Tetrahedron Letters,Vol.24,No.42,pp 4627-4630,1983
Printed in Great Britain

0040-4039/83 $3.00 + .00

ATROPISOMERISM IN A NEW CLASS OF CONDENSED TANNINS BASED ON BIPHENYL AND *O*-TERPHENYL

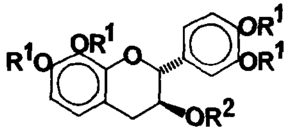
Esmé Jacobs, Daneel Ferreira and David G. Roux
Department of Chemistry, University of the Orange Free State,
P.O. Box 339, Bloemfontein, 9300 South Africa

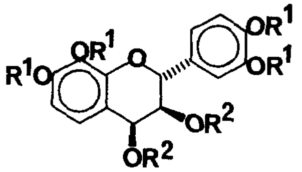
Summary——2,3-*trans*-3',4',7,8-Tetrahydroxyflavan-3-ol, the predominant phenolic component of the heartwood of *Prosopis glandulosa*, serves as precursor for a variety of complex metabolic analogues, including the associated [5,5]- and [5,6]-linked diphenyl type biflavanoids and [5,5:5,6]-*o*-terphenyl triflavanoids. These polyphenyl oligomers provide the first examples of stable rotational isomers and constitute a new class of condensed tannins.

The dark appearance of the heartwood of *Prosopis glandulosa* (mesquite) may be attributed to the presence of a variety of flavanoid analogues based on the 3',4',7,8-tetrahydroxy phenolic substitution pattern, the novel (2*R*,3*S*)-2,3-*trans*-flavan-3-ol[1] (1) predominating. This compound, as well as its (2*R*,3*S*,4*S*)-2,3-*trans*-3,4-*cis*-flavan-3,4-diol analogue (3) present in trace amounts, serve as putative precursors for a variety of polyflavanoid oligomers (e.g. 5, 7, 9 and 11); the last three polyphenol types presumably formed by repetitive condensation *via* free radical mechanisms.

Representative of 'conventional' biflavanoids is a [4,6]-linked 2,3-*trans*-3,4-*trans*:2',3'-*trans* unit (5) which presumably results from electrophilic attack by the 4-carbenium ion generated from the flavan-3,4-diol (3) on the 6-position of the flavan-3-ol (1) (*cf*. ref.[2]). The compound was characterised as its octamethyl ether diacetate (6) [R_F 0.52 in benzene:acetone (8:2 v/v); *m/z* 774 (M^+, 10.6%); $J_{2,3} = J_{3,4} = 9.8$, $J_{2',3'}$ 7.5 Hz; c.d. strongly negative Cotton effect at 200-240 nm (*cf*. ref.[3]); $\lambda_{max.}$ 223, 276 nm, and minimum at 255 nm] with n.m.r. shifts of heterocyclic protons (AMX and ABXY systems for 'upper' and 'lower' units) in agreement with those of known analogues.[2] The bonding position at 6-C was defined by spin-decoupling of 4-CH_2(F) which leads to selective sharpening of 5-H(D) singlet resonance, δ 6.19 ($CDCl_3$).

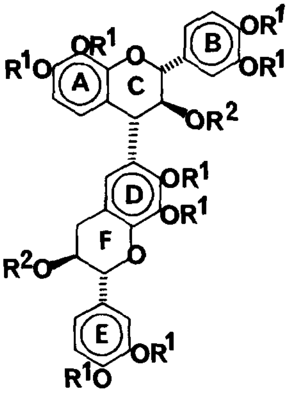
By contrast the isomeric [5,6]-biflavanoid (7), based on a biphenyl linkage, was defined by ^1H n.m.r. spectroscopy in $CDCl_3$ solution of the corresponding derivative (8) [R_F 0.16 in benzene:acetone (8:2 v/v); *m/z* 774 (M^+, 81%)], through the presence of two heterocyclic ABXY systems [2-H, 5.11 and 5.15; 3-H, 5.22 and 5.34; 4-CH_2, 2.38(m, 2 x H); and 2.81(*ax*), 3.08 (*eq*)], and two high-field aromatic singlets, one significantly broadened (δ 6.53) and the other sharp (6.47).[4] Irradiation of the lower field methylene resonances led to selective sharpening of the forementioned broadened aromatic singlet (δ 6.53), thus defining these signals as due to 5-H(D) and 6-H(A) respectively, and hence the interflavanoid bond as [5,6]. The presence of a biphenyl moiety was supported by mass spectrometry with fragment ions *m/z* 331(45%) and 330 (38), representing the A- and D-ring biphenyl residue after two RDA-fragmentations with and without H-transfer, the former process being exceptionally prominent in the tetramethyl ether acetate (2) of the parent compound [*m/z* 167(72%), 166(8.1)]; and by its ultra-violet absorption

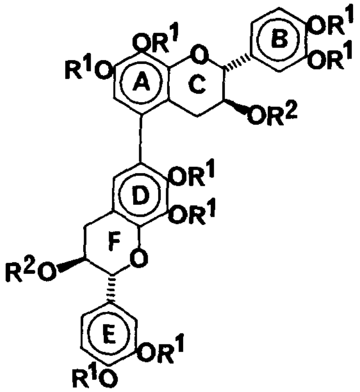




(1) $R^1=R^2=H$ (3)

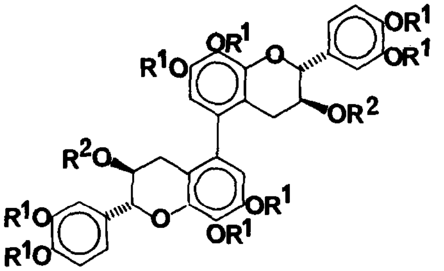
(2) $R^1=Me$, $R^2=Ac$ (4)

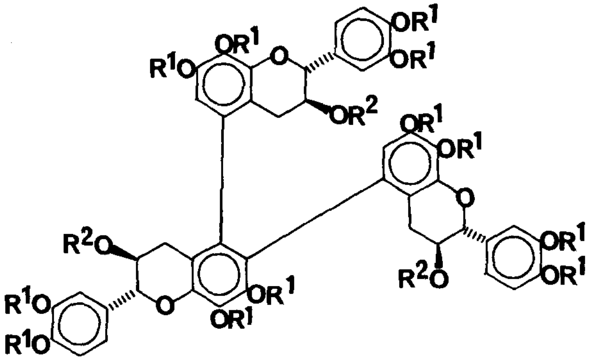




(5) $R^1=R^2=H$ (7)

(6) $R^1=Me$, $R^2=Ac$ (8)





(9) $R^1=R^2=H$ (11)

(10) $R^1=Me$, $R^2=Ac$ (12)

spectrum ($\lambda_{max.}$ 230, 275 nm) which exhibits a shoulder at 255 nm indicative of a degree of conjugation,[5,6] thus contrasting with the absorption minimum shown by the [4,6] isomer (*cf.* above).

Similar spectral characteristics were observed for the corresponding derivatives (10) [two ABXY systems each; *m/z* 774 (M^+, 100, 100%), 331(74, 67), 330(74, 66); $\lambda_{max.}$ 227, ~254(sh.), 273 nm each] of a pair of rotational isomers of the [5,5]-biflavanoid (9). The free phenols were readily resolved by countercurrent distribution [upper phase plates 5 and 6 and lower phase plates 1-3 in a 20 plate H_2O:butan-2-ol:hexane system (5:4:1 by vol.)], and purified on Sephadex LH20 columns [t.l.c. of the methyl ether acetate derivatives, R_F 0.32 and 0.36 resp. in hexane: acetone:EtOAc (12:5:3 by vol.)]. The octamethyl ether diacetate derivatives of the atropisomers were distinguishable from that of the [5,6]-isomer (*cf.* above) by the relative sharpness of both high-field aromatic ^1H resonances of each (singlets, δ 6.19, 6.41 and 6.21, 6.48 resp.) neither of which exhibit sharpening during irradiation of their respective methylene resonances. This establishes their [5,5]-linkages when taken in conjunction with the above spectral evidence.

Extension of the same condensation modes to triflavanoids was evident from the isolation of three out of a possible four atropisomeric dodecamethyl ether acetates (12) [R_F 0.60, 0.56, 0.50 in dichloromethane:acetone (96:4 v/v); *m/z* 1160 (M^+, 49, 13.7, 47%)] of a [5,5:5,6]-*o*-terphenyl analogue (11) with presumed origins in either of the biflavanoids (7) or (9) or in both. These *o*-terphenyl derivatives exhibit the same spectral characteristics as their biphenyl analogues {$\lambda_{max.}$ 222, 253(sh.), 274 nm [*cf.* Dale[6] 232, 252(sh.) nm for unsubstituted *o*-terphenyl]; two sharp singlet ^1H resonances each in the high-field aromatic region (δ 6.42, 6.52; 6.53, 6.56 and 6.53, 6.56 resp.), none of which have long-range coupling with their respective 4-CH_2 resonances} and may be differentiated by the grouping of shifts of their acetoxy proton resonances (δ 1.83, 1.91, 1.96; 1.83, 1.86, 1.88 and 1.60, 1.88, 1.91 resp.). Evidence of a terphenyl structure is supported by the relative prominence of the *m/z* 497 (70% for the R_F 0.60 derivative) fragment ion representative of a triphenyl residue after loss through three mass spectral RDA-processes, each with H-transfer; and by the presence of at least two very strongly shielded methoxy resonances in the region δ 2.92-3.40 in their respective ^1H n.m.r. spectra, indicative of close overlap with and, therefore, the juxtaposition of three aromatic ring systems.

Application of the solvent shift technique of Pelter *et al.*[7] to the methyl ether acetates (8, 10 and 12) of both bi- and triflavanoids gave results which were consistent with the proposed interflavanoid linkages.

The observed atropisomerism for the methyl ether acetate of the [5,5]-biflavanoid (10) is attributable to mutual interaction of the 'rigid' 4-CH_2 functions and of these with the 6-protons, the latter effect being possibly accentuated by the 'buttressing effect' of 7-methoxyl substituents, resulting in retardation of racemization. For the [5,5:5,6]-*o*-terphenyl tannins (11) and derivatives the enthalpy of activation should be accentuated (although synchronized rotation for unsubstituted *o*-terphenyl has been suggested[8]) as indicated by their readily-resolved dodecamethyl ethers [R_F 0.42, 0.50 and 0.27 resp. in dichloromethane:acetone (8:2 v/v)] and considerable albeit incomplete resolution of the free phenols on two-way paper chromatograms. Furthermore, the ^1H n.m.r. spectra of both biphenyl and *o*-terphenyl derivatives (8, 10 and 12) are sharply defined at ambient temperatures, a phenomenon which is symptomatic of 'static' structures for compounds of this class (*cf.* refs.[2,9]) and thus in line with the observed atropisomerism.

The methyl ether acetates of both [5,5]-rotamers (10) (R_F 0.32, 0.36) and also that of the chromophorically related [5,6]-isomer (8) all exhibit positive high-intensity Cotton effects {[θ] x 10^4 2.2, 2.3 and 3.3, 3.9(doublet)} at 225-240 nm in their respective c.d. spectra; absorptions which appear to be independent of atropisomerism or substitution (mode of linkage) and, therefore, mainly diagnostic of absolute configurations at 2-C, although falling within the conjugation band Cotton effect attributed to simple biphenyls.[10] Furthermore, absorptions by each of the isomers in the 210-220 nm region show considerably more intense positive and negative Cotton effects {$[\theta] \times 10^4$ 5.1, -4.5 and -2.5 resp.} which are presumed to be diagnostic of configurational differences about their interflavanoid (biphenyl) bonds, thus defining the R_F 0.36 [5,5]- and [5,6]-isomers as members of the same, and R_F 0.32 [5,5]-isomer of the opposite series.

In this connection the [5,6]-isomer (7) on methylation with excess diazomethane consistently also gives [*cf.* (8)] a heptamethyl ether indicating that the phenolic hydroxyl function *ortho* to the diphenyl link is strongly hydrogen-bonded (*cf.* ref.[11]). The heptamethyl ether triacetate obtained on acetylation [R_F 0.11 in benzene:acetone (8:2 v/v); *m/z* 802(31%); δ 6.56 (broad s, 5-H), 6.41(sharp s, 6-H), 1.96, 1.91(x2) (3 x OAc, including a shielded phenolic acetoxy)] gives high-intensity positive Cotton effects at both 232 and 225 nm {$[\theta] \times 10^4$ 3.7 and 5.25 resp.}. The sign of the latter is taken as indicative of the 'missing' rotamer of the [5,6]-isomer on the basis of the above analysis.

While sp^2-sp^2 C-C bonds between natural flavone and flavanone units are well known,[12] the above to our knowledge represents the first instance of extension of this type of condensation to oligomeric flavans.

ACKNOWLEDGEMENTS——This work is supported by the Sentrale Navorsingsfonds of this University, and by the Research Award Division, C.S.I.R., Pretoria. Mass spectra were recorded by Dr. J.M. Steyn, Department of Pharmacology of this University, and 500 MHz ^{1}H n.m.r. spectra by Mr. I. Antonowitz, National Chemical Research Laboratory, C.S.I.R., Pretoria.

REFERENCES AND NOTES

1. *cf.* Y. Miyauchi, T. Yoshimoto and K. Minami, *Mokuzai Gakkaishi*, 1976, 22, 47.
2. J.J. Botha, D.A. Young, D. Ferreira and D.G. Roux, *J.Chem.Soc., Perkin Trans.* 1, 1981, 1213.
3. J.J. Botha, D. Ferreira and D.G. Roux, *J.Chem.Soc., Chem. Commun.*, 1978, 698.
4. The AB-system (doublets; 5-H, δ 6.72; 6-H, δ 6.53; $J_{5,6}$ 8.5 Hz) of the parent flavan-3-ol methyl ether acetate (2) exhibits relative broadening only of the 5-proton due to benzylic coupling with the 4-CH_2 function.
5. E.L. Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York (1962), p. 177.
6. J. Dale, *Acta Chem. Scand.*, 1957, 11, 650; D. Buza and W. Polaczkowa, *Tetrahedron*, 1965, 21, 3409.
7. M. Ilyas, J.N. Usmani, S.P. Bhatnagar, M. Ilyas, W. Rahman and A. Pelter, *Tetrahedron Letters*, 1968, 5515; R.G. Wilson, J.H. Bowie and D.H. Williams, *Tetrahedron*, 1968, 24, 1407.
8. J. Böhm, *Roczniki Chem.*, 1961, 35, 821.
9. J.J. Botha, P.M. Viviers, D.A. Young, I.C. du Preez, D. Ferreira, D.G. Roux and W.E. Hull, *J.Chem.Soc., Perkin Trans.* 1, 1982, 527.
10. K. Mislow, E. Brunnenberg, R. Records, K. Wellman and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, 85, 1342.
11. G. Aulin-Erdtman and R. Sandén, *Acta Chem. Scand.*, 1963, 17, 1991.
12. H.D. Locksley, *Fortschr. Chem. Org. Naturst.*, 1973, 30, 207.

(Received in UK 8 August 1983)