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TETRAHEDRON

The Formation and Stability of Flavans with 2,3-*cis*-3,4-*cis* Configuration

Johan Coetzee,*[a] Elfranco Malan*[a] and Daneel Ferreira*[b]

[a]Department of Chemistry, University of the Orange Free State, P.O. Box, 339, Bloemfontein, 9300 South Africa

[b]National Center for Natural Products Research, Research Institute of Pharmaceutical Sciences, School of Pharmacy, The University of Mississippi, University, MS 38677

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Abstract: Treatment of 4β-chloroepioritin tri-*O*-methylether with phenylmethanethiol under neutral conditions affords both the 4α- and 4β-substituted epioritin derivatives. The stereochemical course of the reaction is of relevance to the thiolysis of 5-oxy (A-ring) proanthocyanidins and to the conspicuous stability of the 7,8-dihydroxy-2,3-*cis*-3,4-*cis*-flavan-3,4-diols, teracacidin and melacacidin, and of some of their all-*cis* (C-ring) oligomers.

Keywords: Flavanoids; Stereoselection; Neighbouring group effects; Thioethers

INTRODUCTION

Few reactions, if any, have had a more profound effect on the structure elucidation of the 5-oxy (A-ring) proanthocyanidins than their acid-catalyzed degradation using mercaptans[1,2] and phloroglucinol[3] as capture nucleophiles for the C4-carbocations originating from the chain extender flavan-3-ol moieties. The axial C3-hydroxyl group of extender units with 2,3-*cis* configuration controls the stereochemical course of coupling of the nucleophile to the transient carbocation leading in all instances but one[4] to C4-substituted flavan-3-ol units with 3,4-*trans* configuration.

We recently converted epioritin-4α-ol tri-*O*-methyl ether **1** into the 4β-chloroflavan-3-ol derivative **2** and subsequently used the latter compound with its axial C3-OH function as the potential electrophilic flavanyl unit to synthesize a series of novel (4-O-4)- and (4-O-3) bis-teracacinidins[5,6] *via* coupling with the C3- or C4-hydroxyl groups of flavan-3,4-diols, *e.g.* **1**. The stereochemical course of the formation of the (4-O-4)-3,4-*trans* (C-ring) bis-teracacinidin derivative **3** was attributed to an anticipated neighbouring group mechanism.[6,7] The *trans*-diaxial arrangement of the C3-hydroxyl group and the C4-chloro nucleofuge of the 4β-chloroflavan-3-ol **2** permits the formation of a transient protonated epoxide **4** which is prone to nucleophilic attack from the sterically less screened β-face. The unexpected formation of the (4-O-4)-3,4-*cis* (C-ring) bis-teracacinidin **5** was ascribed to conditions incapable of triggering a neighbouring group mechanism hence resulting in an S_N2-type coupling. The generation of the 3,4-*cis* (C-ring) oxyflavanyl

* Corresponding authors. E-mail: dferreir@olemiss.edu; coetzeej@cem.nw.uovs.ac.za

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compound **5**,[6] the formation of the all-*cis* flavan-3,4-diol **1** *via* solvolysis of the 4β-chloroflavan-3-ol **2** and genesis of 4α-benzylsulfanylepicatechin **6** in low concentrations during acid-catalyzed thiolysis of procyanidins with epicatechin-(4β→6)- and (4β→8)-catechin structural units[4] prompted investigation of the thiolysis reaction of the 4β-chloroflavan-3-ol **2** to probe the mechanism of the formation of these all-*cis* flavan derivatives.

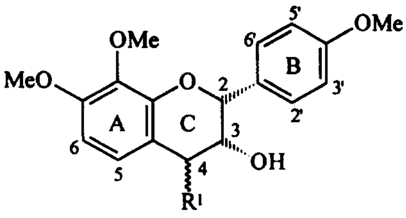
RESULTS AND DISCUSSION

Treatment of a solution of the 2,3-*cis*-3,4-*trans*-4β-chloroflavan-3-ol **2**[5] in anhydrous THF with phenylmethanethiol (2.0 *eq.*) at room temperature (*ca* 22°C) for 15h, afforded a mixture (68% yield) comprising the 4α- and 4β-benzylsulfanylepioritin derivatives **8** (11%) and **9** (89%). These compounds were identified as the 3-*O*-acetyl derivatives **10** and **11** with ^{1}H NMR coupling constants indicating 2,3-*cis*-3,4-*cis* ($J_{2,3}$ = 1.0; $J_{3,4}$ = 4.0 Hz) and 2,3-*cis*-3,4-*trans* ($J_{2,3}$ = 1.5; $J_{3,4}$ = 2.5 Hz) configurations for **10** and **11**, respectively.[4,8] Phase sensitive NOESY experiments confirmed these configurations *via* the selective association between 2- and 4-H(C) for the all-*cis* derivative **10** only. High-amplitude negative ($[\theta]_{244.6}$ -1.96×10^4) and positive ($[\theta]_{245.8}$ $+1.05\times10^5$) Cotton effects in the CD spectra of **10** and **11**, respectively, further validated the 4α- and 4β-benzylsulfanyl substituents in **10** and **11**, resp.

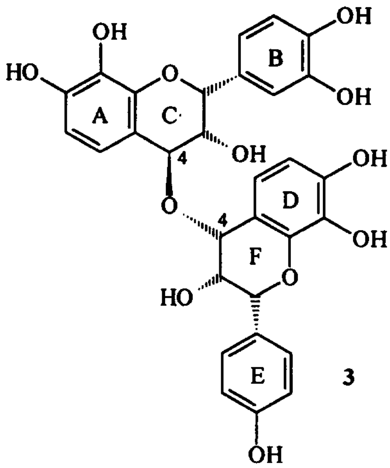
The *ca.* 1:9 ratio of 3,4-*cis*- and 3,4-*trans*-4-benzylsulfanylepioritin derivatives **8** and **9** contrasts with the *ca.* 1:35 – 1:45 ratio of 4α- and 4β-benzylsulfanylepicatechin analogues **6** and **7** formed in the acid-catalyzed thiolysis of the aforementioned procyanidins.[4] Since the degradation reactions were performed at the reflux temperature of a mixture of ethanol, phenylmethanethiol and acetic acid, the ratio of 4α- and 4β-substituted products may be temperature dependent. However, treatment of the 4β-chloroflavan-3-ol **2** with phenylmethanethiol in THF for 15h at –60°C and 60°C consistently gave the same *ca.* 1:9 ratio of 4α- and 4β-benzylsulfanylepioritin derivatives **8** and **9** in similar (*ca.* 70%) yields.

These results presumably indicate the simultaneous formation of the 4α- and 4β-benzylsulfanylepioritins **8** and **9**. The 4α-isomer **8** forms *via* S_N2 attack of the powerful sulphur nucleophile at the σ*-orbital of the polarized near axial C4-Cl bond. The proper alignment for this process is attained by intermolecular hydrogen bonding between the axial C3-OH and the thiol as is depicted in **12**. A sufficiently polarized C4-Cl bond may trigger the neighbouring group mechanism[5,6] to permit the formation of the 4β-benzylsulfanylepioritin **9** *via* intermediacy of the protonated oxirane **4**. The relative rate of the anchimeric process must exceed that of the S_N2 route to explain the dominant formation of the 4β-analogue **9**.

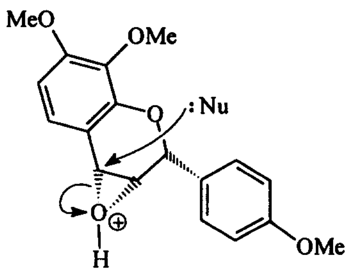
The thermodynamic stabilities of the 4-thiobenzyl ethers **8** and **9** may also influence the ratio in which they are formed. The less stable 4α-benzylsulfanylepioritin **8** may be protonated at sulphur by the acid generated during thiolysis of the 4β-chloroflavan-3-ol **2**. Owing to conformational restraints (see below) the protonated species will then permit a slow conversion into the thermodynamically more stable 4β-thioether **9**.



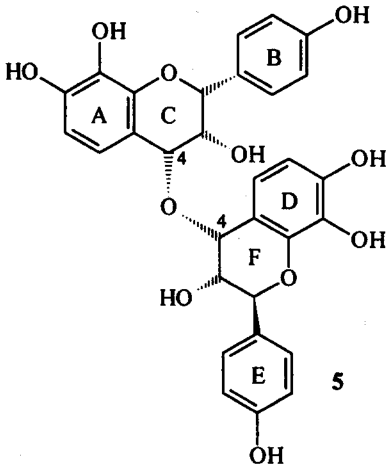
1 R^1=OH,
2 R^1=Cl,



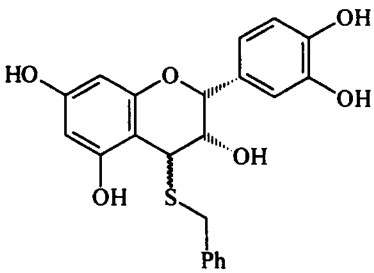
3



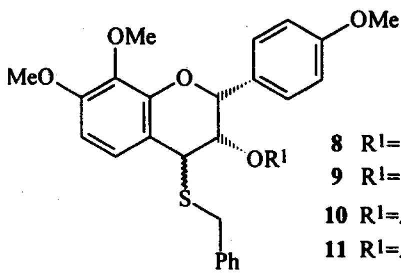
4



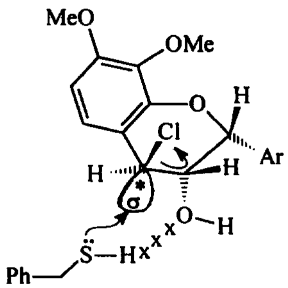
5



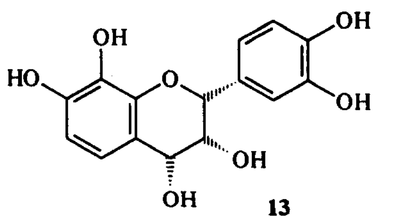
6
7



8 R^1=H,
9 R^1=H,
10 R^1=Ac,
11 R^1=Ac,



12



13

The latter compound should resist C-4 epimerization since enhancement of the nucleofugal properties of the 4-thio functionality by protonation would simply lead to 'activation' of the neighbouring group effect and hence shielding of the α-face at C-4 of oxirane **4**. When the 4α-thiobenzyl ether **8** and phenylmethanethiol in dry THF containing gaseous HCl were stirred at 50°C, the all-*cis* compound was indeed slowly converted into the 4β-benzylsulfanylepioritin **9**, affording a *ca.* 2:1 mixture of analogues **8** and **9** after 3 days. The 4β-thiobenzyl derivative **9** was stable under the same conditions.

A number of factors, *e.g.* the strength of the C4-leaving group bond and the nature of the nucleophile, will influence the energetics of the substitution process and hence the competition between the anchimeric and S_N2 processes. This is also evident from the preferential formation of the 'anchimeric product' **7** in the acid-catalyzed thiolysis of selected procyanidins[4] at *ca.* 80°C and the selective formation of the all-*cis* diol **1** during solvolysis of **2**. The dual nature of the mechanism leading to the formation of 4α- and 4β-epimers during substitution reactions at C-4 of flavans with 3-axial hydroxyl groups is thus firmly established.

The conspicuous resistance of the 4α-thiobenzyl ether **8** to epimerization at C-4 is related to the observed stability of melacacidin **13** under solvolytic conditions. Such inertia towards solvolysis or epimerization was ascribed[7,9] to hydrogen bonding between the axial C3-OH and the heterocyclic oxygen which locks the C-ring in a half-chair conformation with $C_{2eq.}$; $C_{3ax.}$; $C_{4eq.}$ substituents. In this conformation the appropriate C4 σ*-orbital is at an angle of *ca.* 45° above the plane of the A-ring and 'buried' in the heterocyclic ring which screens its overlap by an external nucleophile. Since a C-4 antibonding orbital orthogonal to the A-ring would permit the most effective delocalization of A-ring electron density or stabilization of electron deficiency at C-4, it is now clear why an all-*cis* C-ring configuration is more common for flavonoids with 7,8-dihydroxylated A-rings. These compounds no doubt, would have a reduced need for delocalization[10-12] of the aromatic electron density than their counterparts with more electron-rich resorcinol- and phloroglucinol-type A-rings. It may then also explain the stability and abundance of the flavan-3,4-diol, teracacidin (free phenolic form of **1**) as well as the growing number of dimers with 2,3-*cis*-3,4-*cis*-flavanyl constituent units all possessing 7,8-dihydroxy A-rings and axial C-3 hydroxyl groups.[5,6,13-16]

EXPERIMENTAL

^{1}H NMR spectra were recorded at 298K on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with the solvent as internal standard. Mass spectra were recorded on a VG-70-70E spectrometer and CD spectra on a Jasco J-710 spectropolarimeter. Preparative plates (PLC), 20x20 cm, Kieselgel PF_{254} were air dried and used without prior activation. Methylations were performed with an excess of diazomethane in MeOH-Et_2O over 48h at –15°C and acetylations were in acetic anhydride-pyridine at 25°C.

Formation of the 4α- and 4β-benzylsulfanylepioritin derivatives **8** *and* **9** *at* 22°C.

A solution of (2*R*,3*S*,4*S*)-2,3-*cis*-3,4-*trans*-4-chloro-3-hydroxy-7,8,4′-trimethoxyflavan **2** (95 mg) and phenylmethane thiol (0.068 ml) in dry THF (10 ml) was stirred for 15h at 22°C. The volume was reduced in a stream of N_2 and the products separated by PLC in benzene-Me_2CO (9:1). The ensuing bands [**8**, R_f 0.68 (8.7 mg); **9**, R_f 0.49 (76.2 mg)] were acetylated and purified by PLC in benzene-Me_2CO (19:1) to give products, respectively, at R_f 0.64 (9.6 mg) and 0.67 (80.4 mg). The R_f 0.64 band comprises (2*R*,3*S*,4*R*)-2,3-*cis*-3,4-*cis*-3-acetoxy-4-benzylsulfanyl-7,8,4′-trimethoxyflavan **10** as a *white amorphous solid*, δ_H 7.47-7.28 (m, ArCH₂, 5xH), 7.40 (d, J = 9.0 Hz, H-2′,6′), 7.31 (d, J = 9.0 Hz, H-5), 6.94 (d, J = 9.0 Hz, H-3′,5′), 6.57 (d, J = 9.0 Hz, H-6), 5.59 (dd, J = 1.0, 4.0 Hz, H-3), 5.13 (br.s, J = *ca* 1.0 Hz, H-2), 4.27 (d, J = 4.0 Hz, H-4) 3.92 and 3.87 (each d, J = 13.5 Hz, ArCH_2), 3.89, 3.87, 3.84 (each s, 3xOMe) and 1.99 (s, OAc); m/z, M^+, 480. (Found: M^+, 480.1606. $C_{27}H_{28}SO_6$ requires M, 480.1606); CD $[\theta]_{278.7}$ -5.9×10^3, $[\theta]_{263.6}$ -3.5, $[\theta]_{244.6}$ -1.96×10^4, $[\theta]_{235.7}$ $+1.35\times10^3$, $[\theta]_{230.7}$ -7.85×10^2; IR (cm^{-1}, $CHCl_3$): 1739, 1714, 1610, 1526, 1514.

The R_f 0.67 band afforded (2*R*,3*S*,4*S*)-2,3-*cis*-3,4-*trans*-3-acetoxy-4-benzylsulfanyl-7,8,4′-trimethoxyflavan **11** as a *white amorphous solid*, δ_H 7.51-7.29 (m, ArCH₂, 5xH), 7.36 (d, J = 9.0 Hz, H-2′,6′), 6.92 (d, J = 9.0 Hz, H=3′,5′), 6.76 (d, J = 9.0 Hz, H-5), 6.54 (d, J = 9.0 Hz, H-6), 5.57 (br.s, J = *ca* 1.0 Hz, H-2), 5.29 (dd, J = 1.0, 2.5 Hz, H-3), 3.92 and 4.11 (each d, J = 14.0 Hz, ArCH_2), 3.95 (d, J = 2.5 Hz, H-4), 3.89 (s, OMe), 3.85 (s, 2xOMe), 1.90 (s, OAc); m/z, M^+ 480 (Found: M^+, 480.1605. $C_{27}H_{28}SO_6$ requires M^+, 480.1606); CD $[\theta]_{290.2}$ -7.4×10^3, $[\theta]_{262.9}$ $+6.66\times10^3$, $[\theta]_{245.8}$ $+1.05\times10^5$, $[\theta]_{236.6}$ -2.83×10^3, $[\theta]_{230.3}$ $+1.09\times10^4$, $[\theta]_{220.6}$ $+8.8\times10^3$; IR (cm^{-1}, $CHCl_3$): 1734, 1714, 1614, 1540, 1530, 1516.

Similar treatment of the 4β-chloroepioritin derivative **2** (101 mg) for 15h at –60°C afforded **8** (8.9 mg) and **9** (84.3 mg). At 60°C the 4β-chloroepioritin **2** (120 mg) was converted into a mixture comprising **8** (6.4 mg) and **9** (103.2 mg).

Assessment of the stability of the 4α*-thiobenzyl ethers* **8** *and* **9**.

The thiobenzyl ether **8** (6.3 mg) was dissolved in dry THF (3 ml) containing gaseous HCl [taken from a stock solution of THF which was purged for 30 min with dry HCl (g)]. Phenylmethanethiol (excess) was added, the mixture was stirred at 50°C for 3 days under N_2 and evaporated to dryness. The mixture was resolved by PLC in benzene-Me_2CO (9:1) to give the 4α-benzylsulfanylepioritin derivative **8** (3.2 mg, R_f 0.68) and a further band at R_f 0.49 (2.3 mg). The latter band was acetylated and purified by PLC in benzene-Me_2CO (19:1) to give the 3-*O*-acetyl-4β-benzylsulfanylepioritin derivative **11** (1.5 mg, R_f 0.67).

The 4β-benzylsulfanylepioritin derivative **9** was recovered unchanged after similar treatment.

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