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THE STRUCTURE AND SYNTHESIS OF A 7,8,4′-TRIHYDROXYFLAVAN-EPIORITIN DIMER FROM *ACACIA CAFFRA*

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Key Word Index—*Acacia caffra*; Leguminosae; heartwood; 7,8,4′-trihydroxyflavanone; proteracacinidin; flavan-(4$\beta \rightarrow$6)-epioritin dimer; synthesis.

Abstract—The first (2*S*)-7,8,4′-trihydroxyflavan-epioritin-4α-ol dimer was isolated from the heartwood of *Acacia caffra*. Reduction of 7,8,4′-trihydroxyflavanone to the flavan-4-ol was subsequently used in an acid-catalysed condensation with epioritin-4α-ol to synthesize the dimer. Copyright © 1997 Elsevier Science Ltd

INTRODUCTION

The first flavan–flavanone dimer was isolated from the gum of *Xanthorrhoea preissii* [1]; this was followed by the discovery of flavan–flavan dimers from the red resin of *Daemonorops draco* [2]. Recently, a (2*S*)-7-4′-dihydroxyflavan-*ent*-epiafzelechin dimer was isolated from the leaves of *Cassia fistula* and resulted in the creation of a new class of proanthocyanidins called procassinidins [3, 4].

Reduction of (2*S*)-7,8,4′-triacetoxyflavanone, **2**, isolated from the heartwood of *Acacia caffra* resulted in the expected (2*S*)-7,8,4′-triacetoxyflavan-4-ol, **6**, this was subsequently used in a mild acidic condensation with epioritin-4α-ol to yield 7,8,4′-trihydroxyflavan-(4$\beta \rightarrow$6)-epioritin-4α-ol (**3**) in low concentration.

RESULTS AND DISCUSSION

The flavan-(4$\beta \rightarrow$6)-epioritin-4-ol, **3**, was isolated and purified as the acetate **4** because of the complexity of the original phenolic fraction. The HOMODEC ($CDCl_3$) of compound **4** exhibited an AB/AA′BB′ system and a second AA′BB′ system with a singlet (δ 6.61) in the aromatic region (Table 1). The lower range of the heterocyclic region displayed an AMX-system which is typical for a 2,3-*cis*-3,4-*cis* [5] relative configuration ($J_{2,3}$ = 1.5 H_3 and $J_{3,4}$ = 4.0 Hz).

Irradiation of H-4 (*F*, *d*, δ 6.19) as reference showed a strong association with the singlet at δ 6.61 resulting in substantial sharpening of the peak and was assigned as H-5(D) of compound **4**. This information confirmed the bottom unit to be coupled at the C-6 (D) position. The two dimensional-COSY ($CDCl_3$) of compound **4** showed coupling between a second set of peaks in the higher range of the heterocyclic region, namely δ 4.15(*dd*), δ 5.16(*dd*) and protons underlying the acetoxyl signals in the δ 2.28 region, suggesting a methylene group typical of a flavan system. The ^{1}H NMR (C_6D_6) clearly shifted the two sets of multiplets from under the acetoxyl signals to appear at δ 2.21(*ax*) and δ 2.02(*eq*), respectively. HOMODEC (C_6H_6) confirmed the system to be H-2 (C, *dd*, δ 5.33), H-4 (C, *dd*, δ 4.09) and the methylene group at C-3 of the top unit.

NOE difference spectroscopy showed an association between H-4(C) to H-5(A) of 3.8%, and H-4(C) to H-5(D) of 2.3%, the latter suggesting a preferred conformation with the bottom unit perpendicular to the plane of the C-ring with the 7- and 8-OAc groups above the plane of the heterocyclic ring. Association between 2-H(C) to H-2′,6′(B, 2.5%) and H-2(F) to H-2′,6′(E, 5.2%) confirmed their chemical shifts. No association could be detected between H-2(C) and H-4(C), which validated the assumption that these two protons are on opposite sides of the C-ring. A large positive Cotton effect at $[\theta]_{238.8nm}$ 3.365×10^4 confirmed a 4β configuration at C-4(C) and the absolute stereochemistry of compound **4** could be assigned as (2*S*)-7,8,4′-triacetoxyflavan-(4$\beta \rightarrow$6)-(2*R*, 3*R*, 4*R*)-epioritin-4α-ol. FAB-mass spectrometry confirmed a molecular mass of 882 units thus supporting the structure of compound **4**.

In an attempt to synthesize compound **3** the 7,8,4′-trihydroxyflavanone **1** was isolated from the phenolic extract and the acetate **2** was prepared to ensure its purity. Compound **2** was treated with $NaBH_4$/THF to yield compound **5**, which was identified as (2*S*)-7,8,4′-

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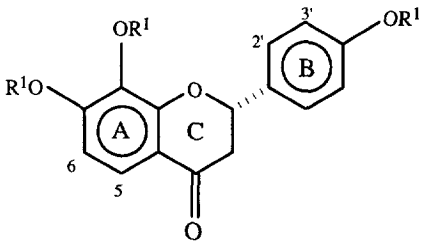

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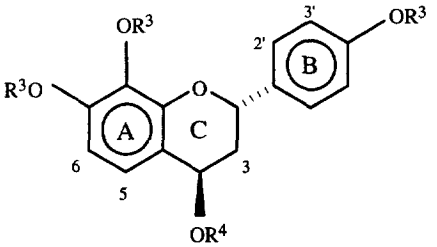
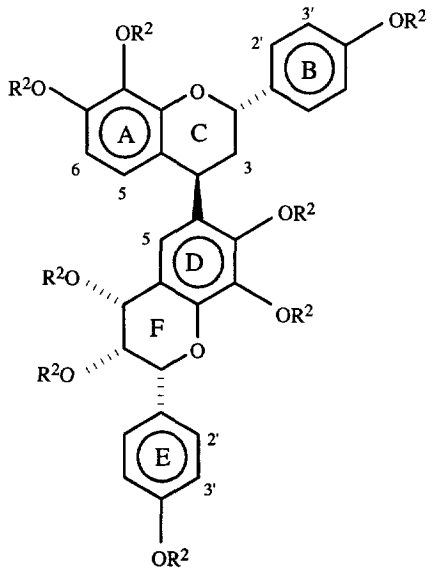


5 $R^3 = Ac$; $R^4 = H$
6 $R^3 = R^4 = Ac$



3 $R^2 = H$
4 $R^2 = Ac$

triacetoxyflavan-4-ol after preparing the acetate **6** (Table 1). Compound **5** was stirred at 25° in a 0.1 M HCl aqueous solution [6] under nitrogen.

The reaction mixture was separated and purified but out of five attempts only once was it successful, yielding 2.4% of compound **4**. The other three theoretical possible dimers could have been present in very low concentrations.

EXPERIMENTAL

General. Exactly the same experimental procedures were followed as was reported previously [7]. The (2*S*)-7,8,4′-trihydroxy-(4$\beta \rightarrow$6)-epioritin-4α-ol **3** was found in the phenolic fr. (R_f between 0.11 and 0.13), using Merck TLC silica gel 5554 in C_6H_6–Me_2CO (8:6×2).

A mixt. of compound **6** (10 mg) and epioritin-4α-ol (30 mg) in 0.1M HCl aq. soln was stirred for 30 min at room temp. The reaction was quenched with excess ice and the reaction mixt. extracted with EtOAc, evapd under red. pres. and the residue analysed.

The plant material was collected at Loskopdam in the Eastern Transvaal and identified by P. Swarts of the NBI at Pretoria.

(*S*)-7,8,4′-*Triacetoxyflavone* (**2**). R_f 0.39 in B:A, 9:1. Non-crystalline, 180 mg. MS: *m/z* 398 (18%) $[M]^+$. ^1H NMR ($CDCl_3$): δ 7.83 (*d*, *J*=8.5 Hz, H-5), 7.42 (*d*, *J*=8.5 Hz, H-2′, 6′), 7.14 (*d*, *J*=8.5 Hz, H-3′,5′), 6.89 (*d*, *J*=8.5 Hz, H-6), 5.49 (*dd*, *J*=3.5 and 13.0 Hz, H-2), 3.04 (*dd*, *J*=13 and 17.0 Hz, H-3ax), 2.87 (*dd*, *J*=3.5 and 17.0 Hz, H-3(eq), 2.30 (s, 2×

Table 1. ^1H NMR (300 MHz) data

Ring	H	**4** ($CDCl_3$)	**4** (C_6D_6)	**6** (C_6D_6)
A	5	6.86 (*d*, 8.5)	6.50 (*d*, 8.5)	7.08 (*dd*, 1.0, 8.5)
	6	6.68 (*d*, 8.5)	6.58 (*d*, 8.5)	6.85 (*d*, 8.5)
B	2′,6′	7.28 (*d*, 8.5)	7.21 (*d*, 8.5)	7.14 (*d*, 8.5)
	3′,5′	7.03 (*d*, 8.5)	6.92 (*d*, 8.5)	7.05 (*d*, 8.5)
C	2	5.11 (*dd*, 3.0, 9.0)	5.33 (*dd*, 3.0, 9.0)	4.74 (*dd*, 2.5, 11.0)
	3	2.27 (under OAc's)	2.21 (*m*, 3.0, 4.0, 13.8, *ax*)	2.15 (*m*, 2.5, 6.0, 13.0, *ax*)
			2.02 (*m*, 9.0, 6.0, 13.8, *eq*)	1.84 (*m*, 11.0, 10.0, 13.0, *eq*)
	4	4.15 (*dd*, 4.0, 6.0)	4.09 (*dd*, 4.0, 6.0)	6.03 (*dd*, 6.0, 10.0)
D	5	6.61 (*br s*)	7.00 (*br s*)	
E	2′,6′	7.39 (*d*, 9.0)	7.10 (*d*, 9.0)	
	3′,5′	7.08 (*d*, 9.0)	7.01 (*d*, 9.0)	
F	2	5.37 (*br s*, 1.5)	4.63 (*br s*, 1.5)	
	3	5.59 (*dd*, 1.5, 4.0)	5.70 (*dd*, 1.5, 4.0)	
	4	6.19 (*d*, 4.0)	6.26 (*d*, 4.0)	
OAc		1.88, 1.93 2.20, 2.24, 2.26, 2.28 (each *s*), 2.27 (2×OAc)	1.54, 1.67, 1.69, 1.70, 1.86, 2.08 (each *s*) 1.83 (2×OAc)	1.76, 1.80, 1.84, 1.86 (each *s*)

OAc), 2.25 (s, 1×OAc).

(S)-7,8,4,4′-*Tetraacetoxyflavan* (**6**). R_f 0.37 in B:A, 9:1. Non-crystalline, 120 mg. MS: *m/z* 442 (16%) $[M]^+$. ^1H NMR (C_6D_6): Table 1.

(S)-7,8,4′-*Trihydroxyflavan*-(4β→6)-*epioritin*-4-*ol* (*octyl acetate*) (**4**). R_f 0.23 in B:A, 9:1 ×2. Non-crystalline 8.0 mg. EI-MS: $[M]^+$ *m/z* 882.2364, $C_{46}H_{42}O_{18}$ requires 882.2366. ^1H NMR: Table 1.

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