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THE NEOFLAVANOID GROUP OF NATURAL PRODUCTS—II.

THE EXAMINATION OF *MACHAERIUM SCLEROXYLON* AND SOME BIOGENETIC PROPOSALS REGARDING THE NEOFLAVANOIDS

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Abstract—*Machaerium scleroxylon* heartwood and sapwood have yielded the new natural products, O-acetyloleanolic aldehyde (I), R-3,4-dimethoxydalbergione (IV), its corresponding quinol (Va), and the benzophenone derivative, scleroin (X), as well as the known dalbergin (IIa) and O-methyldalbergin (IIb). The co-occurrence of the dalbergiones and dalbergins suggests that they have a common biosynthetic origin in which cinnamyl pyrophosphate (or its equivalent) is the postulated precursor of the neoflavanoids. It is suggested that the natural dalbergiones, dalbergins and benzophenones are inter-related as transformation products of neoflavanoids.

IN PART I of this series,[1] it was shown that a new group of natural quinones, the dalbergiones, were characteristic of some members of the *Dalbergia* genus and in view of the close taxonomic relationship between the *Dalbergia* and *Machaerium* genera, a phytochemical examination of the latter genus is also being made. The first species to be examined was *Machaerium scleroxylon* Tul., whose heartwood is now being used in Brazil as a commercial substitute for the true jacaranda wood obtained from *Dalbergia nigra*. The examination of *M. scleroxylon*[2] has provided another member of the dalbergione family and the co-occurrence of a dalbergione with dalbergin (IIa) and O-methyl-dalbergin (IIb) from this species is also of phytochemical interest.

The sapwood of *M. scleroxylon* has yielded β-sitosterol, O-acetyloleanolic aldehyde (I), dalbergin (IIa) and O-methyl dalbergin (IIb). The O-acetyloleanolic aldehyde was identified by consideration of its IR and NMR spectra. These indicated the presence of a quaternary aldehyde group (ν_{max} 2680 and 1710 cm^{-1}; τ 0·58 singlet),

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[1] W. B. Eyton, W. D. Ollis, I. O. Sutherland, O. R. Gottlieb, M. Taveira Magâlhães and L. M. Jackman, Part I of this series, *Tetrahedron* **21**, 2683 (1965).

[2] For a preliminary report see O. R. Gottlieb, M. Fineberg, I. Salignac de Souza Guimarães, M. Taveira Magalhães, W. D. Ollis and W. B. Eyton, *Anais acad. brasil cienc.* **36**, 33 (1964).

one acetoxyl group (ν_{max} 1710 cm^{-1}; τ 7·93 singlet), and one vinyl hydrogen (τ 4·60, triplet; J = 8 c/s), which was compatible with the grouping $-CH_2-\underline{C}\underline{H}=C<$. The other triplet ($\tau$ 5·46; J = 8 c/s) could be assigned to the grouping $AcO-\overline{C}\underline{H}-CH_2-$. The triterpenoid nature of the compound was indicated by its molecular formula, $C_{30}H_{47}O(OAc)$, and the presence of seven quaternary C-methyl groups (singlets at τ 8·85, 9·05, 9·11 and 9·25). Its identity as 3-0-acetyloleanolic aldehyde (I) was confirmed by comparison with an authentic specimen kindly supplied by Dr. M. Shamma. O-Acetyloleanolic aldehyde has not been detected previously as a natural product, although oleanolic aldehyde has been isolated from the catcus *Heliabravoa chende*.[3]

The spectroscopic properties of dalbergin (IIa) and O-methyl-dalbergin (IIb) easily permitted their identification and this was confirmed by comparison with authentic specimens kindly provided by Professor T. R. Seshadri. Previous isolations of these two 4-arylcoumarins (Ia and Ib) have been restricted to the *Dalbergia* species, *D. sissoo*[4] and *D. latifolia*,[5] and their isolation from a *Machaerium* species emphasizes the close botanical relationship between the *Dalbergia* and *Machaerium* genera.

The heartwood extract of *M. scleroxylon* also yielded dalbergin (Ia), O-methyl-dalbergin (Ib), and O-acetyloleanolic aldehyde (II). In addition three other compounds were isolated: a red compound, $C_{15}H_{10}O_2(OMe)_2$, a colourless oil, $C_{15}H_{12}O_2(OMe)_2$ and a yellow compound, $C_{13}H_8O_3(OMe)_2$.

The colour and the UV spectrum [λ_{max} 260 mμ (ε 11,400), 405 mμ (ε 1,000)] of the red compound suggested that it was a quinone and its IR spectrum showed many features in common with the IR spectra of the dalbergiones.[1] Its structure as 3,4-dimethoxydalbergione (III) was uniquely defined by its NMR spectrum. This showed a multiplet (τ 2·5–2·8) assignable to the phenyl group and multiplets characteristic of the $>CH-CH=CH_2$ grouping present in dalbergiones. Two methoxyl groups (singlets, τ 6·00 and 6·05) and one proton (τ 3·65, doublet; J = 1 c/s) were evidently associated with the quinonoid residue. Since the proton at τ 3·65 appeared as a doublet (J = 1 c/s), it must be coupled with the benzylic proton and placed in position 6. It follows that the two methoxyl groups are placed in positions 3 and 4. Permanganate oxidation of 3,4-dimethoxydalbergione (III) gave benzoic acid, reaction with 2,4-dinitrophenylhydrazine gave the 2,4-dinitrobenzeneazophenol (VI), and vigorous catalytic hydrogenation gave the decahydroderivative (VII). The R-configuration (IV) for the 3,4-dimethoxydalbergione was demonstrated by comparison of its optical rotatory dispersion and circular dichroism curves (Fig. 1) with those of R-dalbergione (Fig. 3 of preceding paper[1]). Comparison of the optical rotatory dispersion and circular dichroism curves with the ultra-violet spectrum of 3,4-dimethoxydalbergione discloses electronic transitions characteristic of the quinonoid residue which are not obvious in its UV spectrum.[6]

The colourless oil, $C_{15}H_{12}O_2(OMe)_2$, showed strong absorption in the hydroxyl region of its IR spectrum. It was characterized as a diacetate which was identical with the product (Vb) obtained by sodium dithionite reduction followed by acetylation

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[3] M. Shamma and P. D. Rosenstock, *J. Org. Chem.* **24**, 726 (1959).

[4] V. K. Ahluwalia and T. R. Seshadri, *J. Chem. Soc.* 970 (1957).

[5] S. Balakrishna, M. M. Rao and T. R. Seshadri, *Tetrahedron* **18**, 1503 (1962).
M. M. Rao and T. R. Seshadri, *Tetrahedron Letters* No. **4**, 211 (1963).

[6] C. Djerassi, H. Wolf and E. Bunnenberg, *J. Amer. Chem. Soc.* **84**, 4552 (1962).

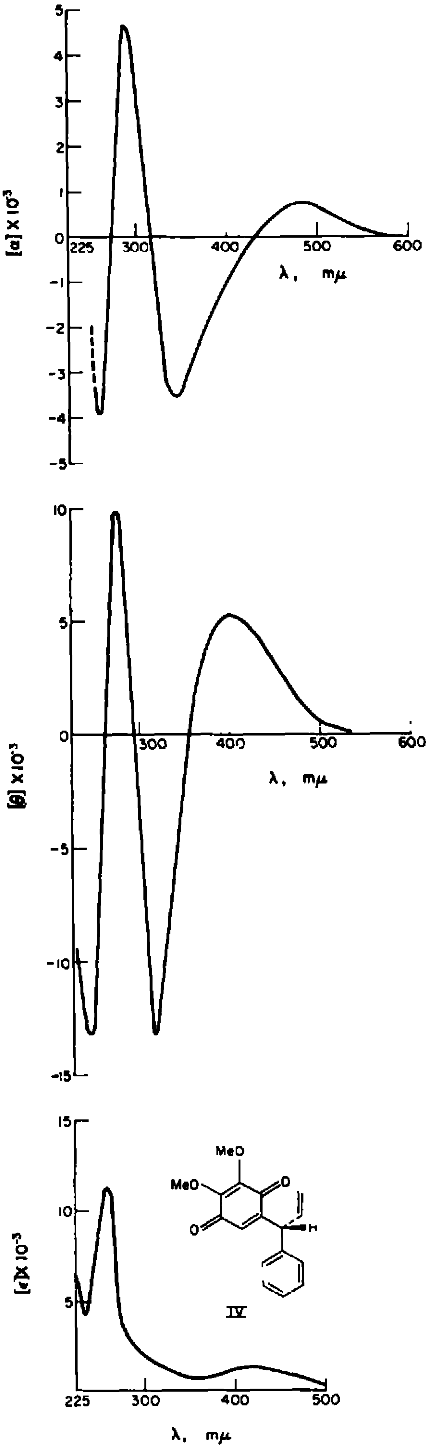
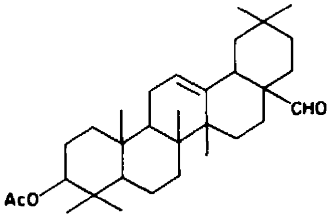
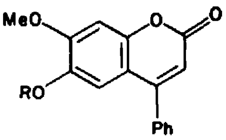


FIG. 1. Optical rotatory dispersion and circular dichroism curves of R-3,4-dimethoxydalbergione (IV) and its ultra-violet spectrum.

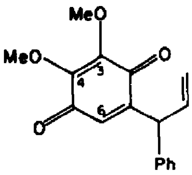
of R-3,4-dimethoxydalbergione. This identified the colourless oil as the quinol (Va). The isolation of quinones and quinols from the same source is comparatively rare, presumably because the quinols are often overlooked.[7] However, the quinol (Va) may be regarded as a structural analogue of latifolin, a quinol methyl ether isolated from *D. latifolia* for which a partial structure has been published.[5,8]



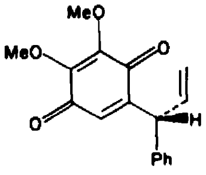
I



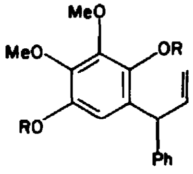
IIa R=H
IIb R=Me



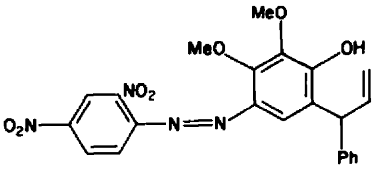
III



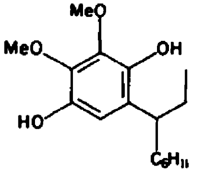
IV



V a R=H
V b R=Ac



VI



VII C_6H_{11}=cyclohexyl

The amount of the yellow compound, $C_{18}H_8O_3(OMe)_2$, called scleroin, which was available precluded extensive degradative investigation. Its IR spectrum indicated the presence of at least two hydroxyl groups in that a band (ν_{max} 3610 cm^{-1}) could be associated with a free hydroxyl group and a second hydroxyl group was obviously chelated with a carbonyl function (ν_{max} 1630 cm^{-1}). The presence of a chelated hydroxyl group was also clearly demonstrated by a sharp low field singlet (τ −2·23) in the NMR spectrum of scleroin. This spectrum also showed the presence of two methoxyl groups (τ 5·85 and 6·02), an unbonded hydroxyl group (broad τ 5.0), one aromatic proton (τ 3·05) and a multiplet (τ 2·18–2·60) showing the deshielding to be

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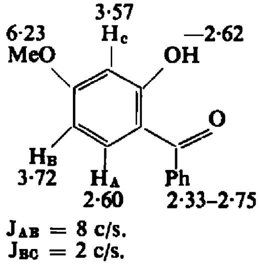
[7] J. Gripenberg, *Acta Chem. Scand.* 12, 1411 (1958).

[8] T. R. Seshadri, *J. Ind. Chem. Soc.* 40, 497 (1963).

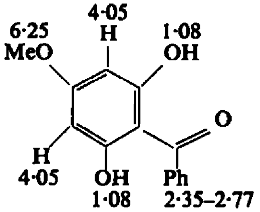
expected for a benzoyl group. The signals (τ −2·23 and 5·0) due to the two hydroxyl groups disappeared on deuteration. Thus scleroin was a benzophenone,

$$\mathrm{Ph—CO—C_6H(OH)_2(OMe)_2},$$

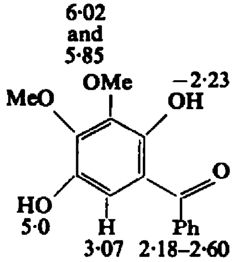
and this proposal was fully supported by comparison of its NMR spectrum with those of 2-hydroxy-4-methoxybenzophenone (VIII)* and cotoin (IX)* as models. However, on this evidence it was not possible to make a final decision regarding the structure of scleroin, but synthesis by Gregson[9] has established that scleroin has the structure X.



VIII*



IX*



X*

Although isolated from different species, a possible biogenetic relation between the dalbergiones and the dalbergins (IIa and IIb) has already been commented upon.[8,10] However, with the demonstrated co-occurrence of dalbergin (IIa), O-methyldalbergin (IIb), R-3,4-dimethoxydalbergione (IV) and the quinol (Va) in the one plant, *M. scleroxylon*, then the probable validity of this proposal is emphasized. The isolation of scleroin (X) from the same source and its close structural similarity to R-3,4-dimethoxydalbergione (IV) lends strong support to earlier proposals made by Geissman and Hinreiner,[11] and later extended by Seshadri,[8,12] concerning the biosynthetic origin of oxygenated benzophenones. Thus, although the structures of naturally occurring benzophenones such as maclurin, cotoin, protocotoin and scleroin

* Chemical shifts and coupling constants are shown in the formulae (VIII), (IX) and (X).

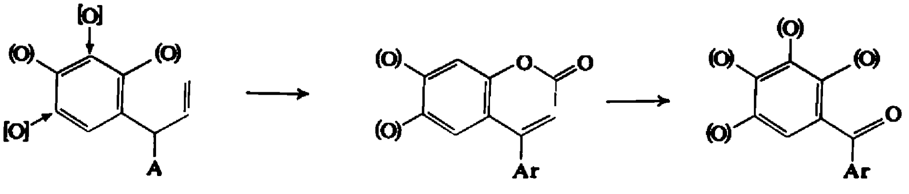
[9] M. Gregson, W. D. Ollis and O. R. Gottlieb, forthcoming publication.

[10] W. B. Eyton, W. D. Ollis, I. O. Sutherland, L. M. Jackman, O. R. Gottlieb and M. Taveira Magalhães, *Proc. Chem. Soc.* 301 (1962).

[11] T. A. Geissman and E. H. Hinreiner, *Bot. Rev.* 18, 208 (1952).

[12] T. R. Seshadri, *Curr. Sci.* 26, 239 (1957).

could well involve chain initiation by benzoyl coenzyme-A and chain extension by malonyl coenzyme-A, in accord with current biosynthetic knowledge,[13] it would seem that the natural co-occurrence of dalbergiones, 4-arylcoumarins, and benzophenones is more in accord with the following oxidative sequence:



Dalbergiones 4-Arylcoumarins **Benzophenones**

It seems probable that the biosynthesis of the C_{15}-neoflavanoid skeleton involves a process which is formally different from that concerned with the generation of the C_{15}-flavonoid and isoflavonoid type structures. The latter biosynthetic sequence formally involves *acylation* by cinnamoyl co-enzyme A[14] and we now suggest[15] that the neoflavanoids are formed by a process involving *alkylation* by cinnamyl pyrophosphate (XI) of a phenolic C_6-unit or its polyketide equivalent. Thus an S_N2 type of reaction (process *a* below) could lead directly to the neoflavanoid skeleton (XII) and it seems possible that the benzylstyrene skeleton (XIII) could be formed by the alternative alkylation process *b*. It may be noted that process *a* is mechanistically similar to the biogenetic proposal (process *c*) recently made by Birch[16] for the formation of natural allylphenols (XIV) by reduction of cinnamyl phosphates.

Our evidence concerning the natural co-occurrence of neoflavanoids (XII) and benzylstyrenes (XIII) will be presented shortly,[17] but it may be noted that the type-structures (XII and XIII) are similar in form to the two types of C_5-isoprenoid residues (XV and XVI) which are frequently associated with the structures of natural phenolic compounds.[18] The two types of isoprenoid residue (XV and XVI) clearly arise by alkylation involving isopentenyl pyrophosphate,[18] and in this connection the recent disclosure[19] of the structures of several natural phenols containing both

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[13] A. J. Birch, *Proc. Chem. Soc.* 3 (1962).

[14] H. Grisebach and W. D. Ollis, *Experienta* **17**, 4 (1960) and Refs there cited; A. C. Neish, *Cinnamic Acid Derivatives as Intermediates in the Biosynthesis of Lignin and Related Compounds* in *Formation of Wood in Forest Trees* p. 219, Academic Press (1964); A. C. Neish, *Major Pathways of Biosynthesis of Plants* in *Biochemistry of Phenolic Compounds* (Edited by J. B. Harborne) p. 295. Academic Press (1964).

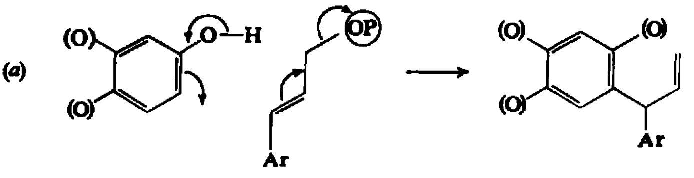
[15] W. D. Ollis, O. R. Gottlieb and M. Taveira Magalhães, *Anais acad. brasil. cienc.* **36**, 35 (1963).

[16] A. J. Birch, *Biosynthetic Pathways* in *Chemical Plant Taxonomy* (Edited by T. Swain) p. 141. Academic Press (1963).

[17] M. Gregson, W. D. Ollis and O. R. Gottlieb, forthcoming publication.

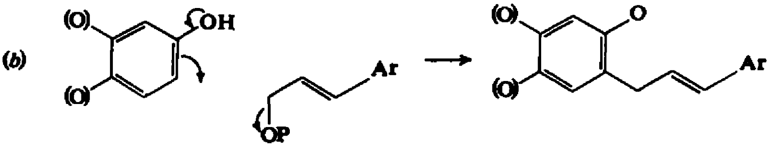
[18] W. D. Ollis and I. O. Sutherland, *Recent Developments in the Chemistry of Natural Phenolic Compounds* (Edited by W. D. Ollis) p. 74. Pergamon (1961).

[19] M. L. Wolfrom, F. Komitsky, G. Fraenkel, J. H. Looker, E. E. Dickey, P. McWain, A. Thompson, P. M. Mundell and O. M. Windrath, *Tetrahedron Letters* No. 12, 749 (1963); *J. Org. Chem.* **29**, 692 (1964).



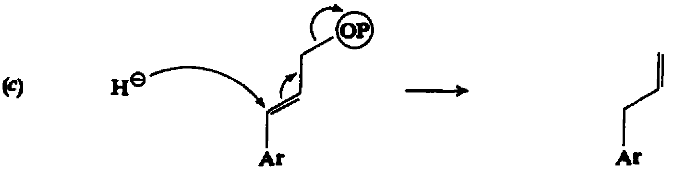
XI

XII*

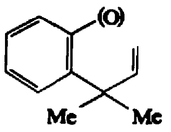


XI

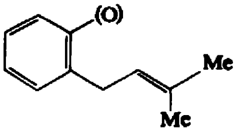
XIII



XIV



XV



XVI

types of C_5-residues (XV and XVI) is relevant. The biogenetic proposals (*a* and *b*) for the formation of the neoflavanoids (XII) and the benzylstyrenes (XIII) are mechanistically analogous to the two types of alkylation offered by isopentenyl pyrophosphate.

EXPERIMENTAL

Extraction of Machaerium scleroxylon *softwood*

Isolation of β-sitosterol, O-acetyloleanolic aldehyde (I), *O-methyldalbergin* (IIb) *and dalbergin* (IIa). The softwood in the form of sawdust (5 kg) was continuously extracted with benzene and this extract after concentration was chromatographed on silica. Successive elution with light petroleum, light petroleum–benzene mixtures, benzene, benzene–chloroform mixtures and chloroform gave a number of fractions which by further chromatography gave four main fractions. The first gave β-sitosterol, m.p. 138–140°, and the second after crystallization from MeOH gave O-acetyloleanolic aldehyde as colourless needles, m.p. 225–228° (Found: C, 79·57; H, 10·20. Calc. for $C_{32}H_{50}O_3$: C, 79·62; H, 10·44%), which was identified from its IR spectrum (ν_{max} in $CHCl_3$, 2680, 1710, 1250

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* As has been suggested in Part I (preceding paper), the term neoflavanoid is used to refer either to the "open" structure (XII) or to its heterocyclic equivalents.

cm^{-1}) and NMR spectrum [τ 0·58 singlet (—C$\underline{\text{H}}$O); τ 4·60 triplet (J = 5 c/s) (—CH$_2$—C$\underline{\text{H}}$=C<); τ 5·46 triplet (J = 8 c/s) (AcO—$\overset{|}{\text{C}}\underline{\text{H}}$—CH$_2$—); τ 7·93 singlet (C$\underline{\text{H}}_3$—CO—O); τ 8·85 singlet (C$\underline{\text{H}}_3$—); τ 9·05 singlet (3C$\underline{\text{H}}_3$—); τ 9·11 singlet (2C$\underline{\text{H}}_3$—); τ 9·25 singlet (C$\underline{\text{H}}_3$—)]. Crystallization of the third and fourth fractions from methanol yielded O-methyldalbergin (80 mg), m.p. 145–146°, and dalbergin (30 mg), m.p. 209–210°. The O-acetyloleanolic aldehyde, dalbergin, and O-methyldalbergin were identical with authentic specimens.

Extraction of Machaerium scleroxylon *heartwood*

Isolation of O-*acetyloleanolic aldehyde* (I), O-*methyldalbergin* (IIb), *dalbergin* (IIa), *scleroin* (X), R-3,4-*dimethoxydalbergione* (IV) *and* R-3,4-*dimethoxydalbergione quinol* (Va). A similar extraction of the powdered heartwood (3 kg) followed by chromatography of the extract (50 g) using benzene, benzene–chloroform mixtures, and chloroform as eluting solvents gave five main fractions. The first fraction was crystallized from MeOH yielding O-acetyloleanolic aldehyde, m.p. 225–228°, and the second fraction consisted of a dark red oil (8·26 g, see below). The third fraction was recrystallized from light petroleum yielding *scleroin* (114 mg) as yellow needles, m.p. 143·5–144·5° (Found: C, 65·50; H, 5·14. $C_{16}H_{14}O_5$ requires: C, 65·69; H, 5·15%.) λ_{max} (in EtOH) 255 mμ (ε 10,300), 293 mμ (ε 10,000), 373 mμ (ε 4,650). ν_{max} (in $CHCl_3$) 3610, 1630 (broad), 1580, 1490, 1120, 960, 947 cm^{-1}. NMR spectrum (in $CDCl_3$) [τ −2·23 singlet (bonded OH); τ 2·60–2·18 multiplet (C_6H_5—); τ 3·07 singlet (aromatic H); τ 5·0 broad (OH); τ 5·85 singlet (OMe); τ 6·02 singlet (OMe)]. The fourth and fifth fractions were rechromatographed and recrystallized from MeOH yielding O-methyldalbergin (800 mg), m.p. 145–146° and dalbergin (700 mg), m.p. 209–210°.

The second fraction (8·26 g) was rechromatographed using light petroleum, light petroleum-benzene mixtures, and benzene as eluting solvents. The earlier fractions deposited crystalline material when dissolved in light petroleum and kept at liquid air temp, whereas the later fractions did not crystallize and were characterized by hydroxyl absorption in their IR spectra. The crystalline fractions were combined and low temp crystallization from light petroleum gave R-3,4-*dimethoxydalbergione* as red needles, m.p. 41–42°. (Found: C, 71·53: H, 5·81; OMe, 21·50. $C_{15}H_{10}O_2(OMe)_2$ requires: C, 71·82; H, 5·67; OMe, 21·8%.) $[\alpha]_D$ 60° ($CHCl_3$). λ_{max} (in EtOH) 260 mμ (ε 11,400), 405 mμ (ε 1,000). ν_{max} (in $CHCl_3$) 1660, 1605, 1140, 995, 930 cm^{-1}. NMR spectrum (in $CDCl_3$) [τ 2·5–2·8 multiplet ($C_6\underline{H}_5$), τ 3·65 doublet (J = 1 c/s) (quinone-$\underline{\text{H}}$), τ 3·7–4·2 multiplet (1$\underline{\text{H}}$), τ 4·6–5·2 multiplet (3$\underline{\text{H}}$), τ 6·00 singlet (OMe), τ 6·05 singlet (OMe)]. ORD in dioxan: c 0·097, 610–500 mμ; c 0·0325, 520–320 mμ; c 0·0097, 350–260 mμ: $[\phi]_{493}$ 2625, $[\phi]_{340}$ −10055, $[\phi]_{295}$ +9525. CD in dioxan: c 0·2132, 540–330 mμ; c 0·0213, 330–280 mμ; c 0·0107, 300–240 mμ: $[\theta]_{520}$ 0, $[\theta]_{400}$ 5300, $[\theta]_{354}$ 0, $[\theta]_{315}$ −13200, $[\theta]_{295}$ 0, $[\theta]_{275}$ 9900, $[\theta]_{262}$ 0, $[\theta]_{245}$ −13200. Treatment of R-3,4-dimethoxydalbergione with Brady's reagent gave the corresponding 2,4-*dinitrobenzeneazophenol* (VI) as red needles, m.p. 193–195° from EtOH (Found: C, 59·27; H, 4·46; O, 23·94; N, 12·30. $C_{23}H_{20}O_7N_4$ requires: C, 59·48; H, 4·34; O, 24·12; N, 12·06%).

The red oil (85 mg) which did not yield crystalline R-3,4-dimethoxydalbergione on cooling was treated with acetic anhydride (6 ml) and pyridine (6 ml) overnight at room temp and then poured into water. Ether extraction yielded an oil (130 mg) which was separated into two fractions (50 and 83 mg) by chromatography on silica and elution with benzene. Distillation (100°/10^{-3} mm) of the larger fraction gave 3,4-dimethoxydalbergione–quinol diacetate (Vb) identical with an authentic specimen (see below).

Oxidation of R-3,4-*dimethoxydalbergione*. A mixture of R-3,4-dimethoxydalbergione (50 mg) and $KMnO_4$ (1 g) in acetone (10 ml) was kept at room temp overnight, then the acetone was removed, water (10 ml) added, and SO_2 was passed through the mixture until it was colourless. Ether extraction followed by sublimation (50°/0·1 mm) gave benzoic acid (10 mg), m.p. 121°.

R-3,4-*Dimethoxydalbergione quinol diacetate* (Vb). Sodium dithionite reduction followed by acetylation (Part I, p. 2695) of R-3,4-dimethoxydalbergione (50 mg) gave an oil (73 mg) which was distilled (100°/10^{-3} mm) giving the *quinol diacetate* as a colourless oil (43 mg). (Found: C, 68·38; H, 6·12. $C_{15}H_{10}(OAc)_2(OMe)_2$ requires: C, 68·09; H, 5·99%.) λ_{max} (in EtOH) 270 mμ (ε 1,000). ν_{max} (in $CHCl_3$) 1770, 1487, 1190, 1020 cm^{-1}. NMR spectrum (in $CDCl_3$) [τ 2·5–2·9 multiplet ($C_6\underline{H}_5$—), τ 3·30 singlet (aromatic $\underline{\text{H}}$), τ 3·3–5·3 multiplet (>C$\underline{\text{H}}$—C$\underline{\text{H}}$=C$\underline{\text{H}}_2$), τ 6·12 singlet (2 OMe), τ 7·72 singlet (OAc), τ 7·85 singlet (OAc)].

Octahydro-R-3,4-*dimethoxydalbergione quinol* (VII). R-3,4-dimethoxydalbergione (250 mg) in glacial acetic acid (5 ml) with PtO_2 catalyst (50 mg) was hydrogenated overnight at atm. press. and room temp. Removal of the catalyst and the acetic acid followed by crystallization from MeOH gave *octahydro*-R-3,4-*dimethoxydalbergione quinol* as colourless plates, m.p. 91–93° (Found: C, 68·99; H, 8·53; OMe, 21·37. $C_{15}H_{20}O_2(OMe)_2$ requires: C, 69·36; H, 8·90; OMe, 21·07%).