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TWO NOVEL COUMARINS FROM *ERIOSTEMON BRUCEI*

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Abstract—Eriobrucinol (**1**) has been related to hydroxyeriobrucinol (**4**) by oxidation of the methyl ether of the latter to a ketone (**8**) and desulphurisation of the derived thioketal. The structures of the coumarins are derived from chemical and spectroscopic arguments. Assignment of the all *cis* configuration for the alicyclic system is supported by evidence for conformational inversion in the 1′ hydroxy derivative (**11**).

The structure of the coumarin bruceol, which had been isolated from *Eriostemon brucei* F. Muell. was described in an early part[1] of this series. More recently we have reexamined extracts of the plant and isolated three new coumarins. One of these had spectral properties suggesting that it may be desoxybruceol and it was identified by comparison with synthetic racemic material.[2] The other coumarins which are phenolic have been named eriobrucinol (**1**) and hydroxyeriobrucinol (**4**) and are the basis of this paper. The identification of the aromatic residue in these compounds follows from spectral data for the coumarins, their methyl ethers and acetates and is confirmed by subsequent degradation. The NMR spectra showed the AB quartets expected for H 3 and H 4 ($J \sim 10$ Hz) together with resonance for a lone aromatic proton. The UV spectrum of eriobrucinol (**1**) showed λ_{max} 217, 335 nm ($\log \epsilon$ 3·99, 3·99) expected for a coumarin with 5- or 7-oxygenation[3] where there is conjugation between oxygen and the CO group. The spectrum, measured in basified solution showed additional maxima at 278 and 405 nm ($\log \epsilon$ 3·99, 3·61) which confirms[3] a phenolic OH group at C 5 or 7. Of these C 5 was chosen since in the acetates (**3**, **6**) H 4 shows its resonance upfield (~0·35 ppm) when compared with the methyl ethers (**2** and **5**). Peri interactions of this type have been well documented.[4] As expected acetylation has little effect on the H 8 resonance and when the spectra are measured in benzene this resonance shows no significant shift. In coumarins H 5, 6 and 7 show benzene shifts from 0·25–0·5 ppm whereas values reported for H 8 are 0·1 ppm.[5] Long range couplings over five bonds in a rigid zig zag pattern are well documented in bicyclic aromatic systems.[6] For the coumarins[7] the most important long range coupling is for H 4 and H 8 (J 0·5–0·7 Hz) and this is evident at 60 MHz as a reduction of the peak height of the H 4 doublet with respect to that from H 3. The reduction was apparent in all the spectra we measured. At 100 MHz $J_{4,8}$ 0·75 was found for **5**. NMR data also establish the location of the side chain at C 6. Apart from resonances for the Me groups the alicyclic protons resonate as multiplets, one of which (H 1′) is a broad doublet separated well downfield from its neighbours and can be assigned a benzylic position. In the 5-acetoxy derivatives (**3**, **6**), this resonance is shifted upfield (0·24, 0·12 ppm) as compared with the methyl ethers (**2**, **5**), a shift which is expected for a peri interaction with acetoxyl. Confirmation of the environment of the phenolic hydroxyl in **4** was obtained by measurement of the Nucler Overhauser Effect between the methoxyl protons and H 1′ and H 4 in **5**. The measurements obtained through the courtesy of Dr. S. Sternhell show NOE effects of 10% and 11% respectively which can only be rationalised in terms of a 5-methoxy-6-alkylated coumarin.

Structural evidence relating to the alicyclic portion was derived from reactions of hydroxyeriobrucinol (**4**) since it contains a convenient chemical handle in the alicyclic system and is much more abundant. In comparison with eriobrucinol (**1**) the NMR spectrum of hydroxyeriobrucinol (**4**) shows a downfield multiplet for H 5′ ($W_{\frac{1}{2}}$ 11 Hz) and this indication of a secondary alcohol is confirmed by oxidation of the methyl ether (**5**) with Jones' reagent to give the ketone (**8**). The IR spectrum of the latter with maxima at 1745 and 1735 cm^{-1} suggests a cyclopentanone as well as the coumarin system. Conversion of **8** to the thioketal and then desulphurisation with Ni provides eriobrucinol methyl ether (**2**) thus relating the natural coumarins.

The NMR spectrum of the ketone (**8**) (Table)

†Part V. P. W. Chow, A. M. Duffield and P. R. Jefferies *Aust. J. Chem.* **19**, 483 (1966).

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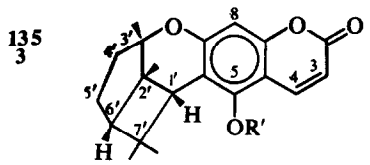
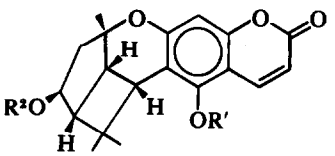
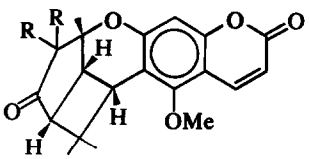


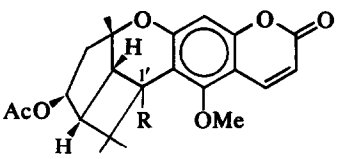
1 R
H
2 Me
3 Ac



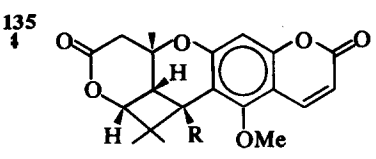
4 R' R²
H H
5 Me H
6 Ac Ac
7 Me Ac



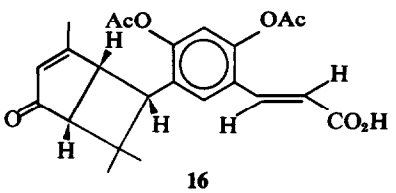
8 R
H
9 D



10 R
Br
11 OH
12 OC_2H_5



R
13 H
14 Br
15 OH



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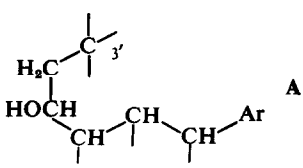
shows an AB quartet (J 18 Hz) which can be assigned[8] to the protons ($4'H_2$) of a methylene group flanked by carbonyl and by a fully substituted carbon atom. Consistently, mild deuteration of **8** with DCl/AcOD gave a d_2 derivative (**9**) whose NMR spectrum lacks this pattern. This spectrum retains the resonances in **8** for the benzyl proton (H 1') which appears as a sharp doublet and is coupled (J 9·0 Hz) to a second proton (H 2') which has an additional coupling (J 8·5 Hz) to a third proton (H 6'). The same AMX like pattern can be seen in the spectrum of hydroxyeriobrucinol methyl ether (**5**) since H 5' is only weakly coupled ($J \sim 1$ Hz) to H 6'. Decoupling the spectrum of **5** provides the coupling constants of H 5' with its vicinal neighbours and as well confirms the couplings assigned to H 2' and 1'. Chemical identification of a benzyl proton followed from bromination of the acetate (**7**) with N-Bromosuccinimide to give a labile bromo derivative (**10**). The NMR spectrum (Table) of the latter showed that the AMX pattern in **7** had been replaced by an AB system (J = 8 Hz) and the methoxyl resonance had been deshielded (0·38 ppm) as expected for a peri interaction with bromine. Exposure of the bromide (**10**) to aqueous media gave the alcohol (**11**) with an analogous NMR spectrum. Similarly, treatment of the bromide with ethanol gave the ethoxy derivative (**12**). Linking of the ketonic function in **8** to the AMX system was obtained by Baeyer-Villiger oxidation of **8** with *m*-chloroperbenzoic acid which gave the lactone **13**.

The NMR spectrum of the lactone showed that a doublet of the AMX system in **8** had shifted downfield to 4·7 δ, clearly due to the introduction of geminal oxygen. That this doublet was not due to the benzylic proton followed from bromination of the lactone with N-Bromosuccinimide which gave the bromo lactone (**14**). The NMR spectrum of **14** showed the AB system due to $H_{4'a4'b}$ as for the parent lactone together with an AX pattern from H 2' and H 6'.

The results so far determined define the protons of the alicyclic system as three tertiary Me groups and



A

Table 1. NMR data for some eriobrucinol methyl ether derivative ($CDCl_3$)

Substituents of 2 5′	1′		7′ Me	7′+3Me	OCH_3	1′H+	2′H+	6′H+	5′H	4′H_2	$J_{4'4'}$	$J_{5'4'}$
H	H	(2)	0·72	1·42, 1·37	3·78	3·25	2·6		*	**	*	*
βOH	H	(5)	0·75	1·45, 1·53	3·78	3·23	2·88	2·43	4·29	2·43, 1·86	14	6, 3
αOH	H	(18)	1·07	1·45, 1·48	3·78	3·25	2·6		4·32†	2·19, 2·03	13	7, 10
O	H	(8)	0·79	1·49, 1·53	3·87	3·63	3·10	2·75	—	2·78, 2·43	18	—
βAcO	H	(7)	0·80	1·45, 1·45	3·75	3·28	2·81	2·44	5·06	2·25, 1·98	14	6, 3
βAcO	Br	(10)	1·07	1·64, 1·64	4·13	—	3·50, 2·66		5·02	*	*	7, 0
βAcO	OH	(11)	0·90	1·39, 1·53	4·00	—	2·70	2·43	5·09	2·35, 1·98	14	6, 4
βAcO	OEt	(12)	1·02	1·42, 1·42	3·86	—	2·82	2·46	5·06	2·21, 1·91	15	6, 0
Lactone		(13)	0·62	1·23, 1·45	3·85	3·54	3·06	4·70	—	2·46, 3·05	17	—
Br "		(14)	0·93	1·63, 1·63	4·10	—	3·71	4·54	—	2·95, 2·44	17	—
HO "		(15)	0·70	1·37, 1·41	4·08	—	2·95	4·70	—	3·06, 2·48	17	—

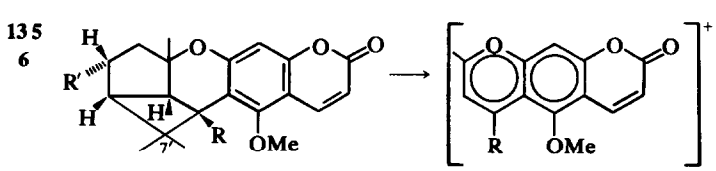
+$J_{1'2'}$ and $J_{2'6'}$ range 7·5–9 Hz, $J_{5'6'}$ 1 Hz;
*obscured
†$J_{5'6'}+J_{2'6'}$ 10 Hz. H 3, 4 and 8 appear in ranges 6·1–6·2, 7·4–7·8, 6·6–6·8 respectively.

The ether oxygen was unmasked and further confirmation of the coumarin system was obtained when the ketone (**8**) was heated briefly in base to give, as major product, an acid characterised as its diacetate (**16**). The NMR spectrum showed the signals expected for a *trans* cinnamic acid (AB doublets 7·81 and 6·64 $J \sim 17$ Hz), a lone aromatic proton (6·9 δ) and an olefinic α proton, (6·13, $W_{\frac{1}{2}}$ 3 Hz) of an αβ-unsaturated ketone coupled to the β-Me resonance[9] (2·14 $CDCl_3$; 1·66 C_6H_6). Tertiary Me resonances were evident at 1·21 and 1·10 together with signals at 2·35 and 2·39 (2 Ac). The IR maxima at 1760, 1705 and 1680 cm^{-1} could be assigned to acetoxyl, cyclopentenone and cinnamic acid groups respectively. The formation of a phenolic OH together with the cyclopentenone carrying a β-Me group is easily rationalised as a β elimination from the ketone (**8**). In contrast with the other compounds in this series the M member of the AMX system now shows its multiplet as the most deshielded member of the group, supporting its new situation allylic to an αβ unsaturated CO group.

The attachment of a methyl and phenol ether groups to C 3′ in **A**, the requirement for a pentacyclic system and the need to incorporate two tertiary methyls and one carbon into **A** leads uniquely to the gross structure **1** for eriobrucinol.

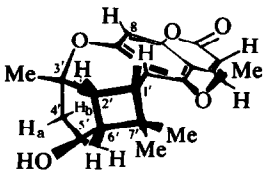
The structures are supported by mass spectra. Most significantly the base peaks correspond to the oxonium ions (**17**) expected for coumarins containing a pyran ring fused to the aromatic nucleus. As required by the 1′ substitution of compounds **10**, **11**, **12**, **14** and **15** their mass spectra showed base peaks retaining the substituent.

Of the sixteen pairs of enantiomers corresponding to the gross structure for hydroxyeriobrucinol (**4**) many are unreasonably strained and not worth serious consideration. However, an all *cis* configuration can be derived independently. The very small coupling for H 5′, H 6′ can only be rationalised if they are *trans* and then only if there is a *cis* relation for H 2′ and H 6′ since in those cases where the latter are *trans* the H 5′ H 6′ dihedrals approach 180° and should give large coupling. Further evidence relating to this point was obtained from the epimer (**18**) obtained by borohydride reduction of the ketone (**8**). In the epimer, H 5′ is now strongly coupled to H 6′. Epimerisation also results in a significant deshielding of the upfield tertiary Me group. This Me group is evidently 7′ α, which will be nearest to the shielding zone of the aromatic ring current. It follows that the OH group in the epimer (**18**) must be *cis* to C 7′ with respect to the cyclopentane ring. Limitation of the configurations of C 1′ and C 3′ comes from a consideration of NMR evidence suggesting that H 1′ approximates coplanarity with the aromatic rings. The near identity of the NOE for OMe and both H 1′ and H 4 suggests that the latter pair may be equivalently placed. In the second place the long range couplings of H 8 to H 4 and H 1′ are virtually equal (~0·75 Hz). For a benzylic coupling of this magnitude to a meta proton it is generally accepted that the mech-



18
R = H, R′ = OH

17



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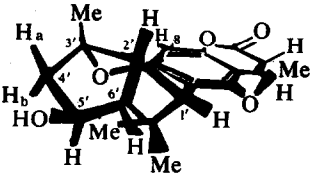

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anism of coupling follows a planar zig zag path. The only configuration which permits near coplanarity of H 1′ with the aromatic system is the all *cis* fusion in (**1**). Whereas other configurations are rigid the all *cis* arrangement can adopt different conformations corresponding to a half chair (**19**) and half boat (**20**) for the dihydropyran ring. The behaviour of eriobrucinol and particularly the 1′ substituted derivatives is simply interpreted in terms of the two conformations. In acetoxy eriobrucinol methyl ether (**7**) the signal due to H 5′ appears as a broad multiplet ($W_{\frac{1}{2}}$ 11 Hz). In the 1′-bromo derivative this multiplet is replaced by a doublet ($J \sim 7$ Hz). Whereas the observed couplings of H 5′ in **7** can be rationalised with the half boat conformation (dihedrals for 5′–αH ~ 20°, (4′ H), ~ 140° (4′ H), ~ 100° (6′ H) the half chair conformation in which two dihedrals are near 100° provides a simple explanation for the doublet character of H 5′. It is to be noted that for a half boat conformation of the bromo derivative repulsion due to virtual coplanarity of the OMe oxygen and bromine atoms can be relieved by conformational inversion when the Br atom moves about 60° from the plane. This interpretation of the NMR data for the bromo derivative is strongly supported by results for the 1′ OH derivative (**11**). The NMR spectrum of this material in deuterochloroform shows the multiplet ($W_{\frac{1}{2}}$ 11 Hz) for H 5′ as for acetoxyeriobrucinol methyl ether, pointing to a half boat conformation. Stabilisation of the half boat conformation by H-bonding to the OMe oxygen will be maximum for coplanarity of these substituents and is evident in the IR spectrum (CCl_4, ν_{max} 3524 cm^{-1}). When the NMR spectrum is determined in pyridine solution the pattern for H 5′ reverts to the doublet observed in the bromo derivative. Evidently solvation with pyridine has destroyed the stabilisation and steric and dipolar effects now favour a half chair conformation. One other compound in the series is the 1′-ethoxy derivative (**12**). This cannot show H-bonding stabilisation and should adopt a half chair conformation in chloroform as for the bromo derivative. The observation of the doublet for H 5′ supports this argument.

An unusual feature of the spectrum of the ethoxy compound is the non equivalence of the methylene protons of the Et group and they appear as doublets of quartets (δ, 3·21, 2·70 J_{gem} 9 Hz), evidently due to restricted rotation, with the high field member exposed to the shielding zone of the aromatic ring.

Conformational mobility of the 1′-hydroxy derivative (**11**) along with evidence presented for the all *cis* configuration in hydroxyeriobrucinol methyl ether requires that the bromination and subsequent solvolysis proceed with retention of configuration. This is to be expected since α-approach to Cl′ is very hindered.

The configuration for the alicyclic portion of eriobrucinol corresponds with that assigned partly by X-ray data to bicyclocannabinol.[10] It is significant to note that the biological origin of the latter is obscured by its lack of optical activity. On the other hand eriobrucinol and its derivatives show high optical rotations.

The absolute configuration of eriobrucinol can be derived in principle by application of the Horeau method[11] to hydroxyeriobrucinol methyl ether, since the substituents of C 5′ are well differentiated. Unfortunately, in esterification, 2-phenylbutyric anhydride reacted sluggishly with the coumarin (**5**). The negative rotation of the recovered acid (α_D − 3·22) provides a tentative assignment for the absolute configuration as in **5**.

EXPERIMENTAL

General experimental details are as described previously.[12] MS were recorded with a Varian Mat CH7 Spectrometer, operating at 70 eV. NMR spectra were recorded on a Varian A60 Spectrometer for $CHCl_3$ or $CDCl_3$ solns, unless otherwise stated and a Bruker Spectrospin High Resolution NMR Spectrometer (90 MHz).

Extraction of E. brucei. The milled leaves and twigs (12·73 Kg) of *E. brucei* collected 257 miles east of Perth on the Great Eastern Highway, Western Australia, were worked up as described,[1] and the Na_2CO_3 soluble extract was washed with ether. Filtration afforded *hydroxyeriobrucinol* (**4**, 33 g) which was crystallised from acetone and then EtOH-water to give solvated needles, m.p. 243°. (Found: C, 67·5; H, 6·90. $C_{19}H_{20}O_5$. C_2H_5OH requires: C, 67·4; H, 7·00%); MS: M^+ 328 ($C_{19}H_{20}O_5$), base peak 229; NMR: (C_5D_5N) δ; 8·34 (4-H, d, J_{3-4} = 10 Hz), 6·66 (8-H, s), 6·31 (3-H), 4·58 (5′-H, m), 3·46 (1′-H, d, $J_{1'-2'}$ = 9 Hz), 2·94 (2′-H), 2·71 (6′-H, d, $J_{2'-6'}$ = 8·5 Hz), 2·38 (4′-H, m), 1·84, 1·52 and 0·96 (each 3H, s); IR: (Nujol mull) ν_{max} 3580, 3280 (broad), 1700, 1665, 1605, 1550, 1440, 1350, 1285, 1250, 1140, 1105, 1075, 995, 970, 960, 920, 875, 825, 765. UV: λ_{max} 232 (ε 10,000) + NaOH 243 (6,000), 279 (7,000) 343 (5,800), 407 (5,500).

The ether soluble portion of the Na_2CO_3 extract was partitioned into MeOH : H_2O (9 : 1) and the soluble portion chromatographed on silicic acid. Elution with $CHCl_3$-light petroleum (2 : 3) afforded first valerenic acid (0·99 g), followed by deoxybruceol (0·63 g); needles (MeOH aq)

m.p. 121–122°, $[\alpha]_D$ −127·4° ($CHCl_3$), whose NMR and IR spectra were identical with synthetic material.[2] Elution with 80% chloroform-light petroleum gave **1** (4·02 g), which was recrystallised from benzene or acetone as needles, m.p. 185°, $[\alpha]_D$ −310°, pyridine. (Found: C, 73·4; H, 6·6. $C_{29}H_{20}O_4$ requires: C, 73·1; H, 6·5%), MS: M^+ 312, base peak 229; NMR: (C_5D_5N) δ; 8·33 (4-H, d, J_{3-4} = 10 Hz), 6·56 (8-H, s), 6·18 (3-H, d, J_{3-4} = 10 Hz), 3·4 (1′-H, m, $J_{1'-2'}$ = 9 Hz), 2·54 (2′-H, t, $J_{1'2'} \sim J_{2'-6'} \sim$ 8·5 Hz), 1·48, 1·39 and 0·86 (each 3H, s); IR: (Nujoll mull) ν_{max} 3300, 1700, 1600, 1505, 1125, 1070, 825; UV: λ_{max} 217 (ε 9,700), 335 (9,700). +NaOH 217 (15,650), 278 (9,700), 340 (7,000), 405 (4, 100).

Derivatives of hydroxyeriobrucinol

The coumarin **4** (1g) in MeOH was added to an ethereal soln of diazomethane. After 12 hr at 0°, excess diazomethane was removed and the ether soln washed with 5% NaOH. The neutral product was crystallised from MeOH to afford *hydroxyeriobrucinol methyl ether* (**5**, 820 mg) m.p. 202° $[\alpha]_D$ − 182° ($CHCl_3$). (Found: C, 69·9; H, 6·5 $C_{20}H_{22}O_5$ requires: C, 70·2; H, 6·5%); MS: M^+ 342, base peak 243; NMR: ($CDCl_3$, Table); IR: (CCl_4) ν_{max} 3625. (Nujol mull) ν_{max} 3500, 1720, 1610, 1555, 1250, 1220, 1140, 1130, 1095, 1075, 995, 960, 925, 874, 840, 825. UV: λ_{max} 225 (9350), 332 (8650).

The *acetate* **7** of the methyl ether prepared with Ac_2O in pyridine, crystallised from MeOH as prisms, m.p. 158·5°, $[\alpha]_D$ −97° ($CHCl_3$). (Found: C, 69·0; H, 6·1. $C_{22}H_{24}O_6$ requires: C, 68·7; H, 6·3%); MS: M^+ 384, base peak 243; NMR: ($CDCl_3$, Table). (C_6H_6) δ; 6·64 (8-H, s), 5·92 (3-H, d, J_{3-4} = 10 Hz), 5·09 (5′ − H, t, $J \sim$ 5 Hz), 3·27 (OMe), 1·7 (Acetate, s), 1·32 (2 × Me, s), 0·8 (Me, s); IR: (CS_2) ν_{max} 1745, 1320, 1230, 1130, 1105, 1075, 825 cm^{-1}.

Hydroxyeriobrucinol **4** was acetylated by the same method as for hydroxyeriobrucinol methyl ether, and the resultant *diacetate* (**6**) crystallised (C_6H_6) as prisms m.p. 190–191°, $[\alpha]_D$ −58° $CHCl_3$. (Found: C, 67·3; H, 5·9. $C_{23}H_{24}O_7$ requires: C, 67·0; H, 5·9%); MS: M^+ 412, base peak 271; NMR: ($CHCl_3$) δ; 7·5 (4-H, d, J_{3-4} = 10 Hz), 6·8 (8-H, s), 6·24 (3-H, d, J_{3-4} = 10 Hz), 5·12 (5′-H, t, $W_{\frac{1}{2}}$ 11 Hz), 3·11 (1′-H, d, $J_{1'-2'}$ = 8 Hz), 2·85 (2′-H, t, $J_{1'-2'}$ $J_{2'-6'} \sim$ 8 Hz), 2·41 (Acetate, s), 2·03 (Acetate, s), 1·48, 1·40 and 0·84 (each 3H, s); IR: (CS_2) ν_{max} 1760, 1745, 1230, 1180, 1130, 1100, 1045, 825. UV: λ_{max} 227 (ε 11,750), 334 (9,900).

Derivatives of eriobrucinol (**1**)

By the same method as for hydroxyeriobrucinol *eriobrucinol methyl ether* (**2**) was obtained as needles m.p. 141° from benzene-light petroleum $[\alpha]_D$ −211°, $CHCl_3$. (Found: C, 73·4; H, 6·8. $C_{20}H_{22}O_4$ requires: C, 73; H, 6·8%); MS: M^+ 326, base peak 243; NMR: ($CDCl_3$, Table). (C_6H_6) δ: 7·5 (4-H, d, J_{3-4} = 10 Hz), 6·64 (8-H, s), 5·92 (3-H, d, J_{3-4} = 10 Hz), 3·38 (OMe), 3·1 (1′-H, m), 2·3 (2′H, 6′H, m), 1·6 (4′-H, 5′-H, m), 1·34, 1·24 and 0·71 (each 3H, s); IR: (CS_2) ν_{max} 1740, 1280, 1240, 1210, 1185, 1120,1095, 1060, 990, 970, 960, 930, 915, 900, 825. UV: λ_{max} 224 (ε 11,200), 333 (10,400).

Acetylation of eriobrucinol (**1**)

By the same method as for hydroxyeriobrucinol, *eriobrucinol acetate* was obtained but failed to crystallise; MS: M^+ 354, base peak 271; NMR: ($CDCl_3$) δ; 7·41 (4-H, d, J_{3-4} = 10 Hz), 6·72 (8-H, s), 6·16 (3-H, d, J_{3-4} = 10 Hz), 3·01 (1′-H, d, $J_{1'-2'} \sim$ 9·5 Hz), 2·59 (2′H, m), 2·4 (6′-H, m), 2·38 (Acetate, s), 1·75 (4′-H, 5′-H, m), 1·36 (2 × Me, s), 0·72 (Me, s); IR: (CS_2) ν_{max} 1775, 1745, 1180, 1135, 1045, 825.

Jones' oxidation of hydroxyeriobrucinol methyl ether (**5**)

The ether **5**, (200 mg) was dissolved in acetone (20 ml) and excess Jones' reagent was added. After 5 min at room temp, excess reagent was destroyed with EtOH and the neutral product isolated with ether, to give the *ketone* **8**, (173 mg). Recrystallisation from chloroform-light petroleum gave needles, m.p. 142–143° $[\alpha]_D$ −193, $CHCl_3$. (Found: C, 70·2; H, 6·3. $C_{20}H_{20}O_5$ requires: C, 70·6; H, 5·9%); MS: M^+ 340, base peak 243; NMR: ($CDCl_3$, Table). (C_6H_6) δ; 6·06 (3-H, d, J_{3-4} = 10 Hz), 3·53 (OMe), 3·42 (1′-H, d, $J_{1'-2'}$ = 9 Hz), 2·75 (2′-H, t), 2·55 (6′-H, d, $J_{2'-6'}$ = 8 Hz), 2·67 (4′-H, d, J_{gem} = 17 Hz), 2·2 (4′-H, d, J_{gem} = 17 Hz), 1·36, 1·24 and 0·77 (each 3H, s); IR: (CH_2Cl_2) ν_{max} 1740, 1728 (CS_2) ν_{max} 1745, 1740, 1240, 1185, 1130, 1070, 920, 820. (CCl_4) ν_{max} 1745, 1735. UV: λ_{max} 240 (ε 12,000), 325 (11,850).

Deuteration of the ketone (**8**)

The ketone **8** was treated with a mixture from acetyl chloride (3·9 g) and D_2O (5 ml) in dioxan (20 ml), equivalent to 2N DCl, at 20° for 3 hr. The mixture was diluted with ether and washed with water. The ether layer gave the 4′, 4′-d_2-ketone (**9**); MS: M^+ 342, base peak 243; NMR: as for **8** except that neither the 18 Hz doublets at 2·78 or 2·43 δ is apparent.

Conversion of hydroxyeriobrucinol methyl ether (**5**) *to eriobrucinol methyl ether* (**2**)

The ketone **8**, (100 mg) in BF_3 etherate (0·5 ml) and ethane dithiol (0·5 ml) were set aside for 3 days. Isolation with ether gave the thioketal; NMR: ($CDCl_3$) δ; 7·73 (4-H, d, J_{3-4} = 10 Hz), 6·51 (8-H, s), 6·12 (3-H, d, J_{3-4} = 10 Hz), 3·76 (OMe), 3·16 (thioketal ethylene protons, s), 1·71, 1·43 and 0·95 (each 3H, s). The thioketal (400 mg) was refluxed for 6 hr with Raney Ni (W7, 5 g) in EtOH (80 ml) containing a small amount of chloroform to solubilise the thioketal. Separation from olefinic material was achieved by preparative TLC. Crystallisation from benzene-light petroleum gave **2**, (m.p. and m.m.p., IR, NMR and MS).

Base-treatment of the ketone (**8**)

The ketone **8**, (510 mg) was heated at 100° in aq 2N NaOH (50 ml) under N_2 for 10 min. Isolation of the acidic products (420 mg) with ether gave a mixture. Chromatography on silicic acid (4 g) and elution with chloroform afforded a phenolic coumarin fraction (80 mg), while the *trans*-cinnamic acid (310 mg) was eluted with 1% MeOH-chloroform; NMR: (acetone) δ 7·5 (4-H, d, J_{3-4} = 17 Hz), 6·4 (3-H, d, J_{3-4} = 17 Hz), 6·1 (8-H, s), 5·6 (5′-H, br, s), 4·9 (3 × OH).

The acid was acetylated (Ac_2O in C_5H_5N) and the *diacetate* (**16**) was recrystallised from ether as needles, m.p. 93–94°, $[\alpha]_D$ −207, $CHCl_3$ (Found: C, 62·5; H, 6·1. $C_{24}H_{26}O_8H_2O$ requires: C, 62·6; H, 6·1%); MS: M^+ 442·1630 (base peak) calc. for $C_{24}H_{26}O_8$: 442·1628; NMR: ($CDCl_3$) δ; 8·33 (CO_2H, s), 7·81 (4-H, d, J_{3-4} = 17 Hz), 6·9 (8-H, s), 6·64 (3-H), 6·13 (4′H, s, $W_{1/2}$ = 3 Hz), 3·76 (OMe + 2′-H), 3·25 (1′-H, d, $J_{1'-2'}$ = 5 Hz), 2·95 (6′-H, d, $J_{2'-6'}$ = 5·5 Hz), 2·35 and 2·39 (2 × acetate, s), 2·14 (3′-Me, s, $W_{1/2}$ 3 Hz), 1·21 and 1·1 (each 3H, s). (C_6H_6) δ; 6·0 (4′-H, br, s), 3·52 (2′-H, t, $J_{1'-2'} \sim J_{2'-6'} \sim$ 6 Hz), 3·24 (OMe + 1′-H), 2·92 (6′-H, d, $J_{2'-6'}$ = 6 Hz), 1·82 and 1·78 (2 × acetate, s), 1·66 (3′-Me, s, $W_{1/2} \sim$ 4 Hz), 1·25 and

1·05 (each 3H, s); IR: (CH_2Cl_2) ν_{max} 3400 (broad), 1775, 1725, 1690. ($CHCl_3$) ν_{max} 1760, 1705, 1680, 1630, 1610. UV: λ_{max} 227 (ϵ 19,300), 268 (10,930).

Baeyer-Villiger oxidation of the ketone (**8**)

The ketone **8**, (200 mg) was dissolved in CH_2Cl_2 (50 ml) and *m*-chloroperbenzoic acid (600 mg, ~6 mmoles) and TsOH (1 mg) were added. After 18 hr reflux, the mixture was concentrated and filtered through alumina. The *lactone* **13** obtained was recrystallised from $CHCl_3$-light petroleum as needles, m.p. 215–217°, $[\alpha]_D$ +347, $CHCl_3$. (Found: C, 67·4; H, 5·8. $C_{20}H_{20}O_6$ requires: C, 67·4; H, 5·7%); M^+ 356, base peak 243; NMR: ($CHCl_3$, Table). (C_6H) δ; 6·58 (8-H, s), 5·83 (3-H, d, J_{3-4} = 10 Hz), 4·2 (6′-H, d, $J_{6'-2'}$ = 8 Hz), 3·32 (OMe), 3·16 (1′-H, d, $J_{1'-2'}$ = 8 Hz), 2·79 (4′-H, d, J_{gem} = 17 Hz), 2·25 (2′-H, t, $J_{1'-2'} \sim J_{2'-6'} \sim$ 8 Hz), 1·88 (4′-H, d, J_{gem} = 17 Hz), 1·17, 0·73 and 0·59 (each 3H, s); IR: ($CHCl_3$) ν_{max} 1745, 1735.

Bromination of acetoxy-eriobrucinol methyl ether (**7**)

The acetate **7**, (100 mg) in CCl_4 (20 ml) containing NBS (60 mg) and benzoyl peroxide (2 mg) were refluxed for 2·5 hr, the solvent was evaporated under reduced pressure and the compound **10** was obtained as a white solid; NMR: (Table).

Nucleophilic substitutions of the bromo compound (**10**)

(a) The compound **10** was chromatographed on alumina (Act. 1), whereon it was converted smoothly to the corresponding alcohol **11**, which crystallised from $CHCl_3$–EtOH (20:1) as needles, m.p. 217° $[\alpha]_D$ = 85, $CHCl_3$. (Found: C, 66·0; H, 6·0. $C_{22}H_{24}O_7$ requires: C, 66·0; H, 6·0%); MS: M^+ 400, base peak 259; NMR: ($CHCl_3$, Table) (Pyridine) δ 6·68 (8-H, s), 6·3 (3-H, d, J_{3-4} = 10 Hz), 5·21 (5′-H, d, $J_{4'-5'}$ = 6 Hz), 3·95 (OMe), 2·93 (2′-H, d, $J_{2'-6'}$ = 9 Hz), 2·6 (6′-H, d, $J_{2'-6'}$ = 9 Hz), 2·1 (4′-H, m), 2·05 (acetate, s), 1·65, 1·60 and 1·12 (3 × Me, s); IR: (CCl_4) ν_{max} 3524 (CS_2) ν_{max} 1740, 1230, 1130, 1065, 1025, 1010, 820.

(b) The bromo compound (**10**) was warmed with EtOH and the ethoxy derivative (**12**) obtained as a resin; MS: M^+ 428, base peak 286; NMR: ($CHCl_3$, Table).

Bromination of the lactone (**13**)

The lactone **13** was treated with NBS as for **7**. The bromo-lactone (**14**) was obtained; NMR: ($CHCl_3$, Table).

Filtration of the bromo-lactone through alumina afforded the *hydroxylactone* (**15**), which crystallised from chloroform-light petroleum as needles m.p. 237–238°, $[\alpha]_D$ +302°, $CHCl_3$.(Found: C, 64·4; H, 5·4. $C_{20}H_{20}O_7$ requires: C, ($CHCl_3$, Table); IR: ($CHCl_3$) ν_{max} 3495, 1750, 1730.

Sodium borohydride reduction of the ketone (**8**)

To the ketone **8** in MeOH excess $NaBH_4$ was added. After stirring for two hr at 20°, the mixture was diluted with H_2O and the neutral products isolated with ether. Filtration in $CHCl_3$ through Al_2O_3 and elution with $CHCl_3$:MeOH gave *5′-epi-hydroxyeriobrucinol methyl ether* m.p. 215–222° (dec); MS: M^+ 342·1472 calc. for $C_{20}H_{22}O_5$: 342·1467. Base peak 243·0657. Calc. for $C_{14}H_{11}O_4$: 243·0657. The spectrum was generally identical with that of **5** except that the M-15 peak was very weak; NMR: ($CHCl_2$, Table); IR: (Nujol) ν_{max} 3510, 1720, 1250, 1240, 1140, 1075, 1060, 830.

Horeau determination[11] *of the absolute stereochemistry at* C-5′

The general procedure used was to dissolve the alcohol in dry pyridine (2 ml/50 mg of substrate) and add approximately 3 mole equivs of (±)-α-phenylbutyric anhydride as described.[11] A control experiment with (–) menthol gave recovered acid $[\alpha]_D$ +21·9°. Under these conditions the acid recovered from esterification of **5** had $[\alpha]_D$ −3·22° requiring the S configuration for the C 5′. The acid was then dissolved in ether and rewashed into bicarbonate solution. After recovery as before, the rotation was measured, again in benzene.

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