The Absolute Configurations of the Animal Metabolite, Equol, Three Naturally Occurring Isoflavans, and One Natural Isoflavanquinone

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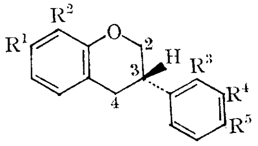
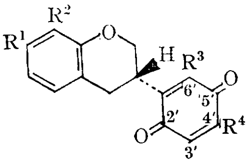
THE isolation[1] of the natural optically active isoflavans (−)-duartin (I), (−)-mucronulatol (II), and (+)- vestitol (III) from *Dalbergia variabilis* and several *Machaerium* species has led us to investigate the absolute configuration of this new group of natural products.

The absolute configuration of (3*S*)-5,7,3′,4′-tetramethoxyisoflavan (IV) follows[2] from its stereospecific synthesis from (2*S*,3*S*)-(+)-catechin tetramethyl ether (V) and its chemical correlation[2,3] with (*S*)-(−)-methylsuccinic acid. The o.r.d. characteristics of the natural isoflavans (I)—(III) have been compared with those of 3(*S*)-5,7,3′,4′-tetramethoxyisoflavan (IV) (Figure 1). For all four compounds, the o.r.d. in the 260—300 $m\mu$ region is characterised by a negative Cotton Effect, and we conclude that the isoflavans (I)—(IV) all have the 3*S*-configuration. Figure 1 clearly shows that the longer wavelength region is unsuitable in these cases for deducing configurational relationships. Thus, (−)-equol[†] (VI) has previously been assigned[2,4] the *R*-configuration at C(3) on the basis of optical rotatory dispersion comparison with (3*S*)-5,7,3′,4′-tetramethoxyisoflavan (IV) in the region 300—360 $m\mu$, but comparison at shorter wavelengths (Figure 1) shows that this configurational assignment[2,4] is incorrect and that (−)-equol also has the *S*-configuration at C(3).[‡] These conclusions were confirmed for (−)-duartin (I) by its oxidative degradation to (*R*)-(+)-paraconic acid (VII) of established absolute configuration.[5] These configurational interrelations have been established with certainty by oxidation of (3*S*)-5,7,3′,4′-tetramethoxyisoflavan (IV), which also gives (*R*)-(+)-paraconic acid (VII).

The absolute configuration of natural (−)-mucroquinone[1] (VIII) was established as 3*S* by comparison of its optical rotatory dispersion characteristics (Figure 2) with those of the isoflavanquinone (IX). The absolute configuration of the quinone (IX) followed from its preparation by oxidation of (+)-dihydrohomopterocarpin (X), since (+)-dihydrohomopterocarpin (X) was shown to have the 3*S*-configuration from the negative Cotton Effect in its optical rotatory dispersion curve in the 260—300 $m\mu$ region (Figure 1).



	R¹	R²	R³	R⁴	R⁵
(I)	OH	OMe	OMe	OH	OMe
(II)	OH	H	OMe	OH	OMe
(III)	OH	H	OH	H	OMe
(VI)	OH	H	H	H	OH
(X)	OMe	H	OH	H	OMe
(XV)	H	H	H	H	H
(XVI)	OMe	H	H	H	OMe
(XVII)	OAc	H	H	H	OAc
(XVIII)	OMe	H	OMe	H	H
(XIX)	OMe	H	OAc	H	H



	R¹	R²	R³	R⁴
(VIII)	OH	OMe	H	OMe
(IX)	OMe	H	H	OMe
(XI)	OH	OMe	OMe	OMe
(XII)	OMe	OMe	OMe	OMe
(XIV)	OMe	H	H	H

[†] We thank Professor F. Wessely for a generous sample of (−)-equol.

[‡] This conclusion has also been reached independently by Professor J. W. Clark-Lewis (private communication), whom we thank for this information.

However, caution must be exercised in the interpretation of the optical rotatory dispersion curves for the isoflavanquinones and comparison of curves is clearly limited to closely related structural types. Thus, the isoflavanquinones (XI) and (XII), although known to be of the 3*S*-configuration from their preparation by oxidation of (3*S*)-(−)-duartin (I) and (3*S*)-(−)duartin 7-methyl ether respectively, have optical rotatory dispersion curves (Figure 2) which are almost enantiomeric in the region 400—500 $m\mu$ with those of the (3*S*)-isoflavanquinones (VIII) and (IX). This, at first sight, could be just a consequence of the different chromophores of these two pairs of quinones, but the n.m.r. spectra of the dihydropyran ring protons [see (XIII), positions 2, 3, and 4] show that there are also interesting conformational differences between the pairs of compounds [(VIII) and (XIV)] and [(XI) and (XII)]. The quinone (XIV) is a synthetic racemate.

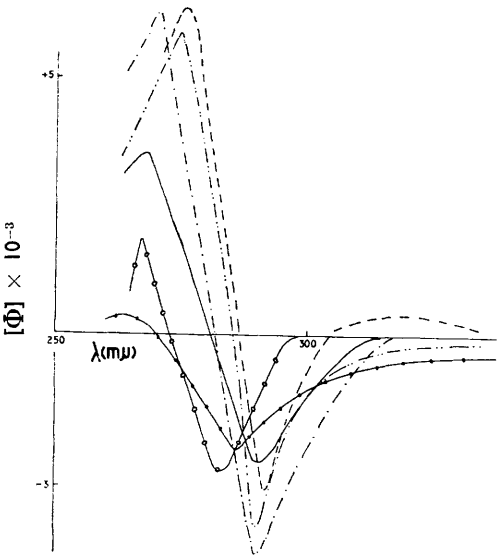
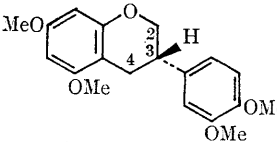
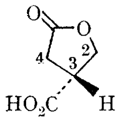


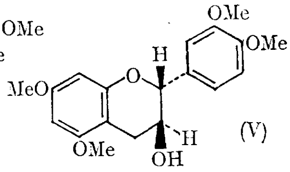
FIGURE 1. *Optical rotatory dispersion curves of isoflavans.* —●— (−)-*Duartin* (I); ——— (−)-*mucronulatol* (II); — — — (+)-*vestitol* (III); —○— (−)-5,7,3′,4′-*tetramethoxyisoflavan* (IV); — · — (−)-*equol* (VI); — · · — (+)-*dihydrohomopterocarpin* (X).



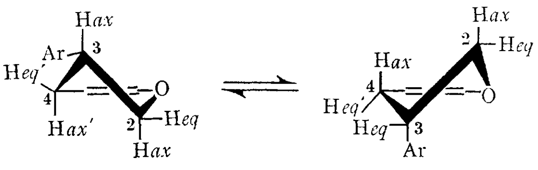
(IV)



(VII)



(V)



(XIIIa) (XIIIb)

The preferred conformation of the dihydropyran ring of the isoflavans is expected to be the half-chair form (XIII) by analogy with cyclohexene and on general considerations of the minimisation of torsional strain. It is not possible to reach a conclusion regarding which of the two possible half-chair conformations (XIIIa) or (XIIIb) is expected to be of lower free energy, since an axial 3-aryl substituent [see (IIIb)] does not result in destabilising 1,3-diaxial interactions characteristic of axially substituted cyclohexane or cyclohexene systems. The n.m.r. spectra of the dihydropyran ring-protons of isoflavans is an ABMXY or ABMXX′ system, which is complex at 60 Mc./sec., but is nearly first order at 220 Mc./sec.,§ so at this frequency, coupling constants may readily be obtained.

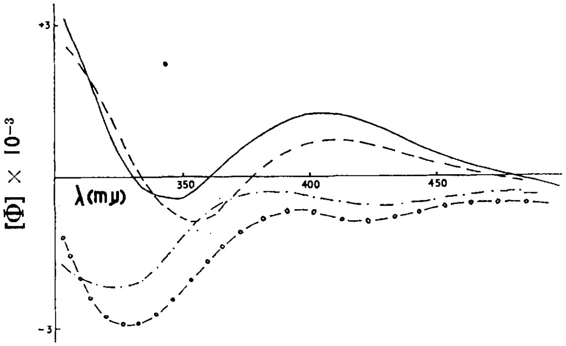


FIGURE 2. *Optical rotatory dispersion curves of isoflavanquinones.* — — — (−)-*Mucroquinone* (VIII); ——— (−)-7,4′-*dimethoxyisoflavan*-2′,5′-*quinone* (IX); —○— (−)-7-*hydroxy*-8, 4′,6′-*trimethoxyisoflavan*-2′,5′-*quinone* (XI); — · — (−)-7,8,4′,6′- *tetramethoxyisoflavan*-2′,5′-*quinone* (XII).

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§ We thank the S.R.C. and Imperial Chemical Industries Limited, Petrochemical and Polymer Laboratory, for the provision of facilities for the determination of these spectra.

Vicinal coupling constants for the dihydropyran ring protons at positions 2, 3, and 4 [*see* (XIIIa) *and* (XIIIb)] *for isoflavans and isoflavanquinones*

	J_{23} (c./sec.)				J_{34} (c./sec.)			
	$2_{eq}3_{eq}$	$2_{eq}3_{ax}$	$2_{ax}3_{eq}$	$2_{ax}3_{ax}$	$3_{eq}4_{eq'}$	$3_{eq}4_{ax'}$	$3_{ax}4_{eq'}$	$3_{ax}4_{ax'}$
Duartin (I)[a]		3·5		10			7·5[c]	
Mucronulatol (II)[a]		3·5		10			7·5[c]	
Vestitol (III)[a]		3·5		10			7·5[c]	
Isoflavan (XV)[b]		3·5		10·5			8·0[c]	
7,4′-Dimethoxyisoflavan (XVI)[b]		3		10·5			8·0[c]	
7,4′-Diacetoxyisoflavan (XVII)[b]		3		10·5			8·0[c]	
7,2′-Dimethoxyisoflavan (XVIII)[b]		3		10·5			5·5	10·5
2′-Acetoxy-7-methoxyisoflavan (XIX)		3·5		10·5			7·0	10·5
(XI)[b]		2		10·5			5	12·5
(XII)[b]		3		10·5			5	12
Mucroquinone (VIII)[b]	2·5		6·5		6	6·5		
(XIV)[b]	3		6·0		6	6·5		

[a] Determined from 60 Mc./sec. spectra; [b] Determined from 220 Mc./sec. spectra; [c] ABMXX′ system, average of J_{MX} and $J_{MX'}$. *eq′* = quasi-equatorial; *ax′* = quasi-axial.

The values for the various vicinal coupling constants of a number of isoflavans are given in the Table. The vicinal coupling constants (J_{23} and J_{34}) for the isoflavans (I)—(III) and the models (XV)—(XIX) are similar in magnitude to those of the isoflavanquinones (XI and (XII), and are consistent[6] with the values expected from the half-chair conformation (XIIIa) in which the 3-aryl or 3-quinonyl substituent occupies an equatorial position. The observed vicinal coupling constants for the isoflavanquinones (VIII) and (XIV) are, however, quite different (see Table) and are consistent with the values expected from a conformational equilibrium in which the conformation (XIIIb) with an axial 3-quinonyl substituent is the major contributor. These conformational differences between the pair of quinones (VIII) and (XIV), which lack the 6′-methoxy-substituent, and the quinones (XI) and (XII), which have a 6′-methoxy-substituent are, certainly related to the atypical optical rotatory dispersion characteristics shown by the two quinones (VIII) and (IX). These differences emphasise that the use of o.r.d. comparisons to establish the absolute configuration of conformationally mobile systems, such as the isoflavans, may be inadequate unless accompanied by evidence concerning the conformations of the compounds involved. The need to revise the configurational assignment of equol also emphasises the need to examine o.r.d. over as wide a wavelength range as possible.

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