenzoate (26) when treated with ammonia under the same conditions did not react, and starting material was recovered on acidification.



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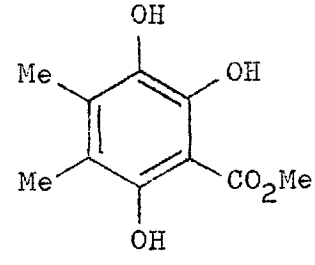
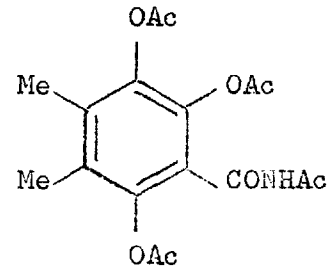


26

Warming the reaction at atmospheric pressure had no effect.

The triphenol (26) was then dissolved in liquid ammonia and the solution sealed in a pressure vessel, at room temperature, for 18 hr. After evaporation of the ammonia, an ultra-violet maximum at 270 mμ showed that the product was quinonoid. The crude product was reduced and acetylated, and a small amount of the major product was separated by t.l.c. on silica gel. The mass spectrum of this compound had the molecular ion at 365 m/e and showed the loss of 4 acetates. This is consistent with the compound being the amide (27).

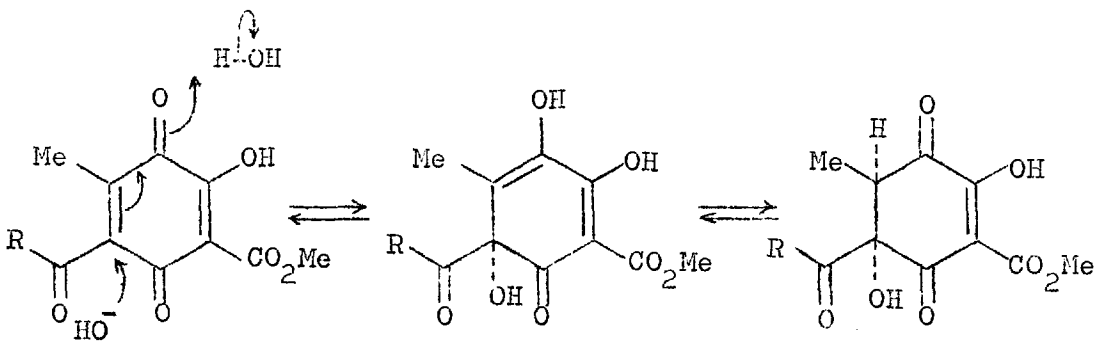


27

Thus this reaction does not provide a useful means of introducing a 4-nitrogen function. The isolation of quinones from the reactions suggests oxidation by the air. As a means of converting ester to amide with the highly substituted compounds the reaction is also unsatisfactory, as the products are intractable and the amide is only obtained in poor yield.

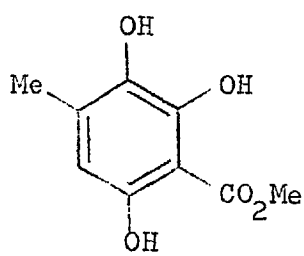
C-12a hydroxylation/dearomatisation reactions.

The possibility of converting a 2-hydroxyquinone to an ene-dione by addition of water was now investigated.



This process may be the one by which the biosynthesis of tetracyclines proceeds, and in the synthetic series would provide a means of 12a-hydroxylation and dearomatisation. The synthesis of model quinones where R = H and OEt was, therefore, carried out.

The triphenol (25) was formylated by treatment with the Gatterman complex and aluminium chloride in ether[10], the aldehyde (28) being obtained in 95% yield.



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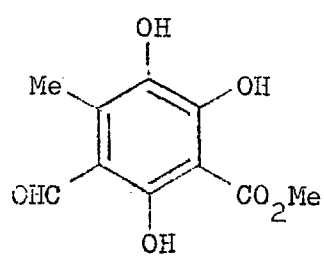

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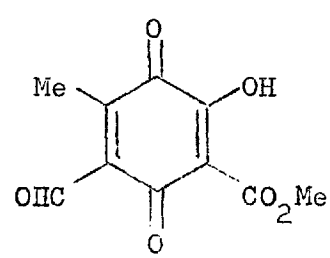
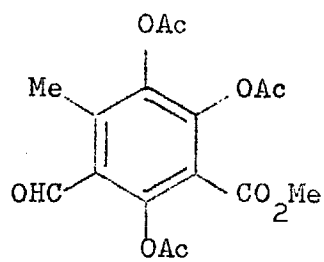


29

Oxidation with 1 mol. of dichlorodicyano-p-benzoquinone (DDQ) in dry chloroform gave a 97% conversion to the quinone (29).

Acetylation of the triphenol aldehyde (28) with acetic anhydride/pyridine on the steam bath provided the triacetate (30). Attempted oxidations of the formyl group with silver oxide, manganese dioxide, oxygen and N-bromosuccinimide were unsuccessful. This difficulty was overcome by modifying the aldehyde to the ethylene ketal (31) by the transketalisation procedure. Treatment with NBS gave the desired oxidation to ester[17] (32). Deacetylation with methanolic hydrogen chloride to the triphenol (33) followed by oxidation with DDQ completed the synthesis of the model quinone (34).



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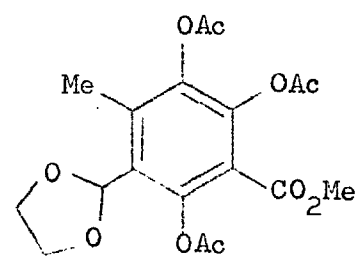
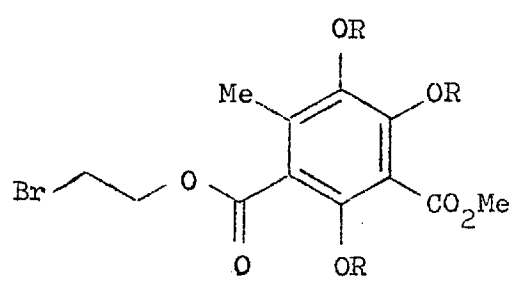
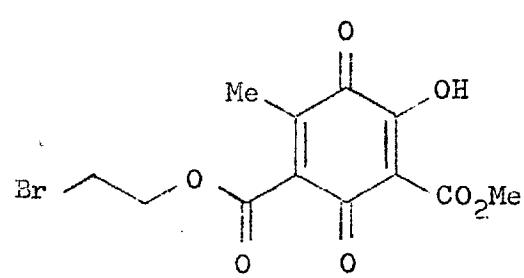


31



	R
32	Ac
33	H



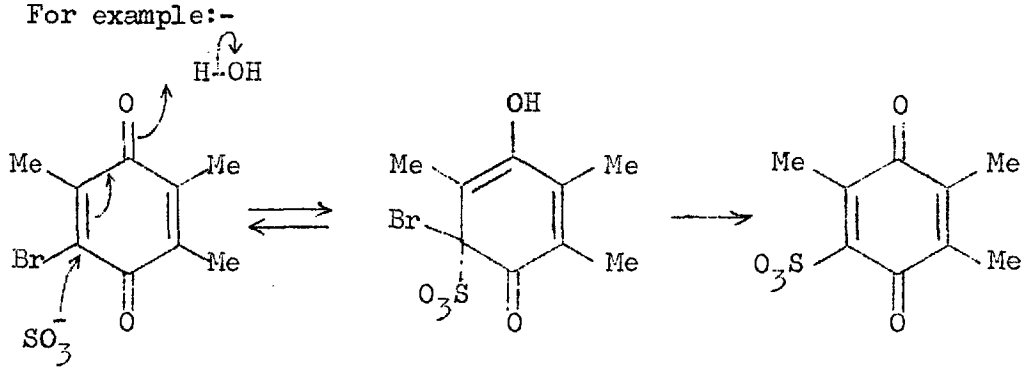
34

To study the hydroxylation reaction small quantities of the quinones were dissolved in aqueous dioxan. An immediate dark red colour developed due to formation of the anion.

Base. N/10 Sodium hydroxide was added dropwise to the stirred solution at room temperature. Aliquots taken over several hours showed no change in the ultraviolet spectrum. Acidification with dilute hydrochloric acid gave unchanged starting material.

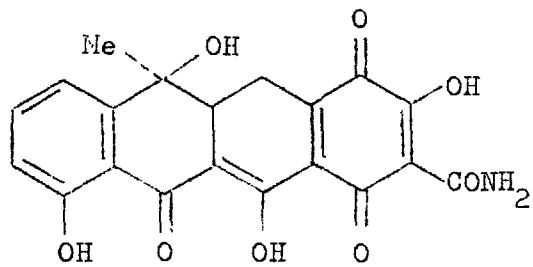
Acid. There was an immediate colour change as the anion was neutralised, but after stirring for 4 hr. with 2N hydrochloric acid, only the hydroxyquinone was present in a chloroform extract.

Examples of additions of nucleophiles to quinones which appear in the literature[18,19] are concerned with quinones in which the substituent at the position of attack is lost in the reverse process. For example:-



Thus it appears likely that if water adds in the desired manner to the model quinones, then it may be lost rapidly in the reverse process.

However, in the case of the tetracyclic quinone (35), if ketonisation takes place after addition of water, then the molecule can form the ketal (36) and so prevent the reverse process.



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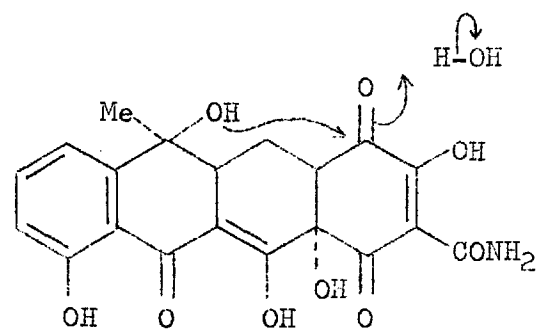
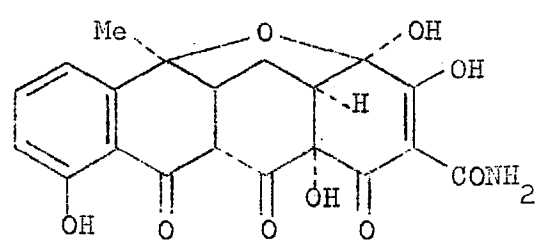
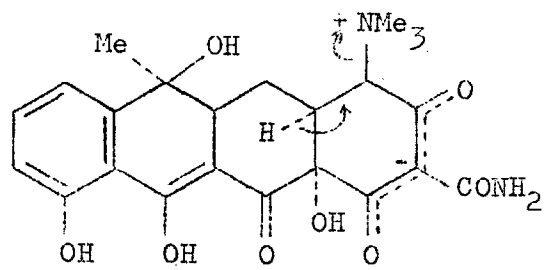




36

Tetracycline base was obtained from the hydrochloride by adjusting the pH of a cooled solution to 4.5 with sodium acetate solution. The crystalline base was dried thoroughly in vacuo, dissolved in dry tetrahydrofuran, and treated with methyl iodide[20]. After 4 days at room temperature an 87% yield of tetracycline methiodide had crystallised. An aqueous solution was again adjusted to pH 4.5 with sodium acetate and tetracycline methyl betaine (37) crystallised. This material was dried for several days in vacuo at room temperature and was then pyrolysed in acetonitrile[21]. After several attempts a 76% yield of the triphenol (38) was obtained by using sufficient dry (distilled three times from calcium hydride) acetonitrile to just cover the solid and then heating the slurry.



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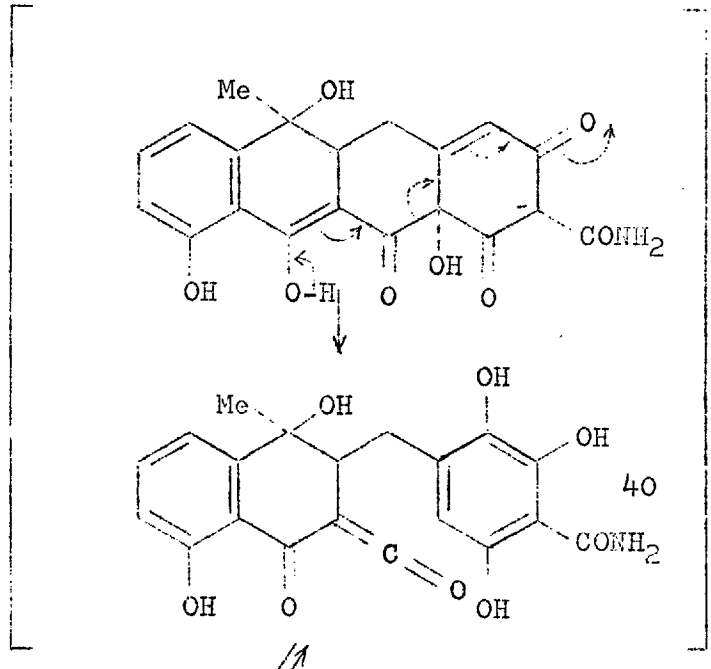
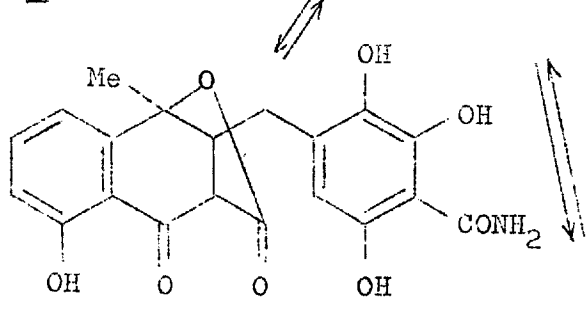
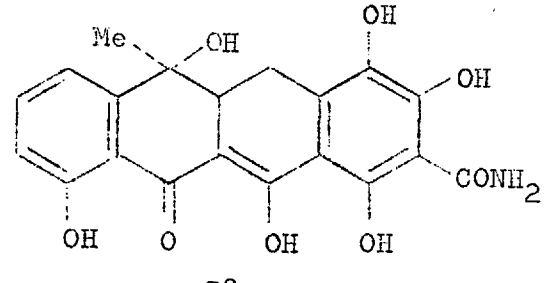

Me
OH
O
CONH2
OH
O-H
O
OH
O
Me
OH
OH
OH
40
CONH2
C
O
OH
O
OH


Me
O
OH
OH
CONH2
OH
O
O
OH

39


OH
Me
OH
OH
CONH2
OH
O
OH
OH

38

This yield represents an improvement over the literature conditions where a larger volume of solvent was used. As the major biproduct of the reaction is the γ-lactone (39), this may provide further insight into the mechanism. Two points should be considered.

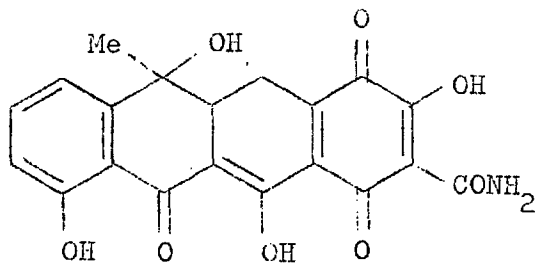
a. If the γ-lactone (39) is isolated as a crystalline solid and is pyrolysed in a small amount of acetonitrile, then some conversion to the triphenol (38) occurs.

b. The solubility of the triphenol (38) in acetonitrile is much less than that of the γ-lactone (39). Thus one would expect the yield of the triphenol to increase as the volume of solvent is decreased and this is, indeed, found in practice.

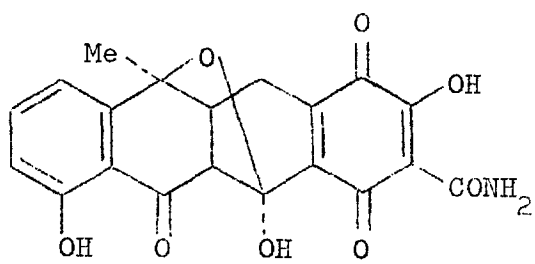
The tetracyclic quinone (35) was prepared from the triphenol by treating a dioxan solution with 1 mol. of DDQ. After filtration, the product was obtained as a red gum on evaporation of the solvent at room temperature. This crystallised on trituration with ether. The n.m.r. spectrum of this compound shows the C-6 methyl signal to be split into two peaks at 8.34 and 8.43 τ. The ultra-violet spectrum is dependent on solvent:

Dioxan	257mμ(18,000), 340mμ(9,190), 382mμ(5,890)
N/100 methanolic HCl.	261mμ(17,600), 342mμ(8,210), 428mμ(12,600)

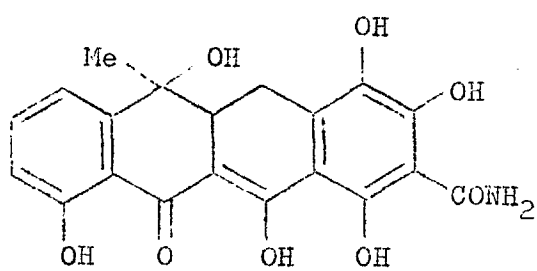
By comparison with the spectroscopic data of other tetracycline derivatives (38, 41, 42, 43) this data has been interpreted as showing that the quinone exists as the 6,12-hemiketal (44) besides the expected form (35).



35



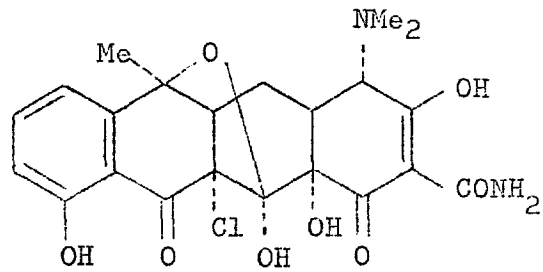
44



38

C-6 methyl at τ 8.34 (DMSO-D_6)

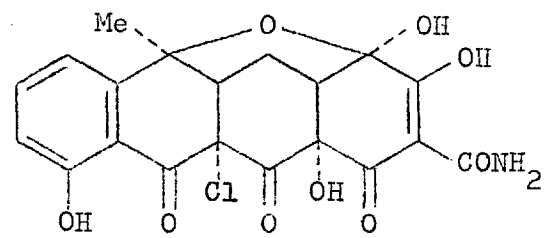
λ_{max} (H_2SO_4, 1% sodium borate)[21] 281 mμ (16,6000), 311 mμ (28,800), 455 mμ (11,200), 520 mμ (8,310).



41

C-6 methyl at τ 8.00 (DMSO-D_6)

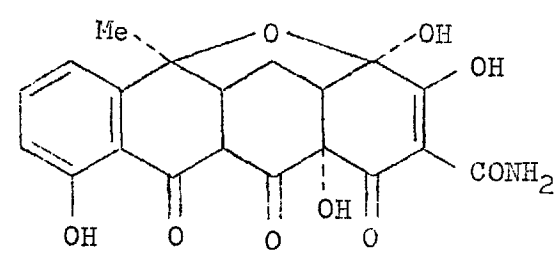
λ_{max} ($^N/_{100}$ methanolic HCl)[22] 258 mμ (21,400), 343 mμ (3,980).



42

C-6 methylat 7.96 (DMSO-D_6).

λ_{max} ($^N/_{100}$ methanolic HCl)[23] 258 mμ (26,300), 343 mμ (4,790).



43

C-6 methyl at 8.21 (DMSO-D_6).

λ_{max} (N/100 methanolic HCl)[23] 268 mμ (25,100), 346 mμ (5,250).

The three hemiketals were prepared by the published routes: 11a-chlorotetracycline-6,12-hemiketal (41) by reaction of amphoteric tetracycline with N-chlorosuccinimide (NClS)[22]; 11a-chloro-4-oxo-4-dedimethylaminotetracycline-4,6 -hemiketal (42) by reaction of the 6,12-hemiketal with NClS in aqueous solution; 4-oxo-4-dedimethylaminotetracycline-4,6-hemiketal by reaction of tetracycline with NClS in aqueous solution.

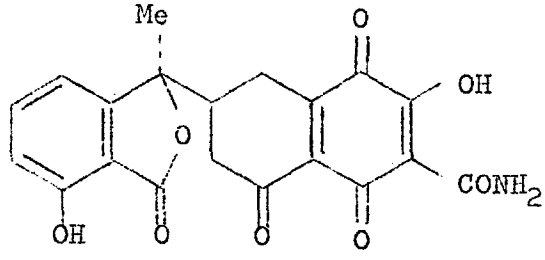
In each hemiketal the C-6 methyl appears at a lower τ -value than in the open system (38). With the 11a-chloro substituted compounds the signal is further deshielded by the presence of the chlorine. The shortening of the chromophere produces the expected reduction in the ultra-violet maxima.

The 4,6-hemiketal (43) was dissolved in methanol and treated with concentrated potassium hydroxide. The expected potassium salt crystallised[23]. The acid stability was tested by warming an aqueous dioxan solution to 100° in the presence of 6N hydrochloric acid. After 15 min. the hemiketal had not been destroyed. Thus the desired product from the hydration of the quinone (35) was stable in relatively severe basic and acidic conditions.

Hydration of the tetracyclic quinone.

a. Base. The quinone was dissolved in THF and was stirred with N/10 sodium hydroxide in an atmosphere of nitrogen. The dark red

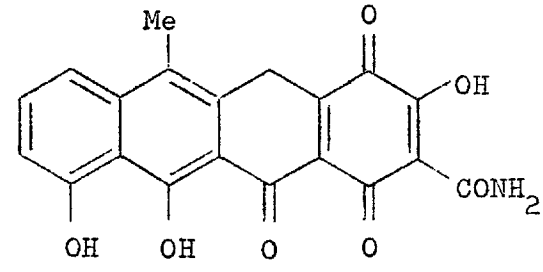
solution initially darkened and then faded rapidly to a deep yellow. After acidification, extraction yielded a yellow-brown solid which had maxima at 257 and 298 mμ and a molecular ion at 397 m/e. This suggests formation of the iso-derivative (45).



45

b. Acid. A solution of the quinone was prepared in 50% aqueous dioxan, acidified with dilute hydrochloric acid and maintained at room temperature. After two hours an aliquot was taken and extracted with chloroform. Evaporation of the solvent gave a red-brown solid. The mass spectrum showed a low intensity ion at 415 m/e and a very much stronger one at 397 m/e. The infra-red spectrum, however, had no band greater than 1700 cm^{-1} in the carbonyl region. This must be present if a 4,6-hemiketal is the product since its formation requires that the 11-ketone is not enolised.

More prolonged acid treatment resulted in the formation of a green-brown solid which had a molecular ion at 381 m/e and λ_{max} 369 and 433 mμ. It is postulated that this compound is the 5a,6-anhydro derivative (46).



46

c. Photolytic hydration. The quinone was dissolved in aqueous dioxan and the solution irradiated with a tungsten filament bulb, the temperature being kept in the range 25-30° by a cooling coil. Short reaction times brought about no change in the substrate and on overnight irradiation, dehydration to a compound with λ_{max} 431 mμ took place. A blank reaction left for the same period gave rise to the same product. Increasing the temperature or alteration of the pH of the solution made no difference to the course of the reaction.

d. Hydration in the presence of metal ions. The quinone was dissolved in dioxan and aqueous solutions of metal salts added, the reaction being followed by taking ultra-violet spectra at intervals. Magnesium ($MgCl_2$), iron ($Fe(NO_3)_3$) and aluminium ($Al_2(SO_4)_3$) ions gave no hydration at room temperature. Warming the solutions dehydrated the quinone.

The steps which must take place in conversion of the quinone (35) to the 4,6-hemiketal (43) may be summarised in 3 stages.

a. Hydration of the 4a,12a-bond on the α-face with the hydroxyl at C-12a.

b. Ketonisation of the 11,12-β-diketone.

c. Intramolecular cyclisation to form the hemiketal.

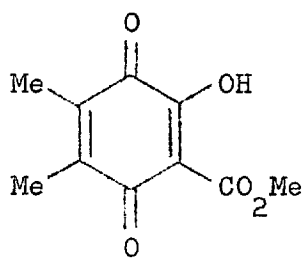
If the 11,12-diketone can be prevented from enolising by blocking with halogen, for example, then only hydration in the correct sense has to occur for the hemiketal to be formed. The two known 11a-halogeno-4,6-hemiketals are the 11a-fluoro and 11a-chloro compounds. Since 11a-chlorine is more easily removed than fluorine it was decided to attempt this simplification by reaction of the tetracyclic quinone with NClS.

The quinone was dissolved in aqueous dioxan, acidified, and treated with NClS. A rapid reaction took place and extraction yielded a yellow solid. This compound had λ_{max} 262 mμ (9,960) and 352 mμ (8,310) and the infra-red spectrum contained absorption bands at 1691, 1721 and 1766 cm^{-1}. This data is in accordance with the chlorination and hydration having occurred but the compound contained chlorine and the n.m.r. spectrum showed the C-6 methyl at 8.27τ. (4,6-hemiketal (43) C-6 methyl at 8.21τ, 11a-chloro-4,6-hemiketal (42) C-6 methyl at 7.96τ). Thus the chlorine was most probably not at C-11a, and in order to elucidate the structure of this compound, the reaction of NClS with a model quinone was studied.

The quinone (47) was dissolved in aqueous dioxan, acidified, and stirred with NClS. A rapid reaction occurred and a pale yellow

oil was obtained by extraction and evaporation of the solvent. Although this oil contained one major product it proved difficult to purify. However, reaction of the quinone with sodium hypochlorite in acid solution gave the same product which was now separated as a colourless crystalline solid. This compound had ν_{max} 3520, 3400, 2560, 1745 and 1723 cm^{-1} and λ_{max} 241 mμ (7,800). The n.m.r. spectrum showed 2 methyl groups on a double bond, an ester methyl and 1 distinguishable hydroxylic proton. The compound contained chlorine.

The structure suggested by this data was the cyclopentenone (48). Confirmation was obtained by methylation with diazomethane to give a more stable diester (49), and oxidation of the α-hydroxyacid with lead tetraacetate to the cyclopentendione (50).



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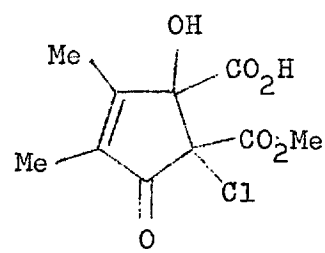

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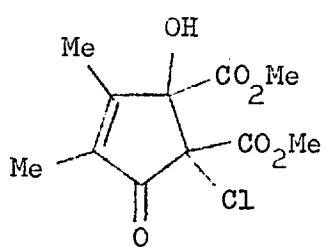

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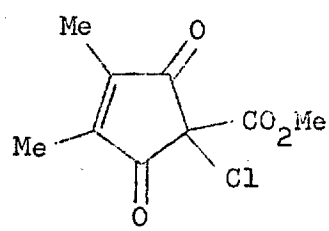
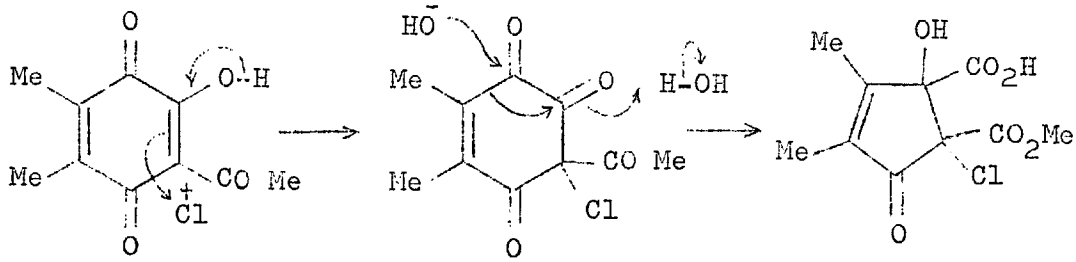


50

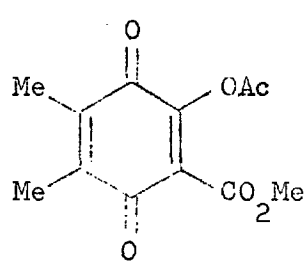
A similar reaction has been reported for the reaction of phenols with chlorinating agents[24], the suggested mechanism being as follows:



Since a ring-contraction of this type would account for the product obtained from the tetracyclic quinone, a method of protecting ring A which would allow 11a-chlorination was sought.

The model quinone (47) was acetylated with acetic anhydride/pyridine to give the acetate (51). However, this compound is hydrolysed rapidly in neutral aqueous solution and therefore the acetate is not a sufficiently stable protecting group. This is not an unexpected result since the acetate possesses considerable anhydride character.

Reaction of the quinone (47) with diazomethane in methanol provided the methyl ether (52).



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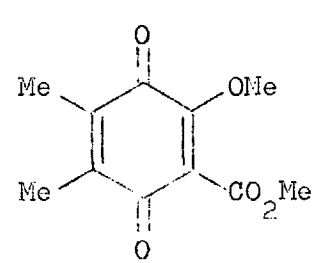


52

This compound was hydrolysed by acid, but was stable in aqueous dioxan for several hours. Treatment of the methoxyquinone with NClS in aqueous dioxan gave no reaction. Thus methylation provides the degree of protection that was required.

The tetracyclic quinone (35) was dissolved in dioxan and methanol and was treated with a solution of diazomethane in ether. A rapid reaction occurred and on evaporation of the solvent a brown solid was obtained. This was purified by rapid chromatography on silica gel. The spectral data showed that the desired methylation had taken place, but a consistently high nitrogen analysis suggested that cyclo addition of diazomethane had also ensued.

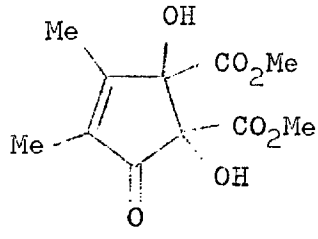
Expoxidation

As the simple addition of water to the 5a,12a-bond had not been achieved, an alternative method of hydroxylation was attempted via epoxidation.

The hydroxyquinone (47) was stirred with basic hydrogen peroxide at room temperature. After the starting material had been consumed acidification yielded an oil which was a mixture of at least ten compounds.

The methoxyquinone (52) was treated with basic peroxide and in this case a 15% yield of a crystalline product was isolated. The infra-red spectrum of this compound contained an absorption at 1751 cm^{-1} and the n.m.r. showed the presence of 2 methyl groups on a double bond, 2 ester methyls and 2 exchangeable protons. Thus a ring

contraction to the cyclopentenone (53) had occurred. Analogous reactions have been reported.[27]



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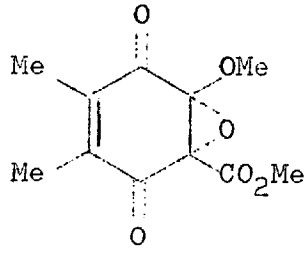


54

An alternative mode of epoxidation was examined with the use of m-chloroperbenzoic acid. Reaction with the methoxyquinone (52) gave a good yield of an epoxide. However, the C-methyl signals appeared at τ 7.97 in the n.m.r. spectrum. Thus the reaction has again taken place on the 2,3-bond, resulting in formation of the epoxide (54).

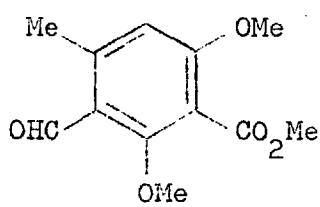
As m-chloroperbenzoic acid is an electrophilic reagent it should be possible to force the reagent to attack the 5,6-double bond by reducing the electron density of the 2,3-bond. However, when the acetoxyquinone (51) was treated with the peracid, no reaction took place.

As the desired hydroxylation of a quinone to an endione could not be brought about an entirely new approach was examined.

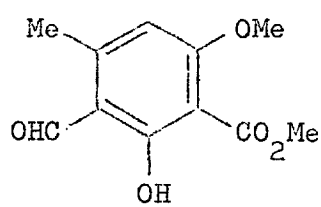
II. 12a-hydroxylation by oxidation of phenols.

Oxidation of phenols to dienones with insertion of an ortho oxygen function has been achieved with lead tetra-acetate[1], sodium periodate[2], and benzoyl peroxide[3]. This type of reaction would provide an excellent means of dearomatisation/hydroxylation of ring A and was, therefore, worthy of investigation.

Studies in the synthesis of tetracyclic intermediates with a 1,2,4-trihydroxy ring A had shown[4] that it was necessary to protect these hydroxy functions as methyl ethers in order to make the A-C cyclisation possible. The problem of demethylation had been investigated on dimethoxy model compounds[4]. Methyl 2,6-dimethoxy-5-formylbenzoate (1) was prepared from methyl p-orsellinate by standard methods. Treatment of a methylene chloride solution of (1) with boron trichloride at -80° provided monodemethylation. The structure of this methoxyphenol was established by acetylation to (3), and comparison with the methoxyacetate (4), of known structure[5].



1



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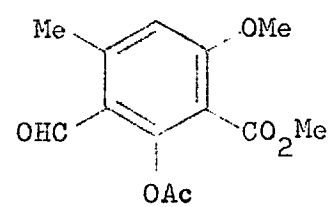

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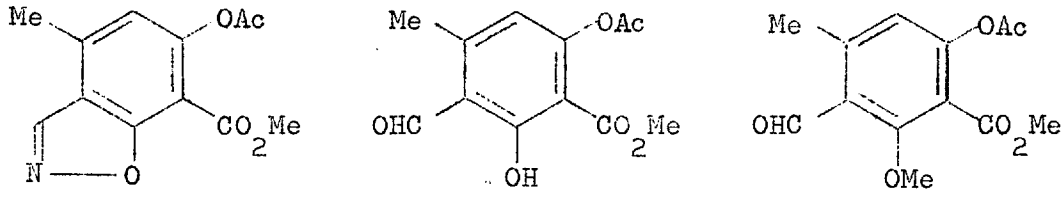


4

The two compounds were isomeric and hence the boron trichloride demethylated the methyl ether ortho to the formyl substituent to give the phenol (2). The oxidation of the hydroxyaldehyde (2) was now examined.

a. $(Et_4N)IO_4$.

The phenol was dissolved in absolute ethanol and was stirred with freshly recrystallised dry $(Et_4N)IO_4$. No reaction could be detected.

b. $NaIO_4$.

An alcohol solution of the phenol was mixed with an aqueous solution of sodium periodate and stirred at room temperature. No reaction took place.

Acidic medium.

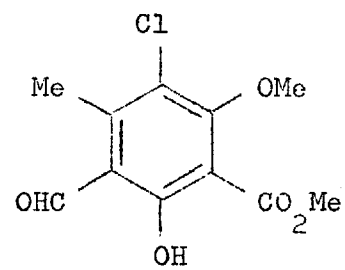
A similar reaction was adjusted to pH 4 immediately after addition of the sodium periodate. There was no reaction on prolonged stirring.

Alkaline medium.

The phenol was dissolved in alcohol, excess aqueous sodium

hydroxide was added followed by the sodium periodate. Acidification with hydrochloric acid and extraction with chloroform provided a new crystalline solid.

The infra-red spectrum of this compound was very similar to that of the phenol (2), but the n.m.r. indicated the absence of an aromatic proton. The compound contained chlorine and the mass spectrum showed the molecular ion at 258 m/e. Thus the product was the chlorophenol (5). The chlorination occurs on work-up for when a similar reaction was acidified with sulphuric acid, only phenol (2) was obtained.



5

c. $Pb(OAc)_4$.

The reaction of the hydroxyaldehyde (2) with lead tetra-acetate was studied extensively. Under forcing conditions; methanol/boron trifluoride etherate, reaction did occur. No characterisable product could be isolated, however, as the reaction gave rise to a complex mixture of products which could not be separated by t.l.c. The infra-red spectrum of the crude mixture suggested that deformylation

had taken place.

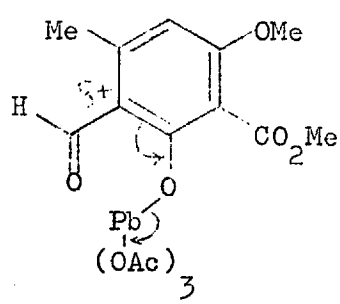
d. $Tl(OAc)_3$.

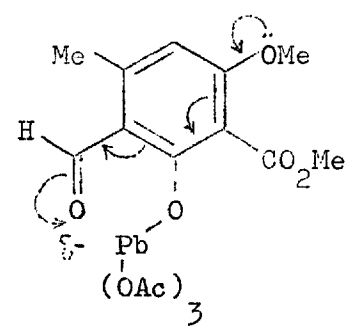
In acetic acid solution thallic acetate proved less powerful than lead tetra-acetate. After prolonged reaction no oxidised products were obtained.

e. $(C_6H_5CO_2)_2$.

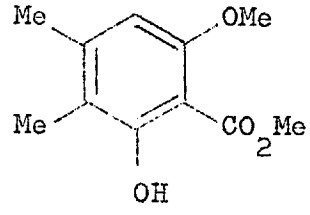
When a benzene solution of the hydroxyaldehyde (2) was warmed to 60-70° in the presence of excess benzoyl peroxide, no reaction occurred.

Lead tetra-acetate appeared to be the most promising of these oxidising agents and its use was, therefore, examined further. Since the lead tetra-acetate oxidation of phenols may require the development of carbonium ion character ortho to the phenol, oxidation may be being prevented by the electron withdrawing formyl substituent.



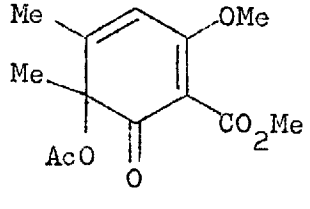


This point was investigated by reducing the aldehyde (2) to the dimethylphenol (6) by hydrogenolysis, and examining the oxidation of this phenol.



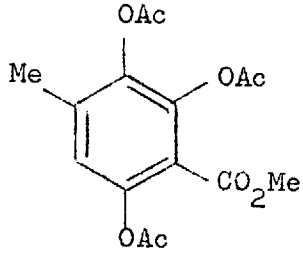
6

When the phenol (6) was treated, in methanol, with lead tetra-acetate and a trace of boron trifluoride etherate, t.l.c. indicated that it was destroyed in 15 min. Work-up by quenching in water and extraction provided a colourless crystalline compound. This material had $\nu_{max.}$ 1733 and 1660 cm^{-1}, and the n.m.r. spectrum showed the presence of an acetate methyl, a methyl signal at 8.55 τ and one aromatic proton. Thus the required oxidation to the dienone (7) had occurred, this being confirmed by the combustion analysis.



7

As the feasibility of the lead tetra-acetate oxidation had been demonstrated a better model compound was sought. Treatment of the triacetate (8) with aluminium trichloride under conditions designed to bring about Fries rearrangement[6], failed to provide the aceto-phenone (9). Similarly acetylation of the triacetate (8) with acetyl chloride did not give an acetophenone.



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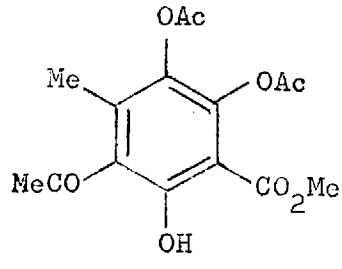

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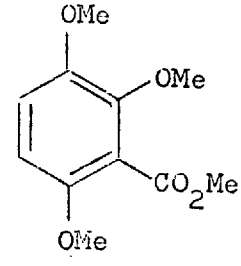
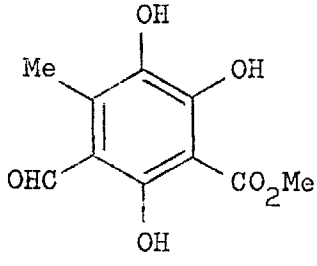


10

Attempted acetylation of the trimethoxyester (10) with acetyl chloride/aluminium chloride only provided demethylated products. Attention was, therefore, returned to trimethoxyaldehydes.

The trihydroxyaldehyde (11) was methylated with dimethyl sulphate/potassium carbonate to yield the trimethoxyaldehyde (12) as an oil. Reaction with boron trichloride in dichloromethane at -80^0 gave a mono demethylated product. In this series the demethylation did not proceed so cleanly as with the dimethoxyaldehyde, but recrystallisation gave the pure phenol. The infra-red spectrum contained maxima at 1733 and 1663 cm^{-1} due to the ester and the hydrogen bonded formyl substituents. The n.m.r. spectrum showed the presence of 1 C-methyl and 3 O-methyl groups, 1 aldehydic proton

and 1 exchangeable proton at -1.9 τ. Hydrogenolysis provided a dimethylphenol for which the ester absorption now appeared at 1660 cm^{-1}. Thus by analogy with the dimethoxy series it was assumed that ortho demethylation had taken place to give the hydroxyaldehyde (13) and the dimethylphenol (14).



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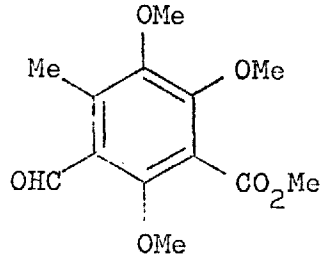
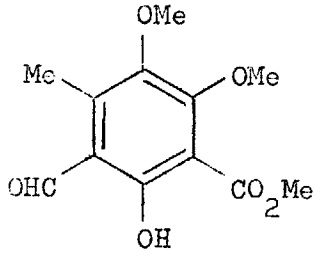


12



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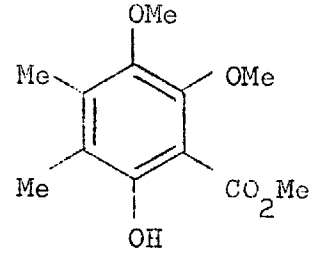
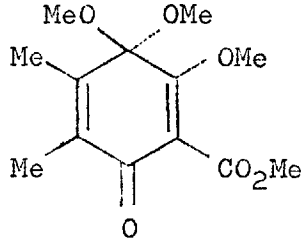


14

The dimethylphenol (14) was dissolved in methanol and was oxidised with lead tetra-acetate in the presence of boron trifluoride etherate. When t.l.c. indicated that the substrate had been consumed the reaction was worked-up by quenching in water. Extraction and evaporation provided a colourless crystalline compound which had $\nu_{max.}$ 1737, 1663, 1650 cm^{-1}.

The n.m.r. spectrum showed methyl group signals at 8.08 (2), 6.78 (2), 6.13 and 6.04 τ. This data fits with the product being the quinone semiketal (15).



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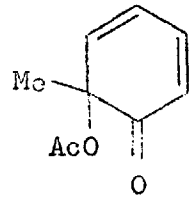
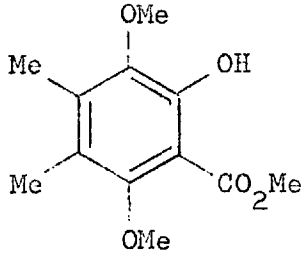


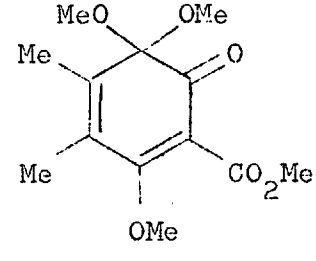
16

However, the ultra-violet spectrum had maxima at 239 mμ (8,120) and 340 mμ (2,660), and this corresponds[7] more closely to the product being a dienone of the type (16) rather than being cross-conjugated as in (15).

The only way this conflicting data may be reconciled is to assume that the boron trichloride demethylation has taken place <u>para</u> rather than <u>ortho</u>. The dimethylphenol would then have the structure (17) and the oxidation product would be the <u>o</u>-quinone semiketal (18). It became necessary, therefore, to synthesise one of the two possible dimethylphenols (14 or 17) by an unambiguous route.

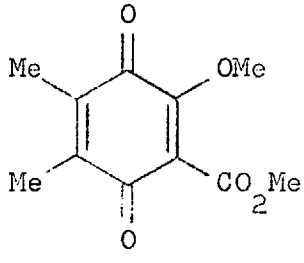


17

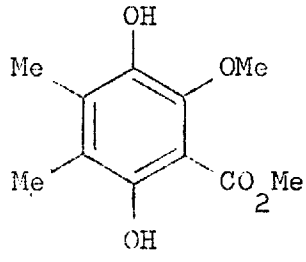


18

The methoxyquinone (19) was hydrogenated over palladium on barium sulphate to provide the crystalline hydroquinone (20).



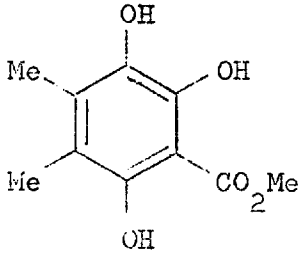
19



20

It was expected that the 3-hydroxyl would methylate more readily than that in the 6-position due to hydrogen bonding with the ester. In practice, however, it was found that treatment with 1.1 mol. of dimethyl sulphate in acetone with potassium carbonate gave an equal mixture of the totally methylated product and the hydroquinone.

An attempt was then made to utilise the o-hydroxyls present in the triphenol (21) to prepare a cyclic derivative. Reaction of the triphenol (21) with acetone dimethylketal in the presence of tosyl acid gave no conversion to the acetonide (22).



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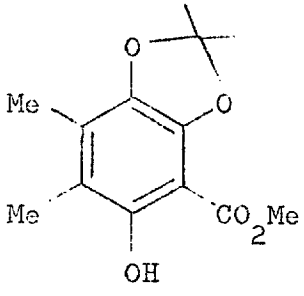
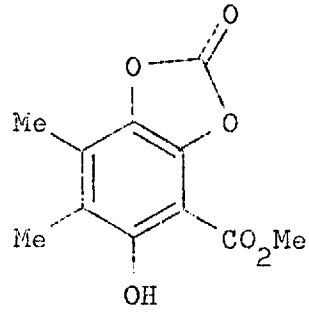


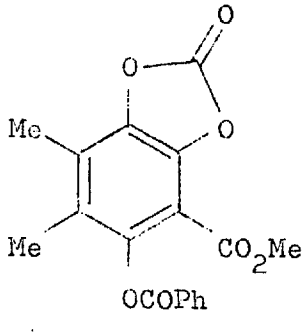
22

The required type of intermediate was obtained by treating a pyridine solution of triphenol (21) with a toluene solution of phosgene at 0° [8]. The cyclic carbonate (23) was produced after quenching in water and extraction. It now remained to protect the 6-hydroxyl so that the carbonate could be removed and the 2 and 3-hydroxyls methylated.

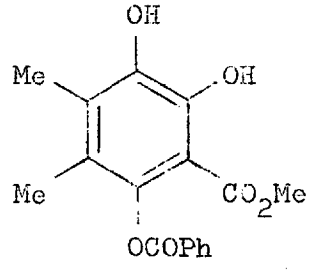


23

When the carbonate (23) was stirred, in acetone, with potassium carbonate and benzyl chloride the only product isolated was the triphenol (21). A satisfactory protection of the phenol was obtained when the carbonate was treated with benzoyl chloride and pyridine. The benzoate (24) crystallised when the reaction mixture was poured onto ice. The cyclic carbonate was removed by treating a THF solution with dilute mineral acid to give the dihydroxydiester (25).

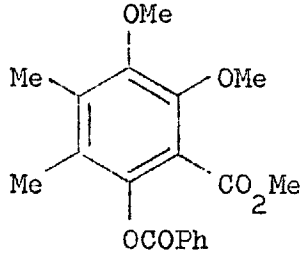


24



25

Reaction of the catechol (25) with dimethyl sulphate/potassium carbonate in acetone readily provided the dimethoxydiester (26). Sodium methoxide in methanol at room temperature rapidly removed the benzoate to give the phenol (14).



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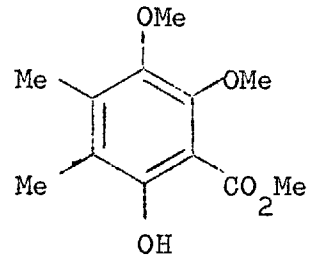
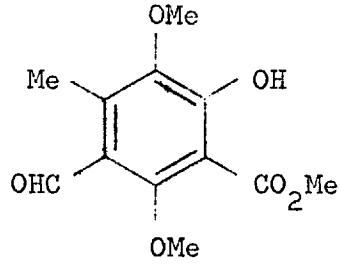


14

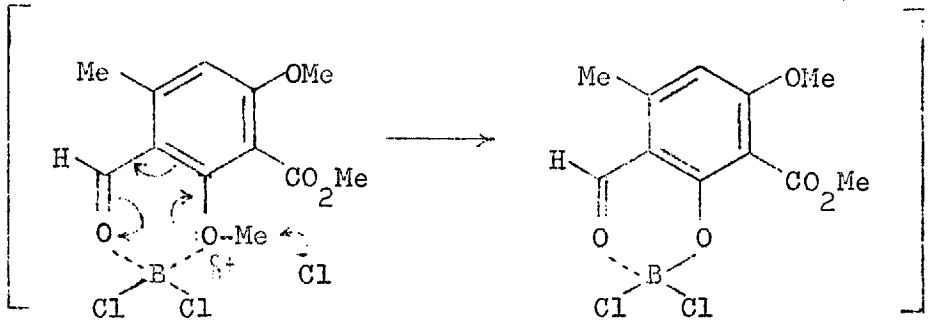
Comparison of this phenol with the one obtained via demethylation of the trimethoxyaldehyde (12) showed them to be dissimilar and isomeric. Thus the product obtained from the reaction of boron trichloride with (12) must be assigned structure (27) and not (13).

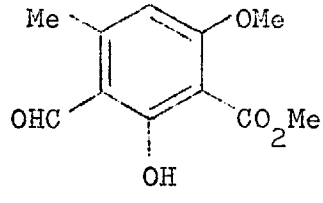


27

Similarly, the dimethylphenol obtained by hydrogenolysis must now be given structure (17).

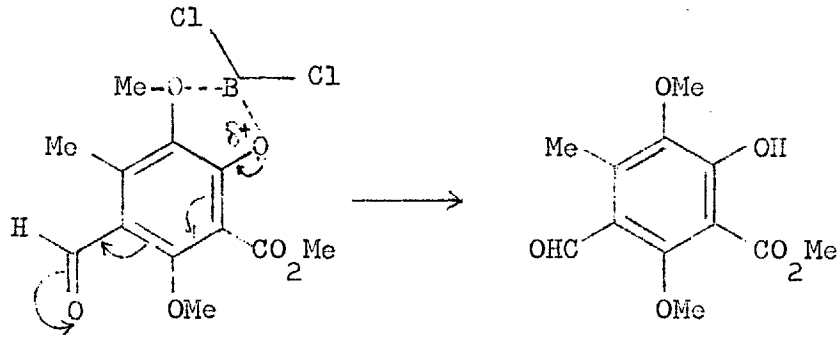
The reason for this <u>para</u> demethylation is not obvious. In the case of the dimethoxy series one may write an intermediate in which the boron trichloride assists attack by nucleophile on the methoxyl group by polarisation:[9]





6

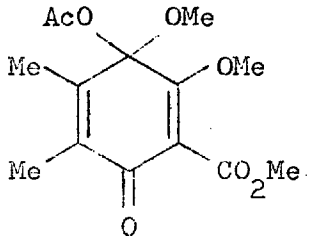
In the trimethoxy series one may write a similar cyclic intermediate between the 2- and 3-methoxyls, with the 2-methoxyl being preferentially removed due to the polarising effect of the formyl group.



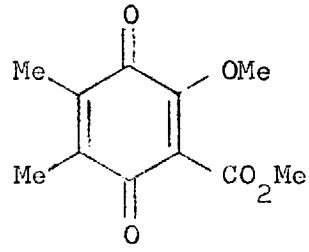
27

The fact that the demethylation does not proceed cleanly in this series may be ascribed to a second demethylation removing the 6-methoxyl to give a resorcinol.

The phenol (14) was now oxidised with lead tetra-acetate in benzene. A rapid reaction took place and the product, after quenching in water and extracting with methylene chloride, was a colourless oil. The n.m.r. spectrum of this oil showed the presence of an acetate at 8.17, 2 C-methyls on a double bond, and a methoxyl on an sp^3 carbon at 6.8 τ. The ultra-violet maxima at 241 mμ (14,300) and 272 mμ (13,300) are in accordance with this product being the p-quinone semiketal (28).



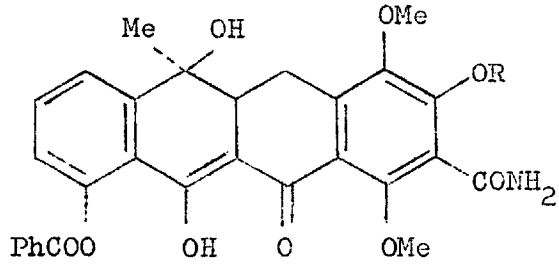
28



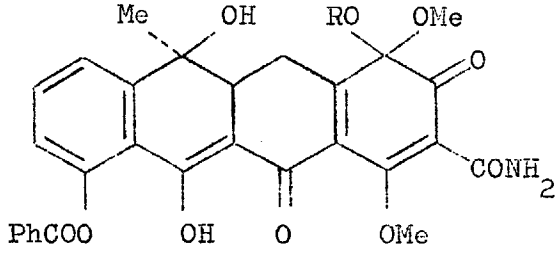
29

Confirmation was obtained by hydrolysis with dilute mineral acid in a two-phase system to provide the previously characterised methoxy-quinone (29).

A possible synthetic tetracyclic product[4,10], is the trimethoxy-amide (30).

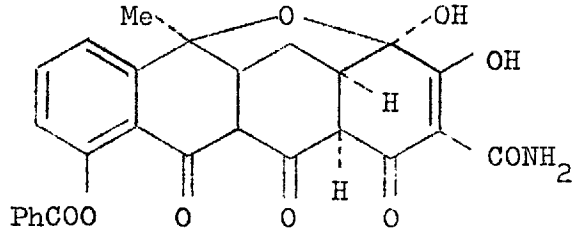


	R
30	Me
31	H



	R
32	Me or Ac

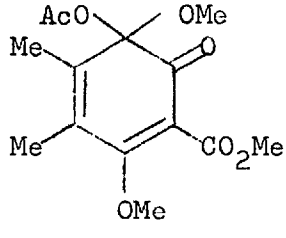
If a selective demethylation can be carried out on this compound without dehydration at the 6-position, then the 3-position should be demethylated to provide (31). Lead tetra-acetate oxidation should provide an o-quinone semiketal (32) which, if the 4a-12a double bond could be reduced on acid treatment, should provide the 4,6-hemiketal (33).



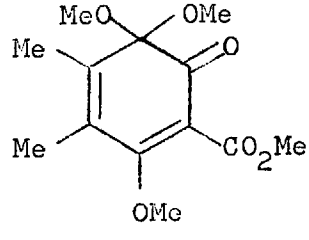
33

Thus continued study of the oxidation of phenols (27) and (17) should be worthwhile.

Reaction of the dimethylphenol (17) with lead tetra-acetate in benzene provided o-quinone semiketal (34). However, this compound was even less stable than the dimethoxy semiketal (18). The reduction of the semiketal (18) was, therefore, studied.

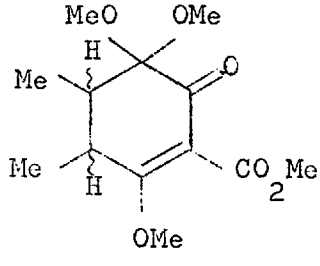


34

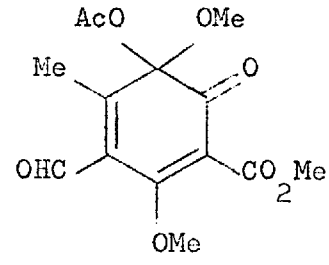


18

Hydrogenation of (18) over palladium on charcoal led to a mixture of 2 compounds. One was identified by t.l.c. as being the phenol (17). The other, separated in an impure state by t.l.c. on silica gel, had $\lambda_{max.}$ 263 mμ (9,600). The n.m.r. spectrum had methyl signals at 8.78, 8.74, 6.78, 6.73, 6.13 and 6.10 τ. Although the signals due to the 2 methine protons could not be identified, and analysis could not be obtained, this data suggests formation of the ketal (35).



35



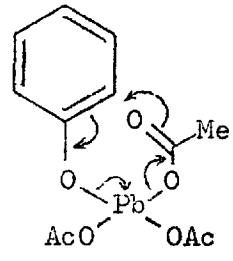
36

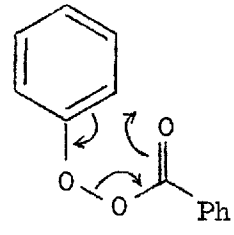
A final oxidation carried out was the treatment of hydroxyaldehyde (27) with lead tetra-acetate. The product obtained after quenching in water and extraction had $\lambda_{max.}$ 224 mμ (13,700) and 333 mμ (2,760). The n.m.r. spectrum showed C-methyl signals at 7.90 and 7.85 τ, O-methyl signals at 6.56, 6.15 and 5.98 τ, and the formyl proton at 0.09 τ. Thus the expected oxidation, with formation of the ketal (36) has occurred.

Thus lead tetra-acetate oxidation should provide a means of converting ring A of tetracyclic intermediates to the dihydro aromatic level, but the desired concomitant hydroxylation had not been achieved.

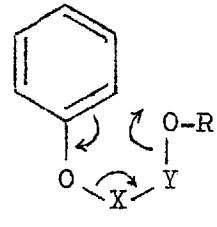
III. Phenol hydroxylation reactions.

It was decided to seek a means of ortho hydroxylating phenols. An accepted mechanism for the reaction of lead tetraacetate[1] or benzoyl peroxide[2] with phenols is indicated below.





Thus one may write a general intermediate (1) in which X and Y may be varied, to suggest analogous oxidations.

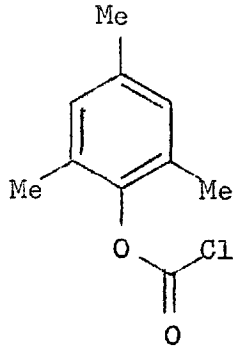


1

Aryl chloroformates.

The first system to be investigated was the reaction of mesityl chloroformate with peroxide, i.e., X = C O, Y = O. Mesityl chloroformate (2) was prepared by the reaction of mesitol with phosgene in the presence of dimethylaniline[3]. The chloroformate

did not react with sodium peroxide in benzene, aqueous benzene or aqueous ether. The major product from a reaction in dimethylformamide was mesitol. Thus the required peroxide is probably being formed but is decomposing, liberating water and carbon dioxide.



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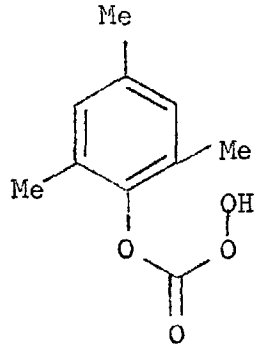
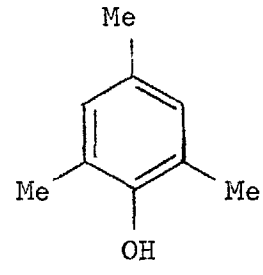
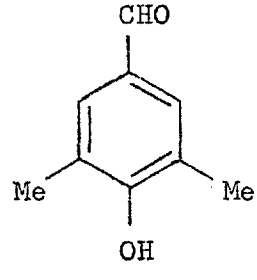




Further study has indicated that a secondary product of the reaction is the aldehyde (3).[4]

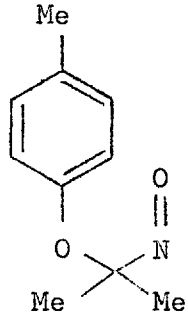


3

In an attempt to obtain a more stable intermediate mesityl chloroformate was stirred with t-butyl hydroperoxide and a trace of pyridine, but on work-up by quenching in water and extraction, mesitol was obtained.

Pyrolysis of 2-(p-cresyl)-2-nitrosopropane.

The suggested reaction was the thermal rearrangement 2-(p-cresyl)-2-nitrosopropane (4), i.e., X = $C(CH_3)_2$, Y = N.

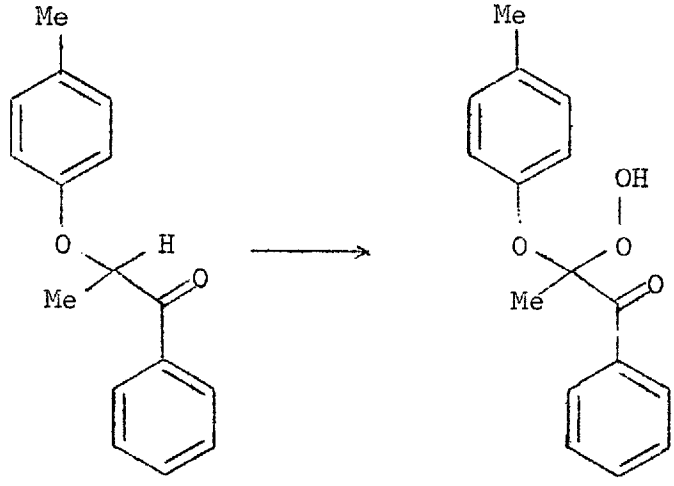


4

Acetoxime was dissolved in aqueous pyridine, cooled to 0^0, and oxidised with bromine[5]. 2-bromo-2-nitrosopropane was isolated as a blue oil and this was stirred, at 0^0, with an aqueous acetone solution of p-cresol anion. The product obtained on acidification and extraction was a brown oil which t.l.c. showed to contain many compounds. Pyrolysis in refluxing benzene increased the number of compounds formed but no single product predominated.

Autoxidation of p-cresyl ethers.

Autoxidation of 2-(p-cresyl)-propiophenone (5) should give a hydroperoxide (6) with the desired type of structure, i.e., X = $C(CH_3)COPh$, Y = O.



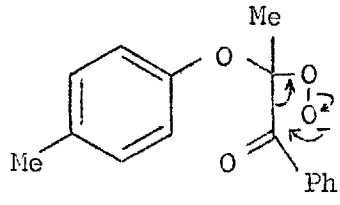
5 6

Propiophenone was brominated in the presence of a catalytic amount of aluminium trichloride to give 2-bromopropiophenone[6]. Treatment with p-cresol and potassium carbonate in refluxing acetone provided 2-(p-cresyl)-propiophenone (5).

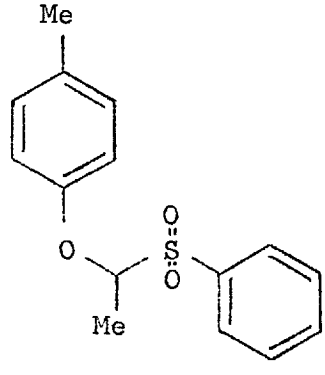
Autoxidation of this compound in t-butanol/dimethyl sulphoxide/ potassium t-butoxide at 0^0 gave a mixture of products. T.l.c. showed one component to be polar so the mixture was methylated with dimethylsulphate/potassium carbonate. A major component of this reaction was identified by t.l.c. and infra-red, and shown to be methyl benzoate.

2-(p-cresyl)-propiophenone does, therefore, undergo the desired autoxidation with formation of the hydroperoxide (6), but under the

conditions of the reaction the hydroperoxide attacks the ketone.



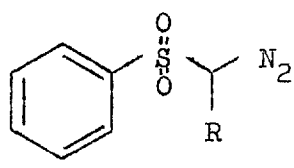
Since formation of the hydroperoxide (6) had been demonstrated it was decided to attempt the synthesis of an active ether of the type (7).



7

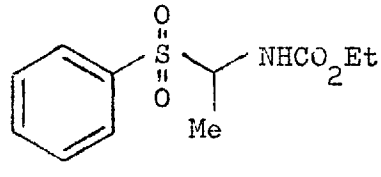
As the aim of the work was to find a means of ortho hydroxylation of phenols, a reagent which would give this type of ether on reaction with a phenol had to be prepared. The diazosulphone (8) might be

such a reagent.



	R
8	Me
9	H

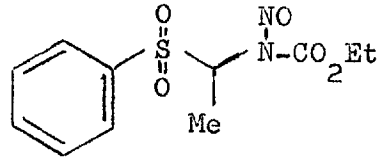
However, diazosulphones are not readily available compounds, but a synthesis of (9) has been published[8]. The intermediate urethane (10) for the preparation of the methyl compound (8) has also been prepared.



10

The urethane (10) was, therefore, prepared and the conversion to the diazosulphone (8) examined. Reduction of benzenesulphonyl chloride with zinc dust in ether gave benzene sulphinic acid[9]. Reaction of the sodium salt with acetaldehyde and urethane in formic acid gave the ester (10) in good yield. Nitrosation with nitrosyl

chloride in dry pyridine at 0^0 gave a 10% yield of the N-nitroso derivative (11) as an oil. Treatment of this compound with sodium methoxide at room temperature gave a 5% yield of an oil showing a weak diazo absorption in the infra-red.

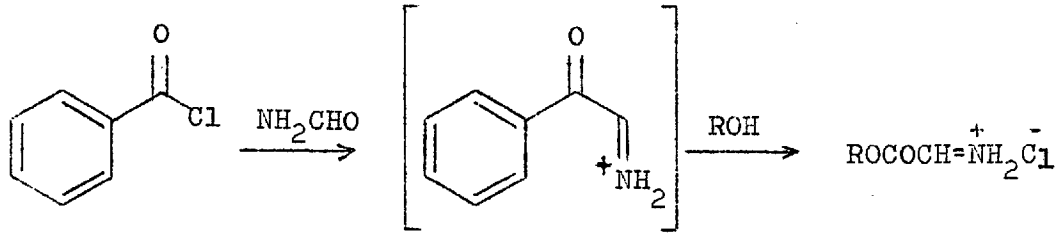


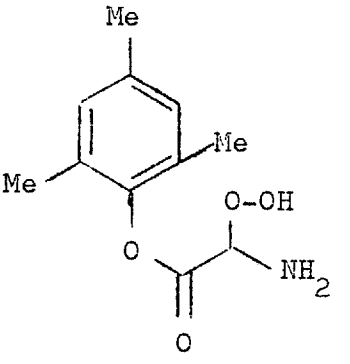
11

Although other methods of N-nitrosation exist, since the subsequent hydrolysis to the diazosulphone is such a poor reaction, this synthesis was not considered to be worthy of further study.

Aryl formididates.

The reaction of aliphatic alcohols with formamide in the presence of benzoyl chloride has been shown to provide alkyl formididates[11].





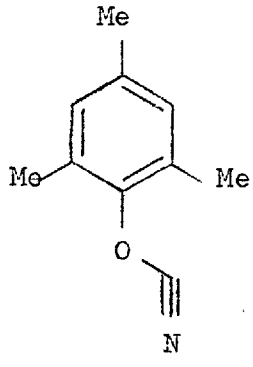
12

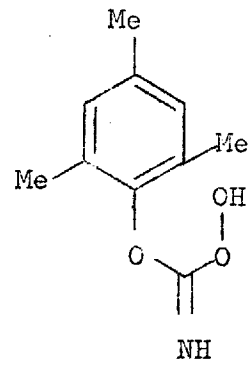
If this reaction was successful with mesitol, reaction with peroxide might provide an intermediate (12) of the type required for the hydroxylation.

In practice, however, it was found that the aryl formididate could not be prepared by this procedure. The only product obtained from a reaction of mesitol, benzoyl chloride and formamide was a colourless, deliquescent solid. This is most probably the intermediate benzoyl compound which does not react further with mesityl anion.

The reaction of mesityl cyanate with peroxide.

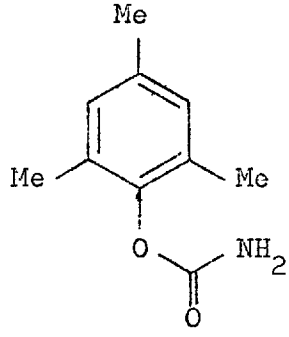
Aryl cyanates have been prepared by the reaction of phenols with cyanogen halide in the presence of triethylamine[12]. Treatment of the cyanate with peroxide should result in the formation of a hydroperoxide (13) of the required structure for a hydroxylation reaction, i.e., X = C NH, Y = O.





13

Mesityl cyanate was prepared by the reaction of mesitol, cyanogen bromide and triethylamine. After removal of the precipitated triethylamine hydrobromide the cyanate was purified by distillation in vacuo. The cyanate was dissolved in petrol and stirred with 87% hydrogen peroxide at room temperature. After 2 hr. the organic phase was separated, washed with water, dried, and evaporated. The solid residue was recrystallised from benzene and had $\nu_{max.}$ 3420, 3340, 3280, 3210, 1700 cm^{-1}. Thus an analogous reaction to that of aryl nitriles and peroxide[13] had been obtained, and the product was the amide (14).



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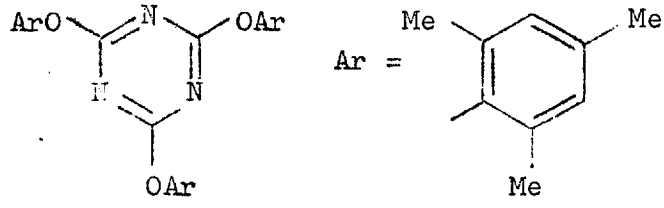
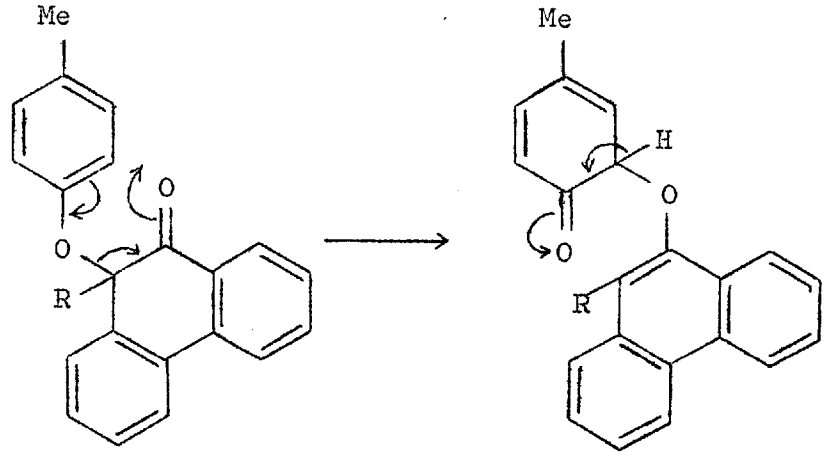


15

Mesityl cyanate was also reacted with t-butyl hydroperoxide in the presence of a trace of p-toluenesulphonic acid. After basic work-up the only product isolated, in very low yield, was the triazine (15), the expected product of trimerisation of the cyanate[14].

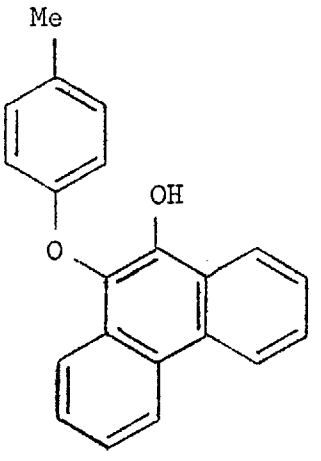
Phenanthrone rearrangement

A possible means of bringing about the ortho hydroxylation would be a cyclic reaction, with transfer of aromaticity, of the type shown below.



The synthesis of such a compound was, therefore, carried out.

Phenanthrene was oxidised to the 9,10-quinone with chromic acid[15]. Reaction with phosphorus pentachloride in benzene at 70° provided 9,9-dichlorophenanthra-10-one[16]. Anhydrous sodium p-cresate was prepared by the action of sodium hydride on cresol and was reacted with the dichlorophenanthrone in dry dimethylsulphoxide. The product, 9,9-di-p-cresylphenanthra-10-one, was reduced with zinc dust in glacial acetic acid to provide 9-p-cresyl-10-hydroxyphenanthrene (16).



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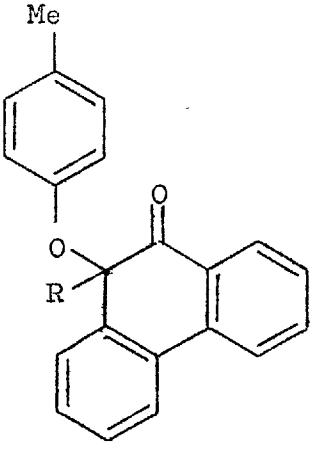


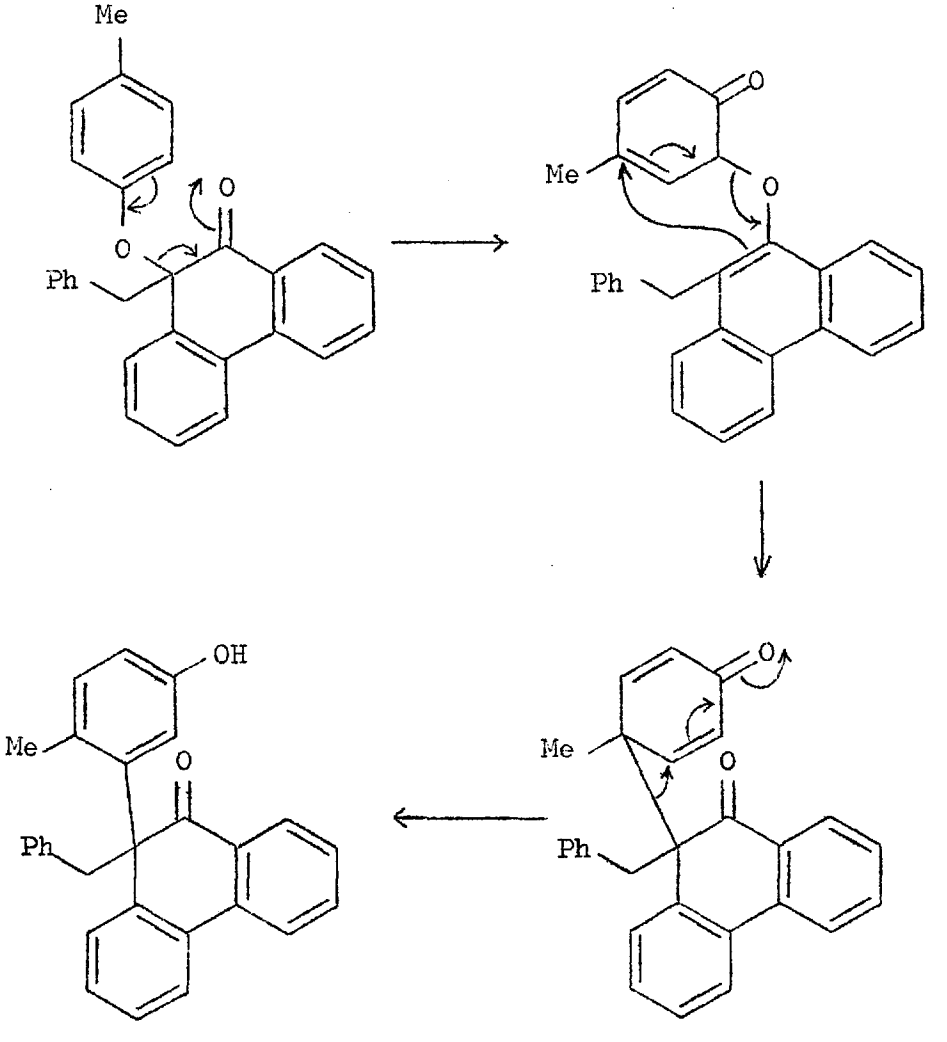
	R
17	Me
18	CH_2Ph

Reaction with methyl iodide in aqueous methanol gave only O-methylation. The required C-alkylation was obtained by preparing the sodium salt of the phenanthrol with sodium hydride and reaction with benzyl bromide in methanol to give (18). This compound had $\nu_{max.}$ 1691 cm^{-1} and in the n.m.r. spectrum the benzylic protons appeared at 6.87 τ, and half the AB quartet due to the aromatic protons on the p-cresyl ring appeared at 3.8-4.0 τ.

Pyrolysis of the benzyl phenanthrone at 190° for 14 min. gave a 20% yield of a crystalline phenol, $\nu_{max.}$ 3200, 1670 cm^{-1}. In the n.m.r. the benzylic protons appeared as a doublet at 6.46 and 6.36 τ, a replaceable proton at 1.78 τ, but the protons on the cresyl moiety were no longer visible. A crystalline acetate was obtained on

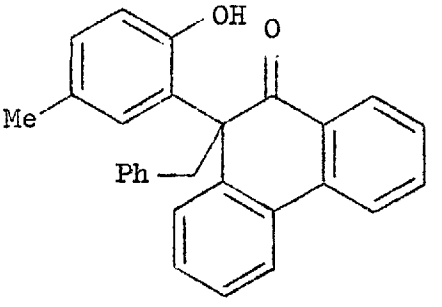
treatment with acetic anhydride/pyridine.

Since the n.m.r. spectra show that the p-cresyl ring has been modified during the pyrolysis, the possible structures of the product must be examined. First, supposing that the desired re-arrangement occurs this may be followed by a 6-electron 6-centre reaction to give the m-substituted phenol (19).



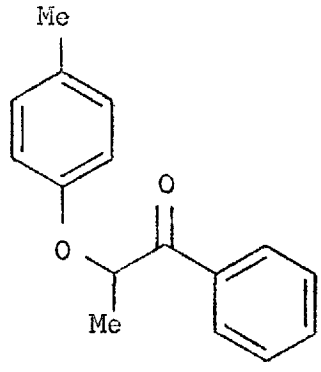
19

Alternatively, the reaction may proceed via a radical intermediate in which case the product will be the o-substituted phenol (20)



20

To distinguish between these two mechanisms the pyrolysis of some similar compounds was studied. The 2-(p-cresyl)-propiophenone (21) had been prepared for the autoxidation experiments and as this possessed a similar structure it was pyrolysed. As the temperature was increased, however, the compound distilled without rearrangement. This lack of reaction may be explained by enolisation preventing the initial rearrangement. Treatment of the propiophenone with methyl iodide and sodium hydride in DMF gave the methylated compound (22)



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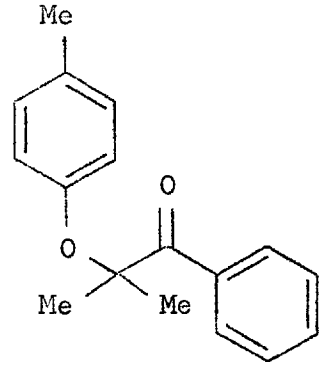
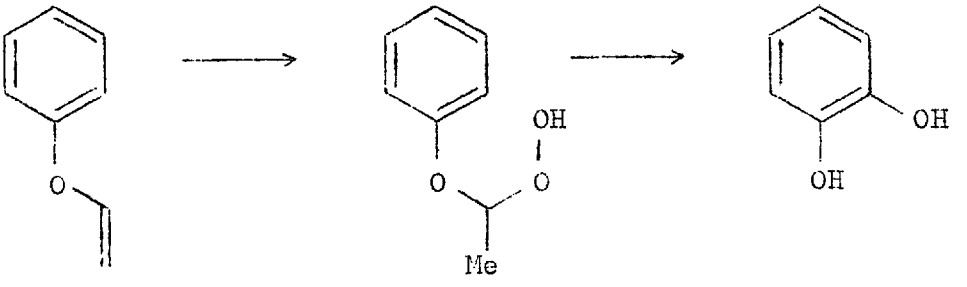


22

which cannot now enolise. Heating to 200° for prolonged periods gave no reaction. This failure to produce an analogous rearrangement indicated that the phenanthrone was probably rearranging by a radical process. Confirmation of this was obtained by heating a solution of the phenol in pyridine with D_2O for 20 hr. The n.m.r. of the deuterated compound showed a 9% reduction in the total integral of the aromatic protons. This corresponds to one proton having been exchanged and indicates that the structure of the phenol is the <u>ortho</u> substituted possibility (20).

The reaction of aryl vinyl ethers with peroxide

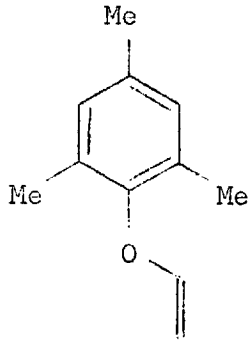
Aryl vinyl ethers should react with hydrogen peroxide to provide a hydroperoxide (22) of the required structure for a cyclic hydroxylation reaction, i.e., X = C-CH_3 , Y = O.



The first model selected was mesityl vinyl ether (23). Since the literature procedure for the preparation of this compound requires vigorous base treatment of the β-bromoethyl ether of mesitol[17], an alternative synthesis was first examined.

The transetherification procedure[18] gave no aryl vinyl ether in the case of the reaction of mesitol and ethyl vinyl ether in the presence of mercuric acetate.

The reaction of mesitol and ethyl bromoacetate provided the ester (24) in high yield[4].



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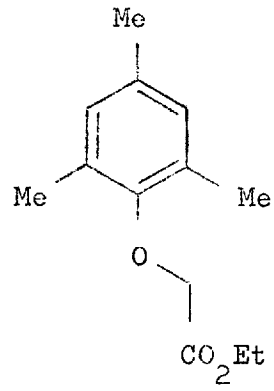
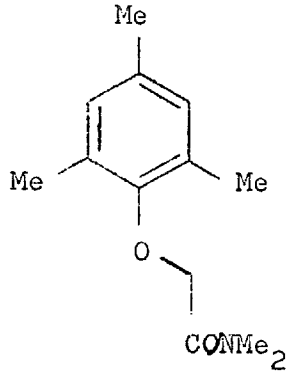


24

Saponification, conversion to the acid chloride with thionyl chloride/ DMF, and reaction with anhydrous dimethylamine gave the amide (25) in almost quantitative yield. Reaction with LAH provided the amine (26) which was oxidised with 30% hydrogen peroxide to the amine oxide (27).



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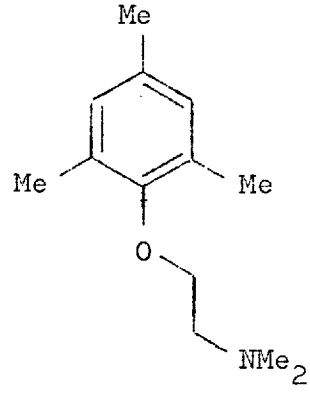

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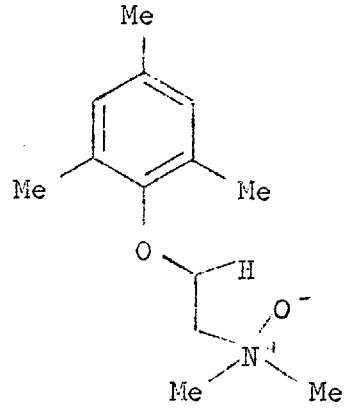


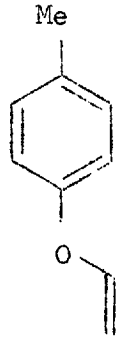
27

An accurate analysis was not obtained for this compound, probably due to hydration. Pyrolysis of the amine oxide at 180°, atmospheric pressure, gave mesityl vinyl ether but in poor yield.

A higher yield was obtained via the β-chloroethyl ether of mesitol, prepared by the reaction of mesitol and the tosylate of β-chloroethanol[19]. Distillation of the chloroether from potassium hydroxide gave the required vinyl ether[17].

The reaction of mesityl vinyl ether with hydrogen peroxide and acid was now examined. A mixture of the vinyl ether and 87% hydrogen peroxide was stirred vigorously at 0° C, and concentrated sulphuric acid added very cautiously. When t.l.c. indicated that the vinyl ether had been consumed the reaction mixture was poured into ice-water and extracted with methylene chloride. The major product was identified as mesitol and the minor products were present in too small quantities for characterisation.

At this time it was decided to continue these studies on p-tolyl vinyl ether (28) as the rearrangement should be more facile and the desired product, 4-methylcatechol (29), was available for comparison with the reaction products.



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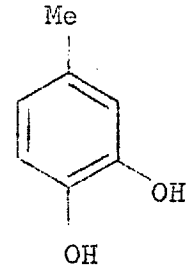
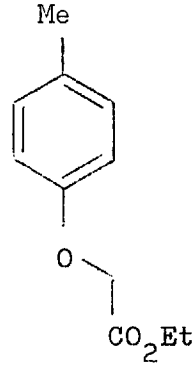


29

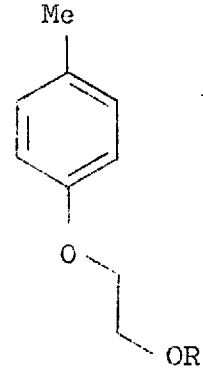
The p-cresyl acetic ester (30)[4] was reduced with LAH to the alcohol (31) which was reacted with p-tosyl chloride/pyridine to give the tosylate (32). Distillation over solid potassium hydroxide gave a 48% yield of p-tolyl vinyl ether. A 23% yield was obtained by distillation of the β-chloroethyl ether of p-cresol from potassium hydroxide.

The reaction of 87% hydrogen peroxide with p-tolyl vinyl ether and concentrated sulphuric acid proved even more liable to explosive decomposition than with mesityl vinyl ether. When carried out under conditions which with ethyl vinyl ether provides α-hydroperoxy ethyl

ether[20], only p-cresol could be identified among the products.

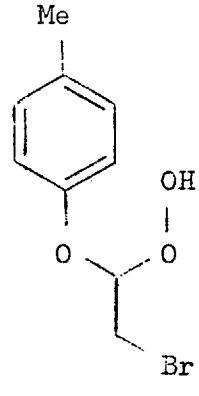


30



	R
31	H
32	Tos

It was then suggested that the α-hydroperoxy-β-bromoethyl (33) should be a more readily available intermediate.

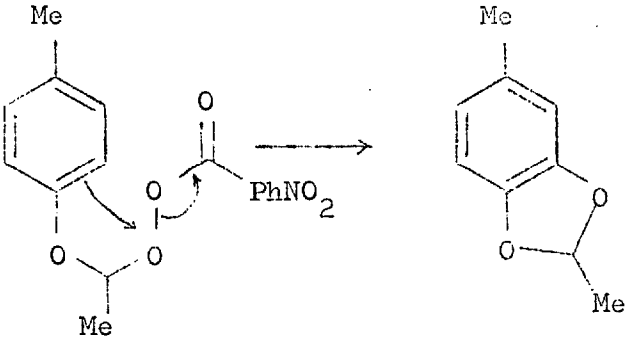


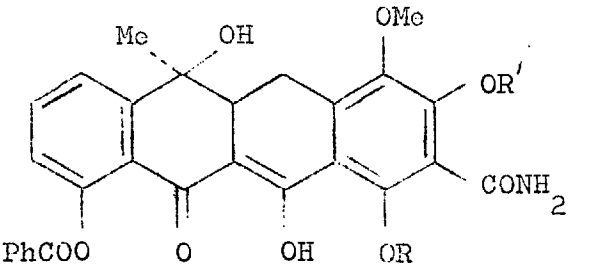
33

Reaction of p-tolyl vinyl ether with hydrogen peroxide and bromine gave a mixture of products. Styrene under the same conditions gave mainly dibromostyrene. Treatment of styrene with hydrogen peroxide, NBS, and sodium carbonate was found to provide a hydroperoxy bromoether. A paper describing a similar preparation of this compound appeared shortly later[21].

The action of hydrogen peroxide, NBS and sodium carbonate on p-tolyl vinyl ether gave a compound which exhibited 95% of the expected oxidising power. Rearrangement of this compound to a catechol could not be achieved. Boron trifluoride in ether gave no reaction whereas aluminium trichloride decomposed the substrate into a series of products, none of which corresponded to 4-methylcatechol. Stirring with p-tosyl acid in benzene at room temperature gave no reaction, but heating provided many products. Simply pyrolysing the hydroperoxide in either benzene or toluene did not decompose the substrate.

In an attempt to prepare a crystalline derivate which could be purified for analysis, the hydroperoxide was stirred with p-nitrobenzoyl chloride and pyridine. A new compound was readily formed, but on work-up by puring into ice-cold hydrochloric acid followed by washing with bicarbonate, an oil was obtained which could not be induced to crystallise. Furthermore, by analogy with the rearrangement of 9-decalyl-hydroperoxide p-nitrobenzoate[22], it was hoped that the ester would rearrange more readily than the hydroperoxide.





34

R= Me or H

R'= H or Me

However, pyrolysis of the peroxyester in chloroform led to a complex mixture of products.

An intermediate which demonstrates the postulated cyclic hydroxylation reaction has not been obtained. With regard to the conversion of a trimethoxy ring A tetracyclic compound to tetracycline, the lead tetra-acetate oxidation appears to be the most promising when a compound of the type (34) becomes available.

EXPERIMENTAL

Unless otherwise specified in the text the following conditions apply to the experiments described in this section.

Melting points were taken on the Kofler block and are uncorrected.

Infra-red spectra were measured in a nujol mull or as thin films on a Unicam S.P.200 spectrometer.

Ultra-violet spectra were measured in absolute ethanol on Unicam S.P.200 or 800 spectrometers.

N.m.r. spectra were measured in deuterochloroform solution with tetramethylsilane as internal standard using a Varian A-60 spectrometer. N.m.r. data is given in terms of τ-values.

Alumina for column chromatography was Brockmann activity 3. Silica gel for t.l.c. was Merck GF_{254}.

Sodium sulphate was used to dry chloroform and methylene chloride extracts.

Methyl p-orsellinate (4).

p-Orsellinic acid was esterified as described by Saraiya and Shah.

Frémy's salt.

Sodium nitrite (17.5 g.) was dissolved in water (50 ml.) and cooled by the addition of crushed ice (100 g.). A solution of sodium metabisulphite (23.8 g.) in water (50 ml.) was added with stirring, and the mixture acidified with glacial acetic acid (10 ml.). After standing for 30 min., 0.88 ammonia solution (7 ml.) was added followed by a solution of potassium permanganate (6.3 g.) in water (200 ml.). The precipitated manganese dioxide was filtered off and saturated potassium chloride solution (250 ml.) added. After crystallisation, the orange salt was filtered off, washed with 5% potassium hydroxide solution, ethanol, acetone, and was dried in air (11.1 g.).

4-carbomethoxy-3-hydroxy-2,5-toluquinone (5).

Methyl p-orsellinate (296 mg.) was dissolved in ethanol (100 ml.) and was stirred vigorously for 1 hr. with a solution of Frémy's salt (3.35 g.) in water (200 ml.). Extraction with chloroform followed by evaporation yielded orange-yellow crystals. Recrystallisation from petrol/benzene yielded fine yellow needles (278 mg., 87.3%), m.p. 115°-116°, $\nu_{max.}$ 3400, 1670, 1590 cm^{-1}. $\lambda_{max.}$ 209 mμ (14,200), 263 mμ (14,900), 327 mμ (1,480). N.m.r. 7.93 and 7.77 (base 7.88) (3 H), 6.03 and 5.97 (base 6.13)(3 H), 3.72 (1 H, singlet), 0.45

(1 H, singlet, exchanged by D_2O). (Found: C, 55.27; H, 4.29. $C_9H_8O_5$ requires C, 55.10; H, 4.11%.)

Methyl 2,3,6-triacetoxy-4-methylbenzoate (6).

a. Quinone (5) (150 mg.) was dissolved, with warming, in sulphurous acid solution (100 ml.). After 2 hr. on the steam bath the solution was cooled to room temperature and was extracted with ether. The extract was evaporated to small volume and the oil stirred with acetic anhydride (3 ml.) and pyridine (3 ml.) at room temperature. After 20 hr. the reaction was quenched in hydrochloric acid (2 N, 25 ml.), and extracted with chloroform. Evaporation provided a sticky solid which, after chromatography on alumina and recrystallisation from methanol, gave colourless nuggets (235 mg., 94.7%).

b. Quinone (5) (26.2 mg.) was dissolved in DMF (5 ml.) and glacial acetic acid (2 ml.). The solution was cooled to 0^0 with stirring, and zinc dust (200 mg.) added. After 5 min. the zinc was filtered off, and work-up as above gave the triacetate (42.7 mg., 97.1%).

c. Quinone (5) (25.4 mg.) was dissolved in benzene and was hydrogenated over 10% palladium on barium sulphate (30 mg.) until uptake ceased. Removal of the catalyst by filtration followed by acetylation as before provided the triacetate (38.3 mg., 91.1%), m.p. $144-145^0$, $\nu_{max.}$ 1780, 1742 cm^{-1}. $\lambda_{max.}$ 204 mμ (30,800), 272 mμ (16,800). N.m.r. 7.74 (12 H, multiplet), 6.17 (3 H, singlet), 3.07 3.07 (1 H, singlet). (Found: C, 55.90; H, 4.76. $C_{15}H_{16}O_8$ requires

C, 55.55; H, 4.97%).

Methyl 2,3,6-triacetoxy-4-formyldiacetoxybenzoate (7).

Methyl 2,3,6-triacetetoxy-4-methylbenzoate (6) (133 mg.) was dissolved in glacial acetic acid (2 ml.) and acetic anhydride (2 ml.). The temperature was kept below 0^0 and concentrated sulphuric acid (0.24 ml.) was added dropwise, followed by chromic oxide (270 mg.) in portions over 1 hr. Stirring was continued for 2 hr. and the reaction quenched in ice-water (25 ml.). The solid was filtered off and recrystallised from petrol/benzene to give colourless needles (37.6 mg., 22.0%), m.p. 125-126°, $\nu_{max.}$ 1768, 1727 cm^{-1}. $\lambda_{max.}$ 205 mμ (25,500), 286 mμ (1,740). N.m.r. 7.8 (15 H, multiplet), 6.14 (3 H, singlet), 2.70 (1 H, singlet), 2.12 (1 H, singlet). (Found: C, 51.99; H, 4.41. $C_{19}H_{20}O_{12}$ requires C, 51.81; H, 4.58%.)

4-carbomethoxy-3,6-dihydroxy-2,5-toluquinone (11).

Methyl 2-formyl-p-orsellinate (10) (525 mg.) was dissolved in acetone (100 ml.) and was added to a solution of Frémy's salt (1.08 g.) in water (100 ml.) containing monopotassium phosphate (M/10, 25 ml.). After stirring for 4 hr. t.l.c. indicated no oxidation had occurred and sufficient 6N. sodium hydroxide was added to increase the pH to 10. On stirring for a further 1 hr., acidification precipitated starting material (500 mg.). Extraction with chloroform yielded an impure yellow solid (8 mg.), $\nu_{max.}$ 1663, 1633 cm^{-1}. The mass spectrum showed the molecular ion at 212 m/e.

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (12).

Methyl 2-formyl-p-orsellinate (1.0 g.) was hydrogenated in glacial acetic acid (100 ml.) over pre-reduced 10% palladium on carbon catalyst (100 mg.) until uptake ceased. The catalyst was filtered off and evaporation of the solvent yielded the crystalline resorcinol (0.82 mg., 96%), m.p. 108-109°, (lit [9] 108°). N.m.r. 7.93 (3 H, singlet), 7.77 (3 H, singlet), 5.94 (3 H, singlet), 3.65 (1 H, singlet), 0.79 (1 H, exchanged by D_2O), -0.14 (1 H, exchanged by D_2O).

4-carbomethoxy-3-hydroxy-6-methyl-2,5-toluquinone (13).

Methyl 2,6-dihydroxy-3,4-dimethylbenzoate (12) (130 mg.) was dissolved in ethanol (50 ml.) and was added to a solution of Frémy's salt (2.0 g.) in water (90 ml.) containing sodium acetate (M , 10 ml.). After stirring for 18 hr., the solution was acidified with dilute hydrochloric acid and extracted with chloroform. Evaporation yielded a yellow oil which crystallised with ether/di-isopropyl ether (132 mg., 94.8%), m.p. 68°, $\nu_{max.}$ 1678, 1660, 1643 cm^{-1}. $\lambda_{max.}$ 208 mμ (9,440), 272 mμ (17,800), 396 mμ (920). N.m.r. 7.92 (6 H, singlet, 6.00 (3 H, singlet), -2.73 to -1.38 (1 H, exchanged by D_2O). (Found: C, 57.14; H, 4.72. $C_{10}H_{10}O_5$ requires C, 57.14; H, 4.80%).

Oxidation of 4-(3',5'-dihydroxy-4'-carbomethoxybenzyl)-2-phenylnaphtho 1,8-bc furan-5-one.

The phenol (14) (90 mg.) was dissolved in DMF (50 ml.) and sodium hydroxide (N/10, 1 eq.). This solution was added slowly to a solution of Frémy's salt (1.0 g.) in water (100 ml.) at pH 10 and 0°. When the addition was completed the reaction was acidified with hydrochloric acid and extracted with chloroform. The product was obtained as a yellow oil on evaporation of the solvent and it was reduced with zinc dust (0.5 g.) in DMF (5 ml.) and glacial acetic acid (2 ml.) at 0°. The zinc dust was filtered off after 3 hr. and the pale yellow product acetylated with acetic anhydride (2 ml.) and pyridine (2 ml.). After stirring for 3 hr. at room temperature the reaction was quenched in ice-cold 2 N hydrochloric acid and extracted with chloroform. T.l.c. showed that this extract contained 6 products. The major component was separated by t.l.c. on silica gel, m.p. higher than 340°; no molecular ion observable in the mass spectrum.

Basic Frémy's salt oxidation of methyl p-orsellinate.

A solution of methyl p-orsellinate (500 mg.) was prepared in DMF (20 ml.) and sodium hydroxide (N/10, 28 ml.). Frémy's salt (5.0 g.) in water (100 ml.) and caustic soda (4 N, 2.5 ml.) was added. The reaction was stirred for 1 hr, acidified with dilute hydrochloric acid and extracted with chloroform. Evaporation yielded a yellow solid which was reduced with zinc dust (5 g.) in DMF (10 ml.) and

glacial acetic acid (10 ml.) at 0°. After removal of the zinc, the product was acetylated with acetic anhydride (3 ml.) and pyridine (3 ml.) at room temperature. Quenching in ice-cold dilute hydrochloric acid and extraction with chloroform yielded an oil. Chromatography on alumina followed by recrystallisation from benzene/petrol yielded colourless crystals of the biphenyl (15) (85 mg.), m.p. 225-227°, $\nu_{max.}$ 1778, 1727 cm^{-1}. $\lambda_{max.}$ 210 mμ (54,800), 285 mμ (5,180). N.m.r. 8.07, 7.70, 6.18 (ratio 2:2:1). The mass spectrum showed a molecular ion at 582 m/e and loss of 6 acetate and 2 methyl ester functions. (Found: C, 55.67; H, 4.47. $C_{30}H_{30}O_{16}$ requires C, 55.75; H, 4.68%.)

Methyl 2,3,6-trihydroxy-4,5-dimethylbenzoate (16)

4-carbomethoxy-3-hydroxy-6-methyl-2,5-toluquinone (13) (150 mg.) was dissolved in dry benzene (2.5 ml.) and hydrogenated over 10% palladium on barium sulphate until uptake ceased. After removal of the catalyst, evaporation of the solvent, recrystallisation from petrol/benzene, and sublimation at 80°, 10^{-4} mm. Hg yielded pale yellow nuggets (145 mg.), m.p. 133-134°, $\nu_{max.}$ 1675 cm^{-1}. $\lambda_{max.}$ 208 mμ (13,600), 224 mμ (11,200), 265 mμ (13,800), 355 mμ (3,630). N.m.r. 7.90 (3 H, singlet), 7.70 (3 H, singlet), 6.95 (3 H, singlet), 5.16-4.21 (1 H, exchanged by D_2O), 1.16-0.70 (1 H, exchanged by D_2O). (Found: C, 56.70; H, 5.80. $C_{10}H_{12}O_5$ requires C, 56.60; H, 5.70%.)

Methyl 2,3,6-triacetoxy-4,5-dimethylbenzoate (17).

4-carbomethoxy-3-hydroxy-6-methyl-2,5-toluquinone (13) (380 mg.) was reduced by stirring with zinc dust (1.0 g.) in glacial acetic acid (10 ml.) at 0°. When the solution became colourless, the zinc was filtered off and the triphenol acetylated with acetic anhydride (5 ml.) and pyridine (5 ml.). After stirring for 18 hr. at room temperature the reaction was quenched in ice-cold hydrochloric acid (2 N, 100 ml.) and extracted with chloroform. Evaporation of the solvent gave a solid, which, after chromatography on alumina and recrystallisation from ethanol, yielded colourless nuggets (503 mg., 76%), m.p. 176-177°, $\nu_{max.}$ 1761, 1722 cm^{-1}. $\lambda_{max.}$ 208 mμ (21,300), 233 mμ (7,160), 278 mμ (4,150). N.m.r. 7.90, 7.85, 7.75, 7.70, 6.17 (all 3 H, singlets). (Found: C, 56.89; H, 5.44. $C_{16}H_{18}O_8$ requires C, 56.80; H, 5.36%.)

Basic Frémy's salt oxidation of methyl 2,6-dihydroxy-3,4-dimethylbenzoate.

Resorcinol (12) (522 mg.) was dissolved in DMF (20 ml.) and sodium hydroxide (N/10, 26 ml.). A solution of Frémy's salt (5 g.) in water (250 ml.) at pH 10 was added and the reaction stirred for 1 hr. at room temperature. Acidification with hydrochloric acid and extraction with chloroform gave a yellow oil which was reduced with zinc/acetic acid and acetylated with acetic anhydride/pyridine in the usual manner to provide methyl 2,3,6-triacetoxy-4,5-dimethyl-

benzoate (17) (235 mg.), m.p. and mixed m.p. 175-177°.

Benzenesulphinic acid.[11]

Benzenesulphonyl chloride (30 g.) was dissolved in ether (150 ml.) and water (2 ml.). Zinc dust (30 g.) was added and the slurry stirred, with cooling until the vigorous reaction subsided. The reaction was then heated to reflux for 1 hr. and the solid filtered off and washed with water. The grey product was stirred with a solution of sodium carbonate (30 g.) in water (150 ml.) at 80-85° for 1 hr. The zinc carbonate was filtered off and the cooled solution acidified with concentrated hydrochloric acid to yield benzenesulphinic acid (13 g.).

N,N-dibenzenesulphonyl hydroxylamine.[12]

Solutions of benzenesulphinic acid (2.0 g.) in water (10 ml.) and sodium nitrite (2.0 g.) in water (10 ml.) were mixed and acidified with dilute hydrochloric acid. The white precipitate was filtered off, dissolved in dilute sodium hydroxide, re-precipitated with dilute sulphuric acid, and recrystallised from alcohol (0.9 g.).

Oxidation of N,N-dibenzenesulphonyl hydroxylamine.

The colourless solid was dissolved in benzene and was treated with aqueous solutions of potassium permanganate and chromic acid. No colouration of the benzene layer was observed. Similarly when a benzene solution was treated with a carbon tetrachloride solution

of bromine or chlorine in the presence of methyl p-orsellinate, no oxidation to quinone took place.

Methyl 2,6-diacetoxy-4,5-dimethylbenzoate (19).

Methyl 2,6-dihydroxy-4,5-dimethylbenzoate (12) (200 mg.) was dissolved in acetic anhydride (10 ml.) and pyridine (10 ml.) and was stirred for 18 hr. at room temperature. The reaction was then quenched in ice-cold hydrochloric acid (2N, 100 ml.) and extracted with chloroform. Evaporation of the solvent, chromatography on alumina and recrystallisation from ethanol yielded colourless needles (210 mg.), m.p. 84-85°, $\nu_{max.}$ 1765, 1720 cm^{-1}. $\lambda_{max.}$ 206 mμ (25,700), 229 mμ (7,850), 282 mμ (1,990). N.m.r. 7.93 (6 H, singlet), 7.73 (3 H, singlet), 7.70 (3 H, singlet), 6.17 (3 H, singlet), 3.13 (1 H, singlet). (Found: C, 60.12; H, 5.68. $C_{10}H_{16}O_6$ requires C, 59.99; H, 5.75%.)

Autoxidation of methyl 2,6-dihydroxy-4,5-dimethylbenzoate.

Resorcinol (12) (136 mg.) was dissolved in hexamethylphosphoramide (10 ml.). Potassium t-butoxide (0.5 g.) was added, and the solution was shaken in an atmosphere of oxygen for 50 min. at room temperature. After acidification with dilute hydrochloric acid and extraction with chloroform, the product was obtained as a yellow oil. Zinc dust reduction and acetic anhydride/pyridine acetylation were carried out in the usual way to yield semi-solid material (80 mg.). T.l.c. showed that this mixed product contained neither the triacetate

(17) nor the diacetate (19).

Tosyl peroxide.[13]

A solution of hydrogen peroxide (100 vol., 10 ml.) in water (15 ml.) was basified with sodium carbonate (4 g.) and cooled to below 0^0. A solution of p-tosyl chloride (1.7 g.) in THF (2 ml.) was added keeping the temperature in the range -5-0^0. The solid (2.0 g.) was filtered off and dried. Addition of potassium iodide and titration of the liberated iodine indicated 43.7% of the expected oxidising power.

Oxidation of methyl p-orsellinate with tosyl peroxide.

Crude tosyl peroxide (0.5 g.) was dissolved in chloroform (10 ml.) and was shaken for 15 min. with a solution of methyl p-orsellinate (80 mg.) in water (10 ml.) and sodium hydroxide ($^N/_{10}$, 0.2 ml.). The dark aqueous layer was acidified and the chloroform layer separated. The orange colour, and formation of a non-running compound on t.l.c. indicated formation of a quinone.

m-Nitrobenzenesulphonyl peroxide.[14]

m-Nitrobenzenesulphonyl chloride (8.8 g.) was dissolved in chloroform (8 ml.) and was added, with shaking, to a solution of potassium carbonate (8 g.) in water (120 ml.), ethanol (60 ml.) and hydrogen peroxide (100 vol., 8 ml.) at -20^0. After 5 min. ethanol (60 ml.) was added and the solid filtered off. The crude solid was

shaken with chloroform (2 x 40 ml.) and the extract evaporated. The sticky product was triturated with ether to provide colourless, crystalline peroxide (390 mg.), m.p. 106° (lit[14] 106°).

Oxidation of methyl p-orsellinate with m-nitrobenzenesulphonyl peroxide.

Methyl p-orsellinate (104 mg.) was dissolved in sodium hydroxide solution (N/10, 25 ml.) and added, with vigorous stirring, to a solution of the peroxide (230 mg., 1 mol.) in chloroform (25 ml.). After 30 min. the solution was acidified and worked-up by reduction and acetylation as before to yield colourless needles of the biphenyl (20) (70 mg., 41.6%), m.p. 180-182°, $\nu_{max.}$ 1777, 1762, 1724 cm^{-1}. $\lambda_{max.}$ 209 mμ (54,800), 287 mμ (6,450). N.m.r. 8.10 (9 H, singlet), 7.87 (3 H, singlet), 7.70 (9 H, singlet), 6.18 (6 H, singlet), 2.98 (1 H, singlet). The mass spectrum showed a molecular ion at 532 m/e, loss of 5 acetate and 2 methyl ester functions. (Found: C, 57.15; H, 4.94. $C_{28}H_{28}O_{14}$ requires C, 57.14; H, 4.80%.)

Oxidation of methyl 2,6-dihydroxy-4,5-dimethylbenzoate with m-nitrobenzenesulphonyl peroxide.

Resorcinol (12)(50 mg.) was dissolved in sodium hydroxide (N/10, 15 ml.) and was stirred, under nitrogen, with a solution of the peroxide (100 mg.) in chloroform (10 ml.). After 30 min. the solution was acidified and worked-up by reduction and acetylation to yield triacetate (17((8.5 mg., 9.8%), m.p. and mixed m.p. 176-177°.

1,2,4-Triacetoxybenzene.[16]

p-Benzoquinone (10.8 g.) was dissolved in acetic anhydride (40 ml.) and boron trifluoride (40% solution in ether, 2 ml.). After standing for 72 hr. the precipitated solid was filtered off and the mother liquor poured into ice-water (200 ml.). The second crop was collected by filtration and the total product crystallised from methanol with treatment by activated charcoal (17.0 g., 67.5%).

1,2,4-Trihydroxybenzene.[26]

1,2,4-Triacetoxybenzene (1.0 g.) was dissolved in methanolic hydrochloric acid (saturated, 150 ml.) and refluxed for 30 min. Evaporation of the solvent provided the greyish solid (0.37 g., 74%).

Reaction of 1,2,4-trihydroxybenzene with ammonia.[15]

1,2,4-Trihydroxybenzene (0.4 g.) was dissolved in water (40 ml.) and .88 ammonia solution (0.9 ml.). After stirring for 3 hr. the solvent was evaporated and the sticky product stirred with ethanol (25 ml.). The residue was filtered off and the ethanol evaporated to give a black, solid product. Acetylation with acetic anhydride (3 ml.) and pyridine (3 ml.) at room temperature provided a product with three components, separated by t.l.c. on silica gel.

a. 2,4-diacetoxy-N,N-diacetylaniline (22).

m.p. 108-109°, $\nu_{max.}$ 1768, 1753, 1709 cm^{-1}. N.m.r. 7.76, 7.72, 2.83 (ratio 2:2:1). The mass spectrum showed a molecular ion at

293 m/e and loss of 4 acetates.

b. 2,4-diacetoxy-N-acetylaniline (23).

m.p. 115°, $\nu_{max.}$ 1761, 1659 cm^{-1}. The mass spectrum showed a molecular ion at 251 m/e and loss of 3 acetates.

c. 2,2',4,4'-tetraacetoxy-N-acetyldiphenylamine (24).

$\nu_{max.}$ (chloroform) 1765, 1681 cm^{-1}. The mass spectrum showed a molecular ion at 443 m/e and loss of 5 acetates.

Reaction of methyl 2,3,6-trihydroxy-4-methylbenzoate with ammonia.

4-carbomethoxy-3-hydroxy-2,5-toluquinone (5) (144 mg.) was dissolved in ethanol (25 ml.) and hydrogenated over 10% palladium on barium sulphate. The catalyst was filtered off and nitrogen bubbled through the solution. After 15 min. the nitrogen was replaced by ammonia which was passed through the solution for 30 min. Acidification gave a solid which on treatment with chloroform, filtration and evaporation, yielded a dark red oil. Zinc dust reduction and acetylation gave a complex mixture of products.

Reaction of methyl 2,3,6-trihydroxy-4,5-dimethylbenzoate with ammonia.

a. Aqueous ammonia. Quinone (13) (119 mg.) was dissolved in ethanol (25 ml.) and was hydrogenated over 10% palladium on barium sulphate. After filtration the solution was diluted with ethanol (15 ml.), degassed with nitrogen for 30 min., and 0.88 ammonia (0.5 ml.) added. The reaction was stirred at room temperature under nitrogen

for 2 hr. when extraction with chloroform yielded a brownish solid (65 mg.). After crystallisation from benzene/petrol this material had Rf, infra-red and ultra-violet spectra identical with the starting triphenol.

b. Liquid ammonia. Triphenol (100 mg.) was suspended in liquid ammonia (20 ml.) and sealed in a pressure bomb at room temperature for 20 hr. Evaporation of the ammonia, zinc dust reduction and acetylation gave a mixed product. The major component, N-acetyl-2,3,6-triacetoxy-4,5-dimethylbenzamide (27), was separated by t.l.c. on silica gel. The mass spectrum showed a molecular ion at 365 m/e and loss of 4 acetates.

Methyl 2,3,6-trihydroxy-4-methyl-5-formylbenzoate (28) [10]

Methyl 2,3,6-trihydroxy-4-methylbenzoate (25) (730 mg.) was dissolved in dry ether (250 ml.) and was stirred with Gatterman complex (4 g.) and aluminium trichloride (5 g.) for 5 hr. Evaporation of the ether gave a dark red oil which was quenched by careful addition of water (300 ml.) containing concentrated hydrochloric acid (10 ml.). The yellow solution was heated on the steam bath for 2 hr. and then cooled at 0^{0} for 18 hr. The solid was filtered off and recrystallised from chloroform to yield the formyl derivative as fine yellow needles (795 mg., 95.4%).

6-formyl-4-carbomethoxy-3-hydroxy-2,5-toluquinone (29)

Methyl 2,3,6-trihydroxy-4-methyl-5-formylbenzoate (28) (76 mg.) was dissolved in dry chloroform (25 ml.), DDQ (77 mg., 1.0 mol.) was added, and the solution stirred at room temperature for $2\frac{1}{2}$ hr. The precipitated hydroquinone was filtered off and the solvent evaporated to yield a yellow solid. Recrystallisation from petrol/benzene gave yellow nuggets (73 mg., 97%), m.p. 145°, $\nu_{max.}$ 1706, 1684, 1664 cm^{-1}. $\lambda_{max.}$ 206 mμ (11,400), 272 mμ (13,500), 376 mμ (470). N.m.r. 7.54 (3 H, singlet), 5.84 (3 H, singlet), -0.56 (1 H, singlet), -2.0 (1 H, very broad, exchanged by D_2O). (Found: C, 53.50; H, 3.78. $C_{10}H_8O_6$ requires C, 53.58; H, 3.60%.)

Methyl 2,3,6-triacetoxy-4-methyl-5-formylbenzoate (30) [30]

Methyl 2,3,6-trihydroxy-4-methyl-5-formylbenzoate (28) (450 mg.) was dissolved in acetic anhydride (15 ml.) and pyridine (15 ml.) and the solution was warmed on the steam bath for 25 min. The reaction was quenched in crushed ice (400 g.) containing concentrated hydrochloric acid (3 ml.). After stirring for 30 min. the solid was filtered off and recrystallised from petrol/benzene (560 mg., 79.6%), m.p. 112-114°, $\nu_{max.}$ 1780, 1735, 1690 cm^{-1}. $\lambda_{max.}$ 219 mμ (28,600), 249 mμ (9,210), 300 mμ (1,780). N.m.r. 7.71 (3 H, singlet), 7.66 (6 H singlet), 7.54 (3 H singlet), 6.13 (3 H, singlet), -0.30 (1 H, singlet). (Found: C, 54.73, H, 4.32. $C_{16}H_{16}O_9$ requires C, 54.55; H, 4.58%.)

Oxidation of methyl 2,3,6-triacetoxy-4-methyl-5- formylbenzoate

Silver oxide. The aldehyde (33 mg.) was dissolved in dry benzene (20 ml.), silver oxide (100 mg.) was added and the slurry stirred vigorously for 20 hr. at room temperature. T.l.c. indicated no oxidation. After heating to reflux for 3 hr., t.l.c. showed no reaction.

Manganese dioxide. The aldehyde (25 mg.) in dry benzene (20 ml.) was refluxed for 18 hr. in the presence of active manganese dioxide (100 mg.). T.l.c. showed no reaction.

Oxygen. The aldehyde (34 mg.) was dissolved in dry benzene (20 ml.), a crystal of azobisisobutyronitrile was added, and the solution stirred, at room temperature, in an atmosphere of oxygen for 18 hr. T.l.c. indicated no oxidation.

The aldehyde (35 mg.) was dissolved in dry benzene (20 ml.) and benzoyl peroxide (5 mg.) added. After irradiation with a low pressure mercury light for 10 min., the solution was stirred in an atmosphere of oxygen for 18 hr. T.l.c. showed no oxidation

N-bromosuccinimide. The aldehyde (108 mg.) was dissolved in carbon tetrachloride (20 ml.). NBS (70 mg.) and triethylamine (0.25 ml.) were added and the solution was refluxed for 20 hr. Filtration, evaporation and trituration with carbon tetrachloride gave a solution which t.l.c. showed to contain only unchanged starting material.

Methyl 2,3,6-triacetoxy-4-methyl-5-formyl ethylenedioxy benzoate (31)

Aldehyde (30) (207 mg.) was dissolved in dry benzene (10 ml.) and was stirred with the ethylene ketal of methylethyl ketone (1.5 ml.) and boron trifluoride (40% ethereal solution, 0.1 ml.) for 15 min. After quenching in water (20 ml.) containing triethylamine (0.5 ml.) the benzene layer was separated and evaporated. Recrystallisation from petrol/benzene provided colourless nuggets (171 mg., 73.4%), m.p. 176-177°, $\nu_{max.}$ 1770, 1720 cm^{-1}. $\lambda_{max.}$ 207 mμ (31,800), 283 mμ (2,140). N.m.r. 7.74 (12 H, multiplet), 6.23 (3 H, singlet), 5.97 (4 H, doublet), 4.09 (1 H, singlet). (Found: C, 54.70; H, 5.01. $C_{18}H_{20}O_{10}$ requires C, 54.54; H, 5.09%.)

Methyl 2,3,6-triacetoxy-4-methyl-5-(2'-bromocarboethoxy)benzoate (32)

The acetal (88 mg.) was dissolved in dry benzene (25 ml.) and was refluxed for 3 hr. with NBS (40 mg.). The solvent was evaporated and the residue stirred with carbon tetrachloride. After filtration, evaporation of the solvent yielded a colourless solid. Recrystallisation from petrol/chloroform gave colourless needles (100 mg., 94.4%), m.p. 94-97°, $\nu_{max.}$ 1770, 1750, 1730, 1720 cm^{-1}. $\lambda_{max.}$ 207 mμ (35,000), 284 mμ (2,070). N.m.r. 7.92 (9 H, singlet), 7.66 (3 H, singlet), 6.39 (2 H, triplet, J = 6 hz), 6.16 (3 H, singlet), 5.35 (2 H, triplet, J = 6 hz). (Found: C, 45.61; H, 3.92; Br, 16.52. $C_{18}H_{19}BrO_{10}$ requires C, 45.46; H, 4.03, Br, 16.82%.)

Methyl 2,3,6-trihydroxy-4-methyl-5-(2'bromocarboethoxy)benzoate (33).

Triacetate (32) (200 mg.) was dissolved in methanolic hydrogen chloride (5 N, 25 ml.) and was stirred, under nitrogen, for 3 hr. at room temperature. After evaporation of the solvent, crystallisation from petrol/ether gave brownish nuggets (102 mg., 69.4%), m.p. 111-113°, $\nu_{max.}$ 3500, 1660, 1640 cm^{-1}. $\lambda_{max.}$ 202 mμ (12,400), 237 mμ (20,700), 247 mμ (16,100), 347 mμ (6,930). N.m.r. 7.50 (3 H, singlet), 6.23 (2 H, triplet, J = 5.82 hz), 5.93 (3 H, singlet), 5.30 (2 H, triplet, J = 5.8 hz), -1.53 (1 H, exchanged by D_2O), -1.90 (2 H, exchanged by D_2O). (Found: C, 41.50; H, 3.53. $C_{12}H_{13}BrO_7$ requires C, 41.27; H, 3.73%.)

4-carbomethoxy-6-(2'-bromocarboethoxy)-3-hydroxy-2,5-toluquinone (34).

Triphenol (33) (48.3 mg.) was dissolved in chloroform (20 ml.) and was stirred with DDQ (33.6 mg., 1 mol.), under nitrogen, for 45 min. at room temperature. The solution was filtered, and evaporation of the solvent provided the orange quinone (45 mg.), m.p. 116-118°, $\nu_{max.}$ 1660, 1640 cm^{-1}. $\lambda_{max.}$ 204 mμ (11,800), 214 mμ (10, 300), 269 mμ (11,700). N.m.r. 7.82 (3 H, singlet), 6.35 (2 H, triplet, J = 5.8 hz), 5.94 (3 H, singlet), 5.30 (2 H, triplet, J= 5.8 hz). (Found: C, 41.64; H, 3.01. $C_{12}H_{11}BrO_7$ requires C, 41.51; H, 3.17%.)

Hydration reactions.

Base. Quinone (29 or 34) (25 mg.) dissolved in dioxan (10 ml.) and water (3 ml.) gave a red solution of the anion (acidification provided

quinone). The solutions were stirred at room temperature and sodium hydroxide solution ($^{N}/10$) added dropwise. The reaction was followed by the ultra-violet of the basic solution. No change was observable. Acidification and extraction with chloroform gave unchanged starting material as judged by IR and UV.

Acid. Quinone (29 or 34) (15 mg.) dissolved in water (25 ml.) and dioxan (10 ml.) and acidified with concentrated hydrochloric acid (2 ml.). There was an immediate colour change as the anion was neutralised, but no change in the UV spectrum was noticed after stirring for 5 hr. Extraction with chloroform gave unchanged starting material.

Tetracycline.

Tetracycline hydrochloride (10 g.) was dissolved in water (200 ml.) and the solution rapidly filtered. Sodium acetate solution was added until the pH was 4.5 and the solution cooled in ice for 1 hr. The pale yellow crystals were filtered off, washed with water, ether, and dried at room temperature in vacuo (8.2 g., 90%).

Tetracycline methiodide.[20]

Tetracycline base (10 g.) (dried for 3 days in vacuo) was dissolved in dry THF (200 ml.) and methyl iodide (24 ml.). The solution was covered and stored for 4 days at room temperature. The cream coloured crystals were filtered off and dried at room temperature in vacuo (11.5 g., 87.0%).

Tetracycline methyl betaine.

Tetracycline methiodide (13.1 g.) was dissolved in water (550 ml.) and filtered rapidly. Sufficient sodium acetate solution was added to give pH 4.5 and the solution cooled in ice for 1 hr. The crystals were filtered off, washed with water, acetone, ether and dried for 3 days in vacuo at room temperature (9.6 g., 93.8%).

4a,12a-anhydro-4-hydroxy-4-dedimethylaminotetracycline (38).

Dry tetracycline methyl betaine (660 mg.) was suspended in dry acetonitrile (4.5 ml., distilled 3 times from calcium hydride) and was refluxed, under nitrogen, for 4 ¾ hr. After cooling the orange crystals were filtered off and dried in vacuo (449 mg., 76.5%).

The mother liquor from the pyrolysis was diluted with petrol and the yellow-brown γ-lactone (39) was precipitated (41 mg.), $\nu_{max.}$ 1760 cm^{-1}.

The γ-lactone (50 mg.) was suspended in dry acetonitrile (0.15 ml.) and warmed. A dark brown solution formed which deposited several crystals of triphenol (38), $\lambda_{max.}$ 280, 311, 455, 520 mμ.

4a,12a-anhydro-4-keto-4-dedimethylaminotetracycline (35).

4a,12a-anhydro-4-hydroxy-4-dedimethylaminotetracycline (38) (1.10 g.) was dissolved in dry dioxan (150 ml.) and stirred, under nitrogen, with DDQ (632 mg., 1 mol.) for 20 hr. The solution was filtered and the solvent evaporated at room temperature to give a dark red oil. Trituration with ether provided a dark red solid

(893 mg., 73.6%), m.p. wide range, greater than 250°, $\nu_{max.}$ 3500, 3400, 3280, 1667, 1625 cm^{-1}. $\lambda_{max.}$ (dioxan) 257 mμ (18,000), 340 mμ (9,190), 382 mμ (5,890). $\lambda_{max.}$ (N/100 methanolic HCl) 261 mμ (17,600), 342 mμ (8,210), 428 mμ (12,600). N.m.r. (DMSO-D_6) 8.36 and 8.43. (Found: C, 60.39; H, 3.54; N, 3.30. $C_{20}H_{15}NO_8$ requires C, 60.45; H, 3.81; N, 3.53%.)

11a-chlorotetracycline-6,12-hemiketal (41).[22]

Anhydrous tetracycline base (490 mg.) was dissolved in glyme (5 ml.) and was stirred for 10 min. at room temperature with freshly recrystallised N-chlorosuccinimide (182 mg.). Water (5.5 ml.) was added and the colourless product filtered off, washed with water, acetone, and dried in vacuo at room temperature (158 mg.), $\lambda_{max.}$ (N/100 methanolic HCl) 260 mμ (21,000), 343 mμ (4,000). N.m.r. (DMSO-D_6) C-6 methyl 8.00.

11a-chloro-4-oxo-4-dedimethylaminotetracycline-4,6-hemiketal (42).[22]

11a-chlorotetracycline-6,12-hemiketal (100 mg.) was slurried in water (5 ml.) and concentrated hydrochloric acid (0.1 ml.). Freshly recrystallised NClS (69.5 mg.) was added and the solution was stirred for 1 hr. at room temperature. The precipitate was filtered off and dissolved in ether. The extract was washed with dilute hydrochloric acid and water, dried and evaporated to yield yellow crystals (79 mg.), $\lambda_{max.}$ (N/100 methanolic HCl) 259 mμ (23,700), 345 mμ (4,090). N.m.r. (DMSO-D_6) C-6 methyl group at 7.96.

4-oxo-4-dedimethylaminotetracycline-4,6-hemiketal (44).[23]

Tetracycline hydrochloride (2.8 g.) was dissolved in water (175 ml.) and concentrated hydrochloric acid (0.5 ml.). Recrystallised NClS (2.0 g.) was added and the reaction stirred at room temperature for 30 min. The precipitated solid was filtered off and dissolved in ether (110 ml.). This extract was washed with water (40 ml., then 4 x 5 ml.), dried and evaporated to yield pale yellow crystals (1.51 g.), $\lambda_{max.}$ ($^{N}/_{100}$ methanolic HCl) 265 mμ (18,200), 342 mμ (4,510). N.m.r. (DMSO-D_6) C-6 methyl at 8.21.

Experiments on the hydration of 4a,12a-anhydro-4-dedimethylamino-4-ketotetracycline.

a. Base

Quinone (35) (19.4 mg.) was dissolved in THF (5 ml.) and stirred, under nitrogen, with sodium hydroxide ($^{N}/_{10}$, 1.5 ml.) for 3 min. After acidification with hydrochloric acid, extraction with chloroform provided a yellow/brown solid (9 mg.), $\nu_{max.}$ 3400, 1780-1600 complex. $\lambda_{max.}$ ($^{N}/_{100}$ methanolic HCl) 257, 298 mμ. The mass spectrum showed the molecular ion at 397 m/e.

b. Acid

Quinone (38 mg.) was dissolved in dioxan (20 ml.) and water (20 ml.). Hydrochloric acid (6 N, 1 ml.) was added and the solution stirred at room temperature. Aliquots (5 ml.) were taken, extracted with chloroform, and the extracts evaporated.

2 hr. Red-brown solid. $\nu_{max.}$ 3500, 3400, 1680-1600 complex. $\lambda_{max.}$ (dioxan) 262 mμ (20,000), 344 mμ (7,260), 378 mμ (7,340), 431 mμ (8,050). The mass spectrum showed a very weak peak at 415 m/e, a strong peak at 397 m/e.

20 hr. Green brown solid. $\nu_{max.}$ 3500 cm^{-1}. $\lambda_{max.}$ (dioxan) 269, 369, 433 mμ. The mass spectrum showed a molecular ion at 381 m/e.

c. Photolytic hydration.

A solution of quinone (91 mg.) was prepared in dioxan (50 ml.) and water (30 ml.). The solution (40 ml.) was irradiated for 20 hr. at 29-30° over a 1 kw. tungsten filament bulb. The remainder was maintained at the same temperature in the absence of light for 20 hr. Extraction of both solutions provided a brown compound which had $\lambda_{max.}$ (dioxan) 260 mμ (19,300), 431 mμ (13,300).

Quinone (126 mg.) was dissolved in dioxan (60 ml.) and water (30 ml.). The solution (70 ml.) was photolysed over a 1 kw. bulb for 15 min. with heating to 60° by a steam coil. A black solution resulted from which no product could be extracted.

Quinone (50 mg.) was dissolved in dioxan (30 ml.) and water (15 ml.). The pH of the solution was adjusted to 8.3 by addition of saturated sodium bicarbonate solution. A blank reaction at room temperature showed the quinone to be still present after 4 hr. Tungsten irradiation for 4hr. and extraction with chloroform provided a product which showed $\lambda_{max.}$ 429 mμ only.

d. Metal ions.

Magnesium. Quinone (18 mg.) was dissolved in dioxan (7 ml.) and an aqueous solution of magnesium chloride (10%, 14 ml.). After stirring to 2 hr. extraction with chloroform gave a red-brown solid, $\lambda_{max.}$ (dioxan) 260, 340, 380 mμ.

Iron. Quinone (20 mg.) was dissolved in dioxan (10 ml.) and ferric nitrate solution (10%, 10 ml.). After stirring for 10 min., no product could be extracted with chloroform.

Aluminium. Quinone (20 mg.) was dissolved in dioxan (10 ml.) and aluminium sulphate solution (10%, 10 ml.). After stirring for 30 min. no product could be extracted with chloroform.

Reaction of 4a,12a-anhydro-4-dedimethylamino-4-ketotetracycline with NClS.

Quinone (35) (110 mg.) was dissolved in dioxan (50 ml.) and water (30 ml.). Concentrated hydrochloric acid (1 ml.) was added, followed by freshly recrystallised NClS (241 mg.) and the solution was stirred for 30 min. at room temperature. The pale yellow solution was filtered and extracted with ether. The extract was washed with water, dried, and evaporated to yield a bright yellow solid (65 mg.), $\nu_{max.}$ 1766, 1721, 1691 cm^{-1}. $\lambda_{max.}$ (dioxan) 261 mμ (17,800), 340 mμ (4,730), 383 mμ (4,450). N.m.r. (DMSO-D_6) C_6 methyl at 8.27.

2-Carbomethoxy-2-chloro-3-hydroxy-3-carboxy-4,5-dimethylcyclopent-4,5-enone (48).

4-Carbomethoxy-3-hydroxy-6-methyl-2,5-toluquinone (206 mg.) was dissolved in dioxan (10 ml.), water (10 ml.) and hydrochloric acid (6 N, 20 ml.). A solution of sodium hypochlorite (10%) was added dropwise until further addition caused effervescence. After stirring for 2 min. the solution was extracted with ether. Evaporation of the solvent provided a pale yellow oil which crystallised on standing. Recrystallisation from petrol/benzene gave colourless nuggets (142 mg.), m.p. 84-85°, $\nu_{max.}$ 3520, 3400, 2560, 1745, 1723 cm^{-1}. $\lambda_{max.}$ 241 mμ (7,800). N.m.r. 8.07 (3 H, singlet), 7.96 (3 H, singlet), 6.21 (3 H, singlet), 4.83 (exchanged by D_2O).

2-Carbomethoxy-2-chloro-3-hydroxy-3-carbomethoxy-4,5-dimethylcyclopent-4,5-enone (49).

Cyclopentenone (48) (71 mg.) was dissolved in dry ether (10 ml.). An ethereal solution of diazomethane was added dropwise until a permanent pale yellow colour was obtained. After standing for 3 min. the solvent was evaporated to yield a colourless solid. Recrystallisation from petrol/chloroform gave colourless needles (69 mg.), m.p. 140-142°, $\nu_{max.}$ 3480, 1750, 1722 cm^{-1}. $\lambda_{max.}$ 239 mμ (10, 400). N.m.r. 7.99, 7.93, 6.26, 6.20 (all 3H, singlet), 5.69 (1 H, singlet, exchanged by D_2O). (Found: C, 47.64; H, 4.57. $C_{11}H_{13}ClO_6$ requires C, 47.74; H, 4.70%.)

2-Carbomethoxy-2-chloro-4,5-dimethylcyclopent-4,5-en-1,3-dione (50).

Cyclopentenone (48) (48 mg.) was dissolved in dry benzene (20 ml.) and was stirred at room temperature with lead tetra-acetate (82 mg.) for 30 min. The solution was filtered, poured into water (100 ml.), and extracted with ether. Evaporation of the solvent provided a colourless solid. Crystallisation from petrol gave needles (31 mg.), m.p. 89-90°, $\nu_{max.}$ 1770, 1709 cm^{-1}. $\lambda_{max.}$ 224 mμ (12,380). N.m.r. 7.84 (6 H, singlet), 6.20 (3 H, singlet). (Found: C, 50.03; H, 4.22; Cl, 16.63. $C_9H_9ClO_4$ requires C, 49.87; H, 4.16; Cl, 16.40%.)

4-Carbomethoxy-3-acetoxy-6-methyl-4,5-toluquinone (51).

Quinone (47) (108 mg.) was dissolved in acetic anhydride (3 ml.) and dry pyridine (distilled from KOH) (3 ml.). After stirring for 30 min. at room temperature, the reagents were removed by evaporation on a high vacuum pump to yield yellow crystals, m.p. 75-76°, $\nu_{max.}$ 1780, 1746, 1668 cm^{-1}, $\lambda_{max.}$ 260 mμ (12,940). N.m.r. 7.91 (6 H, singlet), 7.66, 6.08 (3 H, singlets). (Found: C, 57.20; H, 4.69. $C_{12}H_{12}O_6$ requires, C, 57.14; H, 4.80%.) Stability to water: Acetate (50 mg.) was dissolved in dioxan (5 ml.), water (15 ml.) and sufficient sodium acetate to give pH 7.1. After stirring for 3 min. at room temperature, t.l.c. indicated that the acetate had completely hydrolysed.

4-Carbomethoxy-4-methoxy-6-methyl-4,5-toluquinone (52).

Quinone (47) (204 mg.) was dissolved in methanol (2 ml.) and a solution of diazomethane in ether was added dropwise until no further

colour change was observed. The solvent was evaporated and the solid residue recrystallised from ether/diisopropyl ether to give yellow crystals (180 mg.), m.p. 70-71°, $\nu_{max.}$ 1735, 1672, 1647, 1636, 1616 cm^{-1}. $\lambda_{max.}$ 273 mμ (15,490). N.m.r. 7.96 (6 H, singlet), 6.08, 5.96 (3 H, singlets). (Found: C, 59.98; H, 5.51. $C_{11}H_{12}O_5$ requires C, 58.93; H, 5.39%.) Stability to water: Methoxyquinone (25 mg.) was dissolved in dioxan (1 ml.) and water (5 ml.). After stirring with NClS (30 mg.) for 21 hr. t.l.c. showed no reaction had taken place.

Methylation of the tetracyclic quinone (35).

Quinone (118 mg.) was dissolved in dry dioxan (50 ml.) and methanol (30 ml.). A solution of diazomethane in ether was added until no further colour change occurred. The solvent was evaporated below room temperature and the sticky residue treated with ether to give a brown solid. This material was chromatographed on Florisil, the fraction eluted with ethyl acetate being collected and evaporated to yield a yellow solid (120 mg.), $\nu_{max.}$ 3450, 1700-1600 cm^{-1}. $\lambda_{max.}$ (dioxan) 267 mμ (10,600), 348 mμ (8,510). (Found: C, 59.27, 59.09; H, 5.58, 5.61; N, 5.17, 5.01. $C_{21}H_{17}NO_8$ requires C, 61.32; H, 4.17; N, 3.40%.)

Reaction of 4-carbomethoxy-3-hydroxy-6-methyl-2,5-toluquinone with basic hydrogen peroxide.

Quinone (47) (215 mg.) was dissolved in methanol (4 ml.) and a solution of sodium carbonate (220 mg.) in water (5 ml.). Hydrogen peroxide (50%, 0.4 ml.) was added slowly and the reaction was stirred,

under nitrogen, for 20 hr. at room temperature. T.l.c. indicated that the quinone had been consumed and the solution was acidified with dilute hydrochloric acid and extracted with methylene chloride. Evaporation of the solvent provided a yellow oil which t.l.c. showed to contain at least 10 compounds.

2,3-dicarbomethoxy-2,3-dihydroxy-4,5-dimethylcyclopent-4,5-enone (53).

Methoxyquinone (52) (70 mg.) was suspended in water (2 ml.) and methanol (2 ml.). Sodium hydroxide solution ($^{N}/_{10}$, 0.63 ml.) was added followed by hydrogen peroxide (50%, 0.1 ml.). After stirring at room temperature for 2 hr. the solution was acidified and extracted with methylene chloride. Evaporation of the extract provided a semi-solid material which crystallised with ether (18.1 mg.), m.p. 160-165°, $\lambda_{max.}$ 238 mμ (8,300). N.m.r. 8.12, 8.05, 6.23, 6.20 (3 H, singlets), 5.93 (1 H, exchanged by D_2O). (Found: C, 50.91; H, 5.38. $C_{11}H_{14}O_7$ requires C, 51.16; H, 5.46%.)

2-Carbomethoxy-3-methoxy-2,3-epoxy-5,6-dimethylcyclohex-5,6-en-1,4-dione (54).

Methoxyquinone (52) (54 mg.) was dissolved in dry benzene (5 ml.), m-chloroperbenzoic acid (85%, 100 mg.) was added and the reaction was stirred, under nitrogen, at room temperature for 2 hr. The solvent was evaporated and the residues dissolved in ether (25 ml.). This solution was thoroughly washed with sodium bicarbonate solution followed by water and was dried and evaporated. Treatment of the residues with

diisopropyl ether gave colourless crystals of the epoxide (44.3 mg.), m.p. 92-94°, $\nu_{max.}$ 1762, 1691 cm^{-1}. N.m.r. 7.97 (6 H, singlet), 6.20, 6.08 (3 H, singlets). (Found: C, 54.91; H, 5.08. $C_{11}H_{20}O_6$ requires C, 55.00; H, 5.04%.)

Reaction of acetoxyquinone (51) with m-chloroperbenzoic acid.

Acetoxyquinone (146 mg.) was dissolved in dry benzene (5 ml.) and was stirred with m-chloroperbenzoic acid (232 mg.). T.l.c. showed that no reaction occurred even after prolonged reaction.

II. Methyl 2-hydroxy-4-methyl-6-methoxy-3-formylbenzoate (2).[4]

Dimethoxyaldehyde (1) (500 mg.) was dissolved in dry methylene chloride (50 ml.) and the solution was cooled to -80°. Boron trichloride (3 ml.) was added and the resulting solution was stirred for 8 min. before quenching with water (50 ml.). The organic layer was separated and the aqueous phase extracted with methylene chloride. Evaporation of the combined extracts gave the phenol (447 mg.), $\nu_{max.}$ 1633 cm^{-1}, $\lambda_{max.}$ 238 mμ (14,400), 286 mμ (14,500), 322 mμ (5,200).

Oxidations of phenol (2).

a. $(Et_4N)IO_4$.

The phenol (22.4 mg.) was dissolved in absolute ethanol (10 ml.) and was stirred at room temperature with freshly recrystallised Et_4NIO_4 (33 mg.) for 18 hr. T.l.c. indicated that no reaction had taken place.

b. $NaIO_4$.

Phenol (30 mg.) was dissolved in alcohol (25 ml.) and was stirred for 18 hr. with a solution of sodium periodate (80 mg.) in water (5 ml.). No reaction occurred.

Acid.

Phenol (25 mg.) was dissolved in methanol (10 ml.). A solution of sodium periodate (200 mg.) in water (50 ml.) was added and the pH of the solution immediately adjusted to 4. No oxidation occurred.

Alkali.

Phenol (58 mg.) was dissolved in absolute ethanol (10 ml.) and sodium hydroxide solution ($^{N}/_{10}$, 5 ml.). Sodium periodate (100 mg.) was added and the reaction was stirred at room temperature under nitrogen for 1 hr. Acidification with hydrochloric acid and extraction with chloroform gave methyl 2-hydroxy-4-methyl-5-chloro-6-methoxy-3-formylbenzoate (5) (54 mg.), m.p. 144°, $\nu_{max.}$ 3500, 1738, 1640 cm^{-1}. N.m.r. 7.35 (3 H, singlet), 6.04 (6 H, singlet), -0.32 (1 H, singlet), -2.58 (1 H, exchanged by D_2O). The mass spectrum showed the molecular ion at 258 m/e with a strong M+2 peak. (Found: C, 50.95; H, 4.23; Cl, 13.05. $C_{11}H_{11}ClO_5$ requires C, 51.06; H, 4.26; Cl, 13.73%.)
A similar reaction acidified with dilute sulphuric acid gave only starting material.

c. $Pb(OAc)_4$.

Phenol (180 mg.) was dissolved in dry benzene (15 ml.) and was refluxed with lead tetra-acetate (200 mg.) for 3 hr. T.l.c. showed a small amount of oxidation.

Phenol (50 mg.) was dissolved in glacial acetic acid (25 ml.) and was refluxed with lead tetra-acetate (300 mg.) for 17 hr. Evaporation of the solvent gave a yellow oil. Treatment of the oil with ether, followed by filtration and evaporation provided a pale yellow oil $\nu_{max.}$ 1790, 1740 cm^{-1}.

Phenol (94 mg.) was suspended in dry t-butanol (10 ml.) and was stirred with lead tetra-acetate (200 mg.) and boron trifluoride

etherate (0.3 ml.) at 70°. After 20 min. lead tetra-acetate (50 mg.) was added and the reaction continued for 1 hr. Quenching in water and extraction with methylene chloride provided a yellow solid, m.p. 156-160°, $\nu_{max.}$ 1740, 1730 cm^{-1}. The compound was non-running on silica gel t.l.c. and the mass spectrum indicated that the compound had a high molecular weight, but did not show a distinct molecular ion.

d. $Tl(OAc)_3$.

Phenol (50 mg.) was dissolved in glacial acetic acid (20 ml.) and was refluxed with thallic acetate (100 mg.) for 20 hr. After quenching in water (100 ml.) and extraction with methylene chloride, t.l.c. showed that no oxidation had taken place.

e. $(C_6H_5CO_2)_2$.

Phenol (25 mg.) was dissolved in dry benzene (25 ml.) and was refluxed with benzoyl peroxide (50 mg.). After 20 hr. t.l.c. indicated that no reaction had taken place.

Methyl 2-hydroxy-6-methoxy-3,4-dimethylbenzoate (6).[11]

Hydroxyaldehyde (2) (245 mg.) was dissolved in glacial acetic acid (100 ml.) and was hydrogenated over 10% palladium on charcoal until hydrogen absorption ceased. The catalyst was filtered off, the solvent evaporated, and the residues crystallised from petrol to yield the dimethylphenol (240 mg.).

Oxidation of dimethylphenol (6) with lead tetra-acetate.

Dimethylphenol (50 mg.) was dissolved in dry methanol (10 ml.) and was stirred with lead tetra-acetate (200 mg.) and boron trifluoride etherate (0.25 ml.) at room temperature for 15 min. The reaction was then quenched in water (20 ml.) and extracted with methylene chloride. Evaporation of the solvent and crystallisation from benzene/petrol gave the cyclohexadienone (7) (25.5 mg.), m.p. 180-186°, $\nu_{max.}$ 1733, 1660 cm^{-1}. $\lambda_{max.}$ 224 mμ (9,940), 324 mμ (4,410). N.m.r. 8.55, 8.10, 7.92, 6.12, 6.08 (3 H, singlets). (Found: C, 58.33; H, 6.02. $C_{13}H_{16}O_6$ requires C, 58.20; H, 6.01%.)

Attempted rearrangement of methyl 2,3,6-triacetoxy-4-methylbenzoate (8).

Triacetate (127 mg.) was dissolved in ethylene dichloride (5 ml.) and was refluxed with aluminium trichloride (235 mg.) for 1½ hr. Quenching in ice (100 g.) containing dilute hydrochloric acid (10 ml.), and extraction with chloroform provided a solid diphenol, $\nu_{max.}$ 3430, 3150, 1753, 1659 cm^{-1}. N.m.r. 7.74 (6 H, singlet), 6.09 (3 H, singlet), 3.62 (1 H, singlet), 4.2-4.6 (1 H, exchanged by D_2O), -1.40 (1 H, exchanged by D_2O).

Attempted acylation of methyl 2,3,6-triacetoxy-4-methylbenzoate (8).

Triacetate (131 mg.) was dissolved in acetyl chloride (20 ml.) and was refluxed with aluminium trichloride (500 mg.) for 20 hr. Quenching in water (200 ml.) and extraction with methylene chloride

provided a yellow oil. Treatment with dimethyl sulphate (3 ml.) and potassium carbonate (2 g.) in refluxing acetone (30 ml.) provided a compound identical with methyl 2,3,6-trimethoxy-4-methylbenzoate (10).

Attempted acylation of methyl 2,3,6-trimethoxybenzoate (10).

Trimethoxybenzoate (10)[4] (2.5 g.) was refluxed in ether (150 ml.) with aluminium chloride (14.6 g.) and acetyl chloride (8.7 g.) for 20 hr. After quenching in water (250 ml.) and concentrated hydrochloric acid (10 ml.) the solution was extracted with methylene chloride. The crude product obtained on evaporation of the solvent was chromatographed on silica gel, eluting with ether. Crystallisation of the residue from this fraction from ether/petrol gave a crystalline phenol, $\nu_{max.}$ 3200, 1659 cm^{-1}. N.m.r. 6.23, 6.19, 6.09 (3 H, singlets), 3.14 (2 H, AB quartet), -1.06 (1 H, exchanged by D_2O).

Methyl 2,3,6-trimethoxy-4-methyl-5-formylbenzoate (12).

Triphenol (11) (1.67 g.) was dissolved in acetone (100 ml.) and was refluxed for 4½ hr. with dimethyl sulphate (3.5 g.) and potassium carbonate (3.8 g.). The reaction was then poured into water (200 ml.) and extracted with chloroform. Evaporation of the solvent provided a yellow oil which was purified by chromatography on alumina, eluting with benzene to provide the trimethoxyester (1.52 g.), $\nu_{max.}$ 1731, 1686 cm^{-1}, $\lambda_{max.}$ 227 mμ (16,000), 268 mμ (8,740), 313 mμ (2,390). N.m.r. 7.34, 6.20, 6.08 (all 3 H, singlets), 6.00 (6 H, singlet), -0.40 (1 H, singlet). (Found: C, 58.33; H, 6.15. $C_{13}H_{16}O_6$ requires

C,58.20; H, 6.01%.)

Monodemethylation of methyl 2,3,6-trimethoxy-4-methyl-5-formylbenzoate.

Trimethoxyaldehyde (12) (702 mg.) was dissolved in dry methylene chloride (15 ml.) and the solution was cooled to -80° with stirring. Boron trichloride (2 ml.) was added and the reaction was stirred for 6 min. before quenching by addition of water (25 ml.). The organic layer was separated and the solvent evaporated to yield a solid product. Recrystallisation from benzene/petrol gave methyl 2-hydroxy3,6-dimethoxy-4-methyl-5-formylbenzoate (27) (507 mg.), m.p. 93-95°, $\nu_{max.}$ 1773, 1663 cm^{-1}, $\lambda_{max.}$ 240 mμ (17,500), 277 mμ (7,500), 345 mμ (3,520). N.m.r. 7.43, 6.19, 6.13, 5.95 (all 3 H, singlets), -0.40 (1 H, singlet), -1.90 (1 H, exchanged by D_2O). (Found: C, 56.48; H, 5.42. $C_{12}H_{14}O_6$ requires C, 56.69; H, 5.55%.)

Methyl 2-hydroxy-3,6-dimethoxy-4,5-dimethylbenzoate (17).

Hydroxyaldehyde (27) (266 mg.) was dissolved in glacial acetic acid (100 ml.) and was hydrogenated over pre-reduced 10% palladium on charcoal (50 mg.) until hydrogen absorption ceased. The catalyst was filtered off and the solvent evaporated to yield a solid product. Recrystallisation from petrol gave the dimethylphenol (186 mg.), m.p. 89°, $\nu_{max.}$ 1660 cm^{-1}, $\lambda_{max.}$ 256 mμ (6,010), 327 mμ (1,130). N.m.r. 7.88, 7.79, 6.34, 6.23, 6.04 (all 3 H, singlets), -1.03 (1 H, exchanged D_2O). (Found: C, 59.99; H, 6.52. $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71%.)

Oxidation of dimethylphenol (17) with lead tetra-acetate.

Dimethylphenol (17) (68 mg.) was dissolved in dry methanol (10 ml.) and boron trifluoride etherate (40%, 0.2 ml.) and the solution was stirred with lead tetra-acetate (200 mg.) for $\frac{1}{2}$ hr. Quenching in water (50 ml.) and extraction provided an oil which crystallised with petrol/ethyl acetate. Recrystallisation from petrol/benzene provided colourless crystals of the quinone semiketal (18) (75 mg.), $\nu_{max.}$ 1737, 1663, 1650 cm^{-1}, $\lambda_{max.}$ 239 mμ (8,120), 340 mμ (2,660). N.m.r. 8.08, 6.78 (both 6 H, singlets), 6.13, 6.04 (3 H, singlets).

Methyl 2-methoxy-3,6-dihydroxy-4,5-dimethylbenzoate (20).

Methoxyquinone (19) (172 mg.) was dissolved in dry benzene (20 ml.) and was hydrogenated over 5% palladium on barium sulphate (50 mg.) until hydrogen absorption ceased. The catalyst was filtered off, the solvent evaporated and the residue recrystallised from benzene/petrol to provide the hydroquinone (167 mg.), m.p. 120-121°, $\nu_{max.}$ 1654 cm^{-1}, n.m.r. 7.86, 7.78, 6.26, 6.04 (3 H, singlets), 4.47 and -0.9 (both 1 H, exchanged by D_2O). (Found: C, 58.17; H, 6.06. $C_{11}H_{14}O_5$ requires C, 58.40; H, 6.24%.)

Attempted monomethylation of the hydroquinone (20).

Hydroquinone (44.5 mg.) was dissolved in dry acetone (15 ml.) and was stirred at reflux, under nitrogen, with dimethyl sulphate (24.8 mg., 1.1 mol.) and potassium carbonate (27.2 mg.). After 5 hr.

the reaction was quenched in water (20 ml.) and extracted with methylene chloride. T.l.c. on the extract showed it to contain equal amounts of starting material and the totally methylated compound.

Reaction of methyl 2,3,6-trihydroxy-4,5-dimethylbenzoate with acetone dimethyl ketal.

Triphenol (21) (10 mg.) was dissolved in dry benzene (5 ml.) and acetone dimethylketal (5 ml.), and the solution was refluxed with tosyl acid (2 mg.) and followed by t.l.c. No new compound was formed.

Reaction of methyl 2,3,6-trihydroxy-4,5-dimethylbenzoate with phosgene.

Triphenol (21) (1 g.) was dissolved in toluene (30 ml.), cooled to 0^0, and stirred under nitrogen during the addition of dry pyridine (5 ml.) followed by a toluene solution of phosgene (5%, 10 ml.). After 10 min. reaction, the solution was poured into ice-cold hydrochloric acid (N, 25 ml.). The toluene layer was separated and the aqueous phase was extracted with ether (2 x 100 ml.). The combined extracts were dried and evaporated to yield a colourless solid. Recrystallisation from benzene gave the carbonate (23)(665 mg.), m.p. 167-168°, $\nu_{max.}$ 3180, 1836, 1681 cm^{-1}, $\lambda_{max.}$ 247 mμ (9,970), 327 mμ (3,760). N.m.r. 7.80, 7.65, 6.95 (all 3 H, singlets). (Found: C, 55.48; H, 4.16. $C_{11}H_{10}O_6$ requires C, 55.46; H, 4.23%.)

Reaction of carbonate (23) with benzyl chloride.

Carbonate (23) (168 mg.) was dissolved in dry acetone (50 ml.) and

was refluxed with potassium carbonate (300 mg.) and benzyl chloride (0.2 ml.). After 2 hr. the reaction was quenched in water (25 ml.) and extracted with methylene chloride. Evaporation of the solvent provided the triphenol (21) (85 mg.).

Benzoylation of carbonate (23).

Carbonate (1.27 g.) was stirred in pyridine (15 ml.) with benzoyl chloride (800 mg., 1.1 mol.). After $2\frac{1}{2}$ hr. at room temperature the solution was poured into dilute hydrochloric acid (50 ml.) and ice (100 g.) and the crystalline product filtered off. Crystallisation from benzene/petrol provided the carbonate diester (24) (1.40 g.), m.p. 127-128°, $\nu_{max.}$ 1844, 1829, 1733, 1720 cm^{-1}. N.m.r. 7.81, 7.61, 6.22 (all 3 H, singlets), 2.56 (3 H, multiplet), 1.78 (2 H, multiplet). (Found: C, 63.02; H, 4.23. $C_{18}H_{14}O_7$ requires C, 63.16; H, 4.12%.)

Methyl 6-benzoyloxy-2,3-dihydroxy-4,5-dimethylbenzoate (25).

Carbonate (24) (500 mg.) was dissolved in THF (50 ml.) and dilute hydrochloric acid (50 ml.) was added with shaking. After warming on the steam bath for 10 min., water (50 ml.) was added and the solution was extracted with methylene chloride. Evaporation of the solvent and recrystallisation from benzene/petrol gave the catechol (25) (345 mg.), m.p. 190-192°, $\nu_{max.}$ 3420, 1713, 1672 cm^{-1}. $\lambda_{max.}$ 227 mμ (31,700), 260 mμ (11,200), 331 mμ (3,840). N.m.r. 7.94, 7.73, 6.39 (3 H, singlets), 5.00 (1 H, exchanged by D_2O), 2.75 (3 H, multiplet), 1.7 (2 H, multiplet), -1.27 (1 H, exchanged by D_2O). (Found: C, 64.46; H, 5.01.

$C_{17}H_{16}O_6$ requires C, 64.55; H, 5.10%.)

Methyl 6-benzoyloxy-2,3-dimethoxy-4,5-dimethylbenzoate (26).

Catechol (25) (317 mg.) was dissolved in acetone (30 ml.) and was refluxed with dimethyl sulphate (320 mg., 2.5 mol.) and potassium carbonate (800 mg.). After 2 hr. reaction, the solution was poured into water (100 ml.) and was extracted with methylene chloride. Evaporation of the solvent and crystallisation from petrol gave the diester (26) (300 mg.), m.p. 92-93°, $\nu_{max.}$ 1740 cm^{-1} (broad). $\lambda_{max.}$ 230 mμ (19,000), 275 mμ (2,310). N.m.r. 7.94, 7.76, 6.33, 6.19, 6.10 (3 H, singlets), 2.80 (3 H, multiplet), 1.72 (2 H, multiplet). (Found: C, 66.38; H, 5.89. $C_{19}H_{20}O_6$ requires C, 66.27; H, 5.85%.)

Methyl 2,3-dimethoxy-6-hydroxy-4,5-dimethylbenzoate (14).

Sodium (300 mg.) was dissolved in dry methanol (10 ml.) and a solution of benzoate (26) (300 mg.) in methanol (25 ml.) was added. The reaction was stirred under nitrogen for 5 min. and was worked up by pouring into water, acidifying with hydrochloric acid and extracting with methylene chloride. Purification by chromatography on thick l.c. gave the phenol (190 mg.), m.p. 38°, $\nu_{max.}$ 1662 cm^{-1}. $\lambda_{max.}$ 255 mμ (10,200), 327 mμ (3,920). N.m.r. 7.87, 7.78, 6.26, 6.17, 6.03 (3 H, singlets), -1.30 (1 H, exchanged by D_2O). (Found: C, 59.95; H, 6.56. $C_{12}H_{16}O_5$ requires C, 59.95; H, 6.71%.)

Oxidation of phenol (14) with lead tetra-acetate.

Phenol (66 mg.) was dissolved in dry benzene (15 ml.) and was stirred with lead tetra-acetate (150 mg.) for 15 min. After quenching in water (50 ml.) the benzene layer was separated and the aqueous layer extracted with methylene chloride. Evaporation of the combined extracts provided an oil (55 mg.) which could not be induced to crystallise. $\nu_{max.}$ 1743, 1687, 1639 cm^{-1}, $\lambda_{max.}$ 241 mμ (14,300), 272 mμ (13,300). N.m.r. 8.17 (6 H, singlet), 8.02, 7.96, 6.86, 6.18, 6.00 (3 H, singlets).

Hydrolysis of quinone semiketal (28).

Semiketal (28) (20 mg.) was dissolved in chloroform (3 ml.) and was shaken with dilute hydrochloric acid (3 ml.) for 5 min. at room temperature. The chloroform layer was separated, dried, and evaporated to give an oil. Separation by silica gel t.l.c. gave 3-methoxy-4-carbomethoxy-6-methyl-2,5-toluquinone (29) (8 mg.), m.p. and mixed m.p. 67-68°, $\nu_{max.}$ 1731, 1672, 1648, 1639, 1616 cm^{-1}.

Oxidation of phenol (17) with lead tetra-acetate.

Phenol (10 mg.) was dissolved in dry benzene (5 ml.) and was stirred with lead tetra-acetate (20 mg.) for 2 hr. The solution was poured into sodium bicarbonate solution (20 ml.) and was extracted with methylene chloride. Evaporation of the solvent gave a semi-crystalline product (8 mg.) $\nu_{max.}$ 1743, 1669 cm^{-1}. $\lambda_{max.}$ 239 mμ

(9,760), 335 mμ (1,350). N.m.r. 8.12, 7.89, 6.59, 6.15, 6.03 (3H, singlets).

Hydrogenation of semiketal (18).

Semiketal (18) (8.7 mg.) was dissolved in dry methanol (5 ml.) and was hydrogenated over pre-reduced 10% palladium in charcoal (5 mg.) until 1 mol. had been absorbed. Separation on silica gel t.l.c. gave the cyclohexenone (35), $\nu_{max.}$ 1736, 1678 cm^{-1}, $\lambda_{max.}$ 263 mμ (9,600). N.m.r. 8.78, 8.74, 6.78, 6.73, 6.13, 6.10 (3 H, singlets).

Oxidation of methyl 2-hydroxy-3,6-dimethoxy-4-methyl-5-formylbenzoate (27) with lead tetra-acetate.

Hydroxyaldehyde (27) (56 mg.) was dissolved in dry methanol (15 ml.) and the solution was cooled to 0^0 and stirred with lead tetra-acetate (100 mg.) and boron trifluoride etherate (0.2 ml.) for 5 min. The reaction was quenched in water (50 ml.) and extracted with methylene chloride. Evaporation of the solvent provided a semi-crystalline product (47 mg.), $\nu_{max.}$ 1743, 1731, 1711, 1670, 1644 cm^{-1}, $\lambda_{max.}$ 224 mμ (13,700), 333 mμ (2,760). N.m.r. 7.90, 7.85, 6.56, 6.15, 5.98 (3 H, singlets), 0.09 (1 H, singlet).

III. Mesityl chloroformate (2).[3]

Mesitol (17 g.) was dissolved in benzene (100 ml.) and a vigorous stream of phosgene was passed into the stirred solution, maintaining the temperature below 0^0 with a carbon tetrachloride/carbon dioxide cooling bath. Freshly redistilled dimethyl aniline (17 ml., 1.0 mol.) was then added and the reaction stirred for 10 min. below 0^0.

After quenching with water (15 ml.), the organic phase was separated, washed with dilute hydrochloric acid, dilute caustic soda and then twice with water. The dried ($MgSO_4$) extract was then evaporated and the residual oil distilled, b.p. 69-70^0, 0.5 mm Hg; $\nu_{max.}$ 1783 cm^{-1}.

Reaction of mesityl chloroformate with sodium peroxide.

Benzene. Mesityl chloroformate (37 mg.) was dissolved in dry benzene (10 ml.) and was stirred at room temperature with sodium peroxide (18 mg.). After 4 hr. t.l.c. indicated that no reaction had occurred.

Aqueous benzene. Mesityl chloroformate (37 mg.) was dissolved in benzene (10 ml.) and was stirred with a solution of sodium periodate (38 mg.) in water (5 ml.) at room temperature. After 18 hr. t.l.c. indicated that no reaction had occurred.

Reaction of mesityl chloroformate with t-butyl hydroperoxide.

A solution of mesityl chloroformate (537 mg.) in toluene (10 ml.) was stirred, at 0^0, with a solution of t-butyl hydroperoxide (5 ml.),

toluene (5 ml.) and pyridine (3 ml.). After 2 hr. the reaction was quenched with water (25 ml.), the organic phase separated, washed twice with dilute hydrochloric acid, twice with water and dried. Evaporation yielded a semi-crystalline product which was shown by t.l.c to be mainly mesitol.

Acetoxime.[23]

Hydroxylamine hydrochloride (25 g.) was dissolved in water (40 ml.) and the cooled solution was mixed with a solution of sodium hydroxide (14 g.) in water (40 ml.). Acetone (24 ml.) was added to the stirred solution keeping the temperature below 15^0. When the addition was complete stirring was continued for a further 15 min. and the precipitated oxime was filtered off and dissolved in petrol. The dried (Na_2SO_4) extract was concentrated by evaporation and cooled. Pure acetoxime (20 g.) crystallised.

2-bromo-2-nitrosopropane.[5]

Acetoxime (5 g.) was dissolved in water (50 ml.) and pyridine (6 g.) and the solution was cooled to 0^0 with stirring. Bromine (10 g.) was added dropwise to the cooled solution and a blue oil separated. This was removed from the reaction mixture and used without further purification.

Reaction of 2-bromo-2-nitrosopropane with p-cresol.

p-Cresol (216 mg.) was dissolved in acetone (20 ml.) and sodium hydroxide (N/10, 20 ml., 1 mol.). 2-bromo-2-nitrosopropane (1.5 ml.) in acetone (20 ml.) was added slowly to the stirred cold solution. When the addition was complete the reaction was stirred for 1½ hr. at 0°, acidified with dilute hydrochloric acid and extracted with methylene chloride. The dried extract contained several compounds and yielded a yellow-brown oil on evaporation.

This oil was dissolved in benzene (20 ml.) and refluxed for ½hr. The solvent was then evaporated and the residue acetylated with acetic anhydride (5 ml.) and pyridine (5 ml.). After stirring for 24 hr. at room temperature the reaction was quenched in ice-cold dilute hydrochloric acid (1 N, 25 ml.) and extracted with methylene chloride. This extract, besides a considerable amount of p-cresyl acetate, contained at least 3 other compounds in equal quantity.

2-bromopropiophenone.[6]

Propiophenone (16.1 g.) was dissolved in ether (15 ml.) and was stirred at 0°. Finely powdered aluminium trichloride (150 mg.) and bromine (19.2 g.) were added over 45 min. Ether (15 ml.) was then added and the reaction quenched in water (50 ml.). The organic phase was separated and washed 8 times with water (50 ml.). The ether extract was dried with $MgSO_4$, evaporated; redissolved in methylene chloride and dried with Na_2SO_4 when evaporation gave 2-bromopropiophenone (23 g.).

2-(p-methylphenoxy)-propiophenone (5).[6]

2-bromopropiophenone (3.0 g.) was dissolved in acetone (20 ml.) and was refluxed with p-cresol (1.7 g.) and potassium carbonate (2.8 g.) for 19 hr. The reaction mixture was poured into water (50 ml.) and extracted with ether. The extract was washed with dilute sodium hydroxide, water, dried, and evaporated to yield a yellow solid. Recrystallisation from petrol gave 2-(p-methylphenoxy)-propiophenone, m.p. 49-50°, $\nu_{max.}$ 1689 cm^{-1}. N.m.r. 8.37 (3 H, doublet, J = 7 hz.), 7.80 (3 H, singlet), 4.81 (1 H, quartet, J = 7 hz.), 3.23 (4 H, AB quartet), 2.67 (3 H, multiplet), 2.01 (2 H, multiplet).

Autoxidation of 2-(p-methylphenoxy)-propiophenone.

The propiophenone (296 mg.) was dissolved in t-butanol (5 ml.) and DMSO (5 ml). Potassium t-butoxide (690 mg., 5 mol.) was added and the solution was stirred, at 0°, in an atmosphere of oxygen. After 40 min. when oxygen-absorption had ceased the reaction mixture was acidified with glacial acetic acid at 0°, filtered, diluted with water (25 ml.) and extracted with ether. Evaporation led to a semi-solid product which contained at least six components as judged by t.l.c.

The crude product (200 mg.) was dissolved in acetone (20 ml.) and was refluxed with potassium carbonate (1 g.) and dimethyl sulphate (1 ml.) for 18 hr. After quenching in water (25 ml.), extraction with methylene chloride provided an oil which contained many components. The major product was separated by t.l.c. and shown to be methyl benzoate, $\nu_{max.}$ 1725 cm^{-1}.

α-Methyl-N-(phenylsulphonylmethyl) urethane (10).

Benzene sulphinic acid (6.0 g.) and sodium hydroxide (1.6 g.) were dissolved in water (40 ml.) and to this solution was added urethane (3.56 g.), followed by acetaldehyde (2.0 g.) dissolved in formic acid (8 ml.). The reaction was warmed to 70° for 1 hr. and then cooled to 0° overnight.

The oil which separated was removed, dissolved in chloroform, dried and the solvent evaporated. On treatment with ether/diisopropyl ether the residual oil crystallised (5.8 g.), m.p. 80-90°, $\nu_{max.}$ 3280, 3090, 1700 cm^{-1}. N.m.r. 8.97 (3 H, triplet, J = 7 hz.), 8.39 (3 H, doublet, J = 7.5 hz.), 6.14 (2 H, quartet, J = 7 hz.), 4.97 (1 H, multiplet), 4.31 (1 H, broad doublet), 2.3 (5 H, multiplet).

α-Methyl-N-(phenylsulphonylmethyl)-N-nitrosourethane (11).

The urethane (3.4 g.) was dissolved in dry pyridine (40 ml.) and cooled to 0° with stirring. A stream of nitrosyl chloride was passed into the solution until it became dark red and stirring was then continued for ½ hr. The reaction mixture was poured slowly into ice-water (50 ml.) and extracted with chloroform. The extract was washed 3 times with water (50 ml.), dried, and evaporated to yield an oil (230 mg.), $\nu_{max.}$ 1751 cm^{-1}.

Hydrolysis of α-methyl-N-(phenylsulphonylmethyl)-N-nitrosourethane (11).

The crude N-nitrosourethane was added, with stirring, to a solution of sodium (100 mg.) in dry methanol (20 ml.) at 0°. After 15 min. the

reaction was allowed to warm to room temperature and the stirring was continued for 1 hr. The reaction mixture was extracted with chloroform and the extract washed with water, dried and evaporated to yield a pale yellow oil (6 mg.), $\nu_{max.}$ 2120, 1725, 1710 cm^{-1}.

Mesityl formimidate.[11]

Mesitol (6.8 g.) and formamide (2.25 g.) were dissolved in dry ether (10 ml.) and the solution was added slowly to benzoyl chloride (7.05 g.) in ether (35 ml.) keeping the temperature below 10^0. A small amount of a colourless precipitate appeared after 15 min. and the reaction was allowed to warm to 10^0, and maintained at this temperature for 1 hr. Filtration provided a small amount of a very deliquescent compound. T.l.c. showed the filtrate to contain large quantities of mesitol.

Mesityl cyanate.[12]

Mesitol (13.6 g.) was dissolved in acetone (50 ml.) and the solution cooled to 0^0. Cyanogen bromide (11.0 g., 1.05 mol.) was added followed by triethylamine (12 ml., 1 mol.), keeping the temperature of the stirred reaction below 10^0. After stirring for a further 10 min., the precipitated triethylamine hydrobromide was filtered off and washed three times with acetone (1 ml.). The acetone was removed at 25-30^0 and the residue distilled to give a colourless oil (9.3 g.), b.p. 75-76^0, 0.6 mm Hg., $\nu_{max.}$ 2300 cm^{-1} (strong). (Found: C, 74.24; H, 7.16; N, 8.68. $C_{10}H_{11}ON$ requires C, 74.51;

H, 6.88; N, 8.69%.)

Reaction of mesityl cyanate with peroxide.

Mesityl cyanate (1.0 g.) was dissolved in dry petrol (10 ml.) and was stirred at room temperature with hydrogen peroxide (87%, 5 ml.) for 3 hr. The precipitated crystals were filtered off, washed with petrol, and recrystallised from benzene to provide the amide (14), (0.89 g.), m.p. 203-204°, $\nu_{max.}$ 3420, 3340, 3280, 3210 and 1700 cm^{-1}. N.m.r. 7.83 (9 H, multiplet), 3.84 (2 H, exchanged slowly by D_2O), 3.18 (2 H, broad). (Found: C, 67.24; H, 7.37; N, 8.04. $C_{10}H_{13}NO_2$ requires C, 67.02; H, 7.31; N, 7.82%.)

Reaction of mesityl cyanate with t-butyl hydroperoxide.

Mesityl cyanate (2.0 g.) was dissolved in petrol (15 ml.) and was stirred with t-butyl hydroperoxide (5 ml.) and tosyl acid (20 mg.) at room temperature. The decomposition of the cyanate was followed by t.l.c. and after 1 week the reaction mixture was poured into dioxan (30 ml.), washed with dilute sodium hydroxide and water, extracted with methylene chloride, and the extract dried and evaporated. The semi-solid product was chromatographed on alumina, eluting with petrol. Evaporation of the petrol yielded the s-triazine (15) (207 mg.), m.p. 132-134°, $\nu_{max.}$ 1580, 1568 cm^{-1}. N.m.r. 8.00, 7.78, 3.25 (ratio 6:3:2). (Found: C, 74.43; H, 7.05; N, 8.47. $C_{30}H_{33}N_3O_3$ requires C, 74.51; H, 6.88; N, 8.69%.)

9,10-Phenanthraquinone.[15]

Phenanthrene (25 g.) was added slowly to a vigorously stirred solution of potassium dichromate (75 g.) in water (400 ml.) and concentrated sulphuric acid (125 ml.). After the initial vigorous reaction had subsided potassium dichromate (75 g.) was added and the solution heated to boiling point. Cold water (600 ml.) was added and the solution cooled to 0^0. The crude product was filtered off and washed with water, sodium bicarbonate and ether. Crystallisation from chloroform gave fine orange needles (7.2 g.), m.p. 206-209^0, lit 206^0.

9,9-dichlorophenanthra-10-one.[16]

Phosphorus pentachloride (12.5 g.) was suspended in dry benzene (10 ml.) and was warmed to 70^0. 9,10-Phenanthraquinone (7.2 g.) was added in small quantities. When the addition was complete the dark coloured solution was cooled and the solid was filtered off and washed with benzene and ether. The crude product was added in small portions to vigorously stirred water (50 ml.). Filtration provided fine crystals which were washed with hot and cold water followed by ether (3.4 g.), m.p. 160-165^0, (lit 168^0 from xylene).

Anhydrous sodium p-cresate.

p-Cresol (7.6 g.) was dissolved in dry ether (150 ml.) and sodium hydride (53%, 3.19 g.) was added in small portions to the vigorously

stirred solution. The sodium p-cresate was filtered off, washed with dry ether, and dried in vacuo (9.0 g.).

9,9-di-p-cresyl-phenanthra-10-one.

Sodium p-cresate (1.3 g.) was dissolved in dry DMSO (25 ml.) and the solution warmed to 60°. Dichlorophenanthrone (1.32 g.) was added in portions and when the addition was complete the reaction was stirred for a further 1 hr. keeping the temperature in the range 60-70°. The solution was poured into water (300 ml.) and the green solid filtered off, washed with water and dried in vacuo at room temperature (1.6 g.), $\nu_{max.}$ 1715 cm^{-1}.

9-(p-cresyl) phenanthra-10-ol.

The crude phenanthrone (1.6 g.) was dissolved in glacial acetic acid (150 ml.). Zinc dust (5 g.) was added in portions over 1 hr. to the stirred solution at room temperature. Stirring was continued for 2 hr. when the zinc dust was filtered off and the filtrate poured into water (500 ml.). The precipitated colourless phenanthrol was filtered off, washed with water and dried in vacuo at room temperature (1.4 g.), $\nu_{max.}$ 3540, 1645 cm^{-1}.

Methylation of 9-(p-cresyl) phenanthra-10-ol.

The phenanthrol (300 mg.) was dissolved in methanol (20 ml.) and water (1 ml.) and was stirred, at room temperature, under nitrogen with potassium hydroxide (100 mg.) and methyl iodide (2 ml.). After

2 hr. t.l.c. indicated that a new compound was being formed and the reaction was heated to reflux for a further 2 hr. On quenching in water (50 ml.) and extracting with ethyl acetate, a brown oil was obtained. This was chromatographed on alumina. The fraction eluted with petrol showed $\nu_{max.}$ 1600 cm^{-1} and was the O-methylated compound. Subsequent fractions contained the starting phenanthrol.

9-(p-cresyl)-9-benzylphenanthra-10-one (18).

The phenanthrol (420 mg.) was dissolved in dry ether (25 ml.) and was stirred at room temperature with sodium hydride (53.5%, 63.5 mg.). After $\frac{1}{2}$ hr. the ether was removed by evaporation and the residues dissolved in methanol (40 ml.). Benzyl bromide (2 ml.) was added and the reaction stirred at room temperature for $4\frac{1}{2}$ hr. The solution was then poured into dilute sodium hydroxide (20 ml.) and was extracted with ethyl acetate. Evaporation of the solvent provided a yellow gum which was chromatographed on a thick silica gel plate. After 3 elutions with petrol the major compound was collected as a yellow solid (398 mg.), m.p. 61-63°, $\nu_{max.}$ 1690 cm^{-1}, $\lambda_{max.}$ 246 mμ (27,700), 253 mμ (23,800), 275 mμ (9,670), 285 mμ (7,910), 336 mμ (3,080). N.m.r. 8.01 (3 H, singlet), 6.87 (2 H, singlet), 3.9 (2 H, $\frac{1}{2}$ AB quartet), 2.15-3.5 (15 H, multiplet). (Found: C, 86.15; H, 5.74. $C_{28}H_{22}O_2$ requires C, 86.12; H, 5.68%.)

Pyrolysis of 9-(p-cresyl)-9-benzylphenanthra-10-one.

The phenanthrone (125 mg.) was heated to 190° for 14 min. The yellow residue was dissolved in chloroform and on addition of petrol a solid was precipitated. This was filtered off and recrystallised from petrol/chloroform to yield colourless crystals of 9-(2'-hydroxy-5'-methylphenyl)-9-benzylphenanthra-10-one (20), (37 mg.), m.p. 235-245°, $\nu_{max.}$ 3280, 1670 cm^{-1}, $\lambda_{max.}$ 243 mμ (16,400), 253 mμ (14,200), 281 mμ (7,990), 334 mμ (2,220). N.m.r. ($CDCl_3$ + DMSO-D_6) 7.59 (3 H, singlet), 6.46 (1 H, singlet), 6.38 (1 H, singlet), 3.77-1.93 (16 H, multiplet), 1.78 (1 H, exchanged by D_2O). (Found: C, 86.59; H, 5.33. $C_{28}H_{22}O_2$ requires C, 86.12; H, 5.68%.)

9-(2'-acetoxy-5'-methylphenyl)-9-benzylphenanthra-10-one.

Phenanthrone (20) (15 mg.) was dissolved in acetic anhydride (1 ml.) and pyridine (1 ml.) and the solution was stirred overnight at room temperature. Crystals separated when the reaction mixture was poured into ice-water (20 ml.). These were filtered off and recrystallised from benzene/petrol to yield the acetate (12.5 mg.), m.p. 200-220°, $\nu_{max.}$ 1762, 1675 cm^{-1}, $\lambda_{max.}$ 246 mμ (22,500), 253 mμ (19,700), 273 mμ (9,350), 335 mμ (3,300). N.m.r. 8.82 (3 H, singlet), 7.47 (3 H, singlet), 6.44 (1 H, singlet), 6.27 (1 H, singlet), 3.8-2.0 (16 H, multiplet). (Found: C, 83.52; H, 5.62. $C_{30}H_{24}O_3$ requires C, 83.31; H, 5.59%.)

Pyrolysis of 2-(p-cresyl) propiophenone.

Propiophenone (21) (2 mg.) was heated slowly to 360°. The distillate was collected and was shown by t.l.c. to be pure unchanged starting material.

Methylation of 2-(p-cresyl) propiophenone.

Propiophenone (21) (234 mg.) was dissolved in dry DMF (3 ml.) and was stirred with sodium hydride (53%, 60 mg.) and methyl iodide (1.5 ml.) in an atmosphere of nitrogen. After 2½ hr. t.l.c. showed that the reaction was incomplete and further quantities of sodium hydride (25 mg.) and methyl iodide (1 ml.) were added, and the stirring continued for 20 hr. Quenching in water (20 ml.) and extraction with methylene chloride provided a colourless oil. Chromatography on alumina, eluting with benzene/petrol (1:1), gave a colourless crystalline solid. Recrystallisation from petrol gave 2-(p-cresyl)-2-methylpropiophenone (22), (73.6 mg.), m.p. 61-62°, $\nu_{max.}$ 1674 cm^{-1}, $\lambda_{max.}$ 223 mμ (10,500), 247 mμ (11,500), 284 mμ (1,770). N.m.r. 8.37 (6 H, singlet), 7.81 (3 H, singlet), 3.20 (4 H, AB quartet), 2.63 (3 H, multiplet), 1.70 (2 H, multiplet). (Found: C, 80.60; H, 6.99. $C_{17}H_{18}O_2$ requires C, 80.38; H, 7.13%.)

Pyrolysis of 2-(p-cresyl)-2-methylpropiophenone.

Propiophenone (22) (5 mg.) was heated slowly to 200° and maintained at this temperature for 20 min. After cooling, t.l.c. showed the compound to be unchanged.

Deuteration of 9-(2'-hydroxy-5'-methylphenyl)-9-benzylphenanthra-10-one.

Phenanthrone (20) (40 mg.) was dissolved in pyridine (1 ml.) and D_2O (1 ml.). The solution was sealed in a Carius tube and heated to 70° for 3 days. The solvents were then removed by evaporation and the solid residue dried thoroughly in vacuo. N.m.r. 7.57 (3 H, singlet), 6.72 (1 H, singlet), 6.42 (1 H, singlet), 3.75-1.30 (15 H, multiplet).

Reaction of mesitol with ethyl vinyl ether.[18]

Mesitol (3.4 g.) was dissolved in ethyl vinyl ether (25 ml.) and the solution was refluxed. Mercuric acetate (400 mg.) was added in portions over 3hr. and the solution was then refluxed overnight. After cooling on an ice-bath the reaction mixture was stirred with cold sodium carbonate solution (10%, 25 ml.). The organic phase was separated, dried over solid K_2CO_3 and evaporated. The residue was mesitol as judged by t.l.c.

Ethyl 2-mesitylacetate (24).[4]

Mesitol (27.2 g.) was dissolved in dry acetone (500 ml.) and was refluxed with anhydrous potassium carbonate (80 g.) and ethyl bromoacetate (33.4g.). After 3 hr. the reaction mixture was poured into water (2 l.), extracted with methylene chloride, and the extract evaporated to give ethyl 2-mesitylacetate (30.5 g.).

N,N-Dimethyl mesitylacetamide (25).

Ester (24) (9.0 g.) was suspended in sodium hydroxide solution (4 N, 120 ml.) and was refluxed for 1 hr. After acidification with dilute hydrochloric acid the solution was cooled to 0^0 and the precipitated acid filtered off and dried in vacuo (8.5 g.) $\nu_{max.}$ 1730 cm^{-1}.

The acid (5.0 g.) was dissolved in benzene (100 ml.) and DMF (0.5 ml.). Thionyl chloride (2 ml., 1.1 mol.) was added and the solution was refluxed for $1\frac{1}{2}$ hr. The volume was reduced to half by evaporation and anhydrous dimethylamine (2 ml.) was added at 0^0. After stirring for $\frac{1}{2}$ hr. the reaction was quenched with dilute hydrochloric acid and was extracted with chloroform. Evaporation of the solvent yielded the dimethylamide as an oil (5.25 g.), $\nu_{max.}$ 1680 cm^{-1}. N.m.r. 7.84 (9 H, singlet), 7.13 (3 H, singlet), 6.95 (3 H, singlet), 5.75 (2 H, singlet), 3.34 (2 H, singlet).

N,N-dimethyl-2-mesitylethylamine (26).

Dimethylamide (25) (5.25 g.) was dissolved in dry THF (25 ml.) and was stirred overnight at room temperature with excess LAH. Ethyl acetate (10 ml.) was added and when reaction ceased the solution was poured into water (50 ml.) containing Rochelle salt (2 g.) and was extracted with methylene chloride. This extract was washed thoroughly with dilute hydrochloric acid and the combined acid fractions basified and again extracted with methylene chloride. Evaporation gave an

oil which was distilled to yield the pure amine (3.5 g.), b.p. 96-98°, 0.5 mm. Hg., $\nu_{max.}$ 1490 cm^{-1}. N.m.r. 7.81 (6 H, singlet), 7.76 (9 H, singlet), 7.39 (2 H, triplet, J = 6 hz), 6.27 (2 H, triplet, J= 6 hz), 3.33 (2 H, singlet). (Found: C, 75.23; H, 9.96; N, 7.62. $C_{13}H_{21}NO$ requires C, 75.31; H, 10.21; N, 7.72%.)

N,N-Dimethyl-2-mesitylethylamine-N-oxide (27).

Dimethylamine (26) (2.9 g.) was stirred with hydrogen peroxide (30%, 5 ml.) at room temperature for 17 hr. The reaction was quenched in water (25 ml.) and extracted with ethyl acetate. Evaporation of the solvent provided a semi-solid mass which was recrystallised from acetonitrile (2.5 g.), m.p. 172-3°, $\nu_{max.}$ 3100 cm^{-1}. (Found: C, 60.71; H, 8.71; N, 5.00. $C_{13}H_{21}NO_2$ requires C, 69.92; H, 9.48; N, 6.27%. $C_{13}H_{21}NO_2.2H_2O$ requires C, 60.20; H, 9.72; N, 5.40%.)

Mesityl vinyl ether.

Amine oxide (27) (550 mg.) was heated at 180°, atmospheric pressure, for 1 min. The product, a brown liquid, was dissolved in methylene chloride and dried. The extract was evaporated and the residue distilled to provide mesityl vinyl ether (77 mg.). $\nu_{max.}$ 1660 cm^{-1}, n.m.r. 7.83 (6 H, singlet), 7.74 (3 H, singlet), 5.9 (2 H, multiplet), 3.44 (1 H, multiplet), 3.17 (2 H, singlet).

Tosylate of β-chloroethanol.

Tosyl chloride (95 g.) and β-chloroethanol (100 g.) were refluxed together for 3 hr. The excess chlorohydrin was stripped off on the water pump and the residue washed with dilute sodium hydroxide and extracted with benzene. The extract was dried (K_2CO_3 and Na_2SO_4) and the solvent evaporated. The residue was distilled rapidly to yield the tosylate (70.5 g.), b.p. 145-148°, 2 mm. Hg., $\nu_{max.}$ 1600 cm^{-1}.

β-Chloroethyl ether of mesitol.

Mesitol (5.4 g.) and the tosylate of β-chloroethanol (11 g.) were dissolved in acetone (50 ml.) and were refluxed with anhydrous potassium carbonate (8 g.) for 23 hr. The reaction was quenched in water (100 ml.) and extracted with methylene chloride. The extract was washed with base and water, and then dried and evaporated. Chromatography on alumina, eluting with petrol, followed by distillation gave the pure chloroether (5.1 g.), b.p. 80-85°, 0.3 mm. Hg. N.m.r. 7.82 (9 H, singlet), 6.2 (4 H, multiplet), 3.34 (2 H, singlet). (Found: C, 66.53; H, 7.36; Cl, 17.39. $C_{11}H_{15}ClO$ requires C, 66.46; H, 7.61; Cl, 17.85.)

Mesityl vinyl ether.

Powdered potassium hydroxide (5.6 g.) was suspended in 2-ethoxyethanol (3.6 g.) cooled to 0°. Mesityl β-chloroethylether (2.0 g.) was added and the solution gradually heated until distillation began. Heating was continued until all the liquid phase had been distilled out.

The distillate was poured into water (20 ml.) and the organic phase separated with a little ether. This extract was dried and evaporated, and the residue chromatographed on alumina, eluting with petrol, to yield mesityl vinyl ether (1.16 g.), $\nu_{max.}$ 1660 cm^{-1}.

Reaction of mesityl vinyl ether with hydrogen peroxide.

Mesityl vinyl ether (156 mg.) was stirred at 0^0 with hydrogen peroxide (87%, 5 ml.). Concentrated sulphuric acid (0.1 ml.) was added cautiously; the reaction allowed to warm to room temperature, and stirred for 20 hr. The reaction was quenched in water (50 ml.) and saturated sodium bicarbonate solution (20 ml.) and extracted with chloroform. This extract contained 1 major compound and this was separated by t.l.c. on silica gel to give mesitol (84 mg.).

2-(p-cresyl) ethanol (31).

Ester (30) (20.65 g.) was dissolved in dry THF (250 ml.). LAH (2.5 g.) was added in small portions to the stirred solution. When the addition was complete stirring was continued for $\frac{1}{2}$ hr. and then the excess LAH was destroyed with ethyl acetate. Quenching in dilute hydrochloric acid, extraction with methylene chloride and evaporation provided the alcohol (15.35 g.), $\nu_{max.}$ 3400 cm^{-1}. N.m.r. 7.82 (3 H, singlet), 6.28 (1 H, exchanged by D_2O), 6.23 (4 H, singlet), 3.25 (4 H, AB quartet).

Tosylate of 2-(p-cresyl) ethanol (32).

The alcohol (31) (15.35 g.) was dissolved in dry pyridine (30 ml.) and was stirred, at room temperature with tosyl chloride (21.0 g.). After 3 hr. the reaction was quenched in water and extracted with methylene chloride. Evaporation and crystallisation from ether/petrol gave the tosylate (19.70 g.), $\nu_{max.}$ 1601 cm^{-1}. N.m.r. 7.69 (3 H, singlet), 7.61 (3 H, singlet), 5.83 (4 H, multiplet), 3.20 (4 H, AB quartet), 2.49 (4 H, AB quartet).

p-Tolyl vinyl ether (28).

Tosylate (32) (3 g.) was ground finely with potassium hydroxide (3 g.) and the mixture was placed in a Wood's metal bath at 160°. The temperature was gradually increased to 240° and maintained at this level for 2 hr. to yield p-tolyl vinyl ether (630 mg.), $\nu_{max.}$ 1663 cm^{-1}. N.m.r. 7.73 (3 H, singlet), 5.52 (2 H, multiplet), 3.46 (1 H, multiplet), 3.10 (4 H, AB quartet).

β-Chloroethyl ether of p-cresol.

p-Cresol (10.8 g.) was dissolved in water (10 ml.) containing sodium hydroxide (4.8 g.). The tosylate of β-chloroethanol (23.4 g.) was added and the reaction was heated on the steam bath for 3 hr. with frequent shaking. Sodium hydroxide (5 g.) in water (15 ml.) was added and the solution steam distilled. The β-chloroethyl ether distilled and was separated and dried (9.3 g.), n.m.r. 7.13 (3 H, singlet), 6.08

(4 H, multiplet), 3.10 (4 H, AB quartet).

p-Tolyl vinyl ether.

Powdered potassium hydroxide (35.5 g.) was added to 2-ethoxyethanol (22.2 g.) at 0°. β-Chloroethyl ether of p-cresol (11.1 g.) was added and the reaction warmed until distillation began. The total distillate was collected and was poured into water (50 ml.), and the organic phase was separated, washed twice with water and diluted with chloroform (50 ml.). After drying the solvent was evaporated and the residues distilled to give the vinyl ether (2.0 g.), b.p. 70°, 20 mm. Hg.

Reaction of p-tolyl vinyl ether with hydrogen peroxide.

A solution of hydrogen peroxide (50%, 5 ml.) and concentrated sulphuric acid (20 mg.) was prepared at 0°. A aliquot (1 ml.) was taken and stirred at 0° during the addition of p-tolyl vinyl ether (136 mg.) over ½ hr. The reaction was allowed to warm to room temperature and stirring was continued for 18 hr. T.l.c. showed some starting material to be still present, but the major product (separated by t.l.c. on silica gel) was p-cresol (70 mg.).

Reaction of p-tolyl vinyl ether with peroxide/bromine.

p-Tolyl vinyl ether (191 mg.) in ether (2 ml.) was stirred with an anhydrous solution of hydrogen peroxide in ether (10%, 3 ml.) containing sodium acetate (118 mg.). After cooling to 0°, a solution of bromine

(240 mg.) in ether (15 ml.) was added rapidly. A slight brown colouration persisted and stirring was continued for 15 min. The reaction was quenched in dilute ammonium sulphate solution and the organic phase was washed with sodium bicarbonate and with water. After drying the extract possessed no oxidising power, (addition of KI), and t.l.c. showed it to contain at least 5 products.

Reaction of styrene with peroxide/bromine

Sodium acetate (113 mg.) and anhydrous hydrogen peroxide (10%, 2 ml.) were stirred at -20°. Styrene (143 mg.) was added followed by bromine (220 mg.) in ether (10 ml.). Stirring was continued for 15 min. and then the reaction was quenched in dilute ammonium sulphate solution. After washing with sodium bicarbonate solution and water, the organic phase was dried and evaporated to yield a crystalline solid.

Comparison with an authentic sample of dibromostyrene showed it to contain at least 90% of this compound.

Reaction of styrene with peroxide/NBS.

Anhydrous hydrogen peroxide (10%, 10 ml.) was stirred with sodium carbonate (700 mg.) at -20°. Styrene (334 mg.) in ether (5 ml.) was added followed by freshly recrystallised NBS (620 mg.). After stirring for $5\frac{1}{2}$ hr. the reaction was quenched in dilute ammonium sulphate solution, extracted with ether, and the organic layer washed with bicarbonate and water. Evaporation gave an oil which contained a trace

of dibromostyrene. Iodine titration indicated that the oil contained 80% of the desired bromohydroperoxide.

p-Tolyl-(1-hydroperoxy-2-bromo) ethyl ether (33).

p-Tolyl vinyl ether (168 mg.) was stirred with anhydrous hydrogen peroxide (10 ml.) and sodium carbonate (350 mg.) at -20°. Freshly recrystallised NBS (224 mg.) was added and the reaction was stirred at -20° for 1½ hr. The solution was then poured into sodium bicarbonate solution (5%, 30 ml.), and the organic phase separated and washed with water. Evaporation led to an oil (230 mg.) exhibiting 95% of the expected oxidising power, $\nu_{max.}$ 3500, 1615 cm^{-1}, $\lambda_{max.}$ 220 mμ (11,200), 275 mμ (1,120), 287 mμ (920). N.m.r. 7.70 (3 H, singlet), 6.42 (2 H, doublet, J = 5.5 hz.), 4.55 (1 H, triplet, J = 5.5 hz.), 3.04 (4 H, AB quartet), 0.9 (1 H, exchanged by D_2O).

Attempted rearrangements of p-tolyl-(1-hydroperoxy-2-bromo)ethyl ether.

BF_3. Bromohydroperoxide (200 mg.) was dissolved in dry ether (10 ml.) and was stirred at 0° with boron trifluoride etherate (40%, 1 ml.). After 2 hr. t.l.c. indicated that no reaction had taken place.

$AlCl_3$. Bromohydroperoxide (200 mg.) was dissolved in dry ether (10 ml.) and was stirred at 0°. Aluminium trichloride (0.5 g.) was added in small quantities over 4 hr. The reaction was then quenched in dilute sulphuric acid (20 ml.) and extracted with ether. T.l.c. showed this extract to contain 7 components, none corresponding to 4-methylcatechol.

Acid. Bromohydroperoxide (150 mg.) was dissolved in dry benzene (10 ml.) and was stirred with p-tosyl acid (100 mg.) at room temperature. After 18 hr. stirring t.l.c. showed that no rearrangement had occurred. The reaction was then warmed to 60° for 3 hr., after which time the hydroperoxide had decomposed to many compounds.

Pyrolysis. Bromohydroperoxide (100 mg.) was dissolved in dry benzene (10 ml.) and was warmed to 60° for 3 hr. T.l.c. showed no rearrangement and iodine titration showed that the peroxide had not decomposed.

Hydroperoxide (50 mg.) was dissolved in dry toluene (3 ml.) and was heated to 100° for 3 hr. No rearrangement took place.

Nitrobenzoate of p-tolyl-(1-hydroperoxy-2-bromo) ethyl ether.

Bromohydroperoxide (246 mg.) was dissolved in dry pyridine (2 ml.) and the solution was cooled to 0° with stirring. p-Nitrobenzoyl chloride (200 mg., 1 mol.) was added and the reaction was stirred for 5 min. when it was quenched in ice (20 g.) containing dilute hydrochloric acid (2 ml.) and the crystals obtained dissolved in chloroform. The extract was washed with sodium bicarbonate and water, dried and evaporated to yield an oil (250 mg.).

The ester (20 mg.) was dissolved in chloroform and refluxed for 2 hr. T.l.c. showed the formation of many products.

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