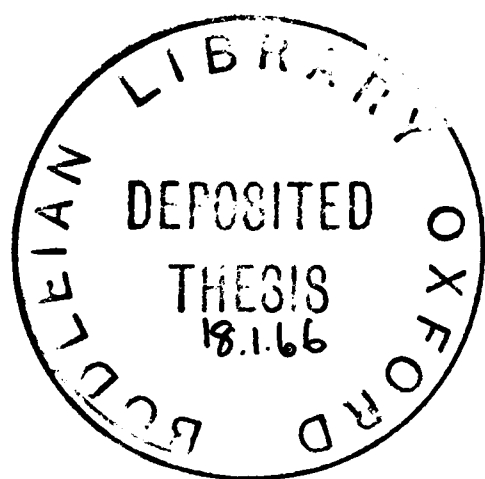


THE SYNTHESIS OF COMPOUNDS
RELATED TO NATURALLY OCCURRING FLAVANOLS

A Thesis submitted
for the
Degree of Doctor of Philosophy
by

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September, 1965.

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TO ELAINE
and our families.

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ACKNOWLEDGEMENTS

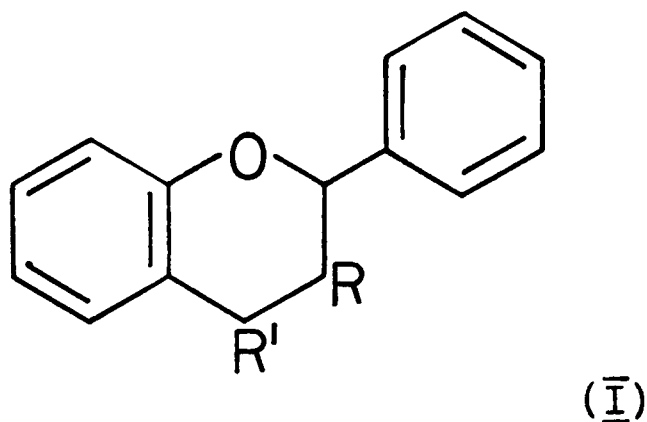
The author wishes to thank Dr. B.R. Brown for his supervision of this work, and for his encouragement during its progress.

The author also thanks Mrs. E.E. Richards and Dr. R.T. Aplin for their valuable advice, and measurements of nuclear magnetic resonance and mass spectra. Thanks are also due to colleagues in the Department whose interest and advice have contributed to this work.

Finally, the author acknowledges a maintenance grant from the D.S.I.R.

A B S T R A C T

Flavanoid compounds exist in many parts of plant life¹ and assume various roles which are not yet fully understood. A study of flavanoids based on the flavan-3-ol ($\bar{\text{I}}$: R=OH, R' $\neq$ H) and the flavan-3:4-diol ($\bar{\text{I}}$: R=R'=OH)



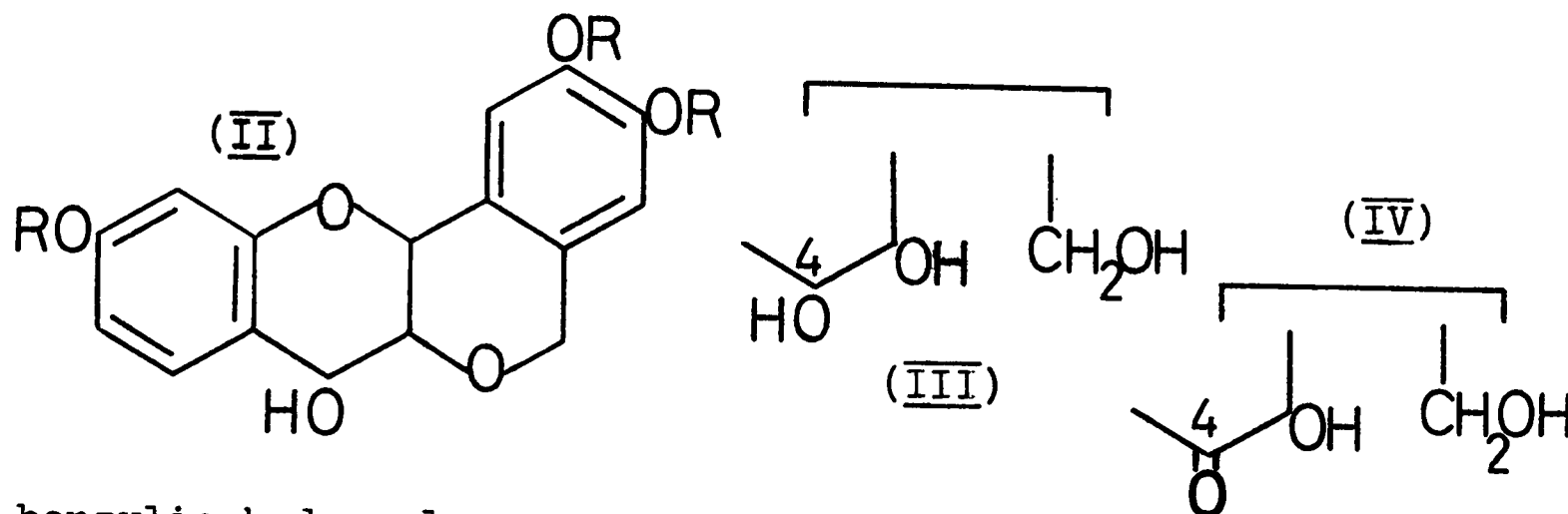
skeleton, is essential for investigation of the functions fulfilled by flavanoids in plants. The synthesis of such flavanoids of particular stereochemistry requires the development of stereospecific methods. Until recently^{2,3}, confusion existed in the knowledge of the stereochemistry of the heterocyclic ring in flavanoids, and particularly the configurations and conformations existing in flavan-4-ols^{4,5} ($\bar{\text{I}}$: R=H, R'=OH).

A number of simple flavan-4-ols have been synthesised, and their benzoates shown, by a strict examination by nuclear magnetic resonance spectroscopy, to exist in a "half chair" conformation, with the oxygen function axial in the α -flavanols and equatorial in the β -flavanols.

Accurate data and interpretation in the α -series has not previously been available; the results for compounds in the β -series are in excellent agreement with those found by other workers.³

Flavan-4 α -ols were synthesised by the oxime route⁵ which has been little used. The route has been shown to be the most reliable of the methods available for the synthesis of flavan-4 α -ols.

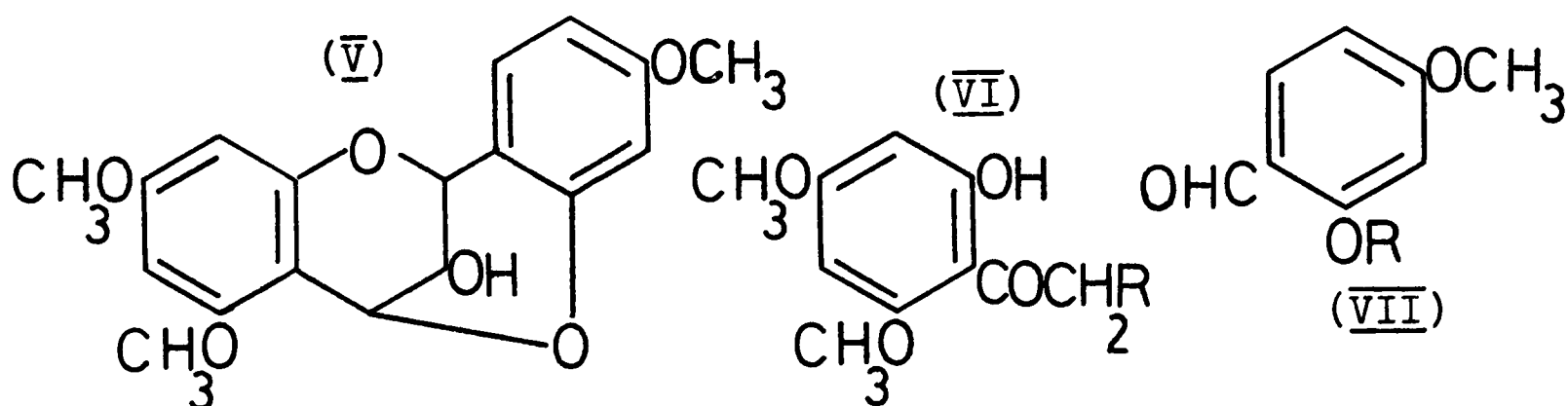
Synthesis of racemic tri-O-methylpeltogynol ($\overline{\text{II}}$: R=CH₃) has been accomplished. (+)-Peltogynol and its isomer peltogynol B, ($\overline{\text{II}}$: R=H), occur in "purple heart", Peltogyne porphyrocardia, a rare Amazonian tree. The critical stage in the synthesis was the specific oxidation of the secondary benzylic hydroxyl group, at the 4-position in the triol ($\overline{\text{III}}$) to the flavan-4-one ($\overline{\text{IV}}$) leaving the primary



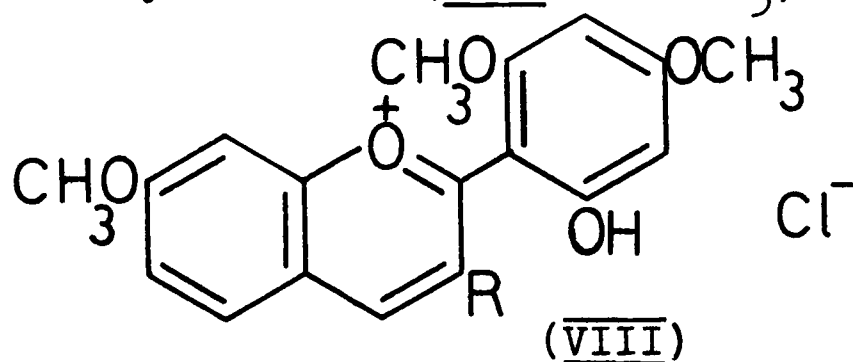
benzylic hydroxyl group present, unoxidised. This was achieved with activated manganese dioxide⁶ under the conditions described by Turner.⁷ Dehydration and reduction

yielded racemic tri-O-methylpeltogynol shown by melting point, infra-red spectroscopy and mass-spectrometry to be structurally identical with the methylated natural product.

Synthesis of tri-O-methylcyanomaclurin (V) which occurs unmethylated in jackwood, Artocarpus integrifolia, was attempted. Failure of phloracetophenone-4:6-dimethyl ether



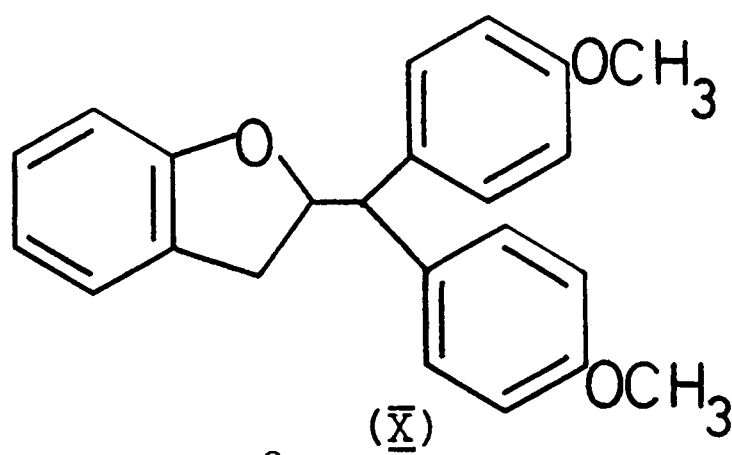
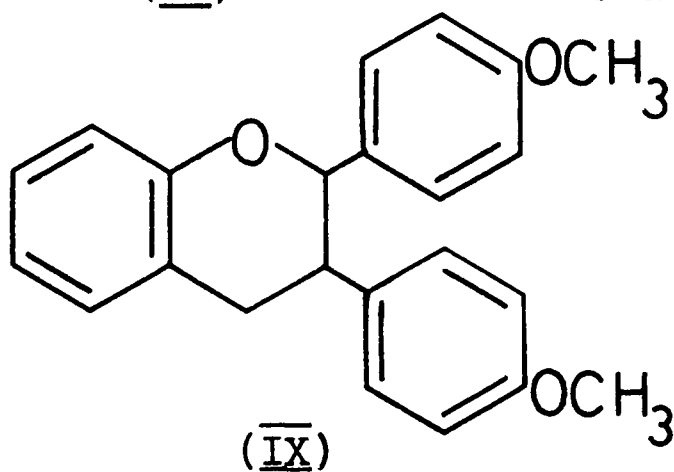
(VI : R=H) to condense with β -resorcylic aldehyde-4-methyl ether (VII : R=H) or with the easily hydrolysed benzoate of the aldehyde (VII : R=COPh) under alkaline conditions, is attributed to the reduction of aldehydic character by the o-phenoxide ion. Condensation was found to occur under acid conditions to yield the flavylum salt (VIII : R=H). A similar flavylum salt (VIII : R=OCH₃) was prepared by



condensation of ω -methoxyphloracetophenone-4:6-dimethyl

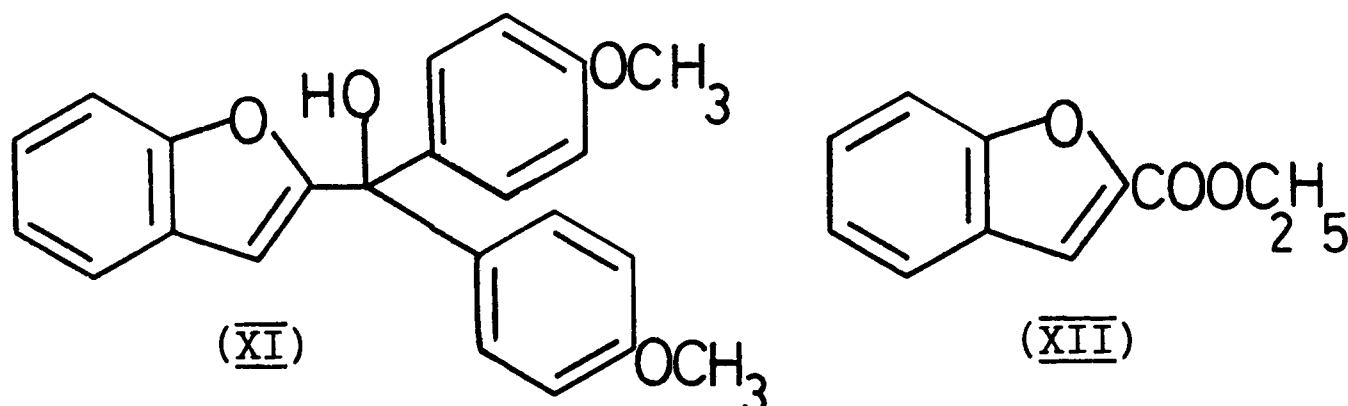
ether (VI : R=OCH₃) with the aldehyde (VII : R=H) under acid conditions. These compounds may be important intermediates in future work on the synthesis of tri-O-methyl-cyanomaclurin.

The condensation of catechins with phenols under acid conditions may be operative in the natural formation of some tannins. Recent studies on such condensations have included the condensation of (+)-catechin with phloroglucinol⁸ to yield a complex condensate, C₂₁H₁₈O₈, whose structure could not be determined at that time. Two mechanisms were postulated for its formation, each of which would give rise to a different product. In a similar experiment, simpler starting materials, 3-hydroxy-4'-methoxyflavan and phenol, were used⁹ and the product treated with dimethyl sulphate and potassium carbonate. The product analysed approximately for the molecular formula C₂₃H₂₂O₃, which represents the flavan (IX) and also the coumaran (X), these structures arising



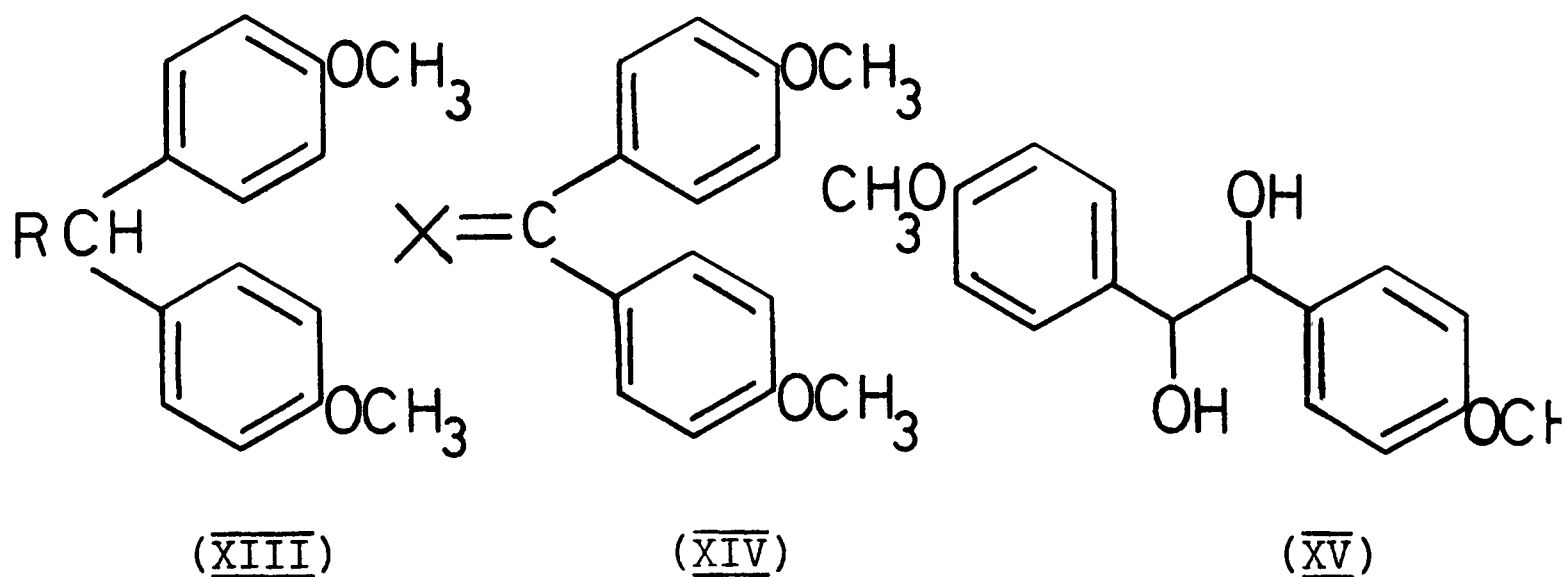
from each of the two mechanisms postulated for this kind of

condensation. The flavan ($\overline{\text{IX}}$) was synthesised and found⁹ to be different from the "methylated condensation product". The coumaran ($\overline{\text{X}}$) has now been synthesised by the hydrogenation and hydrogenolysis of the carbinol ($\overline{\text{XI}}$), which was prepared

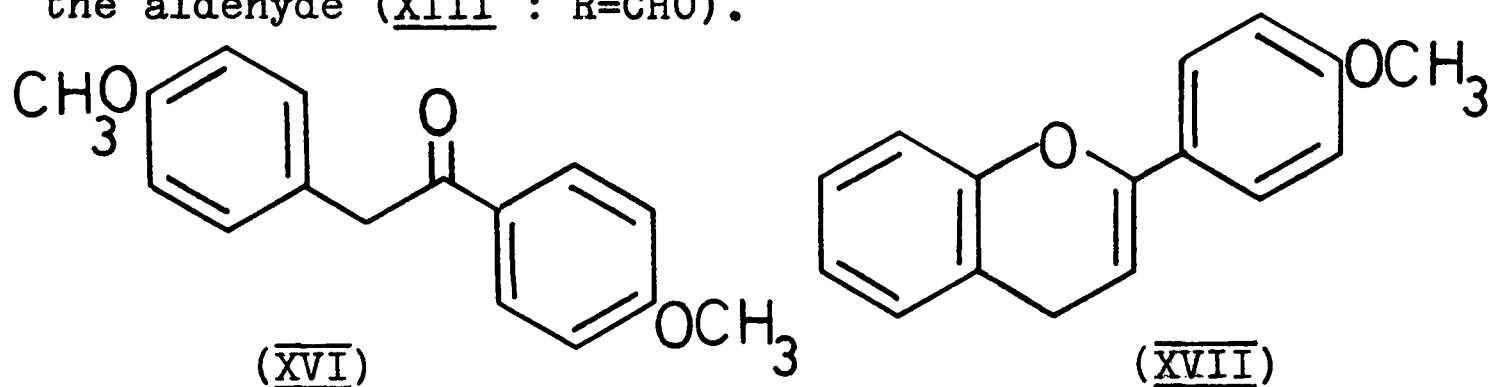


by Grignard reaction of ethyl coumarilate ($\overline{\text{XII}}$) with anisyl magnesium bromide. Ethyl coumarilate ($\overline{\text{XII}}$) was prepared by condensation of salicylaldehyde with ethyl bromoacetate.

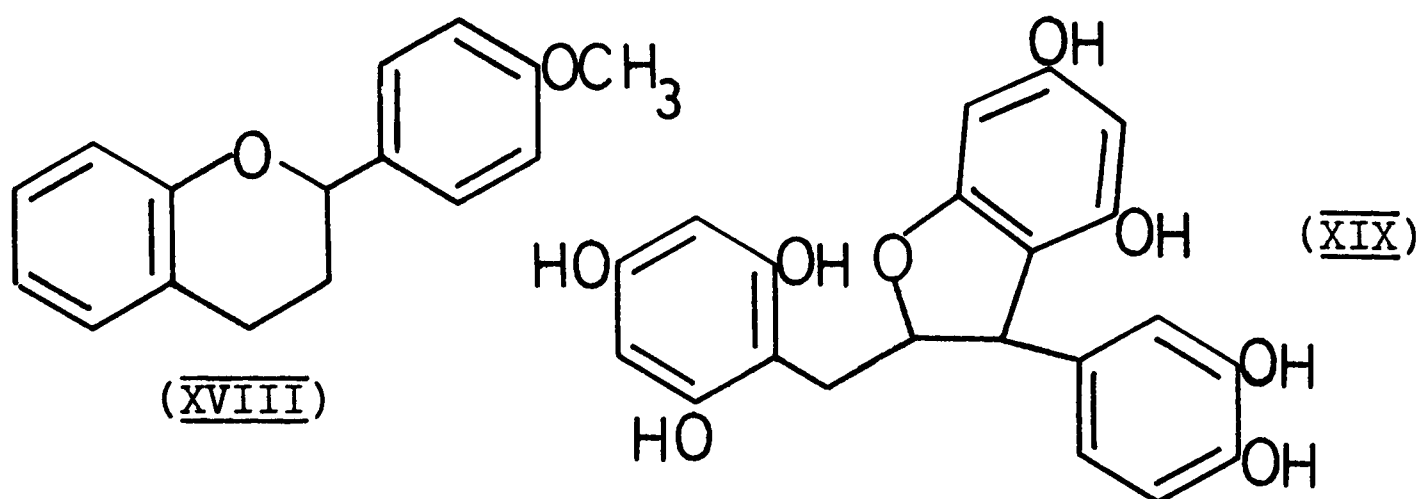
Several attempts had been made to synthesise the coumaran ($\overline{\text{X}}$) by other routes. In one, attempted oxidation of 2:2-dianisylethanol ($\overline{\text{XIII}}$: $\text{R}=\text{CH}_2\text{OH}$) to 2:2-dianisylacetaldehyde ($\overline{\text{XIII}}$: $\text{R}=\text{CHO}$) yielded 1:1-dianisylethylene ($\overline{\text{XIV}}$: $\text{X}=\text{CH}_2$); in another, attempted formation of the Grignard reagent



(XIII : R=MgBr) from the bromide (XIII : R=Br) and carbonation yielded 4:4'-dimethoxybenzophenone (XIV : X=O); and in another, rearrangement of hydroanisoïn (XV) on treatment with sulphuric acid yielded desoxyanisoïn (XVI) and not the aldehyde (XIII : R=CHO).



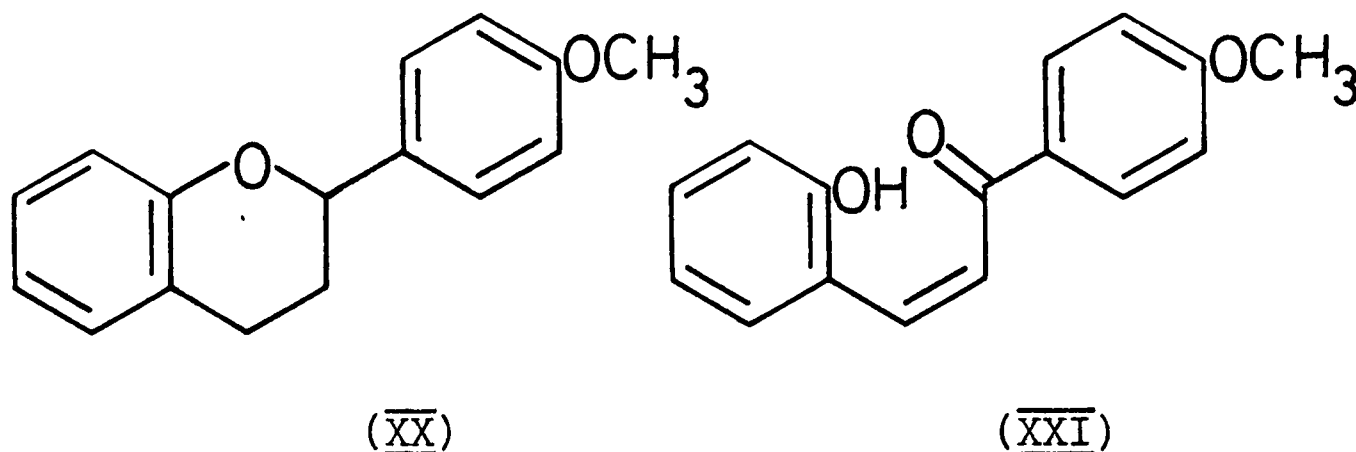
The coumaran (X) was found to be different from the "methylated condensate"⁹. Consequently, the latter was examined by n.m.r. spectroscopy, which revealed that condensation had not taken place and that simple dehydration had given rise to the flav-2-ene (XVII). This was hydrogenated at room temperature to yield the known compound, 4'-methoxyflavan (XVIII).



While this work was in progress, the complex product

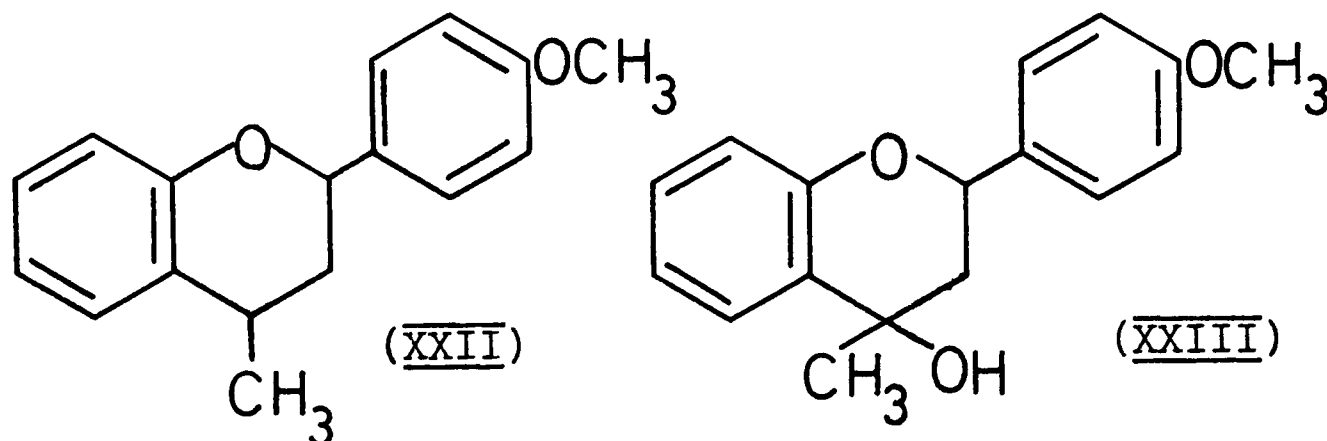
obtained by condensation of (+)-catechin and phloroglucinol⁹ was being investigated and its structure established as a coumaran (XIX) by chemical and mass-spectrometric evidence.¹⁰ The mechanism of its formation was shown to be attack of phloroglucinol on the carbon atom at C₂ in (+)-catechin, opening the heterocyclic ring, followed by dehydration involving the 3-hydroxyl group and one of the o-hydroxyl groups in the phloroglucinol group, a mechanism which would not operate with the simpler starting materials used by Warren⁹.

A convenient route to simple flavans (e.g., (XX)) is by

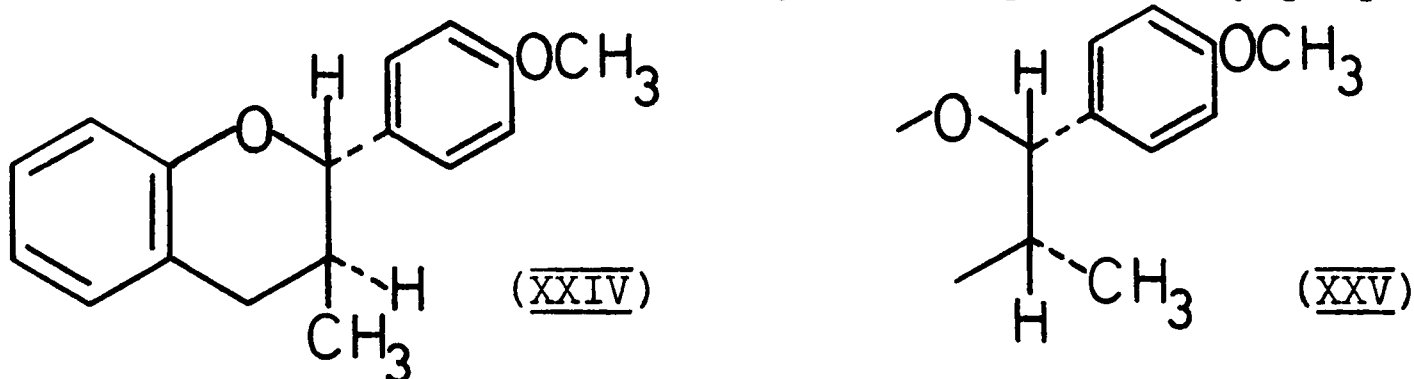


the reduction of 2-hydroxychalcones (e.g., (XXI) with lithium aluminium hydride-aluminium chloride.¹¹ In the reduction of 2-hydroxy-4'-methoxychalcone (XXI) with this reagent, 4'-methoxyflavan (XX) was isolated in 23% yield, together with an alcohol m.p. 136-7° (49%) obtained only when methyl formate was used^{11,12} in the isolation procedure. Reduction of the tosylate of this alcohol with lithium aluminium hydride yielded the methylflavan, C₁₇H₁₈O₂, m.p. 106-7°¹¹. Investigations into

the nature of the methylflavan, m.p. $106-7^{\circ}$ ^{11,12} suggested that it might be a 2:3-trans-3- or a 4-methylflavan. The 4'-methoxy-4-methylflavans (XXII), isomeric at the 4-position, have been synthesised as an inseparable mixture,



by two methods, both of which involved reduction of the flavan-4-ol (XXIII) and which gave a 1:1 mixture of isomers. The n.m.r. spectrum of the mixture shows two discernible superimposed spectra, which confirm the structures (XXII), and which are quite unlike the spectrum¹² of the methylflavan, m.p. $106-7^{\circ}$. However this spectrum¹² is not of sufficient quality to make exact assignments. Accordingly, the spectrum was measured afresh, and an excellent spectrum obtained, which establishes the structure of the methylflavan (XXIV). This is isomeric with the 3-methylflavan previously prepared



(XXV). The future unambiguous synthesis of this 2:3-trans-

3-methylflavan will no doubt confirm the structure (XXIV).

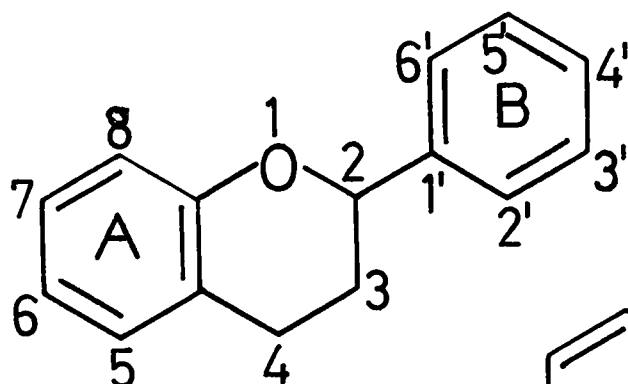
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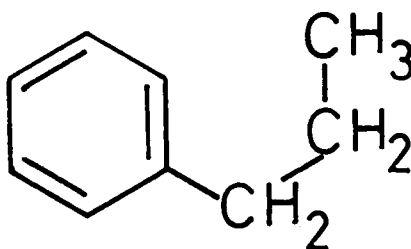
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GENERAL INTRODUCTION

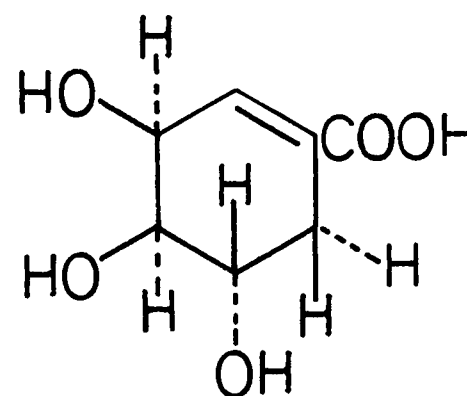
Flavanoids are compounds which are based on the skeleton of flavan (I), and form a large mass of compounds



(I)



(II)



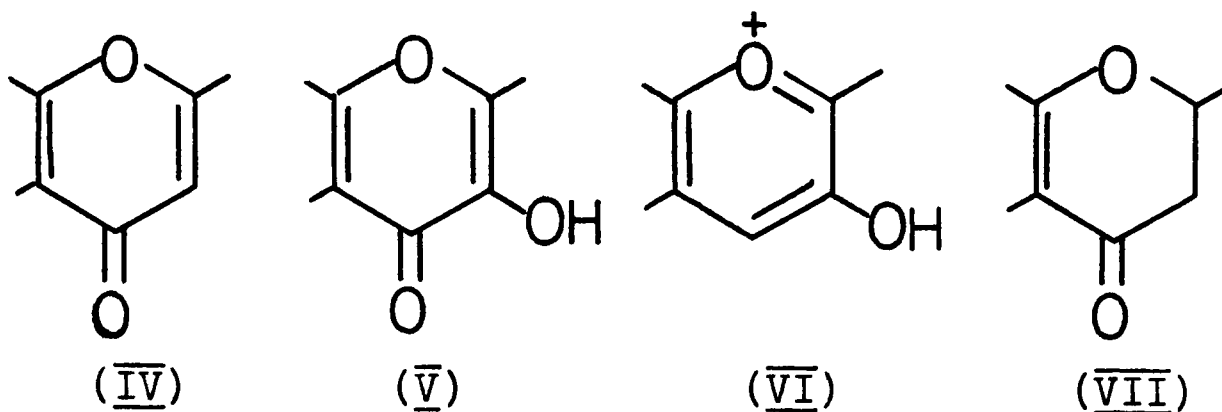
(III)

found in plant life. They may be regarded as being based on a C_{15} skeleton, i.e., $C_6C_3-C_6$, derivatives of the 1-phenyl propane structure (II). The wide occurrence of 1-phenyl propane derivatives in plants¹ indicates that the synthesis of the 1-phenyl propane structure by the shikimic acid (III) pathway,² is one of the fundamental synthetic processes of nature.

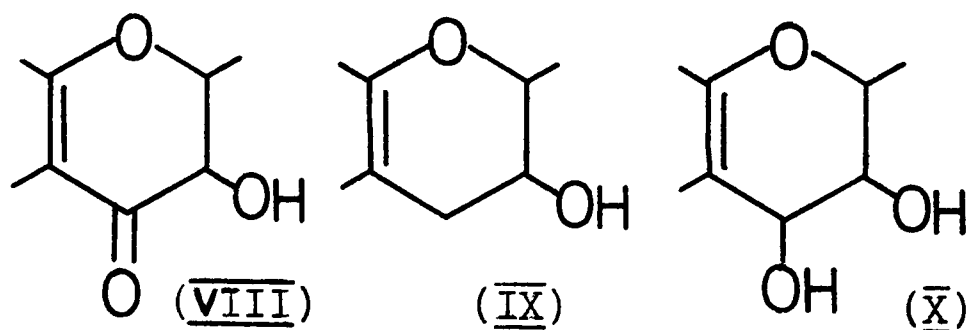
Flavanoids are known to occur as monomers, dimers and polymers in roots, stems, leaves, flowers, pollen, fruit, seeds, bark and wood, and their functions are not completely understood. One major function may be the inhibition of fungal decay in damaged plants.³

The heterocyclic ring in flavanoids can exist in many states of oxidation, and common states are those of

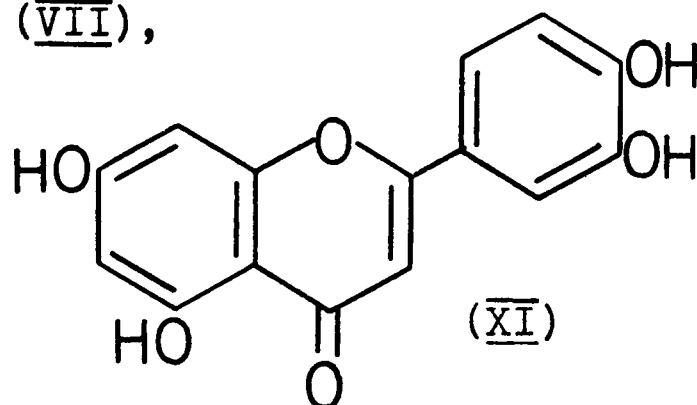
a flavone (IV), a 3-hydroxyflavone (V), a flavylum



salt, usually with a 3-hydroxyl group (VI), a flavanone (VII), a 3-hydroxyflavanone (VIII), a flavan-3-ol (a catechin)(IX),

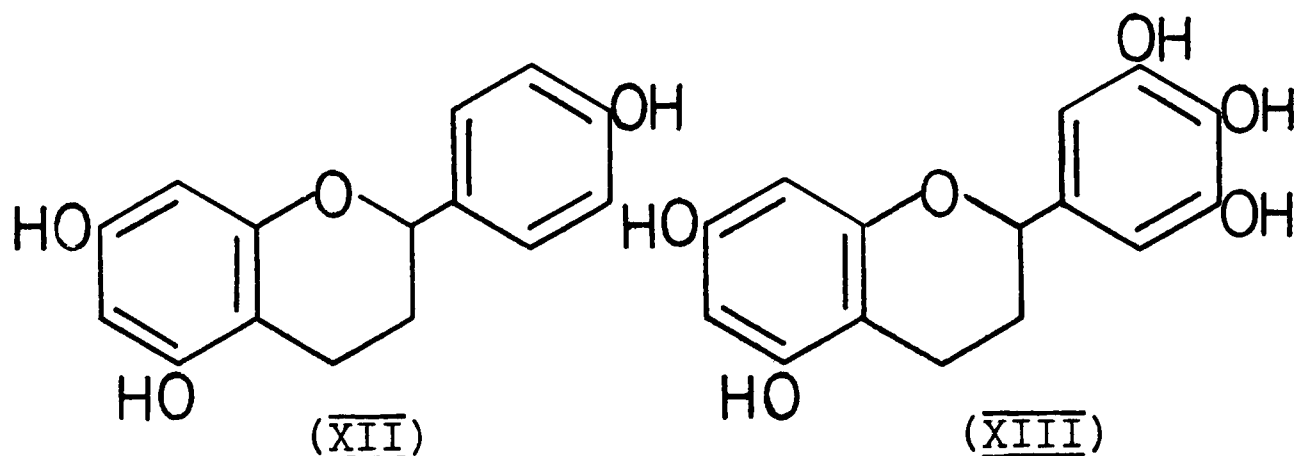


and a flavan-3:4-diol (a leucoanthocyanidin)(X). Examples of the oxidation states (IV)-(X) are provided in the 3':4':5:7- tetrahydroxy compounds, extracted from natural sources, i.e., luteolin (XI), quercetin (V), cyanidin (VI), eriodictiol (VII),

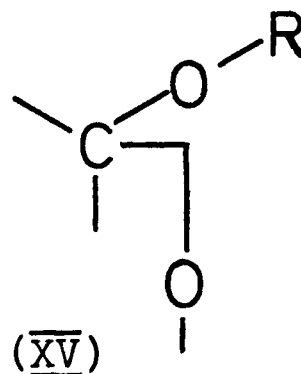
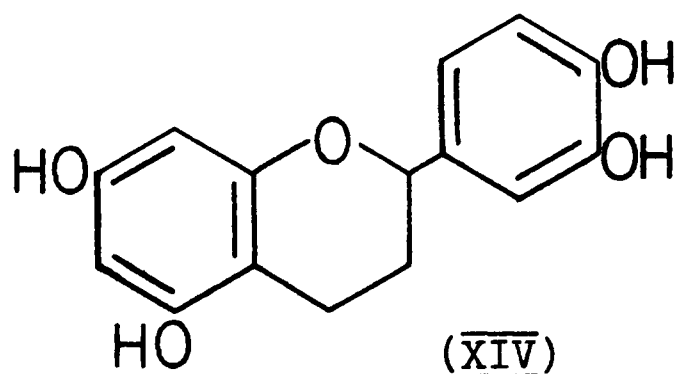


taxifolin (VIII), catechin (IX) and leucocyanidin (X).

Naturally occurring flavanoids are usually hydroxylated in the A and B rings, most commonly at 7- and 4'-, commonly also at 5 and 3'-, often at 5'- and sometimes at the 8-position. Common series of compounds are those known as the pelargonidin series based on the skeleton (XII), the delphinidin series (XIII) and the cyanidin series



(XIV) from which the examples given above have been chosen.



An important group of naturally occurring flavanoids is that of the anthocyanins, which are flavylium salts (VI) to which sugar residues are attached. Glucose is the sugar usually found to be attached, although other sugars are sometimes found. The highly coloured

anthocyanins provide colouring pigments of certain fruits, flowers and leaves, and the (nature) of the sugar residue is thought to be an important factor in the (genetic control) of flower colours.⁴

The sugar residues in anthocyanins occur usually at 3- and 5-positions, and are attached by normal glycosidic links ($\overline{XV}$), which are hydrolysed by dilute acid. The aglycones, produced by hydrolysis of sugar residues from anthocyanins, are flavylium salts ($\overline{VI}$) and are called anthocyanidins. Flavan-3:4-diols ($\overline{X}$), which give rise to anthocyanidins on treatment with mineral acid, especially in the presence of oxygen, are called leucoanthocyanidins.

The Economic Importance of Flavanoids.

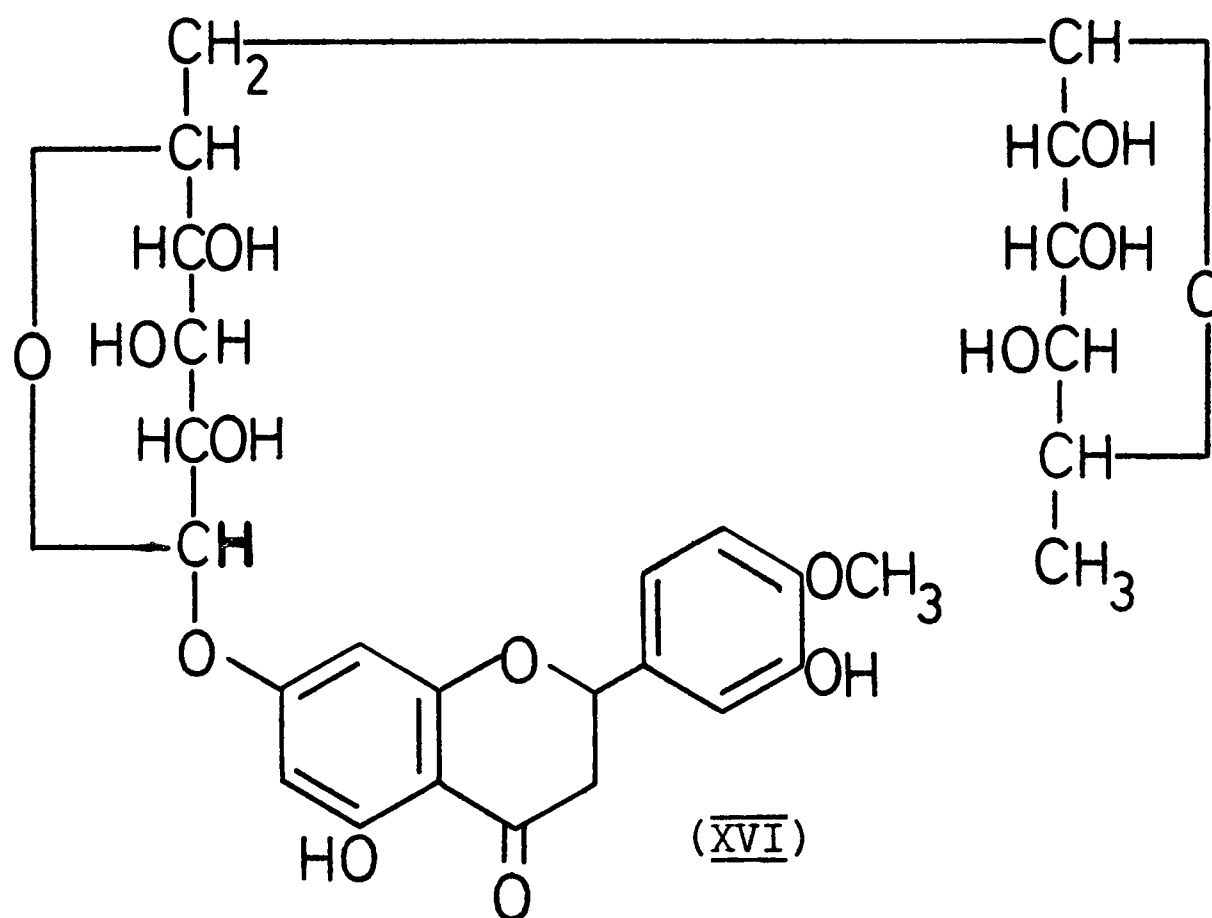
Flavanoids are of importance in tea fermentation. The stimulating effect of tea is due to its caffeine content; other qualities are largely due to the polyphenol content, which may account for 30% of the dry weight of plucked tea shoots. Many flavanoids, notably gallates of catechins, have been detected and isolated,⁵ using, especially, partition chromatography.⁶ A knowledge of such components has been important in the understanding of chemical changes occurring during tea manufacture, and particularly during the fermentation process.

Flavanoids are also of importance in food technology. The Angiospermae, the flowering plants, yield a great many foods, from which flavanoid compounds have been isolated.⁷ These compounds range from related phenols, e.g., catechol, from the onion, Allium cepa,⁸ to leucoanthocyanin polymers, from malted barley, Hordeum vulgare,⁹ and are responsible for colour, both desirable and undesirable, taste, the protection of fats against oxidation, destruction of vitamins and the inactivation of enzymes in foodstuffs.

Flavanoids are of particular importance in the forest products industry. They occur in hard- and softwoods, and interest in them has been shown for a variety of reasons. They inhibit sulphite-pulping, possibly by condensation with lignin¹⁰ or by the formation of a protective layer of a calcium complex on the wood¹¹ and they inhibit fungal decay,³ which is important in connection with the durability of lumber. The occurrence and abundance of certain flavanoids can be of use in chemical taxonomy,¹² and, for a few flavanoids, is such that commercial extraction¹³ is possible. Certain flavanoid polymers are also capable of extraction, and these are of importance in the leather tanning, oil-well drilling and adhesive industries.

The use of flavanoids in pharmacology has now become

important, and the effects of flavanoids have been studied¹⁴ in the treatment of many clinical conditions. In particular, a mixture of flavanoids, containing hesperidin (XVI), known as "vitamin P" has been found to reduce capillary



fragility and permeability.

The complexity and versatility of many flavanoids have been investigated and used, largely through studies of simpler compounds based on the flavan skeleton.

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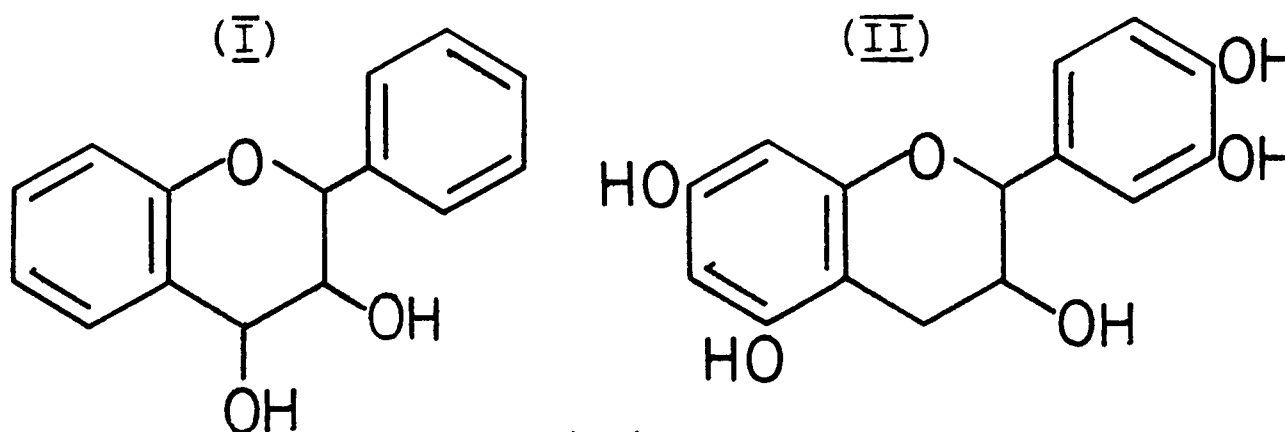
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C H A P T E R I

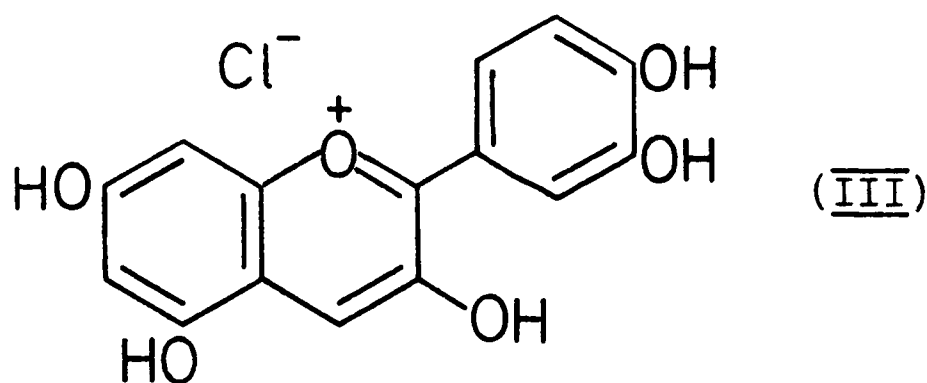
FLAVAN-4-OLSIntroduction

Flavan-3:4-diols (I) have for some time been recognised¹⁻³ as an important class of natural products. They occur



widely in tannin extracts,^{4,5} usually with other flavanoids, the more important of which are flavan-3-ols (catechins), e.g., (II) and the tannins themselves, some of which may be⁶ polymers of flavans.

The natural occurrence of flavan-3:4-diols is relevant also in view of their relationship to the anthocyanidins, or flavylium salts, e.g., cyanidin (III). Treatment of flavan-3:4-diols with acid gives flavylium salts in low yield,



together with large amounts of polymeric materials known as phlobaphenes,^{7,8} so that polymerisation is the preferred path. Catechins could well be a by-product of anthocyanidin formation in nature,^{4,7,9} and catechins have been obtained from flavan-3:4-diols,¹⁰ so that many workers^{4,9,10} now regard flavan-3:4-diols as precursors of condensed tannins. Polymerisation of the diols themselves has been observed,¹¹⁻¹³ and combination of 2:3-diols with catechins has also been suggested.¹⁴

The Stereochemistry of Flavan-3:4-diols.

The growing importance of flavan-3:4-diols has led to considerable interest in the stereochemistry both of the natural products,^{8,15-18} and of those prepared by various synthetic routes.¹⁹⁻²⁷

The easiest synthetic route to flavan-3:4-diols is by reduction of 3-hydroxyflavan-4-ones, and as the usual methods of preparing these compounds, those of Reichel and Steudel²⁸ and Limaye,²⁹ have been shown to give 2:3-trans-stereochemistry,^{24,30} work on the stereochemistry at the 4-position of the reduction products of flavan-4-ones, has been limited^{LARGELY} to 2:3-trans compounds.

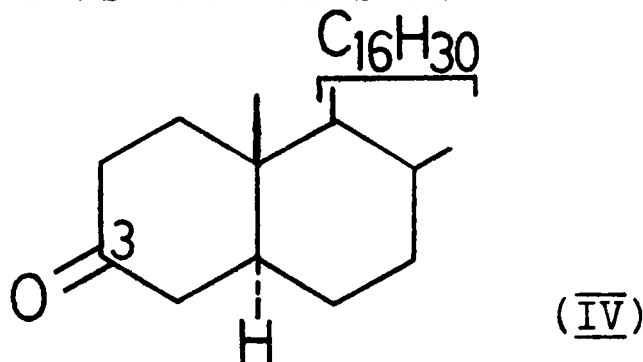
The Reduction of Flavan-4-ones.

Reduction of 3-hydroxyflavan-4-ones by different methods^{20-25,31.} gives different stereochemistry at the 4-position.

It is essential to the development of stereospecific methods of reduction to know which methods give which stereochemistry.

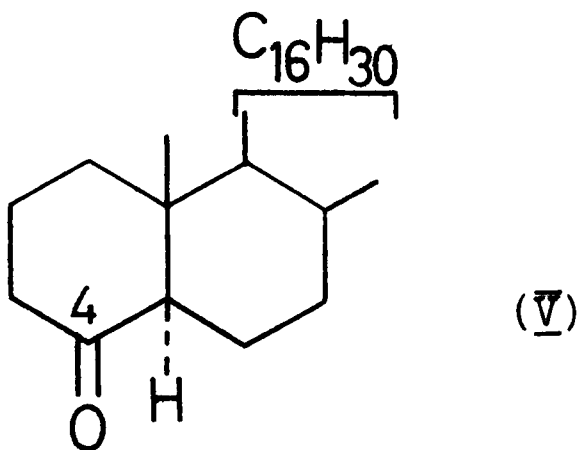
The relevant information for steroidal ketones is relatively well-known,^{32,33} and results are predictable.

5 α -Cholestan-3-one, (IV), for example, is an unhindered ketone and follows the rules laid down by Klyne,³³ viz. that



reduction with lithium aluminium hydride would give an equatorial hydroxyl group and that catalytic hydrogenation in acid solution would give an axial hydroxyl group, but in neutral solution, the equatorial isomer would be obtained.

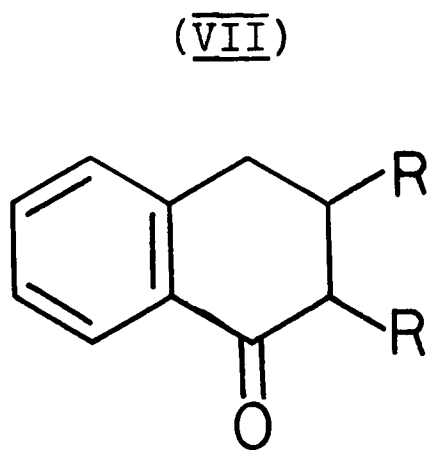
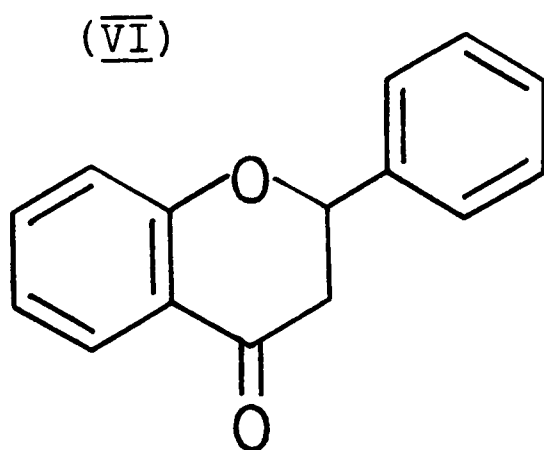
5 α -Cholestan-4-one, (V), on the other hand, behaves



as a typical hindered ketone on reduction,^{34,35} and the axial alcohol is obtained ~~both~~³⁶ on reduction with lithium aluminium hydride, and with a mixture of lithium aluminium hydride and aluminium chloride,³⁵ and on hydrogenation in acetic acid solution.³⁷

Flavanoids do not seem to follow this pattern, a fact which has caused considerable confusion about the assignment of stereochemistry to flavan-3:4-diols^{20-24,35}. In this connection, it must be remembered that the rules involved^{32,33,37} have been developed from work of steroids, and, though applicable to those conformationally rigid molecules, may not apply to relatively labile flavanoid molecules.³⁸ Hardy and Wicker³⁹ have emphasised that the assignment of conformations to the reduction products of substituted cyclohexanones should not be based solely on arguments from such generalised rules, and this seems to be particularly relevant to the flavan-4-ones.

The stereochemical course of reduction of flavan-4-ones, (VI), has been compared⁴⁰ with that of reduction of formally



similar tetral-1-ones, (VII). Several generalisations about the course of reduction by various methods become apparent, only if a revision of the accepted conformations of the two reduction products of flavan-4-one, viz. α - and β -flavan-4-ols, is made.

THE HYDROXYL GROUP IN

Until recently, the conformation of β -flavan-4-ol has been assigned as axial, and that of flavan-4 α -ol as equatorial.²⁷ The conformations of several substituted flavan-4-ols have been assigned, in this way, by analogy. It has been shown, however, by n.m.r. examination of the epimeric 3-bromo-4'-methoxy-6-methylflavan-4 β -ols,⁴¹ that the hydroxyl group in flavan-4 β -ols bears a 2:4-cis relationship to the aryl group at the 2-position, and is equatorial. Other work on flavan-4 β -ols^{42,43} and on flavan-3:4-diols^{44,45} has confirmed this finding, which implies that the hydroxyl group in flavan-4 α -ols bears a 2:4-trans relationship to the aryl group at the 2-position, and is axial.

The Aim of the Present Work.

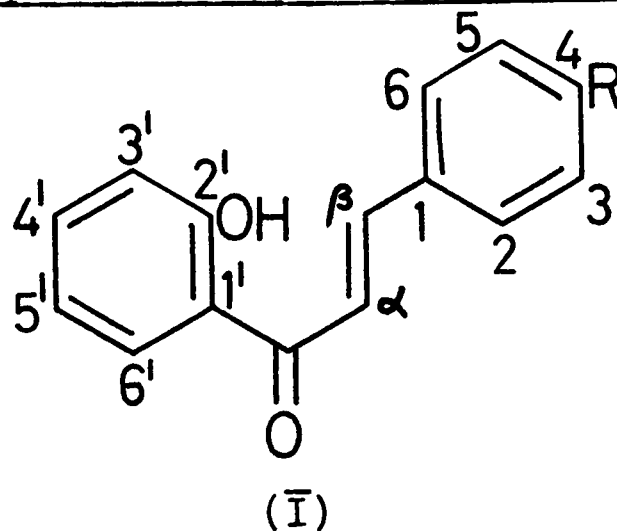
The aim of present work is to synthesise simple compounds in the α - and β -flavan-4-ol series, to examine their nuclear magnetic resonance spectra and to establish the configurations at the 4-position and the conformations of

the heterocyclic ring.

In the course of the synthesis of these simple flavanoids, it was hoped that general procedures would be found, which would be applicable to the syntheses of the naturally occurring flavanoids, peltogynol and cyanomaclurin (Chapters 2 and 3 respectively).

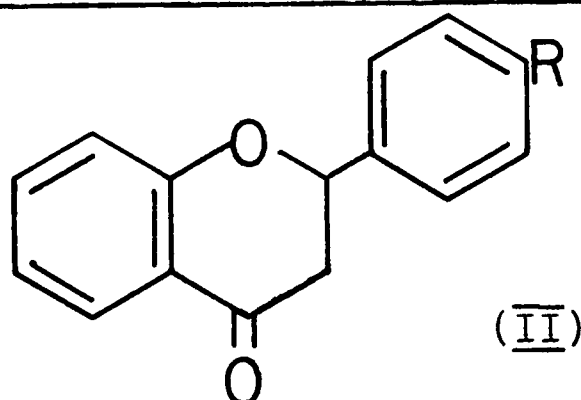
Discussion.

The Preparation of 2'-Hydroxychalcones.



2'-Hydroxychalcone ($\bar{\text{I}}$: R=H), 2'-hydroxy-4-methoxychalcone ($\bar{\text{I}}$: R=OCH₃) and 4-carboxy-2'-hydroxychalcone ($\bar{\text{I}}$: R=COOH) were synthesised in good yield, by the condensation of o-hydroxyacetophenone with benzaldehyde, anisaldehyde and 4-carboxybenzaldehyde respectively, in concentrated, aqueous ethanolic alkali.^{47,48.}

The Preparation of Flavan-4-ones.



Flavan-4-one ($\bar{\text{II}}$: R=H) was prepared in 80% yield by ring-closure of 2'-hydroxychalcone ($\bar{\text{I}}$: R=H) with dilute

aqueous ethanolic alkali.⁴⁸ 4'-Methoxyflavan-4-one

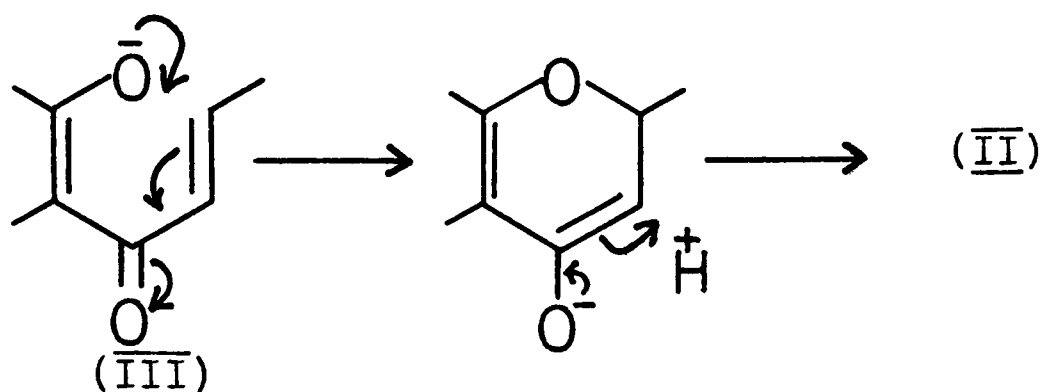
($\overline{\text{II}}$: R=H) was prepared in 57% by ring-closure of 2'-hydroxy-4-methoxychalcone ($\overline{\text{I}}$: R=OCH₃) with dilute ethanolic hydrochloric acid.⁴⁹ Attempts to cause ring-closure with alkali resulted in unchanged chalcone.

The reaction, 2'-hydroxychalcone $\rightleftharpoons$ flavan-4-one, is a reversible one, and one in which, in general, the formation of chalcone is favoured. When a flavan-4-one is treated with alkali, it immediately assumes the intense yellow colour of the chalcone. Chromatographic separation of flavan-4-ones on neutral or alkaline alumina cannot be effected for this reason : equilibria are established, which favour the formation of chalcones. These are strongly absorbed by alumina.

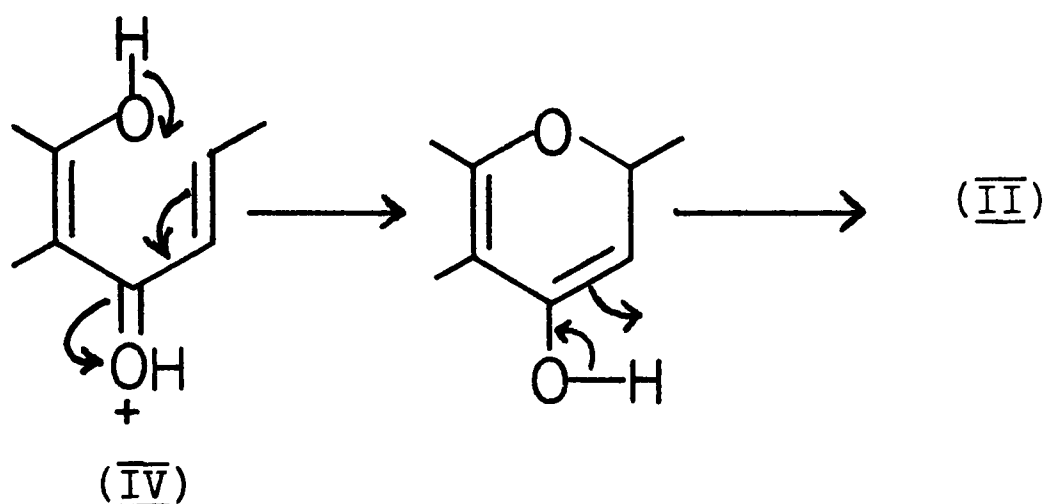
In the case of flavan-4-one, the position of equilibrium is well to the right, and flavan-4-one is produced in high yield from alkaline ring-closure. With 4'-methoxyflavan-4-one, however, the position of equilibrium is to the left; acid ring-closure^{49,50} is used, but the yield is lower.

Attempts to cause ring-closure of 4-carboxy-2'-hydroxy-chalcone in acid and in alkali failed. The position of equilibrium for this chalcone $\rightleftharpoons$ flavanone reaction, is therefore, well to the left. The mechanism of ring-closure by alkali involves attack on the β -carbon atom of the

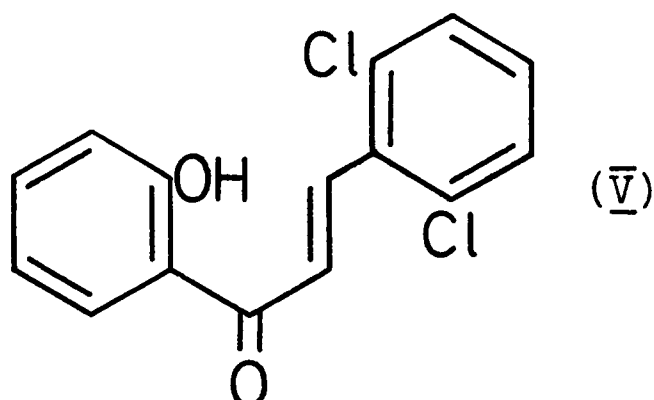
chalcone by the phenoxide ion at the 2'-position (III);



ring-closure by acid proceeds by a similar movement of electrons stimulated by the protonation of the keto group (IV).

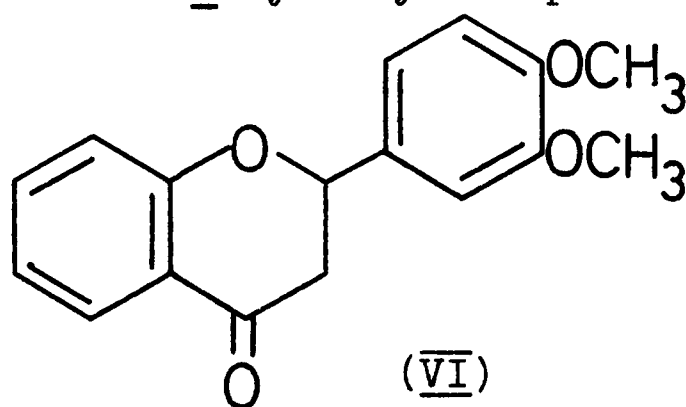


Any factor which reduces the development of a positive charge at the β -carbon atom, will move the position of the equilibrium between chalcone and flavanone towards the left. This has been encountered recently in the attempted ring-closure of 2:6-dichloro-2'-hydroxychalcone (V), by both acid and alkali.⁵¹ The failure to cause ring-closure is suggested to



result from the donation of electrons from the chlorine atoms, which reduces the development of a positive charge on the β -carbon atom. Such an electron donation could arise in the attempted alkaline ring-closure of the carboxychalcone. The carboxylate ion is known to donate electrons into an aromatic ring (e.g., *o*- and *p*- substitution products of electrophilic substitution in sodium benzoate: cf. *m*-substitution in benzoic acid). It is difficult, however, to see why the flavan-4-one is not produced under acid conditions.

3':4'-Dimethoxyflavan-4-one (VI) was prepared in 20% yield by condensation of *o*-hydroxyacetophenone with

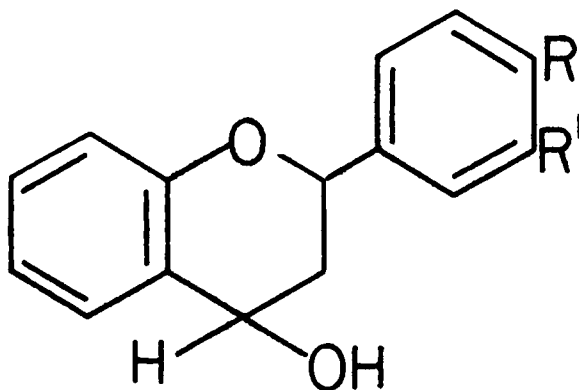


veratraldehyde and ring-closure in dilute aqueous sodium hydroxide solution.⁵² It is reported⁵¹ that the ring-closure of 2'-hydroxy-3:4-dimethoxychalcone in acid and in alkali is difficult.

Flavan-4 β -ols and their derivatives.

Reduction of flavan-4-ones with lithium aluminium

hydride yields flavan-4 β -ols (VII). Flavan-4 β -ol, (VII : R=R'=H), 4'-methoxyflavan-4 β -ol, (VII : R=OCH₃, R'=H) and



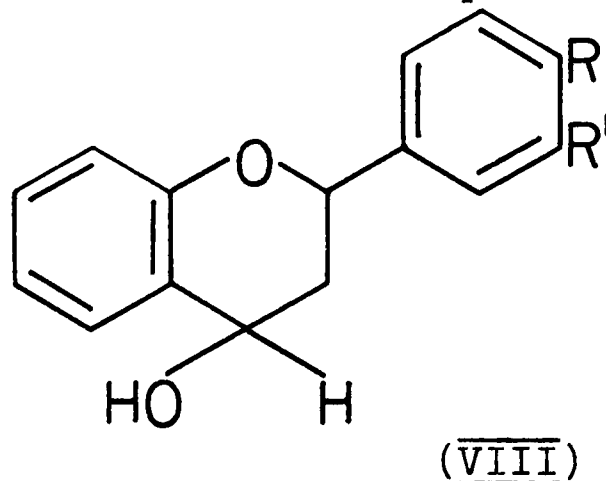
(VII)

3':4'-dimethoxyflavan-4 β -ol (VII : R=R'=OCH₃) were prepared in good yield from the corresponding flavan-4-ones by reduction with lithium aluminium hydride. Acetates of the first two were prepared by treatment with acetic anhydride and pyridine at room temperature. It appears, as will be seen later, that neither flavan-4-ols nor their acetates are suitable for accurate examination by nuclear magnetic resonance spectroscopy. The benzoates, which are much more suitable, were prepared by benzylation of the flavan-4-ols with benzoyl chloride and pyridine. The trimethylsilyl ether of flavan-4 β -ol was prepared in 63% yield by the general procedure of Waiss ⁵³et al. This ^{compound} also proved to be unsatisfactory for a fruitful n.m.r. examination.

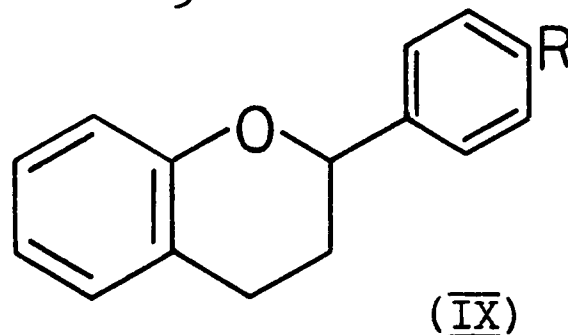
Flavan-4 α -ols and their derivatives.

Reduction of flavan-4-one (II : R=R'=H) with aluminium

⁵⁴amalgam and with magnesium and hydrochloric acid ⁵⁰ has been reported to afford flavan-4 α -ol (VII : R=R'=H) in very low yield. This work has been repeated and confirmed.

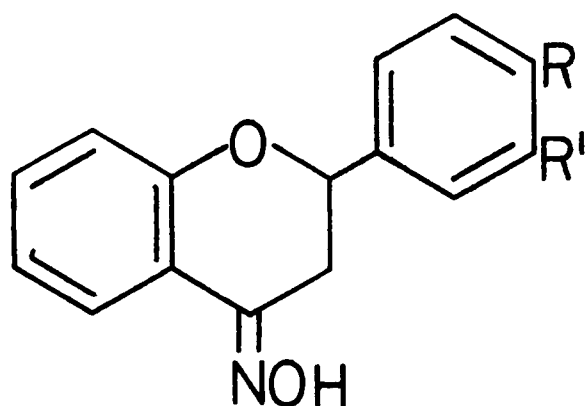
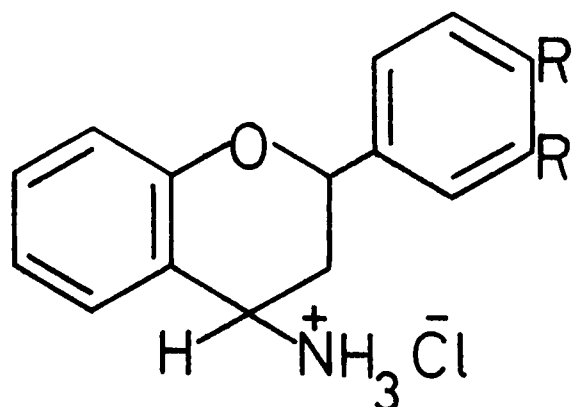


Reduction of flavan-4-one (II : R=H) and of 4'-methoxyflavan-4-one (II : R=OCH₃, R'=H) with the reagent lithium aluminium hydride-aluminium chloride yields flavan (IX : R=H) ⁵⁵ and 4'-methoxyflavan (IX : R=OCH₃) respectively, in good yield.



Reaction of these flavans with lead tetra-acetate in acetic acid yields 4 α -acetoxyflavan and 4 α -acetoxy-4'-methoxyflavan. ⁵⁶ Hydrolysis of the acetates by aqueous ethanolic hydroxide solution yields flavan-4 α -ol (VIII : R=R'=H) and 4'-methoxyflavan-4 α -ol (VIII : $\begin{matrix} R'=H \\ R=OCH_3 \end{matrix}$). This work was repeated and confirmed, though yields from the reactions with lead tetra-acetate were very poor (6-9%). Slightly higher yields (15-22%) were experienced when benzene was used as solvent.

Reaction of flavan-4-one ($\overline{\text{II}}$: $\text{R}=\text{H}$) with hydroxylamine hydrochloride in ethanol and pyridine gives the oxime ($\overline{\text{X}}$: $\text{R}=\text{R}'=\text{H}$). Reduction of this with lithium aluminium

($\overline{\text{X}}$)($\overline{\text{XI}}$)

hydride and treatment with dilute hydrochloric acid yields the amine hydrochloride ($\overline{\text{XI}}$: $\text{R}=\text{R}'=\text{H}$), which, on reaction with nitrous acid in acetic acid, yields a mixture of
²⁷
 flavan-4 α -ol and its acetate. This work has been repeated and confirmed. The syntheses of 4'-methoxyflavan-4 α -ol ($\overline{\text{VIII}}$: $\text{R}=\text{OCH}_3, \text{R}'=\text{H}$) and 3':4'-dimethoxyflavan-4 α -ol ($\overline{\text{VIII}}$: $\text{R}=\text{R}'=\text{OCH}_3$) have been carried out via the formation of the oximes, ($\overline{\text{X}}$: $\text{R}=\text{OCH}_3, \text{R}'=\text{H}$ and $\text{R}=\text{R}'=\text{OCH}_3$) and the amine hydrochlorides, ($\overline{\text{XI}}$: $\text{R}=\text{OCH}_3, \text{R}'=\text{H}$ and $\text{R}=\text{R}'=\text{OCH}_3$). Some care had to be taken with the isolation and purification of the amine hydrochlorides. Decomposition of the reduction mixture with the minimum amount of hydrochloric acid, produces the hydrochloride as a fine white powder, which is collected with difficulty at the pump.

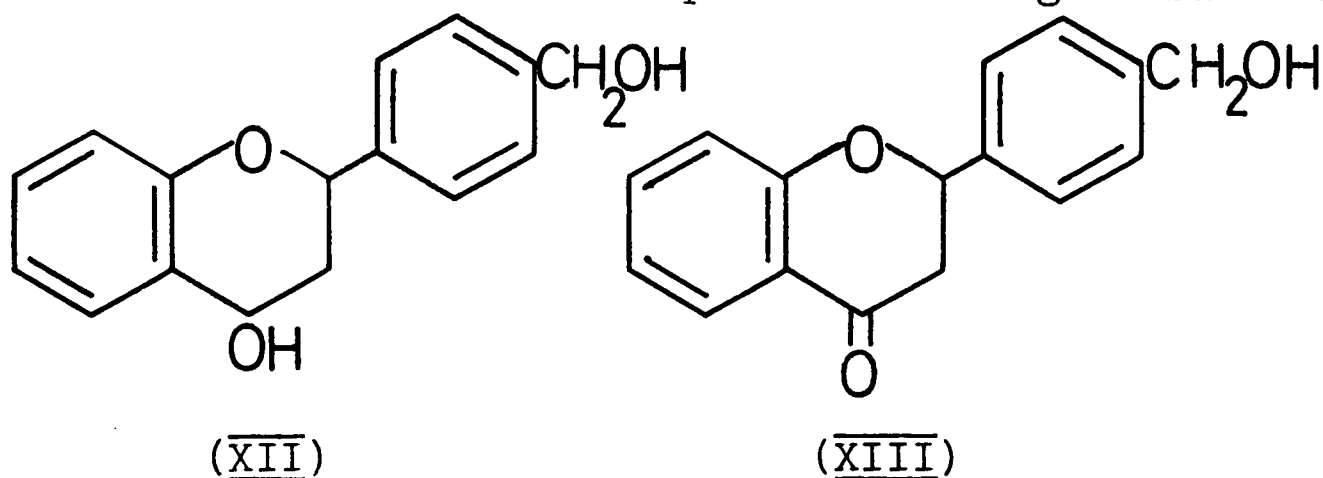
The aqueous layer contains the hydrochloride in solution and careful recrystallisations of the solid and of ^{later crops from} this solution are necessary to obtain pure material in good yield. Acetates of flavan-4 α -ol and of 4'-methoxyflavan-4 α -ol were prepared by treatment with acetic anhydride and pyridine, and benzoates of all three ^{alcohols} were prepared by treatment with benzoyl chloride and pyridine. Other 4 α -substituted flavans have recently been made ⁵¹ via the oxime route. The overall yield of 4 α -benzoate from 4-one is 20-30%; of the methods employed at present to synthesise flavan-4 α -ols and their derivatives, the oxime route thus appears to be by far the most useful.

The preparation of the trimethylsilyl ether of flavan-4 α -ol was attempted using the same conditions as for the 4 β -ol. The product was a mixture of 4 α -ol and its trimethylsilyl ether: its infra-red spectrum showed hydroxyl absorption as well as absorption resulting from the trimethylsilyl ether, and its n.m.r. spectrum showed the presence of two superimposed spectra, one identical to that of flavan-4 α -ol and the other similar to that of the 4 β -trimethylsilyl ether. Experiments were carried out with longer reaction times, each of which yielded the same product.

Oxidations of Flavan-4-ols by Activated Manganese Dioxide.

A number of flavan-4-ols, in dry benzene solution, were treated with ⁵⁷ ~~equal~~ ^{their own} weights of activated manganese dioxide ⁵⁸ at room temperature for 12 days. Oxidation to the corresponding flavan-4-one occurred in good yield. Several flavan-3:4-diols were oxidised in this way, and, under the conditions ⁵⁹ used, no oxidation of the 3-hydroxyl group occurred.

It had been hoped that the specificity of the reagent towards secondary benzylic alcohols in the presence of primary benzylic alcohols ⁵⁸ could be tested by oxidation under these conditions, of the hydroxymethylflavan-4-ol (XII), which could be derived from the product of ring-closure of



4-carboxy-2'-hydroxychalcone (I : R=COOH) by reduction with lithium aluminium hydride. If the ring-closure had been effected, the synthesis of this diol (XII) and its oxidation product (XIII) would have given increased confidence in the use of activated manganese dioxide in the synthesis of tri-O-methylpeltogynol (Chapter 2).

These model oxidations showed that when the number of substituents in the A and B rings increases, the yield decreases and the residual manganese dioxide becomes more finely divided. For example, the oxidation of flavan-4 α -ol to flavan-4-one proceeded in 82% yield, and residual reagent was removed by one filtration through Whatman no. 1. filter paper: the oxidation of 4'-methoxyflavan-3:4-trans- diol to 3-hydroxy-4'-methoxyflavan-4-one proceeded in 65% yield, and residual reagent was removed after five filtrations through the same quality filter paper.

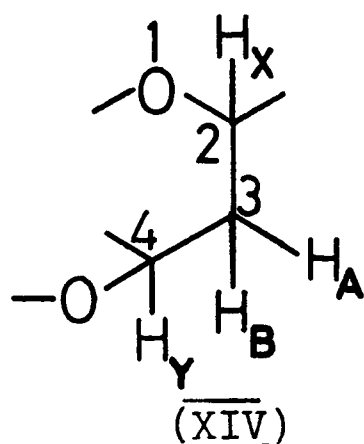
The Examination of Flavan-4-ols by Nuclear Magnetic Resonance Spectroscopy.

The accurate examination of flavan-4-ols by n.m.r. spectroscopy, for conformational studies, is hampered by several considerations. Some of these lie within the technique of n.m.r. spectroscopy: at present, the concentrations of solutions to be examined for fine structural details of signals, have usually to be in excess of 0.1 millimoles in 0.4 ml. of solvent. For simple flavan-4-ols, this means that a solubility of ca. 6% in the solvent chosen is a minimum value. Convenient solvents for examining these spectra are chloroform and benzene, and the solubility of

flavan-4-ols in these solvents rarely reaches this value. An extension of the range of suitable solvents might overcome this limitation.

Another limitation inherent in the technique of n.m.r. spectroscopy lies in the use of spin-spin decoupling units in instruments of relatively low frequency. As the energy of irradiation of a certain portion of a spectrum increases, the signal-to-noise ratio decreases, and it is, at present, impossible to deal with fine structural details of a complex signal on the 60 Mc/s instrument in this Department. This limitation is linked with that of solubility, for to compensate for the lowering of the signal-to-noise ratio on irradiation, the concentration of the solution must be increased greatly if useful information is to be obtained from the spectrum.

Other limitations were found to be intrinsic in the compounds themselves. The system, which was studied, is the ABXY system (XIV), which is manifest as a 24-line spectrum.



{ Throughout this volume, tau values are designated }²⁶
{ as τ . }

The AB part of the spectrum is well-separated from the X and Y portions, and consists of 16 lines at $\tau = 7.0 - 8.5$ ~~p.p.m.~~ The X and Y portions each consist of 4 lines. It was found that in flavan-4-ols, the X and Y signals at $\tau = 4.8 - 5.5$ overlapped to an extent which made exact assignment impossible. Separation of the spectra of H_X and H_Y would occur if an ester of the 4-hydroxyl group were prepared, when H_Y would move downfield.⁶⁰ Acetates were prepared and examined: exact assignments for conformational studies on these compounds, were not possible, for in each case the acetate methyl group appeared in the region $\tau = 7.0 - 8.5$ superimposed on the AB part of the spectrum. Benzoates, however, are suitable for examination, as like the acetates, their solubility in chloroform and benzene is fairly high, and there are no methyl groups present to obscure the AB spectrum. The benzoates of flavan-4 α -ol, 4'-methoxyflavan-4 α -ol, 3':4'-dimethoxyflavan-4 α -ol, and their 4 β -isomers were prepared and examined in deuterio-chloroform and in benzene solution.

4 β -Compounds.

The spectra of the ABXY system in the β -benzoates were identical in the two solvents and consisted of 24 lines.

The H_Y portion, corresponding to the proton at the 4-position was seen as a quartet at $T = 3.3$ to 3.60 , having observed splittings, due to spin-spin interactions with H_A and H_B (H_{3a} and H_{3b}), of 6.6 and $9.0 - 10.2$ cycles per second.

The position of this signal is in accord with the expected decrease in ^{*T value*} ~~chemical shift~~ of a tertiary proton, ^{*attached to*} ~~gem - to~~ ^{*a carbon atom carrying*} an hydroxyl group which has been benzoylated (ca. 1.3 p.p.m).

The H_X portion, corresponding to the proton at the 2-position, was seen also as a quartet, at $T = 4.50 - 4.75$, having observed splittings of 2.4 and 10.2 c/s. The AB portion, corresponding to the protons at the 3-position was seen as a 16-line spectrum at $T = 6.05$ to 7.90 ; the observed splittings were $12.0 - 13.4$, $2.7 - 3.0$, $10.7 - 10.8$, $6.0 - 6.6$ and $9.3 - 9.7$ c/s.

The coupling constants of the ABXY interactions, which are reflected approximately in the observed splittings, were determined from the spectra using the procedure of Pople,⁶¹ Schneider and Bernstein. The coupling constants of the protons at C₂, C₃ and C₄ in the benzoates of flavan-4 β -ols, are: $J_{3a,3b} = 12.9 - 13.4$; $J_{2,3a} = 2.1 - 2.6$; $J_{2,3b} = 10.0 - 10.7$; $J_{4,3a} = 5.5 - 6.3$ and $J_{4,3b} = 9.9 - 10.9$ c/s. These values are in good agreement with other measurements of the coupling constants in flavan-4 β -ols and their derivatives.⁴³

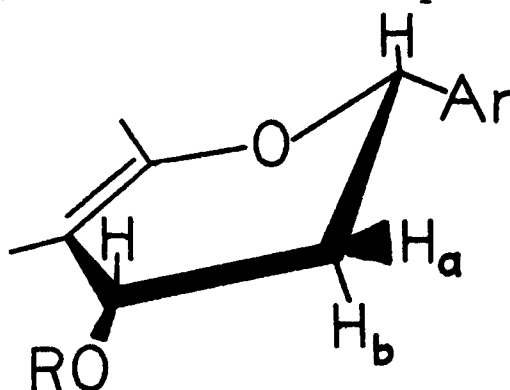
These coupling constants may now be used in studies on the conformation of the heterocyclic ring in flavan-4 β -ols, by translation into dihedral angles, by the calculations of Karplus.⁶² These calculations relate $J_{a,b}$, the magnitude of the coupling constant between protons a and b in the system (XV), to the dihedral angle, ϕ , between the planes



(XV)

$C_1C_2H_a$ and $C_1C_2H_b$. Experimental observations and the calculations are in good agreement and can be expressed as a graph of ϕ° against J c/s.⁶³

The coupling constants measured in flavan-4 β -ols yield the following dihedral angles: $\phi_{2,3a} = 54-58^\circ$ (or $108-110^\circ$), $\phi_{2,3b} = 158-168^\circ$ only, $\phi_{4,3a} = 29-34^\circ$ (or $125-130^\circ$) and $\phi_{4,3b} = 158-175^\circ$ only. The bracketed values of ϕ are alternative values obtained from the graph, which do not apply to this molecule. The dihedral angles above fit a conformational model of the benzoate of flavan-4 β -ol (XVI), which shows that the relationship between the 4-oxygen



(XVI : $R=CO. C_6H_5$)

function and the 2-aryl group is 2:4-cis, which is in agreement with recent publications,⁴³ and that the 4-oxygen function occupies the 4-equatorial position. Although the spectra of the 4 β -ols and their acetates do not enable such a rigorous examination to be made, the structures of their ABXY systems are very similar; from a study of models of the β -compounds examined, it appears that they all possess very similar conformations of the heterocyclic ring.⁴³

4 α -Compounds.

The spectra of the ABXY system in the α -benzoates were not identical in the two solvents. In deuteriochloroform, the H_Y portion, the spectrum of the proton at the 4-position, is seen as a triplet at $T = 3.6-3.8$, with observed splittings of 3.0 and 3.0 c/s. The H_X portion, that due to the proton at the 2-position, is seen as a quartet at $T = 4.4-4.75$, with observed splittings of 5.4-6.0 and 8.4-9.6 c/s. The AB portion, due to the protons at the 3-position, appears as a complex spectrum at $T = 7.2-8.05$.

The H_Y spectrum is seen to differ from that observed in the β -benzoates, as expected. The triplet is a form of a quartet, whose two splittings are equal: further, the inversion of configuration at C₄ is compatible with the

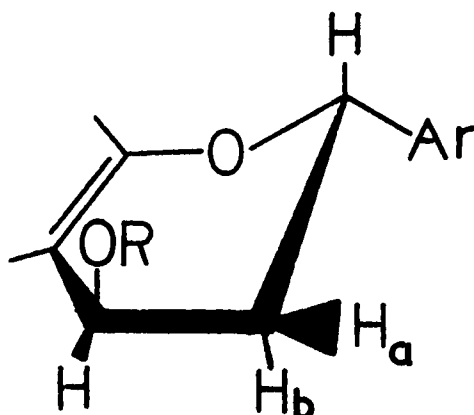
dihedral angles obtained from the splittings of the triplet. However, inversion at C_4 should not cause serious change in the structure of the H_X spectrum unless change in the conformation of the ring has also occurred. The observed splittings of H_X and H_Y for the α -benzoates, which are in agreement with those observed in the α -acetates, also measured in deuteriochloroform, are only compatible with a "boat" conformation, quite unlike the structure (XVI). From a consideration of interatomic distances in various conformations of Dreiding models of 4α -compounds, it was difficult to see why such a conformation should exist.

The spectra of the α -benzoates in deuteriochloroform did not enable a rigorous examination to be made: the AB spectrum, being less well-spread than that observed in β -benzoates, had not been assigned at all. This meant that splittings of the H_X and H_Y spectra had had to be equated with coupling constants without the strict procedure of Pople, Schneider⁶¹ and Bernstein, and it is clear that true coupling constants must be obtained before conformational studies can begin.

The spectra of the α -benzoates were measured in benzene, in an attempt to spread out the AB spectrum. Since benzene is a fairly polar solvent for n.m.r. spectroscopy, it was hoped that it would affect the chemical shift of one of the protons at C_3 with respect to the other, thus increasing the

difference in chemical shift between H_{3a} and H_{3b} , giving rise to an AB spectrum more conducive to exact assignments. This was observed, together with a change in the structure of the H_X spectrum, and the AB spectrum was analysed. A quartet is still observed, at $\tau = 4.45-4.80$, but with observed splittings of 3.3-3.6 and 10.05-10.65 c/s, i.e., similar to those observed in β -benzoates. The complete analysis of the spectra showed the presence of 24 lines (2 superimposed in the H_Y triplet), and the true coupling constants, determined by the Pople, Schneider and Bernstein treatment, are : $J_{3a,3b} = 14.6-14.85$; $J_{2,3a} = 1.6-1.74$; $J_{2,3b} = 11.6-12.4$; $J_{4,3a} = 2.3-2.6$ and $J_{4,3b} = 3.67-3.73$ c/s. Published data of α -compounds is very limited and is confined to sums of coupling constants, obtained from the half-height width of H_X and H_Y spectra. However, the data for the one α -benzoate studied²¹ are in good agreement.

The coupling constants yield the following dihedral angles: $\phi_{2,3a} = 60-61^\circ$ (or $103-104^\circ$), $\phi_{2,3b} = \text{ca. } 180^\circ$ only, $\phi_{4,3a} = 54-56^\circ$ (or $108-110^\circ$) and $\phi_{4,3b} = 48^\circ$ (or 117°), which fit a conformational model of the benzoate of flavan-4 α -ol (XVII), which shows that the relationship between the



(XVII) : $R = CO. C_6H_5$

4-oxygen function and the 2-aryl group is 2:4-trans, and that the 4-oxygen function occupies the 4-axial position.

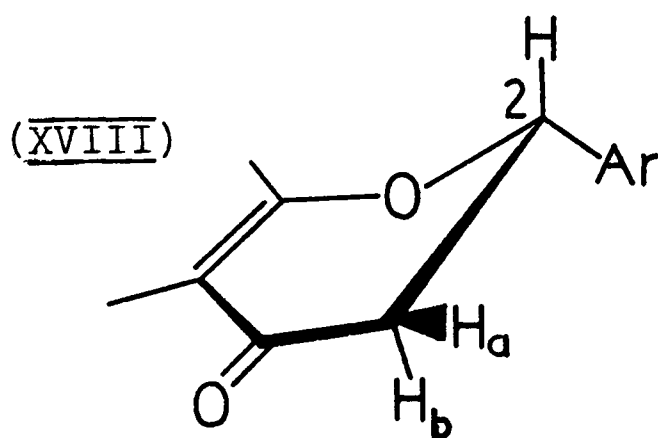
Having analysed the spectrum of an α -compound, it is easy to see that an anomalous spectrum, as observed in chloroform solution, could arise, owing to the relatively small difference in chemical shift of the 3a and 3b protons, approaching the value of $J_{3a,3b}$, the gem-coupling constant.⁶⁴ In benzene solution, the difference in chemical shift, Δ

$T_{3a,3b}$, between the 3a and 3b protons is 21.2 c/s, and $J_{3a,3b}$ is 14.6-14.85 c/s. In deuteriochloroform, $J_{3a,3b}$ ⁶⁵ should be in the range 12-15 c/s, and, calculated from the relative spread of AB spectra in both solutions, $\Delta T_{3a,3b} =$ ca. 16.8 c/s. If $J_{3a,3b}$ has approximately the same value (as it does for the β -benzoates in both solutions) of 14.6-14.85 c/s, the difference between $J_{3a,3b}$ and $\Delta T_{3a,3b}$ would be only about 2 c/s. In the β - compounds, $J_{3a,3b} - \Delta$
 $T_{3a,3b} =$ ca. 15 c/s.

The Examination of other Flavanoids by Nuclear Magnetic Resonance Spectroscopy.

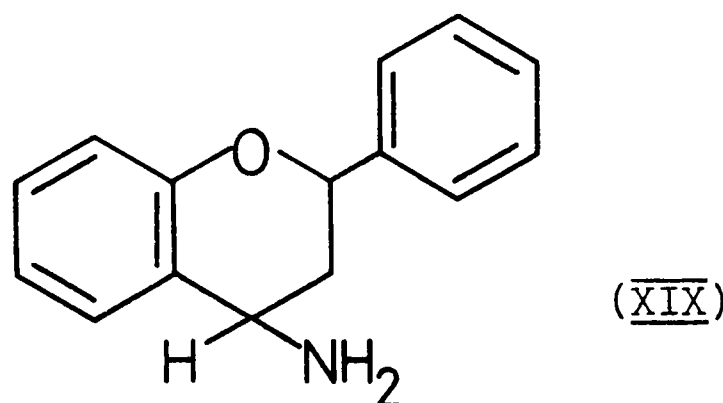
A number of flavanoids have been examined in order to determine the characteristic spectra of flavanoids with particular structures. Several flavans, flavan-4-ones and

2:3-trans-flavan-3:4-diacetates have been examined with a view to establishing the conformations of the heterocyclic ring. Flavans yielded no useful information, since the proton interactions are so complex. Until accurate spin-spin decoupling can be performed on these compounds, it is unlikely that their spectra can be rigorously assigned. Flavan-4-ones appear to exist in the conformation (XVIII), with the ring planar except for the 2-carbon atom, as do



2:3-trans-⁻³⁻hydroxyflavan-4-ones. These findings agree with published work. 2:3-trans-Flavan-3:4-cis-diacetates exist as in conformation (XVII), with the 3-oxygen function occupying the position of H_a; the 3:4-trans-diacetates exist as in conformation (XVI), again with the 3-oxygen function in place of H_a.

The spectrum of 4-aminoflavan (XIX) was measured in



chloroform. A rigorous examination and assignment of the AB part of the spectrum was not possible, owing to the rapid rate of decay of this compound. However, the H_X and H_Y portions of the spectrum are both in excellent agreement with those of 4β - compounds, viz., the C_2 observed splittings of 2.4 and 10.8 c/s (cf. 2.4 and 10.2 c/s), and those for C_4 , 6.6 and 10.8 c/s (cf. 6.6 and 10.2 c/s). There is good reason, therefore, to assign a 4-equatorial position to the amino group. This means that reaction of this compound with nitrous acid gives inversion at the 4-position, with production of 4-axial alcohol and acetate.

One spectrum does not appear to fit the pattern of flavanoids: this is of the trimethylsilyl ether of flavan- 4β -ol. This spectrum has not been examined rigorously, because the H_Y part of the spectrum has moved downfield on silylation to such an extent as to occur in the aromatic absorption at $\tau = 2.5-3.4$, which now integrates for 10 protons. The spectrum in deuterochloroform however, shows the H_X position as a quartet at $\tau = 4.8$ to 5.05, with observed splittings of 5.7 and 8.4 c/s. The AB part of the spectrum is narrow, occurring at $\tau = 7.5-8.3$. These two features indicate the possibility of inversion at the 4-position, on silylation, since this spectrum is similar to the anomalous

spectra of 4 α - compounds in deuteriochloroform. However, if this is the case, then it is difficult to see why flavan-4 α -ol does not silylate completely to give the 4-equatorial trimethylsilyl ether. Perhaps approach of the bulky reagent to the hydroxyl group at the 4-axial position is sterically difficult. Further work on these compounds is required to shed light on the compounds themselves, and on the mechanism of their formation.

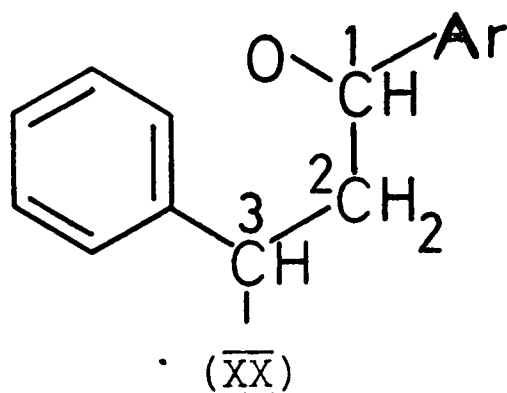
The Reliability of Conformational Analysis by n.m.r. Spectroscopy.

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The calculations of Karplus⁶² have made possible the study of conformations by n.m.r. spectroscopy, and have been applied to many systems, some of which have given rise to anomalous results.⁶⁶ The calculations are based on an open, chain system of aliphatic carbon atoms to which protons are attached. The substitution of these protons by other atoms, or groups such as phenyl, hydroxyl etc., alters the system slightly,⁶⁷ and the exact relationship between coupling constant and dihedral angles may not hold. What is really required is a similar equation particular to each system studied, in order to avoid misuse of the technique.

In the case of flavanoids, the modifications of the

original Karplus system are the substitution of two aryl groups and an oxygen atom in the propane chain (XX). The bond angles of the carbon atom 1, 2 and 3 are still



tetrahedral, and apart from the position of the particular protons in the n.m.r. spectrum, this system should behave normally.

A sufficient number of flavanoid compounds have now been studied to be able to say that the system does behave as expected. Flavanoid compounds of particular known stereochemistry have coupling constants and dihedral angles in accord with molecular models, and probably the more important source of error lies not in the application of the Karplus calculations, but in the use of Dreiding models and a protractor in trying to determine the exact position of an electron cloud.

EXPERIMENTAL SECTION

The following notes apply to all the Experimental Sections :

Melting points were determined on a Kofler block: melting points of mixtures were determined in capillary tubes.

Micro-analyses were carried out by Drs. Strauss and Weiler.

Nuclear magnetic resonance spectra were measured on 60 Mc/s AEI RS2 and Perkin-Elmer R 10 instruments, by Mrs. E.E. Richards. Mass spectra were measured on an AEI MS9 high resolution mass spectrometer by Dr. R.T. Aplin.

Infra-red spectra were measured on a Unicam SP 200 spectrometer except where stated otherwise: ultra-violet spectra were measured on a Unicam SP 800 spectrometer.

Alumina used for chromatography was Grade H (P. Spence and Sons, Ltd.,). 10% Deactivated alumina contained 10 ml. of 10% acetic acid per 100 g., and 5% deactivated, 5 ml. per 100 g. Thin-layer chromatography was carried out on unbaked glass plates coated with "Kieselgel H" silica. Plates were developed by fuming with iodine vapour, except where stated otherwise.

Light petroleum refers to the fraction boiling between 40-60°.

Dry benzene, ether and tetrahydrofuran were prepared by

standing the liquids over sodium wire for 48 hours, distillation and storage over fresh sodium wire. In the case of tetrahydrofuran, a small quantity of benzophenone was added before distillation: the dark blue colour indicates its dryness. Dry pyridine was prepared by distillation and storage over potassium hydroxide pellets. Other common liquid reagents, such as acetic anhydride and benzoyl chloride were redistilled before use. Chloroform, ether and ethyl acetate extracts were dried over anhydrous sodium sulphate.

⁴⁶
2'-Hydroxychalcone : (33g. 80.5%), m.p. 88-9⁰, was prepared by the condensation of benzaldehyde with o-hydroxyacetophenone in strong aqueous ethanolic potassium hydroxide solution; lit. ⁴⁶ m.p. 88-9⁰.

Flavan-4-one : (16.5g. 80%), m.p. 77-8⁰, was prepared from 2'-hydroxychalcone (20.62g.) by ring-closure in dilute aqueous ethanolic potassium hydroxide; lit. ⁴⁸ m.p. 76⁰.

⁶⁸
Flavan-4 β -ol : (3.1g. 70.2%), m.p. 147-8⁰, was prepared by reduction of flavan-4-one (4.38g.) with lithium aluminium hydride; lit. ⁶⁸ m.p. 147-8⁰.

⁶⁸
4 β -Acetoxyflavan : (0.8g. 80%), m.p. 98-9⁰, was prepared

by acetylation of flavan-4 β -ol (0.84g.) with pyridine and acetic anhydride; lit. ⁶⁸ m.p. 97-8 $^{\circ}$.

4 β -Benzoyloxyflavan ⁴² : (836.9 mg. 87%), m.p. 123-5 $^{\circ}$, was prepared from flavan-4 β -ol (658.3 mg.) by benzylation with pyridine and benzoyl chloride, followed by chromatography of the product on 5% deactivated alumina; lit. ⁴² m.p. 120-123 $^{\circ}$.

Flavan-4 β -ol : trimethylsilyl ether - Prepared from flavan-4 β -ol (156.4 mg.) by the general method of Waiss et al. ⁵³ The trimethylsilylether (132.4 mg. 63%) separated from carbon tetrachloride as colourless needles, m.p. 79-80 $^{\circ}$, (Found : C 72.4, H 7.2. C₁₈H₂₂O₂ Si requires 72.45, H 7.4%), $\nu_{\max}$ (nujol) : 1245 (sym. CH₃ def.), 842 and 755 cm⁻¹ (Si - CH₃ Str.), no OH absorption.

4-Oximinoflavan ²⁷ : (15.77g. 98.4%), m.p. 169-171 $^{\circ}$, was prepared from flavan-4-one (15.0g.) by treatment with hydroxylamine hydrochloride and pyridine in boiling ethanol; lit. ²⁷ m.p. 170-171 $^{\circ}$.

4-Aminoflavan Hydrochloride ²⁷ : (3.57g. 46.7%), m.p. 269-272 $^{\circ}$, was prepared from 4-oximinoflavan (7.0 g.) by reduction with lithium aluminium hydride; lit. ²⁷ m.p. 268-270 $^{\circ}$.

4-Aminoflavan ²⁷ : was prepared from an aqueous solution

of a small amount of the hydrochloride by neutralisation with aqueous sodium hydroxide solution. The amine separated from methanol as a yellow oil.²⁷

Reaction of 4-Aminoflavan Hydrochloride with Nitrous Acid²⁷ - A mixture (2.13 g.), m.p. 82-106°, of 4a-acetoxyflavan and flavan-4a-ol resulted from the action of nitrous acid in acetic acid on 4-aminoflavan hydrochloride (3.0g.).

Flavan-4a-ol - The alcohol (1.56g. 60.1%), prepared from the above mixture by hydrolysis with boiling ethanolic potassium hydroxide solution (5%, 60 ml.), separated from light petroleum - benzene as colourless needles, m.p. 119-120°; lit.⁵⁴ m.p. 119°.

Flavan-4a-ol was also prepared in 2.1 and 2.9% yields respectively by reduction of flavan-4-one with aluminium amalgam⁵⁴ and with magnesium and hydrochloric acid.⁵⁰ With aluminium amalgam, flavan-4-one (97.2%) was recovered, and with magnesium and hydrochloric acid, the bis-pinacol (96%) was obtained, m.p. 254-5°; lit.⁵⁰ m.p. 255-6°.

Flavan⁵⁵ : (13g. 82%), m.p. 44-5°, was prepared from flavan-4-one (16.92g.) by reduction with lithium aluminium hydride and anhydrous aluminium chloride; lit.⁵⁶ m.p. 43-4°.

4a-Acetoxyflavan. - (a) 4a-acetoxyflavan (1.16g. 9.1%),

m.p. $85-6^{\circ}$, was prepared from flavan (10g.) by reaction with lead tetra-acetate in acetic acid.⁵⁵ Better, though still poor yields (15-22%) were obtained when benzene was used as solvent.

(b) 4 α -acetoxyflavan (45.1 mg. 95%), m.p. $86-7^{\circ}$, was prepared from flavan-4 α -ol (40 mg.) by acetylation with pyridine and acetic anhydride at room temperature; lit.⁵⁵ m.p. $85-6^{\circ}$.

4 α -Benzoyloxyflavan⁴² : (2.07g. 94%), m.p. $151-2^{\circ}$, was prepared from flavan-4 α -ol (1.51g.) by benzylation with pyridine and benzoyl chloride, followed by chromatography of the product on 5% deactivated alumina: lit.⁴² m.p. $150-151^{\circ}$.

Attempted Synthesis of Flavan-4 α -ol : trimethylsilyl ether.- Flavan-4 α -ol was treated with hexamethyldisilazane and pyridine in a stream of dry nitrogen.⁵³ The product, m.p. $60-70^{\circ}$, was a mixture of flavan-4 α -ol and its trimethyl ether, $\nu_{\max}$ (nujol): 3350 (OH Str.), 1245 (sym. CH₃ def.), 842 and 755 cm⁻¹ (Si - CH₃ Str.).

2'-Hydroxy-4-methoxychalcone⁴⁷ : (23.8g. 64%), m.p. $93-4^{\circ}$, was prepared by condensation of anisaldehyde with o-hydroxyacetophenone in concentrated aqueous ethanolic sodium hydroxide solution; lit.⁴⁷ m.p. $93-4^{\circ}$.

4'-Methoxyflavan-4-one⁴⁹ : (5.7g. 57%), m.p. $91-2^{\circ}$, was

prepared from 2'-hydroxy-4-methoxychalcone (10g.) by ring-closure with dilute hydrochloric acid; lit.⁴⁹ m.p. 91-2°.

4'-Methoxyflavan-4 β -ol⁵⁶ : (2.41g. 94.2%), m.p. 151-2°, was prepared from 4'-methoxyflavan-4-one (2.54 g.) by reduction with lithium aluminium hydride; lit.⁵⁶ m.p. 152-3°.

4 β -Acetoxy-4'-methoxyflavan. - 4'-Methoxyflavan-4 β -ol (1.0g.) was acetylated with pyridine and acetic anhydride at room temperature, to yield 4 β -acetoxy-4'-methoxyflavan (1.15g. 98.9%), which separated from ethanol as colourless prisms, m.p. 127-8°, (Found : C 72.45, H 6.1. C₁₈H₁₈O₄ requires : C 72.5, H 6.05%).

4 β -Benzoyloxy-4'-methoxyflavan. - 4'-Methoxyflavan-4 β -ol (50.61 mg.) was benzoylated with pyridine and benzoyl chloride, followed by chromatography on 5% deactivated alumina, to yield 4 β -benzoyloxy-4'-methoxyflavan (63.96 mg. 90%), which separated from light petroleum as colourless needles, m.p. 93-4°, (Found : C 76.7, H 5.55. C₂₃H₂₀O₄ requires : C 76.6, H 5.55%).

4'-Methoxy-4-oximinoflavan. - A solution of 4'-methoxyflavan-4-one (3.16g.), pyridine (3.2 ml.) and hydroxylamine-hydrochloride (3.2g.) in ethanol, was boiled under reflux for 1 hr. Ethanol was then removed by distillation and the

residue poured into cold water (30 ml.). The white precipitate was collected and recrystallised from aqueous ethanol. 4'-Methoxy-4-oximinoflavan (3.25g. 97%) separated as colourless needles, m.p. $174-5^{\circ}$, (Found : C 71.3, H 5.75, N 5.3. $C_{16}H_{15}NO_3$ requires C 71.4, H 5.6, N 5.2%), $\nu_{\max}$ (nujol): 3300(OH Str.), 1643 cm^{-1} , weak, (C=N Str.)

4-Amino-4'-methoxyflavan Hydrochloride. - A solution of the oxime (3.2g.) in dry ether (975 ml.) and dry tetrahydrofuran (97.5 ml.) was boiled under reflux with lithium aluminium hydride (3.29g.) for 12 hr. The green-coloured reaction mixture was cooled in ice and carefully treated with hydrochloric acid (2N, 500 ml.). 4-Amino-4'-methoxyflavan hydrochloride separated as a fine white powder and was recrystallised from water, from which it separated as colourless needles (2.2g. 63.5%), m.p., after sublimation to prisms at 180° , and after change of crystalline form to blunt needles at 240° , $270-272^{\circ}$, (Found : C 65.8, H 6.2, Cl 12.1, N 4.8. $C_{16}H_{18}ClNO_2$ requires : C 65.85, H 6.2, Cl 12.2, N 4.8%), $\nu_{\max}$ (nujol): $3550\text{ (NH}_3^+\text{ Str.)}$, $1578\text{ (as. NH}_3^+\text{ def.)}$, $1280\text{ (sym NH}_3^+\text{ def.)}$ and $770\text{ cm}^{-1}\text{ (NH}_3^+\text{ rocking)}$.

Reaction of 4-Amino-4'-methoxyflavan Hydrochloride with Nitrous Acid. - 4-Amino-4'-methoxyflavan hydrochloride (2.1g.) was dissolved in acetic acid (50 ml.) and water (50 ml.) and

the solution was added slowly with stirring to a solution of sodium nitrite (5g.) in water (12 ml.) and acetic acid (25 ml.). The mixture was stirred at room temperature for 30 min., at 50° for 40 min., and was then cooled and neutralised with powdered sodium bicarbonate (ca. 100g.). Water was added to promote solution of the bicarbonate, and the mixture was kept at 0° for 12 hr. A buff solid (1.88g.) was collected, washed with water and dried in a vacuum desiccator over calcium chloride. Its infra-red spectrum showed absorption at 3300 (OH Str.) and at 1738 cm^{-1} (acetate C=O Str.). The solid was a mixture of 4'-methoxyflavan-4 α -ol and its acetate.

4'-Methoxyflavan-4 α -ol. - The buff solid (1.87g.) was hydrolysed by treatment with boiling ethanolic potassium hydroxide solution (5%, 60 ml.) for 1 hr. The mixture was cooled, poured into cold water (500 ml.) and kept at 0° for 2 hr. A cream-coloured solid (1.18g. 64%) was collected, washed with water and dried. On recrystallisation from light petroleum - benzene, 4'-methoxyflavan-4 α -ol separated as colourless needles, m.p. 134-5°; lit. ⁵⁶ m.p. 131-2°.

4 α -Acetoxy-4'-methoxyflavan : (105.6 mg. 90.7%), m.p. 70-72°, was prepared from 4'-methoxyflavan-4 α -ol (100 mg.) by acetylation with pyridine and acetic anhydride; lit. ⁵⁶ m.p. 71°.

4 α -Benzoyloxy-4'-methoxyflavan. - 4'-Methoxyflavan-4 α -ol (760 mg.) was benzoylated with pyridine and benzoyl chloride. Chromatography on 5% deactivated alumina gave 4 α -benzoyloxy-4'-methoxyflavan (964 mg. 90%), which separated from light petroleum-benzene as colourless needles, m.p. 137-8 $^{\circ}$, (Found : C 76.6, H 5.55. C₂₃H₂₀O₄ requires : C 76.6, H 5.55%).

3':4'-Dimethoxyflavan-4-one⁵² : (6.69g. 19.7%), m.p. 124-5 $^{\circ}$, was prepared from veratraldehyde and o-hydroxyacetophenone by condensation and ring-closure in dilute aqueous sodium hydroxide solution; lit.⁵² m.p. 125 $^{\circ}$.

3':4'-Dimethoxyflavan-4 β -ol : (1.42g. 94%) was prepared from 3':4'-dimethoxyflavan-4-one (1.5g.) by reduction with lithium aluminium hydride (0.34g.) in dry ether (120ml.). The mixture was boiled under reflux for 3 hr. after which it was decomposed and worked up in the usual way. On recrystallisation from aqueous ethanol, the β -ol separated as colourless plates, m.p. 154-5 $^{\circ}$, (Found: C 71.3, H 6.25. C₁₇H₁₈O₄ requires: C 71.3, H 6.3%), $\nu_{\max}$ (nujol): 3500 cm⁻¹ (OH Str.), no ketone C = O Str.

4 β -Benzoyloxy-3':4'-dimethoxyflavan : (1.41g. 86%) was prepared from 3':4'-dimethoxyflavan-4 β -ol (1.2g.) by benzoylation with pyridine and benzoyl chloride, followed by chromato-

graphy on 5% deactivated alumina. The β -benzoate separated from light petroleum-benzene as colourless needles, m.p. $93-4^{\circ}$. (Found: C 73.9, H 5.7. $C_{23}H_{22}O_5$ requires: C 73.85, H 5.65%), $\nu_{\max}$ (nujol): 1705 cm^{-1} (benzoate C = O Str.), no hydroxyl absorption.

3':4'-Dimethoxy-4-oximinoflavan : (4.95g. 94%) was prepared from 3':4'-dimethoxyflavan-4-one (5.0g.) by treatment with hydroxylamine hydrochloride (5g.) and pyridine (5 ml.) in boiling ethanol (50 ml.) The oxime separated from ethanol as colourless needles, m.p. $156-7^{\circ}$, (Found: C 68.3, H 5.7, N 4.65. $C_{17}H_{17}NO_4$ requires: C 68.25, H 5.7, N 4.7%), $\nu_{\max}$ (nujol): 3300 (OH Str.), 1640 cm^{-1} , weak, (C = N Str.).

4-Amino-3':4'-dimethoxyflavan Hydrochloride : (3.29g. 58%) was prepared from 3':4'-dimethoxy-4-oximinoflavan (4.9g.) by reduction with lithium aluminium hydride (3.31g.) in boiling dry ether (900 ml.) and dry tetrahydrofuran (100 ml.), followed by cautious decomposition of the cooled reaction mixture with the minimum quantity of hydrochloric acid (2N, 470 ml.). The amine hydrochloride separated from water as colourless needles, m.p. $273-4^{\circ}$, (Found: C 63.45, H 6.3, Cl 11.2, N 4.3. $C_{17}H_{20}ClNO$ requires : C 63.45, H 6.2, Cl 11.0, N 4.35%), $\nu_{\max}$ (nujol): 3500 (NH_3^+ Str.), 1680 (as. NH_3^+ def.), 1282 (sym. NH_3^+ def.) and 770 cm^{-1} (NH_3^+ rocking).

3':4'-Dimethoxyflavan-4 α -ol: (1.91g. 67%) was prepared from 4-amino-3':4'-dimethoxyflavan hydrochloride (3.2g.) by treatment with sodium nitrite in acetic acid solution, followed by hydrolysis of the product in boiling ethanolic potassium hydroxide solution. The α -ol separated from light petroleum-benzene as colourless plates, m.p. 123-4 $^{\circ}$, (Found: C 71.3, H 6.3. $C_{17}H_{18}O_4$ requires: C 71.3, H 6.3%), $\nu_{\max}$ (nujol): 3400 cm^{-1} (OH Str.), no NH_3 absorptions.

4 α -Benzoyloxy-3':4'-dimethoxyflavan : (2.05g. 79%) was prepared from 3':4'-dimethoxyflavan-4 α -ol (1.9g.) by benzoylation with pyridine and benzoyl chloride followed by chromatography on 5% deactivated alumina. The α -benzoate separated from light petroleum-benzene as colourless needles, m.p. 137-8 $^{\circ}$, (Found: C 73.7, H 5.65. $C_{24}H_{22}O_5$ requires: C 73.85, H 5.65%), $\nu_{\max}$ (nujol): 1697 cm^{-1} (benzoate C=O Str.), no hydroxyl absorption.

4-Carboxy-2'-hydroxychalcone : (11.4g. 85%) was prepared by condensation of 4-carboxybenzaldehyde and *o*-hydroxyacetophenone in strong aqueous ethanolic sodium hydroxide solution. The carboxychalcone separated from ethanol-ethyl acetate as yellow needles, m.p. 258-261 $^{\circ}$, (Found : C 71.65, H 4.4. $C_{16}H_{12}O_4$ requires: C 71.6, H 4.45%), $\lambda_{\max}$ (ethanol): 355 (inf.) 315 ($\log \epsilon$ 4.38), 226 (inf.) and 205 $\text{m}\mu$ ($\log \epsilon = 2.05$), $\lambda_{\min}$: 262 $\text{m}\mu$.

Attempted Ring-Closure of 4-Carboxy-2'-hydroxychalcone.

<u>Chalcone</u> (g.):	<u>Reagent:</u>	<u>Time:</u>	<u>Product:</u>
0.72	Ethanol (200 ml.) Hydrochloric acid (N, 55 ml.)	24 hr.	Unchanged Chalcone
0.52	Ethanol (164 ml.) Aqueous sodium hydroxide solution (1.5%, 820 ml.)	12 hr.	"
5.0	Ethanol (600 ml.) Aqueous sodium hydroxide solution (1.5%, 1800 ml.) 78°	12 hr.	"
5.33	Methanol (50 ml.) Aqueous sodium hydroxide solution (2N, 5.5 ml.) Hydrogen Peroxide (100 Vol., 9 ml.)	4 hr.	"

The products were identified by their melting-points and by their ultra-violet absorption spectra.

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Oxidations using Activated Manganese Dioxide : carried out on the following compounds, by the general procedure of

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Turner.

(a) Flavan-4 β -ol (666.2 mg.) : the product, flavan-4-one (642.7 mg. 97.4%) separated from ethanol as colourless needles, m.p. and mixed m.p. with authentic sample, 76-8°.

(b) Flavan-4 α -ol (30.37 mg.): the product, flavan-4-one (24.64 mg. 82%) separated from ethanol as colourless needles,

m.p. and mixed m.p. 76-8°.

(c) 4'-Methoxyflavan-4 β -ol (87.99 mg.): the product, 4'-methoxyflavan-4-one (70.6 mg. 81%) separated from light petroleum-ethyl acetate as colourless needles, m.p. and mixed m.p. with authentic sample, 89-91°.

(d) 4'-Methoxyflavan-4 α -ol (36.09 mg.): the product, 4'-methoxyflavan-4-one (28.3 mg. 79%) separated from light petroleum-ethyl acetate as colourless needles, m.p. and mixed m.p., 90-92°.

(e) Flavan-3:4-cis-diol (132.7 mg.): the product, 3-hydroxyflavan-4-one (97.45 mg. 74%) separated from ethyl acetate as cream-coloured needles, m.p. and mixed m.p. with authentic sample, 175-7°.

(f) Flavan-3:4-trans-diol (60.7 mg.): the product, 3-hydroxyflavan-4-one (43.4 mg. 72%) separated from ethyl acetate as cream-coloured needles, m.p. and mixed m.p. 174-7°.

(g) 4'-Methoxyflavan-3:4-cis-diol (56.2 mg.): the product, 3-hydroxy-4'-methoxyflavan-4-one (36.8 mg. 66%) separated from light petroleum - ethyl acetate as cream-coloured needles, m.p. and mixed m.p. with authentic sample, 168-170°.

(h) 4'-Methoxyflavan-3:4-trans-diol (73.2 mg.): the product,

3-hydroxy-4'-methoxyflavan-4-one (47.2 mg. 65%) separated from light petroleum - ethyl acetate as cream-coloured needles, m.p. and mixed m.p., 167-169°.

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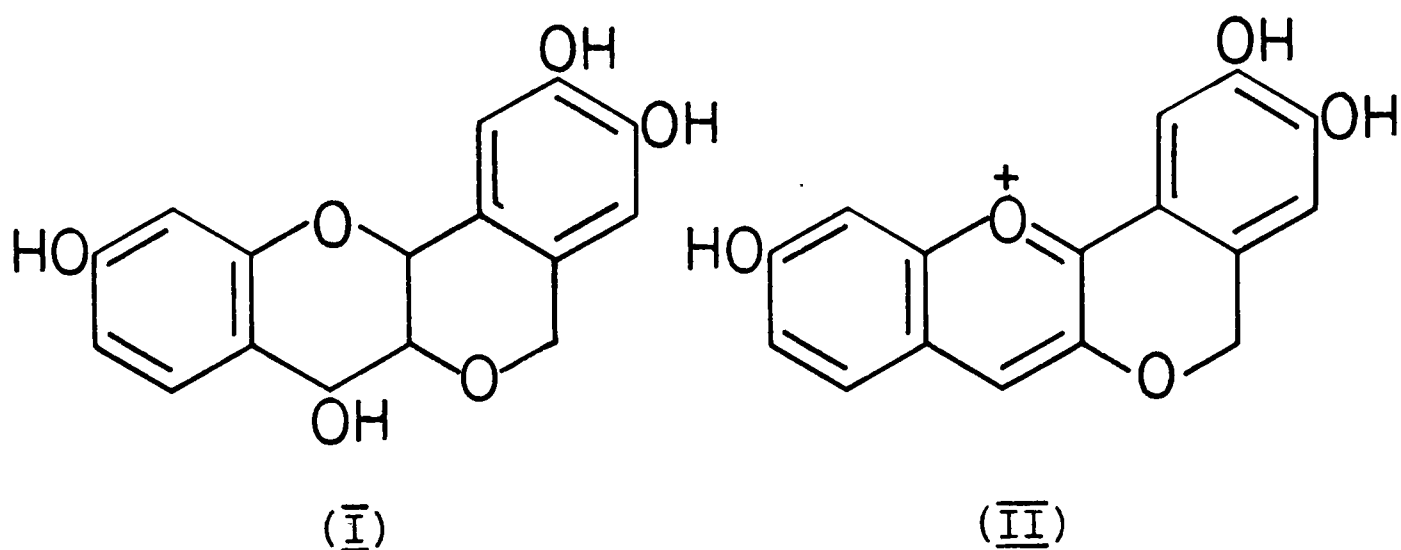
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C H A P T E R 2

PELTOGYNOLIntroduction

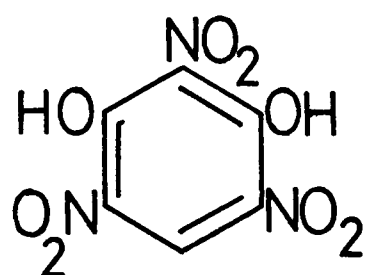
One of the first leucoanthocyanidins (flavan-3:4-diols) to be isolated, characterised and investigated structurally¹ was Peltogynol, (I), which is a constituent of the heartwood



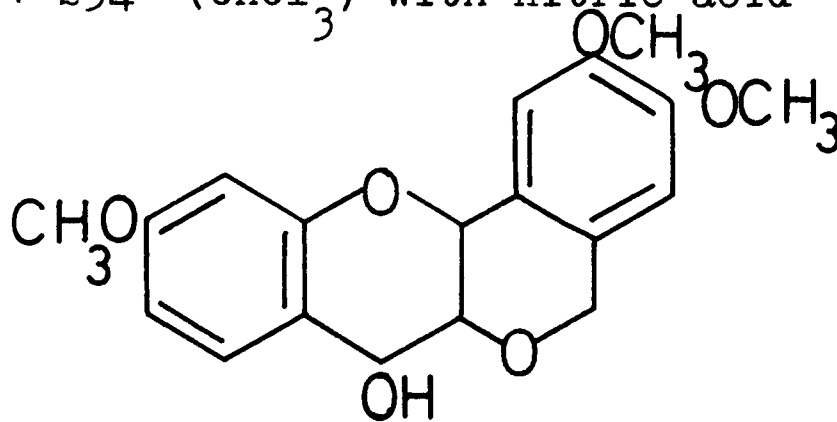
of Peltogyne porphyrocardia, a rare Amazonian tree. Peltogynol is converted into an anthocyanidin (peltogynidin), (II), on treatment with acid in the presence of oxygen. The formation of the anthocyanidin causes the characteristic colouration of the wood when it is exposed to air and light, giving rise to its common name, "purple heart".

Oxidation of peltogynol with nitric acid yielded 2:4:6-trinitroresorcinol (III); oxidation of the trimethyl ether

(IV), m.p. 198° , $[\alpha]_D + 254^{\circ}$ (CHCl_3) with nitric acid

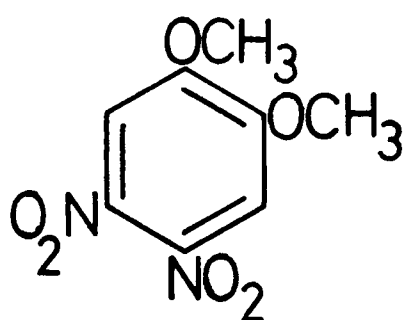


(III)

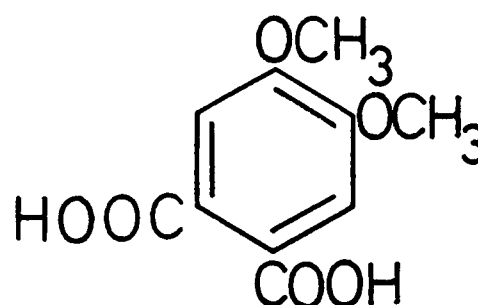


(IV)

yielded 4:5-dinitroveratrole, (V), and with potassium permanganate yielded 4:5-dimethoxyphthalic acid (VI).

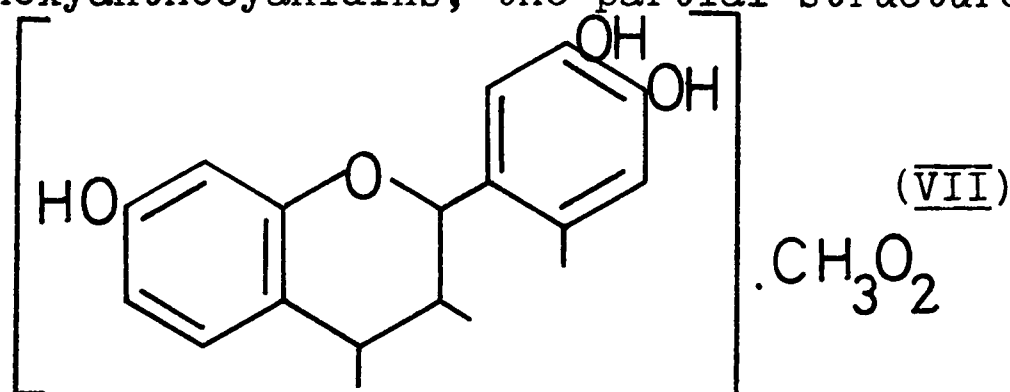


(V)



(VI)

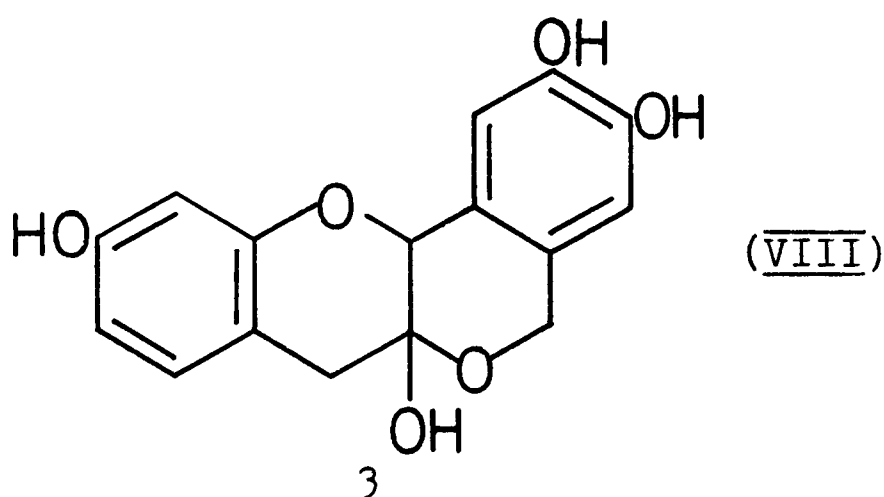
Peltogynol, therefore, contains one catechol and one resorcinol nucleus, and as the fluorescent properties of methylated peltogynidin salts are similar to 7-methoxy- and not 5-methoxyanthocyanidins,¹ the partial structure (VII)



(VII)

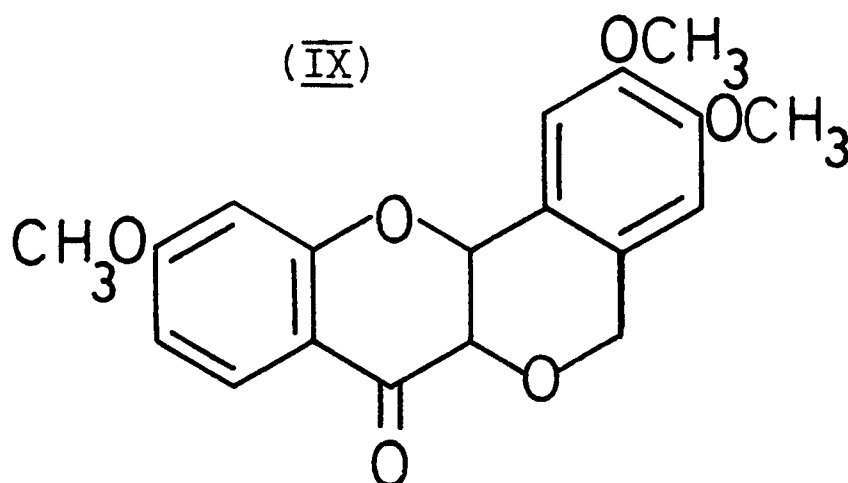
best describes the natural product.

An alkali-insoluble mixture of tri- and tetramethyl ethers is afforded by methylation of peltogynol with methyl sulphate and alkali, and acid hydrolysis of the tetramethyl ether gives a non-phenolic trimethyl ether. This, together with the observation that treatment with 2:4-dinitrophenylhydrazine gives a 2:4-dinitrophenylhydrazone, suggested a^{1,2} hemi-ketal structure, (VIII), supported by limited X-ray data.



It was then suggested³ that as the oxidising powers of 2:4-dinitrophenylhydrazine are known,~~e.g., the formation of~~
~~osazones in sugar chemistry,~~ the formation of a hydrazone might follow after oxidation of the hydroxyl group by the reagent. Accordingly, the trimethyl ether of peltogynol was oxidised with manganese dioxide in chloroform, the product being shown to be a flavan-4-one, (IX), by its infra-red absorption at 1687 cm^{-1} (absence of hydroxyl absorption) and its ultra-violet absorption being that of a resacetophenone derivative. On reduction with sodium borohydride, it re-generated the trimethyl ether of peltogynol. The hemi-ketal

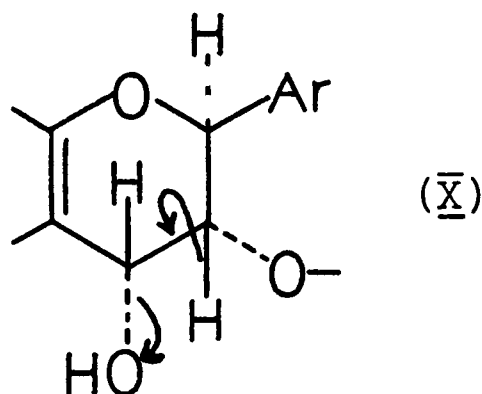
structure, (VIII), was thus discarded and the formula of peltogynol established as (I).



Peltogynol B.

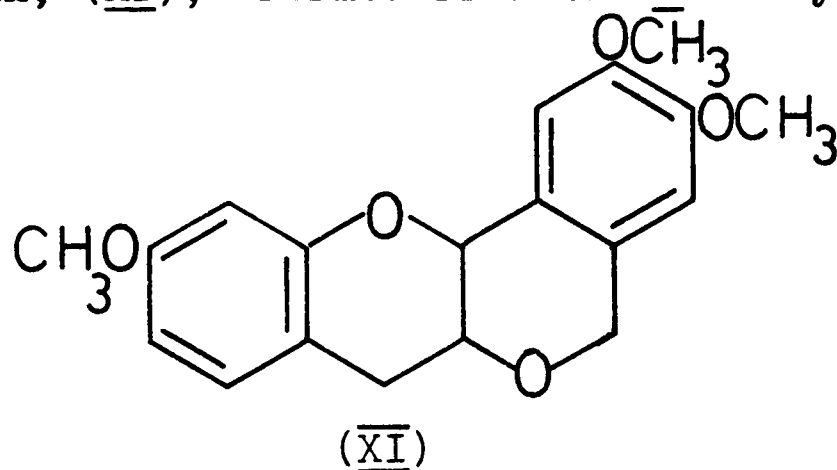
There exists in "purpleheart", together with peltogynol, a stereoisomer, Peltogynol B. Like peltogynol, the isomer affords peltogynidin (II) on treatment with acid, and oxidation of its trimethyl ether, m.p. 140° , with manganese dioxide in chloroform yields the same flavan-4-one, peltogynone, (IX), so that peltogynol B is the 4-epimer of peltogynol.⁴ Since peltogynol is formed by reduction of peltogynone by sodium borohydride, a reagent known to give the equatorial alcohol, the hydroxyl group in peltogynol is most probably in a 4-equatorial position. Peltogynol B, being epimeric with peltogynol at the 4-position, presumably has a 4-axial hydroxyl group. This is supported by the observation that, unlike peltogynol, peltogynol B turns red through

formation of peltogynidin, when heated near the melting point in air. This suggests that trans elimination of the elements of water is possible between the 3-axial hydrogen atom and the 4-axial hydroxyl group ($\bar{X}$)⁴.



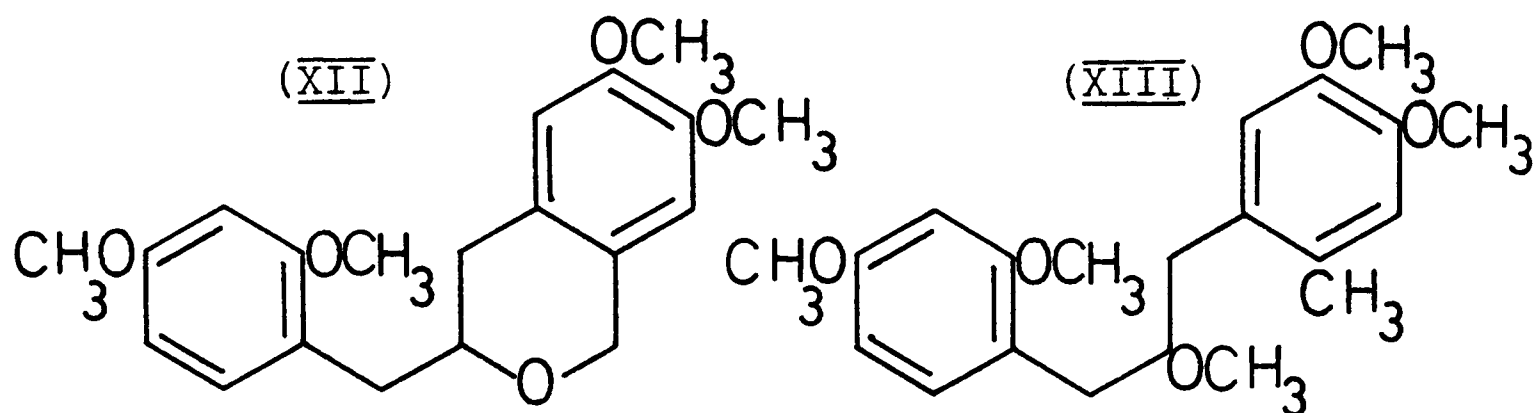
The Absolute Configuration of Peltogynol and Peltogynol B.

The absolute configuration of peltogynol and peltogynol B has recently been established⁵ by determination of the relative configurations of the hydrogen atoms at C₂ and at C₃ in tri-O-methylpeltogynone by n.m.r. spectroscopy, and by determination of the absolute configuration of C₃ by degradation of the flavan, ($\bar{XI}$), formed from tri-O-methylpeltogynol by

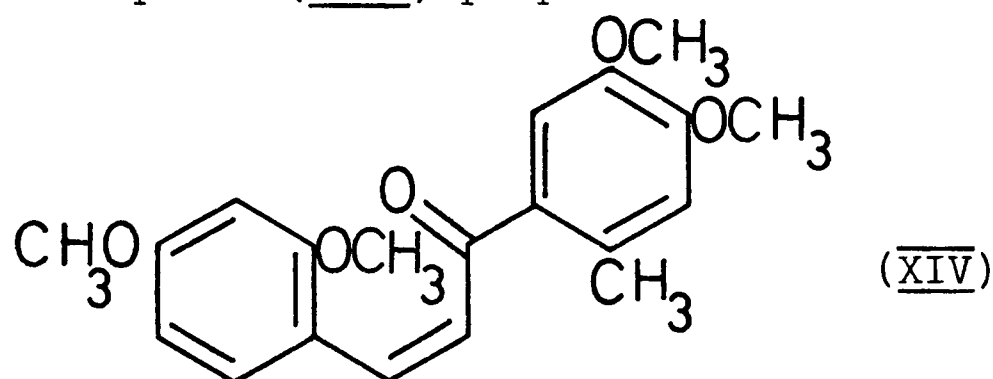


hydrogenolysis. This flavan, ($\bar{XI}$), was degraded by reduction

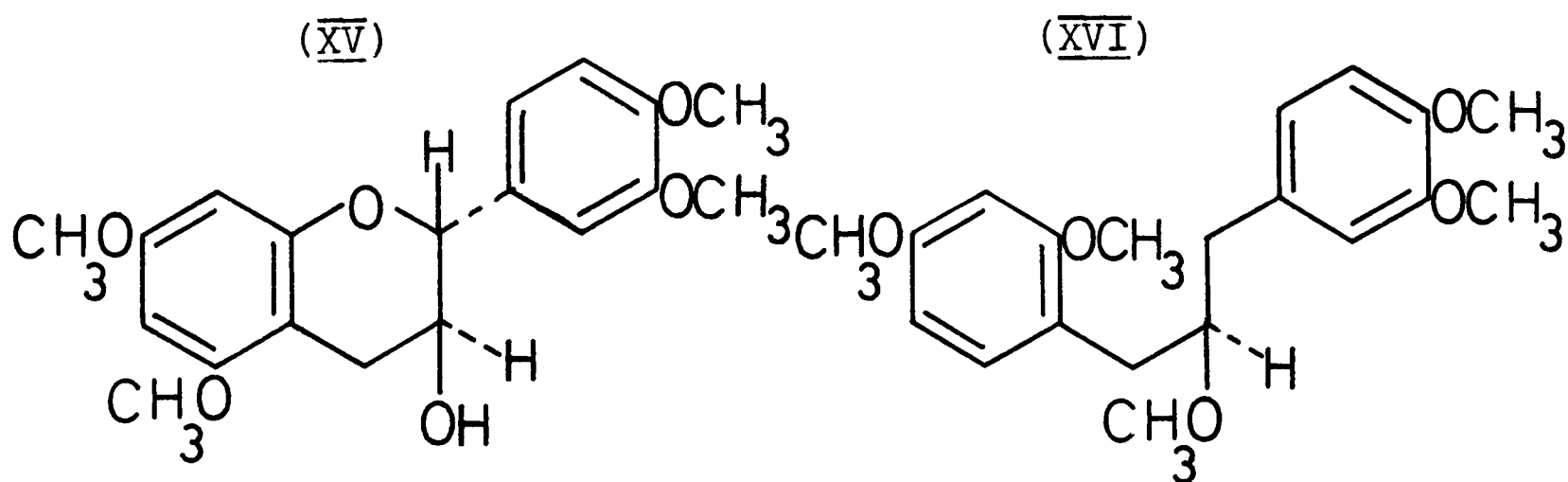
with lithium and ethanol in liquid ammonia, and methylation of the degradation products gave the compounds (XII) and (XIII).



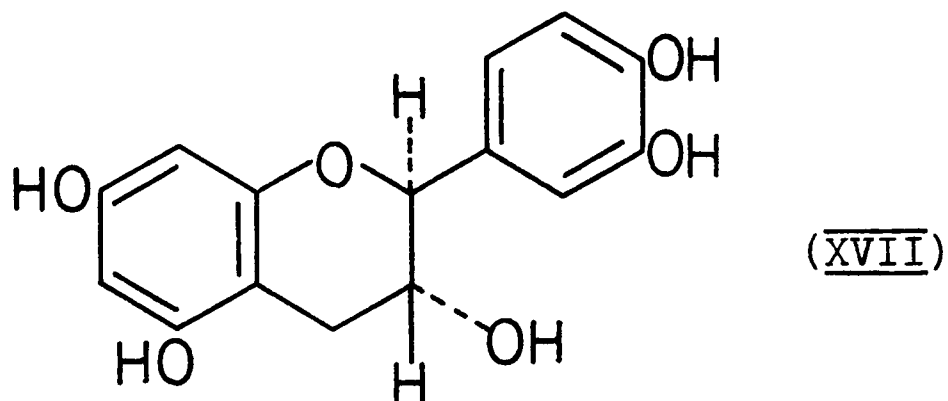
The structure of the (+)- compound (XIII) was established by infra-red and n.m.r. spectroscopy and by comparison with the racemic compound (XIII) prepared from the chalcone (XIV).



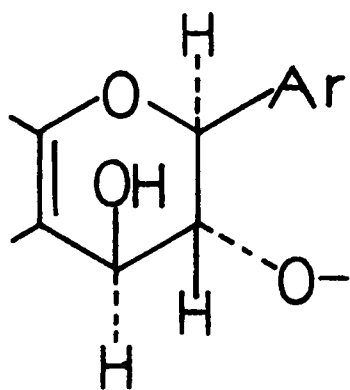
Tetramethyl-(+)-catechin, (XV), was degraded and methylated in like fashion and the (-)- compound (XVI) isolated.



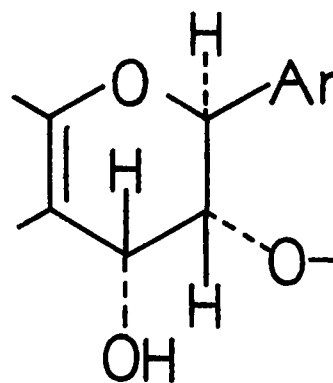
The optical rotatory dispersion curve of this (-)-propan-2-ol, (XVI) was similar in form to, but of opposite sign to that of the (+)- product (XIII). This means that peltogynol must have the same configuration at C_3 as (-)-catechin, whose absolute configuration has been established as the structure (XVII)⁶.



Since the relative configurations of the hydrogen atoms at C_2 and C_3 in peltogynone, are trans, and since the evidence suggests that the relationship between the hydrogen atoms at C_3 and C_4 is trans in peltogynol and cis in peltogynol B, then the absolute configurations of these molecules are the structures (XVIII) and (XIX) respectively.



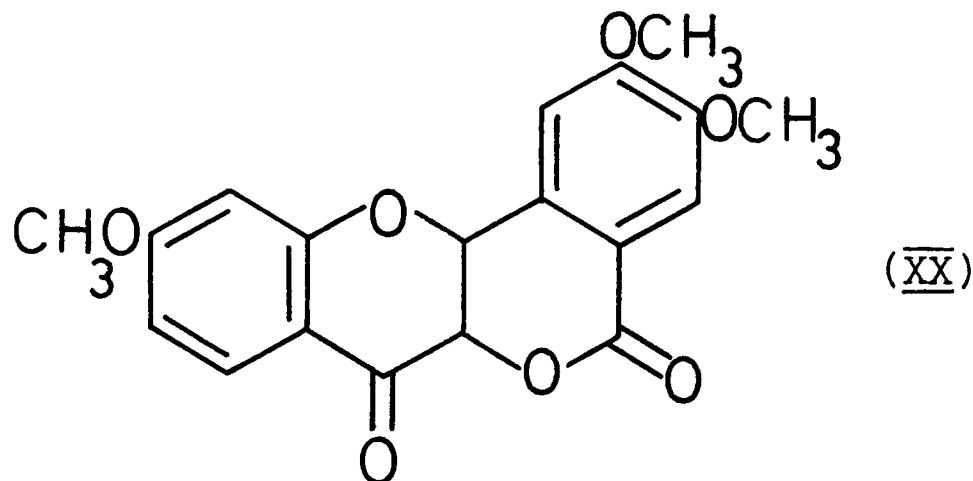
(XVIII)



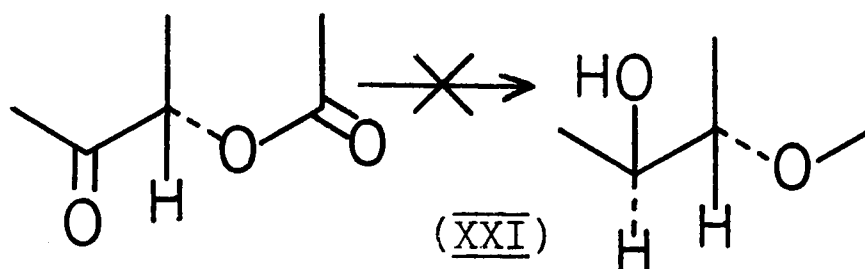
(XIX)

Attempted Synthesis of Tri-O-methylpeltogynol.

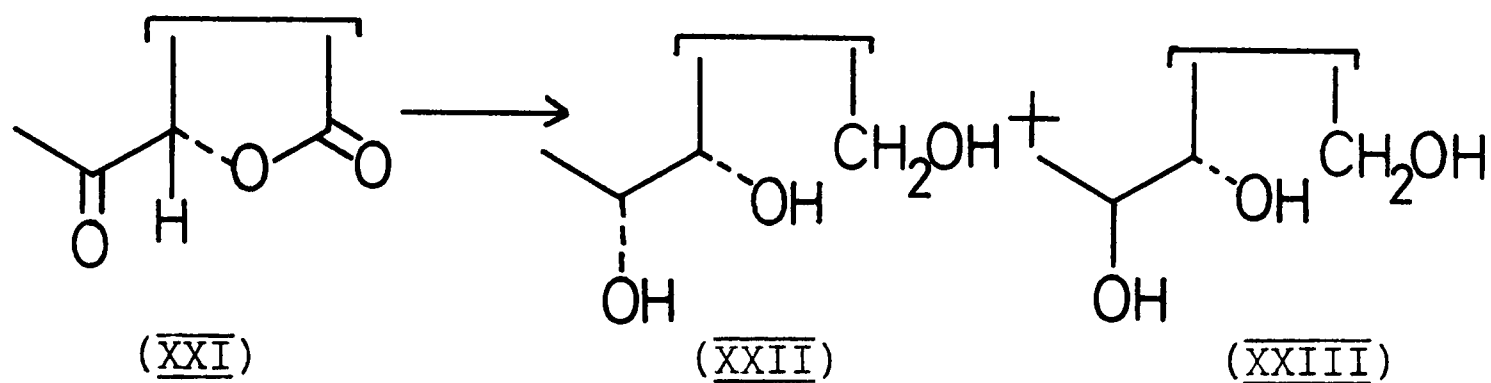
Two attempts have been made to synthesise tri-O-methyl peltogynol. McBride⁷ attempted to reduce the carboxy-flavanonol lactone (XX) with lithium aluminium hydride-boron



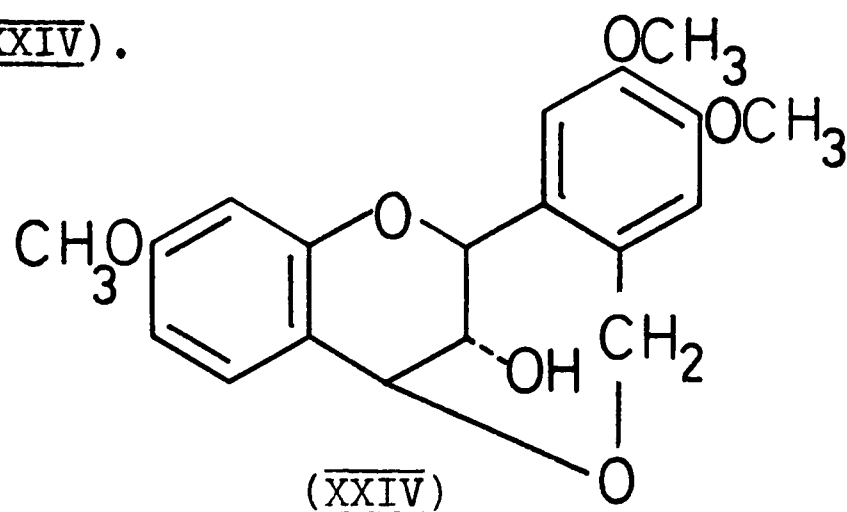
trifluoride, and with sodium borohydride-boron trifluoride, to tri-O-methylpeltogynol (XXI). In accordance with the



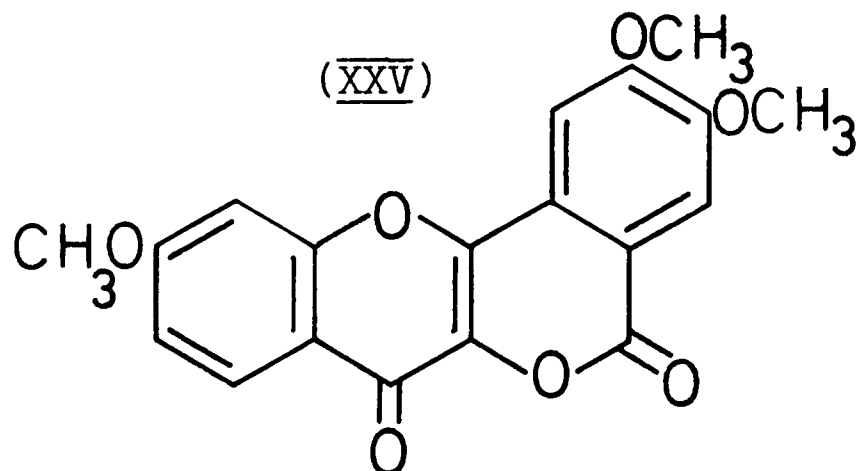
findings of Ayres et al.,⁸ who showed that the lactones of benzoic acid analogues cannot be reduced to cyclic ethers by the diborane-boron trifluoride reagent, McBride recovered the lactone unchanged. He then reduced the lactone with lithium aluminium hydride and separated the 3:4-cis- and trans -triols, (XXII) and (XXIII) respectively. After trying



a variety of reagents, he eventually dehydrated the cis-triol (XXII), and the product, m.p. 137-9°, was not identical with tri-O-methylpeltogynol: it was the seven-membered ring cyclic ether, (XXIV).



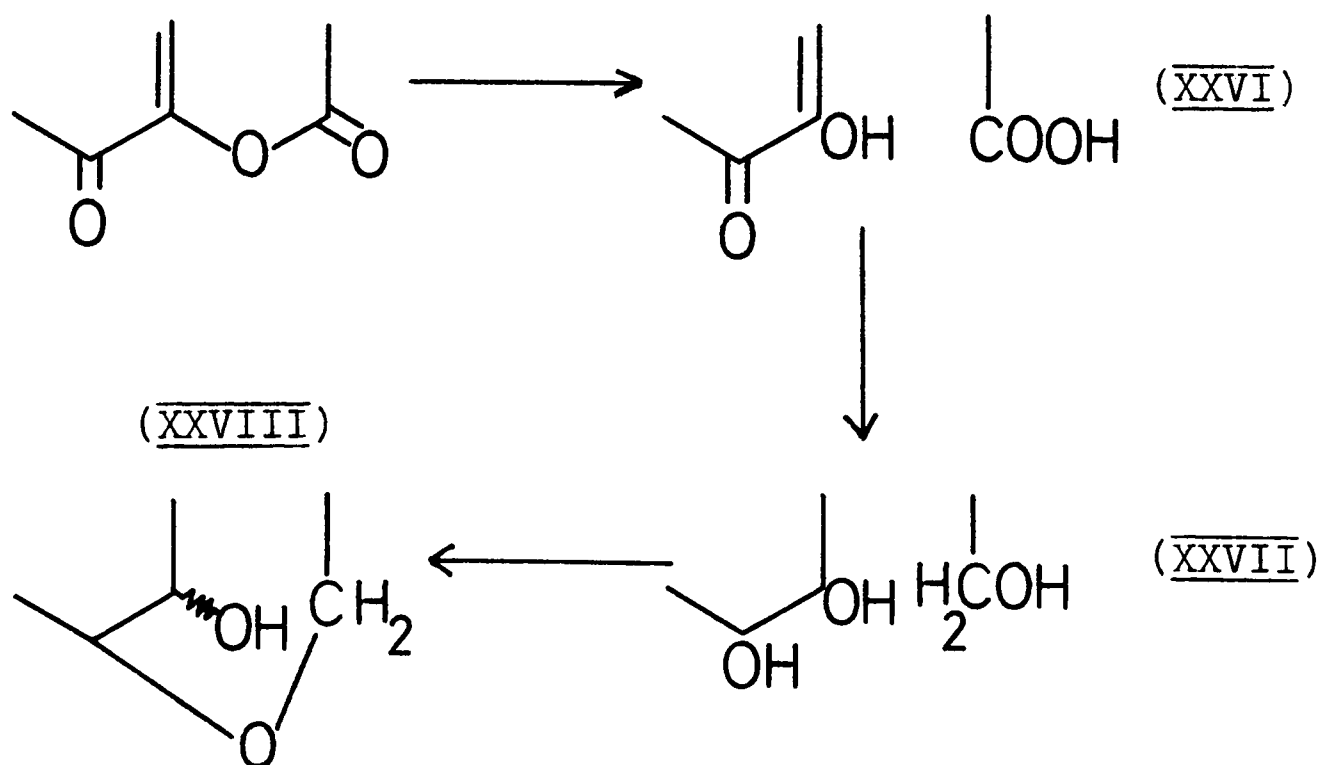
Bryant et al.⁹ prepared the flavonol lactone (XXV),



reduced it with lithium aluminium hydride to a compound

$C_{16}H_{11}O_3(OCH_3)_3$, m.p. $201-2^\circ$, and converted this compound into the corresponding anthocyanidin, peltogynidin chloride by the action of hydrochloric acid in the presence of oxygen. Bryant et al. explain the formation of the compound, m.p. $201-2^\circ$, as a reduction of a lactone carbonyl to a cyclic ether, together with the reduction of an $\alpha\beta$ -unsaturated ketone to a saturated alcohol, and cite examples^{10,11} of this behaviour when lithium aluminium hydride is used. Mention is also made of small differences in the infra-red and n.m.r. spectra of this compound and of authentic tri-O-methylpeltogynol, which are attributable to "stereochemical differences".

In the light of McBride's work, it seems likely that fission of the lactone ring and reduction of the subsequent carboxyflavonol (XXVI) to the triol (XXVII) have occurred.



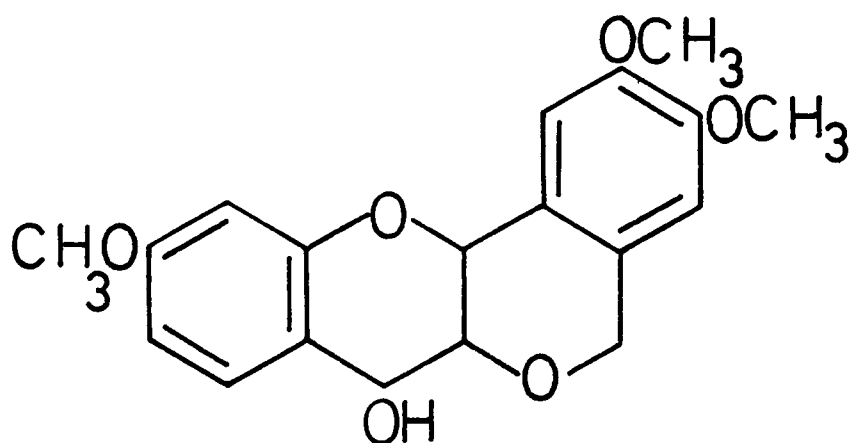
This triol may now dehydrate to yield a seven-membered ring compound, $C_{16}H_{11}O_3(OCH_3)_3$ (XXVIII) not identical with tri-O-methylpeltogynol, and not identical with McBride's compound (XXIV), since it may differ from (XXIV) in the configuration at the 3-position. Like the compound of Bryant et al., that of McBride was also converted into the anthocyanidin, peltogynidin chloride, by the action of hydrochloric acid in the presence of oxygen.

The Aim of Present Work.

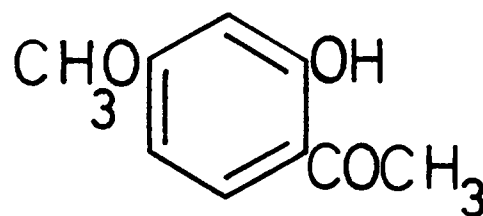
The aim of present work is to synthesise tri-O-methylpeltogynol unambiguously, thereby confirming the structure (I) as that of peltogynol.

DISCUSSION

The synthesis of the trimethyl ether of peltogynol (I),

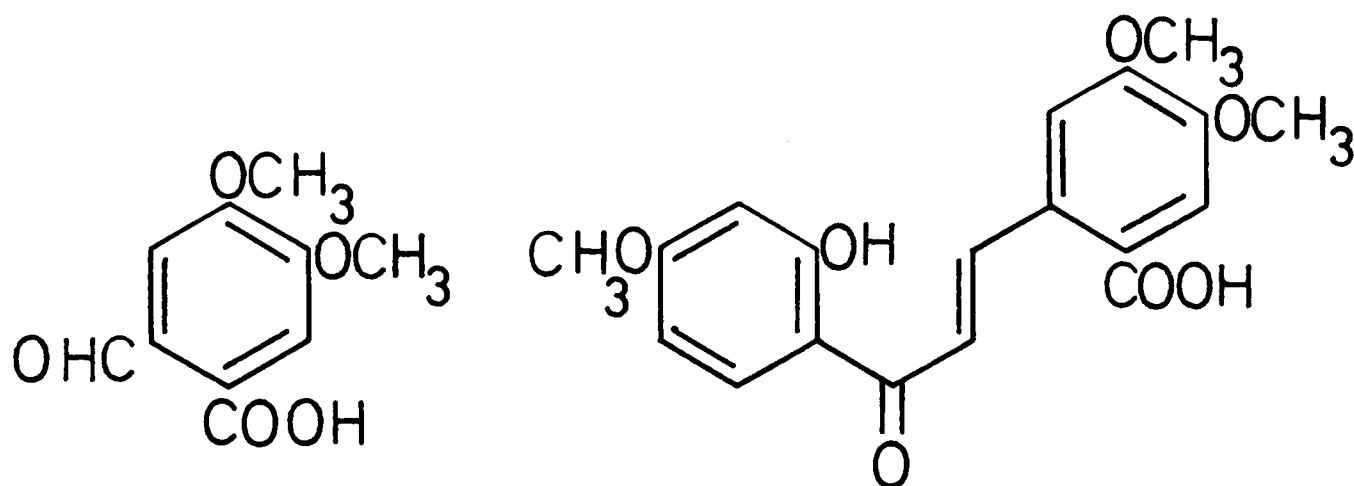


(I)



(II)

was approached in the following way. Condensation of peonol (II) with m-opianic acid (III) in aqueous ethanolic potassium hydroxide solution gives the chalcone (IV) isolated as its

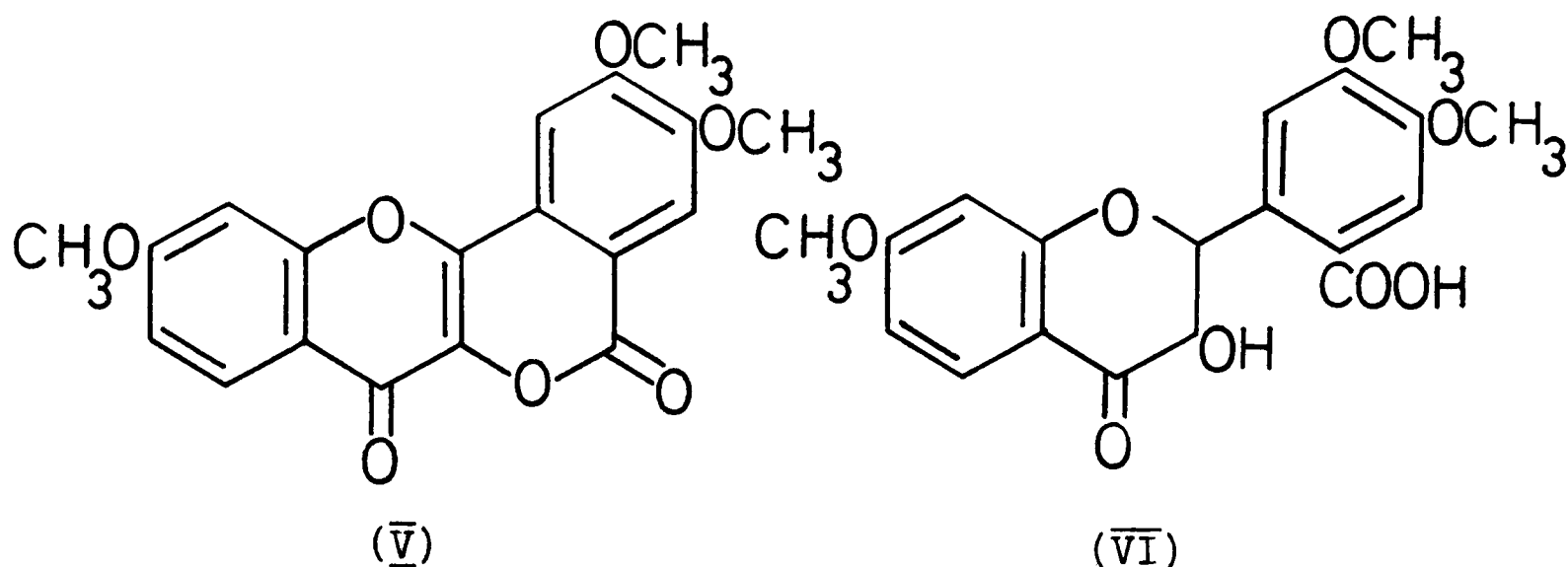


(III)

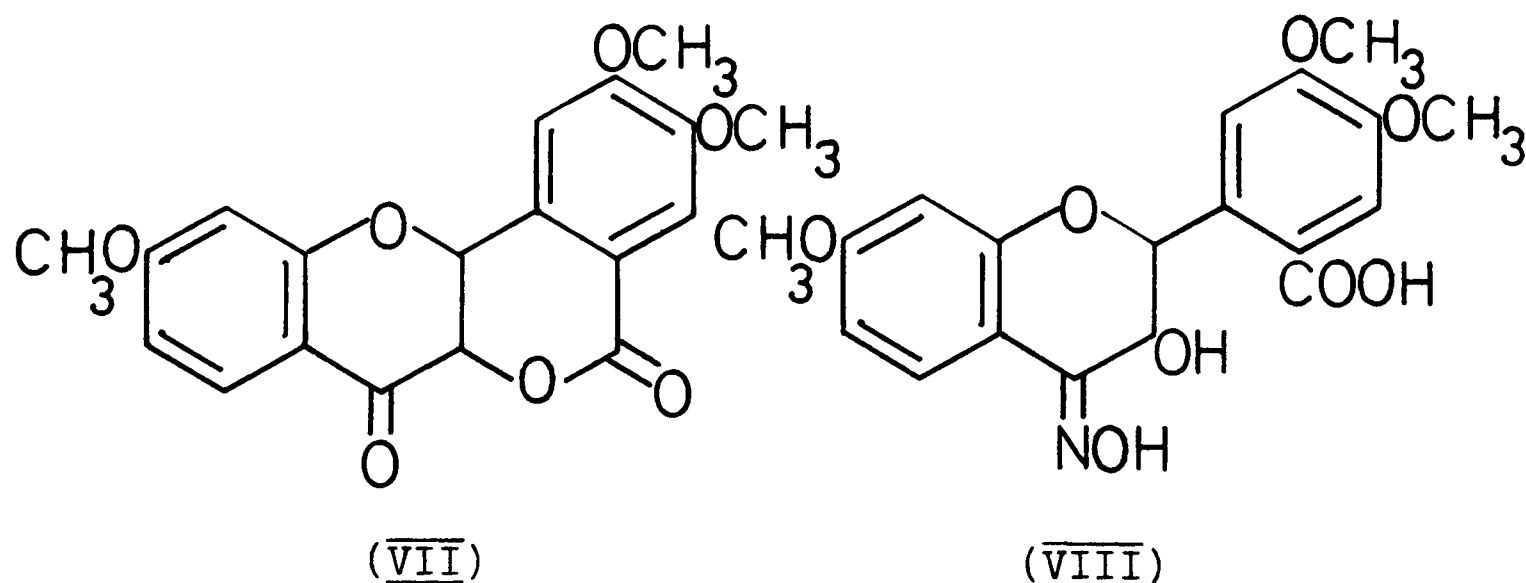
(IV)

dipotassium salt.⁷ Reaction of this with hydrogen peroxide in alkali yields a mixture of unchanged chalcone, the

flavonol lactone (V), and the carboxyflavanonol (VI)⁷. This



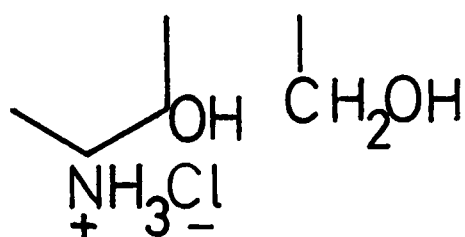
work was repeated and the carboxyflavanonol (VI) isolated, together with its lactone (VII). Lactonisation was found to



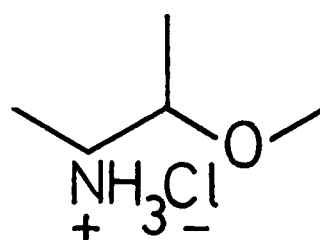
occur easily, by boiling a solution of the carboxyflavanonol (VI) in ethanol, when the very insoluble lactone is precipitated. Starting with the saturated lactone (VII), two possible routes to the trimethyl ether were investigated.

The first route involved oximation of the lactone (VII) to give the oxime (VIII); reduction of this with lithium

aluminium hydride followed by treatment with hydrochloric acid would give the amine hydrochloride (IX). Dehydration of the amine, e.g., by *p*-toluene sulphonic acid in chloroform, would probably yield the ether (X), and reaction of this with



(IX)

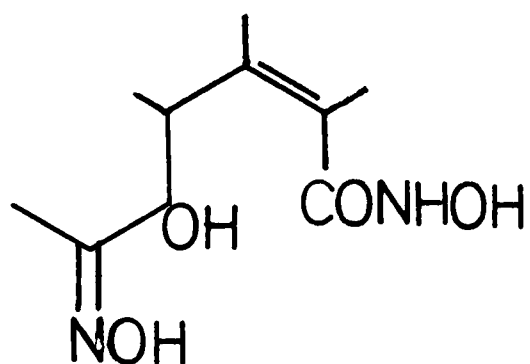


(X)

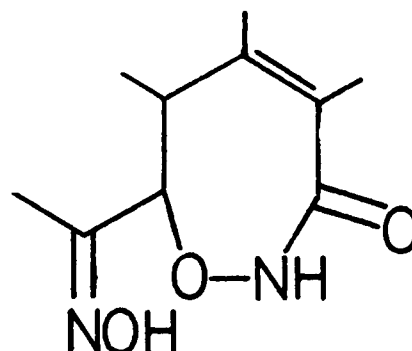
nitrous acid in acetic acid followed by hydrolysis with aqueous ethanolic potassium hydroxide would yield the trimethyl ether of peltogynol B, the 4-axial isomer of peltogynol.

The lactone (VII) is almost completely insoluble in ethanolic pyridine and was treated with hydroxylamine hydrochloride in aqueous sodium hydroxide. The product, m.p. 214-5°, showed hydroxyl absorption at 3400, weak oxime absorption at 1650, and lactam absorption at 1685 cm⁻¹ and analysed for C₁₉H₁₈N₂O₇. Oximation of the 4-keto group had occurred together with reaction of the carboxylate ion in the B ring with the reagent to yield a hydroxamic acid (XI) which had dehydrated to yield, presumably, a cyclic lactam

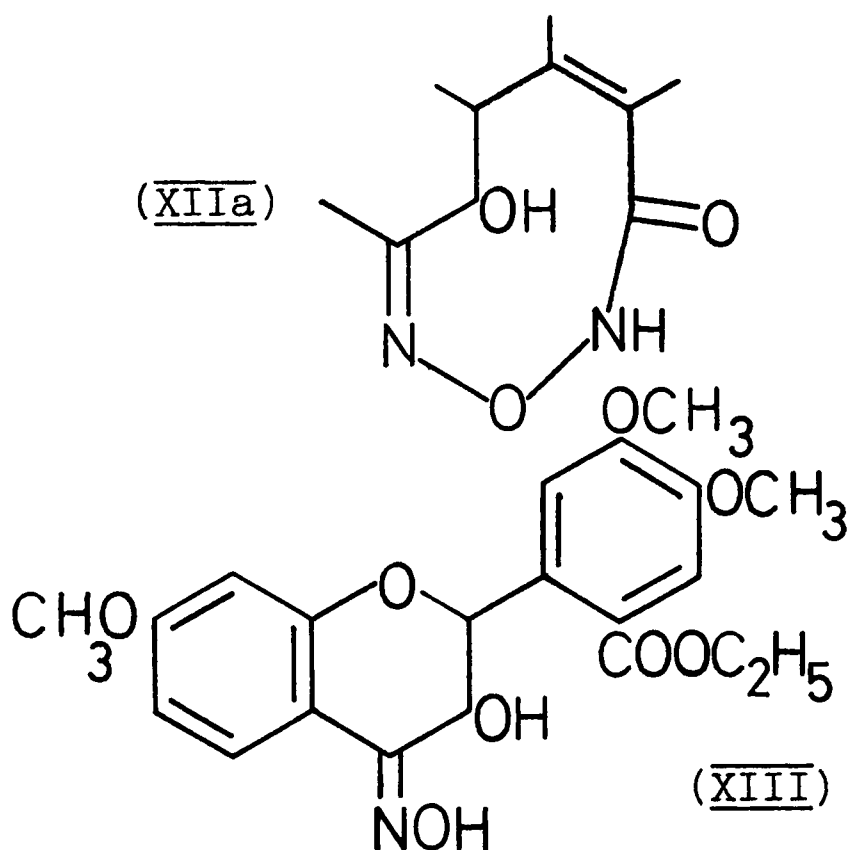
(XII) or (XIIa). Models of these 7- and 9-membered rings are



(XI)



(XII)



(XIII)

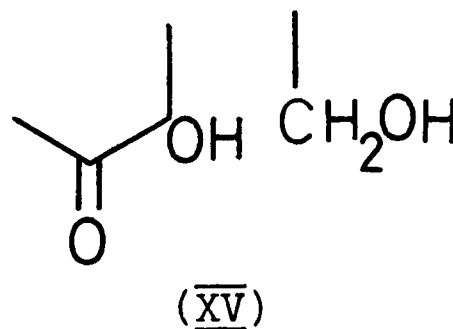
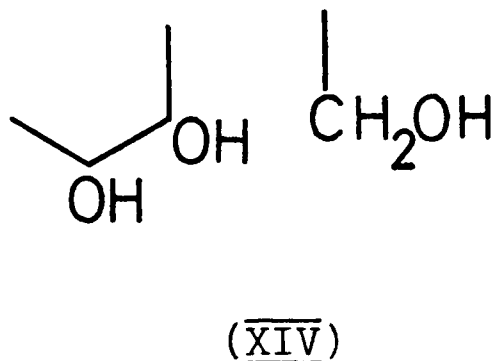
easy to construct.

It was decided not to proceed with this compound further but to try to prepare the ethyl ester of the carboxyflavanonol

(VI) from the lactone (VII), and to oximate this in ethanolic pyridine rather than in alkali, to avoid formation of a hydroxamic acid. The ethyl ester of the acid (VI) was synthesised by extraction of the lactone (VII) with boiling ethanol containing concentrated sulphuric acid (4% v/v). It proved to be fairly soluble in ethanol and attempts were therefore made to form the oxime (XIII) by condensation with hydroxylamine hydrochloride in ethanolic pyridine. Unchanged ethyl ester was recovered at each attempt. The reluctance of 3-hydroxyflavanones to yield oximes in ethanolic pyridine has been reported, but successful oximation has been carried out in aqueous pyridine.¹² The ethyl ester was dissolved in aqueous pyridine containing some ethanol and the solution treated with hydroxylamine hydrochloride. The product, a waxy, cream-coloured solid was shown by analysis and infrared spectroscopy to be a mixture of unchanged ethyl ester and the lactam previously encountered. It appeared, therefore, that the nature of this lactam would have to be investigated further if the synthesis of the trimethyl ether of peltogynol, via the oxime route, were to be successful.

At this time, however, the second route of synthesis was nearing its successful conclusion. This route involved reduction of the lactone (VII) with lithium aluminium hydride

to yield the triol (XIV) (86%). The ethyl ester of the



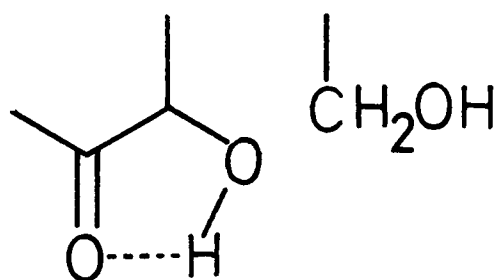
acid (VI) was also reduced with lithium aluminium hydride to yield the same product, a brown gum (79%). The infra-red spectra of these products were identical and showed some carbonyl absorption. Chromatography of solutions of the gum in benzene-chloroform yielded a colourless gum (51.2 mg., 8%), eluted by chloroform, whose infra-red spectrum showed strong hydroxyl absorption and no carbonyl absorption. Previous fractions (92%) had shown small carbonyl absorption, and since the next stage involved oxidation, it was important that no carbonyl compound should be present to interfere with the examination of the oxidation product.

Chromatography of the colourless gum on a silica film in chloroform confirmed the presence of a mixture of 3:4-cis-

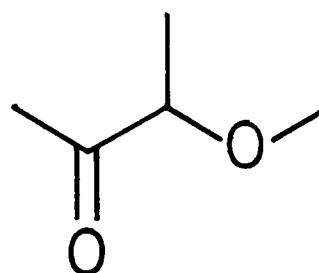
and trans-triols: two spots were observed (R_f 0.47 and 0.50) which became pink on treatment with aqueous ethanolic hydrochloric acid; cf. R_f 0.46 and 0.49⁷. The mixture could not be separated by fractional recrystallisation¹⁵.

The mixture of triols (XIV)¹³ in chloroform was shaken with activated manganese dioxide¹⁴ at room temperature for 12 days. The product after filtration and centrifugation was a sol containing residual manganese dioxide. Evaporation of this sol and treatment of the residual brown powder, softening sharply at 185-90°, with various solvents resulted in sol formation. The infra-red spectrum of the product in chloroform showed hydroxyl absorption at 3200-3600, and a weak carbonyl absorption at 1665 cm^{-1} . This latter is characteristic of a 3-hydroxyflavanone^{-7-METHOXY-}. Hydrogen bonding (XVI) causes the stretching frequency (and/its intensity) of the carbonyl group, to decrease.

(XVI)



(XVII)

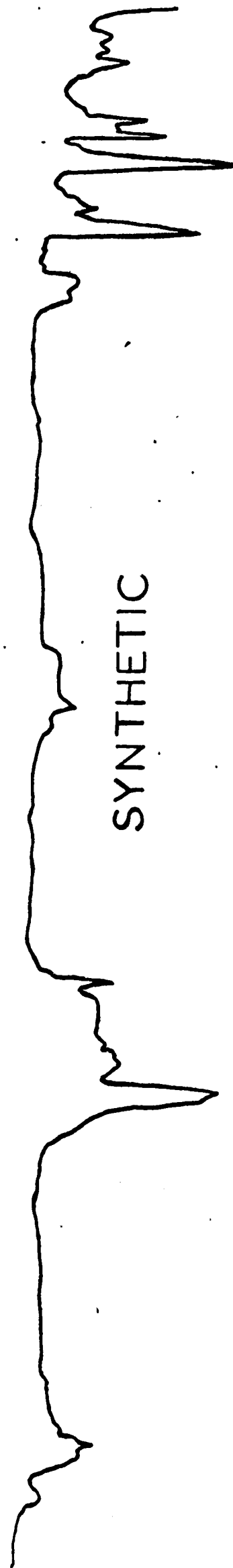
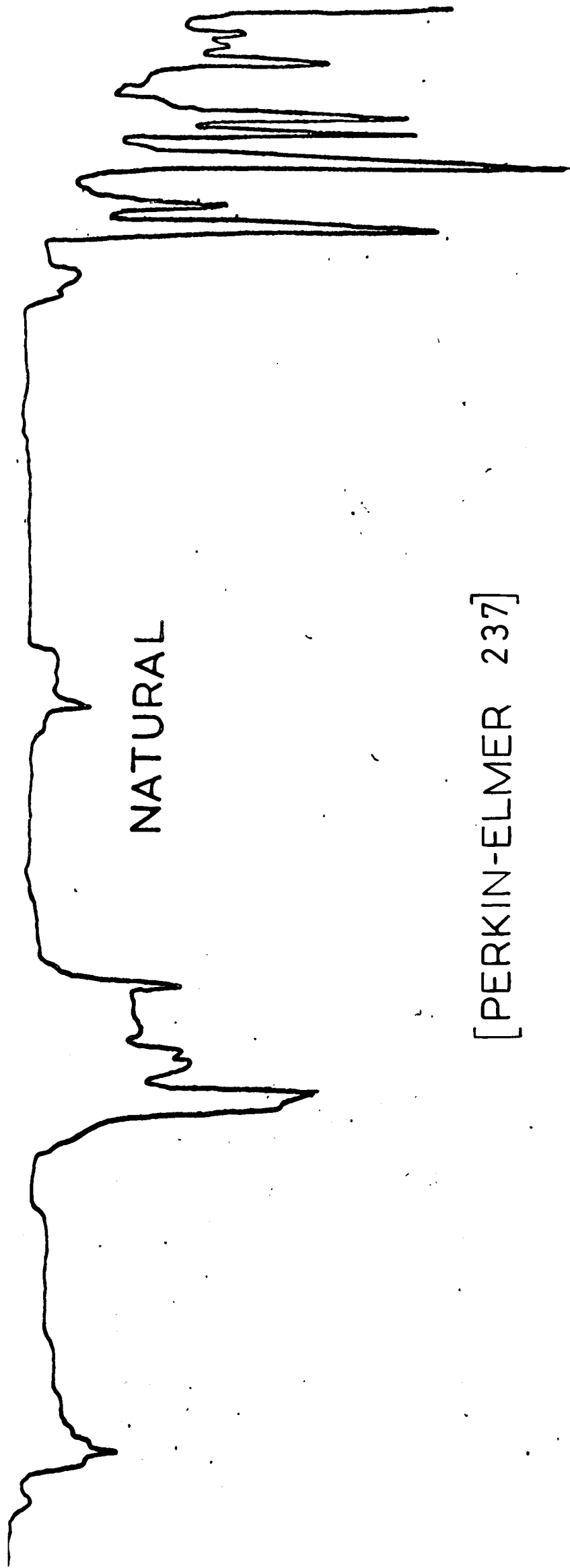


Since the product contained manganese dioxide it was not

suitable for examination by n.m.r. spectroscopy. The brown powder was treated with *p*-toluene sulphonic acid in dimethylsulphoxide at 100° for 15 min. under nitrogen.⁷ The product, a yellow gum (23 mg.) could not be caused to crystallise. Its infra-red spectrum showed no hydroxyl absorption and strong carbonyl absorption at 1690 cm⁻¹. This is absorption characteristic of a flavan-4-one, compares favourably with the carbonyl absorption at 1687 cm⁻¹ of natural peltogynone⁵ and indicates that water has been lost from the hydrogen bonded ketone diol (XVI) to yield the ketone ether (XVII), tri-O-methylpeltogynone. The ketone ether was reduced with lithium aluminium hydride in ether and the colourless product (8.9 mg.) was recrystallised by the gradual evaporation of an ethereal solution, which afforded colourless needles, m.p. 195-7°⁰. The infra-red and mass-spectra of this product, (+)-tri-O-methylpeltogynol, was identical with those of natural (+)-tri-O-methylpeltogynol, m.p. 186-195°⁰ (see pp. 74a-74d).

The Mass Spectrum of (+)-Tri-O-methylpeltogynol.

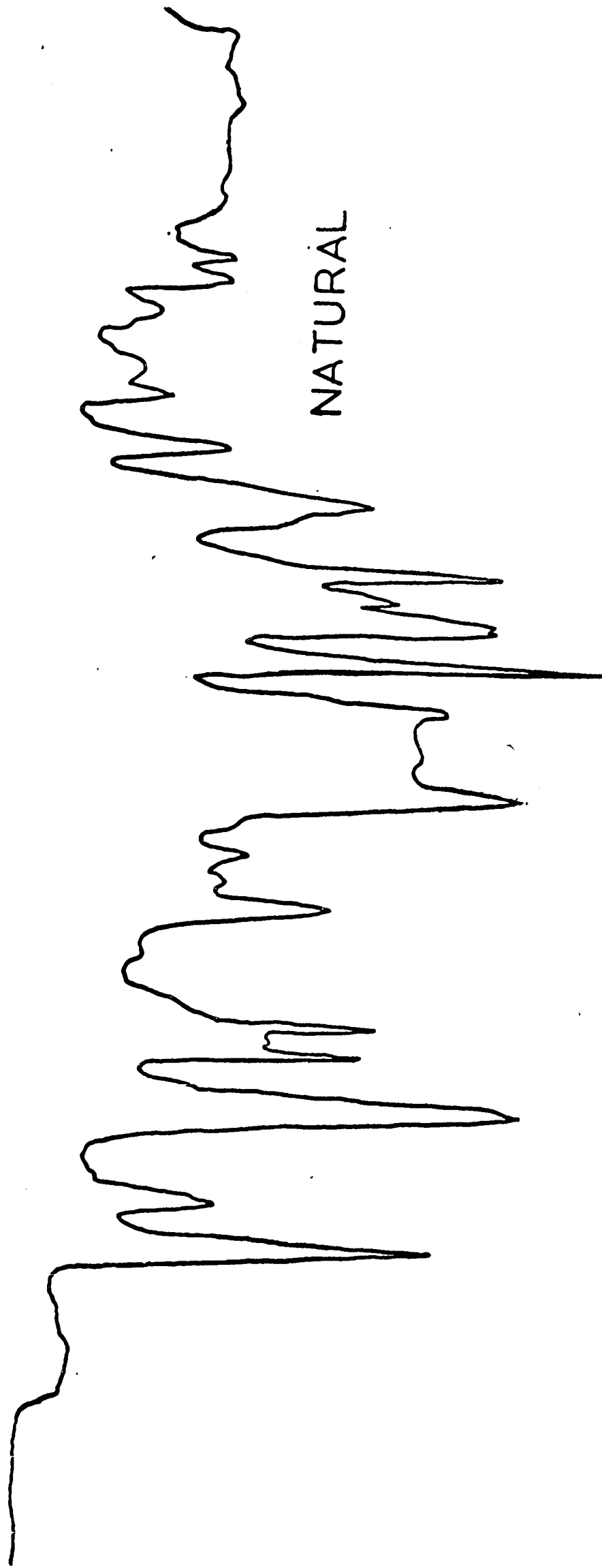
The fragmentation pattern of the trimethyl ether of peltogynol is characteristic in the occurrence of fragments of high mass number at $M/e = 344, 326, 298, 282, 192, 191, 177, 164, 149, 135$ and 121. The sequence of fragmentation is shown below.



3500

CM⁻¹

1500



1800

CM⁻¹

800

100
%
NATURAL

100
%
SYNTHETIC

200
150
100
50
M%

NATURAL

100
%

0

SYNTHETIC

100
%

00

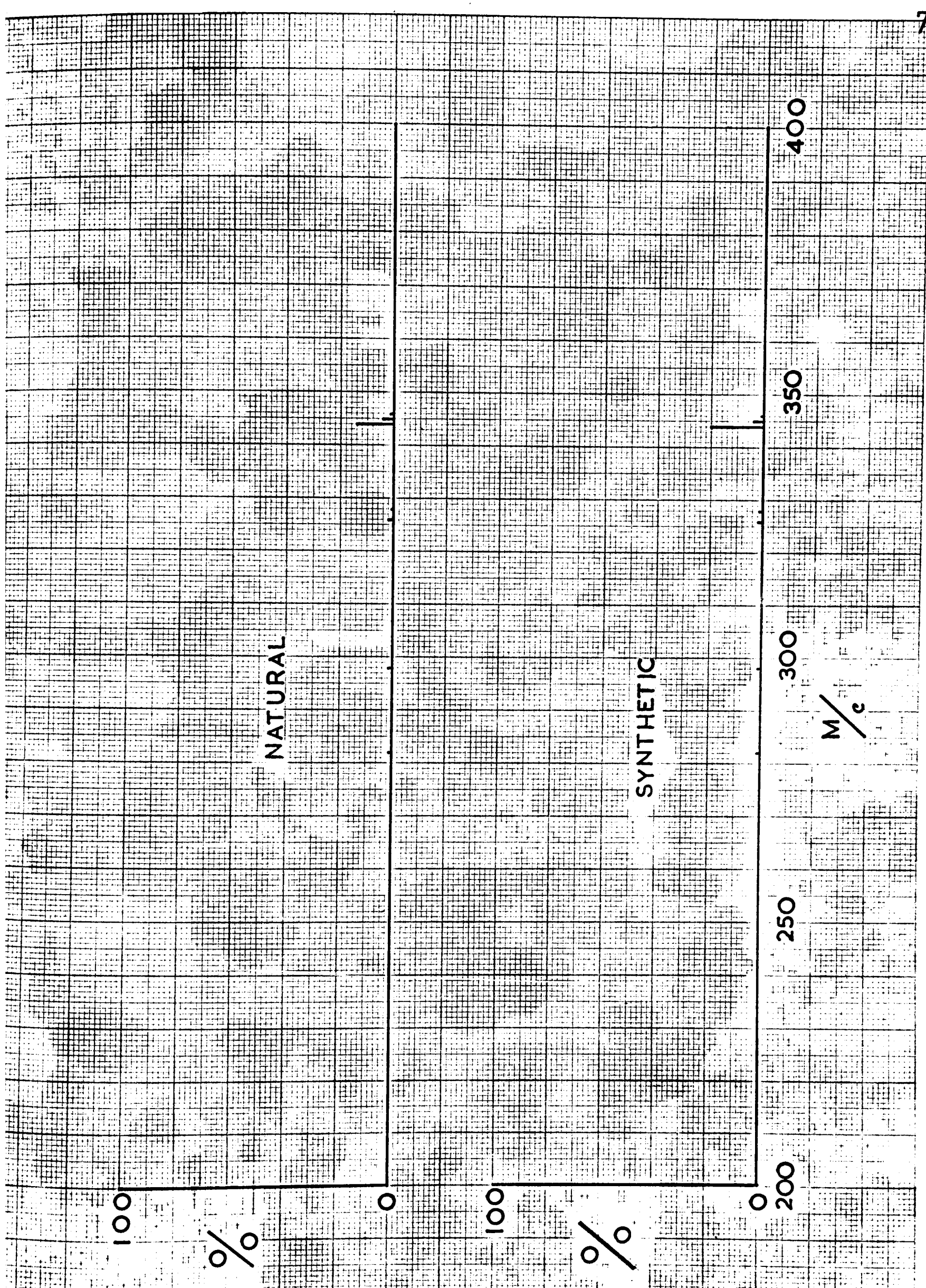
50

100

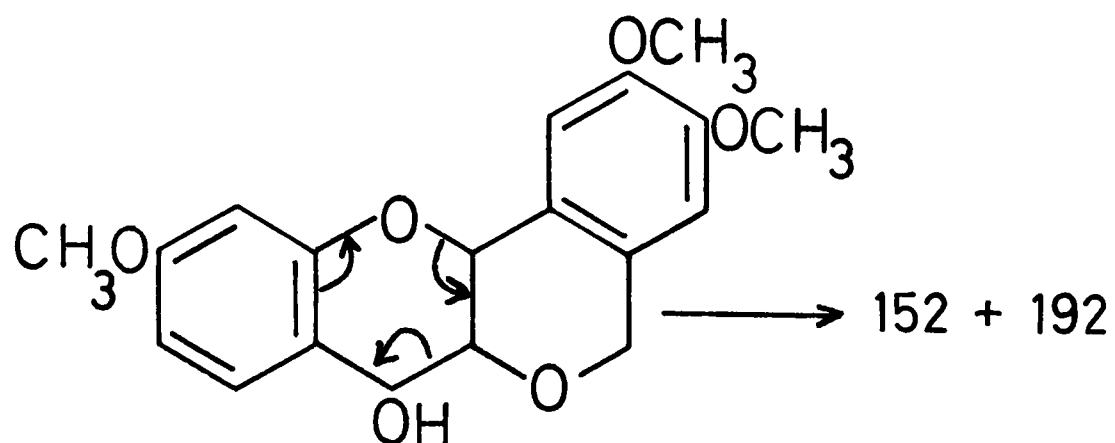
150

200

M/e



The fragmentation pattern is similar to that of the natural product, munduserone,¹⁵ where the main fragmentation is similar to that marked with an asterisk. This fragmentation is represented below (XVIII).



(XVIII)

EXPERIMENTAL SECTION

¹⁶
Veratric Acid : (243 g. 91%), m.p. after loss of water at 90-130°, and after sublimation at ca. 150°, 182-3°, was prepared from veratraldehyde by oxidation with alkaline potassium permanganate; lit. ¹⁶ m.p. 181-2°.

¹⁷
m-Meconine : (67.4g. 26%), m.p. 156-7°, was prepared from veratric acid by condensation with formaldehyde; lit. ¹⁷ m.p. 155-7°.

¹⁸
m-Opianic Acid : (11.0 g. 15.2%), m.p. 185-8°, was prepared from m-meconine by bromination with N-bromosuccinimide, and hydrolysis with hot water; lit. ¹⁸ m.p. 187-8°. The acid was purified via the formation and hydrolysis of the aniline compound (28.7g.), m.p. 209-214°; lit. ¹⁸ m.p. 213-4°.

¹⁹
Resacetophenone : (54.7g. 49.5), m.p. 142-5°, was prepared from resorcinol by condensation with acetic acid in the presence of anhydrous zinc chloride; lit. ¹⁹ m.p. 142°.

²¹
Peonol : (29g. 48.6%), m.p. 46-9°, was prepared from resacetophenone by methylation with methanolic potassium hydroxide and methyl iodide; lit. ²¹ m.p. ca. 50°.

2-Carboxy-2'-hydroxy-4:4':5-trimethoxychalcone:di-

potassium salt⁷ : (17.37g. 84%), was prepared by condensation of m-opianic acid with peonol in aqueous ethanolic potassium hydroxide solution.

2-Carboxy-2'-hydroxy-4:4':5-trimethoxychalcone. - A small amount of the chalcone was prepared from the dipotassium salt by acidification with hydrochloric acid (2N). The chalcone separated from dichloromethane as yellow rhombic plates, m.p., after change of crystalline form to needles at 150°, 230-232° (dec.); lit.⁷ m.p. 231-233° (dec.).

2'-Carboxy-4':5':7-trimethoxyflavanonol and its Lactone - A mixture (11.19g.) of the carboxyflavanonol, its lactone, 2'-carboxy-4':5':7-trimethoxyflavonol lactone and unchanged chalcone, was isolated from the action of hydrogen peroxide on the dipotassium salt of the chalcone (17.3g.) in aqueous solution.⁷ The chalcone (7.14g.) was recovered by extraction with hot chloroform (100 ml.), and the residue was extracted with boiling aqueous ethanol (80%, 200 ml.), the flavonol lactone remaining undissolved. The cold aqueous ethanolic solution deposited the carboxyflavanonol as a cream-coloured solid (3.8g), m.p. 188-194°; lit.⁷ m.p. 188-192°.

On attempted recrystallisation from boiling ethanol, the solid became insoluble, and after prolonged boiling, the lactone of the carboxyflavanonol (3.04g. 21.4%) was collected,

m.p. 230-231^o; lit.⁷ m.p. 226-232^o (dec.).

The Action of Hydroxylamine Hydrochloride on the Carboxy-flavanonol Lactone. - The lactone (232.8 mg.), hydroxylamine hydrochloride (684.78 mg.), water (12 ml.) and aqueous sodium hydroxide solution (8%, 8 ml.) were boiled under reflux for 20 min. The pale yellow solution was cooled to 0^o and acidified. The white precipitate was collected, washed with water and dried. On recrystallisation from aqueous methanol, the product separated as colourless needles, m.p. 214-5^o, (Found : C 59.1, H 4.7, N 7.3. C₁₉H₁₈N₂O₇ requires : C 59.05, H 4.65, N 7.25%), $\nu_{\max}$ (nujol): 1685 (lactam C=O Str.) and 1650 cm⁻¹, weak, (C=N Str.).

2'-Carboethoxy-3-hydroxy-4':5':7-trimethoxyflavan-4-one.-

The flavanonol lactone (482.2 mg.) was placed in a paper thimble under which was a mixture of ethanol (250 ml.) and concentrated sulphuric acid (10 ml.). Above the thimble was a reflux condenser, and the mixture beneath was boiled, the condensing ethanol passing through the thimble on its return to the flask. After 24 hr., the thimble was found to be empty, and the contents of the flask were reduced to 1/10th volume by removal of the ethanol by distillation. The mixture was poured into cold water (400 ml.) and the cream-

coloured solid collected, washed with water and dried. On recrystallisation from ethyl acetate, the ethyl ester of the carboxyflavanonol (506.7 mg. 93%) separated as colourless needles, m.p. $229-30^{\circ}$, (Found : C 62.8, H 5.5, $C_{21}H_{22}O_8$ requires : C 62.8, H 5.5%), $\nu_{\max}$ (nujol); 3450 (OH Str.), 1730 (aryl ester C=O Str.) and 1650 cm^{-1} , weak, (H-bonded aryl ketone C=O Str.).

Attempted Oximation of 2'-Carboethoxy-3-hydroxy-4':5':7-trimethoxyflavan-4-one. - The ethyl ester of the carboxyflavanonol (277.1 mg.) and hydroxylamine hydrochloride (339.5 mg.) were dissolved in ethanol (250 ml.) and pyridine (5 ml.), and the solution boiled under reflux for 30 min. Ethanol was removed by distillation until solid appeared and then the mixture was poured into cold water (400 ml.) when a cream-coloured solid was precipitated. This was collected, washed with water and dried. The product (215.9 mg.) melted at $218-221^{\circ}$ and its infra-red spectrum was identical with that of the starting material.

The Action of Hydroxylamine Hydrochloride on the Ethyl Ester of the Carboxyflavanonol, in Aqueous Pyridine. - The ethyl ester (68.85 mg.) and hydroxylamine hydrochloride (98.5 mg.) were boiled under reflux in water (175 ml.),

ethanol (65 ml.) and pyridine (10 ml.) for 2 hr. The resulting solution was concentrated by distillation to 50 ml., and added to cold water (250 ml.). The white precipitate was collected, washed with water and dried. Recrystallisation from light petroleum-ethyl acetate gave a sticky, white solid, m.p. 110-150°. Elemental analysis and infra-red spectra showed it to be a mixture of starting material and the lactam previously prepared.

2:3-trans-2'-Hydroxymethyl-4':5':7-trimethoxyflavan-
3:4-cis-and trans-diols. - (a) The ethyl ester of the carboxyflavanonol (306 mg.) in a slurry with dry tetrahydrofuran (60 ml.) was boiled under reflux with lithium aluminium hydride (320.1 mg.) for 2 hr. The reaction mixture was cooled in ice and carefully decomposed with wet tetrahydrofuran and hydrochloric acid (2N, 10 ml.). The mixture was extracted with chloroform (3 x 75 ml.), the chloroform solution washed with water and dried. On removal of the solvent by distillation, a brown gum (217.5 mg.) was obtained, $\nu_{\max}$ (chloroform): 3400 strong, (OH Str.) 1730, weak, (ester C=O Str.) and 1660 cm^{-1} weak, (ketone C=O Str.). Attempts to remove the colour from the gum by filtration of the chloroform solution through celite⁷, failed.

(b) The lactone of the carboxyflavanonol (458.5 mg.) was

reduced with lithium aluminium hydride (456.4 mg.) as above in (a). A brown gum (426.8 mg.) was obtained, $\nu_{\max}$ (chloroform): 3400 strong, (OH Str.), 1730, weak, (lactone C=O Str.) and 1695 (ketone C=O Str.).

(c) A solution of the gums (644.3 mg.) in benzene-chloroform (10:2.8^{v/v}, 12.8 ml.) was passed through alumina (10% deactivated, 10g.). The solvent eluted a brown gum (586.4 mg.), $\nu_{\max}$ (chloroform): 3300 (OH Str.), 1730, weak, (lactone and ester C=O Str.), 1695 (lactone ketone C=O Str.) and 1660 cm⁻¹ weak, (ester ketone C=O Str.). Chloroform eluted a colourless gum (51.2 mg.), $\nu_{\max}$ (chloroform): 3400 cm⁻¹, strong, (OH Str.), no carbonyl absorption. This colourless gum could not be caused to crystallise: thin-layer chromatography on silica, in chloroform, yielded 2 spots, R_f 0.47 and 0.50, indicating the presence of the 3:4-cis-and trans-diols.⁷ On treatment with aqueous ethanolic hydrochloric acid, a cherry-red colouration was observed, thus confirming the presence of the 3:4-diol system.

Oxidation of the Diol mixture with Activated Manganese Dioxide. - A solution of the diol mixture (46 mg.) in chloroform (25 ml.) was shaken with activated manganese di-¹³oxide (315.5 mg.) at room temperature for 12 days.¹⁴ The mixture was filtered through fine filter paper, celite,

alumina and silica. Finally, the solution was centrifuged at 3000 r.p.m. for 20 min., leaving a sol of residual manganese dioxide in a solution of the product in chloroform. On removal of the chloroform by distillation, a brown powder remained, which softened sharply at $185-190^{\circ}$, $\nu_{\max}$ (chloroform): 3400 (OH Str.) and 1665 cm^{-1} , weak, (H-bonded aryl ketone).

Dehydration of the Oxidation Product. - The brown powder (80 mg.) was treated with *p*-toluene sulphonic acid (107.4 mg.) in dimethyl sulphoxide (3 ml.) at 100° for 15 min. under nitrogen.⁷ The mixture was cooled and poured into cold saturated aqueous sodium carbonate solution (100 ml.). After 24 hr. at 0° , a brown precipitate formed, which passed through fine filter paper. The mixture was extracted with ether (3x40 ml.), when brown material remained in the aqueous layer. The ethereal solution was washed with water and dried. Removal of solvent by distillation yielded a yellow gum (23.0 mg.), which could not be caused to crystallise, $\nu_{\max}$ (chloroform): 1689 cm^{-1} , strong (aryl ketone C=O Str.), no hydroxyl absorption; cf. 1687 cm^{-1} (aryl ketone C=O Str.) observed in authentic peltogynone trimethyl ether.⁵

(⁺)-Tri-O-methylpeltogynol. - The yellow gum (23.0 mg.) was dissolved in dry ether (25 ml.), and lithium aluminium

hydride (30 mg.) added with cooling. The mixture was stirred and boiled under reflux for 3 hr., after which it was cooled to 0° and decomposed with water and hydrochloric acid (2N, 20 ml.). The ethereal layer was separated and the aqueous layer extracted with ether (3x30 ml.). The ethereal solutions were combined, washed with water and dried. Removal of solvent by distillation yielded a colourless solid (7.9 mg.), m.p. 190-195°. Slow evaporation of an ethereal solution of this solid yielded colourless needles, m.p. 195-7°, $\nu_{\max}$ (chloroform): 3575-3600 cm^{-1} (OH Str.), no carbonyl absorption. A solution of the product in chloroform showed no optical activity.

The product was shown to be the trimethyl ether of peltogynol by comparison of its infra-red and mass-spectra with those of the natural product, m.p. 186-195°. These spectra are reproduced on pages 74a - 74d.

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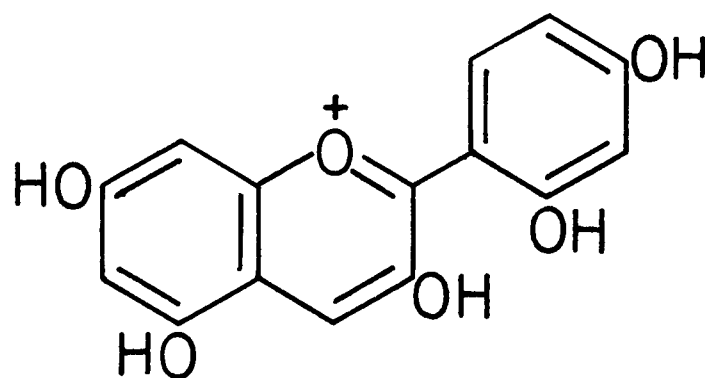
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C H A P T E R 3

CYANOMACLURINIntroduction

Cyanomaclurin occurs in jackwood (Artocarpus integrifolia), an Indian tree. It was first isolated by Perkin and Cope,¹ and investigated by Perkin² and by Appel and Robinson.³

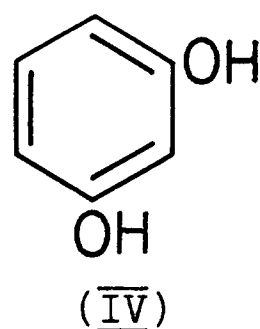
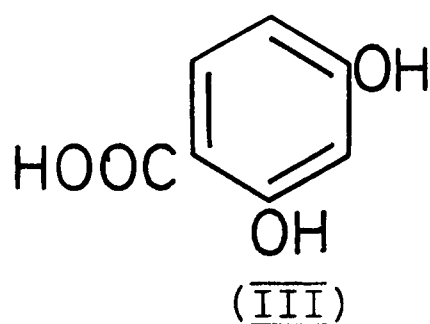
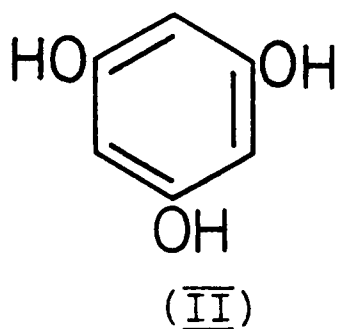
Cyanomaclurin, $C_{15}H_{12}O_6$, m.p. 250° (dec.), $[\alpha]_D + 215^{\circ}$ (ethyl acetate) is a colourless compound, which forms a deep blue solution when heated in alkali: it derives its name from this coloured solution, which closely resembles that produced from morinidin (I). A small quantity of morinidin is



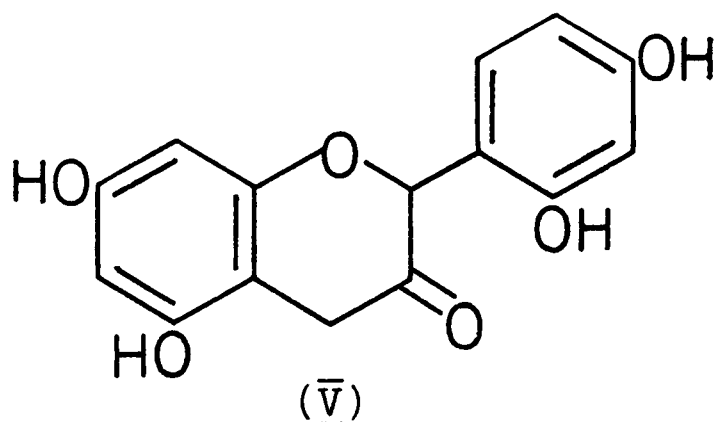
(I)

in fact produced after acidification of an alkaline solution of cyanomaclurin³.

When fused with alkali, cyanomaclurin yielded phloroglucinol, (II), 2:4-dihydroxybenzoic acid, (III), and resorcinol (IV). Perkin² suggested that cyanomaclurin should,

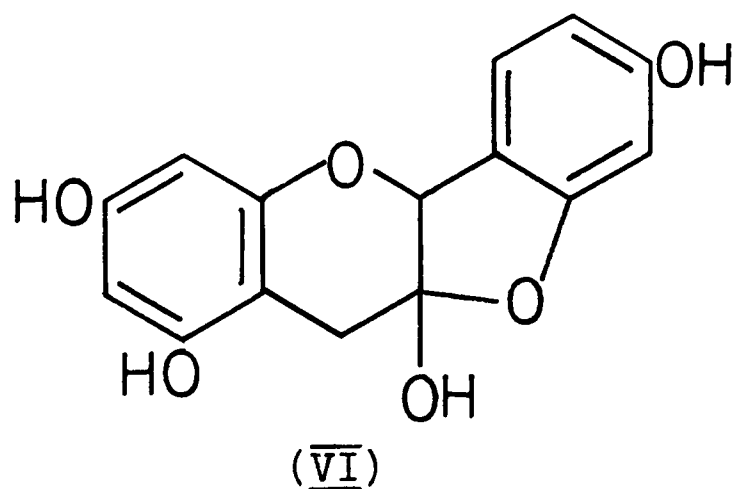


therefore, be regarded as an enol form of the ketone (V).



The Appel-Robinson Structure.

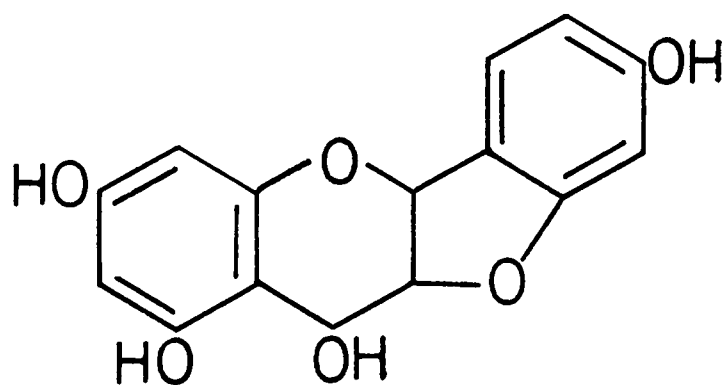
Appel and Robinson³ modified this structure to that of the hemi-ketal (VI), which could accommodate the main features



of the chemistry of cyanomaclurin, provided that the optical stability in alkaline solution, unusual in a hemiketal, could be attributed to some special factor, perhaps a stereochemical one.^{3,4} Cyanomaclurin does not exhibit carbonyl absorption and does not yield a semicarbazone.

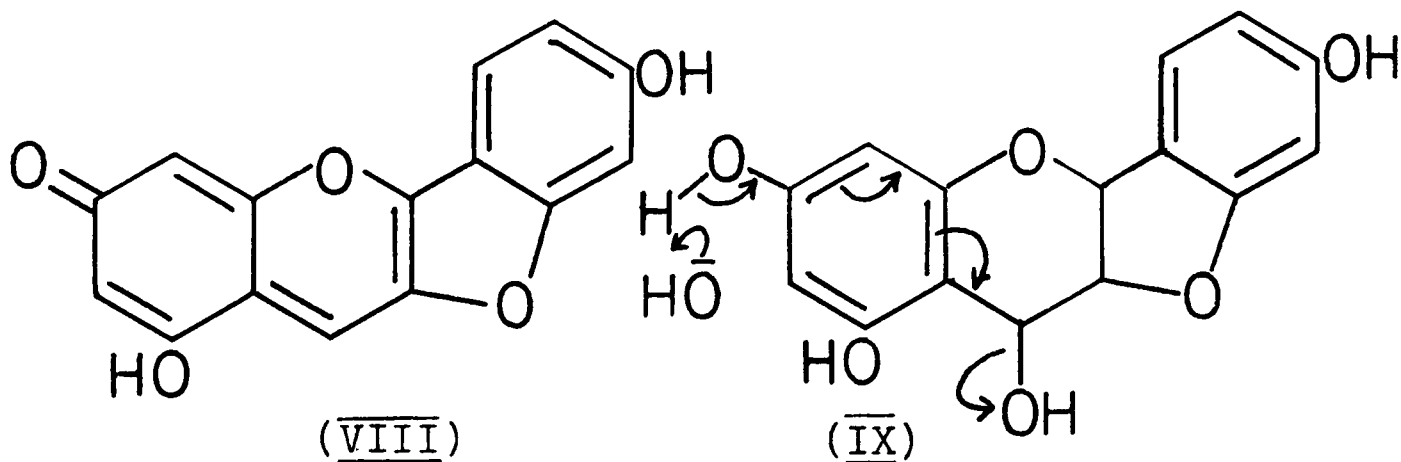
The Dean-King Structure.

It has, therefore, been suggested^{5,6} that the formula, (VII), gives a better description of cyanomaclurin. The blue

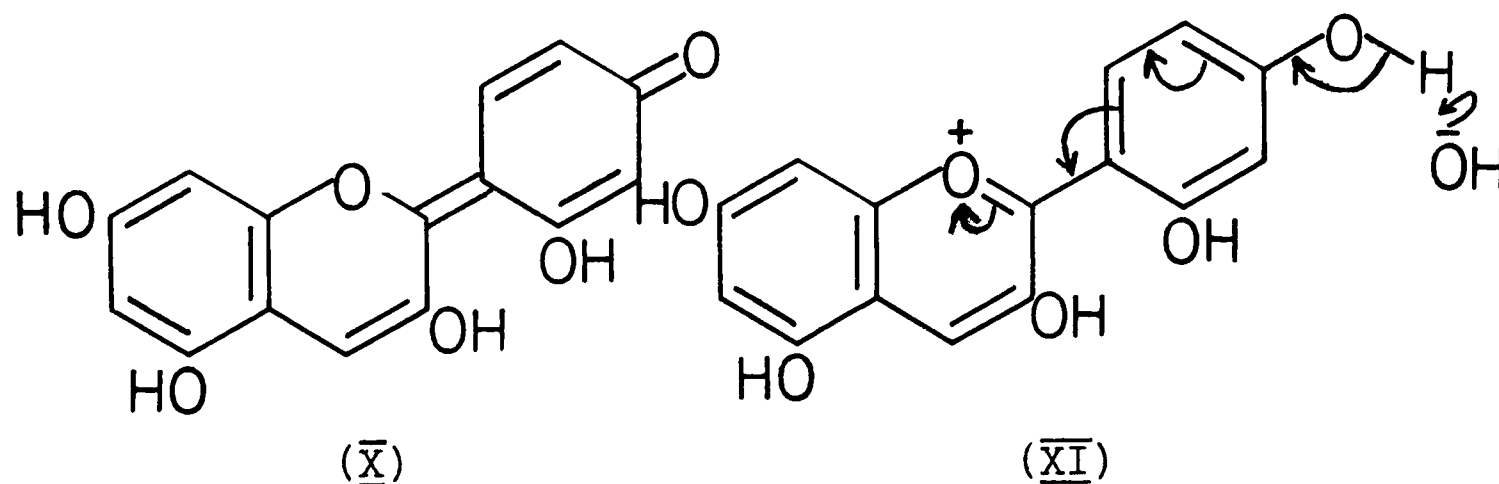


(VII)

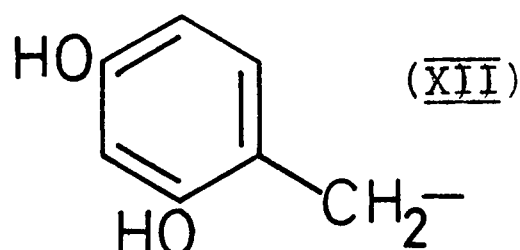
solution in alkali would then be attributed⁵ to the formation of the quinonoid system (VIII), obtained by the movements of electrons shown in (IX), followed by aerial dehydrogenation at



positions 2 and 3. The blue solution of morinidin (I) in alkali is presumably due to a similar quinonoid system (X) obtained by the movements of electrons shown in (XI).



The formula (VII) has received support from Chakravarty and Seshadri,⁷ based on the n.m.r. spectra of cyanomaclurin, tri-O-methyl-cyanomaclurin and of tetra-O-methyl catechin. They claim that the spectrum of the trimethyl ether of cyanomaclurin is incompatible with the hemi-ketal structure (VI), since it does not contain the signal of a benzyl methylene group (XII). Further, they show that the acetate of the



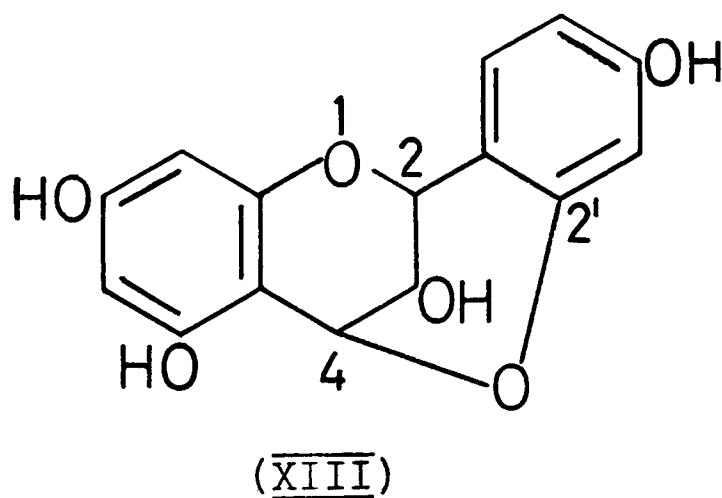
trimethyl ether does not react with N-bromosuccinimide, showing that the benzyl methylene group (XII), present in tetra-O-

methyl catechin and its acetate, which do react with the reagent, is not present in cyanomaclurin as postulated in formula (VI). Chakravarty and Seshadri claim that the n.m.r spectrum of tri-O-methylcyanomaclurin is in accord with formula (VII).

The Nair-Venkatamaran Structure.

8

Nair and Venkatamaran, however, have observed that the inertness of tri-O-methylcyanomaclurin on treatment with manganese dioxide in boiling benzene and towards chromium trioxide in dimethylformamide at 100⁰, both of which result in unchanged trimethyl ether, with no carbonyl absorption in the infra-red spectrum, is not compatible with structure (VII). They suggest that cyanomaclurin is best represented as a 2':4-cyclic ether (XIII). The n.m.r. spectra of cyanomaclurin,



its trimethyl ether and the acetate of the trimethyl ether

are in good agreement with formula (XIII). In particular, the position of the C₃ proton in the trimethyl ether (T = 5.67) is higher than that of the C₂ and C₄ protons (T = 4.61 and 4.68) as expected in formula (XIII), and it is this signal⁹ which moves downfield by approximately 1 p.p.m. on acetylation, to give a signal at 4.6 in the acetate.

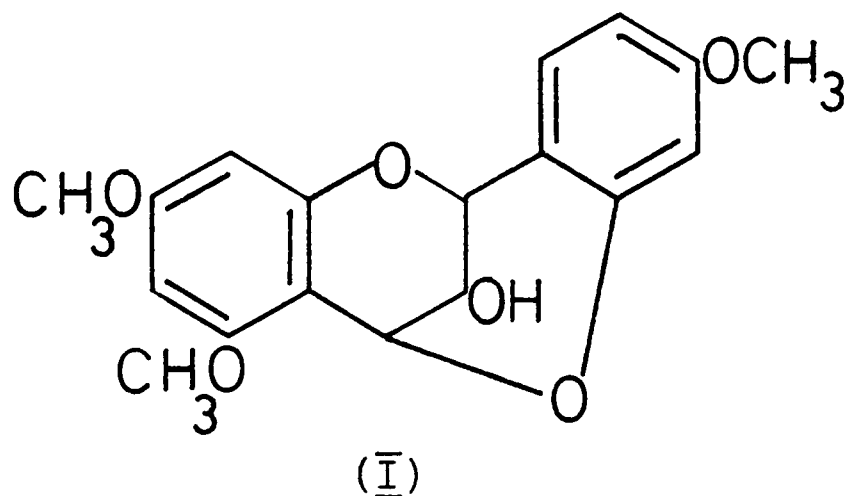
In view of the physical and chemical evidence, it appears possible that cyanomaclurin has the structure shown in formula (XIII).

The Aim of Present Work.

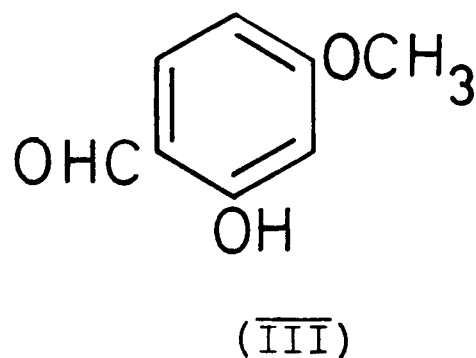
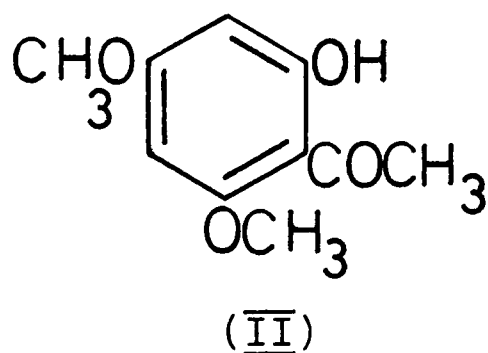
The aim of present work is to synthesise the trimethyl ether of the compound (XIII), thereby proving or disproving its identity with tri-O-methyl cyanomaclurin.

DISCUSSION

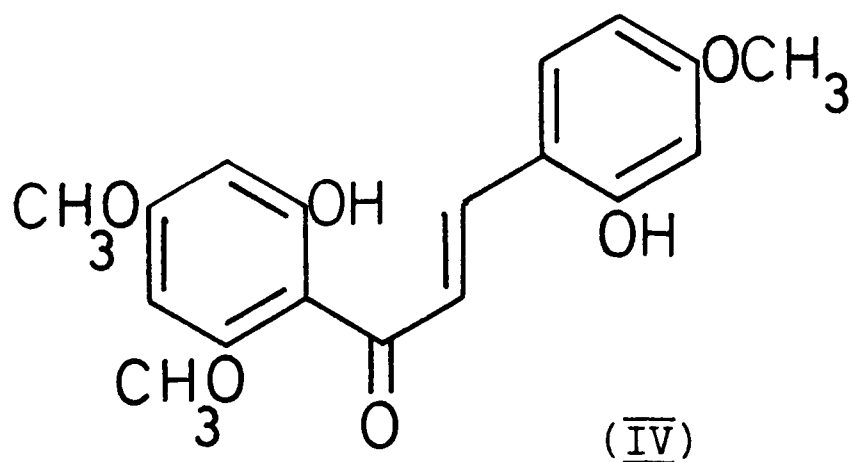
Synthesis of the trimethyl ether of cyanomaclurin (I)



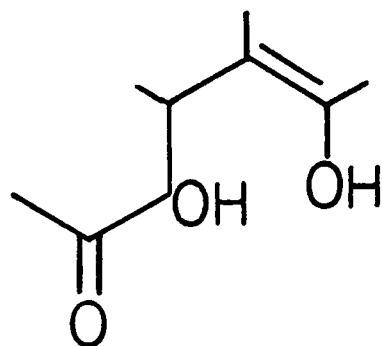
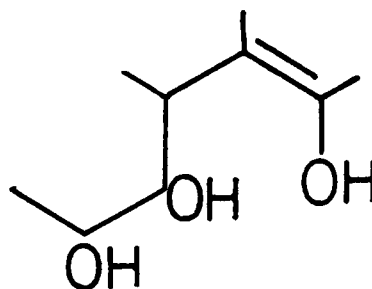
was approached in the following way. Condensation of phloracetophenone-4:6-dimethyl ether (II) with β -resorcylic aldehyde-



4-methyl ether (III) would give the chalcone (IV), which would



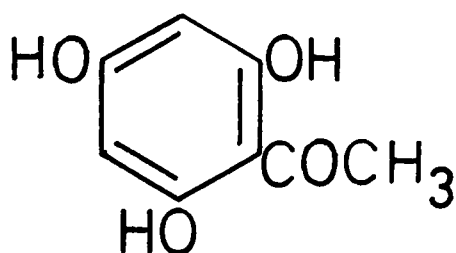
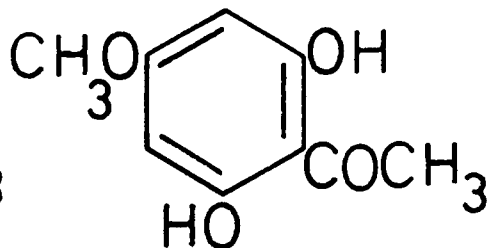
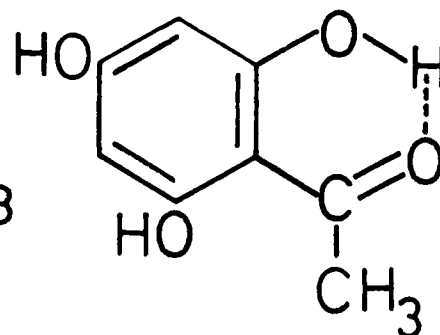
be treated with hydrogen peroxide in alkali¹⁰ to yield the hydroxyflavanone (V). Reduction of this ketone with lithium

(V)(VI)

aluminium hydride would yield the triol (VI), dehydration of which might yield the trimethyl ether of cyanomaclurin or one of its isomers.

Phloracetophenone (VII) was prepared in 45% yield from phloroglucinol, by reaction with acetonitrile in ether.¹¹

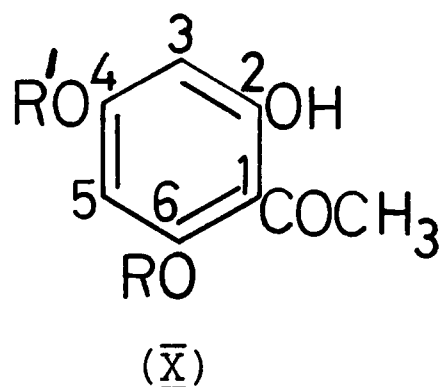
Methylation of phloracetophenone, m.p. 219-221^o, with excess

(VII)(VIII)(IX)

of diazomethane yielded phloracetophenone-4-methyl ether (VIII), m.p. 138-40^o, in 97% yield; lit.¹² m.p. 139-40^o. It had been

expected that methylation with excess diazomethane would yield the dimethyl ether (II), since hydrogen bonding (IX) would prevent only one of the hydroxyl groups from being methylated.

Confirmation of the identity of the product with structure (VIII) was given by the comparison of the nuclear magnetic resonance spectra of phloracetophenone (X : $R=R'=H$), the

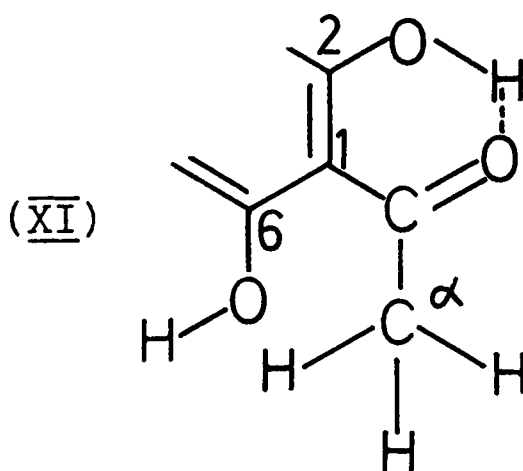


product, m.p. $138-40^{\circ}$, (X : $R=H, R'=CH_3$) and the 4:6-dimethyl ether, (II) and (X : $R=R'=CH_3$), m.p. $85-8^{\circ}$, prepared subsequently in 69% yield by methylation of phloracetophenone with the calculated quantity of dimethyl sulphate and anhydrous potassium carbonate in acetone-benzene.

The spectrum of phloracetophenone shows no methoxyl singlets; that of the compound, m.p. $138-40^{\circ}$, shows one singlet at $\tau = 6.18$ ~~p.p.m.~~ which integrates for three protons, and that of the dimethyl ether shows two singlets at $\tau = 6.14$ and 6.18 , each of which integrates for three protons. In addition to this, the C_3 and C_5 protons appear as a sharp

singlet, integrating for two protons in the spectra of phloracetophenone and of the compound, m.p. $138-40^{\circ}$; this is the expected observation, since the molecules are symmetrical and the C_3 and C_5 protons are therefore completely equivalent. On further methylation, however, to the 4:6-dimethyl ether, the molecule loses its symmetry and the C_3 and C_5 protons become non-equivalent: in the spectrum of the dimethyl ether, they appear as two doublets, each of which is split by 2.4 c/s, which is the usual value for meta-splitting in aromatic rings.⁹

It appears, therefore, that hydrogen-bonding between the 2-phenolic group and the ketone carbonyl also prevents the 6-phenolic group from being methylated by excess of diazomethane. A molecular model of the system (XI) shows that conditions for hydrogen-bonding are most favourable when the



six-membered ring, incorporating carbon atoms 1 and 2, is planar. Under these conditions the α -methyl group is quite

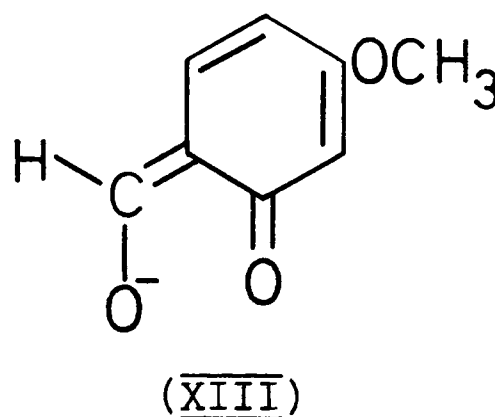
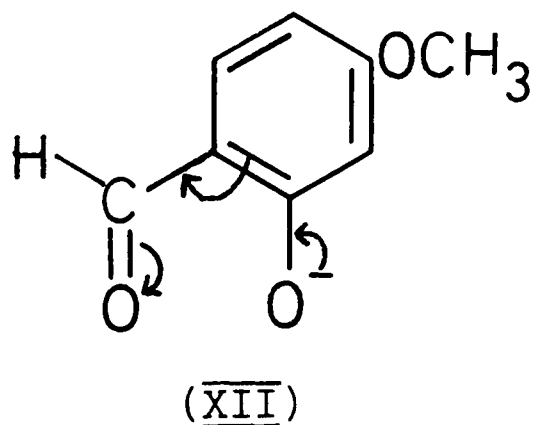
near to the 6-phenolic group, and probably interferes with the approach of the diazomethane molecule. Such shielding may account for the partial methylation of phenolic groups by diazomethane in studies on tannins.¹³

β -Resorcyraldehyde-4-methyl ether (III) was prepared from β -resorcyraldehyde by methylation with the calculated quantity of dimethyl sulphate and sodium hydroxide. The isolation and purification of the product proved troublesome as its solubility in water and in organic solvents is high and its temperature coefficient of solubility in water is low. Steam distillation of the acidified reaction mixture, followed by prolonged cooling of the aqueous distillate, yielded the ether in 22% yield.

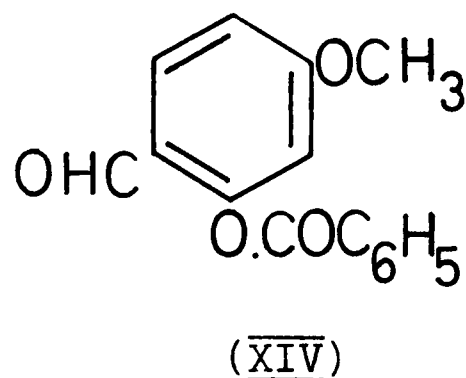
Attempts were then made to condense the methyl ketone (II) and the aldehyde (III) under basic conditions. Aqueous ethanolic solutions of sodium hydroxide, of various strengths were used, from 50% to 5% (w/v), at temperatures ranging from room temperature to 78° and for periods of time of from 1 hr. to 48 hr. In each case, the ketone (II) was recovered in good yield. The identity of these products with the ketone (II) was established by m.p. and mixed m.p., and by a study of their ultra-violet spectra. Several of these spectra showed very small inflexions at 320 and 395 m μ , which can be

attributed to a very small quantity of the chalcone (IV). It is difficult to estimate the ultra-violet absorption of the chalcone (IV), since no data are available for 2:2'-dihydroxychalcones, and furthermore, introduction of methoxyl groups into the aromatic rings produces largely bathochromic, but sometimes hypsochromic shifts in absorptions, and sometimes both.¹³ The general features of the spectra of polyhydroxychalcones, however are absorptions at 340-390 mμ and at 300-320 mμ.¹⁴ On recrystallisation from ethanol, these minor absorptions in the products disappeared, leaving only the characteristic absorption of phloracetophenone-4:6-dimethyl ether (II).

Clearly, the condensation of the methyl ketone (II) with the aldehyde (III) in alkaline solution is inhibited by the presence of the *o*-phenoxide ion (XII), which reduces the carbonyl character of the aldehyde (XIII). The formation of an



o-derivative, might prevent such a reduction of aldehyde character. Accordingly, the benzoate (XIV) of the aldehyde

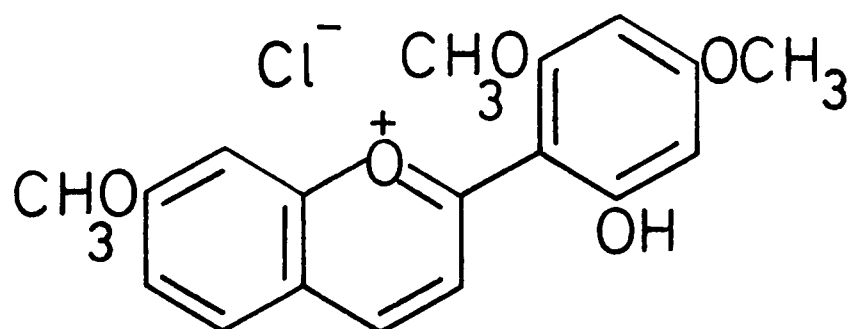


was prepared by the Schotten-Baumann procedure, without a large excess of alkali: with a large excess, the benzoate was hydrolysed yielding the aldehyde (III).

An attempt to condense the benzoate (XIV) with the methyl ketone (II) in dilute alkali, gave a product which proved to be, once again, very largely the methyl ketone (II), showing that hydrolysis of the benzoate occurs more rapidly than condensation with the methyl ketone.

Attempts were then made to condense the aldehyde (III) with the methyl ketone (II) under acid conditions.¹⁵ A solution of the aldehyde and the methyl ketone in dry ethanol was cooled in ice and saturated with dry hydrogen chloride. The colourless solution quickly assumed a purple colour, and was kept at room temperature for 12 hr. On removal of ethanol by distillation and the addition of cold water, a brown solid was isolated. Recrystallisation of this solid from ethanolic hydrochloric acid proved difficult, since its solubility in the solvent is low, as is its temperature coefficient of

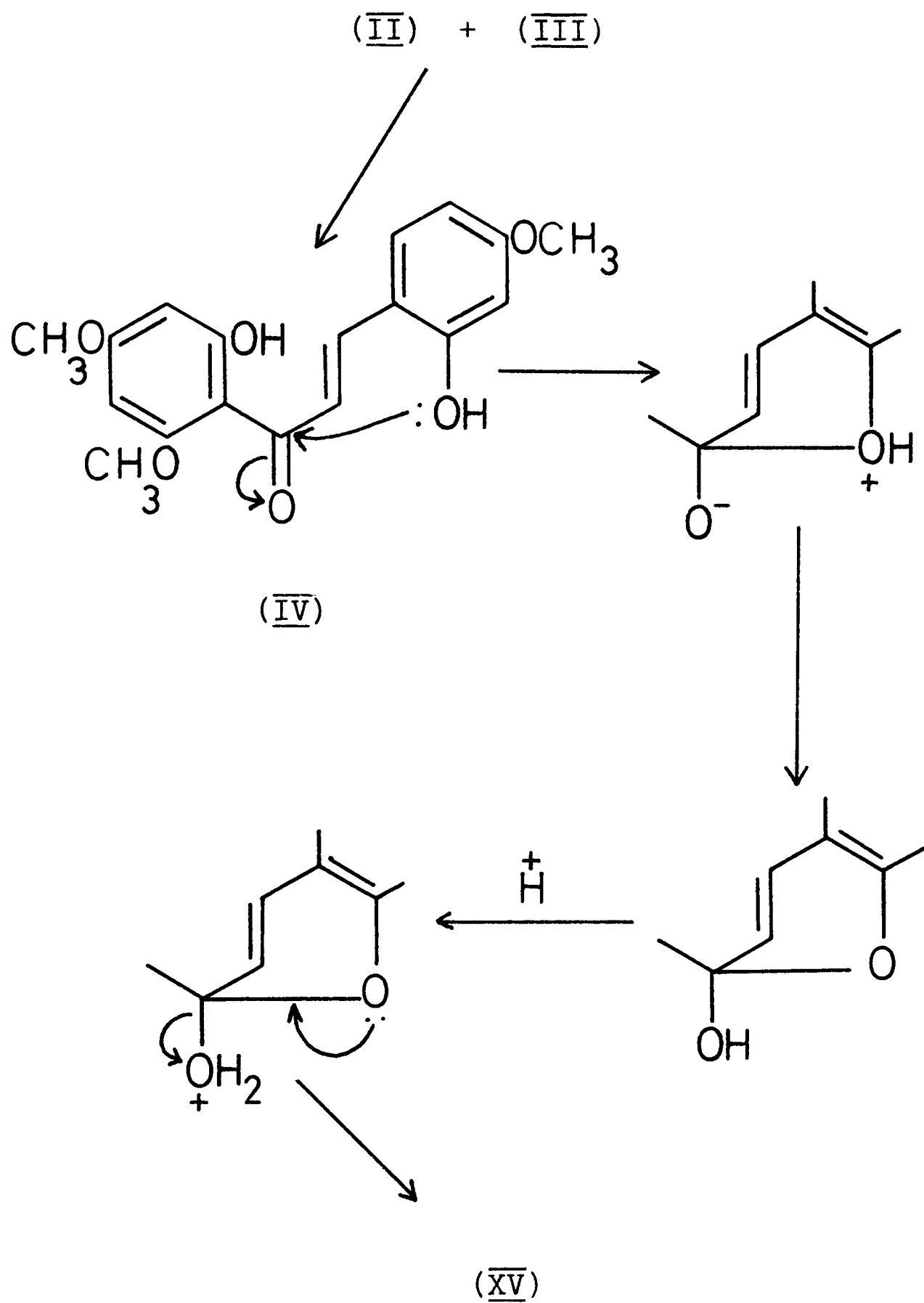
solubility. A pure product was eventually obtained, whose elementary analysis and visible absorption spectrum showed it to be 2'-hydroxy-4':6':7-trimethoxyflavylium chloride (XV).



(XV)

The visible absorption of this compound in ethanol occurred at 480 and 552 (weak inflexion) mμ. Again, comparison with spectra of similar compounds is difficult, since data for 2'-hydroxyflavylium salts is not available. However, absorption by flavylium salts has been seen to occur in the range 483-545 mμ.¹⁶

Clearly condensation has occurred, followed by ring-closure with the aldehyde hydroxyl group, rather than with the hydroxyl group ortho to the methyl ketone group.

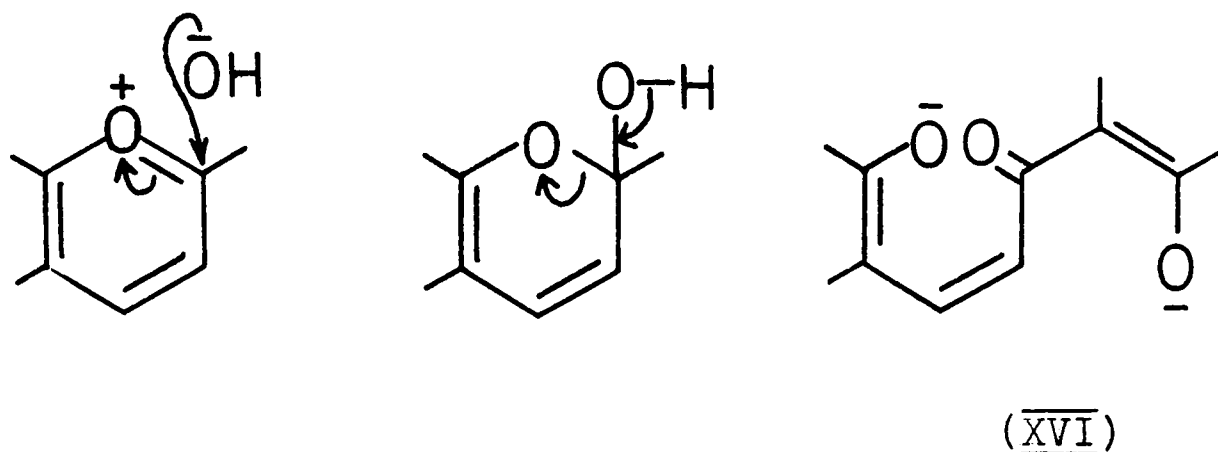


This sequence of events is well-known and was used by Robinson in the synthesis of several anthocyanins and anthocyanidins.¹⁷

Condensation of the benzoate (XIV) with the methyl ketone (II) under the same conditions yielded the same flavylum salt (XV), showing that the benzoate is readily hydrolysed in acid or alkali.

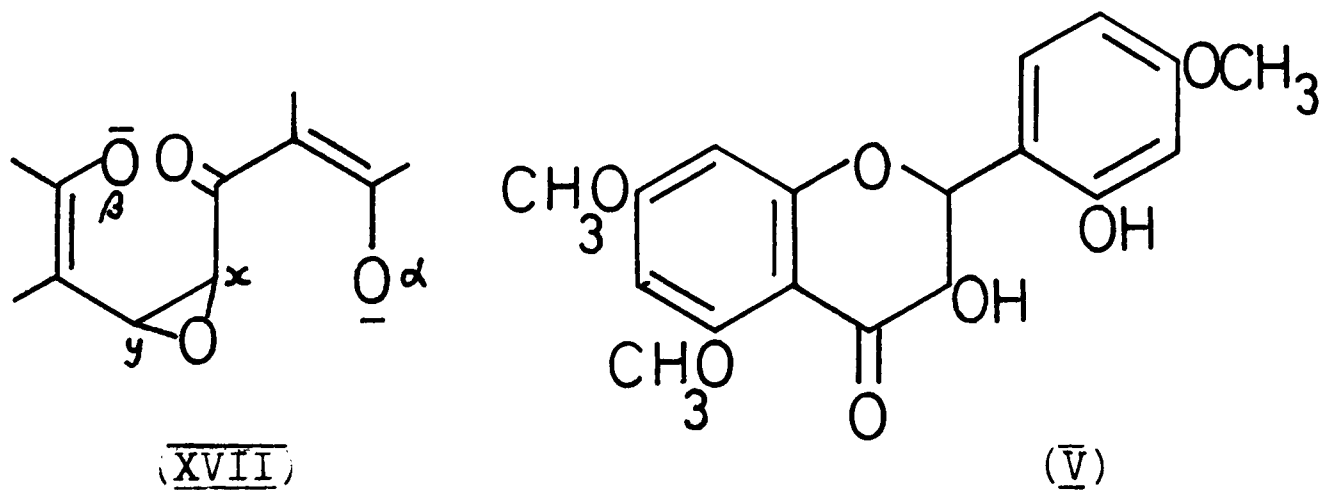
Attempts to prepare the ferrichloride and perchlorate of the flavylum salt failed. Addition of a concentrated solution of ferric chloride in concentrated hydrochloric acid to a solution of the flavylum chloride in ethanol resulted in generation of heat and the precipitation of the flavylum chloride. Similarly, the addition of a strong aqueous solution of perchloric acid to a solution of the flavylum chloride in ethanol, resulted in generation of heat, the production of a red-purple colour and the precipitation of flavylum chloride. Acetic acid was also used as solvent, with the same results.

The flavylum chloride (XV) was treated with methanolic sodium hydroxide at 60° for 30 min., giving rise to a yellow-brown coloured solution. The change in colour from the cherry red solution of the chloride in methanol is attributed to the fission of the ring to give the chalcone ion (XVI).

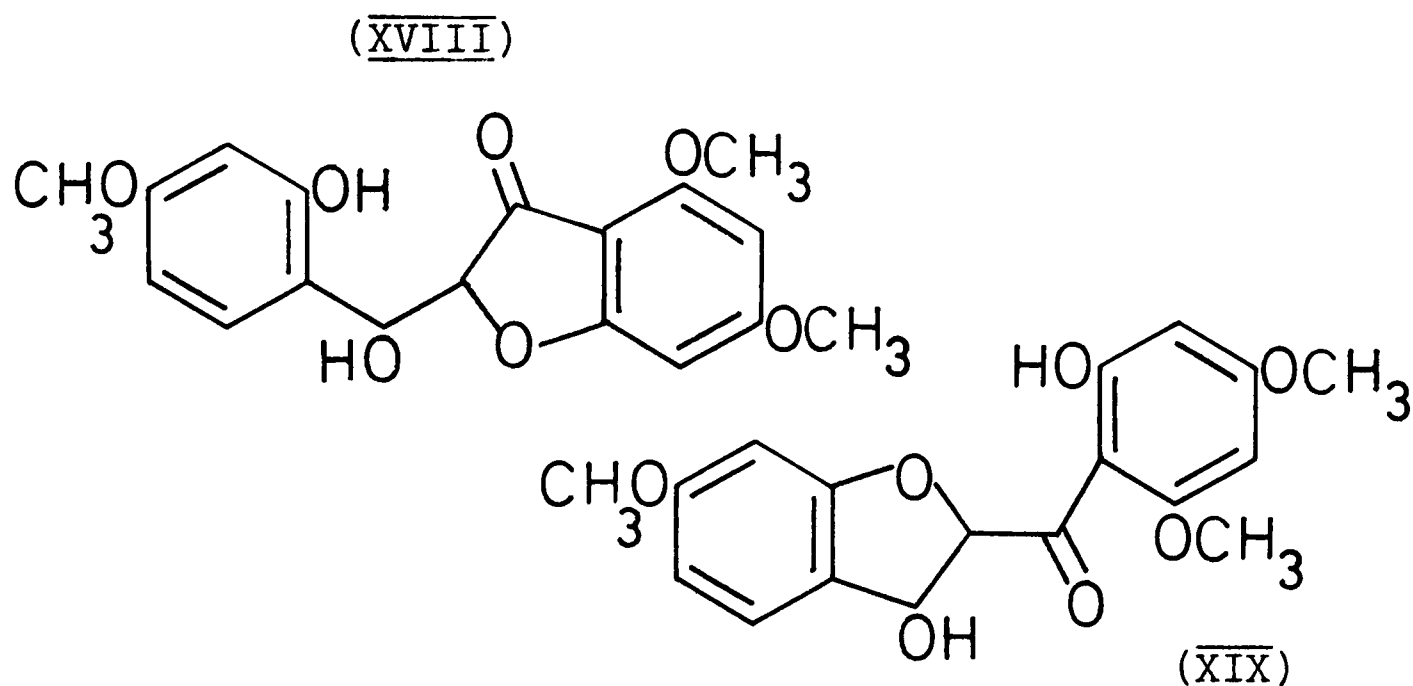


The solution was cooled to 0° , and hydrogen peroxide added slowly. The solution became orange in colour and was kept at room temperature for 8 hr., after which it was poured into cold aqueous hydrochloric acid. Ethyl acetate extraction of this mixture yielded a yellow oil which solidified to a cream-coloured sticky solid, and which could not be recrystallised satisfactorily. The ultra-violet spectrum of the product in ethyl acetate is an amorphous curve, clearly composed of many superimposed absorptions, reaching a maximum at 255 μ . Thin-layer chromatography on Kieselgel gave four spots, confirming that the product was a mixture.

It has been hoped that the epoxide (XVII) formed by the action of hydrogen peroxide on the chalcone ion (XVI),



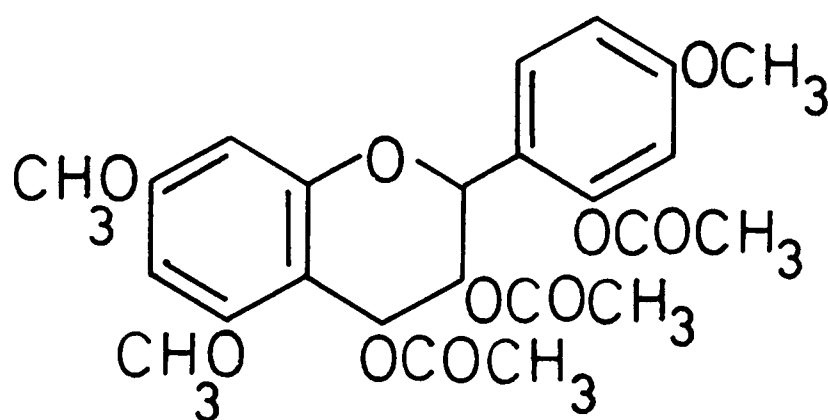
would undergo ring closure by attack of the α -phenoxide ion to the carbon atom y, in a way analogous to the usual¹⁰ preparation of 3-hydroxyflavan-4-ones from chalcones, to give the hydroxy ketone (V). Clearly ring closure is possible also by attack of the α -phenoxide ion on carbon atom x, giving rise to the coumaran-3-one (XVIII): and also by



attack of the β -phenoxide ion on the carbon atom x, giving rise to the coumaran-3-ol(XIX). Other products are also possible, and mention has only been made of the 5- and 6-membered ring products of ring-closure.

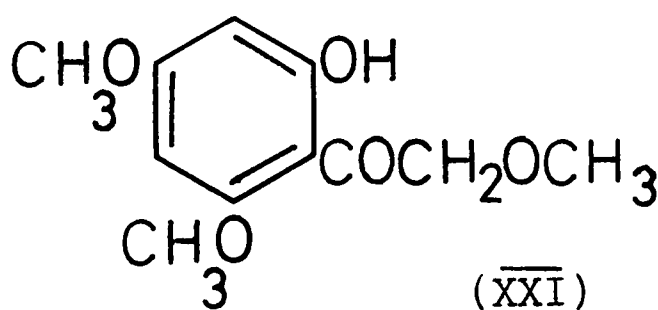
To enable the products of this reaction to be separated, it was decided to reduce the product with lithium aluminium hydride, to acetylate the reduction product and attempt a separation of acetates on alumina. The reduction with lithium

aluminium hydride was effected yielding a brown gum, which could not be caused to crystallise and whose infra-red spectrum showed no carbonyl absorption, and strong hydroxyl absorption at $3200-3400\text{ cm}^{-1}$. Work is still in progress, directed towards the synthesis of the trimethyl ether of cyanomaclurin, via the triacetate, (XX), which will possibly be derived from the mixture of products above, by reduction

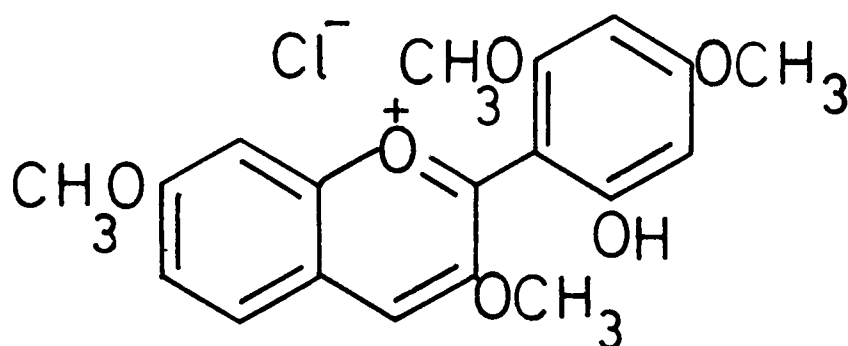
(XX)

and acetylation.

When it became evident that the original synthetic route promised to be abortive, it was decided to investigate a route involving the acid condensation of the aldehyde (III) with the methoxyacetophenone (XXI), which would be expected,

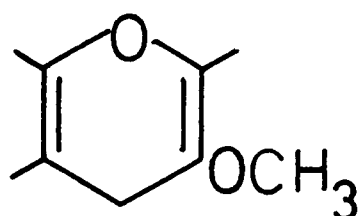
(XXI)

on the basis of work discussed previously, to give the flavylum salt (XXII). Reduction of this salt with lithium

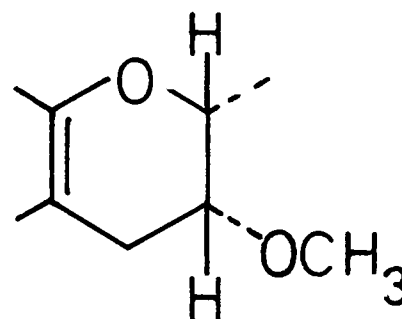


(XXII)

aluminium hydride¹⁸ would be expected to yield the flav-2-ene (XXIII), hydrogenation of which would yield the methoxy-



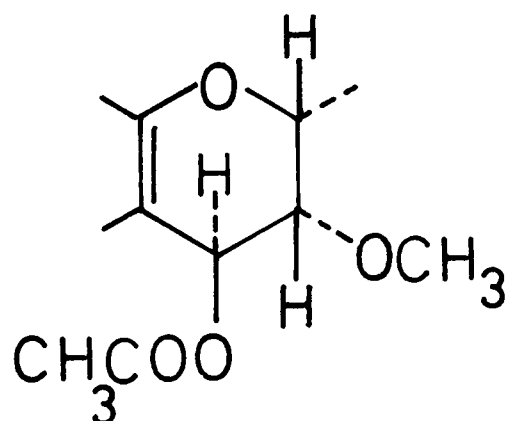
(XXIII)



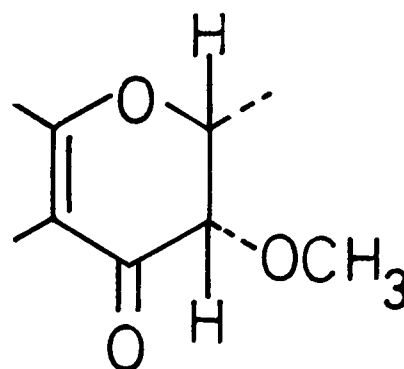
(XXIV)

flavan¹⁹ (XXIV), with 2:3-cis stereochemistry. Reaction of this with lead tetra-acetate would then yield the acetate

(XXV), which on hydrolysis and dehydration would yield the



(XXV)



(XXVI)

tetramethyl ether of cyanomaclurin or one of its isomers. Variation of the configuration of the 4-hydroxyl group after hydrolysis of the acetate (XXV) and prior to dehydration would be possible by means of oxidation with activated manganese dioxide (see Chapter 1) followed by reduction of the resulting ketone (XXVI) with lithium aluminium hydride.

Work on this new synthetic route has begun, and the flavylum salt (XXII) has been prepared. Similar in properties to the salt (XV), it crystallises with reluctance from ethanolic hydrochloric acid with half a molecule of ethanol of crystallisation; it has no melting point; its visible spectrum shows absorption at 484 and 608m μ , (weak inflexion), and it forms no ferrichloride or perchlorate.

It is hoped that further work on the synthesis outlined above, via the flavylium salts (XV) and (XXII), will result in the syntheses of the tri- and tetra-methyl ethers of cyanomaclurin. If the syntheses are unsuccessful, they should at least provide similar compounds with oxygen functions at positions 3 and 4, whose structures may be investigated by the same technique which has been used to give cyanomaclurin the structure (I), viz. nuclear magnetic resonance spectroscopy.

EXPERIMENTAL SECTION

Phloracetophenone¹¹ : (38.5g. 45.6%), m.p. 219-221⁰, was prepared from phloroglucinol by reaction with dry acetonitrile and anhydrous zinc chloride in ether; lit.¹¹ m.p. 218-9⁰.

Phloracetophenone-4-methyl ether: (1.056g. 97.4%), m.p. 138-40⁰, was prepared from phloracetophenone by treatment with an ethereal solution of diazomethane (ca. 1g.), prepared from N-nitrosomethylurea (4g.); lit.¹² m.p. 139-40⁰.

Phloracetophenone-4:6-dimethyl ether : (6.76g. 69.2%), was prepared from phloracetophenone by methylation with dimethyl sulphate (13g.) and anhydrous potassium carbonate (30g.) in dry acetone (30 ml.) and benzene (150 ml.). The reaction mixture was boiled under reflux for 12 hr., and then kept at room temperature for 4 hr. The mixture was filtered and the solid washed well with hot benzene (66 ml.). The filtrate was washed with water (3 x 10 ml.) and extracted with aqueous sodium hydroxide solution (5%, 150 ml.). The yellow alkaline extract was poured into hydrochloric acid (2N, 150 ml.) at 0⁰ and the white precipitate was collected and dried. On recrystallisation from ethanol, the dimethyl ether separated as colourless plates, m.p. 85-8⁰;

lit.²⁰ m.p. 85-8°.

β -Resorcyraldehyde-4-methyl ether²¹ : (22.1g. 22.3%), m.p. 39-40°, was prepared from β -resorcyraldehyde (re-sublimed, m.p. 136-7°) by methylation with dimethyl sulphate and sodium hydroxide in water. Acidification and steam distillation of the reaction mixture gave an aqueous solution, from which the ether separated on cooling; lit.²¹ m.p. 41°.

Attempted Alkaline Condensation of Phloracetophenone-4:6-dimethyl ether with β -Resorcyraldehyde-4-methyl ether. - The acetophenone (2.0g.) and the aldehyde (1.52g.) were dissolved in warm ethanol (25 ml.). An aqueous solution of sodium hydroxide (50%, 5 ml.) was added and the solution kept at 50° for 12 hr. Acidification of the pale yellow solution produced a buff-coloured solid (1.45g.), m.p. 73-7°, which was collected, washed with water and dried. The ultra-violet spectrum of the product, λ_{max} (ethanol): 285 (log ϵ 4.30), 225 (inf.), 211 (log ϵ 3.44), λ_{min} : 242 m μ and its elemental analysis, showed it to be largely the acetophenone, λ_{max} (ethanol): 285 (log ϵ 4.31), 225 (inf.), 211 (log ϵ 3.46), λ_{min} : 242 m μ . The presence of a small inflexion at 325 m μ in the spectrum of the product indicated that a small amount of the chalcone has been formed. The

product separated from ethanol as colourless plates, m.p. and mixed m.p. with authentic sample, $86-7^{\circ}$.

The procedure was repeated with alcoholic potassium hydroxide solution (24%, 70 ml.), as above, and by boiling under reflux for 12 hr. The identical product, phloracetophenone-4:6-dimethyl ether, was obtained.

2-Benzoyloxyanisaldehyde : (0.22g. 52.3%), was prepared from β -resorcyraldehyde-4-methyl ether by benzylation using the Schotten-Baumann procedure. 2-Benzoyloxyanisaldehyde separated from light petroleum-ethyl acetate as colourless blunt needles, m.p. $83-4^{\circ}$, (Found : C 70.4, H 4.7, $C_{15}H_{12}O_4$ requires : C 70.3, H 4.7%), $\nu_{\max}$ (nujol): 1730 (aryl ester C=O Str.), 1698 cm^{-1} (aryl aldehyde C=O Str.), $\lambda_{\max}$ (ethanol): 275 ($\log \epsilon$ 4.17), 232 ($\log \epsilon$ 5.74), 206 ($\log \epsilon$ 2.93), $\lambda_{\min}$: 257, 210 m μ .

Attempted Alkaline Condensation of Phloracetophenone-4:6-dimethyl ether and 2-Benzoyloxyanisaldehyde. - The acetophenone (60 mg.) and the aldehyde (174 mg.) were dissolved in warm ethanol (3 ml.). A solution of sodium hydroxide (8%, 2 ml.) was added, and the solution kept at 50° for 8 hr. The solution was cooled to 0° and acidified with hydrochloric acid (2N, 3 ml.). A buff-coloured solid (53.1

mg.), m.p. $78-81^{\circ}$, separated, and was collected, washed with water and dried. The ultra-violet spectrum of the solid was identical with that of the acetophenone.

The procedure was repeated with aqueous sodium hydroxide (0.8%, 5 ml.) and gave the same product.

Acid Condensation of Phloracetophenone-4:6-dimethyl ether and β -Resorcyraldehyde-4-methyl ether. - The acetophenone (197.4 mg.) and the aldehyde (153.5 mg.) were dissolved in dry ethanol (20 ml.), and the solution cooled to 0° and saturated with dry hydrogen chloride. The colourless solution became dark red and was kept at room temperature for 12 hr. The solution was poured into cold water (150 ml.) and filtered. The dark red finely-divided solid (0.26 g.) was washed with water and dried. On recrystallisation from ethanolic hydrochloric acid, 2'-hydroxy-4':6':7-trimethoxy-flavylium chloride (0.19 g. 54.1%) separated as a brown powder with no m.p., (Found : C 61.9, H 4.7, Cl 10.1. $C_{18}H_{17}ClO_5$ requires : C 61.9, H 4.85, Cl 10.15%), $\lambda_{\max}$ (ethanol): 480 (log ϵ 4.4), 552 (small inf.), $\lambda_{\min}$: 375 m μ .

Attempted Preparation of 2'-Hydroxy-4':6':7-trimethoxy-flavylium Ferrichloride. - A small amount of the chloride was dissolved in ethanol and a concentrated solution of

anhydrous ferric chloride in concentrated hydrochloric acid added. Heat was evolved and a brown precipitate was formed, which was separated, washed with water and dried. Recrystallisation of the product, from ethanol, yielded a brown powder, no m.p. (Found : C 62.0, H 4.85, Cl 10.1. $C_{18}H_{17}ClO_5$ requires : C 61.9, H 4.85, Cl 10.15%).

The procedure was also carried out in glacial acetic acid, and the product, again, was the flavylum chloride.

Attempted Preparation of 2'-Hydroxy-4':6':7-trimethoxy-flavylum Perchlorate. - A small amount of the chloride was dissolved in ethanol and aqueous perchloric acid solution (72%) added. The colour of the solution changed from brown to purple and heat was evolved. The solution was kept at 0° for 48 hr., when no precipitate had formed. The solution was reduced to 1/4 of its volume by removal of ethanol by distillation and poured into cold water. The brown precipitate was collected, washed with water and dried : no m.p., (Found : C 61.95, H 4.8, Cl 10.2, $C_{18}H_{17}ClO_5$ requires : C 61.9, H 4.85, Cl 10.15%).

Acid Condensation of Phloracetophenone-4:6-dimethyl ether and 2-Benzoyloxylanisaldehyde. - The acetophenone (198 mg.) and the aldehyde (259.3 mg.) were dissolved in dry

ethanol (20 ml.) and the solution, cooled to 0° , saturated with dry hydrogen chloride. The colourless solution became red and, after 12 hr. at room temperature, was poured into cold water (150 ml.). The brown precipitate was collected, washed with water and dried (0.22g.), no m.p., (Found : C 62.0, H 4.9, Cl 10.2. $C_{18}H_{17}ClO_5$ requires : C 61.9, H 4.85, Cl 10.15%).

Action of Alkaline Hydrogen Peroxide on 2'-Hydroxy-4':6':7'-trimethoxyflavylium Chloride. - The chloride (180 mg.) was treated with methanol (1.5 ml.) and aqueous sodium hydroxide solution (2N, 0.15 ml.) at 60° for 30 min. The yellow-coloured solution was cooled to 0° and hydrogen peroxide (100 vol., 0.3 ml.) was added slowly, with stirring. The orange mixture was kept at room temperature for 8 hr., after which it was poured into cold aqueous hydrochloric acid (2N, 10 ml.). The yellow mixture was continuously extracted with ethyl acetate, and the extract washed with water and dried. Removal of solvent by distillation yielded a yellow oil (227 mg.) which solidified to a sticky cream-coloured product, which could not be caused to crystallise, $\lambda_{\max}$ (ethanol): broad irregular absorption, reaching a maximum value at 255 m μ , thin-layer chromatography (ethyl acetate):

4 spots (R_f : 0.05, 0.10, 0.16 and 0.23).

Reduction of the Product with Lithium Aluminium Hydride.-

The cream-coloured product (80.1 mg.) was dissolved in dry tetrahydrofuran (40 ml.) and lithium aluminium hydride (96 mg.) added. The mixture was boiled under reflux for 12 hr., cooled to 0° and decomposed carefully with wet tetrahydrofuran and hydrochloric acid (2N, 10 ml.). The mixture was then extracted with ether (4 x 20 ml.) and the ethereal extract washed with water and dried. Removal of solvent by distillation yielded a brown gum (41.0 mg.), which could not be caused to crystallise, $\nu_{\max}$ (chloroform): 3300cm^{-1} , strong, (OH Str.), no carbonyl absorption.

2'-Hydroxy-3:4':6':7-tetramethoxyflavylium Chloride -

ω -Methoxyphloracetophenone-4:6-dimethyl ether (226 mg.), m.p. $102-5^\circ$, and β -resorcyraldehyde-4-methyl ether (152 mg.) were dissolved in dry ethanol (20 ml.), and the solution, cooled to 0° , saturated with dry hydrogen chloride. The colourless solution became red and was kept at room temperature for 12 hr. The reaction mixture was poured into cold water (300 ml.) and the purple-brown precipitate (252.4 mg.) collected, washed with water and dried. On recrystallisation from ethanolic hydrochloric acid, 2'-hydroxy-3:4':6':7-tetra-

methoxyflavylium chloride (207.6 mg. 51.7%) separated as a brown powder, which expelled solvent at ca. 90° and which did not melt, (Found : C 59.9, H 5.6, Cl 8.7. $C_{19}H_{19}ClO_6 \cdot \frac{1}{2} C_2H_5OH$ requires : C 59.8, H 5.5, Cl 8.8%), $\lambda_{\max}$ (ethanol): 484 (log ϵ 4.43), 608 (very small inflexion), $\lambda_{\min}$: 384 m μ .

Attempted Preparations of 2'-Hydroxy-3:4':6':7-tetra-methoxyflavylium Ferrichloride and Perchlorate. - Attempts were made to prepare these derivatives from solutions of the chloride in ethanol and in acetic acid, by treatment with concentrated solutions of anhydrous ferric chloride in concentrated hydrochloric acid, and by treatment with aqueous perchloric acid solutions (72%) respectively; (Found : C 59.75, 59.85, H 5.5, 5.6, Cl 8.7, 8.9. $C_{19}H_{19}ClO_6 \cdot \frac{1}{2} C_2H_5OH$ requires : C 59.8, H 5.5, Cl 8.8%).

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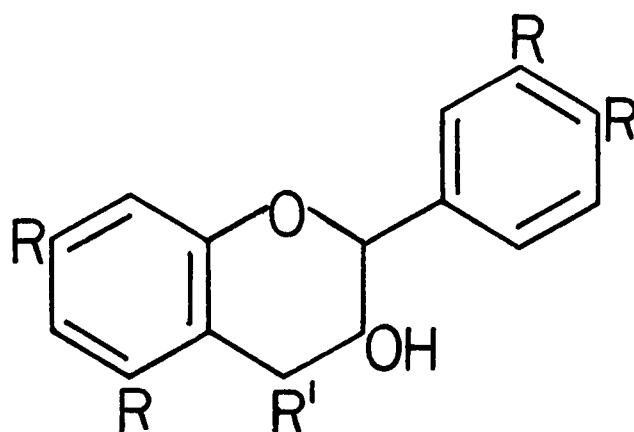
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C H A P T E R 4

THE CONDENSATION OF FLAVAN-3-OLS WITH PHENOLSIntroduction

The skeleton of flavan-3-ol, ($\bar{\text{I}}$: $\text{R}=\text{R}'=\text{H}$), is the

($\bar{\text{I}}$)

basic structure present in many plant products, and together with that of flavan-3:4-diol, ($\bar{\text{I}}$: $\text{R}=\text{H}$, $\text{R}'=\text{OH}$), is of great importance in plant chemistry, especially with reference to the formation of some tannins.

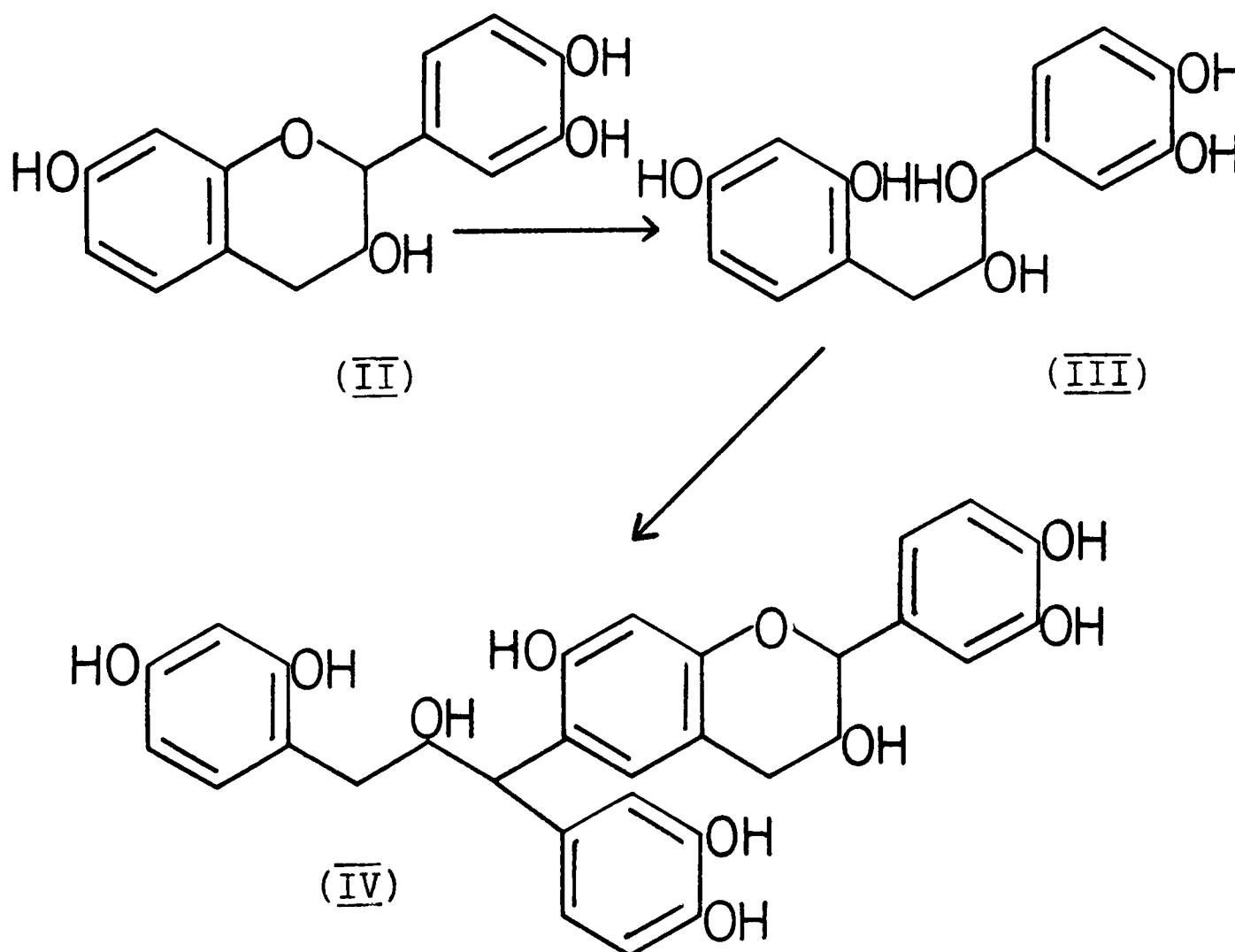
Naturally occurring flavan-3-ols are usually hydroxylated, as is, for example, (+)- catechin, ($\bar{\text{I}}$: $\text{R}=\text{OH}$, $\text{R}'=\text{H}$), which is found in the bush Uncaria gambir. Compounds in which the hydrogen atoms at the 2- and 3-positions are trans, are said to belong to the catechin series, and those in which they

are cis, to the epicatechin series. A diastereoisomer of catechin, (-)-epicatechin, occurs in Acacia catechu.
1-3

Catechins often occur in tannin extracts, and until recently were thought to be the most important of the tannin precursors. Now, however, flavan-3:4-diols are thought to be involved in tannin formation.
4-6.

The Acid Polymerisation of Flavanols.

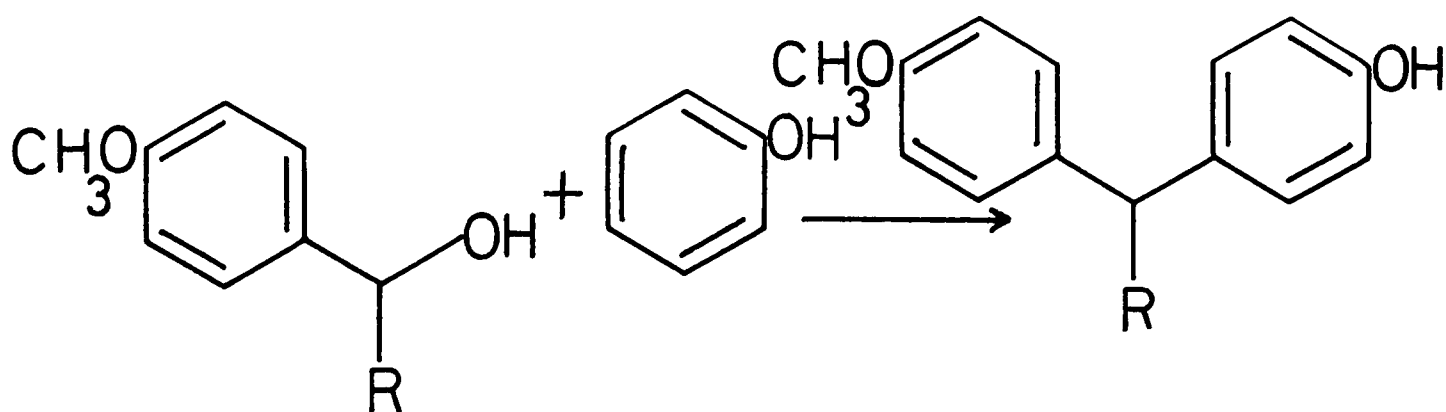
When treated with dilute acid, the condensed tannins undergo further polymerisation, and a number of flavanols are also known to polymerise under the influence of acid. A mechanism for the polymerisation of quebrachocatechin, (II),



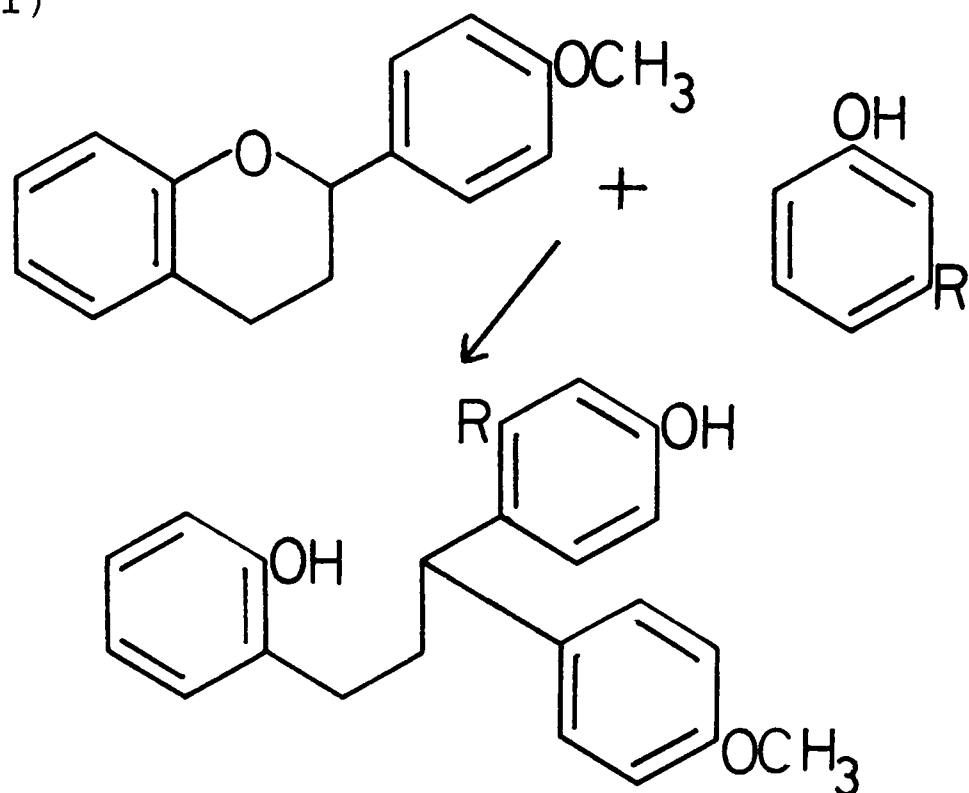
was postulated,² involving ring-opening of one molecule to give a benzyl alcohol, (III), which would then condense with a second molecule as shown. The product, (IV) still contains both the functional groups necessary for further condensation, and polymers may be formed.

A series of hydroxylated flavans was later prepared, and the effect of hydroxyl groups on the ease of polymerisation estimated, by the magnitude of the precipitate formed when each compound was heated with acid for a given period of time.^{7,8.} Compounds with hydroxyl groups in both 7- and 4'-positions invariably gave the heaviest precipitates, and a 5-hydroxyl was found to hinder the reaction. Further support for the mechanism² has been furnished by investigations of condensations between phenols and certain benzyl alcohols, and between phenols and some simple flavans.^{9-13.} The results may be summarised in the reaction schemes below:

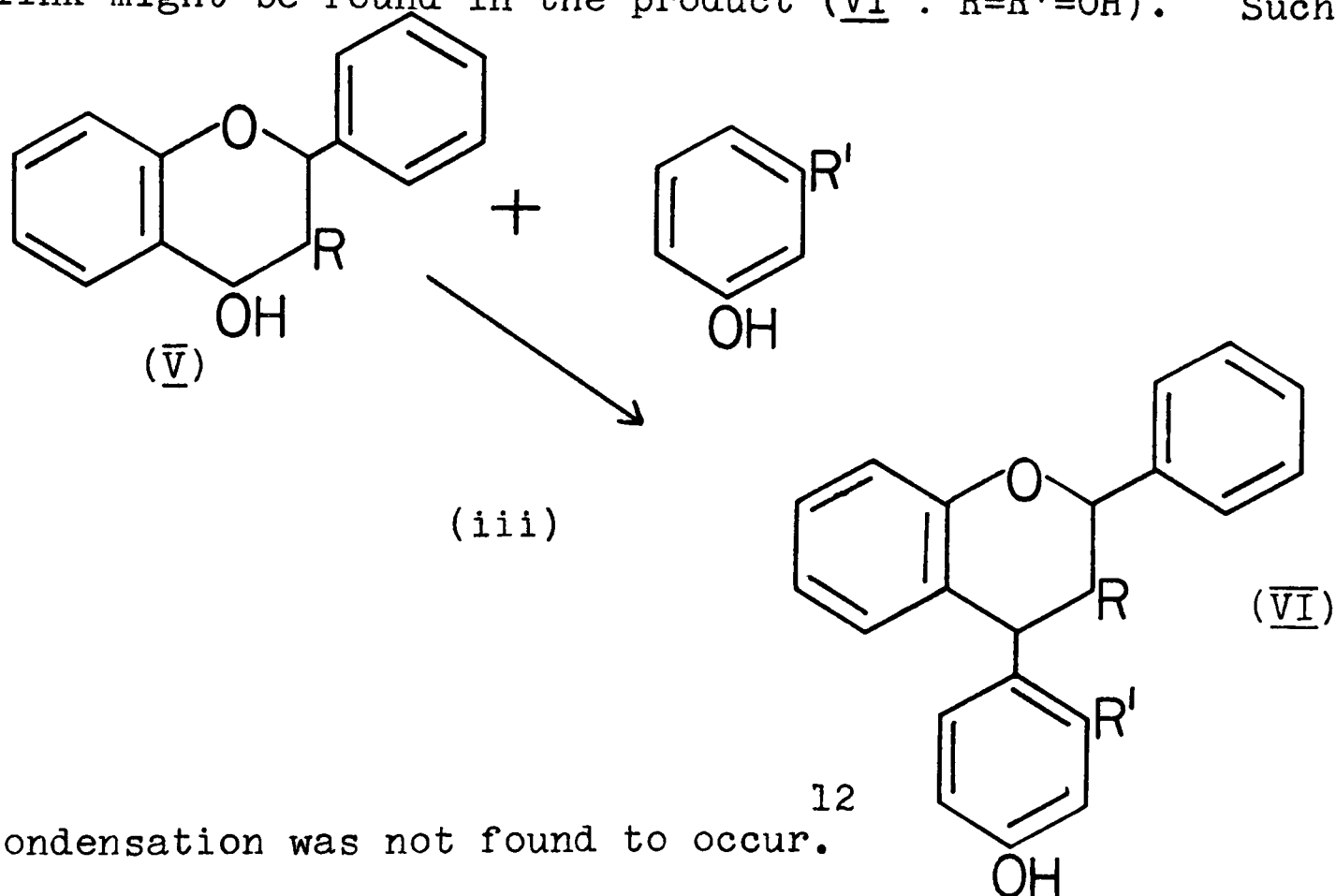
(i)



(ii)



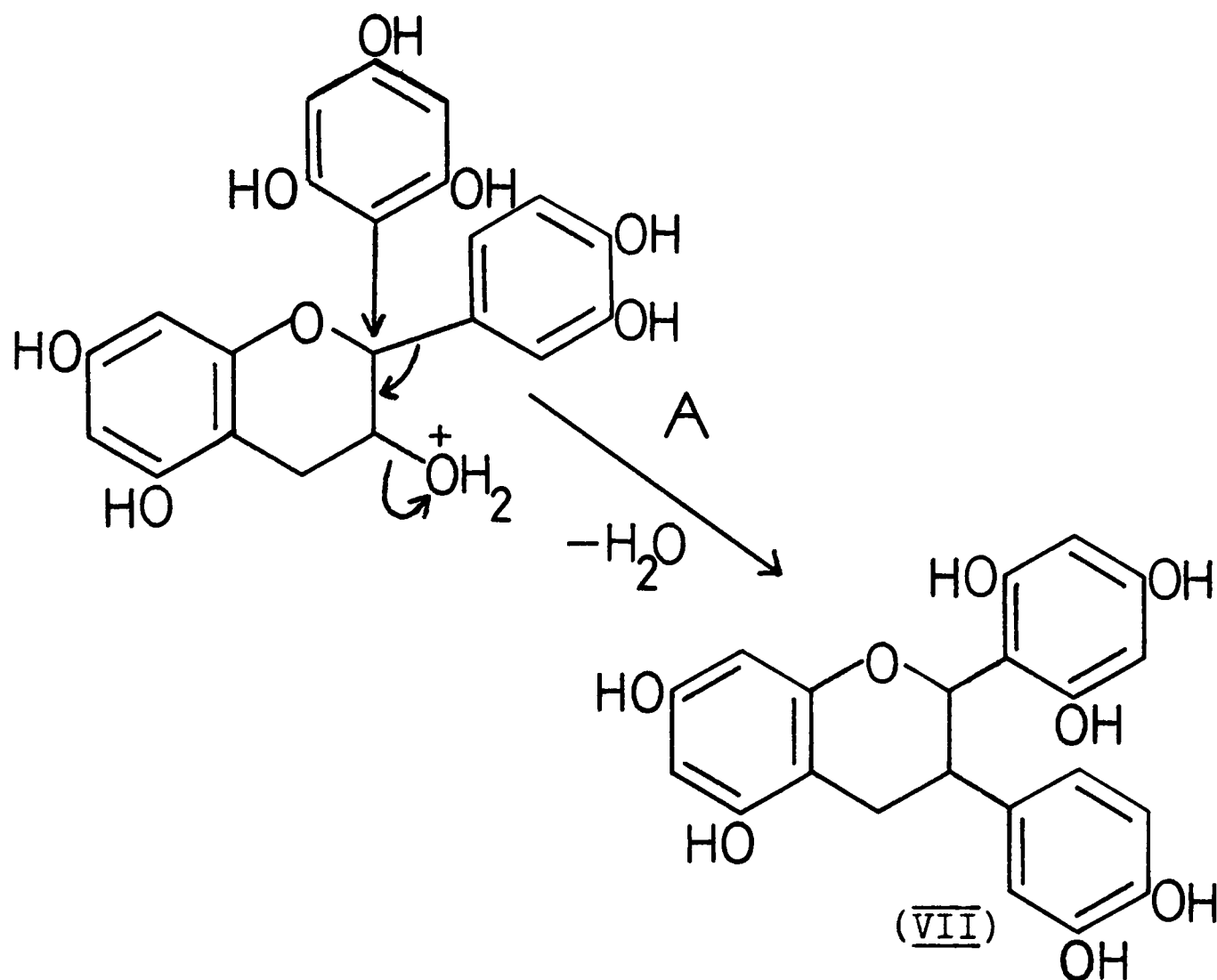
It seemed possible that if flavan-3:4-diols, ($\bar{\text{V}}$: $\text{R}=\text{OH}$), were used, further condensation might occur when the 3-hydroxyl group was cis to the entering aryl group, and an ether link might be found in the product ($\bar{\text{VI}}$: $\text{R}=\text{R}'=\text{OH}$). Such a

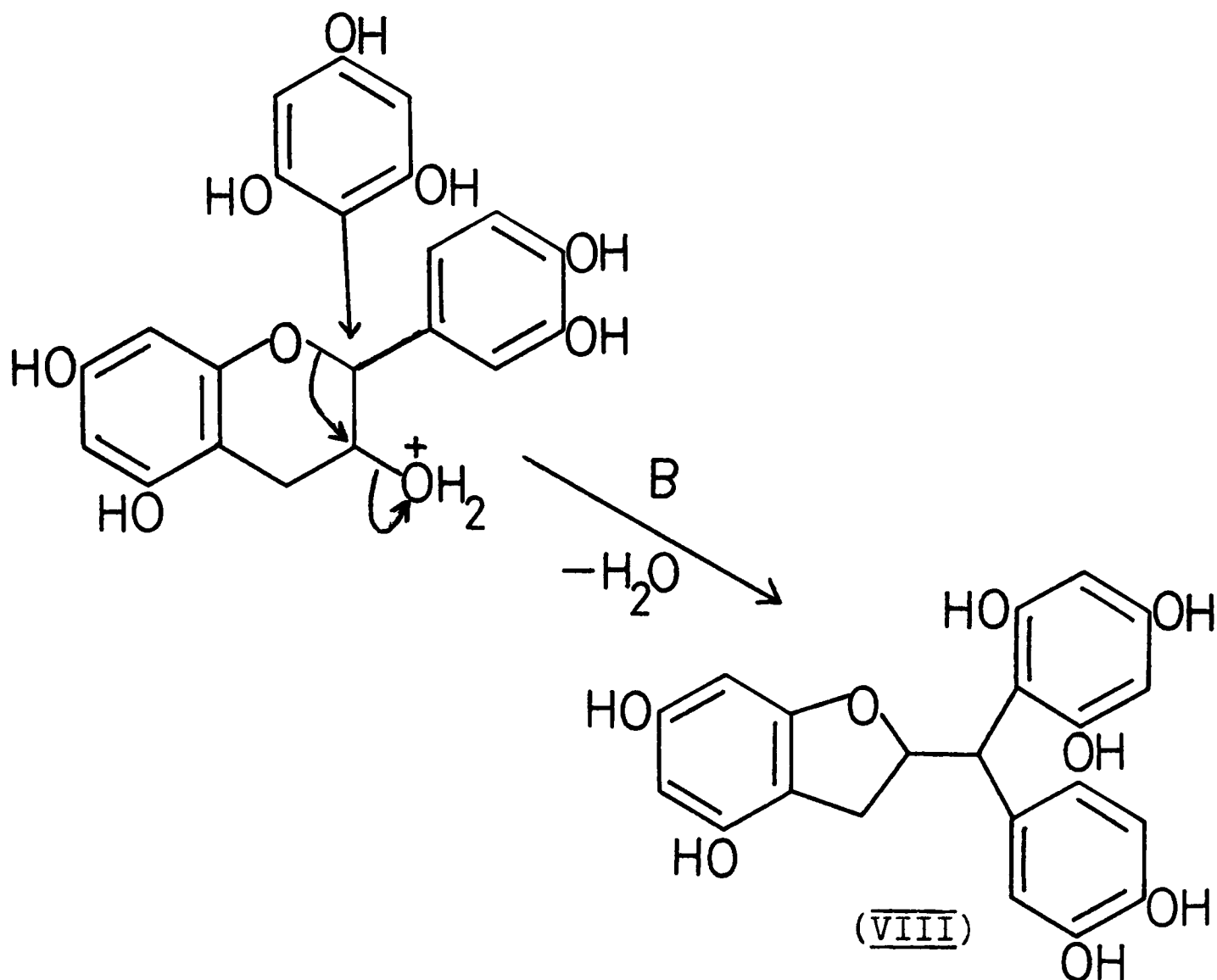


condensation was not found to occur.

The Role of the 3-Hydroxyl Group.

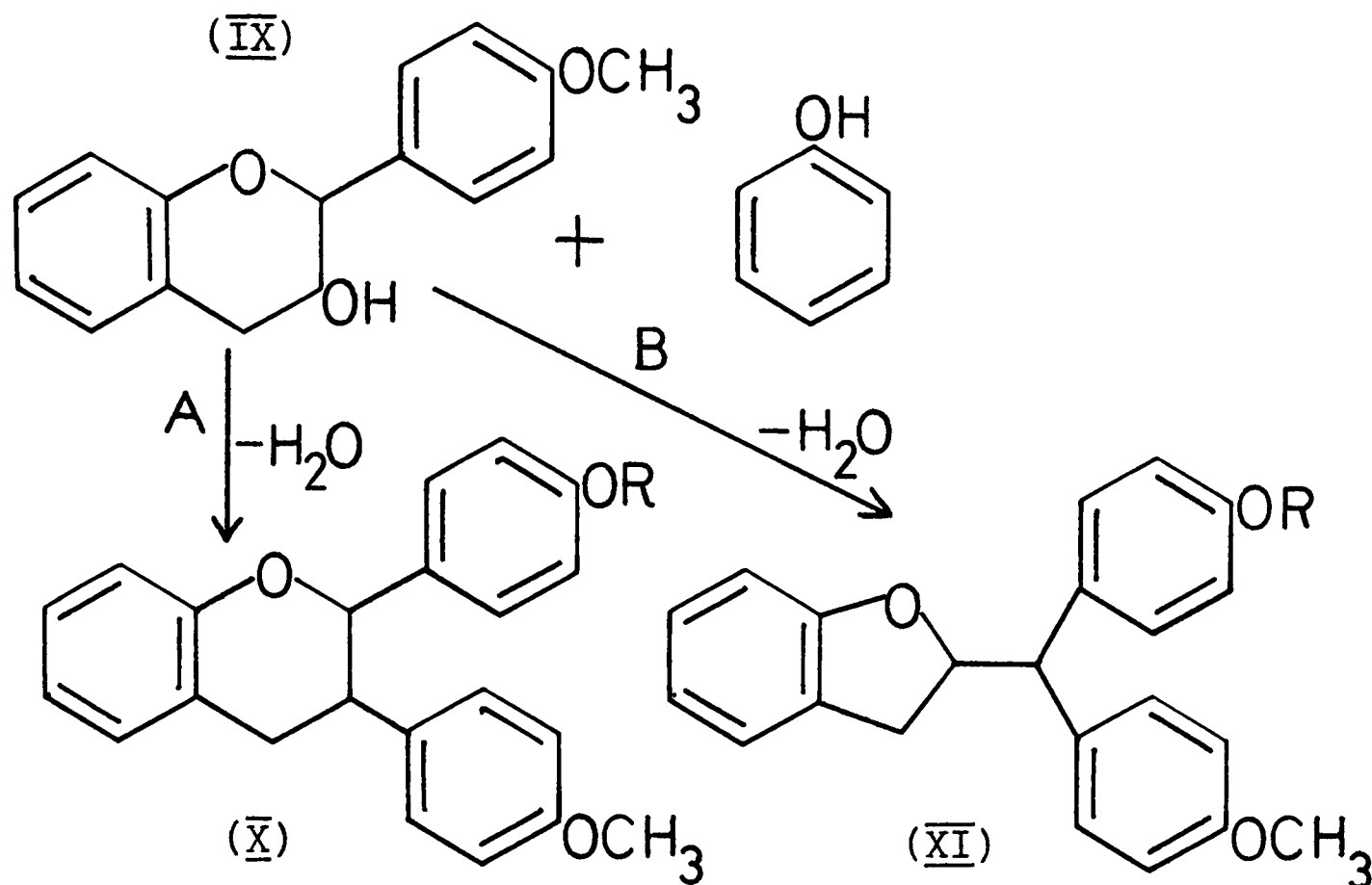
Little attention had been paid to the function of the 3-hydroxyl group in the condensation of catechins until¹⁴ phloroglucinol was condensed with catechin, when a product of formula $C_{21}H_{18}O_8$ was obtained, possessing 7 phenolic hydroxyl groups. This indicates the loss of the 3-hydroxyl group, and two mechanisms, A and B, were suggested for this condensation :





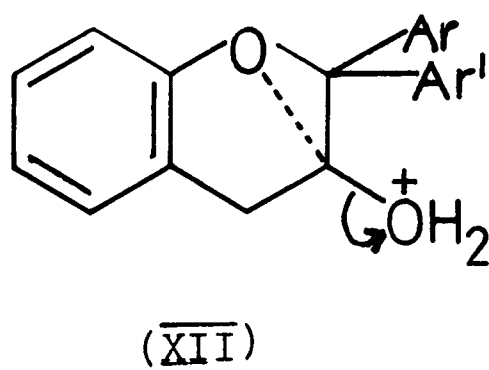
Mechanism A was favoured from steric and electronic considerations, but it proved impossible, at that time, to identify the condensate as either (VII) or (VIII).

In a condensation of this kind, simpler starting materials, such as 3-hydroxy-4'-methoxyflavan (IX) and phenol, should give rise to a product (X or XI; R=H), methylation of which would give a simpler product (X or XI : R=CH₃), which could be identified by synthesis, and the course of the condensation established. This condensation of simpler starting materials was thought to have been effected,¹⁵ and the product methylated, giving a product, m.p. 62-62.5°,

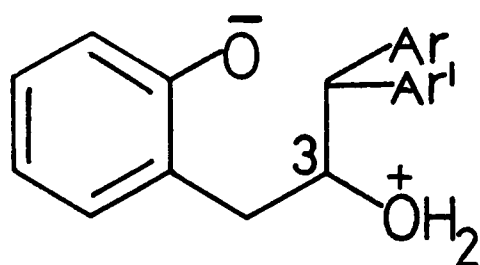


which was not identical with 3-anisyl-4'-methoxyflavan
 ($\bar{X}$: R = CH₃), m.p. 97-8°¹⁶. This suggested that mechanism
 B is operative in such a condensation.

It has been suggested¹⁴ that two factors might militate
 against the B mechanism. These are that (i) the ether
 oxygen atom, as a member of a ring system, is only slightly
 mobile sterically; and that (ii) formation of an oxonium-like
 transition state, ($\bar{XII}$), is unlikely since the available



oxygen orbitals are directed away from C_3 . Such considerations, however, apply only to a concerted reaction, and if the reaction were a two-stage reaction, as suggested in the formation of intermediates such as (III), then an intermediate, (XIII) would be formed, whose oxygen atom is no



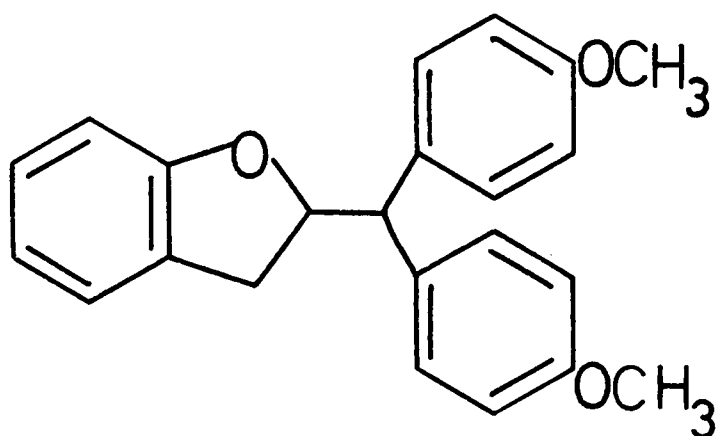
(XIII)

longer held sterically, and whose electron-filled orbitals will direct towards the electrophilic C_3 atom.

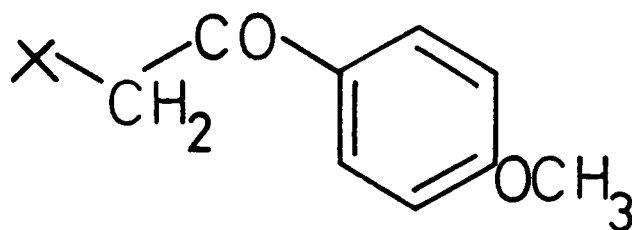
An unambiguous synthesis of 2-dianisylmethylcoumaran, (XI; $R=CH_3$), was therefore required to confirm that mechanism B is operative in such condensations.

DISCUSSION

The synthesis of 2-di-(p-methoxyphenyl)-methylcoumaran (I) was approached in the following way. Chloroacetylchloride

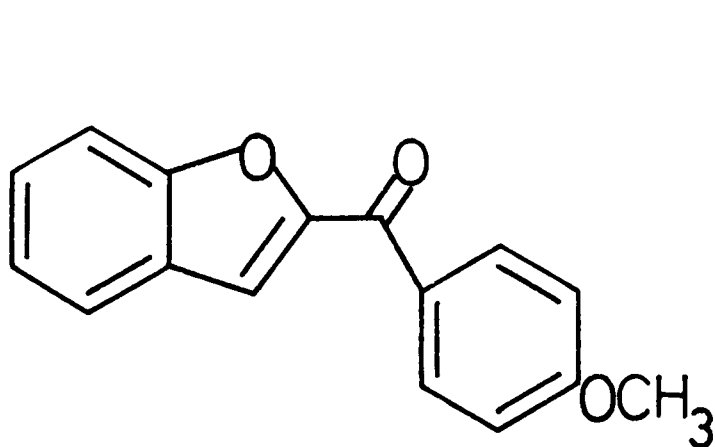


(I)

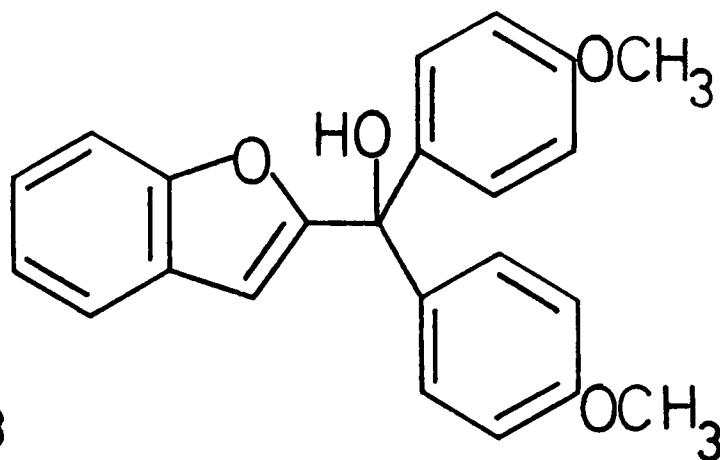


(II)

and bromoacetyl bromide were condensed with anisole in the presence of aluminium chloride,^{16,17} to yield ω -chloro- and ω -bromomethylanisyl ketone in 42 and 27% yield respectively, (II : X=Cl and X=Br). These compounds were condensed with salicylaldehyde in ethanol containing anhydrous potassium carbonate¹⁸ to yield 2-anisoylbenzofuran (III) in 44 and 80%



(III)

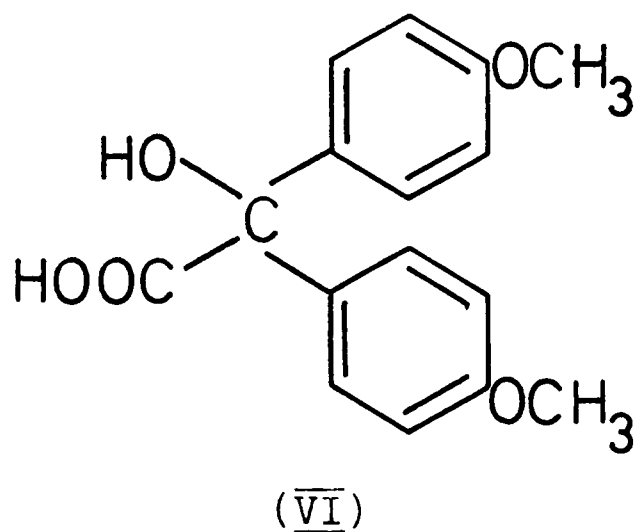
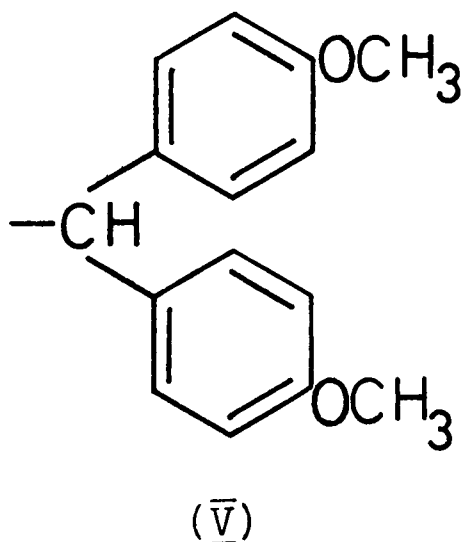


(IV)

yield respectively. The synthesis of 2-di-(p-methoxyphenyl)-hydroxymethylbenzofuran (IV) was attempted by reaction of the ketone (III) with anisylmagnesium bromide and with lithium anisyl under nitrogen, in ether. Starting material and anisole in good yield were recovered in both cases. A molecular model of the ketone (III) shows the carbonyl group to be not easily accessible for reaction with the Grignard reagent. However, it was surprising that the reaction did not occur with the aryl lithium compound as it does react¹⁹ with other hindered ketones.

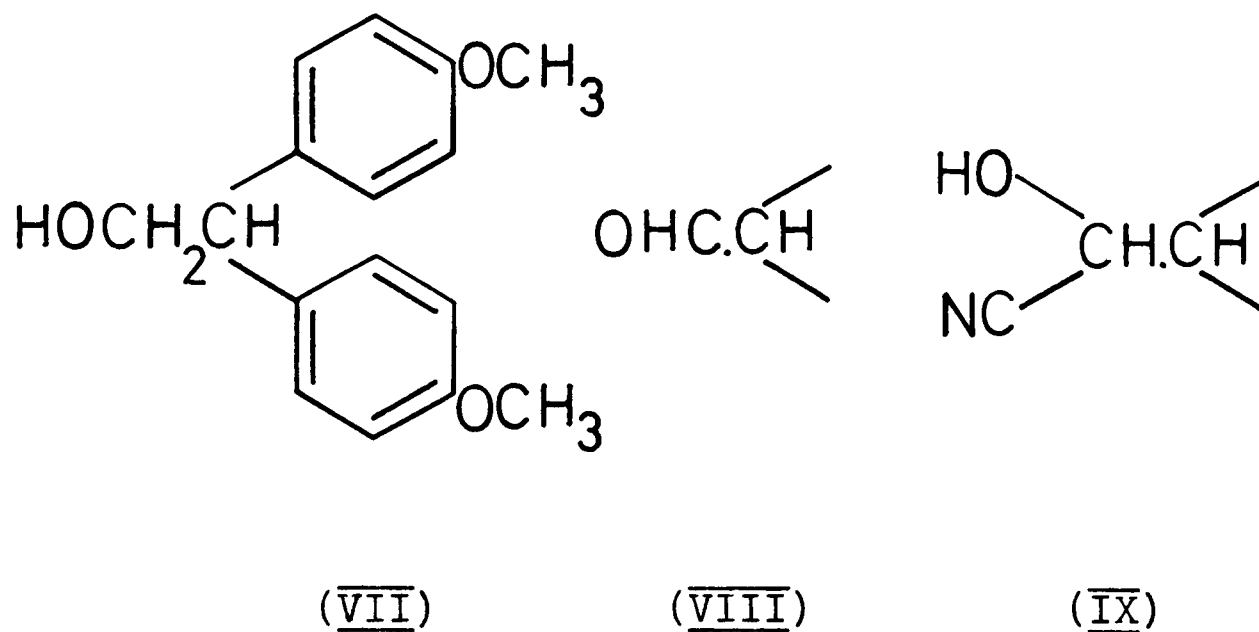
It had been hoped to hydrogenate the $\alpha\beta$ -unsaturated alcohol (IV), to dehydrate and to hydrogenate the product of dehydration yielding the coumaran (I). Since it appeared that the reaction of the ketone (III) with anisylmagnesium bromide was unfruitful, another synthetic route to the coumaran (I) was designed and investigated.

The second synthetic route involved the construction of the dianisylmethyl group (V) preparatory to formation of the

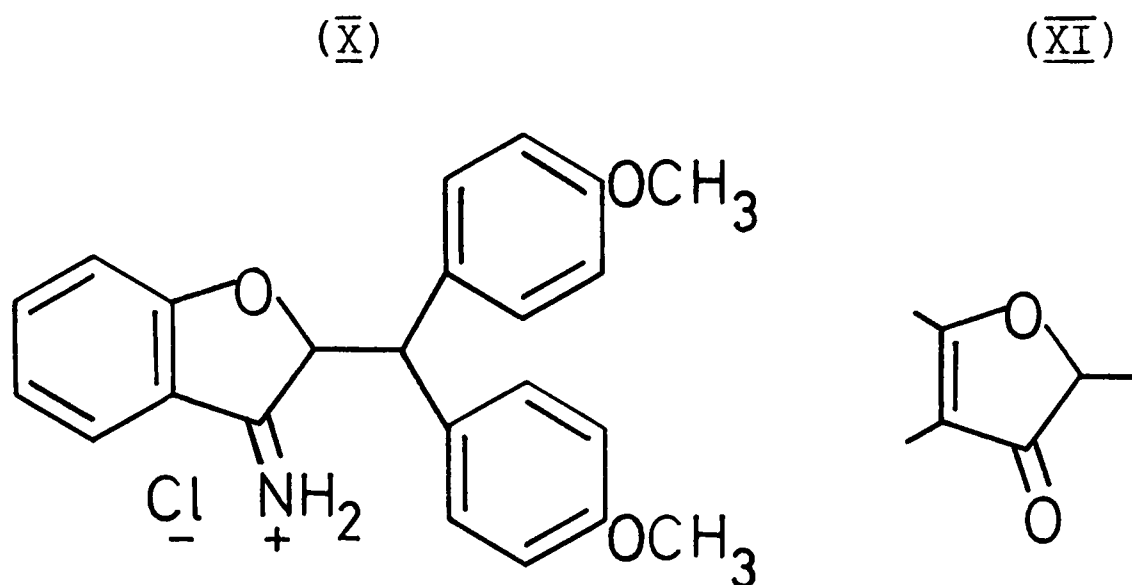


coumaran ring. Anisilic acid (VI) was prepared from anisaldehyde, via the formation of aniso²⁰in and anis²⁰l.

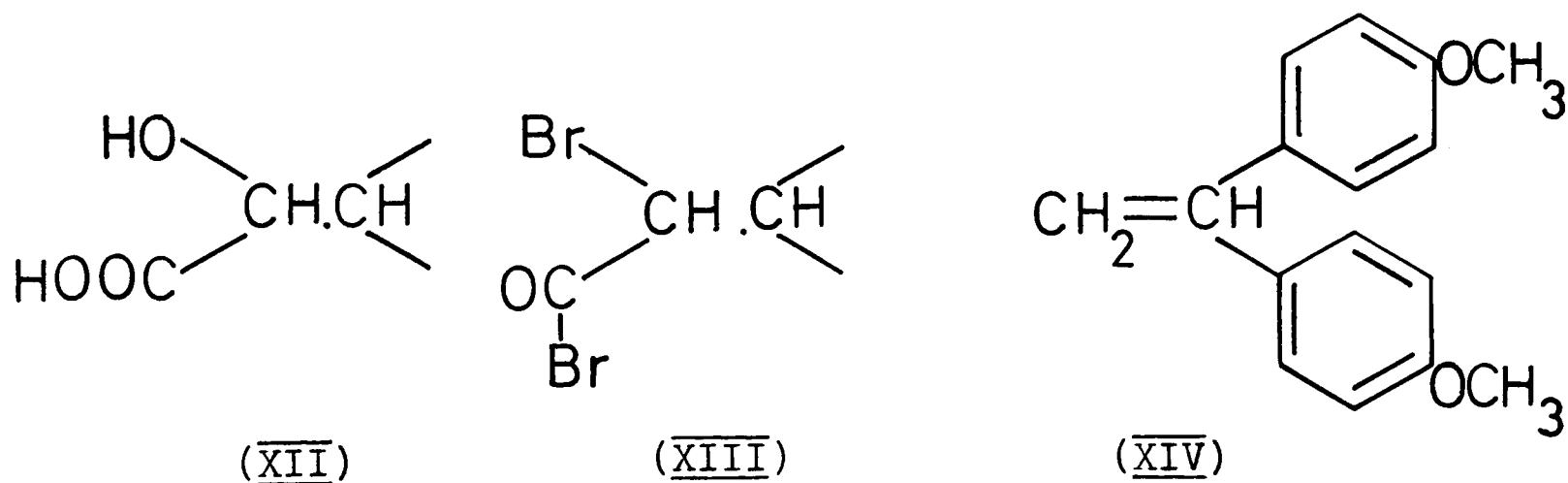
The methyl ester of anisilic acid was prepared by the silver salt method, and was reduced with lithium-aluminium hydride-aluminium chloride²¹ to 2:2-dianisyl ethanol (VII). It was



hoped that oxidation to the aldehyde (VIII) and the addition of hydrocyanic acid to this aldehyde would yield the cyanhydrin (IX). The cyanhydrin might then be condensed directly with phenol, in the presence of a condensing agent such as anhydrous zinc chloride,²² to yield the imine hydrochloride (X), which would be hydrolysed by boiling with water to yield the coumaran-3-one (XI). Alternatively, the cyan-



hydrin (IX) might be hydrolysed to yield the α -hydroxy acid (XII) Condensation of phenol with this by the action of

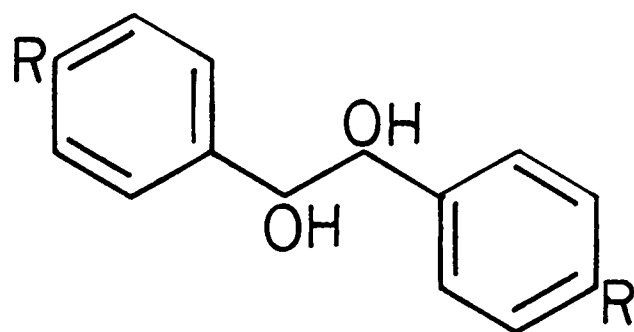
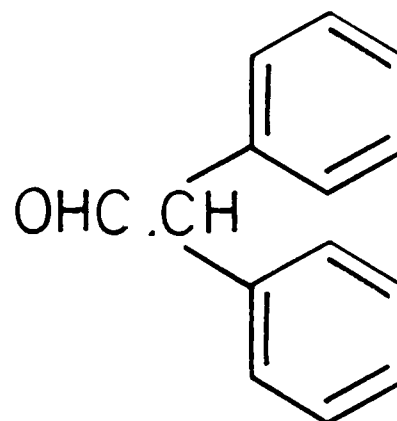


phosphorus pentoxide in benzene²³ or of its bromoacid bromide (XIII) by the action of aluminium chloride in benzene²⁴ might yield the coumaran-3-one (XI). Reduction of this with

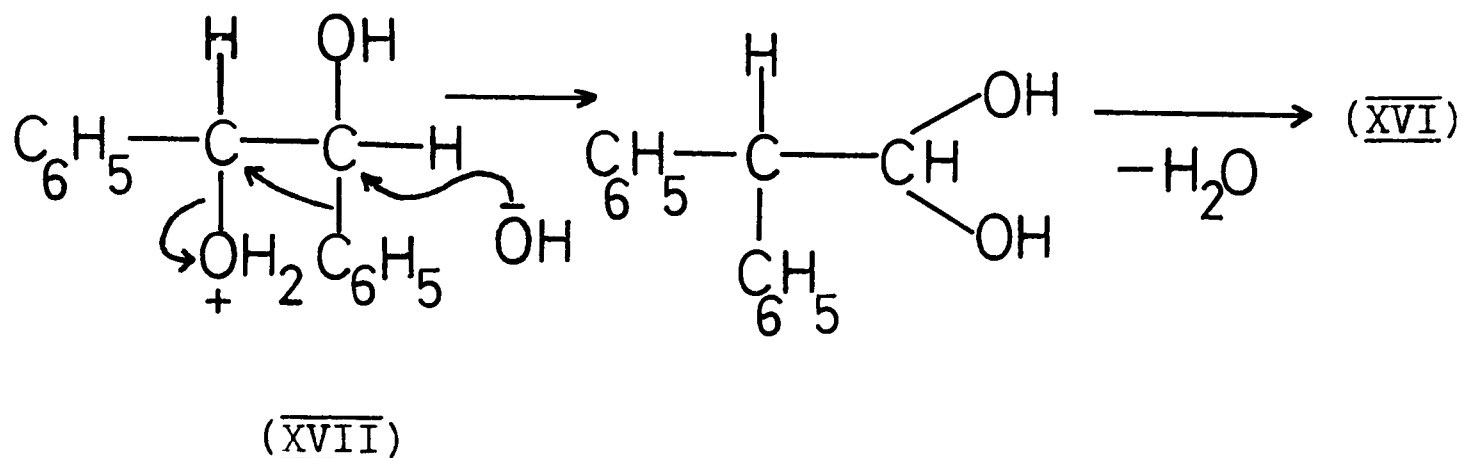
lithium aluminium hydride-aluminium chloride²¹ might yield the coumaran (I).

Attempts were made to oxidise the alcohol (VII) to the aldehyde (VIII) with chromic acid²⁵, activated manganese dioxide²⁶ and with tertiary butylchromate²⁷, all of which are reagents for the specific oxidation of aliphatic primary alcohols to aldehydes. In all cases dehydration occurred and the product was 1:1-dianisyl ethylene (XIV), which was identified by melting point, ultra-violet spectrum and by analysis.

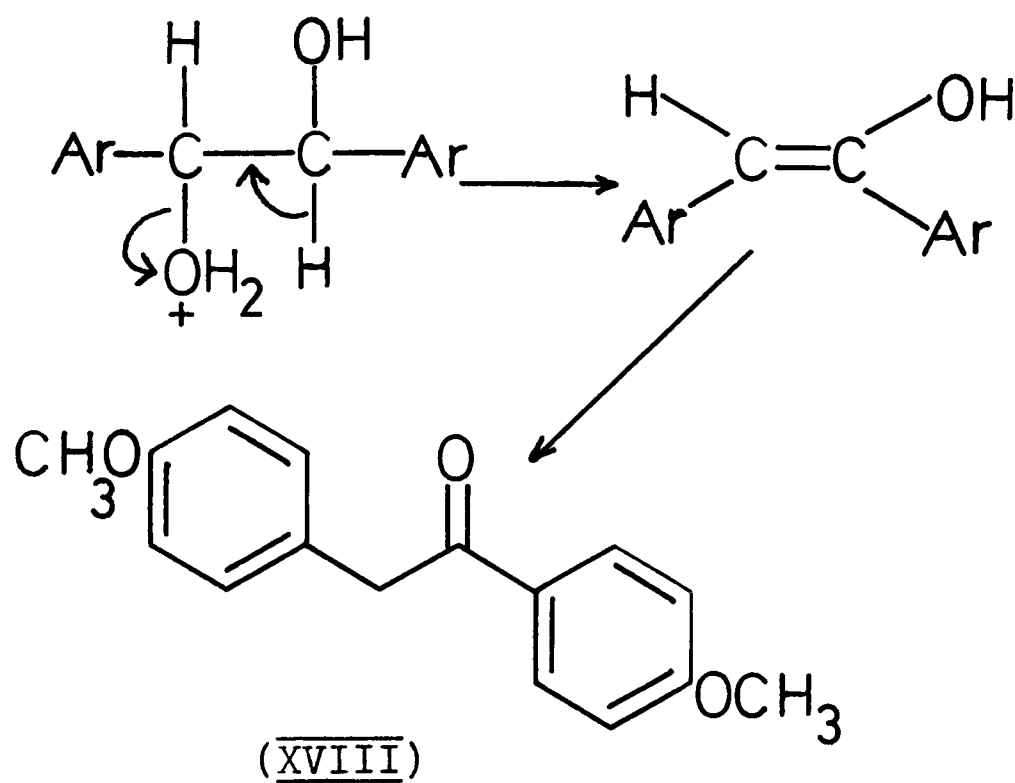
Another synthesis of the aldehyde (VIII) was attempted by treatment of hydroanisoïn (XV : R=OCH₃) prepared from anisoïn by reduction with sodium amalgam²⁸, with boiling 20%

(XV)(XVI)

sulphuric acid. When hydrobenzoïn (XV : R=H) is treated in this way, diphenylacetaldehyde (XVI) is produced²⁹, by Wagner-Meerwein rearrangement (XVII). However, when hydro-

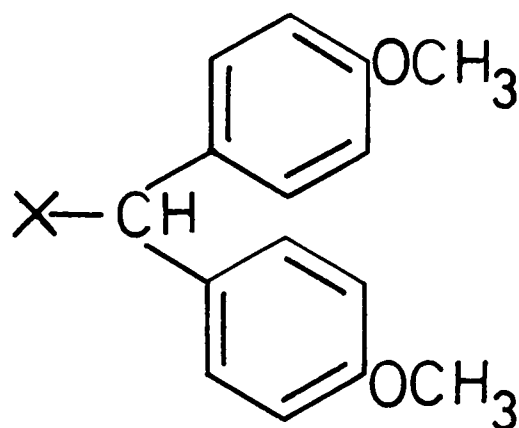
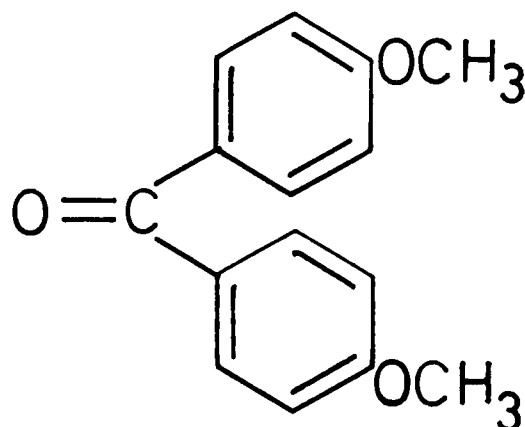


anisoïn was treated in this way, desoxyanisoïn (XVIII) was produced, by simple dehydration and rearrangement of the enol formed.



Desoxyanisoïn was identified by melting point, infra-red spectrum and by analysis.

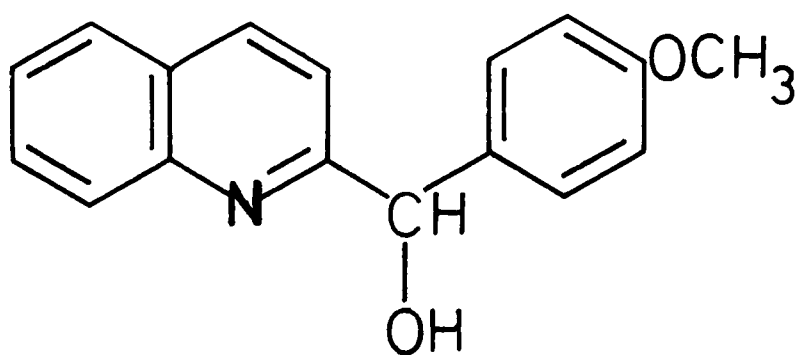
At this point, it was decided to investigate another route to the coumaran (I), again constructing the dianisyl methyl group (V) before formation of the coumaran ring. Reaction of anisaldehyde with anisylmagnesium bromide should yield 4:4'-dimethoxybenzhydrol (XIX : X=OH). Replacement of the hydroxyl group by bromine would yield dianisylbromomethane (XIX : X=Br); the Grignard reagent (XIX : X = MgBr)

(XIX)(XX)

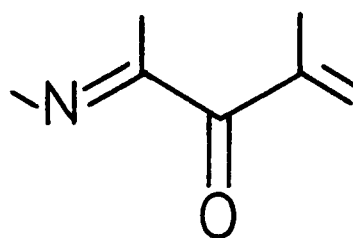
would be prepared by reaction with magnesium, and treatment of this with solid carbon dioxide would yield the carboxylic acid (XIX : X = COOH). Rosenmund reduction of this acid or reduction with lithium aluminium t-butoxide of its chloride would yield the aldehyde (VIII). The synthesis of the coumaran (I) from this aldehyde would be attempted as described above.

Anisaldehyde was treated with anisyl magnesium bromide

and the product was 4:4'-dimethoxybenzophenone (XX), identified by its melting point, 142-3°, infra-red spectrum and by analysis. 4:4'-Dimethoxybenzhydrol (XIX : X=OH) is known to be easily oxidised to the ketone³¹ (XX), and presumably during the decomposition and working-up of the product, oxidation had occurred. An example of the production of a more stable, oxidised, product is afforded in the decarboxylation of quinaldinic acid in anisaldehyde. The expected product, the alcohol (XXI), is easily oxidised in air and the corresponding ketone (XXII) is obtained. The



(XXI)

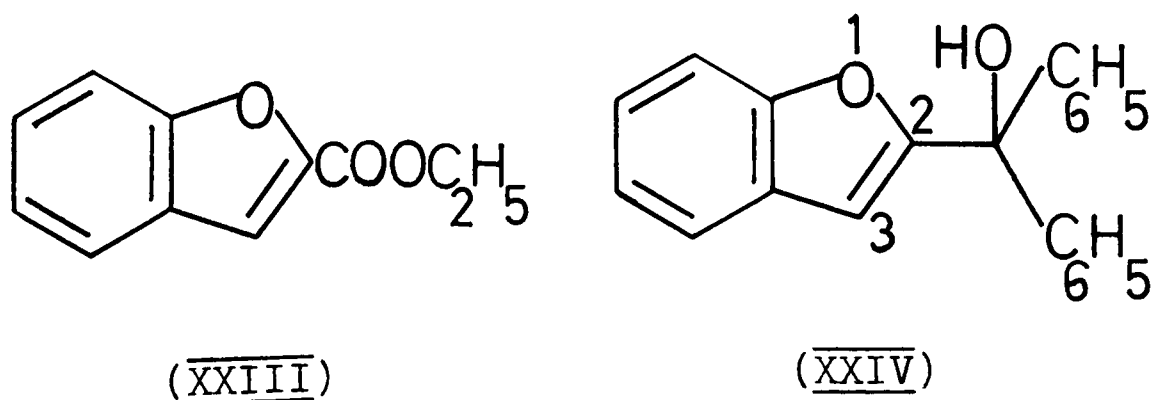


(XXII)

ketone (XX) was hydrogenated in ethyl acetate over Adams catalyst, yielding the benzhydrol (XIX : X=OH), identified by its melting point, 68-70°³¹, and its infra-red spectrum which showed hydroxyl absorption at 3350 cm⁻¹ and absence of

carbonyl absorption. The benzhydrol in dry benzene was then treated with dry hydrogen bromide³³ yielding the bromomethane (XIX : X = Br), identified by its melting point, 67-69°, and its infra-red spectrum which showed C - Br absorption at 650 cm⁻¹ and no hydroxyl absorption. The compound gradually softens and assumes a pink colour. A solution of the bromide in dry ether was boiled under reflux with magnesium for 5 hr., with no signs of reaction. On treatment of the mixture with solid carbon dioxide and acid, the product yielded no carboxylic acid fraction, and was shown by its melting point and mixed melting point, 139-40°, and by its infra-red spectrum to be the benzophenone (XX). Presumably the acid conditions of working-up have hydrolysed the unstable bromide (XIX : X = Br), to the benzhydrol (XIX : X = OH) which has been oxidised to the benzophenone (XX).

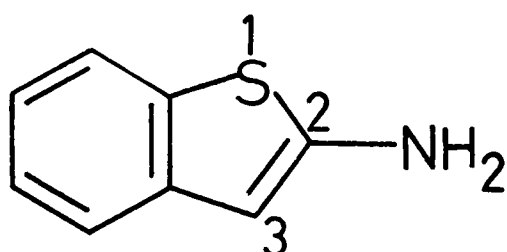
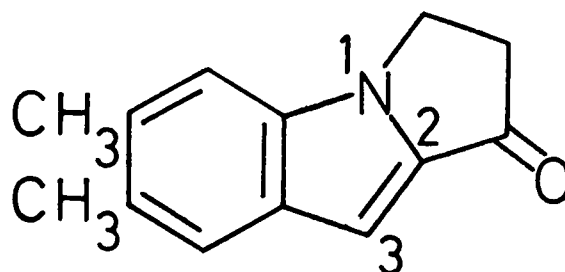
At this date, a report of the action of phenyl magnesium bromide on ethyl coumarilate (XXIII), to yield the carbinol



(XXIV), was published.³⁴ Despite the fact that attempts to synthesise the similar carbinol (IV) by the action of anisyl magnesium bromide on 2-anisoylbenzofuran (III) had failed, it was decided to investigate this reaction afresh, since no obvious reason for its failure could be seen.

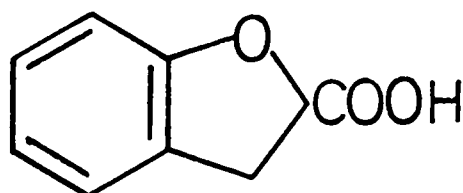
Ethyl coumarilate (XXIII) was prepared from ethyl bromoacetate by condensation with salicylaldehyde in ethanol containing anhydrous potassium carbonate in 59% yield. It was redistilled twice under reduced pressure, to yield a colourless liquid which solidified on cooling and just melted at 24°. The purity of this compound was found to be important in the reaction with anisyl magnesium bromide, which was prepared from carefully redistilled p-bromoanisole and magnesium. The reaction was conducted in boiling dry tetrahydrofuran for 4 hr., and yielded a red oil. Chromatography on alumina yielded 2-di-(p-methoxyphenyl)-hydroxymethylbenzofuran (IV) (35%) as a yellow glass, which could not be caused to crystallise. Its infra-red spectrum showed hydroxyl absorption at ca. 3400 cm⁻¹ and absence of ester carbonyl absorption. The nuclear magnetic resonance spectrum of this compound provided conclusive evidence for its structure. The aromatic protons gave rise to a complex signal at $\tau = 2.4 - 3.4$ ~~p.p.m.~~, which integrates for 12

protons: the proton at the 3-position (XXIV) is seen as a singlet at 3.6, which integrates for 1 proton. N.m.r. data on benzofurans is not available³⁵, but the position of the proton at C₃ is much as expected. The proton at C₃ in 2-aminobenzothiophene (XXV) occurs at $\tau = 3.81$ ³⁶ and that in the compound C₁₃H₁₃NO₂ (XXVI) at $\tau = 3.02$ or 3.15³⁷. However,

(XXV)(XXVI)

the comparison with these compounds only serves as a rough guide, for the systems under consideration are somewhat different because of the different heterocyclic atoms at position 1. In ethyl coumarilate, this proton occurs below

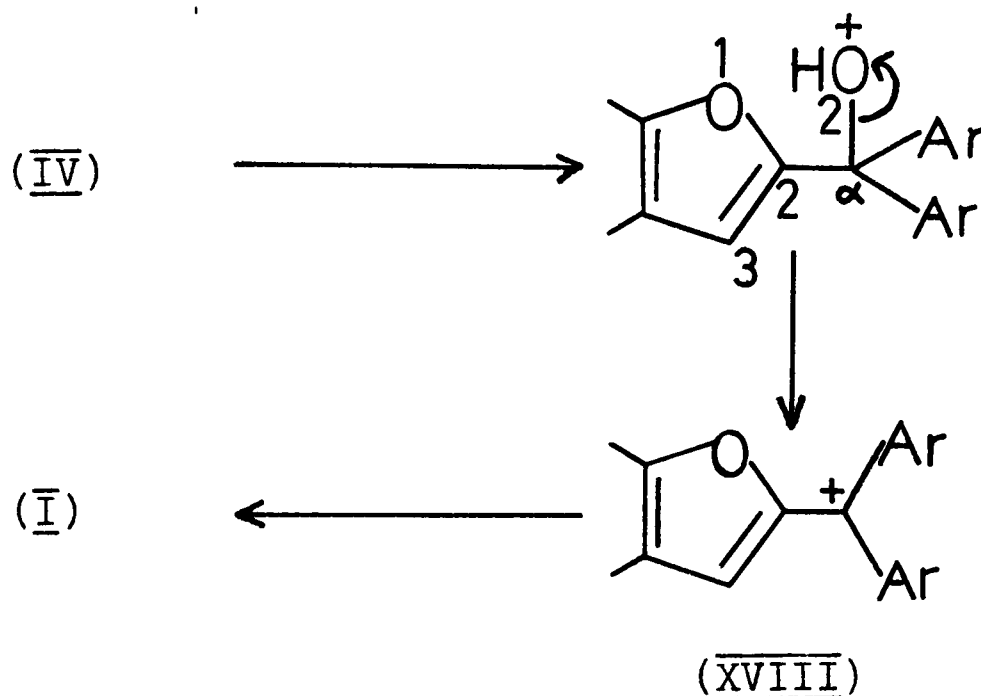
$\tau = 3.0$, together with the other aromatic protons, although the 2:3-double bond is chemically not entirely aromatic, e.g., coumarilic acid may be reduced to coumaranilic acid (XXVII)

(XXVII)

by sodium amalgam^{38,39}; ethyl coumarilate may be easily³⁹ hydrogenated over Adams catalyst to yield ethyl coumaranilate. Yet the aromatic character of the 2:3-double bond in ethyl coumarilate is sufficient that the proton at C₃ shows aromatic character in its n.m.r. spectrum. Whether it is the effect of the carbonyl group at C₂ encouraging its aromatic character, and removal of this on formation of the carbinol (IV) revealing its vinylic character, or whether it experiences a particular shielding effect of the aryl rings in the carbinol (IV), brought about by a particular conformation, is not clear. Studies on similar benzofurans would be necessary to establish the cause of this slight change of aromaticity of the C₃ proton.

The methoxyl groups in the carbinol (IV) give rise to a singlet at $\tau = 6.2$, which integrates for 6 protons. The hydroxyl group is seen as a broad hump, centred at $\tau = 6.3$, which is removed by D₂O exchange.

The carbinol was dissolved in acetic acid, and Adams catalyst added to the purple solution. The colour of the solution probably indicates the generation in acid solution of a carbonium ion, (XXVIII), of the triphenylmethyl type, which could be hydrogenolysed with hydrogenation of the 2:3-double bond. Two moles of hydrogen were taken up at

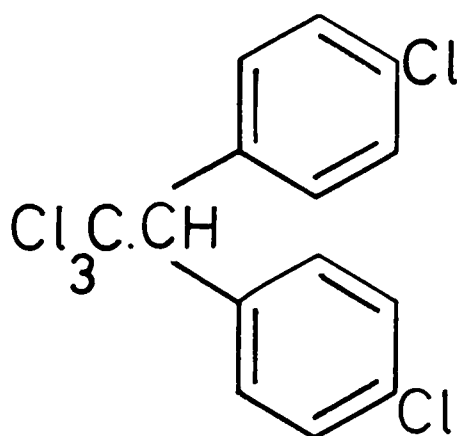


room temperature in $2\frac{1}{2}$ hr., when the solution assumed a pale yellow colour. The product, a cream-coloured solid, m.p. $68-70^{\circ}$, was established as the coumaran (I) by analysis, infra-red and n.m.r. spectroscopy. The infra-red spectrum showed no hydroxyl absorption, aryl-alkyl ether absorption at 1246 and *p*-substituted phenyl absorption at 1038 cm^{-1} . The n.m.r. spectrum showed an aromatic complex at $\tau = 2.2 - 3.7$, which integrated for 12 protons and a thick singlet at $\tau = 4.49$, the signal of the proton attached to the α -carbon atom. This indicates that spin-spin interaction between the protons at C_2 and C_{α} is very small and that the dihedral angle between them is approximately 90° . A molecular model of this coumaran, incorporating this structural detail, shows it to be a necessary part of a "staggered" conformation with the large aryl groups well separated.

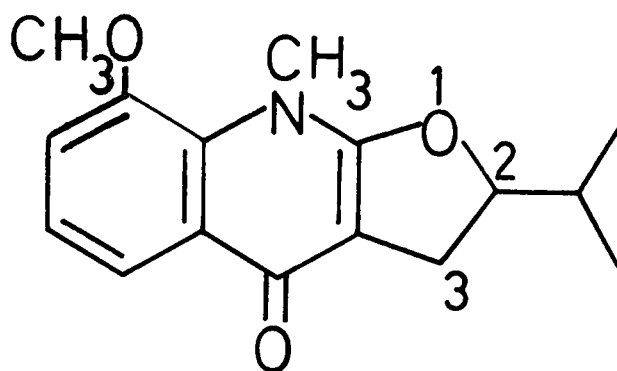
The proton at C_2 is seen as a diffuse quartet at $\tau = 5.47 - 5.60$, which integrates for 1 proton. A quartet arises

from spin-spin interactions with the protons at C_3 , and the very small coupling with the proton at C_a makes the quartet diffuse. The proton at C_3 is seen as a complex at $\tau = 6.0 - 6.6$, which integrates for 2 protons: out of this complex rises a sharp singlet at $\tau = 6.22$ which integrates for 6 protons, this being the signal of two identical methoxyl groups.

The positions of these signals is in accord with those expected: the immediate environment of the benzyl proton at C_a is similar to that in 1:1:1-trichloro-2:2-bis-p-chloro-phenylethane (XXIX) which occurs at $\tau = 4.98$ ⁴⁰; the proton at C_2 has a similar environment to that of the proton at



(XXIX)



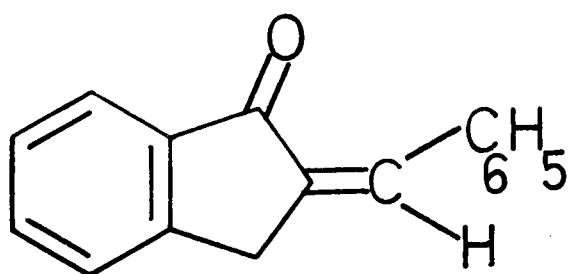
(XXX)

C_2 in lunacrine (XXX)⁴¹, which occurs at $\tau = 5.28$, while the protons at C_3 in the coumaran (I) are similar to those in lunacrine (XXX), which appear at ca. 6.8.

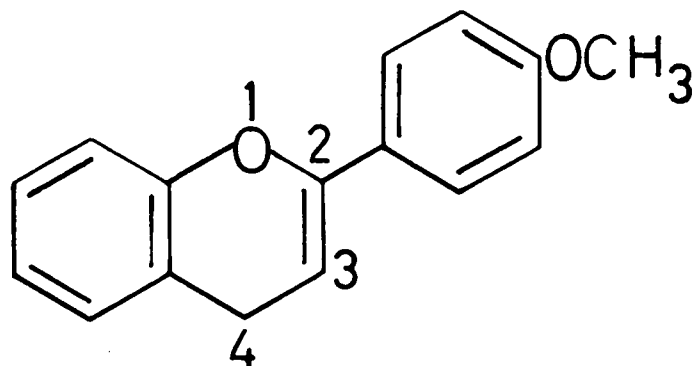
A mixture of this coumaran (I), m.p. $68-70^\circ$, and the

"methylated condensation product", m.p. $62-62.5^{\circ}$, of 3-hydroxy-4'-methoxyflavan and phenol¹⁵ melted at $45-55^{\circ}$, indicating that the compounds were not identical.

The structure of the "methylated condensate"¹⁵ was therefore examined and established by n.m.r. spectroscopy, analysis, and mass spectrometry and hydrogenation. The n.m.r. spectrum showed 8 aromatic protons as a complex at $\tau = 2.3$ to 3.2 and a vinylic proton as a singlet at $\tau = 3.6$. A singlet, which integrates for 2 protons, is seen at $\tau = 5.9$, which is at the position expected for a benzylic methylene group adjacent to a vinyl group, cf. $\tau = 5.96$ in the ketone⁴² (XXXI). The methoxyl group present is seen as a singlet at $\tau = 6.17$, which integrates for 3 protons.



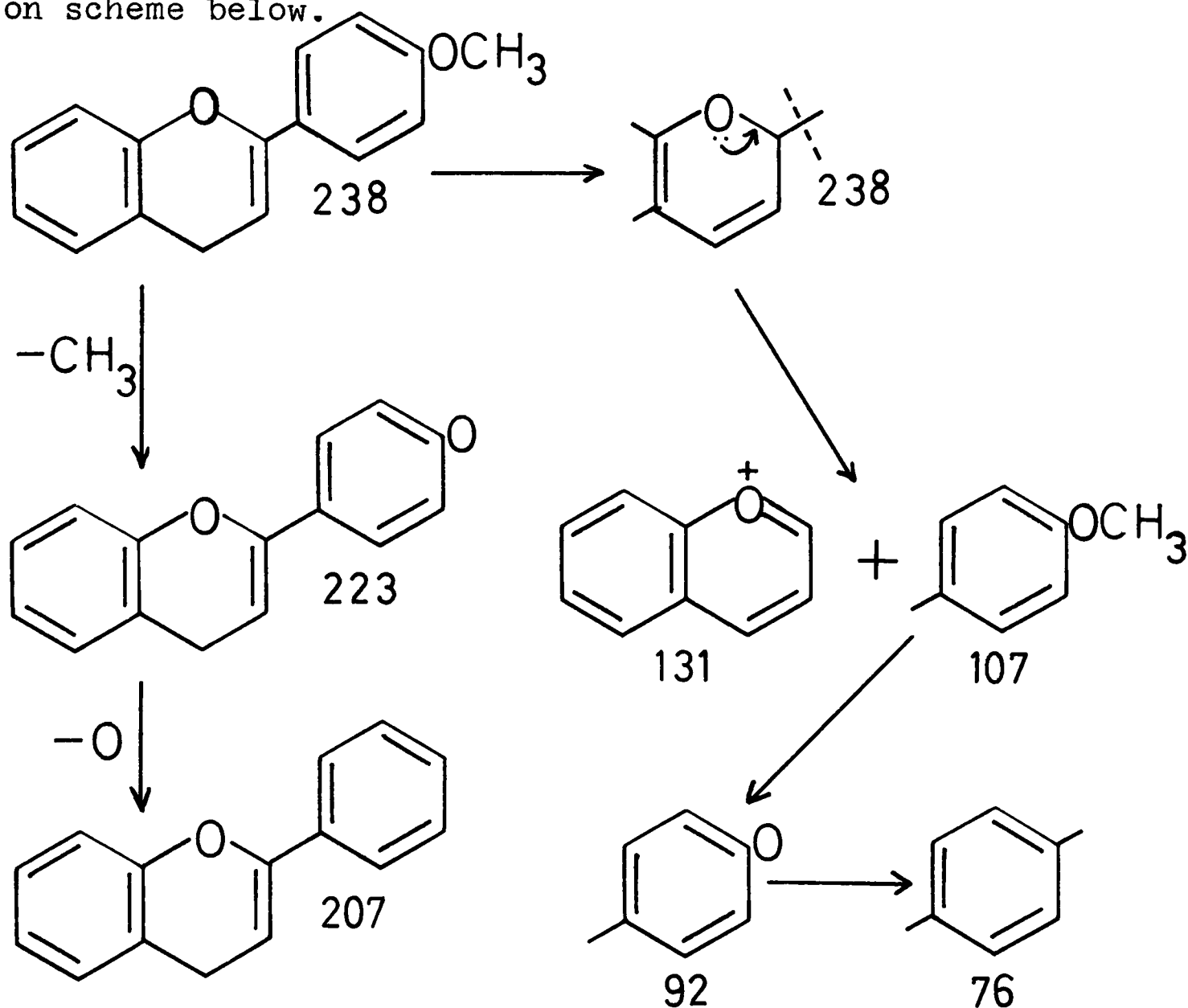
(XXXI)



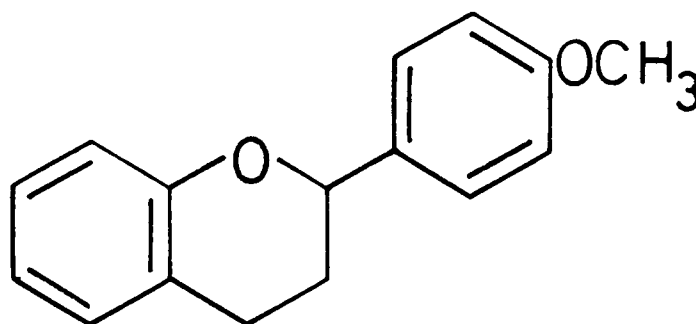
(XXXII)

The elemental analysis of the "methylated condensate" was¹⁵ in poor agreement with the formula $C_{23}H_{22}O_3$, the coumaran (I), and the molecular formula of the flav-2-ene (XXXII),

$C_{16}H_{14}O_2$ is in much better agreement and is established by the n.m.r. spectrum. The fact that no proton at C_2 ($\tau = 4.5 - 5.3$) is seen, clearly indicates the possibility of a 2-ene. In addition, the mass spectrum of the methylated condensate shows the molecular weight to be 238, i.e., that of $C_{16}H_{14}O_2$, as well as fragments of $M/e = 223, 207, 131, 107, 92$ and 76 . These correspond⁴³ to the fragmentation scheme below.



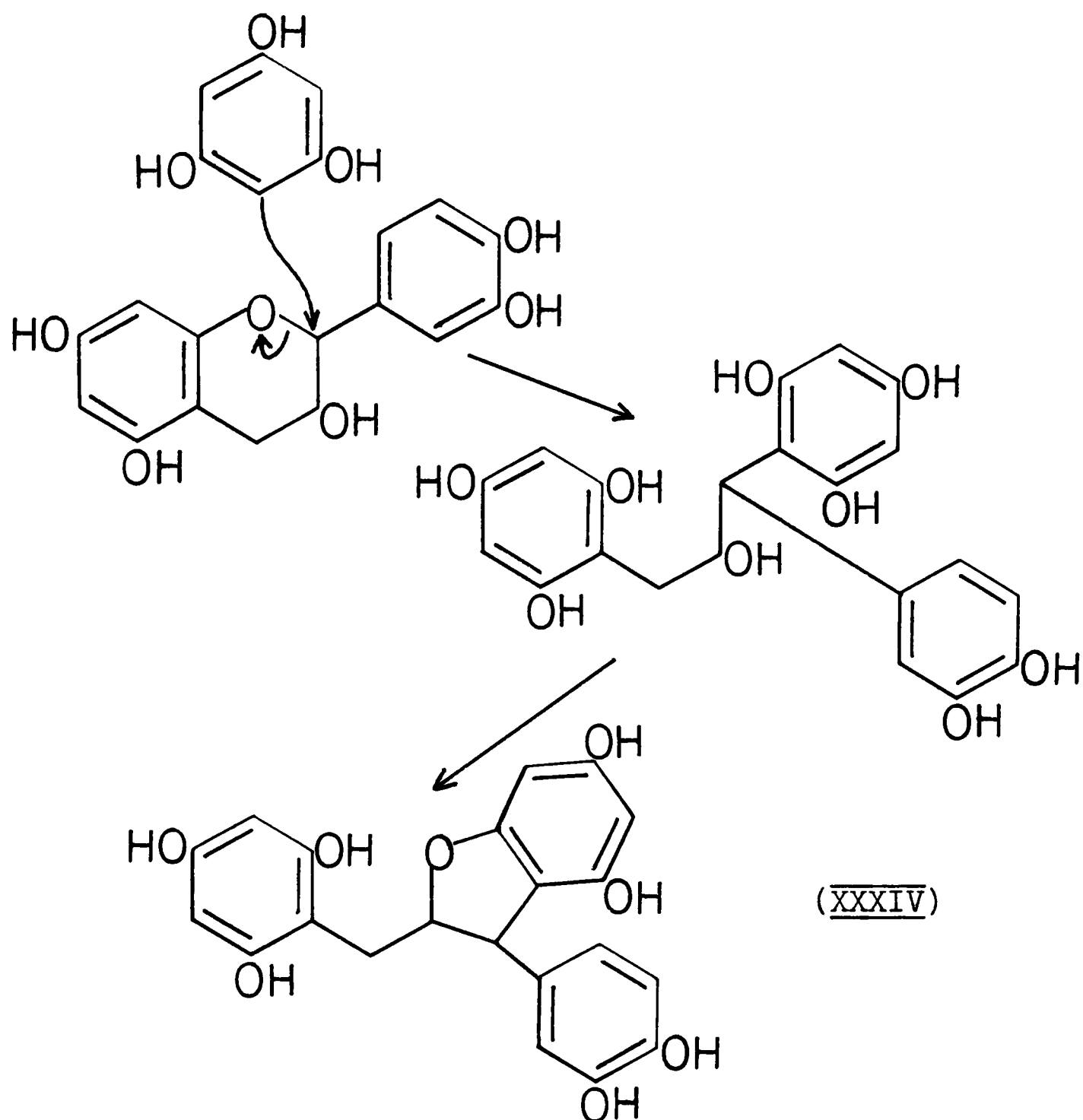
The "methylated condensate"¹⁵ was hydrogenated at room temperature over Adams catalyst and yielded 4'-methoxyflavan (XXXIII), thus establishing the structure of the "methylated condensate" as the flav-2-ene (XXXII). It is



(XXXIII)

clear that condensation of 3-hydroxy-4'-methoxyflavan with phenol has not occurred, but that the flavan has simply dehydrated.

During the course of this work, reports of the elucidation of the complicated structure of the product of condensation of (+)-catechin and phloroglucinol, by chemical and mass-spectrometric evidence,⁴⁴ were published. This evidence established the structure of the condensate as the coumaran (XXXIV), formed by attack of the incoming phenol on C₂ which opens the heterocyclic ring, followed by condensation of the 3-hydroxyl group, not with the A ring hydroxyl, but with the o-hydroxyl present in phloroglucinol.



Further work on the condensations of catechins with phenols may show this mechanism to be important in the natural production of some tannins.

EXPERIMENTAL SECTION.

¹⁶

ω-Chloromethylanisylketone : (8.5g. 41.9%), m.p. 101-2°, was prepared from anisole by the action of chloroacetyl chloride and aluminium chloride; lit. ¹⁶ m.p. 102°.

¹⁷

ω-Bromomethylanisylketone : (26.5g. 26.5%), m.p. 73°, was prepared from anisole by the action of bromoacetyl-bromide and aluminium chloride; lit. ¹⁷ m.p. 73°.

¹⁸

2-Anisoylbenzofuran : (a) (17.6g. 79.5%), m.p. 97-8°, was prepared by the condensation of ω-bromoethylanisylketone with salicylaldehyde; lit. ¹⁸ m.p. 97.5 - 98.5°.

(b) 2-Anisoylbenzofuran (3.1g. 44.2%), m.p. 97-8°, was also prepared by the condensation of ω-chloromethylanisylketone with salicylaldehyde in ethanol containing anhydrous potassium carbonate, as above in (a).

Attempted Synthesis of 2-Di-(p-methoxyphenyl)-hydroxymethylbenzofuran. - (a) 2-Anisoylbenzofuran (5.7 g) in dry ether (150 ml.) was slowly added to anisyl magnesium bromide, prepared from p-bromoanisole (6.4g.) and magnesium turnings (2.4g.) in dry ether (90 ml.) and the mixture boiled under reflux for 30 min. The reaction mixture was worked up in dilute sulphuric acid, and afforded 2-anisoylbenzofuran

(5.2g. 91.2%) and anisole (3.4g. 92.2%).

(b) 2-Anisoylbenzofuran (5.2g.) in dry ether (120 ml.) was slowly added to lithium anisyl, prepared from p-bromoanisole (6.4g.) and freshly cut slices of lithium (0.7g.), and the reaction mixture boiled under reflux for 30 min., the whole being kept in an atmosphere of nitrogen. The mixture was worked up in dilute sulphuric acid, and afforded 2-anisoylbenzofuran (4.8g. 92.3%) and anisole (3.18g. 86.0%).

Experiments (a) and (b) were repeated with times of boiling of 60, 90 and 180 min., and the products were separated on alumina (10% deactivated), being eluted by light petroleum-benzene. Starting material, in yields of 85-89%, and anisole in 80-93% yield, were recovered.

Aniso²⁰lⁿ : (72.8g. 72.8%), m.p. 113-4^o, was prepared from anisaldehyde (100 g.), in boiling aqueous ethanol, by the action of potassium cyanide; lit. ²⁰ m.p. 113^o.

Anisil²⁰ : (53.6g. 75.1%), m.p. 132-3^o, was prepared by oxidation of anisoⁿl (72g.) with Fehling's solution; lit. ²⁰ m.p. 133^o.

Anisilic Acid²⁰ : (48 g. 60%), m.p. 160-2^o, was prepared from anisil (75g.) by fusion with potassium hydroxide; lit. ²⁰ m.p. 164^o.

Silver Anisilate. - Anisilic acid (12.6g.) was dissolved in warm aqueous ammonium hydroxide (5N, 120 ml.) and the solution made very slightly acid with dilute hydrochloric acid. To this cooled solution was added aqueous silver nitrate solution (80%, 10 ml.). The voluminous white precipitate was collected, washed with much water and dried to constant weight (14.92g., 86.4%) in a steam oven, the whole being kept in the dark.

Methyl Anisilate. - The silver salt (14.9g.) and redistilled methyl iodide (7.9g.) in dry benzene (35 ml.) were boiled under reflux for 16 hr. The mixture was cooled and the olive-green precipitate separated and washed with much hot dry benzene. Evaporation of the filtrate and washings yielded a colourless solid, which was recrystallised from light petroleum-benzene. Methyl anisilate (7.85g. 69%) separated as colourless prisms, m.p. 109-111⁰; lit.⁴⁵ m.p. 110-110.5⁰.

2:2-Dianisylethanol. - Methyl anisilate (7.8g.) was suspended in dry ether (100 ml.). Anhydrous aluminium chloride (10.5g.) and lithium aluminium hydride (1.1g.) in dry ether (150 ml.) were added, and the mixture boiled under reflux for 8 hr. The mixture was cooled to 0⁰ and

decomposed carefully with wet ether and hydrochloric acid (2N, 150 ml.). The two layers were separated and the aqueous layer was extracted with ether (2 x 70 ml.). The ethereal layer and extract were washed with dilute hydrochloric acid (30 ml.) and water (30 ml.), and dried. Removal of the solvent by distillation yielded a yellow oil, which solidified. This was recrystallised from light petroleum-benzene, from which 2:2-dianisylethanol (3.26 g. 49%) separated as colourless needles, m.p. $84-5^{\circ}$, (Found : C 74.35, H 7.7, $C_{16}H_{18}O_3$ requires : C 74.4, H 7.7%), $\nu_{\max}$ (carbon disulphide) : 3560 cm^{-1} , no carbonyl absorption.

Attempted Oxidation of 2:2-Dianisylethanol. - (a) 2:2-Dianisylethanol (0.97g.) was dissolved in light petroleum-benzene (2:3 v/v, 125 ml.) and a solution of t-butylchromate in dry light petroleum (75 ml.), formed by the action of chromium trioxide on t-butanol²⁷, added. The mixture assumed a dark red-brown cloudiness and was kept at room temperature for 14 days. The reaction mixture was poured into cold water (600 ml.) containing acetic acid (glacial, 50 ml.) and dilute sulphuric acid (50 ml.), at 0° . Excess of solid oxalic acid was added slowly with stirring, and carbon dioxide was slowly evolved. After 2 days, evolution of carbon dioxide had ceased and excess of oxalic acid was present.

The pale straw-coloured petroleum layer was separated, washed with sodium carbonate solution, dilute hydrochloric acid, and water, and dried. Filtration and removal of solvent by distillation yielded a colourless solid (588.9 mg, 65.3%). On recrystallisation of the solid from benzene, 1:1-dianisylethylene separated as colourless leaflets, m.p. 139-140°, (Found : C 80.0, H 6.65. Calc. for $C_{16}H_{16}O_2$: C 79.95, H 6.65%), $\nu_{\max}$ (nujol): 1630 cm^{-1} (conj. C = C), absence of OH or C = O absorptions, $\lambda_{\max}$ (ethanol): 292 (log ϵ 4.2), 270 (inf.), 223 (log ϵ 3.13) and 206 μ (log ϵ 2.76), $\lambda_{\min}$: 243 and 212 μ ; lit.⁴⁶ m.p. 140°.

The sodium carbonate extract was acidified and extracted with ether (3 x 70 ml.). This ethereal solution was washed with water and dried. Removal of solvent by distillation afforded no residue.

(b) 2:2-Dianisylethanol (93.02 mg.) was dissolved in dry benzene (2 ml.) and the solution was run through a dry column of activated manganese dioxide⁴⁷ (2g.). The column was washed with dry benzene (50 ml.), and the total eluate evaporated, leaving a colourless solid, (72.4 mg. 78%). On recrystallisation from benzene, 1:1-dianisylethylene separated as colourless needles, m.p. and mixed m.p. with the product of (a) above, 139-140°. The infra-red and ultra-

violet spectra, and analysis of the product, were identical to those of the product from (a).

(c) 2:2-Dianisylethanol (1 g.) was dissolved in ether (30 ml.) and the solution was shaken vigorously with a solution of potassium dichromate (387.6 mg.) and concentrated sulphuric acid (0.3 ml.) in water²⁵ (2 ml.) for 12 hr. The ethereal layer was separated, and the aqueous layer extracted with ether (3 x 5 ml.). The ethereal solutions were combined, washed with water and dried. Removal of solvent by distillation yielded a colourless solid, (0.724g. 77.7%). On recrystallisation from benzene, 1:1-dianisylethylene separated as colourless leaflets, m.p. and mixed m.p. with the products of (a) and (b) above, 139-140°.

Hydroaniso²⁸n : (127g. 97%), m.p. 169-172°, was prepared from aniso²⁸n (129.5g.) by reduction with sodium amalgam in wet ether; lit.²⁸ m.p. 167-169°.

Action of Sulphuric Acid on Hydroaniso²⁸n. - Hydroaniso²⁸n (4.0g.) was heated with boiling sulphuric acid (20%, 80 ml.) for 30 min. The reaction mixture was then steam distilled : only water was collected. The mixture was then cooled and extracted with ether (3 x 60 ml.). The ethereal solution was washed with water and dried. Removal of the solvent by

distillation yielded a colourless solid (3.4g.). On re-crystallisation from ethanol, desoxyanisoin (3.01g. 80.5%) separated as colourless leaflets, m.p. $107-9^{\circ}$, (Found : C 74.9, H 6.25. Calc. for $C_{16}H_{16}O_3$: C 74.95, H 6.25%), $\nu_{\max}$ (nujol): 1680 cm^{-1} (aryl ketone C=O Str.), no hydroxyl absorption; lit. ⁴⁸ m.p. $108-9^{\circ}$.

4:4'-Dimethoxybenzophenone. - A solution of redistilled anisaldehyde (13.54 g.) in dry ether (50 ml.) was slowly added to a solution of anisyl magnesium bromide prepared from p-bromoanisole (18.75g.) and magnesium turnings (2.46g.) in dry ether (160 ml.), and the mixture boiled under reflux for 5 hr. The reaction mixture was worked up in the usual way, using sulphuric acid, and removal of ether by distillation yielded a yellow oil (22.7g.), which solidified. On re-crystallisation from methanol, 4:4'-dimethoxybenzophenone (19.49g. 80.4%) separated as colourless plates, m.p. $142-3^{\circ}$, (Found : C 74.5, H 5.75. Calc. for $C_{15}H_{14}O_3$: C 74.4, H 5.75%), $\nu_{\max}$ (nujol): 1654 (diaryl ketone C = O Str.), no hydroxyl or aldehyde absorption; lit. ⁴⁹ m.p. $143-4^{\circ}$.

4:4'-Dimethoxybenzhydrol. - 4:4'-Dimethoxybenzophenone (5.0g.) was dissolved in ethyl acetate (240 ml.). Adams catalyst (271.2 mg.) was added and the mixture hydrogenated

at room temperature and at slight positive pressure. The theoretical quantity of hydrogen (463 ml.) was taken up in 65 min, after which the mixture was quickly filtered and the solvent removed by distillation under reduced pressure, leaving 4:4'-dimethoxybenzhydrol as a colourless crystalline solid (4.67g. 94.1%) m.p. 68-70^o, $\nu_{\max}$ (nujol): 3350 cm⁻¹ (OH Str.), absence of carbonyl absorption; lit.³¹ m.p. 72^o.

Dianisylbromomethane. - 4:4'-Dimethoxybenzhydrol (4.67g.) was dissolved in dry benzene (200 ml.), and the solution saturated with dry hydrogen bromide. The yellow solution was evaporated in a vacuum desiccator at room temperature. The residual colourless crystalline mass, dianisylbromomethane, (5.63g. 95.8%), m.p. 67-69^o, $\nu_{\max}$ (nujol): 650 cm⁻¹ (C-Br Str.), no hydroxyl absorption, gradually softened to a pink sticky solid; lit.³³ m.p. 70^o.

Attempted Carbonation of Dianisylbromomethane. - Dianisylbromomethane (5.63g.) was dissolved in dry ether (400 ml.) and magnesium turnings (0.5 g.) and a crystal of iodine added. The mixture was boiled under reflux for 5 hr., by which time no signs of reaction were seen. The reaction mixture was poured on to solid carbon dioxide and the mixture treated with crushed ice and hydrochloric acid (2N, ca. 60 ml.).

The ethereal layer was separated, and the aqueous layer extracted with ether (3 x 80 ml.). The ethereal solutions were combined and extracted with sodium carbonate solution (10%, 3 x 200 ml.). This carbonate extract was acidified and extracted with ether (4 x 70 ml.). The ethereal solution was washed with water and dried. Removal of solvent by distillation yielded no residue. The ethereal solution left after extraction with sodium carbonate solution was washed with water and dried. Removal of solvent by distillation afforded a colourless solid, (4.16g.), which was recrystallised from light petroleum-benzene, to yield 4:4'-dimethoxybenzophenone (3.97g. 89.4%) as colourless plates, m.p. 139-140°; mixed m.p. with authentic material, 138-140°.

Ethyl Coumarilate. - A mixture of redistilled salicylaldehyde (10 g.), redistilled bromoacetic ester (14.6g.), anhydrous potassium carbonate (14 g.) and ethanol (100 ml.) was boiled under reflux for 5 hr. The mixture was cooled, poured into water (3000 ml.), and the whole extracted with ether (3 x 200 ml.). The ether layer was washed with water, aqueous potassium carbonate solution, and finally, with water. The ethereal solution was dried and the solvent removed by distillation. The product was distilled and bromoacetic ester (1.2g.) was collected, b.p. 168-9° /

762.2 mm., and ethyl coumarilate (9.18g. 59%) collected as a yellow liquid, b.p. $290-4^{\circ}/762.2$ mm. The liquid thickened and solidified on prolonged cooling in an ice-bath and remelted when warmed to room temperature, at 24° , (Found : C 69.5, H 5.25; calc. for $C_{11}H_{10}O_3$: C 69.45, H 5.25%);
 lit.⁵⁰ m.p. 27° , b.p. $274^{\circ}/720$ mm.

2-Di-(p-methoxyphenyl)-hydroxymethylbenzofuran. - A solution of ethyl coumarilate (4.37 g.) in dry tetrahydrofuran (100 ml.) was added slowly, with cooling, to a solution of anisyl magnesium bromide in dry ether (50 ml.), prepared from p-bromoanisole (8.63 g.) and magnesium turnings (1.22g.). After the addition, the mixture was boiled under reflux for 4 hr., cooled and treated with ether (250 ml.), ice (500 g.) and dilute sulphuric acid (2N : 50 ml.). The ethereal layer was separated and the aqueous layer extracted with ether (3 x 100 ml.). The ethereal solutions were combined, washed with dilute sulphuric acid (2N, 50 ml.), water (2 x 30 ml.), saturated sodium metabisulphite solution (50 ml.) and water (2 x 30 ml.), and dried. The solvent was removed by distillation leaving a red oil (8.30 g.), $\nu_{\max}$ (liquid film): 3450 (OH Str.), 1740 cm^{-1} , weak, (ester C = O Str.).

The oil was dissolved in light petroleum-benzene (1:2 v/v, 30 ml.) and the solution passed through alumina

(H, 250 g.). Elution with the same solvent yielded anisole (3.73 g.) and *p*-bromoanisole (0.26g.); with benzene, ethyl coumarilate (0.96g.); and with ether, 2-di-(*p*-methoxyphenyl)-hydroxymethylbenzofuran (2.86 g. 34.6 %). Removal of solvent from the last eluate yielded the benzofuran as a yellow glass, $\nu_{\max}$ (liquid film): 3400 cm^{-1} (OH Str.), no ester carbonyl absorption.

2-Di-(*p*-methoxyphenyl)-methylcoumaran. - The benzofuran (1.908 g.) was dissolved in AnalaR acetic acid (100 ml.) to give a purple solution. Adams catalyst (102.7 mg.) was added, and the mixture hydrogenated at room temperature and at slight positive pressure. 2 Moles of hydrogen (237.4 ml.), were taken up in $2\frac{1}{2}$ hr., when the catalyst was separated and the pale yellow solution was poured into cold water (1000 ml.). Solid sodium carbonate (ca. 100 g.) was added to neutralise the solution, and a pale yellow solid was collected, washed and dried (1.794 g.). On recrystallisation from ethanol (animal charcoal), 2-di-(*p*-methoxyphenyl)-methylcoumaran (1.31 g. 71.4%) separated as pale yellow plates, m.p. $68-70^{\circ}$, (Found : C 79.7, H 6.4, $\text{C}_{23}\text{H}_{22}\text{O}_3$ requires : C 79.8, H 6.35%), $\nu_{\max}$ (nujol): 1246 (aryl-alkyl ether), 1038 cm^{-1} (*p*-substituted phenyl), no hydroxyl absorption.

Hydrogenation of 4'-Methoxyflav-2-ene. - The flavene (12.2 mg.) was dissolved in ethanol (5 ml.) and Adams catalyst (28.2 mg.) added. The mixture was hydrogenated at room temperature and at slight positive pressure, and the theoretical quantity of hydrogen was taken up in 19 min. Removal of the catalyst by filtration and of solvent by distillation yielded 4'-methoxyflavan (11.3 mg. 91.8%) as colourless needles, m.p. and mixed m.p. with authentic material, 82-4°.

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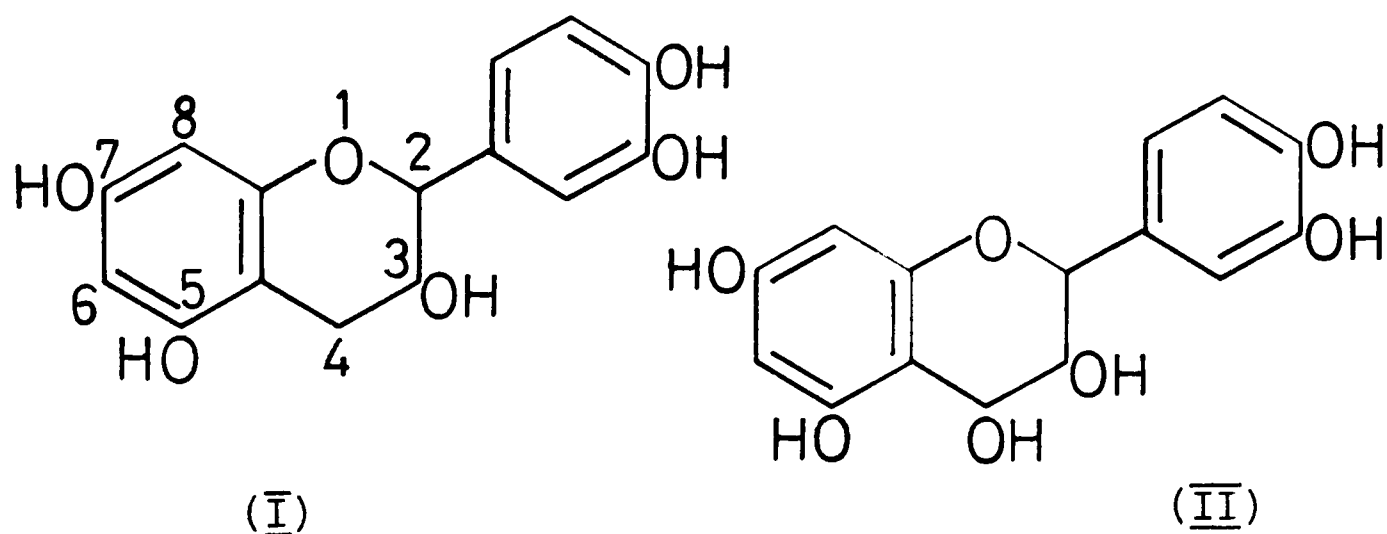
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C H A P T E R 5

3-METHYL AND 4-METHYLFLAVANSIntroduction

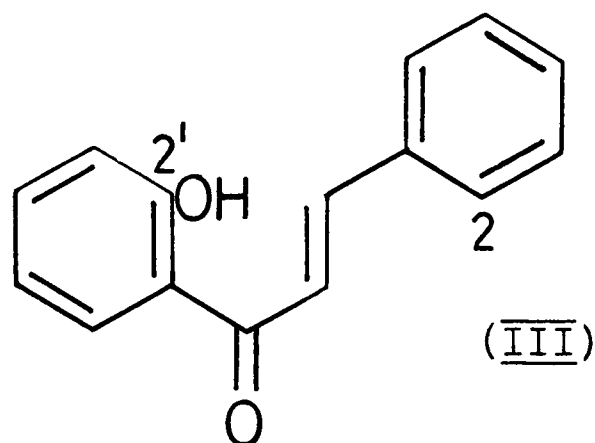
Some condensed tannins are believed to be polymers of¹ polyhydroxyflavanoids, such as catechin (I) and leucocyanidin (II), (see Introductions to Chapters 1 and 4). Such



polymerisation processes could occur by an autoxidative^{2,3} quinone-coupling mechanism or by electrophilic substitution^{4,5} (e.g., at C₆ or C₈) by carbonium ions formed by acid-catalysed fission of the heterocyclic ring or by ionisation at an activated benzyl position (e.g., C₂ or C₄).

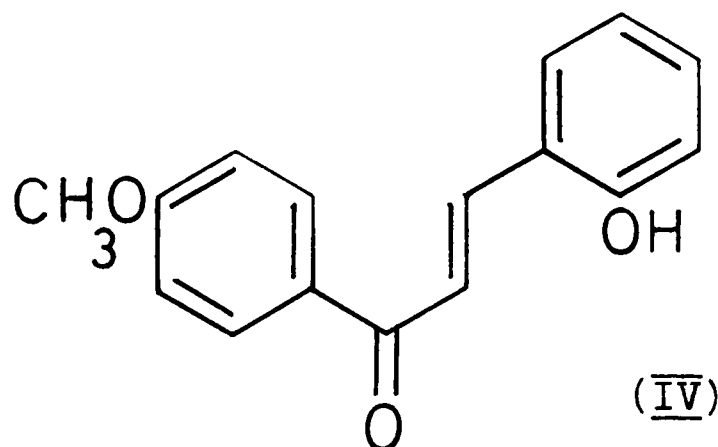
These polymerisation processes can be investigated by

studying condensations between simple flavanoids containing fewer substituents^{6,7}. Flavans for these studies may⁸⁻¹⁰ be synthesised directly from readily available chalcones, e.g. derivatives of (III), by reduction of 2- and 2'-hydroxy-



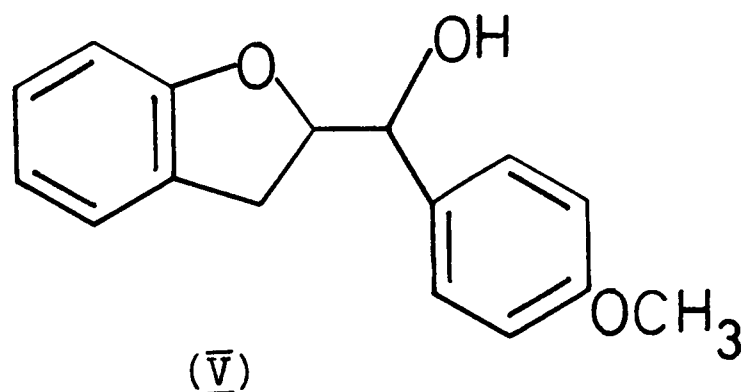
chalcones with lithium aluminium hydride and aluminium^{11,12} chloride.

Arising from these reductions, an interesting observation, on the effect of the use of methyl formate in decomposing lithium aluminium hydride-aluminium chloride reduction mixtures¹³, was made. When 2-hydroxy-4'-methoxychalcone, (IV),



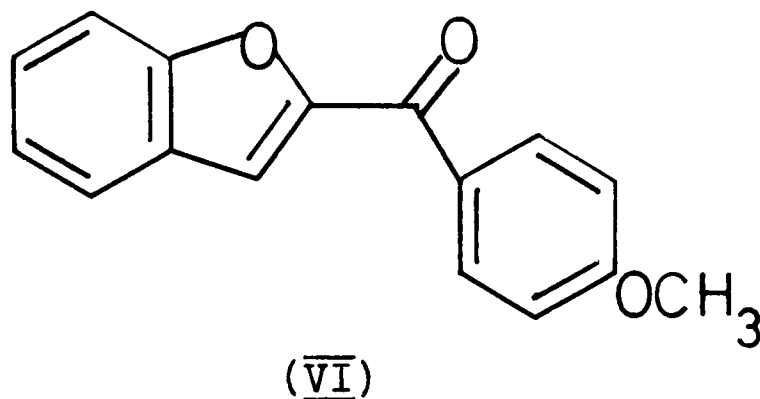
was reduced in the usual way with the mixed reagent, and the reaction mixture decomposed with methyl formate instead of wet ether, a non-phenolic alcohol m.p. $136-7^{\circ}$, (49%) was obtained as well as 4'-methoxyflavan (23%).

The formula of this compound, m.p. $136-7^{\circ}$, agreed tolerably well with analytical data, as $C_{16}H_{16}O_3$. Since the compound was non-phenolic, the only structure consistent with the infra-red and ultra-violet absorption appeared to be the dihydrobenzofuran (V). However, an attempt¹² to de-



hydrate the compound by sublimation at $120-200^{\circ}$ of its acetate, m.p. $105-6^{\circ}$, by cis-elimination, failed, as did an attempt to oxidise the compound by an Oppenauer oxidation, using p-benzoquinone and aluminium isopropoxide in toluene. Finally, the compound, (V) m.p. $98-9^{\circ}$, was synthesised by catalytic hydrogenation of 2-anisoylbenzofuran (VI) at $90-95^{\circ}$ under 60-65 atmospheres of hydrogen in the presence of Raney

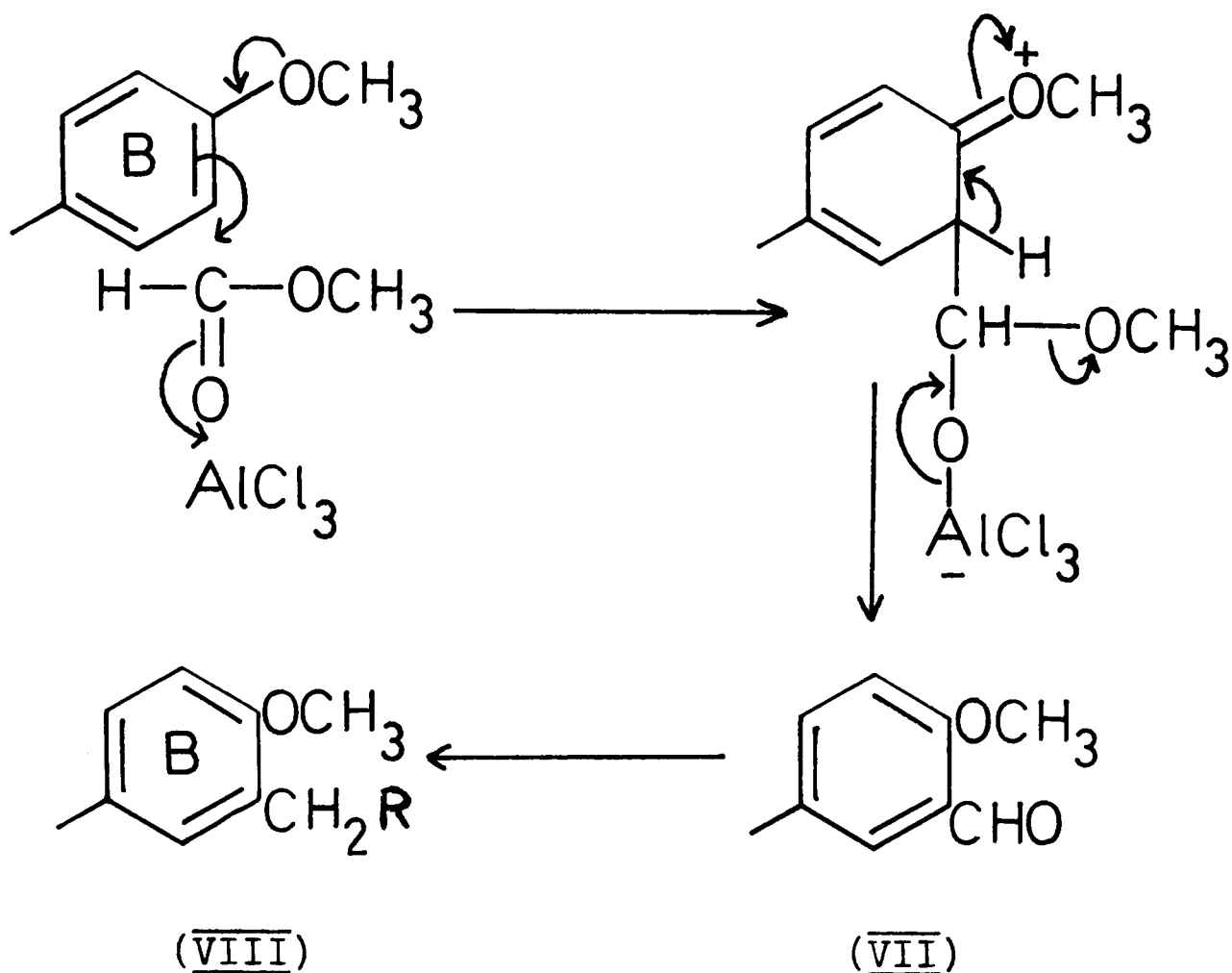
nickel, and was found to be different from the compound,



m.p. $136-7^{\circ}$.

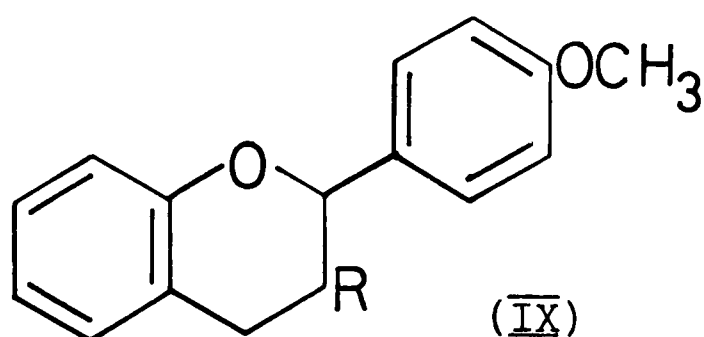
As a result of many elementary microanalyses, it became evident that $C_{17}H_{18}O_3$ was a more appropriate formula than $C_{16}H_{16}O_3$, even though the chalcone, from which the alcohol was prepared, was a C_{16} compound. Derivatives of the alcohol were prepared and their elementary analyses confirmed the presence of a C_{17} skeleton.

Since the compound was only obtained when methyl formate was used to decompose the excess of reducing agent, it seemed likely that methyl formate was the source of the extra carbon atom. It is known that esters can undergo Friedel-Crafts reaction and it was felt that such a reaction might have occurred: substitution by a formyl group could occur to give an aldehyde (VII), which is reduced to the alcohol, (VIII), by the lithium aluminium hydride present. Such a

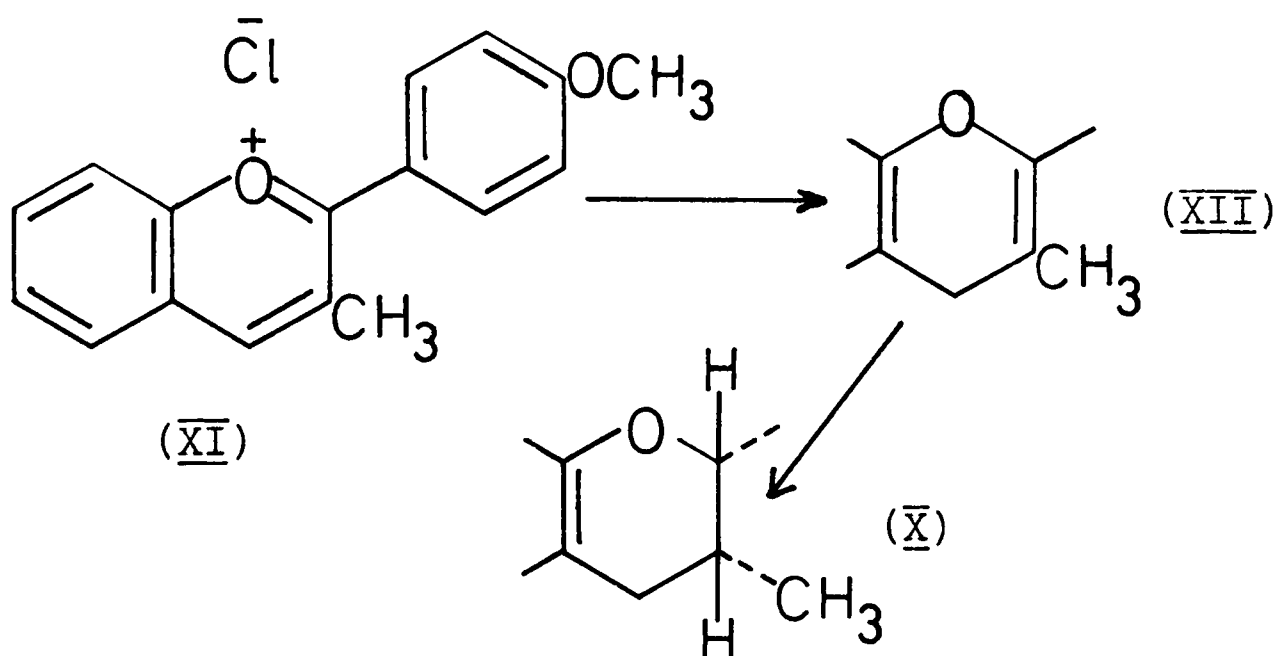


substitution was most likely to have occurred at $\text{C}_{3'}$. 4'-¹⁵Methoxy-3'-methylflavan, (VIII)_A^(R=H), was accordingly synthesised and it was found that it differed from the compound $\text{C}_{17}\text{H}_{18}\text{O}_2$, m.p. $106-7^\circ$. It therefore seemed likely that the compound, m.p. $106-7^\circ$, was either a C_3 -or a C_4 -methyl flavan.

Nuclear magnetic resonance data for the tosylate reduction product, m.p. $106-7^\circ$, and the mass spectrum of the alcohol, m.p. $136-7^\circ$ suggested that these compounds had the



structures ($\overline{\text{IX}}$: $\text{R}=\text{CH}_3$) and ($\overline{\text{IX}}$: $\text{R}=\text{CH}_2\text{OH}$)¹⁵. A synthesis of the methylflavan ($\overline{\text{IX}}$: $\text{R}=\text{CH}_3$) has been attempted¹⁵ and a 3-methylflavan ($\overline{\text{IX}}$: $\text{R}=\text{CH}_3$) was obtained, m.p. $65-66^\circ$, which was not identical with the methylflavan, m.p. $106-7^\circ$, and whose method of synthesis suggests that it is the 2:3-cis-isomer ($\overline{\text{X}}$). The 3-methyl flavylum chloride ($\overline{\text{XI}}$)

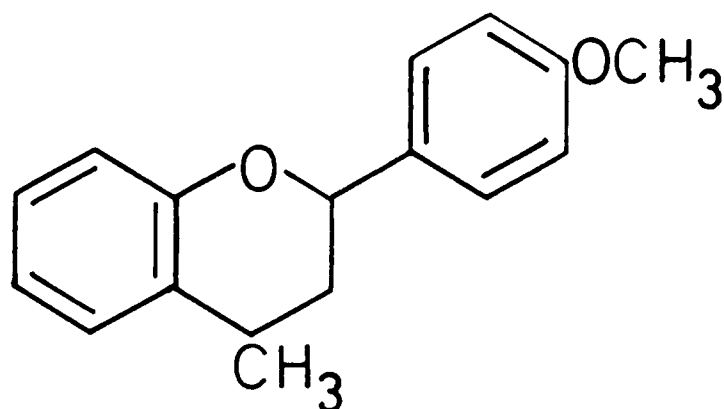


was reduced with lithium aluminium hydride to yield the 3-methylflav-2-ene ($\overline{\text{XII}}$), which was hydrogenated over Raney nickel. cis-Addition of hydrogen to the flav-2-ene ($\overline{\text{XII}}$) would be expected to occur, giving rise to the 2:3-cis-3-methylflavan ($\overline{\text{X}}$).

The Aim of Present Work.

Since no methods are at present available for the

synthesis of 2:3-trans-3-alkylflavans, the aim of present work is to synthesise the 4-methylflavans (XIII) and to show

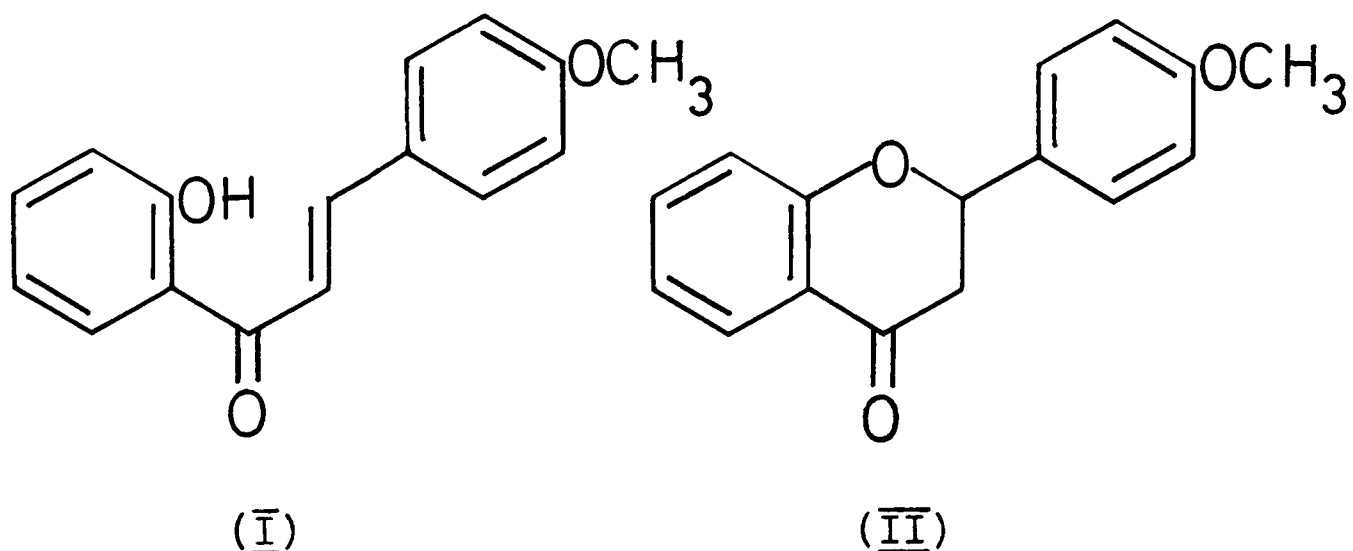


(XIII)

that these are not identical to the methylflavan, m.p. 106-7°, by examination of their n.m.r. spectra. It is hoped that, in view of these spectra and of those of other flavanoids, measured in connection with previous chapters, that the structure of the compound, m.p. 106-7°, and hence that of the alcohol, m.p. 136-7°, may be established.

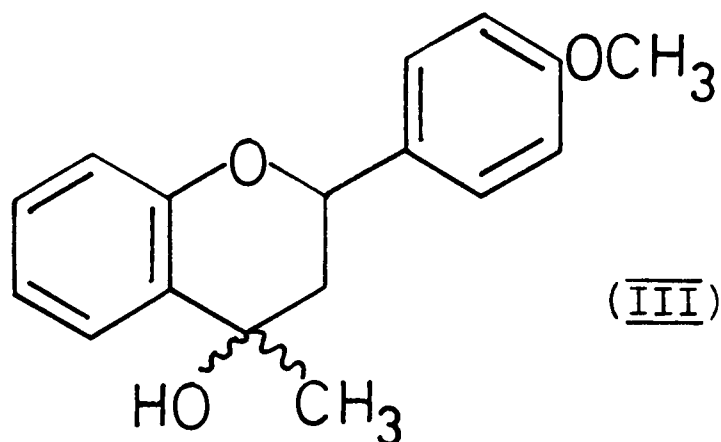
DISCUSSION

The synthesis of 4'-methoxy-4-methylflavan was approached in the following way. 2'-Hydroxy-4-methoxy-chalcone (I) was prepared in 64% yield by the condensation of o-hydroxyacetophenone with anisaldehyde in aqueous ethanolic

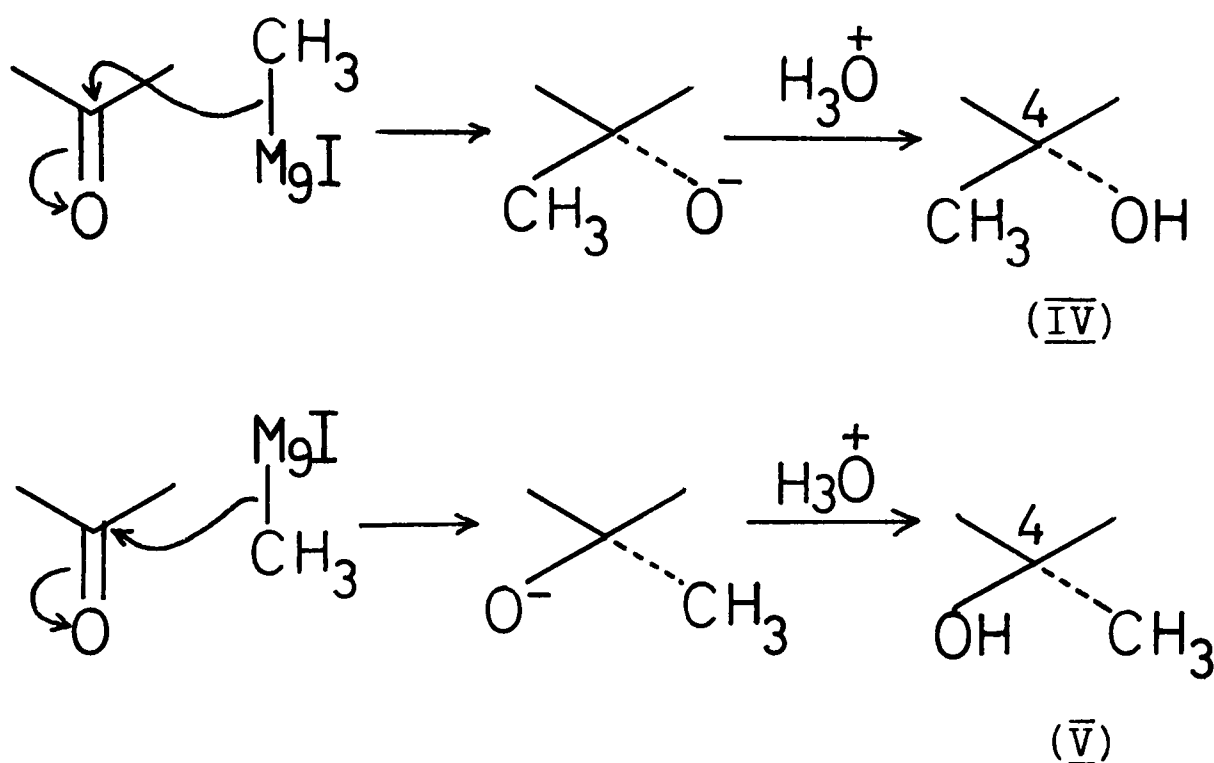


sodium hydroxide solution¹⁶. By ring-closure with ethanolic dilute hydrochloric acid^{15,17}, 4'-methoxyflavan-4-one (II) was prepared in 57% yield.

4'-Methoxy-4-methylflavan-4-ol (III) was then prepared in 72.5% yield from the ketone by reaction with methyl



magnesium iodide in ether. The configuration at the 4-position of this compound, which assumes a green colour on exposure to light, has not been determined. From a consideration of a model of the compound, it appears that attack by the reagent on the 4-position is possible from above or below the heterocyclic ring, giving rise to a 4-axial and a 4-equatorial methyl group respectively, (IV) and (V).



The nuclear magnetic resonance spectrum of this compound confirms the structure (III) and also the presence of only one of the epimers (IV) and (V). There is one sharp singlet at $\tau = 8.3$ ~~p.p.m.~~, the 4-methyl signal, and one sharp singlet at $\tau = 6.16$, the 4'- OCH_3 signal. If the product

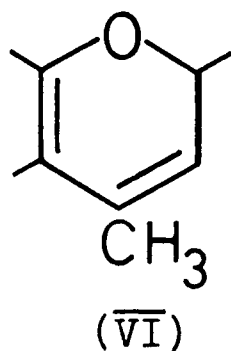
had been a mixture of epimers, two singlets would have been seen for each signal (e.g., n.m.r. spectrum no. 30). Furthermore, the C_2 quartet at $\tau = 4.78 - 4.98$ is a well-defined signal : a mixture of 4-epimers would have given rise to a complex signal, composed of two overlapping quartets (see e.g., n.m.r. spectrum no. 30).

The presence of only one of the epimers ($\overline{IV}$) and ($\overline{V}$) was demonstrated by the sharpness of the melting point, $138-9^\circ$, and by thin-layer chromatography in chloroform solution, which shows one spot, R_f 0.62.

It is important, as will be seen, that this product has one configuration at the 4-position. Presumably, the configuration present is that of an equatorial methyl group and an axial hydroxyl group ($\overline{V}$), since the methyl group is more bulky than the hydroxyl group.

The alcohol ($\overline{III}$) was then treated with p-toluene sulphonic acid in boiling acetic acid, a reagent which has been¹⁸ used to dehydrate 4-arylflavan-4-ols. The product, a bright yellow gum, could not be caused to crystallise, and its infra-red spectrum in chloroform showed no hydroxyl absorption but strong absorption at 1620 cm^{-1} (phenyl conjugated $C=C$). This suggested that the alcohol had lost

water to give 4'-methoxy-4-methylflav-3-ene (VII). Since¹⁸ the instability of flav-3-enes has been observed, it was

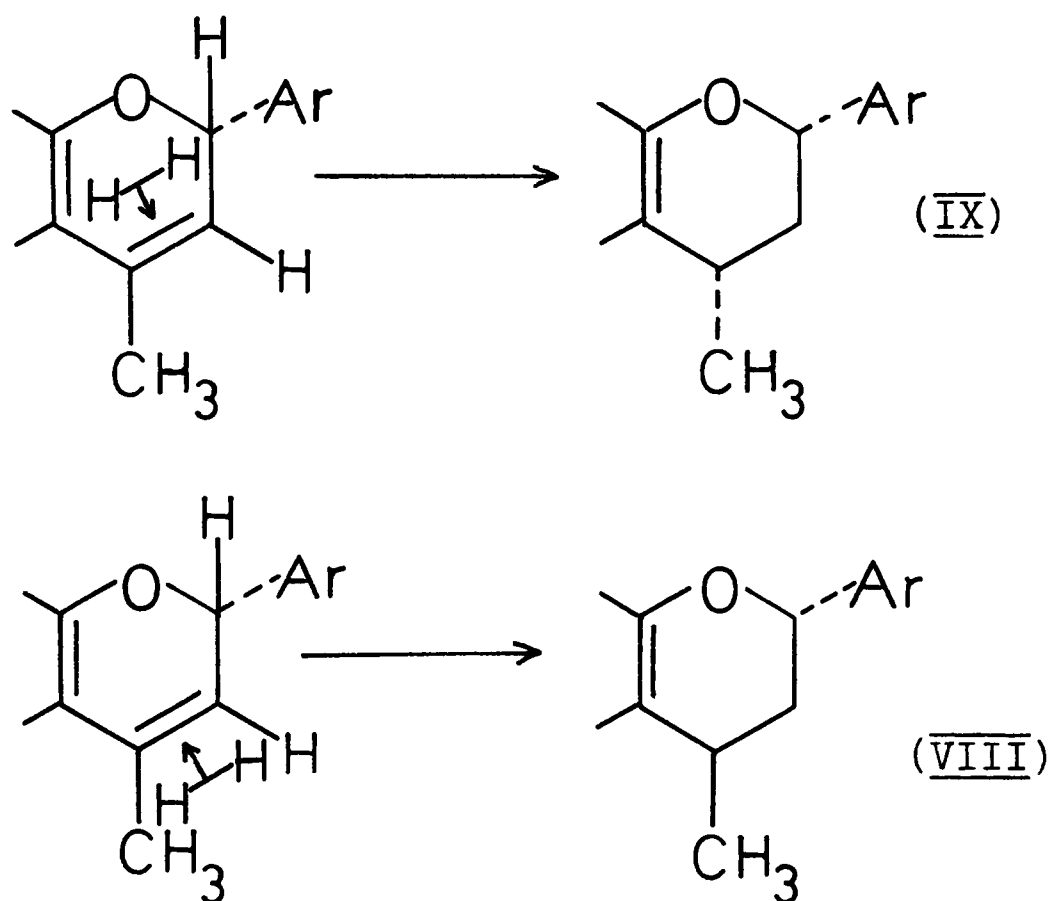


decided not to characterise this compound further, but to hydrogenate the crude product.

A solution of the gum in acetic acid was accordingly hydrogenated over Adams catalyst at room temperature and at slight positive pressure. One mole of hydrogen was taken up in 9 min., and the product, a pale-yellow gum, was chromatographed on alumina, yielding a pale-yellow gum, which could not be caused to crystallise. The n.m.r. spectrum of this gum showed it to be a 1:1 mixture of 4'-methoxy-4 α - and -4 β -methylflavans. Both of the methyl groups present, 4-axial and 4-equatorial, are seen as two doublets at $\tau = 8.54$, 8.65; and $\tau = 8.58$, 8.69, each with splittings of 6.6 c/s (see n.m.r. spectrum no. 31). The methoxyl signal is somewhat thicker than usual, although two separate signals cannot

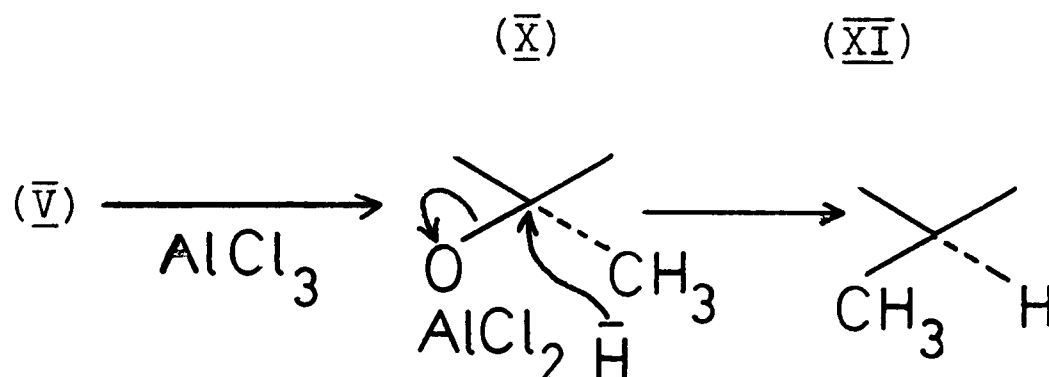
above.

It is clear that on catalytic hydrogenation of the 4-methylflav-3-ene ($\overline{\text{VI}}$), it is possible to obtain both 4-axial and 4-equatorial methylflavans ($\overline{\text{VIII}}$) and ($\overline{\text{IX}}$) by cis-addition of hydrogen.



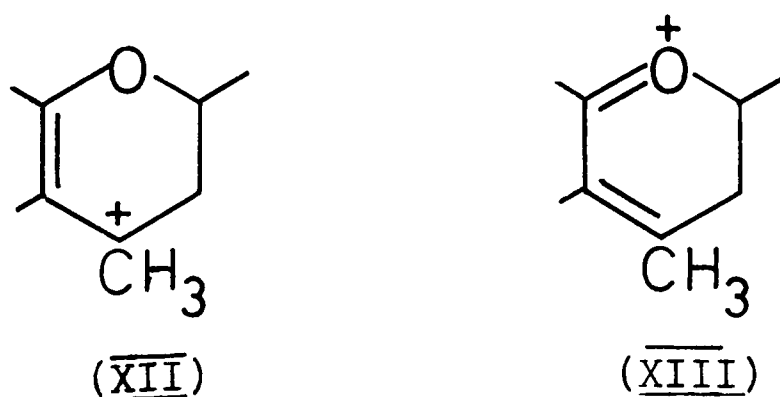
If however, the 4-methylflavan-4-ol ($\overline{\text{V}}$) were reduced²⁰ with lithium aluminium hydride-aluminium chloride to the 4-methylflavan, then such a mixture of epimers might not be formed, assuming that the reduction is effected by an S_{N}^2 reaction of the aluminium chloride complex of the alcohol ($\overline{\text{V}}$)

with hydride ion ($\bar{X}$). If the mechanism of this reduction



is as shown, and if the alcohol ($\bar{III}$) has the 4-equatorial methyl group ($\bar{V}$), then the product might be the 4-axial methylflavan ($\bar{XI}$).

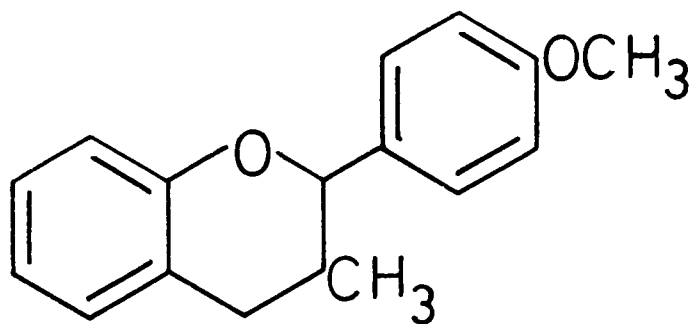
4'-Methoxy-4-methylflavan-4-ol ($\bar{III}$) was reduced with lithium aluminium hydride-aluminium chloride and the product after chromatography on alumina was a pale yellow gum, whose n.m.r. spectrum was identical with that of the product obtained by hydrogenation of the flavene. Both reductions of the alcohol ($\bar{III}$) give rise to a 1:1 mixture of 4-axial and 4-equatorial methylflavans. It seems that in the nucleophilic substitution ($\bar{X}$), the stability of the benzyl carbonium ion ($\bar{XII}$) [possibly stabilised as structure ($\bar{XIII}$)],



generated by loss of the aluminium oxychloride group on approach of hydride ion, allows a time-lag to occur before final attachment of the hydride ion. After such a time-lag, the hydride ion may approach from either above or below the plane of the heterocyclic ring, giving rise to the 1:1 mixture of 4-methylflavans.

The Nuclear Magnetic Resonance Spectrum of the Methylflavan, m.p. 106-7°.

The n.m.r. spectrum of this compound had already been measured¹⁵, and although it lent support to the structure (XIV) for the reduction product of the tosylate of the alcohol,



(XIV)

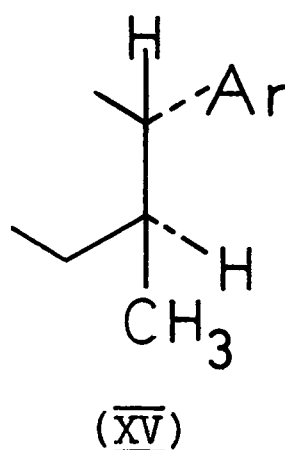
m.p. 136-7°, the quality of the spectrum was such that an unambiguous interpretation was not possible.

Accordingly, the n.m.r. spectrum of the methylflavan, m.p. 106-7°, was re-examined in deuteriochloroform. A well-

defined spectrum resulted, which was different from that of the 4-methylflavans, and which was capable of unambiguous interpretation.

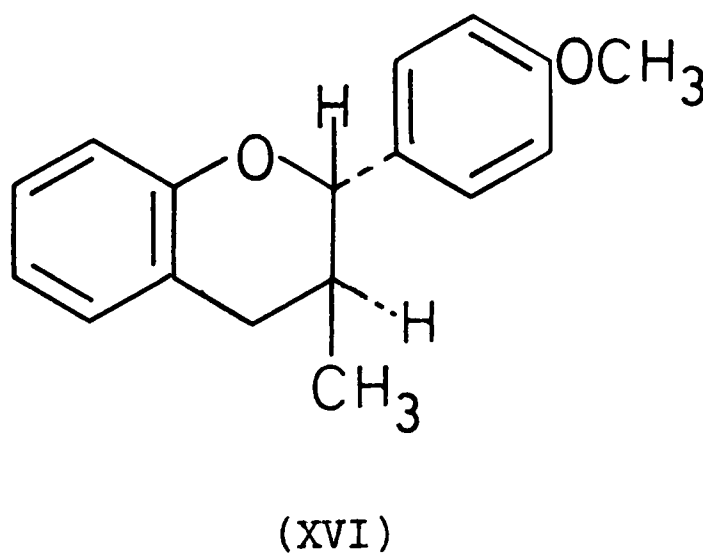
That the compound consisted of only one isomer was shown by the occurrence of one methyl doublet, splitting 6.6 c/s, one methoxyl singlet and one C₂ doublet, splitting 9.0 c/s. The methyl doublet appeared at $\tau = 9.11$ and 9.22, compared with 8.54 and 8.65, and 8.58 and 8.69 for the 4-methyl compounds, which are expected to occur at lower field, since they are adjacent to an aromatic ring (see, e.g., methyl groups at 8.75 and 9.04 ~~p.p.m.~~²¹, being α - and β - to an aromatic ring). The signals of the C₃ and C₄ protons are complex and yield no useful information, beyond the fact that they occur at $\tau = 7.0 - 8.1$, the expected position in the spectrum for protons at the 3- and 4-positions in the hydrocarbon flavans (see e.g., n.m.r. spectra nos. 20, 22, 23 and 24).

The well-defined C₂ doublet at $\tau = 5.35$ and 5.50 confirms that the compound has one substituent at the 3-position, the methyl group, and its splitting, 9.0 c/s, corresponds to a dihedral angle between the C₂ and C₃ protons of ca. 150°²² only. This establishes the relative stereochemistry of the compound at the 2- and 3-carbon atoms as 2:3-trans (XV), and is in accord with results for other 2:3-trans-flavanoids



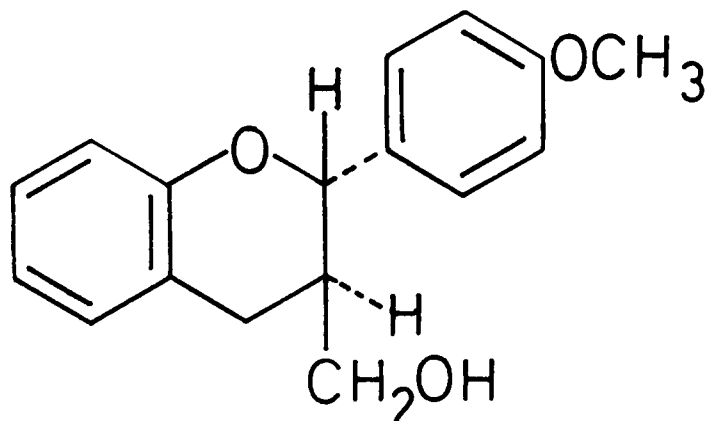
(see e.g., n.m.r. spectra nos. 3, 26 and 27) and contrasts with the results for 2:3-cis-flavanoids (see n.m.r. spectrum no. 33)²³.

The reduction product of the tosylate of the alcohol, m.p. 136-7^o, is, therefore, 4'-methoxy-3-methyl-2:3-trans-flavan (XVI). An unambiguous synthesis of this compound is



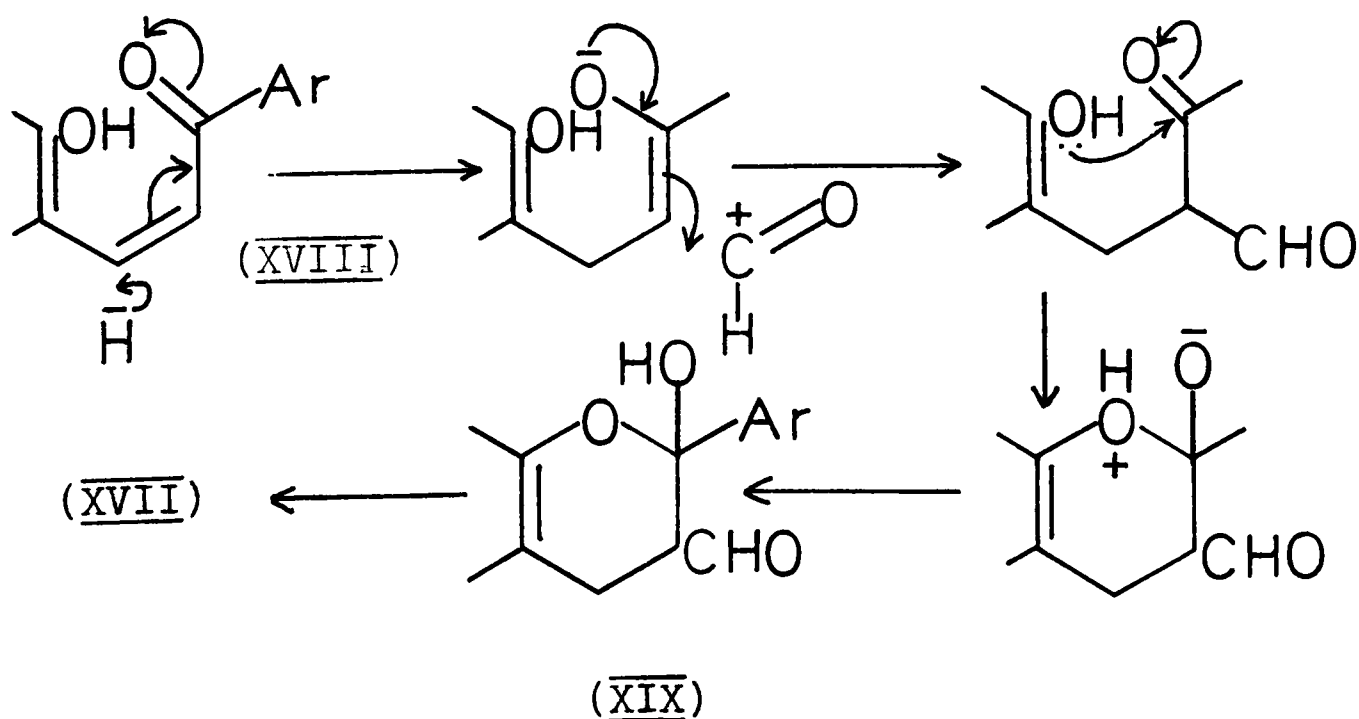
required to verify the structure (XVI). Since no participation of the 3-carbon atom is involved in the tosylation and reduction of the tosylate of the alcohol, m.p. 136-7^o, such

a verification would establish the formula of the alcohol as (XVII).



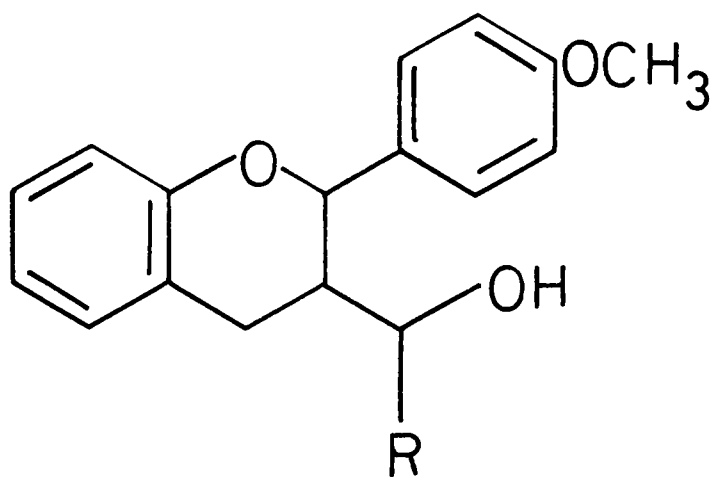
(XVII)

Having established the formula of the alcohol, m.p. 136-7°, as structure (XVII), it is easy to see that its formation could arise by the attack of the ion HCO^+ , generated by methyl formate in the presence of aluminium chloride, at the 3-position during reduction and ring-closure of the chalcone (XVIII). The aldehyde (XIX) would be reduced, and



the hydroxyl group at C₂ replaced, by hydride ions to yield the 3-hydroxymethylflavan (XVII), since at the first addition of methyl formate, lithium aluminium hydride is still present.

Similar reductions of chalcones with lithium aluminium hydride-aluminium chloride followed by treatment with esters other than formates, have been effected¹⁵, and the products have been tentatively assigned¹⁵ the structure (XX), formed



(XX)

by similar mechanisms to that above, involving attack by the ion RCO^+ . Further work on the treatment of such reduction mixtures with appropriate esters, may show this procedure to be a general method of synthesis of 2:3-trans-3-alkylflavans.

EXPERIMENTAL SECTION

4'-Methoxy-4-methylflavan-4-ol. - 4'-Methoxyflavan-4-one (9.34g.) was dissolved in dry ether (150 ml.) and the solution added dropwise to methyl magnesium iodide, prepared from methyl iodide (5.22g.) and magnesium turnings (0.9g), in dry ether (100 ml.). The mixture was boiled under reflux for 2 hr., cooled to 0° and decomposed with cold aqueous acetic acid (4%, 250 ml.): a colourless solid (0.9g.), m.p. 135-7°, was collected.

The ethereal solution was separated, and the aqueous layer extracted with ether (3 x 50 ml.). The ethereal solutions were combined, washed with water and dried. Removal of solvent by distillation yielded a colourless solid (7.7g.), m.p. 134-7°.

On recrystallisation of the combined solids from methanol, 4'-methoxy-4-methylflavan-4-ol (7.2g. 72.5%) separated as colourless needles, which acquire a green colour on prolonged exposure to light, m.p. 138-9°, (Found : C 75.5, H 6.6. $C_{17}H_{18}O_3$ requires : C 75.5, H 6.65%), $\nu_{\max}$ (nujol): 3230 cm^{-1} (OH Str.), no carbonyl absorption, thin-layer chromatography (chloroform): 1 spot (R_f 0.62).

Dehydration of 4'-Methoxy-4-methylflavan-4-ol. - A

solution of 4'-methoxy-4-methylflavan-4-ol (100 mg.) in AnalaR acetic acid (5 ml.) was boiled under reflux with p-toluene sulphonic acid (33.2 mg.) for 2 hr. The mixture was allowed to cool, and was poured into cold water (50 ml.) The green mixture was extracted with ether (3 x 30 ml.) and the ethereal solutions washed with sodium carbonate solution and water, and dried.

Removal of the solvent by distillation yielded a yellow-brown gum (65.1 mg.) which could not be caused to solidify, ν_{max} (chloroform): 1620 cm^{-1} (phenyl conjugated C=C Str.), no hydroxyl absorption.

Hydrogenation of the Dehydration Product. - The gum (64.2 mg.) was dissolved in acetic acid (3 ml.), Adams catalyst (16.9 mg.) added, and the mixture hydrogenated at room temperature and slight positive pressure. The theoretical quantity of hydrogen (6.85 ml.) was taken up in 9 min., when the solution was colourless. Removal of the catalyst by filtration and of the solvent by distillation yielded a yellow gum (61.1 mg.), which could not be caused to crystallise.

Chromatography of the gum, in benzene (5 ml.) on alumina (50g.), yielded a colourless gum (41.2 mg. 63.7%), which could not be caused to crystallise. The infra-red spectrum of the gum showed no phenyl conjugated C=C Str. absorption

at 1620 cm^{-1} : the n.m.r. spectrum showed it to be a 1:1 mixture of 4'-methoxy-4 α -and-4 β -methylflavans.

Attempted Epimerisation of the Mixture of 4-Methylflavans.

The gum (60 mg.) was dissolved in ethanol (5 ml.) and water (1 ml.), and solid potassium hydroxide (87.1 mg.) added. The solution was boiled under reflux for 1 hr., cooled and cold sulphuric acid ($N/2$, 60 ml.) added. The white emulsion formed, was extracted with ether (4 x 20 ml) and the ethereal solution washed with water and dried. Removal of solvent by distillation yielded a colourless gum (40.1 mg.).

Chromatography of the gum, in benzene (5 ml.), on alumina (50 g.), yielded a colourless gum (38.6 mg.), which could not be caused to crystallise. The n.m.r. spectrum of this gum showed it to be a mixture of the 4-methylflavans in the same proportions (1:1) as previously found.

The Reduction of 4'-Methoxy-4-methylflavan-4ol with Lithium Aluminium Hydride and Aluminium Chloride. - To dry ether (40 ml.), stirred and cooled to 0° , was added powdered aluminium chloride (0.4g.) followed by lithium aluminium hydride (0.15g.). The mixture was boiled under reflux for 15 min., cooled to 0° and a solution of 4'-methoxy-4-methylflavan-4-ol (0.27g.) in dry ether (20 ml.) added slowly.

The mixture was then boiled under reflux for 3 hr., after which it was cooled to 0° and decomposed with wet ether, water and hydrochloric acid (2N). The ethereal layer was separated and the aqueous layer extracted with ether (2 x 50 ml.). The ethereal solutions were combined, washed with water (2 x 30 ml.) and dried.

Removal of solvent by distillation yielded a pale yellow gum (0.18g.), which could not be caused to crystallise. Chromatography of a solution of the gum, in benzene (5 ml.), on alumina ("H", 50g.), yielded a pale yellow gum (0.169g.), which could not be caused to crystallise. The infra-red and n.m.r. spectra of the compound showed it to be identical with the 1:1 mixture of 4'-methoxy-4 α - and -4 β -methylflavans previously prepared.

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C H A P T E R VI

NUCLEAR MAGNETIC RESONANCE SPECTRA

Nuclear magnetic resonance spectra of the following compounds were measured on a Perkin Elmer R10 60 Mc/s spectrometer. Spectrum marked with an asterisk, were measured on an AEI RS2 60 Mc/s instrument.

1. Flavan-4-one: solvent:CHCl₃

	<u>T (p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings (c/s):</u>	<u>Inte- gration:</u>
(a)	4.41-4.68	C ₂	quartet	5.4, 10.8	(1)
(b)	6.49-7.33	C ₃	complex		(2)

2. 4'-Methoxyflavan-4-one: CHCl₃

(a)	4.43-4.70	C ₂	quartet	4.8, 11.5	(1)
(b)	6.17	OCH ₃	singlet		(3)
(c)	6.61-7.33	C ₃	complex		(2)

3. 3-Hydroxy-4'-methoxyflavan-4-one: CDCl₃

(a)	1.59-3.01	aromatic complex			(8)
(b)	4.73, 4.93	C ₂	doublet	12.6	(1)
(c)	5.23, 5.44	C ₃	doublet	12.6	(1)

	<u>T (p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings:</u> (c/s)	<u>Inte- gration:</u>
(d)	6.13	OCH ₃	singlet		(3)
(e)	6.0-6.3	OH	broad singlet		(1)
D ₂ O exchange removes the OH signal.					
4.	<u>3':4'-Dimethoxyflavan-4-one</u> : CHCl ₃				
(a)	4.41-4.68	C ₂	quartet	4.8, 11.1	(1)
(b)	6.06, 6.07	OCH ₃	2 sing- lets		(6)
(c)	6.84-7.33	C ₃	complex		(2)
5.	<u>Flavan-4α-ol</u> : CHCl ₃ *				
(a)	4.80-5.50	C ₂ +C ₄	complex		(2)
(b)	7.0-8.5	C ₃ +OH	complex		(3)
6.	<u>4α-Acetoflavan</u> : CDCl ₃				
(a)	3.75-3.85	C ₄	triplet	3.0	(1)
(b)	4.49-4.74	C ₂	quartet	6.0, 8.0	(1)
(c)	7.50-7.90	C ₃ +CO. CH ₃	complex		(5)
7.	<u>4α-Benzoyloxyflavan</u> : CDCl ₃				
(a)	1.80-3.40	aromatic	complex		(14)
(b)	3.60-3.80	C ₄	triplet	3.0	(1)
(c)	4.40-4.75	C ₂	quartet	5.4, 9.6	(1)
(d)	7.35-8.05	C ₃	complex		(2)

~~T (p.p.m.)~~: Assign- Signal: Splittings Inte-
ment: (c/s): gration.

Solvent: benzene

(a)	4.49-.4.74	C ₂	quartet	3.45, 10.65	(1)
(b)	7.53-8.35	C ₃	16-line complex	(14.85) (3.6, 2.85) (11.1, 3.9)	(2)

2nd Order calculations¹ : $J_{3a,3b} = 14.85$, $J_{3a,2} = 1.73$,

$J_{3a,4} = 2.26$, $J_{3b,2} = 12.37$ and $J_{3b,4} = 3.73$ c/s.

8. Flavan-4 β -ol : CHCl₃*

(a)	4.76-5.28	C ₂ ,C ₄	complex		(2)
(b)	7.0-8.5	C ₃ +OH	complex		(3)

9. 4 β -Acetoxyflavan : CHCl₃*

(a)	3.71-3.97	C ₄	quartet	6.0, 9.6	(1)
(b)	4.72-4.94	C ₂	quartet	2.4, 10.8	(1)
(c)	7.0-8.5	C ₃ +CO. CH ₃	complex		(5)

10. 4 β -Benzoyloxyflavan : CDCl₃

(a)	3.33-3.60	C ₄	quartet	6.6, 9.0	(1)
(b)	4.51-4.72	C ₂	quartet	2.4, 10.2	(1)
(c)	6.97-7.90	C ₃	16-line complex	(13.4) (2.85, 6.45) (10.72, 9.67)	(2)

<u>T (p.p.m.):</u>	<u>Assign-</u>	<u>Signal:</u>	<u>Splittings</u>	<u>Inte-</u>
	<u>ment:</u>		<u>(c/s):</u>	<u>gration.</u>

2nd Order calculations¹ $J_{3a,3b} = 13.4$, $J_{3a,2} = 2.09$,
 $J_{3a,4} = 6.32$, $J_{3b,2} = 10.51$ and $J_{3b,4} = 9.88$ c/s.

11. 4 β -Trimethylsilyloxyflavan: CDCl₃

(a)	2.5-3.4	aromatic complex + C ₄		(10)
(b)	4.8-5.0	C ₂	quartet 5.7, 8.4	(1)
(c)	7.5-8.3	C ₃	complex	(2)
(d)	ca.10	Si-CH ₃	complex	(-)

12. 4a-Acetoxy-4'-methoxyflavan : CDCl₃

(a)	3.84-3.95	C ₄	triplet 2.7, 3.0	(1)
(b)	4.63-4.87	C ₂	quartet 6.45, 7.35	(1)
(c)	6.17	OCH ₃	singlet	(3)
(d)	7.60-8.02	C ₃ +CO. CH ₃	complex	(5)

13. 4a-Benzoyloxy-4'-methoxyflavan : CDCl₃

(a)	1.6-3.2	aromatic complex		(13)
(b)	3.6-3.7	C ₄	triplet 3.0	(1)
(c)	4.49-4.73	C ₂	quartet 6.0, 8.4	(1)
(d)	6.14	OCH ₃	singlet	(3)
(e)	7.2-7.9	C ₃	complex	(2)

<u>T (p.p.m.)</u> :	<u>Assign- ment</u> :	<u>Signal</u> :	<u>Splittings (c/s)</u> :	<u>Inte- gration</u> :
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Solvent : benzene

(a)	4.45-4.80	C ₂	quartet	3.3, 10.05	(1)
(b)	6.15	OCH ₃	singlet		(3)
(c)	7.25-8.05	C ₃	16-line complex	(14.6) (4.2, 2.85) (10.8, 3.9)	(2)

2nd Order calculations : $J_{3a,3b} = 14.63$, $J_{3a,2} = 1.74$,
 $J_{3a,4} = 2.34$, $J_{3b,2} = 11.61$ and $J_{3b,4} = 3.67$ c/s.

14. 4'-Methoxyflavan-4 β -ol: CHCl₃*

(a)	4.5-5.5	C ₂ , C ₄	complex		(2)
(b)	6.2	OCH ₃	singlet		(3)
(c)	7.0-8.5	C ₃ +OH	complex		(3)

15. 4 β -Acetoxy-4'-methoxyflavan : CHCl₃

(a)	3.69-3.96	C ₄	quartet	6.71, 10.30	(1)
(b)	4.76-4.99	C ₂	quartet	2.20, 11.45	(1)
(c)	6.15	OCH ₃	singlet		(3)
(d)	7.0-8.5	C ₃ +CO. CH ₃	complex		(5)

16. 4 β -Benzoyloxy-4'-methoxyflavan : CDCl₃

(a)	3.30-3.58	C ₄	quartet	6.6, 10.2	(1)
(b)	4.54-4.75	C ₂	quartet	2.4, 10.2	(1)

<u>T (p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings (c/s):</u>	<u>Inte- gration:</u>
(c) 6.10	OCH ₃	singlet		(3)
(d) 6.95-7.88	C ₃	16-line complex	$\begin{pmatrix} 12.9 \\ 2.7 & 6.0 \\ 10.8 & 9.3 \end{pmatrix}$	(2)

2nd Order calculations¹ : $J_{3a,3b} = 12.9$, $J_{3a,2} = 2.59$,
 $J_{3a,4} = 5.88$, $J_{3b,2} = 10.01$ and $J_{3b,4} = 10.93$ c/s.

17. 4 α -Benzoyloxy-3':4'-dimethoxyflavan : benzene

(a) 4.45-4.68	C ₂	quartet	3.6, 10.2	(1)
(b) 6.14, 6.15	2 OCH ₃	2 sing- lets		(6)
(c) 7.40-8.25	C ₃	16-line complex	$\begin{pmatrix} 14.6 \\ 4.1 & 2.8 \\ 10.4 & 4.3 \end{pmatrix}$	(2)

2nd Order calculations¹ : $J_{3a,3b} = 14.6$, $J_{3a,2} = 1.6$,
 $J_{3a,4} = 2.3$, $J_{3b,2} = 12.1$ and $J_{3b,4} = 3.7$ c/s.

18. 4 β -Benzoyloxy-3':4'-dimethoxyflavan : benzene

(a) 4.92-5.14	C ₂	quartet	2.81, 10.35	(1)
(b) 6.14, 6.17	2 OCH ₃	2 sing- lets		(6)
(c) 6.8-8.2	C ₃	16-line complex	$\begin{pmatrix} 13.2 \\ 3.0 & 6.6 \\ 10.8 & 9.3 \end{pmatrix}$	(2)

T (p.p.m.): Assign- Signal: Splittings Inte-
ment: (c/s): gration:

2nd Order calculations¹ : $J_{3a,3b} = 13.2$, $J_{3a,2} = 2.1$,
 $J_{3a,4} = 5.5$, $J_{3b,2} = 10.7$ and $J_{3b,4} = 10.7$ c/s.

19. Flavan : CHCl_3

(a)	4.73-4.95	C_2	quartet	4.65, 7.95	(1)
(b)	6.53-7.20	C_4	complex		(2)
(c)	7.60-8.05	C_3	complex		(2)

20. 4'-Methoxyflavan : CHCl_3

(a)	4.74-4.95	C_2	quartet	5.25, 7.05	(1)
(b)	6.08	OCH_3	singlet		(3)
(c)	6.8-7.2	C_4	complex		(2)
(d)	7.6-8.1	C_3	complex		(2)

21. 4'-Methoxyflav-2-ene: CDCl_3

(a)	2.3-3.2	aromatic	complex		(8)
(b)	3.6	C_3	singlet		(1)
(c)	5.9	C_4	singlet		(2)
(d)	6.17	OCH_3	singlet		(3)

22. 3':4'-Dimethoxyflavan : CHCl_3

(a)	4.79-5.01	C_2	quartet	5.1, 7.8	(1)
(b)	6.05	2 OCH_3	joint singlet		(6)

	<u>T (p.p.m.)</u> :	<u>Assign- ment</u> :	<u>Signal</u>	<u>Splittings</u> (c/s):	<u>Inte- gration</u> :
(c)	6.8-7.3	C ₄	complex		(2)
(d)	7.6-8.0	C ₃	complex		(2)
23.	<u>4':7-Dimethoxyflavan</u> : CHCl ₃				
(a)	4.82-5.04	C ₂	quartet	5.4, 7.5	(1)
(b)	6.10, 6.14	2 OCH ₃	2 sing- lets		(6)
(c)	6.9 - 7.5	C ₄	complex		(2)
(d)	7.6-8.1	C ₃	complex		(2)
24.	<u>3:4-cis-Diacetoxy-2:3-trans-flavan</u> : CHCl ₃				
(a)	3.74, 3.79	C ₄	doublet	3.0	(1)
(b)	4.35-4.56	C ₃	quartet	3.0, 9.6	(1)
(c)	4.62, 4.79	C ₂	doublet	10.2	(1)
(d)	7.8, 8.2	2 CO. CH ₃	2 sing- lets		(6)
25.	<u>3:4-cis-Diacetoxy-4'-methoxy-2:3-trans-flavan</u> : CHCl ₃				
(a)	3.73, 3.78	C ₄	doublet	3.0	(1)
(b)	4.35-4.57	C ₃	quartet	3.0, 10.2	(1)
(c)	4.65, 4.82	C ₂	doublet	10.2	(1)
(d)	6.17	OCH ₃	singlet		(3)
(e)	7.85, 8.13	2 CO. CH ₃	2 sing- lets		(6)
26.	<u>3:4-trans-Diacetoxy-2:3-trans-flavan</u> : CDCl ₃				
(a)	3.59, 3.71	C ₄	doublet	7.2	(1)

	<u>T(p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings (c/s):</u>	<u>Inte- gration:</u>
(b)	4.24-4.51	C ₃	quartet	7.2, 9.0	(1)
(c)	4.70, 4.85	C ₂	doublet	9.0	(1)
(d)	7.97, 8.09	2 CO. CH ₃	2 sing- lets		(6)
27.	<u>3:4-trans-Diacetoxy-4'-methoxy-2:3-trans-flavan:</u> CHCl ₃				
(a)	3.58, 3.70	C ₄	doublet	7.2	(1)
(b)	4.28-4.55	C ₃	quartet	7.3, 9.2	(1)
(c)	4.82, 4.98	C ₂	doublet	9.6	(1)
(d)	6.16	OCH ₃	singlet		(3)
(e)	7.93, 8.14	2 CO. CH ₃	2 sing- lets		(6)
28.	<u>3:4-trans-Diacetoxy-4'-methoxy-6-methyl-2:3-trans-flavan:</u> CHCl ₃				
(a)	3.62, 3.74	C ₄	doublet	7.2	(1)
(b)	4.31-4.58	C ₃	quartet	7.2, 9.0	(1)
(c)	4.87, 5.02	C ₂	doublet	9.0	(1)
(d)	6.17	OCH ₃	singlet		(3)
(e)	7.69	Ar-CH ₃	singlet		(3)
(f)	7.93, 8.14	2 CO. CH ₃	2 sing- lets		(6)
29.	<u>4'-Methoxy-4-methylflavan-4-ol</u> : CHCl ₃				
(a)	4.74-4.98	C ₂	quartet	5.4, 8.4	(1)
(b)	6.16	OCH ₃	singlet		(3)
(c)	7.65-7.99	C ₃ +OH	complex		(3)

	<u>T(p.p.m.):</u>	<u>Assign-</u> <u>ment:</u>	<u>Signal:</u>	<u>Splittings</u> <u>(c/s)</u>	<u>Inte-</u> <u>gration:</u>
(d)	8.30	C,CH ₃	singlet		(3)
30.	<u>4'-Methoxy-4α and 4β-methylflavan</u> : CDCl ₃				
(a)	2.5-3.2	aromatic	complex		(8)
(b)	4.75-5.15	α C ₂ + β C ₂	2 quart- ets	(4.2, 11.2) ((2.4, 11.4)	(1)
(c)	6.19	OCH ₃	singlet		(3)
(d)	6.56-7.25	α C ₄ + β C ₄	complex		(1)
(e)	7.4-8.2	α C ₃ + β C ₃	complex		(2)
(f)	8.54, 8.65	α or β 4-CH ₃	doublet	6.6	(3)
(g)	8.58, 8.69	β or α 4-CH ₃	doublet	6.6	(3)
31.	<u>4'-Methoxy-3-methyl-2:3-trans-flavan</u> : CDCl ₃				
(a)	2.5-3.3	aromatic	complex		(8)
(b)	5.35, 5.50	C ₂	doublet	9.0	(1)
(c)	6.18	OCH ₃	singlet		(3)
(d)	7.0-8.1	C ₃ +C ₄	complex		(3)
(e)	9.11, 9.22	C.CH ₃	doublet	6.6	(3)
32.	<u>3-Acetoxy-4'-methoxyflavan</u> : CHCl ₃				
(a)	4.35-4.80	C ₂ +C ₃	complex		(2)
(b)	6.12	OCH ₃	singlet		(3)
(c)	6.8-7.1	C ₄	complex		(2)

	<u>τ (p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings (c/s):</u>	<u>Inte- gration:</u>
(d)	7.99	CO.CH ₃	singlet		(3)

33. 2:3-cis-p-Methoxyphenyl-4'-methoxyflavan: CHCl₃

(a)	4.60, 4.65	C ₂	doublet	3.0	(1)
(b)	6.26	2 OCH ₃	joint singlet		(6)
(c)	6.54-6.85	C ₃ +C ₄	complex		(3)

34. 4-Aminoflavan : CHCl₃

(a)	4.68-4.90	C ₂	quartet	2.4, 10.8	(1)
(b)	5.55-5.84	C ₄	quartet	6.6, 10.8	(1)
(c)	7.25-8.55	C ₃ +NH ₂	complex		(4)

D₂O exchange removes half the complex (C), leaving
a complex, $\tau = 7.5-8.2$, which integrates for 2 protons.

35. Veratraldehyde : CDCl₃

(a)	0.13	CHO	singlet		(1)
(b)	2.2-3.3	aromatic	complex		(3)
(c)	6.03, 6.05	2 OCH ₃	2 sing- lets		(6)

36. Veratric acid : dimethyl sulphoxide

(a)	-1.0	COOH	broad singlet		(1)
(b)	2.1-3.2	aromatic	complex		(3)
(c)	6.06, 6.09	2 OCH ₃	joint singlet		(6)

	<u>T (p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings (c/s):</u>	<u>Inte- gration:</u>
37.	<u>m-Meconine</u> : CDCl_3				
(a)	2.73	C_2 or C_5	singlet		(1)
(b)	3.04	C_5 or C_2	singlet		(1)
(c)	4.77	$\text{Ar}.\text{CH}_2.\text{O}$	singlet		(2)
(d)	6.00, 6.05	2 OCH_3	2 sing- lets		(6)
38.	<u>Phloracetophenone</u> : CH_3CN				
(a)	2.1-4.0	3 OH	very broad hump		(3)
(b)	4.1	C_3+C_5	singlet		(2)
(c)	7.4	$\text{CO}.\text{CH}_3$	singlet		(3)
39.	<u>Phloracetophenone-4-methyl ether</u> : CH_3CN				
(a)	4.05	C_3+C_5	singlet		(2)
(b)	6.18	OCH_3	singlet		(3)
40.	<u>Phloracetophenone-4:6-dimethyl ether</u> : CDCl_3				
(a)	3.92, 3.96	C_5 or C_3	doublet	2.4	(1)
(b)	4.06, 4.10	C_3 or C_5	doublet	2.4	(1)
(c)	6.14, 6.18	2 OCH_3	2 sing- lets		(6)
(d)	7.39	$\text{CO}.\text{CH}_3$	singlet		(3)
41.	<u>β-Resorcyal aldehyde</u> : CH_3CN				
(a)	0.29	CHO	singlet		(1)

	<u>T (p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings (c/s):</u>	<u>Inte- gration:</u>
(b)	2.40, 2.54	C ₆	doublet	8.4	(1)
(c)	3.38-3.57	C ₅	quartet	9.0, 2.4	(1)
(d)	3.63, 3.67	C ₃	doublet	2.4	(1)
42.	<u>β-Resorcyll aldehyde-4-methyl ether</u> : CDCl ₃				
(a)	-1.50	CHO	singlet		(1)
(b)	0.28	OH	singlet		(1)
(c)	2.49, 2.62	C ₆	doublet	7.8	(1)
(d)	3.35-3.54	C ₅	quartet	9.0, 2.4	(1)
(e)	3.54-3.58	C ₃	doublet	2.4	(1)
(f)	6.15	OCH ₃	singlet		(3)
43.	<u>2-Benzoyloxyanisaldehyde</u> : CDCl ₃				
(a)	-0.1	CHO	singlet		(1)
(b)	1.6-3.15	aromatic complex			(8)
(c)	6.10	OCH ₃	singlet		(3)
44.	<u>Ethyl coumarilate</u> : CDCl ₃				
(a)	2.2-3.0	aromatic complex			(5)
(b)	5.25-5.80	O.CH ₂	complex		(2)
(c)	8.40-8.90	C.CH ₃	triplet	6.6	(3)
45.	<u>2-Di-(p-methoxyphenyl)-hydroxymethylbenzofuran</u> : CDCl ₃				
(a)	2.4-3.4	aromatic complex			(12)

	<u>T(p.p.m.):</u>	<u>Assign- ment:</u>	<u>Signal:</u>	<u>Splittings (c/s):</u>	<u>Inte- gration:</u>
(b)	3.6	C ₃	singlet		(1)
(c)	6.2	OCH ₃	singlet		(6)
(d)	6.3	OH	broad singlet		(1)

D₂O exchange removes (d).

46.	<u>2-Di-(p-methoxyphenyl)-methylcoumaran</u> : CDCl ₃				
(a)	2.2-3.7	aromatic	complex		(12)
(b)	4.49	C _α	thick singlet		(1)
(c)	5.47-5.60	C ₂	diffuse quartet		(1)
(d)	6.0-6.6	C ₃	complex		(2)
(e)	6.22	2OCH ₃	singlet		(6)

Reference :

1. J.A. Pople, W.G. Schneider and H.J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill, 1959, 133.