Novel Base-catalysed Rearrangements of (−)-Fisetinidol-(+)-catechin Profisetinidins with 2,3-*trans*-3,4-*cis*-Flavan-3-ol Constituent Units

Jan P. Steynberg, Johann F. W. Burger, Desmond A. Young, Edward V. Brandt, Jacobus A. Steenkamp, and Daneel Ferreira*

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

The (−)-fisetinidol-(4β, 8)-(+)-catechin-*O*-methyl ether (**1**) is subject to facile *C*-ring isomerizations in $NaHCO_3$–Na_2CO_3 buffer solution to form a range of novel 8,9-*cis*-9,10-*trans*- and 8,9-*trans*-9,10-*trans*-3,4,9,10-tetrahydro-2*H*,8*H*-pyrano-[2,3-*h*]chromenes (**2**)—(**5**); analogues (**4**) and (**5**) are representative of an unique class of phlobatannins in which the resorcinol *A*- and pyrocatechol *B*-rings are interchanged.

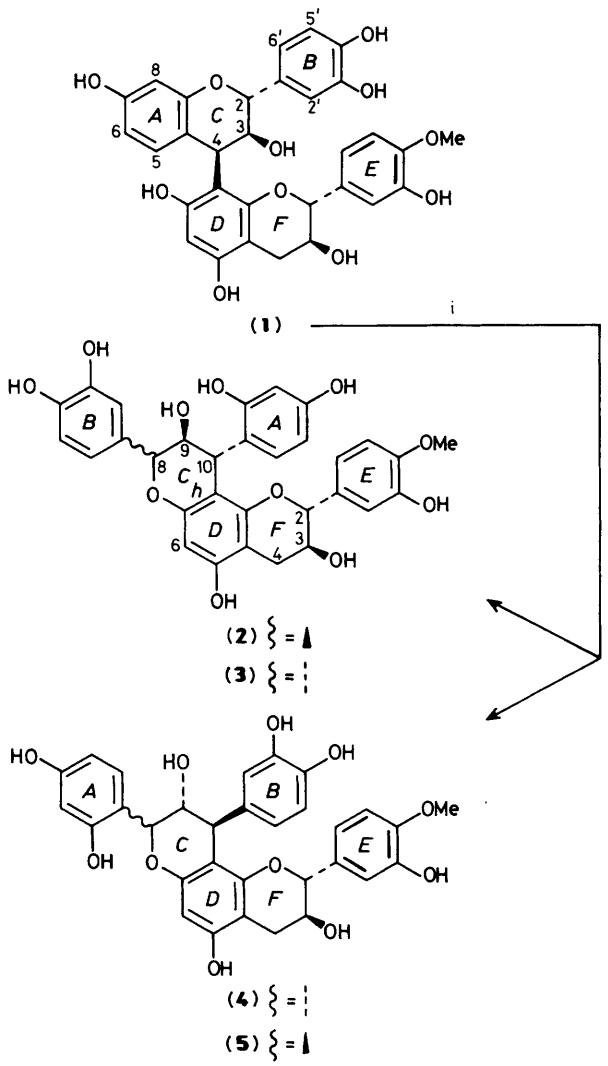
Since many of the industrial applications of condensed tannins involve their dissolution and/or reaction at alkaline pH,[1,2] base-catalysed transformations of this class of natural products have recently received considerable attention.[3—6] Our programme of synthesis of naturally occurring phlobatannins *via* *C*-ring isomerization of oligomeric profisetinidins under mild basic conditions,[4] has revealed the susceptibility of 2,3-*trans*-3,4-*cis*-(−)-fisetinidol units to a novel base-catalysed rearrangement to functionalized tetrahydropyranochromenes in which the resorcinol *A*- and pyrocatechol *B*-rings are interchanged relative to their positions in the more common analogues.

Treatment of the model compound (−)-fisetinidol-(4β, 8)-(+)-catechin-*O*-methyl ether (**1**)† with 0.025 M $NaHCO_3$–0.025 M Na_2CO_3 buffer (pH 10) for 3 h at 50 °C gave complete conversion into four products of stereoselective ring isomerization (**2**)—(**5**) (Scheme 1). These comprise the 8,9-*cis*-9,10-*trans*- and 8,9-*trans*-9,10-*trans*-tetrahydro-2*H*,8*H*-pyrano[2,3-*h*]chromenes (**2**) and (**3**), as well as an isomeric pair (**4**) and (**5**) with interchanged resorcinol *A*- and pyrocatechol *B*-rings.

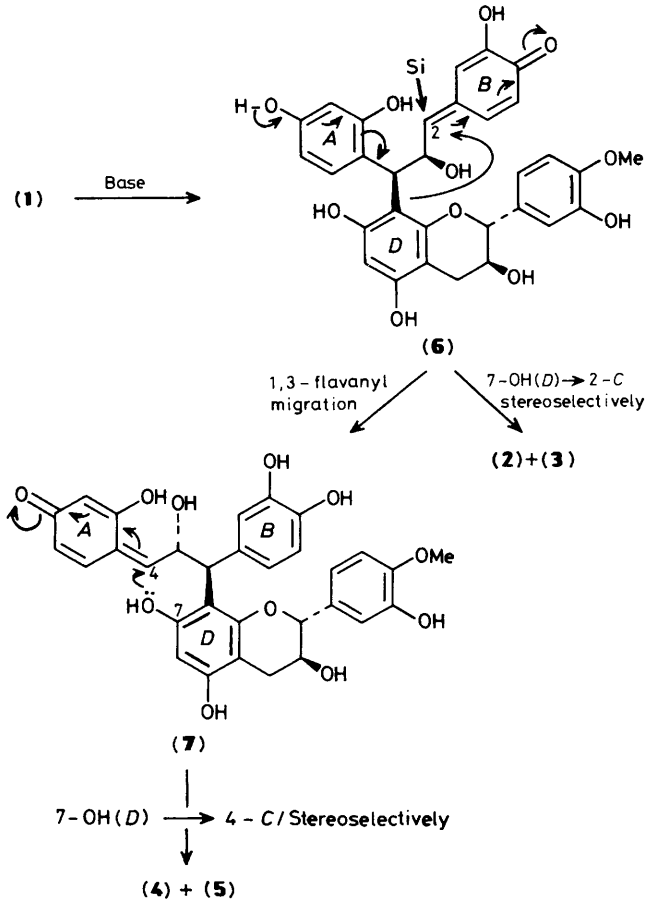
The structures of products (**2**)—(**5**) were established by application of ^{1}H n.m.r. nuclear Overhauser effect (n.O.e.) difference spectroscopy (300 MHz) to their heptamethyl ether diacetates. In each instance n.O.e. associations of 2-OMe (*A*) with 3-H (*A*), and of 4-OMe (*A*) with both 3-H (*A*) and 5-H (*A*) indicated 'liberated' resorcinol moieties characteristic of the structures involved.[4,7] ^{1}H N.m.r. coupling constants of heterocyclic proton resonances [$J_{8,9}$ *ca.* 1.0, $J_{9,10}$ 2.0 Hz for derivatives of (**2**) and (**4**); $J_{8,9}$ 7.0, $J_{9,10}$ 6.0 Hz for derivatives of (**3**) and (**5**)] are consistent with *cis-trans*- and all-*trans* configurations of the respective *C*-rings.[8] Furthermore, the 8,9-*cis*-9,10-*trans* analogues 8-H (*C*) exhibited prominent n.O.e. associations with *ortho*-proton(s) of the aryl ring at 10-C [6-H (*A*) for (**2**) and 2-/6-H (*B*) for (**4**)] indicating a preferred sofa conformation for this heterocycle with near-axial (α) C-10 phenyl substituents. 8- and 10-H (*C*) were correlated with the resorcinol and pyrocatechol rings respectively in derivatives of both (**4**) and (**5**) by spin decoupling experiments using these protons as reference signals.

Subject to the correct allocation of 8- and 10-H (*C*) resonances the above features indicate an interchange of resorcinol *A*- and pyrocatechol *B*-rings in (**4**) and (**5**) when compared to their positions in analogues (**2**) and (**3**). The chemical shifts of 8- and 10-H (*C*) [δ 5.31, 5.36; δ 4.30, 4.14 for derivatives of (**4**) and (**5**) respectively], and thus unambiguous proof for such an *A*/*B*-ring interchange, were confirmed by 2D-heteronuclear correlation of these protons with respectively 8- and 10-C [*e.g.*, δ 67.9, 41.1 for (**4**)]. Notable in the spectra of the groups (**2**), (**3**) and (**4**), (**5**) is the conspicuous deshielding of 6-H (A) [Δδ −0.74, −0.80 in derivatives of (**4**)

† Protected at 4-OH (*E*) to prevent undesired reactions associated with an *E*-ring quinone-methide (*cf.* ref. 4) and available *via* acid-catalyzed condensation of (+)-mollisacacidin [(2*R*, 3*S*, 4*R*)-2,3-trans-3,4-*trans*-3′, 4′, 7-trihydroxyflavan-3,4-diol] and 4′-*O*-methyl-(+)-catechin (*cf.* ref. 11).



Scheme 1. Base-catalysed formation of the series of phlobatannins form the (−)-fisetinidol-(4β,8)-(+)-catechin (**1**). *Reagents and conditions*: i, $NaHCO_3$–Na_2CO_3, 50 °C, 3 h, N_2.



Scheme 2. Proposed route to the formation of *A*/*B*-ring interchanged phlobatannins (**4**) and (**5**).

and (**5**) respectively] in the latter pair relative to the chemical shifts of this proton in the normal *cis-trans*- and all-*trans*-isomers (**2**) and (**3**). Such feature is apparently a characteristic of phlobatannins belonging to the classes (**4**) and (**5**).

In order to establish the sequence of formation of phlobatannins (**2**)—(**5**) from biflavanoid (**1**), aliquots were taken at regular intervals and fully analysed on a Büchi medium pressure liquid chromatography (m.p.l.c.) system, using Sephadex LH-20/ethanol at 0.7—0.8 bar pressure. These results indicated that the (−)-fisetinidol-(+)-catechin (**1**) serves as direct precursor to both groups of phlobatannins (**2**), (**3**), and (**4**), (**5**). Formation of the former pair may be rationalized by stereoselective recyclization involving 7-OH (*D*) and both *Re*- and *Si*-faces in quinone-methide (**6**). Treatment of the thermodynamically less stable 8,9-*cis*-9,10-*trans*-tetrahydropyrano[2,3-*h*]chromene (**2**) under conditions similar to those for its formation did not give equilibration with the all-*trans* isomer (**3**), thus proving their simultaneous genesis from the (4β,8)-biflavanoid (**1**). The observed stereoselectivity contrasts with stereospecific transformation of the 2,3-*trans*-3,4-*trans*-flavan-3-ol unit in (−)-fisetinidol-(4α, 8)-(+)-catechin under similar conditions.[4]

The novel conversion (**1**) → (**4**) + (**5**) is presumably explicable in terms of initial migration of the 'lower' flavanyl moiety to the *Re*-face at 2-C in quinone-methide (**6**) (Scheme 2). Stereoselective pyran recyclization of (**7**) *via* 7-OH (*D*) generates the tetrahydropyrano[2,3-*h*]chromenes (**4**) and (**5**), enantiomerically related to (**2**) and (**3**) with respect to their *C*-rings.

The heptamethyl ether diacetates of the 'normal' analogues (**2**) and (**3**) exhibit intense negative Cotton effects in the 220—240 nm region of their c.d. spectra. These indicate a 10-C aryl substituent below the plane of the *C*/*D*-ring system[9] and thus *R*-absolute configuration at this chiral centre. When taken in conjunction with ^1H n.m.r. coupling constants the c.d. data define the absolute configurations as 2*R*, 3*S*:8*S*, 9*S*, 10*R* for (**2**) and 2*R*, 3*S*:8*R*, 9*S*, 10*R* for (**3**). The same derivatives of the ring interchanged analogues (**4**) and (**5**) showed similar c.d. characteristics than those above thus presumably reflecting similar 9*S*, 10*R* absolute configuration for ring *C*. Such a contradiction may result from significant contributions of *A*-conformers[10] (*F*-ring) reversing the sign of the low-wavelength Cotton effect for 10β-aryl groups. We thus favour the absolute configurations depicted in formulations (**4**) and (**5**) *i.e.* 8*R*, 9*R*, 10*S* (**4**) and 8*S*, 9*R*, 10*S* for (**5**).

Although the mechanism in Scheme 2 is speculative, we have evidence of similar transformations in a variety of profisetinidins and prorobinetinidins with 2,3-*trans*-3,4-*cis*-flavan-3-ol 'upper' units thus demonstrating general applicab-

ility of such a conversion. Furthermore, three of the isomers (**3**), (**4**), and (**5**) have been encountered as 4-O(*E*) demethyl ethers in two species of the Caesalpiniodeae [(**4**) and (**5**) in *Baikiaea plurijuga* and (**3**) from *Guibourtia coleosperma*] presumably indicating mechanisms in Nature similar to those proposed here.

Support by the Foundation for Research Development, C.S.I.R., Pretoria, the Sentrale Navorsingsfonds of this University, and the Marketing Committee, Wattle Bark Industry of South Africa, Pietermaritzburg, is acknowledged.

Received, 18th February 1988; Com 8/00613J

References

1 A. Pizzi, 'Wood Adhesives: Chemistry and Technology,' Marcel Dekker, New York, 1983.
2 R. E. Kreibich and R. W. Hemingway, 'Proceedings of IUFRONTRI Symposium on Wood Adhesives,' 1985, **17**, 1.
3 R. W. Hemingway and L. Y. Foo, *J. Chem. Soc., Chem. Commun.*, 1983, 1035.
4 J. P. Steynberg, D. A. Young, J. F. W. Burger, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1986, 1013.
5 P. E. Laks and R. W. Hemingway, *J. Chem. Soc., Perkin Trans. 1*, 1987, 465, and refs. cited therein.
6 P. E. Laks, R. W. Hemingway, and A. H. Conner, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1875, and refs. cited therein.
7 J. A. Steenkamp, J. P. Steynberg, E. V. Brandt, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1985, 1678.
8 J. W. Clark-Lewis, M. I. Baig, and M. J. Thompson, *Aust. J. Chem.*, 1969, **22**, 2645.
9 J. H. van der Westhuizen, D. Ferreira, and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1220.
10 L. J. Porter, R. Y. Wong, M. Benson, and B. G. Chan, *J. Chem. Res. (M)*, 1986, 830.
11 G. J. Sweeny and G. A. Iacobucci, *J. Org. Chem.*, 1979, **44**, 2298.