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THE NEOFLAVANOID GROUP OF NATURAL PRODUCTS—I

DALBERGIONES—A NEW CLASS OF QUINONES

W. B. EYTON,* W. D. OLLIS,* I. O. SUTHERLAND,*
O. R. GOTTLIEB,† M. TAVEIRA MAGALHÃES,† and L. M. JACKMAN‡

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Abstract—The determination of the structures of four dalbergiones (VII, VIIIa, b and c) is described. Spectroscopic methods established the partial structures (I) for these compounds, and the nature of the $[C_3H_4]$—residue was indicated by the NMR spectra of the dalbergiones and their derivatives. Chemical reduction of the quinonoid residues in the dalbergiones gave quinols, and catalytic reduction of the dalbergiones (VII and VIIIb), followed by atmospheric oxidation, gave the dihydro-dalbergiones (IX and X). Ozonolysis of these dihydro-dalbergiones gave optically active α-ethyl-aryl-acetic acids (V and VI), and the formation of these in association with optical rotatory dispersion results led to the definition of the absolute stereochemistry of the dalbergiones.

The dalbergiones represent a new class of natural quinones belonging to a group of natural products for which we suggest the general name neoflavanoids.§

THE *Dalbergia* genus belongs to the *Leguminosae-Papilionatae* family and in a phytochemical survey of Brazilian members of this genus which is now in progress, a new group of natural quinones has been discovered. These compounds were given the general name of dalbergiones and the elucidation of their structures has already been reported in a preliminary form.[1] Our preliminary communication was followed by

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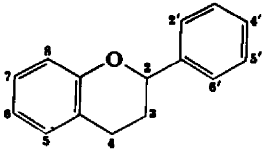
* Department of Organic Chemistry, The University, Bristol, England. (Present address of W.D.O. and I.O.S. Department of Chemistry, The University, Sheffield, England.)

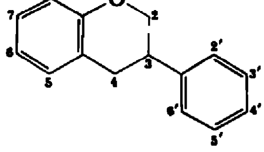
† Departamento de Quimica Orgânica, Universidade de Brasilia, Brasil.

‡ Department of Organic Chemistry, Imperial College, London. (Present address: University of Melbourne, Victoria, Australia.)

§ The studies to be described in this series of papers has indicated to us a need for a general term to describe a group of related natural products which all have a 4-arylchroman type structure. This represents a new class of naturally occurring C_{15}-phenolic compounds; other classes include the flavanoids (2-arylchroman derivatives) (i) and the isoflavanoids (3-arylchroman derivatives) (ii). We now suggest that the term neoflavanoid should be used to describe natural products of the 4-arylchroman type (iii) and that the corresponding numbering systems shown in formulae (i, ii and iii) should be used.



Flavanoid (i)



Isoflavanoid (ii)

(Footnote continued on page 2684)

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

three publications[2–4] describing independent studies of the chemistry of dalbergiones isolated from *Dalbergia nigra* Fr. Allem[2] and *Dalbergia latifolia* Roxb.[3,4] Rao and Seshadri[4] have suggested that the term dalbergenones should be used rather than dalbergiones,[1,2] but the introduction of this new name does not seem to be justified and, in view of its precedence and general acceptance,[6,7] we have continued to use the name dalbergione, originally suggested by Gonçalves da Lima.[5]

The "jacarandás" are among the most valued of the South American timbers. For many years the wood of *Dalbergia nigra* has been extensively used commercially, but recently it has become necessary to use timber from *Machaerium scleroxylon* Tull. as a substitute. *Dalbergia nigra* and *Dalbergia violacea* (Vog.) Malme are considered by botanists[8] to have arisen from a common stock in different environments. *Dalbergia nigra* is endemic in the humid Atlantic forests, whereas *Dalbergia violacea* grows in the dry savannahs of the Brazilian interior. The study of the natural products isolated from the woods of *Dalbergia nigra*[1] and *Dalbergia violacea*[9] is now reported in detail, and it may be noted that the relation between the absolute stereochemistry of the dalbergiones isolated from both these sources is quite unusual.

The dalbergiones were encountered by three groups of investigators before our

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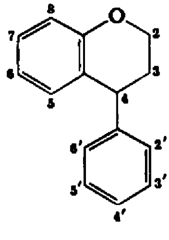
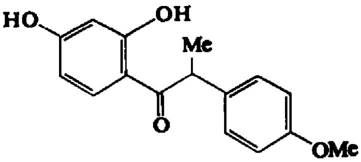
(Footnote continued from page 2683)



Neoflavanoids (iii)



(iv)

Although the dalbergiones are not heterocyclic, just as it is customary to regard natural chalcones as belonging to the flavonoid type and angolensin (iv) as an isoflavanoid, so we suggest that dalbergiones should also be called neoflavanoid to emphasise the relation between the dalbergiones and the dalbergins (Part II, following paper).

The term neoflavanoid was suggested by Dr. T. Swain, Editor of "Phytochemistry", and was discussed with Professor A. J. Birch, Professor L. Crombie, Dr. J. B. Harborne and Dr. J. C. Roberts at the Symposium on *Naturally Occurring Phenolic Compounds* held at the Royal College of Advanced Technology, Salford, on 24–25th September (1964). We thank them for their advice regarding this proposal.

[2] G. B. Marini-Bettelo, C. G. Casinovi, O. Gonçalves da Lima, M. H. Dalia Maia and I. L. d'Albuquerque, *Ann. Chim. Italy* **52**, 1190 (1962).

[3] C. B. Dempsey, D. M. X. Donnelly and R. A. Laidlaw, *Chem. & Ind.* 491 (1963).

[4] M. M. Rao and T. R. Seshadri, *Tetrahedron Letters* No. 4, 211 (1963).

[5] O. Gonçalves da Lima and M. H. Dalia Maia, *Lecture at the Third Annual Meeting Associacão Brasileira de Quimica* Rio de Janeiro, November 6–10 (1961).

[6] D. H. Reid, *Ann. Reports Chem. Soc.* **59**, 318 (1962).

[7] R. H. Thompson, *Quinones—Nature, Distribution and Biosynthesis, Biochemistry of Plant Pigments* (Edited by T. W. Goodwin) p. 309, Academic Press (1965).

[8] C. T. Rizzini, *Simpósio sôbre o Cerrado.* Editôra da Universidade de São Paulo 125 (1963).

[9] For a preliminary report see W. D. Ollis, H. J. P. E. M. Landgraf, O. R. Gottlieb and M. Taveira Magalhães, *Anais Acad. Brasil ciênc.* **36**, 31 (1963).

structural study was first reported.[1] Sandermann *et al.*[10] observed that the rate of drying of polyester finishes on several timbers of the *Dalbergia* genus was slow and in an attempt to isolate the inhibitors, the constituents of several species were examined. A yellow compound, $C_{16}H_{14}O_3$, m.p. 125–126°, was isolated from *Dalbergia retusa* heartwood and an orange compound, $C_{17}H_{16}O_4$, m.p. 109–110°, was obtained from *Dalbergia nigra* heartwood. Compounds with identical m.ps, colours and molecular formulae were reported by Gonçalves da Lima and Dalia Maia[5] in their search for the principles responsible for the antibiotic activity[11] of extracts of *Dalbergia nigra.* In both these studies the suggestion was made that the compounds $C_{16}H_{14}O_3$ and $C_{17}H_{16}O_4$ were naphtha-1,4-quinone derivatives, but we felt that the reported spectroscopic information was incompatible with this tentative proposal. Gottlieb and Magalhães[12] reported the isolation of two substances, J-1 and J-2, from *Dalbergia nigra* heartwood, and it was this material which was first examined.

The examination of Dalbergia nigra. The material J-2[12] was not changed by further recrystallization from several different solvents and it was at first assumed, since J-2 had a sharp m.p. of 111–112°, that it was a pure compound with the molecular formula $C_{30}H_{21}O_4(OMe)_3$. This assumption led, however, to an impossible situation as further structural evidence was acquired, but this was not resolved until it was discovered that J-2 could be separated into two compounds by careful repetitive chromatography. The relation between the molecular formulae of the two substances derived from J-2 suggested that they should be named dalbergione[1] (now called methoxydalbergione*), $C_{15}H_{11}O_2(OMe)$, and methoxydalbergione[1] (now called dimethoxydalbergione*), $C_{15}H_{10}O_2(OMe)_2$. A remarkable result was obtained when an equimolecular *mixture* of methoxydalbergione, m.p. 114–116°, and dimethoxydalbergione, m.p. 109·5–111° was crystallized from cyclohexane. This yielded J-2, m.p. 111–112°, which was unchanged by further crystallization. The significance of this result became clearer at a later stage in the investigation.

J-1 was a pure compound and its molecular formula, $C_{15}H_{11}O_3(OMe)$, coupled with the presence of a strong band (3470 cm^{-1}) in the hydroxyl region of its IR spectrum, suggested that J-1 was hydroxymethoxydalbergione, $C_{15}H_{10}O_2(OH)(OMe)$.This was confirmed by an active hydrogen determination (1 H per molecule).

Methoxydalbergione was yellow and hydroxymethoxydalbergione and dimethoxydalbergione were orange. These colours, in association with their UV spectra (Table 1), suggested that the compounds were quinones, which was supported by the observation that sodium dithionite reduction gave quinols; methoxydalbergione-quinol and dimethoxydalbergione-quinol were characterized as diacetates and hydroxymethoxydalbergione-quinol gave a triacetate. These acetates showed only phenolic acetate

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* It is realised that the original choice[1] of the names dalbergione, methoxydalbergione, and hydroxydalbergione was unfortunate, and in accordance with the nomenclature now proposed, it is suggested that the original names "dalbergione", "methoxydalbergione" and "hydroxydalbergione" should be replaced by methoxydalbergione, $C_{15}H_{11}O_2(OMe)$, dimethoxydalbergione, $C_{15}H_{10}O_2(OMe)_2$ and hydroxymethoxydalbergione, $C_{15}H_{10}O_2(OH)(OMe)$. The substituents should be located as shown in the formulae (IIa, IIb and IIc).

[10] W. Sandermann and E. Schwarz, *Farbe u. Lack.* **62**, 134 (1956); *Chem. Abstr.* **50**, 9755 (1956). W. Sandermann, H. H. Dietrichs and M. Puth, *Holz als Roh und Werkstoff* **18**, 63 (1960).

[11] O. Gonçalves da Lima, M. H. Dalia Maia and I. L. d'Albuquerque, *Rev. Inst. Antib. Recife* **16**, 61 (1961). See *Medical News* 11. May 10 (1963).

[12] O. R. Gottlieb and M. Taveira Magalhães, *J. Org. Chem.* **26**, 2449 (1961).

TABLE 1. ULTRA-VIOLET SPECTRA OF DALBERGIONES AND THEIR DERIVATIVES IN ETHANOL (λ_{max} IN mμ; FIGURES IN PARENTHESES ARE ε)

4-Methoxydalbergione (IIa)		260 (15,150)	
4,4′-Dimethoxydalbergione (IIb)	228 (14,400)	258 (13,700)	333 (1,700)
4′-Hydroxy-4-methoxydalbergione (IIc)	228 (12,700)	262 (13,150)	330 (1,600)
2-Methyl-5-methoxybenzoquinone		262 (17,000)	
4-Methoxytoluene	224 (6,800)		
4-Methoxydalbergione quinol diacetate (IVa)		278 (2,800)	
4,4′-Dimethoxydalbergione quinol diacetate (IVb)	230 (20,300)	278 (4,400)	
4-Methoxy-4′-hydroxydalbergione quinol triacetate (IVc)		279 (2,800)	
Dihydro-4-methoxydalbergione (IIIa)		264 (14,950)	
Dihydro-4,4′-dimethoxydalbergione (IIIb)	223 (13,200)	264 (16,400)	350 (1,400)

absorption (1755–1760 cm^{-1}) in the ester carbonyl region of their IR spectra. A more detailed examination of the UV spectra of the three dalbergiones suggested that they were all derivatives of the 2-alkyl-5-methoxybenzoquinone type in that they all showed maximal absorption at 258–262 mμ, as does 2-methoxy-5-methylbenzoquinone (λ_{max} 262 mμ, ε 17,000). The UV spectra of the dalbergiones were significantly different from those of other *p*-benzoquinones[13,14] and obviously excluded a naphtha-1,4-quinone chromophore[15] as required by earlier structural proposals.[5,10] The UV spectra of dimethoxy- and hydroxymethoxy-dalbergione also showed maxima at 228 mμ, suggesting the presence of the chromophores of the *p*-methoxytoluene (224 mμ, ε 6,800) and *p*-cresol (224 mμ, ε 6,800) types. This was supported by the close correspondence between the observed UV spectra of the three dalbergiones, and summation curves derived from 2-methoxy-5-methylbenzoquinone and the appropriate aryl chromophore. This correspondence excluded direct interaction between the quinonoid and the aryl chromophores in these compounds.

Permanganate oxidation of methoxydalbergione gave benzoic acid, and dimethoxydalbergione similarly gave *p*-anisic acid. No corresponding product was isolated from hydroxymethoxydalbergione, but on biogenetic grounds a structural correspondence between dimethoxy- and hydroxymethoxy-dalbergione was postulated. These considerations suggested that the three dalbergiones could be represented by the partial structures (Ia, Ib and Ic). This was supported by their IR spectra which showed several bands in the C=O and C=C regions, characteristic of substituted *p*-benzoquinones.[16]

Consideration of the undefined C_3H_4 residue in the partial structures (I) was now possible since the three dalbergiones and their derivatives were optically active. This optical activity was retained by the quinols obtained by sodium dithionite reduction since atmospheric oxidation in alkaline solution gave back the optically active dalbergiones. The optical activity of the dalbergiones required them to be either 1,2-disubstituted-cyclopropanes or 3,3,-disubstituted-propenes. The cyclopropane type

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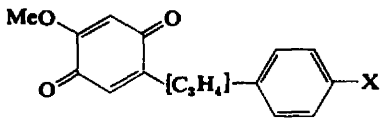
[13] E. Braude, *J. Chem. Soc.* 490 (1945).

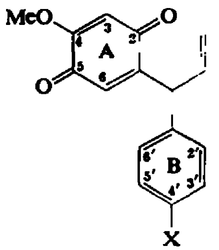
[14] W. Flaig, J. Salfeld and E. Baume, *Liebigs Ann.* **618**, 117 (1958).

[15] R. G. Cooke, A. K. Macbeth and F. L. Winzor, *J. Chem. Soc.* 878 (1939).

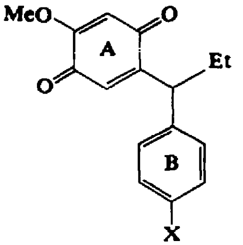
[16] P. Yates, M. I. Ardao and L. F. Fieser, *J. Amer. Chem. Soc.* **78**, 650 (1956).



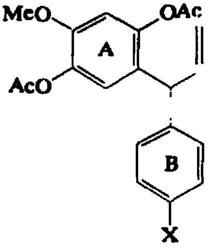
Ia X = H
Ib X = OMe
Ic X = OH



IIa X = H
IIb X = OMe
IIc X = OH



IIIa X = H
IIIb X = OMe



IVa X = H
IVb X = OMe
IVc X = OAc

structure was clearly excluded by the absence of high field signals in the NMR spectra of these compounds (Table 2), whereas the spectra were in full accord with the 3,3-disubstituted-propene structures (II). Complementary evidence in support of this formulation (II) was provided by the IR spectra of the three dalbergiones (IIa, b and c) which all showed absorption bands at approximately 910 and 990 cm^{-1} assignable to a vinyl group. These bands are not apparent in the IR spectra of the dihydro-dalbergiones (IIIa and b), indicating that reduction of the vinyl group occurred in the formation of these compounds. This involved catalytic hydrogenation of the dalbergiones (IIa and IIb) to their dihydro-quinols followed by aerial oxidation in alkaline solution to the dihydro-dalbergiones (IIIa and IIIb). These dihydrodalbergiones were optically active and their NMR spectra (Table 2) fully supported their structures (IIIa and b).

The formation of the dihydro-dalbergiones (IIIa and b) from the dalbergiones (IIa and b) was accompanied by little change in the UV spectra of corresponding pairs (Table 1). This confirmed the absence of direct conjugation of the vinyl group with either the quinonoid or the aryl chromophores in the dalbergiones.

Examination of the NMR spectra of the dalbergiones and their derivatives as summarized in Table 2 immediately indicated the main features of the structures of these compounds, even when interpretation was initially limited to the consideration of chemical shifts and proton integrals. There are, however, some points which merit further comment. No direct proof of the position of the phenolic hydroxyl group in hydroxymethoxydalbergione has so far been provided, but its location as in the structure (IIc) is settled since in the spectrum of the quinol triacetate (IVc) the four aromatic ring B protons form an A_2B_2 system.

TABLE 2. NUCLEAR MAGNETIC RESONANCE SPECTRAL DATA FOR DALBERGIONES AND THEIR DERIVATIVES
60 MC/SEC IN $CDCl_3$

Compound	Ring B protons	Ring A protons	C_3H_4 residue	Methoxyl group(s)	Acetate methyl protons	C_2H_6 residue
4-Methoxydalbergione (IIa)	2·38–3·13 (5) m	3·47 (1) d (J = 0·9)	4·70–5·17 (3) m	6·20 (3) s	—	—
		4·05 (1) s	3·50–4·17 (1) m			
4,4′-Dimethoxydalbergione (IIb)	2·80–3·42 (4) m	3·60 (1) d (J = 0·9)	4·70–5·30 (3) m	6·25 (3) s	—	—
	A_2B_2 system	4·15 (1) s	3·57–4·23 (1) m	6·27 (3) s	—	—
						5·95 (1) t (J ≃ 7·0)
Dihydro-4-methoxydalbergione (IIIa)	2·57–2·90 (5) m	3·47 (1) d (J = 1·0)	—	6·25 (3) s	—	8·15 (2) q (J ≃ 7·0)
		4·12 (1) s				9·13 (3) t (J ≃ 7·0)
						6·00 (1) t (J ≃ 7·0)
Dihydro-4,4′-dimethoxydalbergione (IIIb)	2·67–3·30 (4) m	3·48 (1) d (J = 1·1)	—	6·22 (3) s	—	8·08 (2) q (J ≃ 7·0)
	A_2B_2 system	4·12 (1) s		6·22 (3) s		9·10 (3) t (J ≃ 7·0)
4-Methoxydalbergione quinol diacetate (IVa)	~2·7 (5) m	3·10 (1) s	4·6–5·4 (3) m	6·21 (3) s	7·71 (3) s	
		3·26 (1) s	3·4–4·2 (1) m		7·92 (3) s	—
4,4′-Dimethoxydalbergione quinol diacetate	~3·10 (4) m	3·15 (1) s	4·5–5·5 (3) m	6·23 (3) s	7·75 (3) s	—
(IVb)	A_2B_2 system	3·31 (1) s	3·4–4·2 (1) m	6·23 (3) s	7·89 (3) s	
4-Methoxy-4′-hydroxydalbergione quinol	~2·93 (4) m	3·15 (1) s	4·5–5·5 (3) m	6·22 (3) s	7·74 (6) s	—
triacetate (IVc)	A_2B_2 system	3·29 (1) s	3·4–4·2 (1) m		7·90 (3) s	

Chemical shifts are given on the τ scale and proton integrals in parentheses.
Coupling constants, J, are in c/s.
s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.
The complete analysis of multiplets is discussed in Part III[17] of this series.

The ring A quinonoid protons in the dalbergiones (IIa and b) and the dihydrodalbergiones (IIIa and b) are associated with singlets in the range τ 4·05–4·15, and doublets, τ 3·47–3·60 (J = 0·9–1·1 c/s). In contrast, the ring A protons in the quinol acetates (IVa, b and c)) give rise only to pairs of singlets from which it follows that the aromatic protons on ring A must be *para*-related. These protons must therefore have a corresponding positional relationship in the quinones. In the cases of (IIa, IIb, IIIa and IIIb), the high field quinonoid proton on ring A must be shielded by the adjacent methoxyl group and the doublet character of the signals to be associated with the other quinonoid proton must be due to splitting by the adjacent benzylic —CH= group. This settles the orientation of substituents around ring A of the dalbergione structure. The coupling of quinonoid protons with benzylic protons is positively demonstrated by the NMR spectrum of 2-methoxy-5-methylbenzoquinone. This spectrum shows singlets (τ 6·18 and 4·10) to be assigned to the methoxyl group and adjacent quinonoid proton. The other quinonoid proton gives a quartet (τ 3·50; J = 1·7 c/s) and the methyl group a doublet (τ 7·93; J = 1·7 c/s).

The NMR spectra of the dihydrodalbergiones (IIIa and b) confirm the structures proposed for the dalbergiones in all respects. Most features of their spectra (Table 2) require no further comment, but the position and multiplicities of the signals to be associated with the protons of the C_3H_6 residue establish with certainty the presence of a $>CH—CH_2—CH_3$ group. Clearly the proton [τ 5·95 in (IIIa) and τ 6·00 in (IIIb)] must be attached to a carbon atom which is simultaneously benzylic to ring B and directly attached to the quinonoid ring A.

A more detailed analysis of the NMR spectra of the dalbergiones is given in Part III of this series.[17]

The absolute stereochemistry of the dalbergiones and the recognition of J-2 *as a quasiracemate.* The structures of the dalbergiones (IIa, b and c) having been determined on the evidence which has so far been discussed, it was now necessary to acquire information which would establish their absolute stereochemistry. With this objective, the ozonolysis of the dihydro-4-methoxydalbergione (IIIa) was investigated and this yielded (−)-α-ethylphenylacetic acid of established absolute configuration (V)[18]; this α-ethylphenylacetic acid had the expected specific rotation and gave a *negative* plain optical rotatory dispersion curve.[18] In contrast, the 4,4′-dimethoxydalbergione (IIIb) on ozonolysis gave (+)-α-ethyl-*p*-methoxyphenylacetic acid which gave a *positive* plain optical rotatory dispersion curve. From this it follows that the (+)-α-ethyl-*p*-methoxyphenylacetic acid has the absolute configuration (VI), and it may be concluded that the absolute configuration of the 4-methoxydalbergione isolated from *Dalbergia nigra* is R, as indicated in formula (VII), whereas 4,4′-dimethoxydalbergione *from the same source* has the antipodal S-configuration (VIIIb).

Comparison of the optical rotatory dispersion and circular dichroism curves[19] of the three dalbergiones isolated from *Dalbergia nigra* provided a striking confirmation

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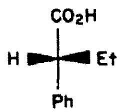
[17] M. F. Barnes, O. R. Gottlieb, W. D. Ollis and I. O. Sutherland. Part III of this series. *Tetrahedron* **21**, 2707 (1965).

[18] P. A. Levene, L. A. Mikeska and K. Passoth, *J. Biol. Chem.* **88**, 40 (1930); K. Mislow and M. Heffler, *J. Amer. Chem. Soc.* **74**, 3668 (1952); B. Sjoberg, *Acta Chem. Scand.* **14**, 273 (1960).

[19] C. Djerassi, H. Wolf and E. Bunnenberg, *J. Amer. Chem. Soc.* **84**, 4552 (1962); **85**, 2835 (1963). R. D. Gillard, *Analyst* **88**, 825 (1963). C. Djerassi and E. Bunnenberg, *Proc. Chem. Soc.* 229 (1963). P. Crabbé, *Tetrahedron* **20**, 1211 (1964).



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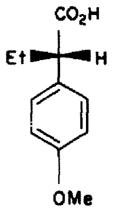
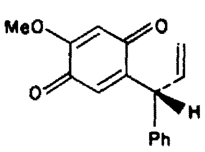
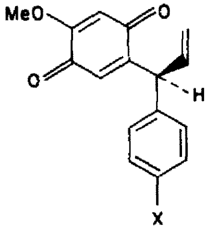


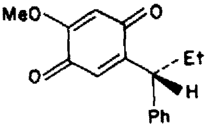
VI



VII



VIIIa, X = H
VIIIb, X = OMe
VIIIc, X = OH



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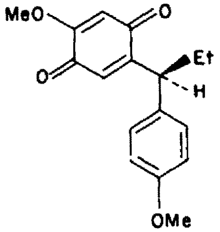

X

(Figs. 1 and 2) of the antipodal relation between R-4-methoxydalbergione (VII) and S-4,4′-dimethoxydalbergione (VIIIb). Furthermore, this antipodal relation was confirmed by comparison of the optical rotatory dispersion curves (Fig. 2) of dihydro-R-4-methoxydalbergione (IX) and dihydro-S-4,4′-dimethoxydalbergione (X). The absolute configuration of 4′-hydroxy-4-methoxydalbergione was settled as shown in the formula (VIIIc), since its optical rotatory dispersion curve (Fig. 1) was similar in form to that of 4,4′-dimethoxydalbergione (VIIIb). The dalbergiones isolated from *Dalbergia nigra* are therefore R-4-methoxydalbergione (VII), S-4,4′-dimethoxydalbergione (VIIIb), and S-4′-hydroxy-4-methoxydalbergione (VIIIc), and the antipodal relation between R-4-methoxydalbergione (VII) and S-4,4′-dimethoxydalbergione (VIIIb) thus accounts for the nature of the compound J-2 originally isolated[12] from *Dalbergia nigra*. It is clear that J-2 is a quasiracemate derived from R-4-methoxydalbergione (VII) and S-4,4′-dimethoxydalbergione (VIIIb).

As far as we are aware, this is the first example of the isolation of a quasiracemate[20] from natural sources, but recently a very interesting example of the isolation of a quasiracemic alkaloid has been described. Laiho and Fales[21] have shown that narcissamine is a quasiracemate of (−)-demethylgalanthamine (XI) and (+)-demethyldihydrogalanthamine (XII). Although it is appreciated that the existence of quasiracemates is a characteristic of the solid state and that these natural products do not exist as such in the plant, it is nevertheless clear that their isolation is of biosynthetic interest.

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[20] For a review see A. Fredga, *Tetrahedron* **8**, 126 (1960).

[21] S. M. Laiho and H. M. Fales, *J. Amer. Chem. Soc.* **86**, 4434 (1964).

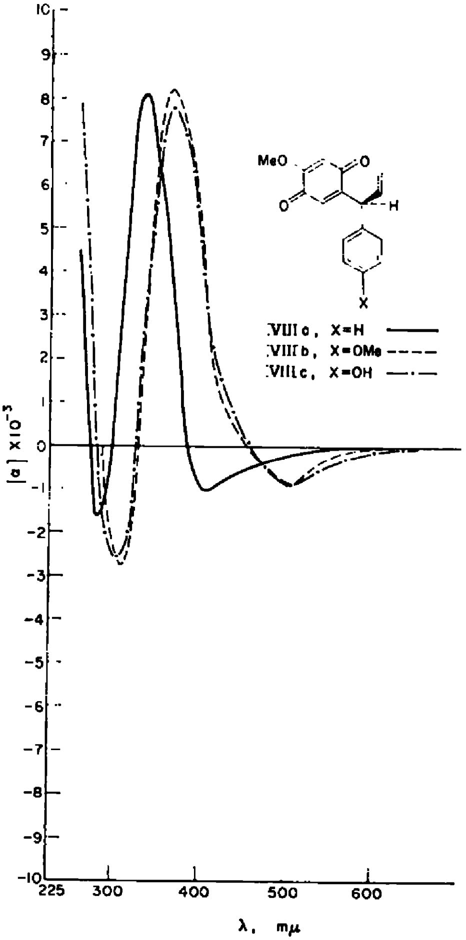

Fig. 1. Optical rotatory dispersion curves of S-4-methoxydalbergione (VIIIa) from *Dalbergia violacea*, S-4,4′-dimethoxydalbergione (VIIIb) and S-4′-hydroxy-4-methoxydalbergione (VIIIc).

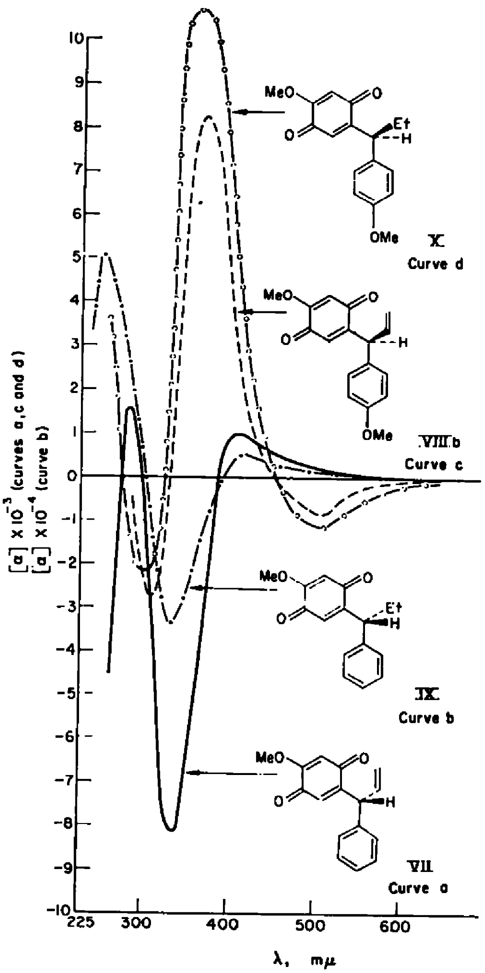

Fig. 2. Optical rotatory dispersion curves of R-4-methoxydalbergione (VII) from *Dalbergia nigra*, S-4,4′-dimethoxydalbergione (VIIIb) from *Dalbergia nigra* and their dihydro-derivatives (IX and X).

Thus, the isolation of quasiracemates may well be due to the stereospecific synthesis of antipodally related natural products of corresponding structural type. This differs from the more frequently encountered circumstance in which asymmetric natural products of corresponding structural type exhibit a stereochemical conformity. A particularly good example of this is provided by the steroids and terpenoids.[22] In this connection the reported isolation of natural products as *true racemates* (where

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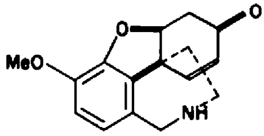
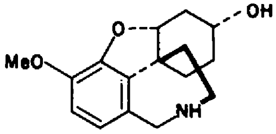
[22] A. I. Scott, F. McCapra, F. Comer, S. A. Sutherland, D. W. Young, G. A. Sim and G. Ferguson *Tetrahedron* **20**, 1339 (1964).

the possibility of racemization during isolation is excluded) is relevant and such cases include the isolation of DL-armepavine,[23] ψ-akuammicine,[24] and DL-fustin.[25]



XI



XII

The antipodal relation between R-4-methoxydalbergione (VII) and S-4,4′-dimethoxydalbergione (VIIIb) is fully supported by their CD curves (Figs. 3 and 4) and the Cotton effects of the ORD curves are seen to be correctly related to the maxima of the CD curves of R-4-methoxydalbergione [370 mμ (positive maximum) and 310 mμ (negative maximum)] and S-4,4′-dimethoxydalbergione [440 mμ (inflexion), 400 mμ (negative maximum), and 338 mμ (positive maximum)]. As has already been noticed by Djerassi[19] in other comparative studies of ORD and CD, it is not possible in these two cases (Figs. 3 and 4) to relate directly their ORD curves to their UV spectra because the transitions corresponding to the observed Cotton effects are much too weak. However, the CD extrema and the corresponding Cotton effects certainly indicate the existence of optically active absorption bands associated with the quinonoid chromophores which are not detectable in their UV spectra (with the exception of λ_{max} 333 mμ in the UV spectrum of S-4,4′-dimethoxydalbergione). This is an example, therefore, of the value of CD studies in the detection of weak electronic transitions associated with the *p*-quinonoid chromophore.

The examination of Dalbergiaviolacea. In view of the close taxonomic relationship between *D. nigra* and *D. violacea*, an examination of the heartwood extract of *D. violacea* was undertaken.[9] A number of compounds including 4-methoxydalbergione and 4′-hydroxy-4-methoxydalbergione has so far been isolated, but although the 4′-hydroxy-4-methoxydalbergione is identical in all respects with the compound (VIIIc) isolated from *D. nigra*, this is not the case with the 4-methoxydalbergione.

The 4-methoxydalbergione isolated from *D. violacea* has the same properties, IR and NMR spectra as the 4-methoxydalbergione (VII) isolated from *D. nigra*, but its specific rotation and ORD curve (Fig. 1) show that it has the absolute S-configuration (VIIIa). This was fully confirmed when it was shown that crystallization of equimolecular amounts of R-4-methoxydalbergione (VII) isolated from *D. nigra* and S-4-methoxydalbergione (VIIIa) isolated from *D. violacea* gave racemic 4-methoxydalbergione identical with the racemate prepared by total synthesis.[17]

This study of the absolute stereochemistry of the natural dalbergiones has revealed two biosynthetic situations of some novelty. 4-Methoxydalbergione of either the R- or the S-type is produced by plants within the same genus, but whereas *D. violacea* produces two dalbergiones of S-configuration, *D. nigra* produces three dalbergiones, of which one has the R-configuration and two have the S-configuration. Among natural phenolic compounds[26] similar situations include the isolation of fustin in one

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[23] S. M. Kupchan, B. Dasgupta, E. Fujita and M. L. King, *J. Pharm. Sciences* **51**, 599 (1962). M. Shamma and W. A. Slusarchyk, *Chem. Revs.* **64**, 59 (1964).

[24] P. N. Edwards and G. F. Smith, *Proc. Chem. Soc.* 215 (1960).

[25] D. G. Roux and K. Freudenberg, *Liebigs Ann.* **613**, 56 (1958).

[26] W. B. Whalley, *The Chemistry of Flavonoid Compounds* (Edited by T. A. Geissman) p. 441. Pergamon, Oxford (1962). J. W. Clark-Lewis, *Revs. Pure Appl. Chem.* **12**, 96 (1962).

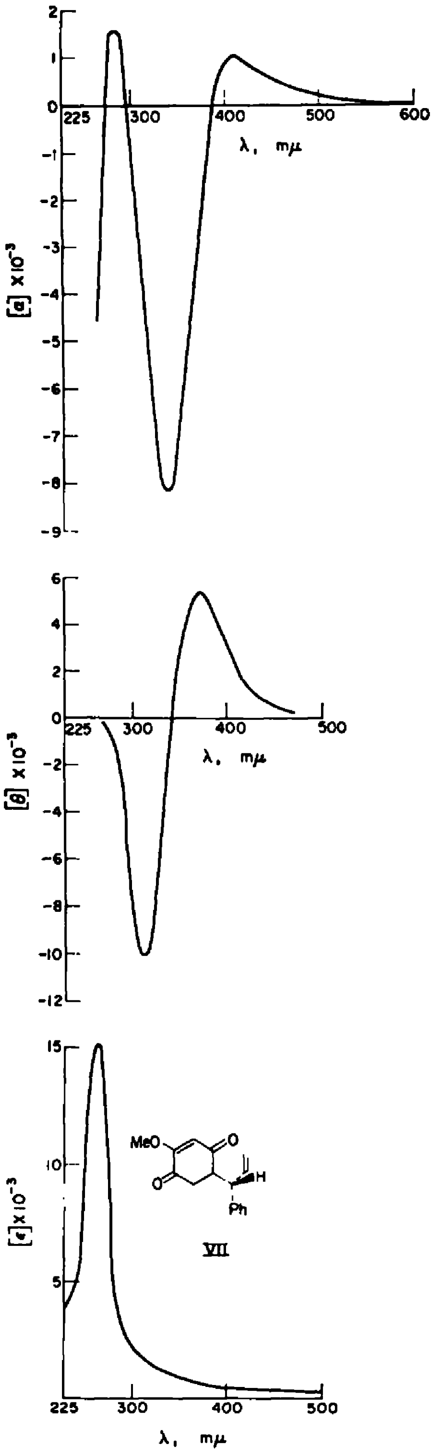

Fig. 3. Optical rotatory dispersion and circular dichroism curves of R-4-methoxydalbergione (VII) and its ultra-violet spectrum.

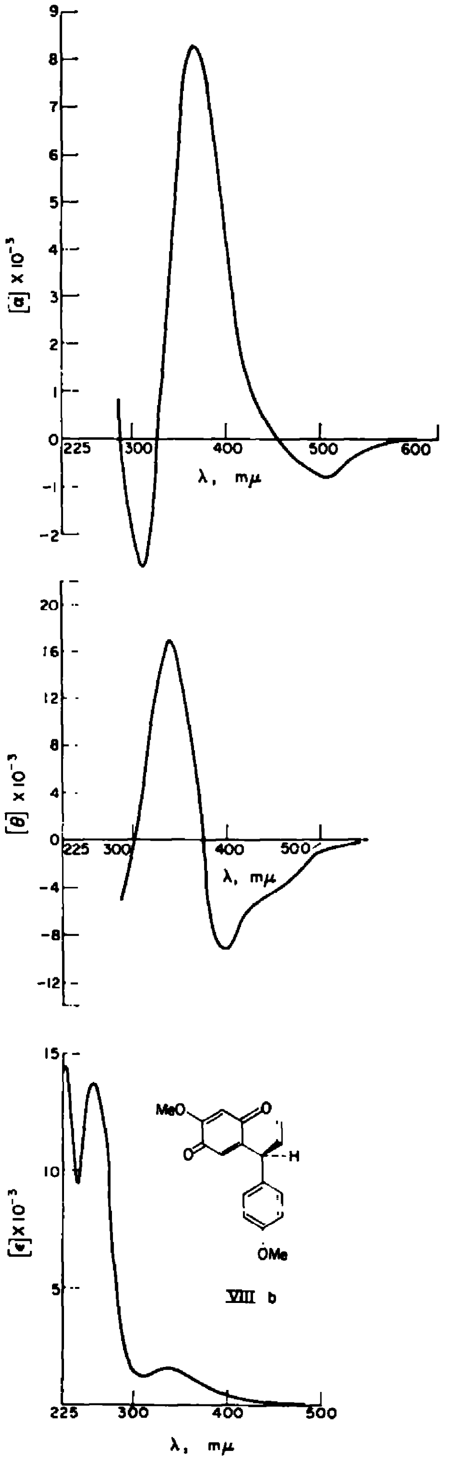

Fig. 4. Optical rotatory dispersion and circular dichroism curves of S-4, 4′-dimethoxydalbergione (VIIIb) and its ultra-violet spectrum.

enantiomeric form from *Rhus cotinus*[27] and in the other form from *Acacia mollissima*.[28] Antipodal forms of 7,3′,4′-trihydroxyflavan-3,4-diol have also been isolated from different plant sources.[29] However, the dalbergiones represent a further stereochemical variant among natural products in that antipodal forms of structurally corresponding types have been shown to exist in a single plant source.

EXPERIMENTAL

NMR spectra were determined on $CDCl_3$ solutions, using a Varian A-60 spectrometer; tetramethylsilane was used as the internal standard. Only significant bands from IR spectra are quoted.

M.ps were determined using a Kofler hot stage microscope and are uncorrected. The m.ps of dalbergiones are dependent upon the rate of heating and a more reliable indication of purity was obtained by chromatographic and spectroscopic examination. Separations by column chromatography were carried out using Hopkin and Williams' M.F.C. grade silica. Merck's Kieselgel G was used for thick and thin layer chromatography. The light petroleum used in chromatographic separations was the fraction b.p. 40–60°.

Extraction of Dalbergia nigra *heartwood*

Isolation of R-4-*methoxydalbergione* (VII), S-4,4′-*dimethoxydalbergione* (VIIIb) *and* S-4′-*hydroxy*-4-*methoxydalbergione* (VIIIc). The finely powdered heartwood (2670 g) was exhaustively extracted with hot benzene and the extract after concentration and standing yielded a partially crystalline precipitate (14·5 g) which by fractional crystallization from acetone gave two fractions.

The less soluble fraction was recrystallized from acetone giving S-4′-*hydroxy*-4-*methoxydalbergione* (2·1 g) as orange rhombs, m.p. 172–178° (dec). (Found: C, 70·99; H, 5·20; OMe, 11·44; active H, 0·37. $C_{15}H_{10}O_2(OH)(OMe)$ requires: C, 71·10; H, 5·22; OMe, 11·49; active H, 0·37%.) λ_{max} (in EtOH) 228 mμ (ε 12,700), 262 mμ (ε 13,150), 330 mμ (ε 1,600). $[\alpha]_D$ −52° (dioxan). ν_{max} (in $CHCl_3$) 1672, 1645, 1600, 1500, 992, 926, 904 cm^{-1}; ν_{max} (in nujol) 3530, 1664, 1639, 1600, 1504, 987, 928 cm^{-1}. ORD in dioxan: c 0·0528, 650–390 mμ; c 0·0105, 400–290 mμ; c 0·0021, 300–250 mμ; $[\phi]_{502}$ −2405; $[\phi]_{366}$ 21160; $[\phi]_{306}$ −7050.

The more soluble fraction was recrystallized from cyclohexane giving the compound J-2 (1·5 g) as yellow needles, m.p. 111–112°. J-2 was recognized as a quasiracemate and a typical separation was achieved as follows. A solution of J-2 (180 mg) in $CHCl_3$ (3 ml) was applied as a series of spots to the starting line of a thick (1 mm) layer chromatoplate (20 × 20 cm). Upward elution with a chloroform–benzene (3:1 v/v) mixture gave a faster-moving yellow band and an orange band. Elution of each of these bands with acetone gave from the yellow band R-4-*methoxydalbergione* (30 mg) as yellow needles, m.p. 114–116°, after recrystallization from cyclohexane. (Found: C, 75·57; H, 5·72; OMe, 12·01. $C_{15}H_{11}O_2(OMe)$ requires: C, 75·57; H, 5·55; OMe, 12·22%.) λ_{max} (in EtOH) 260 mμ (ε 15,150). $[\alpha]_D$ −51° (dioxan), +13° ($CHCl_3$). ν_{max} (in $CHCl_3$) 1672, 1650, 1605, 1195, 1175, 992, 928, 904 cm^{-1}; ν_{max} (in nujol) 1669, 1650, 1605, 1228, 1203, 987, 916, 757, 703 cm^{-1}. ORD in dioxan: c 0·020, 600–325 mμ; c 0·005, 350–285 mμ: $[\phi]_{410}$ 2670, $[\phi]_{385}$ −20885; $[\phi]_{280}$ 4120. ORD in $CHCl_3$: c 0·034, 600–350 mμ; c 0·017, 460–310 mμ; c 0·0042, 340–270 mμ: $[\phi]_{470}$ 2615; $[\phi]_{345}$ −14935; $[\phi]_{280}$ 14935. CD in dioxan: c 0·035, 450–340 mμ, 0·0043, 340–280 mμ: $[\theta]_{370}$ 5410; $[\theta]_{340}$ 0; $[\theta]_{310}$ −10060; $[\theta]_{260}$ 0.

Similarly, extraction of the orange band and recrystallization from cyclohexane gave S-4,4′-*dimethoxydalbergione* (85 mg) as orange needles, m.p. 109·5–111°. (Found: C, 71·88; H, 5·81; OMe, 20·39. $C_{15}H_{10}O_2(OMe)_2$ requires: C, 71·82; H, 5·67; OMe, 21·85%.) λ_{max} (in EtOH) 228 mμ (ε 14,400), 258 mμ (ε 13,700), 333 mμ (ε 1,700). $[\alpha]_D$ −139° ($CHCl_3$), −32° (dioxan). ν_{max} (in $CHCl_3$) 1672, 1645, 1600, 1502, 1200, 992, 928, 905 cm^{-1}; ν_{max} (in nujol) 1667, 1639, 1600, 1505, 996, 985, 928, 919 cm^{-1}. ORD in dioxan: c 0·1146, 610–410 mμ; c 0·0382, 420–390 mμ; c 0·0127, 390–290 mμ: $[\phi]_{505}$ −2400; $[\phi]_{368}$ 23490; $[\phi]_{310}$ −7830. CD in dioxan: c 0·766, 550–420 mμ; c 0·0957, 420–300 mμ; c 0·0479, 350–290 mμ; c 0·00612, 290–260 mμ: $[\theta]_{440}^{infl.}$ −5000; $[\theta]_{400}$ −9200; $[\theta]_{371}$ 0; $[\theta]_{338}$ 16928; $[\theta]_{299}$ 0.

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[27] K. Freudenberg and K. Weinges, *Chem. & Ind.* 486 (1959).

[28] D. G. Roux and E. Paulus, *Biochem. J.* **77**, 315 (1960).

[29] J. W. Clark-Lewis and D. G. Roux, *J. Chem. Soc.* 1402 (1959).

The formation of the quasiracemate J-2. A mixture of R-4-methoxydalbergione (50 mg) and S-4,4′-dimethoxydalbergione (56 mg) was crystallized from cyclohexane giving the quasiracemate (70 mg), m.p. 111–112°, which was unchanged by recrystallization. Its IR spectrum was identical with that of J-2 isolated directly from *D. nigra* heartwood.

Extraction of Dalbergia violacea *softwood and heartwood*

Isolation of β-sitosterol and S-*4-methoxydalbergione* (VIIIa). The finely powdered softwood (3·5 kg) was exhaustively extracted with benzene. This extract was concentrated and the residue was repeatedly extracted with hot light petroleum. The residue from the light petroleum extracts was chromatographed on a silica column with benzene as the eluent. One fraction yielded β-sitosterol, m.p. 138–140°, $[\alpha]_D^{20}$ −23° ($CHCl_3$) which was characterized as its acetate, m.p. 127–128°. A later fraction yielded S-4-methoxydalbergione (150 mg) as yellow needles, m.p. 118–120°. (Found: C, 75·71; H, 5·69; OMe, 11·89. $C_{15}H_{11}O_2(OMe)$ requires: C, 75·57; H, 5·55; OMe, 12·22%.) The UV, IR and NMR spectra of S-4-methoxydalbergione were identical with those of R-4-methoxydalbergione. ORD in dioxan: c 0·0452, 610–340 mμ; c 0·0150, 350–310 mμ; c 0·0030, 290–260 mμ: $[\phi]_{410}$ −2400; $[\phi]_{335}$ 20750; $[\phi]_{280}$ −4215.

The powdered heartwood similarly yielded a light petroleum soluble fraction from which S-4-methoxydalbergione (1·53 g) crystallized directly. The light petroleum insoluble residue was chromatographed on a silica column. Elution with benzene gave S-4-methoxydalbergione (320 mg) and further elution with chloroform–benzene (11:1 v/v) yielded S-4′-hydroxy-4-methoxydalbergione (50 mg).

Oxidation of the dalbergiones. R-4-Methoxydalbergione (50 mg) was added to a solution of $KMnO_4$ (1 g) in acetone (10 ml) and allowed to stand at room temp overnight. The acetone was then removed under diminished press., water (10 ml) was added to the residue, and SO_2 was passed in order to remove excess oxidant. Ether extraction gave a product (18 mg) which was purified by sublimation (50°/0·1 mm) giving benzoic acid (11 mg), m.p. 121°.

S-4,4′-Dimethoxydalbergione (50 mg) similarly gave *p*-anisic acid (12 mg), m.p. 182–184°.

Reversible reduction–oxidation of the dalbergiones. R-4-Methoxydalbergione (25 mg) was dissolved in ether (10 ml) and shaken with aqueous sodium dithionite solution (10 ml, 13%). The initial yellow colour of the mixture rapidly disappeared and ether extraction yielded a colourless oil (20 mg), ν_{max} 3600(OH), 1640, 1600 (aromatic C═C) cm^{-1}. The quinol was easily oxidized and when oxygen was bubbled through an ethereal solution of the quinol in contact with N/10 K_2CO_3 aq, the yellow ethereal solution yielded R-4-methoxydalbergione (5 mg), m.p. 104–108°, after crystallization.

A similar result was obtained with S-4,4′-dimethoxydalbergione.

Reductive acetylation of the dalbergiones to give the quinol acetates (IVa, b and c). An ethereal solution of R-4-methoxydalbergione (50 mg) was reduced with aqueous sodium dithionite and the ethereal layer added quickly to a mixture of acetic anhydride (3 ml) and pyridine (3 ml). The ether was then removed under diminished press. and, after leaving overnight at room temp, water was added; extraction with ether yielded a colourless oil (56 mg) and crystallization from light petroleum gave the *quinol diacetate* (IVa) as colourless needles (19 mg), m.p. 72–73°, $[\alpha]_D^{20}$ −13° ($CHCl_3$), —2° (dioxan), λ_{max} (in EtOH) 278 mμ (ε 2,800), ν_{max} 1760 (phenolic acetate) and 1620 (aromatic C═C) cm^{-1}. (Found: C, 70·34; H, 6·04; OMe, 9·21. $C_{19}H_{17}O_4(OMe)$ requires: C, 70·57; H, 5·92; OMe, 9·13%.)

S-4,4′-Dimethoxydalbergione (50 mg) similarly gave the *quinol diacetate* (IVb; 17 mg) as colourless needles, m.p. 113–115°, from light petroleum, $[\alpha]_D^{20}$ +5° ($CHCl_3$), +30° (dioxan), λ_{max} (in EtOH) 230 mμ (ε 20,300), 278 mμ (ε 4,400), ν_{max} 1760, 1600 cm^{-1}. (Found: C, 67·83; H, 6·14; OMe, 15·54. $C_{19}H_{16}O_4(OMe)_2$ requires: C, 68·09; H, 5·99; OMe, 16·78%.)

S-4′-Hydroxy-4-methoxydalbergione (50 mg) in MeOH (10 ml) was shaken with aqueous sodium dithionite (20 ml, 13%). Water was added to the colourless mixture, the MeOH removed under diminished press., and the quinol extracted with ether (3 × 10 ml). Acetylation as in the preceding experiments yielded the *triacetate* (IVc, 60 mg) as colourless needles, m.p. 126·5–127·5° from cyclohexane, $[\alpha]_D^{20}$ +5° ($CHCl_3$), −2° (dioxan), λ_{max} 279 mμ (ε 2,800), ν_{max} 1755, 1620 cm^{-1}. (Found: C, 65·99; H, 5·54; OMe, 8·09. $C_{21}H_{19}O_6(OMe)$ requires: C, 66·32; H, 5·57; OMe, 7·80%.)

The dihydrodalbergiones (IX and X). R-4-Methoxydalbergione (VII; 340 mg) in EtOH (60 ml) was hydrogenated at room temp and atm. press. with a 5% Pd–C catalyst (300 mg) and during 1 hr the solution became colourless (uptake at N.T.P. = 55·5 ml, theoretical uptake for $2H_2$ = 60·7 ml).

The solution yielded the dihydro-quinol (360 mg) which was oxidized as previously described giving *dihydro*-R-*4-methoxydalbergione* (IIIa; 140 mg) as yellow needles, m.p. 146–147° from cyclohexane. (Found: C, 74·98; H, 6·42. $C_{16}H_{16}O_3$ requires: C, 74·98; H, 6·29%.) λ_{max} (in EtOH) 264 mμ (ε 14,950). $[\alpha]_D$ +37° (dioxan), +82° ($CHCl_3$). ν_{max} (in $CHCl_3$) 1670, 1648, 1600 cm^{-1}. ORD in dioxan: c 0·0826, 610–390 mμ; c 0·0275, 425–320 mμ; c 0·00826, 340–280 mμ; c 0·00175, 300–245 mμ; $[\phi]_{418}$ 13310; $[\phi]_{332}$ −87550; $[\phi]_{260}$ 131660.

S-4,4′-Dimethoxydalbergione (300 mg) similarly gave *dihydro*-S-*4,4′-dimethoxydalbergione* (90 mg) as orange needles, m.p. 159–162°, from cyclohexane. (Found: C, 71·07; H, 6·36. $C_{17}H_{18}O_4$ requires: C, 71·31; H, 6·34%.) λ_{max} (in EtOH) 223 mμ (ε 13,200), 264 mμ (ε 16,400), 350 mμ (ε 1,400). $[\alpha]_D$ −136° (dioxan), −233° ($CHCl_3$). ORD in dioxan: c 0·08, 630–400 mμ; c 0·016, 440–250 mμ; $[\phi]_{504}$ −3805; $[\phi]_{362}$ 30105; $[\phi]_{302}$ −6645.

Ozonolysis of the dihydrodalbergiones (IIIa and b). Ozonized O_2 (3%) was bubbled through a solution of R-dihydro-4-methoxydalbergione (50 mg) in $CHCl_3$ (50 ml) for 3 min (flow rate 6·75 l/hr). Water (4 ml) was then added to the colourless solution which was heated under reflux for 30 min. The acidic product was separated by shaking the $CHCl_3$-extract with 5% $NaHCO_3$ aq and this yielded S-(−)-α-ethylphenylacetic acid (V; 27 mg), ν_{max} 1710 cm^{-1} (CO_2H), which was purified by short path distillation (100°/0·2 mm). It gave a negative plain ORD curve in dioxan,[18] $[\alpha]_D^{20}$ −69° ($CHCl_3$). Its IR spectrum was identical with that of the synthetic racemic acid.

Dihydro-S-4,4′-dimethoxydalbergione (25 mg) similarly gave an acidic product (9 mg), but the degradation could not be satisfactorily carried out on a larger scale. The acidic products from eight ozonolyses were combined and sublimation (150°/1 mm) yielded partially crystalline material (22 mg) which was recrystallized from light petroleum giving R-(+)-α-ethyl-*p*-methoxyphenylacetic acid (VI; 12 mg), m.p. 84–85°, $[\alpha]_D^{20}$ +25° ($CHCl_3$), positive plain ORD curve in dioxan, ν_{max} 1710 cm^{-1} (CO_2H). Its IR spectrum was identical with that of synthetic racemic α-ethyl-*p*-methoxyphenylacetic acid.[20]

Financial support to O. R. G. and M. T. M. by the Conselho Nacional de Pesquisas, Brasil, is acknowledged, and we also wish to thank Professor Carl Djerassi of Stanford University, for the determination of the ORD and CD curves discussed in this paper.

[20] O. S. Madaeva, N. M. Goncharova and V. I. Maksimov, *Zh. Obschei Khim.* **23**, 472 (1953); *Chem. Abstr.* **48**, 5136 (1954).