STUDIES RELATED TO THE SYNTHESIS OF TETRACYCLINE

a thesis presented by

MICHAEL JOHN PEARSON

in partial fulfilment of the requirements

for the award of the degree of

DOCTOR OF PHILOSOPHY

Chemistry Department,
Imperial College,
London, S.W.7.

September 1969.

To Margaret.

ABSTRACT.

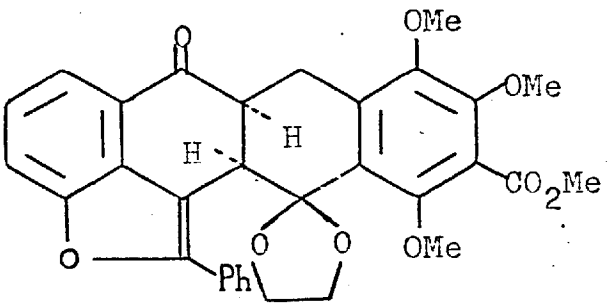
The first section of this thesis describes three aspects of tetracycline chemistry:

1. The chemistry and synthesis of pretetramids.
2. Some recent achievements in tetracycline synthesis.
3. A summary of the results obtained in these laboratories in the field of tetracycline synthesis.

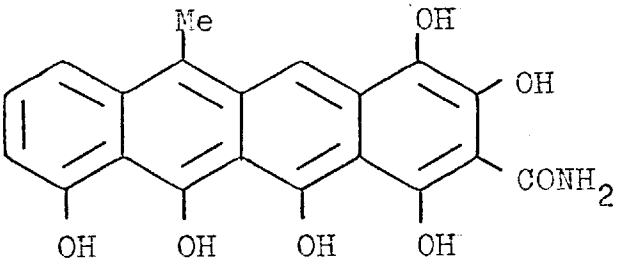
A discussion of the author's work on this project is contained in the second section.

Part I.

An account of the transformation of (A) into 4-hydroxy-6-methylpretetramid (B).

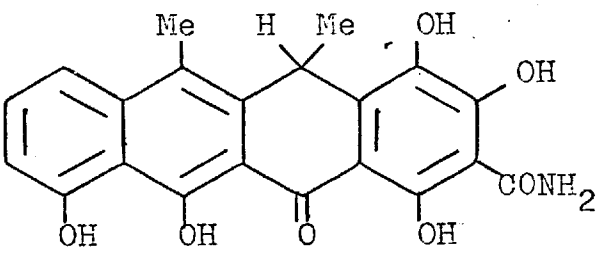


(A)



(B)

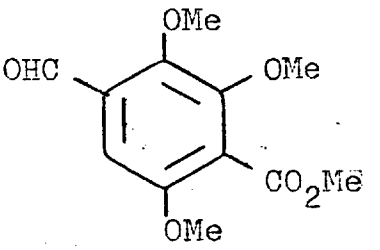
The synthesis of a new pretetramid (C).



(C)

Part II.

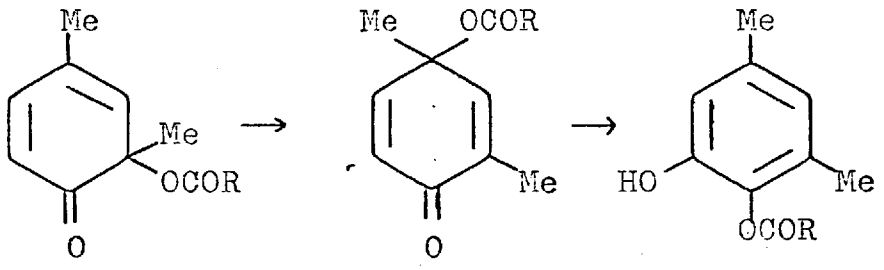
An improved synthesis of (D).



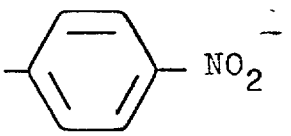
(D)

Part III.

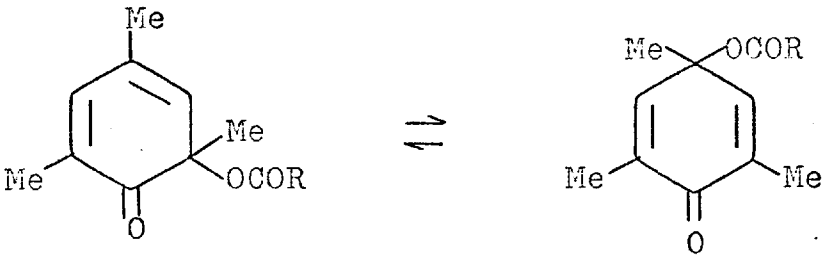
A method of o-acyloxylating phenols. The thermal sigmatropic (3,3) suprafacial migration of an acyloxy-group around the periphery of a cyclohexadienone ring, (E → F → G).



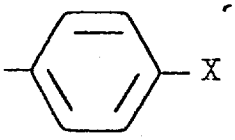
(E) (F) (G)

R = 

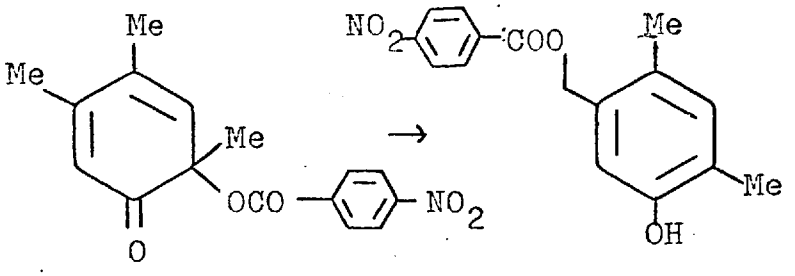
A kinetic study (H ⇌ I)



(H) (I)

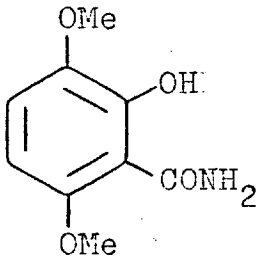
R=  X=H, NO_2, OMe

The rearrangement of (J) to (K)



(J) (K)

The oxidation of (L) to (M)



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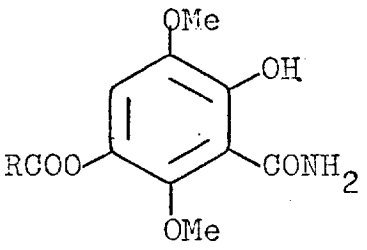

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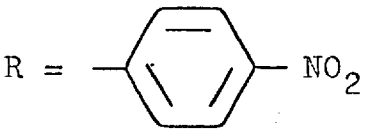

ACKNOWLEDGEMENTS

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The technical staff of the Chemistry Department are thanked for their assistance, expecially Mrs. I. Boston and Mr. K.I. Jones.

The award of a Research Studentship by the Science Research Council is gratefully acknowledged.

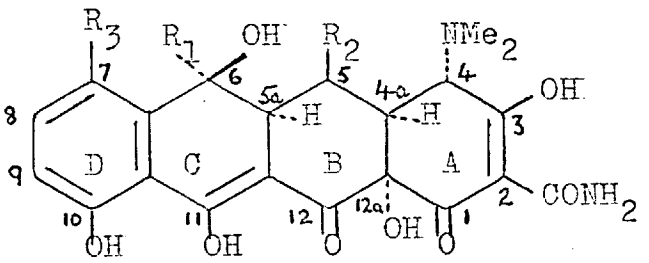
Michael Pearson,
Whiffen Laboratory,
September, 1969.

CONTENTS.

INTRODUCTION

The tetracycline antibiotics consist of a group of closely related hydronaphthacenes that are of interest because of their broad-spectrum antibiotic activity. They are produced by various strains of Streptomyces, or obtained by chemical modification of the natural metabolites.

The first of these substances to be discovered was aureomycin, or 7-chlorotetracycline (1) which was isolated from the culture of Streptomyces aureofaciens[1] in 1948. Terramycin, or 5-hydroxytetracycline (2) was isolated shortly afterwards from Streptomyces rimosus[2]. In 1952 the structures of these complex natural products were elucidated in the laboratories of Chas. Pfizer and Co., Inc., in close co-operation with Woodward[3,4,5]. The parent compound, tetracycline (3) was obtained from Streptomyces albo-niger and was shown to be identical with the hydrogenolysis product of aureomycin[6,7].



(1) R_1=Me, R_2=H, R_3=Cl

(2) R_1=Me, R_2=OH, R_3=H

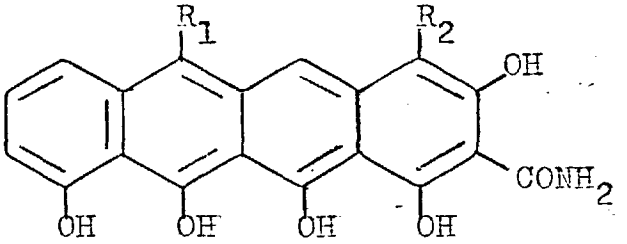
(3) R_1=Me, R_2=R_3=H.

X-ray studies[8] confirmed the chemically assigned structure of aureomycin, and established the relative configurations at the five asymmetric centres. In the case of terramycin, X-ray analysis[9] confirmed the gross structure, but the relative stereochemistry of the C-5 hydroxyl was deduced from n.m.r. evidence[10], and a re-examination of the earlier X-ray data.

The chemistry and synthesis of pretetramids.

Introduction.

Part of the structural elucidation[3] of terramycin (2), involved acid degradation to give a product (4; R_1=CH_3, R_2=H) which was the first fully aromatic compound obtained from tetracycline or its derivatives.



(4)

Later[11], when it was discovered that (4; R_1=CH_3, R_2=H) and related compounds were important intermediates in the biosynthesis of tetracyclines, the name pretetramid was suggested for 1,3,10,11,12-pentahydroxynaphthacene-2-carboxamide (4; R_1=R_2=H).

General Properties

The pretetramids are generally highly crystalline solids, but show no definite melting point, decomposing at 250-300°. Their spectral properties are difficult to measure as they are essentially insoluble in most organic solvents. Their infra-red spectra are not very informative but their ultra-violet absorption spectra are diagnostic. When measured in a sulphuric-boric acid mixture (4; R_1=CH_3, R_2=OH) had λ_{max} (ε), 280 (22,100), 316 (42,100), 467 (15,400), and 520 n.m. (16,500)[12], which is similar to, but easily distinguished from, that of 6-methylpretetramid (4; R_1=CH_3, R_2=H) under the same conditions: λ_{max} (ε), 263 (22,900), 278 (21,600), 341 (14,200), 400 (14,700), and 512 n.m. (13,700)[12].

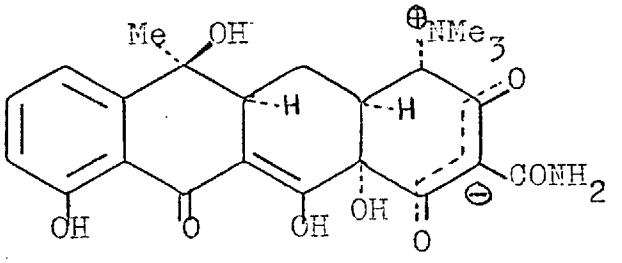
The pretetramids are soluble in dimethylsulphoxide containing 1% magnesium acetate tetrahydrate[12]. The resulting solution is rapidly oxidised in air, but is stable if oxygen is excluded. Material of high purity can be obtained by recrystallisation from hot phenol in the presence of a reducing agent[12].

Synthesis

Pretetramids are readily obtained by degradation of tetracycline derivatives. The route published by Hlavka[13] is illustrative. Pyrolysis of the crystalline betaine (5) in anhydrous acetonitrile causes Hofmann elimination, followed by a ring-opening similar to that formulated for the racemisation of geodin[14]. This sequence provides the phenolic diketone (6) .

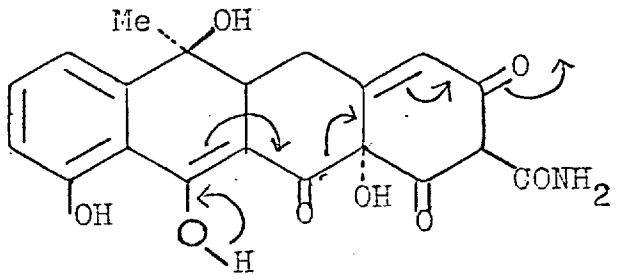
Treatment of (6) with hydrogen iodide in boiling phenol gives 4-hydroxy-6-methylpretetramid (4; R_1=CH_3, R_2=OH).

There is only one published synthesis that does not utilise degradative procedures[15]. Condensation of the substituted naphthalene (7) with 2-hydroxy-phthalic anhydride gave the quinone (8). Reduction of (8) with hydriodic acid containing potassium hyprophosphite provided the pentahydroxynaphthacene (4; R_1=R_2=H), identical in every respect with an authentic specimen obtained by degradation of 6-demethyltetracycline.

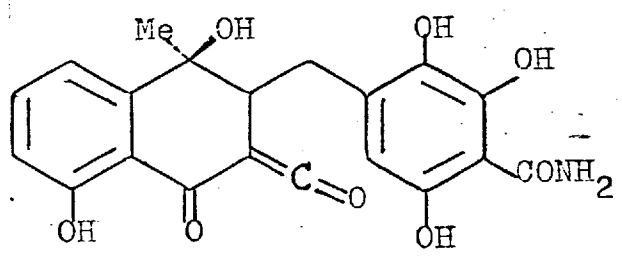

Me
OH
⊕NMe3
H
H
O
CONH2
⊖
OH
O
OH
OH
O

(5)

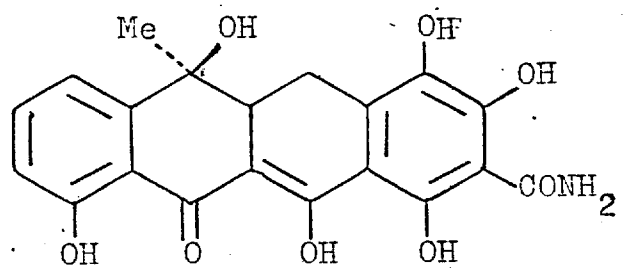
↓ Δ CH_3CN


Me
OH
O
CONH2
OH
O
OH
O
H

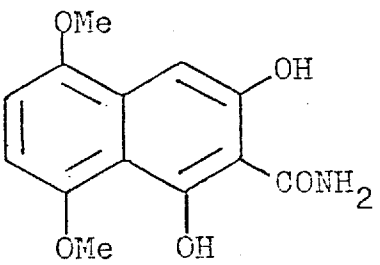
↓


Me
OH
OH
OH
CONH2
C=O
OH
O
OH

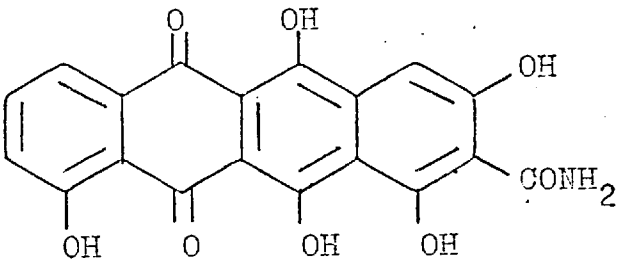
↓


Me
OH
OH
OH
CONH2
OH
O
OH
OH

(6)



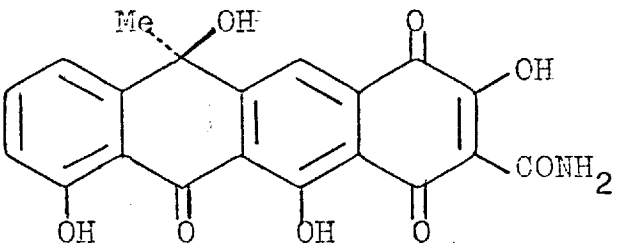
(7)



(8)

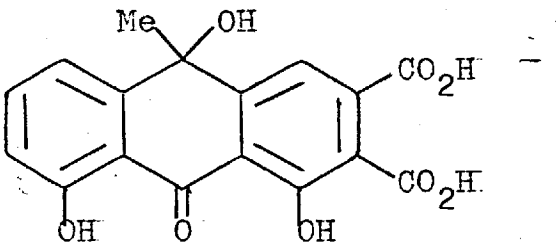
Chemistry

As mentioned previously the pretetramids are readily oxidised when dissolved in an organic solvent. Aerial oxidation of (4; R_1=CH_3, R_2=OH) converts it to the ketonic substance (9)[16]. The change can be reversed by brief treatment with hydrogen iodide in hot phenol. If the reaction is prolonged (ca. 4 hr.)[16], loss of the 4-hydroxyl group takes place to yield 6-methyl-pretetramid (4; R_1=CH_3, R_2=H).



(9)

When both (4; R_1=CH_3, R_2=H) and (4; R_1=CH_3, R_2=OH) are subjected to treatment with alkaline hydrogen peroxide at 60°, ring A is oxidatively cleaved to give racemic 1,8,10-trihydroxy-10-methylanthrone-2,3-dicarboxylic acid (10)[16].



(10)

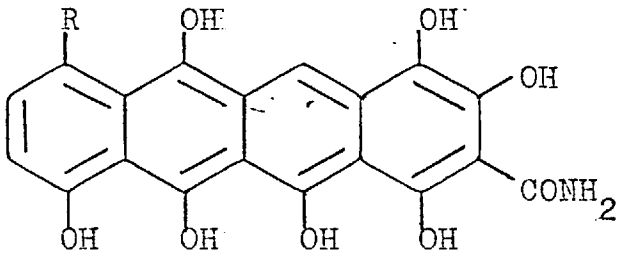
Biosynthetic Importance of the Pretetramids.

Incorporation studies have indicated that tetracycline is derived from nine malonate units initiated by a carbon unit bearing a carboxamido group at C-2[17]. It would also appear from the high yield achieved in the conversion of 6-methylpretetramid (4; R_1=CH_3, R_2=H) to 7-chlorotetracycline, in spite of the number and complexity of the steps involved, that the former is a normal intermediate in the biosynthesis of the 6-methyltetracyclines[11,18]. By analogy it is assumed that (4; R_1=R_2=H) plays a similar role in the biosynthesis of the 6-demethyltetracyclines[19]. The didemethylaminonaphthacenes are not true intermediates, but may be accessible to the biosynthetic pathway by loss of the dimethylamino group[11].

The naphthacene intermediates undergo 12a-hydroxylation[18] and subsequent conversion to anhydrotetracyclines. Oxygenation at C-6 to give 5a,11a-

dehydrotetracyclines, followed by stereospecific reduction, completes the route to the tetracyclines[20].

All attempts to biologically convert the synthetic 4,6-dihydroxypretetramids (11; R=H) and (11; R=Cl) into new tetracyclines have met with no success[13b].



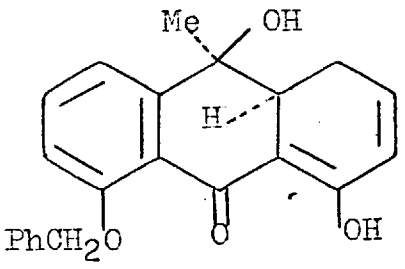
(11)

Recent achievements in the field of tetracycline synthesis.

The large number of functional groups in the tetracycline molecule, coupled with its sensitivity to acid and base, makes its total synthesis a formidable task. However, in recent years two groups have overcome these difficulties and successfully synthesised

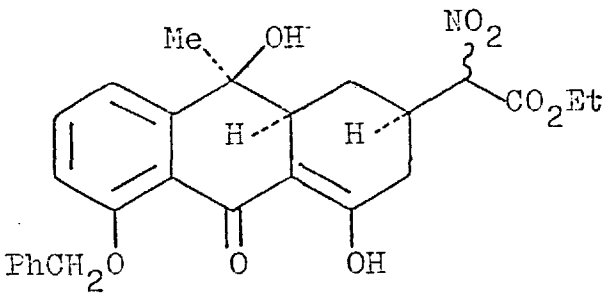
a naturally occurring tetracycline.

The first total synthesis was that due to Shemyakin[21]. Sequential conversion of juglone through six stages gave the dienediolone (12)[22].



(12)

Condensation of the DCB compound (12) with the triethylammonium salt of ethyl nitroacetate gave a mixture of epimeric adducts (13), which was converted by standard methods to the amino ester (14; R=H, R^1=H).



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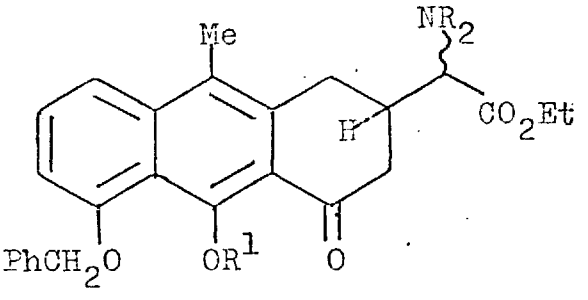
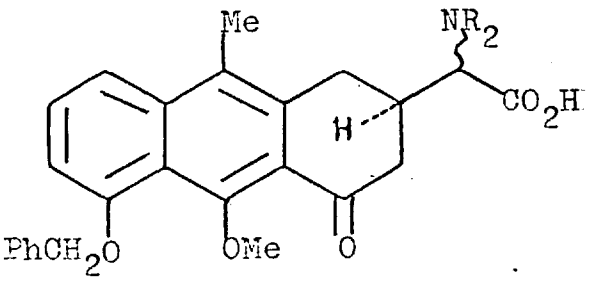


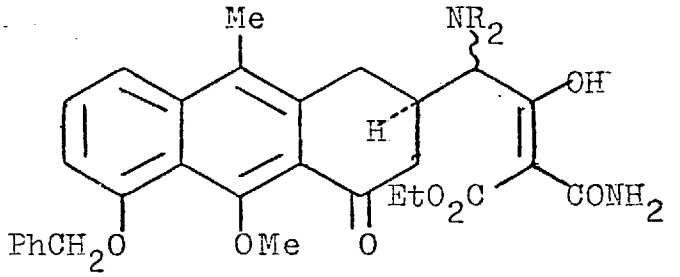
(14)

This compound (14; $R=R^1=H$) was acylated with carboethoxyphthalimide and the product methylated to yield the phthaloyl derivative (14; R_2=Phthal, $R^1=CH_3$). Saponification with dilute potassium hydroxide in aqueous tetrahydrofuran followed by recyclisation of the phthalimido grouping provided the acid (15; R_2= Phthal).



(15)

The latter (15; R_2=Phthal.) was condensed as the chloride with ethyl ethoxymagnesium malonamate and the product (16; R_2=Phthal) cyclised to the hydronaphthacene (17; R=$COC_6H_4CO_2H$-o.), by sodium methylsulphinyl methide in dimethylsulphoxide.



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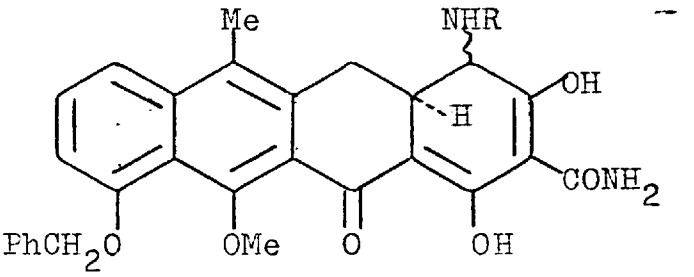
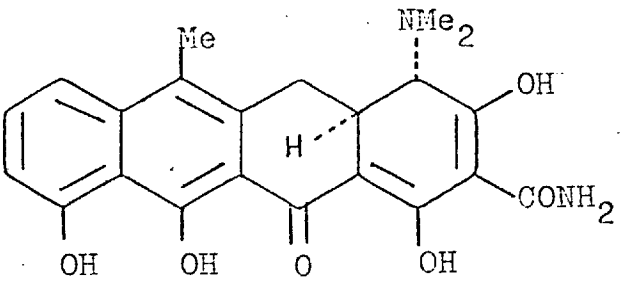


(17)

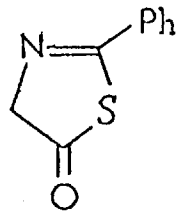
Acid hydrolysis followed by methylation with methyl iodide in tetrahydrofuran completed the synthesis of (±)-12a-deoxy-5a,6-anhydrotetracycline (18).

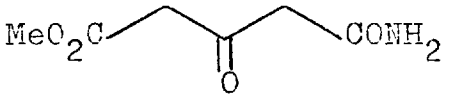


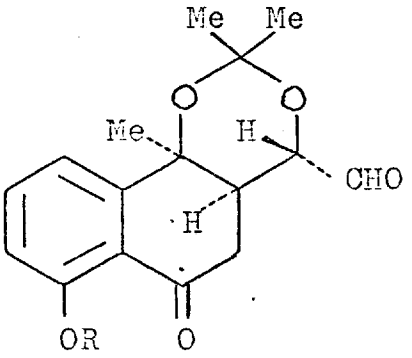
(18)

Since (18) is known[22] and has been converted by 12a-hydroxylation[23] followed by photooxidation-reduction at C-6 to a mixture of tetracycline and 5a-epitetracycline[24], this constitutes a total synthesis[21].

The work of Muxfeldt culminated in the synthesis of dl-terramycin in 1968[25]. Terramycin (2), was assembled using three basic building blocks: the thiazolone (19), methyl 3-oxoglutaramate (20), and the aldehyde (21; R=CH_2OCH_3).

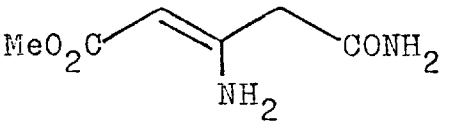






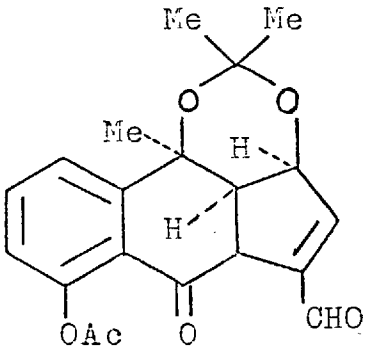
(19) (20) (21)

The thiazolone (19) was readily prepared in two steps from thiobenzoylglycine[26], and methyl 3-oxo-glutaramate (20) was obtained by acid hydrolysis of the enamine (22), formed by controlled reaction of dimethyl 3-oxoglutarate with ammonia in methanol.



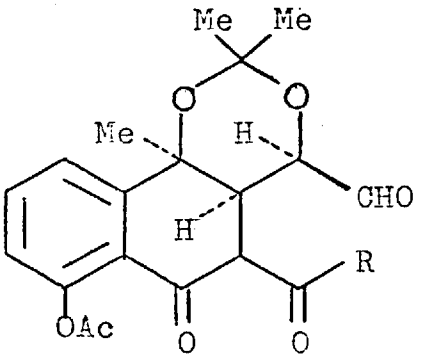
(22)

The starting point for the synthesis of (21; R=CH_2OCH_3) was the diene adduct of juglone acetate and 1-acetoxy-butadiene. Sequential transformations over seven stages gave (23) in high yield.



(23)

Hydrolysis of the crystalline ozonide of (23) afforded a mixture of (24; R=CHO) and (24; R=CO_2H), which on treatment with aqueous sodium carbonate gave a mixture of epimeric aldehydes (21; R=$COCH_3$) and (25).



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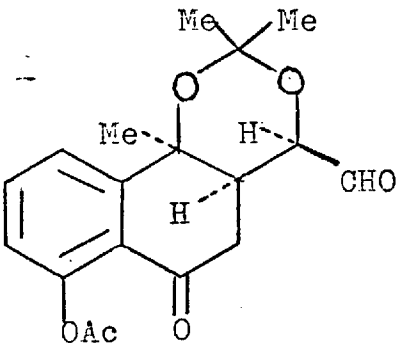
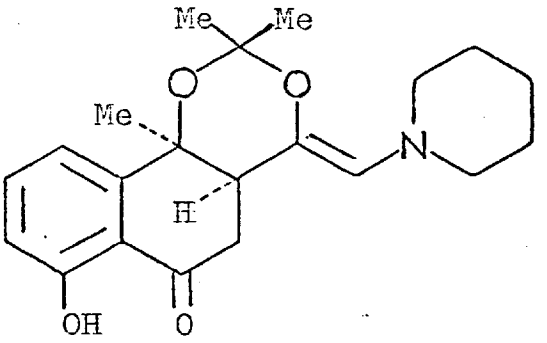


(25)

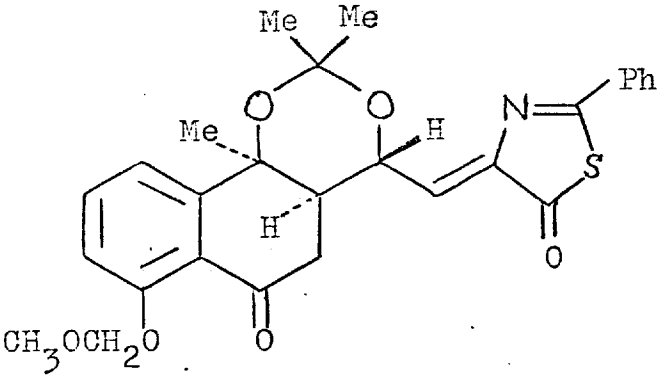
On refluxing this mixture with piperidine in benzene, conversion to the enamine (26) occurred.



(26)

The phenolic hydroxyl was reprotected by methoxymethylation and the aldehyde (21; R=CH_2OCH_3) obtained by stereospecific acid hydrolysis of the enamine function on deactivated silica gel.

The CD compound (21; R=CH_2OMe) was then condensed with (19) to give the thiazolone (27). Base catalysed reaction of (27) with the lithium salt of methyl 3-oxo-glutaramate (20) afforded the tetracyclic compound (28; R=CH_2OCH_3) in approximately 20% yield.



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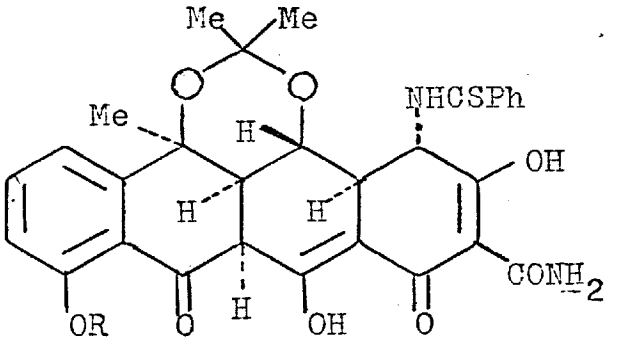
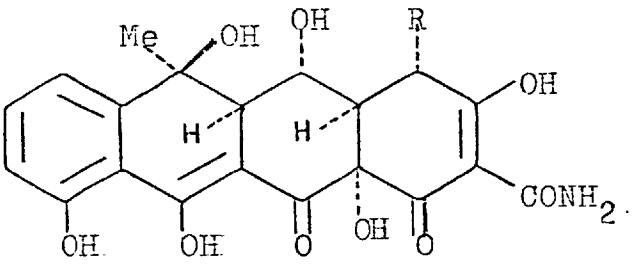


(28)

The methoxymethyl group was removed and the product (28; R=H) hydroxylated in basic media with molecular oxygen. Deketalisation by mild acid treatment then gave (29; R=NHCSPh).



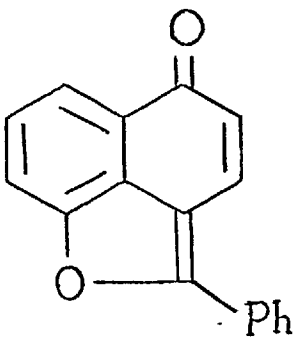
(29)

Methylation with methyl iodide in tetrahydrofuran afforded (29; $R=NH^{+}=C(SCH_3)-C_6H_5\ I^{-}$) which was acid hydrolysed to the crystalline hydrochloride (29; $R=NH_3^{+}Cl^{-}$) without isolation. Final conversion to terramycin was achieved by immediate alkylation of (29; $R=NH_3^{+}Cl^{-}$) with dimethyl sulphate. The pure material was obtained after chromatography of the product on polyamide.

Synopsis of Previous Work[27].

The route proposed for the synthesis of tetracycline was the assembly of an ACD system by the attachment of an aromatic ring A to a protected CD system, the formation of ring B being accomplished by cyclisation. In reviewing previous work it is intended to concentrate on the developments which have relevance to the author's own contribution.

Friedel-Crafts condensation of 1,5-dihydroxy-naphthalene with benzoic acid gave the naphthofuran (30), which was converted to the dihydro compound (31) by hydrogenation over Raney nickel.



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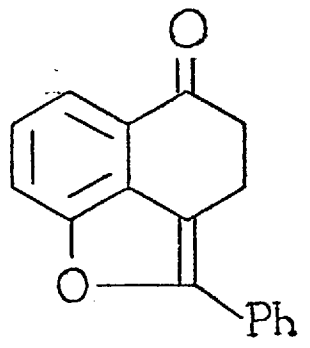
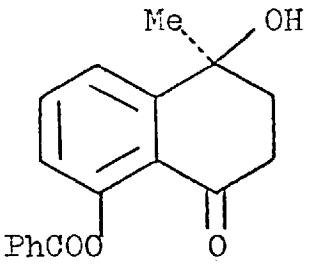


(31)

The utility of (31) lay in its ready transformation to the tetralone (32) via methyl magnesium iodide and ozonolysis. This compound (32) has all the required oxygen functions of the rings C and D of tetracycline.



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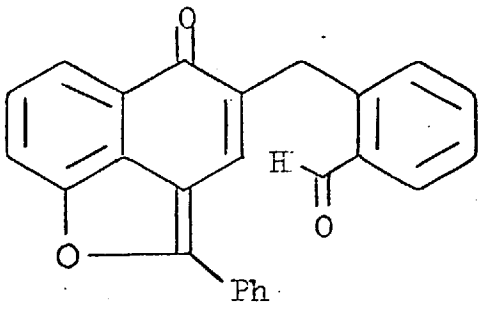
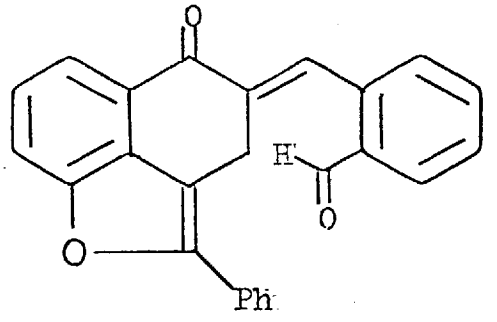


(33)

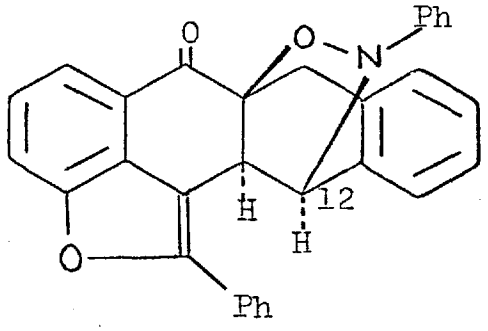


(34)

The active 4-methylene group of (31) provides the point of entry, by condensation with substituted benzaldehydes, into the ACD series of compounds.

Condensation of (31) with o-phthalaldehyde in the presence of triethylamine gave the model aldehyde (33). Under these conditions the initial product (34) isomerised, so that the ACD tricyclic compound (33) was obtained directly. Acid catalysed condensation of (31) with o-phthalaldehyde gave a complex mixture.

At one time the most accessible tetracyclic compound was the isoxazolidine (35).

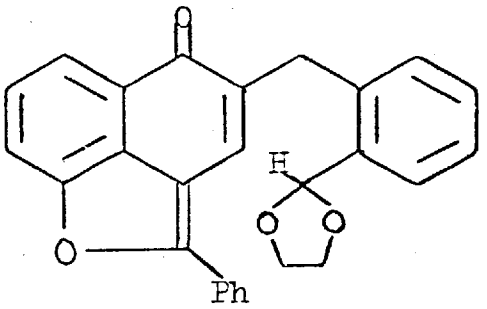


(35)

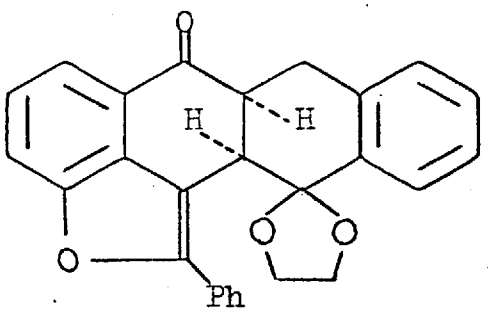
The nitrone derivative of the model aldehyde (33) reacted intramolecularly with the endocyclic double bond of ring C to give (35), the product of 1,3 dipolar addition. The reaction proved successful in producing

tetracyclic compounds when ring A was substituted, but it was not possible to regenerate the 12-keto function.

Eventually a method of cyclisation was found which enabled transformations at C-12 to give the desired keto function. Photolysis of the ACD acetal (36) in the presence of traces of benzoyl peroxide gave the tetracyclic ketal (37) in good yield. It is now known that the observed effect of benzoyl peroxide is due to benzoic acid, its major decomposition product.

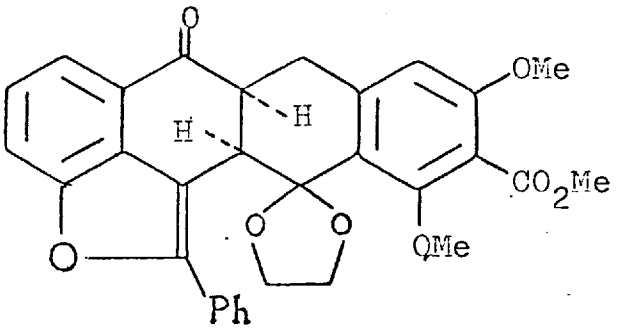


(36)

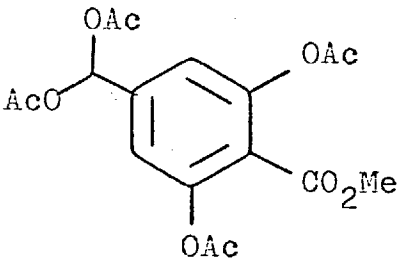


(37)

Further investigation made the tetracyclic dimethoxy ketal (38) readily available in seven steps from the formyl diacetate (39) and the dihydronaphthofuran (31).



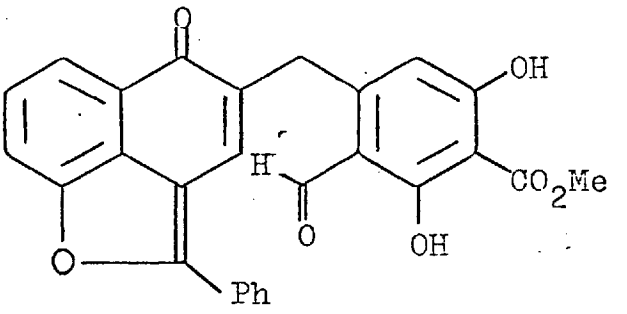
(38)



(39)

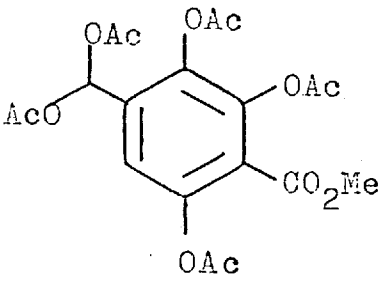
Attention was then focused on the preparation of a tetracyclic compound that emulated the 4-hydroxypretetramids in having a ring A with a 1,2,4-trioxygenation pattern. It was hoped that the final intermediate could be converted into tetracycline by 12a-hydroxylation and to 4-hydroxy-6-methylpretramid (4; $R_1=CH_3$, $R_2=OH$) by aromatisation of rings B and C.

The oxidation of the substituted aldehyde (40) or its ethylene acetal, to give a hydroxyhydroquinone appeared an attractive proposition. However, all attempts to do this failed.



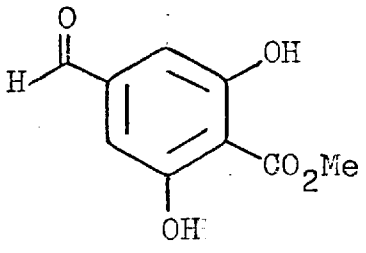
(40)

It was decided, therefore, to construct a suitably substituted 1,2,4-trioxygenated ring A. Methyl-p-orsellinate was converted to the formyldiacetate (41), by oxidation with Fremy's salt, catalytic hydrogenation, acetylation and Thiele oxidation.

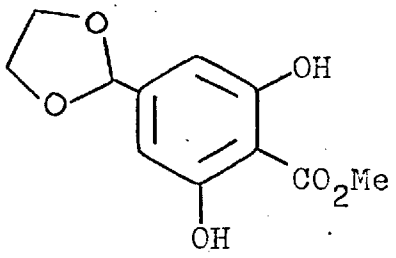


(41)

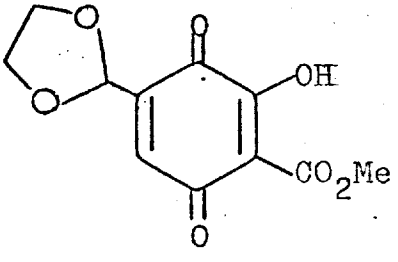
However, condensation of (41) with the dihydronaphthofuran (31) under a variety of conditions gave complex mixtures of pyrlium salts, in various stages of acetylation. It was necessary, therefore, to introduce the hydroxy group after the formyl function. The aldehyde (42), prepared from orcinol was transformed into its ethylene ketal (43) and the latter was oxidised with Fremy's salt to provide the quinone (44).



(42)

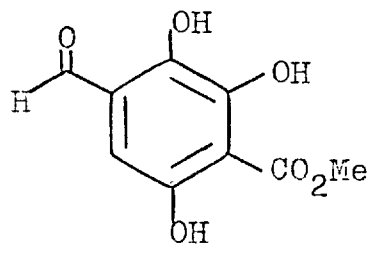


(43)

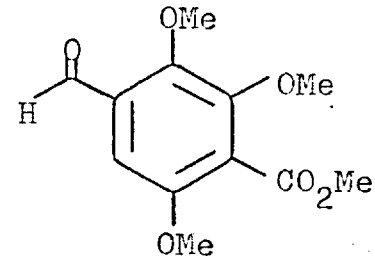


(44)

Catalytic hydrogenation of (44) under non-hydrogenolysing conditions followed by work-up with dilute acid furnished the trihydroxy aldehyde (45).



(45)

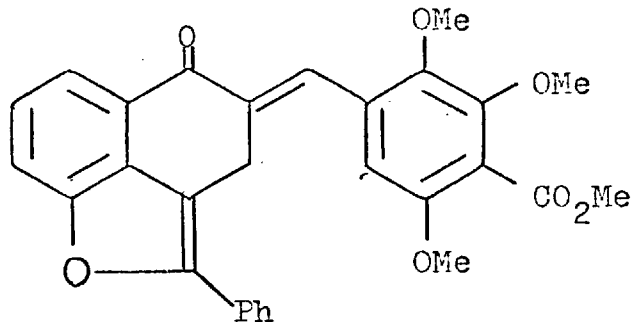


(46)

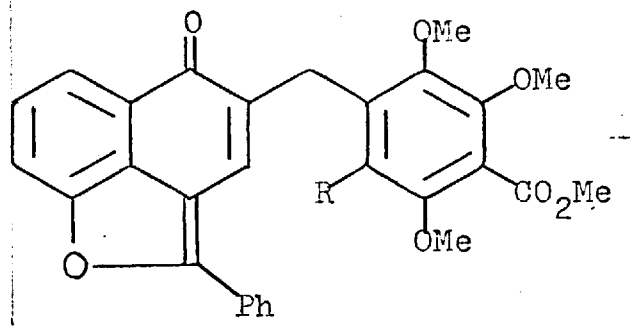
All attempts to condense (45) or its triacetate with the dihydronaphthofuran (31) led to no useful result.

Ultimately the only satisfactory way of protecting the hydroxyl groups was to convert them to methyl ethers. Methylation of (45) in refluxing acetone with dimethyl-sulphate-potassium carbonate gave the required trimethoxy aldehyde (46). Acid condensation of (46) with (31) afforded the exocyclic benzylidene derivative (47).

When this compound was exposed to refluxing triethylamine it rearranged to the endocyclic isomer (48; R=H). Base catalysed condensation gave (48; R=H) directly, but only in moderate yield.



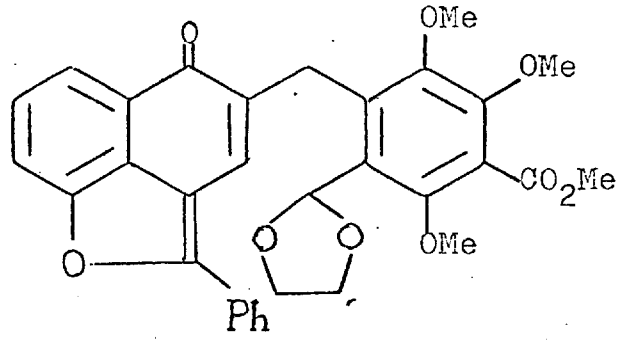
(47)



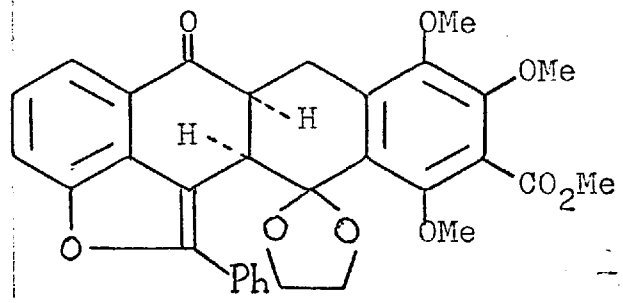
(48)

Formylation of (48; R=H) by prolonged reaction in α,α-dichloromethyl methylether under carefully controlled conditions afforded the aldehyde (48; R=CHO). Conversion to the acetal (49) followed by irradiation of the latter

under established conditions yielded the tetracyclic ketal (50).

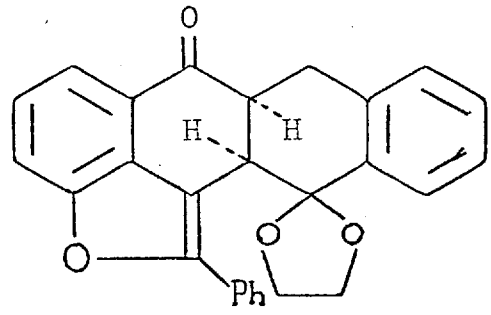


(49)



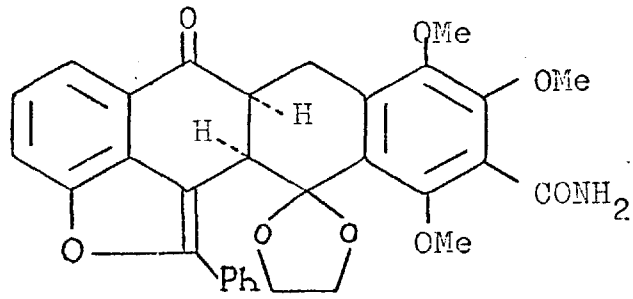
(50)

Transformation of the 6-keto group into a tertiary methyl alcohol had been successfully accomplished on the simple model (37). It was never possible to react completely all the starting material because of enolisation of the 6-carbonyl group.



(37)

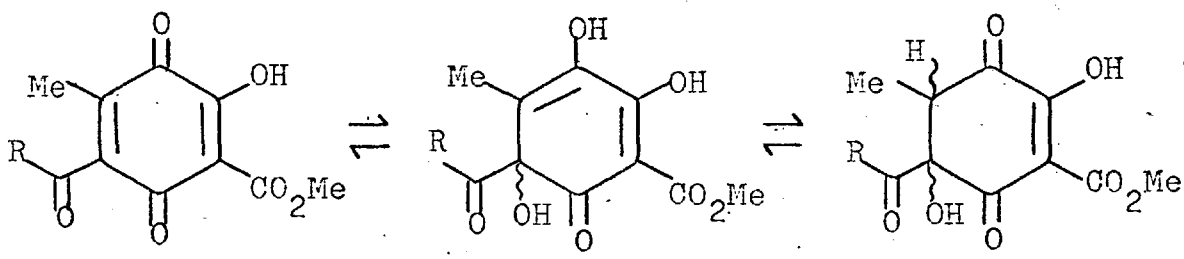
When (50) was treated with methyl lithium attack on the ester function, as well as the desired reaction, took place. Consequently it was decided to convert the ester to an amide, a necessary step anyway, to protect the 2-position against attack by methyl lithium. Work on model compounds indicated that the most applicable method would be base hydrolysis to give the acid, followed by conversion to the acid chloride by treatment with thionyl chloride in benzene containing a catalytic amount of dimethylformamide. Direct work-up with 0.880 ammonia should afford the amide. Part of the author's work was to apply the above procedure to the tetracyclic-ketal (50) and obtain relatively large quantities of the tetracyclic amide (51), in order to investigate its transformation to 4-hydroxy-6-methylpretetramid (4; R_1=CH_3, R_2=OH).



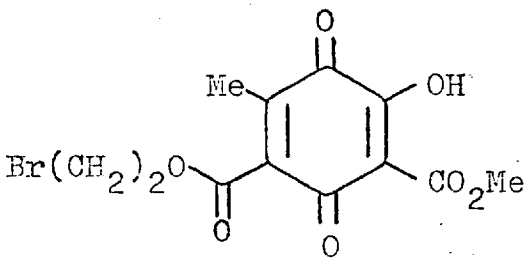
(51)

As the adopted ring A is aromatic and methoxyl-substituted, conversion to tetracycline requires 12a-hydroxylation, followed by reduction, and exposure of the hydroxyl groups. Various approaches have been made in the search for a satisfactory 12a-hydroxylation procedure.

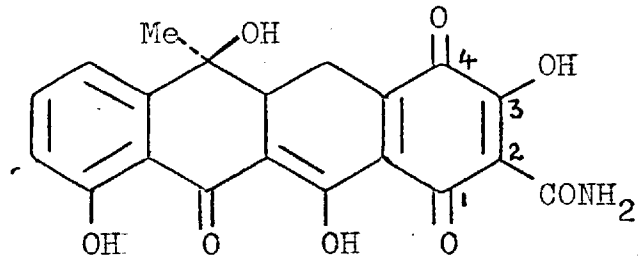
The addition of water to a quinone was tried viz.:



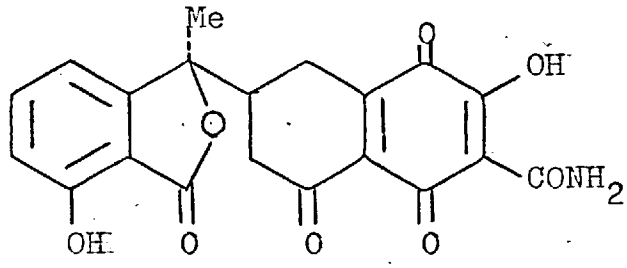
The model quinone (52) was stable to acid and base, and experiments with the tetracyclic quinone (53) were without useful results. Base treatment gave a product assigned the structure (54), whereas acid treatment gave (55).



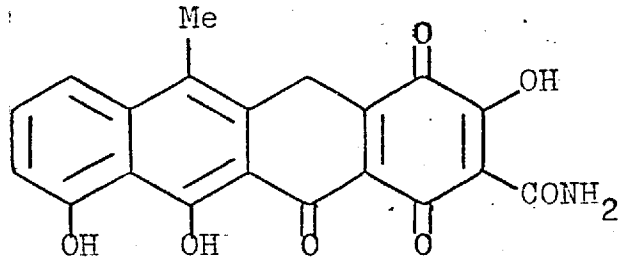
(52)



(53)



(54)

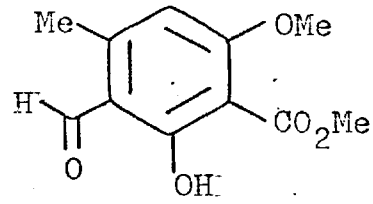


(55)

Photolytic hydration of (53) afforded the anhydro-compound (55) and hydration in the presence of metal ions gave no reaction.

Oxidising agents attacked the 2,3-double bond of (53), and subsequent transformations led to ring contracted products. This conclusion was reached, in the main, from model work.

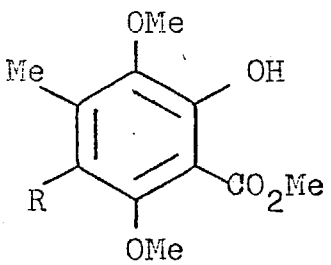
Attempted oxidation of (56) with tetraethyl-ammonium periodate, sodium periodate, thallic acetate or benzoyl peroxide was unsuccessful. Under forcing conditions (56) reacted with lead tetraacetate to give many products.



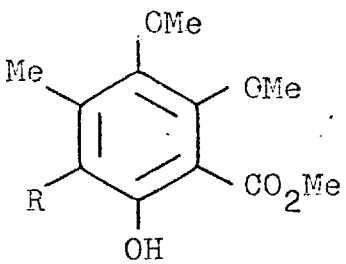
(56)

However, (57; R=CH_3) and (58; R=CH_3) were rapidly oxidised with lead tetraacetate to yield the corresponding

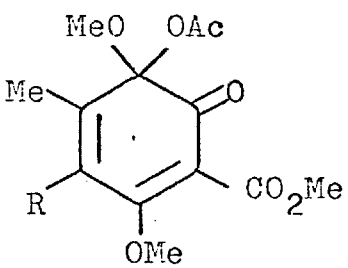
quinone semiketals (59; R=CH_3) and (60; R=CH_3).



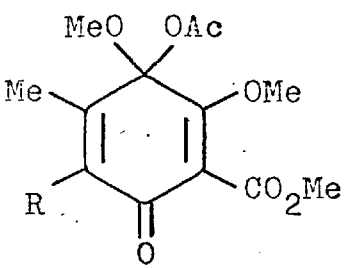
(57)



(58)



(59)



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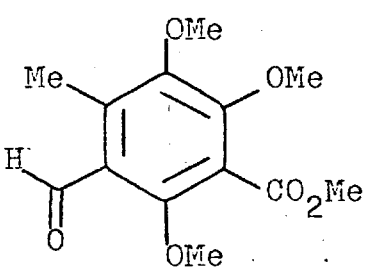
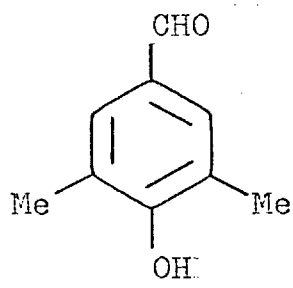


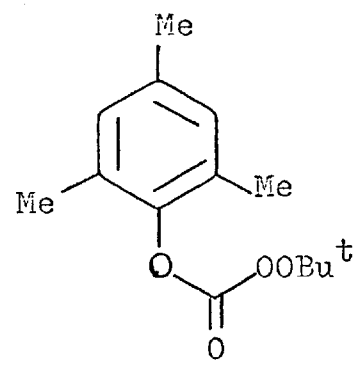
(61)

It was expected that the boron trichloride demethylation of (61) would provide the ortho-demethylated compound (58; R=CHO). In fact para-demethylation occurred and (57; R=CHO) was isolated. This was proved by unambiguous synthesis of (58; R=CHO). Both (57; R=CHO) and (58; R=CHO) were oxidised by lead tetraacetate to give the corresponding quinone semiketals (59; R=CHO) and (60; R=CHO). This procedure thus provided a means of reducing the ring A to the dihydro-aromatic level, but the concomitant '12a-hydroxylation' had not been achieved.

Other approaches involved the preparation of aryl chloroformates. Mesitol chloroformate gave the aldehyde (62), as one of the products from its treatment with sodium peroxide-silver nitrate. The ester (63) yielded mesitol when thermally or photochemically decomposed. Singlet oxygen experiments with mesitol gave the aldehyde (62). Autoxidation of benzhydryl ethers (64) gave benzophenone; the p-cresol entity could not be isolated.



(62)



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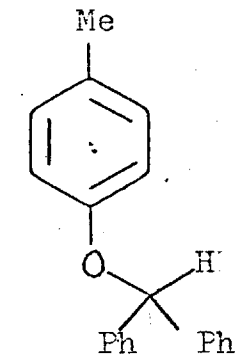
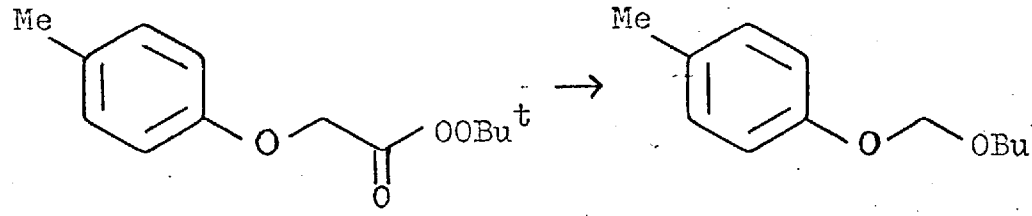


(64)

The perester (65) decomposed to (66) with no intramolecular addition to the p-cresol ring.



(65) (66)

The reaction of arylvinyl ethers with various oxidising systems resulted in no intramolecular oxygenation.

Treatment of p-cresol with benzoyl peroxide in refluxing chloroform yielded, after saponification and sublimation, 4-methyl-catechol. This latter oxidative procedure seemed worthy of further study, and constitutes another part of the author's contribution.

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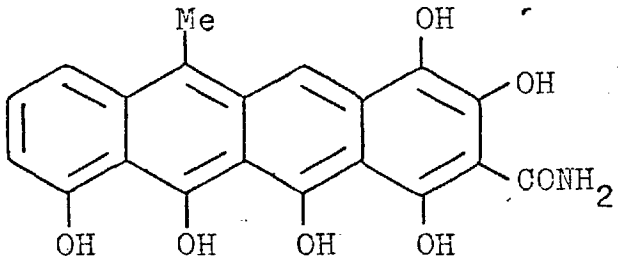
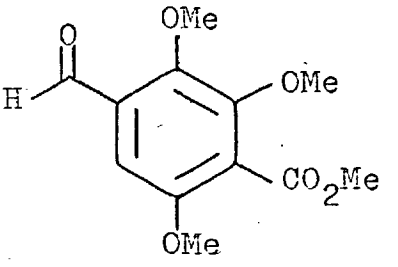
Discussion (Part I).

The Total Synthesis of 4-hydroxy-6-methylpretetramid.

The approach adopted for the total synthesis of 4-hydroxy-6-methylpretetramid (1) was to introduce the ring A oxygenation pattern at an early stage. A suitably constructed ring A (2) was synthesised in six stages from methyl p-orsellinate[1].

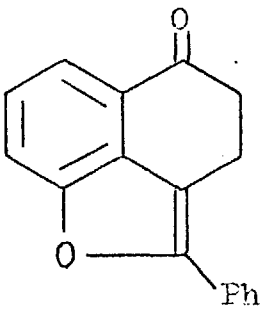


(1)

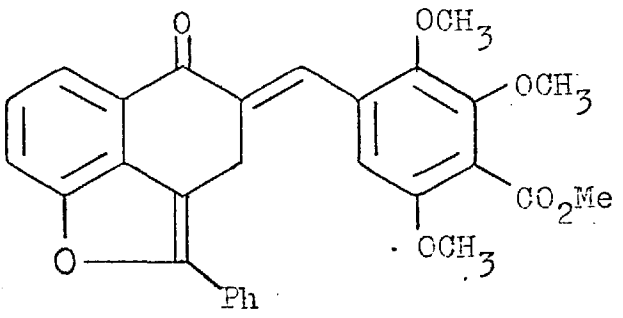


(2)

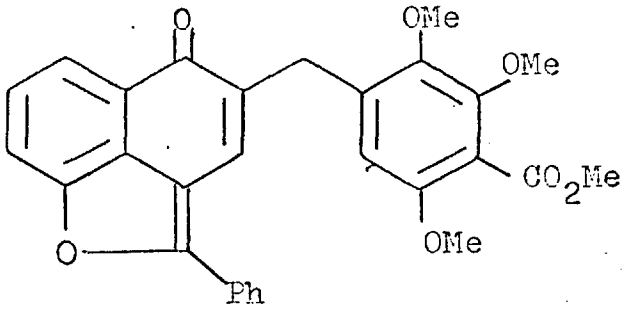
Acid catalysed condensation of the trimethoxyaldehyde (2) with the dihydronaphthofuran (3) afforded the ACD exocyclic compound (4) in high yield. Rearrangement to the endocyclic isomer (5) was achieved by refluxing (4) in dry triethylamine[1].



(3)



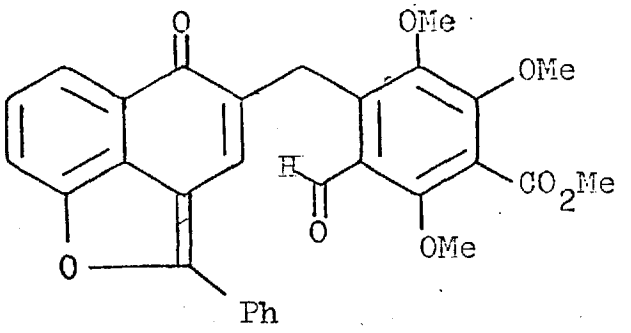
(4)



(5)

The only successful procedure for formylating (5) involved the use of neat α,α-dichloromethyl methylether, with aluminium trichloride as the Lewis acid. A small quantity of nitrobenzene helped to make the reaction homogeneous. Even under these conditions the total reaction time was three days at room temperature. Increasing the temperature caused decomposition to many products. Extensive demethylation also occurs during the reaction and the product must be remethylated before being purified. Small scale experiments (100mg) gave a 70% yield of the aldehyde (6). However, the most

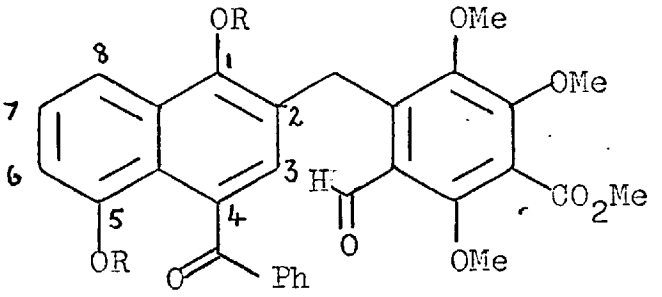
convenient workable scale, yielding 40-45% of the aldehyde (6), utilised approximately 1.5grams of the starting material (5). An attempted large scale reaction (5g.) was very intractable and provided only a small amount of the aldehyde (6; ca. 10%).



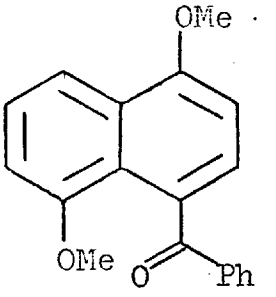
(6)

When the formylation reaction was quenched with ice-water containing a few drops of dilute hydrochloric acid, a different product (7; R=H) was isolated. Methylation with dimethylsulphate in acetone using potassium carbonate as the base gave the ether (7; $R=CH_3$). In the n.m.r. spectrum the formyl proton appeared as a sharp singlet at -0.3τ and there were six O-methyl signals. The characteristic naphthofuran

chromophore was not present in the ultra-violet spectrum, and comparison with the known dimethoxy naphthalene (8) confirmed the structure (7; R=Me). The 5-O-methyl signal appeared at 6.59τ in both compounds.

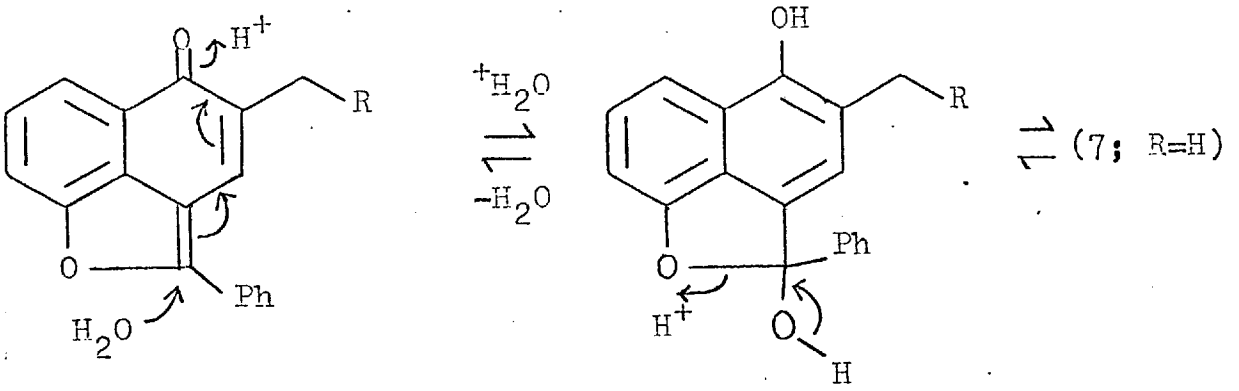


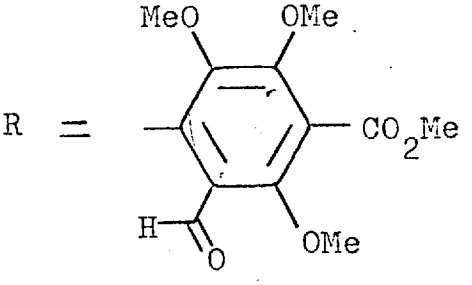
(7)



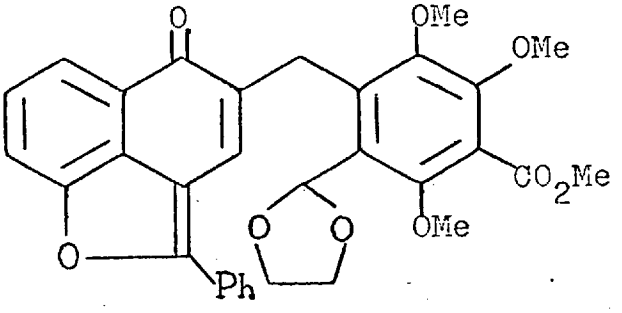
(8)

The formation of (7; R=Me) demonstrates the only intrinsic disadvantage of the naphthofuran, namely, its susceptibility to undergo conjugate addition reactions viz.:





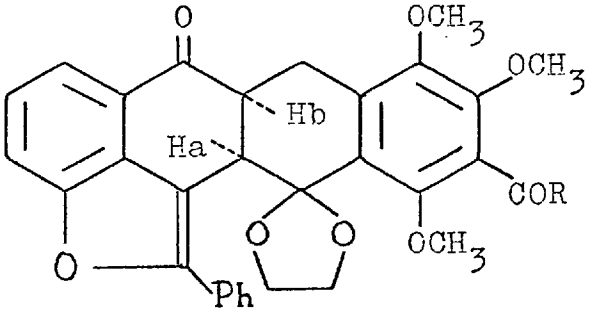
The aldehyde (6) was converted into its ethylene acetal (9) by treatment with ethylene glycol in benzene containing a trace of p-toluenesulphonic acid[1].



(9)

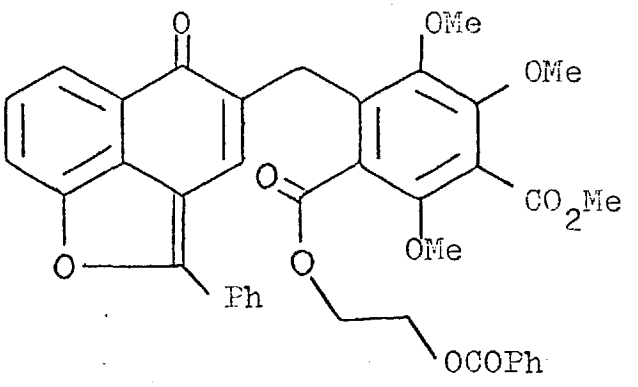
When (9) was photolysed in benzene containing a trace of benzoyl peroxide, using a tungsten lamp, the reaction was slow (4 days) and the yield only moderate

(35-40%). Subsequent studies[2] have shown that the reaction requires one equivalent of benzoic acid, the observed effect of benzoyl peroxide being due to benzoic acid, its major decomposition product. When equivalent quantities of benzoic acid and the acetal (9) were irradiated, the product (10; R=OCH_3) was formed at a reasonable rate (12 hours) and in consistent yields of 65%.



(10)

A yellow by-product was also isolated (25%), in which the naphthofuran chromophore was still intact. The infra-red spectrum had a very intense band at 1715cm^{-1}, suggesting the structure (11). This was confirmed by the n.m.r. spectrum which was practically identical to that of (5) except for four extra aromatic protons and a four proton multiplet at 5.52τ. The formation of (11) is not unexpected, since the photolytic conversion of acetals to esters is a well known process[3].



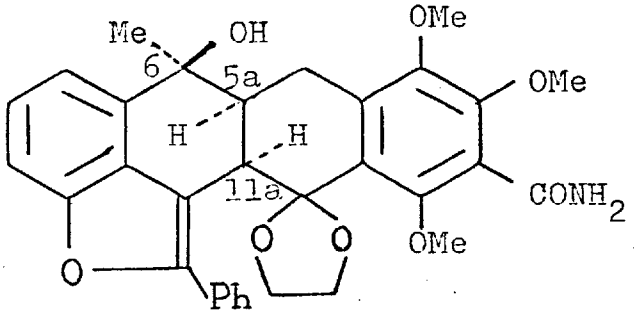
(11)

A mechanism for the formation of (10; R=OCH_3) has been proposed[1] involving thermal enolisation leading to photocyclisation of the resulting triene. Sigmatropic rearrangement and equilibration of the 6a-position then gives the observed product.

At this stage it was decided to substitute the methoxycarbonyl by a carbamoylgroup, for two reasons. Firstly to protect it from attack by methyl lithium, used to generate the 6-methyl alcohol, and secondly because the carbonyl function at C-2 in the pretetramids is an amide and not an ester.

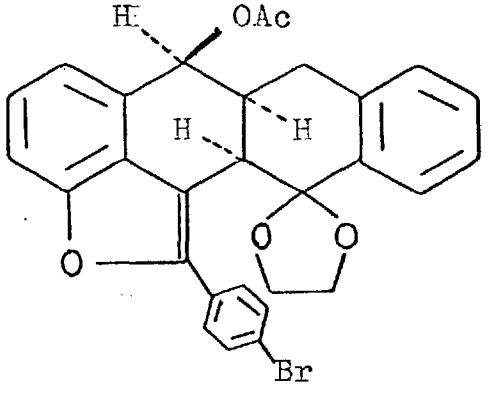
Saponification of the tetracyclic ester (10; R=OMe) in aqueous ethanol, containing a large excess of potassium hydroxide, proceeded smoothly to give the acid (10; R=OH). This was not characterised but treated with equivalent amounts of thionyl chloride-dimethylformamide in benzene at room temperature. Work-up by addition of 0.880 ammonia yielded the amide (10; $R=NH_2$). The amide protons appeared at 3.95τ in the n.m.r. spectrum, and Ha gave rise to a doublet at 5.62τ (J_{ab}=5cps), consistent with a <u>cis</u> BC ring fusion.

Treatment of (10; $R=NH_2$) with ethereal methyl lithium in benzene-ether afforded the required alcohol (12). Even with a large excess of the reagent it was never possible to destroy all of the starting material owing to enolisation of the 6-keto function.



(12)

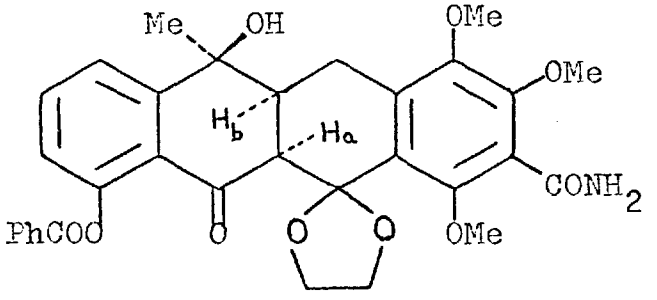
The n.m.r. spectrum of (12) showed the tertiary methyl group as a singlet at 8.27τ, while the hydroxyl proton signal was obscured by the ketal and methoxyl signals. The stereochemistry at C-5a and C-6 is the same as that in tetracycline itself, since all nucleophilic additions to the 6-ketone, in principle, involve reagent approach from the relatively unhindered α-face. X-ray studies[2] on the bromo-acetate (13) have confirmed the cis stereochemistry of the protons at C-5a,6 and 11a, and extending hydride attack at C-6 to Me^-, one would assume the same relative stereochemistry for (12).



(13)

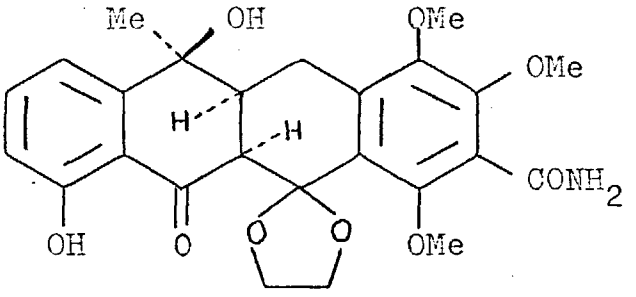
Ozonolysis of the methyl alcohol (12) in chloroform-methanol containing a trace of pyridine at -76° gave an ozonide. The reaction was monitored by observing the disappearance of the 309n.m. ultra-violet maximum, since

it was necessary to avoid excess ozone, which caused decomposition to many products. The ozonide was reduced with triphenylphosphine to yield the ketobenzoate (14). ν_{max} 3450, 3315, 3185, 1738, 1698, 1678, 1658, 1610cm^{-1}. λ_{max} 228, 283 n.m. The n.m.r. spectrum demonstrated the presence of three O-methyl groups, and the tertiary methyl group appeared as a singlet at 8.29τ. Ha gave rise to a doublet at 5.63τ (J_{ab}=5cps) consistent with the stereochemistry shown below (14).



(14)

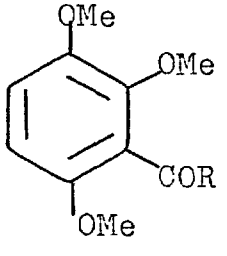
Studies[4] in the dimethoxy series of compounds indicated that the 10-benzoate was relatively resistant to even the most vigorous demethylating conditions. Therefore (14) was saponified with sodium methoxide in methanol to provide the phenol (15) in good yield, ν_{max} 3515, 3480, 3295, 1670, 1640cm^{-1}. λ_{max} 260.5, 334 n.m. The phenolic hydroxyl appeared as a sharp singlet at -2.02τ.



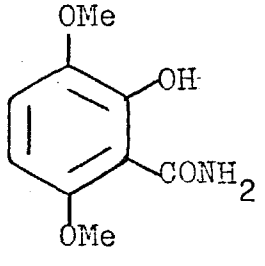
(15)

Before attempting to demethylate any of this material it was decided to investigate the demethylation of a suitable 1,2,4-trimethoxy model compound.

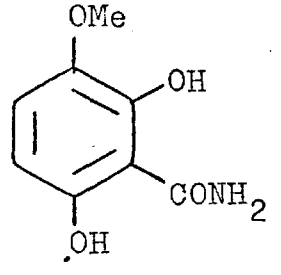
Dakin oxidation[5] and in situ methylation of o-vanillin gave 1,2,4-trimethoxy benzene. Lithiation with methyl lithium followed by carboxylation with dry ice gave the crystalline acid (16; R=OH). Conversion to the amide (16; $R=NH_2$) was effected by treatment of (16; R=OH) with thionyl chloride-dimethyformamide in benzene, followed by work-up with 0.880 aqueous ammonia.



(16)



(17)



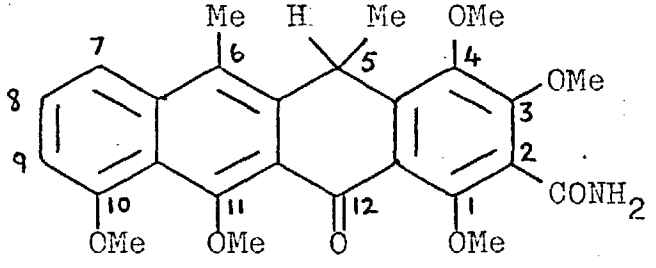
(18)

When the amide (16; R=NH_2) was exposed to an excess of boron trichloride under a variety of conditions, the only product was the monohydroxy compound (17). Hydrogen bromide in glacial acetic acid at 60° and hydrogen iodide in refluxing benzene brought about the same transformation. Confirmation of the structure of (17) is presented later in Part III.

Use of the more potent demethylating agent, boron tribromide at room temperature, gave the di-demethylated product (18) in 44% yield. Increasing the temperature caused decomposition to material which stayed at the origin on t.l.c. The structure of (18) is based upon its n.m.r. spectrum which showed one O-methyl signal at 6.15τ and two exchangeable protons at 2.15τ and -2.7τ. Hydrogen iodide in glacial acetic acid afforded (17) at room temperature and (18) at 100°. However, prolonged reaction at 100° yielded many products.

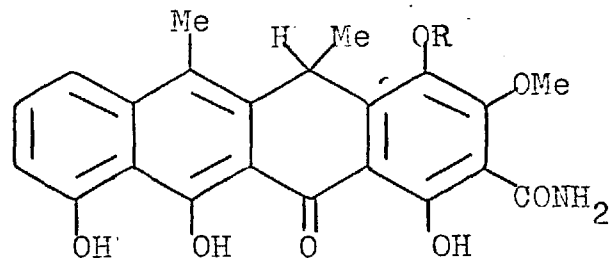
The resistance of (16; R=NH_2) to undergo complete demethylation was rather surprising. However, it was thought that the greater basicity of the naphthacene system might cause this transformation to be accomplished on the keto-phenol (15).

With this in mind 4-hydroxy-6-methylpretetramid (1) was methylated, in the hope of obtaining a better model compound on which to practise the demethylation step. The major product (30%) was a pale yellow crystalline compound with ν_{max} 3445, 3340, 1690, 1672cm^{-1}. The ultra-violet spectrum 377, 310, 274, 249, 228n.m. was indicative of an anthrone chromophore, rather than a naphthacene chromophore. The n.m.r. spectrum showed the presence of five O-methyl groups, two amide protons and an aryl methyl group. A three proton doublet at 8.52τ (J=7.0cps), and a one proton quartet at 5.07τ (J=7.0cps) were indicative of C-methylation. This data allows the structure (19) to be written. The alternative with ring C ketonic was dismissed because of the "peri-interaction" between C-4 and C-5 when C-5 is sp^2 hybridised.



(19)

Exposure of (19) to hydrogen iodide in refluxing phenol for 20 minutes gave a new crystalline demethylated compound. The n.m.r. spectrum indicated that one methoxyl group remained, and more significantly a three proton doublet at 8.62τ showed ring B was still ketonic. The structure (20; R=CH_3) was confirmed by the mass spectrum M^+ 409 m/e, 408 m/e, 391 m/e.



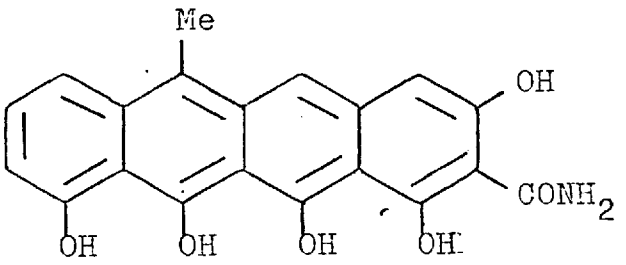
(20)

The fully demethylated compound (20; R=H) separated at reflux when the reaction time was extended (1 1/4 hours) and more hydrogen iodide added. The mass spectrum, M^+ 395 m/e, 378 m/e, and ultra-violet spectrum, run in concentrated sulphuric-boric acid, 533, 353, 319, 277, 273, 265 n.m. support the structure (20; R=H). Ring B is again ketonic, there being a doublet methyl signal in the n.m.r. scan.

Having achieved complete demethylation in a high yield, this procedure was now transferred to the totally

synthetic material, namely (15).

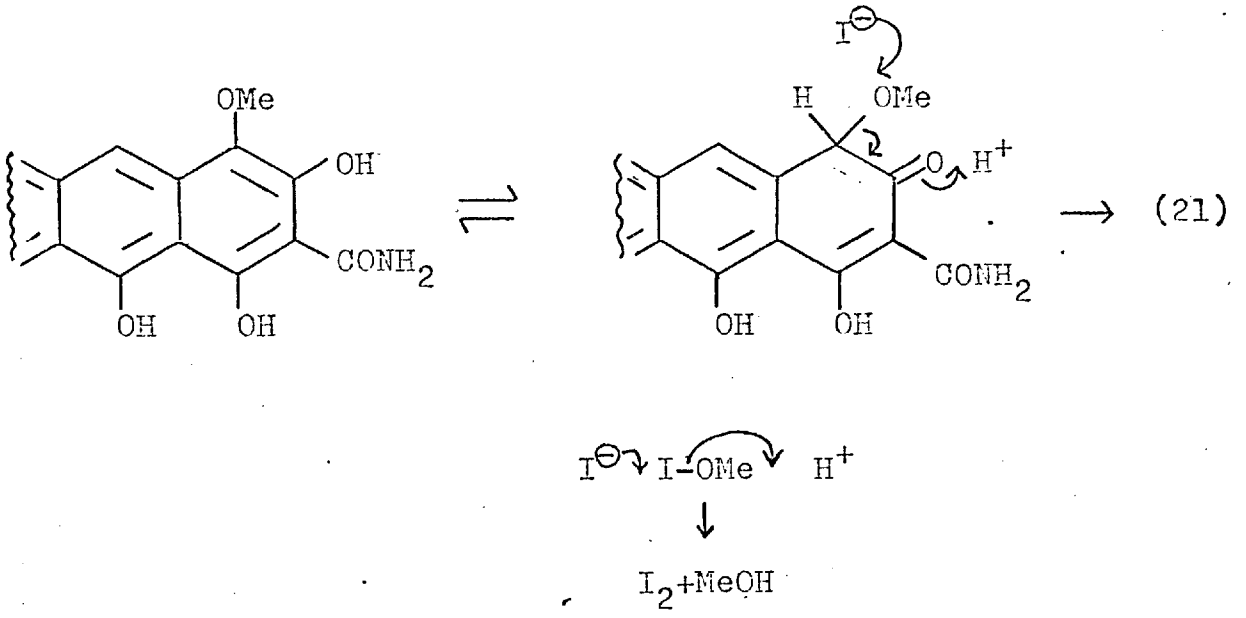
When (15) was exposed to the above demethylation conditions, 6-methylpretetramid (21) was obtained in 20% yield.



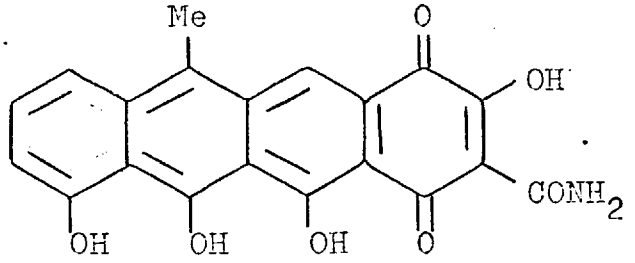
(21)

Recrystallisation from boiling phenol containing a trace of hydrogen iodide provided pure material, identical in all respects with an authentic sample prepared by degradation of tetracycline[6,7,8].

It seems probable that the 4-oxygen function is lost before demethylation occurs at that position, since the conversion[8] of 4-hydroxy-6-methylpretetramid (1) to 6-methylpretetramid (21), by treatment with hydrogen iodide in refluxing phenol, requires a reaction time in excess of that used above (15→21). A number of mechanisms for the reductive removal of the 4-methoxyl can be written. A possibility is as follows:-



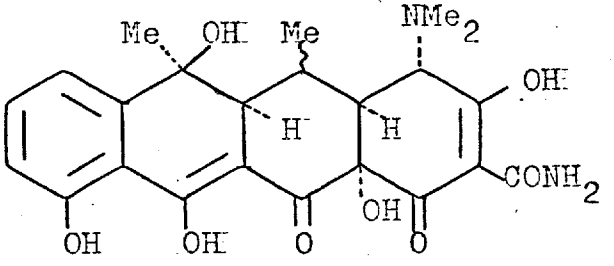
In the case of (20; R=Me) demethylation and not loss of the O-methyl group takes place. The sp^3 hybridisation at C-5 prevents C-4 becoming sp^3 hybridised because of the steric buttressing that would result between the C-4 and C-5 substituents. Since (21) has been oxidised[9] to the quinone (22), and (22) has been reduced to 4-hydroxy-6-methylpretetramid (1), this route constitutes a total synthesis of 4-hydroxy-6-methylpretetramid (1) and 6-methylpretetramid (21).



(22)

The overall yield of (21) from methyl-p-orsellinate in the 18-step synthesis is 0.2%.

It was thought that since a new pretetramid (20; R=H) had been prepared, it might be worthwhile investigating its biological conversion to the corresponding new tetracycline (23).



(23)

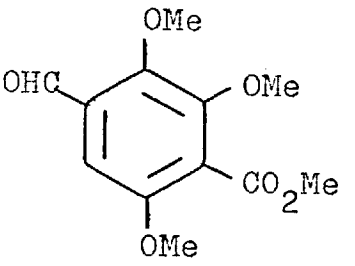
The biological conversion of 4-hydroxy-6-methyl-pretetramid (1) to a tetracycline has been achieved in high yield by McCormick[11]. However, our preliminary experiments utilising (1) were unsuccessful, possibly due to the strain of Streptomyces aureofaciens used. A sample of (20; R=H) was, therefore, sent to McCormick's group. They found[10] that no conversion to a tetracycline took place, under conditions which had previously proved successful[11] with 4-hydroxy-6-methylpretetramid (1). This dramatic effect may in some way be due to ring B being aromatic in (1) and ketonic in (20; R=H).

The compound (20; R=H) also exhibits anomalous behaviour on prolonged treatment with hydriodic acid in boiling phenol. It was unaffected under conditions[8] which bring about the reductive cleavage of the 4-hydroxyl group of (1) (see page 16). This observation, which has been confirmed by Hlavka and his co-workers at Lederle[12], is presumably due to electronic or steric factors brought about by the ketonic nature of ring B.

Discussion (Part II).

An improved ring A synthesis.

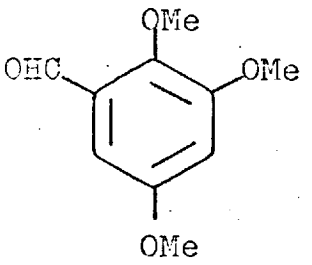
Two sources of the 1,2,4-trimethoxybenzene ring A system have been investigated[1]. The first, necessitating an oxidation-reduction sequence to introduce the required oxygenation pattern, was briefly described in part I. Although the yield at each stage leading to (1) from orcinol is excellent, the synthesis has the disadvantage of involving a considerable number of stages.



(1)

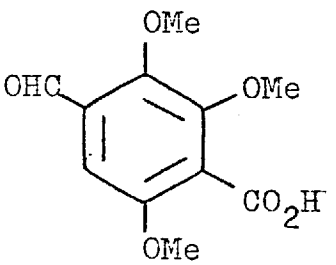
The second route utilised o-vanillin as the starting material. Following the literature procedure[2] o-vanillin was subjected to Elbs persulphate oxidation to

give, after acid hydrolysis and methylation, the aldehyde (2) in 10% yield.



(2)

Conversion of (2) to its ethylene ketal and carboxylation of the latter with methyl lithium - dry ice provided the acid (3).

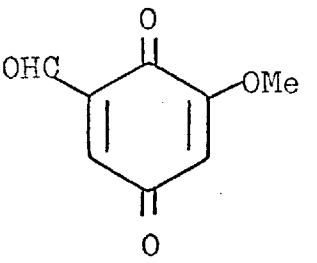


(3)

Treatment of (3) with diazomethane yielded the required trimethoxy aldehyde (1). This synthesis involves only five stages, as compared with ten stages from orcinol.

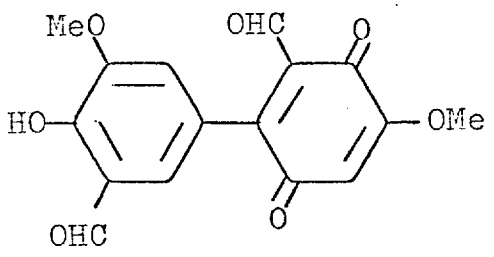
However, owing to the poor yield in the oxidation stage, the overall yield is only 2%. It was thought that this could be improved by processing each reaction.

With this in mind o-vanillin was oxidised with Fremy's salt in the hope of obtaining the quinone (4). Reduction of (4) followed by methylation should then give (2).



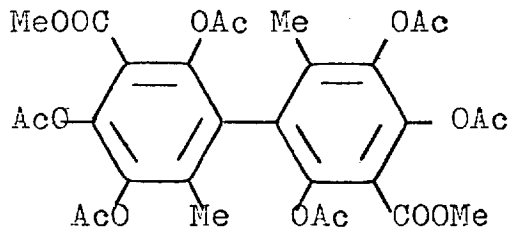
(4)

A pale yellow crystalline product was isolated in low yield, ν_{max} 1660, 1640 cm^{-1}. The mass spectrum exhibited a molecular ion at 316 m/e indicating that the product was dimeric, with structure (5).



(5)

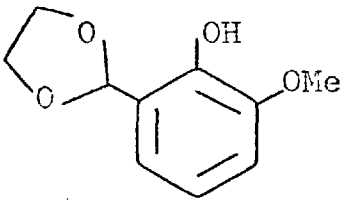
The formation of (5) was not altogether unexpected since it has been previously shown that methyl p-orsellinate dimerises to (6) when treated with basic Fremy's salt. The compound (6) was isolated after reduction, followed by acetylation[3].



(6)

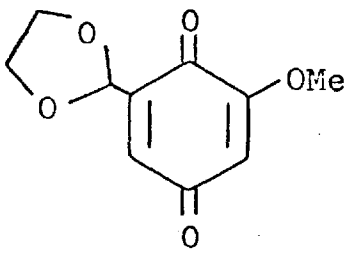
Protection of the aldehyde as its ethylene ketal should prevent dimerisation taking place. Treatment of o-vanillin with ethylene glycol in benzene, containing a trace of p-toluenesulphonic acid monohydrate, with

provision for the removal of water, provided the crystalline acetal (7) in 60% yield.

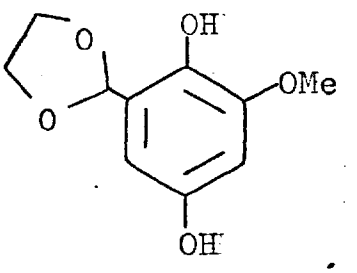


(7)

o-Hydroxyacetals are sensitive to both acids and bases and oxidation of (7) with Fremy's salt under the usual conditions[1] led to dimerisation, owing to the initial loss of the acetal to give o-vanillin. However, adding the solid acetal (7) to the total reaction mixture at pH 7.2, provided an excellent yield of the quinone (8), ν_{max} 1675, 1645, 1600 cm^{-1}.

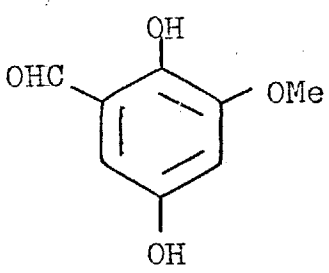


(8)

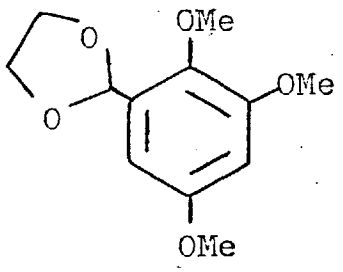


(9)

Singlets at 5.95τ (4H) and 4.06τ (1H) in the n.m.r. scan showed that the ethylene acetal was intact. The two olefinic protons gave rise to signals at 3.20τ and 4.06τ. Hydrogenation was best accomplished over palladium on barium sulphate, to avoid hydrogenolysis, and was carried out in dry benzene. The product (9) was an unstable oil and on treatment with dilute acid (or even contact with hot chloroform) yielded the known dihydroxy-aldehyde (10)[2].



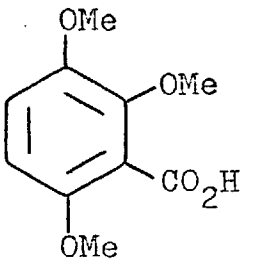
(10)



(11)

The dihydroxyacetal (9) was best methylated immediately with dimethylsulphate-potassium carbonate in refluxing acetone to give the trimethoxyacetal (11).

The total product was chromatographed on alumina to provide pure (11) as a thick oil. The n.m.r. spectrum revealed the presence of the acetal function, three O-methyl groups, and two aromatic protons. Removal of the acetal protecting group under acidic conditions gave the known[2] crystalline aldehyde (2). When the acetal (11) was treated with an excess of ethereal methyl lithium at reflux, and the reaction was quenched with cardice snow, the acid (3) was obtained. The yield was moderate (40%), even though carboxylation[1] of 1,2,4-trimethoxybenzene under indentical conditions affords (12) in 80% yield.



(12)

Methylation of (3) with diazomethane in ether provided (1), identical in all respects with an authentic specimen.

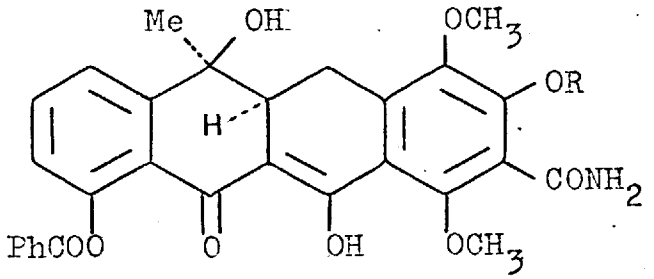
This modification of the second route gives (1) in an overall yield of approximately 20% from o-vanillin and so represents a ten-fold improvement over that obtained previously. Although an extra stage is necessary, the route is more convenient from a practical point of view. The reactions would easily be scaled up to provide large quantities of (11) for carboxylation, the only step which proceeds in relatively poor yield.

Discussion (Part III).

Examination of 12a-hydroxylation.

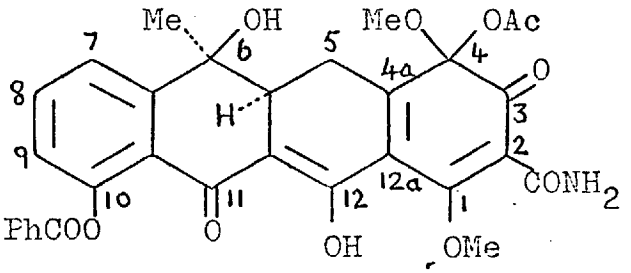
The route adopted has ring A aromatic. The work described in this section discusses a way of introducing the 12a-hydroxyl group into the ring A of a "tetracycline like" molecule, with concomitant dearomatisation to a cyclohexadienone system. The oxidation of phenols to ortho-dienones has been achieved with lead tetra-acetate[1] and sodium periodate[2]. However, as outlined in the synopsis (pages 42 -44), previous work indicated that only lead tetra-acetate showed any utility[3].

It was envisaged that if (1; R=Me) could be selectively demethylated, without dehydration at the 6-position to give (1; R=H), then lead tetra-acetate oxidation should provide the o-quinone semiketal (2).

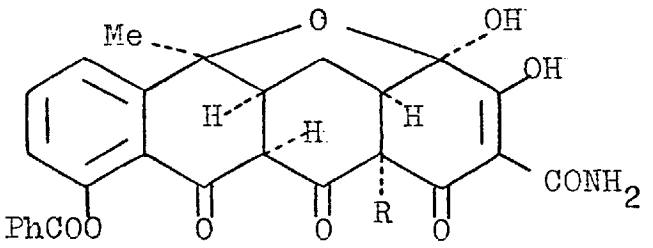


(1)

Reduction of the 4a,12a double bond followed by mild acid treatment should yield the 4,6-hemiketal (3; R=H).

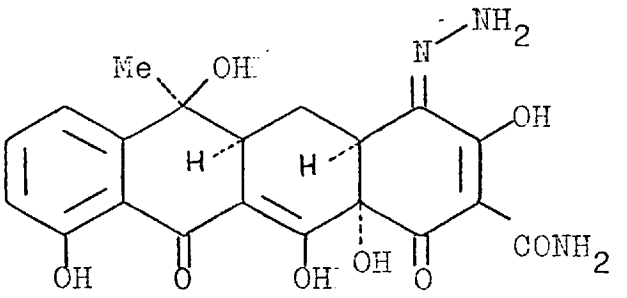


(2)



(3)

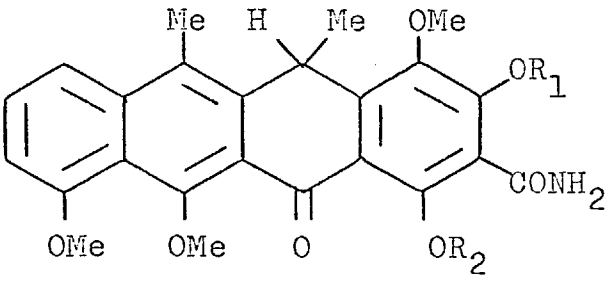
The tetracycloxide (3; R=OH) is prepared from tetracycline hydrochloride by treatment with N-chloro-succinimide in water[4]. Reaction of (3; R=OH) with hydrazine gives the hydrazone (4). Reduction of the latter followed by methylation provides tetracycline.



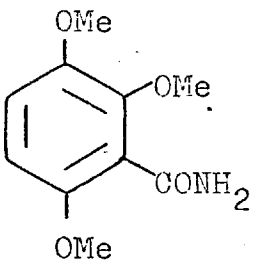
(4)

Therefore, the synthesis of (3; R=OH) would constitute a total synthesis of tetracycline, and synthesis of (3; R=H) a total synthesis of 12a-deoxytetracycline.

In the hope of obtaining a model compound more suitable than those used previously, the pentamethoxy naphthacene (5; R_1=R_2=Me) was reacted with hydrogen bromide in glacial acetic acid at room temperature. A new crystalline demethylated product was quickly formed. On the basis of the n.m.r. scan and the mass spectrum, there are two structures that can be written for this compound, (5; R_1=H, R_2=Me) or (5; R_1=Me, R_2=H).



(5)



(6)

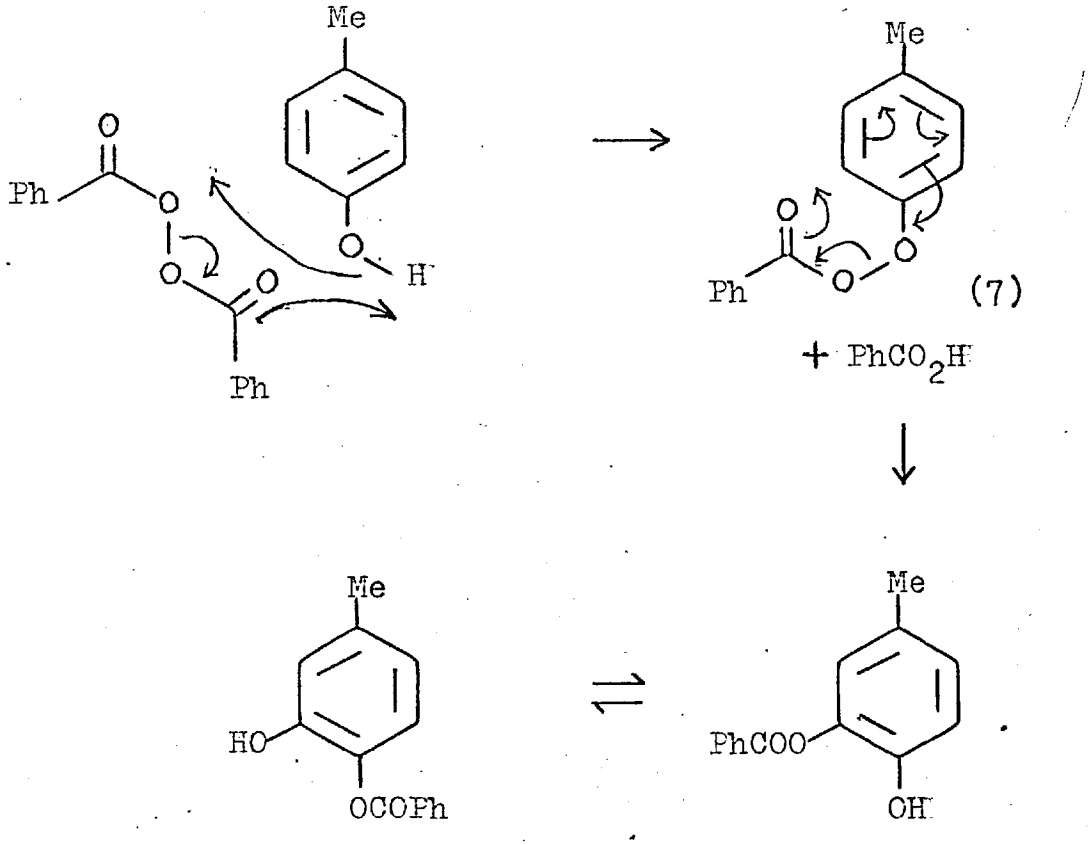
However, oxidation of the demethylated material with lead tetra-acetate gave many products. Similar treatment of the simple amide (6) also yielded a complex mixture.

The use of lead tetra-acetate was, therefore, abandoned and attention was transferred to the oxidation of phenols with benzoyl peroxide, a reaction that had also shown some early promise.

Treatment of phenols (having at least one ortho-position unsubstituted) with benzoyl peroxide in refluxing chloroform affords[5] monobenzoylated catechols. It has been stated that under these conditions, 2,6-dimethylphenol gave 4-benzoyloxy-2,6-dimethylphenol and

the corresponding diphenoquinone. Similarly[6] mesitol was reported to give 4-benzoyloxy-2,4,6-trimethyl-cyclohexa-2,5-dienone. The latter was isolated by distillation or by crystallisation after treatment with benzoyl chloride in refluxing pyridine.

The mechanism of these acyloxylations has been investigated and the reaction is believed to take place as illustrated below with p-cresol[7,8].

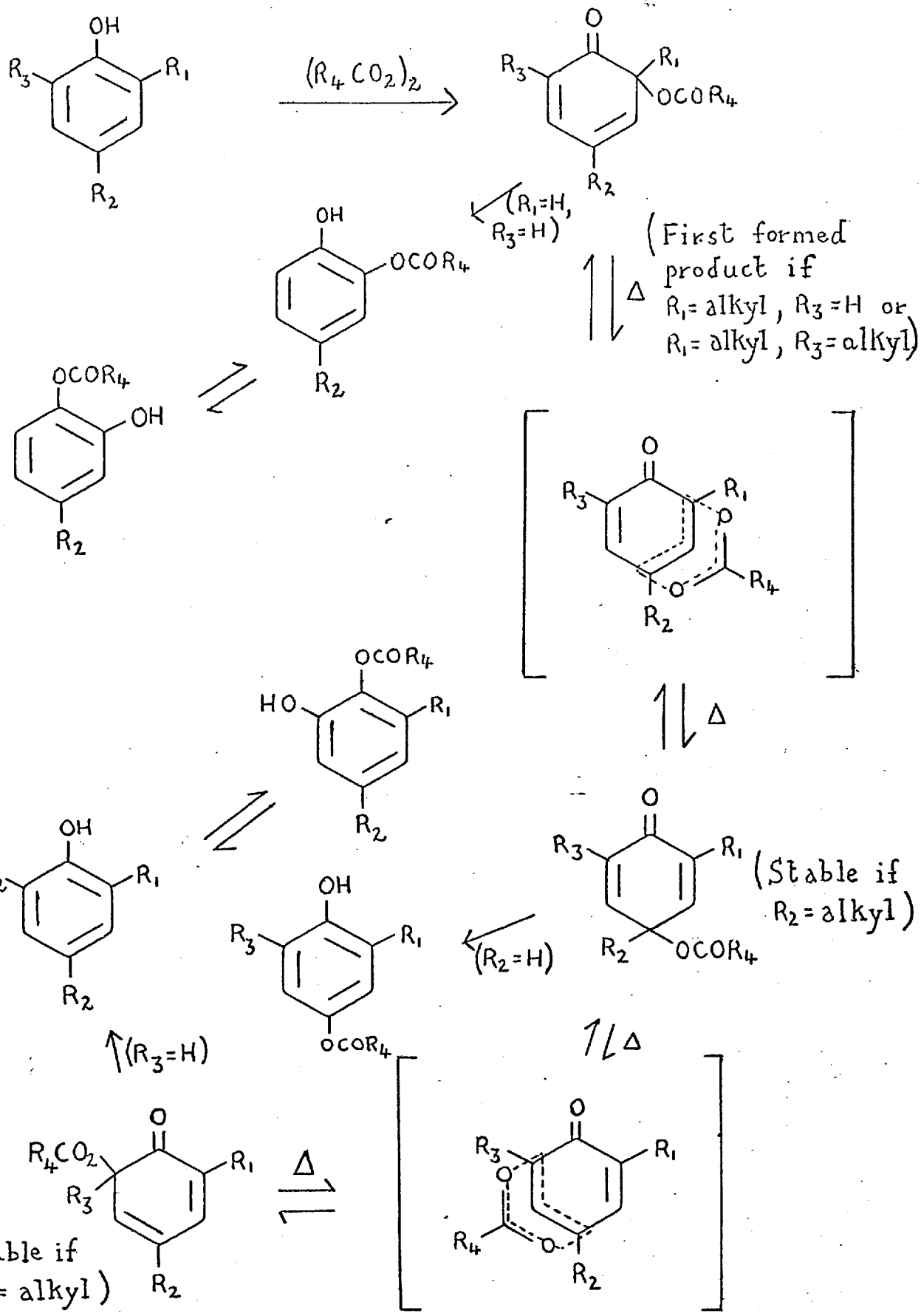


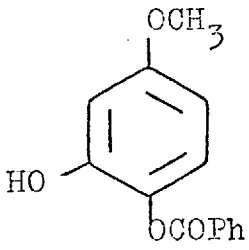
It is generally held[9] that the p-benzoyloxy compounds are formed by p-attack of benzoate anion on the intermediate of type (7), and not by 'Claisen-type' rearrangements of initially formed o-isomers. Indeed where this latter type of rearrangement has been observed, it has involved pyrolysis at 450°, and has been a minor pathway in a free-radical sequence[10,11].

In contrast, based on the discussion to follow, it is evident that the reaction of a phenol with an acyl peroxide always results in preponderant o-acyloxylation. Subsequent products are formed by thermal sigmatropic (3,3) suprafacial[12] migration of the acyloxy group around the periphery of the cyclohexadienone ring. Diagrammatically this hypothesis may be represented as in Figure 1.

It was thought that the more nucleophilic phenolate anion would react with benzoyl peroxide under conditions much less vigorous than those used for the phenol itself. p-Methoxyphenol is rapidly oxidised by benzoyl peroxide in refluxing chloroform to the compound (8)[5].

FIGURE I


OH
R3
R1
R2
(R4CO2)2
O
R3
R1
OCOR4
R2
(R1=H, R3=H)
OH
OCOR4
R2
(First formed product if R1= alkyl, R3=H or R1= alkyl, R3=alkyl)
OCOR4
OH
R2
O
R3
R1
O
R4
O
R2
OCOR4
HO
R1
R2
OH
R4CO2
R1
R2
OH
R3
R1
OCOR4
(R2=H)
O
R3
R1
R2
OCOR4
(Stable if R2=alkyl)
(R3=H)
O
R4CO2
R3
R1
R2
Δ
(Stable if R3 = alkyl)
O
R3
R1
O
R4
O
R2

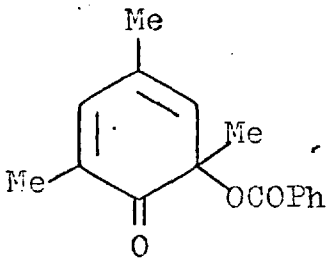


(8)

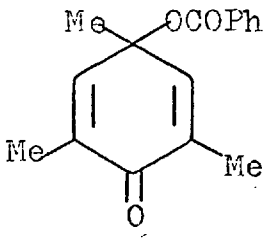
The sodium salt was prepared and reacted with benzoyl peroxide in dry glyme at room temperature. Direct attack on the carbon-oxygen double bond occurred to give a good yield of p-methoxyphenyl benzoate. This result is not surprising and can be compared with the standard preparation of perbenzoic acid, by the action of methoxide ion on benzoyl peroxide[13].

The use of a more hindered phenol was then tried, in an attempt to bring about the desired attack on the peroxide linkage (see page 81). Anhydrous sodium mesitate, prepared by the action of sodium hydride on mesitol, was reacted with benzoyl peroxide in dry ether at -20°. After work-up and chromatography on alumina, the

crystalline product (9) was obtained in excellent yield. ν_{max} 1710, 1667, 1658cm^{-1}, λ_{max} 231.5, 275, 283, 312 n.m. The n.m.r. spectrum showed a three proton singlet at 8.53τ, a six proton multiplet at 8.09τ, two one-proton multiplets at 4.16τ and 3.36τ, and five aromatic protons.



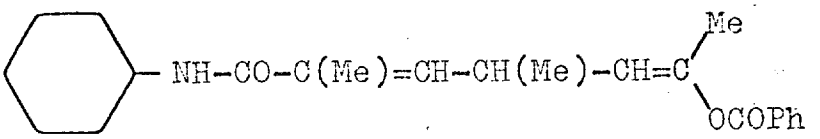
(9)



(10)

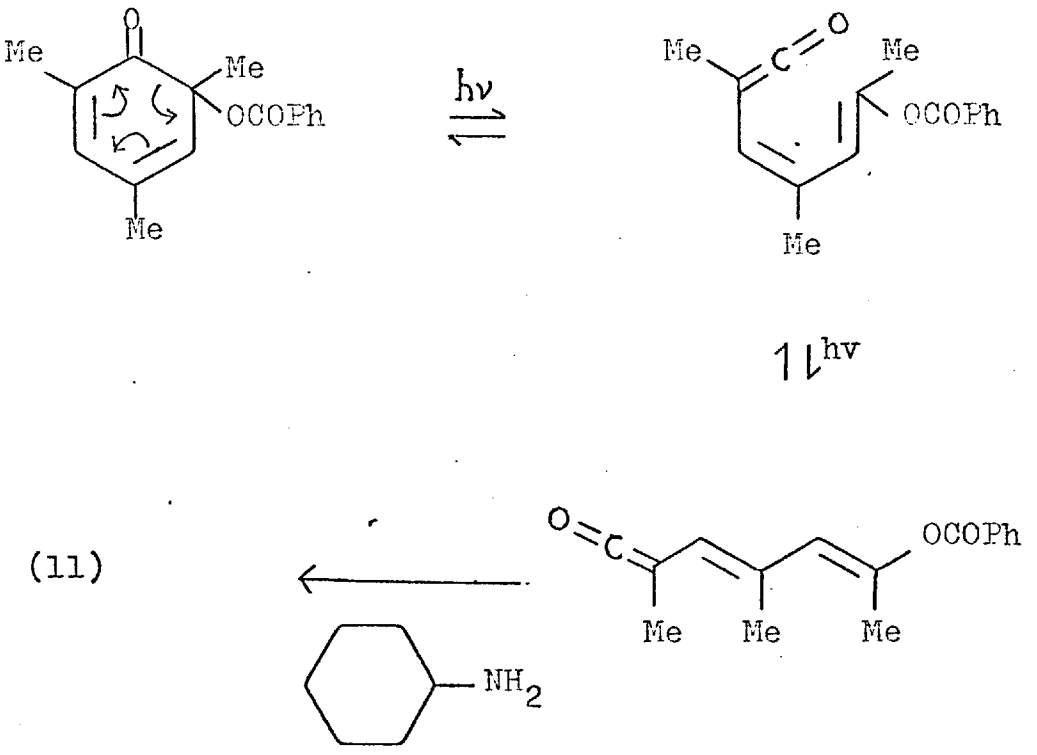
When the reaction reported[6] to give (10) was repeated, (9) was isolated in high yield.

Conclusive evidence that (9) was indeed an o-dienone was obtained by photolysis[14] in tetrahydrofuran containing cyclohexylamine with a high pressure mercury lamp, to yield the amide (11). Its spectroscopic data was in agreement with the assigned structure, ν_{max}^{film} 3400, 3320, 1725, ca. 1650 (broad)cm^{-1}.



(11)

Under the above conditions an o-dienone is rearranged to an unsaturated keten, which is trapped by the nucleophile, cyclohexylamine. The excess of cyclohexylamine used is sufficiently basic to isomerise the unstable $\beta\gamma,\delta\varepsilon$-diene which has unfavourable 1,3 interactions between the three methyl groups, to the more stable unconjugated diene system[14], viz.

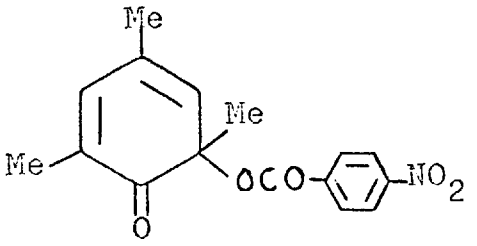


It was found that heating (9) on a Kofler block at 120° (m.p. 113°) for thirty minutes gave a mixture of o- and p-dienones. Since the work-up conditions used by the same workers[6] who isolated the p-dienone employed treatment of the product with benzoyl chloride-pyridine, the o-dienone (9) was exposed to these conditions, and to pyridine at reflux alone. In both cases a steady state was reached after approximately one hour in which 40% of the o-dienone and 60% of the p-dienone were present by

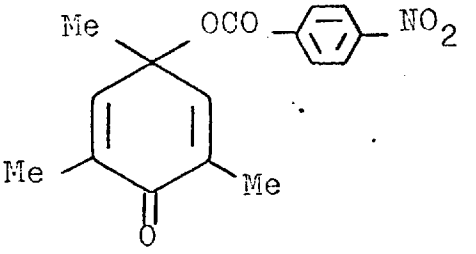
n.m.r. Prolonged reaction did not alter the situation, but merely caused slight decomposition. The same equilibrium was established in toluene in about five hours.

The pure p-dienone (10) was isolated by chromatography on thin silica plates, ν_{max} 1722, 1635cm^{-1}, λ_{max} 239 n.m. The n.m.r. spectrum was that of a symmetrical molecule, showing one methyl group at 8.35τ, two methyl groups at 8.07τ, and two olefinic protons as a singlet at 3.26τ.

Reaction of mesitol with the more electrophilic bis-p-nitrobenzoyl peroxide gave (12) ν_{max} 1720, 1675, 1665, 1530, 1355cm^{-1}, λ_{max} 258, 295(sh) n.m. The n.m.r. spectrum again confirmed the structure. When (12) was rearranged as above, a mixture of o- and p-dienones was formed in the same ratio 2:3, but at a faster rate. Chromatography as in the previous case afforded the pure p-dienone (13) ν_{max} 1728, 1635, 1530, 1355cm^{-1}, λ_{max} 253 n.m. The structure and symmetry of the molecule was evident from the n.m.r. spectrum.

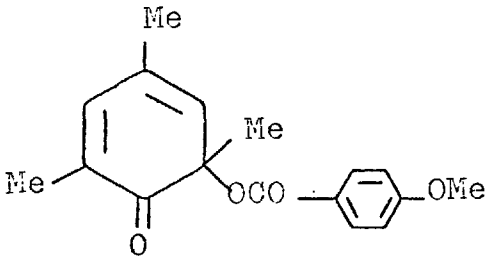


(12)

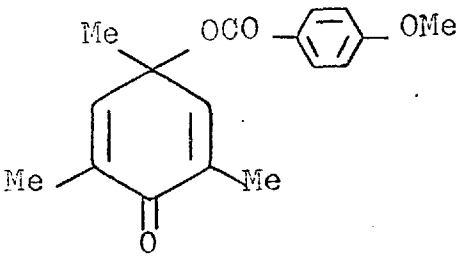


(13)

Since it was intended to study the kinetics of this rearrangement at a later date an o-dienone of type (9) or (12) was required with an electron donating substituent in the phenyl ring. Consequently anisoyl peroxide was prepared and reacted with mesitol to give a good yield of the o-dienone (14), ν_{max} 1700, 1665, 1655, 1600cm^{-1}, λ_{max} 259, 310 n.m. Its n.m.r. spectrum was again entirely compatible with the assigned structure (14).



(14)



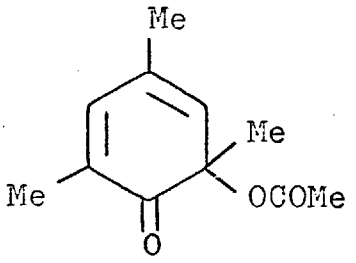
(15)

Rearrangement of (14) provided the expected mixture of o- and p-dienones, at a slightly slower rate than in the case of (9). The pure p-isomer (15) was isolated in the usual way, ν_{max} 1705, 1670, 1635, 1600, 1255cm^{-1}, λ_{max} 258 n.m. The n.m.r. was that expected from a symmetrical p-dienone.

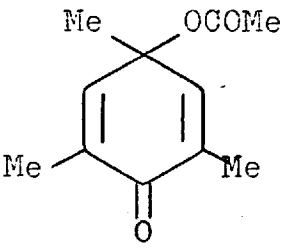
In all these rearrangements it is possible to establish the same ratio of o:p-dienone starting with the pure p-dienone.

When the known o-dienone (16), prepared by oxidation of mesitol with lead tetra-acetate[15], was

exposed to refluxing pyridine for 24 hours, a mixture of o- and p-dienones was formed in the ratio 2:3, according to the n.m.r. scan. The pure p-dienone (17) was never isolated as the mixture did not separate on t.l.c., even on eluting the plate several times. On refluxing the o-dienone (16) in toluene for 24 hours, no rearrangement took place.

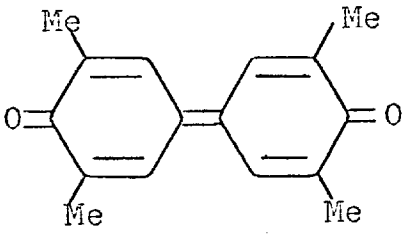


(16)

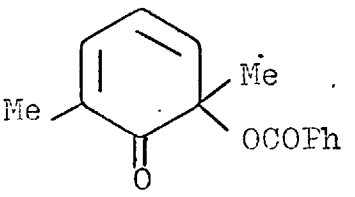


(17)

Having demonstrated the case when R_2=Me (see Figure 1), the case where R_2=H was investigated. Treatment of 2,6-dimethylphenol with benzoyl peroxide in refluxing chloroform gave the red diphenoquinone (18; 50%) and the o-dienone (19;25%) ν_{max} 1725, 1675cm^{-1}, λ_{max} 231, 275(sh), 284(sh), 304 n.m. The methyl signals at 8.68τ and 8.08τ in the n.m.r. spectrum confirmed the structure (19).

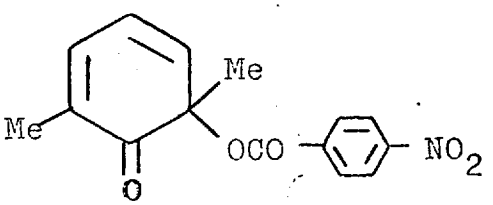


(18)



(19)

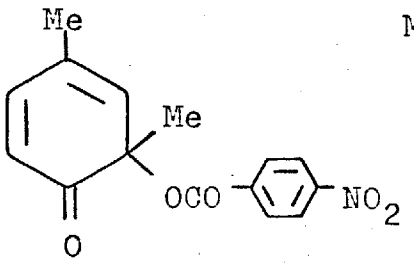
Reaction of the sodium salt of 2,6-dimethylphenol with benzoyl peroxide in ether at -20°, provided a better yield of the o-dienone (19; 50%) and gave only a trace of the diphenoquinone (18; 1%). The use of bis-p-nitrobenzoyl peroxide in chloroform on 2,6-dimethylphenol yielded the expected o-dienone (20), ν_{max} 1720, 1660, 1535, 1350cm^{-1}, λ_{max} 259, 299(sh) n.m.



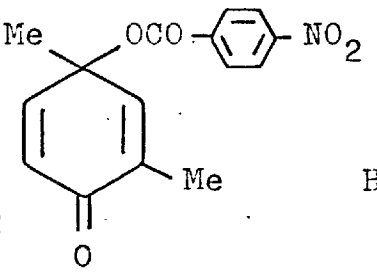
(20)

Prolonged exposure (120 hours) of (19) to refluxing pyridine gave 4-benzoyloxy-2,6-dimethylphenol, along with unchanged starting material. Similar treatment (40 hours) of (20) resulted in the formation of 4-(p-nitrobenzoyloxy)-2,6-dimethylphenol in excellent yield. Attempted rearrangement of either (19) or (20) in refluxing toluene brought about very little change in t.l.c. or the infra-red spectrum after 24 hours.

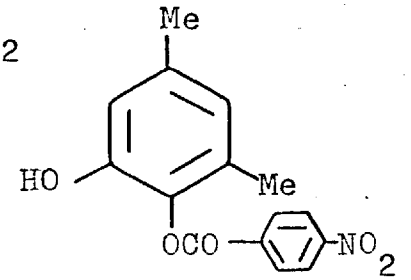
The case with R_1=R_2=Me and R_3=H was now examined. 2,4-Dimethylphenol reacted with bis-p-nitrobenzoyl peroxide in chloroform at 40° to give the o-dienone (21; 33%), a trace of p-dienone (22; 3%) and the catechol mono-p-nitrobenzoate (23; 40%). All spectra were consistent with the assigned structures.



(21)



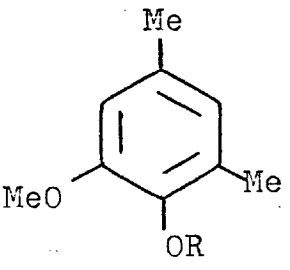
(22)



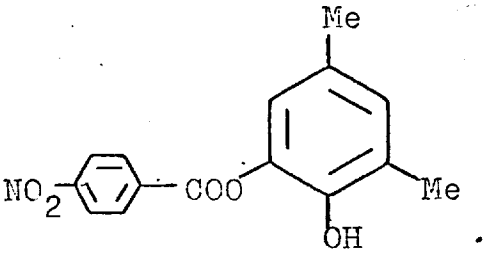
(23)

When (21) was refluxed in toluene, t.l.c. demonstrated that the p-dienone (22) was formed first, and slowly rearranged to the catechol derivative (23). Total rearrangement required approximately 40 hours. On repeating the process in dry pyridine, a period of only six hours was necessary for complete conversion to (23). The final product was identical in all respects with the catechol derivative obtained from the oxidation of 2,4-dimethylphenol.

The structure of (23) was established as follows. Treatment of (23) with diazomethane and saponification of the product gave the known ether (24; R=H), with the same melting-point as literature[6]. The methyl ether (24; R=H) was benzoylated and the benzoate (24; R=COPh) shown to be identical with an authentic specimen, prepared by the procedure of Cosgrove and Waters[6].



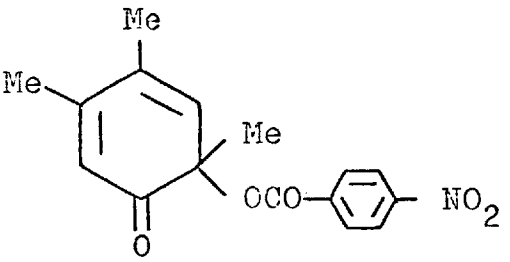
(24)



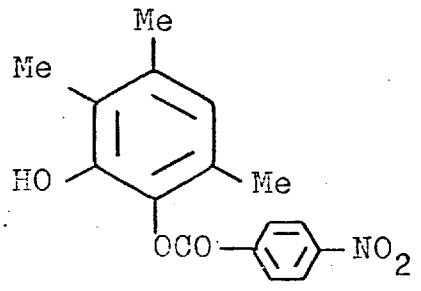
(25)

The formation of (23) is presumably due to migration of the p-nitrobenzoyl group in (25), which should be the initial product of the rearrangement.

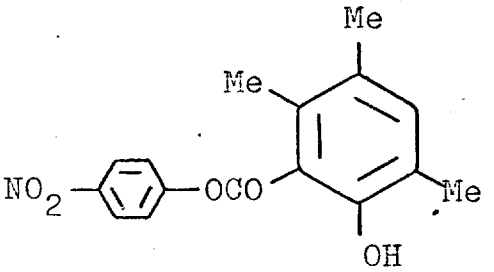
When the case $R_1=R_2=Me$, $R_3=H$ was investigated the o-dienone of 2,4,5-trimethylphenol was also prepared and rearranged. Oxidation of the phenol with bis-p-nitrobenzoyl peroxide under the established conditions provided the required o-dienone (26) and an inseparable mixture of catechol derivatives (27) and (28).



(26)

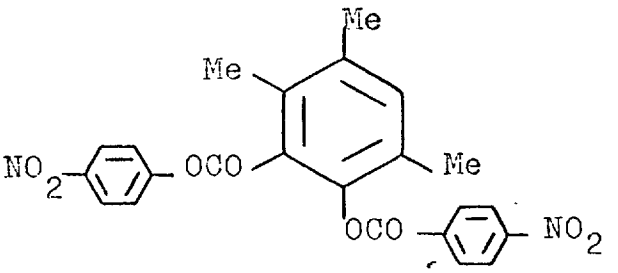


(27)



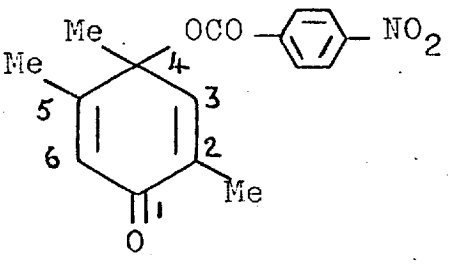
(28)

Treatment of the mixture, (27) and (28), with p-nitrobenzoyl chloride in pyridine afforded (29).



(29)

When the o-dienone (26) was dissolved in toluene and the solution refluxed, rearrangement to the p-dienone (30) occurred.

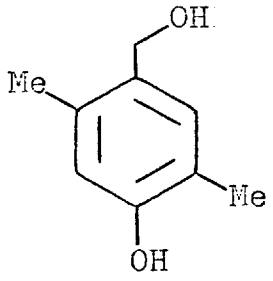


(30)

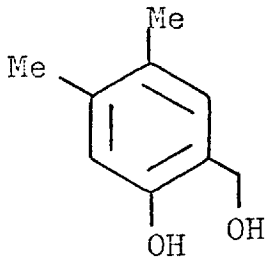
After 14 hours n.m.r. showed that the total product consisted of the p-dienone (30; 83%), along with

some unchanged o-dienone (26; 17%). No trace of either (27) or (28) was detected by n.m.r. or t.l.c. The marked steric effect of the 5-methyl group in blocking rearrangement to the vacant o-position is somewhat surprising, since the resultant aromatisation of the system should provide the necessary driving force.

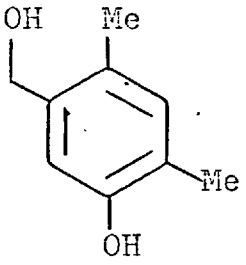
A somewhat more dramatic rearrangement occurred when (26) was refluxed in pyridine. A new product was rapidly formed via the p-dienone (3), but t.l.c. indicated that it was not (27) or (28). The purified product, obtained in 52% yield, had ν_{max} 3520, 1720, 1530 and 1352cm^{-1}. The n.m.r. spectrum indicated that oxidation of one of the methyl groups had taken place, with concomitant aromatisation. The product formed a di-p-nitrobenzoate on treatment with p-nitrobenzoyl chloride (one equivalent) in pyridine, and on saponification with sodium methoxide in methanol gave a phenolic benzyl alcohol, one of the three possible isomers (31), (32) or (33).



(31)



(32)



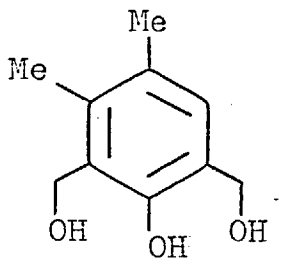
(33)

Each of these was synthesised by an unambiguous route in orderto determine the correct structure of the rearrangement product.

Treatment[16] of 2,5-dimethylphenol with formaldehyde/base provided (31) in excellent yield. The compound (31) formed a di-p-nitrobenzoate and on hydrogenolysis gave 2,4,5-trimethylphenol, identical in all respects with an authentic sample. However, its spectral data and melting-point indicated that it was not the required benzyl alcohol.

Exposure of 3,4-dimethylphenol to formaldehyde/base gave two products, which were isolated by preparative t.l.c. The less polar product was (32), since it formed

a di-p-nitrobenzoate and yielded 2,4,5-trimethylphenol on hydrogenolysis with 10% palladium/carbon in acetic acid. The other compound (34) resulted from further reaction of (32). Treatment with p-nitrobenzoyl chloride in pyridine gave a tri-p-nitrobenzoate and hydrogenolysis afforded 2,3,4,6-tetramethylphenol. The latter had the expected n.m.r. and a melting-point identical with literature[17].

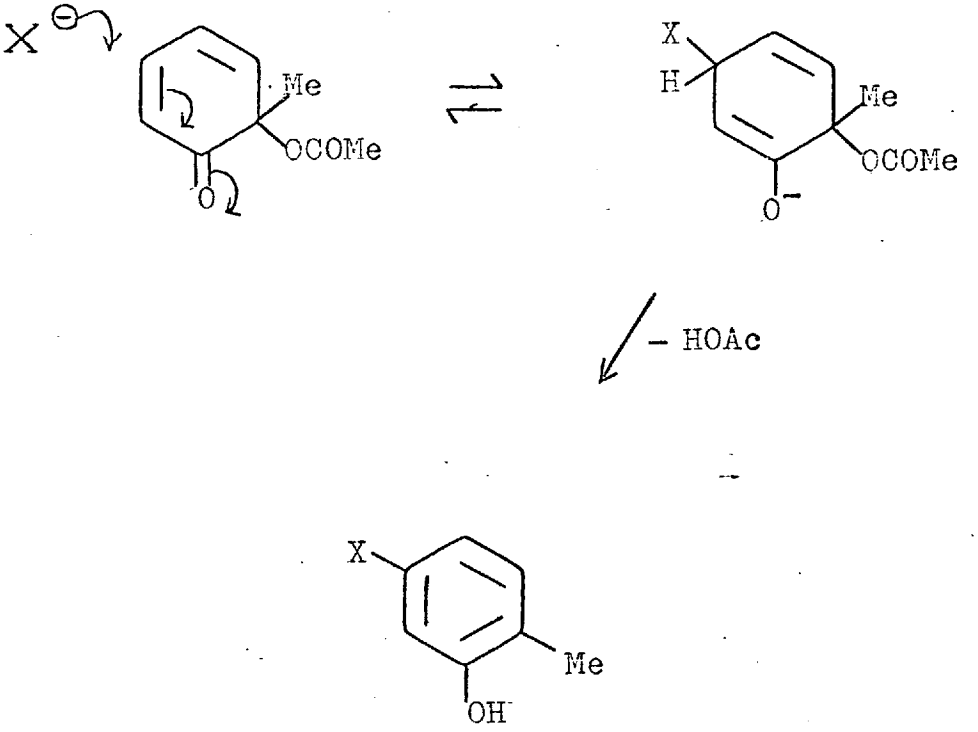


(34)

Comparison of (32) with the saponified rearrangement product by the usual technique (m.p., mixed m.p., infra-red) showed them to be different. There now remained the

problem of unambiguously synthesising (33).

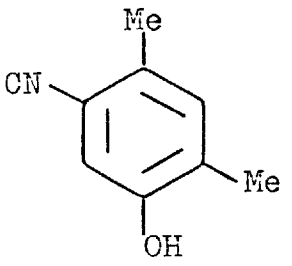
It is known that o-quinol acetates[18,19] react with nucleophiles to furnish m-substituted phenols. An addition/elimination mechanism has been suggested[18], viz.



o-(p-Nitrobenzoyloxy)-dienones should react even more readily than the o-quinol acetates, and it was envisaged that if cyanide ion was used as the

nucleophile, subsequent conversion of the nitrile function to a benzyl alcohol would be relatively straightforward.

The nitrile (35) was prepared by reaction of the o-dienone (21) with potassium cyanide in dry dimethylformamide at room temperature, ν_{max} 3400, 2230cm^{-1}.

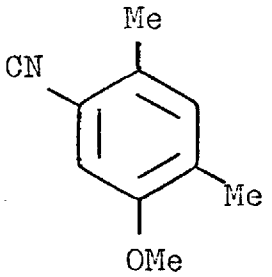


(35)

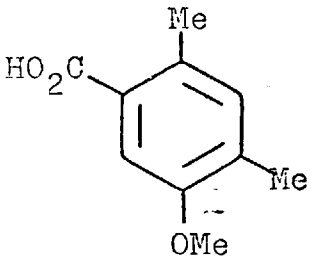
Saponification of (35) in aqueous ethanolic potassium hydroxide led to recovery of starting material in high yield. Overnight treatment of the nitrile (35) with hydrogen chloride in dry methanol gave unchanged starting material on quenching the reaction with water.

Attempted hydrolysis of (35) in concentrated sulphuric acid/water resulted in considerable decomposition and afforded no useful product.

In order to facilitate base hydrolysis the phenolic hydroxyl was protected by methylation with dimethyl-sulphate/potassium carbonate in acetone to provide (36). Treatment of (36) with a large excess of potassium hydroxide proceeded slowly to yield the acid (37), ν_{max} 3000, 1685cm^{-1}.



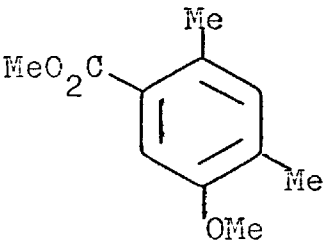
(36)



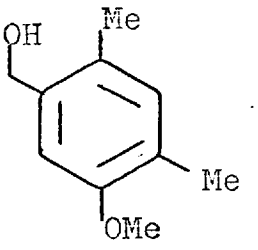
(37)

When (37) was refluxed in dry methanol containing a trace of concentrated sulphuric acid the ester (38) was formed in excellent yield. Since attempted

demethylation of (38) with an excess of boron trichloride at room temperature gave only starting material after work-up, it was decided to reduce the ester (38) directly. Reduction with lithium aluminium hydride in dry ether yielded the benzyl alcohol (39), ν_{max} 3310, 3210, 1620, 1278cm^{-1}.



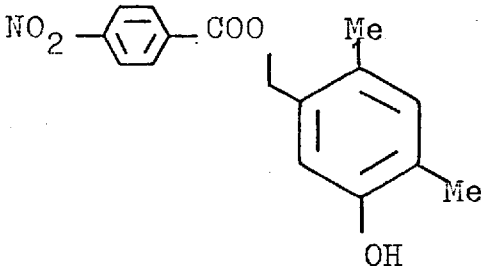
(38)



(39)

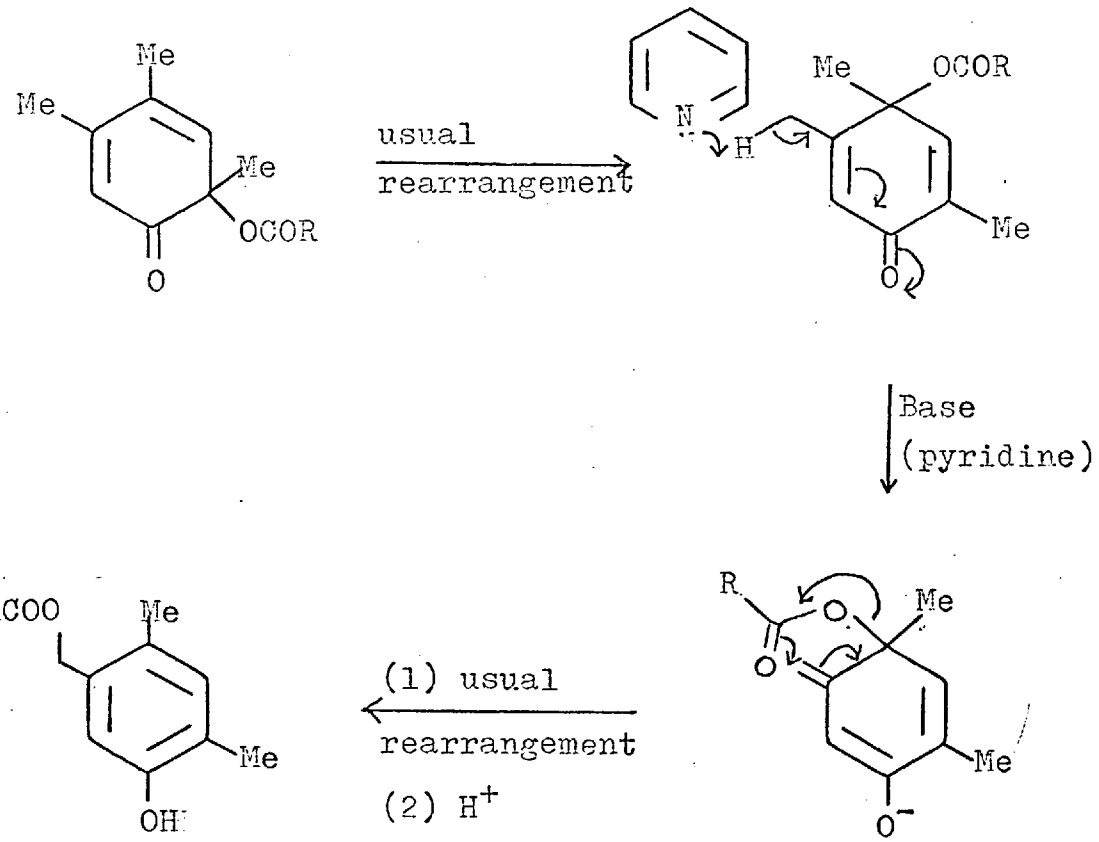
The n.m.r. scan showed the presence of two olefinic methyl groups and one O-methyl group. The benzylic hydrogens appeared as a sharp singlet at 5.39τ, and the aromatic protons gave rise to singlets at 3.27τ and 3.19τ. There was one exchangeable proton at 8.13τ.

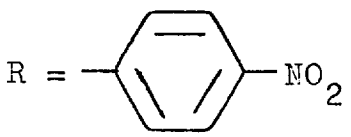
When the saponified rearrangement product was treated with dimethylsulphate under the usual conditions, the product was identical in all respects with the benzyl alcohol (39). Consequently the rearrangement product has the structure (40), and saponification gives the m-hydroxybenzyl alcohol (33).



(40)

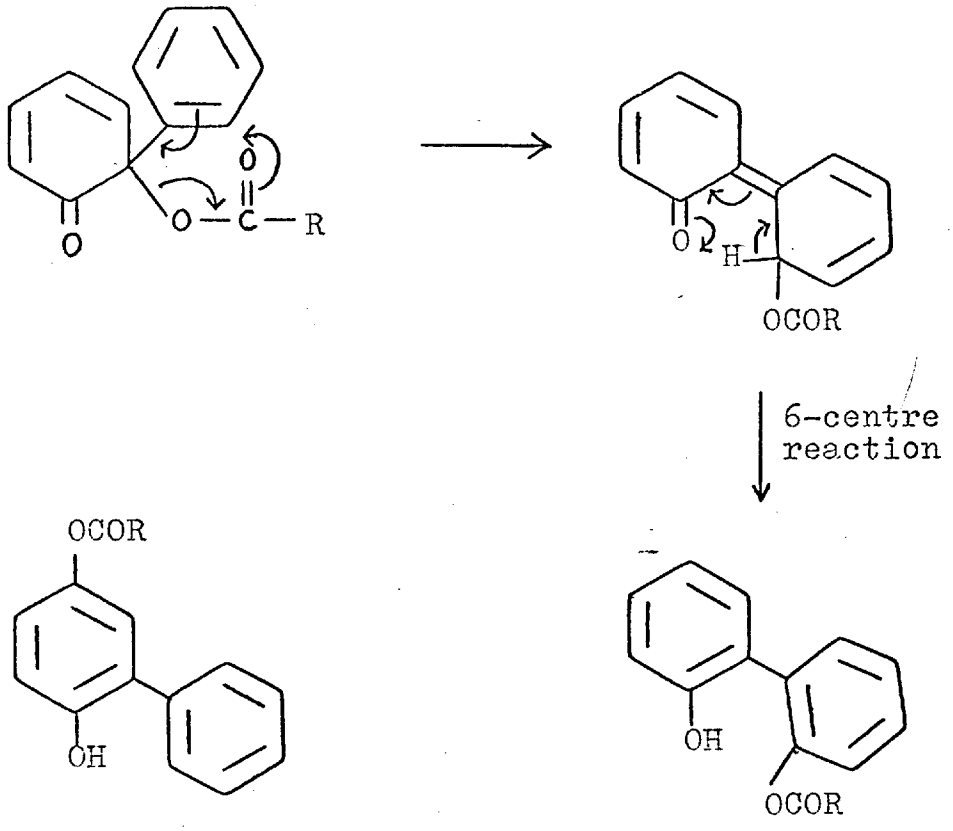
The formation of (40) on refluxing (26), or indeed (30), in pyridine can be rationalised as follows.





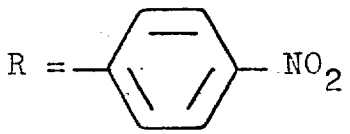
Rearrangement to (40) does not occur in toluene since the removal of a proton from the 5-methyl group cannot take place.

Theoretically for the case R_1=Ph, R_2=R_3=H, R_4= $C_6H_4NO_2$-p (figure 1, page 83), it should be possible to rearrange the p-nitrobenzoyloxy group into the phenyl ring, as well as to the p-position, viz.

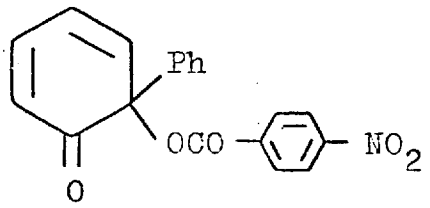


normal rearrangement product

(42)

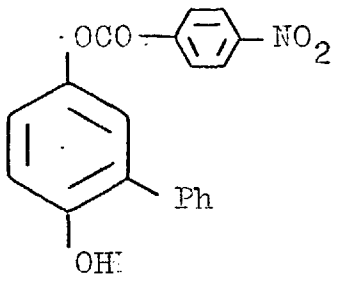


It was decided, therefore, to prepare the o-dienone (41). Oxidation of 2-hydroxybiphenyl with bis-p-nitrobenzoyl peroxide provided (41) in 13% yield, ν_{max} 1715, 1675, 1525, 1350cm^{-1}, λ_{max} 259, 295(sh.) n.m.



(41)

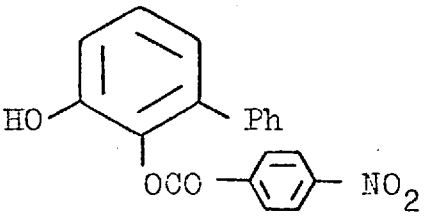
When (41) was refluxed in toluene it was slowly converted to a mixture of two more polar compounds. Separation of thin silica plates gave the less polar product as a thick oil, $\nu_{max}^{CHCl_3}$ 3520, 3260, 1732, 1540, 1350cm^{-1}. Saponification of this oil with sodium methoxide in methanol gave 2,5-dihydroxybiphenyl, identical in all respects with an authentic sample prepared by hydrogenation of 2-phenylbenzoquinone over 10% palladium-carbon. The quinone[20] was obtained by Fremy's salt oxidation of 2-hydroxybiphenyl. The oil must, therefore, be the normal rearrangement product (42).



(42)

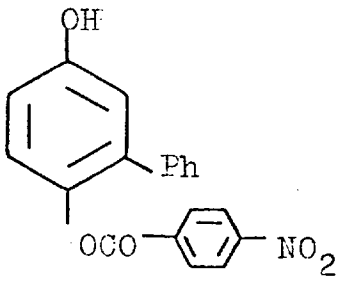
The more polar compound was isolated as a crystalline solid ν_{max}^{Nujol} 3410, 1745, 1720, 1535, 1350cm^{-1}, $\nu_{max}^{CHCl_3}$ 3520, 3260, 1740, 1540, 1350cm^{-1}. Treatment of the product with sodium methoxide gave a dihydroxybiphenyl, the n.m.r. spectrum showing the presence of eight aromatic protons and two exchangeable protons. However, comparison with an authentic specimen of 2,2[1]-dihydroxybiphenyl indicated that they were different. All the possible homonuclear dihydroxybiphenyls are known compounds[21] and the sharp-melting product had a melting-point that corresponded to that quoted in the literature for

2,3-dihydroxybiphenyl[21]. Consequently the second rearrangement product was assigned the structure (43).

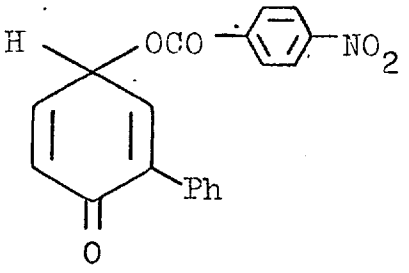


(43)

Rearrangement of (41) in refluxing pyridine proceeded more rapidly than in toluene. The major products were (42) and (43) but a trace of 2,3-dihydroxybiphenyl was isolated along with another compound, ν_{max} 3475, 1735, 1530, 1355cm^{-1}. The formation of the catechol by loss of the p-nitrobenzoate group from (43) was not unexpected in hot pyridine. The unknown compound gave 2,5-dihydroxybiphenyl on saponification and, therefore, has structure (44). Presumably (44) must be formed by a benzoate transfer process, catalysed by the pyridine.



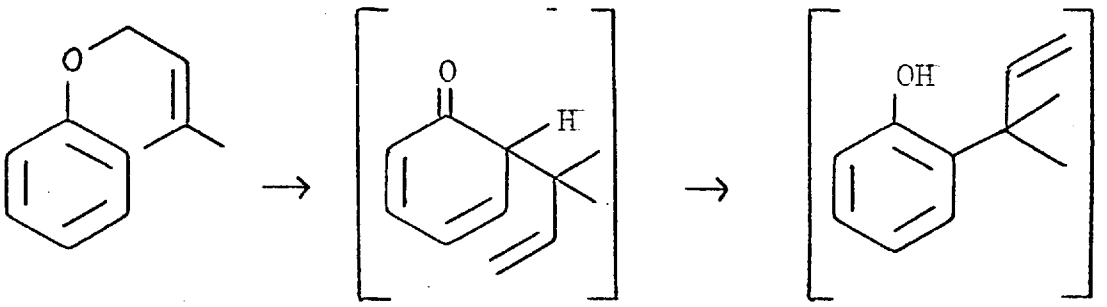
(44)



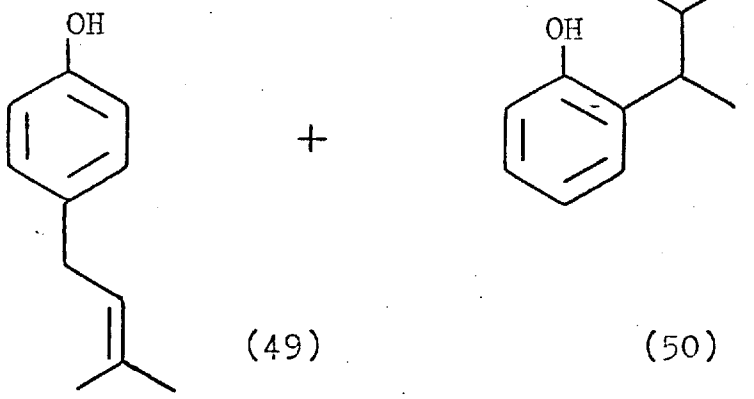
(45)

Unless a completely new mechanism is invoked, the formation of (43) can be explained by assuming that the rate of rearrangement of the intermediate (45) to give (43) is greater than the rate at which enolisation takes place to yield (42). This has some precedent in the Claisen rearrangement of γγ-dimethylallylphenyl ether (46) indiethylaniline, to give a high yield of 4-(γγ-dimethylallyl)phenol (49)[22]. The other product (50) isolated arises from an abnormal Claisen rearrangement. Clearly steric interactions in the ortho-dienone (47) and 2-(αα-dimethylallyl)phenol (48) (which is the intermediate

for the abnormal product (50) allow further sigmatropic rearrangements to give thermodynamically more stable products, viz.

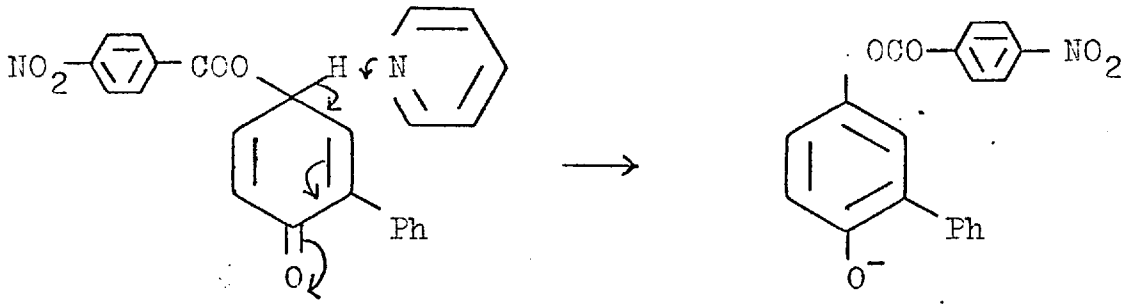


(46) (47) (48)



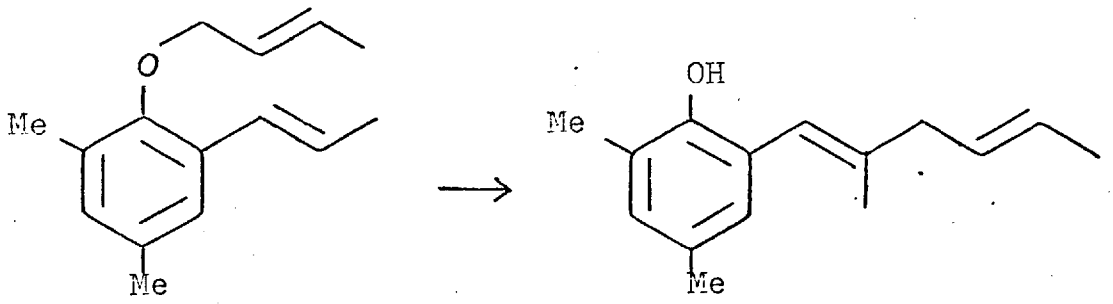
(49) (50)

The formation of (43) in pyridine, in approximately the same yield as in toluene, is surprising, since the rate of enolisation in the former solvent would be expected to be considerably more rapid than in the latter.

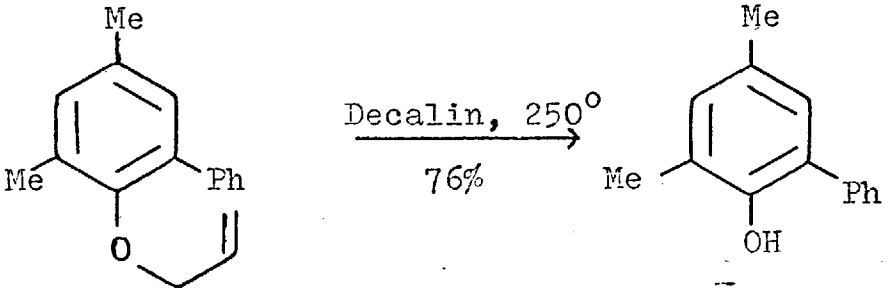


This could be rationalised by an ortho-ortho[1] rearrangement. Although the latter is not allowed by the Woodward-Hoffmann selection rules[12], a number of such rearrangements have been postulated to account for experimental phenomena and reaction products[23,24,25].

No rearrangement of the p-nitrobenzoyloxy group of (41) into the phenyl ring was observed, doubtless because the loss of aromaticity of that ring, necessary for the first step, was energetically too unfavourable. Although the 'out-of-ring' Claisen rearrangement has been observed ((51) → (52))[26], when the olefinic unit acting as the allyl acceptor was part of a second phenyl ring (53), disproportionation to the corresponding parent phenol took place on pyrolysis[27]. This indicates that the second phenyl ring acts as a blocking group and not as an allyl acceptor.

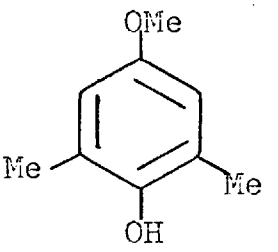


(51) (52)



(53)

Further studies involved the oxidation of phenol itself, and the preparation and oxidation of 2,6-dimethyl-4-methoxyphenol (54) and the boron trichloride demethylation product of (6).



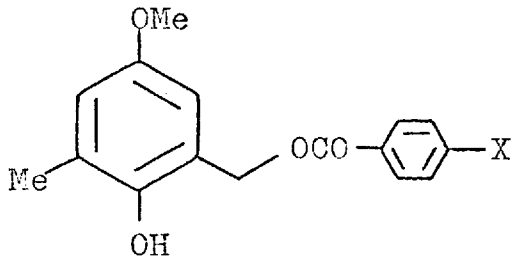
(54)

Phenol was slowly oxidised by bis-p-nitrobenzoyl peroxide in chloroform at 60°, a trace of starting material still being present after three days. Base saponification of the total product followed by sublimation gave catechol in an overall yield of 18%. In an attempt to obtain a better yield, sodium phenate was treated with bis-p-nitrobenzoyl peroxide at room temperature. However, the only product formed was p-nitrophenyl benzoate.

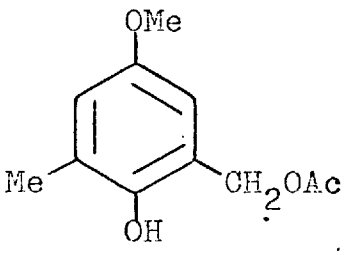
As mentioned previously (page 84) p-methoxyphenol has been oxidised with benzoyl peroxide to give the compound (8)[5]. At this time it was of particular interest to attempt the oxidation of a phenol with an electron releasing group in the p-position, that could form a cyclohexadienone, in order to assess the effect of such

a substituent. 2,6-Dimethyl-4-methoxyphenol (54) was chosen for this purpose and because of its relationship to ring A.

Treatment[28] of 2,6-dimethylphenol with Fremy's salt gave 2,6-dimethylbenzoquinone, which on reduction over 10% palladium-carbon afforded the hydroquinone. Methylation of 2,6-dimethylhydroquinone with one equivalent of dimethylsulphate and anhydrous potassium carbonate gave 2,6-dimethyl-4-methoxyanisole, and the major product (54). Oxidation of (54) with benzoyl peroxide proceeded rapidly in refluxing chloroform to give (55; X=H) in excellent yield, ν_{max} 3370, 1690cm^{-1}. The n.m.r. spectrum showed a two proton singlet at 4.81τ, consistent with the oxidation of an aryl methyl group. Use of bis-p-nitrobenzoyl peroxide at room temperature afforded an analogous product (55; X=NO_2).

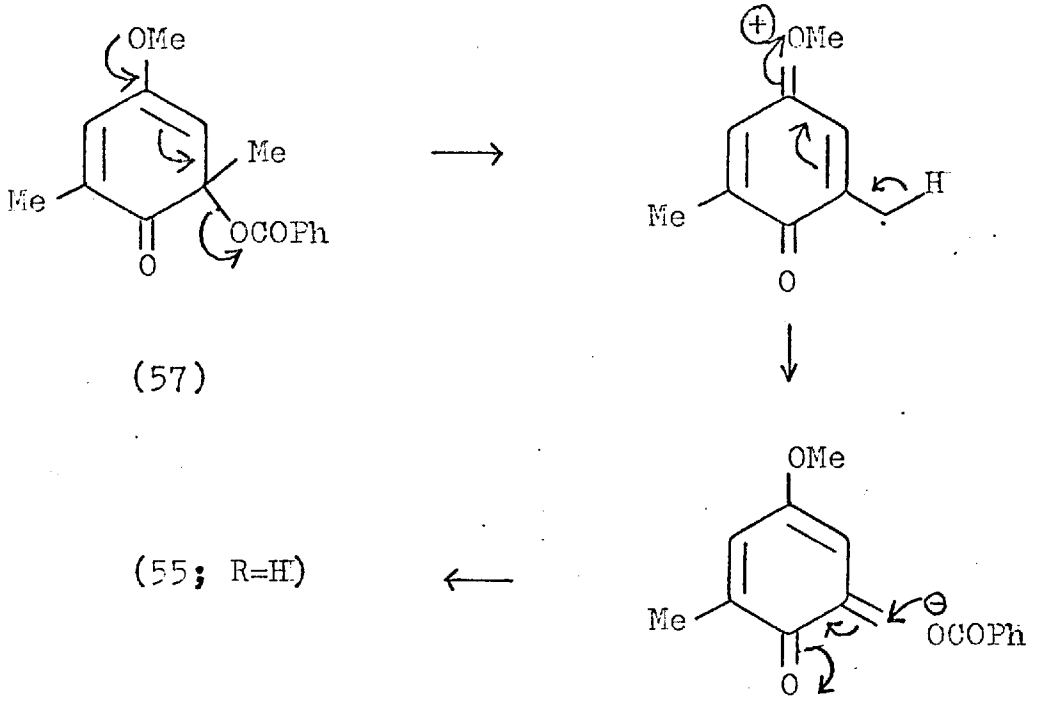


(55)



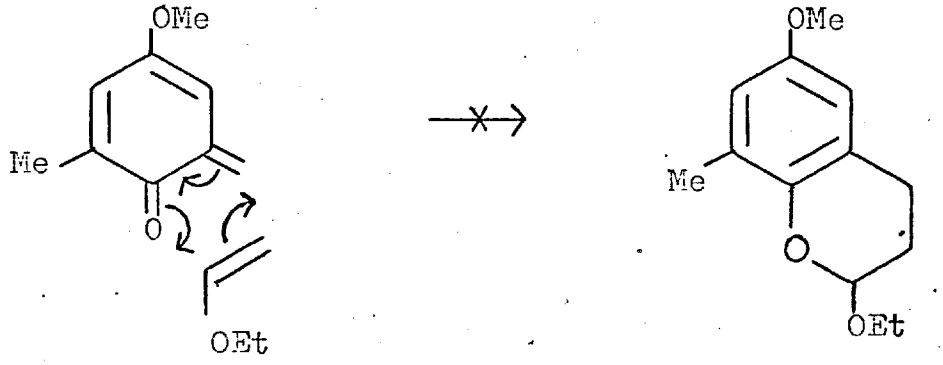
(56)

The result is very unusual but not unexpected since the lead tetra-acetate oxidation of (54) gave (56)[28]. It would appear that in overall substrate to product terms that a C-H bond has been oxidised in preference to an O-H phenol bond. This would not be expected, and in detail has not occurred. The O-H bond is oxidised to the o-dienone (57), then elimination followed by addition gives the more thermodynamically stable-product, viz.



(58)

Attempts were now made to trap the ortho-quinone methide (58). Oxidation of (54) with bis-p-nitrobenzoyl peroxide in ethylvinyl ether afforded a high yield of (55; $X=NO_2$), no trapping being observed, viz.

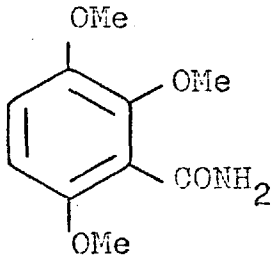


(58)

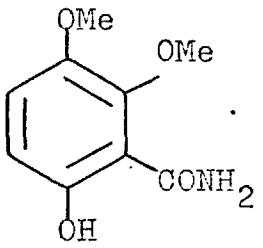
Addition of acetate ion to the reaction mixture in dry glyme gave 32% of (56) and 68% of (55; X=NO_2) according to the n.m.r. scan. The formation of (56), although as the minor product, is good evidence for an o-quinone methide intermediate.

Attention was now focused on the more electrophilic sodium salt of (54). When benzoyl peroxide was added to a solution of the sodium salt in glyme at -20°, two main products were formed, 2,6-dimethylbenzoquinone and (55; X=H), in the ratio 2:1. Repeating the reaction at -76° gave only a trace of quinone and mainly (55; X=H).

Having thoroughly studied the oxidation of several simple phenols by aroyl peroxides, it was decided to investigate the oxidation of a suitable ring A model. The trimethoxyamide (6) was prepared as described in Part I. Demethylation with boron trichloride gave a good yield of a monodemethylated product assigned the structure (59).



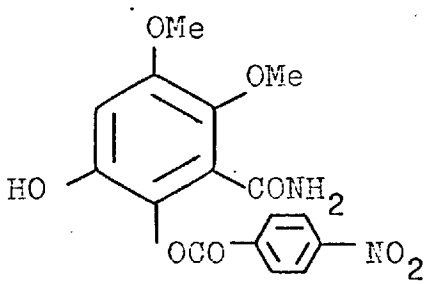
(6)



(59)

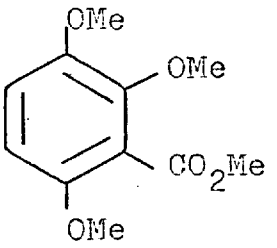
When (59) was treated with benzoyl peroxide in refluxing chloroform the reaction was extremely slow, even with a large excess of the oxidising agent. However, it was encouraging to find that t.l.c. indicated one product was being formed. Consequently attention was transferred to the more electrophilic bis-p-nitrobenzoyl peroxide. Oxidation in chloroform at 60° proceeded smoothly overnight to give one compound. The crystalline product, ν_{max} 3480, 3250, 3195, 1727, 1675, 1530, 1357cm^{-1}, was not an o-dienone. The n.m.r. spectrum showed the presence of two O-methyl groups, but lacked the aromatic

AB quartet of the starting material. One aromatic proton was present, besides those of the p-nitrobenzoyloxy group. The amide was intact and there was one low field exchangeable proton. All this data, and the elemental constitution, $C_{16}H_{14}N_2O_8$ acquired from the microanalysis, allows the structure (60) to be written.

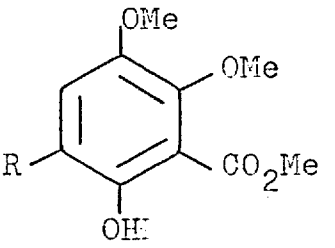


(60)

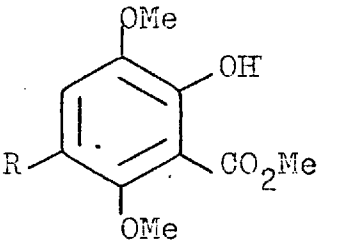
While this oxidation was being carried out, the trimethoxyester (61) was demethylated with boron trichloride, in connection with further model work, to give two products (62; R=H) and (63; R=H) in approximately equal amounts[29].



(61)

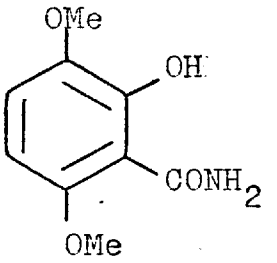


(62)



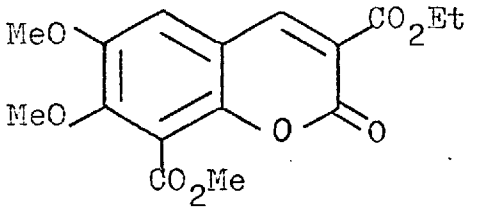
(63)

Therefore, it was thought best to firmly establish the structure of the hydroxybenzamide as (59) and not (64).

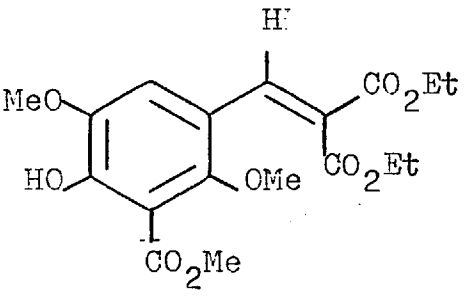


(64)

The two hydroxyesters (62; R=H) and (63; R=H) were reacted with α,α-dichloromethyl methylether/aluminium chloride in dry dichloromethane to provide the corresponding formyl derivatives (62; R=CHO) and (63; R=CHO). The aldehyde (62; R=CHO) gave the 3-carbethoxy coumarin derivative (65) on treatment with diethylmalonate in refluxing ethanol containing a few drops of piperidine and glacial acetic acid. Similar treatment of (63; R=CHO) afforded (66).



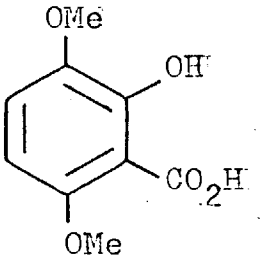
(65)



(66)

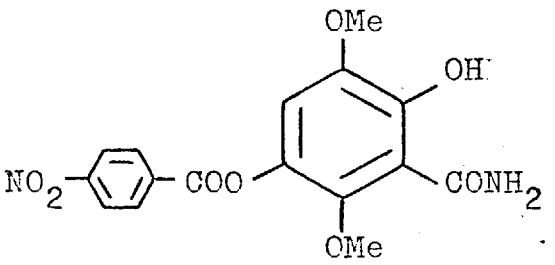
Saponification of the monodemethylated amide with a large excess of potassium hydroxide in aqueous ethanol was extremely slow, giving only 39% of the corresponding acid after 72 hours, the remaining product being starting material. When the acid was methylated with diazomethane

the ester (63; R=H) was formed, identical in all respects with the authentic sample. Consequently the acid must be given the structure (67) and the hydroxyamide structure (64) and not the previously assigned (59).



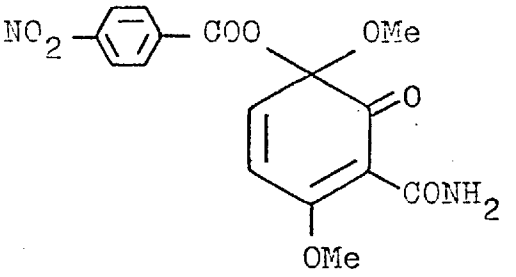
(67)

The structure of the oxidation product (60) must now also be reassigned as (68).



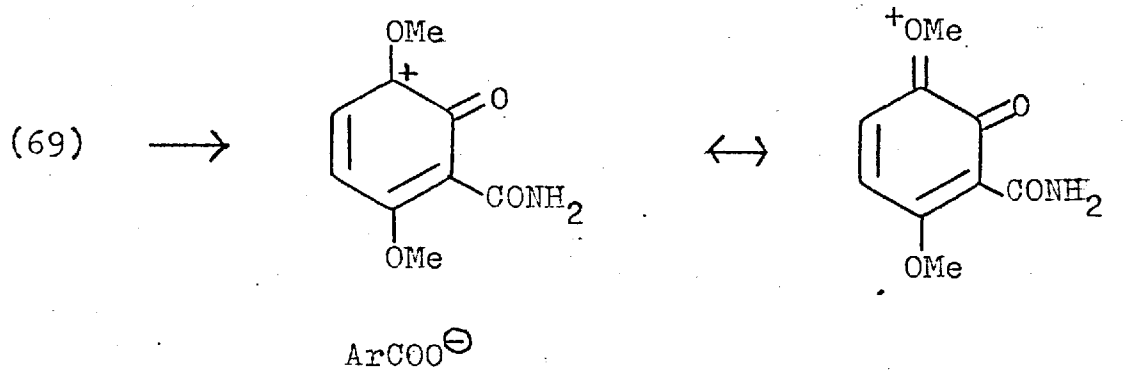
(68)

The formation of (68) is readily explained by assuming that the o-dienone (69) is the initial product which then rearranges to give the observed product with concomitant aromatisation.

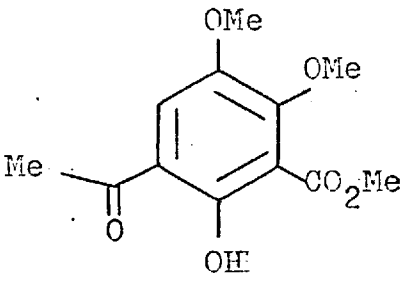


(69)

The rearrangement may be concerted, but an ion-pair mechanism is a possibility, since the positive charge can be stabilised by the methoxyl group.

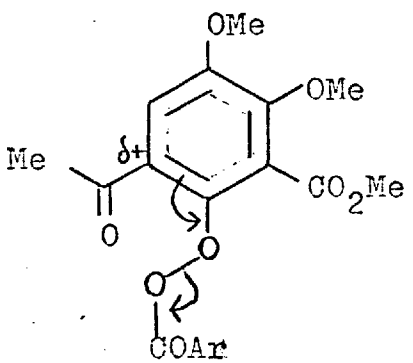


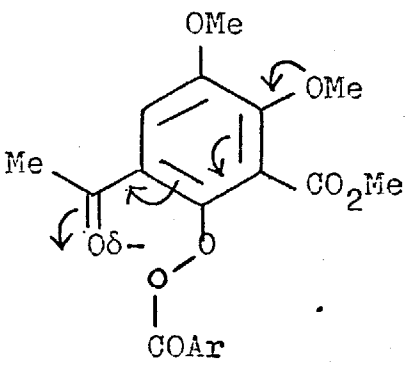
A more advanced model (70) was not oxidised by bis-p-nitrobenzoyl peroxide[29].



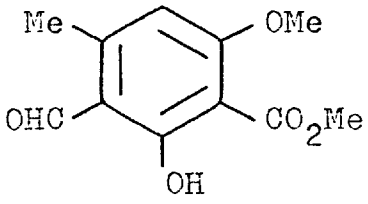
(70)

Since the oxidation of phenols by aroyl peroxides may require the development of carbonium ion character ortho to the phenol, oxidation is doubtless being prevented by the electron withdrawing acetyl substituent, as follows.

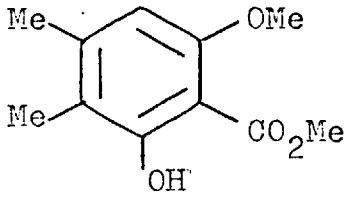




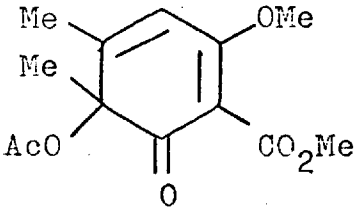
This effect has also been observed in the lead tetra-acetate oxidation studies carried out by L. Bould[3]. The aldehyde (71) was resistant to the oxidising agent but its hydrogenolysis product (72) was readily attacked to yield (73).



(71)

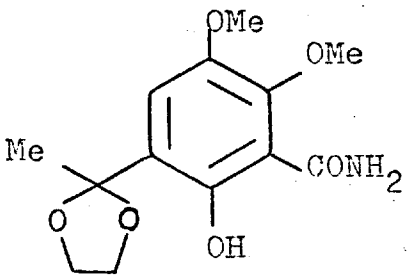


(72)



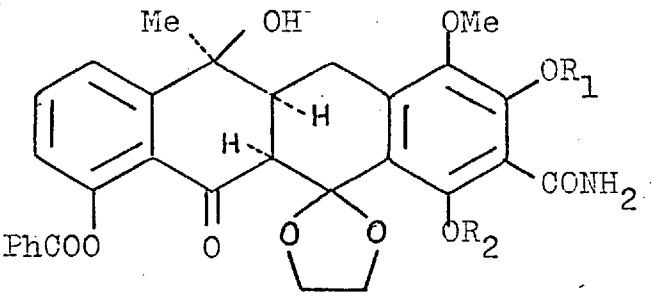
(73)

For further model work the preparation and oxidation of (74) should be worthwhile.



(74)

With regard to the conversion of a trimethoxy ring A tetracyclic compound to tetracycline, the peroxide oxidation procedure may prove useful when a compound of type (75) becomes available.

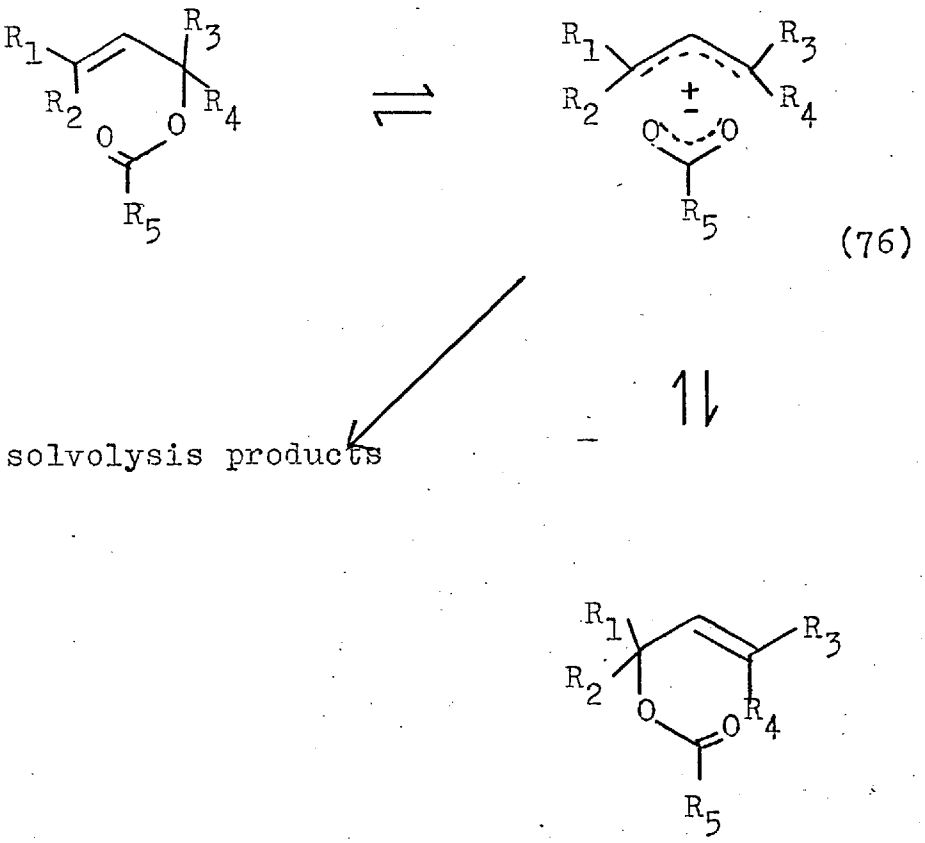


(75) R_1=H R_2=Me or
R_1=Me R_2=H.

Kinetics and mechanism of the rearrangement.

The isomeric rearrangement accompanying solvolysis of esters of allylic alcohols has been extensively studied[33,34]. On the basis of a detailed analysis of the effect of solvents and temperature on racemization,

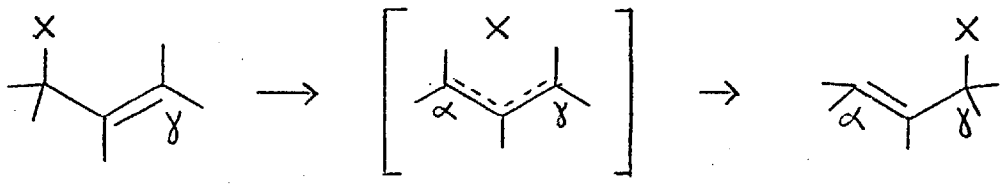
solvolysis and isotopic exchange rate constants, Goering and co-workers[33b] have suggested that in polar solvents solvolysis and isomeric rearrangement proceed through a common intermediate (76) with allylic systems such as 5-methyl-2-cyclohexyl[35-37] and α,γ-dimethylallyl[38,39]. The intermediate (76) has been described as an ion-pair.



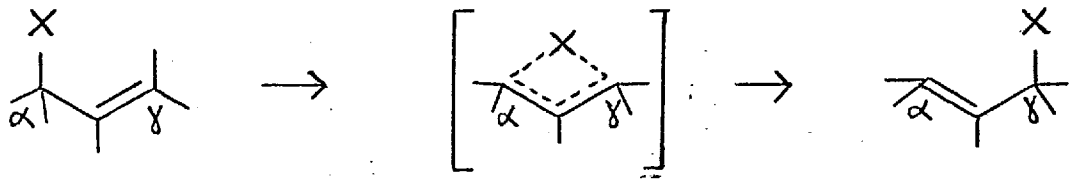
(76)

In the case of the thermal isomerisation of 1-phenylallyl p-nitrobenzoate to cinnamyl p-nitrobenzoate in chlorobenzene solvent, Braude and Turner[40] have observed that the acyl oxygen atom of the starting material becomes exclusively the alkyl oxygen atom in the rearranged product. Whereas they prefer a synchronous cyclic rearrangement mechanism, Winstein[41] has stated that the facts do not preclude an intimate ion-pair intermediate.

Winstein[42] has also pointed out that on should anticipate a spectrum of merging ion-pair and non-ionic cyclic rearrangements. The fundamental difference between mechanisms for cyclic and non-cyclic reactions is one of timing[43]. In an extreme non-cyclic reaction mechanism, the bond between the migrating group and the carbon atom to which it was originally attached (α-carbon) is essentially completely broken before the onset of bonding between the migrating group and the migrating terminus (γ-carbon), as illustrated below.



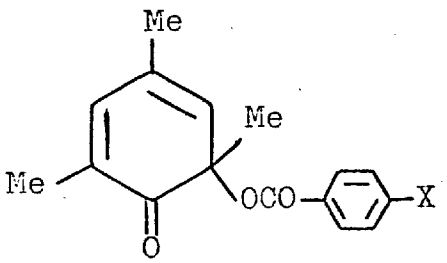
In contrast, the transition state for a cyclic reaction is characterised by significant bonding between the γ-carbon and the migrating group before completion of bond breaking between the α-carbon and the migrating group, viz.



Several examples of the latter type, which involve very little charge separation in the transition state, have been reported. For example, the allylic rearrangement of α,α-dimethyallyl azide[44] and the isomerisation of

allylic thiocyanates[45] and thionbenzoates[46] to isothiocyanates and thiolbenzoates respectively, display very small sensitivities to solvent ionising power, indicative of a relatively non-polar transition state.

In our studies the rearrangement of (21) to (23) in toluene, showed no response to free radical inhibitors. A radical pathway would be expected on pyrolysis in the gas phase at 450°, and indeed under such conditions the o-dienone (16) has been shown to give a mixture of dimeric products[10,11], presumably resulting from cleavage of (16) into acetyl and phenoxyl radicals. Since no such products are formed on rearranging (77; X=H, NO_2, OMe) in refluxing toluene, a radical mechanism appears improbable.



(77)

The rates of rearrangement of (77; X=H, NO_2, OMe) in xylene were followed by means of ultra-violet spectroscopy. In the case of (77; X=H) and (77; X=OMe) the rate constants were calculated by assuming that the equilibrium mixture contains 40% of (77; X=H) and (77, X=OMe) (n.m.r. evidence). No true equilibrium position could be obtained from the ultra-violet spectrum, owing to the formation of traces of coloured products, which obscured the region in the spectrum being examined. This difficulty was not encountered in the case of (77; X=NO_2) and the rate constants were calculated from the observed absorbance values at equilibrium. The results are tabulated below; (see page 213 for calculation details).

X	Temp°C	$10^5 K sec^{-1}$	X	Temp°C	$10^5 K sec^{-1}$
H	86.8	1.19			
H	96	2.75			
H	108	10.38	OMe	96	1.28
NO_2 [a]	79	3.38	OMe	108.5	5.63
NO_2 [b]	86.8	8.33	OMe	115	9.83
NO_2 [c]	97	24.0			
NO_2 [d]	96	111.0			

[a] A_∞ = 44.3% A_0 [b] A_∞ = 50.8 A_0

[c] A_∞ = 54.6% A_0 [d] in dimethylformamide.

A_0 = initial absorbance. A_∞ = equilibrium absorbance.

X	Activation energy[a]	Entropy of activation[b]
H	27.6	-7 (at 96°C)
NO_2	28.2	-2 (at 97°C)
OMe	29.7	-3 (at 96°C)

[a] $k.cal.mole^{-1}$. [b] $cal.\ mole^{-1}deg.^{-1}$

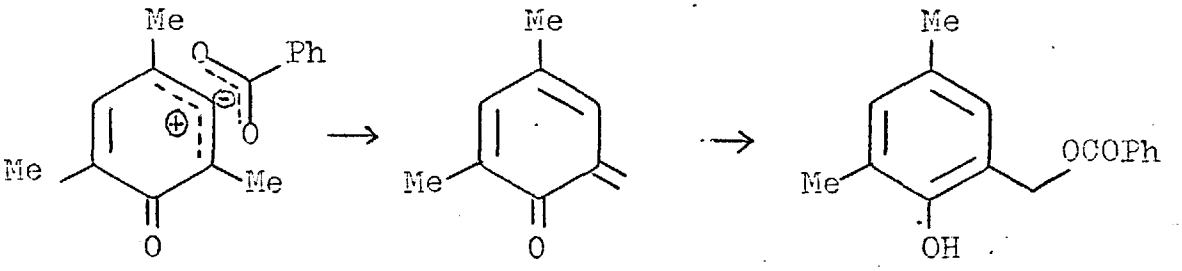
[a] Estimated reliability ± 10%.

The rearrangement is kinetically first order with respect to dienone (77; X=H, OMe, NO_2) and the relative rates for the rearrangement are approximately 10:1:0.5 (NO_2:H:OMe). Pocker[47] has observed an almost identical rate effect in his studies on the rearrangement of 1-phenylallyl benzoate and 1-phenylallyl p-nitrobenzoate, in chlorobenzene, to the corresponding cinnamyl derivatives.

Previous observations (page 91) indicated that the o-dienone (16) rearranged at a considerably slower rate than (77; X=H, NO_2, OMe). The ease of migration of the leaving group is, therefore, acetate $\ll$ p-methoxybenzoate $<$ benzoate $<$ p-nitrobenzoate, i.e., in the order of stability of the leaving group as an anion. This would tend to support an intimate ion-pair mechanism. However, Winstein and Robinson[41] have stated that in their view the best criterion for ionization is sensitivity of the reaction to ionising power of the medium.

Qualitative observation shows that all the rearrangements previously described proceed at a faster rate in pyridine than in toluene. A quantitative estimate of the effect of solvent was obtained by measuring the rate of rearrangement of (77; X=NO_2) in dimethylformamide, a solvent of high dielectric constant, relative to xylene. The rate was enhanced approximately five times, an effect that would be considered small[45a].

The relative insensitivity of the reaction to solvent polarity and the smallness of the substituent effects strongly indicates that the reaction proceeds by way of a cyclic transition state. The D.M.F. presumably stabilises any charge separation in the transition state enabling the reaction to be more polar. Another factor weighing against an ion-pair mechanism is the absence of any products of type (78). If an ion-pair were formed, elimination of a proton to give a quinone methide (79) and subsequent capture of (79) by benzoate anion, might be expected, viz.



(79) (78)

This has precedence in the oxidation of (54) with benzoyl peroxide to yield (55; X=H), via an o-quinone methide intermediate, as described previously (page 117).

The values obtained for the activation energy are reasonably consistent with the observed rate effects, within experimental error. The negative entropies of activation, although very approximate, provide some support for the conclusion that the reaction proceeds through a cyclic transition state. Similar values have been observed for the Claisen and Cope rearrangements[43], and for the rearrangement of allylic thionbenzoates to thiolbenzoates[43].

On the basis of the results obtained, it would appear that the acyloxy group migrates by a mechanism which involves very little change in charge separation between the ground state and the transition state.

EXPERIMENTAL.

Unless otherwise stated, the following data applies to experiments described in this section.

Melting points were measured on a Kofler block and are uncorrected. Infra-red spectra were taken in chloroform or in a nujol mull on a Unicam S.P. 200 spectrometer. Ultra-violet spectra were measured in ethanol on a Unicam S.P. 800 spectrometer. Mass spectra were taken with an A.E.I. MS9 high resolution mass spectrometer. N.m.r. spectra were measured in deuterochloroform solution with tetramethylsilane as internal standard using a Varian A-60 spectrometer. The following refers to the n.m.r. data, which is given in terms of τ values: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), bs (broad singlet) and m (multiplet).

Solvents were dried, when necessary, by standard techniques. Sodium sulphate was used to dry solutions of organic compounds. Evaporation of solutions was effected *in vacuo*.

Petrol refers to the fraction (40-60°).

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

Experimental to Part I.

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

Methyl 2,6-diacetoxy-4-formyldiacetoxy-benzoate was hydrolysed in refluxing aqueous methanolic hydrogen chloride, and the resulting dihydroxyaldehyde converted to the dihydroxyacetal. This was oxidised with Fremy's salt and the product reduced and methylated to give the aldehyde (2). The details are reported by P.D. Magnus[1].

4-(2^1,3^1,5^1-Trimethoxy-4^1-methoxycarbonyl-benzyl)-2-phenyl-naphtho (1,8-bc) furan-5-one (5).

The aldehyde (2) was condensed with the dihydronaphthofuran (3) in acetic acid containing a trace of concentrated sulphuric acid. Exposure of the product (4) to refluxing triethylamine overnight provided (5) in excellent yield. The experimental details are reported by P.D. Magnus[1].

4-(2^1,3^1, 5^1-Trimethoxy-4^1-methoxycarbonyl-6^1-formylbenzyl)-2-phenylnaphtho (1,8-bc) furan-5-one (6).

The endocyclic benzylidene compound (5; 1.5g.) in α,α-dichloromethyl methylether (40ml) and dry nitrobenzene (3ml) was cooled to -76° (CO_2/acetone). Aluminium trichloride (5.5g) was added in portions whilst the solid melted, and warmed to room temperature over 1-2 hours. After 3 days the dark red solution was quenched at 0° in ice-water (50ml) and dichloromethane (50ml). After stirring for 15 minutes the dichloromethane layer was separated, dried, and evaporated, to yield a dark oil. Methylation of this oil in acetone (100ml) containing potassium carbonate (7g) and dimethylsulphate (10ml) was accomplished in 2 hours with stirring at reflux. The cooled suspension was poured into water (100ml) and extracted with dichloromethane (2x100ml). Evaporation of the dried extract gave a dark oil Chromatography of this material on alumina eluting with petrol removed the nitrobenzene. Elution with chloroform gave the aldehyde (6) as an oil. Chromatography on three thick plates (36"x12") of silica gel eluting with chloroform-benzene-ethylacetate (10:6:1)

gave a yellow oil, which crystallised on trituration with ether. Yield 720mg. Thin layer chromatography on silica in benzene-chloroform (1:1) just separates (6) from (5). The aldehyde (6) has m.p. 164°, $\nu_{max}^{CHCl_3}$ 1728, 1688, 1640cm^{-1}, λ_{max} 400, 265, 207 n.m. (ε, 26,100, 14,500, 33,600). The n.m.r. spectrum has signals at 6.30 (3Hs), 6.12 (3Hs), 6.07 (6Hs), 5.65 (2Hd; J=1cps), 0.00 (1Hs) and 9 aromatic protons. When the reaction was carried out on a larger scale (5; 5g) the yield of the aldehyde (6) was only 668mg.

When the formylation reaction was quenched in ice/water containing a few drops of hydrochloric acid a by-product was isolated by thick layer chromatography. Methylation with dimethylsulphate-potassium carbonate in refluxing acetone gave (7; R=Me) m.p. 134.5°, ν_{max} 1728, 1675 cm^{-1}, λ_{max} 328, 313, 303, 230.5 n.m. (ε, 6.620, 10,550, 11,450, 63,300). The n.m.r. spectrum had signals at 6.59 (3Hs), 6.47 (3Hs), 6.18 (3Hs), 6.13 (3Hs), 6.08 (3Hs), 5.94 (3Hs), 5.33 (2Hs), 3.24 (1Hs), -0.42 (1Hs) and 8 aromatic protons. (Found, C, 68.70; H, 5.37; $C_{32}H_{30}O_9$ requires C, 68.81; H, 5.41%).

4-(2^1,3^1, 5^1-Trimethoxy-4^1-methoxycarbonyl-6^1-formyl-ethylenedioxy- benzyl)-2-phenylnaphtho (1,8-bc) furan-5-one (9).

Treatment of the aldehyde (6) with ethylene glycol in benzene, containing a trace of p-toluenesulphonic acid monohydrate, with provision for the removal of water, gave the crystalline acetal (9) in 95% yield. The details are reported by P.D. Magnus[1].

cis-6a,12a-(12-Ethylenedioxy)-8,9,11-trimethoxy-10-methoxycarbonyl-6a,7,12,12a-tetrahydro-1-phenylnaphthaceno (1,12-bc) furan-6-one (10; R=OMe).

The acetal (9; 355mg) dried overnight in vacuo, was dissolved in dry benzene (140ml), and dry benzoic acid (120mg) added. The solution was irradiated under nitrogen with a 750 watt tungsten lamp. All the starting material had disappeared after 12 hours and t.l.c. indicated the formation of a bright blue fluorescent compound (steel blue with acid). The reaction was worked-up by evaporation and chromatography on thick silica plates, to yield the ketal (227mg) m.p. 249-250°

(dichloromethane-diisopropylether). The spectral data of (10; R=OMe)are reported by P.D. Magnus[1].

The by-product (11; 74mg) was isolated by elution of the requisite band from the silica plate. ν_{max} 1715, 1640 cm^{-1}. λ_{max} 400 n.m. The n.m.r. spectrum had signals at 6.28 (3Hs), 6.20 (3Hs), 6.12 (3Hs), 6.09 (3Hs), 5.96 (2Hm), 5.52 (4Hm), 2.60 (3Hm) and 2.15 (2Hm).

cis-6a,12a-(12-Ethylenedioxy)-8,9,11-trimethoxy-10-carboxy-6a,7,12,12a-tetrahydro-1-phenylnaphthaceno (1,12-bc) furan-6-one (10; R=OH).

The tetracyclic ester (10, R=OMe; 525 mg) was suspended in ethanol (50ml) and water (50ml), and nitrogen was vigorously bubbled through the suspension. Potassium hydroxide (6.5g) was added and the mixture refluxed for 6 hours. During this time the substrate went into solution, and thin layer chromatography (chloroform-ethylacetate-acetic acid 1:1:trace) indicated that a new polar fluorescent compound had been formed. The pale brown solution was cooled to 0^{o}, dichloro-methane added, and the reaction neutralised with 6-N

hydrochloric acid. The dichloromethane layer was separated and the aqueous phase extracted with dichloromethane. Evaporation of the dried extracts gave a pale yellow crystalline residue (10, R=OH; 284mg). This compound was not characterised but converted to the amide (10, R=NH_2).

cis-6a,12a-(12-Ethylenedioxy)-8,9,11-trimethoxy-10-carboxamido-6a,7,12,12a-tetrahydro-1-phenylnaphthaceno (1,12-bc) furan-6-one (10, R=NH_2).

The crude dry acid (10, R=OH; 284mg) was dissolved in dry benzene (25ml) and dry dimethylformamide (96mg. 2.2mm) added. To this stirred solution under nitrogen at room temperature was added thionyl chloride (40mg; 2.5mm). After 1 1/2 hours at 25° no acid remained. To this mixture was added 0.880 ammonia (20ml) and the whole vigorously stirred for 10 minutes, whilst nitrogen bubbled through the emulsion. Extraction of the emulsion with dichloromethane gave, after drying and evaporation, a crystalline residue. Chromatography on silica-gel

thick plates provided the pure amide (10, R=NH_2, 265mg), crystallisation from benzene-diisopropylether gave m.p. 192-194°, $\nu_{max}^{CHCl_3}$ 3405, 3524, 2942, 1694, 1684, 1594 cm^{-1}, ν_{max}^{Nujol} 3350, 3200, 1690, 1684, 1668 cm^{-1}, λ_{max} 354, 306, 294, 278, 209 n.m. (ε, 13,300; 12,500; 15,100; 22,000; 60,100). The n.m.r. spectrum had signals at 6.05 (6Hs), 6.25 (3Hs), 5.62 (1Hd, J_{AB}=5cps), 7.36 (1Hm), 7.19 (1Hm), 6.06 (1Hm), 6.0-6.6 (4Hm), 3.95 (2Hbs), and 8 aromatic protons. (Found; C, 68.66; H, 4.91; N, 2.59 $C_{31}H_{27}O_8N$ requires C, 68.75; H, 5.03; N, 2.59%). (Carried out with P.D. Magnus).

cis-6a,12a-(12-Ethylenedioxy)-8,9,11-trimethoxy-10-carboxamido-6a,7,12,12a-tetrahydro-1-phenylnaphthaceno (1,12-bc) furan-6α-methyl-6β-ol (12). –

The ketoamide (10, R=NH_2; 54mg) was dissolved in dry benzene (5ml) and ether (15ml) at room temperature under nitrogen. Methyl lithium (1.6ml., 1.3M, 20mm) was added, and the solution became black. After 15 minutes 10% ammonium chloride solution (10ml) was added, and the mixture extracted with dichloromethane. The dried

extract was evaporated at room temperature and the residue chromatographed on thin silica plates. The compound was eluted from the silica with chloroform-ether to give the alcohol (12; 38mg) (67%). Recrystallisation from benzene-petrol gave m.p. 159-160°, $\nu_{max}^{CHCl_3}$ 3505, 3405, 1678 cm^{-1}, ν_{max}^{Nujol} 3485, 3360, 3205, 1678, 1665 cm^{-1}, λ_{max} 323, 309, 295, 251, 210 n.m. (ε, 22,800; 30,600; 23,700; 8,500; 54,800). The n.m.r. spectrum had signals at 8.27 (3Hs), 6.06 (6Hs), 6.24 (3Hs), 5.90-7.50 (9H, complex multiplets), 3.98 (2Hbs), and 8 aromatic protons. (Found; C, 69.15; H, 5.82; N, 2.59; $C_{32}H_{31}O_8N$ requires C, 68.93; H, 5.60; N, 2.51%). The mass spectrum exhibits a molecular ion at 557 m/e corresponding to $C_{32}H_{31}O_8N$, 539 m/e (M^+-18), base peak 295 m/e.

cis-5a,11a-12-Ethylenedioxy-1,3,4-trimethoxy-2-carboxamido-6β-hydroxy-6α-methyl-10-benzoyloxy-11-oxo-5,5a,6,11,11a,12-hexahydronaphthacene (14).

The alcohol (12; 70mg) was dissolved in dry chloroform

(30ml) and dry methanol (30ml). To this stirred solution was added dry pyridine (5 drops), followed by cooling the mixture to -76° (acetone/CO_2 bath). Ozonised oxygen was passed through the solution, and portions were withdrawn and inspected by the disappearance of the ultra-violet maximum at 309 n.m. After 5 minutes the reaction was 97.5% complete. Nitrogen was bubbled through the solution for 30 minutes, then triphenylphosphine (35mg. 2 equiv.) was added dropwise in dry chloroform (1ml) at -76°. After a further 1 hour at -76° the reaction was allowed to warm to room temperature. The solvents were evaporated at room temperature and the pyridine removed overnight under vacuum. The crude product was chromatographed on thin silica plates to give (14, 52mg) m.p. 248° ν_{max}^{Nujol} 3450, 3315, 3185, 1738, 1698, 1678, 1658, 1610 cm^{-1}, $\nu_{max}^{CHCl_3}$ 3500, 3400, 1680, 1700, 1727, cm^{-1}, λ_{max} 283, 228 n.m. (ε, 3,500; 28,000). The n.m.r. spectrum had signals at 8.29 (3Hs), 6.33 (3Hs), 6.28 (3Hs), 6.17 (3Hs), 5.63 (1Hd, J=5cps), 7.12 (1Hm), 6.77 (1Hm), 6.0-7.5 (6H complex multiplet), 4.02 (2Hbs), and 8 aromatic protons. The compound was characterised as the phenol (15).

cis-5a,11a-12-Ethylenedioxy-1,3,4-trimethoxy-2-carboxamido-6β-hydroxy-6α-methyl-10-hydroxy-11-oxo-5,5a,6,11,11a,12-hexahydronaphthacene (15).

The ketobenzoate (14; 20mg) was dissolved in dry methanol (15ml). To this solution under nitrogen was added a solution of sodium methoxide in methanol (0.5ml) (sodium 20mg., in methanol 10ml). After 4 hours water was added to the solution followed by dichloromethane. Solid carbon dioxide was added to the vigorously stirred mixture, and after a few minutes the organic phase was separated, dried and evaporated. The crude product was chromatographed on a thin silica plate to give the keto-phenol (15; 10mg) m.p. 218-220°. ν_{max}^{Nujol} 3515, 3480, 3350, 3295, 3150, 1672, 1642, 1612 cm^{-1}, λ_{max} 334, 260.5, 207 (ε, 2,600; 10,700; 42,500). The n.m.r. spectrum had signals at 8.28 (3Hs), 6.31 (3Hs), 6.18 (3Hs), 6.10 (3Hs), 5.5-7.8 (9Hm), 3.77 (2Hbs), 2.5-3.3 (3Hm), -2.00 (1Hs - exchanged by D_2O). (Found, C, 61.77; H, 5.77; N, 2.62; $C_{25}H_{27}O_9N$ requires C, 61.85; H, 5.61; N, 2.89%).

1,2,4-Trimethoxybenzene[5].

Vanillin (30g) was dissolved in 1N potassium hydroxide (175ml) and hydrogen peroxide (50%; 18ml - diluted to 100ml) added slowly. The temperature rose to 45°. To the dark solution at 30° was added with external cooling (ice-bath) 20% sodium hydroxide in four portions (100ml). Each stepwise addition was followed by dimethylsulphate (4x30ml). After stirring for 2 hours the solution was extracted with ether (4x100ml). The dried extract was evaporated and the residue distilled at 128°/1mm to yield 24g. of trimethoxybenzene, ν_{max} 3008, 3000, 2940, 2815, 1610, 1599 cm^{-1} (thin film).

2,3,6-Trimethoxybenzoic (16; R=OH).

1,2,4-Trimethoxybenzene (3.12g. 20mm), was dissolved in dry ether (32ml). To this magnetically stirred solution under nitrogen was added ethereal methyl lithium (35ml; 1.3M) through a serum cap. The white suspension was refluxed for 3 hours, then rapidly poured onto crushed dry ice and vigorously shaken. Water was added to the mixture and the whole warmed to room temperature. The

mixture was neutralised with 6N-hydrochloric acid and extracted with dichloromethane. The dried extracts were evaporated to yield the acid (16; R=OH; 3.2g). Crystallisation from benzene-petrol (60-80°) gave long needles, m.p. 148-149° (lit. m.p. 148-149°)[13], ν_{max} 3300-2500, 1724 cm^{-1}.

2,3,6-Trimethoxybenzamide (16; $R=NH_2$).

2,3,6-Trimethoxybenzoic acid (16, R=OH; 1.5g) was dissolved in dry benzene (45ml) under nitrogen. To this solution was added thionyl chloride (975mg) and dry dimethylformamide (0.45ml). The solution was refluxed for 2 hours then poured into 0.880 ammonia (75ml). After vigorously stirring for 5 minutes the mixture was extracted with chloroform. The dried extract was evaporated to give the amide (16, $R=NH_2$; 1.3g) as needles; m.p. 158°, ν_{max} 3420, 3300, 3160, 1678, 1664 cm^{-1}. The n.m.r. spectrum had signals at 6.20 (3Hs), 6.18 (3Hs), 6.10 (3Hs), 3.88 (2Hbs), 3.41 (1Hd, J_{AB}=9.4cps), 3.11 (1Hd, J_{AB}=9.4cps).

3,6-Dimethoxy-2-hydroxybenzamide (17).

A. Treatment of 2,3,6-trimethoxybenzamide (16; $R=NH_2$) with

boron trichloride.

i) The trimethoxyamide (16, R=NH_2; 50mg) was dissolved in dry methylene dichloride (5ml), and the solution cooled to -76° (acetone/CO_2). A few drops of boron trichloride were added, and after 5 minutes the reaction was quenched by careful addition of water. The dried organic extract was evaporated to give the crude product (40mg). T.l.c. indicated that some starting material remained, but the main product was the monophenol (17). Two recrystallisations from benzene-petrol (60-80°) gave the pure hydroxybenzamide (17; 20mg) m.p. 152-153°. ν_{max}^{Nujol} 3420, 3200, 1650, 1610 cm^{-1}, $\nu_{max}^{CHCl_3}$ 3500, 3400, 1652 cm^{-1}. The compound (17) has been previously reported by P.D. Magnus as the product from the attempted formylation of (16; R=NH_2) with α,α-dichloromethyl methylether-aluminium trichloride in benzene. The product prepared above had the same infra-red spectrum and t.l.c. behaviour as an authentic sample.

ii) The amide (16, R=NH_2, 100mg) was dissolved in dry

methylene dichloride (10ml) at room temperature, and a few drops of boron trichloride were added. After a few minutes the reaction was worked-up as above to give the pure monophenol . Recrystallisation from benzene-petrol gave needles (17; 67mg).

iii) Treatment of the amide (16, R=NH_2; 50mg) in dry dichloromethane (10ml) with a large excess of boron trichloride overnight at room temperature, gave predominately the hydroxybenzamide (17), along with material which stayed at the origin on t.l.c.

B. Treatment of (16, R=NH_2) with hydrobromic acid.

The trimethoxyamide (16, R=NH_2; 50mg) was dissolved in glacial acetic acid (2ml) and hydrobromic acid in glacial acetic acid (10drops) added. All the starting material was consumed in 1 hour at 60° (t.l.c.). After 14 hours water was added and the solution extracted with dichloromethane. The extracts were washed with aqueous sodium bicarbonate, water and dried. Evaporation of the solvent and recrystallisation of the crude product from benzene-petrol (60-80°) gave (17; 34mg). Identical in all respects with the authentic sample.

C. Treatment of (16, R=NH_2) with hydriodic acid.

The amide (16, R=NH_2; 25mg) was dissolved in dry benzene (2ml) under nitrogen, and a large excess of 57% analar hydriodic acid (0.5ml) was added. The reaction was stirred at room temperature overnight. The solution was extracted with sodium thiosulphate and the organic layer separated and dried. Evaporation of the benzene gave white crystals (17; 21mg).

2,6-Dihydroxy-3-methoxybenzamide (18).

A.i) The trimethoxyamide (16, R=NH_2, 100mg) was dissolved in dry dichloromethane (10ml) at room temperature, and a few drops of boron tribromide were added. After 5 minutes the reaction was quenched by the careful addition of water, and then dilute sodium hydroxide. The aqueous layer was acidified over dichloromethane with concentrated hydrochloric acid. Evaporation of the dried extract gave the crude prodict (45mg). Recrystallisation from benzene-petrol (60-80°) with charcoaling gave white crystals (18; 39mg) m.p. 168-169°. ν_{max} 3405, 3310, 3185, 1650, 1618 cm^{-1}.

The n.m.r. spectrum had signals at 6.15 (3Hs), 3.73 (1Hd, J_{AB}=9cps), 3.11 (1Hd, J_{AB}=9cps), 2.54 (1Hbs), 2.15 (1Hs - exchanged by D_2O), 1.93 (1Hbs) and ~2.7 (1Hs - exchanged by D_2O). (Found; C, 52.46; H, 4.95; N, 7.65; $C_8H_9O_4N$ requires C, 52.47; H, 4.97; N, 7.57%).

ii) When the above experiment was repeated in refluxing chloroform overnight, usual work-up gave the dihydroxy-benzamide (t.l.c.). The t.l.c. plate also showed some material which remained on the origin.

B. Treatment of the trimethoxyamide (16, R=NH_2) with hydriodic acid.

The amide (16, R=NH_2; 150mg) was dissolved in glacial acetic acid (2ml) and 57% analar hydriodic acid added. The mixture was stirred at 100° for 3 1/2 hours and then worked-up in the usual way. T.l.c. on the crude product indicated the presence of the di-demethylated compound (18), along with two other products. Prolonged reaction caused decomposition to several compounds.

1,3,4,10,11-pentamethoxy-5,6-dimethyl-5-H-12-oxo-2-carboxamido-5,12-dihydronaphthacene (19).

4-Hydroxy-6-methylpretetramid (1) was methylated in dry acetone using methyl iodide and potassium carbonate. The details are reported by P.D. Magnus[1]. The product has m.p. 249-250° ν_{max} 3445, 3340, 1690, 1672 cm^{-1}.

1,3,10,11-tetrahydroxy-4-methoxy-5,6-dimethyl-5-H-12-oxo-2-carboxamido-5,12-dihydronaphthacene (20; R=Me).

The pentamethoxynaphthacene (20; 50mg) was dissolved in phenol (2ml), under nitrogen, and 57% hydriodic acid (5 drops) added to the refluxing solution. After 20 minutes the solution was cooled and the red-brown precipitate filtered, washed with benzene, chloroform and petrol to give a light orange powder. Recrystallisation from chloroform-petrol (60-80°) gave (20, R=Me; 35mg). The compound did not melt but decomposed at ca. 250°. ν_{max} 3480, 3385, 3300, 3240, 1670, 1628, 1590, 1570 cm^{-1}. λ_{max}^{EtOH} 456, 373, 323, 270.5, 227.5 n.m.

(ε, 17,700; 8,800; 8,200; 33,900; 27,900). The n.m.r. spectrum, run in pyridine at 60°, had signals at 8.62 (3Hd, J=7cps), 7.55 (3Hs), and 6.01 (3Hs). The lower field protons were obscured by the solvent. (Found; C, 64.47; H, 4.76; N. 3.39; $C_{22}H_{19}NO_7$ requires C, 64.54; H, 4.68; N, 3.42%). The mass spectrum exhibited a molecular ion at 409 m/e corresponding to $C_{22}H_{19}NO_7$.

1,3,4,10,11-pentahydroxy-5,6-dimethyl-5-H-12-oxo-2-carboxamido-5,12-dihydronaphthacene (20; R=H).

The pentamethoxynaphthacene (20; 67mg) was dissolved in phenol (1ml), under nitrogen, and 57% hydriodic acid (20 drops) was added to the refluxing solution. After 1 1/4 hours, long orange needles separated at reflux. The solution was cooled to 60°, and the crystals were filtered from the warm phenol and washed with benzene, chloroform and petrol (60-80°). The pale orange crystals were extracted three times with hot chloroform (to remove any (20; R=Me)), and then dried *in vacuo* at 100° to yield pure (20, R=H, 48mg). The product did not melt but began

to decompose at 280°. ν_{max} 3580, 3480, 3410, 3260, 1658, 1625, 1590 cm^{-1}. λ_{max} 533, 353 (sh.), 319, 277.5, 273.5, 265, 237 n.m. (ε, 24,800; 10,200; 25,000; 24,000; 24,900; 23,400; 19,600), run in concentrated sulphuric acid/ saturated sodium borate (99:1). (Found; C, 63.61; H, 4.31; N, 3.55; $C_{21}H_{17}NO_7$ requires C, 63.80; H, 4.33; N, 3.54%). The mass spectrum exhibited a molecular ion at 395 m/e corresponding to $C_{21}H_{17}NO_7$.

6-Methylpretetramid (21).

The keto-phenol (15; 20mg) was dissolved in phenol (1ml) and 57% hydriodic acid (5 drops) added to the refluxing solution under nitrogen. The solution was cooled after 1 1/4 hours and benzene (2ml) added. The precipitate was filtered and washed with benzene. Two crystallisations from boiling phenol containing a trace of hydriodic acid gave pure 6-methylpretetramid (21; 4mg). ν_{max} 1685, 1661, 1630, ca. 1595 cm^{-1}. λ_{max} (H_2SO_4/H_3BO_3; 99:1) 262, 277, 339, 398, 512 n.m. (ε, 23,900; 22,800; 13,700; 15,600; 13,800) (reported[8] λ_{max} 263, 278, 341, 400, 512 n.m. (ε, 22,900; 21,600;

14,200; 14,700; 13,700). An authentic[6,7] specimen had λ_{max} 262, 277, 339, 398, 512 n.m., (ε, 22,900; 20,900; 15,200; 17,100; 15,500). The mass spectrum of the synthetic material exhibited a molecular ion at 365 m/e corresponding to $C_{20}H_{15}NO_6$.

Treatment of (20; R=H) with hydriodic acid.

The pretetramid (20, R=H; 50mg) was dissolved in refluxing phenol (2ml) under nitrogen and 57% hydriodic acid (20 drops) added. After 4 hours the reaction mixture was cooled to ca. 60° and filtered. The precipitate was washed with benzene and extracted three times with hot chloroform. The infra-red and u.v. spectra of the product were the same as starting material. The mass spectrum exhibited a molecular ion at 395 m/e corresponding to $C_{21}H_{17}NO_7$ (starting material).

Experimental to Part II.

Oxidation of o-vanillin with Fremy's salt.

o-Vanillin (2g) was dissolved in acetone (100ml) and water (200ml). Disodium hydrogen phosphate was added until the solution reached pH 8.3. Freshly prepared Fremy's salt (20g) was added to this solution followed by water (400ml). The pH was adjusted to 7.2 with disodium hydrogen phosphate, and the solution was stirred at room temperature for 15 minutes. Extraction with chloroform and evaporation of the dried extract gave a pale yellow solid (100mg). Recrystallisation from chloroform-ether gave yellow needles of the dimer (5; 75mg), m.p. 268-270° ν_{max} 1660, 1640 cm^{-1}. (Found; C, 60.73; H, 3.98; $C_{16}H_{12}O_7$ requires C, 60.76; H, 3.82). The mass spectrum exhibited a molecular ion at 316 m/e corresponding to $C_{16}H_{12}O_7$.

2-Hydroxy-3-formylethylenedioxyanisole (7).

o-Vanillin (25g) was dissolved in sodium dried benzene (700ml) under nitrogen, and ethylene glycol (25ml) followed by p-toluenesulphonic acid monohydrate (100mg)

added. The mixture was vigorously refluxed, allowing the condensate to percolate through a thimble packed with calcium hydride. After 4 hours the solution was cooled to room temperature and triethylamine (2ml) added. The benzene solution was washed with 1% aqueous sodium bicarbonate solution followed by water. Evaporation of the dried benzene extract gave a thick oil which crystallised on trituration with petrol. Recrystallisation from benzene-petrol gave large white crystals of the acetal (7; 18.9g) m.p. 73-74° ν_{max} 3400, 1600, 1275, 1062cm^{-1}. The n.m.r. spectrum had signals at 6.25 (3Hs), 5.99 (4Hd), 3.92 (1Hs), 3.32 (1Hs - exchanged by D_2O), and three aromatic protons. (Found; C, 61.42; H, 6.13; $C_{10}H_{12}O_4$ requires C, 61.22; H, 6.16%).

2-Methoxy-6-formylethylenedioxy-p-benzoquinone (8).

Disodium hydrogen phosphate solution was added to water (2.5 litre) until the pH was 7.2. Fremy's salt (90g) was added in portions along with sufficient phosphate solution to maintain the pH at 7.2. Acetone (500ml) was

then added followed by the solid acetal (7; 9g). The reaction was shaken for 5-10 minutes in a large separating funnel and then extracted with benzene. The dried extracts were evaporated at room temperature to approximately 20ml., and the pale yellow crystalline product filtered and dried (8; 7.6g). The semi-crystalline residue (1.4g) resulting from evaporation of the filtrate was essentially t.l.c. pure quinone. The total product (9g; 95%) was of adequate purity to be used directly for the next stage. It is advisable to store the material protected from light at 0^{o}. The quinone, recrystallised from chloroform-ether has m.p. 136-137^{o}. ν_{max} 1675, 1650, 1628, 1600, 1235cm^{-1}, λ_{max} 357, 256 n.m. (ε, 4,000; 11,500). The n.m.r. spectrum had signals at 6.13 (3Hs), 5.95 (4Hs), 4.06 (1Hs) and 3.20 (1Hm). (Found; C, 56.91; H, 4.71; $C_{10}H_{10}O_5$ requires C, 57.14; H, 4.80%).

2,5-Dihydroxy-3-formylethylenedioxyanisole (9).

The quinone (8; 630mg) was dissolved in dry analar benzene (100ml) and hydrogenated over 10% palladium on barium sulphate. When the uptake of hydrogen ceased

(68ml; theoretical 67.2ml) the solution was filtered under nitrogen and the filtrate evaporated at room temperature to give a thick oil (9; 625mg). ν_{max}^{Film} 3450, 1610cm^{-1}. The n.m.r. spectrum had signals at 6.39 (3Hs), 6.09 (4Hd), 4.03 (1Hs), 3.78 (1Hs - exchanged by D_2O), 3.31 (1Hbs - exchanged by D_2O) and two aromatic protons.

2,5-Dihydroxy-3-methoxybenzaldehyde (10).

The acetal (9; 100mg) was dissolved in tetrahydrofuran (2ml) and dilute hydrochloric acid (1ml) added. The solution was poured into water and extracted with dichloromethane. Evaporation of the dried extract and recrystallisation of the residue from benzene gave small yellow prisms (10; 50mg) m.p. 142-143° (lit. m.p. 143°)[2]. ν_{max} 3380, 3180, 1650, 1630, 1600, 1142cm^{-1}. The n.m.r. spectrum had signals at 6.13 (3Hs), 3.31 (2Hm), 1.08 (2Hbs - exchanged by D_2O) and 0.00 (1Hs).

2,5-Dimethoxy-3-formylethylenedioxyanisole (11).

The acetal (9; 2g) in dry acetone (200ml) under nitrogen was treated with anhydrous potassium carbonate

(4g) and dimethylsulphate (4ml). The mixture was refluxed and mechanically stirred for 20 hours. The cooled suspension was poured into water and extracted with dichloromethane. The extract was washed with 5% sodium bicarbonate solution, followed by water and dried. Evaporation of the dichloromethane gave the crude product (2.3g). Chromatography over alumina eluting with benzene gave the required trimethoxyacetal (11) as a colourless oil (2.00g). ν_{max}^{Film} 1605, 1070cm^{-1}. The n.m.r. spectrum had signals at 6.26 (6Hs), 6.20 (3Hs), 6.03 (4Hd), 4.06 (1Hs) and 3.60 (2Hq). (Found; C, 60.48; H, 6.73; $C_{12}H_{16}O_5$ requires C, 59.99; H, 6.71%).

2,3,5-Trimethoxybenzaldehyde (2).

The trimethoxyacetal (11; 100mg) was dissolved in tetrahydrofuran (2ml) and dilute hydrochloric acid (1ml) added. The solution was poured into water and extracted with dichloromethane. The dried extract was evaporated to give the aldehyde (2; 70mg). Recrystallisation from petrol gave silky white needles m.p. 63-64° (lit. m.p. 63°).[2]

ν_{max} 1686, 1610, 1258cm^{-1}. The n.m.r. spectrum had signals at 6.22 (3Hs) 6.15 (3Hs), 6.08 (3Hs), -0.25 (1Hs) and 3.25 (2Hq).

Methyl 2,3,6-trimethoxy-4-formylbenzoate (1)[1].

The trimethoxyacetal (11; 945 mg) was treated with a large excess of ethereal methyl lithium (1oml; 1M) under nitrogen. After 6 hours at reflux solid carbon dioxide was added to the reaction mixture. When the mixture had warmed to room temperature 6N hydrochloric acid was added to hydrolyse the acetal. After 30 minutes the mixture was extracted with benzene. Evaporation of the dried benzene layer gave the acid (3) which was not characterised but treated in ether with redistilled ethereal diazomethane at 0°. The residue from evaporation of the ether was chromatographed on alumina eluting first with petrol and then benzene to give the required aldehyde (1; 480mg). The material was identical with that prepared from orcinol.

Experimental to Part III.

Sodium salt of p-methoxyphenol.

p-Methoxyphenol (1.24g) was dissolved in dry ether (25ml) and sodium hydride (50%, 0.48g) was added in small portions to the vigorously stirred solution. The sodium salt was filtered off, washed with dry ether, and dried *in vacuo* (1.44g).

Reaction of sodium p-methoxyphenate with benzoyl peroxide.

Sodium p-methoxyphenate (438mg) was dissolved in dry glyme (15ml) and the solution cooled to -20°C. Benzoyl peroxide (736mg., 1eq.) was added in small portions over a period of 15 minutes. The reaction was allowed to come to room temperature and was left overnight. The pale yellow suspension was poured into water and extracted with methylene dichloride. The organic layer was washed with aqueous sodium bicarbonate and water. Evaporation of the dried extract and crystallisation of the residue from methanol gave p-methoxyphenyl benzoate (605mg) m.p. 87° (lit. 87°)[30] ν_{max} 1720cm^{-1}.

Anhydrous sodium mesitate.

Mesitol (2.04g) was dissolved in dry benzene (40ml) and sodium hydride (0.72g:50%) was added in small portions to the stirred solution. After stirring at room temperature for 30 minutes, the sodium salt was filtered off, washed with dry benzene, and dried *in vacuo* (2.30g).

6-Benzoyloxy-2,4,6-trimethylcyclohexa-2,4-dienone (9).

a). Reaction of sodium mesitate with benzoyl peroxide.

Sodium mesitate (474mg) was dissolved in dry ether (30ml) and the solution cooled to -20°. Benzoyl peroxide (726mg. 1eq.) was added in portions over a period of 15 minutes. After a further hour at -20° the reaction was poured into aqueous sodium bicarbonate. The ether layer was washed with water, dried and evaporated. The oily residue was chromatographed on alumina, eluting with benzene to give a pale yellow oil that crystallised on contact with methanol m.p. 112-113° (9; 503mg). ν_{max} 1710,

1667, and 1658cm^{-1}, λ_{max} 231.5, 275, 283, 312n.m. (ε 17,700; 2,400; 2,500; 3,700). The n.m.r. spectrum had signals at 8.53 (3Hs), 8.09 (6Hd), 4.16 (1Hm), 3.36 (1Hm), 2.59 (3Hm) and 2.04 (2Hm). (Found; C, 74.74; H, 6.44; $C_{16}H_{16}O_3$ requires C, 74.98; H, 6.25%).

b). Oxidation of mesitol with benzoyl peroxide.

4-Benzoyloxy-2,4,6-trimethylcyclohexa-2,5-dienone (10).

Mesitol (136g) and benzoyl peroxide (2.42g) were refluxed in dry chloroform (25ml) for 14 hours. The pale orange solution was worked-up as above. Chromatography on alumina gave the o-dienone (9; 2.09g) and a small quantity of the p-dienone (10; 90mg) m.p. 127-130° (methanol). ν_{max} 1722, 1635cm^{-1}, λ_{max} 239 n.m. (ε, 23,600). The n.m.r. spectrum had signals at 8.35 (3Hs), 8.07 (6Hs), 3.26 (2Hs), 2.56 (3Hm) and 2.05 (2Hm). (Found; C, 74.76; H, 6.41; $C_{16}H_{16}O_3$requires C, 74.98; H, 6.25%).

6-Benzoyloxy-N-cyclohexyl-2,4-dimethylhepta-2,5-dienamide (11).

The o-dienone (9; 74mg) was dissolved in dry tetrahydrofuran (T.H.F.) (25ml) and cyclohexylamine (75mg) added. The solution was irradiated under nitrogen in a pyrex vessel, using a high pressure mercury lamp[14]. The reaction was complete in 20 minutes, according to t.l.c. The solvent was removed and ether (10ml) added to the residue. The organic layer was washed with dilute hydrochloric acid (5ml; ca. 1N) and then water (5ml). The ethereal solution was dried and evaporated. Chromatography on thin silica plates afforded the product as a t.l.c. pure oil (11; 91mg), ν_{max}^{film} 3400, 3320, 1725, ca. 1650(broad)cm^{-1}. The n.m.r. spectrum had signals at 8.78 (3Hd; J=7cps), ca. 8.48 (10Hm), 8.16 (3Hs), 8.05 (3Hs), 6.67 (2H, very broad multiplet), 5.42 (1Hm), 4.26 (1Hbs), 3.83 (1Hm), 2.52 (3Hm) and 1.96 (2Hm).

Pyrolysis of (9) on a Kofler block.

When the o-dienone (9; ca. 5mg) was heated at 120° (m.p. 113°) on a Kofler block for 30 minutes, t.l.c. showed

that a mixture of o- and p-dienones was formed.

Treatment of (9) with benzoyl chloride-pyridine.

The o-dienone (9; 250mg) was dissolved in dry pyridine (3ml) and benzoyl chloride (100mg) added. The solution was refluxed and the reaction followed by t.l.c. and infra-red spectroscopy. A steady state was established after approximately an hour. After 5 hours the cooled solution was poured into ether and washed with water, dilute hydrochloric acid and water. Evaporation of the dried organic extract gave a dark oil, which was chromatographed on alumina, eluting with benzene, to afford a mixture (120mg) in which 40% of the o-dienone and 60% of the p-dienone were present (by n.m.r).

Treatment of (9) and (10) with refluxing pyridine.

(a) The o-dienone (9; 200mg) was dissolved in dry pyridine (50ml) and the solution refluxed for 2 hours. Equilibrium was set up after approximately one hour. The cooled solution was worked-up as above to give the same mixture (195mg) of o- and p-dienones (by n.m.r.).

(b) Similar treatment of the p-dienone (10; 20mg) in dry pyridine (10ml) gave an identical mixture (17mg) of o- and p-dienones (by n.m.r.).

Treatment of (9) and (10) with refluxing toluene.

(a) The o-dienone (9; 100mg) was refluxed in dry toluene (30ml). According to infra-red spectroscopy and t.l.c., equilibrium was established in approximately 5 hours. The toluene was evaporated and the crystalline residue shown to be a clean mixture of o- and p-dienones in the ratio 2:3.

(b) Similar treatment of the p-dienone (10; 20mg) in dry toluene (10ml) gave the same mixture of dienones (by n.m.r.).

6-p-Nitrobenzoyloxy-2,4,6-trimethylcyclohexa-2,4-dienone (12).

Mesitol (680mg) and bis-p-nitrobenzoyl peroxide (1.66g) were dissolved in dry chloroform (50ml) and the solution stirred at 40° overnight. The final suspension

was poured into aqueous sodium bicarbonate, the chloroform layer washed with water, dried and evaporated to give a pale yellow solid. Recrystallisation from methanol gave pale yellow nuggets of the o-dienone (12; 1.4g) m.p. 116-117°. ν_{max} 1720, 1675, 1665, 1530 and 1355cm^{-1}, λ_{max} 258, 295(sh) n.m. (ε 16,600; 7,000). The n.m.r. spectrum had signals at 8.47 (3Hs), 8.04 (6Hs), 4.12 (1Hm), 3.28 (1Hm), 1.8 (4Hs). (Found; C, 63.64; H, 5.09; N, 4.66; $C_{16}H_{15}NO_5$ requires C, 63.78; H, 4.98; N, 4.65%).

Treatment of (12) and (13) with refluxing pyridine.

(a) The o-dienone (12; 200mg) was dissolved in dry pyridine (40ml) and the solution refluxed for 1 hour. Equilibrium was established after ca. 30 minutes. The cooled solution was worked-up in the usual way to give a crystalline residue (180mg). The n.m.r. spectrum was indicative of a mixture containing ca. 40% of the o-dienone and 60% of the p-dienone. The p-dienone (13) was isolated by chromatography of the mixture on several thin silica plates. Recrystallisation from methanol gave (13; 90mg) m.p. 131.5-132.5°. ν_{max} 1728, 1635, 1530, 1355cm^{-1}, λ_{max} 253 n.m. (22,700). The n.m.r. spectrum

had signals at 8.30 (3Hs), 8.07 (6Hs), 3.25 (2Hs) and 1.80 (4Hd). (Found; C, 63.97; H, 5.17; N, 4.63; $C_{16}H_{15}NO_5$ requires C, 63.78; H, 4.98; N, 4.65%).

b) Similar treatment of the p-isomer (13; 20mg) in dry pyridine (10ml) gave an identical mixture (15mg) of o- and p-dienones (by n.m.r.).

Treatment of (12) and (13) with refluxing toluene.

a) The o-dienone (12; 200mg) was refluxed in dry toluene (40ml). A steady state was reached after approximately 2 hours. After 3 hours the toluene was evaporated and the residue examined by n.m.r. spectroscopy, which indicated that a mixture containing 40% of the o-dienone and 60% of the p-dienone had been formed.

b) When the p-dienone (13; 20mg) was refluxed in dry toluene (5ml) for the same time, an identical mixture of dienones was obtained, according to the n.m.r. spectrum.

6-p-Methoxybenzoyloxy-2,4,6-trimethylcyclohexa-2,4-dienone (14).

Mesitol (1.36g) and anisoyl peroxide (3.02g) were dissolved in dry chloroform (50ml) and the solution was refluxed for 18 hours. The solution was cooled and washed with aqueous sodium bicarbonate and water. Evaporation of the dried organic extract gave a dark oil, which was chromatographed on alumina, eluting with benzene, to provide the pure dienone (14; 2.11g) as a t.l.c. pure oil. This slowly crystallised on addition of methanol to give pale yellow crystals m.p. 75-77°. ν_{max} 1700, 1665, 1655 and 1600cm^{-1}, λ_{max} 259, 310 n.m. (ε 24,000; 4,000). The n.m.r. spectrum had signals at 8.54 (3Hs), 8.08 (6Hs), 6.20 (3Hs), 4.14 (1Hm), 3.33 (1Hm), 3.14 (2Hd; J_{AB}=9cps) and 2.08 (2Hd; J_{AB}=9cps). (Found; C, 71.22; H, 6.30; $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%).

Treatment of (14) and (15) with refluxing pyridine.

a) The o-dienone (14; 80mg) was refluxed in dry pyridine (50ml) for 1 1/2 hours at which time equilibrium had been established (usual control). Work-up in the

normal way gave a mixture (75mg), in which 40% of the o-dienone and 60% of the p-dienone were present (by n.m.r.). Chromatography of the product on several thin silica plates gave the pure p-dienone (15; 36mg). Crystallisation from petrol gave white needles m.p. 115°. ν_{max} 1705, 1670, 1635, 1600, 1255cm^{-1}, λ_{max} 258 n.m. (ε29,500). The n.m.r. spectrum had signals at 8.32 (3Hs), 8.17 (6Hs), 6.13 (3Hs), 3.21 (2Hs), 3.09 (2Hd; J_{AB}=9cps) and 2.04 (2Hd; J_{AB}=9cps). (Found; C, 71.44; H, 6.19; $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%).

b) On rearranging the p-dienone (15; 20mg) in dry pyridine (10ml) under identical conditions the same mixture (15mg) of dienones was isolated (by n.m.r.)

Treatment of (14) and (15) with refluxing toluene.

a) When the o-dienone (14; 50mg) was rearranged in dry toluene (50ml) equilibrium was established in about 5-6 hours. The solvent was evaporated and the residue examined by n.m.r. The latter showed a mixture of the o- and p-dienones in the ratio 2:3.

b) Similar treatment of the p-dienone (15; 10mg) in refluxing toluene (10ml) afforded the same mixture of dienones (by n.m.r.).

6-Acetoxy-2,4,6-trimethylcyclohexa-2,4-dienone (16)[15].

Mesitol (2.0g) was dissolved in dry benzene (24ml) and treated with lead tetraacetate (5.2g) in benzene (12ml). After a few minutes stirring at room temperature t.l.c. indicated that the reaction was complete. Water (100ml) was added and the benzene layer separated, dried and evaporated to yield the cyclohexadienone (16), 1.65g m.p. 81-83° (lit. m.p. 82-84°)[15]. ν_{max} 1725, 1662 and 1665cm^{-1}. The n.m.r. spectrum had signals at 8.10 (6Hs), 8.68 (3Hs), 7197 (3Hs), 4.22 (1Hs) and 3.37 (1Hs).

Treatment of (16) with refluxing pyridine.

The o-dienone (16; 100mg) was dissolved in dry pyridine (30ml) and the solution refluxed. After 3 1/2 hours t.l.c. showed no change, but a new band was present at 1640cm^{-1} in the infra-red spectrum. The reaction was continued for a total of 24 hours when this new band

showed no further increase. T.l.c. still showed only on spot corresponding to the o-dienone (16). Usual work-up gave a dark oil which was chromatographed on alumina to give an oil (55mg) which eventually crystallised. ν_{max} (total product) 1738, 1670, 1650(sh) and 1640cm^{-1}. T.l.c. showed only one spot, even on eluting the plate several times, however, the n.m.r. spectrum was consistent with a mixture containing approximately 35% of the o-dienone and 65% of the p-dienone. Signals assignable to the p-isomer appeared at 8.48 (3Hs), 8.12 (6Hs), 8.00 (3Hs), 3.35 (2Hs). The pure p-dienone (17) was never isolated, as no separation on t.l.c. could be achieved with several different solvent systems.

Treatment of (16) with refluxing toluene.

The o-dienone (16; 100mg) was refluxed in dry toluene (40ml). There was very little change in the infra-red spectrum even after 24 hours.

6-Benzoyloxy-2,6-dimethylcyclohexa-2,4-dienone (19).

a) 2,6-Dimethylphenol (122g) and benzoyl peroxide (2.42g) were refluxed in dry chloroform (30ml) for 12 hours. The deep red solution was washed with aqueous sodium bicarbonate and water. Evaporation of the dried chloroform layer gave a deep red gummy residue, which when triturated with ether left the diphenoquinone (18; 600mg) as a red insoluble powder. Crystallisation from chloroform-ether gave deep red crystals m.p. 208° (lit. m.p. 210-215°)[6]. ν_{max} 1640, 1595cm^{-1}. The ether washings were evaporated and chromatographed on alumina to give the crystalline o-dienone (19; 605mg) m.p. 66°. ν_{max} 1725, 1675cm^{-1}, λ_{max} 231, 275(sh), 284(sh), 304 n.m., (ε18,100; 3,000; 3,600; 4,700). The n.m.r. spectrum had signals at 8.56 (3Hs), 8.08 (3Hd), 3.96 (1Hs), 3.89 (1Hs), 3.31 (1Hm), 2.59 (3Hm), and 2.05 (2Hm). (Found; C, 74.41; H,5.97; $C_{15}H_{14}O_3$ requires C, 74.36; H, 5.82%).

b) Sodium 2,6-diemthylphenate (432mg) (prepared from the phenol and sodium hydride in benzene in the usual way),

was dissolved in dry ether (20ml) at -20°, and benzoyl peroxide (726mg) was added in portions over 15 minutes. The suspension was allowed to warm to room temperature and then filtered. The precipitate was washed with aqueous sodium bicarbonate and water and dried in vacuo to give the diphenoquinone (18; 20mg). The initial ether filtrate was evaporated and chromatographed on alumina eluting with benzene to provide the o-dienone (19; 375 mg).

4-Benzoyloxy-2,6 dimethylphenol.

The o-dienone (19; 57mg) was refluxed in dry pyridine (25ml), and the rearrangement followed by t.l.c. After 24 hours there was a trace of a slower running compound. Starting material was still present after a further 4 days. The cooled solution was worked-up in the usual way and the product recrystallised from petrol (60-80°) as colourless plates (23mg) m.p. 142° (lit. m.p. 140°)[6]. ν_{max} 3525, 1720cm^{-1}. The n.m.r. spectrum had signals at 7.76 (6Hs), 3.18 (2Hs), 2.44 (4Hm, containing one exchangeable proton), and 1.85 (2Hm). The mother

liquor from the crystallisation was essentially pure starting material (19; 28mg). Attempted rearrangement of (19; 30mg) in refluxing toluene (10ml) gave only starting material after 4 days (t.l.c.).

6-p-Nitrobenzoyloxy-2,6-dimethylcyclohexa-2,4-dienone (20).

2,6-Dimethylphenol (112mg) and bis-p-nitrobenzoyl peroxide (332mg) were stirred at 40° in dry chloroform (8ml) for 12 hours. The yellow solution was washed with aqueous sodium bicarbonate and water, dried and evaporated to give a yellow oil. Triturating with ether and filtering gave the diphenoquinone (18; 20mg). The ethereal filtrate was evaporated and chromatographed on alumina eluting with benzene to afford the crystalline o-dienone (20; 201mg). Recrystallisation from methanol gave needles m.p. 154-155°. ν_{max} 1720, 1660, 1535 and 1350cm^{-1}, λ_{max} 259, 299(sh) n.m., (ε 13,900; 6,700). The n.m.r. spectrum had signals at 8.41 (3Hs), 8.01 (3Hd), 3.80 (1Hs), 3.73 (1Hs), 3.13 (1Hm) and 1.78 (4Hs). (Found; C, 62.91; H, 4.46; N, 4.80; $C_{15}H_{13}NO_5$ requires C, 62.72; H, 4.56; N, 4.88%).

4-(p-Nitrobenzoyloxy)-2,6-dimethylphenol.

The o-dienone (20; 55mg) was refluxed in dry pyridine (35ml). After 40 hours t.l.c. showed only a trace of starting material remained. The cooled solution was poured into water and extracted with dichloromethane. The organic layer was washed thoroughly with water, dilute hydrochloric acid and water, dried and evaporated. The crude product was recrystallised twice from benzene-petrol to give pale yellow needles (37mg) m.p. 224°. ν_{max} 3520, 1725, 1535, 1355cm^{-1}. The n.m.r. spectrum had signals at 7.72 (6Hs), 3.18 (2Hs), 2.50 (1Hs, exchanged by D_2O) and 1.67 (4Hs). (Found; C, 62.64; H, 4.57; N, 4.76; $C_{15}H_{13}NO_5$ requires C, 62.72; H, 4.56; N, 4.88%).

On refluxing (20; 10mg) in dry toluene (5ml) for 24 hours t.l.c. showed only starting material.

Oxidation of 2,4-dimethylphenol with bis-p-nitrobenzoyl peroxide.

2,4-Dimethylphenol (0.814g) and bis-p-nitrobenzoyl

peroxide (2.214g) were dissolved in dry chloroform (40ml) and the solution was stirred at 40° for 8 hours. The cooled reaction mixture was poured into aqueous sodium bicarbonate and the chloroform layer separated, washed with water, dried, and evaporated. Methylene dichloride (2ml) was added to the residue which was then cooled at 0° overnight. Pale yellow crystals of the catechol derivative (23; 250mg) were obtained. Recrystallisation from carbon tetrachloride gave m.p. 160° ν_{max} 3450, 1720, 1530 and 1350cm^{-1}. The n.m.r. spectrum had signals at 7.88 (3Hs), 7.75 (3Hs), 3.45 (1Hs), 3.35 (1Hs), 1.66(4Hs) and 1.13 (1Hs - exchanged by D_2O). (Found; C, 62.68; H, 4.62; N, 4.88; $C_{15}H_{13}NO_5$ requires C, 62.72; H, 4.56; N, 4.88%).

The mother liquors from the crystallisation were chromatographed on silica gel to give a further quantity of (23; 530mg), the o-dienone (21; 632mg) and a trace of p-dienone (22; 55mg). Recrystallisation of the o-dienone from methanol gave long needles m.p. 147-149° ν_{max} 1715, 1680, 1655, 1530, 1350cm^{-1}, λ_{max} 258.5, 295 n.m.(sh) (ε, 15,100; 6,100). The n.m.r. spectrum had signals at

8.44 (3Hs), 8.00 (3Hd), 3.95 (1Hbs), 3.78 (1Hd), 3.05 (1Hm) and 1.77 (4Hs). (Found; C, 62.50; H, 4.58; N, 4.60; $C_{15}H_{13}NO_5$ requires C, 62.72; H, 4.56; N, 4.88%).

Crystallisation of the p-dienone from methanol gave m.p. 170-171° ν_{max} 1670, 1640, 1525, 1355cm^{-1}, λ_{max} 253 n.m. (ε 20,500). The n.m.r. spectrum had signals at 8.25 (3Hs) 8.07 (3Hd), 3.72 (1Hd), 3.19 (2Hm) and 1.81 (4Hd). (Found; c, 62.76; H, 4.67; N, 4.67; $C_{15}H_{13}NO_5$ requires C, 62.72; H, 4.56; N, 4.88%).

Treatment of (21) and (22) with refluxing pyridine.

a) The o-dienone (21; 50mg) was refluxed in dry pyridine (15ml) and the rearrangement followed by t.l.c. After 1 1/2 hours only a trace of the o-compound remained, there being two new spots corresponding to the p-isomer and the catechol derivative. On refluxing the solution for a further 4 hours complete conversion to the catechol derivative occurred. Usual work-up gave an oil which was purified on thin silica plates. Recrystallisation from

carbon tetrachloride gave (23; 38mg) m.p. 160°. Mixed melting-point with the product (23) from the oxidation of 2,4-dimethylphenol showed no depression. The n.m.r. spectrum was identical to that of (23).

b) Similar rearrangement of the p-dienone (22; 20mg) in dry pyridine (5ml) for 3 hours gave (23; 13mg), identical in all respects with an authentic sample.

Treatment of (21) with refluxing toluene.

The o-dienone (21; 120mg) was refluxed in dry toluene (35ml) and the rearrangement followed by t.l.c. After 39 hours complete conversion to the catechol derivative had taken place, along with a small amount of decomposition to material which stayed at the origin on t.l.c. The toluene was evaporated and the solid residue chromatographed on silica plates to furnish the pure rearranged material (23; 94mg), which was identical in all respects with the authentic sample.

2,4-Dimethyl-6-methoxyphenol (24; R=H).

The catechol derivative (23; 1.2g) in dry T.H.F. (25ml) was treated with diazomethane (from 1.2g of nitrosomethylurea) at -10° during 48 hours. After removal of most of the ether, unchanged phenolic material was extracted with alkali and the remaining ethereal solution dried and evaporated to give an oil (0.75g). This was suspended in dry methanol (25ml) under nitrogen, and sodium methoxide (1 eq.) in emthanol (1.5ml) added. After stirring for 15 minutes the solution was poured into water and extracted with dichloromethane. The dried extracts were evaporated to give a dark oil which was chromatographed on alumina eluting first with petrol and then benzene to provide the required phenol (24, R=H; 100mg) m.p. 31-33° (lit. m.p. 32-33°)[6]. ν_{max} 3530, 1380, 1365, 1232 and 1218cm^{-1}. The n.m.r. spectrum had signals at 7.83 (3Hs), 7.80 (3Hs), 6.19 (3Hs), 4.39 (1Hs - exchanged by D_2O), and 3.50 (2Hs).

2,4-Dimethyl-6-methoxyphenylbenzoate (24; R=COPh).

The phenol (24, R=H; 40mg) was dissolved in dry pyridine (2ml) and benzoyl chloride (45mg) added. The solution was left overnight, poured into 1N hydrochloric acid (10ml) and cooled at 0° for a few hours. The solid was filtered, washed with water and dried *in vacuo*. Recrystallisation from aqueous methanol gave m.p. 73°. An authentic smaple prepared by the method of Cosgrove and Waters[6] had m.p. 72-73°. Mixed melting-point gave no depression. ν_{max} 1725, 1265cm^{-1}. The n.m.r. spectrum had signals at 7.87 (3Hs), 7.71 (3Hs), 6.28 (3Hs), 3.38 (2Hs), 2.51 (3Hm) and 1.84 (2Hm).

Oxidation of 2,4,5-trimethylphenol with bis-*p*-nitrobenzoyl peroxide.

2,4,5-Trimethylphenol (906mg) and bis-*p*-nitrobenzoyl peroxide (2.22g) were dissolved in dry chloroform (50ml) and the solution stirred at 40°C for 4 hours. The cooled reaction mixture was washed with aqueous sodium bicarbonate

and water. Evaporation of the dried organic layer gave a pale yellow oil. Methylene dichloride (5ml) was added and the solution kept at 0° overnight. Pale yellow crystals (410mg) of (27) and (28) were obtained. A second crop (120mg) was obtained from the mother liquors ν_{max} 3400, 1710, 1535 and 1355cm^{-1}. The n.m.r. spectrum of the mixture run in deuterochloroform containing a trace of D_6-dimethylsulphoxide had signals at 7.77(s), 7.85(s), 7.92(s), 7.99(s) (all methyl signals); 3.43 (s), 3.19 (s) (ring proton); 1.90(s), 1.82(s) (hydroxyl signal, D_2O exchanged); 1.75 (4Hs).

The mixture (150mg) of (27) and (28) was treated with p-nitrobenzoyl chloride (140mg) in dry pyridine (3ml). The solution was stirred overnight at room temperature and then poured into ice-water (50ml). The white precipitate was filtered, washed thoroughly with water and dried *in vacuo*. The crude solid was recrystallised from chloroform-methanol to give white nuggets of (29; 192mg) m.p. 228°. ν_{max} 1745, 1530 and 1350cm^{-1}. The n.m.r. spectrum had signals at 7.88 (3Hs), 7.80 (3Hs), 7.68 (3Hs), 2.94 (1Hs) and 1.80 (8Hs). (Found; C, 61.06; H, 4.18; N, 5.96;

$C_{23}H_{18}N_2O_8$ requires C, 61.33; H, 4.03; N, 6.22%).

The mother liquors from the crystallisation of (27) and (28) were chromatographed on alumina eluting with benzene to give (26; 805mg). Recrystallisation from methanol gave (26) m.p. 142-144°. ν_{max} 1720, 1672, 1535 and 1352cm^{-1}, λ_{max} 258.5, 295(sh) n.m. (ε 15,000; 6.300). The n.m.r. spectrum had signals at 8.47 (3Hs), 8.03 (3Hd), 7.88 (3Hd), 3.98 (1Hm), 3.90 (1Hm) and 1.79 (4Hs). (Found; C, 63.78; H, 4.97; N, 4.55; $C_{16}H_{15}NO_5$ requires C, 63.78; H, 4.98; N, 4.65%).

Treatment of (26) with refluxing toluene.

The o-dienone (26; 105mg) was dissolved in dry toluene (30ml) and the solution refluxed for 14 hours. The solvent was evaporated and the n.m.r. spectrum of the total product indicated that the product consisted mainly of the p-dienone (30; 85%) along with some o-dienone (26; 15%). Chromatography on thin silica plates gave (30; 80mg). Recrystallisation from methanol gave

m.p. 162-163° (changes crystalline form on the block before melting). ν_{max} 1720, 1675, 1645, 1527 and 1352cm^{-1}, λ_{max} 253 n.m. (ε 25,600). The n.m.r. spectrum had signals at 8.32 (3Hs), 8.06 (6Hm), 3.85 (1Hd), 3.30 (1Hd) and 1.79 (4Hd). (Found; C, 63.69; H, 5.13; N, 4.52; $C_{16}H_{15}NO_5$ requires C, 63.78; H, 4.98; N, 4.65%).

Treatment of (26) with refluxing pyridine.

The o-dienone (26; 200mg) was refluxed in dry pyridine (50ml). After 1/2 hour t.l.c. showed three spots corresponding to the o-dienone, the p-dienone (30) and a new compound that was not (27) or (28). The deep red solution was cooled and worked-up in the usual way. The crude product (40; 130mg) was chromatographed on silica plates. Recrystallisation from benzene-petrol gave pale yellow needles (40; 105mg) m.p. 145°. ν_{max} 3520, 1720, 1530 and 1352cm^{-1}. The n.m.r. spectrum had signals at 7.78 (3Hs), 7.71 (3Hs), 5.08 (1Hs, D_2O exchanged), 4.68 (2Hs), 3.16 (1Hs), 3.04 (1Hs) and 1.79 (4Hs). (Found; C, 63.87; H, 4.99; N, 4.48; $C_{16}H_{15}NO_5$ requires C, 63.78; H, 4.98; N, 4.65%).

Treatment of (40; 50mg) in dry pyridine (3ml) with p-nitrobenzoyl chloride (31mg) gave the di-p-nitrobenzoate derivative m.p. 184-185° (chloroform-methanol). ν_{max} 1725, 1715, 1530 and 1350cm^{-1}. The n.m.r. spectrum had signals at 7.77 (3Hs), 7.59 (3Hs), 2.80 (2Hm), 1.79 (4Hs) and 1.67 (4Hs). (Found; C, 61.22; H, 3.84; N, 6.08; $C_{23}H_{18}N_2O_8$ requires C, 61.33; H, 4.03; N, 6.22%).

2,4-Dimethyl-5-hydroxybenzyl alcohol (33).

The rearranged material (40; 140mg) was dissolved in dry methanol (60ml) under nitrogen at room temperature, and a solution of sodium methoxide in methanol (7ml; 4mg. sodium per ml.) added. After 1 hour water was added to the solution followed by dichloromethane. Solid carbon dioxide was added to the vigorously stirred mixture, and after a few minutes the organic phase was separated, dried and evaporated to give a semi-solid residue. Addition of a small amount of benzene and cooling gave white crystals of the alcohol (33; 50mg). Recrystallisation from benzene gave m.p. 143°. ν_{max} 3330, 3090, 1285 and 1197cm^{-1}. The

n.m.r. spectrum had signals at 7.82 (6Hs), 6.14 (1Hbs - D_2O exchanged), 5.49 (2Hs), 3.19 (1Hs), 3.14 (1Hs) and 1.84 (1Hbs - D_2O exchanged). (Found; C, 70.82; H, 7.82; $C_9H_{12}O_2$ requires C, 71.03; H, 7.95%).

2,5-Dimethyl-4-hydroxybenzyl alcohol (31)[16].

2,5-Dimethylphenol (8g) was dissolved in aqueous sodium hydroxide (66ml; 5%) and aqueous formaldehyde solution (4.5ml; 40%) added. The mixture was stirred for 4 hours at room temperature, and then dilute acetic acid added until the solution was neutral. The precipitate was filtered, washed with a little water and dried *in vacuo* overnight. The crude product (31; 7.5g) was recrystallised from ethyl acetate to give white plates m.p. 175° (lit. m.p. 175°)[16]. ν_{max} 3455, 3230, 1295 and 1205cm^{-1}. The n.m.r. spectrum had signals at 7.85 (3Hs), 7.78 (3Hs), 5.67 (1Hbs- D_2O exchanged), 5.58 (2Hs), 3.43 (1Hs), 3.03 (1Hs) and 1.52 (1Hs- D_2O exchanged). (Found; C, 70.38; H, 7.91; $C_9H_{12}O_2$ requires C, 71.03; H, 7.95%).

Treatment of (31; 152mg) in dry pyridine (5ml) with p-nitrobenzoyl chloride (272mg) gave the di-p-nitrobenzoate derivative m.p. 201-202° (chloroform-methanol), ν_{max} 1725, 1718, 1530 and 1355cm^{-1}. The n.m.r. spectrum had signals at 7.79 (3Hs), 7.58 (3Hs), 4.61 (2Hs), 2.93 (1Hs), 2.66 (1Hs), 1.78 (4Hd) and 1.68 (4Hd). (Found; C, 61.20; H, 3.88; N, 6.26; $C_{23}H_{18}N_2O_8$ requires C, 61.33; H, 4.03; N, 6.22%).

Hydrogenolysis of (31).

2,5-Dimethyl-4-hydroxy-benzylalcohol (31; 500mg) was hydrogenated over 10% palladium/carbon in glacial acetic acid (25ml). When the uptake of hydrogen ceased (89ml; theoretical 75ml), the solution was filtered into water and extracted with dichloromethane. The extracts were washed with water, aqueous sodium bicarbonate, water and dried. Evaporation of the solvent gave 2,4,5-trimethyl-phenol (342mg). Recrystallisation from petrol gave m.p. 70-71°, mixed melting-point with an authentic sample gave no depression. The n.m.r. and infra-red spectra were identical with those of an authentic sample.

Treatment of 3,4-dimethylphenol with formaldehyde-base.

3,4-Dimethylphenol (8g) was dissolved in aqueous sodium hydroxide (60ml; 5%) and aqueous formaldehyde solution (6ml; 40%) added. The solution was stirred at room temperature for 2 days and then cooled in an ice-bath. Dilute acetic acid was added dropwise until the solution was neutral. The pale brown precipitate was filtered, washed with cold water and dried in vacuo. The crude product was recrystallised from benzene with charcoaling to give white crystals (6.1g). T.l.c. indicated the product was a mixture of two compounds, later shown to be (32) and (34).

Some of the product (500mg) was chromatographed on thick silica plates to give the two pure compounds (32; 193mg) and (34; 236mg).

4,5-Dimethyl-2-hydroxybenzyl alcohol (32) was recrystallised from benzene as white plates m.p. 102-104°, resolidified as needles which melted at 115.5-116.5°. ν_{max} 3490, 3230, 1380, 1300, 1285 and 1205cm^{-1}. The n.m.r. spectrum had signals at 7.85 (6Hd), 7.43 (1Hbs- D_2O exchanged), 5.28

(2Hs), 3.37 (1Hs), 3.24 (1Hs) and 3.02 (1Hbs - D_2O exchanged). (Found; C, 70.85; H, 8.00; $C_9H_{12}O_2$ requires C, 71.03; H, 7.95%).

Benzoylation of (32; 60mg) with p-nitrobenzoyl chloride (150mg) in pyridine (5ml) gave white needles m.p. 173° (chloroform-methanol) ν_{max} 1730, 1720, 1527 and 1355cm^{-1}. The n.m.r. spectrum had signals at 7.74 (6Hs), 4.70 (2Hs), 3.02 (1Hs), 2.72 (1Hs), 1.90 (3Hd) and 1.72 (4Hs). (Found; C, 61.23; H, 4.33; N, 6.23; $C_{23}H_{18}N_2O_8$ requires C, 61.33; H, 4.03; N, 6.22%).

The slower running product (34) was recrystallised from benzene as white needles m.p. 114.5-115°. ν_{max} 3500, 3350, 1385, 1212 and 1030cm^{-1}. The n.m.r. spectrum had signals at 7.84 (6Hs), 5.35 (6Hd- containing 2 exchangeable protons), 3.17 (1Hs) and 1.07 (1Hs - D_2O exchanged). (Found; C, 66.16; H, 7.90; $C_{10}H_{14}O_3$ requires C, 65.91, H, 7.74%).

Treatment of (34; 90mg) in dry pyridine (5ml) with p-nitrobenzoyl chloride (280mg) gave the tri-p-nitrobenzoate derivative of (34) m.p. 203-205° (chloroform-methanol).

ν_{max} 1730, 1710, 1530 and 1350cm^{-1}. The n.m.r. spectrum had signals at 7.58 (3Hs), 7.53 (3Hs), 4.67 (2Hs), 4.55 (2Hs), 2.53 (1Hs), 1.93 (4Hs), 1.87 (4Hs) and 1.72 (4Hs). (Found; C, 58.67; H, 3.51; N, 6.40; $C_{31}H_{23}N_3O_{12}$ requires C, 59.13; H, 3.68; N, 6.67%).

Hydrogenolysis of (32).

4,5-Dimethyl-2-hydroxybenzyl alcohol (32) was hydrogenated under the conditions used for (31). After the usual work-up, 2,4,5-trimethylphenol was obtained, identical in all respects with an authentic specimen.

Hydrogenolysis of (34).

Hydrogenolysis of (34) as above gave 2,3,4.6-tetramethylphenol. Recrystallisation from petrol gave white needles m.p. 80° (lit. 80°)[17]. ν_{max} 3415, 1580, 1480 and 1220cm^{-1}. The n.m.r. spectrum had signals at 7.95 (12Hs), 3.23 (1Hs) and 5.59 (1Hs - D_2O exchanged).

5-Cyano-2,4-dimethylphenol (35).

The o-dienone (21; 634mg) was dissolved in dry dimethylformamide (30ml) and solid potassium cyanide (175mg) added. After 1 hour the reaction mixture had crystallised and t.l.c. showed no starting material. Water was added and the solution extracted with dichloromethane. The extracts were washed with dilute sulphuric acid, aqueous sodium bicarbonate, water, and dried. Evaporation of the solvent gave pale yellow crystals (35; 302mg). Filtration through a short column of alumina afforded white crystals (35; 285mg). Recrystallisation from benzene-petrol gave m.p. 124-125°. ν_{max} 3400, 2230, 1230 and 1160cm^{-1}. The n.m.r. spectrum had signals at 7.75 (3Hs), 7.60 (3Hs), 4.28 (1Hbs- D_2O exchanged) and 2.96 (2Hs). (Found; C, 73.65; H,6.07; N, 9.53; C_9H_9NO requires C, 73.45; H, 6.16; N, 9.52%).

Attempted base hydrolysis of (35).

The nitrile (35; 72mg) was dissolved in ethanol (2ml) and potassium hydroxide (400mg) dissolved in water (2ml) added. The mixture was refluxed for 30 hours,

neutralised with concentrated hydrochloric acid, and extracted with chloroform. The dried extract was evaporated to give a crystalline residue (35; 70mg). The infra-red spectrum of the total product showed no carbonyl absorption and a strong nitrile band at 2230cm^{-1}.

Attempted acid hydrolysis of (35).

The nitrile (35; 50mg) was suspended in concentrated sulphuric acid (4ml) and water (2ml), and the mixture refluxed for 5 hours. The solution was extracted with chloroform and the dried extracts evaporated to give the crude product (5mg). The infra-red spectrum of the total product had 3560, 1710 and 1680cm^{-1}.

Treatment of (35) with hydrogen chloride in methanol.

The nitrile (35; 20mg) was dissolved in dry methanol (2ml) and dry hydrogen chloride bubbled through the solution for 5 hours. The solution was left overnight and then poured into water and extracted with dichloromethane. The dried extracts were evaporated to give

(35; 19mg). The infra-red spectrum of the total product was identical with that of the starting material (35).

5-Cyano-2,4-dimethylanisole (36).

The nitrile (35; 170mg) was dissolved in dry acetone (5ml) and dimethylsulphate (218mg) and potassium carbonate (450mg) added. The suspension was refluxed for 1 1/2 hours under nitrogen with stirring, then poured into water and extracted with dichloromethane. Evaporation of the dried extracts gave white crystals of (36; 180mg). Recrystallisation from 60-80° petrol gave long needles m.p. 73.5°. ν_{max} 2210 and 1267cm^{-1}. The n.m.r. spectrum had signals at 7.80 (3Hs), 7.58 (3Hs), 6.21 (3Hs), 3.07 (1Hs) and 2.97 (1Hs). (Found; C, 74.36; H, 6.89; N, 8.69; $C_{10}H_{11}NO$ requires C, 74.51; H, 6.88; N, 8.69%).

2,4-Dimethyl-5-methoxybenzoic acid (37).

The ether (36; 170mg) was dissolved in ethanol (5ml) and potassium hydroxide (450mg) dissolved in water (5ml) added. The solution was refluxed for 48 hours,

acidified with concentrated hydrochloric acid and extracted with chloroform. Evaporation of the dried extracts gave the crystalline acid (37; 175mg). Recrystallisation from benzene-petrol gave white needles. m.p. 170°. ν_{max} 3000 (very broad) 1685, and 1260cm^{-1}. The n.m.r. spectrum had signals at 7.77(3Hs), 7.44 (3Hs), 6.16 (3Hs), 2.98 (1Hs), 2.47 (1Hs) and -1.70 (1Hbs - D_2O exchanged). (Found; C, 66.50; H, 6.49; $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%),

2,4-Dimethyl-5-methoxybenzyl alcohol (39).

The acid (37; 152mg) was dissolved in dry methanol (3ml) and concentrated sulphuric acid (50mg) added.. The solution was refluxed for 8 hours, poured into water and extracted with ether. The extracts were washed with aqueous sodium bicarbonate, water and dried. Evaporation of the ether gave the ester (38; 145mg) as an oil. ν_{max} 1718, 1262 and 1240cm^{-1}. Attempted demethylation of (38) with boron trichloride in dry dichloromethane at room temperature gave only starting material on working-up after several hours. Therefore, the ester (38; 140mg) was taken up in dry ether (3ml) and lithium aluminium hydride (20mg) added at room temperature with stirring.

Aqueous ammonium chloride was carefully added and the mixture extracted with ether. The dried extracts were evaporated to give (39; 100mg). Sublimation under reduced pressure (0.1mm/30°) gave long needles m.p. 53.5-54°. ν_{max} 3310, 3210, 1620, and 1278cm^{-1}. The n.m.r. spectrum had signals at 8.13 (1Hbs - D_2O exchanged), 7.82 (3Hs), 7.76 (3Hs) 6.20 (3Hs), 5.39 (2Hs), 3.27 (1Hs), and 3.19 (1Hs). (Found; C, 72.40; H, 8.40; $C_{10}H_{14}O_2$ requires C, 72.26; H, 8.49%).

Methylation of (33).

The benzyl alcohol (33; 22mg) was dissolved in dry acetone (3ml) and dimethylsulphate (60mg) and anhydrous potassium carbonate (120mg) added. The stirred suspension was refluxed under nitrogen for 6 hours, until no starting material remained. The cooled reaction mixture was poured into water and extracted with dichloromethane. Evaporation of the dried extracts gave the crude product. Sublimation (0.1mm/30°) afforded long needles of (39; 15mg) having the same infra-red spectrum, m.p., and mixed m.p. as the authentic sample.

6-(p-Nitrobenzoyloxy)-6-phenylcyclohexa-2,4-dienone (41).

2-Hydroxybiphenyl (1.02g) and bis p-nitrobenzoyl peroxide (2.988g) were refluxed in dry chloroform (40ml) for 12 hours. The deep red solution was worked-up in the usual way to give a dark oil. Chromatography on alumina, eluting with benzene, afforded the crystalline o-dienone. Recrystallisation from chloroform-methanol gave pale yellow needles (41; 250mg) m.p. 173° ν_{max} 1715, 1675, 1525 and 1350cm^{-1}. λ_{max} 259, 295(sh) n.m. (ε 19,200; 6,500). The n.m.r. spectrum had signals at 3.85 (1H double doublet), 3.45 (2Hm), 2.55 (6Hm) and 1.71 (4Hs). (Found; C, 67.96; H, 4.08; N, 4.07; $C_{19}H_{13}NO_5$ requires C, 68.06; H, 3.91; N, 4.18%).

Treatment of (41) with refluxing toluene.

The o-dienone (41; 70mg) was dissolved in dry toluene (30ml) and the solution refluxed for 72 hours, at which time t.l.c. showed no starting material remained. The two close running products were separated on silica

plates to give the less polar fraction as a pale yellow oil (42; 26mg). $\nu_{max}^{CHCl_3}$ 3520, 3260, 1730, 1538 and 1350cm^{-1}. The n.m.r. spectrum had signals at 4.73 (1Hbs - D_2O exchanged), 2.93 (3Hm), 2.57 (5Hs) and 1.67 (4Hs).

The more polar fraction was isolated as an oil which eventually crystallised (43; 34mg). Recrystallisation from chloroform-petrol gave m.p. 126-127°. ν_{max}^{Nujol} 3410, 1745, 1720, 1535 and 1353cm^{-1}, $\nu_{max}^{CHCl_3}$ 3520, 3260, 1740, 1540 and 1350cm^{-1}. The n.m.r. spectrum, run in deuterochloroform containing a trace of D_6-DMSO had signals at 6.92 (1Hbs - D_2O exchanged), 2.72 (8Hm) and 1.78 (4Hs). (Found; C, 68.00; H, 4.12; N, 4.10; $C_{19}H_{13}NO_5$ requires C, 68.06; H, 3.91; N, 4.18%).

Saponification of (42).

The less polar fraction (42; 25mg) was dissolved in dry methanol (2ml) and sodium methoxide (1 eq.) added in dry methanol (0.1ml). After magnetically stirring for 5 minutes under nitrogen the solution was neutralised with CO_2 followed by quenching in water. The aqueous mixture was extracted with dichloromethane. Evaporation of the dried extracts gave an oil (24mg) which was chromatographed

on a thin silica plate to give 2,5-dihydroxybiphenyl (10mg). Recrystallisation from aqueous ethanol gave m.p. 95-98° (lit. m.p. 96-98°)[31]. The infra-red and n.m.r. spectra and t.l.c. behaviour were identical to those of an authentic specimen prepared as indicated below.

2,5-Dihydroxybiphenyl.

2-Hydroxyphenol was oxidised with Fremy's salt to give 2-phenylbenzoquinone[20]. m.p. 113-114° (ethanol) (lit. m.p. 114°)[20]. ν_{max} 1652, 1640 and 1630cm^{-1}. The n.m.r. spectrum had signals at 3.19 (3Hs) and 2.55(5Hs).

2-Phenylbenzoquinone (2g) was dissolved in benzene (40ml) and hydrogenated over 10% palladium on carbon (uptake 250ml). The solution was filtered and evaporated. Crystallisation from aqueous ethanol gave 2,5-dihydroxybiphenyl (1.4g), m.p. 95-97° (lit. m.p. 96-98°)[31]. ν_{max} 3500, 3250 and 1595cm^{-1}. The n.m.r. spectrum had signals at 5.38 (1Hs - D_2O exchanged), 5.14 (1Hs - D_2O exchanged), 3.25 (3Hm) and 2.56 (5Hs).

Saponification of (43).

The more polar fraction (43; 25mg) was dissolved in dry methanol (2ml) and sodium methoxide (1 eq.) added in dry methanol (0.1ml), under nitrogen. Usual work-up after 5 minutes gave an oil (21mg). Chromatography on a thin silica plate gave 2,3-dihydroxybiphenyl (8mg). Sublimation at 100°/1mm provided pure material m.p. 111-113° (lit. m.p. 112-113°)[21]. ν_{max} 3460, 3350, 1612, 1585 and 1570cm^{-1}. The n.m.r. spectrum had signals at 5.03 (2H broad multiplet - D_2O exchanged), 3.17 (3Hs) and 2.58 (5Hs).

Treatment of (41) with refluxing pyridine.

The o-dienone (41; 105mg) was refluxed in dry pyridine (50ml) until t.l.c. showed no starting material remained (9 hours). Usual work-up gave a dark oil (95mg), which was chromatographed on thin silica plates to give (42; 24mg), (43; 39mg), (44; 13mg) and a trace of 2,3-dihydroxybiphenyl (4mg). The compound (44) had ν_{max} 3480, 1735, 1530, 1352cm^{-1}.

Saponification of (44).

The compound (44; 10mg) was dissolved in dry methanol (2ml) under nitrogen, and sodium methoxide (1 eq.) added in dry methanol (0.05ml). Usual work-up after 5 minutes, followed by preparative t.l.c. on silica gave 2,5-dihydroxybiphenyl, identical in all respects with the authentic sample.

Oxidation of phenol with bis-p-nitrobenzoyl peroxide.

Phenol (1.88g) and bis-p-nitrobenzoyl peroxide (6.64g) were dissolved in dry chloroform (120ml) and the solution was refluxed for 3 days. Work-up in the normal way gave the crude product (3.98g). This was suspended in methanol (20ml) and T.H.F. (20ml), under nitrogen. Potassium hydroxide (3g) in methanol-water (10ml; 1:1) was added, and the reaction immediately darkened and became homogeneous. After 1 hour at room temperature the solution was neutralised with 6N-hydrochloric acid and extracted with chloroform. The extracts were washed with aqueous sodium bicarbonate to remove p-nitrobenzoic acid, dried and evaporated to yield a dark oil. Sublimation of

this oil at 50°/1mm gave catechol (18%) m.p. 104-105° (lit. m.p. 105°)[30].

Reaction of sodium phenate with bis-p-nitrobenzoyl peroxide.

Sodium phenate (58mg) (prepared from phenol and sodium hydride in benzene in the usual way) was dissolved in dry glyme (4ml) and the solution cooled to -20°. Bis-p-nitrobenzoyl peroxide (166mg) was added in portions during 5 minutes. The reaction mixture was allowed to warm to room temperature and was left overnight. Water was added and the solution extracted with dichloromethane. The organic extracts were washed with aqueous sodium bicarbonate, water and dried. Evaporation of the solvent gave the crude product. Two recrystallisations from methanol gave long needles of phenyl-p-nitrobenzoate (49mg) m.p. 129° (lit. m.p. 126°)[30]. ν_{max} 1730, 1530, 1350cm^{-1}. T.l.c. of the mother liquors showed no trace of catechol-mono-p-nitrobenzoate, but indicated the presence of phenyl-p-nitrobenzoate, phenol and unreacted bis-p-nitrobenzoyl peroxide.

Preparation of 2,6-dimethyl-4-methoxyphenol (54)[28].

2,6-Dimethyl-4-methoxyphenol (54) was prepared from 2,6-dimethylphenol using the procedure developed by P.D. Magnus[28]. m.p. 77° (lit. m.p. 77°)[32] ν_{max} 3330, 1624cm^{-1}.

Reaction of 2,6-dimethyl-4-methoxyphenol with benzoyl peroxide.

2,6-Dimethyl-4-methoxyphenol (54; 101mg) and benzoyl peroxide (161mg) were dissolved in dry chloroform (8ml) and the solution was refluxed for 30 minutes. Work-up in the usual way gave a thick oil, which crystallised on triturating with petrol (55; X=H; 160mg). Recrystallisation from petrol gave m.p. 66-67°. ν_{max} 3370, 1690cm^{-1}. The n.m.r. spectrum had signals at 7.83 (3Hs), 6.38 (3Hs), 4.81 (2Hs), 3.43 (2Hs), 2.68 (4Hm - one hydrogen exchanged by D_2O) and 2.08 (2Hm). (Found; C, 70.43; H, 5.92; $C_{16}H_{16}O_4$ requires C, 70.57; H, 5.92%).

Reaction of (54) with bis-p-nitrobenzoyl peroxide.

2,6-Dimethyl-4-methoxyphenol (54; 76mg) and bis-p-nitrobenzoyl peroxide (166mg) were dissolved in dry chloroform (10ml) and the solution was stirred at room temperature. After 1 hour t.l.c. showed none of the starting materials were present. Usual work-up gave a pale orange crystalline solid (55, X=NO_2; 136mg). Recrystallisation from benzene-petrol gave pale orange needles m.p. 133°. ν_{max} 3505, 1705, 1532, 1360cm^{-1}. The n.m.r. spectrum had signals at 7.76 (3Hs), 6.26 (3Hs), 4.63 (2Hs), 4.55 (1Hs - exchanged by D_2O), 3.27 (2Hs) and 1.78 (4Hs). (Found; C, 60.69; H, 4.63; N, 4.41; $C_{16}H_{15}NO_6$ requires C, 60.56; H, 4.73; N, 4.42%).

Attempts to trap the quinone methide (58).

(a) Reaction in ethylvinyl ether.

The phenol (54; 50mg) and bis-p-nitrobenzoyl peroxide (111mg) were dissolved in dry ethylvinyl ether (50ml) and the solution stirred overnight at room

temperature. After the usual work-up the n.m.r. spectrum of the total product indicated that no trapping had occurred.

(b) Acetate ion.

2,6-Dimethylphenol-4-methoxyphenol (54; 76mg) and bis-p-nitrobenzoyl peroxide (166mg) were dissolved in dry glyme (10ml; previously refluxed with anhydrous potassium acetate for 2 hours), and anhydrous potassium acetate added. After 1 hour at room temperature the reaction was poured into water and the solution extracted with dichloromethane. The extracts were washed with aqueous sodium bicarbonate, water, dried and evaporated. The n.m.r. spectrum of the total product showed that some trapping had taken place, 68% of the usual product (55; X=NO_2) and 32% of (56) being present.

Sodium 2,6-dimethyl-4-methoxyphenate.

2,6-Dimethyl-4-methoxyphenol (54; 101mg) was dissolved in dry glyme (5ml) and sodium hydride (32mg of a 50% dispersion; previously washed with benzene) was added. The suspension was refluxed for 1 hour, cooled

and filtered. The solution of the sodium salt was used in the next experiments.

Reaction of sodium 2,6-dimethyl-4-methoxyphenate with benzoyl peroxide.

(a) At -20°.

The solution of the sodium salt (50mg) in glyme (2.5ml) was cooled to -20° and benzoyl peroxide (80mg) added in small portions over a period of 5 minutes. After a further 30 minutes the reaction mixture was poured into water and extracted with dichloromethane. The organic extracts were washed with sodium bicarbonate, water, dried and evaporated. T.l.c. indicated that a number of products had been formed, the main ones being (55; X=H) and 2,6-dimethylbenzoquinone, in the ratio 1:2.

(b) At -76°.

The above experiment was repeated at -76° and the total product examined by n.m.r. The major product was

(55; X=H ca. 60%) with only a trace of 2,6-dimethyl-benzoquinone.

3,6-Dimethoxy-2-hydroxybenzamide (64).

This was prepared as described in Part I, page 151.

Oxidation of (64) with benzoyl peroxide.

The hydroxyamide (64; 20mg) and benzoyl peroxide (25mg) were refluxed in dry chloroform in the dark. After 8 hours t.l.c. showed very little reaction. Addition of a further quantity of benzoyl peroxide (100mg) and refluxing for a further 4 days also had no real effect. After the usual work-up t.l.c.-showed mainly starting materials, with a trace of a compound slightly less polar than the amide, (64) $\nu_{max}^{CHCl_3}$ (total product) 3530, 3420, 1780, 1760, 1740, 1655, 1606cm^{-1}.

Oxidation of (64) with bis-p-nitrobenzoyl peroxide.

The amide (64; 357mg) was dissolved in dry chloroform (25ml) and bis-p-nitrobenzoyl peroxide (602mg) added. The solution was refluxed in the dark for 14 hours with

magnetic stirring. Usual work-up gave an orange solid (560mg). T.l.c. showed one new spot, slightly less polar than the starting amide (64). Chromatography on silica plates gave pure material. Recrystallisation from chloroform-ether gave pale orange needles (68; 150mg) m.p. 198.5°. ν_{max} 3480, 3250, 3195, 1727, 1530, 1357cm^{-1}. The n.m.r. spectrum had signals at 6.16 (3Hs), 6.11 (3Hs), 3.82 (2H; broad multiplet), 3.11 (1Hs), 1.60 (4Hs) and -3.43 (1Hs - D_2O exchanged). (Found; C, 53.23; H, 3.86; N, 7.50; $C_{16}H_{14}N_2O_8$ requires C, 53.04; H, 3.90; N, 7.73%).

The experimental procedures for compounds (62; R=H or CHO), (63; R=H or CHO), (65), (66), (67) and (70) are reported by S. Djokic[29].

Rearrangement of (21) in the presence of radical traps.

The o-dienone (21; 15mg) was dissolved in dry toluene (5ml) and cyclohexene (430mg:100eq.) or norbornadiene (550mg:100eq.) added. The solution was refluxed and rearrangement to (23) was complete in the expected time (40 hours). The product was identical in

all respects with an authentic sample.

Kinetics.

The rearrangement of (77; X=H or OMe) was followed by observing the decrease in the ultra-violet maximum at 310n.m. In the case of (77; $X=NO_2$) the decrease in absorption at 325n.m. was measured. The temperature was varied by using an apparatus in which the solution of (77) was immersed in the vapour of different refluxing solvents. The refluxing solvents used were benzene, triethylamine, n-propanol, toluene and n-butanol.

An example of a typical run with (77; $X=NO_2$) is given below.

Temperature:- 97° Concentration:- 0.216g/l (xylene)

A_0=1.43 A_∞ =0.78

A_0 = initial absorbance A_t= absorbance at time t (secs)

A_∞ = absorbance at equilibrium.

A_t	t	$\log_{10}\frac{A_0-A_\infty}{A_t-A_\infty}$	A_t	t	$\log_{10}\frac{A_0-A_\infty}{A_t-A_\infty}$
1.405	300	0.0170	1.15	2400	0.2447
1.365	600	0.0457	1.12	2700	0.2944
1.32	900	0.0805	1.10	3000	0.3078
1.265	1200	0.1272	1.075	3300	0.3581
1.235	1500	0.1549	1.05	3600	0.3815
1.20	1800	0.1897	1.035	3900	0.4237
1.19	2100	0.2001			

A plot of $\log_{10}\frac{A_0-A_\infty}{A_t-A_\infty}$ against t gave a straight line of slope $\frac{k}{2.303}$, where k is the rate constant.

Slope = $\frac{0.48}{77\text{x}60} = \frac{k}{2.303}$. Therefore k = $2.4\text{x}10^{-4}\text{sec}^{-1}$.

If k_1 and k_2 are the rate constants at temperatures (^oK) T_1 and T_2, then the activation energy (E) can be calculated from the formula

$$E = \frac{1.98 \text{ x } 2.303 \text{ x } (\log k_2 - \log k_1)}{\frac{1}{T_1} - \frac{1}{T_2}}$$

Since the rate constant was found at three temperatures (page 133), three values for E were obtained for each rearrangement. The mean value of these is the activation energy quoted on page 133.

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