The chemistry of dispirotetraenediones

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THE CHEMISTRY OF

DISPIROTETRAENEDIONES

by

IVOR EDWARD WILLIAMS, G.R.I.C.

A Doctoral Thesis

submitted in partial fulfilment of the requirements

for the award of

Doctor of Philosophy of

Loughborough University of Technology

August 1976

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Department of Chemistry

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A literature survey of the oxidative coupling of phenols and phenolic ethers has been carried out and is included.

The thermal decomposition of dispiro(5,0,5,3)pentadeca-1,4,8,11-tetraene-3,10-dione, prepared by oxidation of the appropriate diphenol, has been studied in both solution and in the solid state. The decomposition in ethanol occurs by approximately first order kinetics at 74°C, the rate is not completely insensitive to concentration, however, suggesting a second order component. Decomposition in benzene is kinetically less regular; it is characterised by a slow initial phase followed by a more rapid reaction leading to complete decomposition. Addition of benzoyl peroxide has no effect on the decomposition rate in benzene; however, addition of 2,6-di-t-butyl-4-methyl phenol accelerates the decomposition in both benzene and ethanol.

In dimethyl sulphoxide the decomposition of the bisdione has been studied by $^1H$ n.m.r. spectroscopy. The product is entirely aromatic and comparison of signal strengths for aryl and hydroxylic hydrogen indicates the involvement of both carbon–carbon and carbon–oxygen coupling.

The decomposition of the bisdienone in the solid state proceeds much more rapidly than in solution, the studies being carried out using infra-red spectroscopy and differential calorimetry. Investigations using e.s.r.

(i)
have shown that free radicals are produced during the decomposition in the solid state.

Attempts to prepare ortho-para coupled analogues, by oxidation of appropriate phenols surprisingly gave only carbon-oxygen coupled products.

Attempts to prepare a bridged bisdienone system which would be expected to be thermally more stable than the non-bridged forms proved to be unsuccessful.

The synthesis of N-acetyl-14-azadispiro(5,0,5,4)hexadeca-1,4,8,11-tetraene-3,10-dione has been achieved via the oxidative coupling of the corresponding diphenol. The $^1$H n.m.r. spectrum is complex but the structure of the bisdienone has been proved by a series of experiments involving deuterium labelled precursors. Attempts to convert this bisdienone and its N-trifluoroacetyl homologue to mesembrine type alkaloids were unsuccessful.
ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to Professor Kirby for his considerable help and encouragement throughout the course of this work and to Dr. Heaney for many helpful discussions.

I am indebted to the Science Research Council for a research studentship and to both Loughborough University of Technology and the University of Glasgow for the privilege of working in their laboratories. I would like to thank the technical staff at both universities for the services which they provided.

Finally my thanks are due to my wife for typing the manuscript and for her understanding and help throughout the work.
CHAPTER ONE

GENERAL INTRODUCTION
Oxidative Coupling of Phenols and Phenolic Ethers

Coupling of Phenolate Radicals.

It has been recognised for some time\textsuperscript{1,2} that a considerable diversity of structural types can be derived from the oxidation of phenols with such reagents as ferric chloride or potassium ferricyanide. It was these pioneering investigations of Pummerer which placed the radical theory of coupling of phenols on a sound basis.

Phenolate radicals are formed from phenolate anions by removal of one electron or alternatively, from phenols by loss of a proton as well as removal of one electron. They are more stable than alkyl radicals, because of the spread of the odd electron by resonance over the ortho and para positions of the aromatic ring. The combined evidence of chemical reactivity\textsuperscript{3,4}, paramagnetism\textsuperscript{5,6,7,8} and e.s.r. studies\textsuperscript{8,9}, for the existence of phenolate radicals is now quite formidable.

Once phenolate radicals have been generated, they may be converted into stable molecular products by several processes. Reduction gives back the parent phenol,\textsuperscript{6,7,8} coupling with reactive molecules such as oxygen, bromine and nitrogen dioxide, affords non-radical products and self coupling furnishes dimers. The latter can be formed by carbon - carbon, carbon - oxygen or, in principle, oxygen - oxygen coupling as shown below.
When coupling has occurred, the dimers, where possible, tautomerise to the corresponding phenolic product.
Examples of para - para coupling, type (1), are provided by the formation of 4,4'-dihydroxydiphenyl (7) from the lead tetra-acetate oxidation of phenol$^{10}$, 3,3'-dimethyl-4,4'-dihydroxydiphenyl (8) from the anodic oxidation of o-cresol$^{11}$ and (9) from the oxidation of anthrol$^{12,13}$.

Some examples of ortho - ortho coupling, type (2), are provided by dehydrodivanillin (10), obtained by oxidation of vanillin$^{14}$, dehydrodieugenol (11)$^{15}$, and dehydrodi-o-cresol (12)$^{10}$, all prepared from the appropriate precursor in a similar manner.
The ortho-para coupling (3) does not occur as frequently as the ortho-ortho (2) and para-para coupling (1). The best authenticated example of ortho-para coupling is the formation of Pummerer's ketone (13) by oxidation of para-cresol and subsequent addition of the hydroxyl group to the dienone system.
a-Naphthol yields, by oxidation with ferric chloride, all three possible carbon - carbon coupling products\textsuperscript{17,18}.

Dimeric ethers, types (4) and (5), are not normally produced in high yields. They have however been detected in anodic oxidations in addition to other products\textsuperscript{11,19,20}.

The formation of quinol ethers is preferentially intramolecular when the phenol residues to be coupled are already linked. An example of ether formation is the oxidation of 2,4'-dihydroxydiphenyl ether with silver oxide to give the dienone (14) in 1 - 2\% yield\textsuperscript{21}. 
Ether formation is further illustrated by the oxidation of the diphenol (15) to the dienone (16) in 83% yield\textsuperscript{22}. Ether formation is favoured when carbon - carbon coupling is sterically hindered; this is well illustrated by comparing the yields of ethers in the two oxidations which produce the ethers (14) and (16) respectively.

An example of quinol ether production by oxidative dimerisation is given in the oxidation of the phenol (17) to the quinol ether (18)\textsuperscript{23}. 

\begin{equation} \text{But} \quad \text{But} \quad \text{But} \quad \text{But} \quad \text{But} \quad \text{But} \quad \text{But} \end{equation}
In a few cases dimers of the type (6) have been reported as stable products of phenolic oxidations. Recent re-examination of the structures however, has shown these to be of the quinol ether type (4) or (5). There appear to be no authentic examples of diaryl peroxides; presumably the C - C bond is too weak and the phenolate radicals couple in other ways (cf. (15) \( \rightarrow \) (16)).

The formation of trimeric and polymeric products can be explained as a consequence of further oxidation of the dehydro-dimers.

If the phenolate radical, generated by oxidation, has large unreactive groups in the positions ortho and para to the oxygen, dimerisation is inhibited because all possible positions of reaction are sterically protected.
When 2,4,6-tri-t-butylphenol is oxidised with potassium ferricyanide under nitrogen the phenolate radical (19) can be isolated as dark blue crystals or as a stable blue solution because dimerisation is sterically hindered$^7,32$. In the presence of oxygen the phenolate radical (19) forms the peroxide (20).

![Chemical structures](image)

Additional stability is gained if the blocking groups on the phenolate radical can delocalise the free electron as is illustrated by the 2,4,6-triphenyl-
phenolate radical which is reported to be inert to oxygen\textsuperscript{26,29}. If the blocking group on the radical (21) has an $\alpha$-hydrogen atom the radical will undergo bimolecular disproportionation to the quinone methide (22) and the starting phenol (23)\textsuperscript{33}.

The stability of the quinone methide is dependent upon the nature of $R$. If both $R$ groups are hydrogen the quinone methide is very unstable; this has caused some debate as to its existence\textsuperscript{34}. If the quinone methide (22) is stabilised by substituents ($R = \text{CH}_3$, or $\text{Ph}$) it can be isolated\textsuperscript{33,35,36}.
Phenol Coupling in Synthesis and Biosynthesis.

The involvement of phenolic oxidative coupling in biosynthesis and its versatile synthetic applications have long been appreciated and have been well reviewed. Up to the time of the writing of these reviews synthetic oxidations had been confined, in the main, to a small number of inorganic oxidants.

The use of these oxidants has now been extended further and, additionally, a number of other methods of phenolic oxidative coupling have now been developed. This survey will be confined mainly to the most recent applications, classified for convenience under the various oxidising systems.

**Ferric chloride and potassium ferricyanide.**

The two reagents, ferric chloride and potassium ferricyanide, which were among the first used in synthetic phenolic oxidation, are still employed extensively at the present time. The method of use remains unchanged, that is potassium ferricyanide in alkaline solution using a single or a two phase system, or ferric chloride in neutral or acidic solution. Both oxidants have been applied to the oxidation of simple and complex phenols.

One of the more prominent recent users of these two reagents for phenolic oxidative coupling is Kametani. The isoquinoline alkaloids are probably the major group
of alkaloids whose biosynthesis is thought to involve phenol oxidation and it is in this field that Kametani has concentrated his interests in phenol oxidative coupling. The work done by him has been covered in recent reviews\textsuperscript{39,40} and can be illustrated by the following examples.

Following the isolation of several groups of alkaloids, androcymbine\textsuperscript{41}, melanthioidene\textsuperscript{42}, kreysiginine\textsuperscript{43} and kreysiginone\textsuperscript{44}, by Battersby, which are derived biogenetically by phenolic oxidation of 1-phenethylisoquinolines, Kametani anticipated the presence of homoerythrine type alkaloids and investigated their synthesis by phenolic oxidation\textsuperscript{45,46}. In this work substituted \textit{N}-phenethyl-3-phenylpropylamines were oxidised in a two phase system using potassium ferricyanide and sodium carbonate. Other systems involving potassium ferricyanide and ferric chloride were not successful for this oxidation. Two homoerythrinadienone type compounds were synthesised in this manner. Following this work three homoerythrina alkaloids were isolated by an Australian group\textsuperscript{47}, thus substantiating Kametani's assumption.

An example of the successful use of ferric chloride as an oxidising agent is given by the oxidation of 1,2,3,4-tetrahydro-7-hydroxy-1-(2-hydroxy-4-methoxyphenethyl)-6-methoxy-2-methylisoquinoline(52) and a methoxy analogue(53) to give 	extit{ortho}-dienone type homoproaporphines\textsuperscript{48}(54,55).
Ferric chloride has been used successfully in a number of phenolic oxidative coupling reactions by Frank. In one such example\textsuperscript{49} he found that laudanosoline (25) and norlaudanosoline (24) may be converted into aporphines (27,28) surprisingly easily and in good yields.
(24) $R = R_1 = H$

(25) $R = \text{Me, } R_1 = H$

(29) $R = R_1 = \text{Me}$

(68) $R = \text{COCl}, R_1 = \text{Me}$

(27) $R = R_1 = \text{H}; 63\%$

(28) $R = \text{Me, } R_1 = \text{H}; 52\%$

(65) $R = R_1 = \text{Me}; 53\%$

(69) $R = \text{COCl}, R_1 = \text{Me}; 7\%$
It was found that this reaction was only successful if carried out using 0.2 molar ferric chloride. If a more dilute solution, or potassium ferricyanide, is used as oxidant the desired product is not obtained. The explanation offered is that the ferric chloride forms a complex (26) with the pyrocatechol hydroxyl groups and, at the same time, oxidises the compound to the aporphine. This complex formation hinders the formation of an ortho-quinone intermediate which would not lead to the desired product. This appears to be one of the best methods available for aporphine synthesis.

Crinine and about thirty similar Amaryllidaceae alkaloids are formed in the plant cell by oxidative coupling of norbelladine derivatives as predicted by Barton and Cohen and verified by isotope experiments. Based on this biosynthetic pathway the ring system of the crinine alkaloids was easily prepared by phenolic oxidative coupling of a norbelladine derivative (30; R = OMe).
The amine group was first protected by trifluoroacetylation. Oxidation with ferric chloride gave a dienone and the crinine ring system was then completed by hydrolysis with sodium carbonate.

Frank has also used ferric chloride as the oxidant in the synthesis of ergot pigments by the oxidative coupling of phenols\textsuperscript{51}. Ferric chloride has been applied to the formation of polymers by oxidative coupling of phenols\textsuperscript{52}. In this work 2,6-xylenol was coupled using ferric chloride and conditions were studied to optimise yields.

The synthesis of the isoquinoline alkaloid cularine (57), was carried out independently by two different groups\textsuperscript{53,54} by the same route using potassium ferri-cyanide to oxidise 1,2,3,4-tetrahydro-8-hydroxy-1-(3-hydroxy-4-methoxybenzyl)-7-methoxy-2-methylisoquinoline (56) to give a carbon - oxygen - carbon linkage.
Heterogeneous oxidising agents.

Heterogeneous reaction conditions, in which a metal oxide, such as manganese dioxide or lead dioxide, is the oxidising agent, have also been used for oxidative coupling of phenols for a considerable period. In the main, these systems have been applied to simple phenols with varying degrees of success. These reagents, often suffer from poor selectivity and usually give a mixture of quinone dimers and polymers, the product distribution varying widely with the nature of the reagent.

In an attempt to improve selectivity another heterogeneous system, silver carbonate on celite, has been introduced. In neutral media, selective oxidative coupling of hindered phenols, such as 2,6-dimethyl and 2,6-di-t-butylphenol, was effected to yield the corresponding diphenoquinones. When this reagent was applied to natural products for oxidative coupling only low yields of oxidised products were obtained.

Copper complexes and molecular oxygen.

Copper complexes, which involve cupric or cuprous chloride and an amine are now being used extensively by workers interested in the preparation of polyphenylene oxides by phenol oxidative coupling. In reactions involving copper complexes the products can vary depending on the reaction conditions and the amine used. When morpholine or piperidine, for example, are used in
an oxygen atmosphere dimers and trimers containing carbon - oxygen - carbon bonds, carbon - carbon bonds and carbon - nitrogen bonds, have been reported. The type of product obtained is, of course, influenced by the substituents on the phenol ring. The mechanism of the reaction involved in the oxidative coupling of phenols using copper complexes has been investigated and it has been found that the reaction only takes place when the copper is not fully co-ordinated. In complexes where the copper atom is firmly bound in chelate groups such as ethylacetylacetonate no electron transfer occurs.

**Enzymic oxidation.**

It has been considered for some time that oxidative coupling in Nature is assisted by enzymes. Following the work of Barton, who oxidised α-cresol to Pummerer's ketone using hydrogen peroxide/peroxidase, and Baxter who attempted, unsuccessfully, to oxidise benzylisoquinolines in a similar way, Kametani examined the use of enzymes for isoquinoline alkaloid synthesis. In his first paper, head - to - tail coupling of 1,2,3,4-tetrahydro-7-hydroxy-1-(4-hydroxyphenethyl)-6-methoxy-2-methylisoquinoline (58), using hydrogen peroxide and peroxidase obtained from potato peelings, to yield promelanthioidine (59) was reported. When the same isoquinoline was oxidised using *Wasabia japonica* peroxidase and hydrogen peroxide again a dimer was obtained but this time it was linked head - to - head (60).
This approach to the synthesis of isoquinoline alkaloids and other similar reports has been of little preparative value due to formation of complicated mixtures or poor yields. Therefore, until recently, it has not been used widely as an alternative to chemical methods of oxidation. In contrast, the use of the purified enzyme horseradish peroxidase has been recently reported to effect oxidative coupling of isoquinolines in preparative yields. (13) - (+)-Laudanosoline hydrobromide (61) and (1R) - (-)-laudanosoline methiodide (62) were oxidised to dibenzopyrrocoline (63) and the quaternary aporphine (64) (carbon - carbon coupling) in yields of 81% and 63% respectively.
These results may lead to an increase in the use of enzymes in the oxidative coupling of phenols.

**Manganese tris(acetylacetonate).**

The complex, manganese tris(acetylacetonate), showed considerable promise as an oxidising agent for phenolic coupling when it was first introduced. It was used to dimerise 1-naphthol in over 60% yield and was also applied to the coupling of 2,6-disubstituted phenols in good yields. It offers the advantage of solubility in organic solvents and it does not over-oxidise; potassium ferricyanide will oxidise 2,6-di-t-butylphenol to the diphenoquinone whereas manganese tris(acetylacetonate) yields the diphenol.
Few examples of the use of this reagent have been reported and therefore its scope remains unknown. Two examples where it has been used are in the preparation of polyphenylene oxides from 2,6-xylenol\(^74\) and the intramolecular coupling of 1,14-bis(3,5-dihydroxyphenyl)-tetradecane\(^75\).

**Vanadium oxytrichloride.**

An oxidising agent whose use in the field of oxidative coupling of phenols has been reported more frequently is vanadium oxytrichloride. This was first reported by Schwartz\(^76\), who used it to effect the intramolecular coupling of 1-(3-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (31) to yield the spirodienone (71).
He also carried out this oxidation using potassium ferricyanide, ferric chloride and manganic tris(acetylacetonate). The yield of 76% obtained using vanadium oxytrichloride shows that it offers considerable advantages over the other reagents which gave yields of 4%, 7% and 10% respectively. In all the above experiments Schwartz was unable to detect any ortho - para coupled products. Schwartz also claims that this reagent has the advantage of being incorporated into the diphenol prior to the oxidation reaction thus allowing the electron transfer step to be carried out in high dilution, to avoid polymerisation, without a large excess of oxidising agent.

Having shown the great potential of this reagent, Schwartz then sought to apply it to biogenetic - type synthesis of phenolic alkaloids. His first success was in the synthesis of (\(\ddagger\)) maritidine from 0- methyl­norbelladine (30; \(R = H\)). This method offers an alternative to that reported by Frank (see above) who used ferric chloride.

The trifluoroacetyl derivative of 0 - methyl norbelladine was oxidised and (\(\ddagger\)) epimaritidine was obtained from the product by hydrolysis followed by sodium borohydride reduction and methylation. Epimerization was accomplished by refluxing in dilute hydrochloric acid. The yield for the oxidation step was 24%, double that obtained in using ferric chloride.

Schwartz followed this by oxidising reticuline (29),
as the perchlorate, to isoboldine (65) in 53% yield using vanadium oxytrichloride\textsuperscript{77}. This same reaction has also been attempted by Kametani\textsuperscript{56}, using vanadium oxytrichloride, potassium ferricyanide and silver carbonate on celite, but with little success.

Vanadium oxytrichloride has been applied successfully in a model reaction for the biosynthesis of Erythrina alkaloids\textsuperscript{78}, the oxidation step being effected in 34% yield.

These results indicate that the reagent may be of general utility in the oxidative coupling of benzyltetrahydroisoquinolines.

Carrick\textsuperscript{79} compared vanadium oxytrichloride with vanadium tetrachloride for the oxidative coupling of phenols. He found that, whereas vanadium tetrachloride oxidation of phenol produced \textit{para} - \textit{para}, \textit{ortho} - \textit{para} and \textit{ortho} - \textit{ortho} coupled dimers in the ratio of 8:4:1, vanadium oxytrichloride did not produce any coupling. He did however find that phenols with lower oxidation potentials were coupled by this reagent, 1-naphthol and 2-naphthol were coupled in 56% and 65% yields respectively. He considers the reaction to occur by rearrangement of electrons in a complex containing at least two phenoxide (or phenol) residues and at least one metal centre, because of the volume of hydrogen chloride evolved.
Electrochemical oxidation.

Electrochemical coupling of phenols has not been assiduously pursued until quite recently. Although carbon-carbon and carbon-oxygen-carbon dimers were obtained by Fitcher and his co-workers\textsuperscript{80,81} using lead dioxide anodes, it was not until the publication of Vermillion and Pearl\textsuperscript{82}, which includes a voltammetric study and some preparative examples, that interest was fully aroused in this field. One example which they reported was the coupling of vanillin to dehydrodivanillin (10) in about 65\% yield. Shortly afterwards this technique was applied to the electro-oxidation of phenolic tetrahydroquinolines. This was followed by papers by Johnston\textsuperscript{84} on hydroxyacetophenones and Kametani\textsuperscript{85} on p-cresol. Johnston coupled several hydroxyacetophenones and obtained reasonable yields (7 - 53\%) of carbon-carbon dimers. Kametani obtained low yields of a carbon-carbon dimer (12), a carbon-oxygen-carbon dimer and Pummerer's ketone (13).

Since his first publication in the field of electro-chemical oxidative coupling of tetrahydroisoquinolines\textsuperscript{83}, Bobbitt has carried out extensive studies in this field and has recently published a comprehensive summary of the work done by himself and other authors\textsuperscript{86}. It would seem that, from the viewpoint of isoquinoline alkaloid synthesis and biosynthesis, electro-oxidative coupling
produces good yields of intermolecular coupled products while for intramolecular coupled products mediocre yields are obtained.

One advantage which electro-oxidative coupling offers is that, by controlling the potential, one can perform selective oxidations and, indeed, can selectively oxidise certain functionalities.

A further advantage which has been reported by Miller\textsuperscript{87} is that electrochemistry allows non-phenolic materials to be oxidatively coupled, thus eliminating the necessity for utilising easily oxidised phenolates; carbon - oxygen - carbon coupling is also eliminated. In this work Miller reports a one - step, high - yield conversion of 1-benzyltetrahydroisoquinolines to morphinandienones. He selected laudanosine (32) and its 0 - benzyl derivatives (33 - 36) for detailed study.
Following Miller's work, Tobinaga\textsuperscript{88,100} used 
electro-oxidative coupling in the total synthesis of 
some alkaloids including oxocrinine and oxomaritididine.
In his synthesis, he prepared oxomaritidine by oxidising 
the dimethyl ether of (30; $R = H$), protected as its $N$-
trifluoroacetyl derivative, electrochemically.

The product was hydrolysed to yield the oxomaritidine. 
Oxocrinine was prepared in a similar way from the
corresponding methylenedioxy compound. In both these syntheses the oxidation step was effected in 62% yield. This is a considerable improvement on the yields obtained in the chemical methods already described for this type of transformation using ferric chloride\(^\text{50}\) and vanadium oxytrichloride\(^\text{89}\).

**Ferric chloride - dimethylformamide.**

Whilst trying a variety of oxidising agents under various conditions for intermolecular and intramolecular oxidative coupling of phenols, Tobinaga\(^\text{90,100}\) found that ferric chloride in dimethylformamide yielded a complex of molecular formula \(\left\{\text{Fe(DMF)}_3\text{Cl}_2\right\}\left\{\text{FeCl}_4\right\}\). This complex was used to effect oxidative coupling of phenols under mild conditions.

The use of the complex in this field was illustrated by coupling 1-(3,4-dimethoxy-5-hydroxyphenyl)-3-(3-methoxy-4-hydroxyphenyl)propane to the corresponding diene in 67% yield. The corresponding phenols with the 3,4-dimethoxy groups and the 3-methoxy group replaced by hydrogen were also oxidised in 67% yield and 39% yield respectively.

\(\text{p- Cresol was oxidised using this complex to Pummerer's ketone (13) in 28% yield. Tobinaga also used the complex in the biogenetic - type synthesis of (}^{4}\) - oxomaritidine}\(^\text{91}\). The synthesis followed essentially the route employed by Schwartz\(^\text{89}\). The yield obtained by Tobinaga for the oxidation step was 35%, showing some
improvement on Schwartz's vanadium oxytrichloride method, but was considerably lower than the yield obtained electrolytically for the same type of coupling.

This complex has one disadvantage over the vanadium oxytrichloride in that three times as much oxidant is required to effect coupling. The complex is used in a two phase system.

**Thallium trifluoroacetate.**

In his continuing search for effective intramolecular oxidative phenol coupling methods for use in alkaloid synthesis, Schwartz\textsuperscript{93} examined thallium (III) trifluoroacetate. This reagent had been used by Taylor\textsuperscript{92} for the oxidation of phenols to \( p \)-quinones. The potential utility of the method was demonstrated by oxidising 1-(3,4-methylenedioxyphenyl)-3-(4-hydroxyphenyl)propane (66) to the corresponding dienone (67) in 87% yield using a suspension of one molar equivalent of thallium trifluoroacetate in anhydrous methylene chloride.
The method was then extended to the Amaryllidaceae alkaloid system with ease, but with a substantial decrease in yield. In the synthesis of (2) - oxocrinine the 3,4-methylenedioxy derivative of norbelladine was oxidised using thallium trifluoroacetate in 19% yield, substantially less than that obtained by Tobinaga \(^8\) electrochemically. When thallium trifluoroacetate was used in the synthesis of \(\alpha\) - methylandroccymbine from 1,2,3,4-tetrahydro-7-hydroxy-6-methoxy-1-(3,4,5-trimethoxyphenethyl)-2-methylisouquinoline, an overall yield of 20% was obtained. The amino group was protected as the borane derivative and regenerated by oxidation and hydrolysis. Oxidation of the free amine led to a myriad of products, while use of the \(\text{N} -\) trifluoroacetyl
protecting group gave a 10% yield of the dienone.

Oxidation of the N-trifluoroacetyl derivative of norreticuline (68) with thallium trifluoroacetate produces the isoboldine analogue (69) (7%) and the corresponding para-ortho coupled product (70) (11%) which had previously proved elusive. Only one other example of para-ortho coupling has been reported, the reaction being carried out in very low yield (0.03%), and the product detected via isotope dilution techniques. The oxidant was potassium ferricyanide.

Ceric sulphate.

During a classical cyclisation of a benzylisoquinoline, Kupchan discovered that spraying thin-layer chromatograms with acidic ceric sulphate caused the phenol (37) to develop an orange-red colour reminiscent of the quinonoid oxaporphine (38).

![Chemical structures](image-url)

(37) \( R = R_1 = H \)
(39) \( R = Me, \ R_1 = OMe \)
He then carried out a preparative experiment using acidic ceric sulphate as the oxidising agent and isolated (38) in 25% yield. Other oxidising agents were studied with the results shown in the table below.

<table>
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<tr>
<th>Oxidant</th>
<th>Medium</th>
<th>Yield of (38)</th>
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<tbody>
<tr>
<td>Ceric sulphate</td>
<td>10% aqueous sulphuric acid</td>
<td>25%</td>
</tr>
<tr>
<td>Cobalt hydroxide</td>
<td>10% aqueous sulphuric acid</td>
<td>15%</td>
</tr>
<tr>
<td>Chromium trioxide</td>
<td>Aqueous sulphuric acid / acetic acid</td>
<td>25%</td>
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<td>Manganese dioxide</td>
<td>Trifluoroacetic acid</td>
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<td>Thallium trifluoroacetate</td>
<td>Trifluoroacetic acid</td>
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<td>59%</td>
</tr>
<tr>
<td>Molybdenum oxytetrachloride</td>
<td>Trifluoroacetic acid / chloroform</td>
<td>62%</td>
</tr>
</tbody>
</table>

Vanadium oxytrifluoride.

Following these observations Kupchan applied vanadium oxytrifluoride to the oxidative coupling of non-phenolic benzylisoquinolines94.

The first reaction which he reported was the oxidation of papaverine (39) to give an intermolecularly coupled dimeric product linked 6'→ 6' in 80% yield. The apparent absence of intramolecular coupled product was
attributed to protonation of the nitrogen, resulting in a general deactivation of the isoquinoline moiety. Accordingly laudanosine (32) was selected as an alternative substrate since protonation of the isolated nitrogen was expected to exert a lessened effect upon the reactivity of the phenyl ring in the tetrahydroisoquinoline. In this example intramolecular coupling occurred 1'→8 to yield glaucine in 43% yield. To investigate the effect of acylation of nitrogen on the course of the oxidation a solution of (I) - N - formylnorlaudanosine was oxidised with vanadium oxytrifluoride. In this reaction the 1' - 8 coupled product, N - formylnor-glaucine, was isolated in only 6% yield, the major product being the spirodienone (40) (55%).
The spirodienone (40) was treated in methanol with dry hydrogen chloride to give the corresponding ketal; this was then treated with lithium aluminium hydride to give \( O \)-methylerbidine (41; \( R = Me \)).

Dibenzazonine derivatives related to (41; \( R = Me \)) have been shown to be effective in vitro and in vivo precursors of the erythrinan alkaloids. Kupchan therefore suggested that this synthetic route from phenethyl benzylisoquinolines, via the 'neoproerythrinadienone' (40), to (41; \( R = Me \)) may have important implications for the biosynthesis of the Erythrina alkaloids. This publication by Kupchan appears to report the first successful chemical oxidative coupling of non-phenolic substrates.

Kupchan has since reported the synthesis of another dibenzazonine (41; \( R = H \)). Oxidative coupling, with vanadium oxytrichloride, of the benzyl isoquinoline (1) - \( N \) - trifluoroacetylnorprotosinomenine was carried out to yield the \( para \) - \( para \) coupled spirodienone in 40% yield. Hydrolysis with sodium hydroxide followed by reduction with sodium borohydride produced the dibenzazonine (41; \( R = H \)). The oxidation step was carried out in 11% yield using vanadium oxytrichloride as oxidant.

Molybdenum oxytetrachloride.

Despite the success achieved in effecting oxidative coupling of the phenolic benzylisoquinoline (37) using molybdenum oxytetrachloride (see preceding table) only
one other example of its use in this field has been found, this was in the dimerisation of phenol$^{61}$ to give a $20\%$ yield of the para-para coupled product.

Miscellaneous.
Compounds which have found isolated application in the oxidative coupling of simple phenols include potassium dichromate$^{63}$ and phloroacetophenone$^{64}$. 
CHAPTER TWO
THE SYNTHESIS AND REACTIONS OF
DISPIROTETRAENEDIONES
Introduction.

The biosynthesis of mesembrine (47) was considered to proceed from the O-methylnorbelladine (31) via **para - para** coupling as outlined below.

![Chemical structures](image-url)
Attempts were made to carry out the proposed sequence.
chemically. When the oxidative coupling of the 0-methylnorbelladine (31) was carried out, the bisdienone (42) appeared to be produced as judged by development of characteristic dienone bands in the infra-red spectrum of the crude products. However there was no evidence for the production of any of the other intermediates in the proposed sequence and no pure dienone product could be isolated. The failure of this sequence was attributed to the unexpected thermal lability of the bond linking the dienone rings compared with the bond which was required to cleave as shown in the scheme. To examine this further, a study of the corresponding carbocyclic system was undertaken. Preliminary studies showed that the bisdienones (48) and (49) underwent thermal decomposition in neutral alcoholic solution to yield the corresponding benzylic ethers (50) and (51) respectively.
A more detailed study of the synthesis and reactions of dispirotetraenediones has since been carried out and is reported in this thesis. The work described had three principle aims which were as follows. Firstly to study the thermal decomposition of these dienones and elucidate, if possible, the mechanism of their polymerisation in
solution and in the solid state. The second objective was to examine a range of bisdienone types in the hope of finding representatives which might yield useful polymers on heating. The third aim was to explore the application of bisdienone intermediates in alkaloid synthesis.
Discussion.

The bisdienones of the type studied were prepared by the oxidation of the corresponding diphenol. The diphenol, 1,3-bis(4-hydroxyphenyl)propane (75), was prepared initially\(^97\) by the following route. Anisole was treated with acetic anhydride, using orthophosphoric acid as catalyst, to produce 4-methoxyacetophenone (72) which was then condensed with anisaldehyde to give 4,4′-dimethoxychalcone (73). The chalcone was hydrogenated catalytically to 1,3-bis(4-methoxyphenyl)propane (74) which was then demethylated to yield the diphenol (75). The synthesis was carried out in good yield up to the demethylation step. The demethylation was effected by heating under reflux in glacial acetic acid and hydroiodic acid to give a 24\% yield of the diphenol (75). In an attempt to improve the yield demethylation was carried out using hydrobromic acid in glacial acetic acid; after optimisation of the conditions an improved yield of 44\% of the diphenol (75) was obtained. Eventually, efficient demethylation was achieved by heating the ether under gentle reflux in a solution of potassium hydroxide in diethylene glycol. This method proved the most successful, giving the diphenol (75) in 82\% yield.

The diphenol (75) was converted to the bisdienone (48) in 20\% yield\(^97\), by oxidation with alkaline potassium ferricyanide, using a two phase medium of water and benzene.
Methods were sought to improve the yield for the oxidation step. Dilution of the oxidation medium by 25% proved helpful in that it improved the yield of bisdienone (4₈) by approximately 5%. Further dilution did not produce any significant improvement in the yield of bisdienone (4₈). However, variations in the time for the addition of the potassium salt of the diphenol (7₅) to the oxidation medium were unsuccessful. It appeared that the addition time of one hour initially used was the optimum time. A more significant increase in yield of bisdienone (4₈) was achieved by changing the organic phase of the reaction medium from benzene to chloroform which resulted in an increase in yield of the bisdienone (4₈) to 57%.

\[
\begin{align*}
\text{OMe} & \quad \text{OMe} \\
\text{C} & = \text{O} \\
\text{Me} & \\
\text{Me} \\
\end{align*}
\]

(7₂)

\[
\begin{align*}
\text{OMe} & \\
\text{C} & = \text{O} \\
\text{CHO} \\
\end{align*}
\]

(7₃)

\[
\begin{align*}
\text{MeO} & \quad \text{O} \\
\text{CH=CH} & \quad \text{CH=CH} \\
\text{OMe} & \\
\end{align*}
\]

(7₄)
Following the preliminary investigation, a more detailed study of the thermal decomposition of the bisdienone \((48)\) was carried out in both solution and the solid state. In solution the decomposition was studied in ethanol and benzene, by ultra-violet spectroscopy, and in dimethyl sulfoxide by proton magnetic resonance spectroscopy. The bisdienone \((48)\) has a characteristic shoulder at 256 nm (in ethanol) in the ultra-violet spectrum. Dilute ethanolic solutions remained virtually unchanged for several days.
at 20°C97 but at 74°C the absorption at 256 nm diminished and was replaced by a phenolic absorption at 278 nm. The disappearance of this shoulder as a function of time was used to follow the decomposition rate of the bisdienone (48) in both benzene and ethanol. Samples of the ethanolic solution were sealed in ampules and stored in a water bath at 74°C. Ampules were removed at regular intervals, cooled and the ultra-violet spectrum of the reaction mixture was then determined. For the decomposition in benzene a similar procedure was adopted except that the benzene was removed, by evaporation under nitrogen, after each ampule had been taken from the bath. The residue was then dissolved in ethanol and the ultra-violet spectrum determined.

When examining the decomposition in ethanol, although the kinetics appeared to be approximately first order, it was found that the rate was not completely insensitive to the initial concentration of the dienone; for example, increasing the concentration of the dienone in ethanol from 0.00876 mg per ml to 0.08937 mg per ml reduced the half life ($t_{1/2}$) from 2635 minutes to 2160 minutes. This suggests the presence of a second order component.

The decomposition of the bisdienone in benzene at 74°C was kinetically less regular. This process was characterised by a slow initial phase, or induction period, followed by a more rapid reaction leading to complete decomposition in ca. 24 hours. Moreover, an
increase in the initial concentration of the bisdienone (48) increased the reaction rate, the rate curve assuming a smooth sigmoid shape.

**Decomposition of the bisdienone (48) in benzene solution.**

1. Dienone (48) in benzene @ 3 mg/100 ml.
2. Dienone (48) in benzene @ 9 mg/100 ml.
3. Dienone (48) in benzene @ 3 mg/100 ml. with added 2,6-di-t-butyl-4-methylphenol (76).

![Absorbance vs Time Graph](image-url)
In a communication\textsuperscript{97}, following the preliminary investigation, it was proposed that the bisdienone (48) decomposed by cleavage of the central bond linking the dienone rings, to give, possibly, a diradical which then polymerised. When 2,6-di-t-butyl-L-methylphenol (76) was added to a solution of the dienone (48) in either ethanol or benzene the reaction rate was increased, the induction period in benzene solution was eliminated and the reaction in benzene was complete in ca. 6 hours, (See figure 1 above). In ethanol the reaction was complete, in the presence of (76), in ca. 60 hours. The difference in reaction times indicates that the initial central bond cleavage, if this is the rate limiting step, is much slower in ethanol than in benzene. In the presence of two moles of this radical trapping agent the diphenol (75) was formed in benzene and ethanol in substantial amounts along with 1,2-bis(3,5-di-t-butyl-L-hydroxyphenyl)ethane (77). The formation of these products is consistent with the reaction's occurring by a radical process and the relatively slow rate in ethanol is also better explained by a radical rather than ionic process. The phenolic products could have been obtained by two radical reaction sequences, as shown below.
Pathway 1

(85)

(75)
Pathway 2
The fact that addition of dibenzoyl peroxide to a benzene solution of the dienone (48) did not have any catalytic effect on the decomposition (see figure 1 above) supports the idea (pathway 1) that central bond cleavage to yield the diradical (85) is the slow step, at least in this solvent.

It has been shown by Dalgleish\textsuperscript{103}, and by Mahoney and Weiner\textsuperscript{104,105}, that the coupling of phenoxy radicals may be reversible. As a result of their studies on the dimerisation of phenoxy radicals Mahoney and Weiner\textsuperscript{104} propose that the formation of the initial bisdienone may be reversible, and the rate-controlling step is the enolisation of this bisdienone. The results of their mechanistic studies were consistent with the following reaction scheme.
During the present studies the validity of this mechanism for the dimerisation of 2,6-di-t-butylphenol (81) has been demonstrated. The phenol (81) was oxidised, following a similar procedure to that of Kharasch and Joshi\textsuperscript{108}, to the corresponding bisdienone (82), which was known to isomerise, in protic solvents, to the corresponding
diphenol (84). In contrast, when the bisdienone (82) was heated alone at 160°C for 20 minutes it yielded the starting phenol (81) and the corresponding diphenoquinone (83), in a molar ratio of 2 : 1. This result is easily explained if (82) dissociates to give phenoxy radicals (cf. 79 to 78) which attack (82) to yield (83) and (81).

In solution the bisdienone (82) isomerises slowly to the corresponding diphenol (84), the isomerisation being catalysed by polar solvents. In order to determine the kinetic isotope effect associated with this process, for comparison with the value given by Mahoney and Weiner\textsuperscript{105}, the corresponding 4,4'-dideuterobiisdienone was prepared as follows. The phenol (81) was deuteriated in the 4 position by heating under reflux in a mixture of sodium deuteroxide and dimethylformamide. The deuteriophenol was then oxidised to the corresponding dideuterobiisdienone using the same method as for the phenol (81). Analysis by proton magnetic resonance, and by mass spectral techniques, revealed that the isotopic purity was greater than 95%.

The isomerisation of both the bisdienone (82) and dideuterobiisdienone was followed by ultra-violet spectroscopy using cyclohexane, containing 8% ethanol, as solvent at 30°C. A plot of log (A - A\textsubscript{∞}) versus time (t), where A is the absorbance (at 233 nm) at time t and A\textsubscript{∞} is the absorbance after infinite time, gave a straight line indicating first order kinetics. The slope, -2.303/k\textsubscript{1}, gave the rate constant, k\textsubscript{1}. The experiments were carried out in duplicate and the following rate constants were
obtained.

<table>
<thead>
<tr>
<th></th>
<th>Bisdienone (82)</th>
<th>Dideuteriobisdienone</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1(30^\circ C)$</td>
<td>$5.5 \times 10^{-3}\text{min}^{-1}$</td>
<td>$1.3 \times 10^{-3}\text{min}^{-1}$</td>
</tr>
<tr>
<td></td>
<td>$5.4 \times 10^{-3}\text{min}^{-1}$</td>
<td>$1.5 \times 10^{-3}\text{min}^{-1}$</td>
</tr>
</tbody>
</table>

That is there is an apparent four fold isotope effect for the isomerisation. This is smaller than the value, $10 \pm 2$, reported by Mahoney and Weiner\textsuperscript{105} for the isomerisation of the transient dimer derived from 3,5-di-t-butylphenol but their experiments were conducted in an aprotic solvent (benzene).

If the reaction scheme proposed by Mahoney and Weiner\textsuperscript{104} is applied to the decomposition of the bisdienone (48) it might be expected that the initial coupling product (type 79) of the diradical (type 78) might reverse to (78) competitively with enolisation to produce (80). In benzene, but not in ethanol the enolisation process (79) $\longrightarrow$ (80) would initially be slow but could be catalysed by the phenolic end product. This product catalysis would account for the sigmoid nature of the rate curve. In agreement with this tentative explanation, addition of the product-like compound (75) to benzene solutions of the bisdienone (48) eliminated completely the "induction period" in the thermal decomposition. A similar addition in ethanol had no effect upon the decomposition rate. Experiments
were then carried out with the deuteriated bisdienone (86) to determine, by the deuterium isotope effect, whether the process of the type \((79) \rightarrow (80)\) is kinetically important for the system being studied. The deuteriated compound (86) was prepared by oxidation of the corresponding tetradeuteriated phenol following the same procedure as for the preparation of the dienone (48). The tetradeuteriated phenol was prepared by heating the phenol (75) under reflux in sodium deuteroxide. When the decomposition of the bisdienone (86) was followed in benzene solution the "induction period" and the overall reaction time were both increased when compared with the bisdienone (48) decomposition at the same concentration; the "induction period" was approximately doubled as was the total reaction time (see figure 2), thus showing a deuterium isotope effect. In ethanol a deuterium isotope effect was not observed. These results indicate that the decomposition of the bisdienone (48) follows the mechanism proposed and the rate-controlling step in benzene is the enolisation of the dienone (type 79) formed by reversible coupling of the initial diradical (type 78).
Decomposition of the bisdienones $\text{(48)}$ and $\text{(86)}$ in benzene solution at concentration of 9 mg/100 ml.

Figure 2
The polymerisation of the dienone (48) was also studied qualitatively by proton magnetic resonance spectroscopy in hexadeuteriodimethyl sulphoxide at 70°C. During the polymerisation the olefinic proton signals disappeared to be replaced by aromatic (\(\delta = 3.00\) and 3.30, \(J = 10\) Hz) and hydroxylic (\(\delta = 0.86\)) proton signals. When the signal strengths for the aromatic and hydroxylic protons were compared at the end of the reaction a ratio of 5 : 1 was found, thus indicating that both carbon–carbon and carbon–oxygen coupling are probably involved in the polymerisation. If only carbon–carbon coupling was involved a ratio of 3 : 1 would be observed whereas if carbon–oxygen coupling was the only mode of polymerisation a ratio of 7 : 1 would be observed. These values would apply strictly for a high polymer; chain termination by, for example, hydrogen transfer could produce intermediate ratios.

The decomposition of the bisdienone (48) was followed in the solid state using infra-red spectroscopy, ultra-violet spectroscopy and differential scanning calorimetry. The reaction proceeds much more rapidly in the solid state than in solution. For the studies using infra-red spectroscopy the dienone (\(\sim 2\) mg) was dispersed in potassium bromide (\(\sim 300\) mg), a disc was made and the disappearance of the carbonyl peak at 1665 cm\(^{-1}\) with time was followed. Although the reaction proceeds in the solid
state at an appreciable rate at ambient temperatures, decomposition being complete in approximately three weeks, the studies were carried out at elevated temperatures of 60° and 74°C. At both temperatures a similar mode of decomposition to the decomposition in benzene was observed, that is a smooth sigmoid rate curve was obtained when a plot of log(% transmittance) vs time, was made. The "induction period" was approximately 40 minutes at 60°C and 35 minutes at 74°C, with the reaction being complete within 4 hours at both temperatures.

When a potassium bromide disc containing the dienone (48) was irradiated with ultra-violet light at room temperature again a smooth sigmoid rate curve for the disappearance of the carbonyl peak in the infra-red spectrum was produced with the reaction being completed in 36 hours.

In all the infra-red spectroscopy studies no detectable difference in reaction rate occurred in a nitrogen atmosphere rather than in air.

The decomposition of the solid using ultra-violet spectroscopy was followed by heating samples of known weight (~1mg) in sealed ampules at 74°C, opening ampules at regular intervals, dissolving the solid in ethanol and running the ultra-violet spectrum. Using this technique it was found that the solid bisdienone completely decomposed in 20 minutes at 74°C.

The third system used for the study of the decomposition
of the bisdienone (48) in the solid state was differential scanning calorimetry (D.S.C.). D.S.C. is a thermal analysis system which is capable of giving direct quantitative measurement of changes in thermal energy. In this technique the sample to be analysed is placed in the calorimeter in a small cell along with an empty reference cell. The two cells are mounted on separate platforms. In the calorimeter the sample and reference cells are temperature programmed and maintained at the same temperature by means of a closed-loop negative feed-back of the power supplied to each. Any thermal transition in the sample requires differential power to be supplied to the sample reference system and this is the quantity which is recorded as the ordinate in D.S.C. Conversely, any energy liberated or absorbed by the sample is balanced by an equivalent change in the energy input to the reference cell. The scan consists of a series of positive and negative peaks corresponding to exothermic and endothermic changes in the sample. The area under the D.S.C. peak is a direct measure of the energy involved in the corresponding thermal transition.

D.S.C. scans on the trimethylene bisdienone (48) were carried out at both constant temperatures and with constant heating rates. In the constant temperature scans the sample, in the cell, is heated to the required
temperature rapidly (64°C per minute) from the starting temperature of 30°C and then held at that temperature until the scan is complete. Scans were carried out at 55°, 60°, 65°, 70°, and 74°C. The scans all showed a smooth exothermic peak and also confirmed the observations from the other solid state studies, namely that the reaction proceeds much more rapidly in the solid state than in solution. As would be expected, the reaction rate increased with increase in temperature, the exothermic reaction at 55°C being over in 9 minutes whereas the reaction at 74°C was completed in 7 minutes. A typical constant temperature scan is shown in Figure 3.
In the scans at a constant heating rate again a smooth exothermic peak was observed. Heating rates of 3°, 5° and 10°C per minute were used. As the heating rate increased, corresponding increases in the temperatures at which the exotherm began and the exotherm peak was reached, were observed:

<table>
<thead>
<tr>
<th>Heating rate (°C per min.)</th>
<th>Temp. at beginning of exotherm</th>
<th>Exotherm peak temp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>40°C</td>
<td>68°C</td>
</tr>
<tr>
<td>5</td>
<td>44°C</td>
<td>74°C</td>
</tr>
<tr>
<td>10</td>
<td>49°C</td>
<td>80°C</td>
</tr>
</tbody>
</table>

As indicated earlier, the area under the peak is directly related to the energy evolved during the reaction ($-\Delta H$). In order to determine the energy evolved quantitatively the instrument is first calibrated using compounds of known heat output to give a calibration coefficient (E).

\[
\Delta H = \frac{E \times A \times \Delta Ts \times Ts}{M \times a} \text{ m cal/mg.}
\]

$A =$ peak area in sq. ins.

$\Delta Ts =$ Y axis sensitivity setting in °C/in.

$Ts =$ X axis sensitivity setting in °C/in.

$M =$ sample mass in mg.

$a =$ heating rate in °C/min.
E = calibration coefficient.

\( \Delta H = \) enthalpy or heat content.

E is obtained by substituting known values of \( \Delta H \) in the above equation for the standards, thus obtaining E values at different peak maximum temperatures. These values of E are then plotted against the temperature at which the heat output was a maximum; for samples which are of unknown \( \Delta H \) the temperature at which their D.S.C. curve peaks is noted and the value of E at that temperature is obtained from the calibration graph and substituted in the above equation to obtain \( \Delta H \). A typical scan at a constant heating rate is shown in Figure 4.
Enthalpy (ΔH) values determined in the above manner showed that the decomposition of the trimethylene bisdienone (48) showed an exotherm of $25 \pm 0.5$ k cal/mole for the three different heating rates. The deuteriated bisdienone (86) showed the same enthalpy of decomposition.

During the D.S.C. examination of the bisdienone (48) it was observed that the sample had changed from a white crystalline material to a pink amorphous solid on completion of the scan. If ethanol was added to the solid the pink colouration was discharged and an off-white solid remained in suspension. This sequence was interpreted as follows. Decomposition of the bisdienone (48) involved (see above) formation of phenoxy radicals, some of which were being trapped in the solid matrix giving a pink colouration. Addition of ethanol caused swelling of the polymer and allowed the trapped radicals to react further. In support of this theory electron spin resonance (e.s.r.) spectra were determined for the system. The following experiment was carried out in the University of York by the kind co-operation of Professor R. O. C. Norman. A sample was heated for 30 seconds at $60^\circ$C; it became pink and gave a single, broad e.s.r. line, of width ca. 10 gauss. There was no other signal in the range 0 - 400 gauss. After one minute at $70^\circ$C the pink colour became darker and the intensity of the signal was increased by approximately a factor of ten.
After several minutes at $70^\circ C$ the sample became darker still, but the intensity of the signal was, to, a first approximation, unchanged. The final concentration of radicals present in the system was ca. $10^{16}$ per gram, to the nearest order of magnitude. This corresponds to the trapping of ca. 1 in $10^6$ of the phenoxy radicals which might be generated by homolytic cleavage of the bisdienone. Ethanol treatment of the pink solid once again caused bleaching and also the complete disappearance of the e.s.r. signal.

Since the rapid thermal decomposition of the bisdienone (48) appeared to involve reversible cleavage of the central bond to give a diradical, which then polymerised, the effect of blocking the ortho positions with bulky t-butyl groups was explored. The phenol (75) was readily t-butylated with isobutylene and concentrated sulphuric acid in benzene to give the corresponding tetra-t-butyl phenol (87). This was oxidised with alkaline potassium ferricyanide in an aqueous ethanolic solution to yield the desired bisdienone (88) in 38% yield.
This tetra-t-butyl derivative (88) was thermally much more stable than the parent bisdienone (48). The derivative (88), when heated under reflux in ethanol, showed no significant decomposition (u.v. control) during a period which led to the complete reaction of the parent bisdienone (48). However, heating under reflux in ethanol for 7 days did yield two major products. These were identified as the corresponding benzylic ether (89) (55%) and the starting phenol (87) (22%). The formation of (89) accords with the mechanism proposed for the parent bisdienone decomposition but
(87) must have arisen by reduction or disproportionation. As expected, the t-butyl groups prevented polymerisation of the postulated diradical, while still allowing Michael addition of ethanol to the quinone methide intermediate (90) proposed in the preliminary communication\textsuperscript{97}. Decomposition of the bisdienone (88) in benzene for 5 days or toluene for 2 days, under reflux, yielded an oily product which was not fully identified. However, the ultra-violet spectrum had a maximum at 308 nm. which, when compared with the spectra for (91) and (92) which have maxima at 303 nm. and 312 nm. respectively, suggests the presence of the quinone methide (90).

\[
(90) R_1 = R_2 = \text{tBu}, R_3 = H, \\
R_4 = \text{CH}_2
\]

\[
(91) R_1 = R_2 = \text{tBu}, R_3 = H, R_4 = \text{Me}.
\]

\[
(92) R_1 = R_2 = \text{Me}, R_3 = H, R_4 = \text{Me}.
\]

The infra-red spectrum of this oil showed both carbonyl
(1660 cm\(^{-1}\)) and hydroxyl bands (3655 cm\(^{-1}\)) to be present. However the mass spectrum of the oil showed a peak with an m/e 32 units higher than that required by the proposed quinone methide (90). When the oil was heated under reflux in ethanol for 14 hours the benzylic ether (89) was formed. This product would be expected from Michael addition of ethanol to the quinone methide (90). In the presence of benzene alone there are no polar species available to allow decomposition of the quinone methide in this manner. All attempts to purify the product from the benzene reaction by thin layer chromatography proved completely unsuccessful in that each time a plate was run more products appeared, presumably owing to decomposition of the compound on the plate.

\[ \text{But}^t \text{O} \]

\[ \text{But}^t \]

\[ \text{But}^t \text{O} \]

\[ \text{But}^t \]

(88)

\[ \text{But}^t \text{O} \]

\[ \text{But}^t \]

\[ \text{But}^t \text{O} \]

\[ \text{But}^t \]

64
Differential scanning calorimetry confirmed the increased thermal stability produced by the introduction of the four t-butyl groups. A scan of the tetra-t-butyl bisdienone (88) showed no exotherm or endotherm prior to the melting point of the compound at 153°C. Melting produced the expected endotherm which was quickly followed by an exotherm suggesting that as soon as the compound liquefied decomposition occurred.

Following the successful improvement in the yields in the reaction sequence leading to the trimethylene bisdienone (48) attempts were made to improve the yield.
in the production of the tetramethylene bisdienone (49).

1,4-Bis(4-methoxyphenyl)buta-1,3-diene (93) was prepared by condensing two moles of anisaldehyde with one mole of succinic acid in the presence of lead monoxide using acetic anhydride as solvent. An amorphous solid was obtained when the reaction mixture was cooled and poured into benzene and the precipitate washed with aqueous ammonium chloride and water. The product proved very insoluble and was reduced as a suspension in benzene by catalytic hydrogenation to give the tetramethylene compound (94). Demethylation was achieved using the potassium hydroxide / diethylene glycol system used in the trimethylene sequence. Oxidation of the diphenol (95) using chloroform rather than benzene as the organic phase, as for the trimethylene compound (48), improved the yield of the bisdienone (49) from 15% to 23%.

Although the sequence leading to the production of the diphenol (95) offers no advantage in yield over the sequence used by Richardson and Reid98, the number of steps involved is reduced from seven to three. In their route Richardson and Reid condensed succinic anhydride and anisole to give p-anisoylpropionic acid which was reduced to the butyric acid. The acid chloride was prepared, using thionyl chloride, and was condensed with anisole. The crude ketone obtained was reduced and demethylated using hydrobromic acid in acetic acid to yield the
1,4-di(4-hydroxyphenyl)butane (95). Both ketones were reduced by the Clemmensen method.

\[
\text{2 MeO-} \quad \text{CHO} \quad + \quad \text{COOH} \quad \text{COOH} \quad \rightarrow
\]

\[
\text{MeO-} \quad \text{(CH}_2\text{)}_4 \quad \text{OMe} \quad \rightarrow
\]

\[
\text{MeO-} \quad \text{(CH}_2\text{)}_4 \quad \text{OMe} \quad \rightarrow
\]

\[
\text{HO-} \quad \text{(CH}_2\text{)}_4 \quad \text{OH} \quad \rightarrow
\]

\[
\text{(49)}
\]

\[
\text{(93)}
\]

\[
\text{(94)}
\]

\[
\text{(95)}
\]
Differential scanning calorimetry showed little difference in thermal stability in the solid state between tetramethylene (49) and trimethylene (48) dienones. Using a heating rate of 5°C/min, an exothermic peak was produced beginning at 49°C with a maximum at 85°C. The decomposition was exothermic to the extent of $20.0 \pm 0.4$ k cal/mole.

With a view to investigating the reactions of the ortho-para analogues of (48) and (49) the syntheses of the appropriate phenols were carried out. The proposed route for the trimethylene analogue (96) was similar to that for the para-para trimethylene phenol (75), that is via a chalcone (97) and reduction. The diphenol (96) had been previously synthesised by Carpenter and Hunter. They prepared 2,4'-dihydroxychalcone (97) from 4-hydroxyacetophenone and salicylaldehyde, and reduced the chalcone to 1-(4-hydroxyphenyl)-3-(2-hydroxyphenyl)-propan-1-one (102). The ketone (102) was reduced by the Clemmensen method to the trimethylene compound (96).
In an attempt to reduce the number of stages in the
synthetic route it was decided to try and complete the reduction of both the double bond and the ketone by catalytic hydrogenation as was done in the synthesis of the para - para linked phenol (75). Catalytic hydrogenation of the chalcone (97) in ethanol over 10% palladium on charcoal produced 4'-hydroxyflavan (98). This was identified by acetylation and methylation to give the corresponding 4'-acetoxyflavan (99) and 4'-methoxyflavan (100) respectively. It was initially thought that the reduction had proceeded to the benzylic alcohol (101). Although the mass spectrum showed the flavan as the molecular ion it was thought that dehydration had taken place in the mass spectrometer. The acetylation was therefore carried out to determine the number of hydroxyl groups present in the compound.

(98) \( R = \text{OH} \)

(99) \( R = \text{OAc} \)

(100) \( R = \text{OMe} \)
Perchloric acid was added to an ethanolic solution of the chalcone (97) and this was subjected to catalytic hydrogenation over 10% palladium on charcoal; again 4'-hydroxyflavan (98) was produced with none of the required product being isolated. Catalytic hydrogenation over Raney Nickel was even less successful with mainly starting material being recovered. It was then decided to revert to the method of Carpenter and Hunter. The double bond in the chalcone was reduced by catalytic hydrogenation over 5% palladium on charcoal, in ethanol, to give the ketone (102). Clemmensen reduction of this ketone (102) gave 4'-hydroxyflavan (98) and a product which appeared to be the required phenol (96), but it could not be obtained as a solid. The preparation of the tosylhydrazone of the ketone (102) as a route to the hydrocarbon was considered as a possibility but when the reaction was carried out only the starting materials could be isolated. It was considered that if the benzylic alcohol (101) was prepared this could be reduced to the hydrocarbon by preparing the tosyl derivative and reducing it with lithium aluminium hydride or by reacting the alcohol with constant boiling hydroiodic acid. With this in mind the chalcone (97) was reduced using sodium borohydride but none of the required alcohol (101) was obtained and the only products isolated were 4'-hydroxyflavan (98) and the ketone (102). Having had no success with
the indirect routes, attention was returned to catalytic hydrogenation. Although hydrogenation of the chalcone (97) in glacial acetic acid, in the presence of perchloric acid, over 10% palladium on charcoal gave 4'-hydroxyflavan (98) as the major product, some of the required phenol (96) was obtained as a pure solid. In an attempt to improve the yield of required phenol (96) the reduction was carried out under pressure using both 10% palladium on charcoal and Raney Nickel as catalysts at both ambient and elevated temperatures. No improvement in yield was observed. It was finally discovered that a yield of 31% of the required phenol (96) could be obtained by making regular additions of palladium on charcoal to the reduction medium under ambient conditions. Although all the spectral and analytical data for the 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (96) were in accordance with the structure, the melting point of 63°C differed considerably from that reported by Carpenter and Hunter99 which was 90°C.

The preparation of the tetramethylene analogue (103) proved to be more straightforward. 2-Methoxybenzyl alcohol (104) prepared from the corresponding aldehyde (105) was converted into 2-methoxybenzyl chloride (106) with thionyl chloride and pyridine in benzene. 4-Methoxy-cinnamaldehyde (107) was prepared from anisaldehyde and acetaldehyde under basic conditions. The aldehyde (107) and the benzyl chloride (106) were then combined in a
Wittig type reaction by first treating the 2-methoxybenzyl chloride (106) with triethylphosphite under reflux, then adding base and then the 4-methoxycinnamaldehyde (107) in dimethylformamide to yield the 1-(4-methoxyphenyl)-4-(2-methoxyphenyl)buta-1,3-diene (108). The butadiene (108) was reduced by catalytic hydrogenation to give the tetramethylene compound (109). Demethylation with potassium hydroxide in diethylene glycol gave the required diphenol (103).
Oxidation of both diphenols (96) and (103), using potassium ferricyanide / potassium hydroxide in a two phase medium, did not produce the expected carbon - carbon coupled bisdienones. Instead only the carbon - oxygen coupled products (110) and (111) were isolated.

\[
\begin{align*}
\text{(112)} & \quad n = 2 \\
\text{(96)} & \quad n = 3 \\
\text{(103)} & \quad n = 4
\end{align*}
\]

\[
\begin{align*}
\text{(113)} & \quad n = 2 \\
\text{(110)} & \quad n = 3 \\
\text{(111)} & \quad n = 4
\end{align*}
\]

The first indication that the expected carbon - carbon coupled compounds were not formed was obtained from the ultra-violet spectra. Instead of the absorptions being
at a higher wavelength than that recorded for the para-para coupled products (48) and (49), which might be expected due to the extended conjugation, the only absorptions observed for the oxidation products of the diphenols (96) and (103) were at 219 nm. and 216 nm. respectively. The n.m.r. spectrum of the products from the oxidation of (96) and (103) also showed that the expected carbon-carbon coupled products were not in fact obtained. In both cases one methylene peak occurs at lower field than the others, this being the benzylic methylene which is moved to lower field by the influence of the aromatic ring. The trimethylene compound (110) gave a multiplet at 6.85 - 7.25 \( \tau \) and the tetramethylene compound (111) a multiplet at 6.80 - 7.20 \( \tau \), the other methylene groups absorbing as multiplets in the region of 7.35 - 8.40 \( \tau \) and 7.30 - 8.43 \( \tau \) respectively. This agrees with the n.m.r. spectrum of the dimethylene compound (113) which has been isolated by other workers and gives two triplets at 7.15 \( \tau \) and 7.95 \( \tau \) for the methylene groups.

It is unlikely that the formation of the 8-membered ring in (111) would occur faster than that of the 6-membered ring in the expected bisdienone. It would therefore seem more probable that the bisdienones are produced initially and then reverse thermally, even at room temperature, to the corresponding diradicals which
can undergo carbon-oxygen coupling to produce, eventually, the thermodynamically stable products (110) and (111).

Differential scanning calorimetry only showed the expected endotherm corresponding to the melting point for the trimethylene compound (110) in a scan up to 150°C. No peaks were observed for the tetramethylene compound (111) which was only isolated as an oil.

If the proposal that the tetramethylene bisdienone (49) decomposes by intramolecular 1,5-hydrogen transfer in competition with polymerisation is correct, then a bisdienone which cannot readily undergo 1,5-hydrogen transfer should polymerise more efficiently than the tetramethylene bisdienone (49). A system which would meet these requirements is the bisdienone (114). Moreover, formation of (114) from the corresponding diphenol, involving linkage of cis groups, might proceed faster and in better yield.

\[
\begin{align*}
\text{(114)}
\end{align*}
\]
The synthesis of this compound (114) was therefore attempted.

The route selected to synthesise the required diphenol started with the Diels - Alder addition of maleic anhydride to a diphenylbutadiene. It has been reported\textsuperscript{110} that the Diels - Alder reaction of bis-1,4\textsubscript{7}(4-methoxyphenyl)-buta-1,3-diene (93) with maleic anhydride did not work, therefore 1,4-diphenyl-1,3-butadiene (115) was selected as the diene for the reaction. The Diels - Alder adduct (116) was obtained in good yield by heating the two components under reflux in xylene. The olefinic bond in the cyclohexene ring of the adduct (116) was reduced by catalytic hydrogenation, and the anhydride (117) was hydrolysed by base to the diacid (118); again both reactions proceeded in very good yield. All attempts to remove the carboxylic acid groups proved unsuccessful. Lead tetraacetate was used in benzene, in dimethyl sulfoxide, in the presence of oxygen and in the absence of oxygen; in each case the only product isolated was \( p \)-terphenyl (119). Decarboxylation attempts using copper chromite in quinoline yielded the corresponding anhydride (117) as did an attempted decarboxylation by pyrolysis. As decarboxylation was proving a problem it was decided to attempt to introduce the required phenolic hydroxyl groups directly into the diacid; again this proved unsuccessful. The first method tried was nitration.
but this produced a mixture of six products in equal proportions and was therefore considered unsuitable.
The second method tried was that of McKillop and Taylor\textsuperscript{111} using thallium trifluoroacetate. The only identifiable material produced which was soluble in aqueous alkali was triphenylphosphine oxide.

\begin{align*}
(115) \ R &= \ H \\
(93) \ R &= \ O\text{Me} \\
(116) \ R &= \ H \\
(121) \ R &= \ O\text{Me}
\end{align*}
Attention was then turned to the corresponding mono-carboxylic acid (120), again produced by the Diels-Alder reaction, this time using acrylic acid instead of maleic anhydride as the dienophile, followed by catalytic hydrogenation. Decarboxylation of this acid (120) was attempted using copper chromite in quinoline, which yielded \( p \)-terphenyl (119) and an anhydride; and pyrolysis, from which starting material was recovered. A decarboxylative bromination, using the Hunsdiecker reaction, was attempted, again without success. Nitration of the mono-acid (120)
yielded a myriad of products which resulted in this approach to the required diphenol being abandoned.

As difficulty had been experienced in getting para-substitution in the two acids (118) and (120), it was decided to reinvestigate the reaction of bis-1,4-(4-methoxyphenyl)buta-1,3-diene (93) with maleic anhydride. The butadiene (93), used earlier for the preparation of bis-1,4-(4-hydroxyphenyl)butane (95), was heated under reflux with maleic anhydride in xylene; the butadiene (93) remained in suspension. The heating was continued for 16 hours after which time a brown-black solid remained undissolved and was removed by filtration. Chromatography
of the xylene soluble material yielded less than 10% of what appeared to be the required product (121) on examination of the n.m.r. and i.r. spectra. Using other solvents or solvent-free reactions at different temperatures gave no improvement in the yield. Since it was thought that the problem might be associated with the purity of the amorphous butadiene (93), the method for its preparation was modified. Again one mole of succinic acid was condensed with two moles of anisaldehyde in the presence of lead monoxide with acetic anhydride as solvent. However, when the reaction was complete, instead of pouring the reaction mixture into benzene, aqueous acetic acid was added and the solution was then allowed to cool. This method yielded a fluorescent pale yellow crystalline product (93) which could be recrystallised from toluene. When (93) and maleic anhydride were heated in xylene under reflux, both components dissolved and, after 3 days, the required adduct (121) was obtained in 65% yield. The adduct (121) had a low solubility in most solvents and therefore a large volume of solvent was required to effect the catalytic hydrogenation of the cyclohexene ring to the cyclohexane (147). Reduction of the adduct (121) in suspension was very slow, therefore the anhydride (121) was hydrolysed to the diacid (122) and reduction was attempted with diimide, but without success. It was found, however, that the diacid (122)
was more soluble in organic solvents than the anhydride (121) and reduction to the diacid (123) could be effected readily and in good yield by catalytic hydrogenation. Due to the difficulty encountered earlier with decarboxylation no attempt was made to effect decarboxylation on the reduced diacid (123). Instead the diacid (123) was demethylated using potassium hydroxide in diethylene glycol. This occurred with concurrent isomerisation of the diacid groups to give the cis-3, cis-6-di(4-hydroxyphenyl)cyclohexane cis-1, trans-2-dicarboxylic acid (124). That isomerisation had occurred was shown by methylation of the dimethoxy diacid (123) and the dihydroxy diacid (124). The two products (125) and (126) had different melting points and spectroscopic properties.

Attempted oxidation of the diphenol diacid (124) in aqueous alcoholic solution, using potassium ferricyanide and potassium hydroxide, only produced an insoluble polymeric material. In order to be able to carry out a two-phase oxidation, the dimethyl ether diacid (123) was reduced with diborane to the diol (127), which was in turn demethylated using potassium hydroxide / diethylene glycol to give cis-1, cis-2-bis(hydroxymethyl) cis-3, cis-6-di(4-hydroxyphenyl)cyclohexane (128). Isomerisation was shown, as expected, not to have taken place during the demethylation of the diol by acetylation to give the tetra-acetoxy compound (129). Examination of the n.m.r.
The spectrum of (129) showed a single signal (τ 7.73) for both aryl acetoxy groups and another (τ 8.18) for both alkyl acetoxy groups. Unless accidental coincidence of signals has occurred, this excludes epimerisation during demethylation. However, two-phase oxidation of the diphenol dialcohol (128) did not prove any more successful than the oxidation of the diphenol diacid (124) in that no products could be isolated from the organic phase.
During the course of their continuing search for new representatives of the *Sceletium* group of alkaloids, Arndt and Kruger\textsuperscript{112} isolated three new members, joubertiamine (130), dihydrojoubertiamine (131), and dehydrojoubertiamine (132). Although the basic skeleton of these new alkaloids resembles that of mesembrine (47), these are the first *Sceletium* alkaloids known containing only one oxygen function in the aromatic ring.

\[
\begin{align*}
\text{(130)} & \quad \text{(131)} & \quad \text{(132)} \\
\end{align*}
\]

In an attempt to see if this system could be approached via phenol oxidative coupling, the synthesis of the bisdienone (134) was undertaken.
Phenolic systems of the type (133) have been prepared successfully on previous occasions\textsuperscript{113,114} via the condensation of the corresponding benzyloxyamine and benzyloxyaldehyde, to give the Schiff's base, followed by reduction of the imine group with sodium borohydride. Debenzylation by hydrogenolysis then yielded the required phenolic amine.
This approach was therefore applied to the synthesis of the phenolic amine (133; R = H). 4-Benzhydrylbenzaldehyde (135) was prepared from the hydroxyaldehyde (137) with benzyl chloride in the presence of anhydrous potassium carbonate with acetone as solvent. O-Benzyltyramine (136) was prepared from 4-benzhydrylbenzaldehyde (135) by treatment with nitromethane to give the 4-benzhydryl-ω-nitrostyrene (138) which was reduced with lithium aluminium hydride to the amine (136). N-(4-Hydroxyphenethy1)-4-hydroxybenzylamine (133; R = H) was then prepared as described above.
(135) + (136) → (139) → (140)

(133; R = H)
In an effort to reduce the number of steps and also increase the overall yield in this synthetic route, the preparation of the Schiff's base from \( \text{4-hydroxybenzaldehyde (137)} \) and tyramine (141), obtained by decarboxylation of tyrosine, was attempted and successfully carried out. The imine (142) was reduced as before by sodium borohydride to the required amine (133; \( R = H \)). This offers advantages over the previous route in that the preparation of 4-benzyloxybenzaldehyde (135) and O-benzyltyramine (136), and the debenzylation step are eliminated from the synthetic sequence to be replaced by the single reaction for the preparation of tyramine (141). The overall yield of the phenolic amine (133; \( R = H \)) was increased from 18\% to 50\% by using the direct condensation of the phenols.

\[
\text{HO--CH}_2\text{CHO} + \text{H}_2\text{N}-(\text{CH}_2)_2\text{OH} \rightarrow \text{HO--CH}==\text{N}-(\text{CH}_2)_2\text{OH}
\]

137 141 142
In order to protect the amine group for the phenolic oxidation step the \(N\)-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; \(R = H\)) was acetylated using acetic anhydride in pyridine in a nitrogen atmosphere. The \(O\)-acetyl groups were removed by alkaline hydrolysis to give \(N\)-acetyl-\(N\)-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; \(R = Ac\)). Two-phase alkaline ferricyanide oxidation of the diphenol amine (133; \(R = Ac\)) gave one major product in 70% yield. The infra-red spectrum of the compound showed the expected dienone bands at 1668 and 1625 cm\(^{-1}\), and also the \(N\)-acetyl carbonyl band at 1647 cm\(^{-1}\). The ultra-violet spectrum showed a maximum at 234 nm with an \(\epsilon\) value of 22,060 which is very similar to the spectrum obtained for the tetramethylene bisdienone (49). The n.m.r. spectrum however proved to be complex and could not readily be interpreted.

In order to determine whether the oxidation product obtained was the expected one a series of experiments were carried out aimed at simplifying the n.m.r. spectrum and thus allowing it to be interpreted unambiguously.

\(L\)-Hydroxybenzaldehyde (137) and tyramine (141) were both deuteriated at the 3 and 5 positions by heating under reflux in \(LN\) DCl. 2,6-Dideuterietyramine (144) was prepared by deuteration, under forcing conditions, of tyrosine in the 2, 3, 5 and 6 positions followed by decarboxylation. The decarboxylation also replaced the
deuterium atoms at the 3 and 5 positions with protons. Condensation of the deuteriated aldehyde (145) with the undeuteriated amine (141) and condensation of the two deuteriated amines (144) and (146) with the undeuteriated aldehyde (137), followed by oxidation of the phenols, gave a set of specifically deuteriated bisdienones (143 a, b and c). The n.m.r. spectrum of each was compared with that of the undeuteriated compound and unambiguous assignments of signals were made confirming the structure (143) for the latter.

![Chemical Structures]

(145)  (146)  (144)
The tetramethylene bisdienone (49) is symmetrical and, as expected, its n.m.r. spectrum (CDCl₃) showed a sharp quartet ($J = 10$Hz) for the $\alpha$ ($\tau$ 3.71) and $\beta$ ($\tau$ 2.91) protons of the two equivalent dienone rings. Initially, the bisdienone (143) was expected to show, at the most, two quartets for the protons in the two non-equivalent rings. In fact, the spectrum (CDCl₃) was more complex, although a sharp quartet ($\tau$ 2.86 and 3.63, $J \approx 10$Hz) did stand out clearly above a set of weaker, overlapping signals. For this reason, structures containing one dienone ring and one aromatic ring were at first considered though later excluded with the help of the deuteriated derivatives (143a, b and c). The n.m.r. spectrum of (143a) showed the sharp quartet (see above) accompanied by a pair of singlets ($\tau$ 2.97 and 3.06) of unequal intensity. In the spectra of (143b) and (143c) the sharp dienone quartets had collapsed to singlets at, respectively, $\tau$ 2.86 and 3.63, allowing the signals from the other ring to be seen clearly. These were found to be comprised of a pair of quartets ($\tau$ 2.97 and 3.53) and ($\tau$ 3.06 and 3.55) of unequal intensity but with the same coupling constant, $J = 10$Hz. The chemical shifts of the low-field doublets of each quartet corresponded with those of the two singlets in the spectrum of (143a). It was also noticed that the N-acetyl signal of all these bisdienones appeared as two singlets ($\tau$ 7.71 and 7.88) in a ratio of ca 5 : 6.
These results may be interpreted as being due to restricted rotation of the N-acetyl group, giving rise to two different environments for the 8, 9, 11 and 12 protons.

\[
\text{Me} \quad \text{O}^- \\
\text{N}^+ \\
\text{C}_8 \quad \text{B} \\
\text{O}^- \\
\text{Me} \\
\text{C} \\
\text{12} \\
\text{11} \\
\text{10} \\
\text{A} \\
\text{9} \\
\text{8} \\
\text{7} \\
\text{6} \\
\text{5} \\
\text{4} \\
\text{3} \\
\text{2} \\
\text{1} \\
\text{0}
\]

(143)

On the n.m.r. time scale (143) would appear as an unequal mixture of two species. The protons of ring A would resonate in slightly different positions depending on whether they were being influenced by the oxygen or the methyl group. The olefinic protons in ring C are too far from the N-acetyl group to be influenced significantly by it. The presence of two different rotamers would also, of course, explain the two signals for the N-acetyl methyl group.

Decomposition of the N-acetyl dienone (143) in neutral ethanol at 74°C proceeded in a similar manner to
that of its carbocyclic analogues (48) and (49). The decomposition was approximately first order with a half life of 18 hours. The major product (51%) from the decomposition was the benzylic ether (148). The structure followed from the appearance of the appropriate molecular ion in the mass spectrum and also from the n.m.r. spectrum which showed an ethoxy group and only one proton on the carbon atom between the aromatic ring and the nitrogen. The ultra-violet spectrum also indicated the presence of a phenolic group in the product by showing a base shift from 289 nm to 308 nm.

\[ \text{HO} \quad \text{Nac} \quad \text{O} \quad \text{OH} \]

\[ \text{HO} \quad \text{OEt} \quad \text{Nac} \quad \text{(CH}_2\text{)}_2 \quad \text{OH} \]

\[ (143) \quad 96 \quad (148) \]
Differential scanning calorimetry showed the \( N \)-acetyl dienone (143) to have slightly greater thermal stability than its trimethylene and tetramethylene analogues (48) and (49) in the solid state in that it did not begin to decompose until a temperature of 90°C was reached at a heating rate of 5°C/min. The decomposition was again accompanied by an exotherm, the peak occurring at 134°C, with an enthalpy value of 27 K cal/mole.

Attempts to remove the acetyl group from the \( N \)-acetyl dienone (143) all proved unsuccessful. The standard methods, such as trifluoroacetic acid in methylene chloride, hydrogen chloride in acetic acid and triethylxonium fluoroborate in methylene chloride all led to the decomposition of the dienone system, as determined by ultra-violet spectroscopy, before the \( N \)-acetyl group was removed.

In an attempt to avoid this decomposition the corresponding \( N \)-trifluoroacetyl phenol (133; \( R = \text{CF}_3\text{CO} \)) was prepared by treatment of the amine (133; \( R = \text{H} \)) with trifluoroacetic anhydride in pyridine followed by aqueous work-up. This type of system has been successfully oxidised using vanadium oxytrichloride\(^89\). However, the oxidation of \( N \)-trifluoroacetyl-\( N \)-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; \( R = \text{CF}_3\text{CO} \)) using vanadium oxytrichloride, according to the method of Schwartz\(^76\),
did not yield any product in high enough yield to be identified. Oxidation of the diphenol (133; \( R = \text{CF}_3\text{CO} \)) with activated manganese dioxide did yield the expected dienone (149), but it could not be obtained as a solid, and the structure could not therefore be confirmed by analysis; the mass spectrum did not show the expected molecular ion. Attempts at the removal of the \( N \)-trifluoroacetyl group by hydrolysis using potassium carbonate in aqueous methanol led to a mixture of products, none of which could be identified.

\[
\begin{align*}
\text{Oxidation of the diphenol (133; } R = \text{CF}_3\text{CO) } &\text{ did yield the expected dienone (149), but it could not be obtained as a solid, and the structure could not therefore be confirmed by analysis; the mass spectrum did not show the expected molecular ion. Attempts at the removal of the } N \text{-trifluoroacetyl group by hydrolysis using potassium carbonate in aqueous methanol led to a mixture of products, none of which could be identified.}
\end{align*}
\]

\[
\begin{align*}
\text{OH} &\quad \text{O} \\
\text{CH}_2 &\quad \text{N} \quad \text{C} \quad \text{CF}_3 \\
\text{N} \quad \text{C} \quad \text{CF}_3 &\quad \text{OH} \\
\text{CH}_2 &\quad \text{OH} \\
\end{align*}
\]

(133; \( R = \text{CF}_3\text{CO} \) )

(149)
CHAPTER THREE
EXPERIMENTAL
**General Methods**

Solutions of products in organic solvents were dried over anhydrous magnesium or sodium sulphate before evaporation of the solvent. Solvents were dried by standard methods and distilled before use. Petrol refers to the light petroleum fraction b.p. 60 - 80°C. Thin layer and preparative layer chromatography used silica (Merck PF$_{254}^\prime$) or alumina (Merck GF$_{254}^\prime$) as support spread as 0·5 mm layers. Column chromatography was carried out on silica (Fisons) and 'Camag' alumina (Brochmann).

Melting points were determined on a Kofler hot-stage apparatus. Infra-red spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer. Ultra-violet spectra were recorded using Unicam SP800 and SP8000 spectrometers. $^1$H Nuclear magnetic resonance spectra were recorded at 60 MHz on Perkin-Elmer R10 and Varian T60 spectrometers and at 100MHz on a Varian HA100 spectrometer. Tetramethylsilane was used as an internal standard. Mass spectra were recorded with A.E.I. MS9 and MS12 instruments.
Preparation of 4-methoxyacetophenone (72)

Anisole (10.7 g, 0.1 mol), acetic anhydride (16.2 g, 0.16 mol) and ortho phosphoric acid (0.7 g) were heated under reflux, with stirring, for 4 hours. The reaction mixture was allowed to cool to room temperature and then diluted with chloroform (40 ml). The chloroform solution was then washed with water (4 x 100 ml), sodium bicarbonate (2 x 100 ml of a 10% solution) and water (2 x 50 ml). The chloroform solution was then dried and the solvent removed in vacuo. Distillation of the crude product gave the ketone (72) as a colourless liquid which solidified on cooling (4.6 g, 31%), b.p. 110°C (4 mm Hg), m.p. 37.5°C (lit. 38 - 39°C); \( \tau \) (CDCl\(_3\)) 2.07, 3.10 (q, \( J = 10\) Hz, Ph), 6.19 (s, OMe) and 7.51 (s, C-Me); \( \nu \) max (KBr) 2845, 1685, 1608, 1361, 1260 and 835 cm\(^{-1}\).

Preparation of 4,4'-dimethoxychalcone (73)

Anisaldehyde (3.6 g, 0.027 mol) and 4-methoxyacetophenone (72) (4.0 g, 0.027 mol) were dissolved in absolute ethanol (13 ml). A solution prepared by dissolving sodium (0.3 g) in methanol (6.5 ml) was cooled and added to the ethanolic solution. This reaction mixture was maintained at room temperature for 1 hour, after which time a solid crystalline mass was formed. The reaction mixture was then maintained at 0°C for 2 hours. The solid chalcone (73) was filtered off, washed with cold 80% methanol and dried.
at room temperature (5.4 g, 76%), m.p. 100°C (lit. 97 - 99°C); δ (CDCl₃) 1.94, 3.04 (q, J = 10Hz, Ph), 2.20, 2.60 (q, J = 16Hz, 2-CH, 3-CH), 6.18 (s, OMe) and 6.20 (s, OMe); ν max (KBr) 2845, 1663, 1600, 1573, 1510, 824 and 812 cm⁻¹.

Preparation of 1,3-bis(4-methoxyphenyl)propane (74)

The chalcone (73) (4.0 g) was dissolved in glacial acetic acid (160 ml) and 10% Pd/C (160 mg) was added. The material was then hydrogenated at ambient temperature and atmospheric pressure. Uptake of hydrogen was complete in 24 hours. The catalyst was then removed by filtration and the acetic acid removed in vacuo. The residual liquid was taken up in chloroform (160 ml) and the chloroform solution extracted with 10% aqueous sodium carbonate (2 x 50 ml) and water (2 x 50 ml). The chloroform solution was dried and evaporated to yield a colourless oil which gave (74) as colourless needles on standing; (3.8 g, 100%); m.p. 42.5 - 44°C (from ethanol), (lit. 43 - 45°C);

δ (CDCl₃) 2.89, 3.16 (q, J = 10Hz, 2 x Ph), 6.26 (s, 2 x OMe), 7.44 (t, J = 8Hz, 1-CH₂ and 3-CH₂) and 7.8 to 8.3 (m, 2-CH₂); ν max (KBr) 2840, 1618, 1585, 1515, 1245 and 1038 cm⁻¹.

Preparation of 1,3-bis(4-hydroxyphenyl)propane (75) using hydroiodic acid as demethylating agent

1,3-Bis(4-methoxyphenyl)propane (74) (1.6 g) in acetic
acid (10 ml) and hydroiodic acid (9·7 ml) was heated under reflux for 10 hours. The solvent was then removed in vacuo to leave a dark brown oil which was dissolved in chloroform. This solution was then washed with water (3 x 25 ml), 5% aqueous sodium thiosulphate (2 x 25 ml) and water (2 x 25 ml). The chloroform solution was dried, and the solvent evaporated to yield a dark brown oil. The oil was dissolved in 1N potassium hydroxide solution (25 ml). The alkaline solution was washed with chloroform, acidified and extracted with chloroform. Drying and evaporation of the chloroform yielded a yellow oil which solidified on standing. Recrystallisation from benzene / petrol yielded white crystals of the diphenol (75) (347 mg, 24%), m.p. 103 - 104°C (lit. 99-106°C); \[\text{CD}_3\text{CO}] 2.16 (s, 2 x OH exchangeable with deuterium oxide), 2.98, 3.20 (q, J = 10Hz, 2 x Ph), 7.47 (t, J = 8Hz, 1-CH$_2$ and 3-CH$_2$) and 7.8 to 8.3 (m, 2H$_2$); $\nu_{\text{max}}$ (KBr) 3350, 1618, 1601, 1516, 1455, 1240 and 828 cm$^{-1}$.

Preparation of 1,3-bis(4-hydroxyphenyl)propane (75) using hydrobromic acid as the demethylating agent

1,3-Bis(4-methoxyphenyl)propane (74) (2.56 g) was heated under reflux with a mixture of glacial acetic acid (13.0 g) and constant boiling hydrobromic acid (5.0 g). The heating was continued for 4½ hours after which time all the starting material had reacted, as determined by
thin layer chromatography. Removal of the solvent in vacuo yielded a dark brown oil. The oil was dissolved in chloroform, the solution was washed with 10% sodium bicarbonate (3 x 50 ml) and water (3 x 50 ml), dried and the chloroform evaporated. The brown oily material was then dissolved in 1N potassium hydroxide solution (100 ml). The alkaline solution was then washed with ether, acidified and extracted with chloroform (4 x 50 ml). The chloroform solution was dried and the solvent removed by evaporation to yield an oily solid. This was recrystallised from benzene / petrol to yield the diphenol (75) as needles (1·0 g, 44%), m.p. 105°C (lit. 99 106°C). This product was identical in all respects to the product obtained using hydroiodic acid as demethylating agent.

**Preparation of 1,3-bis(4-hydroxyphenyl)propane (75) using potassium hydroxide in diethylene glycol as demethylating agent**

Potassium hydroxide (7·5 g) was dissolved in digol (20 ml) at 90°C. 1,3-Bis(4-methoxyphenyl)propane (74) (1·0 g) was added to the solution at 110°C. The temperature was then raised to 210°C with the removal of a distillate. The temperature was maintained at 210° - 220°C for 7 hours under a gentle reflux. The digol solution was then poured into ice water (180 ml) with rapid stirring. The aqueous solution was washed with chloroform (2 x 15 ml) and then
acidified with concentrated hydrochloric acid to pH 4. The acidified solution was extracted with chloroform (5 x 20 ml). The chloroform extracts were washed with saturated sodium bicarbonate (2 x 10 ml) and water (2 x 10 ml). The chloroform solution was then dried and evaporated to leave a brown oily solid. This was percolated in chloroform through a short column of grade III neutral alumina using chloroform as eluent and the solution evaporated to give an off-white solid. Recrystallisation from benzene / petrol yielded white needles of the diphenol (75) (730 mg, 82%), m.p. 106°C (lit. 99 106°C). This product was identical in all respects to the products from the two previous methods.

**Oxidation of 1,3-bis(L-hydroxyphenyl)propane (75)**

The diphenol (75) (500 mg) was dissolved in water (200 ml) containing potassium hydroxide (500 mg). This solution was added over 1 hour, under nitrogen, to a vigorously stirred mixture of water (100 ml), containing potassium ferricyanide (5 g) and chloroform (400 ml). When the addition was complete stirring was continued for a further 30 minutes. The mixture was then filtered using a water suction pump. The two layers were then separated and the chloroform layer quickly washed with water (100 ml). The chloroform solution was then dried and evaporated at room temperature to leave an off-white solid.
The solid was purified by passage through a grade III neutral alumina (5 g) column. The product was eluted with methylene chloride (75 ml). Removal of the solvent left the dienone (48) as a white crystalline solid, (281 mg, 57%), m.p. decomposes on heating. The product was spectroscopically identical with an authentic sample.97.

Determination of the decomposition rate of the bisdienone (48) in ethanol

The bisdienone (48) was dissolved in ethanol, which had previously been distilled from potassium hydroxide and zinc, at a known concentration. Aliquots of this solution were taken and sealed in ampules, which had been washed with dilute sodium bicarbonate solution, water and ethanol and placed in a water bath at 74°C. An ethanolic solution of the bisdienone (48) has a characteristic shoulder at 256 nm in the ultra-violet spectrum. The decomposition was followed by removing ampules from the bath at regular intervals and running the ultra-violet spectrum of the cooled solution. The absorption at 256 nm diminished with time and was replaced by a phenolic absorption at 278 nm. A plot of absorbance at 256 nm versus time was made to determine the rate of decomposition of the bisdienone (48).

Decompositions were carried out at different
concentrations and a constant dilution factor was used as necessary to run the ultra-violet spectra.

**Determination of the decomposition rate of the bisdienone (48) in benzene**

The bisdienone (48) was dissolved in benzene, which had previously been distilled from sodium, aliquots of this solution were sealed in ampules and placed in a water bath at 74°C, as for the ethanol samples. Ampules were removed at regular intervals and the benzene evaporated using a stream of nitrogen. The residue was taken up in ethanol and the ultra-violet spectrum determined. The rate of decomposition of the bisdienone was determined as for the ethanolic decomposition.

**Reaction of the dienone (48) with 2,6-di-t-butyl-4-methylphenol (76) in benzene.**

The dienone (48) (60 mg, 0.27 mmol) and 2,6-di-t-butyl-4-methylphenol (76) (120 mg, 0.55 mmol) were heated under reflux in benzene for 16 hours under nitrogen. Evaporation of the benzene yielded a yellow solid. This was separated by p.l.c. on silica, developing with chloroform / ethanol (97 : 3), into the starting phenol (75) (15 mg, 25%), m.p. 107°C, mixed mp 105°C, spectroscopically identical, and 1,2-bis(3,5-di-t-butyl-4-hydroxyphenyl)ethane (77) (101 mg, 85%), m.p. 173°-175°C (from ethanol)
(lit. $^{117}$ 174 - 175°C); $\tau$ (CDCl$_3$) 3.01 (s, 2 x Ph), 4.98 (s, 2 x OH exchangeable with deuterium oxide), 7.18 (s, 1-CH$_2$, 2-CH$_2$), 8.59 (s, 4 x t-Bu); $\nu_{\text{max}}$ (KBr) 3650, 2960, 1605, 1435, 1230, 875, 780 and 770 cm$^{-1}$.

Reaction of the dienone (48) with 2,6-di-t-butyl-4-methylphenol (76) in ethanol

The reaction was carried out as for the reaction in benzene. The two products isolated were the starting phenol (75) (60%), m.p. 106°C, mixed mp 106°C, and 1,2-bis(3,5-di-t-butyl-4-hydroxyphenyl)ethane (77) (97%), m.p. 173°C - 174°C, mixed m.p. 173°C - 174°C. This compound was spectroscopically identical to the product from the reaction in benzene.

Deuteriation of 1,3-bis(4-hydroxyphenyl)propane (75)

The phenol (75) (1.14 g) was dissolved in deuterium oxide (5 ml) to which sodium (345 mg) had previously been added. The solution was heated under reflux for 48 hours, cooled, diluted with water, acidified and extracted with chloroform. The chloroform solution was dried and the solvent evaporated. The phenol was again subjected to exchange in alkaline deuterium oxide (as above). The product showed the following spectroscopic features; $\tau$ (CDCl$_3$) 3.00 (s, 2 x 2'-CH, 2 x 6'-CH), 4.83 (b.s., 2 x OH exchangeable with deuterium oxide), 7.23 to 7.70.
(m, 1-CH₂, 3-CH₂) and 7.80 to 8.50 (m, 2-CH₂); mass spectrometry showed complete exchange of four protons with deuterium.

Preparation of 3,5,3',5'-tetra-t-butyl-1,1'-dihydro-2,5,2',5'-bis-cyclohexadiene-4,4'-one (82)

A benzene solution of 2,6-di-t-butylphenol (81) (4.12 g in 50 ml) was added, dropwise, under a current of nitrogen to a well stirred mixture of potassium ferrocyanide (24 g), water (100 ml), benzene (200 ml) and potassium hydroxide (4 g), over a period of half an hour. The resultant red coloured mixture was chilled and the two layers separated. The organic layer was then washed with water (2 x 50 ml), dried and the solvent evaporated at room temperature. The resulting solid material was washed with petrol (35 ml) to leave the bis-dienone (82) as a pale yellow solid (2.9 g, 71%), which was recrystallised from dry, freshly distilled petrol; m.p. 150°C (decomp.) (lit. 108 151° - 152°); r (CCl₄) 3.54 (d, J = 3 Hz, 2'-CH, 6'-CH), 6.62 (m, 1'-CH), and 8.82 (s, 4 x t-Bu); ν max (KBr) 2960, 1668, 1662, 1635, 1467, 1460, 1370, 1253, 960, 932, 872 and 740 cm⁻¹; λ max (hexane) 244 nm (ε, 16,500).

Evaporation of the petrol washings yielded 3,5,3',5'-tetra-t-butyl-4,4'-diphenooquinone (83) (0.5 g, 13%);
m.p. 245°C (lit. 246°C) (from ethanol); \( \tau \) (CCl\(_4\))

2·33 (s, 2-CH, 6-CH, 2′-CH, 6′-CH), and 8·60 (s, 4 x t-Bu);

\( \nu_{\text{max}} \) (KBr) 2940, 1650, 1620, 1570, 1485, 1463, 1365, 1092, 1043, 898, 882, 842 and 820 cm\(^{-1}\); \( \lambda_{\text{max}} \)
(hexane) 260 (\( \epsilon \), 4,300), 270 (\( \epsilon \), 4,300) and 418 nm
(\( \epsilon \), 84,000).

Recrystallisation of the dienone (82) from wet solvents or polar solvents results in isomerisation to

\( 4,4'\)-dihydroxy-3,5,3',5'-tetra-t-butyldiphenyl (84),
m.p. 185°C (lit. 185°C); \( \tau \) (CCl\(_4\)) 2·68 (s, 2-CH,
6-CH, 2′-CH, 6′-CH), 4·83 (s, 2 x OH exchangeable with deuterium oxide), and 8·50 (s, 4 x t-Bu);

\( \nu_{\text{max}} \) (KBr) 3600, 2940, 1118, 1220, 1132, 1095 and 862 cm\(^{-1}\); \( \lambda_{\text{max}} \)
(ethanol) 265 nm (\( \epsilon \), 18,000).

**Thermal decomposition of 3,5,3′,5′-tetra-t-butyl-1,1′-dihydro-2,5,2′,5′-bis-cyclohexadiene-4,4′-one (82)**

The dienone (82) (100 mg) was heated in an evacuated sealed tube at 160°C for 20 minutes. The tube was cooled, the products dissolved in chloroform and separated by p.l.c. on silica (petrol) to afford, 3,5,3′,5′-tetra-t-butyl-4,4′-diphenoquinone (83) (46 mg, 47%), m.p. 215°C (lit. 215°C), spectrosopically identical with an authentic sample, and 2,6-di-t-butylphenol (81) (43 mg, 42%), m.p. 35° - 37°C (lit. 35° - 38°C), spectrosopically identical with an authentic sample.
Deuteriation of 2,6-di-t-butylphenol (81)

Sodium (230 mg) was dissolved in deuterium oxide (10 ml) and 2,6-di-t-butylphenol (81) (4.12 g) was added followed by dry dimethylformamide (50 ml) to dissolve the phenol. A dark green-blue coloured solution was obtained, which was heated under reflux for 48 hours, cooled and poured into water (100 ml). The product was extracted with petrol (3 x 25 ml) and the organic solution was dried and evaporated. The deuteriated phenol was purified by distillation, b.p. 83° - 85°C (1 mm Hg) (lit. 118 133°C, 20 mm Hg; δ (CDCl₃) 2.78 (s, 3-CH, 5-CH), 4.80 (s, OH) and 8.55 (s, 2 x tBu).

Preparation of 1,3-bis(3,5-di-t-butyl-4-hydroxyphenyl)-propane (87)

1,3-Bis(4-hydroxyphenyl)propane (75) (1.14 g) was dissolved in benzene (5 ml). Concentrated sulphuric acid (0.035 ml) was added and the temperature raised to 60° - 63°C. Isobutylene gas was bubbled slowly through the solution at 60°C for 45 minutes. The solution was diluted with benzene (15 ml) and the organic phase washed with dilute sodium hydroxide (3 x 3 ml) and water until neutral (4 x 5 ml). The benzene solution was dried and then evaporated to yield 1,3-bis(3,5-di-t-butyl-4-hydroxy-phenyl)propane (87) as an oily solid which was recrystallised from ethanol (816 mg, 36%), m.p. 124° - 126°C

(Found: C, 82.0; H, 11.0%. \(C_{31}H_{48}O_2\) requires C, 82.2; H, 11.0%.)
H, 10·7%; $\tau$ (CDCl$_3$) 2·99, (2 x Ph), 4·99 (s, 2 x OH exchangeable with deuterium oxide), 7·2 to 7·6 (m, 3 x CH$_2$) and 8·57 (s, 4 x tBu); $\nu_{\text{max}}$ (KBr) 3660, 2940, 1435, 1235 and 875 cm$^{-1}$.

**Oxidation of 1,3-bis(3,5-di-t-butyl-4-hydroxyphenyl)propane (87) in aqueous ethanol**

The diphenol (87) (250 mg) was dissolved in ethanol (100 ml) containing potassium hydroxide (250 mg). This solution was added over 1 hour, under nitrogen, to a vigorously stirred aqueous ethanol solution (200 ml, 1 : 1) of potassium ferricyanide (2·5 g). When the addition was complete the solution was stirred for a further 1 hour during which period the colour changed from pale yellow to dark brown. The aqueous ethanol solution was then extracted with benzene (4 x 50 ml). The benzene was evaporated at room temperature to leave an impure oil. The oil was purified by passing through a grade III alumina column and eluting with petrol to yield 2,4,9,11-tetra-t-butyl-dispiro(5,0,5,3,7)hexadeca-1,4,8,11-tetraene-3,10-dione (88) as a yellow crystalline solid which was recrystallised from ethanol (94 mg, 38%), m.p. 153·5$^\circ$ - 155$^\circ$C; (Found: C, 83·0; H, 10·2%.

C$_{31}$H$_{46}$O$_2$ requires C, 82·6; H, 10·3%) $\tau$ (CDCl$_3$) 3·60 (s, $\beta$ -dienone protons), 7·86 (b.s. 3 x CH$_2$) and 8·83 (s, 4 x tBu); $\nu_{\text{max}}$ (KBr) 2960, 1665, 1645, 1370, 1250, 111.
896 and 870 cm\(^{-1}\); \(\lambda_{\text{max}}\) (EtOH) 242 mm (\(\epsilon = 27,000\)) and 264 mm (\(\epsilon = 22,000\)).

The decomposition of the tetra-t-butylated bisdienone (88) in ethanol

The bisdienone (88) (55 mg) was heated under reflux in ethanol (100 ml), in a nitrogen atmosphere, for 7 days. The ethanol was removed in vacuo to give a brown oil. The oil was separated, by p.l.c. on silica and developing with benzene / petrol (40 : 60), into two major components. The first component was identified as 1,3-bis(3,5-di-t-butyl-4-hydroxyphenyl)propane (87) (12 mg, 22%) spectroscopically identical with an authentic sample. The second component, isolated as an oil, was shown to be 1-ethoxy-1,3-bis(3,5-di-t-butyl-4-hydroxyphenyl)propane (89) (33 mg, 55%). The oil decomposed on attempted distillation under vacuum; m/e 496.3914 (m\(^+\), \(C_{33}H_{52}O_3\) requires m, 496.3916); \(\tau\) (CDCl\(_3\)) 2.95 (s, Ph), 3.04 (s, Ph), 4.93 (s, OH, exchangeable with deuterium oxide), 5.03 (s, OH, exchangeable with deuterium oxide), 5.93 (d/d, \(J = 8\) Hz, \(J = 6\) Hz, 1-CH), 6.55 to 6.85 (m, 0-CH\(_2\)-CH\(_2\)), 7.20 to 7.60 (m, 3-CH\(_2\)), 7.85 to 8.20 (m, 2-CH\(_2\)), 8.56 (s, 4 x tBu) and 8.80 (t, CH\(_3\)); \(\nu_{\text{max}}\) (CHCl\(_3\)) 3660, 2960, 2880, 1435, 1155, 1120, 910 and 650 cm\(^{-1}\).
The decomposition of the tetra-t-butylated bisdienone (88) in toluene

The bisdienone (88) (86 mg) was heated under reflux in dry distilled toluene (500 ml) in a dry oxygen free nitrogen atmosphere for 52 hours. After this time the maximum in the ultra-violet spectrum due to the bisdienone (88) had disappeared to be replaced by a maximum at 308 nm. The toluene was therefore removed in vacuo to yield a yellow oil (80 mg). All attempts to purify this oil led to the disappearance of the ultra-violet peak at 308 nm. τ (CDCl₃) 3.00 (b.d., J = 2.5 Hz, β proton in dienone), 3.12 (s, Ph), 3.15 (b.d., J = 2.5 Hz, β proton in dienone), 3.63 (m, vinyl proton), 4.98 (s, OH, exchangeable with deuterium oxide), 7.25 (m, 2 x CH₂), 8.62 (s, 2 x tBu), 8.73 (s, tBu) and 8.80 (s, tBu); νmax (CHCl₃) 3655, 1660, 1635 and 1615 cm⁻¹; λmax (cyclohexane) 308 nm.

Preparation of bis-1,4(4-methoxyphenyl)buta-1,3-diene (93)

Anisaldehyde (7.5 g, 55 mmol) succinic acid (3.0 g, 25 mmol) and lead monoxide were added to acetic anhydride (10 ml) and the mixture was stirred. The mixture was heated under reflux for 4 hours. The solution was then cooled and poured into benzene (100 ml). The solid product was removed by filtration and washed with hot benzene, ammonium chloride solution and finally water. Due to its
low solubility a suitable solvent for recrystallising the butadiene (93) could not be found. It was therefore isolated as a pale yellow amorphous solid (2·1 g, 30%), m.p. 219°C (lit. 222·5 - 223·5°C) \( \nu_{\text{max}} (\text{KBr}) \) 3010, 2950, 1605, 1505, 1300, 1255, 850 and 800 cm\(^{-1}\).

**Preparation of 1,4-bis(4-methoxyphenyl)butane (94)**

1,4-Bis(4-methoxyphenyl)buta-1,3-diene (93) (5 g) was suspended in benzene (200 ml), 10% palladium on charcoal (200 mg) was added and the material hydrogenated at ambient temperature and atmospheric pressure. Uptake of hydrogen was complete in 5 hours, the product remaining in solution. The catalyst was removed by filtration and the benzene was evaporated to yield the butane (94) as a crystalline product (4·5 g, 90%), m.p. 79 - 80°C (from ethyl acetate) (lit. 78 - 79°C); \( \tau (\text{CDCl}_3) \) 2·96, 3·26 (q, \( J = 10\text{Hz} \), 2 x Ph), 6·28 (s, 2 x OMe), 7·25 to 7·70 (m, 1-CH\(_2\), 4-CH\(_2\)), 8·20 to 8·64 (m, 2-CH\(_2\), 3-CH\(_2\)); \( \nu_{\text{max}} (\text{KBr}) \) 2930, 2850, 1605, 1585, 1515, 1245, 1030, 830, 810 and 750 cm\(^{-1}\).

**Preparation of 1,4-bis(4-hydroxyphenyl)butane (95)**

1,4-Bis(4-methoxyphenyl)butane (94) was demethylated by the method described for the demethylation of 1,3-bis(4-methoxyphenyl)propane (74) using potassium hydroxide / diethylene glycol. The product (95) had 114
This compound was spectroscopically identical to an authentic sample of the diphenol.

**Oxidation of 1,4-bis(4-hydroxyphenyl)butane (95)**

The diphenol (95) was oxidised with potassium ferricyanide using the method described for 1,3-bis(4-hydroxyphenyl)propane (75) to yield the bisdienone (49) (23%) which was spectroscopically identical to an authentic sample.

**Preparation of 2,4'-dihydroxychalcone (97)**

4-Hydroxyacetophenone (6·8 g) and salicylaldehyde (6 g) were dissolved in ethanol (20 ml). The solution was stirred under nitrogen and potassium hydroxide (13·5 g) in water (15·5 ml), was added dropwise at room temperature. When the addition was complete the temperature was raised to 53°C and maintained at this temperature for 16 hours. The solution was then cooled and acidified with 6N-hydrochloric acid (32 ml). Mustard coloured needles of the chalcone (97) separated out and were recrystallised from aqueous ethanol (7·9 g, 65%), m.p. 177°C (decomp.) (lit. 178°C); τ [(CD₃)₂SO] series of multiplets from 1·8 to 2·5 (2 x Ph and olefinic protons) and 4·28 (s, 2 x OH, exchangeable with deuterium oxide); νmax (KBr) 3250, 1655, 1608, 1590, 1565, 1345, 1230 1169 and 834 cm⁻¹.
Catalytic hydrogenation of 2,4'-dihydroxychalcone (97) in ethanol over 10% palladium on charcoal

The chalcone (97) (4 g) in ethanol (30 ml) was hydrogenated over 10% palladium on charcoal (160 mg) at ambient temperature and atmospheric pressure. One molar equivalent of hydrogen was taken up in 5 hours, when the rate of uptake decreased until uptake of hydrogen appeared to be complete after 10 days. The solution was then filtered and the solvent evaporated. The resultant oil was chromatographed over a silica column with benzene / petrol (3 : 1) to yield 4'-hydroxyflavan (98) which was recrystallised from benzene (0.7 g, 19%), m.p. 99°C (Found: C, 80.0; H, 6.4%. C_{15}H_{14}O_{2} requires C, 79.6; H, 6.2%) 7[(CD_{3})_{2}SO] O·60 (s, 1 x OH, exchangeable with deuterium oxide), 2.80, 3.25 (q, J = 9Hz, Ph), 2.7 to 3.4 (m, 5-CH, 6-CH, 7-CH, 8-CH), 5.06 (d/d, J = 9Hz, 3Hz, 2-CH), 6.85 to 7.45 (m, 4-CH_{2}) and 7.75 to 8.3 (m, 3-CH_{2}); ν_{max} (KBr) 3650 to 3100, 1620, 1590, 1520, 1492, 1260, 1111, 1073, 1047, 830 and 755 cm⁻¹.

Catalytic hydrogenation of 2,4'-dihydroxychalcone (97) in ethanol / perchloric acid over 10% palladium on charcoal

The chalcone (97) (1 g) in ethanol (10 ml) and perchloric acid (0.1 ml) was hydrogenated as before over 10% palladium on charcoal (100 mg). Uptake of hydrogen appeared to be complete after 8 days. The solution was
then filtered and the solvent removed. The residue was taken up in benzene (50 ml) and washed with sodium bicarbonate solution (3 x 10 ml) and water (2 x 10 ml). The solution was dried and evaporated to yield a colourless oil, which was chromatographed on silica to yield 4'-hydroxyflavan (98) (291 mg, 31%), m.p. 99°C, mixed m.p. 98°C. None of the required fully reduced hydrocarbon (96) was obtained.

Catalytic hydrogenation of 2,4'-dihydroxychalcone (97) over Raney nickel

The chalcone (97) (500 mg) was dissolved in ethanol (10 ml). Raney nickel (ca. 60 mg of W2) was added and the material was hydrogenated at room temperature and atmospheric pressure until no further uptake of hydrogen was observed. The catalyst was removed by filtration and the solvent evaporated to leave a pink oil. This oil was shown to be mainly starting material (97) by t.l.c., but p.l.c. separation afforded a minor proportion of a product which showed strong carbonyl absorption in the infra-red region and was not investigated further.

Catalytic hydrogenation of 2,4'-dihydroxychalcone (97) to 1-(4-hydroxyphenyl)-3-(2-hydroxyphenyl)propan-1-one (102)

The chalcone (97) (24 g) was dissolved in ethanol (15 ml) and 5% palladium on charcoal (150 mg) added. The
material was hydrogenated until one mole equivalent of hydrogen was absorbed. The catalyst was removed by filtration and the solvent evaporated. The residual oil was crystallised from aqueous ethanol to yield white needles of the ketone (102) (1.33 g, 54%), m.p. 113 - 114°C, (lit 103 - 104°C); \( ^{1}{H} \text{NMR} \) \( (\text{CD}_3)_{2}SO \) 2.19, 3.22 (q, \( J = 10 \text{Hz}, 3\text{-Ph} \)), 2.82 to 3.38 (m, 1-Ph), 3.98 (b.s., 2 x OH, exchangeable with deuterium oxide) and 6.64 to 7.30 (m, 2-CH\(_2\), 3-CH\(_2\)); \( \nu_{\text{max}} \) (KBr) 3350, 1670, 1610, 1590, 1210, 982, 845 and 766 cm\(^{-1}\).

**Clemmensen reduction of 1-(4-hydroxyphenyl)-3-(2-hydroxyphenyl)propan-1-one (102)**

The ketone (102) (400 mg) in ethanol (10 ml) was heated under reflux with amalgamated zinc (200 mg) and concentrated hydrochloric acid. No products were observed after 50 hours and more zinc (600 mg) was added and the mixture heated under reflux for a further 48 hours after which time all the starting material had been consumed. The zinc was removed by filtration, the solvent evaporated and the residue was dissolved in benzene (100 ml). The benzene solution was washed with sodium bicarbonate solution (3 x 25 ml) and water (2 x 25 ml) and the solution was dried and the solvent evaporated. The residue was purified by p.l.c. on silica developed in chloroform / ethanol (95 : 5).
Two major bands were obtained, one of which corresponded to 4'-hydroxyflavan (98) (30 mg, 8%), m.p. 98°C, mixed m.p. 98°C. The second product (77 mg, 20%) appeared, from its spectral data, to be the required 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (96). \( \delta \) (CDCl₃) 2.70 to 3.50 (m, 2 x Ph), 4.68 (b.s.; 2 x OH, exchangeable with deuterium oxide), 7.40 (J = 6 Hz, 1-CH₂, 3-CH₂) and 7.80 to 8.40 (m, 2-CH₂); \( \nu \) max (CHCl₃) 3610, 3340, 2930, 1612, 1598, 1510, 1488, 1455, 1170 and 830 cm\(^{-1}\).

It could not however be obtained as a solid.

Reduction of 2,4'-dihydroxychalcone (97) with sodium borohydride

The chalcone (97) (500 mg) was dissolved in ethanol (5 ml) and sodium borohydride (100 mg) was added to the stirred solution over half an hour. The solution was then heated under reflux for 2 hours, cooled, acidified with dilute hydrochloric acid and extracted with chloroform. The chloroform extracts were dried and evaporated and the residue was chromatographed on silica p.l.c. plates using chloroform / ethanol (95 : 5). Extraction of a band at \( R_f \) ca. 0.7 yielded 4'-hydroxyflavan (98) (170 mg, 34%), m.p. 99°C, mixed m.p. 98°C. Extraction of a band at \( R_f \) ca. 0.5 yielded 1-(4-hydroxyphenyl)-3-(2-hydroxyphenyl)-propan-1-one (102) (166 mg, 33%), m.p. 112°C, mixed m.p. 111°C. Starting material (97) (146 mg) was also isolated.
Attempted preparation of the tosyl hydrazone of 1-(4-hydroxyphenyl)-3-(2-hydroxyphenyl)propan-1-one (102)

The ketone (102) (242 mg) and toluene-4-sulphonyl hydrazide (600 mg) were dissolved in methanol (10 ml) and the solution was heated under reflux for 12 hours. When the solution was allowed to cool no product crystallised and t.l.c. analysis of the solution showed that only starting materials were present. Infra-red spectrometry showed a strong carbonyl band.

Catalytic hydrogenation of 2,4'-dihydroxychalcone (97) in glacial acetic acid over 10% palladium on charcoal

The chalcone (97) (4 g) was suspended in glacial acetic acid (100 ml) containing three drops of perchloric acid. 10% Palladium on charcoal (200 mg) was added and the material was hydrogenated at ambient temperature and pressure. Uptake of hydrogen ceased after 5 days, then the catalyst was removed by filtration and the glacial acetic acid evaporated. The residue was dissolved in chloroform (100 ml) and the solution was washed with sodium bicarbonate solution (3 x 25 ml) and water (3 x 25 ml). The organic layer was dried and solvent evaporated to yield an oil which crystallised on standing. The crystalline mixture was chromatographed over a column of silica. Elution with petrol - benzene (1 : 3) gave 4'-hydroxyflavan (98) (2.24 g, 59%), m.p. 120
98°C, mixed m.p. 98°C. Elution with benzene - chloroform (4 : 1) gave 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (96) (0.74 g, 19%), m.p. 62 - 63°C (from benzene) (lit. 90°C) (Found: C, 79.0; H, 7.0. Calc. for C_{15}H_{16}O_{2}: C, 78.9; H, 7.1%); τ (CDCl₃) 2.70 to 3.40 (m, 2 x Ph), 5.25 (b.s., 2 x OH, exchangeable with deuterium oxide), 7.20 to 7.60 (m, 1-CH₂, 3-CH₂) and 7.75 to 8.45 (m, 2-CH₂); ν max (KBr) 3650, to 3100, 1618, 1600, 1518, 1456, 1225, 830 and 755 cm⁻¹.

**High pressure catalytic hydrogenation of 2,4'-dihydroxychalcone (97) in glacial acetic acid over 10% palladium on charcoal**

The chalcone (97) (4 g) was suspended in glacial acetic acid (100 ml) containing three drops of perchloric acid. 10% Palladium on charcoal (200 gm) was added and the material was hydrogenated at ambient temperature and a pressure of 2000 p.s.i. After 8 days the carbonyl group was no longer present. Work up as in the previous experiment yielded 4'-hydroxyflavan (98) (2.64 g, 70%), m.p. 98°C, mixed m.p. 98°C and 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (96) (200 mg, 5%), m.p. 61 - 62°C, mixed m.p. 60°C.
High pressure catalytic hydrogenation of 2,4'-dihydroxychalcone (97) in glacial acetic acid over Raney Nickel

The procedure was as for the previous experiment. The major product was 4'-hydroxyflavane (98) with only a trace of the required 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (96) (20 mg, 0.5%).

This reaction was also carried out at 60°C with the same result.

Catalytic hydrogenation of 2,4'-dihydroxychalcone (97) in glacial acetic acid with regular additions of 10% palladium on charcoal

The chalcone (97) (3 g) was suspended in glacial acid (75 ml) containing three drops of perchloric acid. 10% Palladium on charcoal (150 mg) was added and the material was hydrogenated at ambient temperature and pressure. Further portions of catalyst (50 ml) were added at intervals of 24 hours for 5 days. After this time hydrogen uptake ceased, the catalyst was removed by filtration and the glacial acetic acid evaporated. The residue was dissolved in chloroform (75 ml) and the solution was washed with sodium bicarbonate solution (3 x 25 ml) and water (3 x 25 ml). The organic layer was dried and the solvent evaporated to yield an oil. The oil was chromatographed over a column of silica. Elution with
petrol - benzene (1 : 3) gave 4'-hydroxyflavan (98) (1.6 g, 41%), m.p. 99°C, mixed m.p. 98°C. Elution with benzene - chloroform (4 : 1) gave 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (96) (1.2 g, 31%), m.p. 63°C, mixed m.p. 63°C.

Oxidation of 1-(2-hydroxyphenyl)-3-(4-hydroxyphenyl)propane (96)

The diphenol (96) (250 mg) was dissolved in a solution of potassium hydroxide (250 mg) in water (50 ml). This solution was added over 1 hour, under nitrogen, to a vigourously stirred mixture of a solution of potassium ferricyanide (2.5 g) in water (100 ml) and benzene (250 ml). When the addition was complete the mixture was stirred for a further 30 minutes, then filtered and the two layers separated. The benzene layer was quickly washed with water (100 ml), dried and evaporated at room temperature to leave a colourless oil. The oil was purified by chromatography through a neutral grade III alumina column in methylene chloride. The spirodienone (100) was then recrystallised from petrol (47 mg, 19%), m.p. 86 - 87°C (Found: C, 79.6; H, 6.3. C_{15}H_{14}O_{2} requires C, 79.6; H, 6.2%); ν (CDCl₃) 2.60 to 3.20 (m, Ph), 2.99, 3.84 (q, J = 10Hz, α and β 'dienone' protons), 6.85 to 7.25 (m, benzylic methylene) and 7.85 to 8.40 (m, Ph-CH₂-CH₂-CH₂); ν max 2940, 1667, 1640, 1590 and 1225 cm⁻¹; λ max (EtOH) 219 nm (ε 6,010).
Preparation of 4'-acetoxyflavan (99)

4'-Hydroxyflavan (98) (100 mg) was acetylated according to the method of Kirby and Tiwari to yield 4'-acetoxyflavan (99) (98 mg, 83%), m.p. 112°C (from benzene / petrol) (Found: C, 76.4; H, 6.2. C_{17}H_{16}O_{3} requires C, 76.1; H, 6.0%). \(\delta(CDCl_3)\) 2.57, 2.89 (q, J = 9Hz, Ph), 2.45 to 3.25 (m, 5-H, 6-H, 7-H, 8-H), 4.96 (d/d, J = 9Hz, J = 3Hz, 2-CH), 6.80 to 7.45 (m, 4-CH_{2}), 7.70 (s, OAc) and 7.70 to 8.05 (3-CH_{2}); \(\nu_{max}(KBr)\) 2950, 2910, 1760, 1607, 1582, 1485, 1240, 1215, 1185, 913 and 758 cm\(^{-1}\).

Preparation of 4'-methoxyflavan (100)

4'-Hydroxyflavan (98) (50 mg) was methylated using the method of Gillis to give the methyl ether (100) (47 mg, 91%), m.p. 82 - 83°C (from petrol) (lit. 83 - 84°C); \(\delta(CDCl_3)\) 2.68, 3.12 (q, J = 9Hz, Ph), 2.66 to 3.28 (m, 5-CH, 6-CH, 7-CH, 8-CH), 5.03 (d/d, J = 8Hz, J = 4Hz, 2-CH), 6.22 (s, OMe), 6.82 to 7.40 (m, 4-CH_{2}) and 7.76 to 8.02 (m, 3-CH_{2}); \(\nu_{max}(KBr)\) 2997, 2960, 2835, 1612, 1580, 1512, 1487, 1235, 1030, 810 and 760 cm\(^{-1}\).

Preparation of 2-methoxybenzyl alcohol (104)

2-Methoxybenzaldehyde (105) (3.0 g) in dry ether (20 ml) was slowly added to a stirred suspension of lithium aluminium hydride (850 mg) in dry ether (20 ml). The mixture was then heated under reflux for 6 hours, when water was added dropwise to decompose excess reagent.
The precipitate was removed by filtration and the organic solution dried and evaporated to yield the crude product, which was purified by distillation under reduced pressure; (2.7 g, 89%), b.p. 87 - 88°C (0.02 mm Hg) (lit.121 80 - 82°C, 0.01 mm Hg); $\nu_{\text{max}}$ (liq. film) 3350, 2940, 2840, 1608, 1595, 1495, 1465, 1243, 1050, 1030 and 755 cm$^{-1}$.

Preparation of 2-methoxybenzyl chloride (106)

A solution of 2-methoxybenzyl alcohol (104) (2.7 g), thionyl chloride (4.5 g) and pyridine (0.06 g) in benzene (24 ml) was heated under reflux for 2 hours. The solution was then concentrated and diluted with ether. The ethereal solution was washed with water, dried and distilled under reduced pressure to yield 2-methoxybenzyl chloride (106) (2.8 g, 91%), b.p. 78 - 79°C (3 mm Hg) (lit.121 52 - 54°C, 0.1 mm Hg); $\nu_{\text{max}}$ (liq. film) 2970, 2840, 1610, 1594, 1495, 1470, 1440, 835, 700 and 670 cm$^{-1}$.

Preparation of 4-methoxycinnamaldehyde (107)

Anisaldehyde (13.6 g) was suspended in aqueous sodium hydroxide (200 ml of 1% solution) and acetaldehyde gas was bubbled through the suspension for 10 hours. The suspension was then extracted with chloroform (4 x 25 ml) and the combined chloroform extracts were washed with water and dried. Fractional distillation gave pure 4-methoxycinnamaldehyde (107) (3.8 g, 23%), b.p. 121 -
122°C (3 mm Hg), m.p. 56 - 58°C (lit. 122°C); \( \nu_{\text{max}} \) (liq. film) 3010, 2950, 2840, 1675, 1605, 1510, 1360, 1130, 820 and 755 cm\(^{-1}\).

**Preparation of 1-(2-methoxyphenyl)-4-(4-methoxyphenyl)-buta-1,3-diene (108)**

Triethylphosphite (5 ml) and 2-methoxybenzyl chloride (106) (3·0 g) were heated under reflux for 1 hour, when evolution of ethyl chloride ceased. The product was then cooled to room temperature and poured into a flask containing freshly prepared sodium methoxide (1·2 g). Dimethylformamide (20 ml) was added and the solution was stirred vigourously with cooling in an ice bath. A solution of 4-methoxycinnamaldehyde (107) (3·2 g) in dimethylformamide (10 ml) was added dropwise to the thoroughly chilled solution. The flask was then removed from the ice bath and allowed to stand at room temperature for 30 minutes. Water (10 ml) was added followed by methanol (5 ml). Crystals of 1-(2-methoxyphenyl)-4-(2-methoxyphenyl)buta-1,3-diene (108) which separated were recrystallised from methanol (1·5 g, 28%), m.p. 116 - 116·5°C (Found: C, 80·9; H, 6·8; \( \text{C}_{18}\text{H}_{16}\text{O}_2 \) requires C, 81·2; H, 7·0%). \( \tau \) (CDCl\(_3\)) 2·40 to 3·40 (m, 2 x Ph, 1-H, 2-H, 3-H, 4-H), 6·18 (s, OMe) and 6·20 (s, OMe) \( \nu_{\text{max}} \) (KBr) 2940, 2840, 1635, 1601, 1510, 1485, 1250, 1030, 995 and 750 cm\(^{-1}\).
Preparation of 1-(2-methoxyphenyl)-4-(4-methoxyphenyl)-butane (109)

The butadiene (108) (1.4 g) was dissolved in benzene (120 ml) and hydrogenated at ambient temperature and atmospheric pressure over 10% palladium on charcoal (50 mg). When hydrogen uptake ceased the catalyst was filtered off and the pure 1-(2-methoxyphenyl)-4-(4-methoxyphenyl)butane (109) was obtained by distillation under reduced pressure (1.2 g, 85%), b.p. 180°C (1.0 mm Hg) (Found: C, 80.4; H, 8.3. C₁₈H₂₀O₂ requires C, 80.0; H, 8.2%) \( \gamma (\text{CDCl}_3) \)

2.92, 3.20 (q, \( J = 10 \text{Hz} \), Ph), 2.80 to 3.35 (m, Ph), 6.20 (s, OMe), 6.23 (s, OMe), 7.20 to 7.60 (m, 1-CH₂, 4-CH₂) and 8.20 to 8.55 (m, 2-CH₂, 3-CH₂); \( \nu_{\text{max}} \) (liq. film) 2940, 2960, 2840, 1615, 1605, 1590, 1510, 1495, 1245, 1035 and 750 cm\(^{-1}\).

Preparation of 1-(2-hydroxyphenyl)-4-(4-hydroxyphenyl)-butane (103)

The dimethoxy compound (109) (1.1 g) was added to a mixture of dry diethylene glycol (20 ml) and potassium hydroxide (7.5 g) at 100°C. The temperature was raised to 210°C and the solution was maintained under reflux at 210°C for 8 hours, allowed to cool and poured into ice water (200 ml) with rapid stirring. The aqueous solution was washed with chloroform (2 x 25 ml) and acidified with hydrochloric acid. The acidic solution was extracted with
chloroform (4 x 25 ml) and the chloroform extracts were washed with sodium bicarbonate solution (2 x 25 ml) and water (3 x 25 ml). The organic solution was dried and evaporated to yield a pink oil which crystallised on standing. The 1-(2-hydroxyphenyl)-4-(4-hydroxyphenyl)-butane (103) was recrystallised from benzene (890 mg, 90%), m.p. 114 - 115°C (Found: C, 79·2; H, 7·6. C₁₆H₁₈O₂ requires C, 79·3; H, 7·5%); ν[(CD₃)₂SO] 1·52 (s, 2 x OH, exchangeable with deuterium oxide), 3·05, 3·30 (q, J = 10Hz, Ph), 2·85 to 3·45 (m, Ph), 7·20 to 7·65 (m, 1-CH₂, 4-CH₂) and 8·20 to 8·60 (m, 2-CH₂, 3-CH₂); νmax (KBr) 3470, 3350, 2915, 2850, 1610, 1590, 1512, 1450, 1240, 1190, 825, 760 and 745 cm⁻¹.

Oxidation of 1-(2-hydroxyphenyl)-4-(4-hydroxyphenyl)-butane (103) to the spirodienone (111)

This phenol (103) was oxidised in a similar manner to the homologous trimethylene phenol. The spirodienone (111) (18 mg, 7%) could not be obtained as a solid m/e 240·1155 (M⁺, C₁₆H₁₆O₂ requires M, 240·1150); ν (CDCl₃) 2·55 to 3·15 (m, Ph), 2·85, 3·70 (q, J = 10Hz, α and β 'dienone' protons), 6·80 to 7·20 (m, benzylic methylene) and 7·80 to 8·43 (m, Ph-CH₂-CH₂-CH₂-CH₂); νmax (CHCl₃) 2930, 2850, 1670, 1630, 1480, 1440, and 860 cm⁻¹; λmax (EtOH) 216 nm.
Preparation of cis-3,cis-6-diphenylcyclohex-4-ene-cis-1,cis-2-dicarboxylic acid anhydride (116)

trans, trans-1,4-Diphenyl-1,3-butadiene (115) (1.03 g, 5 mmol) and maleic anhydride (0.46 g, 4.6 mmol) were dissolved in xylene (5 ml). The solution was heated under reflux for 7 hours and then allowed to cool. The white crystalline product (116) which separated was filtered off, washed with xylene and ethanol and recrystallised from chloroform (1.21 g, 81%), m.p. 205-206°C (lit. 123 206°C); δ (CDCl₃) 2.64 (s, 2 x Ph), 3.46 (s, 4-H, 5-H) and 6.05 (s, 1-H, 2-H, 3-H, 6-H); ν max (KBr) 1855, 1770, 1601, 1500, 1250, 955, 940, 930 and 740 cm⁻¹.

Catalytic hydrogenation of cis-3,cis-6-diphenylcyclohex-4-ene-cis-1,cis-2-dicarboxylic acid anhydride (116)

cis-3,cis-6-Diphenylcyclohex-4-ene-cis-1,cis-2-dicarboxylic acid anhydride (116) (500 mg) was suspended in glacial acetic acid (10 ml) and 10% palladium on charcoal (50 mg) was added. The material was hydrogenated at ambient temperature and atmospheric pressure. Uptake of hydrogen was complete in 12 hours. The insoluble product and catalyst were removed by filtration and washed with water. The product was separated from the catalyst by Soxhlet extraction with chloroform. Evaporation of the chloroform yielded an off white solid which was recrystallised from chloroform to yield white crystals of cis-3,cis-6-
diphenylcyclohexane—cis-1,cis-2-dicarboxylic acid anhydride (117) (485 mg, 97%), m.p. 220 – 221°C (lit. 123 220 – 222°C); \[
\delta \left( \left[ \text{CD}_3 \right]_2 \text{SO} \right) \]
2.68 (s, 2 x Ph), 6.02 (m, 1-H, 2-H, 3-H, 6-H) and 7.69 to 8.05 (m, 4-H, 5-H); \[
\nu_{\text{max}} \] (KBr) 1860, 1780, 1601, 1500, 995, 947, 920, 910, 760, 750 and 700 cm\(^{-1}\).

Hydrolysis of cis-3,cis-6-diphenylcyclohexane-cis-1,cis-2-dicarboxylic acid anhydride (117)

The anhydride (117) (340 mg) was suspended in aqueous sodium bicarbonate solution (10 ml) and the mixture was heated under reflux until the anhydride had dissolved. The solution was filtered, acidified with dilute hydrochloric acid and the product removed by filtration. The cis-3,cis-6-diphenylcyclohexane-cis-1,cis-2-dicarboxylic acid (118) was recrystallised from aqueous ethanol (332 mg, 92%), m.p. 208 – 209°C (lit. 124 209 – 211°C); \[
\delta \left( \left[ \text{CD}_3 \right]_2 \text{SO} \right) \]
1.65 (b.s., 2 x OH), 2.53 to 3.10 (m, 2 x Ph), 6.70 (b.s., 1-CH, 2-CH, 3-CH, 6-CH), 7.20 to 7.75 (m, 4-CH, 5-CH) and 7.85 to 8.35 (m, 4-CH, 5-CH); \[
\nu_{\text{max}} \] 3650 to 2800, 1725, 1200, 750 and 695 cm\(^{-1}\).

Decarboxylation of cis-3,cis-6-diphenylcyclohexane-cis-1,cis-2-dicarboxylic acid (118) with lead tetraacetate in dimethyl sulfoxide under nitrogen

The diacid (118) (318 mg) was dissolved in dimethyl
sulphoxide (15 ml) and pyridine (90 mg) was added followed 
by lead tetraacetate (466 mg). The solution was stirred 
overnight under nitrogen, then poured into water and the 
aqueous suspension extracted with ether (3 x 25 ml). 
The combined ether extracts were washed with dilute 
sodium hydroxide (2 x 10 ml), dilute hydrochloric acid 
(2 x 10 ml) and finally water (3 x 10 ml). The ethereal 
solution was dried and evaporated to yield a crude gum. 
P.I.C. yielded p-terphenyl (119) (91 mg, 40%), m.p. 
213°C (lit. 213°C). The compound was spectroscopically 
identical with an authentic sample.

Decarboxylation of cis-3, cis-6-diphenylcyclohexane-cis-1, 
cis-2-dicarboxylic acid (118) using lead tetraacetate in 
benzene, under nitrogen

The diacid (118) (256 mg) was dissolved in dry benzene 
(12.5 ml) and pyridine (105 mg). Lead tetraacetate (310 mg) 
was added to the mixture under a nitrogen atmosphere and 
the mixture stirred for 2 days. The precipitated lead 
diacetate was removed by filtration and the solution was 
washed with water (2 x 2.5 ml), dilute sodium hydroxide 
(2 x 2.5 ml), dilute hydrochloric acid (2 x 2.5 ml) and 
finally water (3 x 2.5 ml). The solution was dried and 
the benzene evaporated to yield p-terphenyl (119) (118 mg, 
61%), m.p. 212°C (lit. 213°C) after separation by 
p.l.c. on silica with petrol / benzene (50 : 50). The
p-terphenyl (119) was spectroscopically identical with an authentic sample.

Decarboxylation of cis-3,cis-6-diphenylcyclohexane-cis-1, cis-2-dicarboxylic acid (118) using lead tetraacetate in the presence of oxygen.

Oxygen was bubbled through pyridine (10 ml, dist. from barium oxide) for approximately 15 minutes. The diacid (118) (972 mg) and lead tetraacetate (1.17 g) were added and the solution heated at 68°C. Carbon dioxide was evolved and after 10 minutes the reaction mixture was cooled, poured into excess dilute nitric acid and extracted with ether (3 x 25 ml). The organic layer was washed with aqueous sodium bicarbonate (3 x 10 ml), brine (3 x 10 ml) and water (2 x 10 ml). The ethereal solution was dried and evaporated. P.l.c. on silica of the crude product with benzene / petrol (50 : 50) yielded p-terphenyl (119) (390 mg, 53%), m.p. 212°C (lit. 118 213°C). The compound was spectroscopically identical with an authentic sample.

Attempted decarboxylation of cis-3,cis-6-diphenylcyclohexane-cis-1,cis-2-dicarboxylic acid (118) using copper chromite in quinoline.

The diacid (118) (324 mg), copper chromite (30 mg) and quinoline were heated at 240°C for 14 hours. The
reaction mixture was then cooled, diluted with ether (100 ml) and filtered. The ethereal solution was washed with dilute hydrochloric acid (3 x 10 ml), dilute sodium hydroxide (3 x 10 ml) and brine (3 x 10 ml). The ethereal solution was dried and evaporated to yield the anhydride (117) (244 mg, 80%), m.p. 219 - 220°C (lit. 123 220 - 222°C), mixed m.p. 219°C. The compound was spectroscopically identical to an authentic sample of the 3,6-diphenylcyclohexane-1,2-dicarboxylic acid anhydride (117).

Attempted decarboxylation of cis-3,cis-6-diphenylcyclohexane-cis-1,cis-2-dicarboxylic acid (118) by pyrolysis

The diacid (118) (648 mg) was passed through a flow pyrolysis tube at 450°C, at reduced pressure, under a stream of nitrogen. A white solid was trapped at the end of the tube. This solid was shown, by comparison, to be cis-3,cis-6-diphenylcyclohexane-cis-1,cis-2-dicarboxylic acid anhydride (117) (596 mg, 97%), m.p. 220 - 221°C (lit. 123 220 - 222°C), mixed m.p. 219 - 220°C.

Nitration of cis-3,cis-6-diphenylcyclohexane-cis-1,cis-2-carboxylic acid (118)

The diacid (118) (100 mg) in glacial acetic acid (2 ml) was slowly added to a mixture of concentrated nitric acid (4 ml) and glacial acetic acid (1.5 ml),
the temperature being kept at 0°C throughout the addition. The mixture was stirred for half an hour, poured onto ice and extracted with benzene (3 x 25 ml). The organic layer was washed with water (3 x 10 ml), dried and evaporated to yield a crude gum (30 mg). T.l.c. showed the gum to consist of six components in approximately equal proportions and the experiment was abandoned.

Preparation of cis-2,cis-5-diphenylcyclohex-3-ene-cis-1-carboxylic acid (150)

1,4-Diphenylbutadiene (20 g, 97 mmol) and acrylic acid (8 g, 125 mmol) were heated under reflux in xylene (50 ml) for 12 hours. The solution was allowed to cool to room temperature and extracted with dilute sodium hydroxide (3 x 50 ml). The xylene solution was dried and the solvent removed in vacuo to recover the unreacted diene (3.6 g). The basic solution was acidified and extracted with benzene. The benzene solution was dried and evaporated to yield the adduct and the unreacted acrylic acid. The product (150) was recrystallised from aqueous ethanol, (13.2 g, 49%), m.p. 176°C (lit. 128 178°C); \( \gamma \) (CDCl₃) 0.83 (s, OH, exchangeable with deuterium oxide), 2.70 (s, Ph), 2.79 (s, Ph), 4.08 (s, 3-H, 4-H), 5.95 to 6.25 (m, 1-H), 6.35 to 7.15 (m, 2-H, 5-H) and 7.95 to 8.25 (m, 6-CH₂); \( \nu_{max} \) (KBr) 3600 to 2400, 1795, 1603, 1495, 1455, 1212, 760, 745 and 700 cm⁻¹.

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Catalytic hydrogenation of cis-2,cis-5-diphenylcyclohex-3-ene-cis-1-carboxylic acid (150)

The acid (150) (5 g) was dissolved in dilute sodium hydroxide (50 ml) and 10% palladium on charcoal (100 ml) was added. The material was hydrogenated at ambient temperature and atmospheric pressure. Uptake of hydrogen was complete in 16 hours. The catalyst was removed by filtration and the solution was acidified and extracted with benzene (4 x 25 ml). The benzene solution was dried and evaporated to yield cis-2,cis-5-diphenylcyclohexane-1-carboxylic acid (120) (4.8 g, 94%), m.p. 145°C (from aqueous ethanol) (lit.123 146°C); T (CDCl₃) -2.30 (s, OH, exchangeable with deuterium oxide), 2.40 to 3.00 (m, 2 x Ph), 6.25 to 6.60 (m, 1-H), 6.70 to 7.35 (m, 2-H, 5-H), 7.70 to 8.18 (m, 3-CH₂, 4-CH₂) and 8.20 to 8.62 (m, 6-CH₂);

\[ \gamma_{\text{max}} \text{(KBr)} \] 3650 to 2300, 1702, 1603, 1495, 1450, 1265, 755 and 700 cm⁻¹.

Decarboxylation of cis-2,cis-5-diphenylcyclohexane-cis-1-carboxylic acid (120) using copper chromite in quinoline

The acid (120) (278 mg) was dissolved in quinoline (1 ml). Copper chromite (20 mg) was added and the mixture was heated under reflux for 16 hours. The cooled solution was diluted with ether (25 ml), washed with dilute hydrochloric acid (4 x 5 ml), dilute sodium hydroxide (3 x 5 ml) and water (3 ml). The ether
solution was dried and evaporated. P.l.c. of the resultant oil (115 mg) on silica using benzene/petrol (50:50), yielded \( \text{p-terphenyl} \) (119) (36 mg, 15%), m.p. 212°C (lit. \( \text{118} \) 213°C). The compound was spectroscopically identical with an authentic sample. The other major product (56 mg) showed a characteristic anhydride band in the I.R. and was not identified further.

Attempted decarboxylation of \text{cis-2,cis-5-diphenylcyclohexane-cis-1-carboxylic acid} (120) by pyrolysis

The acid (120) (500 mg) was passed through a flow pyrolysis tube at 600°C, at reduced pressure in a nitrogen atmosphere. The material isolated at the outlet was shown to be starting material (120) (470 mg, 94%).

Nitration of \text{cis-3,cis-6-diphenylcyclohexane-cis-1-carboxylic acid} (120)

The monoacid (120) was nitrated using the same procedure as for the diacid (118).

Again a multicomponent gum (20 mg) was obtained and the experiment was abandoned.

Attempted decarboxylative bromination of \text{cis-2,cis-5-diphenylcyclohexane-cis-1-carboxylic acid} (120)

A solution of the acid (120) (2.8 g) and bromine (0.79 g) in \( 1,1,2,2\)-tetrachloroethane was added dropwise
to a stirred suspension of red mercuric oxide (2.16 g) in 1,1,2,2-tetrachloroethane (60 ml) at 35°C over a period of 45 minutes. The solution was cooled and filtered. The solid was washed with tetrachloroethane and the organic solution dried over calcium chloride. Allyl alcohol was added to remove the excess bromine and the solvent was removed in vacuo. Starting material (170) was recovered (2.6 g, 93%).

**Attempted hydroxylation of dimethyl cis-3,cis-6-diphenyl-cyclohexane-cis-1,cis-2-dicarboxylate using thallium trifluoroacetate**

The diester was prepared by the addition of diazomethane to the diacid in ethanol/ether. The procedure of MacKillop and Taylor for hydroxylation was then followed.

The only base soluble material isolated was triphenylphosphine oxide, m.p. 156°C (lit. 156 ± 157°C). This product was identical in all respects to an authentic sample.

**Preparation of bis-1,4-(4-methoxyphenyl)buta-1,3-diene (93)**

Anisaldehyde (6.9 g, 50 mmol) and succinic acid (3.0 g, 25 mmol) were dissolved in acetic anhydride (15 ml). Litharge (11.1 g) was added and the mixture was heated under reflux for 5 hours. Acetic acid (20 ml of 80%) was added and the solution was allowed to cool.
butadiene (93) crystallised on cooling and was recrystallised from toluene (2.4 g, 36%), m.p. 224°C (lit. 222.5 - 223.5°C); $\nu_{\text{max}}$ (KBr) 3008, 2955, 2835, 1600, 1505, 1300, 1250, 1175, 1028, 982, 847 and 800 cm$^{-1}$.

**Reaction of 1,4-bis(4-methoxyphenyl)buta-1,3-diene (93) with maleic anhydride**

The butadiene (93) (5.3 g, 20 mmol) and maleic anhydride (1.96 g, 20 mmol) were suspended in xylene (1,000 ml). Both compounds dissolved when the temperature was increased and the solution was heated under reflux for 3 days. On cooling a white crystalline solid separated out. The adduct (121) was separated from the unreacted diene (93) by chromatography through a short silica column. Elution with benzene gave the unreacted diene (93) followed by cis-3, cis-6-di(4-methoxyphenyl)cyclohex-4-ene-1,2-dicarboxylic acid anhydride (121) which was recrystallised from benzene (4.75 g, 65%), m.p. 220 - 221°C. (Found: C, 72.7; H, 5.6. C$_{22}$H$_20$O$_5$ requires C, 72.5; H, 5.5%) $\tau$ [(CD$_3$)$_2$SO] 2.78 and 3.13 (q, J = 9Hz, 2 x Ph), 3.66 (s, 4-H, 5-H), 6.13 (b.s., 1-H, 2-H, 3-H, 6-H) and 6.22 (s, 2 x OMe); $\nu_{\text{max}}$ (KBr) 2835, 1840, 1768, 1612, 1518, 1250 and 945 cm$^{-1}$. 138
Catalytic hydrogenation of cis-3, cis-6-di(4-methoxyphenyl)-cyclohex-4-ene-cis-1, cis-2-dicarboxylic acid anhydride (121)

The anhydride (121) (500 mg) was dissolved in ethyl acetate (500 ml), 10% palladium on charcoal (50 mg) was added and the anhydride was hydrogenated at ambient temperature and atmospheric pressure. One mole equivalent of hydrogen was taken up after 48 hours. The catalyst was removed by filtration and the solvent evaporated. The residue was recrystallised from benzene to yield pure cis-3, cis-6-di(4-methoxyphenyl)cyclohexane-cis-1, cis-2-dicarboxylic acid anhydride (147) (496 mg, 98%), m.p. 238°C (Found: C, 72.2; H, 5.9. C_{22}H_{22}O_{5} requires C, 72.1; H, 6.0%). \( \gamma \) \([\text{CD}_{3}]_{2}S\text{O}\) 2.78, 3.14 (q, J = 9 Hz, 2 x Ph), 6.00 to 6.55 (m, 1-H, 2-H, 3-H, 6-H) and 7.86 to 8.14 (m, 4-CH_{2}, 5-CH_{2}); \( \nu \) \text{max} (KBr) 2940, 2840, 1850, 1780, 1612, 1513, 1298, 1182, 1035, 995, 940 and 900 cm\(^{-1}\).

Hydrolysis of cis-3, cis-6-di(4-methoxyphenyl)cyclohex-4-ene-cis-1, cis-2-carboxylic acid anhydride (147)

The anhydride (147) (5 g) was suspended in a solution of sodium bicarbonate (5 g) in water (100 ml) and the mixture was heated under reflux for 18 hours. The solution was cooled, filtered and acidified. The off white solid which separated out was collected by filtration and recrystallised from benzene to afford cis-3, cis-6-di(4-methoxyphenyl)cyclohex-4-ene-cis-1, cis-2-dicarboxylic acid anhydride.
acid (122) (4·7 g, 89%), m.p. 204 - 205°C (Found: C, 69·0; H, 6·0. C_{22}H_{22}O_6 requires C, 69·1; H, 5·8%); τ (CDCl₃) 1·00 (s, 2 x OH, exchangeable with deuterium oxide), 2·73, 3·26 (q, J = 9 Hz, 2 x Ph), 3·70 (s, 4-H, 5-H), 5·95 to 6·25 (m, 3-H, 6-H), 6·28 (s, 2 x OMe) and 6·50 to 6·70 (m, 1-H, 2-H); ν max (KBr) 3650 to 2200, 1740, 1610, 1510, 1240, 1175, 1020 and 815 cm⁻¹.

Atypical reduction of cis-3,cis-6-di(4-methoxyphenyl)cyclohex-4-ene-1,2-dicarboxylic acid (122)

The diacid (122) (1·93 g) was dissolved in aqueous sodium hydroxide solution (920 mg in 10 ml). Bis-hydroxylammonium sulphate (0·82 g) was added to the solution followed by hydroxylamine-O-sulphonic acid (1·24 g), which dissolved with the evolution of nitrogen. A further portion of sodium hydroxide (300 mg) was added to maintain a clear solution. The solution was stirred at room temperature for 16 hours. Acidification yielded complete recovery of starting material (122).

Catalytic hydrogenation of cis-3,cis-6-di(4-methoxyphenyl)cyclohex-4-ene-1,2-dicarboxylic acid (122) with 10% palladium on charcoal in ethanol

The diacid (122) (5 g) was dissolved in ethanol (100 ml) and 10% palladium on charcoal (250 mg) was added. The material was hydrogenated at ambient temperature and
atmospheric pressure for 6 hours. The catalyst was removed by filtration and the solvent was evaporated.

Recrystallisation of the product from methanol yielded pure cis-3,cis-6-di(4-methoxyphenyl)cyclohexane-cis-1,cis-2-dicarboxylic acid (123) (4.95 g, 96%), m.p. 226°C

(Found: C, 68.9; H, 6.3. C_{22}H_{24}O_{6} requires C, 68.7; H, 6.3%); \nu[(CD_3)_2SO] 2.2 to 3.6 (b, 2 x OH, exchangeable with deuterium oxide), 2.65 to 3.21 (q; J = 9Hz, 2 x Ph), 6.24 (s, 2 x OMe), 6.45 to 6.66 (m, 1-H, 2-H, 3-H, 6-H), 6.90 to 7.40 (m, 4-H, 5-H) and 7.70 to 8.20 (m, 4-H, 5-H);

\nu_{\text{max}} (KBr) 3640 to 2250, 1715, 1612, 1513, 1245, 1180, 1035 and 1020 cm\(^{-1}\).

Methylation of cis-3,cis-6-di(4-methoxyphenyl)cyclohexane-cis-1,cis-2-dicarboxylic acid (123)

The diacid (123) (100 mg) was dissolved in methanol / ether (10 ml of 1 : 1) and an ethereal solution of diazomethane (excess) was then added to the cooled solution with stirring. The solution was stirred for a further period of 30 minutes, when the solvent and excess diazomethane were removed by evaporation. The product was dissolved in ether (10 ml), washed with aqueous sodium bicarbonate (2 x 5 ml) and water (2 x 5 ml). The ethereal solution was dried and the solvent evaporated to yield dimethyl-cis-3,cis-6-di(4-methoxyphenyl)cyclohexane-cis-1, cis-2-dicarboxylate (125) which was recrystallised from
benzene (98 mg, 92%), m.p. 127 - 128°C (Found: C, 69.9; H, 7.0. \( \text{C}_{24}\text{H}_{28}\text{O}_6 \) requires C, 69.9; H, 6.8%); \( \tau \) (CDCl\(_3\)) 2.73, 3.19 (q, \( J = 9\) Hz, 2 x Ph), 6.22 (s, 2 x -OMe), 6.64 (s, 2 x CO\(_2\)Me), 6.5 to 6.8 (m, 1-H, 2-H, 3-H, 6-H), 7.15 to 7.50 (m, 4-H, 5-H), 7.80 to 8.20 (m, 4-H, 5-H);
\( \nu_{\text{max}} \) (KBr) 2950, 2838, 1738, 1610, 1512, 1242, 1208, 1180, 1027 and 810 cm\(^{-1}\).

Demethylation of cis-3,cis-6-di(4-methoxyphenyl)cyclohexane-
cis-1,cis-2-dicarboxylic acid (123)

The method described for the demethylation of 1,3-bis(4-methoxyphenyl)propane (74), using potassium hydroxide / diethylene glycol as demethylating agent, was used. The washing with aqueous sodium bicarbonate was omitted from the work up procedure. The crude product was recrystallised from ethylacetate / petrol to yield pure cis-3,cis-6-di(4-hydroxyphenyl)cyclohexane-cis-1,
trans-2-dicarboxylic acid (124) (2.24 g, 60%), m.p. 236 - 237°C; (Found: C, 69.2; H, 5.8. \( \text{C}_{22}\text{H}_{22}\text{O}_6 \) requires C, 69.1; H, 5.8%); \( \tau \) (CD\(_3\))\(_2\)CO 0.5 to 1.6 (b.s., 4 x OH); 2.73, 3.24 (q, \( J = 9\) Hz, 1 x Ph), 2.94, 3.28 (q, \( J = 9\) Hz, 1 x Ph), 6.22 to 6.44 (m, 1 proton), 6.62 to 6.85 (m, 3-CH, 6-CH), 7.15 to 7.55 (m, 1 proton), 7.75 to 8.50 (m, 4-CH\(_2\), 5-CH\(_2\) ); \( \nu_{\text{max}} \) (KBr) 3700 to 2300, 1725, 1612, 1595, 1513, 1220 and 830 cm\(^{-1}\).
Methylation of \(\text{cis-3, cis-6-di(4-hydroxyphenyl)cyclohexane-cis-1, trans-2-dicarboxylic acid (124)}\)

The dimethyl ether was prepared by the method of Gillis\(^{120}\). The dimethyl ether dimethyl ester was then prepared as described for the preparation of dimethyl cis-3, cis-6-di(4-methoxyphenyl)cyclohexane-cis-1, cis-2-dicarboxylate (125). Recrystallisation of the crude product from ethanol yielded pure dimethyl cis-3, cis-6-di(4'-methoxyphenyl)cyclohexane-cis-1, trans-2-dicarboxylate (126) (97 mg, 84%), m.p. 140 - 141°C; (Found: C, 70.2; H, 7.0. \(\text{C}_{24}\text{H}_{28}\text{O}_{6}\) requires C, 69.9; H, 6.8%); \(\nu\) (CDCl\(_3\)) 2.76, 3.18 (q, \(J = 9\text{Hz}\), 1 x Ph), 2.92, 3.20 (q, \(J = 9\text{Hz}\), 1 x Ph), 6.23 (s, 2 x OMe), 6.18 to 6.40 (m, 1 proton), 6.48 to 6.98 (m, 3-CH, 6-CH), 6.54 (s, 1 x -C'0-OMe), 6.64 (s, 1 x -C'0-OMe), 7.05 to 7.46 (m, 1 proton), and 7.76 to 8.44 (m, 4-CH\(_2\), 5-CH\(_2\)). \(\nu\)\(_\text{max}\) (KBr) 2940, 2925, 2830, 1725, 1606, 1508, 1240, 1170, 1022 and 820 cm\(^{-1}\).

Oxidation of \(\text{cis-3, cis-6-di(4-hydroxyphenyl)cyclohexane-cis-1, trans-2-dicarboxylic acid (124)}\)

The oxidation was carried out using the method used for the oxidation of the tetra-t-butyl phenol (87); the only difference being that the solution was neutralised after the oxidation so as to be able to extract the product into the organic phase. Neutralisation resulted in a polymeric product at the solvent interface.
Reduction of cis-3,cis-6-di(4'-methoxyphenyl)cyclohexane-
cis-,cis-2-dicarboxylic acid (123) to the diol (127)

All apparatus was dried in an oven and cooled under dry nitrogen.

The diacid (123) (2 g) was dissolved in dry tetrahydrofuran (100 ml) and the solution was cooled to 0°C under a stream of dry nitrogen. A one molar solution of diborane in tetrahydrofuran (12 ml) was added slowly to the cold solution. A clear solution was obtained. The reaction was allowed to warm to ambient temperature and stirred for 14 hours. A mixture of water and tetrahydrofuran (200 ml) of (1:1) was added slowly to destroy the excess diborane and the clear solution was saturated with potassium carbonate. The two layers were separated and the aqueous layer extracted with ethyl acetate (2 x 50 ml). The ethyl acetate extracts were combined with the tetrahydrofuran layer. The combined organic phases were dried and evaporated to yield a white crystalline product, which was recrystallised from methanol to yield pure cis-1,cis-2-bis(hydroxymethyl) -
cis-3,cis-6-di(4'-methoxyphenyl)cyclohexane (127) (1.72 g, 93%), m.p. 146 - 147°C. (Found: C, 74.0; H, 7.8. C_{22}H_{28}O_{4} requires: C, 74.1; H, 7.9%); δ (CDCl_{3}) 2.71, 3.13 (q, J = 9 Hz, 2 x Ph), 6.19 (s, 2 x OMe), 6.25 to 6.60 (m, 2 x -CH_{2}-O), 6.70 to 7.0 (m, 3-H, 6-H), 7.4 to 8.2 (m, 1-CH, 2-CH, 4-CH_{2}, 5-CH_{2}) and 8.10 (s, 2 x OH, exchangeable with deuterium oxide); ν_{max} (KBr) 3600 to 3150, 2940, 2875, 2840, 1610, 1510, 1250, 1180, 1033 and
Demethylation of \(\text{cis-1, cis-2-bis(hydroxymethyl)-cis-3, cis-6-di(4-methoxyphenyl)cyclohexane (127)}\)

The method described for the demethylation of 1,3-bis(4-methoxyphenyl)propane (74), using potassium hydroxide / digol as demethylating agent, was used.

Pure \(\text{cis-1, cis-2-bis(hydroxymethyl)-cis-3, cis-6-di(4-hydroxyphenyl)cyclohexane (128)}\) was obtained by recrystallisation from ethyl acetate (630 mg, 67%), m.p. 248 - 249°C (Found: C, 73.4; H, 7.6. \(\text{C}_{20}\text{H}_{24}\text{O}_{4}\) requires C, 73.1; H, 7.4); \(\text{T} \left(\text{CD}_{3}\right)\text{SO} \) 0.89 (b.s. 2 x OH, exchangeable with deuterium oxide), 2.83, 3.34 (q, \(J = 9\)Hz, 2 x Ph), 6.00 to 6.25 (m, 2 x OH, exchangeable with deuterium oxide), 6.30 to 7.16 (m, 2 x \(-\text{CH}_2\text{-O}, 3\text{-CH}, 6\text{-CH}\) and 7.55 to 8.38 (m, 1-CH, 2-CH, 4-CH\(_2\), 5-CH\(_2\) ); \(\nu_{\text{max}}\) (KBr) 3650 to 3000, 2940, 1615, 1600, 1515, 1455, 1245, 1180, 1038, 1020, 837 and 830 cm\(^{-1}\).

Acetylation of \(\text{cis-1, cis-2-bis(hydroxymethyl)-cis-3, cis-6-di(4-hydroxyphenyl)cyclohexane (128)}\)

The diphenol dialcohol (50 mg) was acetylated using the method of Kirby and Tiwari\(^\text{119}\). Recrystallisation from benzene yielded \(\text{cis-1, cis-2-bis(acetoxyethyl)-cis-3, cis-6-di(4-acetoxyphenyl)cyclohexane (129)}\) (71 mg, 94%), m.p. 175 - 176°C. (Found: C, 67.9; H, 6.6. \(\text{C}_{28}\text{H}_{32}\text{O}_{8}\) requires 145
C, 67.7; H, 6.5%; \( \tau \) (CDCl₃) 2.68, 2.93 (q, \( J = 9Hz \), 2 x Ph), 5.86 to 6.08 (m, 2 x -CH₂-O), 6.47 to 6.95 (m, 3-CH, 6-CH), 7.23 to 8.10 (m, 1-CH, 2-CH, 4-CH₂, 5-CH₂), 7.73 (s, 2 x OAc) and 8.18 (s, 2 x OAc); \( \nu_{\text{max}} \) (KBr) 1757, 1740, 160, 1510, 1370, 1260, 1040 and 918 cm⁻¹.

Preparation of 4-benzyloxybenzaldehyde (135)

4-Hydroxybenzaldehyde (137) (12.2 g, 0.1 mol) benzyl chloride (13.9 g, 0.11 mol) and anhydrous potassium carbonate (13.8 g) were heated in acetone under reflux for 12 hours. The solution was filtered and the acetone removed by evaporation to yield the crude product (135), which was recrystallised from aqueous ethanol (14.9 g, 70%), m.p. 71°C (lit. 126 72°C); \( \tau \) (CDCl₃) 0.12 (s, CHO), 2.18, 2.95 (q, \( J = 9Hz \), O-Ph-CHO), 2.60 (s, Ph-CH₂) and 4.85 (s, Ph-CH₂); \( \nu_{\text{max}} \) (KBr) 2830, 2740, 1690, 1602, 1575, 1510, 1260, 1155, 1020, 832 and 734 cm⁻¹.

Preparation of \( \beta \)-benzyltyramine (136)

\( \beta \)-Benzyltyramine (136) (1.75 g, 35%) was prepared from 4-benzyloxybenzaldehyde (135) (5 g) \textit{via} the 4-benzyloxy-w-nitrostyrene (138) using the method of Bruce⁵¹⁴, m.p. 206 - 208°C (lit.¹¹³ 202 - 204°C); mixed m.p. with an authentic sample showed no depression.
Condensation of Q-benzyltyramine (136) and 4-benzzyloxybenzaldehyde (135) and reduction of the product imine

The aldehyde (135) (1.06 g, 5 mmol) was dissolved in dry methanol (20 ml) and a solution of the amine (136) (1.13 g, 5 mmol) in dry methanol (5 ml) was added. The solution was stirred for 3 hours, until no carbonyl absorption was detectable by I.R. spectroscopy. The mixture was then cooled to 0°C and excess sodium borohydride was added slowly. On completion of the addition the reaction was allowed to warm to room temperature and was stirred for 12 hours. Excess methanol was then removed in vacuo and water (50 ml) was added, followed by dilute hydrochloric acid to destroy the excess sodium borohydride. The pH was adjusted to between 7 and 8 and the solution was extracted with ether (3 x 25 ml). The combined ether extracts were washed with water, dried and acidified by dropwise addition of ethanolic hydrochloric acid. The amine (140), isolated as the hydrochloride, was filtered off and recrystallised from ethanol (1.5 g, 72%), m.p. 262 - 263°C (Found: C, 75.7; H, 6.7; N, 3.5; Cl, 8.0. C29H30ClNO2 requires C, 75.7; H, 7.0; N, 3.0; Cl, 7.7%); \[\text{\text{\textsuperscript{1}H NMR}}\] 2.40 to 3.16 (m, 2 x Ph-CH\(_2\)), 2.63 (s, 2 x Ph-CH\(_2\)), 4.83 (s, Ph-CH\(_2\)), 4.88 (s, Ph-CH\(_2\)), 5.92 (b.s., Ph-CH\(_2\)-N) and 7.00 (b.s., Ph-CH\(_2\)-CH\(_2\)-N); \(\nu\text{ max (KBr)}\) 2930, 2770, 1612, 1583, 1513, 1445, 830, 814, 740, 730 and 695 cm\(^{-1}\).
Debenzylation of N-(4-benzyloxyphenethyl)-4-benzyloxybenzylamine (140)

The amine hydrochloride (140) (600 mg) was suspended in methanol (25 ml) and 10% palladium on charcoal (60 mg) was added followed by concentrated hydrochloric acid (0.1 ml). The material was hydrogenolysed at ambient temperature and atmospheric pressure. Uptake of hydrogen was complete in 12 hours. The product remained in solution and the catalyst was removed by filtration. The methanol was evaporated and the N-(4-hydroxyphenethyl)-4-hydroxybenzylamine hydrochloride (133, R = H) was washed with water and recrystallised from aqueous ethanol (260 mg, 71%), m.p. 232 - 233°C (lit. 234°C); δ \left[\text{CD}_3\right]_2\text{SO} 0.03 to 1.18 (b.s., 2 x OH, -NH\text{H}^+\text{3}, exchangeable with deuterium oxide), 2.78, 3.28 (q, J = 9Hz, Ph), 3.10, 3.38 (q, J = 9Hz, Ph), 6.05 (s, Ph-CH\text{2}-N), 7.66 (s, Ph-CH\text{2}-CH\text{2}-N); υ_{\text{max}} (KBr) 3445, 3180, 2960, 2800, 1612, 1598, 1515, 1232, 830 and 875 cm\text{⁻¹}.

Preparation of tyramine (141)\text{I14}

Tyrosine (5 g) in diphenylamine (50 g) was heated at 280°C to 50°C under a nitrogen atmosphere. The reaction mixture was dark in colour and the tyrosine was in suspension. After about 20 minutes a pale yellow clear solution was obtained. The solution was heated for a further 10 minutes, then allowed to cool to approximately 90°C and
poured into 60°-80° petrol (600 ml) with rapid stirring. Stirring was continued for 20 minutes and the solid material was removed by filtration, ground up and resuspended in stirred 60°-80° petrol (4.00 ml) for a further 20 minutes. The solid was recovered by filtration, dried and dissolved in hot ethanol and filtered while hot, to remove any unreacted tyrosine. The tyramine (141) was recrystallised from a mixture of ethanol and ether (2.9 g, 76%), m.p. 161 - 163°C (lit. 165°C); $\gamma\left[(CD_{3})_{2}SO\right] 2.98, 3.30 (q, J = 9Hz, Ph), 6.08 (b.s., OH, NH$_2$) and 7.06 to 7.76 (m, 2 x CH$_2$); $\nu_{\text{max}}$ (KBr) 3345, 3290, 2930, 2850, 1610, 1595, 1512, 1465, 1265, 832 and 822 cm$^{-1}$.

Preparation of N-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; R = H) from tyramine (141) and 4-hydroxybenzaldehyde (137)

The method described for the preparation of N-(4-benzyloxyphenethyl)-4-benzyloxybenzylamine (140) was used. The amine hydrochloride was recrystallised from aqueous ethanol (1.16 g, 66%), m.p. 233 - 235°C (lit. 234°C). This product was spectroscopically identical to the material prepared by debenzylation of N-(4-benzyloxyphenethyl)-4-benzyloxybenzylamine (140).

N-Acetylation of N-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; R = H)

The amine hydrochloride (133; R = H) (5 g) was dissolved
in acetic anhydride (60 ml) and pyridine (96 ml). The solution was stirred, under nitrogen, for 14 hours at room temperature. The solution was adjusted to pH ~ 4 and extracted with chloroform (3 x 100 ml). The combined chloroform extracts were washed with dilute hydrochloric acid (3 x 50 ml) and water (3 x 50 ml), dried and evaporated. The resultant oil was dissolved in 50% aqueous ethanol (50 ml) and potassium hydroxide pellets (1·3 g) were added. The solution was stirred for 24 hours at room temperature under an atmosphere of nitrogen. The excess ethanol was removed in vacuo and water (50 ml) was added to the remaining solution. The aqueous solution was washed with chloroform (2 x 25 ml) and acidified to yield a brown oil, which, on the addition of benzene, separated out at the interface. The oil and benzene were separated from the water layer and the benzene was removed in vacuo. Ethanol (3 x 50 ml) was added to the oil and removed in vacuo in order to dry the oil, which was then dissolved in ethanol and filtered to remove inorganic impurities. Evaporation of the ethanol yielded N-acetyl-N-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; R = Ac) as an oil which solidified on trituration with chloroform (3·6 g, 62%), m.p. 162°C (from methanol) (Found: C, 71·3; H, 6·8; N, 4·8. \( \text{C}_{17}\text{H}_{19}\text{NO}_3 \) requires C, 71·6; H, 6·7; N, 4·9%); \( [\text{CD}_3]_2\text{SO} \) 0·72 to 1·11 (m, 2 x OH, exchangeable with deuterium oxide), 3·05 to 3·66 (m, 2 x Ph), 5·73 (b.s., Ph-CH\(_2\)-N), 6·56 to 6·86 (m, CH\(_2\)-CH\(_2\)-).
N), 7.20 to 7.65 (m, Ph-CH₂-CH₂), 8.01 (s, COCH₃) and 8.13 (s, COCH₃); \( \nu_{\text{max}} \) (KBr) 3600 to 2400, 1610, 1590, 1505, 1440, 1220, 830 and 820 cm⁻¹.

Oxidation of N-acetyl-N-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; R = Ac)

The diphenol (133; R = Ac) (500 mg) was dissolved in water (200 ml) containing potassium hydroxide (500 mg) and the solution was added, over a period of 1 hour, under an atmosphere of nitrogen, to a vigorously stirred mixture of water (100 ml) containing potassium ferricyanide (5 g) and methylene chloride (400 ml). Stirring was continued for a further 30 minutes after the completion of the addition. The emulsion obtained was broken by filtration through a celite filter bed. The two layers were separated and the organic layer washed with water (100 ml). The methylene chloride solution was dried and evaporated to leave an oil. Chromatography over grade III acidic alumina yielded an oil which solidified on trituration with petrol/chloroform. White crystals of N-acetyl-14-azadispiro(5,0,5,4,) hexadeca-1,4,8,11-tetraene-3,10-dione (143) were obtained on recrystallisation from ethyl acetate / petrol (348 mg, 70%), m.p. decomp. on heating above 90°C.

(Found: C, 72.3; H, 6.6; N, 4.7. \( \text{C}_{17}\text{H}_{17}\text{NO}_3 \) requires C, 72.1; H, 6.1; N, 4.9%); \( \tau \) (CDCl₃) 2.80 to 3.34 (m, 1-CH, 5-CH, 8-CH, 12-CH), 3.34 to 3.86 (m, 2-CH, 4-CH, 9-CH, 11-CH), 6.16 (s, 13-CH₂), 6.32 (s, 13-CH₂), 5.80 to 6.10 (m, 15-CH₂), 7.78 (s, N-COCH₃), 7.93 (s, N-COCH₃) and 7.60 to 8.18
Deuteriation of \( \text{L-hydroxybenzaldehyde (137) at the 3 and 5 positions} \)

\( \text{L-Hydroxybenzaldehyde (137) (5 g) was suspended in 4N-DCl (prepared by dissolving thionyl chloride in deuterium oxide). The solid dissolved on warming and the solution was heated under reflux for 16 hours, then basified and filtered to remove the base insoluble material. The basic solution was washed with chloroform (2 x 25 ml), acidified and extracted with chloroform. The organic layer was dried and the solvent evaporated to leave the deuteriated product (145) (2.4 g, 48%), n.m.r. spectroscopy showed that approximately 70% of the 3 and 5 protons had been exchanged by deuterium. The procedure was repeated on the partially deuteriated material. N.m.r. and mass spectrometry showed that over 95% of protons at the 3 and 5 positions had been exchanged by deuterium; } \tau \text{ [(CD)\textsubscript{2}CO]} - 1.1 (s, CH\textsubscript{3}), -0.5 (b.s., OH, exchangeable with deuterium oxide), 2.83 (s, 2-CH, 6-CH).

Deuteriation of \( \text{tyramine (141) at the 3 and 5 positions} \)

\( \text{Tyramine (141) (5 g) was dissolved in 4N-DCl (20 ml) and heated under reflux for 16 hours. The pH was adjusted to between 8 and 9 and the solution evaporated to dryness.} \)
The solid product was extracted with ethanol to separate the tyramine from the inorganic materials. Evaporation of the ethanol produced tyramine hydrochloride. This was dissolved in water, the pH of the solution was adjusted to between 8 and 9 and the solution again evaporated to dryness. The resultant solid was extracted with ethanol and evaporation of the ethanol gave the free amine (146) which was recrystallised from ethanol (4.6 g, 92%), m.p. 160 - 162°C (lit. 128 165°C). N.m.r. and mass spectrometry showed that greater than 95% exchange of hydrogen by deuterium in the 3 and 5 positions had occurred; \[ \gamma \left[ \left( CD_2 \right)_2 SO \right] \]
3.03 (s, 2-CH, 6-CH), 6.28 (b.s., OH), 7.16 (b.s., Ph-CH$_2$-CH$_2$-N).

Preparation of DL-(2, 3, 5, 6, $\alpha^2$H$_5$) tyrosine

Tyrosine was suspended in 10N DCl (prepared by dissolving thionyl chloride in deuterium oxide) and the suspension was heated under an atmosphere of nitrogen in a sealed tube at 175°C for 72 hours. (It was essential to maintain this temperature because temperatures greater than 180°C yielded a charred product and temperatures lower than 170°C did not yield the required deuteriated product.) The reaction was poured into water and the pH was carefully adjusted to 6 with dilute sodium hydroxide. Tyrosine crystallised out when the solution was cooled. N.m.r. spectrometry showed the $\alpha$, 2, 3, 5 and 6 protons to be completely exchanged.
Preparation of N-acetyl-N-(4-hydroxyphenethyl)-3,5-dideuterio-4-hydroxybenzylamine

The preparation was carried out using 3,5-dideuteriobenzaldehyde (145) and tyramine (141) following the method described earlier for the protiated compounds. Overall yield 39%, m.p. 160°C; T [(CD$_3$)$_2$SO] 0.4 to 1.1 (b.s., 2 x OH), 2.80 to 3.18 (m, 2-CH, 6-CH, 2-CH, 6-CH), 3.34 (d, J = 8Hz, 3-CH, 5-CH), 3.35 (q., J = 8Hz, 3-CH, 5-CH), 5.61 (s, Ph-CH$_2$-N), 5.67 (s, Ph-CH$_2$-N), 6.56 to 6.86 (m, N-CH$_2$-CH$_2$), 7.20 to 7.60 (m, CH$_2$-CH$_2$-Ph), 7.96 (s, COCH$_3$), 8.10 (s, COCH$_3$).

Oxidation of N-acetyl-N-(4-hydroxyphenethyl)-3,5-dideuterio-4-hydroxybenzylamine

The oxidation was carried out as for the protiated diphenol (133; R = Ac) to yield the dienone (143a): T (CDCl$_3$) 2.86, 3.63 (q, J = 10Hz, 1-CH, 2-CH, 4-CH, 5-CH), 2.97 (s, 8-CH, 12-CH), 3.06 (s, 8-CH, 12-CH), 6.14 (s, 13-CH$_2$), 6.30 (s, 13-CH$_2$), 5.80 to 6.50 (m, 15-CH$_2$), 7.71 (s, N-COCH$_3$), 7.88 (s, N-COCH$_3$) and 7.60 to 8.18 (m, 16-CH$_2$).

Preparation of N-acetyl-N-(3,5-dideuterio-4-hydroxyphenethyl)-4-hydroxybenzylamine

The preparation was carried out using 3,5-dideuterietylamine (146) and 4-hydroxybenzaldehyde (137) following the procedure described earlier for the protiated compounds,
with an overall yield of 42%, m.p. 161°C; $\gamma [(\text{CD}_3)_2\text{SO}]$

0.8 to 2.1 (b.s., 2 x OH), 2.80 to 3.18 (m, 2-CH, 6-CH, 2-CH, 6-CH), 3.18 to 3.60 (m, 3-CH, 5-CH), 5.62 (s, Ph-CH$_2$N), 5.67 (s, Ph-CH$_2$N), 6.56 to 6.86 (m, N-CH$_2$-CH), 7.20 to 7.60 (m, CH$_2$-CH$_2$-Ph), 7.96 (s, COCH$_3$) and 8.10 (s, COCH$_3$).

Oxidation of N-acetyl-N-(3,5-dideuterio-4-hydroxyphenethyl)-4-hydroxybenzylamine

The oxidation was carried out as for the protiated diphenol (133; R = Ac) to yield the dienone (143b): $\gamma (\text{CDCl}_3)$ 2.86 (s, 1-CH, 5-CH), 2.97, 3.53 (q, $J = 10$Hz, 8-CH, 9-CH, 11-CH, 12-CH), 3.06, 3.55 (q, $J = 10$Hz, 8-CH, 9-CH, 11-CH, 12-CH), 6.14 (s, 13-CH$_2$), 6.30 (s, 13-CH$_2$), 5.80 to 6.50 (m, 15-CH$_2$), 7.71 (s, N-COCH$_3$), 7.88 (s, N-COCH$_3$) and 7.60 to 8.18 (m, 16-CH$_2$).

Preparation of N-acetyl-N-2-(2,6-dideuterio-4-hydroxyphenyl)-1-deuterioethyl-4-hydroxybenzylamine

$\alpha,2,3,5,6$-Pentadeuteriotyrosine was decarboxylated as described earlier for the preparation of protiated tyramine (141). This yielded a product with deuterium in the 2,6 and $\alpha$ positions of tyramine (144). This was then condensed with 4-hydroxybenzaldehyde (137) and acetylated as described earlier, with an overall yield of 45%, m.p. 162°C; $\gamma [(\text{CD}_3)_2\text{SO}]$ 0.5 to 0.9 (m, 2 x OH), 2.96
(d, J = 8 Hz, 2-CH, 6-CH), 3.00 (d, J = 8 Hz, 2-CH, 6-CH),
3.14 to 3.40 (m, 3-CH, 5-CH, 3-CH, 5-CH), 5.62 (s, Ph-CH$_2$ -N),
5.67 (s, Ph-CH$_2$ -N), 6.58 to 6.80 (m, N-CH$_2$-CH$_2$), 7.20 to
7.55 (m, CHD-CH$_2$-Ph), 7.96 (s, COCH$_3$) and 8.10 (s, COCH$_3$).

Oxidation of N-acetyl-N-2-(2,6-dideuterio-4-hydroxyphenyl)-
1-deuterioethyl-4-hydroxybenzylamine

The oxidation was carried out as for the protiated
diphenol (133; R = Ac) to yield the dienone (143c):

(133c; R = Ac)

N-Trifluoroacetylation of N-(4-hydroxyphenethyl)-4-
hydroxybenzylamine

The amine hydrochloride (133; R = H) (1 g) was dissolved
in pyridine (2.5 ml) and trifluoroacetic anhydride (10 ml)
was added slowly, with cooling. The solution was stirred
for 30 minutes and then poured onto a mixture of
chloroform and ice. The chloroform layer was washed
with 0.1 N hydrochloric acid (3 x 10 ml) followed by
water (3 x 10 ml), dried and evaporated to yield a brown
oil which crystallised from benzene. The N-trifluoroacetylated
N-(4-hydroxyphenethyl)-4-hydroxybenzylamine (133; R = CF$_3$CO)

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was recrystallised from benzene (930 mg, 67%), m.p. 147 - 148°C. (Found: C, 60.4; H, 4.8; N, 4.4. \( \mathrm{C}_{17}\mathrm{H}_{16}\mathrm{F}_{3}\mathrm{NO}_{3} \) requires: C, 60.2; N, 4.7; N, 4.1%); \( \mathrm{\tau} \left[\left(\mathrm{CD}_{3}\right)_{2}\mathrm{SO}\right] \) 1.60 (b.s., OH, exchangeable with deuterium oxide), 1.84 (b.s., OH, exchangeable with deuterium oxide), 2.60 to 3.40 (m, 2 x Ph), 5.37 (s, Ph-\( \mathrm{CH}_{2}-\mathrm{N} \)), 5.53 (s, Ph-\( \mathrm{CH}_{2}-\mathrm{N} \)), 6.23 to 6.70 (m, \( \mathrm{N}-\mathrm{CH}_{2}-\mathrm{CH}_{2} \)) and 7.02 to 7.40 (m, \( \mathrm{CH}_{2}-\mathrm{CH}_{2}-\mathrm{Ph} \)); \( \nu_{\text{max}} \) (KBr) 3350, 3230, 1662, 1612, 1596, 1515, 1235, 1212, 1195, 1175, 1155 and 835 cm\(^{-1}\).

Oxidation of \( \mathrm{N}-\text{trifluoroacetyl-}N-(4\text{-hydroxyphenethyl})-4\text{-hydroxybenzylamine} \) (133; \( \mathrm{R} = \mathrm{CF}_{3}\mathrm{CO} \))

The diphenol (133; \( \mathrm{R} = \mathrm{CF}_{3}\mathrm{CO} \)) (100 mg) was dissolved in chloroform (40 ml) and manganese dioxide (300 mg) (prepared by ozonolysis of potassium permanganate by the method of Belew and Tek-Ling\(^{130} \)) was added. The suspension was stirred under nitrogen for 6 hours when the oxidant was removed by filtration and fresh manganese dioxide was added to the solution. This procedure was repeated at regular intervals until no further conversion of diphenol (133; \( \mathrm{R} = \mathrm{CF}_{3}\mathrm{CO} \)) to product could be detected by t.l.c. (approx, 48 hours). The manganese dioxide was removed by filtration and the product dienone was separated from the starting phenol by passage through an acidic grade III alumina column with methylene chloride as eluent. The \( \mathrm{N}-\text{trifluoroacetyl-14-azadispiro(5,0,5,4)hexadiene-1,4,8,11-teraene-3,10-dione} \) (149) produced (11 mg, 11%) could

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not be crystallised; \( \tau (\text{CDCl}_3) 2.98, 3.68 \, (q, J = 10\,\text{Hz}, 
1-\text{CH}, 2-\text{CH}, 4-\text{CH}, 5-\text{CH}), 2.95 \text{ to } 3.30 \, (m, 8-\text{CH}, 12-\text{CH}), 
3.69 \, (d, J = 10\,\text{Hz}, 9-\text{CH}, 11-\text{CH}), 5.8 \text{ to } 6.40 \, (m, 15-\text{CH}_2), 
6.09 \, (s, 13-\text{CH}_2), 6.22 \, (s, 13-\text{CH}_2) \) and 7.86 \text{ to } 8.10 
\, (m, 16-\text{CH}_2); \nu_{\text{max}}(\text{CHCl}_3) 2930, 1695, 1675, 1633, 1615, 
1514, 1168, 1147 \text{ and } 860 \, \text{cm}^{-1}.

Decomposition of the N-acetyldienone (143) in ethanol

The dienone (143) (240 mg) was dissolved in ethanol 
(500 ml), under nitrogen, and heated under reflux for 
5 days. Evaporation of the ethanol yielded the benzyllic 
ether (148) as a brownish solid which was recrystallised 
from ethanol (140 mg, 51\%), m.p. 246 - 250°C (decomp.), 
M/e 329,1614 \,(m^+, \text{C}_{19}\text{H}_{23}\text{NO}_4 \text{ requires } M, 329,1627); \tau 
\left[\text{(CD}_3\right)_2\text{SO}\right] 0.10 \text{ to } 0.90 \, (b.s., 2 \times \text{OH, exchangeable with} 
deuterium oxide), 2.8 \text{ to } 3.4 \, (m, 2 \times \text{Ph}), 5.40 \text{ to } 5.80 
\, (m, \text{Ph-CH-N}), 6.54 \, (q, J = 7\,\text{Hz}, \text{O-CH}_2\text{-CH}_3), 6.65 \text{ to } 6.95 
\, (m, \text{N-CH}_2\text{-CH}_2), 7.15 \text{ to } 7.6 \, (m, \text{CH}_2\text{-CH}_2\text{-Ph}), 7.90 \, (s, \text{NCOCH}_3), 
8.13 \, (s, \text{NCOCH}_3), 8.90 \, (t, J = 7\,\text{Hz, O-CH}_2\text{-CH}_3); \nu_{\text{max}}(\text{KBr}) 
3650 \text{ to } 3000, 2920, 1710, 1620, 1510, 1430, 1420, 1260 \text{ and} 
815 \, \text{cm}^{-1}.
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