SYNTHESIS OF SOME
BENZOFURANOID COMPOUNDS

by

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The work described in this thesis is my own, except where otherwise stated. It was carried out in the Research School of Chemistry, The Australian National University from 1971 to 1974 during the tenure of a Commonwealth Post-Graduate Scholarship.

Brenn R. Worth.
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B. R. Worth
This thesis is divided into six chapters. Chapter I serves as a brief review of the chemistry of benzofuran molecules in general and introduces the "cyperaquinones" and "scabequinones", novel classes of quinones from species of Cyperaceae. A proposed, general synthetic route to benzofurans, suitable as intermediates in syntheses of natural products, is outlined in Chapter I and its investigation and applications, particularly with regard to an intramolecular, base induced cyclisation reaction, are discussed in Chapter II.

Chapter III describes an unambiguous total synthesis of cyperaquinone (1) and conicaquinone (4) from phloroglucinol. A mass spectrometric technique for the determination of the orientation of the three-ring system is also described.

Chapter IV deals with alternate total syntheses of (1) and (4), together with that of demethylcyperaquinone (5). A possible route to dihydrocyperaquinone (2) and tetrahydrocyperaquinones (6) and (7) is also given.

A total synthesis of (±) scabequinone (15) is dealt with in Chapter V while the last chapter outlines an approach to the total synthesis of pterocarpanoid compounds.

A portion of the work described in this thesis has been published:


Reprints of these articles are included at the end of the text.
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CHAPTER I

INTRODUCTION

[Chemical structures]
Since 1967 Wells and co-workers have carried out an extensive phytochemical survey covering over 100 species from 29 genera of the family Cyperaceae found in northern Queensland. A new class of naturally occurring quinones, the "cyperquinones", was obtained along with other pigments from the roots and rhizomes of these plants.

Of the seven major quinones (1)-(7) found (Fig. 1) cyperquinone (1), the parent of the series, was by far the most widespread. Its structure, and those of the related quinones was established by spectroscopic methods. The 2,6-oxygenation pattern was favoured over the corresponding 2,5-pattern, as in (8) chiefly on biogenetic grounds.

These quinones were the first examples containing the benzo[1,2-b; 5, 4-b']difuran ring system (9) in natural products.

Dimeric derivatives (10)-(14) of these quinones, the "dicyperquinones A-E" (Fig. 2), were isolated from the roots of Cyperus conicus, while C. scaber yielded two 6,7-dihydro-5H-furo[3,2-g]benzopyran-4, 9-quinones, scabequinone (15) and dihydroscabequinone (16).
FIG. 1

1 cyperaquinone

2 dihydrocyperaquinone

3 hydroxycyperaquinone

4 conicaquinone

5 demethylcyperaquinone

6 tetrahydrocyperaquinone A

7 tetrahydrocyperaquinone B
FIG. 2

A 10

B 11

C 12 R = R' = CH₃
D 13 R = CH₃, R' = CH₂OH
E 14 R = R' = CH₂OH
The proposed biogenetic origin of the "cyperaquinones" and "scabequinones" is shown in Figs. 3 and 4. The precursor (17) is presumably derived by cyclisation of a polyketide chain and attachment of an isoprene unit. Addition of C_1 as a methoxyl function would then give rise to preremirol (18). The related, co-occurring natural products remirol (19) and isoevodionol (20) are then presumed to be formed by cyclisation and dehydrogenation. Further hydroxylation, cyclisation and oxidation of (19) would then lead to dihydrocyperaquinone (2) where the one-carbon unit introduced forms the α-carbon of the β-methylbenzofuran ring system. The other members of the "cyperaquinone series" could then arise by a series of enzymatic dehydrogenation, hydrogenation, oxidation and decarboxylation processes.

The route proposed for the biosynthesis of the "scabequinones" (Fig. 4) involving the addition of two externally derived C_1 units followed by hydroxylation to (21) is supported by the co-occurrence of scabediol (22) with the quinones (15) and (16) in C. scaber. The existence of the proposed progenitor (21) earns credence from the occurrence in C. brevibracteatus of breviquinone (23) and hydroxybreviquinone (24). The biogenetic introduction of a methylene function, as opposed to a methyl group, as a C_1 unit is unusual. A similar situation arises in the reported biosynthetic pathway to the rotenoid amphorigenin (25) from the isoflavone (26).
FIG. 4

An alternative and perhaps more direct method of introduction of the C1 unit would be a somocysteine reaction of a biologically activated thiol group as shown in Fig. 3.

The structures proposed to be the best methods to confirm the structures proposed to support the proposed biosynthetic pathways.

The chemistry of these molecules has been the subject of several reviews and new compounds of these classes have been shown to possess various forms of biological activity.
An alternative and perhaps more likely method of introduction of the C\textsubscript{1} unit would be a concerted insertion of a biologically activated methylene function as shown in Fig. 5.

Rickards\textsuperscript{12} has shown that dihydrocyperaquinone, scabequinone and scabediol all inhibit growth of the fungus \textit{Phytophthora cinnamomi}. Dihydrocyperaquinone possesses rotenoid-like activity as well as acting as a powerful fish toxin but is not a human toxin.\textsuperscript{5}

Unambiguous total synthesis of these molecules was considered to be the best method to confirm the structures proposed and to support the proposed biosynthetic pathways.

A variety of preparative methods for benzofurans\textsuperscript{13-15} is available but few are generally applicable when substitution patterns displayed by natural products such as dibenzofurans, rotenoids, furocoumarins, pterocarpans, coumestans and the morphine alkaloids (Fig. 6) are required. The chemistry of these molecules has been the subject of several reviews\textsuperscript{13,15-17} and many compounds of these classes have been shown to possess varying forms of biological activity.
FIG. 5

[Chemical structures and reactions depicted in the image]
FIG. 6

usnic acid

rotenone

psoralene

pterocarpin

coumestrol

morphine

cyperaquinone
Synthetic routes to simple benzofurans have been reviewed and can be grouped into three classes according to ring closure by formation of the 1-2, 2-3 or 3-3a bond.¹⁴

Typical examples of the first type include the spontaneous lactonisation reactions of o-hydroxyphenylacetic acids to yield 2-keto-2,3-dihydrobenzofurans.+  

Elimination of hydrogen halide from o-hydroxy-β-haloethyl (or vinyl) benzenes is a commonly used route to α-substituted dihydrobenzofurans and benzofurans. These and other methods of preparation which involve similar elimination of HX may be summarised as follows:

A typical example is found in Perkin's¹⁸ original synthesis of benzofuran-2-carboxylic acid (27) from coumarin (28).

+ Throughout this thesis nomenclature will be based on the benzofuran moiety¹⁴; benzofuran, dihydrobenzofuran, benzofuran-2-carboxylic acid and 3-keto-2, 3-dihydrobenzofuran replacing the older names coumarone, coumaran, coumarilic acid and coumaran-3-one, respectively.
Readily available \( \alpha \)-allyl phenols are also useful starting materials for the synthesis of \( \alpha \)-substituted benzofurans. Acid catalysed cyclisation of these compounds yields dihydrobenzofurans but here substitution at the \( \beta \) or \( \gamma \) position of the side chain may give rise to mixtures of dihydrobenzofurans and chromans.

The \( \alpha \)-allyl phenols are normally formed via Claisen rearrangement of the corresponding allyl ethers but with compounds substituted in the benzenoid ring, isomeric products may again be formed.

The second class of synthetic routes encompasses ring closures involving formation of the 2-3 bond. Commonly used methods require either an internal mixed Claisen condensation;
or an internal aldol condensation;

Reactions of the third group effect ring closure through 3-3a bond formation and usually employ internal Friedel Crafts type alkylation or cyclodehydration reactions.

Photochemical cyclisations of phenyl allyl ethers are also included in this class.
All of the schemes discussed above involve formation of benzofurans by closure of the heterocyclic ring. Elix and co-workers have utilised an approach based on elaboration of the benzenoid ring \textsuperscript{19}. Diels Alder addition of selected dienophiles to 2-vinyl furans gave the requisite benzofurans (Fig. 7). However, the two diene systems available for reaction led to mixtures of products. The method does provide a route to benzofurans substituted only in the benzenoid ring. Through an extension of this method they were able to prepare polyfunctionalised dibenzofurans using Diels Alder addition to 2-vinylbenzofuran derivatives.\textsuperscript{20-27}

The method did have limitations; yields were sometimes low and mixtures of products were often obtained. It is noteworthy that use of 2-(S-methoxyvinyl) benzofurans yielded dibenzofurans with a 3-oxygen substituent; a feature of all known naturally occurring dibenzofurans.\textsuperscript{28}

Furocoumarins\textsuperscript{13,16,29} are a common source of the benzofuran moiety. Direct synthesis of the linear system as found in psoralene (29) is difficult since 6-hydroxybenzofurans (30) are most readily substituted at the 2-position and umbelliferones (31) at C\textsubscript{8}. 

\[
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\end{align*}
\]
FIG. 7

Condensation of derivatives of 781 with cyclic enones also give rise to the corresponding furanocarbons. These are converted to benzo[b]furanones, and ultimately to a benzofuranone nucleoside, by known methods involving, alternatively, methylation with methyl halides. 29-32 has resulted in improved methods for the synthesis of psoralene and its derivatives.

Approaches to the anti-fungal agent, the phorone, 47 have been confined to partial synthesises from either the corresponding furanone or psoralene compounds.

Kohler and Treadwell 114 in 1960 reported the first synthesis of the phorone ring system (73) and the diazenic derivative (74) from the imidazole (71) by reduction and subsequent acid catalyzed
Perkin condensation of the aldehyde (32) with malic acid followed by dehydrogenation has been used to prepare psoralene 13.

Condensation of derivatives of (30) with malic acid may also give rise to the corresponding furocoumarins. These methods, based on building the pyrone ring on to a benzofuran nucleus are generally inefficient due to the harsh conditions required. However, extensive work by several authors 30–33 has resulted in improved methods for the synthesis of psoralene and its derivatives.

Approaches to the anti-fungal agents, the pterocarpans 17, have been confined to partial syntheses from either the corresponding isoflavone or coumestan compounds.

Suginome and Iwadare 34 in 1960 reported the first synthesis of the pterocarpanoid ring system (33) and the conjugated derivative (34) from the isoflavone (35) by reduction and subsequent acid catalysed
cyclisation (Fig. 8).

Fukui and co-workers\textsuperscript{35} utilised a second approach to these compounds. Reduction of the corresponding coumestans (36) with lithium aluminium hydride followed by recyclisation and saturation of the conjugated intermediates gave the required pterocarps (Fig. 9). This method was used to prepare pterocarpin (37), maackiain (38) and 4-methoxypterocarpin (39). The conversion of (36) to (40) has also been accomplished by reduction with diborane.\textsuperscript{36}

Bevan et al.\textsuperscript{37} found that pterocarpin (37), when treated with acid, gave the isoflavene (41). Oxidation of the acetate (42) with osmium tetroxide followed by alkali treatment afforded the 6a-hydroxy-derivative, (±)-pisatin (43). A number of similar partial syntheses of pterocarps have been reported\textsuperscript{15,17,38,39} but the use of naturally occurring precursors obviously limits the applicability of these methods.

All known pterocarps\textsuperscript{17} have oxygen substituents at C\textsubscript{3} and C\textsubscript{9} and a review of the literature shows that many naturally occurring benzofurans incorporate the 6-oxygenated benzofuran unit (44). An ideal synthesis of benzofurans would thus allow the preparation of
FIG. 9

37 $R = \text{OCH}_3$; $R' = \text{H}$; $R''$, $R''' = \text{OCH}_2\text{O}$

38 $R = \text{OH}$; $R' = \text{H}$; $R''$, $R''' = \text{OCH}_2\text{O}$

39 $R = R' = \text{OCH}_3$; $R''$, $R''' = \text{OCH}_2\text{O}$
part skeletons such as (44), appropriately substituted for the elaboration of natural products and, for the purpose of synthesis of the "cyperaquinones" and "scabequinones", would provide access to benzofurans substituted in the 8-position of the heterocyclic ring.

The observation by Lahey and MacLeod\textsuperscript{30,31} that geiparvarin (45) cyclised, on treatment with mild aqueous base, presumably via the aldehyde (46), to psoralene (29) provided the basis for a possible general synthetic route to 6-oxygenated benzofurans for use as intermediates in the synthesis of natural products. It had also been reported\textsuperscript{40} that sodium ethoxide catalysed cyclisation of (47) gave the linear furocoumarin (48) although on repeating this work Esse and Christensen\textsuperscript{33} obtained (48) in only 4% yield.

Thus it was envisaged that appropriate substitution in the side chain of (49) would lead to ideal intermediates (50) for the synthesis
of various naturally occurring benzofurans. For example with (49), 
\[ R=H, R' = CH_3, \] 
the reaction should afford the \( \beta \)-methylbenzofuran (51) suitable as an intermediate in the synthesis of the "cyperaquinones" and "scabequinones" while use of the cyclohexanonyl side chain compound (52) would be expected to give 3-hydroxydibenzofuran (53) via the tetrahydro-derivative (54).

The preparation of linear furocoumarins by this route has already been mentioned and an intermediate of the type (55) might be expected to cyclise to the pterocarpan skeleton (56).
The investigation and applications of this cyclisation reaction will be discussed in subsequent chapters.
in 1961 Inouye and Nakano observed that the naturally occurring coumarins, periwinkle flavonoids (45), on treatment with oxalyl chloride gave the benzilidene coumarin derivatives (46) in 10% yield. These authors proposed retro-aldol fragmentation of (45) with concurrent cyclisation of the intermediate aldehyde (47) to (46). The cyclisation of this aldehyde initiated the work presented here.

CHAPTER II

CYCLISATION REACTION

A similar cyclisation had been reported by Inouye et al. and claimed that sodium ethoxide catalysed the cyclisation of the ketone (47) to 6-methylchromanone (48). On repeating this work, however, Kane and Christiano claimed (48) to (51) 41% yield but were unsuccessful in their attempt to cyclise the aldehyde (51) under a variety of acidic and basic conditions.

An interesting side chain was observed when high yield alcohols were prepared Kumofuran. In 1968 Bhatia and Mitta reported phenothiazine of these molecules (53) to give, among other products, 6-methylphenothiazine (55) as an ortho-quinoneimine and subsequent cyclisation of the phenothiazine system.
In 1963 Lahey and MacLeod observed that the naturally occurring coumarin, geiparvarin (45), on treatment with mild aqueous base gave the linear furocoumarin psoralene (29) in 58% yield. These authors proposed retro-aldol fragmentation of (45) with concomitant cyclisation of the intermediate aldehyde (46) to (29). The cyclisation of this aldehyde initiated the work presented here.

A similar conversion had been reported by Ray et al. who claimed that sodium ethoxide catalysed the cyclisation of the ketone (47) to \(\beta\)-methylpsoralene (48). On repeating this work, however, Esse and Christensen obtained (48) in only 4% yield and were unsuccessful in their attempts to cyclise the aldehyde (57) under a variety of acidic and basic conditions.

Acetonyloxy side chain compounds have been used elsewhere to prepare benzofurans. In 1968 Dirania and Hill reported photolysis of these molecules (58) to give, among other products, \(\alpha\)-methylbenzofurans (59) via an ortho-rearrangement and subsequent cyclisation of the phenolic intermediates (60).
Dehydrocyclisation of 3-(m-substituted phenoxy) butanones has been reported\textsuperscript{43} to yield mixtures of 4- and 6-substituted-2,3-dimethylbenzofurans. In the cases where R=OH or OAc, however, only very low yields of the benzofurans were observed.

In the course of their work on geiparvarin, Lahey and MacLeod prepared 7-(2-oxoethoxy)coumarin (46) and cyclised it to (29) by the action of 5% potassium hydroxide solution under reflux in an atmosphere of nitrogen. This synthesis\textsuperscript{51} of the biologically active\textsuperscript{44} psoralene in four simple steps from resorcinol was a considerable improvement over previously published methods.

The generality of this cyclisation reaction has been demonstrated by the synthesis of the linear furocoumarins (48), (64)-(66) from their corresponding ketone precursors (47), (61)-(66).

\begin{align*}
\text{R} & = \text{R'} = \text{CH}_3 \\
\text{R} & = \text{C}_6\text{H}_5, \text{R'} = \text{H} \\
\text{R} & = \text{C}_6\text{H}_5, \text{R'} = \text{CH}_3
\end{align*}

In each case, the \textsuperscript{1}H n.m.r. spectrum of the single product showed two signals for the para-oriented aromatic proton absorptions. No AB patterns due to ortho-protons from the possible angular

\* Prepared by Dr. J. K. MacLeod, Research School of Chemistry, Australian National University.
furocoumarin isomers (e.g. (67)) were observed.

![Image of furocoumarin isomer](image)

The furocoumarin (68)\(^{41}\), a key intermediate in the synthesis of cyperaquinnone\(^{45}\) (Chapter IV) was likewise obtained from (70) by the action of aqueous base.

![Image of reaction products](image)

Thus the cyclisation proceeds with regiospecificity giving rise, in these cases, to the linear three-ring system. The overall reaction may be regarded as an electrophilic substitution at the position para- to the phenoxide ion formed in base (Fig. 10). The intermediate carbinol (71), which is readily dehydrated to the \(10\) aromatic system, resembles to some extent the product from an aldol condensation. The two reactions are, however, dissimilar due to the fundamental differences in the reactants of each.

The cyclisation reaction is, however, closely related to the \(\text{Ar}_1\text{-5 cyclisation of } \text{p-hydroxyphenyl-C}_4\text{ compounds of the type (72) discussed by Baird and Winstein}^{46}\). Other workers have demonstrated the synthetic utility of these \(\text{Ar}_1\text{-5 cyclisations to spiro dienones.}

![Image of reaction mechanism](image)
For example, Corey et al.\textsuperscript{47} cyclised (74) using potassium tert-butoxide in tert-butanol, to obtain (75), an intermediate in their synthesis of cedrol (76). Crandall and Lawton\textsuperscript{48} cyclised (77) under similar conditions to give the same intermediate (75). Masamune\textsuperscript{48} has utilised Ar\textsubscript{1-5} participation for the preparation of intermediates in the synthesis of several diterpenes and diterpene alkaloids, while Beames and Mander\textsuperscript{50} have reported similar transformations.

These reactions, however, all led to spiro compounds of the type (73).

Duggan and Murphy\textsuperscript{51} treated (78) with base to obtain a mixture of the tetralins (79) and (80).
We have successfully applied this new method to the synthesis of several simple 6-hydroxybenzofuran derivatives.\textsuperscript{41} For example, the monoacetyoxyl ether of resorcinol (81) readily cyclised in refluxing 1N potassium hydroxide solution to yield (after acidification) 6-hydroxy-3-methylbenzofuran\textsuperscript{52} (51) in 75\% yield. Similarly, the methoxy analogue (82) was obtained from (83) in high yield. This benzofuran (82) was required as an intermediate in the synthesis of cyperaquinone\textsuperscript{45} (Chapter III) and an efficient preparation of the compound was essential. It was found that treatment of (83) in aqueous-methanolic potassium hydroxide solution at 55-60° for 2 hr under nitrogen, removal of the methanol under reduced pressure and acid work-up gave a very high yield of (82) contaminated with only a small amount of the dimer (84). An almost quantitative yield of (82) could be obtained if the acidification step was carried out below 5°, minimising formation of the dimer.

Again in each case the only product formed was that arising from cyclisation to the position para- to the intermediate phenoxide ion.

The susceptibility of benzofurans to electrophilic attack at position-2 is well known and formation of the dimer (84) is presumably acid catalysed as shown:
Indeed acid catalysed dimerisation of benzofurans has been reported\textsuperscript{53}. Cavell and MacMillan\textsuperscript{54} have isolated the benzofuran dimer (85) in the preparation of (86). The dimer (87) was also reported. These workers found that even brief exposure of the phenol (88) to dilute acid led to formation of (87).

Structural identification of (84) was possible from its \textsuperscript{1}H n.m.r. spectrum. The aromatic protons of the dihydro-benzofuran system appeared as two doublets at 6.02 and 5.98 with $J$ 2.5Hz. The benzofuran ring shows aromatic proton doublet absorbances at 6.44 and 6.24 with $J$ 2.5Hz. No signal for an $\alpha$-proton of the benzofuran system was observed in the region of 6.7-8. The two methyl groups appeared as singlets at 61.96 and 1.80. Two doublets centred at 64.58 and 4.36 with $J$ 9Hz were attributed to the two $\alpha$-protons of the dihydrobenzofuran system.

Treatment of (82) with methanolic hydrochloric acid solution slowly gave rise to (84) as the only product.
Utilisation of the cyclic ketone \(^{47}\) (89) in the cyclisation reaction afforded the furocoumarin (90) which was subsequently dehydrogenated (D.D.Q/C\(_6\)H\(_6\)) to the linear four-ring system (91)* (Fig. 11). In an analogous manner (92) gave 3-hydroxydibenzofuran (53) in high yield via the benzofuran (54).\(^{41,55}\)

It is noteworthy that all products from the cyclisation reaction have a 6-oxygenated benzofuran moiety (44); the same as that found in the naturally occurring furocoumarins, dibenzofurans, pterocarpans and benzodifurans discussed in Chapter I.

The synthetic utility of this method is demonstrated by its application to the syntheses of the natural products dealt with in subsequent chapters.

The epoxy acetate (93) was prepared, from (94), with the intention of extending the cyclisation method, discussed above, to the preparation of chroman derivatives. Selective cleavage of the acetate functionality, however, was not possible (Fig. 12) – basic hydrolysis gave a polyhydroxy compound which could not be isolated in a pure state. Failure of this route is not surprising since the epoxide would be expected to undergo facile cleavage in the presence of alkali. Peracid oxidation of the phenol (95)\(^{56}\) gave rise to intractable coloured material possibly due to formation of quinonoid products.

The epoxy phenol (96), if obtained, would be expected to cyclise, \(^*\)

\* Prepared by Dr. J. K. MacLeod, Research School of Chemistry, Australian National University.
FIG. 11

\[ \text{89} \rightarrow \text{90} \]

\[ \text{91} \]

\[ \text{92} \rightarrow \text{54} \]

\[ \text{53} \]
FIG. 12

\[ \text{94} \xrightarrow{\text{reaction}} \text{93} \]

\[ \text{95} \xrightarrow{\text{reaction}} \text{96} \]

\[ \text{96} \xrightarrow{\text{OH}^-} \]

\[ \text{\(\sigma^*\)} \xrightarrow{\text{\(H^+\)}} \text{\(\sigma^-\)} \]

\[ \text{\(\sigma^-\)} \]

\[ \text{97} \]

The reaction sequence depicted in Figure 12 shows the transformation of compound 94 through intermediate 93, then 95 to 96, followed by the reaction with OH\(^-\) to form 97. The reaction is catalyzed by \(H^+\), as indicated by the arrow.
in base to the 3-hydroxy chroman (97) as shown in Figure 12.

The cyclisation reaction may also be applicable to the synthesis of 3-substituted-6-hydroxyindoles (98). In this case selective alkylation of m-amino phenols would give the required precursors.
EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected.

Ultraviolet spectra were measured on a Unicam SP 800 spectrometer, in ethanol solution unless otherwise stated.

Infra-red spectra were measured on a Perkin Elmer 257 spectrometer, in nujol mulls, unless otherwise stated.

Mass spectra were recorded on an A.E.I. M.S. 902 spectrometer.

Nuclear magnetic resonance (n.m.r.) spectra were recorded on a Varian HA-100, a JEOL C-60, or a JEOL MH-100 spectrometer. Chemical shift values are quoted in units of δ parts per million with respect to the signal from tetramethylsilane. Abbreviations used to describe the multiplicity of signals are: singlet, s; doublet, d; multiplet, m; triplet, t; quartet, q; broad, b.

Solvents and reagents were distilled or recrystallised prior to use.

Analytical t.l.c. was, unless otherwise stated, carried out on Kieselgel G₂₅₄ or Alumina G (type E) layers of 0.1 mm thickness and preparative scale separations employed layers of 1.0 mm thickness.
4-Methyl-7-phenacyloxycoumarin (63)

A solution of 7-hydroxy-4-methylcoumarin (17.6g, 100mmole) and phenacyl bromide (24.0g, 120mmole) in acetone (350 ml) under reflux was stirred with anhydrous potassium carbonate (20g) for 10 hr. The cooled solution was filtered and evaporated under reduced pressure to give the ketone (63), (25.5g, 87%), as colourless needles from ethanol, m.p. 164-6°. (Found: C, 73.5; H, 5.1. C_{16}H_{14}O_{4} requires: C, 73.5; H, 4.8%). vmax 1725 (lactone), 1700 (CO), 1625 (C=C) cm⁻¹; δ (CDCl₃) 8.00 (d, 1, H₅, J 9Hz), 7.6-7.4 (m, 5, phenyl), 6.92 (dd, 1, H₆, J 9, 2.5Hz), 6.99 (d, 1, H₆, J 2.5Hz), 6.12 (bs, 1, H₃), 5.37 (s, 1, OCH₂CO), 2.38 (bs, 3, CH₃).

4-Methyl-6-phenylpsoralene (66)

The ketone (63) (2.94g, 10mmole) was heated in potassium hydroxide solution (150 ml) under reflux in an atmosphere of nitrogen for 6 hr. The solution was cooled, acidified with 40% phosphoric acid and kept at 5° overnight. The precipitate was removed by filtration, dried and recrystallised from ethanol to give the psoralene derivative (66) (1.95g, 70%) as colourless needles, m.p. 183-184.5° (Found: C, 78.3; H, 4.5. C_{18}H_{12}O_{3} requires: C, 78.3; H, 4.4%). vmax 1705 (lactone), 1625 (C=C), 1605 (C=C furan) cm⁻¹; δ (CDCl₃) 7.94 (s, 1, H₇), 7.80 (s, 1, H₅), 7.7-7.5 (m, 5 phenyl), 7.45 (s, 1, H₉), 6.25 (bs, 1, H₃).

7-Acetonyloxy-8-hydroxycoumarin (69)

The ketone (69) was prepared by the method of Ray et al.⁴⁰ in 50% yield, m.p. 137-8° (lit.⁴⁰ 132-3°). vmax. 3500-3200 (OH), 1700 (CO) cm⁻¹; δ (DMSO-d₆) 8.06 (d, 1, H₄, J 10Hz), 7.28 (d, 1, H₅, J
9Hz), 6.92 (d, 1, H6, J 9Hz), 6.35 (d, 1, H3, J 10Hz), 4.11 (s, 2, OCH2CO), 1.51 (s, 3, COCH3); m/e 234 (M+, 92%), 192 (73), 191 (100).

7-Acetonyloxy-8-methoxycoumarin (70)

Methylation of (69) with methyl iodide and anhydrous potassium carbonate in acetone gave the methyl ether (70) in 95% yield, m.p. 67-95° (lit. 40 81-2°), (Found: C, 63.0; H, 5.1. Calc. for C13H12O5: C, 62.9; H, 4.9%) vmax 1720 (CO) cm⁻¹; δ (CDCl3) 7.79 (d, 1, H4, J 10Hz), 7.36 (d, 1, H5, J 9Hz), 7.00 (d, 1, H6, J 9Hz), 6.34 (d, 1, H3, J 10Hz), 4.68 (s, 2, OCH2CO), 4.00 (s, 3, OCH3), 2.44 (s, 3, COCH3); m/e 248 (M+, 100%), 206 (47), 205 (65), 191 (78).

6-Methylxanthotoxin (68)

A solution of (70) (6.0 g, 24mmole) in 1N potassium hydroxide solution (300 ml) was refluxed for 24 hr under an atmosphere of nitrogen. The cooled solution was acidified with 40% phosphoric acid and extracted with ether (3 x 150 ml). The combined ether extract was dried and evaporated to an oil. Column chromatography on alumina with chloroform afforded the furocoumarin (68) (2.0g, 36%) as colourless needles from ethanol, m.p. 132-132.5° (lit. 40 155°), (Found: C, 68.0; H, 4.5. Calc. for C13H10O4: C, 67.8; H, 4.4%). vmax 1725 cm⁻¹; δ 7.80 (d, 1, H4, J 10Hz), 7.52 (bs, 1, H7), 7.27 (s, 1, H5), 6.36 (d, 1, H3, J 10Hz), 4.24 (s, 3, OCH3), 2.24 (bs, 3, CH3); m/e 230 (M+, 100%), 215 (28), 202 (10), 187 (41).

Resorcinol monoacetonyl ether monobenzenesulphonate (81)

Resorcinol monobenzenesulphonate 57 was alkylated with chloroacetone and anhydrous potassium carbonate in acetone to give
the ketone (81) in 90% yield. The product was purified by molecular distillation at 80°C/0.003mm. (Found: C, 58.5; H, 4.6; S, 10.3. 
C₁₅H₁₄S₀₅ requires: C, 58.8; H, 4.6; S, 10.5%). vmax. (liquid film) 1730 cm⁻¹; δ (CDCl₃) 7.9-6.5 (complex envelope, 9, aromatic protons), 4.46 (s, 2, OCH₂CO), 2.20 (s, 3, COCH₃).

6-Hydroxy-3-methylbenzofuran (51)

The above ketone (81) (5.0g, 16.4mmole) was dissolved in hot methanol (15 ml) and the resulting solution added slowly to a 1N potassium hydroxide solution under reflux in an atmosphere of nitrogen. The mixture was refluxed for 4 hr, cooled, acidified at 0-5°C and the product collected by filtration. Recrystallisation from hot petroleum spirit (60-80°C) gave the benzofuran (51) (1.4g, 75%) as colourless needles m.p. 104-5°C (lit. 103°C). vmax. 3400-3200 cm⁻¹; δ (CDCl₃) 7.30 (d, 1, H₄, J 8Hz), 7.26 (bs, 1, H₂), 6.93 (d, 1, H₇, J 2.5Hz), 6.76 (dd, 1, H₅, J 8, 2.5Hz), 2.18 (bs, 3, CH₃).

Phloroglucinol monomethyl ether monoacetyloxy ether monobenzenesulphonate (83)

Phloroglucinol monomethyl ether monobenzenesulphonate was alkylated with chloroacetone and anhydrous potassium carbonate in acetone to give the ketone (83) in 95% yield. The product recrystallised from ethanol as colourless needles m.p. 90°C (Found: C, 56.6; H, 5.1; S, 9.3. C₁₆H₁₆S₀₆ requires: C, 56.6; H, 5.1; S, 9.5%). vmax. 1730 (CO) cm⁻¹; δ (CDCl₃) 7.5-8.0 (complex envelope, 5, phenyl), 6.40 (t, 1, aromatic proton, J 2.5Hz), 6.18 (d, 2, aromatic protons, J 2.5Hz), 4.64 (s, 2, OCH₂CO), 3.70 (s, 3, OCH₃), 2.14 (s, 3, COCH₃).
6-Hydroxy-4-methoxy-3-methylbenzofuran (82)

A solution of (83) (9.4g, 25mmole) in methanol (150 ml) was added dropwise to 20% aqueous methanolic potassium hydroxide solution (85 ml) at 55-60° under nitrogen. The solution was stirred at this temperature for 2 hr and the methanol removed under reduced pressure. The residue was diluted to 500 ml with water and acidified at 0-5° with 40% phosphoric acid. The precipitate was collected by filtration, washed with cold water, dried and recrystallised from petroleum spirit (60-80°) to give the benzofuran (82) (4.0g, 90%) as colourless needles m.p. 102-3° (Found: C, 67.3; H, 5.7. C10H10O3 requires: C, 67.4; H, 5.7%). vmax. 3300 (OH), 1625 (C=C) cm⁻¹; δ (CDCl₃) 7.12 (bs, 1, H₂), 6.50 (d, 1, H₇, J 2.5Hz), 6.19 (d, 1, H₅, J 2.5Hz), 5.06 (bs, 1, OH, D₂O exchangeable), 3.80 (s, 3, OCH₃), 2.28 (bs, 3, CH₃); λmax. 258nm (log ε, 4.20), λinf1. 287 (3.20); m/e 178 (M⁺, 100%), 163 (87), 135 (10).

The benzofuran dimer (84)

The phenol (82) (0.5g) was stirred in a solution of 40% phosphoric acid (20 ml) and methanol (30 ml) for 4 hr. The methanol was removed under reduced pressure and the residue diluted with water (20 ml) and extracted with ether (2 x 20 ml). The combined ether extract was dried and evaporated. Recrystallisation of the remaining solid from benzene afforded the dimer (84) (0.4g, 80%) as colourless prisms m.p. 200-201° (Found: C, 67.3; H, 5.6. C₂₀H₂₀O₆ requires: C, 67.4; H, 5.7%). vmax. 3300 (OH), 1620 (C=C) cm⁻¹; δ ((CD₃)₂CO) 8.30 (bs, 1, OH, D₂O exchangeable), 6.44 (d, 1, benzofuran H₇, J 2.5Hz), 6.24 (d, 1, benzofuran H₅, J 2.5Hz), 6.02 (d, 1, dihydrobenzofuran H₇ or H₅, J 2.5Hz), 5.98 (d, 1, dihydrobenzofuran H₇ or H₅, J 2.5Hz), 4.58 (d, 1, dihydrobenzofuran H₂, J 9Hz), 4.36
Resorcinol cyclohexan-2-onyl ether benzenesulphonate (92)

Resorcinol monobenzenesulphonate was alkylated with 2-chlorocyclohexanone and anhydrous potassium carbonate in acetone to give the ketone (92) in 70% yield. The product was purified by molecular distillation at 120°/0.002mm. (Found: C, 62.8; H, 5.7; S, 8.7. C₁₅H₁₆SO₅ requires: C, 62.5; H, 5.7; S, 9.3%). νmax. 1720 (CO) cm⁻¹ 6 (CDCl₃) 8.0-6.5 (complex envelope, 9, aromatic protons), 4.51 (m, 1, OCHCO), 2.7-2.1 (envelope, 2, COCH₂), 2.1-1.7 (envelope, 6, remaining methylene protons); m/e 346 (M⁺, 100%), 302 (35), 282 (6), 250 (36), 206 (8), 185 (27), 141 (95).

3-Hydroxy-6, 7, 8, 9-tetrahydrodibenzofuran (54)

The ketone (92) (6.9g, 20mmole) in hot methanol (40 ml) was added to 1N potassium hydroxide solution (300 ml) under reflux in an atmosphere of nitrogen. The solution was refluxed for a further 8 hr, cooled, acidified with 40% phosphoric acid and extracted with ether (2 x 150 ml). The combined ether extract was dried and evaporated. The residue was then extracted with hot hexane to give the phenol (54) (2.8g, 74%) as colourless needles m.p. 106-7° (Found: C, 76.8; H, 6.5. C₁₂H₁₂O₂ requires: C, 76.6; H, 6.4%). νmax. 3250 (OH), 1615 (C=C) cm⁻¹ 6 (CDCl₃) 7.20 (d, 1, H₁, J 8Hz), 6.90 (d, 1, H₄, J 2Hz), 6.70 (dd, 1, H₂, J 8, 2Hz), 5.20 (bs, 1, OH, D₂O exchangeable), 2.62 (m, 4, CH₂C=CCH₂), 1.90 (m, 4, remaining methylene protons); m/e 188 (M⁺, 100%), 187 (25), 160 (100).
3-Hydroxydibenzofuran (53)

The derivative (54) (2.0 g, 10.6 mmole) and 2,3-dichloro-5, 6-dicyano-1,4-benzoquinone (DDQ) (5.0 g, 22 mmole) were heated in dry benzene (50 ml) under reflux with stirring for 10 hr. The mixture was filtered and the filtrate evaporated. Recrystallisation of the residue from water gave the dibenzofuran (53) (1.25 g, 65%) as colourless needles m.p. 140-141° (lit. 141-141.5°). \( \text{vmax. } 3300 \text{ (OH)} \text{ cm}^{-1} \); \( \delta \) (CDCl\(_3\)) 7.9-7.2 (complex envelope, 4, H\(_6\), 7, 8, 9), 7.31 (d, 1, H\(_1\), J 9 Hz), 7.02 (d, 1, H\(_4\), J 2 Hz), 6.83 (dd, 1, H\(_2\), J 9, 2 Hz); m/e 184 (\( M^+ \), 100%), 155 (9), 128 (16), 127 (8).

Resorcinol monoallyl ether monoacetate (94)

The ether (94) was prepared according to the method of Kaufman. The product was obtained as a colourless liquid in 90% yield, b.p. 143°/16 mm. (lit. 82°/0.05 mm). \( \text{vmax. } 1760 \text{ (CO) cm}^{-1} \); \( \delta \) (CDCl\(_3\)) 7.25 (t, 1, H\(_5\), J 8 Hz), 6.8-6.6 (m, 3, remaining aromatic protons), 6.0 (m, 1, CH-CH\(_2\)), 5.40 (dd, 1, terminal olefinic proton, J 16, 1 Hz), 5.26 (dd, 1, terminal olefinic proton, J 10, 1 Hz), 4.48 (d, 2, OCH\(_2\), J 6 Hz), 2.24 (s, 3, COCH\(_3\)); m/e 192 (\( M^+ \), 39%), 150 (100), 135 (11), 122 (18), 43 (73), 41 (83).

Resorcinol-2',3'-epoxypropyl ether monoacetate (93)

The olefin (94) (4.0 g, 20.8 mmole) and \( m \)-chloroperbenzoic acid (4.3 g, 25 mmole) were heated in dichloromethane (160 ml) under reflux for 10 hr. The mixture was cooled, filtered and evaporated to an oil. Column chromatography on silica with dichloromethane gave the epoxide (93) (3.16 g, 73%). The product was purified by molecular distillation at 110°/0.03 mm, (Found: C, 63.6; H, 5.9. C\(_{11}\)H\(_{12}\)O\(_4\))
requires: C, 63.5; H, 5.8%. \(\nu_{\text{max.}}\) (liquid film) 1755 (CO) cm\(^{-1}\);
\(\delta\) (CDCl\(_3\)) 7.25 (t, 1, H\(_5\), J 9Hz), 6.85-6.60 (m, 3, H\(_2\), H\(_6\)), 4.20 (dd, 1, terminal epoxide proton, J 12, 4Hz), 3.92 (dd, 1, terminal epoxide proton, J 12, 5Hz), 3.34 (m, 1, terminal-epoxide methine proton), 2.88 (t, 1, Ar-OCH\(_3\)), 2.72 (dd, 1, Ar-OCH\(_3\)), 2.25 (s, 3, COCH\(_3\)); m/e 208 (M\(^{+}\), 31%), 166 (100), 136 (10), 123 (16), 57 (19), 43 (74).

Resorcinol monoallyl ether (95)

The penol (95) was prepared in 76% yield by the method of Kaufman et al.\(^{56}\), b.p. 104°/0.8mm. (lit.\(^{56}\) 102°/0.7mm). \(\nu_{\text{max.}}\) 3300 (OH) cm\(^{-1}\); \(\delta\) (CDCl\(_3\)) 7.16 (t, 1, H\(_5\), J 8Hz), 6.65-6.40 (m, 3, H\(_2\), H\(_6\)), 6.30-5.90 (m, 1, -CH=CH\(_2\)), 5.44 (dd, 1, terminal olefinic proton, J 16, 1 Hz), 5.32 (dd, 1, terminal olefinic proton, J 10, 1 Hz), 4.52 (d, 2, -OCH\(_2\)-, J 6 Hz).
CHAPTER III

TOTAL SYNTHESIS OF "CYPERAQUINONES"

It was envisaged that such an intermediate, with appropriate modifications, would provide a valuable approach to the "cyperaquinones". Compound (82) prepared by this method (Chapter II) had a free hydroxyl function available for the elaboration of the 3-substituted form while the 6-methoxy group provided a latent quinone function; the proposed conversions involved cleavage of the methyl ether and subsequent oxidation of the lactone group.

A highly efficient synthesis of (82) was achieved utilizing

In part, the method of compounds** for selective hydrolysis of

The route to phloroglucinol-succinonaphthyl ether methanesulphonate (83) is shown in Fig. 11; utilization of (83) proceeded with
The "cyperaquinones" (fig. 1) were shown, spectrally, to incorporate the novel benzo[1,2-b;5,4-b']difuran-4,8-quinone system (99). Hence synthesis of the ring system was of interest for both structure confirmation and to allow access to these novel natural products and their analogues for the purpose of further biological investigations.

Synthesis of these molecules required unambiguous formation of the linear three ring system. The cyclisation reaction discussed in Chapter II affords the 6-oxygenated benzofuran skeleton (44), and it was envisaged that such an intermediate with appropriate modifications would provide a suitable approach to the "cyperaquinones". Compound (82) prepared by this method (Chapter II) had a free hydroxyl function available for the elaboration of the α-substituted furan while the 4-methoxy group provided a latent quinone function; the proposed conversion involved cleavage of the methyl ether and subsequent oxidation of the formed phenol.

A highly efficient synthesis of (82) was achieved utilising, in part, the method of Kampouris for selective hydrolysis of benzenesulphonate esters of polyhydric phenols to prepare (103). The route to phloroglucinol monoacetyl ether monobenzenesulphonate (83) is shown in fig. 13. Cyclisation of (83) proceeded with
FIG. 13

\[ \text{HO-} \text{OH} \xrightarrow{\text{Bso-Obs}} \text{Bso-Obs} \]

102

\[ \text{Bso-Obs} \xrightarrow{\text{OH}} \text{Bso-Obs} \]

101

\[ \text{HO-} \text{Ome} \xrightarrow{\text{Bso-Obs}} \text{Ome} \text{Ome} \]

103

\[ \text{Ome} \text{Ome} \xrightarrow{\text{Bso-Obs}} \text{Bso-Obs} \]

83

\[ \text{OH} \]

82
regiospecificity to give (82) (Chapter II). This key intermediate (82) was prepared in 66% overall yield from phloroglucinol. The six reactions involved all proceeded in good yield and were readily adaptable to large scale preparations.

By analogy with the known\textsuperscript{13,14} condensations of salicylaldehyde derivatives with \(\alpha\)-bromo ketones to give 2-acyl benzofurans (Chapter I) it was envisaged that the required linear three-ring system could be obtained via the 5-formyl compound (104). Benzofurans have been shown to undergo formylation\textsuperscript{58} at position-2, while 2,3-dihydrobenzofurans are prone to electrophilic attack\textsuperscript{59} at position-5. Formylation of the 6-hydroxy compound (105) gives (106)\textsuperscript{59}. Furthermore, benzofurans are notoriously acid labile and reduction to dihydrobenzofurans is usually necessary before attempting Friedel Crafts type reactions.

\[
\begin{align*}
\text{105} & \quad \text{106} \\
& \quad R=H \\
& \quad R=\text{OMe}
\end{align*}
\]

In order to direct formylation to the required position of the nucleus it was first necessary to reduce the furan double bond. This was accomplished in virtually quantitative yield by hydrogenation in ethanol over palladium on carbon catalyst. The \textsuperscript{1}H n.m.r. spectrum of (107) showed characteristic\textsuperscript{3} absorbances for the two non-equivalent \(\alpha\)-protons; a triplet at \(\delta\) 4.61 with \(J\) 8 Hz and a doublet of doublets centred at \(\delta\) 4.10 with \(J\) 8.4 Hz. The dihydrobenzofuran \(\beta\)-proton appeared as a multiplet at \(\delta\) 3.50, while the three proton doublet at \(\delta\) 1.27 with \(J\) 7 Hz was attributed to the \(\beta\)-methyl group.

Treatment of the phenol (107) with the Vilsmeier-Haack reagent\textsuperscript{60,61} (dimethylformamide and phosphorous oxychloride) gave only a low yield of the 7-formyl derivative (108). The mass spectrum of (108) showed the following fragment ions; \(m/e\) 208 (\(M^+\), 55%), 193 (100), 165 (16),
but no peak at $m/e$ 190 ($M^+ - 18$), due to loss of water was observed. Electron impact studies\textsuperscript{62} of ortho-methoxy aromatic carbonyl compounds have shown that fragment ions due to $[M - H_2O]^+$ species are observed in the mass spectra. Studies\textsuperscript{62} with deuterium labelled compounds showed that the elements of the water molecule lost arose from both the hydrogen and the oxygen atom of the formyl group together with one of the hydrogen atoms of the methoxyl function as shown:

![Chemical Structure](image)

Thus the directing effect of the methoxyl group led to formation of the undesired 7-aldehyde, added proof of the position of cyclisation in (82). Alternative "ortho-cyclisation" of (83) would have given (109), reduction and subsequent formylation of which would by necessity have given an o-methoxy formyl compound.

![Chemical Structure](image)

The use of N-methylformanilide in place of dimethylformamide in the Vilsmeier-Haack reaction\textsuperscript{60} has been reported to alter the position of attack. Treatment of pyrene with N-methylformanilide and phosphorous oxychloride gave pyrene-3-aldehyde\textsuperscript{63} while use of dimethylformamide afforded pyrene-1-aldehyde\textsuperscript{64}. In our case, however the phenol (107) when treated with N-methylformanilide and phosphorous oxychloride gave only the 7-formyl compound (108) in very low yield.

An alternative approach to the synthesis of aromatic aldehydes involved the use of $\alpha,\alpha$-dichloromethyl methyl ether with titanium
In view of these results it was necessary to block the 3-position prior to formation. Oxidation of (110) with bromine in chloroform 107 gave the desired product (108) in moderate yield. The only product observed was (108), which was identical in every way to the anti-cholesan side-chain of the isoleucine methyl ester in disaccharide methyl ester after permethylation (111) as the only product observed. The presence of (108) in this reaction is in accordance with the proposed structure for the parent compound at the position of the acetate group (112). The acetate group is observed in the 1H NMR spectrum at 6.5 ppm as a doublet of doublets reflecting the presence of the acetate group, respectively, to give the diastereomers (111) and (112).
tetrachloride catalyst\textsuperscript{65}. Treatment of (107) with this reagent in dichloromethane however, also afforded (108) as the only product.

In view of these results it was necessary to block the 7-position prior to formylation. Bromination of (107) with bromine in chloroform gave the 7-bromo derivative (110) in 70-80\% yield together with a small amount of the unstable dibromide (111). Formylation of (110) with dimethylformamide and phosphorous oxychloride then gave a very low yield of the bromo-aldehyde (112). However the use of titanium tetrachloride and \(\alpha,\alpha\)-dichloromethyl methyl ether in dichloromethane afforded (112) in 94\% yield. The mass spectrum of this formyl derivative showed a significant \([M - H_2O]^+\) fragment ion at \(m/e\) 268/270, each peak constituting 40\% of the intensity of the base peak (\(m/e\) 164). The \(d_3\) analogue (113) was prepared from (101) firstly by \(d_3\)-methylation and then via the normal route outlined in figs. 13 and 14. Its mass spectrum showed the expected\textsuperscript{68} fragment ion at \(m/e\) 270/272 (each peak 20\% of the intensity of the base peak) due to loss of HDO from the molecular ion at \(m/e\) 289/291, confirming the ortho-relationship between the methoxyl and formyl groups.

Condensation of (112) and chloroacetone in acetone with anhydrous potassium carbonate yielded the linear three-ring system (114). The aromatic proton, \(H_3\) appeared as a singlet at \(\delta\) 7.62 in the \(^1\text{H n.m.r.}\) spectrum of (114). Dehydrogenation of (114) with DDQ\textsuperscript{66} in refluxing benzene proceeded smoothly to give the difuran (115). The \(^1\text{H n.m.r.}\) spectrum of (115) showed the two aromatic protons, \(H_3\), a singlet at \(\delta\) 7.79 and \(H_6\), a broad singlet at \(\delta\) 7.35. The methyl group at \(C_5\) appeared as a broad singlet at \(\delta\) 2.38 due to allylic coupling with \(H_6\).
With the desired benzodifuran system now available, it was necessary to cleave the methyl ether to gain access to the 1,4-quinone system via the phenol (116). Demethylations of aryl methyl ethers have been accomplished with boron tribromide. Treatment of (115) however, with this reagent led to intractable tar. The failure of an acidic demethylating agent was not surprising in view of the acid lability of phenolic benzofurans.

Feutrill and Mirrington required a non-acidic reagent for the demethylation of aromatic methoxy compounds and have reported the use of thioethoxide anion, an extremely powerful nucleophile, in dipolar aprotic solvents for the cleavage of aryl methyl ethers. The methoxy compound (115) was efficiently demethylated to the required phenol (116) using 2.5 equivalents of potassium thioethoxide in dimethylformamide at 70°. This phenol was obtained as a sticky pale yellow solid which decomposed on standing in the presence of sunlight and also in ethereal solution. Due to its instability the compound was not purified but treated immediately with Fremy's reagent (potassium nitroso disulphonate) in dimethylformamide and a phosphate buffer solution to yield an orange-yellow quinone, identical in all respects (m.p., mixed m.p., i.r., u.v., n.m.r. and mass spectra) with the natural product conicaquinone (4). The concomitant loss of a halogen substituent para- to the hydroxyl in such oxidations has been reported.
Methyltriphenylphosphorane, prepared from methyltriphenylphosphonium iodide and sodium methoxide in a mixture of tetrahydrofuran and dimethylformamide (2:1)\textsuperscript{73}, converted (115) to the isopropenyl derivative (117) in high yield. The \textsuperscript{1}H n.m.r. spectrum of (117) showed broad singlet signals for the two terminal olefinic protons at δ 5.84 and 5.20. The methyl of the isopropenyl function showed broad singlet absorbance at δ 2.14 while H\textsubscript{3} appeared as a singlet at δ 6.80.

Treatment of (117) with boron tribromide also led to tarry material and attempted demethylation with thioethoxide ion\textsuperscript{69} in dimethylformamide at 70\degree\textsuperscript{a} and at 100\degree\textsuperscript{a} was unsuccessful; analysis of the reaction mixture by t.l.c. showed only starting material to be present. When this latter reaction was repeated however, using hexamethylphosphoramide (HMPA)\textsuperscript{74} as solvent, the aryl methyl ether was cleaved cleanly to yield the required phenol (118).

This phenol was less stable than (116) and rapidly decomposed in solution giving rise to coloured (blue) products. Careful work-up of the demethylation product and immediate reaction with Fremy's salt\textsuperscript{70} however, led to a good overall yield of the quinone (1) which was identical in all respects (m.p., mixed m.p., i.r., u.v., n.m.r. and mass spectra) to the natural product cyperaquinone\textsuperscript{3,5}(1)

This unambiguous total synthesis\textsuperscript{45} of conicaquinone and cyperaquinone confirms the original structural assignments\textsuperscript{3,5} by Wells and co-workers and provides ready access to analogues of these
natural products.
EXPERIMENTAL

General experimental notes are given in Chapter II, experimental section.

Phloroglucinol tribenzenesulphonate (100)

The triester (100) was prepared in 95% yield according to the method of Kampouris\(^5\), m.p. 121-2\(^o\) (lit.\(^5\) 122\(^o\)).

Phloroglucinol dibenzenesulphonate (101)

Controlled hydrolysis of (100) according to the method of Kampouris\(^5\) gave the phenol (101) in 90% yield, m.p. 120\(^o\) (lit.\(^5\) 120-1\(^o\)).

Phloroglucinol monomethyl ether dibenzenesulphonate (102).

Methylation of the phenol (101) with methyl iodide and anhydrous potassium carbonate in acetone gave the methyl ether (102) in 95% yield, m.p. 92\(^o\) (lit.\(^5\) 92\(^o\)).

Phloroglucinol monomethyl ether monobenzenesulphonate (103)

Controlled hydrolysis of (102) using the method of Kampouris\(^5\) gave the phenol (103) in 90% yield, m.p. 112\(^o\) (lit.\(^5\) 111-2\(^o\)).

Phloroglucinol monoacetonyl ether monomethyl ether monobenzenesulphonate (83)

The procedure is given in Chapter II, experimental section.
6-Hydroxy-4-methoxy-3-methylbenzofuran (82)

The procedure is given in Chapter II, experimental section.

2,3-Dihydro-6-hydroxy-4-methoxy-3-methylbenzofuran (107)

The benzofuran (82) (8.9g, 50 mmole) and 10% palladium on carbon catalyst (1g) were shaken in ethanol (200 ml) under 1 atm of hydrogen for 6 hr. The mixture was filtered through a celite pad and the ethanol removed under reduced pressure to give the dihydro-derivative (107) (8.9g, ca. 100%) as a clear oil, b.p. 146°/1 mm, (Found: C, 66.7; H, 7.0. C₁₀H₁₂O₃ requires: C, 66.6; H, 6.7%). v_max. (liquid film) 3380 (OH) cm⁻¹; δ(CDCl₃) 5.95 (s, 2, H₅ and H₇), 5.10 (bs, 1, OH, D₂O exchangeable), 4.61 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.10 (dd, 1, dihydrofuran α-proton, J 8,4 Hz), 3.50 (m, 1, dihydrofuran β-proton), 3.75 (s, 3, OCH₃), 1.27 (d, 3, CH₃, J 7 Hz); m/e 180 (M⁺, 35%), 165 (100), 137 (34), 107 (30).

2,3-Dihydro-7-formyl-6-hydroxy-4-methoxy-3-methylbenzofuran (108)

(a) The phenol (107) (0.5g, 2.78mmole), phosphorous oxychloride (0.61g, 4 mmole) and dimethylformamide (0.29g, 4 mmole) were heated to 80° in dry toluene (10 ml) for 80 hr. The solution was poured into a mixture of water (50 ml), 1N sodium hydroxide solution (50 ml) and ethanol (10 ml). This aqueous solution was boiled for 5 min., cooled, acidified with 40% phosphoric acid and extracted with ether (2 x 40 ml). The dried ether extract was evaporated to give an oil which was shown by t.l.c. analysis to contain (107) together with a compound of higher Rf. Preparative t.l.c. (40 x 20 cm. plate, silica, benzene-chloroform (1:1)) gave the aldehyde (108) (0.087g, 15%) as
pale yellow needles from hexane, m.p. 84-85.5° (Found: C, 63.0; H, 6.0. C₁₁H₁₂O₄ requires: C, 63.5; H, 5.8%). v max. (CHCl₃ solution) 1625 cm⁻¹; 6 (CDCl₃) 11.70 (s, 1, OH, D₂O exchangeable), 9.94 (s, 1, CHO), 5.92 (s, 1, H₅), 4.74 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.22 (dd, 1, dihydrofuran α-proton, J 8.4 Hz), 3.84 (s, 3, OCH₃), 3.50 (m, 1, dihydrofuran β-proton), 1.29 (d, 3, CH₃, J 7 Hz); m/e 208 (M⁺, 55%), 193 (100), 165 (16).

(b) The above reaction was repeated using N-methylformanilide (0.54g, 4mmole) in place of dimethylformamide. The aldehyde (108), identical to that obtained from (a), was obtained in 10% yield.

(c) Titanium tetrachloride (0.57g, 0.33 ml, 3.0 mmole) in dichloromethane (5 ml) was added to a solution of the phenol (107) (0.45g, 2.5mmole) and α,α-dichloromethyl methyl ether (0.35g, 3mmole) in dichloromethane (5 ml) at 0° under nitrogen. The solution was stirred at this temperature for 30 min. and then at 25° for 1 hr. The mixture was washed with water (2 x 10 ml) and extracted with 1N sodium hydroxide solution (2 x 10 ml). The combined alkaline extract was washed with ether (5 ml), acidified with 40% phosphoric acid and extracted with dichloromethane (2 x 20 ml). The extract was dried and evaporated to give the aldehyde (108) (0.34g, 65%) identical to that obtained under conditions (a) and (b) above.

7-Bromo-2,3-dihydro-6-hydroxy-4-methoxy-3-methylbenzofuran (110)

The dihydrobenzofuran (107) (9.0g, 50mmole) in chloroform (180 ml) was treated with bromine (8.0g, 2.35 ml, 50mmole) in
chloroform (90 ml) at 0°. The solution was washed with water (3 x 100 ml), dried and evaporated under reduced pressure. The residue was extracted with hot petroleum spirit (60-80°) to give the bromide (110) (9.0 g, 70%) as colourless needles m.p. 106° (Found: C, 46.3; H, 4.4; Br, 31.0. C\textsubscript{10}H\textsubscript{11}BrO\textsubscript{3} requires: C, 46.3; H, 4.3; Br, 30.8%). \textsuperscript{\textsuperscript{vmax.} 3420 (OH) cm\textsuperscript{-1}; \textsuperscript{6} (CDCl\textsubscript{3}) 6.14 (s, 1, H\textsubscript{5}), 5.42 (bs, 1, OH, D\textsubscript{2}O exchangeable), 4.70 (t, 1, dihydrofuran \ensuremath{\alpha}-proton, J 8 Hz), 4.19 (dd, 1, dihydrofuran \ensuremath{\alpha}-proton, J 8,4 Hz), 3.75 (s, 3, OCH\textsubscript{3}), 3.60 (m, 1, dihydrofuran \ensuremath{\beta}-proton), 1.30 (d, 3, CH\textsubscript{3}, J 7 Hz); \textit{m/e} 260 (M\textsuperscript{+}, 40%), 258 (M\textsuperscript{+}, 40%), 245 (70), 243 (70), 165 (12), 164 (100).

From the mother liquors there was obtained a small amount of a viscous oil which, although it was not sufficiently stable for accurate analysis was shown to be the dibromide (111). \textsuperscript{vmax.} 3400 (OH) cm\textsuperscript{-1}; \textsuperscript{6} (CDCl\textsubscript{3}) 5.80 (bs, 1, OH, D\textsubscript{2}O exchangeable), 4.66 (t, 1, dihydrofuran \ensuremath{\alpha}-proton, J 8 Hz), 4.15 (dd, 1, dihydrofuran \ensuremath{\alpha}-proton, J 8,4 Hz), 3.80 (s, 3, OCH\textsubscript{3}), 3.70 (m, 1, dihydrofuran \ensuremath{\beta}-proton), 1.32 (d, 3, CH\textsubscript{3}, J 7 Hz); \textit{m/e} 340 (M\textsuperscript{+}, 50%), 338 (M\textsuperscript{+}, 98%), 336 (M\textsuperscript{+}, 52%), 325 (50), 323 (100), 321 (52), 244 (83), 242 (70).

\textbf{7-Bromo-2,3-dihydro-5-formyl-6-hydroxy-4-methoxy-3-methylbenzofuran (112)}

\textbf{(a)} The bromo-phenol (110) (0.52 g, 2 mmole), phosphorous oxychloride (0.61 g, 4 mmole) and dimethylformamide (0.29 g, 4 mmole) were heated to 80° in dry toluene (10 ml) for 80 hr. The solution was poured into water (50 ml), ethanol (10 ml) and 1N sodium hydroxide solution (50 ml). This aqueous solution was then boiled for 5 min., cooled, acidified and extracted with ether (2 x 40 ml). The dried ether extract was evaporated to an oil which gave the aldehyde (112) (0.058 g, 10%) after recrystallisation from \textit{n}-hexane, m.p. 97° (Found: C, 45.9; H, 4.0; Br, 27.9.
C\textsubscript{12}H\textsubscript{11}BrO\textsubscript{4} requires: C, 46.0; H, 3.7; Br, 27.8%. $\nu_{\text{max.}}$

(CDCl\textsubscript{3} solution) 1625 cm\textsuperscript{-1}; 6 (CDCl\textsubscript{3}) 13.16 (s, 1, OH, D\textsubscript{2}O exchangeable), 9.95 (s, 1, CHO), 4.83 (t, 1, dihydrofuran $\alpha$-proton, $J$ 8 Hz), 4.38 (dd, 1, dihydrofuran $\alpha$-proton, $J$ 8.4 Hz), 4.02 (s, 3, OCH\textsubscript{3}), 3.80 (m, 1, dihydrofuran $\beta$-proton), 1.40 (d, 3, CH\textsubscript{3}, $J$ 7 Hz); m/e 288 ($M^+$, 94%), 286 ($M^+$, 95%) 273 (60), 271 (69), 270 (40), 268 (40), 255 (20), 253 (20), 242 (20), 240 (20), 164 (100).

(b) Titanium tetrachloride (4.7g, 3.3 ml, 30mmole) in dichloromethane (50 ml) was added to a solution of the bromo-compound (110) (6.5g, 25mmole) and $\alpha,\alpha$-dichloromethyl methyl ether (3.45g, 30mmole) in dichloromethane (30 ml) at 0° under nitrogen. The solution was stirred at this temperature for 30 min. and then at 25° for 1 hr. The mixture was washed with water (2 x 30 ml) and extracted with 1N sodium hydroxide solution (2 x 60 ml). The alkaline solution was acidified with 10N hydrochloric acid and extracted with dichloromethane. This latter extract was dried (MgSO\textsubscript{4}) and evaporated under reduced pressure to give the aldehyde (112) (6.7g, 94%), as pale yellow needles from petroleum spirit (60-80°), m.p. 97°, identical to that obtained in (a).

2-Acetyl-8-bromo-5,6-dihydro-4-methoxy-5-methylbenzo[1,2-b;5,4-b']difuran (114)

The aldehyde (112) (6.0g, 21mmole) was stirred with chloroacetone (2.3g, 25mmole) in refluxing acetone (70 ml) in the presence of anhydrous potassium carbonate (4g) for 6 hr. The solid residue from the filtrate was recrystallised from methanol to give the ketone (114) (5.6g, 82%) as pale yellow needles m.p. 143° (Found: C, 51.9; H, 3.9; Br, 24.6. C\textsubscript{14}H\textsubscript{13}BrO\textsubscript{4} requires: C, 51.7; H, 4.0; Br, 24.6%). $\nu_{\text{max.}}$
1665, 1615 cm\(^{-1}\); \(\delta (\text{CDCl}_3)\) 7.62 (s, 1, H\(_3\)), 4.78 (t, 1, dihydrofuran \(\alpha\)-proton, \(J\) 8 Hz), 4.30 (dd, 1, dihydrofuran \(\alpha\)-proton, \(J\) 8,4 Hz), 4.15 (s, 3, OCH\(_3\)), 3.75 (m, 1, dihydrofuran \(\beta\)-proton), 2.58 (s, 3, COCH\(_3\)), 1.37 (d, 3, CH\(_3\), \(J\) 7 Hz); \(\lambda_{\max}\) 260 nm (log \(\varepsilon\), 4.11), 327 (4.39); 

\(m/e\) 326 (\(M^+\), 100%), 324 (\(M^+\), 95%), 311 (33), 309 (34), 230 (73).

2-Acetyl-8-bromo-4-methoxy-5-methylbenzo[1,2-b;5,4-b']difuran (115)

The ketone (114) (5.0g, 15.4mmole) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (3.6g, 15mmole) were heated in refluxing benzene (100 ml) for 6 hr. The cooled reaction mixture was filtered through a small plug of alumina (grade II) and the eluate evaporated under reduced pressure to give the difuran (115) (4.7g, 95%) as yellow needles from methanol, m.p. 209-210° (Found: C, 51.8; H, 3.3; Br, 24.7. 

\(C_{14}H_{11}BrO_4\) requires: C, 52.0; H, 3.4; Br, 24.8%). \(\lambda_{\max}\) 1670, 1610 cm\(^{-1}\); \(\delta (\text{CDCl}_3)\) 7.79 (s, 1, H\(_3\)), 7.35 (bs, 1, H\(_6\)), 4.22 (s, 3, OCH\(_3\)), 2.66 (s, 3, COCH\(_3\)), 2.38 (bs, 3, CH\(_3\)); \(\lambda_{\max}\) 269 nm. (log \(\varepsilon\), 4.39), 313 (4.22); \(\lambda_{\text{infl}}\) 346 (3.51); 

\(m/e\) 324 (\(M^+\), 91%), 322 (\(M^+\), 91%), 309 (100), 307 (100), 267 (15), 265 (15).

2-Acetyl-8-bromo-4-hydroxy-5-methylbenzo[1,2-b;5,4-b']difuran (116)

The methyl ether (115) (0.5g, 1.56mmole) was heated to 70° under nitrogen together with potassium hydroxide (0.22g, 3.9mmole) and ethane thiol (0.24g, 3.9mmole) in dimethylformamide (15 ml) and water (0.5 ml) for 3 hr. The solution was cooled, poured into ice cold 3N hydrochloric acid solution (100 ml) and extracted with ether (2 x 50 ml). The combined ether extracts were washed with water, dried (MgSO\(_4\)) and evaporated to a semi-solid yellow residue (115) (0.45g, 95%) which was homogeneous on t.l.c. but slowly decomposed on standing; \(\lambda_{\max}\) 3130, 1650, 1625 cm\(^{-1}\).
2-Acetyl-5-methylbenzo[1,2-b;5,4-b']difuran-4,8-quinone (4); conicaquinone

A solution of potassium nitroso disulphonate (0.175 g, 0.65 mmole) in M/15 potassium dihydrogenphosphate solution (4 ml) was added to the crude phenol (115) (0.1 g, 0.32 mmole) in dimethylformamide (3 ml). The mixture was shaken for 20 min., cooled and the precipitate collected by filtration. The dark red solid was dried and recrystallised from benzene/hexane to give the quinone (4) (0.04 g, 50%) as yellow needles m.p. 189-190° (lit. 5 189-191°), mixed m.p. with an authentic sample of conicaquinone 189-191°. \( \nu_{\text{max.}} \) 1690, 1680, 1665 cm\(^{-1}\); \( \delta \) (CDCl\(_3\)) 7.75 (bs, 1, H\(_6\)), 7.49 (s, 1, H\(_3\)) 2.61 (s, 3, COCH\(_3\)), 2.37 (bs, 3, CH\(_3\)); m/e 244 (M\(^+\), 60%), 229 (100), 43 (19).

8-Bromo-2-isopropenyl-4-methoxy-5-methylbenzo[1,2-b;5,4-b']difuran (117)

The ketone (115) (3.0 g, 9.3 mmole) in tetrahydrofuran (25 ml) and dimethylformamide (12 ml) was added to a solution of methyltriphenylphosphorane (prepared from methyltriphenylphosphonium iodide (12.1 g, 30 mmole) and sodium methoxide (1.6 g, 30 mmole) in tetrahydrofuran (60 ml) and dimethylformamide (30 ml)) at 40° under nitrogen. The solution was stirred at 45° for 2 hr., poured into cold water (500 ml) and extracted with n-hexane (3 x 250 ml). The combined, dried (MgSO\(_4\)) extract was filtered through a small plug of alumina (grade II). The eluate afforded the olefin (117) (2.8 g, 94%) as pale yellow needles from methanol, m.p. 128-130° (Found: C, 56.3; H, 4.3; Br, 24.6. \( \text{C}_{15}\text{H}_{13}\text{BrO}_3 \) requires: C, 56.1; H, 4.1; Br, 24.9%). \( \nu_{\text{max.}} \) 1610 cm\(^{-1}\); \( \delta \) (CDCl\(_3\)) 7.30 (bs, 1, H\(_6\)), 6.80 (s, 1, H\(_3\)), 5.84 (bs, 1, terminal olefinic proton), 5.20 (bs, 1, terminal olefinic proton), 4.14 (s, 3, OCH\(_3\)), 2.36 (bs, 3, furan \( \beta -\text{CH}_3\)), 2.14 (bs, 3, H\(_2\text{C} = \text{C(\text{CH}_3)}-\)); \( \lambda_{\text{max.}} \) 259 nm. (log. \( \varepsilon \), 4.40), 268 (4.41), 295 (4.24), 304 (4.27); m/e 322 (M\(^+\), 66%), 320 (M\(^+\), 66%), 307 (100), 305 (100).
8-Bromo-4-hydroxy-2-isopropenyl-5-methylbenzo[1,2-b;5,4-b']difuran (118)

The methyl ether (117) (0.5g, 1.6mmole) was heated to 70° under nitrogen together with potassium hydroxide (0.22g, 3.9mmole) and ethane thiol (0.24g, 3.9mmole) in hexamethylphosphoramide (10 ml) and water (0.5 ml) for 3 hr. The solution was cooled, poured into ice cold 3N hydrochloric acid solution (70 ml) and extracted with ether (2 x 50 ml). The combined ether extracts were dried (MgSO₄) and evaporated under reduced pressure to yield a cream, light sensitive solid (118) (0.46g, 95%). This solid was homogenous on t.l.c. but decomposed rapidly on standing at room temperature or in solution.

2-Isopropenyl-5-methylbenzo[1,2-b;5,4-b']difuran-4,8-quinone (1; cyperaquinone)

A solution of potassium nitroso disulphonate (0.175g, 0.65mmole) in M/15 potassium dihydrogenphosphate solution (4 ml) was added to the crude phenol (118) (0.1g, 0.32mmole) in dimethylformamide (3 ml). The mixture was shaken for 20 min., cooled and the red precipitate isolated by vacuum filtration. This solid was recrystallised from benzene/hexane to give the quinone (1) (0.04g, 50%), m.p. 174-178°. This product was sublimed (150°/1mm) and recrystallised from benzene/hexane to give cyperaquinone as bright red needles, m.p. 180-181° (lit.3,5 182-3°), mixed m.p. with an authentic sample, 181-182°. vmax. 1665 cm⁻¹; δ (CDCl₃) 7.47 (bs, 1, H₆), 6.71 (s, 1, H₃), 5.86 (bs, 1, terminal olefinic proton), 5.30 (bs, 1, terminal olefinic proton), 2.34 (s, 3, H₂C = C(CH₃)- ), 2.11 (bs, 3, furan β-CH₃); m/e 242 (M⁺, 100%).
CHAPTER IV

ALTERNATIVE TOTAL SYNTHESIS
OF "CYPERAQUINONES"

In this chapter, the alternative total synthesis of "cyperaquinones" is described. The approach utilized involved the use of pyrogallol as a key intermediate derived from the quinone ring of the cyparissoside system. This method provided a more feasible alternative to the earlier syntheses.

The intramolecular base-catalyzed cyclization, as described in Chapter III, was again used to form the 2-methylbenzofuranoid system of the key intermediate (68). However, in contrast to the earlier syntheses, the second 2-substituted furan ring was derived by contraction of the pyrrole ring of the cyparissoside system in (68) (Fig. 12). The corresponding intermediate for the synthesis of deacetylcyperaquinone (3), cypaquinone (13a) was commercially available although the total synthesis had been reported earlier.

Daphnetin (130) was prepared by the known procedure from pyrogallol and maleic acid. Subsequent elaboration with tropacogenone...
The total syntheses of cyperaquinone (1) and conicaquinone (4) have been described in Chapter III.

\[
\begin{align*}
1 & : R=CH_3, R'=CH_2 \\
4 & : R=CH_3, R'=O \\
5 & : R=H, R'=CH_2
\end{align*}
\]

In this chapter alternative total syntheses of (1) and (4) together with that of demethylcyperaquinone (5), a minor constituent of *Cyperus compressus*, are reported. In the previous synthesis it was shown that the natural products (1) and (4) contained oxygenation patterns based on the phloroglucinol nucleus. In this work the presence of 1,2,3-oxygenation as in pyrogallol has been utilised. Indeed pyrogallol provided a cheap, readily available alternative to phloroglucinol used as starting compound for the earlier synthesis.

The intramolecular base catalysed cyclisation, described in Chapter II, was again used to form the \( \beta \)-methylbenzofuranoid system of the key intermediate (68). However, in contrast to the earlier synthesis, the second \( \alpha \)-substituted furan ring was derived by contraction of the pyrone ring of the coumarin system in (68) (fig. 15). The corresponding intermediate for the synthesis of demethylcyperaquinone (5), xanthotoxin (119) was commercially available although its total synthesis has been reported.

Daphnetin (120) was prepared by the known procedure from pyrogallol and malic acid. Subsequent alkylation with chloroacetone
FIG. 15

The cyclisation of (68) under basic conditions has already been discussed (Chapter II) and although, for individual reactions, yields of up to 63% were realised only 36% of the desired product (70) could be obtained reproducibly. Attempts to cyclise (69) under basic conditions were unsuccessful. Starting materials recovered from several attempts at cyclisation were shown to yield benzo[1,3]dioxocin-5-carboxylic acids.

Controlled hydroxylation of the linear compounds (68) and (119) in ethanal over 185°C palladium black or Raney nickel gave the corresponding hydroxy compounds (69) and (120) which were shown to be present by F.I.R. analysis but were readily reduced during recrystallisation of the dihydro derivatives.

68  R= Me

119  R= H
in the presence of sodium ethoxide catalyst \(^{40}\) gave the ketone (69). Preferential 7-0-alkylation of daphnetin derivatives has been reported\(^{80-82}\) and in our hands, the 7-alkoxy derivative (69) was the only product isolated. The absence of any 7,8-dialkoxy compound was presumably partly due to intramolecular hydrogen bonding in (69). Methylation of (69) with methyl iodide and anhydrous potassium carbonate gave (70) in high yield.\(^{40}\)

The cyclisation of (70) under basic conditions has already been discussed (Chapter II) and although, for individual reactions, yields of up to 65% were realised only 36% of the desired product (68) could be obtained consistently. Attempts to cyclise (69) under basic conditions were unsuccessful. Starting material was recovered from several attempts.

The pyrone ring of 3-bromocoumarin systems has been contracted by the action of aqueous base to yield benzofuran-2-carboxylic acids\(^{18}\) (Chapter I). Since bromine adds readily to the 6-7 double bond of the furocoumarin ring system\(^{83}\) selective reduction of the furan ring was necessary to allow bromination specifically at the 3-position. Controlled hydrogenation of the linear furocoumarins (68) and (119) in ethanol over 10% palladium on carbon catalyst\(^{83}\) afforded the corresponding dihydrofuran derivatives (121) and (122) in better than 80% yield. Traces of the corresponding tetrahydro derivatives (123) and (124) were shown to be present by t.l.c. analysis but were readily removed during recrystallisation of the dihydro compounds.
Treatment of (121) and (122) with bromine in chloroform gave the 3-bromo-compounds (125) and (126) by the known sequence of addition of bromine followed by elimination of hydrogen bromide. In the $^1$H n.m.r. spectrum of each compound $H_4$ appeared as a singlet at $\delta 8.00$.

By analogy with Perkin's synthesis of benzofuran-2-carboxylic acid$^{18}$ (Chapter I), treatment of (125) and (126) with refluxing 1N potassium hydroxide solution followed by acid work-up afforded the carboxylic acids (127) and (128) respectively. The furan $\beta$-protons, $H_3$, of the two acids (127) and (128) appeared as singlets at $\delta 7.52$ and 7.76 respectively in the $^1$H n.m.r. spectra. The corresponding acid chlorides (129) and (130) were prepared using thionyl chloride,$^84$ and subsequent reaction with lithium dimethyl copper$^{85}$ in tetrahydrofuran at $-78^\circ$ gave the respective methyl ketones (131) and (132) in high yield.
Dehydrogenation of (131) and (132) using DDQ in refluxing benzene proceeded smoothly to yield (133) and (134) respectively. The $^1$H n.m.r. spectrum of (133) showed; $H_3$, a singlet at $\delta 7.44$ and $H_6$, a broad singlet at $\delta 7.40$, while that of (134) showed; $H_3$, a singlet at $\delta 7.45$; $H_5$ a doublet at $\delta 6.75$ with $J 2$ Hz and $H_6$, a doublet at $\delta 7.60$ with $J 2$ Hz.

The two ketones (133) and (134) were also obtained via the alternate route outlined in fig. 16. In this approach the acids (127) and (128) were esterified with diazomethane to give (135) and (136). Dehydrogenation of these esters and subsequent hydrolysis gave the carboxylic acids (139) and (140) which yielded the ketones (133) and (134) on treatment of the corresponding acid chlorides with lithium.
FIG. 16

The three quinones prepared in this synthetic route were identical in all respects with the corresponding naturally occurring compounds.

This synthesis of (S) confirms the previously assigned structure of demethylyperasperonin.

It was envisaged that this route would allow the preparation of 5,6,7-dihydroxypseudopine (133) and extrahynokynone (134) and (135) in yields of greater than 80%.

The spectra of these compounds (see Experimental) show an absorption at 385 nm in DMSO, and in the UV spectra a strong band at 385 nm and a shoulder at 380 nm in DMSO.

The three quinones prepared in this synthetic route were identical in all respects with the corresponding naturally occurring compounds.

This synthesis of (S) confirms the previously assigned structure of demethylyperasperonin.

It was envisaged that this route would allow the preparation of 5,6,7-dihydroxypseudopine (133) and extrahynokynone (134) and (135) in yields of greater than 80%.

The spectra of these compounds (see Experimental) show an absorption at 385 nm in DMSO, and in the UV spectra a strong band at 385 nm and a shoulder at 380 nm in DMSO.
Dimethyl copper reagent as before.

Methyltriphenylphosphorane in tetrahydrofuran/dimethylformamide (2:1) converted these ketones to the corresponding isopropenyl derivatives (141) and (142) in yields of greater than 80%. The $^1$H n.m.r. spectra of these compounds (see experimental) showed the expected signals arising from the isopropenyl functions while the $H_3$-signals appeared at $\delta 6.60$ and $6.52$ for (141) and (142) respectively.

Demethylation of the aryl methyl ethers (133), (141), and (142) with potassium thioethoxide in dimethylformamide gave the unstable phenols (143), (144) and (145) which were oxidised by Fremy's reagent to the quinones: conicaquinone (4) [73% from (133)]; cyperaquinone (1) [69% from (141)]; and demethylcyperaquinone (5) [75% from (142)], respectively.

\[
\begin{align*}
143 & \quad R=CH_3, \quad R'=O \\
144 & \quad R=CH_3, \quad R'=CH_2 \\
145 & \quad R=H, \quad R'=CH_2
\end{align*}
\]

The three quinones prepared via this synthetic route were identical in all respects with the corresponding naturally occurring compounds. This synthesis of (5) confirms the previously proposed structure of demethylcyperaquinone.

It was envisaged that this route would also allow the preparation of dihydrocyperaquinone (2) and tetrahydrocyperaquinones A and B, (6) and (7) via the ketone (146) or the carboxylic acid (147). For this approach it was necessary to selectively reduce the $\alpha$-substituted furan
double bond of (133) or the corresponding acid (139).

The reduction of the carbon-carbon double bond of $\alpha,\beta$-unsaturated carbonyl compounds has been effected by metal/ammonia reduction.\textsuperscript{86} Allan\textsuperscript{5} however, showed that the reduction of the "cyperaquinone" system by this method led to products of allylic oxygen cleavage; compounds of the type (148).

Sodium borohydride has been reported\textsuperscript{87} to reduce $\alpha,\beta$-unsaturated ketones to the corresponding saturated alcohols together with the
allylic alcohols. Using (134) as a model system however, reduction

\[
\text{R} \quad \text{OH} \\
\text{CHO} \quad + \\
\text{R} \quad \text{OH}
\]

with sodium borohydride afforded only the allylic alcohol (149).

Corey has reported the selective reduction of \(\alpha,\beta\)-unsaturated carbonyl compounds with diisobutylaluminium hydride in toluene at \(-78^\circ\). Again reduction of (134) with this reagent afforded only (149).

Hydridoiron complexes have also been used to selectively reduce \(\alpha,\beta\)-unsaturated carbonyl compounds. The reagent prepared from iron pentacarbonyl and 1,4-diazabicyclo[2.2.2]octane (DABCO) in moist hexamethylphosphoramide (HMPA) was unsuccessful in reducing the ketone (133).

Reductions of \(\alpha,\beta\)-unsaturated carboxylic acids to the corresponding saturated acids have been accomplished by reaction of the sodium salt of the acid with sodium amalgam. Maung utilised this method for the reduction of benzofuran-2-carboxylic acid (27) to (150). In our hands the acid (147) was obtained from (139) in high

\[
\text{CO}_2\text{H} \quad \text{CO}_2\text{H}
\]
yield using this procedure.

The natural product\textsuperscript{3,5} dihydrocyperaquinone, [\(\alpha\)]\textsubscript{D}\textsuperscript{-35\degree}, has an asymmetric centre at C\textsubscript{2} and it was therefore desirable to resolve the acid (147) into its enantiomeric forms. The \textsuperscript{1}H n.m.r. spectrum (fig. 17) of the corresponding methyl ester (151), with added "europium optishift II" reagent\textsuperscript{93} enabled ready distinction between the two optical isomers, thus providing a simple method for checking the optical purity of the acid after resolution.

Attempts to resolve (147) with optically active alkaloid bases (quinine, ephedrine, brucine and strychnine) were unsuccessful.

Salts of metal complex cations such as \textit{cis-}
\textsuperscript{dinitrobis(ethylenediamine)cobalt\textsuperscript{III}} bromide are readily resolved into their enantiomers\textsuperscript{94} and use of these antipodal reagents has proved successful in the resolution of N-protected \(\alpha\)-amino acids.\textsuperscript{95-97} Both \(d\) and \(l\)-enantiomers of \textit{cis-}[Co(en)\textsubscript{2}(NO\textsubscript{2})\textsubscript{2}]Br were available\textsuperscript{97} and the corresponding acetates reacted with the sodium salt of (147) to give the desired crystalline complex carboxylate salts. Repeated crystallisation from water provided: \(d\textit{-cis-}[Co(en)\textsubscript{2}(NO\textsubscript{2})\textsubscript{2}]\text{-d-(147)}, [\alpha]\textsubscript{D}\textsuperscript{+97\degree};\) and \(l\textit{-cis-}[Co(en)\textsubscript{2}(NO\textsubscript{2})\textsubscript{2}]\text{-l-(147)}, [\alpha]\textsubscript{D}\textsuperscript{-92\degree}. The yield from this resolution method was however quite low and this, together with the scarcity of material forced the postponement of this investigation.

The proposed route to dihydrocyperaquinone and tetrahydrocyporquiouinones A and B is shown in fig. 18. The main disadvantage is expected to be the possible racemisation at C\textsubscript{2} of the ketone (152) during Wittig reaction to give (153). This problem could be avoided by the use of neutral conditions; butane-epoxide\textsuperscript{98} to generate the ylid from methyltriphenylphosphonium iodide. The n.m.r. "europium optishift" reagent\textsuperscript{93} mentioned earlier should provide a
FIG. 17

$^1$H n.m.r. spectra (CDCl$_3$)
FIG. 18
PROPOSED ROUTE TO DIHYDROCYPERAQUINONE
AND TETRAHYDROCYPERAQUINONES A AND B.

\[
\begin{align*}
&\text{OMe} \\
&\begin{array}{c}
\text{147 resolved} \\
\end{array} \\
&\text{OMe} \\
&\text{154} \\
&\text{OMe} \\
&\text{153} \\
&\text{OH} \\
&\text{152} \\
&\text{6} \\
&\text{7} \\
&\text{2}
\end{align*}
\]
simple method for checking optical purity of the intermediates.

Reduction of (147) would be expected to yield the diastereomeric acids (154) which could then be converted to tetrahydrocyperaquinones A and B, (6) and (7). Allan has described the separation of (6) and (7) by preparative chromatography.
EXPERIMENTAL

General experimental notes are given in Chapter II, experimental section.

Daphnetin (120)

Von Pechmann condensation \(^{79}\) of pyrogallol and malic acid gave the phenol (120) in 25% yield, m.p. 253-5° (lit. \(^{79}\) 255-6°).

7-Acetonyloxy-8-hydroxycoumarin (69)

The procedure is given in Chapter II, experimental section.

7-Acetonyloxy-8-methoxycoumarin (70)

The procedure is given in Chapter II, experimental section.

6-Methylxanthotoxin (68)

The procedure is given in Chapter II, experimental section.

6,7-Dihydro-6-methylxanthotoxin (121)

The benzofuran (68) (4.0g, 17.4mmole) and 10% palladium on carbon catalyst (1g) were shaken in ethanol (300 ml) under 1 atm. of hydrogen for 50 min. The mixture was filtered through a celite pad and the filtrate evaporated to give the dihydroderivative (121) (3.6g, 89%) as colourless needles from ethanol, m.p. 124.5-125° (Found: C, 67.0; H, 5.2. \(\text{C}_{13}\text{H}_{12}\text{O}_{4}\) requires: C, 67.2; H, 5.2%).

\(\nu_{\text{max}}\) 1720 cm\(^{-1}\) \(\delta\) (CDCl$_3$) 7.60 (d, 1, H$_4$, \(J\) 10 Hz), 6.92 (s, 1, H$_5$), 6.20 (d, 1, H$_3$, \(J\) 10 Hz), 4.82 (t, 1, dihydrofuran \(\alpha\)-proton, \(J\) 8 Hz),
4.18 (dd, 1, dihydrofuran α-proton, $J$ 8.4 Hz), 4.00 (s, 3, OCH$_3$),
3.64 (m, 1, dihydrofuran β-proton), 1.36 (d, 3, CH$_3$, $J$ 7 Hz); m/e
232 ($M^+$, 100%), 217 (67)

6,7-Dihydroxanthotoxin (122)

Hydrogenation of xanthotoxin (119) (10.0g) as described above
for the preparation of (121) gave the dihydro-derivative (122) (8.3g,
82%) as colourless needles from ethanol; m.p. 160-160.5° (lit. 99,83
163°; 160-161°). v max. 1715 cm$^{-1}$. $\delta$ (CDCl$_3$) 7.52 (d, 1, H$_4$, $J$ 10 Hz),
6.92 (s, 1, H$_5$), 6.13 (d, 1, H$_3$, $J$ 10 Hz), 4.69 (t, 2, dihydrofuran
α-protons, $J$ 9 Hz), 4.00 (s, 3, OCH$_3$), 2.25 (t, 2, dihydrofuran β-protons,
$J$ 9 Hz); m/e 218 ($M^+$, 100%), 203 (12), 190 (31), 175 (17).

3-Bromo-6,7-dihydro-6-methy1xanthotoxin (125)

To a solution of (121) (4.0g, 17.3mmole) in chloroform (40 ml)
was added, dropwise over a period of 1 hr, a solution of bromine (4g,
1.37 ml, 25.0mmole) in chloroform (300 ml). The solution was stirred
at room temperature for a further 3 hr, washed with 5% sodium
bisulphite solution (3 x 50 ml), and evaporated to give the bromo-
derivative (125) (5.0g, 93%) as cream needles from ethanol; m.p. 124-5°
(Found: C, 50.4; H, 3.6; Br, 25.6. C$_{13}$H$_{11}$BrO$_4$ requires: C, 50.2;
H, 3.6; Br, 25.7%). v max. 1705 cm$^{-1}$; $\delta$ (CDCl$_3$) 8.00 (s, 1, H$_4$), 6.90
(s, 1, H$_5$), 4.86 (t, 1, dihydrofuran α-proton, $J$ 8 Hz), 4.20 (dd, 1,
dihydrofuran α-proton, $J$ 8.4 Hz), 4.00 (s, 3, OCH$_3$), 3.6 (m, 1,
dihydrofuran β-proton), 1.36 (d, 3, CH$_3$, $J$ 7 Hz); m/e 312 ($M^+$, 98%),
310 ($M^+$, 100%), 297 (42), 295 (43), 269 (14), 267 (14), 241 (5),
239 (5).
3-Bromo-6,7-dihydroxanthotoxin (126)

Bromination of (122) (8.0g, 36.7mmole) in chloroform (80 ml) with bromine (8.0g, 50.0mmole) in chloroform (600 ml) over a period of 4 hr. gave the bromo-derivative (126) (9.9g, 91%) as cream needles from ethanol; m.p. 205.5-207° (Found: C, 48.1; H, 3.3; Br, 26.7. C_{12}H_{9}BrO_{4} requires: C, 48.5; H, 3.1; Br, 26.9%). v_max. 1710 cm^{-1}; δ (CDCl_{3}) 8.00 (s, 1, H_{4}), 7.00 (s, 1, H_{5}), 4.80 (t, 2, dihydrofuran α-protons, J 9 Hz), 4.08 (s, 3, OCH_{3}), 3.33 (t, 2, dihydrofuran β-protons, J 9 Hz); m/e 298 (M^{+}, 100%), 296 (M^{+}, 100%), 283 (8), 281 (8), 269 (9), 267 (9), 255 (10), 253 (10), 227 (13), 225 (13).

5,6-Dihydro-8-methoxy-5-methylbenzo[1,2-b;5,4-b'] difuran-2-carboxylic acid (127)

A solution of (125) (4.0g, 12.9mmole) in 1N potassium hydroxide solution (160 ml) was heated under reflux for 2 hr, cooled and acidified with conc. hydrochloric acid. The precipitate was collected by filtration, washed with water, dried and recrystallised from methanol to give the carboxylic acid (127) (3.0g, 94%) as colourless needles, m.p. 210-212° (Found: C, 63.1; H, 5.0. C_{13}H_{12}O_{5} requires: C, 62.9; H, 4.9%). v_max. 1675 cm^{-1}; δ (DMSO-d_{6}) 7.52 (s, 1, H_{3}), 7.20 (s, 1, H_{4}), 4.76 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.10 (dd, 1, dihydrofuran α-proton, J 8,4 Hz), 4.00 (s, 3, OCH_{3}), 3.58 (m, 1, dihydrofuran β-proton), 1.28 (d, 3, CH_{3}, J 7 Hz); m/e 248 (M^{+}, 100%), 233 (14), 205 (10).

5,6-Dihydro-8-methoxybenzo[1,2-b;5,4-b']difuran-2-carboxylic acid (128)

The bromo-derivative (126) (9.5g, 32.0mmole) was heated in refluxing 1N potassium hydroxide solution (400 ml) for 2 hr. The
solution was cooled, acidified with conc. hydrochloric acid and the precipitate collected by filtration. Recrystallisation from methanol gave the acid (128) (6.95g, 93%) as colourless needles, m.p. 256-260° (Found: C, 61.7; H, 4.6. C₁₂H₁₀O₅ requires: C, 61.5; H, 4.3%). νmax. 1665 cm⁻¹; δ (DMSO-d₆) 13.5 (bs, 1, CO₂H), 7.76 (s, 1, H₃), 7.46 (s, 1, H₄), 4.80 (t, 2, dihydrofuran α-protons, J 9 Hz), 4.12 (s, 3, OCH₃), 3.36 (t, 2, dihydrofuran β-protons, J 9 Hz); m/e 234 (M⁺, 100%), 219 (18), 199 (23).

2-Acetyl-5,6-dihydro-8-methoxy-5-methylbenzo[1,2-b;5,4-b'] difuran (131)

The acid (127) (1.0g, 4.0mmole) was heated in refluxing, redistilled thionyl chloride (5 ml) for 1.5 hr. The solution was diluted with dry benzene and the solvents removed under reduced pressure to give the crude acid chloride (129). νmax. 1740 cm⁻¹.

The crude acid chloride (129) from above in dry tetrahydrofuran (20 ml) was added at -78° to a solution of lithium dimethyl copper [prepared from methyl lithium (15.0 ml of a 1.6M solution, 24.0mmole) and anhydrous cuprous iodide (2.04g, 12mmole) in dry tetrahydrofuran (30 ml) at 0°] under nitrogen. The solution was stirred for 20 min., quenched with water (20 ml) and allowed to attain room temperature. The mixture was filtered (twice) through a small plug of celite. The tetrahydrofuran was removed under vacuum and the residue extracted with ether (2 x 50 ml). The ether extract was dried (Na₂SO₄) and evaporated to give, after molecular distillation (150°/0.001 mm), the ketone (131) (0.84g, 85%), (Found: C, 68.5; H, 5.5. C₁₄H₁₄O₄ requires: C,68.3; H, 5.4%). νmax. (liquid film) 1670 cm⁻¹; δ (CDCl₃) 7.39 (s, 1, H₃), 7.05 (s, 1, H₄), 4.78 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.17 (dd, partly obscured, 1, dihydrofuran α-proton), 4.16 (s, 3, OCH₃),
7.30 (s, 1, H₃), 7.01 (s, 1, H₄), 4.65 (t, 2, dihydrofuran α-protons, J \(= 9 \) Hz), 4.13 (s, 3, OCH₃), 3.25 (t, 2, dihydrofuran β-protons, J \(= 9 \) Hz), 2.51 (s, 3, COCH₃); \( m/e \) 232 (\( M^+ \), 100%), 217 (28), 189 (10), 161 (13).

2-Acetyl-5,6-dihydro-8-methoxybenzo[1,2-b;5,4-b']difuran (132)

The acid (128) (6.5g, 27.8mmole) was heated in refluxing thionyl chloride (30 ml) for 1.5 hr. The solution was diluted with dry benzene and the solvents removed under reduced pressure to give the crude acid chloride (130), \( \nu_{\max} \) 1740 cm\(^{-1}\).

The crude acid chloride (130) from above in dry tetrahydrofuran (120 ml) was added at \(-78^\circ\) to a solution of lithium dimethyl copper [prepared from methyl lithium (105 ml of a 1.6M solution, 167mmole) and anhydrous cuprous iodide (14.2g, 83.5mmole) in dry tetrahydrofuran (210 ml) at 0°] under nitrogen. The solution was stirred for 20 min., quenched with water (120 ml) and allowed to attain room temperature. The mixture was filtered (twice) through a plug of celite. The tetrahydrofuran was removed under vacuum and the aqueous layer extracted with ether (2 x 300 ml). The ether extract was dried (Na₂SO₄) and evaporated to give the ketone (132) (5.65g, 88%) as cream needles from ethanol; m.p. 76-8° (Found: C, 67.4; H, 5.0.

\( \text{C}_{13}\text{H}_{12}\text{O}_4 \) requires: C, 67.2; H, 5.2%). \( \nu_{\max} \) 1670 cm\(^{-1}\); \( \delta \) (CDCl₃) 7.30 (s, 1, H₃), 7.01 (s, 1, H₄), 4.65 (t, 2, dihydrofuran α-protons, J \(= 9 \) Hz), 4.13 (s, 3, OCH₃), 3.25 (t, 2, dihydrofuran β-protons, J \(= 9 \) Hz), 2.51 (s, 3, COCH₃); \( m/e \) 232 (\( M^+ \), 100%), 217 (28), 189 (10), 161 (13).

2-Acetyl-8-methoxy-5-methylbenzo[1,2-b;5,4-b']difuran (133)

(a) The ketone (131) (0.5g, 2.0mmole) and DDQ (0.5g, 2.2mmole) were heated in refluxing benzene (20 ml) for 14 hr. The cooled
solution was filtered through a small plug of alumina (grade II) and the filtrate evaporated to give the ketone (133) (0.4g, 80%) as pale yellow needles from acetone/hexane, m.p. 94° (Found: C, 68.4; H, 5.0. C_{14}H_{12}O_4 requires: C, 68.9; H, 5.0%).

\[ \text{vmax. } 1670 \text{ cm}^{-1}; \delta (\text{CDCl}_3) 7.44 (s, 1, H_3), 7.40 (bs, 1, H_6), 7.24 (s, 1, H_4), 4.53 (s, 3, OCH}_3), 2.54 (s, 3, COCH}_3), 2.18 (bs, 3, CH}_3); \text{ m/e } 244 (M^+, 100%), 229 (71). \]

(b) The acid (139) (0.2g, 0.81mmole) was treated with thionyl chloride and then with lithium dimethyl copper as described in the preparation of (131) to give the ketone (133) (0.16g, 81%) identical to that obtained above.

2-Acetyl-8-methoxybenzo[1,2-b;5,4-b']difuran (134)

(a) The ketone (132) (5.0g, 21.5mmole) and DDQ (5.0g, 22.0mmole) were heated in refluxing benzene for 12 hr. The cooled solution was filtered through a small plug of alumina (grade II) and the filtrate evaporated to give the ketone (134) (4.4g, 89%) as pale yellow needles from acetone/hexane, m.p. 101-3° (Found: C, 67.6; H, 4.3. C_{13}H_{10}O_4 requires: C, 67.8; H, 4.4%).

\[ \text{vmax. } 1670 \text{ cm}^{-1}; \delta (\text{CDCl}_3) 7.60 (d, 1, H_6, J 2 \text{ Hz}), 7.45 (s, 1, H_3), 7.36 (s, 1, H_4), 6.75 (d, 1, H_5, J 2 \text{ Hz}), 4.37 (s, 3, OCH}_3), 2.57 (s, 3, COCH}_3); \text{ m/e } 230 (M^+, 100%), 215 (58). \]

(b) The acid (140) (0.2g, 0.86mmole) was treated with thionyl chloride and then with lithium dimethyl copper as described in the preparation of (132) to give the ketone (134) (0.16g, 80%) identical to that obtained above.
5,6-Dihydro-8-methoxy-5-methylbenzo[1,2-b;5,4-b']difuran-2-carboxylic acid methyl ester (135)

Treatment of the acid (127) with an ethereal solution of diazomethane gave the methyl ester (135) as colourless needles from aqueous methanol, m.p. 49-51° (Found: C, 63.7; H, 5.2. \( \text{C}_{14}\text{H}_{14}\text{O}_5 \) requires: C, 64.1; H, 5.4%). \( \text{v}_{\text{max}} \) 1700 cm\(^{-1}\); \( \delta \) (CDC\(_3\)) 7.44 (s, 1, \( \text{H}_3 \)), 7.05 (s, 1, \( \text{H}_4 \)), 4.82 (t, 1, dihydrofuran \( \alpha \)-proton, \( J \) 8 Hz), 4.2 (m, 1, partly obscured, dihydrofuran \( \alpha \)-proton), 4.20 (s, 3, OCH\(_3\)), 3.94 (s, 3, CO\(_2\)CH\(_3\)), 3.6 (m, 1, dihydrofuran \( \beta \)-proton), 1.34 (d, 3, CH\(_3\), \( J \) 7 Hz); \( m/e \) 262 (\( M^+ \), 100%), 247 (36), 231 (7), 219 (15), 191 (23).

5,6-Dihydro-8-methoxybenzo[1,2-b;5,4-b']difuran-2-carboxylic acid methyl ester (136)

Treatment of the acid (128) with an ethereal solution of diazomethane gave the ester (136) as colourless needles from ethanol, m.p. 78.5-79.5° (Found: C, 63.2; H, 4.9. \( \text{C}_{13}\text{H}_{12}\text{O}_5 \) requires: C, 62.9; H, 4.9%). \( \text{v}_{\text{max}} \) 1700 cm\(^{-1}\); \( \delta \) (CDC\(_3\)) 7.41 (s, 1, \( \text{H}_3 \)), 7.07 (s, 1, \( \text{H}_4 \)), 4.68 (t, 2, dihydrofuran \( \alpha \)-protons, \( J \) 9 Hz), 4.19 (s, 3, OCH\(_3\)), 3.94 (s, 3, CO\(_2\)CH\(_3\)), 3.28 (t, 2, dihydrofuran \( \beta \)-protons, \( J \) 9 Hz); \( m/e \) 248 (\( M^+ \), 100%), 233 (12), 217 (9), 205 (14).

8-Methoxy-5-methylbenzo[1,2-b;5,4-b']difuran-2-carboxylic acid methyl ester (137)

The ester (135) (0.52g, 2.0mmole) and DDQ (0.5g, 2.2mmole) were heated in refluxing benzene for 8 hr. The cooled solution was filtered through a small plug of alumina (grade II) and the filtrate evaporated to give the ester (137) (0.45g, 89%) as colourless needles from methanol, m.p. 106.5-107.5° (Found: C, 64.9; H, 4.7. \( \text{C}_{14}\text{H}_{12}\text{O}_5 \) requires: \( \text{C}, 64.7; \text{H}, 4.7 \)).
8-Methoxybenzo[1,2-b;5,4-b']difuran-2-carboxylic acid methyl ester (138)

Dehydrogenation of the ester (136) (0.5g, 2.0mmole) with DDQ (0.5g, 2.2mmole) as described above for the preparation of (137) gave the ester (138) (0.44g, 90%) as colourless needles from methanol, m.p. 113-114° (Found: C, 63.2; H, 4.3. C_{13}H_{10}O_S requires: C, 63.4; H, 4.1%). \( \nu_{\text{max.}} 1710 \text{ cm}^{-1} \); \( \delta (\text{CDCl}_3) 7.60 (d, 1, H_6, J 2 \text{ Hz}), 7.48 (s, 1, H_3), 7.35 (s, 1, H_4), 6.74 (d, 1, H_5, J 2 \text{ Hz}), 4.36 (s, 3, OCH}_3), 3.92 (s, 3, CO_2CH_3); m/e 246 \left( M^+, 100\% \right), 231 (57), 215 (10).

8-Methoxy-5-methylbenzo[1,2-b;5,4-b']difuran-2-carboxylic acid (139)

The ester (137) (0.52g, 2.0mmole) was suspended in 1N potassium hydroxide solution (20 ml) under reflux. After 1 hr the solution was cooled, acidified with conc. hydrochloric acid and the precipitate collected by filtration. Recrystallisation from methanol gave the acid (139) (0.43g, 88%) as colourless needles, m.p. 215-220° (Found: C, 63.6; H, 4.4. C_{13}H_{10}O_S requires: C, 63.4; H, 4.1%). \( \nu_{\text{max.}} 1675 \text{ cm}^{-1} \); \( \delta (\text{DMSO-d}_6) 7.60 (bs, 1, H_6), 7.55 (s, 1, H_3), 7.27 (s, 1, H_4), 4.10 (s, 3, OCH}_3), 2.21 (bs, 3, CH_3); m/e 246 \left( M^+, 100\% \right), 231 (83), 204 (7), 203 (6), 202 (4), 175 (24).

8-Methoxybenzo[1,2-b;5,4-b']difuran-2-carboxylic acid (140)

The ester (138) (0.4g, 1.6mmole) was hydrolysed by the method described above for the preparation of (139) to give the acid (140) (0.33g, 89%) as colourless needles from methanol m.p. 238-9° (Found:
C, 61.8; H, 3.7. C_{12}H_{8}O_{5} requires: C, 62.1; H, 3.5%. \nu_{\text{max}} 1675 cm^{-1}; \delta (\text{DMSO-}d_{6}) 7.91 (d, 1, H_{6}, J 2 \text{ Hz}), 7.58 (s, 1, H_{3}), 7.47 (s, 1, H_{4}), 6.90 (d, 1, H_{5}, J 2 \text{ Hz}), 4.12 (s, 3, OCH_{3}); m/e 232 (M^{+}, 100%), 217 (74).

2-Isopropenyl-8-methoxy-5-methylbenzo[1,2-b;5,4-b']difuran (141)

A solution of the ketone (133) (0.25 g, 1.0 mmole) in tetrahydrofuran (2 ml) and dimethylformamide (1 ml) was added to a solution of methyltriphenylphosphorane [prepared from methyltriphenylphosphonium iodide (1.21 g, 3 mmole) and sodium methoxide (0.16 g, 3 mmole) in tetrahydrofuran (6 ml) and dimethylformamide (3 ml)] at 40° under nitrogen. The solution was stirred at 40-50° for 2.5 hr, poured into cold water (30 ml) and extracted with n-hexane (3 x 30 ml). The combined ether extracts were dried (Na_{2}SO_{4}) and filtered through a small plug of alumina (grade II). The filtrate was evaporated to give the olefin (141) (0.22 g, 88%), evaporatively distilled at 95°/0.001 mm (Found: C, 74.1; H, 6.0. C_{12}H_{14}O_{3} requires: C, 74.4; H, 5.8%). \delta (CDCl_{3}) 7.35 (bs, 1, H_{6}), 7.11 (s, 1, H_{4}), 6.60 (s, 1, H_{3}), 5.74 (bs, 1, terminal olefinic proton), 5.09 (bs, 1, terminal olefinic proton), 4.28 (s, 3, OCH_{3}), 2.12 (s, 3, H_{2}C=CH(CH_{3})-), 2.01 (bs, 3, CH_{3}); m/e 242 (M^{+}, 100%), 227 (31).

2-Isopropenyl-8-methoxybenzo[1,2-b;5,4-b']difuran (142)

The ketone (134) (3.0 g, 13 mmole) was treated with a solution of methyltriphenylphosphorane as described above for the preparation of (141) to give the olefin (142) (2.52 g, 85%), evaporatively distilled at 90°/0.001 mm (Found: C, 73.6; H, 5.4. C_{14}H_{12}O_{3} requires: C, 73.7; H, 5.3%). \delta (CDCl_{3}) 7.52 (d, 1, H_{3}, J 2 \text{ Hz}), 7.12 (s, 1, H_{4}), 6.68 (d,
1, H_5, J 2 Hz), 6.52 (s, 1, H_3), 5.80 (bs, 1, terminal olefinic proton), 5.12 (bs, 1, terminal olefinic proton), 4.32 (s, 3, OCH_3), 2.04 (bs, 3, H_2C=C(CH_3)-); m/e 228 (M^+, 100%), 213 (33).

2-Acetyl-8-hydroxy-5-methylbenzo[1,2-b;5,4-b']difuran (143)

The methyl ether (133) (0.1g, 0.41mmole) was heated to 75° under nitrogen in a solution of potassium hydroxide (0.056g, 1mmole), ethane thiol (0.062g, 1mmole) and water (0.1 ml) in dimethylformamide (3 ml), for 3 hr. The cooled solution was poured into ice cold 3N hydrochloric acid (20 ml) and extracted with ether (2 x 30 ml). The dried (Na_2SO_4) ethereal solution was evaporated to an oil (0.09g, 96%) which was homogeneous on t.l.c. (silica; benzene/chloroform/methanol, 10:5:1) but slowly decomposed on standing.

2-Isopropenyl-8-hydroxy-5-methylbenzo[1,2-b;5,4-b']difuran (144)

The methyl ether (141) (0.1g, 0.41mmole), potassium hydroxide (0.056g, 1mmole), ethane thiol (0.062g, 1mmole) and water (0.1 ml) were heated to 75° under nitrogen in dimethylformamide (3 ml) for 4 hr. The cooled solution was poured into ice cold 3N hydrochloric acid (20 ml) and extracted with ether (2 x 30 ml). The dried (Na_2SO_4) ethereal solution was evaporated to an oil (144) (0.09g, 95%) which was homogeneous on t.l.c. but slowly decomposed on standing.

2-Isopropenyl-8-hydroxybenzo[1,2-b;5,4-b']difuran (145)

The methyl ether (142) (1.0g, 4.4mmole) was heated to 75° under nitrogen together with potassium hydroxide (0.6g, 10.7mmole), ethane thiol (0.66g, 10.7mmole) and water (1.0 ml) in dimethylformamide (30 ml) for 7 hr. The solution was cooled, poured into ice cold 3N
hydrochloric acid (200 ml) and extracted with ether (2 x 200 ml). The combined ether extracts were dried (Na₂SO₄) and evaporated to an oil (145) (0.91g, 97%) which was homogeneous on t.l.c. but slowly decomposed on standing.

**2-Acetyl-5-methylbenzo[1,2-b;5,4-b']difuran-4,8-quinone, conicaquinone (4)**

To a solution of the crude phenol (143) (0.09g, 0.39mmole) in dimethylformamide (3 ml) was added a solution of potassium nitroso disulphonate (0.215g, 0.8mmole) in M/15 potassium dihydrogen phosphate solution (5 ml). The mixture was shaken for 20 min., cooled and filtered. The precipitated solid was dried and recrystallised from benzene/hexane to give the quinone (4) (0.072g, 76%), m.p. 189-190° (lit.⁵ 189-191°), mixed m.p. 189-191°. vmax. 1690, 1680, 1665 cm⁻¹; δ (CDCl₃) 7.53 (q, 1, H₆, J 1 Hz), 7.47 (s, 1, H₃), 2.60 (s, 3, COCH₃), 2.35 (d, 3, CH₃, J 1 Hz); m/e 244 (M⁺, 60%), 229 (100), 43 (20); λmax. 426 nm (log. ε, 3.49), 319 (3.55), 261 (4.38).

**2-Isopropenyl-5-methylbenzo[1,2-b;5,4-b']difuran-4,8-quinone, cyperaquinone (1)**

A solution of potassium nitroso disulphonate (0.215g, 0.8mmole) in M/15 potassium dihydrogen phosphate (5 ml) was added to the crude phenol (144) (0.09g, 0.39mmole) in dimethylformamide (3 ml). The mixture was shaken for 20 min., cooled and the red precipitate collected by filtration. Recrystallisation from benzene/hexane gave the quinone (1) (0.07g, 73%) as bright red needles m.p. 181-182° (lit.³ 5 182-3°), mixed m.p. 181-3°. vmax. 1665 cm⁻¹; λmax. 473 nm (log. ε, 3.49), 347 (3.41), 259 (4.36); δ (CDCl₃) 7.46 (bs, 1, H₆), 6.71 (s, 1, H₃), 5.86 (bs, 1, terminal olefinic proton), 5.30 (bs, 1, terminal olefinic proton), 2.32 (s, 3, H₂C=C(CH₃)⁻), 2.10 (bs, 3, CH₃);
2-Isopropenylbenzo[1,2-b;5,4-b']difuran-4,8-quinone, demethylcyperaquinone (5)

A solution of potassium nitroso disulphonate (2.4g, 9.0mmole) in M/15 potassium dihydrogen phosphate (50 ml) was added to the crude phenol (145) (0.91g, 4.25mmole) in dimethylformamide (30 ml). The mixture was shaken for 20 min., cooled and the precipitate collected by filtration. The dark red solid was recrystallised (twice) from hexane to give the quinone (5) (0.75g, 77%) as maroon needles m.p. 139-141° (lit.3,5 138-140°), mixed m.p. 139-141°. v_max. 1665 cm⁻¹;
λ_max. 467 nm (log. ε, 3.40), 333 (3.50), 256 (4.52); δ (CDCl₃) 7.68 (d, 1, H₅, J 2 Hz), 6.84 (d, 1, H₅, J 2 Hz), 6.72 (s, 1, H₃), 5.85 bs, 1, terminal olefinic proton), 5.29 (bs, 1, terminal olefinic proton), 2.08 (bs, 3, H₂C=O(CH₃)⁻); m/e 228 (M⁺, 100%), 115 (16).

2-(1'-Hydroxyethyl)-8-methoxybenzo[1,2-b;5,4-b']difuran (149)

(a) The ketone (134) (0.23g, 1mmole) in isopropanol (5 ml) was added to a solution of sodium borohydride (0.091g, 0.5mmole) at 0°. The solution was stirred at room temperature for 5 hr, poured into ice water (10 ml), saturated with sodium chloride and extracted with ether (2 x 20 ml). The dried ether extract was evaporated to give the alcohol (149) (0.18g, 72%) after molecular distillation at 90°/0.003 mm. v_max. (liquid film) 3400 cm⁻¹; δ (CDCl₃) 7.55 (d, 1, H₅, J 2 Hz), 7.16 (s, 1, H₄), 6.72 (d, 1, H₅, J 2 Hz), 6.56 (s, 1, H₃), 5.00 (q, 1, -CH(OH)-CH₃, J 6 Hz), 4.32 (s, 3, OCH₃), 2.86 (bs, 1, OH, D₂O exchangeable), 1.60 (d, 3, CH₃, J 6 Hz); m/e 232 (M⁺, 100%), 217 (74), 202 (30), 190 (16), 89 (13), 43 (25).
(b) A solution of diisobutyl aluminium hydride (0.6 ml of a 25% solution in benzene, 1.1 mmole) was added to a solution of the ketone (134) (0.23 g, 1 mmole) in dry toluene (15 ml) at -78° under nitrogen. After 2 hr the reaction was quenched with saturated sodium sulphate solution (20 ml). The organic layer was separated, dried (Na₂SO₄) and evaporated to give the alcohol (149) (0.19 g, 82%) identical to that obtained above in (a).

Reduction of the ketone (133) with hydridoiron complex

A solution of iron pentacarbonyl (0.784 g, 4.0 mmole) and DABCO (0.224 g, 2.0 mmole) in a 98:2 v/v mixture of HMPA and water (2.0 ml) was stirred under nitrogen for 10 min. The ketone (133) (0.23 g, 1.0 mmole) was added and the solution stirred at room temperature for 24 hr. Excess reducing agent was destroyed by addition of an ethereal solution of iodine. The solution was diluted with water (5 ml) and extracted with ether (2 x 20 ml). The ether extract was washed with sodium thiosulphate solution and then with water, dried and evaporated.

Analysis of the residue by t.l.c. showed only starting material (133) to be present.

2,3-Dihydro-8-methoxy-5-methylbenzo[l,2-b;5,4-b']difuran-2-carboxylic acid (147)

To a solution of the acid (139) (3.1 g, 12.6 mmole) and sodium hydroxide (0.51 g, 12.8 mmole) in water (35 ml) was added, over a period of 1 hr, pulverised 5% sodium amalgam (31 g). The mixture was stirred for a further 1.5 hr, and the aqueous layer separated, filtered, acidified with conc. hydrochloric acid and extracted with dichloromethane (2 x 40
The extracts were combined, dried (MgSO₄) and evaporated to give the acid (147) (2.9g, 92%) as colourless needles from aqueous methanol, m.p. 58-60°. v_max. 1710 cm⁻¹; δ (DMSO-d₆) 7.36 (bs, 1, H₆), 6.80 (s, 1, H₄), 5.10 (dd, 1, -CH-CO₂H, J 10.6 Hz), 3.80 (s, 3, OCH₃), 3.3 (m, 2, Ar-CH₂-CH-CO₂H), 1.95 (bs, 3, CH₃).

The acid (147) was treated with an ethereal solution of diazomethane to give the ester (151), which was purified by molecular distillation at 120°/0.05 mm (Found: C, 64.0; H, 5.1. C₁₄H₁₄O₅ requires: C, 64.1; H, 5.4%). v_max. (liquid film) 1740 cm⁻¹; δ (CDCl₃) 7.32 (bs, 1, H₆), 6.92 (s, 1, H₄), 5.30 (dd, 1, -CH-CO₂H, J 10.6 Hz), 4.20 (s, 3, OCH₃), 3.80 (s, 3, CO₂CH₃), 3.5 (m, 2, Ar-CH₂-CH-CO₂H), 2.16 (bs, 3, CH₃); m/e 262 (M⁺, 100%), 230 (24), 215 (12), 203 (46), 202 (15), 187 (19), 175 (27).

**Attempted resolution of (147) via alkaloid salts**

The natural alkaloids brucine, quinine, ephedrine and strychnine were used. The use of brucine typifies the method.

The racemic acid (147) (0.248g, 1mmole) and (-)-brucine (0.394g, 1mmole) were dissolved in hot acetone (10 ml) and the solution allowed to cool. This solution was then divided into several aliquots, each evaporated to an oil and triturated with different solvents (e.g. ether, ethyl acetate, acetone, methanol, ethanol and water). No crystalline salt was obtained but the aqueous solution deposited crystals of (-)-brucine after 2 days.

\[
d-\text{cis-[Co(en)₂(NO₂)₂]-d-(147)}
\]

To a solution of d-cis-dinitrobis(ethylenediamine)cobalt
bromide (1.029 g, 3 mmole) in water (10 ml) at 95-100° was added silver acetate (0.5 g, 3 mmole), and the mixture was shaken for 5 min., and filtered. To the hot filtrate was added a solution of the acid (147) (0.744 g, 3 mmole) and sodium hydroxide (0.125 g, 3.1 mmole) in water (20 ml). The solution was filtered and kept at ca 5° overnight. The yellow $d$-$\sigma$-$[\text{Co(en)$_2$(NO)$_2$}]$-$d$-(147), (0.32 g), $[\alpha]_D + 54^\circ$, was collected by filtration and recrystallised (four times) from water to give the pure salt (0.05 g), $[\alpha]_D + 97^\circ$. The original filtrate from the $d$-$d$-salt was treated with potassium iodide (1 g) and allowed to stand at 5° overnight. The insoluble $d$-$\sigma$-$[\text{Co(en)$_2$(NO)$_2$}]$ iodide was removed by filtration. The filtrate was cooled, acidified with 6N hydrochloric acid and extracted with ether (2 x 20 ml). The ether extract was washed with saturated sodium chloride solution (10 ml), dried and evaporated to give partly resolved (147) (0.35 g), $[\alpha]_D - 24^\circ$.

$l$-$\sigma$-$[\text{Co(en)$_2$(NO)$_2$}]$-$l$-(147)

A solution of $l$-$\sigma$-$d$-dinitrobis(ethylenediamine)cobalt acetate was prepared as above from the corresponding bromide (0.49 g, 1.42 mmole) and silver acetate (0.237 g, 1.42 mmole) in water (5 ml). To this solution was added a solution of the partly resolved acid from above (0.35 g, 1.42 mmole) and sodium hydroxide (0.057 g, 1.42 mmole). Cooling at ca 5° overnight gave the $l$-$l$-salt (0.3 g), $[\alpha]_D - 39^\circ$. Four recrystallisations from water gave the pure salt (0.04 g), $[\alpha]_D - 92^\circ$. 
CHAPTER V

TOTAL SYNTHESIS OF

(±) SCABEQUINONE
The family Cyperaceae is a rich source of novel quinones,\textsuperscript{2,3} the biogenesis of which has been proposed\textsuperscript{1,5} to involve the incorporation of a methylene moiety into a C\textsubscript{13} aromatic precursor to produce compounds containing a 3-methylbenzofuran or a 3-isopropylchroman system (see Chapter I). *Cyperus scaber* (R. Br) Boeck yielded the two 6,7-dihydro-5H-furo[3,2-\textit{g}][1]benzopyran-4,9-quinones\textsuperscript{9}, scabequinone (15) and dihydroscabequinone (16) which possess both the 3-methylbenzofuran unit and the 3-isopropylchroman moiety.\textsuperscript{7}

\begin{align*}
&\textbf{15} \\
&\textbf{16}
\end{align*}

Synthetic routes to benzofurans have been discussed (Chapter I) and there are many methods for the preparation of chroman systems (155). These cyclic ethers are usually formed by the internal alkylation of an ortho-substituted phenol or by Friedel-Crafts type cyclisation of substituted phenyl-C\textsubscript{3} ethers:

\begin{align*}
\text{OH} & \xrightarrow{X} \text{O} \\
& \text{O} \\
& \text{O}
\end{align*}

These and other methods leading to chromans have been adequately reviewed.\textsuperscript{13,16,100}
There were two obvious approaches to the synthesis of scabequinone (15); linear annelation of a furan ring to a preformed chroman system; or cyclisation of the side chain of a suitable benzofuran intermediate to form the pyran ring.

For either approach the problem of ensuring linear alignment of the three-ring system existed.

The dihydrobenzofuran (107), available from the synthesis of cyperaquinone (Chapter III), provided an ideal starting compound for the second type of approach. The first route investigated involved an extension of the condensation reactions of salicylaldehyde derivatives with α-bromo ketones to give 2-acylbenzofurans. It was envisaged that use of β-halogeno ketones in this reaction would lead to 3-acylchromans. Thus the aldehyde (112) prepared earlier (Chapter III) was expected to condense with 4-chlorobutan-2-one to give (156). Only starting material (112) was recovered from this reaction and attempts to condense the corresponding iodo ketone with (112) in refluxing acetone or dimethylformamide were unsuccessful. The failure of this reaction was not surprising in view of the low activity of β-halogeno ketones relative to the corresponding α-halogeno compounds.
The second route investigated comprised initial formation of a 2,3-dihydro-7H-furo[3,2-g][1]benzopyran system (157) and subsequent functionalisation at the 6-position.

Several authors\textsuperscript{101-105} have reported Claisen rearrangement of Aryl prop-2-ynyl ethers to yield chromene derivatives and this type of reaction was thought to provide the simplest approach to the desired chromene system (157).

Alkylation of the phenol (107) with propargyl bromide gave the ether (159) which, when heated in refluxing N,N-diethylaniline for 2 hr, gave a mixture of the chromenes (157) and (160) (fig. 19).

In order to assign the correct structures to these two isomers, the olefins were hydrogenated in ethanol with 10\% palladium on carbon catalyst to give (161) and (162) which were formylated using a,a-dichloromethyl methyl ether and titanium tetrachloride.\textsuperscript{65} The mass spectra of the aldehydes obtained, (163) and (164), were used to determine the alignment of the three rings in each compound.\textsuperscript{62} The 70 ev mass spectrum of (164) showed a fragment ion at \( m/e \) 230 (7\% relative intensity) representing a loss of H\(_2\)O from the molecular ion at \( m/e \) 248 (100\%). At low voltage the rearrangement process under investigation was expected to predominate\textsuperscript{106,107} and the 12 ev spectrum of (164) showed only one fragment ion; \( m/e \) 230 (7\%). This
The ortho-relationship between the formyl and methoxy functions in (164) is more detailed in Figure 19. The more specific chroma-4-ol derivative was therefore the desired intermediate for the synthesis of

In order to functionalize the 6-position of (160), the route described was necessary. It was shown to produce a 2:1 mixture of the isomeric compounds as indicated above. Reaction of the formyl Grignard reagent would be expected to lead to the 6-substituted derivatives (163). Attention to epoxidation either (157) or (160) with epoxides under various conditions gave a solid residue which had E2=0 on several F.T.I.R. systems and appeared to be a polymeric material. Similar results were obtained from attempted peroxide oxidation of (157) and (160).

Kaiser et al. have shown that hydration of the chroma-3-ol side to the chroma-4-ol derivatives was usually trace amounts of the corresponding chroma-3-ols. It was, however, considered worthwhile to attempt hydration of these systems, (157) and (160),

FIG. 19

107 → OMe

159

OMe

161

OMe

162

OMe

163

OMe

164
loss of water from (164) under electron bombardment demonstrated the ortho-relationship between the formyl and methoxyl functions\textsuperscript{62} in (164) (a more detailed explanation of the technique is given in Chapter III). The mass spectrum of (163) showed no peak at $m/e$ 230, thus indicating the linear alignment of the ring system. The chromene (157) was therefore the desired intermediate for the synthesis of scabequinone.

In order to functionalise the 6-position of (157) via the route outlined below it was necessary to epoxidise or hydrate the double bond in the direction shown. Reaction of (165) with Grignard reagents would then be expected to lead to the 6-substituted derivatives (158). Attempts to epoxidise either (157) or (160) with $m$-chloroperbenzoic under various conditions\textsuperscript{108,109} gave a solid residue which had $R_f$=0 on several t.l.c. systems and appeared to be polymeric material. Similar results were obtained from attempted performic acid oxidations\textsuperscript{110} of (157) and (160).

Clark-Lewis et al\textsuperscript{111} have shown that hydroboration/oxidation of chrom-3-enes leads to the chroman-4-ol derivatives with only trace amounts of the corresponding chroman-3-ols. It was, however considered worthwhile to attempt hydroboration of these systems, (157) and (160),
with several of the hindered alkylborane reagents \(^1\text{12,113}\) (diisoamylborane, \(^1\text{114,116}\) diisopinocampheyl-borane \(^1\text{114,115,117}\) and 9-borabicyclo[3,3,1]nonane \(^1\text{118}\) ) developed by Brown and co-workers. Hydroboration of (157) and (160) with these reagents followed by chromic acid oxidation \(^1\text{119}\) of the intermediate alkylboranes gave, in each case, mixtures of at least four products (by t.l.c.) none of which could be obtained in a pure state. The infrared spectra of the crude mixtures showed the absence of carbonyl absorbance in the region of 1720 cm\(^{-1}\) expected from ketones of the type (165). No attempt was made to identify these products.

The third route to the scabequinone system involved the cyclisation of a benzofuran intermediate already substituted with a six carbon side chain progenitor of the 3-isopropylchroman unit.

Isopropyl bromomethyl ketone* was prepared by treatment of isobutyryl chloride with two equivalents of diazomethane followed by reaction of the intermediate diazomethyl ketone with anhydrous hydrogen bromide. \(^1\text{120}\) Condensation of this \(\alpha\)-bromo ketone with (107) gave the ether (166) in high yield. Methyltriphenylphosphorane converted (166) to the allyl ether (167) which underwent a Claisen rearrangement in refluxing N,N-diethylaniline \(^1\text{102,104}\) to give a mixture (ratio ca 1:1) of the isomeric ortho-allyl phenols (168) and (169). A similar mixture of (168) and (169) was obtained by pyrolysis of (167) in a sealed tube at 190\(^\circ\).

\*Roussel \textit{et al} \(^1\text{121}\) have reported a more facile preparation of this \(\alpha\)-bromo ketone by direct bromination of isopropyl methyl ketone.
The 7-bromo derivative (110) (see Chapter III) was used to overcome the formation of isomeric products in the Claisen rearrangement. Condensation of (110) with isopropyl bromomethyl ketone followed by Wittig reaction on (170) gave the required allyl ether (171).

Pyrolysis of (171) in a sealed tube at 150°, 180° and 200° in each case, gave a mixture of products. Analysis of the crude mixtures by t.l.c. and n.m.r. spectroscopy indicated the presence of the desired ortho-allyl phenol (172) together with (168) and (169) (ratio ca 1:2:1) presumably due to a competing debromination reaction. Similar results were obtained by heating (171) in refluxing N,N-diethylaniline and in refluxing decalin. Attempted Claisen rearrangement of (171) in trifluoroacetic acid at 25° was also unsuccessful. Treatment of (171) however, in refluxing N,N-dimethylaniline (redistilled from acetic anhydride to remove any monomethyl impurity) under reflux for 70
min. gave a mixture (by t.l.c.) containing mostly the desired compound (172) which was isolated in 65-75% yield from a small amount of starting material (171) and an unidentified product. The $^1$H n.m.r. spectrum of (172) showed a singlet at $\delta$ 3.20 for the two benzylic protons of the six carbon side chain and a broad signal, $D_2O$ exchangeable, at $\delta$ 5.28 for the phenolic proton. No signals were present downfield of $\delta$ 5.28. The mass spectrum of (172) showed the expected molecular ion at $m/e$ 340/342.

With the benzofuran carrying the required six carbon side chain now available it was necessary to functionalise the terminal position of the olefin (172) and subsequently form the chroman (174) by elimination of HX.

$$\text{Br}$$

$$\text{R}$$

175 $R=H$, $X=OH$
176 $R=Ac$, $X=OH$
177 $R=H$, $X=Br$
178 $R=Ac$, $X=Br$
174 $R=Br$
179 $R=H$

Although free radical anti-Markownikov addition of HX to olefins has been used extensively for the preparation of primary halides, treatment of (172) with anhydrous hydrogen bromide in the presence of benzoyl peroxide initiator gave an intractable residue. The addition of borane to terminal olefins however, provides an efficient and very selective route to primary alcohols or halides. Brown et al have reported the base induced reaction of organoboranes with bromine as a convenient procedure for the anti-Markownikov hydrobromination of olefins. Hydroboration of (173) followed by
in-situ treatment of the intermediate alkylborane with bromine and sodium methoxide, gave a mixture of products (t.l.c.). No pure product could be isolated from several attempts.

Hydroboration of the acetate (173) followed by alkaline peroxide oxidation\textsuperscript{126} gave a mixture of the primary alcohols (175) and (176) (ratio ca 2:1). These hydroxy compounds were converted to the primary bromides (177) and (178) respectively by reaction with tri-n-octylphosphine and carbon tetrabromide.\textsuperscript{127} The phenolic compound (172) was hydroborated in the presence of excess borane and subsequent oxidation with alkaline peroxide\textsuperscript{126} gave the primary alcohol (175) in 80\% yield. Treatment of either (177) or (178) with warm aqueous methanolic potassium hydroxide solution gave the desired chroman (174) in good yield. Extending the reaction time for the bromination of (175) also led to the formation of the chroman (174) as the only product.

The bromine atom introduced as a blocking group was quantitatively removed from (174) to give (179) by hydrogenolysis in ethanol with 10\% palladium on carbon catalyst. The \textsuperscript{1}H n.m.r. spectrum of (179) showed a singlet at $\delta 6.06$ for the aromatic proton.

The \textsuperscript{1}H n.m.r. spectrum of the alcohol (175) (fig. 20) showed splitting patterns for the benzylic protons of the side chain, similar to those observed for the protons on C\textsubscript{5} of scabequinone\textsuperscript{7} (fig. 21). The spectrum of the cyclised compound (179) (fig. 20) showed one of the C\textsubscript{7} protons as a pair of triplets at $\delta 4.50$ and 4.38 while the signal due to the other proton was obscured in the region $\delta 3.8$ (cf: spectrum of (15), fig. 21).

In earlier syntheses (Chapters III and IV) DDQ\textsuperscript{66} proved the
FIG. 20

$^1$H n.m.r. spectra (CDCl$_3$)
reagent of choice for the dehydrogenation of 2,3-dihydrobenzofuran systems. This reagent was however, ineffectual in promoting the dehydrogenation of (179). Attempted benzylic bromination/dehydrobromination was also unsuccessful in introducing the furan double bond since reaction of (179) with N-bromosuccinimide in carbon tetrachloride gave an almost quantitative yield of the aromatic bromo-compound (174). Starting material (179) was recovered almost quantitatively from attempted dehydrogenation with 10% palladium on carbon catalyst in refluxing xylene. When diphenyl ether was used as solvent for this reaction, the desired benzofuran (180) was isolated in 58% yield. The \( ^1H \) n.m.r. spectrum of (180) (fig. 21) showed signals characteristic of the 3-isopropylchroman system (see experimental and fig. 21) and a broad singlet at \( \delta 7.12 \) for \( H_2 \).

![Chemical structure](image)

Demethylation of (180) with potassium thioethoxide in dimethylformamide at 80° was complete after 12 hr. The phenol (181) was unstable at room temperature and in chloroform solution and was therefore oxidised immediately with Fremy's reagent.\(^{20}\) The quinone (15) [obtained in 78% yield from (180)] was identical to natural scabequinone\(^{5,7}\) in all respects (m.p., mixed m.p., i.r., u.v., n.m.r. and mass spectra) except optical rotation.

The crude phenol (181) was esterified with \( d-10 \)-camphorsulphonyl chloride to give the diastereomeric esters (182) as a viscous oil.
$^1$H n.m.r. spectra (CDCl$_3$)
which could not be induced to crystallise. Attempts to separate the
diastereoisomers (182) by g.l.c. and preparative t.l.c. were unsuccessful
thus preventing preparation of optically active (+)-scabequinone.

Natural (+)-scabequinone, $[\alpha]_D^o + 166^\circ$, was hydrogenated in
ethanol over 10% palladium on carbon catalyst to give the dihydroquinol
(183). Aerial oxidation of crude (183) gave a mixture of diastereomeric
quinones (16) with $[\alpha]_D^o + 142^\circ$. The red solid (16) was recrystallised

$$\text{183}$$

(4 times) from hexane to give a crop of large needles (ca 5-10 mm long)
together with a minor amount of small prisms. The needles were hand
separated and recrystallised from hexane (3 times) to give
dihydrosclavequinone $^5$ $[\alpha]_D^o + 42^\circ$, identical* to the natural product in
all respects.

* Allan $^5$ has reported natural dihydrosclavolin to have $[\alpha]_D^o + 64^\circ$,
however measurements carried out in these laboratories on a sample
of the natural product consistently gave a value of $[\alpha]_D^o + 41^\circ$. 

\begin{align*}
\text{16 & OH} \\
\text{O & OH}
\end{align*}

\begin{align*}
\text{183 & OH} \\
\text{O & OH}
\end{align*}
EXPERIMENTAL

General experimental notes are given in Chapter II, experimental section.

Optical rotations were measured on a Perkin Elmer P22 spectropolarimeter.

2,3-Dihydro-4-methoxy-3-methyl-6-(prop-2-ynyloxy) benzofuran (159)

The phenol (107) (18.0g, 100mmole) and redistilled propargyl bromide (13.1g, 110mmole) together with anhydrous potassium carbonate (20g) were stirred in refluxing acetone (360 ml) for 10 hr. The cooled solution was filtered and evaporated under reduced pressure. The residue was recrystallised from methanol to give the ether (159) (18.5g, 85%) m.p. 58-9°. $\nu_{\text{max.}}$ 3300, 2120 cm$^{-1}$; $\delta$ (CDCl$_3$) 6.06 (m, 2, H$_5$,7), 4.60 (s, 2, OCH$_2$C=CH), 4.58 (t, 1, dihydrofuran $\alpha$-proton, $J$ 8 Hz), 4.10 (dd, 1, dihydrofuran $\alpha$-proton, $J$ 8,4 Hz), 3.76 (s, 3, OCH$_3$), 3.5 (m, 1, dihydrofuran $\beta$-proton), 2.49 (t, 1, -C=CH, $J$ 2 Hz), 1.27 (d, 3, CH$_3$, $J$ 7 Hz); $m/e$ 218 ($M^+$, 82%), 217 (25), 203 (100), 190 (30), 187 (20), 175 (60).

The chromenes (157) and (160)

The ether (159) (4.0g, 18.4mmole) was heated in refluxing N,N-diethylaniline (80 ml) for 2 hr. The cooled solution was poured into ice cold 20% sulphuric acid solution (500 ml) and extracted with ether (2 x 250 ml). The ether extracts were combined, washed with water, dried (MgSO$_4$) and evaporated under reduced pressure. The residual oil was chromatographed on 4 preparative t.l.c. plates (silica, 1 m x 20 cm; benzene). Separation of the higher Rf bands gave the
chromene (160) (1.8 g, 45%) as a viscous oil; \( \text{vmax. } 1630 \text{ cm}^{-1} \); 6 (CDCl\(_3\)) 6.60 (sextet, 1, olefinic proton, \( J 10.1 \text{ Hz} \)), 6.04 (s, 1, aromatic proton), 5.64 (sextet, 1, olefinic proton, \( J 10.4 \text{ Hz} \)), 4.79 (m, 2, chromene \( \alpha \)-protons), 4.68 (t, 1, dihydrofuran \( \alpha \)-proton, \( J 8 \text{ Hz} \)), 4.18 (dd, 1, dihydrofuran \( \alpha \)-proton, \( J 8.4 \text{ Hz} \)), 3.80 (s, 3, OCH\(_3\)), 3.55 (m, 1, dihydrofuran \( \beta \)-proton), 1.28 (d, 3, CH\(_3\), \( J 7 \text{ Hz} \)); \( m/e \) 218 (\( M^+ \), 90%), 217 (50), 203 (100), 187 (10), 175 (25).

Separation of the lower Rf bands gave the chromene (157) (1.7 g, 43%) as a viscous oil \( \text{vmax. } 1625 \text{ cm}^{-1} \); 6 (CDCl\(_3\)) 6.74 (sextet, 1, olefinic proton, \( J 10.1 \text{ Hz} \)), 6.18 (s, 1, aromatic proton), 5.68 (sextet, 1, olefinic proton, \( J 10.4 \text{ Hz} \)), 4.76 (m, 2, chromene \( \alpha \)-protons), 4.66 (t, 1, dihydrofuran \( \alpha \)-proton, \( J 8 \text{ Hz} \)), 4.14 (dd, 1, dihydrofuran \( \alpha \)-proton, \( J 8.4 \text{ Hz} \)), 3.86 (s, 3, OCH\(_3\)), 3.60 (m, 1, dihydrofuran \( \beta \)-proton), 1.32 (d, 3, CH\(_3\), \( J 7 \text{ Hz} \)); mass spectrum identical to that of (160).

The aldehyde (163)

The chromene (157) (1.1 g, 5 mmole) was hydrogenated in ethanol (30 ml) over 10% palladium on carbon catalyst (0.2 g) under 1 atm. of hydrogen for 2 hr. The mixture was filtered through a celite pad and evaporated to give the chroman (161) (1.1 g, ca 100%) as a clear oil; \( m/e \) 220 (\( M^+ \), 40%), 205 (100), 177 (34).

Titanium tetrachloride (1.14 g, 6 mmole) in dichloromethane (10 ml) was added to a solution of the chroman (161) (1.1 g, 5 mmole) and \( \alpha,\alpha \)-dichloromethyl methyl ether (0.7 g, 6 mmole) in dichloromethane (10 ml) at 0° under nitrogen. The solution was stirred at this temperature for 30 min. and then at 25° for 1 hr. The mixture was washed with water (2 x 20 ml), dried (MgSO\(_4\)) and evaporated to give the aldehyde (163) as a viscous oil (1.0 g, 81%). \( \text{vmax. } 1670 \text{ cm}^{-1} \); \( m/e \) 248 (\( M^+ \), 68%), 233 (100), 205 (27), 177 (42).
The aldehyde (164)

The chromene (160) (1.1g, 5mmole) was hydrogenated as described above for the preparation of (161) to give the chroman (162) (1.1g, ca 100%) as a colourless solid from methanol; m.p. 72-4°; m/e 220 (M⁺, 33%), 205 (100), 177 (35).

Formylation of (162) (1.1g, 5mmole) using the method described for the preparation of (163) gave the aldehyde (164) (0.95g, 77%), as pale yellow needles from n-hexane, m.p. 101-2°. v_max. 1670 cm⁻¹; m/e (70 ev) 248 (M⁺, 100%), 247 (15), 234 (12), 233 (79), 231 (15), 230 (7), 219 (20), 215 (19), 205 (35), 202 (65), 177 (52); m/e (12 ev) 248 (M⁺, 100%), 230 (7).

Isopropyl bromomethyl ketone

The bromo-ketone was prepared by the method of Catch et al. in 45% yield; bp 87°/50mm (lit. 86°/50mm).

The ketone (166)

The phenol (107) (1.8g, 10mmole), isopropyl bromomethyl ketone (2.0g, 12mmole) and anhydrous potassium carbonate (3g) were stirred in refluxing acetone (40 ml) for 12 hr. The cooled solution was filtered and evaporated under reduced pressure. The residue was purified by molecular distillation at 95°/0.005 mm. to give the ketone (166) (2.19g, 83%) (Found: C, 68.3; H, 7.5. C₁₅H₂₀O₄ requires: C, 68.2; H, 7.6%). v_max. 1710 cm⁻¹; δ (CDCl₃) 6.10 (d, 1, H₅ or H₇, J 2 Hz), 6.00 (d, 1, H₇ or H₅, J 2 Hz), 4.62 (s, 2, OCH₂CO), 4.60 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.14 (dd, 1, dihydrofuran α-proton, J 8,4 Hz), 3.82 (s, 3, OCH₃), 3.50 (m, 1, dihydrofuran δ-proton), 2.94 (seven line multiplet, 1,
-CH(CH$_3$)$_2$, 1.30 (d, 3, dihydrofuran β-CH$_3$, $J$ 7 Hz), 1.14 (d, 6, -CH(CH$_3$)$_2$, $J$ 6 Hz).

The olefin (167)

The ketone (166) (1.32g, 5mmole) in tetrahydrofuran (12) and dimethylformamide (6) was added to a solution of methyltriphenylphosphorane (prepared from methyltriphenylphosphonium iodide (6.05g, 15mmole) and sodium methoxide (0.8g, 15mmole) in tetrahydrofuran (30 ml) and dimethylformamide (15 ml)) at 40° under nitrogen. The solution was stirred at 40-45° for 2 hr, poured into cold water 250 ml) and extracted with n-hexane (2 x 150 ml). The hexane extracts were dried (MgSO$_4$) and filtered through a small plug of alumina (grade II). The eluate afforded the olefin (167) (1.25g, 95%) as a viscous oil, purified by molecular distillation at 80°/0.002 mm (Found: C, 73.5; H, 8.6. C$_{16}$H$_{22}$O$_3$ requires: C, 73.3; H, 8.5%). δ (CDCl$_3$) 6.12 (s, 2, HS,7), 5.20 (bs, 1, terminal olefinic proton), 5.08 (bs, 1, terminal olefinic proton), 4.70 (t, 1, dihydrobenzofuran α-proton, $J$ 8 Hz), 4.53 (s, 2, Ar-OC=CH$_2$), 4.19 (dd, 1, dihydrofuran α-proton, $J$ 8,4 Hz), 3.84 (s, 3, OCH$_3$), 3.60 (m, 1, dihydrofuran β-proton), 2.50 (m, 1, -CH(CH$_3$)$_2$), 1.34 (d, 3, dihydrofuran β-CH$_3$, $J$ 7 Hz), 1.16 (d, 6, -CH(CH$_3$)$_2$, $J$ 6 Hz).

The phenols (168) and (169)

The allyl ether (167) (1.0g, 3.8mmole) was heated in refluxing N,N-diethylaniline (20 ml) for 8 hr. The cooled solution was poured into ice cold 20% sulphuric acid solution (100 ml) and extracted with ether (2 x 80 ml). The ether extract was dried and evaporated to an oil. Chromatography on silica (one 1 m x 20 cm plate) with benzene/chloroform/methanol, 10:5:1, gave the phenol (168) (0.35g, 35%) as a viscous oil (Found: C, 73.2; H, 8.5. C$_{16}$H$_{22}$O$_3$ requires: C, 73.3;
H, 8.5%); $\nu_{\text{max}}$ 3450 cm$^{-1}$; $\delta$ (CDCl$_3$) 6.12 (s, 1, H$_7$), 5.34 (bs, 1, OH, D$_2$O exchangeable), 4.88 (bs, 1, terminal olefinic proton), 4.68 (bs, 1, terminal olefinic proton), 4.64 (t, 1, dihydrofuran $\alpha$-proton, $J$ 8 Hz), 4.10 (dd, 1, dihydrofuran $\alpha$-proton, $J$ 8.4 Hz), 3.76 (s, 3, OCH$_3$), 3.60 (m, 1, dihydrofuran $\beta$-proton), 3.40 (s, 2, side chain benzylic protons), 2.37 (m, 1, $-\text{CH}(\text{CH}_3)_2$), 1.36 (d, 3, dihydrofuran $\beta$-CH$_3$, $J$ 7 Hz), 1.16 (d, 6, $-\text{CH}(\text{CH}_3)_2$, $J$ 6 Hz); and the phenol (169) (0.4 g, 40%) as a viscous oil (Found: C, 73.3; H, 8.6. C$_{16}$H$_{22}$O$_3$ requires: C, 73.3; H, 8.5%); $\nu_{\text{max}}$ 3450 cm$^{-1}$; $\delta$ (CDCl$_3$) 6.00 (s, 1, H$_5$), 5.40 (bs, 1, OH, D$_2$O exchangeable), 4.92 (bs, 1, terminal olefinic proton), 4.84 (bs, 1, terminal olefinic proton), 4.60 (t, 1, dihydrofuran $\alpha$-proton, $J$ 8 Hz), 4.12 (dd, 1, dihydrofuran $\alpha$-proton, $J$ 8.4 Hz), 3.76 (s, 3, OCH$_3$), 3.53 (m, 1, dihydrofuran $\beta$-proton), 3.40 (s, 2, side chain benzylic protons), 2.30 (m, 1, $-\text{CH}(\text{CH}_3)_2$), 1.30 (d, 3, dihydrofuran $\beta$-CH$_3$, $J$ 7 Hz), 1.10 (d, 6, $-\text{CH}(\text{CH}_3)_2$, $J$ 6 Hz).

7-Bromo-2,3-dihydro-4-methoxy-3-methyl-6-(3'-methyl-2'-oxobuty1)benzofuran (170)

The phenol (110) (13.0 g, 55 mmole), isopropyl bromomethyl ketone (9.1 g, 55 mmole) and anhydrous potassium carbonate (20 g) were stirred in refluxing acetone (250 ml) for 12 hr. The cooled solution was filtered and evaporated under reduced pressure. Recrystallisation of the residue from methanol gave the ketone (170) (15.8 g, 92%) as colourless needles m.p. 79-80° (Found: C, 52.6; H, 5.9; Br, 22.6. C$_{15}$H$_{19}$BrO$_4$ requires: C, 52.5; H, 5.6; Br, 23.3%). $\nu_{\text{max}}$ 1710 cm$^{-1}$; $\delta$ (CDCl$_3$) 6.04 (s, 1, H$_5$), 4.84 (t, 1, dihydrofuran $\alpha$-proton, $J$ 8 Hz), 4.69 (s, 2, OCH$_2$CO), 4.32 (dd, 1, dihydrofuran $\alpha$-proton, $J$ 8.4 Hz), 3.84 (s, 3, OCH$_3$), 3.7 (m, 1, dihydrofuran $\beta$-proton), 3.24 (m, 1, $-\text{CH}(\text{CH}_3)_2$, $J$ 6 Hz), 1.32 (d, 3, dihydrofuran $\beta$-CH$_3$, $J$ 7 Hz), 1.20 (d, 6, CH(CH$_3$)$_2$,
$J$ 6 Hz); $m/e$ 344 ($M^+$, 96%), 342 ($M^+$, 96%), 329 (100), 327 (100), 301 (3), 299 (3), 273 (13), 271 (13).

7-Bromo-2,3-dihydro-6-(2'-isopropylallyl)-4-methoxy-3-methylbenzofuran (171)

The ketone (170) (13.0 g, 38 mmole) in tetrahydrofuran (130 ml) and dimethylformamide (65 ml) was added to a solution of methyltriphenylphosphorane (prepared from methyltriphenylphosphonium iodide (40.4 g, 100 mmole) and sodium methoxide (5.4 g, 100 mmole) in tetrahydrofuran (200 ml) and dimethylformamide (100 ml)) at 40° under nitrogen. The solution was stirred at 40-45° for 3 hr, poured into cold water (2.5 l) and extracted with $n$-hexane (3 x 1 l). The extracts were dried (MgSO$_4$), filtered through a small plug of alumina (grade II) and evaporated. The residue was purified by molecular distillation at 120°/0.003 mm to give the allyl ether (171) (12.0 g, 93%) as a clear viscous liquid (Found: C, 57.0; H, 6.3; Br, 23.3.

C$_{16}$H$_{21}$BrO$_3$ requires: C, 56.4; H, 6.2; Br, 23.4%). 6 (CDCl$_3$) 5.92 (s, 1, H$_5$), 5.13 (bs, 1, terminal olefinic proton), 4.98 (bs, 1, terminal olefinic proton), 4.64 (t, 1, dihydrofuran $\alpha$-proton, $J$ 8 Hz), 4.48 (s, 2, OCH$_2$-C=CH$_2$), 4.11 (dd, 1, dihydrofuran $\alpha$-proton, $J$ 8.4 Hz), 3.76 (s, 3, OCH$_3$), 3.60 (m, 1, dihydrofuran $\beta$-proton), 2.50 (m, 1, -CH(CH$_3$)$_2$), 1.28 (d, 3, dihydrofuran $\beta$-CH$_3$, $J$ 7 Hz), 1.16 (d, 6, -CH(CH$_3$)$_2$, $J$ 6 Hz); $m/e$ 342 ($M^+$, 80%), 340 ($M^+$, 80%), 327 (40), 325 (40), 314 (4), 312 (4), 299 (11), 297 (11), 273 (8), 272 (5), 271 (8), 270 (5), 261 (90), 193 (100).
7-Bromo-2,3-dihydro-6-hydroxy-5-(2'isopropylallyl)-4-methoxy-3-methylbenzofuran (172)

The allyl ether (171) (4.0g, 11.7mmole) was heated in redistilled N,N-dimethylaniline (80 ml) under reflux for 70 min. The solution was cooled (ice) and poured into ice cold 20% sulphuric acid solution (300 ml) and extracted with ether (2 x 100 ml). The ether extract was extracted with 1N sodium hydroxide solution (5 x 50 ml). The combined alkaline extract was washed with ether (10 ml), acidified at 0-5° with conc. hydrochloric acid and extracted with ether (3 x 50 ml). Evaporation of the dried (MgSO₄) ethereal solution and molecular distillation at 110°/0.003 mm gave the phenol (172) (2.8g, 70%) as a clear viscous oil (Found: C, 56.7; H, 6.4; Br, 23.2. C₁₆H₂₁BrO₃ requires: C, 56.3; H, 6.2; Br, 23.4%). vmax. 3500 cm⁻¹; δ (CDCl₃) 5.32 (bs, 1, OH, D₂O exchangeable), 4.66 (bs, 1, terminal olefinic proton), 4.64 (t, 1, dihydrobenzofuran α-proton, J 8 Hz), 4.32 (bs, 1, terminal olefinic proton), 4.12 (dd, 1, dihydrofuran α-proton, J 8,4 Hz), 3.68 (s, 3, OCH₃), 3.64 (m, 1, dihydrofuran β-proton), 3.26 (s, 3, side chain benzylic protons), 2.32 (m, 1, -C≡(CH₃)₂), 1.32 (d, 3, dihydrofuran β-CH₃, J 7 Hz), 1.10 (d, 6, -CH(CH₃)₂, J 6 Hz); m/e 342 (M⁺, 98%), 340 (M⁺, 100), 327 (80), 325 (81), 299 (29), 297 (30), 273 (51), 271 (53).

Treatment of (172) with acetic anhydride in pyridine in the normal manner gave the acetate (173), in 90% yield, as colourless prisms from methanol, m.p. 84-5° (Found: C, 57.0; H, 6.1; Br, 19.9. C₁₆H₂₃BrO₄ requires: C, 56.4; H, 6.1; Br, 20.8%). vmax. 1760 cm⁻¹; δ (CDCl₃) 4.68 (bs, 1, terminal olefinic proton), 4.64 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.34 (bs, 1, terminal olefinic proton), 4.14 (dd, 1, dihydrofuran α-proton, J 8,4 Hz), 3.72 (m, 1, dihydrofuran β-proton), 3.70 (s, 3, OCH₃), 3.16 (s, 2, side chain benzylic protons),
2.20 (m, 1, -CH(CH₃)₂), 2.16 (s, 3, OCOCH₃), 1.36 (d, 3, dihydrofuran β-CH₃, J 7 Hz), 1.08 (d, 6, -CH(CH₃)₂, J 6 Hz); m/e 384 (M⁺, 45%), 382 (M⁺, 46%), 342 (92), 340 (100), 327 (50), 325 (50), 304 (20), 299 (20), 297 (20).

The alcohols (175) and (176)

(a) The acetate (173) (5.6g, 14.6mmole) was dissolved in dry tetrahydrofuran (50 ml) and a 1.2M solution of diborane in tetrahydrofuran (12.5 ml, 15mmole) added at 0° under nitrogen. After 1.5 hr, excess diborane was destroyed with water (2 ml) and a 30% solution of hydrogen peroxide (16.7 ml, 14.7mmole) was added together with sufficient 1N sodium hydroxide solution to maintain a pH of ca 8. The solvent was removed under vacuum and the residue diluted with water (50 ml) and acidified with 2N hydrochloric acid solution. The mixture was extracted with ether (2 x 100 ml) and the dried (MgSO₄) extracts evaporated under reduced pressure. The residue was chromatographed on silica (150g) with benzene/ether (20:1). The first band eluted gave the acetate (176) (1.46, 25%) as a viscous oil, v max. 3450-3250, 1760 cm⁻¹. ¹H n.m.r. spectrum identical to that of (175) plus a 3 proton singlet at δ 2.40 for OCOCH₃. Later fractions gave the alcohol (175) (2.8g, 54%) as a clear glass after molecular distillation at 110°/0.001 mm (Found: C, 53.6; H, 6.2. C₁₆H₂₃BrO₄ requires: C, 53.5, H, 6.5%). v max. 3200-3400 cm⁻¹; δ (CDCl₃) 4.70 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.20 (dd, 1, dihydrofuran α-proton, J 8.4 Hz), 3.82 (s, 3, OCH₃), 3.66-3.8 (m, 1, dihydrofuran β-proton), 3.32-3.62 (m, 2, -CH₂OH), 2.70-2.98 (octet, 1, side chain benzylic proton), 2.50 (dd, 1, side chain benzylic proton, J 14,10 Hz), 1.82 (m, 2, -CH(CH₃)₂ and -CHCH(CH₃)₂), 1.33 (d, 3, dihydrofuran β-CH₃, J
The alcohol (175) (4.2g, 80%) identical to that obtained above.

The primary bromide (178)

The alcohol (176) (0.2g, 0.43mmole) and carbon tetrabromide (0.43g, 1.3mmole) were dissolved in ether (5 ml). Tri-n-octylphosphine oxide (0.48g, 1.3mmole) was added dropwise and the mixture stirred at room temperature for 8 hr. The solution was poured into water (30 ml) and extracted with pentane (2 x 30 ml). Evaporation of the dried (MgSO$_4$) extract gave the primary bromide (178) (0.2g, 86%) as a viscous oil; v$_{\text{max.}}$ 1760 cm$^{-1}$; $^1$H n.m.r. spectrum - identical to that of (178) (see below) plus a 3 proton singlet at $\delta$ 2.42; m/e 466 ($M^+$, 5%), 464 ($M^+$, 9%), 462 ($M^+$, 5%), 424 (15), 422 (28), 420 (15), 273 (100), 271 (100).

The primary bromide (177)

Using the method described above for the preparation of (178), the alcohol (175) (0.4g, 1.1mmole) gave the bromide (177) (0.42g, 90%) as a viscous oil; v$_{\text{max.}}$ 3400 cm$^{-1}$; $\delta$ (CDCl$_3$), 4.85 (t, 1, dihydrofuran $\alpha$-proton, $J$ 8 Hz), 4.35 (dd, 1, dihydrofuran $\alpha$-proton, $J$ 8, 4 Hz), 3.92 (s, 3, OCH$_3$), 3.82 (m, 1, dihydrofuran $\beta$-proton), 3.46 (d, 2, CH$_2$Br, $J$ 4 Hz), 2.6 (m, 2, side chain benzylic protons), 1.80 (m, 2, $-CH(\text{CH}_3)_2$), 1.32 (d, 3, dihydrofuran $\beta$-CH$_3$, $J$ 7 Hz), 1.00 (d, 6, $-CH(\text{CH}_3)_2$, $J$ 6 Hz); m/e 424 ($M^+$, 30%), 422 ($M^+$, 55%), 420 ($M^+$, 30%), 273 (100), 271 (100).
9-Bromo-6-isopropyl-4-methoxy-3-methyl-2,3,6,7-tetrahydro-5H-furo[3,2-g][1]benzopyran (174)

(a) The acetate (178) (0.2g, 0.43mmole) was heated to 50-60° in a mixture of 1N sodium hydroxide solution (5 ml) and methanol (2 ml) for 4 hr. The cooled solution was diluted with water (10 ml) and extracted with ether (2 x 10 ml). The dried (MgSO₄) extract was evaporated to give the chroman (174) (0.13g, 88%) as a colourless viscous liquid after molecular distillation at 110°/0.03 mm (Found: C, 56.7; H, 6.1; Br, 22.7. C₁₆H₂₁BrO₃ requires: C, 56.3; H, 6.2; Br, 23.4%). δ (CDCl₃) 4.70 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.44 (sextet, 1, dihydropyran α-proton, J 10,2 Hz), 4.20 (dd, 1, dihydrofuran α-proton, J 8,4 Hz), 3.84 (s, 3, OCH₃), 3.78 (m, partly obscured, 2, dihydrofuran β-proton and chroman α-proton), 2.80 (m, 1, chroman γ-proton), 2.30 (dd, 1, chroman γ-proton, J 18,10 Hz), 1.62 (m, 2, -CH-CH(CH₃)₂), 1.34 (d, 3, dihydrofuran β-CH₃, J 7 Hz), 1.00 (d, 6, CH(CH₃)₂, J 6 Hz); m/e 342 (M⁺, 96%), 340 (M⁺, 100%), 327 (87), 325 (90), 273 (10), 272 (15), 271 (15), 270 (15), 247 (31), 246 (58).

(b) Treatment of the phenol (177) with aqueous-methanolic sodium hydroxide solution as described in (a) above gave the chroman (174) in 94% yield.

(c) The alcohol (175) (4.0g, 11mmole) was treated with carbon tetrabromide (11.6g, 35mmole) and tri-n-octylphosphine (13.0g, 35mmole) as described for the preparation of (177). The mixture was stirred at room temperature for 24 hr, poured into cold water (200 ml) and extracted as before. The chroman (174) (3.0g, 80%), obtained by chromatography on silica with benzene
was identical to that obtained above.

(d) The chroman (179) (0.13g, 0.5mmole) and recrystallised
N-bromosuccinimide (0.1g, 0.55mmole) were stirred in
refluxing carbon tetrachloride (5 ml) for 10 hr. The cooled
solution was filtered through a small plug of alumina (grade
II) and the eluate evaporated under reduced pressure to give
the chroman (175) (0.165g, 98%) identical to that obtained
above.

6-Isopropyl-4-methoxy-3-methyl-2,3,6,7-tetrahydro-5H-
furo[3,2-g][1]benzopyran (179)

The bromo-derivative (174) (2.5g, 7.3mmole) was dissolved in
ethanol (60 ml) and shaken with 10% palladium on carbon catalyst
(0.5g) under 1 atm. of hydrogen for 12 hr. The solution was filtered
through a celite pad and the filtrate evaporated to give the
chroman (179) (1.8g, 94%) as a viscous, colourless liquid after
molecular distillation at 105°/0.005 mm (Found: C, 73.2; H, 8.5.
C_{16}H_{22}O_{3} requires: C, 73.3; H, 8.5%). δ (CDCl_{3}) 6.06 (s, 1, H_{3}),
4.56 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.22 (sextet, 1,
dihydrofuran α-proton, J 10,2 Hz), 4.05 (dd, 1, dihydrofuran α-proton,
J 8,4 Hz), 3.84 (s, 3, OCH_{3}), 3.45-3.80 (m, 2, dihydrofuran β-proton
and chroman α-proton), 2.62-2.96 (m, 1, chroman γ-proton), 2.28 (dd,
1, chroman γ-proton, J 18,10 Hz), 1.62 (m, 2, -CH-CH(CH_{3})_{2}), 1.31
(d, 3, dihydrofuran β-CH_{3}, J 7 Hz), 1.01 (d, 6, -CH(CH_{3})_{2}, J 6 Hz);
m/e 262 (M^{+}, 55%), 248 (17) 247 (100), 219 (4), 193 (4), 192 (9),
177 (30).
6,7-Dihydro-6-isopropyl-4-methoxy-3-methyl-5H-furo[3,2-g][1]benzopyran (180)

The chroman (179) (0.8g, 3mmole) and 10% palladium on carbon catalyst (0.4g) were stirred in refluxing diphenyl ether (4 ml) for 5 hr. The cooled solution was diluted with pentane (20 ml) and filtered through a small plug of alumina (grade II). The pentane eluate was discarded and elution with benzene afforded the benzofuran (180) (0.47g, 58%) after molecular distillation at 110°/0.005 mm (Found: C, 73.7; H, 7.6. C_{16}H_{20}O_{3} requires: C, 73.8; H, 7.7%).

δ (CDCl₃) 7.11 (bs, 1, H₂), 6.68 (s, 1, H₉), 4.24 (sextet, 1, chroman α-proton, J 10,2 Hz), 3.82 (s, 3, OCH₃), 3.75 (t, 1, chroman α-proton, J 10 Hz), 2.96 (octet, 1, chroman γ-proton, J 18,4,2 Hz), 2.48 (dd, 1, chroman γ-proton, J 18,10 Hz), 2.31 (bs, 3, furan - CH₃), 1.62 (m, 2, -CH-CH(CH₃)₂), 1.02 (d, 6, -CH(CH₃)₂, J 6 Hz); m/e 260 (M⁺, 100%), 191 (16), 190 (19), 175 (5).

6,7-Dihydro-4-hydroxy-6-isopropyl-3-methyl-5H-furo[3,2-g][1]benzopyran (181)

The methyl ether (180)(0.2g, 0.77mmole) was heated to 80° under nitrogen together with potassium hydroxide (0.11g, 2.0mmole) and ethane thiol (0.12g, 2.0mmole) in dimethylformamide (6 ml) and water (0.2 ml) for 12 hr. The cooled solution was poured into ice cold 3N hydrochloric acid solution (40 ml) and extracted with ether (2 x 30 ml). The ether extract was dried (Na₂SO₄) and evaporated under reduced pressure to give the phenol (181) (0.17g, 91%) as a pale yellow oil which was homogeneous on t.l.c. but slowly decomposed on standing.
6,7-Dihydro-6-isopropyl-3-methyl-5H-furo[3,2-g][1]benzopyran-4,9-quinone (15); scabequinone

A solution of potassium nitroso disulphonate (0.37g, 1.4mmole) in M/15 potassium dihydrogenphosphate solution (7 ml) was added to the crude phenol (181) (0.17g, 0.65mmole) in dimethylformamide (4 ml). The mixture was shaken for 20 min, cooled and the orange precipitate collected by filtration. Recrystallisation from benzene/hexane gave (+) scabequinone (15) (0.15g, 85%) as yellow needles m.p. 116-118°, mixed m.p. 118-120° (lit.7 119-20°). vmax. 1695, 1645, 1605 and 1580 cm⁻¹; δ (CDCl₃) 7.44 (q, 1, H₂, J 1 Hz), 4.48 (sextet, 1, chroman α-proton, J 10,2 Hz), 3.80 (t, 1, chroman α-proton, J 10 Hz), 2.70 (octet, 1, chroman γ-proton, J 18,4,2 Hz), 2.30 (d, 3, furan β-CH₃, J 1 Hz), 2.14 (dd, 1, chroman γ-proton, J 18,10 Hz), 1.66 (m, 2, -CH-CH(CH₃)₂), 1.04 (d, 6, -CH(CH₃)₂, J 6 Hz); λmax. 435 nm (log ε, 2.81), 325 (3.84), 270 (3.98), 222 (4.30); m/e 260 (M⁺, 100%), 245 (35), 217 (87); [α]D 0.0°.

The quinol (183)

Scabequinone (15) (0.5g), [α]D +166°, and 10% palladium on carbon catalyst (0.2g) were stirred in ethanol (35 ml) under 1 atm. of hydrogen for 3 hr. The solution was filtered through a celite pad and evaporated to give the quinol (183) (0.5g, ca 100%) as a yellow oil.

Dihydroscebequinone (15)

The quinol (183) (0.5g) was dissolved in chloroform (100 ml) and air bubbled through for 2 days. The orange solution was evaporated to give a red solid (0.5g, ca 100%), [α]D +142°. This solid was
recrystallised (3 times) from n-hexane to give long needles of the red quinone (0.26g). The larger needles (ca 5-10 mm in length) were separated with the aid of tweezers and recrystallised (3 times) from n-hexane to give dihydroscaebquinone (15) (0.1g, 20%) as red needles m.p. 140-141° (lit. 5 140-141°) mixed m.p. 140-141°. vmax. 1675, 1650 cm⁻¹; [α]D + 42°; δ (CDCl₃) 4.76 (t, 1, dihydrofuran α-proton, J 8 Hz), 4.41 (sextet, 1, chroman α-proton, J 10,2 Hz), 4.24 (dd, 1, dihydrofuran α-proton, J 8,4 Hz), 3.72 (t, 1, chroman β-proton), 3.5 (m, 1, dihydrofuran β-proton), 2.60 (octet, 1, chroman γ-proton, J 18,4,2 Hz), 2.06 (dd, 1, chroman γ-proton, J 18,10 Hz), 1.64 (m, 2, -CH−CH(CH₃)₂), 1.34 (d, 3, dihydrofuran β-CH₃, J 7 Hz), 1.00 (d, 6, -CH(CH₃)₂, J 6 Hz); λmax. 447 nm (log ε, 2.35), 311 (4.00); m/e 264 (36%), 262 (M⁺, 100%).
CHAPTER VI

AN APPROACH TO THE TOTAL SYNTHESIS OF PTEROCARPANS

Typical structural differences from pterocarpin itself are exemplified by pisatin (43), amygdalin (45), ssemblein (46), phaeoclit (47), lepocarpin (48) and phaeoclim (49) (Fig. 22).

Pisatin and phaeoclaim are known to be inhibitory to a wide range of phytopathogenic fungi and these and other pterocarpins are considered to play a major role in natural disease resistance of the host plant. Perrin and Cruickshank have investigated the antifungal activity of most of the known pterocarpins (together with some synthetic analogues) towards Helminthis fructicosus (Wilt.) honey.

They were able to deduce two broad requirements for activity: (a) the aromatic rings A and B must not lie in the same plane and (b) small oxygen containing substituents are required on the periphery of the molecule, particularly at C1 and C9. Introduction of a hydroxyl function at C12 does not affect the activity but a double bond at
During 1940 Spath and Schlager\textsuperscript{130} and Robertson \textit{et al.}\textsuperscript{131} determined the structures of two naturally occurring compounds previously isolated from the heartwoods of \textit{Pterocarpus} species by Cazeneuve.\textsuperscript{132} Pterocarpin and homopterocarpin were shown to have structures (37) and (184) respectively.

![Chemical Structure](image)

37 $R, R' = -\text{OCH}_2\text{O}$

184 $R=\text{H}$, $R' = \text{OCH}_3$

By 1972, 28 pterocarpans and related derivatives had been listed.\textsuperscript{17, 133-136} Their chemistry and biogenetic relationship to the isoflavonoids and coumestans has been the subject of several reviews.\textsuperscript{13, 15, 17}

Typical structural differences from pterocarpin itself are exemplified by pisatin (43), anyhydrovariablin (185), neodulin (186), phaseollin (187), leiocarpin (188) and phaseollidin (189) (fig. 22).

Pisatin and phaseollin are known to be inhibitory to a wide range of phytopathogenic fungi and these and other pterocarpans are considered to play a major role in natural disease resistance of the host plant. Perrin and Cruickshank\textsuperscript{137} have investigated the antifungal activity of most of the known pterocarpans (together with some synthetic analogues) towards \textit{Monilinia fructicola} (Wint.) Honey. They were able to deduce two broad requirements for activity: (a) the aromatic rings A and D must not lie in the same plane and (b) small oxygen containing substituents are required on the periphery of the molecule, particularly at $C_3$ and $C_9$. Introduction of a hydroxyl function at $C_{6a}$ does not affect the activity but a double bond at
FIG. 22

Such antipodes of natural phenocarpanes were found to be active antifungal agents. Thus syntheses of these natural products need only yield the racemic compounds in order to provide equivalent activity.

It was envisaged that a convergent total synthesis, utilizing the base-catalyzed cyclization procedure discussed in Chapter II, would provide access to phenocarpanes with a wide range of substitution key intermediates e.g. (186) could, on the basis of the methods described in Chapter II, be converted to the corresponding phenocarpan compound (181) or, by suitable deoxygenation, give anhydrosvarliftos (183).

This route would provide phenocarpanes with oxygen substituents that are (as required for antifungal activity). In view of the low biological activity and isolation of pisatin, 17, 18 the hydroxy derivatives were the isolable fraction of this reaction.

The phenolic intermediates, e.g. (173) are readily available.

Fused-ring molecules such as (181), necessary to provide a route to compounds such as (187) and (189), have been reported in the literature. 19, 19

The bromocaranes (185), proved more difficult synthetic problem. Information regarding bromocaranes was sparse. Cyclization problem...
C₆₆-C₈₈ leads to loss of activity.

Both antipodes of natural pterocarpans were found to be active antifungal agents. Thus syntheses of these natural products need only yield the racemic compounds in order to provide equivalent activity.

Pterocarpans are available by partial synthesis from the corresponding coumestan or isoflavone compounds (Chapter I) but the availability of the naturally occurring starting materials limits the utility of these routes.

It was envisaged that a convergent total synthesis, utilising the base catalysed cyclisation reaction discussed in Chapter II, would provide access to pterocarpans with a wide range of substitution patterns. The key intermediate e.g. (190) (fig. 23), would, on the basis of previous results (Chapter II), be expected to cyclise in base to give either the 6a-hydroxy compound (191) or, by dehydration, the 6a-11a double bond derivative (192). Methylation of (192) would then give anhydrovariablin (185).

This route would provide pterocarpans with oxygen substituents at C₃ and C₉ (as required for antifungal activity). In view of the stable occurrence and isolation of pisatin (43), the 6a-hydroxy derivatives, e.g. (191) may be isolable from the cyclisation reaction. The phenolic intermediates, e.g. (193) are readily available. Functionalised molecules such as (194), necessary for the proposed route to compounds such as (187) and (189), have been reported in the literature.

The bromoketone (195) proved a more difficult synthetic problem. Information regarding chroman-3-ones was sparse. Cyclisation
FIG. 23

193

\[
\text{MeO} + \text{HO}^\text{-}\text{Ac} \rightarrow \text{Br}
\]

195

\[
\text{MeO} \quad \text{MeO}
\]

190

\[
\text{MeO} \quad \text{MeO}
\]

192

\[
\text{MeO} \quad \text{MeO}
\]

191

Other routes involving 3-ene and chroman-3-one include hydronoration/oxidation of 2,3-chromene \(^{242} (293)\) as the corresponding coumarine or chromeno, \(28\) and \(293\) respectively.
of (196) had been reported\textsuperscript{140} to yield (197) although the identity of this product has been questioned. The diester (198) was reported to cyclise to (199).\textsuperscript{140}

\begin{center}
\begin{align*}
\text{196} & \quad \text{198} \\
\text{197} R = \text{C}_6\text{H}_5 & \quad 199 R = \text{CO}_2\text{Et}
\end{align*}
\end{center}

Dean\textsuperscript{15} has discussed the cyclisation of derric acid (200) to the enol acetate (201) under the influence of sodium acetate and acetic anhydride.\textsuperscript{141}

\begin{center}
\begin{align*}
\text{200} & \quad \text{201}
\end{align*}
\end{center}

Other routes to chroman-3-ones and chroman-3-ols include the hydroboration/oxidation of 2,3-chromenes\textsuperscript{142} (202) or the corresponding coumarins or chromenes, (28) and (203) respectively.\textsuperscript{143}
Our initial attempts at synthesis of the chroman-3-ol (206) via hydroboration/oxidation of the chrom-3-ene (207) or (208) were abandoned after the failure of similar reactions in an approach to the synthesis of scabequinone (Chapter V) and in view of the report by Clark-Lewis et al. that hydroboration/oxidation of chrom-3-enes gave preferentially chroman-4-ols.

Since chrom-2-enes were reported to produce chroman-3-ols by hydroboration/oxidation, the route outlined below was investigated.
Reduction of the lactone (209) however, with diisobutylaluminium hydride did not give a clean product although the presence of a band at 3400 cm\(^{-1}\) in the infrared spectrum suggested the presence of the hemiacetal (210).

At this time Collier and Porter\(^{144}\) reported thallium \(^{\text{III}}\) oxidation of aryl allyl ethers to give the corresponding chroman-3-ols in yields of up to 70%. This represented the simplest published route to these 3-hydroxy compounds. In our hands the allyl ether (211) gave the required chroman-3-ol (206) in 65% yield.

Initial attempts to oxidise (206) to the ketone (212) were
unsuccessful; starting material (206) was recovered almost quantitatively from reaction with several reagents (DDQ/CH₂Cl₂, Jones’ reagent, CrO₃/pyridine complex, Al(O-i-C₃H₇)₃, RuO₄, CuO/290°, nickel peroxide). Reaction of (206) with DMSO/AC₂O gave a mixture of at least two products (t.l.c.), however no pure compound could be isolated. Earlier reports suggest that this latter oxidation may have given the methylthiomethyl ether (213). Attempted dehydrogenation of the acetate (214) with DDQ in refluxing benzene was also unsuccessful.

Only two successful oxidations of chroman-3-ol derivatives have been reported. Both used the method developed by Pfützer and Moffat; employing DMSO, dicyclohexylcarbodiimide (DCC) and a proton source (e.g. pyridinium trifluoroacetate or monophenyl phosphate). Oxidation of (206) using this procedure was successful and gave (212) in 64% yield. The ¹H n.m.r. spectrum of (212) showed the expected singlet signals for the methylene protons at δ 3.50 and 4.42.

The protons on C₄ of (212) are expected to be very labile (both benzylic and α- to a carbonyl group) and should readily allow bromination (NBS/CCl₄) at this position to give (195).

Investigations aimed at preparing (195) and using it in the synthesis outlined earlier (fig. 23) to give (190), (191) and (192) are still proceeding.
EXPERIMENTAL

General experimental notes are given in Chapter II, experimental section.

Resorcinol monopropargyl ether monobenzenesulphonate (204)

Resorcinol monobenzenesulphonate (12.5 g, 50mmole) and propargyl bromide (6.6 g, 55mmole) together with anhydrous potassium carbonate (20 g) were stirred in refluxing acetone (250 ml) for 10 hr. The cooled solution was filtered and evaporated under reduced pressure to give the ether (204) (12.5 g, 87%) after molecular distillation at 110°/0.003 mm. $v_{\text{max}}$ 3280, 2130 cm$^{-1}$; $\delta$ (CDCl$_3$) 8.2-6.6 (broad envelope, 9, aromatic protons), 4.61 (d, 2, OCH$_2$C=CH, $J$ 2 Hz), 2.50 (t, 1, -C=CH, $J$ 2 Hz).

Resorcinol monomethyl ether monopropargyl ether (205)

Monomethyl resorcinol (12.4 g, 100mmole), propargyl bromide (13.2 g, 110mmole) and anhydrous potassium carbonate (20 g) in refluxing acetone (250 ml) as for the preparation of (204) gave the ether (205) (14.6 g, 90%) as a colourless liquid b.p. 80°/0.05 mm (Found: C, 74.2; H, 6.3. C$_{10}$H$_{10}$O$_2$ requires: C, 74.1; H, 6.2%). $v_{\text{max}}$ 3280, 2140 cm$^{-1}$; $\delta$ (CDCl$_3$) 7.20 (t, 1, H$_5$, $J$ 9 Hz), 6.56 (m, 3, H$_2$, H$_3$), 4.64 (d, 2, OCH$_2$C=CH, $J$ 2 Hz), 3.76 (s, 3, OCH$_3$), 2.52 (t, 1, -C=CH, $J$ 2 Hz); $m/e$ 162 ($M^+$, 70%), 161 (100), 147 (32), 134 (20), 131 (26).

7-Benzenesulphonyloxychrom-3-ene (207)

The ether (204) (7.2 g, 25mmole) was heated in refluxing N,N-diethylaniline (140 ml) for 8 hr. The solution was cooled and poured into cold 20% sulphuric acid solution (500 ml) and extracted...
with ether (2 x 200 ml). The ether extracts were combined, washed with 20% sulphuric acid solution (50 ml), dried (MgSO₄) and evaporated under reduced pressure to give the chromene (207) (5.1g, 70%) as a clear viscous liquid after molecular distillation at 120°/0.005 mm.

\[ \text{vmax. 1605 cm}^{-1}; \ \delta (\text{CDCl}_3) 7.9-6.3 \text{ (complex envelope, 9, aromatic protons and H}_4) , 5.70 \text{ (eight line multiplet, 1, H}_3) , 4.72 \text{ (eight line multiplet, 2, OCH}_2-) ; \ m/e 288 (M}^+, 57%), 287 (15), 150 (35), 148 (40), 147 (30), 134 (100). \]

7-Methoxy chrom-3-ene (208)

Treatment of the ether (205) (8.1g, 50mmole) in refluxing N,N-diethylaniline (160 ml) as for the preparation of (207) gave the chromene (208) (6.6g, 82%) as a clear viscous liquid after molecular distillation at 100°/0.002 mm. (Found: C, 73.8; H, 6.2. C₁₀H₁₀O₂ requires: C, 74.1; H, 6.2%).

\[ \text{vmax. 1605 cm}^{-1}; \ \delta (\text{CDCl}_3) 7.0 \text{ (m, 1, H}_4) , 6.81 \text{ (d, 1, H}_5, J 8 \text{ Hz)} , 6.40 \text{ (dd, 1, H}_6, J 8,2 \text{ Hz)} , 6.33 \text{ (d, 1, H}_8, J 2 \text{ Hz)} , 5.63 \text{ (eight line multiplet, 1, H}_3) , 4.72 \text{ (m, 2, OCH}_2-) , 3.76 \text{ (s, 3, OCH}_3) ; \ m/e 162 (M}^+, 75%), 161 (100), 147 (27), 146 (18). \]

3,4-Dihydro-7-methoxycoumarin (209)

A solution of 7-methoxycoumarin (3.5g, 20mmole) and 10% palladium on barium sulphate catalyst (0.5g) in 2N sodium hydroxide solution (150 ml) was shaken under 3 atm. of hydrogen for 15 hr. The mixture was filtered through a celite pad cooled in ice and acidified with conc. hydrochloric acid. The precipitated solid was removed by filtration, dried and dissolved in refluxing benzene (150 ml) containing a few crystals of para-toluenesulphonic acid. The water azeotrope was removed during reflux and after 7 hr the solution was
cooled and evaporated under reduced pressure to give the lactone (209) (2.6g, 75%) as colourless needles from acetone/hexane, m.p. 37-8° (Found: C, 67.3; H, 5.5. C₁₀H₁₀O₃ requires: C, 67.4; H, 5.7%). v_max. 1760 cm⁻¹; δ (CDCl₃) 7.12 (d, 1, H₅, J 8 Hz), 6.68 (dd, 1, H₆, J 8,2 Hz), 6.64 (d, 1, H₇, J 2 Hz), 3.84 (s, 3, OCH₃), 3.15-2.70 (complex envelope, 4, methylene protons); m/e 178 (M⁺, 100%), 150 (28), 149 (11), 137 (15), 136 (32).

Resorcinol monoallyl ether monomethyl ether (211)

Alkylation of resorcinol monomethyl ether with allyl bromide and anhydrous potassium carbonate in acetone gave the ether (211) in 89% yield, b.p. 82°/0.5mm (lit. 125°/14 mm).

3-Hydroxy-7-methoxychroman (206)

The allyl ether (211) (8.2g, 50mmole) and thallium triacetate (20.9g, 55mmole) were dissolved in 2.5M sulphuric acid solution (210 ml). The solution was stirred at 40-45° for 48 hr, cooled, diluted to 600 ml with water and extracted with ether (3 x 250 ml). The ether extracts were combined, washed with 5% sodium bicarbonate solution (2 x 50 ml), saturated sodium chloride solution (50 ml), dried (Na₂SO₄), and evaporated under reduced pressure. The residue was chromatographed on silica (350g) with benzene/ether (9:1) to give the alcohol (206) (5.8g, 65%) as a clear oil, after molecular distillation, which crystallised on standing, m.p. 56-8° (Found: C, 66.5; H, 6.5. C₁₀H₁₂O₃ requires: C, 66.7; H, 6.7%). v_max. 3400 (broad) cm⁻¹; δ (CDCl₃) 6.91 (d, 1, H₅, J 8 Hz), 6.46 (dd, 1, H₆, J 8,2 Hz), 6.40 (bs, 1, H₇), 4.20 (eight line multiplet, 1, CH-CH), 4.06 (bs, 2, protons on C₂), 3.74 (s, 3, OCH₃), 2.86 (octet,
2, protons on $C_4$, $J$ 18,16,4 Hz), 2.10 (bs, 1, OH, $D_2O$ exchangeable):

$m/e$ 180 ($M^+$, 98%), 162 (7), 161 (11), 137 (68), 136 (100), 108 (51), 44 (30), 43 (15).

Treatment of (206) with acetic anhydride in pyridine in the normal manner gave the acetate (214) as a viscous oil, purified by molecular distillation at 80°/0.01 mm. $\nu_{max.}$ 1740 cm$^{-1}$; $\delta$ (CDCl$_3$) 6.90 (d, 1, $H_5$, $J$ 8 Hz), 6.44 (dd, 1, $H_6$, $J$ 8,2 Hz), 6.40 (bs, 1, $H_8$), 5.22 (m, 1, CHOAc), 4.12 (bs, 2, protons on $C_2$), 3.70 (s, 3, OCH$_3$), 2.92 (octet, 2, protons on $C_4$, $J$ 18,16,4 Hz), 2.00 (s, 3, OCOCH$_3$).

**3-Oxo-7-methoxychroman (212)**

A solution of trifluoroacetic acid (0.16 ml, 2mmole) and dry pyridine (0.32 ml, 4mmole) in dry benzene (10 ml) was added to the alcohol (206) (0.72g, 4mmole) and anhydrous DMSO (6 ml) in dry benzene (10 ml) at 25° under nitrogen. The solution was cooled to ca 5° and dicyclohexylcarbodiimide (2.24g, 12mmole) added in small portions over 15 min. The mixture was stirred at 25° for 12 hr. Ether (100 ml) and a solution of oxalic acid (1.52g, 12mmole) in dry methanol (10 ml) were added and the stirring continued for a further 30 min. Water (100 ml) was added and the mixture filtered. The ether layer was separated, washed with 5% sodium bicarbonate solution (2 x 20 ml) and water (20 ml), dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was chromatographed on silica (30g) with hexane/ether (3 : 1) to give the ketone (212) (0.45g, 64%) after molecular distillation at 95% 0.01 mm.

$\nu_{max.}$ (liquid film) 1725 cm$^{-1}$; $\delta$ (CDCl$_3$) 6.90 (d, 1, $H_5$, $J$ 8 Hz), 6.30 (dd, 1, $H_6$, $J$ 8,2 Hz), 6.27 (bs, 1, $H_8$), 4.22 (s, 2, chromone $\gamma$-protons), 3.78 (s, 3, OCH$_3$), 3.50 (s, 2, chroman-$\alpha$-protons); $m/e$ 178 ($M^+$, 100%), 150. (32), 149 (40), 136 (12), 135 (10), 121 (22); measured mass: 178.06282 C$_{10}$H$_{10}$O$_3$ requires: 178.06300.
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The naturally-occurring macroline polyene antibiotic, 17-deoxynojirimycin, has been shown to undergo a stereospecific condensation, followed by reduction, to generate the linear


disaccharide precursor \( \text{I, } \beta_1 = \beta_2 = \beta_3\).

Formal synthesis of \( \text{I, } \beta_1 = \beta_3 = \beta_4 \) was accomplished in two steps: condensation of \( \text{II, } \beta_1 = \beta_2 = \beta_3 \) and the subsequent ring closing step. Condensation of \( \text{II, } \beta_1 = \beta_2 = \beta_3 \) is shown in Figure 1.

Previous reports have shown that the 4-methyl derivatives of \( \text{I, } \beta_1 = \beta_2 = \beta_3 \) to be the corresponding furanocarbazoles \( \text{III, } \beta_1 = \beta_2 = \beta_3 \) under a variety of acidic and basic conditions. Also in repetition of the earlier work of \( \text{IV, } \beta_1 = \beta_2 = \beta_3 \) they obtained the 4-methylfuranocarbazoles \( \text{V, } \beta_1 = \beta_2 = \beta_3 \) in only 4% yield.

\[ \text{I} \]

\[ \text{II} \]

\[ \text{III} \]

\[ \text{IV} \]

\[ \text{V} \]
SYNTHESIS OF BENZOFURANOID SYSTEMS. I.
FUROCOUMARINS, BENZOFURANS AND DIBENZOFURANS

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The naturally-occurring coumarin geiparvarin (I) on treatment with mild aqueous base, was shown to undergo a retro-Aldol condensation followed by cyclisation to generate the linear furocoumarin psoralene (II, \( R_1 = R_2 = H \): 58\%).\(^1\) The postulated intermediate in this cyclisation process, 7-(2-oxoethoxy)coumarin (III, \( R_1 = R_2 = H \)) was synthesised\(^2\) and on similar base treatment\(^1\) gave psoralene in reasonable yield (30\%). Esse and Christensen\(^2\) had previously reported that they were unsuccessful in attempts to cyclise the 4-methyl derivative of 7-(2-oxoethoxy)coumarin (III, \( R_1 = H, R_2 = CH_3 \)) to the corresponding furocoumarin (II, \( R_1 = H, R_2 = CH_3 \)) under a variety of acidic and basic conditions. Also on repetition of the earlier reported work of Ray\(^3\) on the sodium ethoxide catalysed cyclisation of 7-acetonyloxy-coumarin (III, \( R_1 = CH_3, R_2 = H \)) they obtained the 8-methylpsoralene (II, \( R_1 = CH_3, R_2 = H \)) in only 4\% yield.

\[
\begin{align*}
&\text{I} \\
&\text{II} \\
&\text{III}
\end{align*}
\]

Since our method of synthesis of psoralene involves only four simple steps starting from resorcinol and malic acid (von Pechmann condensation; etherification with allyl bromide; ozonolysis; base-catalysed cyclisation) this offers a considerable improvement over other
published methods of total synthesis of this biologically active compound. We now report the application of this base-catalysed cyclisation process to the preparation of other linear furocoumarins and to the synthesis of benzofurans and dibenzofurans.

Condensation of chloroacetone or phenacyl bromide with umbelliferone (7-hydroxycoumarin) or its 4-methyl derivative in acetone/K₂CO₃ gave (III, R₁ = CH₃ or C₆H₅, R₂ = H or CH₃) in high yield. Treatment of these four compounds in refluxing 0.1N aqueous KOH for 6 hours followed by cooling and acidification gave the respective α-substituted furocoumarins (IV, R₁ = CH₃ or C₆H₅, R₂ = H or CH₃) in better than 80% yield of recrystallised product. The PMR spectra of these compounds confirmed that cyclisation had occurred in one direction only to give the linear furocoumarin skeleton.

The mechanism of this reaction can be described as a type of intramolecular aldol condensation in which the phenoxide ion (a), formed on base hydrolysis of the pyrone ring, promotes attack at the exocyclic carbonyl function through the resonance-stabilised carbanion generated at the position para to the phenoxide ion, viz, a → b. The irreversibility of the process is established by abstraction of the proton from the newly formed ring junction to regenerate the coumarinic acid salt c. On acidification the pyrone ring is reformed and following protonation of the alkoxy ion, water is spontaneously eliminated from the labile α-hydroxydihydrofuran ring system to give the psoralene derivative (II).

As an extension of the method, we have successfully applied it to the synthesis of 6-hydroxybenzofuran derivatives. The mono-acetonyl ether of resorcinol (IV, R₁ = H, R₂ = H) when treated under reflux with aqueous 0.1N KOH for 4 hours underwent cyclisation to furnish...
6-hydroxy-3-methylbenzofuran, \( \text{m.p.} \ 104-105^\circ \) (V, \( R_2 = H \); 75%). The mono-methylether (IV, \( R_1 = \text{CH}_3, \ R_2 = H \)) did not undergo base catalysed cyclisation and was recovered essentially unchanged.

The acetonyl ether of the mono-benzenesulphonate ester of phloroglucinol mono-methylether \( ^6 \) (IV, \( R_1 = \text{SO}_2\text{O}, \ R_2 = \text{OCH}_3 \)) under similar basic conditions after initial rapid hydrolysis of the ester moiety cyclised cleanly to the benzofuran (V, \( R_2 = \text{OCH}_3 \), m.p. 102-103\(^\circ \)) (95%). In both cases cyclisation took place only to the ring position \textit{para} to the free phenol. The final acidification step had to be carried out cautiously to avoid acid-catalysed formation of the dimer (VI).

To illustrate further the utility of this synthetic method, we prepared in good yield the dibenzofuran derivative (IX) by condensation of 2-bromocyclohexanone with 7-hydroxycoumarin to give (VII), m.p. 169-170\(^\circ \), followed by treatment with aqueous KOH under reflux. The isolated product (VIII), m.p. 148-150\(^\circ \), was readily dehydrogenated with DDQ in benzene to the functionalised dibenzofuran (IX), m.p. 202-203\(^\circ \). Similarly, resorcinol mono-benzenesulphonate, after etherification with 2-bromocyclohexanone, base hydrolysis/cyclisation and dehydrogenation, gave the dibenzofuran (X), \( \text{m.p.} \ 140-141^\circ \).
We are presently engaged in an extensive investigation of the scope of this reaction and its use in the synthesis of other naturally-occurring compounds of biological interest.

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SYNTHESIS OF BENZOFURANOID SYSTEMS. II.

TOTAL SYNTHESIS OF CYPERAQUINONE AND CONICAQUINONE

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The difurobenzoquinone cyperaquinone, a constituent of a number of species of Cyperaceae, has been shown mainly on spectroscopic evidence to have structure (I). This compound and its derivatives represent a novel type of naturally-occurring ring system whose biogenesis and biological activity are of some considerable interest. Conicaquinone (II) has been extracted in low yield from the roots of Cyperus conicus Boeck and its structure was assigned solely from UV, IR, NMR and mass spectral data. We now wish to report the total synthesis of both compounds (I) and (II).

6-Hydroxy-4-methoxy-3-methylbenzofuran (IV), m.p. 103°, was prepared by the base catalysed cyclisation of the mono-acetonyl mono-methyl ether of phloroglucinol mono-benzenesulphonate (III) as previously described. The overall yield of (IV) in six steps from phloroglucinol was 73%. Hydrogenation to the dihydrobenzofuran (V), b.p. 144°/1 mm, was followed by bromination (Br₂ in CHCl₃ at 0°) to block the more reactive 7-position (VI, m.p. 103°) prior to formylation using dichloromethylmethylether/titanic chloride in dichloromethane to produce (VIla), m.p. 96°. The substitution pattern in (VIla) was confirmed by its mass spectrum which showed an [M - H₂O⁺] ion (40% RI) characteristic of an o-methoxybenzaldehyde whereas the aldehyde obtained by formylation of the unbrominated dihydrobenzofuran (V) showed no mass spectrometric loss of H₂O from its molecular ion. Preparation of the d₃-methoxy derivative (VIIb) and observation of an [M - DDO⁺] ion in its mass spectrum substantiated the assignment.

Condensation of (VIla) with chloroacetone in acetone/K₂CO₃ gave (VIII), m.p. 141-142°, which was dehydrogenated to the benzodifuran derivative (IX), m.p. 208-209°, using DDQ in benzene. Demethylation of (IX) with 2.5 equivalents of sodium thioethoxide in DME afforded the bromophenol (X), m.p. 243-245°, which was oxidized by Fremy's salt to (II), m.p. 189-190°.
The synthetic compound (II) was identical in all respects (m.p., mixed m.p., UV, IR, NMR, mass spectra) with naturally-occurring conicaquinone.

The action of the ylid, generated from methyltriphenylphosphoniumiodide by sodium methoxide in DMF/THF on (IX) produced the isopropenyl benzodifuran, (XI), m.p. 128-130\(^\circ\)C, which demethylated cleanly with sodium thioethoxide in HMPT at 70\(^\circ\)C. The product (XII), extremely acid labile and light sensitive, was oxidised by Fremy's salt to give (I), m.p. 182-183\(^\circ\)C, identical in all respects with cyperaquinone from natural sources.\(^1\)

We are now in the process of synthesising other naturally-occurring derivatives of cyperaquinone.\(^1\)

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Total Synthesis of (±)-Scabequinone

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Summary The synthesis of (±)-scabequinone, a novel 5H-furo[3,2-g][1]benzopyran-4,9-quinone from Cyperus scaber, is reported.

The family Cyperaceae is a rich source of quinones, the biogenesis of which has been suggested to involve, in part, the incorporation of a methylene group into a C14 aromatic precursor (C4 + C5 + C4) to produce compounds containing a β-methylbenzofuran (C4 + C5 + C4) or a 3-isopropylchroman (C4 + C5 + C4) system. The structure (1) suggested for scabequinone, a major component of Cyperus scaber (R.Br.) Boeck, which possesses both of these ring systems, has now been confirmed by total synthesis.

The substituted dihydrobenzofuran (2), whose preparation in eight steps from phloroglucinol has been reported, was condensed with 1-bromo-3-methylbutan-2-one in MesCO-K2CO3 to produce (3), m.p. 79-80°. Treatment of the derived ketone with methyltriphenylphosphorane gave (4), b.p. 95°/0.03 mm, in high yield. This substituted allyl ether underwent a Claisen rearrangement in NN-dimethylaniline under reflux to afford compound (5), having the desired aromatic substitution pattern and six-carbon progenitor of the 3-isopropylchroman ring system. Cyclisation of this side-chain to give (8), b.p. 105°/0.03 mm, was effected by hydroboration-peroxide oxidation of the exocyclic double bond to give exclusively the primary alcohol (6), followed by bromination [(C6H5)2P-CBr4], to (7), and treatment of the bromide with aqueous base.

The aromatic bromine substituent used as a blocking group was quantitatively removed from compound (8), by hydrogenolysis (10% Pd-C), and subsequent aromatisation to the benzofuran system (9) carried out using palladised charcoal in diphenyl ether under reflux. Dichlorodicyanoquinone (DDQ) was ineffectual in promoting this dehydrogenation.

Demethylation of the aryl methyl ether (9) with the thioethoxide ion in DMF proceeded smoothly to give the unstable phenol (10) which was oxidised by Fremy’s salt.

† All compounds reported have been fully characterised and their structures are consistent with u.v., i.r., n.m.r., m.s. data and microanalysis.
to the quinone (1), m.p. 116-118°. The racemic synthetic compound (1) was found to be identical in all respects (m.p. mixed m.p., u.v., i.r., $^1$H n.m.r., mass spectra) except optical rotation with naturally occurring (+)-scabequinone.

Attempts to resolve the phenol (10) via its (+)-camphor-10-sulphonate have proved unsuccessful.

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