THE CHEMISTRY OF FLAVONOIDS AND MODEL BENZYL ALCOHOLS RELATED TO FLAVANDIOLS

A THESIS

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by

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SUMMARY

Extractives from *Acacia cambagei* and *Acacia salicina* were found to contain (±)-7,8,3',4'-tetrahydroxydihydroflavonol, (±)-7,8,3',4'-tetrahydroxyflavanone, 7,8,3',4'-tetrahydroxyflavonol, and traces of melacacidin, isomelacacidin and O-ethylisomelacacidin (an artefact from isomelacacidin and ethanol). (-)-7,8,3',4'-Tetrahydroxyflavanone had been isolated earlier from the sapwood of *A. salicina*.

A 2,3-*cis*-3-methoxyflavanone has been synthesized by oxidation of the corresponding 2,3-*cis*-3,4-*cis*-3-methoxyflavan-4-ol with manganese dioxide and its configuration was established by n.m.r. measurements. Attempts to epimerize the 2,3-*cis*-3-methoxyflavanone to the *trans*-isomer were unsuccessful. Oxidation of the corresponding flavan-3,4-diol with manganese dioxide apparently gave an unstable *cis*-dihydroflavonol.

A study of the reactivity of some simple model benzyl alcohols related to flavandiols has been made. The investigation was undertaken primarily to provide an explanation for the significant difference in the reactivity of the benzylic 4-hydroxyl group in melacacidin (a flavan-2,3-*cis*-3,4-*cis*-diol) and isomelacacidin (the epimeric *cis*-*trans*-diol). A number of model benzyl alcohols of the phenylpropan-1-ol, tetralol, and tetralin-1,2-diol type has been synthesized. A correlation between the n.m.r. spectra and configuration and conformation has been made for the tetralin compounds. It was found (as expected) that there was a clear distinction between

observed values of spin-spin coupling constants for the 1,2-*cis*- and 1,2-*trans*-compounds. The Karplus equation was used to calculate approximate values for dihedral angles from observed spin-spin coupling constants and these values were used to infer the conformations of the reduced ring in the tetralin compounds. The reactivity of the simpler model benzyl alcohols towards methyl-ether formation showed that these flexible systems behave differently from the more rigid systems. These alcohols did not form methyl ethers probably because of faster reactions. Methyl-ether formation was observed, however, with 6-methoxytetralol. N.m.r. spectral analysis showed that *cis*-1,2-dihydroxy-6-methoxytetralin reacted with methanolic hydrochloric acid to give a mixture of *cis*- and *trans*-methyl ethers. This study has suggested that the more rigid systems (3-phenyltetralins) should provide better model compounds for a detailed study of the stereochemical contributions to reactivity. As the electronic contributions from the fused aromatic ring are the same in melacacidin and isomelacacidin the greater reactivity of the latter is attributed to the conformation of the benzylic hydroxyl group (quasi-axial) and the presence of a neighbouring *trans*-hydroxyl group.

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STATEMENT

The work described in this thesis incorporates no material previously submitted for a degree or diploma in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person except where due reference is made in the text.

V. Nair

ACKNOWLEDGEMENTS

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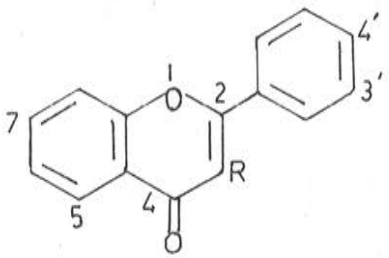
INTRODUCTION.

THE OCCURRENCE OF FLAVONOID COMPOUNDS IN NATURE.

Flavonoid compounds are extremely widely distributed in the plant kingdom. They represent a large number of types with different properties. Many of these occur naturally as glycosides.

Flavones (1, R = H) and the related flavonols (1, R = OH) form the largest family of naturally occurring oxygen heterocyclic compounds. Their importance, as plant pigments, is exceeded only by



(1)

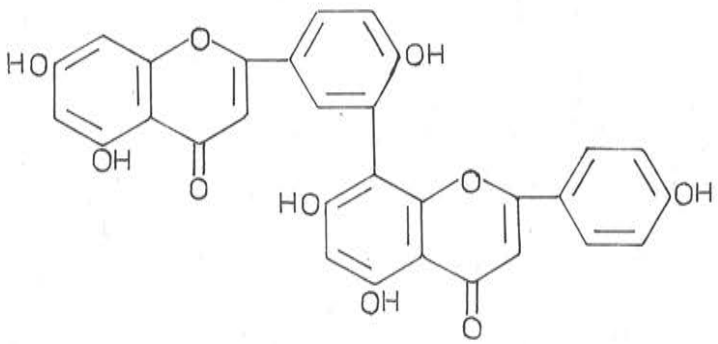
anthocyanins, chlorophyll and carotenes. Pigments related to flavones are often referred to loosely as anthoxanthidins. Most obvious as pigments in flower petals, flavones occur in all parts of plants, including the fruits, pollen, roots and heartwoods.

Although the number of naturally occurring flavones and flavonols is very large, there is little structural diversification, the main difference being in the manner in which the parent nucleus is hydroxylated or alkoxylated. It is believed that these compounds play a vital role in plant life but little is known about the specific nature of this role.[1] Numerous physiological activities have been attributed to them, but many of these have been strongly disputed.[1]

The hydroxyl (or alkoxyl) groups in flavones are found in a

large number of cases at positions 5 and 7 which implies that ring A in these cases is derived from phloroglucinol. Ring B, however, is usually found to have hydroxyl (alkoxyl) groups at the 4'-position or at both the 3'-and 4'-positions. The differences in hydroxylation (or alkoxylation) reflect a difference in the biosynthetic origin of ring A and ring B.

Flavones of the type (2) are probably derived by oxidative coupling of simple flavones.[1]



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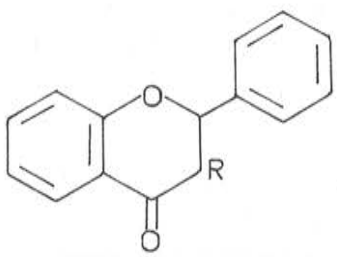
Flavanones (3, R = H) can be looked upon as the 2,3-dihydro-derivatives of flavones and it is quite common for a flavanone and its corresponding flavone to exist together in a plant.[2]



(3)

The hydroxylation patterns and other structural features in the flavanone series are much the same as those in the flavone series. It is found that on the whole flavanones do seem to be associated more closely than flavones with heartwoods, bark and roots, and less so with leaves and petals.[3]

The most significant feature in flavanone chemistry is the reversible acid or base, catalysed ring opening (4 $\rightleftharpoons$ 5) which gives the chalcone. It is thus doubtful whether a chalcone such as okanin (6) isolated from Acacia harpophylla,[7] is really a natural product or is formed during the isolation procedure from the corresponding flavanone. Most probably all naturally occurring flavanones are optically active in vivo, but during isolation, some are racemized completely whilst others suffer partial racemization.[15]

The first 3-hydroxyflavanone or dihydroflavonol (3, R = OH) to be examined was fustin by Schmid in 1886. The structure (7) of this compound was elucidated by Oyamada in 1939.[1] As acyloins, naturally occurring dihydroflavonols are very easily oxidized to the corresponding enols, the flavonols.[4] As with flavanones, all the naturally occurring dihydroflavonols are optically active. With one exception ((-)fustin) the optically active dihydroflavonols isolated from natural sources are dextrorotatory in most solvents.[16]

The third group of flavonoid compounds that is of interest in the present work is the leucoanthocyanidins. The flavan-3,4-diol nucleus (8) is the basis of many naturally occurring leucoanthocyanidins. King and Bottomley[5] isolated melacacidin (9) as an amorphous powder

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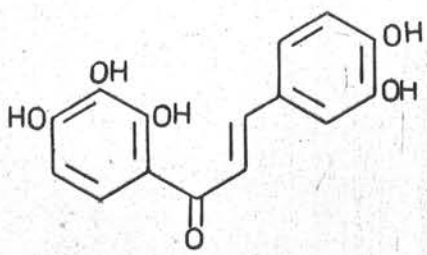

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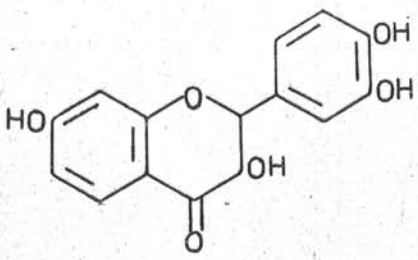
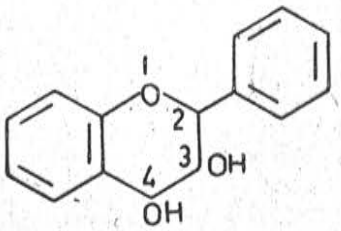


(7)

from the heartwood of Australian blackwood (Acacia melanoxylon) by extraction with ether. They showed that it had the structure (9). King and Clark-Lewis[6] later confirmed this structure by synthesis of (±)-melacacidin tetramethyl ether by catalytic reduction of the corresponding flavonol (10, R = OMe) and further supported this by proof that melacacidin yields the expected anthocyanidin 3,7,8,3',4'-pentahydroxyflavylium chloride (11). The leucoanthocyanidin has since been found in other Acacia species[7] where it occurred together with its 4-epimer, isomelacacidin. Teracacidin (12), which is closely related to melacacidin was isolated from Acacia orites,[8] together with its 4-epimer, isoteracacidin. Two other important leucoanthocyanidins which show a similar regularity in the arrangement of phenolic groups are (+)-mollisacacidin[9] (13) and (-)-mollisacacidin[10,11] (14).

Condensation products derived from compounds (13) and (14), are important in the tannin industry. Tannins have molecular weights in the range of 600 to 2000 and it appears that they are condensed polymers derived from monomeric leucoanthocyanidins of molecular weight about 300, and to a lesser extent from the corresponding catechins.[12]

The distribution and interrelationship of flavonoid compounds is important in consideration of their biogenesis. Certain classes of flavonoid compounds are found to occur together: flavonol, flavanone, 3-hydroxyflavanone, leucoanthocyanidin and catechin. The



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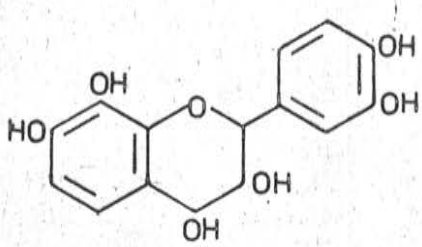

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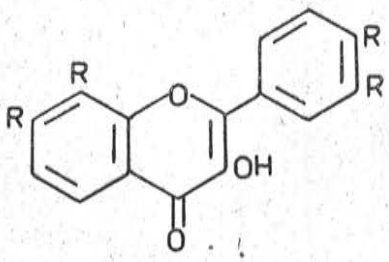

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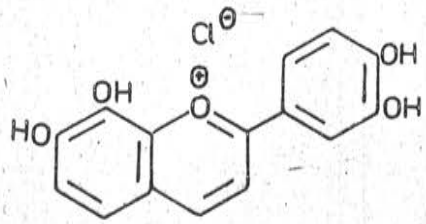

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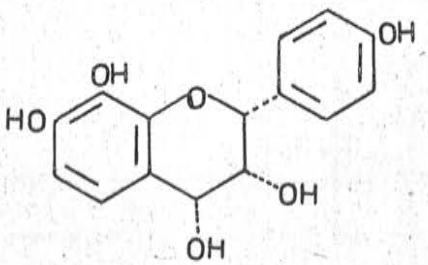

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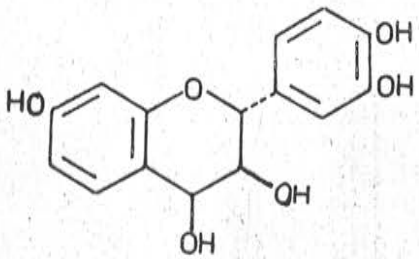

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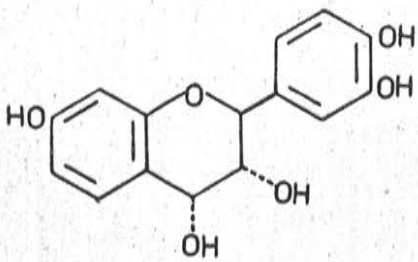
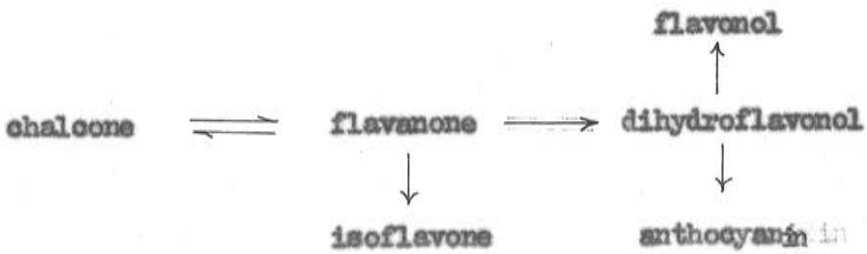


(14)

flavan ring system is thought to arise biosynthetically by the condensation of two units, A and B (Fig. 1). A is thought to arise

Fig. 1

by the folding of β-polyketones through the polyketide pathway[13] and B is thought to be derived from sugars through the shikimic acid route.[14] Grisebach and his co-workers[17] have postulated the following biosynthetic relationship between the more important flavonoids:

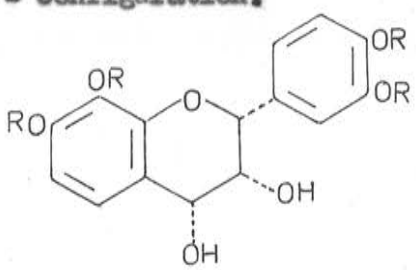


STEREOCHEMISTRY, CONFORMATION AND REACTIONS OF FLAVAN-3,4-DIOLS AND RELATED COMPOUNDS.

Stereochemistry and conformation of flavan-3,4-diols.

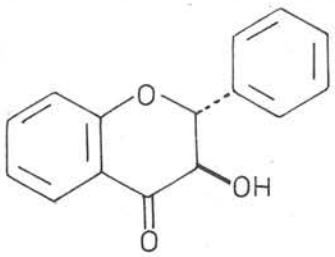
Consideration of the flavan-3,4-diol system (8) shows that there are two aspects to the problem of the stereostructure of these compounds: (i) the three centres of asymmetry (C_2, C_3 and C_4) giving rise to the possibility of four racemates, (ii) the conformation of the heterocyclic ring.

King and Clark-Lewis[6] synthesized racemic melacacidin tetramethyl ether (15, R = Me) by catalytic hydrogenation of the corresponding flavonol (10, R = OMe). On the basis of this catalytic hydrogenation of a planar molecule and the formation of cyclic derivatives[5,6] (-) and (±)-melacacidin tetramethyl ethers were assigned the 2,3-cis - 3,4-cis - configuration.



(15)

Dihydroflavonols are more easily reduced than flavonols and because of their 2,3-trans configuration[18] (16) they are useful starting materials for the preparation of 2,3-trans-flavan-3,4-diols.



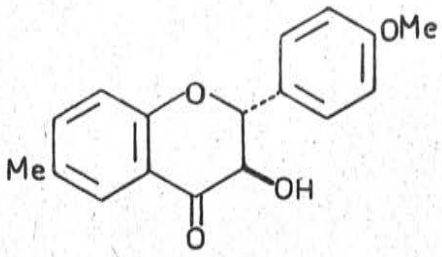
(16)

However, the 3,4-configurations of the reduction products of 2,3-trans dihydroflavonols have only recently been established.[19,20] Brown and his co-workers showed that reduction of 3-hydroxy-4'-methoxy-6-methyl-flavenone (17) with lithium aluminium hydride gave the trans-trans-diol (19) as the predominant product whereas reduction with lithium aluminium hydride - aluminium chloride mixture gave the trans - cis - diol (19).

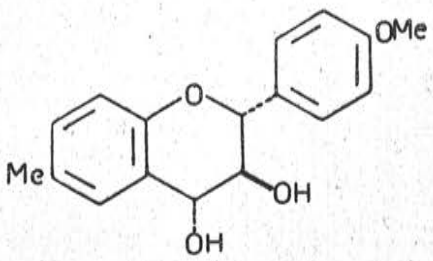
2,3-cis-Flavan-3,4-trans-diols are the least accessible of the four racemic forms of flavan-3,4-diols. The diacetate of this diol was prepared by Joshi, Kulkarni and Kashikar from the 3-bromoflavenone via the 3-bromoflavan-4-ol. Clark-Lewis and Williams[39] prepared the cis - trans - diacetate (21) from the cis-cis-diol (20) by acetylation of the latter with acetic acid, acetic anhydride and potassium acetate.

Synthesis by unequivocal methods of the racemates of flavan-3,4-diols and comparison of the products with naturally occurring compounds represents the classical approach to the determination of their geometrical configurations.

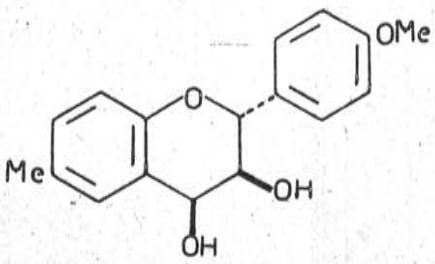
The stereochemistry of flavan-3,4-diols can be related to the flavan-3-ols by hydrogenolysis of the 4-hydroxyl group,[23,24] but the


OMe
O
Me
OH
O

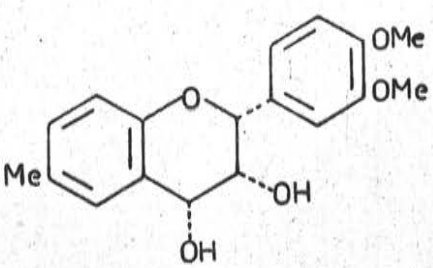
(17)


OMe
O
Me
OH
OH

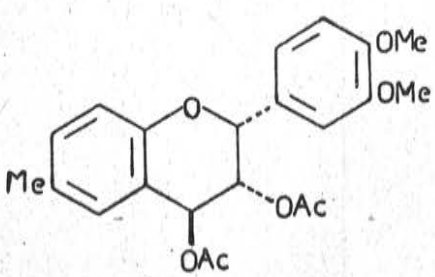
(18)


OMe
O
Me
OH
OH

(19)

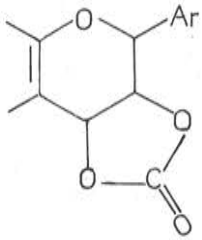

OMe
OMe
O
Me
OH
OH

(20)


OMe
OMe
O
Me
OAc
OAc

(21)

only chemical evidence for the configurations at the 3-and 4-positions relates to the formation of cyclic derivatives and to the relative rates of oxidation with lead tetraacetate.[25] The formation of cyclic carbonates (22) and isopropylidene derivatives (23) was used by several workers[5,6,23] to distinguish cis-diols from trans-diols. This



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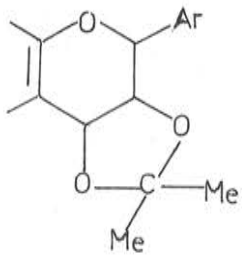


(23)

method, however, is unreliable as both 3,4-cis- and 3,4-trans-carbonates and cis-isopropylidene derivatives from both 3,4-cis- and 3,4-trans-diols have been reported.[19,25,26] The latter method has limited use as difference in rates of oxidation of 2,3-trans-3,4-cis- and 2,3-trans-3,4-trans-diols is small. Both isomers however, are oxidized at rates considerably slower than the 2,3-cis-3,4-trans-compounds.[27]

Philbin, Wheeler and their co-workers[28] used hydrogen bonding studies to assign 3,4-cis- and 3,4-trans- configuration to flavan-3,4-diols.

Nuclear magnetic resonance spectroscopy however, is the most suitable method for the determination of the relative stereochemistry of flavan-3,4-diols and related compounds. Examination of the coupling constants between the 2,3- and 3,4-protons defines the configuration.[25,29,30] A 2,3-cis-configuration is associated with low spin-

spin coupling constants but much larger coupling constants are observed for 2,3-trans-compounds. There is similarly a clear distinction in the spin-spin coupling constants of the 3,4-protons.[29] Coupling constant data can also be used to give an approximate idea of the dihedral angles (from the Karplus equation[31]) and hence the conformation of the heterocyclic ring. Nuclear magnetic resonance data indicate that the preferred conformation of the heterocyclic ring in flavan systems is a half-chair.[29]

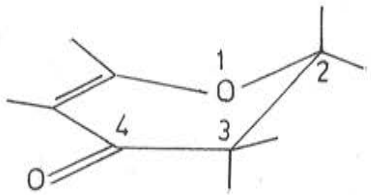
Stereochemistry and conformation of 3-substituted Flavanones.

The stereochemistry of 3-hydroxyflavanones (dihydroflavonols) can be related to that of the flavan-3-ols by hydrogenation[32] and the naturally occurring dihydroflavonols, together with those synthesized by the cyclization of suitable precursors, are the thermodynamically more stable trans-isomers. The cis-isomers in this series have not been fully characterized.[18,33,34,38]

The value of the 2,3-coupling constant for the trans-compounds lies close to the upper limit observed[35] for the interaction of 1,2-diaxial protons. The 2(ax)H,3(ax)H-trans-structure of naturally occurring dihydroflavonols and of the appropriate synthetic members is in accordance with their chemical properties.[18,32] They are dehydrated, but only with great difficulty. This is because the 2-hydrogen atom and the 3-hydroxyl group do not possess a trans anti-parallel arrangement. The 2- and 3-hydrogens are readily removed by various mild oxidative processes.

The geometry postulated by Philbin and Wheeler[36] (24) for 3-substituted flavanones gives a value for the dihedral angle of

2,3-diaxial substituents close to 180°. The carbonyl group is co-planar with the aromatic ring A. Clark-Lewis, Jackman and Spotswood[30]



(24)

noted that the co-planarity of the carbonyl group with ring A is supported by the observation that the 2,3-coupling constants in flavanones are not altered by the presence of a 5-hydroxyl substituent, even though a hydroxyl group in this position enters into very strong hydrogen bonding which necessitates co-planarity of the carbonyl group with ring A. (τ value for 5-hydroxylic proton is -2.93).

The n.m.r. data for trans-3-bromoflavanones[30,37] show a lower coupling constant ($J_{2,3}$ 8.5 c/s) which implies considerable distortion of conformation (24). For cis-3-bromoflavanones[37] $J_{2,3}$ is 1.8 c/s and this is accommodated by conformation (24) with little distortion.

Stereochemistry and conformation of 1,2,3,4-tetrahydronaphthalene-1,2-diols.

Kuhn[40] has suggested that consideration of the infrared stretching frequencies for the OH....O and OH....π hydrogen-bonded

species as well as for the free hydroxyl functions permits discussion of the stereochemistry of tetralin-diols (Table 1).

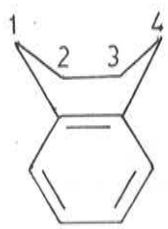
Table 1.

Hydroxyl stretching frequencies of cyclic glycols and arylalkyl alcohols in carbon tetrachloride (cm^{-1}).

Compound	Free	OH....π	OH....O
Benzyl alcohol	3632	3615	
β-Phenylethanol	3631	3604	
cis-cyclohexane-1,2-diol	3626		3587
trans-cyclohexane-1,2-diol	3634		3602
cis-tetrahydronaphthalene-1,2-diol		3618	3575
trans-tetrahydronaphthalene-1,2-diol		3615	3582

The higher frequency is attributed to free hydroxyl groups and the lower to bonded hydroxyl groups. Kuhn[40] suggested that the separation between these two bands ($\Delta\nu$) is a measure of the proximity of the two hydroxyl groups. The closer the hydroxyl groups are to each other, the stronger will be the hydrogen bond and the greater will be $\Delta\nu$. The tetrahydronaphthalene diols then, reveal a greater strength of the hydrogen bond in the cis than in the trans-diol. The reduced ring in tetrahydronaphthalene is suggested[40] as being either in a boat form (25) or a semi-puckered form (26). The

values for $\Delta\nu$, according to Kuhn,[40] suggest that the cis-compound



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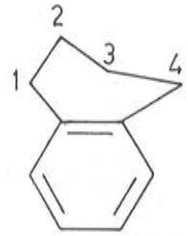


(26)

is in the semi-puckered form with the hydroxyl groups in positions 3 and 4 and that the trans-compound is either in the boat form or in the semi-puckered form with the hydroxyl groups in positions 1 and 2.

There is, surprisingly, very little in the literature about the conformation of tetralols and tetralin diols. No report on the correlation of n.m.r. spectral data and configuration and conformation has been made. In this work n.m.r. spectral data for some simple tetralin derivatives are presented together with some ideas on the stereochemistry and conformation of these compounds. Analogies with the flavan system[30] and tetrahydroquinoline[41] are made. However, the stereochemistry and conformation of a carbocyclic system cannot be deduced from a system with a hetero-atom in the reduced ring. A comparison is made with cyclohexane and cyclohexene[42] in connection with the rate of inversion and the conformational barrier to inversion. Brief references are made to work on the conformation of cyclohexane-1,2-diols.[43,44]

Reactions of the benzylic hydroxyl group in Flavan-3,4-diols and some simple benzyl alcohols.

Melacacidin (15, R = OH) and its 4-epimer, isomelacacidin

undergo some interesting reactions which involve the p-hydroxybenzyl alcohol system in these flavan-3,4,-diols.[49]

Crude extracts from Acacia heartwoods were shown by paper chromatography to contain melacacidin and two other monomeric leucoanthocyanidins, isomelacacidin and O-ethylisomelacacidin[7] (also described in present work). Separation of these compounds was simplified after it was discovered that O-ethylisomelacacidin was an artefact very readily formed from isomelacacidin and ethanol under acidic conditions. The ethyl ether has a higher distribution coefficient (ethyl acetate/phosphate buffer system, pH 7.0) than melacacidin and was conveniently separated in a counter-current distribution apparatus. Melacacidin and O-ethylisomelacacidin were obtained crystalline by Mortimer but isomelacacidin was obtained as an amorphous powder. The structure of isomelacacidin was inferred largely from the properties of its ethyl derivative.[7]

Some interesting observations on the reactions of the benzylic hydroxyl groups at C_4 in these flavan-3,4-diols were made:[49]

(i) Melacacidin was converted under aqueous mildly acidic conditions into isomelacacidin. The reaction involves the epimerization of a quasi-equatorial benzylic hydroxyl group to the quasi-axial conformation possibly through an oxonium ion intermediate. It appears to be an equilibrium reaction which favours isomelacacidin. (Fig. 3). A competing reaction here is condensation to give polymers. Epimerization at the 4-position has been noted with other flavan-3,4-diols[8] and with peltogynol.[45] (27, R = H.)

Djerassi and his co-workers[46] have noted a similar epimerization in the case of ring B oxygenated estrogens and postulated an oxonium ion intermediate for the reaction (Fig. 2). Methyl-ether formation was expected at the benzylic position under the conditions of the reactions but instead only an inversion at this position was noted.

(ii) Isomelacacidin formed an ethyl ether or methyl ether with retention of configuration when treated with ethanol or methanol and an acid catalyst, whereas melacacidin did not. A similar trend has been observed with teracacidin (12) and its 4-epimer isoteracacidin.[8]

MELACACIDIN ⟶ ISOMELACACIDIN

0.5N AcOH

50% conversion in 1 hr at 100°

0.1N HCl

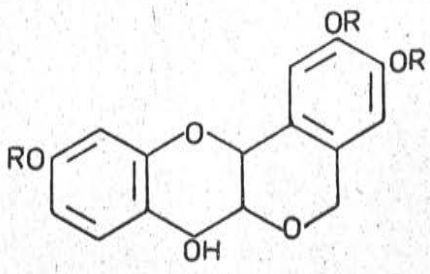
90% conversion in 10 min at 100°

ISOMELACACIDIN ⟶⟵ O-ETHYLISOMELACACIDIN

0.1N AcOH/EtOH

50% conversion to ether
in 1 hr at 100°

Fig. 3



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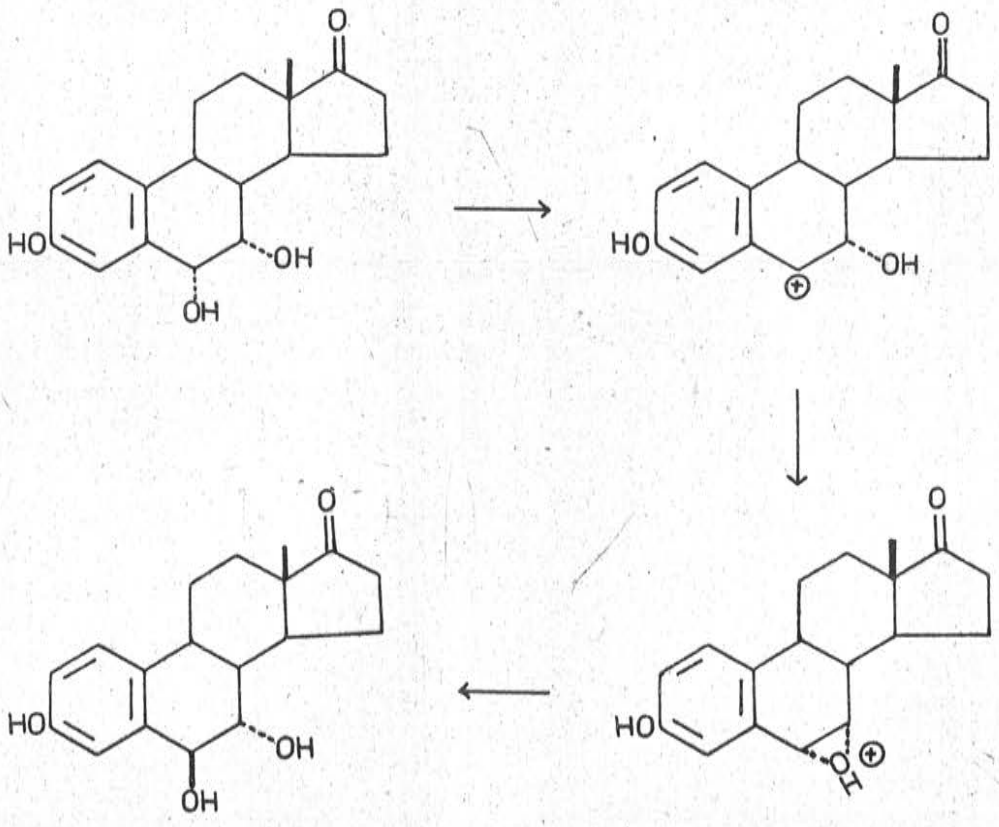
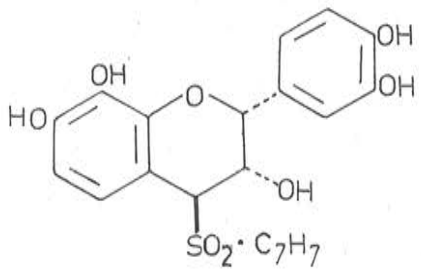


Fig. 2

(iii) Isomelacacidin reacted readily (more readily than melacacidin) with toluene-p-sulphinic acid to give the sulphone (28). Melacacidin required stronger acidic conditions for this reaction and gave the same sulphone (28) as isomelacacidin. It appears that epimerization to isomelacacidin occurs prior to reaction.

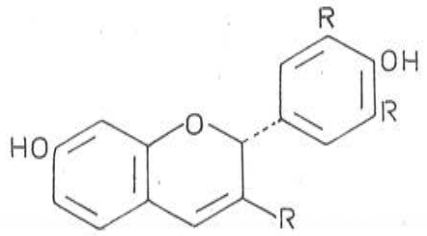


(28)

(iv) The anthocyanidin formed from O-ethylisomelacacidin by treatment with hot 3N-hydrochloric acid was indistinguishable from 3,7,8,3',4'-pentahydroxyflavylium chloride (11) similarly derived from melacacidin. The reaction is indicative of the extreme lability of the benzylic ethoxyl group.

(v) Roux and Drewes[47] studied the redness induced by light and pyrolysis in the formation of anthocyanidins from flavan-3,4-diols and flavan-4-ols. The redness is attributed to loss of the elements of water from the 3-H and 4-OH positions of these compounds resulting in formation of a flav-3-ene (29, R = H, OH), and subsequent oxidation of the 2-H to form the anthocyanidin which exists in the 7-keto form

of the anhydro-base (30, R = H, OH). The effect of light or pyrolysis is considered to be similar to the mineral acid induced conversion of flavan-3,4-diols into anthocyanidins.



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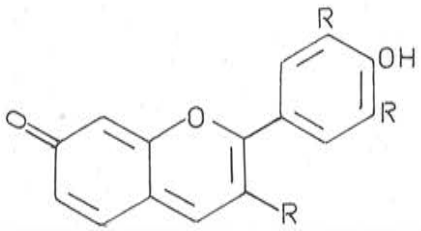

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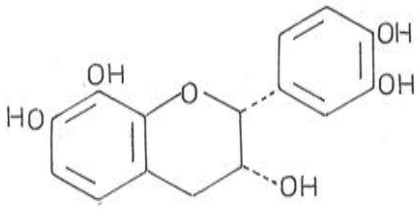
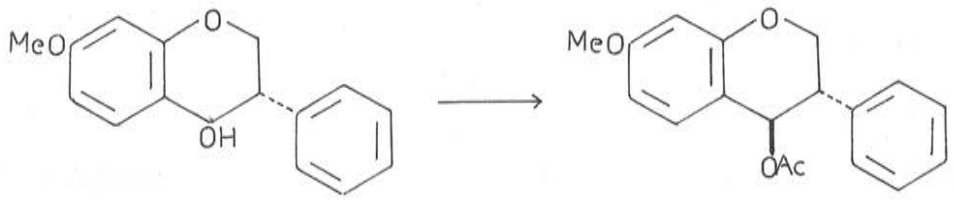
(vi) The benzylic hydroxyl group in melacacidin and isomelacacidin underwent hydrogenolysis to give the corresponding cis-flavan-3-ol (31).



(31)

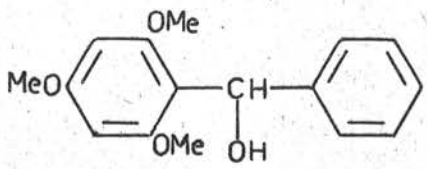
(vii) Some recent work by Inoue[48] on the reactions of 7-methoxyisoflavan-4-ols (32) is of interest here as the 4-hydroxyl group is part of an active benzyl alcohol system. Reaction of 7-methoxyisoflavan-4β-ol (cis) and 4α-ol (trans) with acetic acid at 50° gave in both cases 4α-acetoxy-7-methoxyisoflavan (33). With the unsubstituted isoflavan-4-ol however, unchanged starting material was obtained. Inoue suggested that because of its quasi-equatorial conformation and trans-configuration, the 4α-ol is more stable than the 4β-ol and that reactions which proceed through the planar sp^2 hybridized form of C_4 (carbonium ion) give the 4α- or trans-product.



(32) (33)

All the reactions discussed above involve the 4-position where the hydroxyl group is part of an activated benzyl alcohol system. The reactions of benzyl alcohols in general are therefore relevant to this work and some important aspects of them are reviewed at this stage.

Kenyon and his co-workers[49-52] studied the reactions of reactive benzyl alcohols and suggested that these compounds react readily by unimolecular alkyl-oxygen fission. Dismutation reactions, bis-ether formation and ethyl ether formation were observed under appropriate conditions.[49a] They found[50] that 2,4,6-trimethoxydiphenylmethanol (34) acted as a powerful aralkylating agent towards a variety of compounds. When (34) was allowed to stand at room temperature for several days in ethanol containing 1.5% sulphuric acid, 2,4,6,2',4',6'-hexamethoxytriphenylmethane (35) and benzaldehyde were obtained. It was observed[51,52] that the unimolecular heterolysis was facilitated by the presence of electron releasing substituents. Thus, 2,4-dimethoxydiphenylmethanol (36) and 1-(2,4-dimethoxyphenyl)ethanol (37) reacted with a facility between those of the corresponding 2- or 4-monomethoxy- and 2,4,6-trimethoxy- compounds, and 4-methyldiphenylmethanol (38) and 2,4,6-trimethyldiphenylmethanol (39) reacted less



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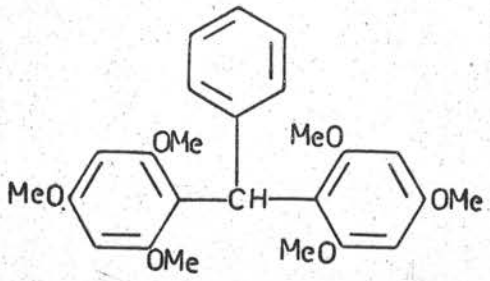

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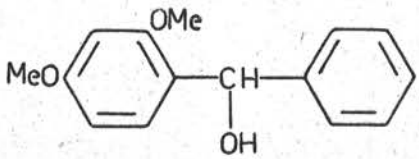

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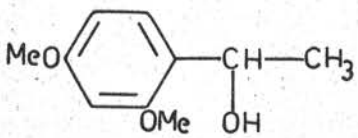

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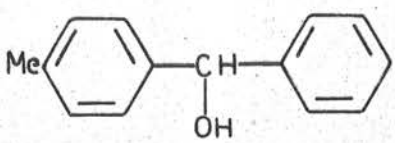

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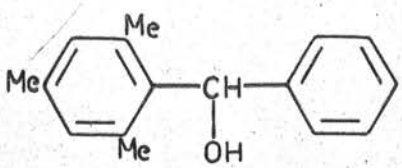
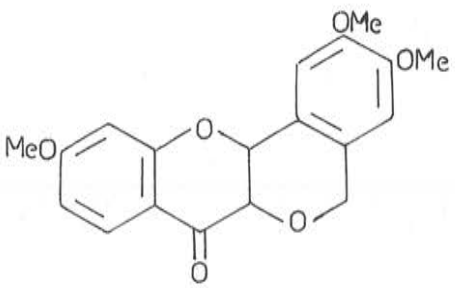


(39)

readily than the analogous methoxy-substituted compounds.

Numerous other reactions of benzyl alcohols, for example, hydrogenolysis with chloroaluminium hydrides,[53] condensation with phenols,[54] reaction with sulphinic acid,[55] and reaction with thiosulphate[56] have been studied but are not of direct interest to the present work and are not discussed.

Manganese dioxide has been used extensively for the oxidation of allylic and benzylic alcohols to aldehydes and ketones.[57-60] Hassal and his co-workers[45] oxidized tri-O-methylpeltogynol (27, R = Me) to tri-O-methylpeltogynone (40) with manganese dioxide in chloroform. Manganese dioxide has been employed for oxidizing



(40)

selectively only one of the hydroxyl groups in diols.[61] Whether the oxidation of benzyl alcohols with manganese dioxide proceeds *via* free radical intermediates[60] or *via* carbonium ions[57] remains obscure.[62]

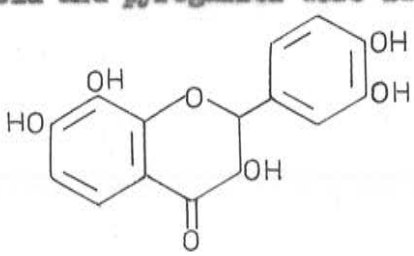
DISCUSSION

FLAVONOID COMPOUNDS FROM NATURAL SOURCES.

Extractives from Acacia cambagei.

Extractives from the heartwood of A. cambagei contained a considerable proportion of intractable phenolic material, apparently polymeric in nature.

7,8,3',4'-Tetrahydroxyflavonol (10, R = OH) was isolated from the ether extractive and further flavonol was obtained from the cold ethanol percolate. The structure of the flavonol was established by degradation with potassium hydroxide, by acetylation which gave the penta-acetate (10, R = OAc) and by methylation which gave penta-methoxyflavone (10, R = OMe). In the micro-degradation both 3,4-dihydroxybenzoic acid and pyrogallol were identified.



(41)

The ether extractive was found to contain 7,8,3',4'-tetra-hydroxydihydroflavonol (41), chromatographically identical with the racemic dihydroflavonol from A. excelsa.[7] The structure of the dihydroflavonol from A. cambagei and A. excelsa was established by methylation with methyl iodide-acetone-potassium carbonate, with dimethyl sulphate-acetone-potassium carbonate or with diazomethane which gave 3,7,8,3',4'-pentamethoxyflavone (10, R = OMe) identical

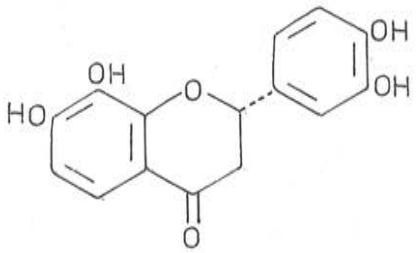
with a sample prepared from 7,8,3',4'-tetramethoxyflavonol. Dehydrogenation of the dihydroflavonol therefore occurs very easily. Row and Sastry[63] reported the occurrence of this dihydroflavonol in the heartwood of Albizzia odoratissima. For reasons which shall be presented below it is believed that the presence of the dihydroflavonol in this Albizzia wood has not been established.

The cold ethanol percolate contained a small proportion of monomeric leucoanthocyanidin which was also present in the acetone extractive, and was identified as melacacidin (15, R = H) by paper chromatographic examination and ultraviolet light absorption spectra of the leucoanthocyanidin and the derived anthocyanidin (11). Using an authentic sample of 3,7,8,3',4'-pentahydroxyflavylium chloride[7] a spectroscopic estimation of the yield of the anthocyanidin derived from the crude natural leucoanthocyanidin was made (Found: 34.9%). Confirmation of the identification of melacacidin by preparation of derivatives could not be achieved owing to difficulties encountered in separating the crude monomer from accompanying polymer.

The cold ethanol percolate of the heartwood was shown by paper chromatography to contain two other monomeric leucoanthocyanidins, isomelacacidin and O-ethylisomelacacidin. O-ethylisomelacacidin, an artefact very readily formed from isomelacacidin and the ethanol used in the extraction procedure,[7] was easily separated from melacacidin by counter-current procedures because of its enhanced distribution ratio in the ethyl acetate/phosphate buffer system. As in the case of melacacidin, the crude monomer could not be separated from the

accompanying polymer.

The sapwood contained a much smaller proportion of the flavenol and dihydroflavenol, and also yielded a small quantity of racemic 7,8,3',4'-tetrahydroxyflavanone (42). The structure of the flavanone was established by degradation with potassium hydroxide and by methylation which gave 7,8,3',4'-tetramethoxyflavanone. The compound gave



(42)

a blue-purple colour when submitted to the Horowitz test for flavanones.[64,65] The flavanone underwent a base catalysed ring opening to the corresponding chalcone as was evidenced by observation of its ultraviolet spectrum which showed a bathochromic shift of 40 mμ in the absorption maximum of the long-wave band on addition of base.

The bark of A. cambagei did not contain any easily isolable flavonoids. A light-sensitive aliphatic ester was found in the extractive.

Extractives from Acacia salicina.

Acacia salicina was found to contain 7,8,3',4'-tetrahydroxyflavenol (10, R = OH) and (±)-7,8,3',4'-tetrahydroxydihydroflavonol (41). A. Salicina was also found to contain (-)-7,8,3',4'-tetra-

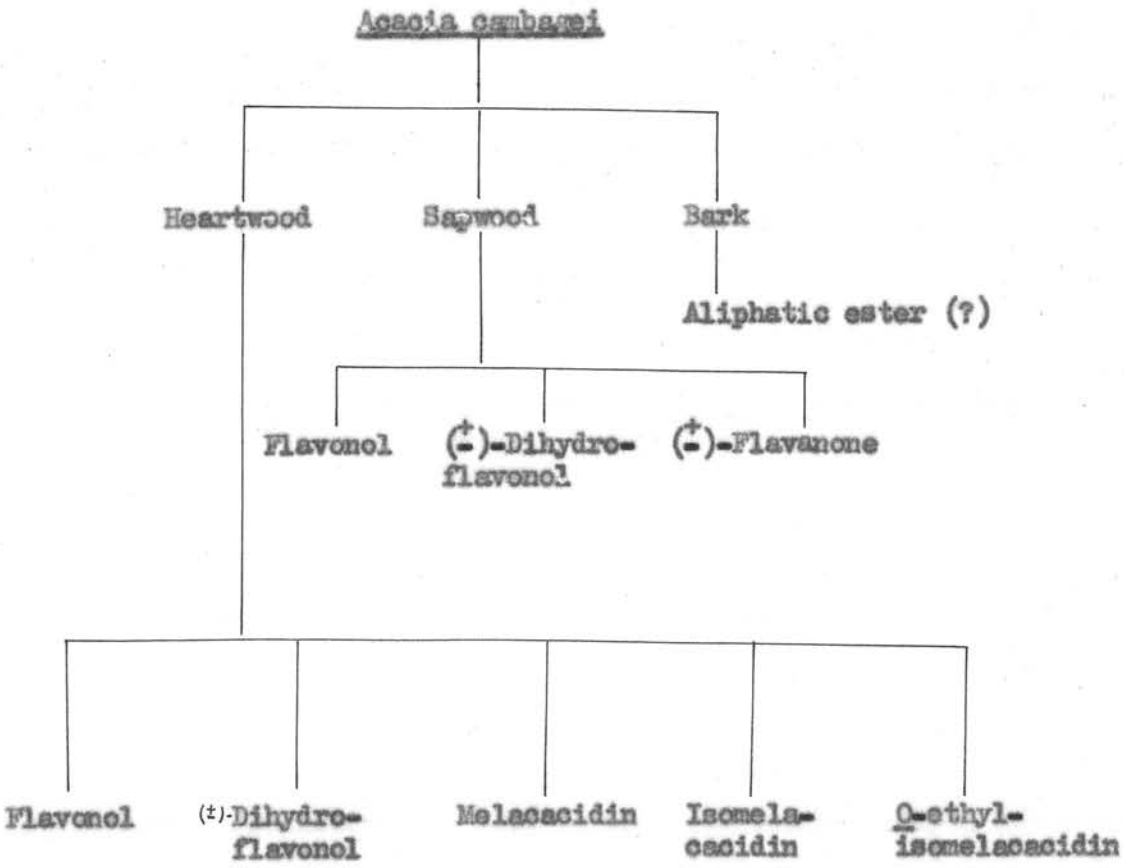

Acacia cambagei
Heartwood
Sapwood
Bark
Aliphatic ester (?)
Flavonol
(±)-Dihydro-flavonol
(±)-Flavanone
Flavonol
(±)-Dihydro-flavonol
Melacacidin
Isomela-cacidin
O-ethyl-isomelacacidin

Fig. 4

hydroxyflavanone (42) and the corresponding chalcone (okanin).[2] A small quantity of racemic flavanone was also isolated. The bark of the wood sample contained a cinnamic acid, possibly caffeic acid.

The flavonol and dihydroflavonol were very conveniently separated by chromatography over cellulose powder using chloroform-ethanol-water as the eluting solvent.

(-)-7,8,3',4'-Tetrahydroflavanone has not been previously isolated. Its laevorotation indicates that it possesses the 2S-configuration[66] (42) like other optically active flavanones obtained from natural sources. Methylation was accompanied by racemization as the resulting 7,8,3',4'-tetramethoxyflavanone was indistinguishable from a synthetic sample.[2,6]

The existence of optically active and racemic flavanone in a single species further supports previous observations[67] that optically active flavanones are readily racemized to (±)-flavanones by the action of acid, alkali or by thermal means. This ready racemization is ascribed to the ease of the chalcone-flavanone interconversion. The presence of racemic flavanone in Acacia species, and particularly the occurrence of the laevorotatory form in A. salicina, supports the suggestion[7] that okanin (6) obtained from A. harpophylla was in fact formed from this flavanone during isolation and it is probable therefore that 7,8,3',4'-tetrahydroxyflavanone is a constituent of A. harpophylla heartwood.

Most probably the racemic 7,8,3',4'-tetrahydroxydihydroflavonol (41) isolated from A. salicina and A. cambagei was optically active

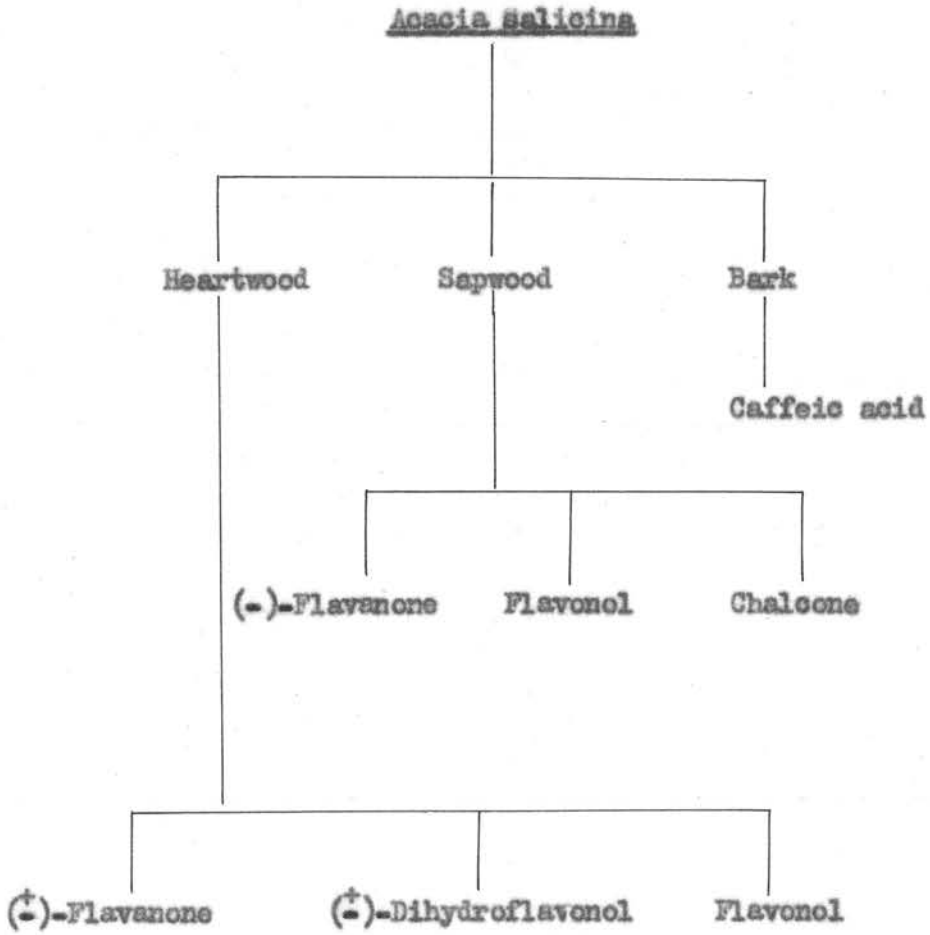
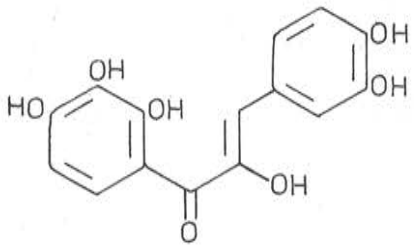

Acacia salicina
Heartwood
Sapwood
Bark
Caffeic acid
(-)-Flavanone
Flavonol
Chalcone
(±)-Flavanone
(±)-Dihydroflavonol
Flavonol

Fig. 5

in vivo but suffered racemization during the extraction procedure presumably by way of a chalcone-type intermediate (43).



(43)

The reported occurrence of 7,8,3',4'-tetrahydroxydihydroflavonol in Albizzia odoratissima[63] rests not on isolation of the compound but on methylation of a brown gum, which was said to give (+)-3,7,8,3',4'-pentamethoxyflavanone. Methylation of a dihydroflavonol to a 3-methoxyflavanone is without precedent. When dehydrogenation occurs though, methylation leads to a 3-methoxyflavone as discussed above in connection with the structure of 7,8,3',4'-tetrahydroxydihydroflavonol and also discussed later (page 41) in connection with the attempted synthesis of trans-3-methoxyflavanone. The m.p., wavelengths of ultraviolet light absorption maxima, and carbonyl stretching frequency of the methylation product reported as "(+)-3,7,8,3',4'-pentamethoxyflavanone" are consistent with its being 3,7,8,3',4'-pentamethoxyflavone (refer Table 2). On this basis then, the recorded rotation is evidently erroneous. Other puzzling features of the "dihydroflavonol" chemistry are also explicable if the methylation product is the pentamethoxyflavone. Thus partial demethylation of the pentamethoxyflavone with

with aluminium chloride is unexceptional and would account for the phenolic material, m.p. 140-142°, reconverted into the pentamethoxyflavone by diazomethane. Demethylation of the pentamethoxyflavone with hydrogen iodide could lead to the tetrahydroxyflavonol monohydrate, consistent with the analytical data, and again converted by diazomethane into the pentamethoxyflavone. It is clear also from the recorded data that the synthetic "pentamethoxyflavanone" had suffered dehydrogenation and is likewise the pentamethoxyflavone. The results obtained by Row and Sastry[63] are therefore consistent with the presence in the brown gum of either 7,8,3',4'-tetrahydroxyflavonol or -dihydroflavonol (or both) but do not distinguish between these possibilities.

Table 2.

Physical data on 3,7,8,3',4'-pentamethoxy- flavone and -flavanone.

Compound	m.p.	Ultraviolet light absorption λ_{max} (mμ)	Infrared absorption of carbonyl group λ_{max} (cm^{-1})
3-Methoxyflavone	153°	250,347	1625
cis-3-Methoxyflavanone (synthetic)	110°	288	1665
3-Methoxyflavanone (Row and Sastry)	146-148°	248,346	1623

Simple procedures frequently suffice for the isolation of pure

compounds from sapwoods and heartwoods,[5,6] but with Acacia gambacei and Acacia salicina the extractives were complex and only small quantities of pure compounds were isolated after preliminary extraction with different solvents, followed by counter-current distribution, and then preparative paper chromatography.

The co-occurrence of flavonoid compounds with the same hydroxylation pattern, and a simple chemical interrelationship lends further support to current views on their biosynthesis.[1,13,14]

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SYNTHESIS, STEREOCHEMISTRY AND CONFORMATION OF (±) 2,3-cis-3-SUBSTITUTED FLAVANONES.

It has been shown both by chemical and physical methods that naturally occurring dihydroflavonols and those synthesized by chemical reduction of flavonols and by ring closure of suitable precursors have the 2,3-trans-configuration.[30,32,67] These compounds are the thermodynamically more stable isomers.[32] The cis-isomers in this series have not been fully characterized.[18,33,34]

In the present work a convenient synthesis of a 2,3-cis-3-methoxyflavanone is described. A possible route to the synthesis of a 2,3,-cis-3-hydroxyflavanone is discussed.

2,3-cis-3,7,8,3',4'-Pentamethoxyflavanone (46).

3,7,8,3',4'-Pentamethoxyflavone (44) was conveniently prepared by cyclization[5] of 2'-hydroxy-3,4,3',4'-tetramethoxychalcone and methylation of the resulting flavonol.

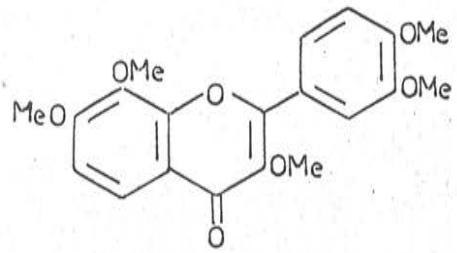
Hydrogenation of flavonols at high temperatures and pressures represents the only suitable method for the preparation of 2,3-cis-flavan-3,4,-cis-diols. The catalyst used for this hydrogenation is Raney nickel. There are, however, many complications involved in the use of this catalyst.[68] Low yields of the cis-cis-diols are usually obtained and undesirable side reactions such as hydrogenolysis of the benzylic hydroxyl group play an important role.[69] Very little is known about the mechanism of this hydrogenation of a planar molecule. A catalyst described as nickel boride[70] was found to be

excellent for the reduction of the flavone (44) to the cis-cis-diol derivative (45). A much higher yield (69% as compared to 16% with Raney nickel) was obtained and a shorter reaction time (12 hr as compared to 22 hr with Raney nickel) was required. Another advantage is the small amounts of catalyst required for this reduction. The catalyst appears to work well with other flavones and flavonols[71] and could be used for αβ-unsaturated ketones in flavonoids of most types.

The 3-methoxyflavan-4-ol (45) from the above hydrogenation was found to be dimorphic. Examples of dimorphism have been reported in other flavan compounds.[20,72]

The n.m.r. spectrum of the diol derivative (Table 3) was analysed by a first order procedure and established the configuration of the 3-methoxyflavan-4-ol (45) as 2,3-cis-3,4-cis. The resonance of the 3-proton appeared as a quartet with spin-spin coupling constants $J_{2,3}$ 0.9 c/s and $J_{3,4}$ 4.5 c/s. The signal of the 4-proton was a doublet with $J_{3,4}$ 4.4. c/s. The signal of the 2-proton was unresolved and appeared as a single peak.

The hydroxyl group at C_4 in the flavan-4-ol (45) is part of a benzyl alcohol system and should undergo oxidation readily with manganese dioxide, a specific reagent for the oxidation of allylic and benzylic alcohols. The oxidation of tri-O-methylpeltogynol with this reagent has already been discussed in the introduction. Bloch[73] used X-ray crystallography to study the various forms of manganese dioxide and suggested that only the α and γ forms of manganese dioxide



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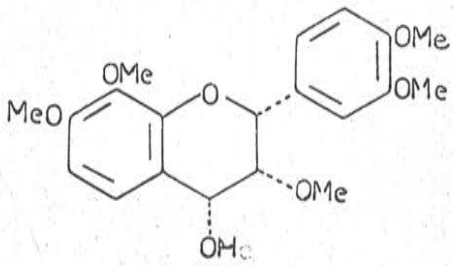

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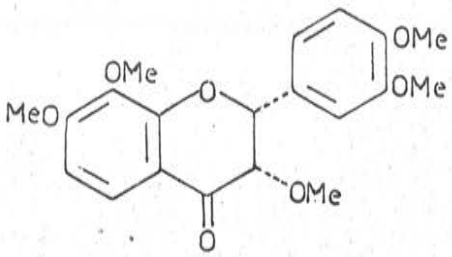


(46)

are "active" enough for the oxidation of allylic and benzylic alcohols. For the purposes of the present work "active" manganese dioxide was prepared by the method of Attenburrow and his co-workers.[59]

The mechanism of this oxidation reaction is not fully understood. Evans[57] suggested that carbonium ions probably play an important role and that the compounds that are more readily oxidized are those that would be expected to form the more stable carbonium ions. The reaction is said[57] to be triphasic - absorption of substrate, oxidation, and desorption of product. Pratt and van der Castle[60] studied the oxidation of a variety of phenylcarbinols and proposed a free-radical mechanism (Fig. 6). Gritter, Dupre and Wallace[62] proposed

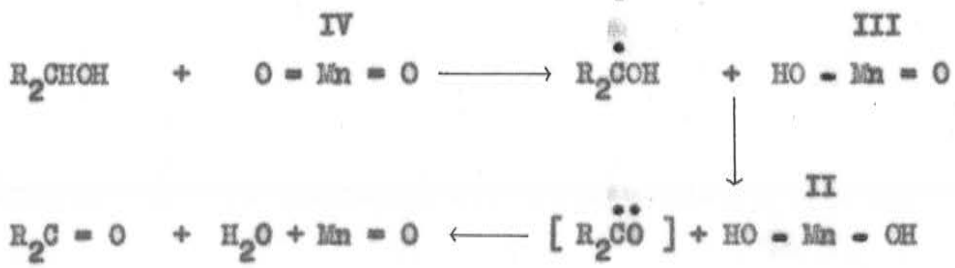


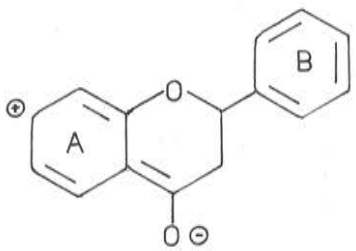
Fig. 6

a mechanism which is based on the presence of cationic impurities in manganese dioxide.

Oxidation of the 3-methoxyflavan-4-ol (45) to the 3-methoxyflavanone (46) proceeded smoothly. The reaction was followed by determining the infrared spectra of aliquots of the reaction mixture taken out as the reaction proceeded. A similar oxidation with nickel peroxide[74] gave a mixture of 3-methoxyflavanone and 3-methoxyflavone.

The n.m.r. spectrum (Table 3 and Fig. 7) established the 2,3-configuration as cis. The absorption arising from the 2- and 3- protons appeared as an AB quartet with spin-spin coupling constant $J_{2,3}$ 2.5 c/s. Because of the greater deshielding by the 2-aryl group than by the carbonyl the 2-proton resonance occurs at a lower field than that of the 3-proton.[30] If we use the conformation for 3-substituted flavanones (24) postulated by Philbin and Wheeler[36] in which the dihedral angle of the 2ax, 3eq - substituents is close to 60°, then the calculated coupling constant from the Karplus equation is 1.7 c/s. Thus the observed value of the 2,3-coupling constant in this cis-compound in which the methoxyl group is axial is accommodated by conformation (24) without appreciable distortion.

The ultraviolet light absorption spectrum (Fig. 8) showed a maximum at 288 mμ. The band is associated with absorption in the benzoyl grouping (47). The introduction of methoxyl groups into the A ring primarily increases the resonance contribution of this ring and tends to increase the wavelength and intensity of maximum absorption of the band.[79]



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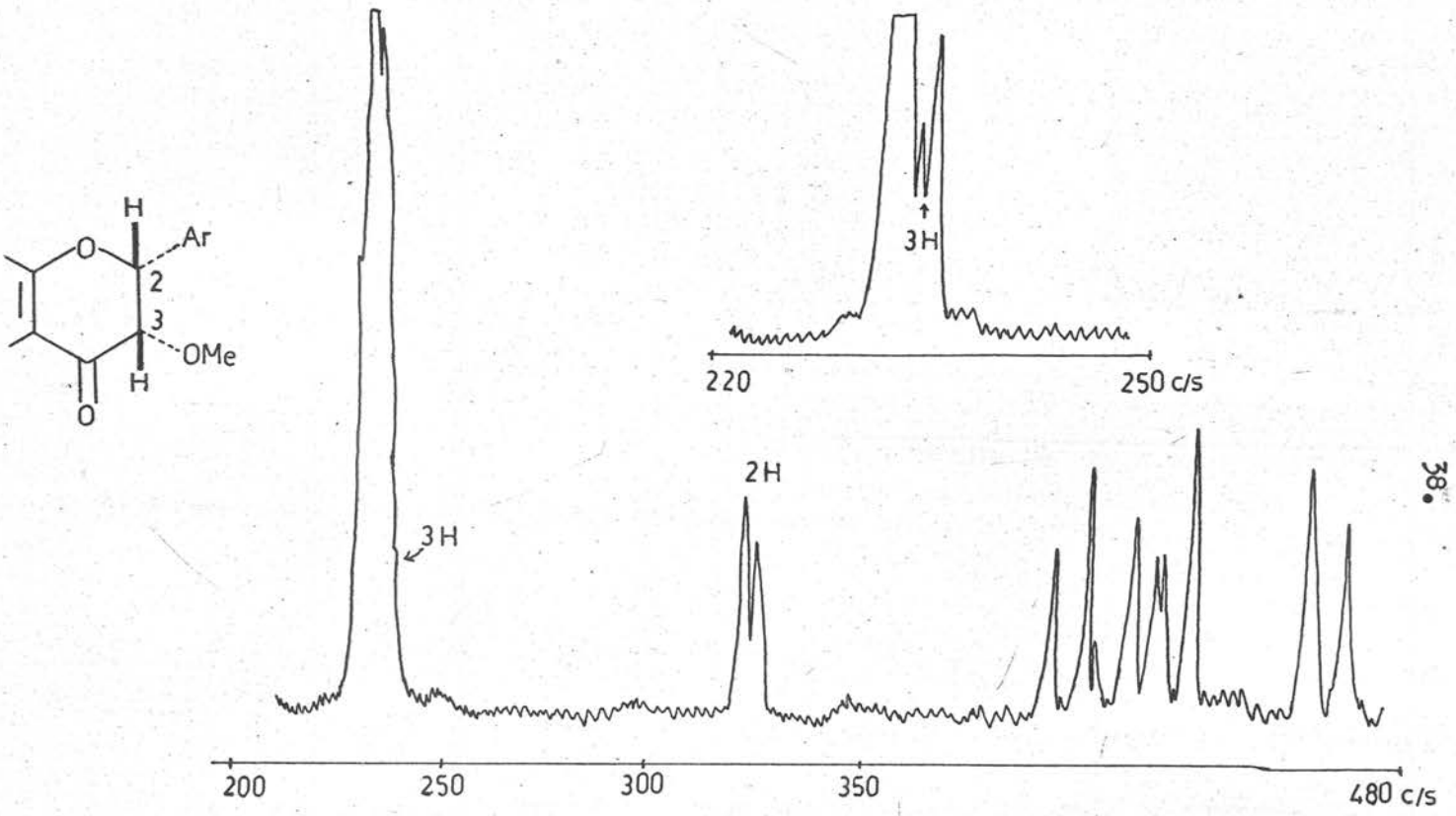


Fig. 7.

The 60 Mc/s n.m.r. spectrum of 2,3-cis-3,7,8,3',4'-pentamethoxy-flavanone in deuterochloroform.

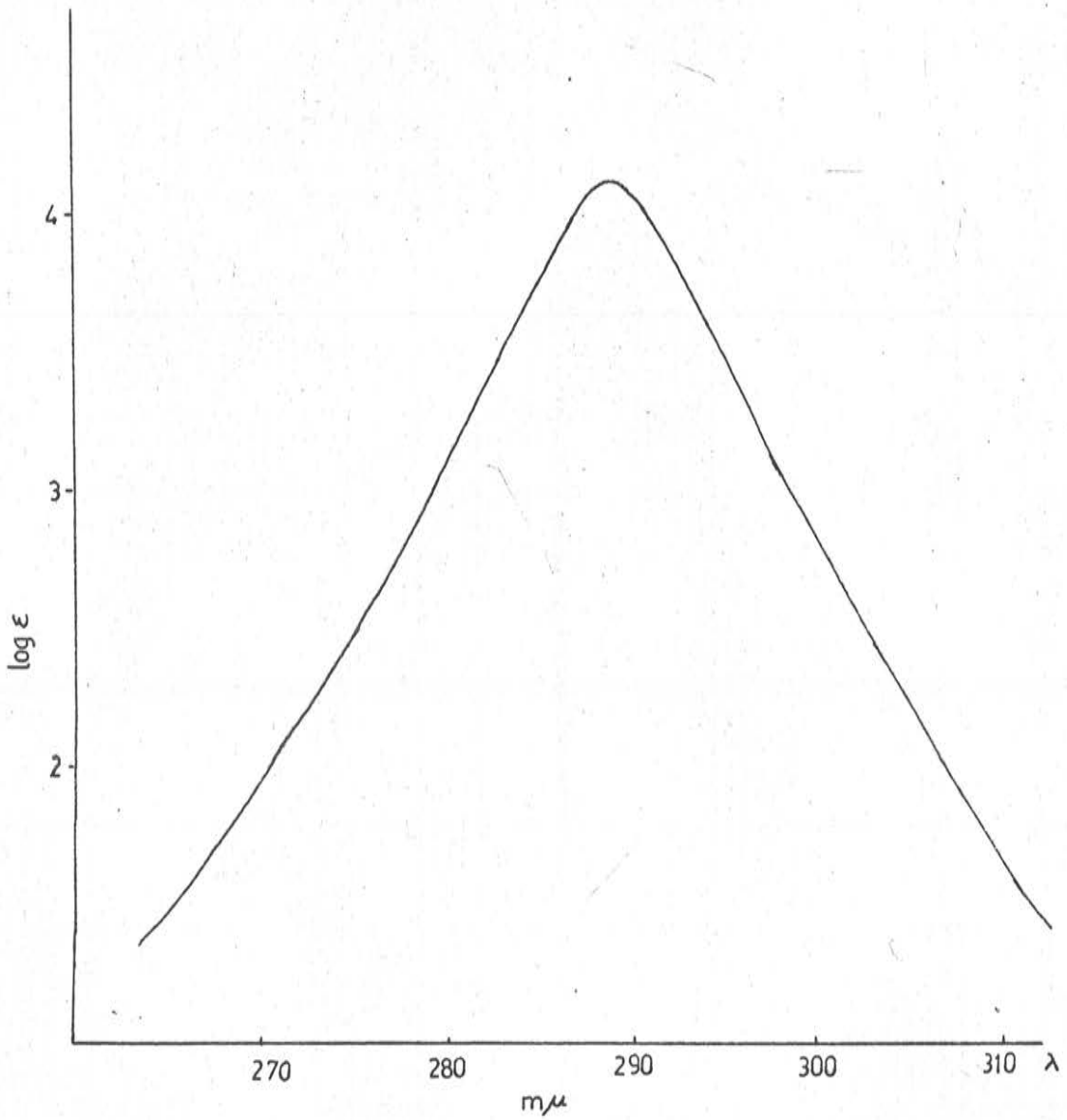


Fig. 8.

Ultraviolet absorption spectrum of 2,3-*cis*-3,7,8,3',4'-pentamethoxyflavanone in ethanol.

Catalytic hydrogenation over nickel boride and reduction with sodium borohydride in methanol of 2,3-cis-3-methoxyflavanone (45) gave in both cases, 2,3-cis-3,4-cis-3-methoxyflavan-4-ol (45). The cis-cis-product is expected with catalytic hydrogenation but the preponderance of this product in the case of reduction with sodium borohydride has to be explained.

The concepts of "steric approach control" and "product development control" were used by Dauben and his co-workers[75] to explain the reduction products of substituted cyclohexanones. Dauben's hypothesis[75] on reductions with complex hydrides was based on the assumption that solvation of the borohydride ion did occur in a solvent such as methanol. This assumption was criticized by Wheeler and Huffman[76] who claimed that the borohydride ion is not solvated. However, the findings of Eliel and Haubenstock[77] strongly suggest that borohydride is solvated in at least some of the common solvents used for reductions as this seems the most likely explanation for the variation in steric result.

The use in the reduction reaction of the flavanone of sodium borohydride and methanol does lead to stereospecificity of reduction as only one compound was isolated and in high yield. An explanation in terms of Dauben's concept of "steric approach control" appears to be preferable here to explain the all cis-product. The approach of a fairly large solvated borohydride species from the equatorial side is subject to steric interference by the neighbouring axial methoxyl group (Fig. 9). It is probable then that in the transition state the

attacking solvated borohydride species approaches from the axial side.

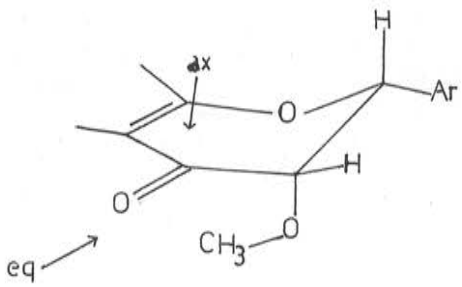
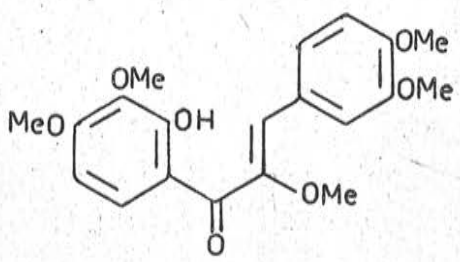


Fig. 2.

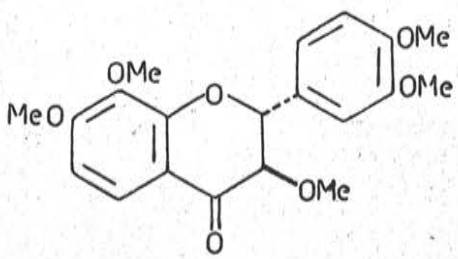
Attempts to epimerize 2,3-cis-3-methoxyflavanone (46) to the trans-isomer (49) were unsuccessful. Dehydrogenation occurred readily in most of the epimerization experiments studied, leading to the production of the 3-methoxyflavone (50).

Attempts to synthesize the trans-isomer (49) were also unsuccessful. Methylation of 2,3-trans-dihydroflavonol (58) by several methods including one used recently for the methylation of sugar hydroxyl groups[81] did not give the desired 3-methoxyflavanone (49) but the 3-methoxyflavone (50). Methylation of a dihydroflavonol to a 3-methoxyflavanone is without precedent, although, when dehydrogenation occurs, methylation leads to the 3-methoxyflavone.

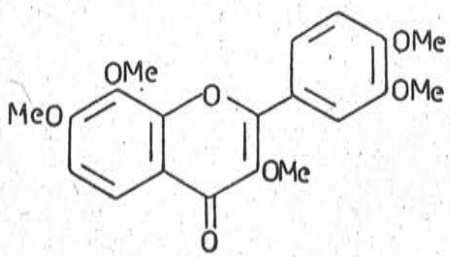
Cyclization of 2'-hydroxy-α-3,4,3',4'-pentamethoxychalcone (48) under normal Algar-Flynn-Oyamada (AFO) reaction conditions gave


OMe
OMe
MeO
OH
OMe
O

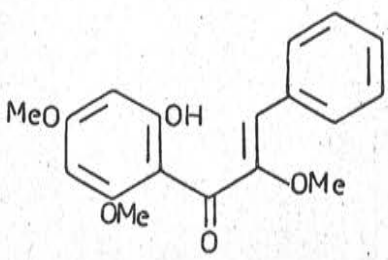
(48)


OMe
OMe
OMe
MeO
O
OMe
O

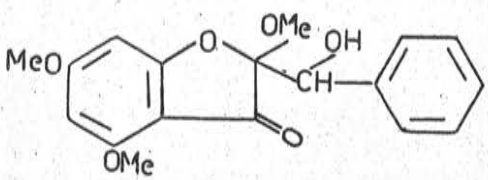
(49)


OMe
OMe
OMe
MeO
O
OMe
O

(50)


MeO
OH
OMe
OMe
O

(51)


MeO
O
OMe
OH
CH
O
OMe

(52)

a compound whose physical properties were consistent with its being 3,7,8,3',4'-pentamethoxyflavone (50). Recent work by Philbin and her co-workers[80] showed that oxidation of 2'-hydroxy-α-4',6'-trimethoxychalcone (51) under AFO conditions gave 2α-hydroxybenzyl-2,4,6-trimethoxycoumaran-3-one (52) in 80% yield. Our result can be reconciled with this if the existence of a controlling steric effect in the behaviour of 6'-methoxychalcones is accepted. The mechanism[72] of production of flavonols (56) and aurones (54) involves the production of a ketone-epoxide (53) from which a dihydroflavonol (55, route i) or a "hydrated-aurone" (54, route II) is formed. The presence of a methoxyl substituent in the 6'-position of the chalcone displaces the keto-group from the plane of the nucleus. This is said to produce steric inhibition of resonance from the 2'-O^--ion which promotes activation of the α-carbon of the chalcone.[75] A hydroxyl group in the 2- or 4- position causes resonance expulsion of the β-epoxide bond with consequent dihydroflavonol formation.[72]

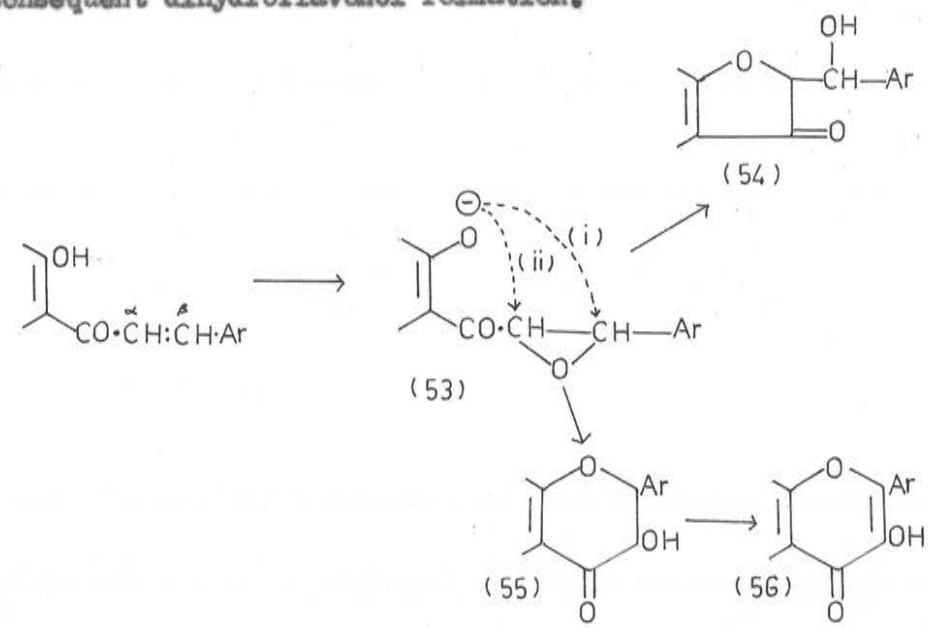


Table 3.

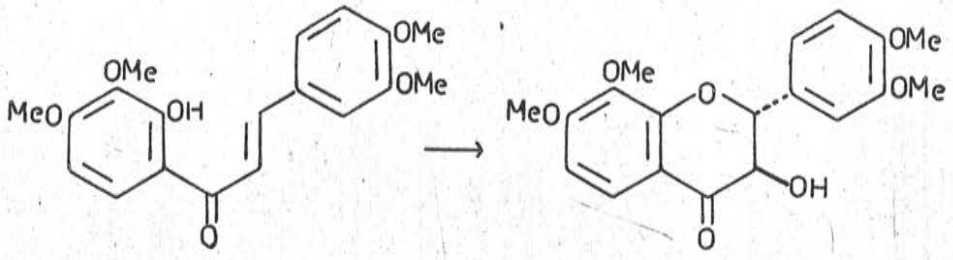
Chemical shifts and coupling constants of heterocyclic ring protons of 3-substituted and 3,4-disubstituted flavans.

No.	Compound	3 Subst.	4 Subst.	$J_{2,3}$	$J_{3,4}$	τ 2H	τ 3H	τ 4H	Configuration
45	Flavan-4-ol	OMe	OH	0.9	4.5	4.92	6.33	5.07	cis-cis
46	Flavanone	OMe		2.5		4.58	6.07		cis
	$NaBH_4$ reduction of (46)	OMe	OH	1.0	4.4	4.87	6.28	5.02	cis-cis
58	Dihydroflavonol	OH		12.1		5.47	4.93		trans
61 R=Ac	3-Acetoxyflavan	OAc		1.25		4.87	4.56	6.90	cis

2,3-trans-7,8,3',4'-Tetramethoxydihydroflavonol

Cyclization of 2-hydroxy-3,4-3',4'-tetramethoxychalcone (57) to the corresponding 2,3-trans-dihydroflavonol (58) was effected with benzyltrimethylammonium hydroxide (Triton B) and hydrogen peroxide in ethanol by the method of Brown and MacBride.[20] This method is superior to the oxidative ring closure with alkaline hydrogen peroxide (AFO reaction conditions) and to the alternative cyclization of acetoxychalcone dibromide with aqueous acetone and aqueous sodium carbonate. The difficulty with the AFO reaction procedure usually arises from the insolubility of the potassium and sodium salts of 2'-hydroxychalcones. Substitution of benzyltrimethylammonium hydroxide for sodium or potassium hydroxide yields salts that are more soluble which enables cyclizations to proceed well.[20]

The n.m.r. spectrum of the dihydroflavonol confirmed its 2,3-trans-configuration (Table 3). The value of the 2,3-coupling constant lies close to the upper limit observed[35] for the interaction of 1,2-diaxial protons. The high value for this coupling constant lends further support to the view[30] that these trans-compounds exist almost exclusively in the conformation with the 2,3-substituents equatorial. The spectrum also gives evidence for the presence of strong intramolecular hydrogen bonding between the 3-hydroxyl group and the carbonyl group. The signal of the hydroxyl proton in the corresponding 3-hydroxyflavan[83] is centred at τ 8.0. The downfield shift of this proton in the dihydroflavonol by 4.1 p.p.m. is ascribed as being due to a large extent to strong intramolecular hydrogen bonding. The


OMe
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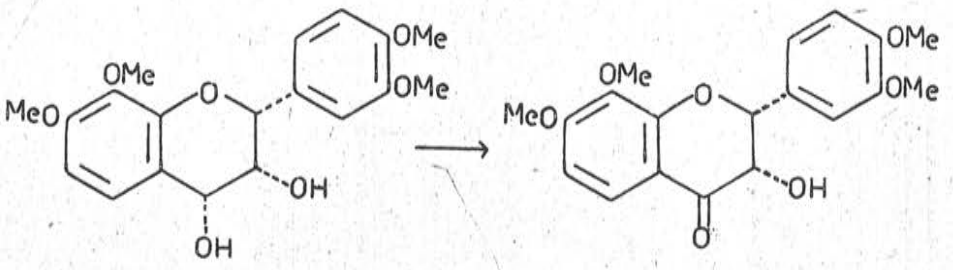
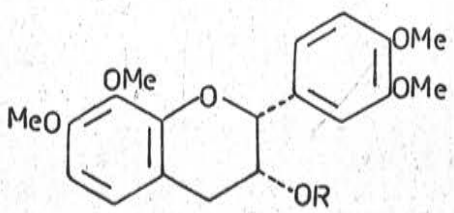
MeO
OH
O
OMe
OMe
MeO
O
OH
O

(57) (58)


OMe
OMe
MeO
O
OH
OH
OMe
OMe
MeO
O
OH
O

(59) (60)


OMe
OMe
MeO
O
OR

(61)

theoretical basis for such hydrogen-bond shifts has been discussed by Bernstein, Pople and Schneider.[82]

Oxidation of 7,8,3',4'-tetramethoxyflavan-3,4-diol with manganese dioxide.

The cis-cis-diol (59) required for oxidation was prepared by catalytic (nickel boride) hydrogenation of the corresponding flavonol. It was discovered that prolonged hydrogenation resulted in hydrogenolysis of the benzylic hydroxyl group at C_4 with the production of cis-3-hydroxyflavan (61, R = H).

Oxidation of the cis-cis-diol (59) with manganese dioxide required a longer period of time than for the 3-methoxyflavan-4-ol (45) probably because of the presence of strong intramolecular hydrogen bonding in the former. The structural assignment of the oxidation product, 2,3-cis-dihydroflavonol (60), is based on its infrared spectral data (Table 4), its lower stability compared to the trans-isomer and its decomposition product.

The trans-dihydroflavonol (58) appears to be the thermodynamically more stable isomer. The instability of the cis-isomer is attributed to the stereochemical arrangement of the 2-hydrogen atom and the 3-hydroxyl group. Their trans anti-parallel (diaxial) conformation facilitates dehydration to the flavone. In the cis-3-methoxyflavanone a trans diaxial arrangement exists between the 2-hydrogen atom and the 3-methoxyl group but dehydration is not possible in this case and the compound is relatively more stable.

Table 4.

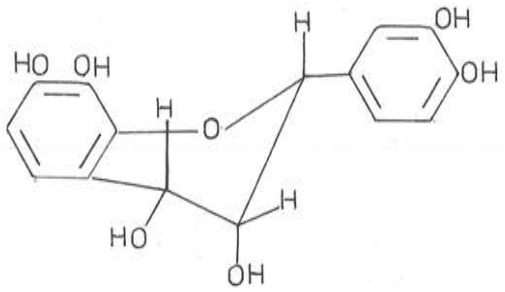
Carbonyl stretching frequencies of flavones and flavanones.

Compound	ν_{max} (cm^{-1})
3-Methoxyflavone (44)	1625 (Nujol)
3-Hydroxyflavone	ca 1627 (Nujol)
cis-3-Methoxyflavanone (45)	1665 (Nujol), ca 1665 ($CHCl_3$)
trans-3-Hydroxyflavanone (58)	1680 (Nujol), 1680 ($CHCl_3$)
cis-3-Hydroxyflavanone (60)	ca 1680 (Nujol)

***

SYNTHESIS, STEREOCHEMISTRY, CONFORMATION AND REACTIVITY OF MODEL BENZYL ALCOHOLS.

Our interest in the reactivity of benzyl alcohols arose from the observed differences in chemical properties between melacacidin (62) and its 4-epimer isomelacacidin (63).



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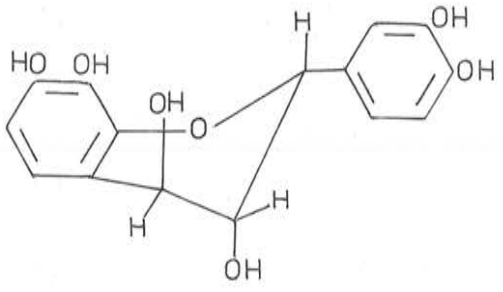


(63)

The benzylic 4-hydroxyl group is quasi-equatorial in melacacidin and quasi-axial in isomelacacidin when the two molecules are in their preferred conformations and this has been confirmed by n.m.r. evidence.[29] Apart from this steric consideration, there are two other associated factors which may contribute to the reactivity of the benzylic hydroxyl group in melacacidin and isomelacacidin - an activating group in the para position and the presence of a neighbouring hydroxyl group.

The reactivity of benzyl alcohols is attributed to their ability to form benzyl carbonium ions which are stabilized by resonance. Electron releasing groups in the para position further stabilize the electron deficient aromatic system.[84] Clark-Lewis postulated[49] that

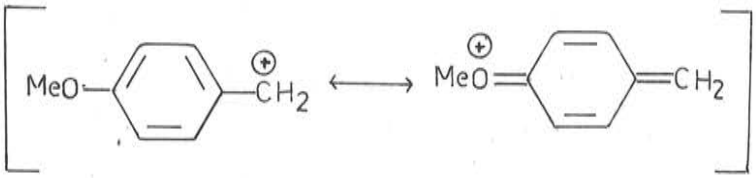


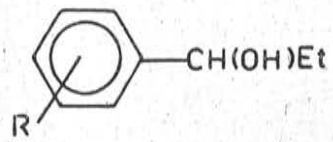
Fig. 10

when the benzylic hydroxyl group in the above flavan-3,4-diols is quasi-axial resonance stabilization of the incipient carbonium ion is possible and hence formation of carbonium ion (a reactive species) is favoured. The quasi-equatorial conformation of the 4-hydroxyl group (62) renders the formation of the carbonium ion less favourable probably because the vacant p-orbital is directed away from the π-orbital system of the aromatic ring. The acidity of a quasi-equatorial hydroxyl group may be expected to be higher than the epimeric quasi-axial hydroxyl group because the electronic requirements for enhanced acidity are the reverse of those for carbonium ion formation.[27] Further stabilization of the 4-carbonium ion is possible by neighbouring group participation and this should be more favourable in the case of isomelacacidin (63) where the leaving group and the neighbouring group are in a trans anti-parallel arrangement. This proposal would also account for the retention of configuration observed in ethyl - or methyl-ether formation.

The above naturally occurring leucoanthocyanidins are too complex for elucidation of the contribution of the various factors influencing reactivity and so it is desirable to synthesize simpler related systems of known configuration and to study their reactions.

To study the electronic effects alone a series of simple benzyl alcohols of the phenylpropan-1-ol type (64) is desirable. Model compounds for the flavan system which will show steric as well as electronic effects are tetralin derivatives. The tetralin diols, especially those with a 3-aryl substituent would be very interesting analogues of the flavan system.

The reason for this investigation was primarily to provide an explanation of the significant difference in the reactivity of the 4-hydroxyl group in melacacidin and isomelacacidin in some sensitive reactions. This difference is most clearly seen in the formation of benzyl ether and it was decided to extend the study to the formation of methyl ether in model benzyl alcohols. This is a very wide field for investigation and a start has been made by synthesis of model compounds and study of their behaviour which has provided experimental support for some of the reasons for the difference in chemical reactivity of the flavandiols.



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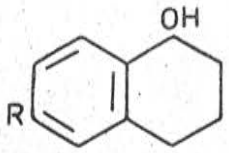

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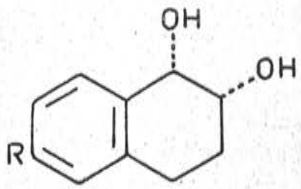

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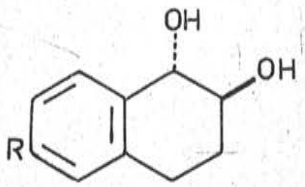

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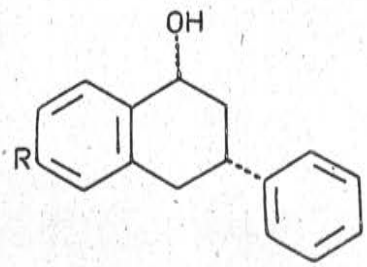

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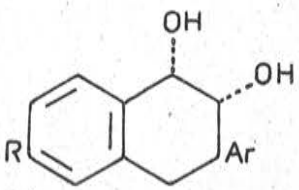

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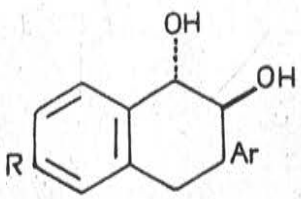


(70)

Synthesis of Model Benzyl Alcohols and Derivatives.

Samples of high purity are required for stereochemical and reactivity studies and purification in a lot of cases presented a major problem. The purification procedures and precautions are referred to in the experimental section.

1-Phenylpropan-1-ol and the related p-methyl- and p-methoxy-derivatives were prepared by standard procedures.

1-(3,4-Dimethoxyphenyl)propan-1-ol [64, R = 3,4 $(OMe)_2$]

This was prepared by reaction of ethylmagnesium bromide and veratraldehyde by the method of Roberti, York and MacGregor.[85] It was found however, that to obtain very pure samples of the benzyl alcohol, the exact amount of Grignard reagent had to be determined by titration.

1-(2,4,6-Trimethoxyphenyl)propan-1-ol [64, R = 2,4,6$(OMe)_3$]

Reaction of phosphorus oxychloride, formanilide and phloroglucinol trimethyl ether gave 2,4,6-trimethoxybenzaldehyde.[50] The benzyl alcohol was best prepared from the aldehyde by reaction with ethylmagnesium bromide, careful decomposition of the complex and fractionation of the product under reduced pressure in an atmosphere of nitrogen.

1-Hydroxy-1,2,3,4-tetrahydronaphthalene (65, R = H)

Reduction of α-tetralone with lithium aluminium hydride pro-

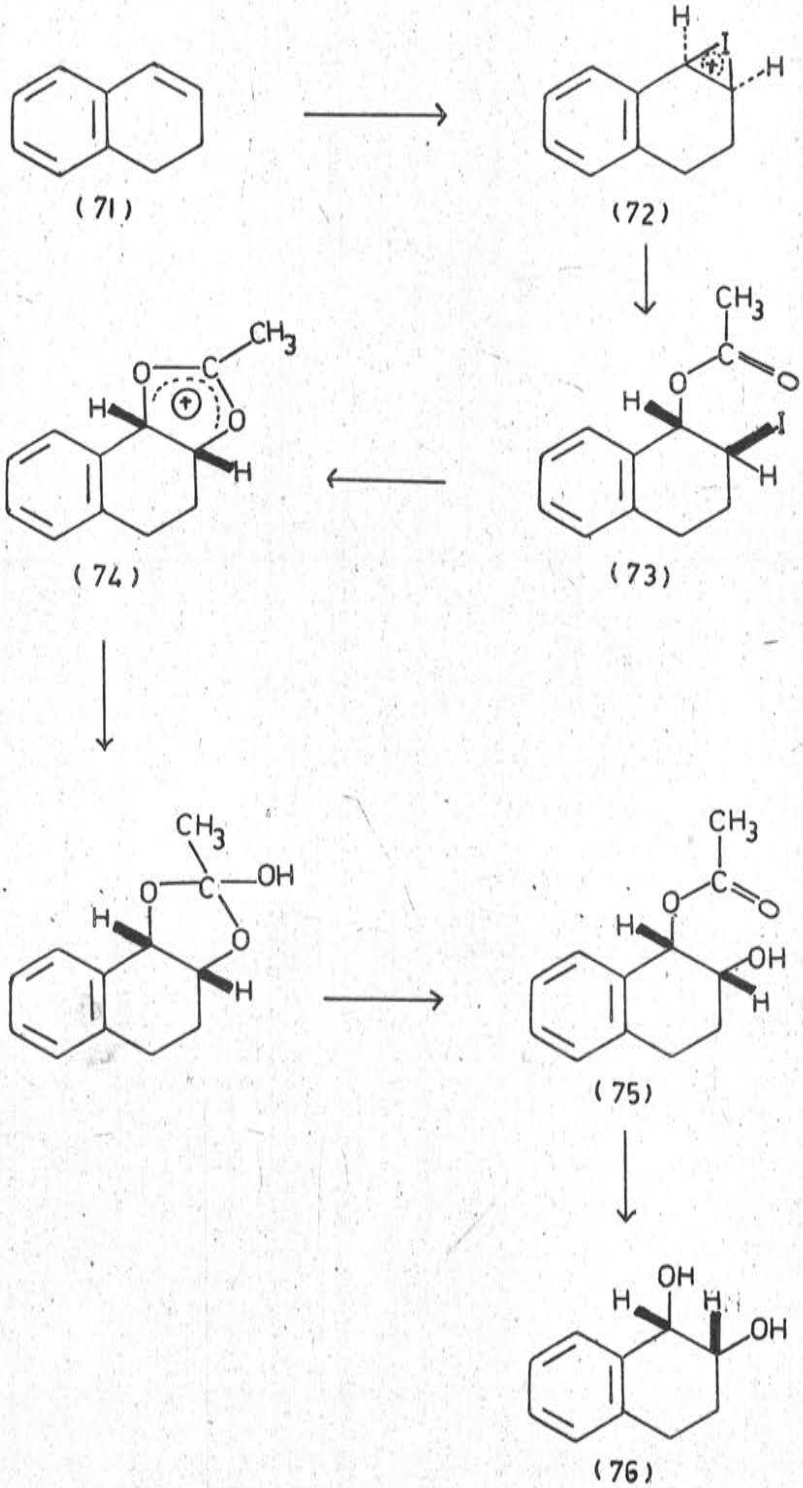
ceeded smoothly to give the tetralol (65) in high yield.

cis-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (66, R = H)

1,2-Dihydronaphthalene (71) was prepared by dehydration of α-tetralol (65, R = H) with potassium hydrogen sulphate. cis-Hydroxylation of this olefin was then carried out by Woodward's procedure with iodine and silver acetate in wet acetic acid.[86] This method depends on the ability of a neighbouring carboxyl group to interact with a carbonium ion. When the solvent contains at least a molar proportion of water the intermediate opens to give a cis-product.[87] The hydroxylation is envisaged as occurring in several stages.[86,88,89] Reaction between iodine and silver acetate is said to produce the following species: $IOAc \rightleftharpoons I^{\oplus} + AcO^{\ominus}$. Interaction of $I^{\oplus}$ with dihydronaphthalene produces the species (72). trans-Diaxial opening of this bridged iodonium ion gives the trans-iodoacetate (73). This reacts with acetoxyl group participation to give the cyclic oxonium ion (74) with inversion of configuration. Under moist conditions this ion must be hydrolysed by attack upon the acetyl carbon atom. Alkaline hydrolysis of the monoacetate (75) then gives the cis-diol (76).

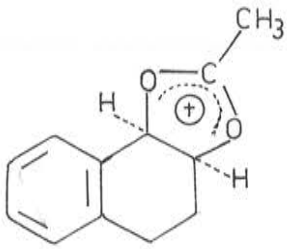
Hydroxylation of the dihydronaphthalene (71) with potassium permanganate[90] gave a lower yield and an impure product.

The cis-diacetate and the cis-carbonate of the diol were prepared for n.m.r. studies.


(71)
(72)
(73)
(74)
(75)
(76)

trans-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (67, R = H)

The trans-diol was prepared by trans-acetoxylation of 1,2-dihydronaphthalene[91] followed by reduction with lithium aluminium hydride of the diacetate. Low yields of the diol were obtained from this reaction. Naphthalene was obtained as a side product. The reaction probably proceeds through a cyclic oxonium ion (77) as attack by an acetate ion then would give a trans-product.



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The trans-diacetate and the trans-carbonate of the diol were prepared for n.m.r. studies.

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (65, R = OMe)

6-Methoxytetralin (78) was prepared in excellent yields by the method of Stork[92] by reducing β-naphthyl methyl ether with W4 Raney nickel under very mild acidic conditions. The reduction proceeded very rapidly and it was found that less hydrogenolysis occurred when methanol was used as solvent instead of ethanol. Oxidation of 6-methoxytetralin with chromic acid gave the ketone (79). Reduction of this ketone with lithium aluminium hydride gave the 6-methoxytetralol

(65, R = OMe). Platinum oxide was found to be an unreliable catalyst for the above reduction. In one such reduction 6-methoxydecalol was produced.

An alternative route to 6-methoxytetralol from 6-methoxytetralin involved acetoxylation of the activated benzylic 1-position with lead tetra-acetate and subsequent reduction of the tetralyl acetate (80) with lithium aluminium hydride.

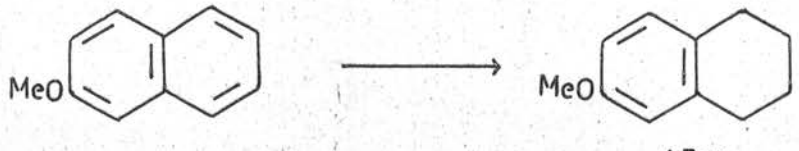
cis-1,2-Dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (66, R = OMe)

cis-Hydroxylation of 7-methoxy-1,2-dihydronaphthalene (81) with osmium tetroxide proceeded smoothly to give the cis-diol (66, R = OMe) in good yield and in a high state of purity. This stereospecific hydroxylation is thought to proceed through an osmate ester complex[93] (82).

trans-1,2-Dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (67, R = OMe)

trans-Hydroxylation of 7-methoxy-1,2-dihydronaphthalene (81) could not be achieved successfully with performic acid. The dihydronaphthalene (81) underwent undesirable side reactions in the presence of formic acid used in the hydroxylation procedure.

The epoxide (83) of the dihydronaphthalene (81) was prepared by reaction with perbenzoic acid in chloroform.[94] trans-Hydrolytic ring opening of the epoxide ring was effected in dimethyl sulphoxide under basic conditions.[95] In base-catalysed epoxide-cleavage reactions large rate enhancements are produced with dimethyl sulphoxide



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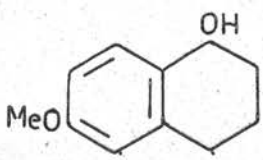
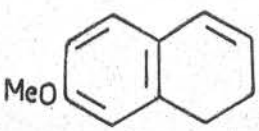
(79) (80)





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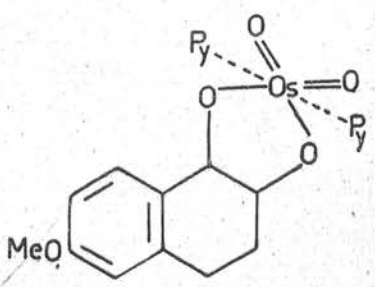

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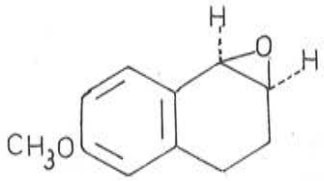
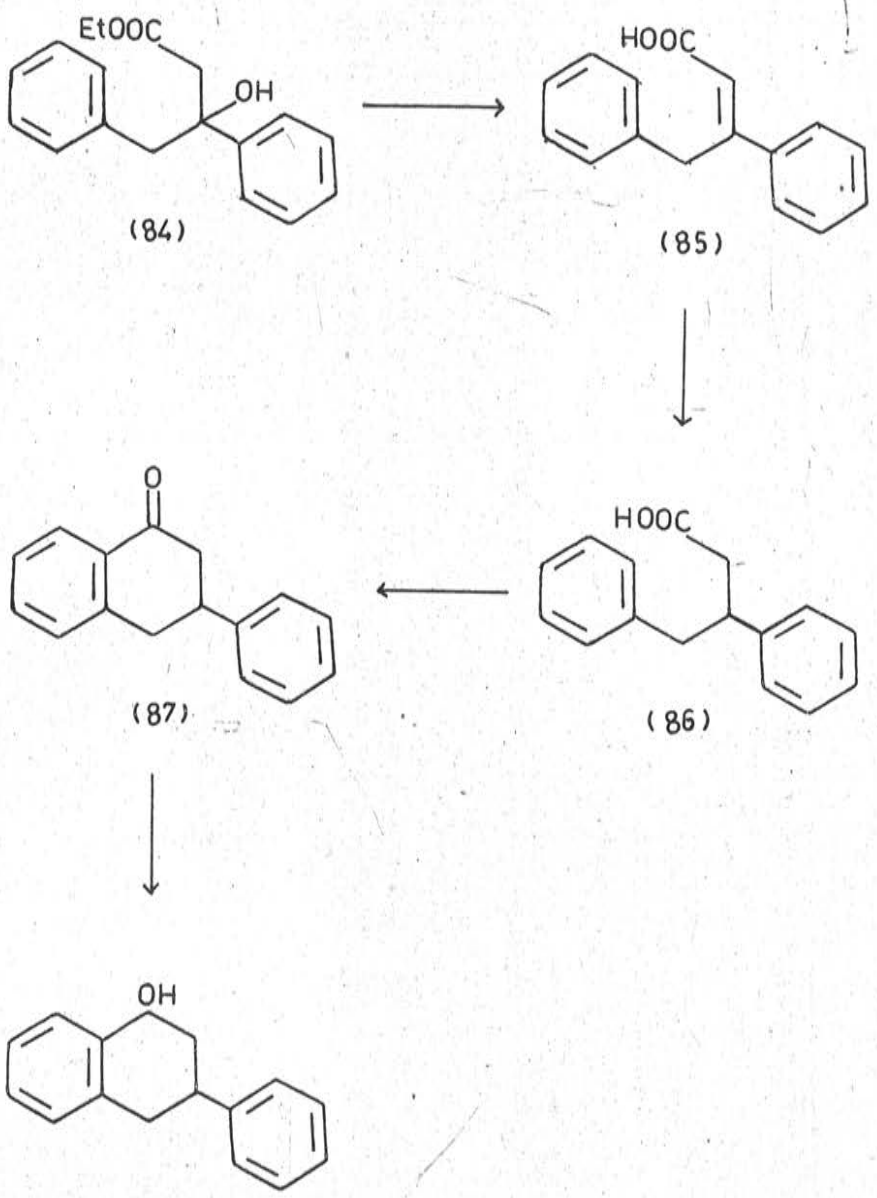


(83)

as solvent because of its high polarity and low solvating power for anions.[96] In a system such as this, one would expect the rule of diaxial opening to be obeyed.[97] There is evidence[98,99] to suggest that the diaxial opening involves fission of the benzylic C-O bond preferentially..

1-Hydroxy-3-phenyl-1,2,3,4-tetrahydronaphthalene (68, R = H).

The preparation of ethyl-β-hydroxy-βγ-diphenylbutyrate (84) by the Reformatsky reaction of deoxybenzoin and ethyl bromoacetate[100] was the first step in the synthesis of this compound. Hydrolysis of the ester and dehydration of the resulting β-hydroxy acid with hydriodic acid and red phosphorus gave β-benzylcinnamic acid (85). The reduction of this benzylcinnamic acid was carried out with 5% palladium on charcoal catalyst. Both Raney nickel and nickel boride were found to be unsatisfactory for this reduction. βγ-Diphenylbutyric acid (86) was cyclized in high yields to 1-oxo-3-phenyltetralin (87) with phosphorus pentachloride and stannic chloride. This method of cyclization, first used by Johnson[101] for the preparation of α-tetralone, was found to be superior to that using concentrated sulphuric



(84) (85) (86) (87)

acid. Reduction of the ketone (87) with lithium aluminium hydride gave 1-hydroxy-3-phenyltetralin.

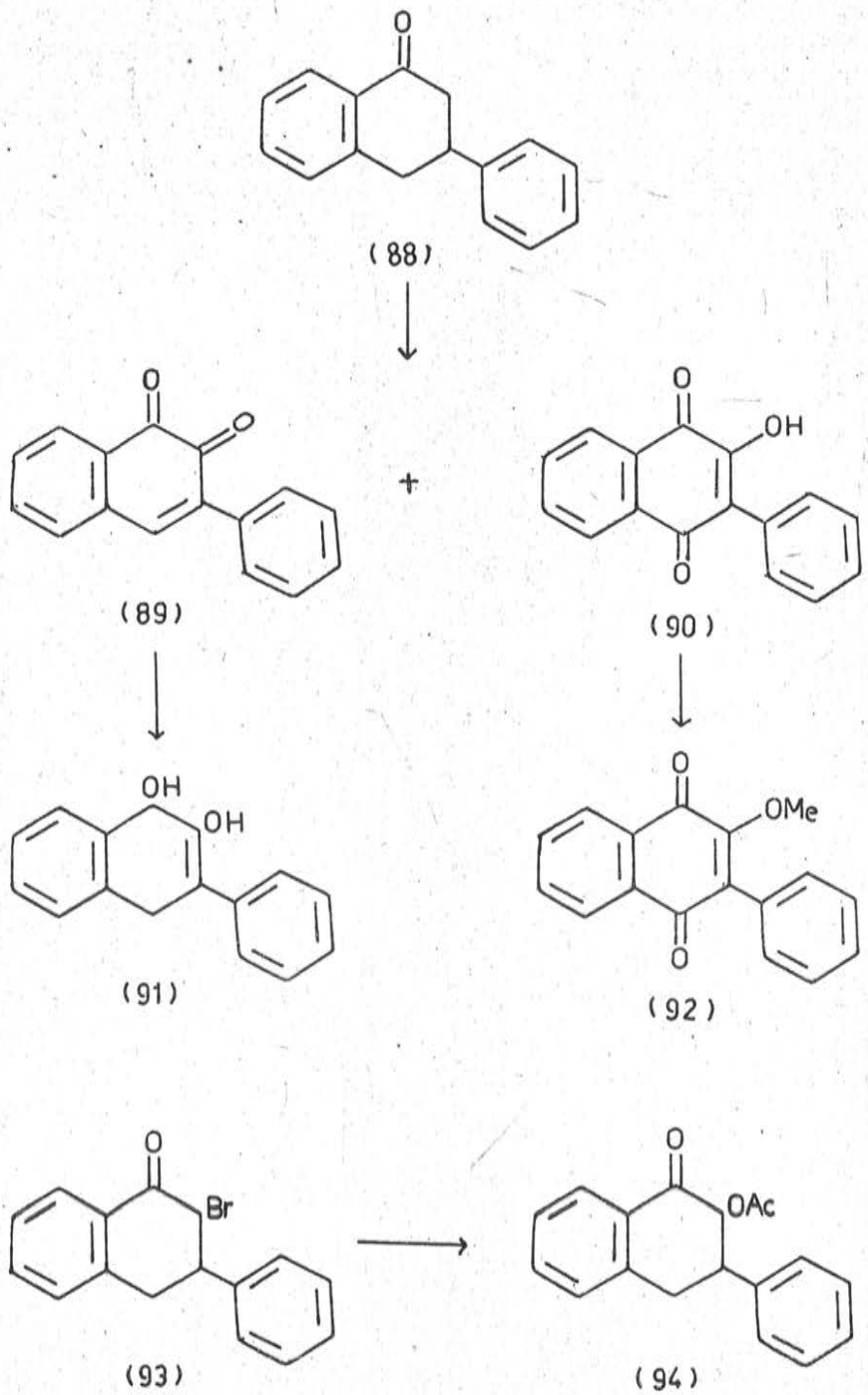
The n.m.r. spectrum of the compound (Table 7) indicated that the 1- and 3- protons were diaxial. This seems to suggest that the reduction of the ketone (87) with lithium aluminium hydride in diethyl ether gives as the predominant product, the compound with the 1-hydroxyl group equatorial. Eliel and Haubenstock[102] found that the stereochemistry of the reduction of 3,3,5-trimethylcyclohexanone with lithium aluminium hydride in diethyl ether was independent of the proportion of reactants and the order of their addition, and gave in all cases, 55 ± 3% of the axial alcohol.

1,2-Dihydroxy-3-phenyl-1,2,3,4-tetrahydronaphthalene (69,70, R = H)

Two routes to the synthesis of 1,2-dihydroxy-3-phenyltetralins have been investigated.

(i) Oxidation of 1-oxo-3-phenyltetralin (88) with selenium dioxide under mild conditions gave a mixture of 1,2-naphthaquinone (89) and 2-hydroxy-1,4-naphthaquinone (90). Mixtures of this kind have been reported for the oxidation of the corresponding 3-methyl compound with selenium dioxide.[103] Compound (90) was characterized as its methoxyl derivative (92). The 1,2-naphthaquinone (89) appeared to enolize easily and reduction with lithium aluminium hydride gave 1,2-dihydroxy-3-phenyldihydronaphthalene (91).

(ii) Bromination of conformationally rigid ketones under suitable conditions is said to furnish axial α-bromoketones.[104] Replacement


O
(88)
O
O
(89)
+
O
OH
O
(90)
OH
OH
(91)
O
OMe
O
(92)
O
Br
(93)
O
OAc
(94)

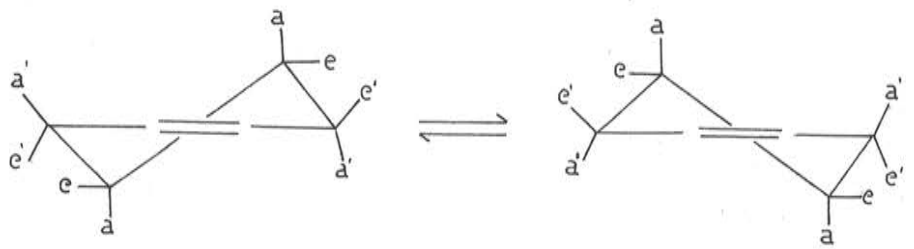
of the bromine atom with an acetoxyl group and reduction of the acetate with lithium aluminium hydride should furnish one or more diols in this series. There are analogies for these reactions in the flavan series.[37]

1-Oxo-3-phenyltetralin was smoothly converted into the α-bromoketone (93) with a chilled solution of bromine in ether. Replacement of the bromine atoms by acetoxyl groups by heating with potassium acetate in acetic acid gave only small yields of 2-acetoxy-1-oxo-3-phenyltetralin (94) and this, only after prolonged heating.

Stereochemistry and Conformation of Model Benzyl Alcohols.

It is assumed that a half-chair conformation is generally adopted by the reduced ring in preference to a half-boat conformation owing to lower repulsive non-bonded interactions involved in the former.[105,106,107] The n.m.r. spectrum of 1-hydroxy-1,2,3,4-tetrahydronaphthalene (Fig. 11) gives a strong indication that the reduced ring is not a rigid half-chair, but a rapidly inverting half-chair. The resonance of the benzylic 1-proton appears as a broad band centred at τ 5.55 (Table 6). If the averaging effects resulting from inversion were not present the signal of this proton would have appeared as a quartet (X part of ABX system).

In tetrahydronaphthalene itself it would be reasonable to assume that equal proportions of conformations (95) and (96) are present but the observed spectral data of 1-hydroxy-1,2,3,4-tetrahydronaphthalene at room temperature does not permit estimation of the relative population of the two conformations. This can only be achieved by a study



(95) (96)

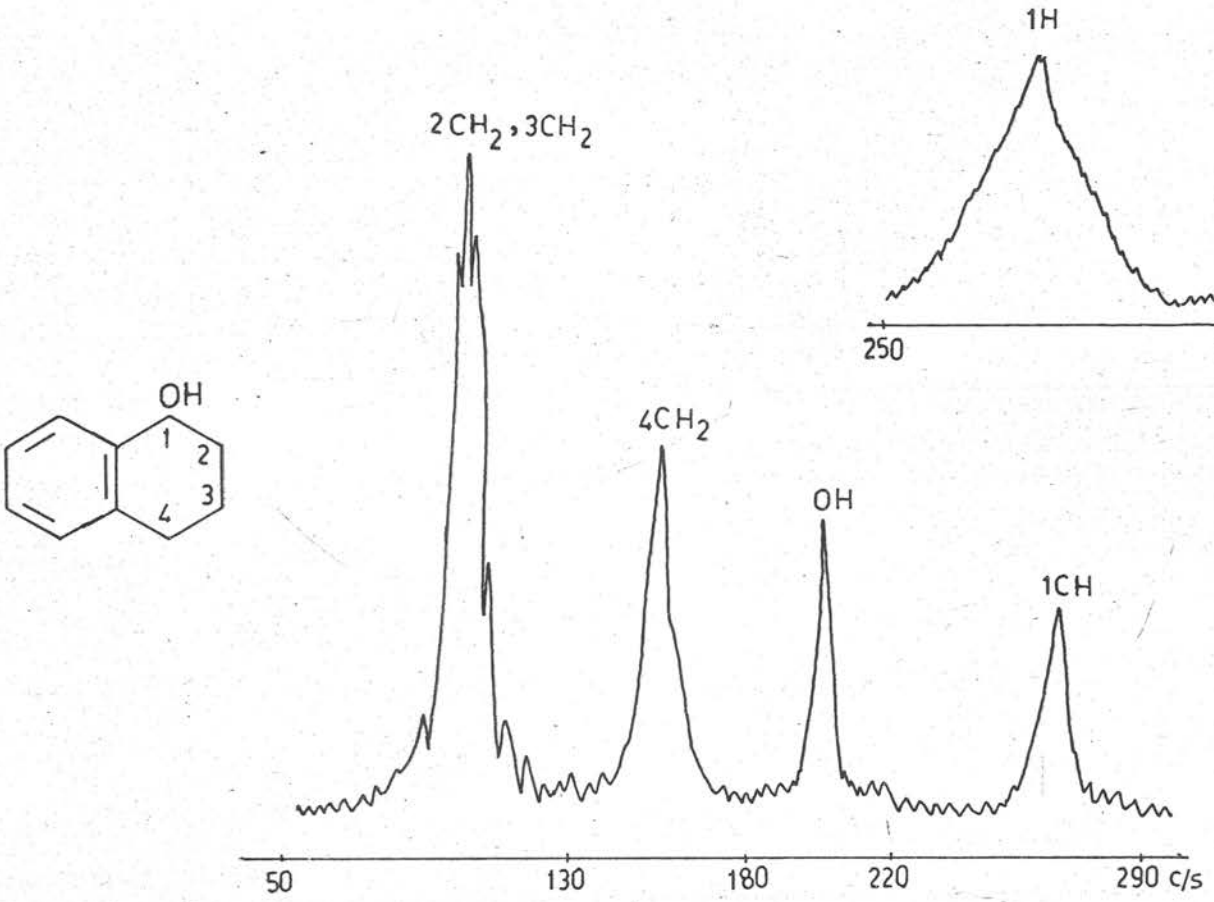


Fig. 11.

The 60 Mc/s n.m.r. spectrum of 1-hydroxy-1,2,3,4-tetrahydro-naphthalene in carbon tetrachloride.

of the n.m.r. spectrum determined at low temperatures[108] where the rate of the chair-chair interconversion is slowed sufficiently so that the mean lifetime in any given conformation is larger than the inverse frequency separation due to the two kinds of hydrogens.

From a study of scale models and by analogy with cyclohexene itself,[42] it is suggested that the intermediate in the ring inversion is the boat form (Fig. 12). The calculated value of ΔF^{*} (from k value) for the process A⟶B (Fig. 12) is 5.3 kcal./mole for cyclohexene.[42] For cyclohexane it is 10.1 kcal./mole.[108] The average lifetime at 25° of a cyclohexene molecule before inversion is of the order of 10^{-9} sec. and for cyclohexane it is 2.6×10^{-5} sec.[42] Tetrahydronaphthalene is a much more rigid system than cyclohexene and cyclohexane and the average lifetime of a particular conformation would be expected to be much higher especially when substituents are introduced into the reduced ring. The presence of intramolecular hydrogen bonding (as with diols) will also contribute to the increase in lifetime of a particular conformation. A higher ΔF^{*} value for interconversion is also expected in this system especially when substituents are present as this will increase the number of eclipsing interactions in the transition state.[109]

The spectra of 1,2-disubstituted tetralin derivatives were analysed by first-order procedures. The benzylic 1-proton showed a clean doublet. The 2-proton constitutes the X part of an ABXY system (Fig. 13). Diols are not very convenient compounds to use for n.m.r. work because of their low solubility in carbon tetrachloride and

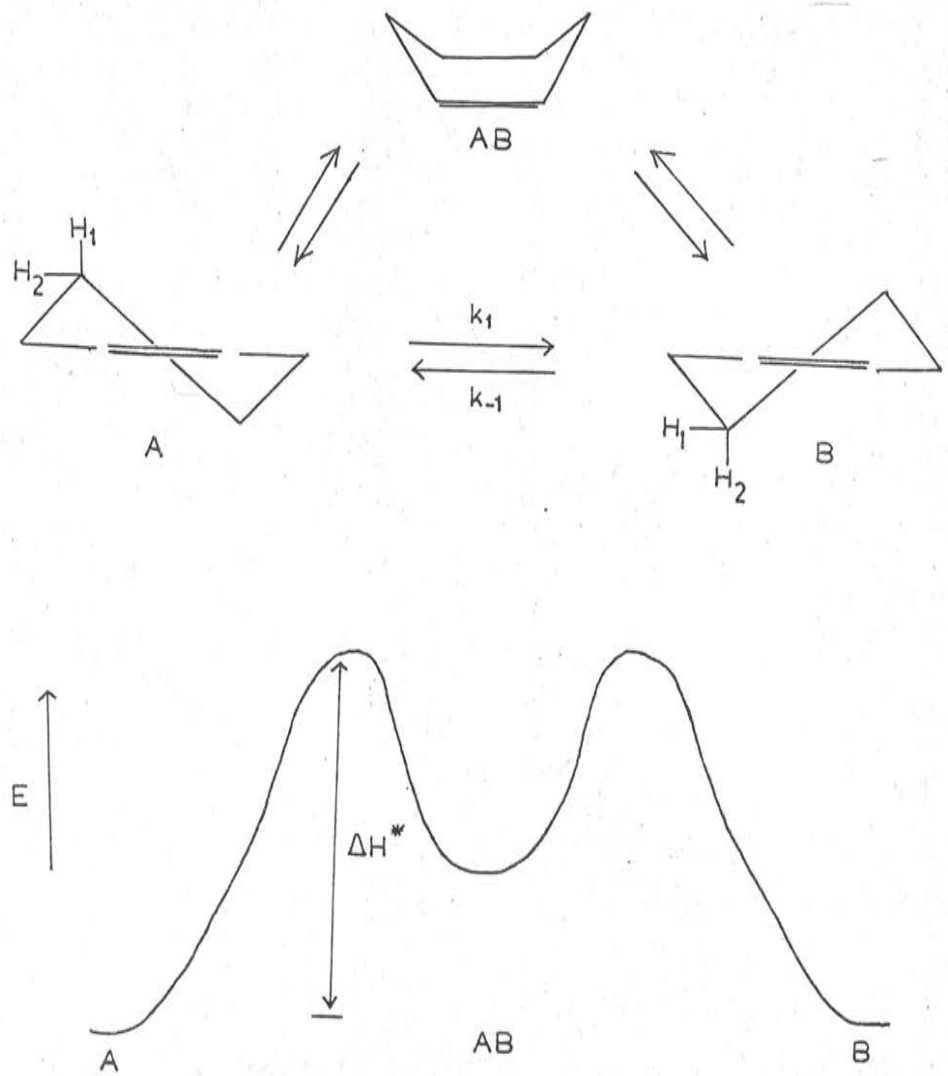


Fig. 12.

Diagrammatic representation of the interconversion barrier in tetrahydronaphthalene.

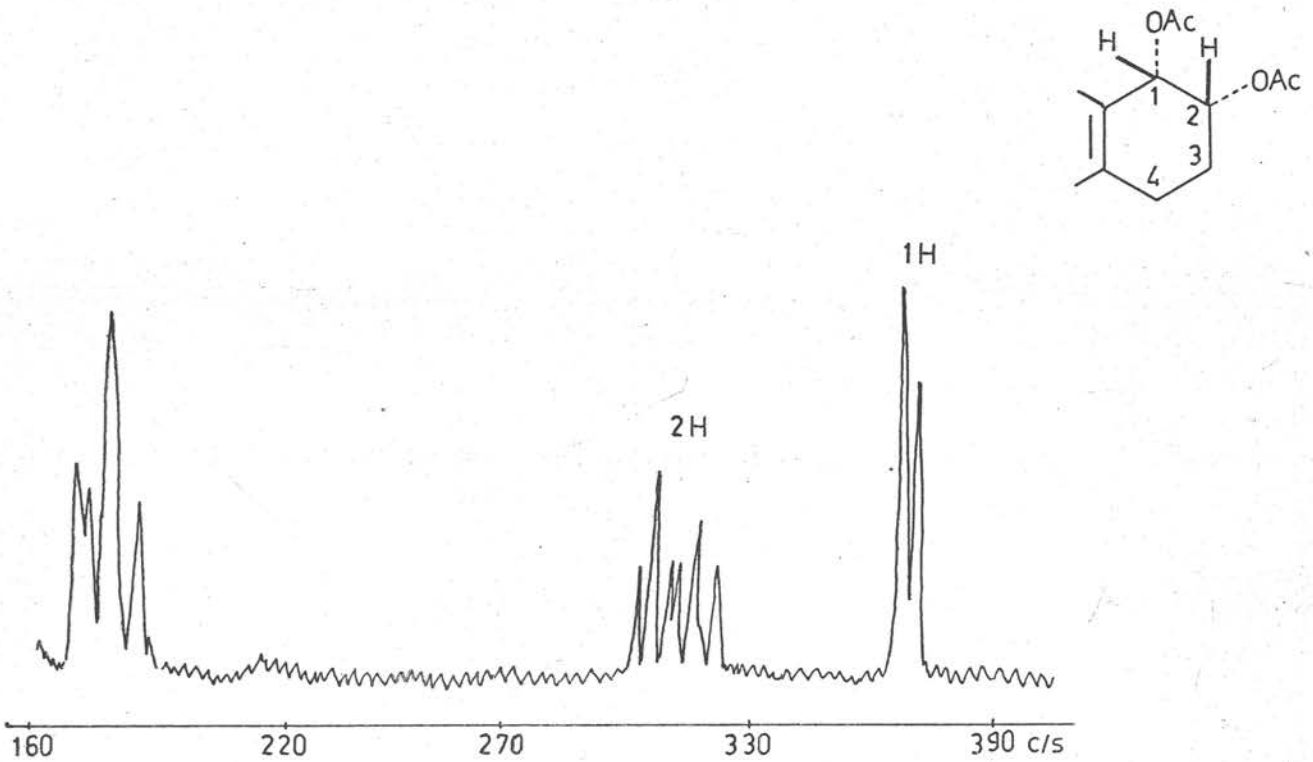


Fig. 13.

The 60 Mc/s n.m.r. spectrum of tetralin-cis-diol diacetate in deuterochloroform.

deuterated chloroform. Diol diacetates are much more suitable because of their higher solubility and because the resonance lines associated with the benzylic proton on the acetate bearing carbon atom are displaced downfield from the other protons (deshielding effects of acetate group).

The n.m.r. spectral data presented in Table 6 allow some generalizations to be made on the correlation between observed spin-spin coupling constants and configurations of the tetralin diols and diacetates. A clear distinction is found between the coupling constants for the 1,2-cis- and 1,2-trans - compounds. The 1,2-cis coupling constants have values close to 3.4 c/s whereas values greater than 5.6 c/s are found for the trans-compounds.

The valence-bond σ-electron calculation of Karplus[31,110] which uses a non-ionic six electron six orbital fragment (HCC'H) to determine the contact interaction gives an approximate relation between the coupling constant (J) and the dihedral angle (φ). For a C-C bond

$$J_{HH'} = A + B \cos \phi + C \cos 2\phi$$

length of 1.543 A° and sp^3 hybridized carbon, the constants A = 4.22, B = -0.5 and C = 4.5 c/s. In principle then, the Karplus equation can be used to predict spin-spin coupling constants approximately. Conversely, observed values of coupling constants can be used to evaluate dihedral angles and these approximate values can be used to determine the conformation of molecules.

Table 5 shows the various dihedral angles for C-1 and C-2 protons measured on Dreiding models together with the calculated coupling constants.

Table 5.

Dihedral angles and calculated coupling constants in tetralin models

Bond conformation	1ax 2eq	1ax 2ax	1eq 2ax	1eq 2eq
Dihedral angle	52	172	53	62
Coupling constants (c/s)	2.8	9.0	2.7	1.5

For tetralin trans-diacetate the observed coupling constant $J_{1,2}$ must represent the average coupling between the hydrogens in the two half-chair conformations (95 and 96).

$$J_{aa} + J_{ee} = 2J_{1,2} = 10.5 \quad \text{(calculated)}$$

$$J_{aa} + J_{ee} = 2J_{1,2} = 11.2 \quad \text{(observed)}$$

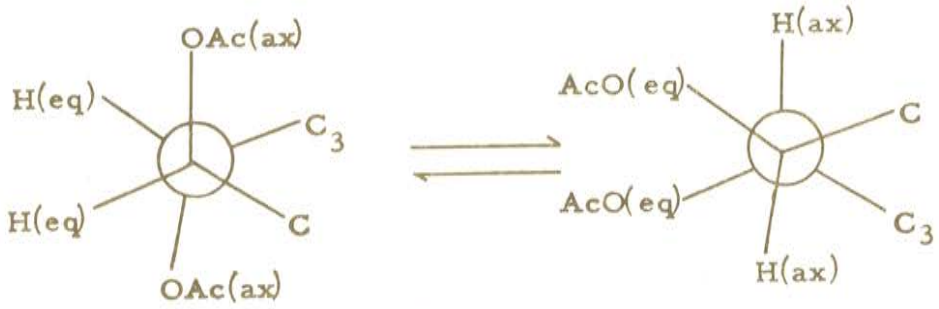
As the parameters of the Karplus equation are strongly dependent on the nature of the -CH-CH- fragment to which it is applied and because data on other tetralin derivatives are not available, it is difficult to decide from the above whether the two half-chair conformations are thermodynamically equivalent and therefore equally populated. It is doubtful though that the two rapidly inverting conformations will be

Table 6.

Chemical shifts and coupling constants of reduced ring protons in substituted tetralins.

Compound	1 Substituent	2 Substituent	1,2 Stereochem	$J_{1,2}$	τ 1H	τ 2H	τ 3Hs	τ 4Hs
65, R=H	OH				5.55	8.25	8.25	7.26
65, R=OCH_3	OH				5.30	8.12	8.12	7.27
66, R=H	OH	OH	cis	3.3	5.43	ca.6·4 ~~6.28~~	8.13	7.20
Diacetate of 66, R=H	OAc	OAc	cis	3.4	3.05	4.77	7.96	7.03
99	Carbonate		cis	7.8	4.25	4.84	7.95	7.18
67, R=H	OH	OH	trans	8.2	5.44	6.23	7.98	7.14
Diacetate of 67, R=H	OAc	OAc	trans	5.6	3.93	4.82	7.90	7.10
100	Carbonate		trans	10.6	4.79	5.75	7.84	7.04
66, R=OCH_3	OH	OH	cis	3.4	5.39	ca.6·4 ~~7.00~~	8.28 ~~to~~	ca.7·2 ~~8.28~~
67, R=OCH_3	OH	OH	trans	ca10.4	5.48	ca.6·4 ~~7.02~~	8.13 ~~to~~	ca.7·2 ~~8.13~~

equally populated as the acetoxyl groups will prefer equatorial conformations. The two half-chair conformations are better appreciated from the projection formulae (97,98), the view as seen along the 1-2 bond being shown.



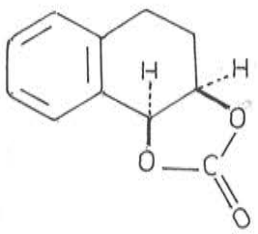
(97) (98)

For the trans-diols the observed values of $J_{1,2}$ suggest that the conformation with two hydroxyl groups equatorial will be more populated. It can be shown that about 80% of tetralin-trans-diol (67, R=H) resides in the conformation with the two hydroxyl groups equatorial. This reveals the greater repulsion of the acetoxyl groups than the hydroxyl groups in the gauche orientation and also the strength of the hydrogen bond in the diol. Intramolecular hydrogen bonding would increase the lifetime of the conformation with the hydroxyl groups in the equatorial positions.

For the cis-diols and diacetates the dihedral angles ϕ_{ae} and ϕ_{ea} are very nearly equal and so a value for $J_{1,2}$ of about 2.8 c/s is expected. This is in general agreement with the observed value (3.4 c/s), although the slightly higher observed value could be attributed to slight distortion of the half-chair in these diols and

diacetates.

The n.m.r. spectra of the carbonates of cis- and trans-tetralin-1,2-diols showed the benzylic 1-proton as a doublet with $J_{1,2}$ 7.8 c/s for cis- and $J_{1,2}$ 10.6 c/s for the trans-carbonate. First-order analysis of the resonance of the 2-methine proton gave $J_{1,2}$ 7.8 c/s (cis) and $J_{1,2}$ 10.6 c/s (trans). These values are much larger than those generally observed for the diols and diacetates (Table 6), and also much larger than the values that would be expected from the Karplus equation (Jaq = 2.8 c/s and Ja,a = 9.0 c/s). This indicates considerable distortion of the half-chair conformation.



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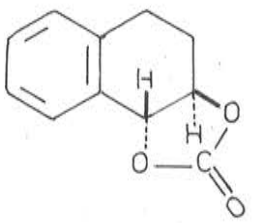
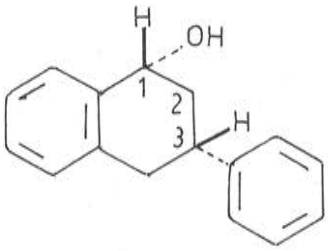


(100)

Scale models show that the carbonates possess rigid conformations. For the cis-carbonate (99) the observed $J_{1,2}$ of 7.8 c/s means that a considerable decrease in dihedral angle has occurred. Scale models show that in the trans-carbonate (100) the 1- and 2- protons are rigidly axial in type.

The n.m.r. spectra (Fig. 14 and Table 7) of 1-hydroxy-3-phenyltetralin (101) and its acetate showed the benzylic 1-proton as a symmetrical quartet (X part of ABXY system). The resonance of the 2-methylene protons (AB part of ABXY) was found to be too complex to analyse by first-order procedures and spin-spin decoupling experiments

did not simplify the signals.



(101)

If it is assumed that $J_{1,2ax}$ has the same sign as $J_{1,2eq}$ then the J values are additive.[111] Then:

$$J_{1,2ax} + J_{1,2\,eq} = 16.2\ c/s \quad \text{(observed for acetate)}$$

$$J_{1,2ax} + J_{1,2\,eq} = 16.4\ c/s \quad \text{(observed for alcohol)}$$

$$J_{1ax\ 2eq} + J_{1ax\ 2\ ax} = 11.8\ c/s \quad \text{(calculated)}$$

$$J_{1eq\ 2ax} + J_{1eq\ 2eq} = 4.2\ c/s \quad \text{(calculated).}$$

These values show that the benzylic 1-proton is axial, and if it is assumed that the preferred conformation of the bulky 3-phenyl group is equatorial then the 1- and 3- protons are diaxial and cis. The n.m.r. spectrum (Fig. 14) also gives a strong indication that the system is a rigid one and not a rapidly inverting one. The 3-phenyl group anchors the reduced ring of the molecule in a fixed conformation.

Table 7.

Chemical shifts and coupling constants of reduced ring protons in 3-phenyltetralins.

Compound	1 Subst.	1,3 Stereochem.	$J_{1ax\ 2ax}$	$J_{1ax\ 2eq}$	τ 1H	τ 2H	τ 3H	τ 4Hs
(101)	OH	cis	10.3	6.1	5.06	7.79	7.07	7.07
Acetate of (101)	OAc	cis	9.9	6.3	3.81	7.75	6.95	6.95

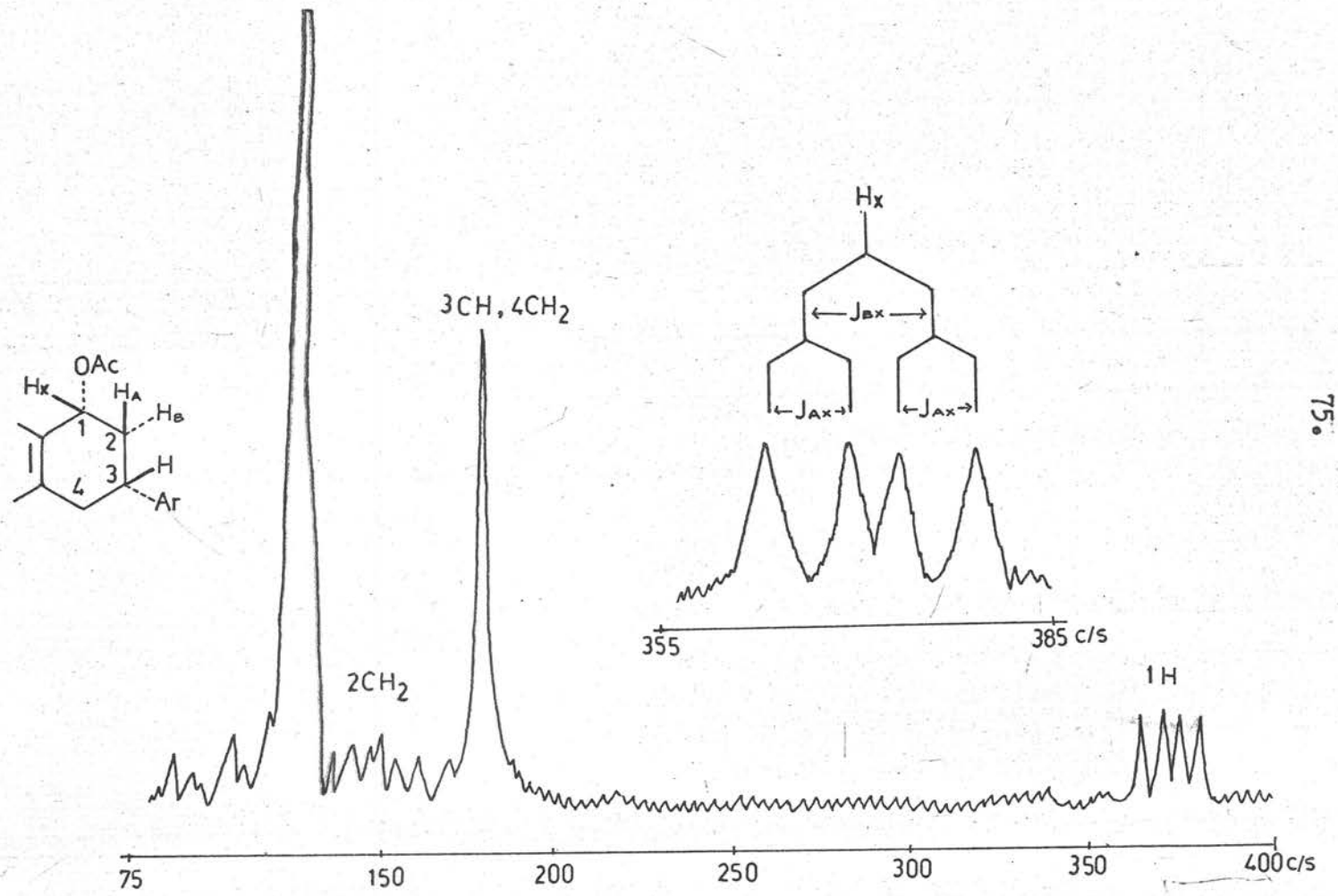


Fig. 14.

The 60 Mc/s n.m.r. spectrum of 1-acetoxy-3-phenyltetralin in deuterochloroform.

Reactivity of Model Benzyl Alcohols.

The product analysis study with 1-phenylpropan-1-ol and derivatives showed that our ability to do a careful investigation of the requirements for methyl-ether formation was severely limited by the fact that flexible systems such as these undergo faster competing reactions which seem to predominate.

In benzyl alcohols of this type alkyl-oxygen heterolysis occurs readily especially when an electron releasing group is present in the ortho or para position as this will facilitate resonance stabilization of the incipient carbonium ion. The fate of the carbonium ion will depend upon the conditions of the reaction but one might anticipate the following reactions:

(i) Loss of a proton leading to formation of olefin,

(ii) Acid-catalysed reaction of the olefin with the carbonium ion to give a dihydro-dimer.

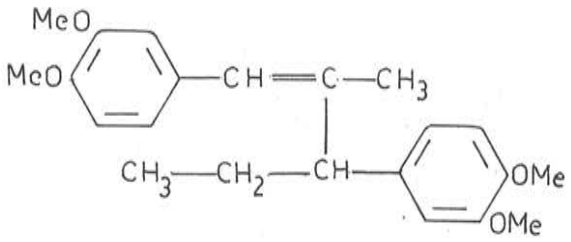
(iii) Acid-catalysed formation of bis-ether.

(iv) Disproportionation to a phenylpropane derivative.

(v) Methyl-ether formation.

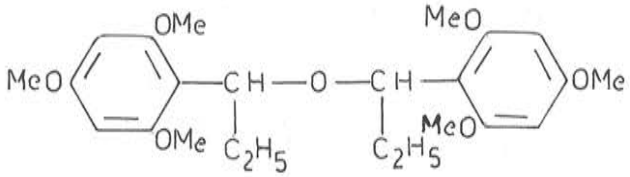
Formation of olefin was observed in every case with these simple benzyl alcohols.

1-(3,4-Dimethoxyphenyl)propan-1-ol [64, R = 3,4(OMe)$_2$] underwent further acid-catalysed reaction to the dimer (102). Analogous reactions have been reported in the literature.[112a]



(102)

1-(2,4,6-trimethoxyphenyl)propan-1-ol [64, R = 2,4,6(OMe)$_3$] was found to be an extremely reactive benzyl alcohol. In the presence of even very small amounts of acid it suffered dehydration rapidly. When the benzyl alcohol was heated with methanol in the complete absence of acid no observable change took place as was evidenced by vapour phase chromatographic analysis. Under very mild acidic conditions and high benzyl alcohol concentration, bis-1-(2,4,6-trimethoxyphenylpropyl)ether (103) was formed.



(103)

Under stronger acidic conditions the benzyl alcohol underwent a disproportionation reaction to give 1,1-di-(2,4,6-trimethoxyphenyl) propane (105). In order to postulate a possible mechanism for the formation of the disproportionation product, the reactions of 1,3,5-trimethoxybenzene with 1-(2,4,6-trimethoxyphenyl)propan-1-ol,

acetaldehyde and propionaldehyde in methanol under acidic conditions were studied. The formation of the diphenylpropane (105) was observed only in the reaction with the benzyl alcohol.

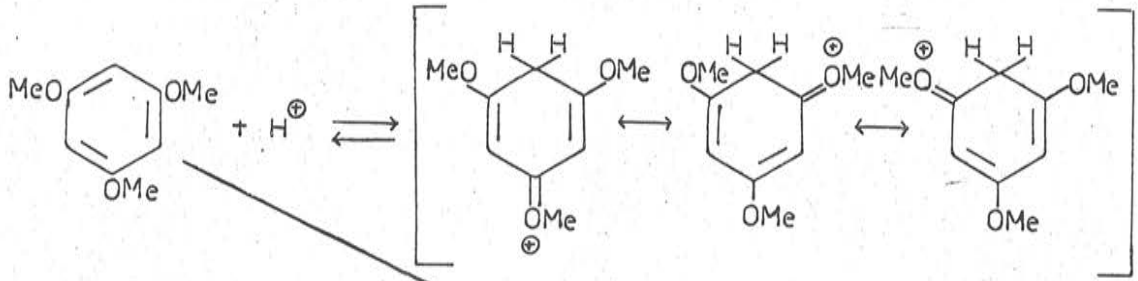
Kresge and Chiang[112] considered the protonation of 1,3,5-trimethoxybenzene under acidic conditions to be on carbon and with good evidence. Schubert and Quacchia[113,114] used n.m.r. data as direct evidence for the C-protonated structure (104). The reaction between 1,3,5-trimethoxybenzene and the benzyl alcohol can be envisaged as shown in Fig. 15. The formation of the diphenylpropane from the benzyl alcohol and methanol under acidic conditions can be suggested as proceeding through the intermediate (106).

The reactivity studies on these simple benzyl alcohols with respect to methyl-ether formation show that these behave differently compared to the more rigid benzyl alcohol systems. Whether methyl-ether formation occurs to a very small extent or not is not known. The reactions do show the marked effect of activating ortho and para groups on alkyl-oxygen heterolysis.

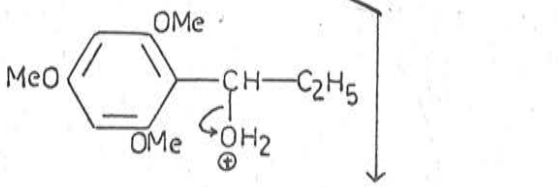
The tetralols and the tetralin-1,2-diols are closer analogues to the flavan system and one might anticipate methyl-ether formation with some of these benzyl alcohols. Numerous difficulties arose in establishment of the best conditions for methyl-ether formation. Where possible, the products of the reactions were isolated and analysed. Thin-layer chromatographic analysis and n.m.r. spectral analysis proved invaluable in this respect.

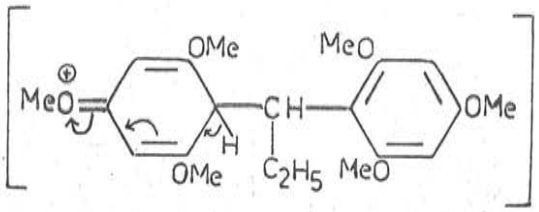
1-Hydroxytetralin (65, R = H) was found to be stable under

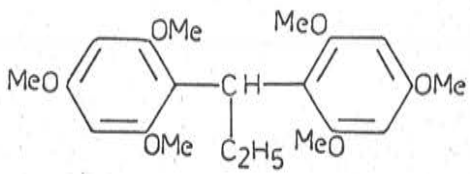
Fig. 15



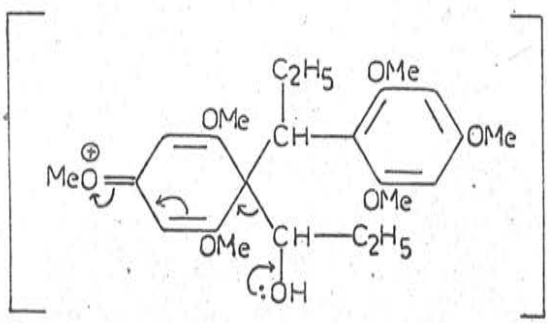
(104)







(105)



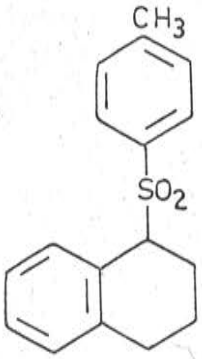
(106)

the conditions used for methyl-ether formation. It formed a sulphone (107). However, the conditions for the formation of sulphones are not so rigid as the more sensitive reaction with very dilute methanolic acids.

1-Hydroxy-6-methoxytetralin (65, R = OCH_3) underwent dehydration to 7-methoxy-1,2-dihydronaphthalene (81) readily even in the presence of traces of acid. Two other undesirable though interesting compounds were isolated. Under very low acid concentrations and high concentrations of the tetralol, bis-(6-methoxy-1,2,3,4-tetrahydro-1-napthyl)ether (110) was formed. The structure of the compound was confirmed by n.m.r. spectral evidence.

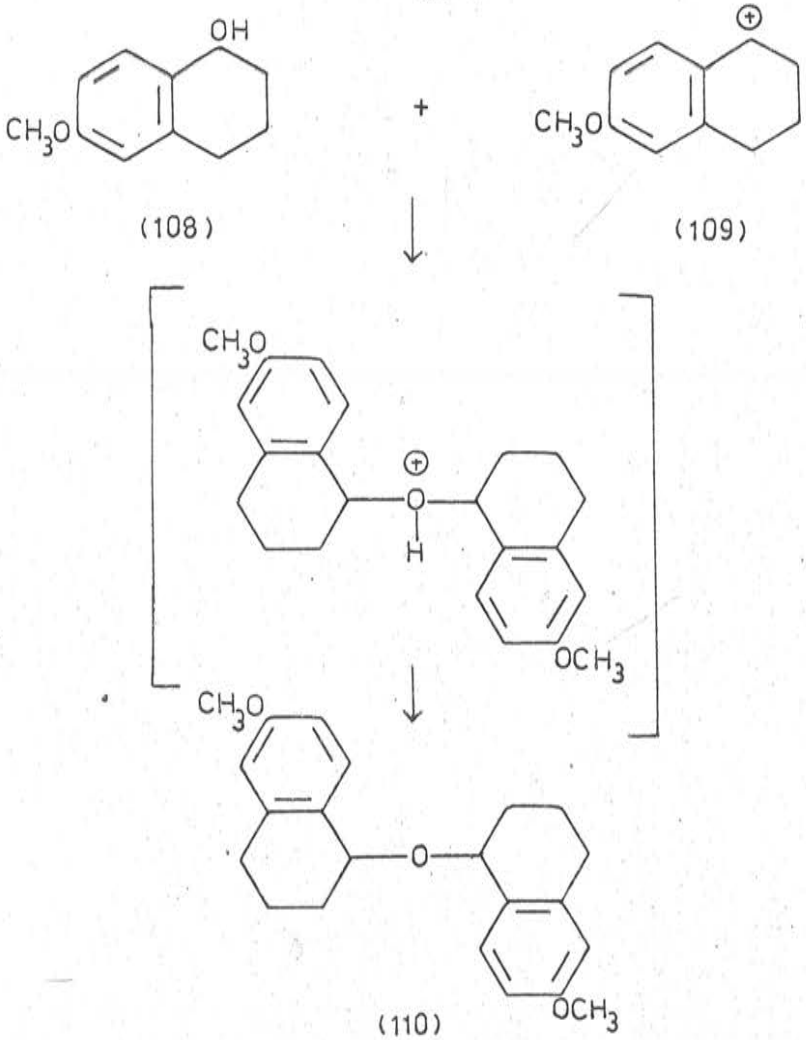
If the mechanism of formation of the bis-ether (110) shown in (Fig. 16) is acceptable then any difference in basicity between methanol and 6-methoxytetralol (108) has to be explained because in the reaction mixture there will exist a competition between these two for the species (109). From the present work it appears that in a reaction mixture where the concentration of 6-methoxytetralol is relatively high (> 1M) the basicity of the tetralol is much greater than that of methanol possibly due to the presence of a strong electron releasing substituent in the para position.

The bis-ether (110) was found to be unstable under relatively strong acidic conditions. When heated with 1% methanolic hydrochloric acid it gave 7-methoxy-1,2-dihydronaphthalene (81) as the major product. A small amount of 2-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-3,4-dihydro-6-methoxynaphthalene (111) was also present. An authentic



(107)

Fig. 16

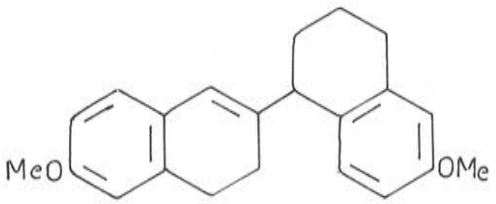


(108) (109)

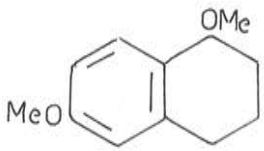
(110)

sample of this dihydrodimer was prepared by dehydration of 6-methoxytetralol (108) with 48% aqueous hydrobromic acid.[115]

6-Methoxytetralol in stronger acidic solutions (> 0.2%) did not give the bis-ether. The presence of the olefin and the dihydro-dimer (111) was noted.



(111)



(112)

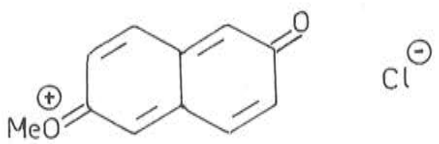
It became obvious from the above work that for methyl-ether formation and isolation a low tetralol concentration and a very low acid concentration was required. 1,6-Dimethoxytetralin (112) was obtained in high yield when the tetralol (0.125M solution) was treated with 0.001% methanolic acetic acid. The structure of the methyl ether was assigned on n.m.r. spectral evidence (see experimental section).

The methyl ether (112) was found to be unstable under even mildly acidic conditions. When heated with 0.1% methanolic hydrochloric acid it decomposed to give the olefin (81). The reaction is indicative of the extreme lability of the benzylic methoxyl group.

The tetralin-diols (66, 67, R = H) did not form methyl ethers. The cis-diol, on prolonged heating with 3% methanolic hydrochloric

acid, was converted to the trans -diol but only to a very small extent (reaction mixture probably contaminated with water). The epimerization probably proceeds through an oxonium ion intermediate. An intermediate of this kind was proposed by Djerassi[46] to explain inversion in ring B oxygenated estrogens.

6-Methoxytetralin diols (66, 67, R = OCH_3) were found to be more reactive than their unsubstituted analogues. When heated in the presence of 0.1% methanolic hydrochloric acid the diols turned a red colour. The redness is attributed to formation of a conjugated keto-compound (113).



(113)

The reactivity of cis-1,2-dihydroxy-6-methoxytetralin (66, R = OMe) was of particular interest to the present work as this system is a relatively close analogue of melacacidin. The n.m.r. spectral analysis of the reaction product of this diol with 0.01% methanolic hydrochloric acid showed the presence of a mixture of cis- and trans-tetralyl methyl ethers (115, 116). The signal of the 1-methoxyl group was centred at τ 6.84 and that of the 6-methoxyl group at τ 6.25. A symmetrical doublet centred at τ 5.85 with spin-spin coupling constant $J_{1,2}$ 3.3. c/s was assigned to the benzylic 1-proton of the cis-methyl

ether (115). The benzylic 1-proton of the corresponding cis-diol (refer Table 6) showed a doublet centred at τ 5.43. This downfield shift in the case of the diol is attributed to greater deshielding of the benzylic 1-proton by the hydrogen-bonded hydroxyl group than by the methoxyl group. A quartet centred at τ 6.03 with ~~spin-spin coupling constant $J_{1,2}$ ca 3.5 c/s and $J_{1,2}$ ca 7.4 c/s~~ splittings of ca. 3.5 and 7.4 c/s in the mixture of products was assigned to the ~~benzylic~~ 2-proton ~~of the cis- and trans-methyl ethers~~.

A possible mechanism for the formation of the cis- and trans-methyl ethers is proposed (Fig. 17). Loss of the benzylic 1-hydroxyl group by acid-catalysed alkyl-oxygen heterolysis results in the formation of a carbonium ion (114) which is stabilized by resonance. Since the three bonds attached to the central carbon of a carbonium ion are co-planar, the nucleophile (methanol) can attack from either side to give a mixture of cis- and trans-products (S_N1 mechanism). An S_N2 mechanism proceeding through an oxonium ion (117) would account for the inversion of configuration and the trans-product.[99]

In the trans-diol (67, R = OMe) there is the possibility of greater neighbouring group participation because of the favourable stereochemical arrangement of the hydroxyl groups. However, the small amounts of pure trans-diol available did not allow any detailed study with this compound.

The studies with the tetralin compounds show the greater reactivity of the 6-methoxytetralol as compared to the corresponding diols. This is attributed to the greater rigidity of the reduced

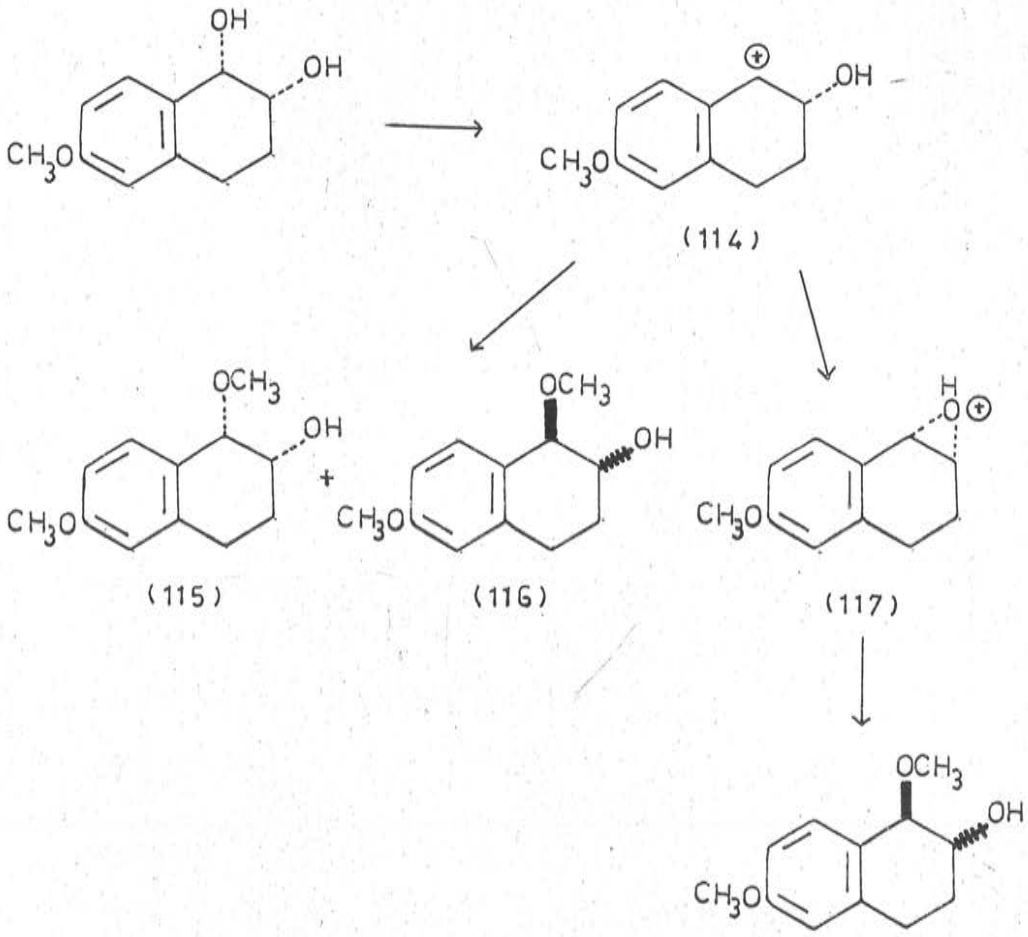

OH
OH
CH3O
OH
CH3O
(114)
OCH3
OH
CH3O
(115)
+
OCH3
OH
CH3O
(116)
OH
CH3O
(117)
OCH3
OH
CH3O

Fig. 17

ring and to the presence of strong intramolecular hydrogen bonding in the case of the diols. Melacacidin does not react with methanolic acetic acid and this was also noted in the case of the cis-diol (66, R = OMe). Williams[71] observed the presence of two ethyl ethers in the reaction of melacacidin with ethanolic hydrochloric acid. A similar observation was made with the tetralin-cis-diol. A mechanism similar to that outlined above (Fig. 17) can be suggested for the formation of the cis-cis- and cis-trans-ethyl ethers in the case of melacacidin.

The present investigation suggests that more rigid systems (3-phenyltetralins), where the hydroxyl groups have fixed conformations (see p.72) should provide better model compounds for a detailed study of the stereochemical contributions to reactivity.

The presence of an activating group in the para position on reactivity is shown clearly in the present work. As the electronic contributions from the fused aromatic ring are the same in melacacidin and isomelacacidin the greater reactivity of the latter is attributed to the conformation of the benzylic hydroxyl group (quasi-axial) and to the presence of a neighbouring trans-hydroxyl group.

***

EXPERIMENTAL

GENERAL

The nuclear magnetic resonance spectra were recorded by Dr. T. McL. Spotswood and Mr. R.L. Paltridge with a Varian D.P. 60 instrument at 60 Mc/s. The spectra were calibrated with a Muirhead-Wigan decade oscillator (D890A) using side-bands generated from the signal of tetramethylsilane used as internal standard.

The infrared spectra were recorded with Perkin-Elmer Spectrometers (137 and 237).

The ultraviolet spectra were recorded with a Perkin-Elmer Model 137 UV spectrophotometer and an Optica recording spectrophotometer.

Vapour phase chromatographic analyses were carried out using a Perkin-Elmer Model 800 gas chromatograph with flame ionization detector and three feet Apiezon columns.

Countercurrent distribution experiments were carried out using a Towers 50-tube (50 ml) automatic countercurrent distribution apparatus.

Microanalyses were carried out by the C.S.I.R.O. Microanalytical Service under the supervision of Dr. W. Zimmerman.

EXTRACTION WORK

General Experimental Conditions.

Origins of Wood samples.

Wood specimens were collected by Mr. W.T. Jones, C.S.I.R.O., Brisbane, from botanically identified *Acacia cambagei* (herbarium number WTJ 899) and *Acacia salicina* (sample number 6128) and supplied by the courtesy of the C.S.I.R.O. Chemical Research Laboratories, Melbourne.

Extraction Apparatus and General Extraction Procedure.

Hot extractions of the wood material were carried out in a cylindrical stainless-steel container totally enclosed within a stainless-steel shell with a copper coil water condenser at the top. The detachable bottom portion served as a boiler and receiver for extract from the wood. The wood container had a hole in the bottom and condensed solvent percolated directly through to the receiver. As the container was completely surrounded by the vapour of boiling solvent in an enclosed system, the extraction occurred at the boiling point of the solvent.

Cold extractions were effected by continuous percolation of cold solvent through the wood sample in the steel container.

All solvents used in extraction work were redistilled before use. The wood samples were ground to a powder before extraction.

Paper Chromatography.

Analytical paper chromatography was carried out on Whatman No. 1 paper by the descending technique. The paper was not equilibrated with the solvent and no special temperature regulation procedure was used.

The three main developing solvents used were: (1) sec-Butanol-water (2) 2% Acetic acid-water (3) Butan-1-ol-acetic acid-water (4:1:5) (BAW). BAW was made up immediately before use.

R_f values are given with respect to the point of maximum concentration except where streaks occur and these are given as a range from the rear to the front of the spot.

The following reagents were used for the detection of polyphenols on chromatograms:

(a) 1% solution of ferric chloride in ethanol.

(b) Ferric chloride-potassium ferricyanide reagent.

(c) 3% Toluene-p-sulphonic acid was used for detecting leucoanthocyanidins.

Preparative paper chromatography was carried out on Whatman 3MM paper and 1/16 in. seed test paper.

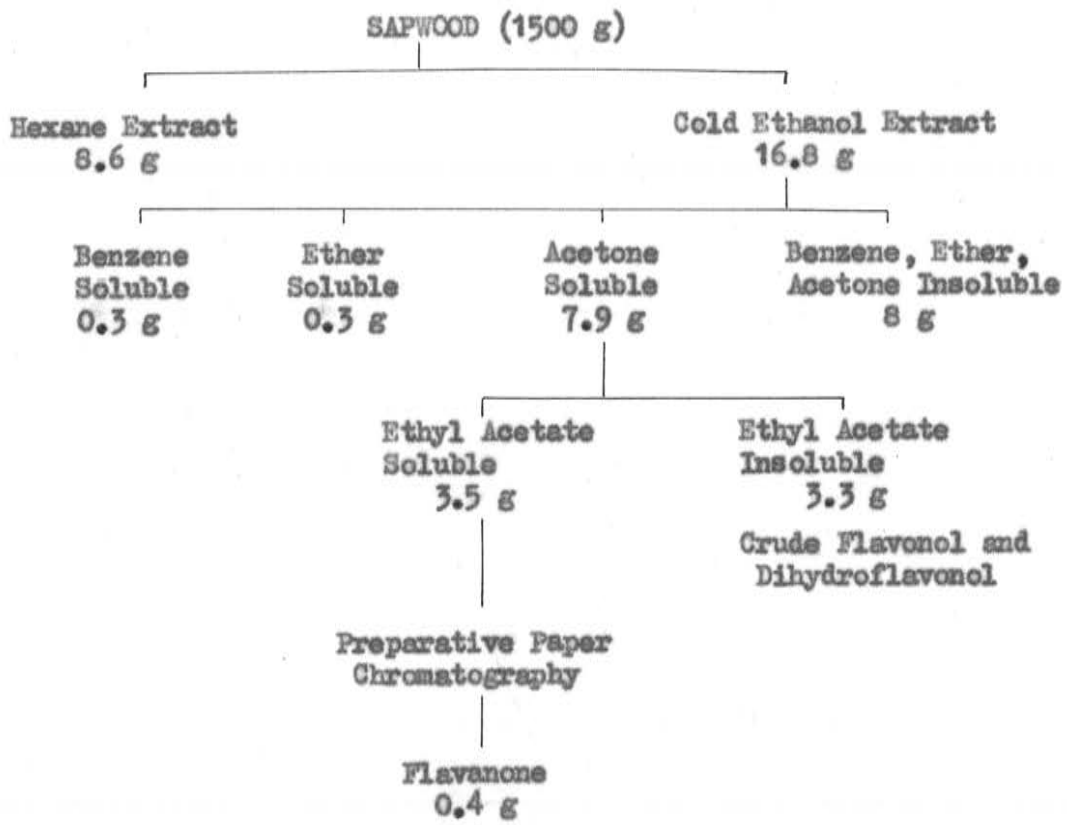
Extraction of Acacia cambagei.

(i) Sapwood.

The milled sapwood (1500 g) was extracted with hot hexane

before percolation with cold ethanol. The ethanol extractive (16.8 g) was sparingly soluble (0.3 g) in ether and was extracted with acetone. The acetone-soluble residue (7.9 g) was mixed with a little warm ethyl acetate and filtered from undissolved brown powder (3.3 g) which, after purification on a cellulose column, was found by paper chromatography to consist mainly of 7,8,3',4'-tetrahydroxy-flavonol and -dihydroflavonol.

The ethyl acetate soluble portion (4.6 g) was dissolved in methanol (10 ml) and streaked on two seed test papers (18 x 22 x 1/16 in.). Development with ascending 2% acetic acid gave a light brown non-fluorescent zone (R_F 0.23-0.35) from which crude 7,8,3',4'-tetrahydroxyflavanone (0.4 g) was obtained.



Identification of Constituents

(±)-7,8,3',4'-Tetrahydroxyflavanone (42)

Attempts to crystallize the crude flavanone from water and from an acetone-methanol mixture (1:1 v/v)[116] were unsuccessful. Preparative paper chromatography on Whatman 3MM paper gave a chromatographically homogeneous sample which was used for further study. The flavanone had R_F 0.77 ($Bu^sOH - H_2O$) and R_F 0.23 (2% acetic acid). It gave a magenta colour with Mg/HCl said to be characteristic of flavanones. A paper chromatogram of the flavanone developed with 2% acetic acid was dried and sprayed with a 2% solution of sodium borohydride in methanol. After some minutes the chromatogram was fumed with hydrochloric acid gas. A blue-purple spot (R_F 0.25) appeared slowly and was completely developed in 3 minutes. The test is said to be very useful for the detection of flavanones.[64,65]

Light absorption in 95% ethanol: λ_{max} 293 mμ (log ε 4.13), λ_{min} 258 mμ (log ε 3.40), and an inflection at 235 mμ (log ε 4.15). Addition of a drop of 1N NaOH resulted in a bathochromic shift of 40 mμ in the absorption maximum of the long-wave band. Shimokariyama[3] reported for the racemic compound in 98% ethanol: λ_{max} at 235 (log ε 4.15) and 291 mμ (log 4.12), and λ_{min} at 257 mμ (log ε 3.30). The infrared spectrum (Nujol) showed a strong sharp carbonyl absorption at 1650 cm^{-1}.

Micro-degradation of the flavanone with potassium hydroxide under anhydrous condition for 15 minutes gave 3,4-dihydroxybenzoic acid. A spot on the paper chromatogram at R_F 0.53 (2% acetic acid)

was possibly due to the presence in the degradation product of 3,4-dihydroxybenzaldehyde.

Methylation of the crude flavanone (0.1 g) in acetone with methyl iodide (2 ml) and potassium carbonate (1.5 g) gave 7,8,3',4'-pentamethoxyflavanone, m.p. 140-142°, and undepressed by admixture with synthetic 7,8,3',4'-tetrahydroxyflavanone,[6] m.p. 143°.

7,8,3',4'-Tetrahydroxyflavonol (10, R = OH) and (±)-7,8,3',4'-tetrahydroxydihydroflavonol.(41)

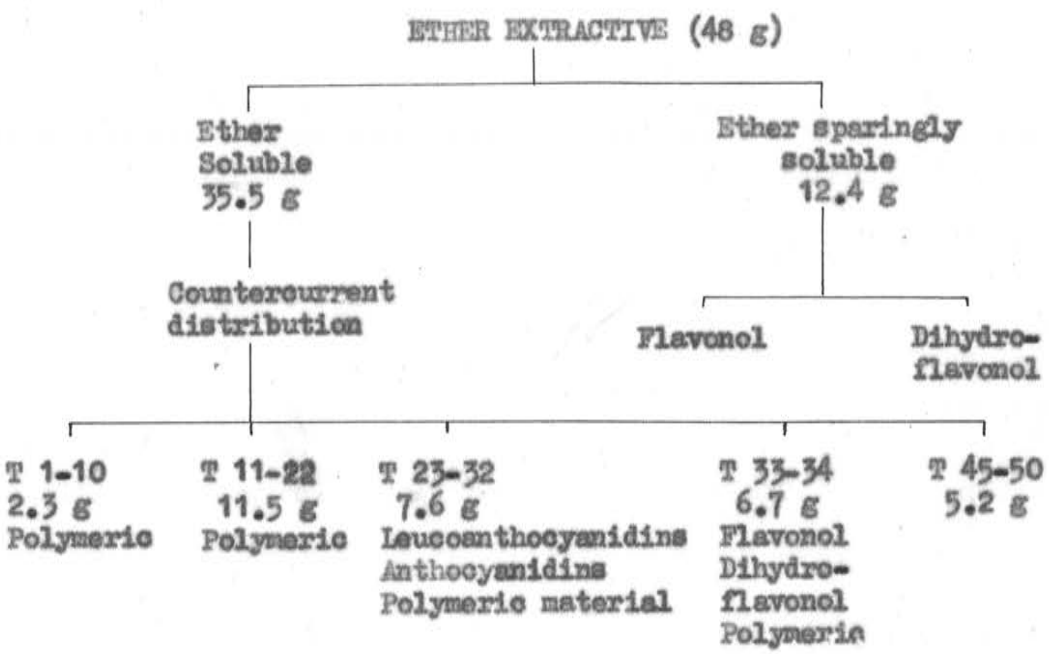
The flavonol and dihydroflavonol were purified by chromatography over powdered cellulose and identified by microdegradation and comparative paper chromatography with authentic samples extracted from the heartwood of A. cambagei and A. salicina.

(ii) Heartwood.

The milled heartwood (7200 g) of A. cambagei was extracted by continuous hot percolation with light petroleum (b.p. 40-60°) for 24 hr and gave a white amorphous powder (1.2 g, 0.01%) and an orange waxy extractive (60 g, 0.8%). The white amorphous substance is possibly a triterpene but its presence in small quantities and the difficulty encountered in purifying it precluded further investigation.

Ether extraction of the heartwood for 30 hr gave a brown solid (48 g, 0.7%). Percolation to exhaustion with cold ethanol gave a viscous extractive (335 g, 4.7%) and percolation with hot acetone for 20 hr then yielded a dark resinous extractive (229 g, 3%).

The ether extractive (48 g) was digested with hot ether (300 ml) and an undissolved mixture (12.4 g) of 7,8,3',4'-tetrahydroxyflavonol and-dihydroflavonol was removed by filtration; it was separated by treatment with hot methanol into a fraction rich in flavonol (8.3 g) and a fraction rich in dihydroflavonol (1.8 g). These were identified by paper chromatographic comparison with the compounds isolated from A. excelsa[7] as well as by degradation and preparation of derivatives (below). The portion of the ether extractive that was readily soluble in ether contained a considerable amount of intractable phenolic material, apparently polymeric in nature as evidenced by extensive streaking in paper chromatograms of the fractions from the countercurrent distribution of the material. (see block diagram.)

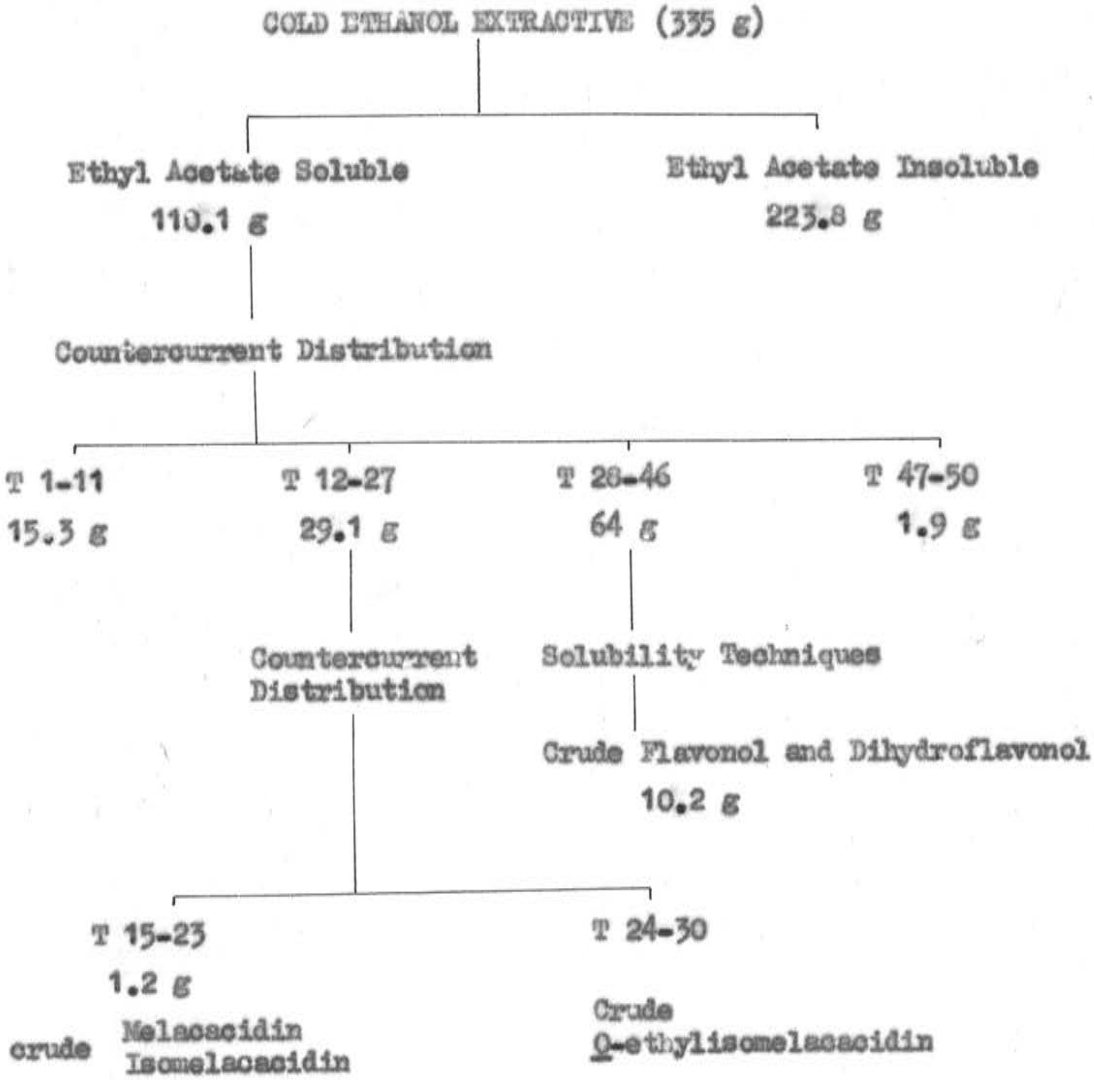


The viscous residue (335 g) from the ethanol percolate was extracted with hot ethyl acetate (ca 600 ml) and the soluble portion (110 g) was distributed between ethyl acetate and 0.067M phosphate buffer at pH 7.0 in a 50 tube (50 ml) countercurrent machine. Tubes 28-46 gave a crude mixture of 7,8,3',4'-tetrahydroxy-flavonol and -dihydroflavonol (10.2 g).

The ethyl acetate-soluble portion (17.3 g) from tubes 12-27 was submitted to another countercurrent distribution. Tubes 15-23 (peak at T 20) in the second distribution were found to contain melacacidin, R_F 0.47 (2% acetic acid) and isomelacacidin, R_F 0.57, identified by comparative paper chromatographic examination, and concentration gave a residue (1.2 g). Tubes 24-30 were found by paper chromatographic examination to contain some O-ethylisomelacacidin.

Table showing countercurrent distribution of A. cambagei heartwood polyphenols.

Tube Extent	Peak Tube	R_F (2% Acetic Acid)	Identity
1 - 14		Streaks	Polymeric
15 - 23	20	0.47	Melacacidin
		0.57	Isomelacacidin
		Streaks	Polymers
24 - 30	?	0.65	O-ethylisomel.
		Streaks	Polymers
31 - 50	41	0.01	Flavonol
		0.04	Dihydroflavonol



The ethyl acetate-soluble portion (65 g) of the acetone extractive was submitted in two portions to countercurrent distribution between ethyl acetate and 0.067M- phosphate buffer (pH 7). Tubes 15-25 which contained melacacidin and isomelacacidin were combined and the residue (15.3 g) submitted to another countercurrent distribution. From this, a light brown residue (3.4 g), containing

a mixture of melacacidin and isomelacacidin was obtained. Attempts to separate melacacidin and isomelacacidin by countercurrent distribution were unsuccessful. In the separation of O-ethylisomelacacidin from melacacidin and its 4-epimer, isomelacacidin by countercurrent distribution procedures use was made of the enhanced distribution ratio of O-ethylisomelacacidin in the ethyl acetate-water system. O-ethylisomelacacidin was an artefact from isomelacacidin and ethanol. The presence of a considerable proportion of intractable polymeric phenolic material presented further difficulties in separating the crude monomers.

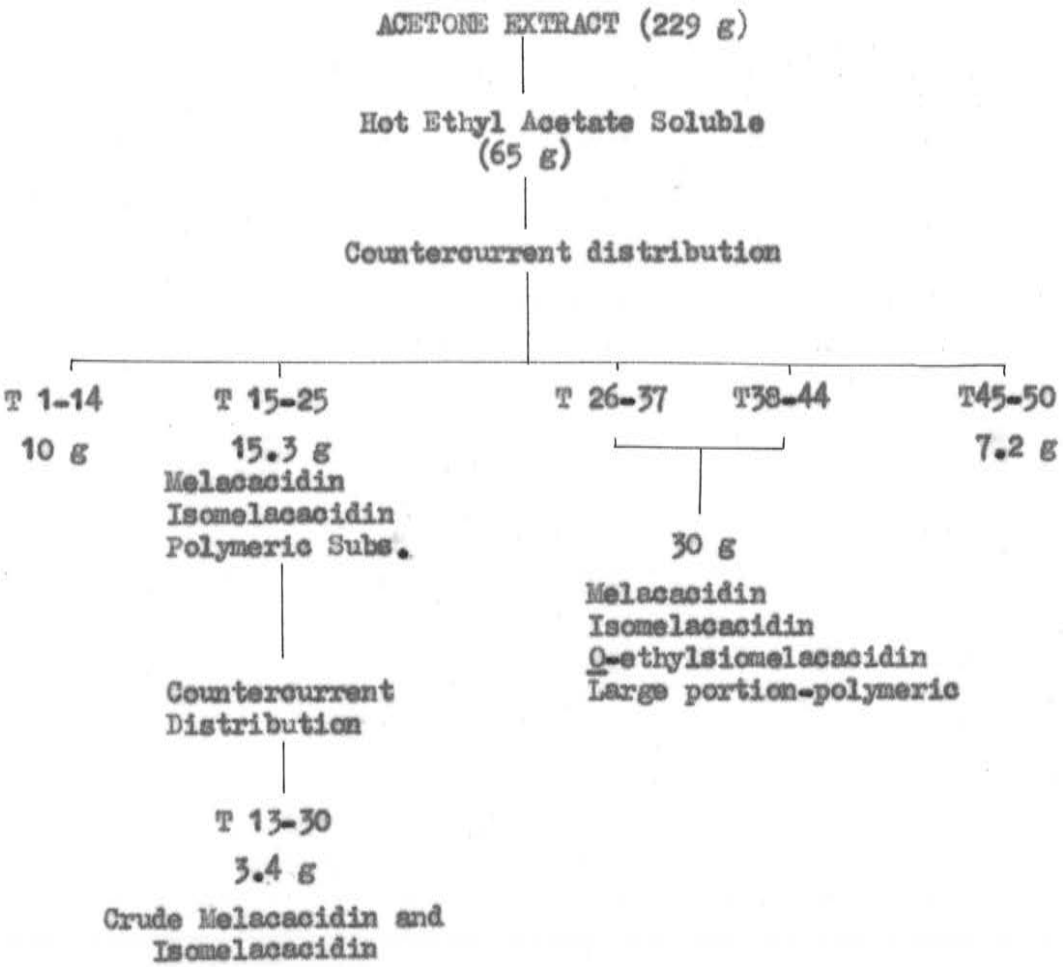


Table showing countercurrent distribution of A. cambagei heartwood polyphenols

Tube extent	Peak Tube	R_F (2% Acetic acid)	Identity
1 - 12		Streaks	Polymeric
13 - 30	25	0.47 0.58	Melacacidin Isomelacacidin
30 - 50			Dark brown resin

The ether soluble portion of the dry ethanol extractive showed the presence in it of ketonic flavonoids and the Lindstedt and Erdtman method of isolation[117] was carried out. The ethereal solution was shaken successively with saturated aqueous sodium bicarbonate, with a saturated solution of sodium carbonate, with dilute sodium hydroxide (0.2%) and then with stronger sodium hydroxide solution (5%). Each aqueous extract was acidified with dilute sulphuric acid and extracted with ether. Almost all the ketonic flavonoid was found in the sodium carbonate extract (4.2 g). The crude ketonic flavonoid was chromatographed on magnesium trisilicate and gave a bright yellow amorphous compound (1.3 g) which was shown by paper chromatographic examination and methylation to be 7,8,3',4'-tetrahydroxyflavonol.

Identification of Constituents.

7,8,3',4'-Tetrahydroxyflavonol (10, R = OH).

The crude flavonol (1.0 g) isolated from the ether extraction was chromatographed twice over magnesol using water saturated ethyl acetate as the eluting solvent. A yellow amorphous material (0.2 g) was obtained. The flavonol gave a streak on paper chromatograms (R_F 0.35 - 0.51, Bu^3OH - H_2O) and a bright yellow fluorescence under ultraviolet light. The infrared spectrum of the flavonol (in Nujol) showed a broad O-H absorption band and a carbonyl band at 1620 cm^{-1}.[5] Härhammer and Wagner[118] pointed out that in flavones substituted at C_4', ring B becomes a p-substituted benzene ring and the spectrum shows bands at 810 and 830 cm^{-1} which represents the γ-vibration of the p-substituted ring B. The above flavonol showed absorption peaks at 840, 820, 788, and 745 cm^{-1}. Comparison with the infrared spectrum of quercetin suggested the possibility of a 3,4-hydroxylation pattern in ring B.

Alkali Fusion:

Micro-degradation with potassium hydroxide under anhydrous conditions for twenty minutes gave pyrogallol and 3,4-dihydroxybenzoic acid, identified by comparison of R_F with that of authentic samples and by spraying with 1% alcoholic ferric chloride (green with 3,4-dihydroxybenzoic acid - R_F 0.46 in 2% acetic acid, yellow-brown with pyrogallol - R_F 0.61).

3,7,8,3',4'-Penta-acetoxyflavone.

The crude flavonol (0.6 g) was acetylated with acetic anhydride (6 ml) and sodium acetate (1 g). Crystallization (twice) of the crude penta-acetoxyflavone from ethanol gave yellow prisms, m.p. 171-173° (lit.[119] m.p. 173°).

3,7,8,3',4'-Pentamethoxyflavone.

The crude flavonol (1.12 g) was methylated in dry acetone with excess dimethyl sulphate (4 ml) and potassium carbonate (8 g) for 16 hr. Repeated crystallization of the crude product (1.08 g) from ethanol gave 3,7,8,3',4'-pentamethoxyflavone as white needles, m.p. 153° alone and when mixed with a synthetic sample.[42]

(Found: C, 64.4; H, 5.5. Calc. for $C_{20}H_{20}O_7$: C, 64.5; H, 5.4%).

Light absorption in 95% ethanol: λ_{max} at 250 mμ (ε 22,600) and 347 mμ (ε 21,800), and inflection at 318 mμ (ε 14,300); λ_{min} at 278 mμ (ε 5,200). The infrared spectrum (Nujol) showed $\nu_{c=o}$ at 1625 cm^{-1}.

(±)-7,8,3',4'-Tetrahydroxydihydroflavonol.

The crude dihydroflavonol isolated above was purified by chromatography over cellulose powder using chloroform-methanol-water (27:3:10) as the eluant.[120] Further purification was carried out by preparative paper chromatography using Whatman 3MM paper. The compound in ethanol gave a stable deep-red colour with Mg/HCl. A chromatographically homogeneous sample gave a positive result in a

test said to be specific for dihydroflavonols.[121] It was chromatographically indistinguishable from the material obtained from A. excelsa.[7] On paper chromatograms it gave a blue fluorescence under ultraviolet light, R_F 0.79 (Bu^sOH-H_2O), R_F 0.70 (BAW). It had $[\alpha]_D$ 0° (0.25% in ethanol). The dihydroflavonol was found to be unstable to traces of acid, and paper chromatograms, when sprayed with ethanolic 3% toluene-p-sulphonic acid, gave a yellow colour immediately.

3,7,8,3',4'-Pentamethoxyflavone.

Methylation of the dihydroflavonol (0.2 g) in dry acetone with dimethyl sulphate (1.5 ml) and potassium carbonate (2 g) under nitrogen (the mixture turned yellow immediately) gave 3,7,8,3',4'-pentamethoxyflavone (0.1 g), m.p. 152-153°, alone and when mixed with authentic 3,7,8,3',4'-pentamethoxyflavone.

Methylation of the dihydroflavonol with diazomethane and also with methyl iodide-acetone-potassium carbonate gave the same product.

Methylation of the dihydroflavonol from A. excelsa, also gave the pentamethoxyflavone, m.p. 151°, not depressed by admixture with authentic material, but depressed by authentic (±)-7,8,3',4'-tetramethoxydihydroflavonol, m.p. 166°.

Melacacidin.

The crude melacacidin was purified for further investigation

by preparative paper chromatography on Whatman 3MM paper using 2% acetic acid as the developing solvent, R_F 0.45, and R_F 0.42 (Bu^sOH-H_2O). Light absorption in 95% ethanol: λ_{max} 283 mμ and λ_{min} 256.

Attempted crystallizations of crude melacacidin from ethanol and acetic acid were unsuccessful as extensive polymerization occurred when the solution was left standing. A solution in methanol was left standing at 0° for six months and deposited a crystalline material, m.p. 84-86° which is possibly a partial methylation product of the flavan-3,4-diol.

3,7,8,3',4'-Pentahydroxyflavylium chloride.

When heated with 3N-HCl-propan-2-ol (1:4 v/v) the leucoanthocyanidin developed a bright red colour (λ_{max} in 95% ethanol:542 mμ). The anthocyanidin formed was identified by comparative paper chromatography with an authentic sample of 3,7,8,3',4'-pentahydroxyflavylium chloride.[7] It had R_F 0.40 (3N-HCl-90% formic acid, 1:1 v/v) and turned blue when sprayed with a 1% solution of aluminium chloride and when exposed to ammonia vapour.

Using the authentic sample of the anthocyanidin (λ_{max} 542 mμ, log ε = 3.97 and extinction 0.699 of a solution containing 0.006 g in 250 ml of 95% ethanol) estimation of the yield of the anthocyanidin derived from the natural leucoanthocyanidin was made.

(Found: 34.9%).

7,8,3',4'-Tetramethoxyflavan-3,4-diol and -diacetate.

Attempts to obtain a crystalline derivative by methylation of the crude flavan-3,4-diol were unsuccessful mainly due to difficulty encountered in separation of the methylated material from the accompanying polymeric substances.

Crude melacacidin (1 g) was methylated using methyl iodide-tetrahydrofuran-potassium carbonate. The product was worked up in the usual way and chromatographed over deactivated alumina but the light yellow oil (0.2 g) obtained, failed to crystallize. This methylated product was acetylated using acetic anhydride and pyridine but all attempts to crystallize the product were unsuccessful.

(iii) Bark.

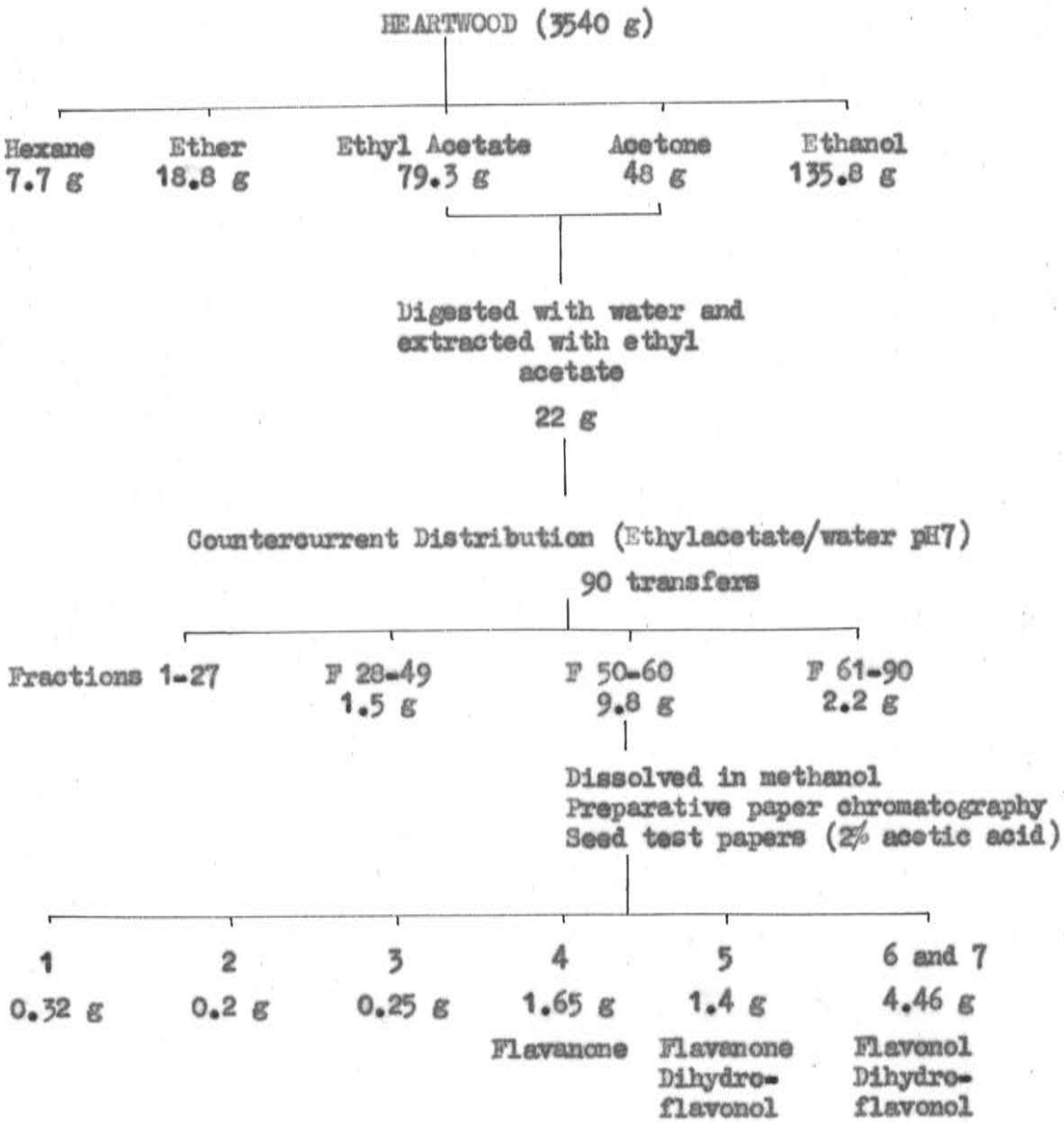
The milled bark (1360 g) was extracted by continuous hot percolation with hot acetone for 20 hr and gave 7.2 g of a lumpy brown deposit and 89.4 g of viscous extractive. The brown solid was soluble in dilute alkali but insoluble in all the common organic solvents. It is possible that the solid is a resin acid.

The viscous residue (89.4 g) was leeched with ether and the ether soluble bright yellow solid (6.3 g) was chromatographed over alumina and gave a yellow oil (4.8 g), b.p. 120°/1mm. The compound was found to be sensitive to sunlight (a sample containing 2 mgs in 10 ml of benzene turned from yellow to colourless within 1½ hr). The infrared spectrum of the oil suggested that it was possibly an aliphatic ester.

Extraction of Acacia Salicina.

(i) Heartwood.

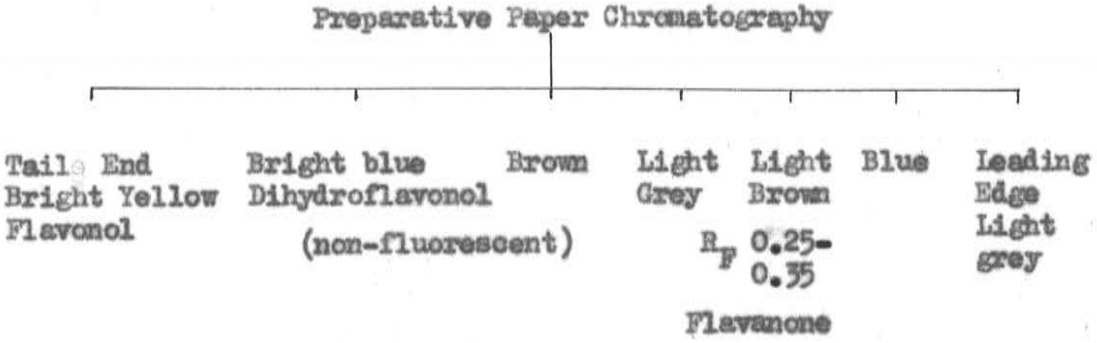
The heartwood of A. salicina was extracted by Clark-Lewis[2] and the block diagram shows how further separation was carried out. The method of separation is similar to that described for A. cambagei.



Separation, Purification and Identification of Constituents.

(±)-7,8,3',4'-Tetrahydroxyflavanone.

A portion of section 4 from the above paper chromatogram (1.36 g) was chromatographed over cellulose powder. The partly purified material (1.11 g) was submitted to preparative paper chromatography using Whatman 3MM paper with descending 2% acetic acid for 5 hr. Examination of the paper under ultraviolet light showed seven zones.



The non-fluorescent brown band (R_F 0.25 - 0.35) was excised, extracted with ethanol, and the ethanol removed. The dry extract (0.5 g) was suspended in water and the aqueous solution extracted continuously with ether. Removal of ether left a dark brown powder (0.36 g) consisting mainly of 7,8,3',4'-tetrahydroxyflavanone R_F 0.25 (2% acetic acid), R_F 0.72 (butan-1-ol).

The compound was identified by its degradation products, its infrared and ultraviolet spectra and by methylation to the tetramethoxyflavanone (see preceding section on isolation of this flavanone from A. cambagei).

7,8,3',4'-Tetrahydroxyflavonol and (±)-7,8,3',4'-Tetrahydroxydihydroflavonol.

A convenient method of separating the flavonol from the dihydroflavonol has been found and will be described here. Zone 6 (2.7 g) from the seed test paper chromatogram above was purified by passage through a cellulose column using water saturated ethyl acetate as the eluant. A second chromatography over cellulose powder using chloroform: ethanol:water (27:3:10 by volume) as the eluting solvent[120] was carried out. Fraction 1 gave pure dihydroflavonol (0.06 g), R_F 0.76 (Bu^sOH-H_2O). Fractions 2 to 8 (1.0 g) contained a mixture of flavonol and dihydroflavonol, R_F 0.44, R_F 0.76 (Bu^sOH-H_2O). Fractions 9 to 12 gave pure flavonol (0.45 g).

The flavonol and dihydroflavonol were identified by comparative paper chromatographic examination, micro-degradation and methylation.

(ii) Bark.

The bark of A. salicina (1674 g) was extracted with light petroleum (b.p. 40-60°) (5.8 g of oily extractive) followed by percolation to exhaustion with cold ethanol (12.6 g of red extractive). The ether soluble portion of the dry ethanol extractive showed the presence of a cinnamic acid, R_F 0.29, 0.66 (2% acetic acid) R_F 0.86 (Bu^sOH). The two blue fluorescent spots appear to be the cis- and trans-forms of the cinnamic acid. This is possibly caffeic acid.

(iii) Sapwood.

The sapwood of A. salicina (2770 g) was extracted by Clark-Lewis.[2] The ethyl acetate extractive gave, after countercurrent distribution and preparative paper chromatography, (-)-7,8,3',4'-tetrahydroxyflavanone, m.p. 126-127° (water), $[\alpha]_D^{17}$ - 11.9° (1% in MeOH), $[\alpha]_D^{17}$ - 11.8° (1% in acetone-water, 1:1). The structure of the compound was established[2] by degradation and methylation, and by its n.m.r. spectrum which showed the X quartet typical of the ABX spectra of flavanones.

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SYNTHESIS OF 3-SUBSTITUTED FLAVANONES

2'-Hydroxy-3,4,3',4'-Tetramethoxychalcone.

2-Hydroxy-3,4-dimethoxyacetophenone[122] (13 g) and veratraldehyde (11 g) in ethanol (130 ml) were condensed with the aid of potassium hydroxide (25 g, 50% solution) as described by Crabtree and Robinson.[123] The precipitated 2'-hydroxy-3,4,3',4'-tetramethoxychalcone (20.2 g) crystallized from 90% ethanol in slender yellow needles (14.6 g, 64%), m.p. 125° (lit.[123] m.p. 125°).

3,7,8,3',4'-Pentamethoxyflavone (44)

The foregoing chalcone (14.6 g) was converted into the flavonol with alkaline hydrogen peroxide as described by King and Bottomley.[5] The flavonol crystallized from methanol in yellow prisms (4.9 g, 33%), m.p. 219-221° (lit.[5] m.p. 220-221°). Methylation of the flavonol (4.9 g) with dimethyl sulphate (3 g) and anhydrous potassium carbonate (30 g) in acetone (150 ml) for 5 hr gave 3,7,8,3',4'-pentamethoxyflavone which crystallized from methanol in needles (3.5 g, 69%), m.p. 153° (lit.[5] m.p. 151°).

2,3-cis-3,4-cis-3,7,8,3',4'-Pentamethoxyflavan-4-ol (45)

(a) Reduction with Raney nickel catalyst.

W5 Raney nickel catalyst was prepared by the method of Adkins and Billica[124] and stored under ethanol at 0° for one month. A small portion of this was then deactivated further by heating under reflux in ethanol for 8 hr. A 1:1 mixture of this deactivated and

the one month old Raney nickel was used for the reduction reaction.

3,7,8,3',4'-Pentamethoxyflavone (1 g) was dissolved in ethanol (80 ml) and hydrogenated for 22 hr at 100° and 100 atm. over the Raney nickel (1 g) described above. Removal of the catalyst by filtration and concentration of the filtrate gave 2,3-cis-3,4-cis-3,7,8,3',4'-pentamethoxyflavan-4-ol (0.15 g, 16%). Crystallization from ethanol gave fine white needles, m.p. 151-152°.

(b) Reduction with nickel boride catalyst.

The nickel boride catalyst was prepared in the aqueous state by the method of Brown and Brown.[70] Nickel acetate (1.2 g) was dissolved in water (100 ml) and then flushed with nitrogen. To the magnetically stirred solution, 30ml of a 1M solution of sodium borohydride in water was added slowly over 50 seconds. When the vigorous effervescence had subsided the nickel boride was stirred for a further minute and then collected with the aid of a centrifuge. It was washed several times with water and then with ethanol.

3,7,8,3',4'-Pentamethoxyflavone (0.77 g) in ethanol (100 ml) was hydrogenated for 12 hr at 80° and 70 atm. over the nickel boride catalyst described above. Removal of the catalyst by filtration and concentration of the filtrate gave a white crystalline compound (0.33 g, 69%) which was chromatographed over deactivated alumina (20 g containing 10% by weight of water). Crystallization from methanol then gave 2,3-cis-3,4-cis-3,7,8,3',4'-pentamethoxyflavan-4-ol as opaque prisms, m.p. 151°.

(Found: C, 64.3; H, 6.4. $C_{20}H_{24}O_7$ requires C, 63.8; H, 6.4%).

The n.m.r. spectrum (in CCl_4/30% $CDCl_3$ and after D_2O exchange) showed the 3H as a quartet centred at τ 6.33 with coupling constants $J_{2,3}$ 0.9 c/s and $J_{3,4}$ 4.5 c/s. The 4H showed a doublet centred at τ 5.07 with coupling constant $J_{3,4}$ 4.4 c/s. The signal of the 2H was a singlet at τ 4.92. The aromatic methoxyl groups absorbed at τ 6.08 and the 3-methoxyl appeared at τ 6.99. The aromatic protons showed a multiplet centred at τ 3.16.

Dimorphism in 2,3-cis-3,4-cis-3,7,8,3',4'-pentamethoxyflavan-4-ol.

The flavan-4-ol described above appeared to be dimorphic. It crystallized from chloroform, carbon tetrachloride or chloroform-carbon tetrachloride mixtures as small white needles, m.p. 127-128°. From methanol it crystallized as opaque white prisms, m.p. 151-152°. Mixed m.p. of a 1:1 mixture of compound m.p. 127-128° with compound m.p. 151-152° showed no depression of the m.p. of the latter. The individual compounds and a 1:1 mixture were spotted on thin-layer silica gel plates and developed by ascending method using 5% ethanol/chloroform. A single spot appeared in each case when the plate was fumed with iodine. All three spots had the same R_F value.

2,3-cis-3,7,8,3',4'-pentamethoxyflavanone (46)

(a) Oxidation with manganese dioxide.

"Active" manganese dioxide was prepared by the method of Attenburrow and his co-workers[59] and heated at 100° for 15 mins before each oxidation.

The foregoing flavan-4-ol (0.7 g) was oxidized with finely powdered manganese dioxide (10 g) in chloroform (120 ml) for 11 hr during which time the hydroxyl band disappeared from the infrared spectra of aliquots of the solution. Filtration of the manganese dioxide and evaporation of the chloroform under reduced pressure gave a light yellow viscous oil (0.45 g, 66%). A further 0.095 g of yellow oil was obtained when the manganese dioxide was suspended in water, decomposed with sulphur dioxide, and extracted with chloroform. The yellow oil crystallised on trituration with methanol (2 ml). Further recrystallizations from methanol gave pure 2,3-cis-3,7,8,3',4'-pentamethoxyflavanone as white prisms (0.2 g), m.p. 109.5-110.5° (Found: C, 64.1; H, 6.1. $C_{20}H_{22}O_7$ requires C, 64.2; H, 5.9%).

The n.m.r. spectrum (in $CDCl_3$) showed a one proton doublet (B part of AB system) centred at τ 4.58 due to the 2H, with coupling constant $J_{2,3}$ 2.5 c/s. The 3H appeared as a doublet at τ 6.07 being partly obscured by the aromatic methoxyl protons which showed an intense absorption at τ 6.08. The absorption of the 3-methoxyl protons occurred at τ 6.59 and the aromatic protons showed a multiplet centred at τ 2.98.

Light absorption in 95% ethanol: λ_{max} at 288 mμ (log ε 4.25). The infrared spectra showed: ν_{max} (Nujol) 1665 cm^{-1}, ν_{max} ($CHCl_3$) 1665 cm^{-1} (carbonyl).

(b) Oxidation with nickel peroxide.

Nickel peroxide was prepared by the method of Nakagawa,

Konaka and Nakata.[74] A solution of sodium hydroxide (4.2 g) in sodium hypochlorite (30 ml of a 6% solution) was added dropwise to a solution of nickel sulphate (13 g) in water (30 ml) and stirred for 15 mins at 25°. The resulting nickel peroxide was collected by filtration, washed with water, dried over anhydrous calcium chloride and crushed to a fine powder (6 g).

2,3-cis-3,4-cis-7,8,3',4'-Pentamethoxyflavan-4-ol (0.5 g) was oxidized with nickel peroxide (2 g) in benzene (50 ml) for 5 hr. Removal of the nickel peroxide by filtration and evaporation of the benzene gave a bright yellow oil (0.3 g). Light absorption of the product in 95% ethanol: λ_{max} 250, 350, and 290 mμ and λ_{min} at 278 mμ. This shows that a mixture of 3,7,8,3',4'-pentamethoxyflavone and 3,7,8,3',4'-pentamethoxyflavanone is present. The infrared spectrum (Nujol) showed $\nu_{C=O}$ at 1630 cm^{-1} and 1670 cm^{-1}.

Reduction of 2,3-cis-3,7,8,3',4'-Pentamethoxyflavanone.

(a) Reduction with sodium borohydride.

Sodium borohydride (0.2 g) was slowly added to a solution of 2,3-cis-3,7,8,3',4'-pentamethoxyflavanone (0.25 g) in methanol (100 ml). The mixture was shaken gently for a ½ hr and left to stand overnight at room temperature. A drop of acetic acid was then added to decompose any unreacted sodium borohydride. On reduction of volume, white, needle-shaped crystals (0.2 g, 80%) separated out. Chromatography over deactivated alumina (20 g containing 10% by weight of water) gave a single compound, 2,3-cis-3,4-cis-3,7,8,3',4'-penta-

methoxyflavan-4-ol, as the 50% benzene/ether eluate. The flavan-4-ol crystallized from methanol as needles, m.p. 127-128°. The n.m.r. spectrum (in $CDCl_3$) showed the 3H as a quartet centred at τ 6.28 with coupling constants $J_{2,3}$ 1.0 c/s and $J_{3,4}$ 4.4. c/s. The signal of the 4H was a doublet centred at τ 5.02 with coupling constant $J_{3,4}$ 4.2 c/s and the 2H showed a singlet at τ 4.87. The aromatic methoxyl protons absorbed at τ 6.08 and 3-methoxyl protons appeared at τ 6.86. The benzylic hydroxyl proton appeared surprisingly as a split peak centred at τ 7.55. The aromatic protons showed a multiplet centred at τ 2.99.

(b) Reduction with nickel boride.

The flavanone (0.08 g) in ethanol (50 ml) was hydrogenated catalytically at room temperature and 35 atm. hydrogen pressure using nickel boride. The reaction product (0.064 g, 80%) was chromatographed over deactivated alumina. The flavan-4-ol crystallized from methanol as white prisms, m.p. 152° alone and when mixed with a sample of 2,3-cis-3,4-cis-3,7,8,3',4'-pentamethoxyflavan-4-ol.

2,3-trans-7,8,3',4'-Tetramethoxydihydroflavonol (58)

2'-Hydroxy-3,4,3',4'-tetramethoxychalcone (12.0 g), 40% aqueous benzyltrimethylammonium hydroxide (Triton B) (40 g) and aqueous ethanol (300 ml of 70%) were treated at 0° with hydrogen peroxide (90 ml, 6%).[20] The reaction mixture was stirred for 3 hr and aqueous sodium bisulphite (60 ml, 4%) was added followed by

dilute hydrochloric acid (50 ml). The temperature was maintained at ca 10° throughout the additions. The light yellow compound which precipitated was collected, washed with aqueous ethanol (40 ml., 50%) and crystallized from methanol to give 2,3-trans-7,8,3',4'-tetramethoxydihydroflavonol as white needles (8.1 g, 64.5%), m.p. 166° (lit.[6] m.p. 166°). wrong ref

The dihydroflavonol slowly oxidized to the corresponding flavonol when left standing in solution at room temperature. Oxidation to the flavonol occurred much more readily on an alumina column.

Light absorption in 95% ethanol: λ_{max} 286 mμ. ν_{max} ($CHCl_3$) 3460 cm^{-1} (OH), 1680 cm^{-1} (c = o). The n.m.r. spectrum (in $CDCl_3$) showed an intense resonance centred at τ 6.10 due to the methoxy groups, a one proton doublet centred at τ 5.47 with spin-spin coupling constant $J_{2,3}$ 12.3 c/s due to the 3H and another doublet centred at τ 4.93 with spin-spin coupling constant $J_{2,3}$ 12.1 c/s due to the 2H. A one-proton doublet at τ 3.29 was assigned to the 2'-H of the B ring and another at τ 2.30 was assigned to the 5H (deshielded because adjacent to the carbonyl group). The ortho spin-spin coupling constants in both cases were of the order of 9.1 c/s. The absorption of the 3',6,6'-protons (2',5',6') centred at τ 3.91 was partly obscured by the singlet at τ 3.90 due to the 3-hydroxyl group and also by the absorption of the chloroform present in the solvent.

Attempted synthesis of 2,3-cis-7,8,3',4'-Tetramethoxydihydroflavonol (60)

2,3-cis-3,4-cis-7,8,3',4'-Tetramethoxyflavan-3,4-diol (59)

7,8,3',4'-Tetramethoxyflavonol (2 g) in ethanol (125 ml) was hydrogenated for 20 hr at 90°/70 atm. over nickel boride catalyst.[70] Removal of the catalyst by filtration and concentration of the filtrate gave a light yellow oil which was chromatographed over deactivated alumina. Elution with 50% benzene/ether gave the cis-cis-diol which crystallized slowly from this solvent mixture as prisms (0.9 g, 45%), m.p. 132-133°, (lit.,[6] m.p. 135-136°). The diol also crystallized from benzene/ether as needles, m.p. 84-85° (possibly dimorphic). ν_{max} (in $CHCl_3$) : 3540 cm^{-1}, and a broad band of lower intensity centred at 3400 cm^{-1} (OH.....O).

Prolonged hydrogenation of 7,8,3',4'-tetramethoxyflavonol resulted in hydrogenolysis of the benzylic hydroxyl group and the corresponding cis-flavan-3-ol was produced. The compound crystallized from ethanol as needles, m.p. 123-125° (lit.[125] 118-119°). $\nu_{max.}$ (Nujol): 3540 cm^{-1}.

Acetylation of the foregoing flavan-3-ol gave the acetate as prisms, m.p. 138-139° (lit.[125] m.p. 137°). The n.m.r. spectrum (in $CDCl_3$) showed an intense singlet at τ 8.10 due to the acetoxyl group, and ~~a symmetrical quartet centred at τ 6.90 due to benzylic 4-CH_2 with the sum of the spin-spin coupling constants $J_{AX} + J_{BX}$ 11.6 c/s for the ABXY system. The methoxyl groups~~ methoxyl absorption at τ 6.10. The 3H (τ 4.56) and 4-CH_2 (τ 6.90) showed absorptions typical of ABX spin systems. The 2-proton doublet occurred at τ 4.87 ($J_{2,3}$ ca. 1.2 c/s) and the aromatic protons absorbed as a multiplet centred at τ 3.17.

~~resonance at τ 6.10, the 2H a doublet centred at τ 4.87 with spin-spin coupling constant $J_{2,3}$ 1.25 c/s, and the 3H a poorly resolved band centred at τ 4.56. The aromatic protons showed a multiplet centred at τ 3.17.~~

Oxidation of 2,3-cis-3,4-cis-7,8,3',4'-tetramethoxyflavan-3,4-diol with manganese dioxide.

The diol (0.75 g) was oxidized with finely powdered manganese dioxide (8 g) in chloroform (100 ml) for 24 hr during which time a carbonyl band (1680 cm^{-1}) appeared in the infrared spectra of aliquots of the solution. Filtration of the manganese dioxide and evaporation of the chloroform under reduced pressure gave a yellow viscous oil (0.6 g, 80%).

The compound was found to be very unstable and attempts to crystallize it or chromatograph it resulted in further decomposition. The n.m.r. spectra of the product did not show the AB quartet typical of the spectra of dihydroflavonols. The infrared spectrum ($\nu_{c=o}$ 1630 cm^{-1}) and ultraviolet spectrum (λ_{max} 240 and 350 mμ) showed that the cis-dihydroflavonol had decomposed possibly to the corresponding flavone during the working up and purification procedures.

Attempted synthesis of 2,3-trans-3,7,8,3',4'-pentamethoxyflavanone.

(i) Methylation of the 3-hydroxyl group.

(a) With methyl iodide and barium oxide in dimethyl sulphoxide.

2,3-trans-7,8,3',4'-tetramethoxydihydroflavonol (0.5 g) in

dimethyl sulphoxide (15 ml) was methylated with methyl iodide and barium oxide[81] at room temperature for 3 days. The reaction mixture was then worked up. An ultraviolet spectrum of the product indicated that dehydrogenation and methylation to the pentamethoxyflavone had occurred.

(b) With boron trifluoride and diazomethane

The trans-dihydroflavonol (0.1 g) and boron trifluoride (1 drop) were dissolved in ice cold methylene chloride and the mixture cooled further in an ice-salt bath. A cold ethereal solution of diazomethane (from 0.2 g of nitrosomethylurea) was added dropwise to the mixture which was then left to stand in an ice-bath for 2 hr. The reaction mixture was washed with 2N potassium hydroxide solution with water and then dried (Na_2SO_4). Removal of solvent and chromatography of the residue over silica gel gave a yellow compound (0.04 g) as the benzene/ether eluate. The compound showed an intense yellow fluorescence under ultraviolet light. Light absorption in 95% ethanol: λ_{max} 288, 365 mμ. This showed that a large proportion of the product was the tetramethoxyflavonol (pentamethoxyflavone shows a blue fluorescence under ultraviolet light and its ultraviolet spectrum shows λ_{max} at 250 and 347 mμ).

(ii) Cyclization of 2'-hydroxy-α-3,4,3',4'-pentamethoxychalcone

2'-Hydroxy-α-3,4,3',4'-pentamethoxychalcone (48) was prepared by condensing together 2-hydroxy-ω,3,4-trimethoxyacetophenone[126] and veratraldehyde with the aid of a 50% solution of potassium

hydroxide (yield: 50%). Cyclization of the chalcone (48) with alkaline hydrogen peroxide gave a yellow amorphous compound (yield: 10%). Light absorption in 95% ethanol: λ_{max} at 250, 350 mμ; λ_{min} at 280 mμ. The infrared spectrum (Nujol) showed an intense carbonyl absorption at 1630 cm^{-1}. This suggested that the product was the 3-methoxyflavone (50) and not the desired 3-methoxyflavanone (49).

Attempted epimerization of 2,3-cis-3,7,8,3',4'-pentamethoxyflavanone to the 2,3-trans-isomer.

Epimerization reactions were carried out on a small scale and the products were identified either spectroscopically or by thin-layer chromatography.

(i) Attempted thermal epimerizations were carried out by heating the cis-flavanone in methanol at reflux temperatures. Thermal epimerizations were carried out both in the presence of air and under nitrogen. The reaction time in each case was 3/4 hr. In all cases, ultraviolet spectroscopy and thin-layer chromatography showed the presence of only two compounds in the reaction mixture, the cis-flavanone and the corresponding 3-methoxy-flavone.

(ii) Attempted epimerization on an alumina column was also carried out. The cis-flavanone (0.07 g) was chromatographed on slightly deactivated alumina (15 g containing 5% by weight of water). Elution with 50% benzene/ether gave the same flavanone (0.06 g).

(iii) No change was observed when the compound was heated for 2 minutes at 40° with 0.5% methanolic sulphuric acid.

(iv) No change was observed when a dilute methanolic solution of the flavanone was heated under nitrogen for 2 min at 50° in the presence of sodium acetate. When the reaction was carried out in the presence of air the reaction mixture turned a light yellow and thin-layer chromatographic examination showed the presence of a small amount of 3-methoxyflavone.

(v) Attempts to epimerize the cis-compound by heating with benzene and toluene at reflux temperatures were unsuccessful.

(vi) Epimerization reactions with catalytic amounts of boron trifluoride were also unsuccessful.

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SYNTHESIS OF MODEL BENZYL ALCOHOLS

(a) Phenylpropan-1-ol type.

1-Phenylpropan-1-ol (64, R = H)

Propiophenone (36.2 g, b.p. 100-102°/18 mm) was reduced with sodium borohydride and gave 1-phenylpropan-1-ol as a colourless oil (28.9 g, 78.5%), b.p. 101-102°/13 mm, n_D^{21} 1.5195 (lit.[127] b.p. 106-108°/18 mm).

1-(p-Methylphenyl)propan-1-ol (64, R = p-Me)

The Friedel and Crafts reaction using propionic anhydride (65 g), anhydrous aluminium chloride (150 g) and dry toluene (300 ml) gave p-tolylethyl ketone (63.2 g, 85.5%, b.p. 131-134°/21 mm). The ketone (26.6 g) in methanol (200 ml) was reduced to the corresponding alcohol (22.7 g, 84%) with an alkaline solution of sodium borohydride (4 g in 30 ml of 0.2N sodium hydroxide). Fractionation gave a colourless oil, b.p. 80-81°/0.3 mm (lit.[128] b.p. 114°/12-13 mm).

1-(p-Methoxyphenyl)propan-1-ol (64, R = p-MeO)

This benzyl alcohol was prepared by the method of Allred, Sonnenberg and Winstein.[129] To the Grignard reagent prepared from p-bromoanisole (50 g, b.p. 100°/16 mm, n_D^{20} 1.5646) and magnesium (6.5 g) in ether (200 ml) was added, as rapidly as possible, freshly distilled propionaldehyde (15.5 g) in ether (200 ml). After an additional stirring time of ½ hr, the reaction mixture was decomposed with a saturated solution of ammonium chloride to give 1-(p-methoxy-

phenyl)propan-1-ol as a light yellow oil (31.0 g, 70%). Fractionation under reduced pressure gave a colourless oil, b.p. 102°/0.7 mm, n_D^{23} 1.5180 (lit.[129] b.p. 120.5-121°/4 mm, n_D^{25} 1.5257).

1-(3,4-Dimethoxyphenyl)propan-1-ol [64, R = 3,4(OMe)$_2$]

Ethyl magnesium bromide was prepared from ethyl bromide (45 ml, 0.6 mole) and magnesium turnings (14.5 g, 0.6 mole). The amount of Grignard reagent formed was estimated by titration. The reaction mixture was allowed to attain room temperature and the magnesium particles permitted to settle. A 10 ml sample was collected with the aid of a pipette and added to a conical flask containing 100 ml of distilled water. Sufficient standard acid (0.24N) was added, the solution heated to 50°, and the excess acid was then back titrated with standard sodium hydroxide (15.5 ml of 0.19N). The titration results indicated that 0.36 equivalents (47.7 g) of ethyl magnesium bromide was formed.

Ethyl magnesium bromide (47.7 g, 0.36 mole) was reacted with half the equivalent amount of veratraldehyde[85] (30 g, 0.18 mole) and the resulting complex was decomposed with a saturated solution of ammonium chloride to give 1-(3,4-dimethoxyphenyl)propan-1-ol as a light yellow oil. Distillation gave a colourless oil (22 g, 62%). For reactivity studies further purification was carried out by fractionation, b.p. 106-107°/1.3 mm, n_D^{27} 1.5288 (lit.[85] b.p. 102-103°/0.2 mm).

1-(2,4,6-Trimethoxyphenyl)propan-1-ol [64, R= 2,4,6(OMe)$_3$]

Phloroglucinol trimethyl ether was prepared by methylation of phloroglucinol by the method of Clark-Lewis.[130]

2,4,6-trimethoxybenzaldehyde was prepared by the method of Kenyon and Mason.[50] Phosphorus oxychloride (7 g) was added to a solution of phloroglucinol trimethyl ether (14 g) and formanilide (10 g) in dry ether (100 ml). The reaction mixture was left standing at room temperature overnight, the solvent then removed, the residue decomposed with aqueous sodium hydroxide (600 ml, 5%) and the alkaline solution steam distilled. On cooling, the non-volatile residue precipitated out. Crystallization from benzene-petroleum ether (b.p. 60-80°) gave shiny yellow elongated plates (9.2 g, 64%), m.p. 120° (lit.[50] m.p. 118°).

Ethyl magnesium bromide was prepared from ethyl bromide (8 g, 0.072 mole) and magnesium (1.7 g, 0.072 mole) in dry ether (100 ml). 2,4,6-Trimethoxybenzaldehyde (7.2 g, 0.036 mole) in dry benzene (150 ml) was slowly added to a stirred solution of the Grignard reagent over the period of an hour. Stirring was continued for a further half hour, the reaction mixture allowed to stand overnight at room temperature and decomposed with a saturated solution of ammonium chloride. The ether-benzene layer was separated, the aqueous layer extracted with ether and the combined organic extracts washed with water and dried (Na_2SO_4). Removal of the solvent under reduced pressure and distillation of the residue under nitrogen gave 1-(2,4,6-trimethoxyphenyl)propan-1-ol a viscous oil (8.0 g, 96%). Careful fractionation

under nitrogen gave a sample which showed a single peak when injected in the vapour phase chromatograph, b.p. 148°/2.7 mm, n_D^{30} 1.5371 (Found: C, 64.9; H, 7.3. $C_{12}H_{18}O_4$ requires C, 63.7, H, 8.0%).

This benzyl alcohol is very reactive and has to be stored at 0° under nitrogen. It decomposes when left standing at room temperature.

The above benzyl alcohol was also prepared by reduction of 1-(2,4,6-trimethoxyphenyl)propan-1-one. To a solution of phloroglucinol trimethyl ether (30 g) in dry ether (150 ml) was added powdered zinc chloride (4 g) and ethyl cyanide (19.6 g). A fast stream of dry hydrochloric acid gas was bubbled through the solution for 1½ hr and the reaction mixture was left standing at 0° for 2 days. The slender white needles of the ketimine hydrochloride which separated out were collected, washed with ether and decomposed by boiling in water for 2 hr. The resulting ketone crystallized from methanol (charcoal) in colourless prisms (4.5 g, 11.2%), m.p. 82-83°.

1-(2,4,6-Trimethoxyphenyl)propan-1-one (4 g) was reduced with lithium aluminium hydride (2 g) to give 1-(2,4,6-trimethoxyphenyl)propan-1-ol as a viscous oil (2.6 g, 65%), b.p. 160-163°/7 mm, n_D^{23} 1.5289.

(b) Tetralols and tetralin diols.

1-Hydroxy-1,2,3,4-tetrahydronaphthalene (65, R = H)

Commercial α-tetralone was purified by distillation under

reduced pressure, b.p. 127-129°/13 mm, n_D^{17} 1.5690 (lit.[131] b.p. 120-122°/9 mm, n_D^{20} 1.5704).

α-Tetralone (43.5 g) was reduced with lithium aluminium hydride (10 g) to give 1-hydroxy-1,2,3,4-tetrahydronaphthalene (33.4 g, 77%), b.p. 134-135°/13.5 mm, n_D^{18} 1.5637 (lit.[131] b.p. 89°/1 mm n_D^{20} 1.5642).

The n.m.r. spectrum (in CCl_4) showed the benzylic 1-proton as a broad unsplit peak at τ 5.55, a four proton multiplet centred at τ 8.25 due to $2CH_2$ and $3CH_2$ and a broad unresolved peak at τ 7.26 ($4CH_2$). The benzylic hydroxyl proton appeared as a singlet at τ 6.62 and the aromatic protons showed a multiplet centred at τ 2.99.

1-Hydroxy-1,2,3,4-tetrahydronaphthalene was also prepared by oxidation of tetralin with lead tetraacetate[132] and reduction of the resulting 1-tetralyl acetate with lithium aluminium hydride.

cis-1,2,-Dihydroxy-1,2,3,4-tetrahydronaphthalene (66, R = H)

1-Hydroxy-1,2,3,4-tetrahydronaphthalene (25 g) was heated at 110° for 4 hr in the presence of potassium hydrogen sulphate (5 g) to give 3,4-dihydronaphthalene (13.5 g, 61%), b.p. 90-92°/16 mm, n_D^{18} 1.5825 (lit.[131] b.p. 70-72°/1 mm, n_D^{20} 1.5820).

(i) Hydroxylation using potassium permanganate.

cis-Hydroxylation of 3,4-dihydronaphthalene was carried out initially by the method of Straus and Rohrbacher[90] using potassium permanganate. The method was found to be unsatisfactory as low

yields (ca 17%) and mixtures of cis and trans isomers were obtained (see n.m.r. data below).

The n.m.r. spectrum (in $CHCl_3$) of the diol (leaflets from benzene, m.p. 102°) showed the benzylic 1-proton as a quartet, centred at τ 5.43 (triplet after deuterium oxide exchange). One would have expected a symmetrical doublet for the 1-proton after deuterium oxide exchange. The presence of a triplet indicates a mixture of cis- and trans-diols. Calculated (approximately) spin-spin coupling constants $J_{1,2}$ (cis) 3.3 c/s and $J_{1,2}$ (trans) 9.2 c/s. The signal of 2H was a quintet centred at τ 6.28, the 3-methylene protons showed a multiplet centred at τ 8.13, and the resonance of the 4-benzylic protons appeared at τ 7.20. The aromatic protons showed a multiplet at τ 2.79.

(ii) Hydroxylation by the Woodward procedure[86,89]

To a solution of 3,4-dihydronaphthalene (10 g, 0.077 mole) in glacial acetic acid (300 ml) containing 2.5 ml of water, silver acetate (32.3 g, 0.195 mole) was added. Over the period of a half hour finely pulverized iodine (19.5 g, 0.077 mole) was added, and the reaction mixture stirred vigorously at room temperature until all the iodine was consumed, and then for a further 3 hr at 90°. The reaction mixture was cooled and the precipitated silver salts filtered off and washed with ether. Removal of the solvents gave a yellow oil (10.5 g).

A portion of the foregoing mixture of mono- and -diacetates

(5 g) was dissolved in ethanol (50 ml) and heated under reflux with aqueous sodium hydroxide (20 ml of 40%) for 1½ hr. Water (100 ml) was added, the ethanol removed by distillation under reduced pressure and the residue extracted with chloroform (2 x 100 ml). The combined extracts were washed with sodium bisulphite (30 ml of 40%) and dried (Na_2SO_4). Removal of the chloroform gave the crude diol as a brown oil (3.1 g, 52%). Chromatography over alumina (ether as eluant) and crystallization from benzene gave cis-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene as shiny white plates, m.p. 102° (lit.[90] m.p. 102°).

cis-1,2,-Diacetoxy-1,2,3,4-tetrahydronaphthalene.

The foregoing diol (0.1 g) was acetylated with acetic anhydride (4 ml) and pyridine (2 ml) for 48 hr at room temperature. The reaction mixture was poured slowly onto a mixture of ice and water and worked up in the usual way. The cis-diacetate crystallized from petroleum ether (b.p. 60-80°) as plates (0.115 g, 76%), m.p. 79-80° (lit.[90] m.p. 78.6-79.2).

The n.m.r. spectrum (in $CDCl_3$) showed the benzylic proton as a doublet centred at τ 3.85 with spin-spin coupling constant $J_{1,2}$ 3.4 c/s. The 2-proton signal was a multiplet (X part of ABXY system) at τ 4.77 and the benzylic 4-protons appeared as a two proton multiplet centred at τ 7.03. Acetoxyl protons showed absorptions at τ 7.92, 7.96 and partly obscured the multiplet centred at τ 7.96 due to the 3-methylene group. The resonance of the aromatic protons appeared at τ 2.80.

Carbonate of cis-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene (99)

Preparation of the carbonate of the cis-diol was carried out by the method of King and Clark-Lewis[6] with slight modifications.

Ethylchloroformate (2 ml) in benzene (7 ml, containing a little dioxan), was slowly added to an ice-cooled solution of the cis-diol (0.1 g) in triethylamine (2 ml). The reaction mixture was allowed to stand at room temperature for an hr and extracted with ether. The combined extracts were washed thoroughly with water and dried ($MgSO_4$). Removal of the ether and crystallization of the residue from petroleum ether (b.p. 60-80°) gave the cis-carbonate as white plates (0.06 g, 51.5%), m.p. 81°

(Found: C, 69.5; H, 5.6. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%).

The infrared spectrum (in Nujol) showed $\nu_{C=O}$ at 1785 cm^{-1}.

The n.m.r. spectrum (in $CDCl_3$) showed the benzylic 1-H as a doublet centred at τ 4.25 with spin-spin coupling constant $J_{1,2}$ 7.8 c/s. The 2-proton signal was a quintet (X part of ABXY system) centred at τ 4.84 and the benzylic 4-protons appeared as a multiplet centred at τ 7.18. The 3-methylene protons showed a multiplet centred at τ 7.95 and the resonance of the aromatic protons appeared at τ 2.67.

trans-1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (67, R = H)

The first step in the trans hydroxylation - trans acetoxylation - was carried out by the method of Criegee[132] with slight modifications. 1,2-Dihydronaphthalene (10 g), lead tetraacetate

(40 g) and acetic acid (40 ml) were stirred together vigorously for 1 hr at 70°. The reaction mixture was poured into water, extracted with ether and the combined ether extracts washed with water and dried (Na_2SO_4). Removal of ether gave a light brown oil (9 g) containing a mixture of diacetoxytetrahydronaphthalene and naphthalene.

The crude mixture from the above acetoxylation (9 g) was reduced with lithium aluminium hydride (3 g), and the product chromatographed over alumina. Naphthalene (ca 2 g) was removed almost entirely in the earlier fractions and the diol (3.2 g, 25% overall yield) was eluted with 50% ether/benzene. The trans-diol crystallized from benzene as needles, m.p. 112° (lit.[132] m.p. 112-113°).

The n.m.r. spectrum (in $CDCl_3$) showed the benzylic 1-proton as a doublet centred at τ 5.44 with spin-spin coupling constant $J_{1,2}$ 8.2 c/s. The signal of the 3-methylene protons was a multiplet centred at τ 7.98 and the 4-benzylic protons appeared as a quartet centred at τ 7.14. A three-proton multiplet centred at τ 6.23 was due to the two hydroxyl protons and the proton at the 2-position. The resonance of the aromatic protons was centred at τ 2.71.

trans-1,2,-Diacetoxy-1,2,3,4-tetrahydronaphthalene.

The foregoing trans-diol (0.15 g) was acetylated with acetic anhydride and pyridine. Trans-1,2,-diacetoxytetralin crystallized from petroleum ether (b.p. 60-80o) in colourless prisms (0.12 g, 79%),

m.p. 85° (lit.[90] m.p. 84°).

The n.m.r. spectrum (in $CDCl_3$) showed the benzylic 1-proton as a doublet centred at τ 3.93 with spin-spin coupling constant $J_{1,2}$ 5.6 c/s. The signal of the 2-proton was a multiplet centred at τ 4.82 and the benzylic 4-protons showed a two-proton triplet (unresolved) at τ 7.10. Acetoxyl groups showed absorptions at τ 7.89, 7.96 and partly obscured the multiplet centred at τ 7.90 due to the 3-methylene group. The aromatic protons showed an intense resonance at τ 2.80.

Carbonate of trans-1,2-dihydroxy-1,2,3,4-tetrahydronaphthalene (100)

The carbonate of the trans-diol was prepared as described above for the cis-diol. The trans-carbonate crystallized from petroleum ether (b.p. 60-80°) as plates (yield: 43%), m.p. 114-116°, $\nu_{c=o}$ (Nujol) 1785 cm^{-1}. The trans-carbonate appeared to be less stable than the cis-carbonate and decomposed when chromatographed over alumina.

The n.m.r. spectrum (in $CDCl_3$) showed the benzylic 1-proton as a doublet centred at τ 4.79 with spin-spin coupling constant $J_{1,2}$ as 10.6 c/s. The 2-proton signal was a multiplet (X part of ABXY system) centred at τ 5.75 and the benzylic 4-protons appeared as a multiplet centred at τ 7.04. The 3-methylene protons showed a multiplet centred at τ 7.84. The resonance of the aromatic protons appeared at τ 2.73. The ~~trans-carbonate appeared to be contaminated with a little of the cis-isomer as a doublet centred at τ 4.31 with spin-spin coupling constant 7.7 c/s was present in the spectrum.~~ spectrum showed that the product was a mixture of cis- and trans-carbonates (ca. 1:1).

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (65, R = OMe)

β-Methoxynaphthalene (m.p. 71°), prepared by methylation of β-naphthol with methanol and conc. sulphuric acid, was reduced to 6-methoxytetralin with Raney nickel by the method of Stork.[92]

To a suspension of β-naphthyl methyl ether (20 g) in methanol (100 ml) was added W4 Raney nickel[124] (several ml in methanol) and glacial acetic acid (2 ml). The mixture was hydrogenated at 100°/100 atm. for one hr and the catalyst removed by filtration. Removal of the solvent and distillation gave 6-methoxytetralin as a colourless oil (17.9 g, 87%) b.p. 126-128°/15 mm, n_D^{20} 1.5433 (lit.[92] b.p. 134-137°/17 mm). (Less hydrogenolysis of the methoxy group occurred in this reaction when methanol was used as solvent instead of ethanol. It was found that increase in reaction time also resulted in increase in hydrogenolysis.)

Chromic acid (18 g) in water (10 ml) and glacial acetic acid (50 ml) was added with stirring at 5-10° to 6-methoxytetralin (18 g) in glacial acetic acid (100 ml).[133] The addition took 1½ hr and the reaction mixture was stirred for a further 2 hr and then left to stand at room temperature overnight. The acetic acid was removed under reduced pressure, the residue dissolved in water (5000 ml) and extracted repeatedly with ether. The combined ether extracts were washed with aqueous potassium carbonate (10%), water, and then dried ($MgSO_4$). Removal of ether and distillation of the residue gave a yellow oil which solidified on cooling (6.7 g, 34%) b.p. 163-166° (lit.[133] b.p. 164-166°). 1-Oxo-6-methoxy-1,2,3,4-tetrahydronaph-

thalene crystallized from benzene-petroleum ether (b.p. 60-80°) in yellow plates (4.9 g), m.p. 77° (lit.[133] m.p. 77.5°).

6-Methoxytetralone (10 g) in dry ether (300 ml) was reduced with lithium aluminium hydride (2.2 g) in ether (100 ml). The complex formed was decomposed with water, the ether layer separated and the aqueous layer extracted with ether. The combined ether extracts were washed thoroughly with water (6 x 100 ml) and dried (Na_2SO_4). Removal of the solvent and fractionation of the residue under nitrogen gave 1-hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene as a colourless viscous oil (7 g, 69%), b.p. 130°/1.5 mm, n_D^{20} 1.5632 (lit.[115] b.p. 175°/16 mm).

(Found: C, 74.1; H, 7.9. Calc. for $C_{11}H_{14}O_2$: C, 73.9; H, 7.8%).

The n.m.r. spectrum (in $CDCl_3$) showed a single broad peak at τ 5.30 (benzylic 1-proton), a multiplet centred at τ 8.12 (2- and 3-methylene protons, hydroxyl proton), an unresolved signal at τ 7.27 (benzylic 4.CH_2), an intense resonance at τ 6.24 (methoxyl) and a multiplet centred at τ 3.07 (aromatic protons).

Reduction of the 6-methoxytetralone was also carried out catalytically using platinum oxide. This was found to be an unreliable method as the presence of 6-methoxydecalol was noted in one of the reductions.

An alternative route to 6-methoxytetralol involved acetoxylation of 6-methoxytetralin with lead tetra-acetate[115] and subsequent reduction of the tetralyl acetate (b.p. 156-160°/6mm, lit.[115]

b.p. 144-149°/3 mm) with lithium aluminium hydride (overall yield: ca 30%).

2-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)3,4-dihydro-6-methoxy-naphthalene (111)

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (1 g) was shaken with hydrobromic acid (20 ml, 48%, v/v) for 3 hr.[115] The solution turned pink after a few minutes and after 3 hr a light brown ball was formed. This was collected and crystallized from petroleum ether (b.p. 40-60°) to give the dimer as flat prisms (0.51 g, 51%), m.p. 75-76° (lit.[115] m.p. 73-74°). Light absorption in 95% ethanol: λ_{max} 275 mμ (log ε 4.24). The n.m.r. spectrum (in $CDCl_3$) showed a one proton singlet at τ 3.86 due to the benzylic olefinic proton, a multiplet centred at τ 8.06 (six methylene protons) and a "triplet" centred at τ 7.25 due to the ~~six~~ five benzylic protons. The methoxyl protons showed an intense signal at τ 6.26 and the resonance of the aromatic protons was centred at τ 3.24.

cis-1,2,-Dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (66, R = OMe)

1-Hydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (4 g) was dehydrated with powdered potassium bisulphate (1 g) by heating at 110° for a half hour. Distillation gave 7-methoxy-1,2-dihydronaphthalene (2.6 g, 72%) as a pale yellow oil, b.p. 134°/16 mm, n_D^{20} 1.5838 (lit.[134] b.p. 94-95°/2-3 mm, $n_D^{26.5}$ 1.5837).

Cis-hydroxylation of this olefin was carried out using osmium tetroxide. The olefin (0.95 g) in ether (30 ml) and pyridine (3 ml) was added to a cold solution of osmium tetroxide (1.5 g) in ether (40 ml). The mixture set to a brown mass almost immediately and was left to stand at 0° for an hour. The adduct was collected, washed with ether and shaken with mannitol (10 g) in 10% aqueous potassium hydroxide (100 ml). After 15 hr the reaction mixture was extracted with methylene chloride, the combined extracts washed with water and dried (Na_2SO_4). Removal of the solvent and crystallization of the residue from benzene gave cis-1,2-dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene as colourless needles (0.84 g, 73%), m.p. 117.5-118.5°,

(Found: C, 67.5; H, 7.4. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.3%).

The n.m.r. spectrum (in $CDCl_3$) showed the benzylic 1-proton as a doublet centred at τ 5.39 with spin-spin coupling constant $J_{1,2}$ 3.4 c/s, a seven-proton multiplet between τ 7.08 and τ 8.28 (3.CH_2, 4.CH_2, 2-CH (OH), 1CH(OH), ~~2CH(OH)~~), intense signal at τ 6.22 (methoxyl) and a multiplet centred at τ 3.07 due to aromatic protons.

trans-1,2-Dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (67, R = OMe)

Trans hydroxylation of 3,4-dihydronaphthalene was carried out by preparation of the epoxide and then effecting trans-hydrolytic ring opening of this oxirane using dimethyl sulphoxide as solvent.[95]

7-Methoxy-1,2-dihydronaphthalene (1 g) in chloroform (30 ml)

and perbenzoic acid[94] (0.95 g) in chloroform (50 ml) were stirred together for 1 hr at 0°. The reaction mixture was left standing at 0° for 20 hr, then washed with aqueous sodium hydroxide (3 x 30 ml) and water and dried.

The crude epoxide from the above reaction was hydrolysed for 6 hr at 80° with 0.3N potassium hydroxide in 85% dimethylsulphoxide. The reaction mixture was worked up in the usual way and a light brown oil (0.8 g, 66%) was obtained. Chromatography over deactivated alumina and crystallization from ether-petroleum ether gave trans-1,2-dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene as colourless plates, m.p. 119-120°.

(Found: C, 68.0; H, 7.3. $C_{11}H_{14}O_3$ requires C, 67.8; H, 7.3%).

The n.m.r. spectrum (in $CDCl_3$) showed the benzylic 1-proton as a doublet centred at τ 5.48 with spin-spin coupling constant $J_{1,2}$ ca 10.4 c/s, a seven proton multiplet between τ 7.02 and τ 8.13 (due to 3-CH_2, 4-CH_2, ~~2-CH(OH)~~, 1-OH and 2-OH), an intense signal at τ 6.22 (methoxyl) and a multiplet centred at τ 2.91 due to aromatic protons.

1-Hydroxy-3-phenyl-1,2,3,4-tetrahydronaphthalene (68, R = H)

Ethyl-β-hydroxy-βγ-diphenylbutyrate was synthesized by the Reformatsky reaction as described by Spring[100] but with slight modifications.

Deoxybenzoin[100] (60 g) in dry toluene (250 ml) was placed

in a flask containing shiny zinc wool (22 g, cleaned by washing with 5% hydrobromic acid, water, alcohol and acetone and drying for an hour at 100°). The mixture was gently heated and stirred vigorously with the addition of a little redistilled ethyl bromoacetate (b.p. 60°/16 mm, n_D^{25} 1.4512). The reaction mixture was brought slowly to reflux temperature when a vigorous reaction set in. The heating was discontinued and the remaining ethyl bromoacetate (total 54 g) was added at a rate which kept the reaction mixture at reflux temperature. After addition, heating under reflux was carried out for a further 2 hr when the solid zinc complex separated out. The reaction mixture was cooled, the complex decomposed with ice-cold sulphuric acid (15%) the separated toluene layer collected and washed with dilute sulphuric acid and dried. Evaporation of the toluene gave a yellow solid residue (45 g, 54%). Chromatography over alumina and crystallization from petroleum ether (b.p. 60-80°) gave ethyl-β-hydroxy-βγ-diphenylbutyrate as slender needles (30 g), m.p. 58° (lit.[100] m.p. 57-58°).

The foregoing ester (15 g) was hydrolysed with potassium hydroxide (10 g), water (50 ml) and ethanol (100 ml). β-Hydroxy-βγ-diphenylbutyric acid crystallized from 85% ethanol as needles (10.3 g, 76.5%), m.p. 120° (lit.[100] m.p. 120°).

β-Hydroxy-βγ-diphenylbutyric acid (6 g) was refluxed for 3 hr. with red phosphorus (5 g) and hydriodic acid (50 ml, 55%). The reaction mixture was cooled, diluted with water, the aqueous layer

decanted and the viscous red residue extracted with dilute potassium hydroxide. The alkaline solution was acidified and worked up. β-Benzylcinnamic acid (4.3 g, 77%) crystallized from 85% ethanol as colourless prisms (3.1 g), m.p. 169° (lit.[100] m.p. 169°).

The foregoing benzylcinnamic acid (10 g) was hydrogenated in glacial acetic acid (60 ml) with 5% palladium on charcoal catalyst (2.5 g) at room temperature and 10 atm. hydrogen pressure for 1½ hr. βγ-Diphenylbutyric acid (9.1 g, 90%) crystallized from petroleum ether (b.p. 60-80°) as colourless prisms (6.8 g), m.p. 95-96° (lit.[100] 95°).

The cyclization procedure of the foregoing acid was carried out as described by Johnson[101] for the preparation of α-tetralone. βγ-Diphenylbutyric acid (6 g, 0.025 mole) was dissolved in dry thiophene-free benzene (60 ml). To this cooled stirred solution phosphorus pentachloride (6.3 g, 0.03 mole) was added during a few minutes. After the addition, the reaction mixture was heated under reflux for 5 min, cooled to room temperature and then further to -10° using an ice-salt mixture. Anhydrous stannic chloride (13.2 g, 6 ml, 0.05 mole) in dry benzene (30 ml) was added slowly to the reaction mixture, the temperature being maintained below 15°. The reaction mixture was then stirred at 0-10° for a ½ hr and the complex decomposed by the addition of 100 g of ice followed by conc. hydrochloric acid (50 ml). The two phase mixture was heated under reflux until no hydrochloric acid gas was evolved (about ½ hr). It was cooled, the separated benzene layer collected and the aqueous

layer extracted with ether. The combined benzene-ether extracts were washed with water, 10% aqueous sodium carbonate, again with water and finally with a saturated solution of sodium chloride and then dried. Removal of the solvent gave 1-oxo-3-phenyl-1,2,3,4-tetrahydronaphthalene as a yellow oil which crystallized on trituration with petroleum ether (b.p. 60-80°) as colourless prisms (5.1 g, 92%), m.p. 65-66° (lit.[100] m.p. 65°). ν_{max} (Nujol) 1665 cm^{-1} (c=o).

(Found: C, 86.7; H, 6.4. Calc. for $C_{16}H_{14}O$: C, 86.5; H, 6.4%).

Cyclization of βγ-diphenylbutyric acid with conc. sulphuric acid gave a lower yield (< 30%) of the ketone.

1-Oxo-3-phenyltetralin (1.5 g) in dry ether (50 ml) was reduced with lithium aluminium hydride (0.2 g) in ether (100 ml) to 1-hydroxy-3-phenyl-1,2,3,4-tetrahydronaphthalene (1.3 g, 86%). Crystallization from petroleum ether (b.p. 60-80°) gave fine white needles, m.p. 113.5-114.5°.

(Found: C, 85.5; H, 7.2. $C_{16}H_{16}O$ requires C, 85.7; H, 7.2%).

The n.m.r. spectrum (in $CDCl_3$) showed the resonance of the benzylic 1-proton as a quartet (X part of ABXY system) centred at τ 5.06 with the sum of the spin-spin coupling constants $J_{AX} + J_{BX}$ 16.4 c/s. A three-proton multiplet centred at τ 7.79 was assigned to the 2-methylene protons and the 1-hydroxyl proton. The benzylic protons showed a strong resonance at τ 7.07 and the aromatic protons absorbed at τ 2.53. Double irradiation experiments to simplify the

signals of the methylene protons (AB of ABXY) were unsuccessful.

Synthesis of βγ-diphenylbutyric was carried out at the outset by the method of Braun and Manz.[135] α-Phenylcinnamic acid was reduced with Raney nickel to αβ-diphenylpropionic acid which was converted into the propanol derivative by Beauvault-Blanc reduction of the corresponding ester. Reaction of the propanol with hydrobromic acid gave diphenyl propyl bromide which was converted to βγ-diphenylbutyric acid through the nitrile. This method, however, was found to be unsatisfactory as the yields especially in the latter steps were very low.

1-Acetoxy-3-phenyl-1,2,3,4-tetrahydronaphthalene.

1-Hydroxy-3-phenyltetralin (0.25 g) was acetylated with acetic anhydride (4 ml) and pyridine (2 ml) at room temperature for 27 hr and the reaction mixture worked up in the usual way. 1-Acetoxy-3-phenyl-1,2,3,4-tetrahydronaphthalene crystallized from petroleum ether (b.p. 60-80°) as colourless needles (0.1 g, 34%), m.p. 76°. (Found: C, 81.0; H, 6.7. $C_{18}H_{18}O_2$ requires C, 81.2; H, 6.8%).

The n.m.r. spectrum (in $CDCl_3$) showed the resonance of the benzylic 1-proton as a quartet (X part of ABXY system) centred at τ 3.81 with the sum of spin-spin coupling constants $J_{AX} + J_{BX}$ 16.2 c/s. The 2-methylene protons showed a multiplet (AB part of the ABXY system), partly obscured by the acetoxyl group absorption and centred at τ 7.75. A three-proton multiplet centred at τ 6.95 was assigned to the benzylic protons at C_3 and C_4. The acetoxyl group protons

showed an intense resonance at τ 7.86 and the aromatic protons absorbed at τ 2.8.

Possible routes to the synthesis of 1,2-dihydroxy-3-phenyl-1,2,3,4-tetrahydronaphthalene (69, 70 R = H)

Two routes to the synthesis of 1,2-dihydroxy-3-phenyl-tetralins have been investigated.

(i) Oxidation of 1-oxo-3-phenyl-1,2,3,4-tetrahydronaphthalene with selenium dioxide.

1-Oxo-3-phenyltetralin (1 g) was oxidized with selenium dioxide (1 g) in moist dioxan (25 ml) at 60° for 3 hr. The reaction mixture was poured into water, extracted with ether and the combined ether extracts washed with saturated aqueous potassium carbonate, water and dried ($MgSO_4$). The red oily residue obtained on removal of the ether crystallized from ethanol in red needles (0.4 g). The oxidation product appeared to be a mixture of two compounds and fractional crystallization gave a compound, m.p. 160-161°, ν_{max} (Nujol) 1650, 1680 cm^{-1} (carbonyl), no hydroxyl absorption. Light absorption in 95% ethanol: λ_{max} at 263 mμ (broad band). The physical data is consistent with the compound being the 1,2-naphthaquinone (89) (lit.[136] m.p. 156°).

(Found: C, 81.3; H, 4.2. Calc. for $C_{16}H_{10}O_2$: C, 82.0; H, 4.3%).

The second compound from the above oxidation was 2-hydroxy-

3-phenyl-1,4-naphthaquinone (90) (characterised as shown below). Mixtures of this kind have been reported in the oxidation of 1-oxo-3-methyl-1,2,3,4-tetrahydronaphthalene with selenium dioxide.[103]

1,2-Dihydroxy-3-phenyl-1,2-dihydronaphthalene (91)

The mixture of naphthaquinones (1 g) from the selenium dioxide oxidation was reduced with an excess of lithium aluminium hydride (0.25 g). The reaction mixture was worked up in the usual way and then separated into a phenolic fraction (soluble in aqueous sodium hydroxide) and a non-phenolic fraction (ether layer after extraction with sodium hydroxide).

The ether layer (non-phenolic) was washed thoroughly with water and dried (Na_2SO_4). The residue obtained on removal of ether was chromatographed over alumina (60 g). Fractions 4 to 11 (benzene/ether eluant) were combined, the solvents removed and the residue (0.5 g) triturated with benzene when a white amorphous material separated out. Crystallisation from carbon tetrachloride gave 1,2-dihydroxy-3-phenyl-1,4-dihydronaphthalene (?) as slender needles, m.p. 112-113°.

(Found: C, 78.1; H, 5.8. $C_{16}H_{14}O_2.\frac{1}{2}H_2O$ requires C, 77.8; H, 6.1%). The infrared spectrum showed a broad hydroxyl absorption peak at 3250 cm^{-1} but no carbonyl absorption.

2-Hydroxy-3-phenyl-1,4-naphthaquinone (90)

The phenolic fraction from the above reduction was worked

up and a yellow oil (0.25 g) was obtained. Crystallization from ether-petroleum ether (b.p. 40-60°) gave 2-hydroxy-3-phenyl-1,4-naphthaquinone (90) as prisms (0.15 g), m.p. 146-147° (lit.[137] m.p. 147°). The infrared spectrum (Nujol) showed a sharp absorption at 3400 cm^{-1} (OH) and two carbonyl peaks at 1630 and 1650 cm^{-1}. Methylation of the naphthaquinone (0.15 g) with methyl iodide-acetone-potassium carbonate for 3 hr gave 2-methoxyl-3-phenyl-1,4-naphthaquinone which crystallized from ether-petroleum ether (b.p. 60-80°) as prisms (0.1 g, 64%), m.p. 122-123° (lit.[138] m.p. 122-123°).

(Found: C, 77.6; H, 4.7. Calc. for $C_{17}H_{12}O_3$: C, 77.3; H, 4.6%).

(ii) 1-Oxo-2-bromo-3-phenyl-1,2,3,4-tetrahydronaphthalene (93)

To a chilled solution of 1-oxo-3-phenyltetralin (1 g) in ether (100 ml) was added a few drops of a cold ethereal solution of bromine. The solution was stirred until the reaction started (½ min) and the colour of the bromine disappeared. The remaining portion of the bromine solution (total 0.72 g, 0.24 ml in 25 ml of ether) was then introduced dropwise into the reaction mixture. After the addition (½ hr) the reaction mixture was stirred for a further ½ hr and the ether removed. 1-Oxo-2-bromo-3-phenyltetralin (1.3 g, 96%) crystallized from petroleum ether (b.p. 40-60°) as light yellow prisms, m.p. 144-145°.

(Found: C, 64.3; H, 4.35; Br, 26.5. $C_{16}H_{13}OBr$ requires C, 63.8; H, 4.32; Br, 26.6%). The infrared spectrum showed a strong absorption at 1675 cm^{-1} (carbonyl) and a marked absorption at 745 cm^{-1}

(C - Br).

1-Oxo-3-acetoxyl-3-phenyl-1,2,3,4-tetrahydronaphthalene (94)

The foregoing bromoketone (0.25 g) was heated with acetic acid and anhydrous potassium acetate at 65° for 6 hr. The reaction mixture showed no change. However, prolonged heating (70 hr) at 65° gave a small amount of the acetoxyl compound (94) as evidenced by the infrared spectrum which showed two carbonyl absorption peaks (1675 cm^{-1}, 1730 cm^{-1}).

REACTIONS OF MODEL BENZYL ALCOHOLS

Product analysis.

Reactions were carried out in anhydrous methanolic hydrochloric acid and methanolic acetic acid in sealed ampules. The reaction temperatures and acid concentrations (w/w) are specified.

Vapour phase chromatography (V.P.C.) was used to indicate purity and to follow the path of the reactions of the simple benzyl alcohols. All samples containing anhydrous hydrochloric acid were passed through an ion-exchange amberlite IRA 400 resin column (regenerated with sodium carbonate solution) before injection into the vapour phase chromatograph.

Thin-layer chromatography was used extensively as a guide in product analyses. Thin-layer plates were coated with Kieselgel G approximately 480 μ thick. The plates were activated at 80° for 10 hr. The plates were developed with chloroform and an "overrun" period of 10 min was used. The R_f. value of a particular compound varied slightly from plate to plate and, unless otherwise indicated, the identity of compounds that were formed in the reactions were confirmed by running them alongside authentic samples. The compounds on the plates were revealed by exposure to iodine vapour which gave yellow to brown spots.

Solvents and Reagents.

B.D.H. Reagent grade acetic acid was purified by distilla-

tion from potassium permanganate through a fractionating column. The distillate was dried over triacetyl borate and redistilled from the borate. The main fraction, b.p. 116-117° was collected. Solutions of methanolic acetic acid were prepared directly before use.

Anhydrous methanolic hydrochloric acid was prepared by passing dry hydrochloric acid gas through dry redistilled A.R. methanol. The acidity of the solution was determined by titration with a standard solution of sodium hydroxide. The acid solution was stored at 0°.

Samples of olefins for V.P.C. work were prepared directly before use by dehydration of the corresponding benzyl alcohols with potassium hydrogen sulphate.

Phenylpropan-1-ol (64, R = H).

This showed no change when heated at 40° for 6 hr with methanol containing 3% acetic acid. After two days with 1% methanolic hydrochloric acid at 40° a little dehydration was observed.

1-(p-Methylphenyl)propan-1-ol (64, R = p-Me)

Reaction temperature	40°
Methanolic HCl acid conc.	1%
Benzyl alcohol conc.	0.1M

After 21½ hr V.P.C. analysis showed that about 40% conversion to the olefin had occurred. After 35½ hr the chromatogram showed 3 peaks with retention times:

4 min 37 sec (propan-1-ol), 4 min 48 sec (unknown),

4 min 57 sec (olefin).

1-(p-Methoxyphenyl)propan-1-ol (64, R = p-MeO).

The reactivity of this compound was found to be greater than that of the foregoing compound but the reaction products appeared to be of the same type.

1-(3,4-Dimethoxyphenyl)propan-1-ol [64, R = 3,4(OMe)$_2$]

(i)	Reaction temp.	40°
	Reaction time	48 hr
	Acetic acid conc.	1%
	Propan-1-ol conc.	0.1M

V.P.C. analysis showed the presence of four compounds with retention times:

(a) 3 min 4 sec (minor - unknown)

(b) 3 min 50 sec (major - unreacted alcohol)

(c) 4 min (major - olefin)

(d) 4 min 50 sec (minor - unknown).

(ii) Conditions as for (i) except 1% methanolic HCl used. After 3½ hr the reaction mixture showed the presence of a little of the olefin. After 19½ hr however, the reaction mixture showed the presence of two other compounds with retention times almost the same as the two unknown peaks in (i).

(iii) The propan-1-ol (1 g) was heated with 2% methanolic HCl for 10 hr at 50°. The reaction mixture was allowed to stand at room temperature for 2 days and then worked up. The product crystallized from methanol as white needles, m.p. 94°. The infrared spectrum (Nujol) showed no hydroxyl absorption but a peak at 1610 cm^{-1} (c = c). Light absorption in 95% ethanol: λ_{max} 288 mμ, λ_{min} 255 mμ. The compound is probably the dimer (102) of the olefin. (Found: C, 74.1; H, 7.9. $C_{22}H_{28}O_4$ requires C, 74.3; H, 7.9%). Molecular weight (Rast) : 290.

1-(2,4,6-Trimethoxyphenyl)propan-1-ol [64, R = 2,4,6$(OMe)_3$]

The formation of a number of compounds was noted in this case.

(i) Dehydration to the olefin occurred even under very low concentrations of acid.

(ii) Under relatively strong acidic conditions (> 3%) a disproportionation product, 1,1-di-(2,4,6-trimethoxyphenyl)propane (105) was formed (yield: ca 5%). The compound crystallized from methanol as white prisms, m.p. 127-128°. (Found: C, 66.9; H, 7.5. $C_{21}H_{28}O_6$ requires C, 67.0; H, 7.5%). The n.m.r. spectrum (in CCl_4) showed a symmetrical triplet centred at τ 9.22 (methyl protons), a quartet centred at τ 8.02 (methylene protons) and an intense signal at τ 6.37 (methoxyls). A triplet centred at τ 5.49 was assigned to the methine proton and an intense

resonance at τ 4.07 to the aromatic protons. The relative integrated intensities over the spectrum were 3 : 2 : 18 : 1 : 4.

(iii) Under very mild acidic conditions (0.1%) and high propan-1-ol concentrations (ca 2M) the formation of bis-1-(2,4,6-trimethoxyphenylpropyl)ether (103) was noted. The bis-ether crystallized from methanol as colourless prisms (yield : ca 10%), m.p. 144-145°. (Found: C, 66.2; H, 7.9. $C_{24}H_{34}O_7$ requires C, 66.3; H, 7.9%). The n.m.r. spectrum (in $CDCl_3$) showed a 1 : 2 : 1 triplet centred at τ 9.28 (methyl protons), a quintet centred at τ 8.08 (methylene protons), an intense signal centred at τ 6.30 (2,6,2',6' methoxyls) and a signal at τ 6.17 (4,4' methoxyls). A triplet centred at τ 5.44 was assigned to the ether linkage protons and an intense resonance at τ 3.90 to the aromatic protons. The relative integrated intensities over the spectrum were 6 : 4 : 18 : 2 : 4.

(iv)

Reaction temp.	40°
HCl conc.	1%
Propan-1-ol conc.	0.1M

The reaction mixture turned yellow within 15 sec of the addition of acid. V.P.C. analysis of the reaction mixture after 1½ hr showed one major peak (unreacted propan-1-ol, retention time: 4 min 25 sec) and two minor peaks (2 min 32 sec - olefin, 5 min 36 sec - unknown). Thin-layer chromatographic analysis showed that the unknown compound was probably the disproportionation product (105), R_F 0.38.

(v) A sample of the propan-1-ol in methanol (0.1M) in the absence of acid did not show any observable change when heated for 18 hr at 40°.

(vi) 1,3,5-trimethoxybenzene was reacted with an excess of the propan-1-ol in methanol under acidic (1%) conditions and the reaction mixture worked up. The m.p., infrared spectrum and R_F value of the product were identical with that of the diphenylpropane (105). Reaction of the trimethoxybenzene with acetaldehyde and with propionaldehyde under similar conditions did not give the diphenylpropane.

1-Hydroxy-1,2,3,4-tetrahydronaphthalene (65, R = H)

The tetralol did not show any observable change when reacted with 3% methanolic acetic acid or 1% methanolic HCl acid even after 54 hr.

It formed a sulphone (107) when heated with sodium p-toluenesulphinate dihydrate, dil. HCl acid and acetic acid. The sulphone crystallized out slowly from the reaction mixture, m.p. 127-129°.

(Found: C, 71.8; H, 6.5. $C_{17}H_{18}SO_2$ requires C, 71.5; H, 6.3%). The infrared spectrum (Nujol) showed a strong absorption at 1130 cm^{-1} (s = o) but no hydroxyl absorption.

6-Methoxy-1-hydroxy-1,2,3,4-tetrahydronaphthalene (65, R = OMe)

(i) The tetralol (0.4M) in 1% methanolic HCl acid was heated for 18 hr at 40°. Product analysis showed that 7-methoxy-1,2-

dihydro-naphthalene and its dimer were the predominant products. The n.m.r. spectrum (in $CDCl_3$) showed a two-proton multiplet centred at τ 7.89 (3-methylene protons), a quartet at τ 7.22 (benzylic protons), a signal at τ 6.22 (methoxyl), and a multiplet centred at τ 4.10 (olefinic 2-proton). A doublet centred at τ 3.58 with coupling constant J 9.9 c/s was assigned to the benzylic 1-proton (olefinic). A multiplet centred at τ 3.23 was due to the aromatic protons. The integrated intensities over the spectrum were 2 : 2 : 3 : 1 : 1 : 3.

(ii) Reaction (i) was repeated but a time of 1½ hr was used. Product analysis showed that the dihydronaphthalene (R_F 0.83) and a small amount of 2-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-3,4-dihydro-6-methoxynaphthalene (111) (R_F 0.78) was present in the reaction mixture.

(iii) The tetralol (1.2M) in 0.001% methanolic HCl acid was allowed to stand at room temperature for two days. bis-(6-Methoxy-1,2,3,4-tetrahydro-1-naphthyl)ether (110) crystallized out slowly from the reaction mixture as needles (ca 5% yield), m.p. 99-100°.

(Found: C, 77.7; H, 7.8. $C_{22}H_{26}O_3$ requires C, 78.1; H, 7.7%). The n.m.r. spectrum (in $CDCl_3$) showed a multiplet centred at τ 8.01 due to the methylene protons, a partly resolved triplet centred at τ 7.28 (benzylic protons), and a resonance at τ 6.25 (methoxyls). A triplet centred at τ 5.44 was assigned to the protons in the ether linkage and a multiplet at τ 3.07 was assigned to the aromatic protons. The integrated intensities over the spectrum were 8 : 4 : 6 : 2 : 6.

The bis-ether (0.02 g) in 1% methanolic HCl acid (3 ml) was heated at 40° for 18 hr. The reaction mixture showed the presence of three compounds: (a) 7-methoxy-1,2-dihydronaphthalene, R_F 0.81 (major), (b) the dihydro-dimer (111), R_F 0.72 (minor), (c) unreacted bis-ether, R_F 0.21 (minor).

(iv) A sample of the tetralol (0.4M) in methanol was heated at 40° for 6 hr. No change was observed.

(v) The tetralol (0.06M) in 3% methanolic acetic acid was heated at 40° for 1 hr. Product analysis showed the presence of the dihydronaphthalene, unreacted tetralol and a compound at R_F 0.37 (methyl ether ?).

(vi) The tetralol (0.125M) in 0.001% methanolic acetic acid was heated at 40° for 24 hr. Thin-layer chromatography showed the presence of one compound at R_F 0.47. The reaction was stopped and the solvent and acid completely removed. The n.m.r. spectrum (in CCl_4) of the product (methyl ether) showed a multiplet centred at τ 8.14 (methylene protons), a broad unresolved band at τ 7.35 (benzylic 4-protons), two intense signals at τ 6.71 (benzylic 1-methoxyl) and τ 6.29 (6-methoxyl), and a broad band at τ 5.86 (benzylic 1-proton). The absorption of the aromatic protons was centred at τ 3.33. The relative integrated intensities over the spectrum were 4 : 2 : 3 : 3 : 1 : 3.

The tetralyl methyl ether was found to be unstable in the presence of even small amounts of acid. When heated with 0.1% methanolic HCl acid it decomposed to give the dihydronaphthalene (81).

1,2-Dihydroxy-1,2,3,4-tetrahydronaphthalene (66,67, R = H)

The tetralin cis- and trans- diols were found to be very stable under the conditions used for methyl-ether formation. However, prolonged heating of the cis- diol (R_F 0.41 in 1% ethanol-chloroform) with 3% methanolic HCl acid gave a little of the trans-diol (R_F 0.33) (reaction mixture was probably contaminated with water even though precautions were taken to exclude water from the reaction).

1,2-Dihydroxy-6-methoxy-1,2,3,4-tetrahydronaphthalene (66,67, R = OMe)

(i) The cis- and trans- diols (0.05M) in 0.1% methanolic HCl acid were heated at 40° for 15 hr. The reaction mixtures turned red in colour. The infrared spectra of the reaction products showed strong absorption at ca 1700 cm^{-1} (carbonyl).

(ii) Both diols were found to be unreactive in the presence of 1% methanolic acetic acid.

(iii) The cis- diol (0.1M) in 0.01% methanolic HCl acid was heated at 40° for 12 hr and the solvent and acid removed. The n.m.r. spectrum (in $CDCl_3$) of the product showed a multiplet centred at τ 7.93 (3-methylene protons, 2-hydroxyl proton and 2-proton), a triplet centred at τ 7.13 (benzylic 4-protons), a resonance at τ 6.84 (methoxyl group of methyl ether) and a signal at τ 6.25 (6-methoxyl). A doublet centred at τ 5.85 was assigned to the benzylic 1-proton of the cis-methyl ether. A quartet centred at τ 6.03 was assigned to

the benzylic 1-proton of the *cis*- and *trans*- methyl ethers. The aromatic protons showed a multiplet at τ 3.03.

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X. 7,8,3′,4′-TETRAHYDROXYFLAVANONE AND 7,8,3′,4′-TETRAHYDROXYDIHYDROFLAVONOL FROM ACACIA SPECIES

By J. W. Clark-Lewis and V. Nair

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