Interconversion of Neoflavanoids

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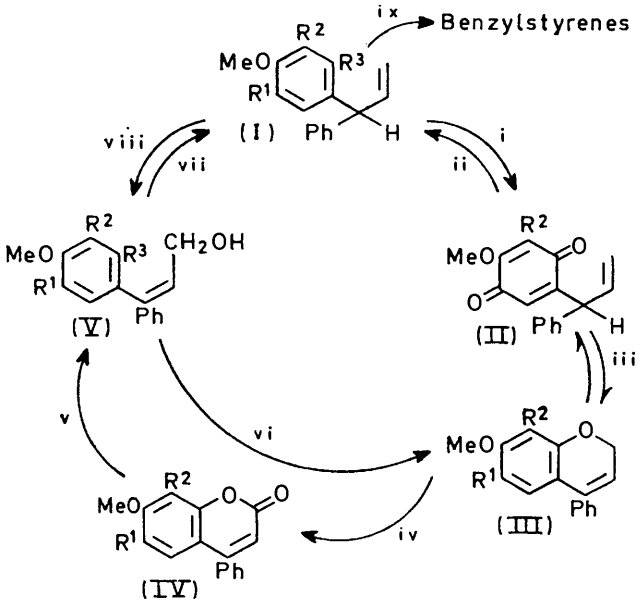
Quantitative yields have been obtained in the interconversion of neoflavanoids (II) ⇌ (IV). An alternative pathway is considered for the synthesis of 4-arylcoumarins without a 6-hydroxy-substituent.

THE isolation, in minor quantities, of closely related neoflavanoids often of similar configuration [1,2] from the genera Dalbergia and Macherium (*Leguminosae-Lotoideae*) emphasised the advantages of a system of chemical interconversions of members of a series. High yield biological-type conversions have been achieved; for example, 3,3-diarylpropenes [4-methoxydalbergiquinol (Ia)] have been converted into the corresponding 4-arylcoumarins [dalbergin (IVa; R = OH)] *via* the 4-arylchromens [dalbergichromen (IIIa; R^1 = OH)] (see Scheme). The compounds prepared were used as standards in phytochemical searches of unexplored Dalbergia species.[3]

Proposals for the biosynthesis of the neoflavanoids include a bio-oxidative sequence [4] resulting in the formation of the 4-arylcoumarin or alternatively a bio-reductive sequence [5] commencing with the 4-arylcoumarin. In the latter case, it is suggested that the 4-arylcoumarins arise by cyclisation of the corresponding cinnamic ester. The former proposal envisages *C*-alkylation of polyphenols with cinnamyl pyrophosphate [6] under mild acid catalysis, giving the dalbergiquinols.

Ollis and his associates [7] have demonstrated the reversible oxidation–reduction of a dalbergiquinol (Ia) to a dalbergione (IIa) and subsequently reported [1] the isomerisation of the quinone (IIb) to the neoflavene kuhlmannene (IIIb; R^1 = OH) by chromatography on neutral alumina. We have found this method unsatisfactory for cyclisation of 4-methoxydalbergione (IIa) and 3′-acetoxy-4,4′-dimethoxydalbergione (IIc). Quantitative yields of the isomeric neoflavenes (IIIa—c; R^1 = OH) were obtained by treatment of the dalbergiones (IIa—c) with *NN*-dimethylaminopyridine in chloroform at room temperature. Refluxing the dalbergiones with pyridine [8] resulted in slightly reduced yields of neoflavenes.

A selection of oxidising reagents was tested for the conversion of the chromens (IIIa—d) to the 4-arylcoumarins (IVa—d); for example SeO_2 in refluxing dioxan gave a 50% yield and CrO_3 in pyridine at 21° also gave 50%. The conversion was obtained in 95% yield in all cases with CrO_3 in pyridine at 55° for 5 h.



a; $R^1 = R^3$ = OH (OAc), R^2 = H
b; $R^1 = R^3$ = OH (OAc), R^2 = OMe
c; $R^1 = R^3$ = OH (OAc), R^2 = H; C_6H_3-3-OH-4-OMe for Ph
d; $R^1 = R^2$ = H, R^3 = OAc

SCHEME Reagents: i, O_2–0·1N-K_2CO_3,[7] if R^1 = H *m*-chloroperbenzoic acid–toluene-*p*-sulphonic acid–$CHCl_3$;* DDQ–C_6H_6;* ii, sodium dithionite (13%);[7] iii, neutral alumina,[8] reflux in C_5H_5N;[8] *NN*-dimethylaminopyridine–$CHCl_3$;* iv, CrO_3–pyridine,* SeO_2–dioxan;* v, LAH–Et_2O;[5] vi, IR 120 H^+ form–C_6H_6;[8] HCl–EtOH;* vii, LAH–$AlCl_3$–Et_2O;[5] $SnCl_2$–HOAc,[5] Zn–HCl–HOAc,[5] DMF–Zn–HCl;[5] viii, $Hg(OAc)_2$–HOAc,* SeO_2–HOAc;* ix, BF_3.[9]

* Present paper.

Among literature examples of oxidation of methylene groups are the conversion of a chromenocoumarin into

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[2] B. J. Donnelly, D. M. X. Donnelly, A. M. O'Sullivan, and J. P. Prendergast, *Tetrahedron*, 1969, **25**, 4409, and unpublished work.
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[4] W. D. Ollis and O. R. Gottlieb, *Chem. Comm.*, 1968, 1396.
[5] S. K. Mukerjee, T. Saroja, and T. R. Seshadri, *Indian J. Chem.*, 1970, **8**, 21, and references therein; T. R. Seshadri, *Phytochemistry*, 1972, **11**, 881.
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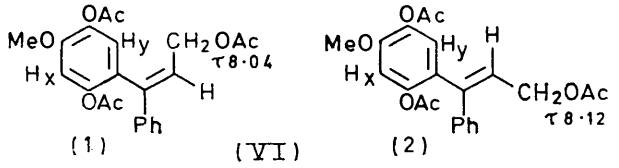
[7] W. B. Eyton, W. D. Ollis, I. O. Sutherland, O. R. Gottlieb, M. Taveira Magalhães, and L. H. Jackman, *Tetrahedron*, 1965, **21**, 2683.
[8] S. K. Mukerjee, T. Saroja, and T. R. Seshadri, *Tetrahedron*, 1971, **27**, 799.
[9] D. Kumari, S. K. Mukerjee, and T. R. Seshadri, *Tetrahedron Letters*, 1967, 1153.

di-*O*-methylcoumestrol,[10] isoflav-3-ene into 3-arylcoumarin,[11] and 4-phenyl-1-thio- and 1-seleno-chromen [12] into the corresponding coumarins.

The 3,3-diarylpropenes (Ia—c) contain a hydroxy-group at C-5, essential for quinone formation and subsequent isomerisation to the neoflavene As a 6-hydroxy-substituent is absent from all neoflavanoids isolated to date from Guttiferae [13] and from exostemin [14] isolated from a member of the Rubiaceae, a more general route to neoflavenes and hence coumarins *via* the allylic alcohols or epoxides was investigated.

Oxidation of dalbergiquinol diacetate (Ia; $R^1 = R^3 = OAc$) by an equimolar amount of $Hg(OAc)_2$ in AcOH [15] at reflux gave 60% metallic Hg and a total conversion of 60% from which the allylic alcohols [as their acetates (VI1 and 2)] were identified. The



configurations (1) and (2) were assigned by application of the intramolecular nuclear Overhauser effect (NOE). In the isomer (VI2), the proton resonance at τ 3·04 (6-H, H_y) is enhanced on irradiation at the frequency

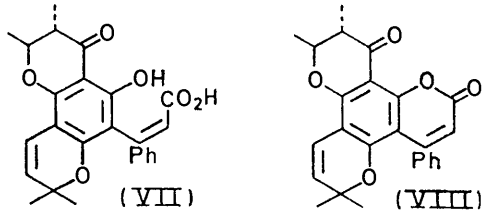
NOE measurements on 3-(2,5-diacetoxy-4-methoxy phenyl)-3-phenylallyl acetates (VI1 and 2)

Protons irradiated	Proton observed	% Enhancement (1)	% Enhancement (2)
OMe	H_x	30	28
CH_2O	H_y	12	0
C=CH	H_y	0	18

of the ethylenic proton. Irradiation at the frequency of the methoxy-group causes no enhancement in the peak area of H_y but causes 28% enhancement in H_x (3-H) at τ 3·36.

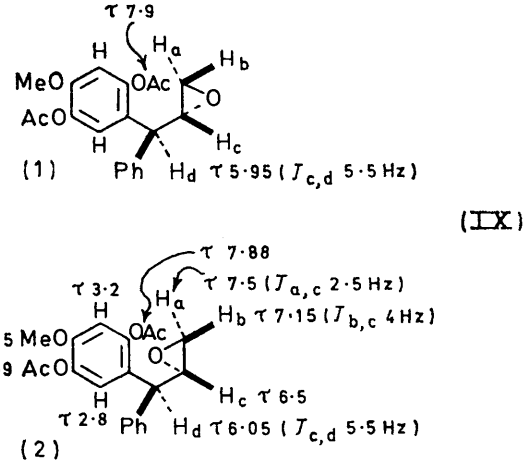
The isomers (VI1 and 2) gave rise to two distinct allylic acetate resonances (τ 8·04 and 8·12) in the ratio 3 : 1. The major isomer (VI1) underwent smooth cyclodeacetylation, and reacetylation leads to the corresponding neoflavene (IIIa). Further confirmation of the configurational assignment of compound (VI1) was obtained by comparison with the product from reduction [lithium aluminium hydride (LAH)] [5] and subsequent acetylation of dalbergin (IVa). The replacement of $Hg(OAc)_2$ by SeO_2 led to formation of a 1 : 1 mixture of allylic alcohols.

The further oxidation of the allylic alcohol to αβ-unsaturated acid and immediate cyclisation to the lactone would be consistent with the existence of intermediates like calophyllic acid (VII) in the biogenesis of inophyllolide (VIII) (*Calophyllum inophyllum*). Polonsky *et al.*[16] have shown by labelling experiments that callophyllic acid (VII) is a precursor of the 4-arylcoumarin (VIII).



Cyclodeacetylation of the allylic acetates with ethanolic HCl was quantitative in yield.

The route to the coumarins *via* the epoxides was abandoned due to low yields at the rearrangement stage and difficulty in separating the isomeric mixture (IX1 and 2). A partial separation was achieved by fractional crystallisation. The assignment of the configurations (1) and (2) is based on differences in chemical shift values of H_d and 2-OAc in the spectra of the two isomers. The major isomer (2) is the epoxide formed by approach of the *m*-chloroperbenzoic acid to the less hindered side of the double bond.



A recent publication shows the conversion under acetylating conditions of an epoxide into a 2,2-dimethyl-2*H*-chromen.[17]

[10] W. J. Bowyer, J. N. Chatterjea, J. P. Dhoubhadel, B. D. Handford, and W. B. Whalley, *J. Chem. Soc.*, 1964, 4213.
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[17] J. Bohlmann and U. Bühmann, *Chem. Ber.*, 1972, **105**, 863.

The Scheme shows the possible interconversions (and the reagents) of the neoflavanoids including those detailed in the present paper.

EXPERIMENTAL

M.p.s were measured on a Köfler hot-stage apparatus. 60 MHz N.m.r. spectra were measured for $CDCl_3$ solutions (Me_4Si as internal reference). Merck Kieselgel $HF_{254+366}$ was used for t.l.c.

4-Methoxydalbergione (IIa).—To a solution of 4-methoxydalbergiquinol (40 mg) in dry benzene (1 ml) was added a solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in dry benzene (1·5 ml). The solution was stirred for 5 min and the reduced DDQ ($DDQH_2$) was filtered off. Removal of the benzene gave the dalbergione (35 mg).

3,4-Dimethoxydalbergione (IIb).—A mixture of 3-(2-hydroxy-3,4-dimethoxyphenyl)-3-phenylpropene (400 mg), *m*-chloroperbenzoic acid (400 mg), and toluene-*p*-sulphonic acid (15 mg) in chloroform was stirred for 24 h. The chloroform solution was washed successively with aqueous Na_2SO_3 and $NaHCO_3$ and dried. Purification by t.l.c. of the red oil obtained by evaporation of the solvent gave the title compound (62 mg).

Isomerisation of 4-Methoxydalbergiones (IIa—c).*—An equimolar solution of the 4-methoxydalbergiones and *NN*-dimethylaminopyridine in $CHCl_3$ was stirred at room temperature for 12 h. Acetic anhydride was added and the mixture was left for a further 12 h. The neoflavenes (IIIa—c) were precipitated on dilution with ice–water. *Melannene acetate* (IIIc; R^1 = OAc) crystallised from aqueous EtOH as prisms, m.p. 135—136° (Found: C, 65·7; H, 5·2. $C_{21}H_{20}O_7$ requires C, 65·6; H, 5·2%), $\nu_{max.}$ (KBr) 1750 (Ac) and 1610 cm^{-1}, τ 4·31 (t, 3-H), 5·18 (d, AX_2, J_{AX} 4·0 Hz, 2-H_2), 6·12(s) and 6·18(s) (2 × OMe), and 7·69 and 7·75 (s, 2 × OAc), $\lambda_{max.}$ (MeOH) 243sh (log ε 4·46), 285 (4·03), and 315 (4·03) nm. The products (IIIa and b; R^1 = OAc) are acetates of dalbergichromen [8] and kuhlmannene [1] respectively.

Formation of Allylic Alcohols. 3-(2,5-*Diacetoxy*-4-*methoxyphenyl*)-3-*phenylallyl Acetates* (VI1 *and* 2).—An equimolar mixture of 4-methoxydalbergiquinol diacetate (Ia; $R^1 = R^3$ = OAc) (300 mg) and $Hg(OAc)_2$ (300 mg) in glacial acetic acid (150 ml) was refluxed for 72 h. The Hg formed was collected by filtration. Removal of the acetic acid under reduced pressure gave a black residue which was dissolved in Et_2O and washed with aqueous NaOH (5%) and water. T.l.c. (silica gel, $CHCl_3$) afforded a solid (230 mg) which was shown by n.m.r. spectrometry to be a 3 : 1 mixture of the isomeric acetates (VII and 2). Addition of EtOH yielded a solid (VI2), m.p. 147·5° (Found: C, 66·2; H, 5·5. $C_{22}H_{22}O_7$ requires C, 66·3; H, 5·5%), $\nu_{max.}$ (KBr) 1760, 1725, and 1610 cm^{-1}, τ 2·74 (s, aromatic ring B), 3·04 (s, 6-H), 3·36 (s, 3-H), 4·04 (t, ethylenic 2-H), 5·28 (d, AX_2, J_{AX} 4 Hz, CH_2OAc), 6·19 (s, OMe), 7·7, 7·93 (s, 2 × OAc), and 8·12 (s, CH_2OAc).

* (*S*)-3′-Hydroxy-4,4′-dimethoxydalbergione, a new natural product from *Dalbergia melanoxylon*. Details will be published shortly.

The filtrate was evaporated to yield a solid which crystallised from EtOH as needles of (VI1), m.p. 110° (Found: C, 66·5; H, 5·7%), $\nu_{max.}$ (KBr) 1760, 1725, and 1620 cm^{-1}, τ 2·74 (s, ring B), 3·08 (s, 6-H), 3·25 (s, 3-H), 3·82 (t, ethylenic 2-H), 5·39 (d, AX_2 s, J_{AX} 4 Hz, CH_2OAc), 6·16 (s, OMe), 7·7, 7·93 (s, OAc), and 8·04 (s, CH_2OAc). No depression in m.p. was observed on admixture with the product of reduction (LAH–Et_2O) and subsequent acetylation of dalbergin.

A solution of 4-methoxydalbergiquinol diacetate (350 mg) and SeO_2 (150 mg) in HOAc (30 ml) was refluxed for 3 h. Filtration and evaporation of the acetic acid gave a residue which was treated with ice–water. The solid obtained was dissolved in Et_2O, washed ($NaHCO_3$ and H_2O), dried, and evaporated. The n.m.r. spectrum of the oil indicated a 1 : 1 mixture of alcohols (VI).

3-(2-Acetoxy-4-methoxyphenyl)-3-phenylallyl Acetates [(Vd) *and Isomer*].—A mixture of 3-(2-acetoxy-4-methoxyphenyl)-3-phenylpropene [6] (750 mg) and $Hg(OAc)_2$ (110 mg) in HOAc (75 ml) was refluxed for 48 h. The procedure for isolation of compounds (VI1 and 2) was adopted and gave an oil (500 mg). N.m.r. spectroscopy indicated a 5 : 1 mixture of the isomeric allylic acetates.

Cyclodeacetylation. 3-Acetoxydalbergichromen.[8]—3-(2,5-Diacetoxy-4-methoxyphenyl)-3-phenylallyl acetate (VI) (120 mg), EtOH (25 ml), and HCl (5 ml; 10%) were refluxed for 24 h. The residue, obtained by evaporation of EtOH, was acetylated. Purification (t.l.c.) gave 3-acetoxydalbergichromen (IIIa) as an oil (45 mg).

The mixture (5 : 1) of allyl acetates [(Vd) and isomer] in EtOH (12 ml) was treated with HCl (1 ml; 10%). The mixture was refluxed gently for 2 h. 7-Methoxy-4-phenylchromen [8] (IIId) was obtained in 80% yield.

Oxidation of Neoflavenes (IIIa—d).—The neoflavenes (IIIa—d) were stirred at 50—60° in CrO_3–pyridine for 5 h. Quantitative yields of dalbergin acetate (IVa), kuhlmannin acetate [1] (IVb), melannein diacetate [2] (IVc), and 7-methoxy-4-phenylcoumarin (IVd) were isolated and found to be identical (n.m.r., t.l.c., and m.p.) with authentic samples.

3-(2,5-Diacetoxy-4-methoxyphenyl)-3-phenylpropene Epoxides (IX1 *and* 2).—A mixture of 4-methoxydalbergiquinol diacetate (Ia; $R^1 = R^3$ = OAc) (400 mg) and *m*-chloroperbenzoic acid (400 mg) was refluxed in EtOAc for 72 h. A $CHCl_3$ extract of the mixture was washed successively with Na_2SO_3 and $NaHCO_3$. Evaporation of the dried solvent gave an oil (45%) which afforded needles on addition of EtOH, m.p. 115—116°. The n.m.r. spectrum indicated a 4 : 1 mixture of two isomeric epoxides (IX1 and 2). Recrystallisation from EtOH gave the *epoxide* (IX1) as needles, m.p. 122·5° (Found: C, 67·0; H, 5·8. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·7%). The filtrate yielded a second crop, m.p. 85—86°. N.m.r. spectrum showed the isomers (1) and (2) in ratio 1 : 1·5.

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