Condensed Tannins: Condensation Mode and Sequence During Formation of Synthetic and Natural Triflavonoids

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Summary The first synthesis of 4,8:4,6-linked all-*trans*- and 2,3-*trans*-3,4-*trans*: 2′,3′-*trans*: 2″,3″-*trans*-3″,4″-*cis*-bi[(−)-fisetinidol]-(+)-catechins and recognition of their distribution in nature gives an insight into the mode and sequence of condensations leading to such key triflavonoid intermediates during tannin formation; the synthesis taken in conjunction with c.d. spectra established their absolute configurations.

THE versatility of the direct method of synthesis of condensed tannins[1] by generation of 4-carbocations from flavan-3,4-diols under extremely mild conditions and their substitution on the strongly nucleophilic A-rings of flavan-3-ols (catechin units) to form biflavonoid tannin prototypes of varying absolute configuration, has been confirmed by its application to a range of units of differing stereochemistry and structure.[2] The association of such related compounds in a number of natural sources has been confirmed by their isolation.[2] The study has also been extended to the synthesis of natural triflavonoids and has given results of both structural and biochemical significance.

Coupling of the flavan-3,4-diol, (+)-mollisacacidin (**1**), with the synthetic 4,8-linked all-*trans*-(−)-fisetinidol-(+)-catechin (**2**)[1,3] under the same conditions[1] results in the regiospecific condensation at the vacant 6-position of the 'lower' (+)-catechin unit of the biflavonoid, in preference to the competing 6-position on the 'upper' (−)-fisetinidol unit (see below), to form the novel 4,8:4,6-linked all *trans*-(**3**) and 2,3-*trans*-3,4-*trans*: 2′,3′-*trans*: 2″,3″-*trans*-3″,4″-*cis*-bi-[(−)-fisetinidol]-(+)-catechin (**4**) triflavonoid tannins in almost equal proportion (*ca.* 20% yield). The products were not separable as either free phenols or decamethyl ethers, but their decamethyl ether triacetates were readily resolved by t.l.c. after two developments in benzene–acetone (9:1 v/v), R_F 0·22 and 0·32, respectively. These derivatives, $C_{61}H_{64}O_{19}$, were characterized by elemental analysis, mass spectrometry and 360 MHz ^1H n.m.r. Fourier transform spectrometry at *ca.* 200 °C in Me_2SO.

Under these conditions the n.m.r. spectra are characterized by the presence to high field in aromatic region of two ABC systems attributable to the resorcinol A-ring protons of two (−)-fisetinidol units and the conspicuous absence of the high field singlet which differentiates the residual 6-proton on the A-ring of the 'lower' (+)-catechin unit of the biflavonoid (**2**) starting material (*cf.* ref. 1). Taken in conjunction these indicate introduction of a second (−)-fisetinidol unit at the latter position, and that the synthetic triflavonoid tannins, (**3**) and (**4**), therefore, consist of two (−)-fisetinidol units 4,8- and 4,6-linked to (+)-catechin. The regiospecific condensation at the 6-position of the 'lower' (+)-catechin unit of the biflavonoid (**2**) is unexpected in our view considering the low order of 4,6- (5·5%) compared with 4,8-coupling (44·5%) in the condensation of (+)-mollisacacidin (**1**) with (+)-catechin,[1] and the high yield (46%) of 4,6-linked biflavonoids resulting from similar but regiospecific coupling with (−)-fisetinidol under the same conditions.[2]

The reaction follows the expected[1,4] stereochemical course. Coupling constants evident [360 MHz (*ca.* 200 °C) and 80 MHz (*ca.* 167 °C) spectra] from the low-field heterocyclic protons at τ 4·17 (triplet, $\Sigma|J_S|$ 19·0)† and 4·19 (t, $\Sigma|J_S|$ 19·0) for the methyl ether acetate of (**3**) and at τ

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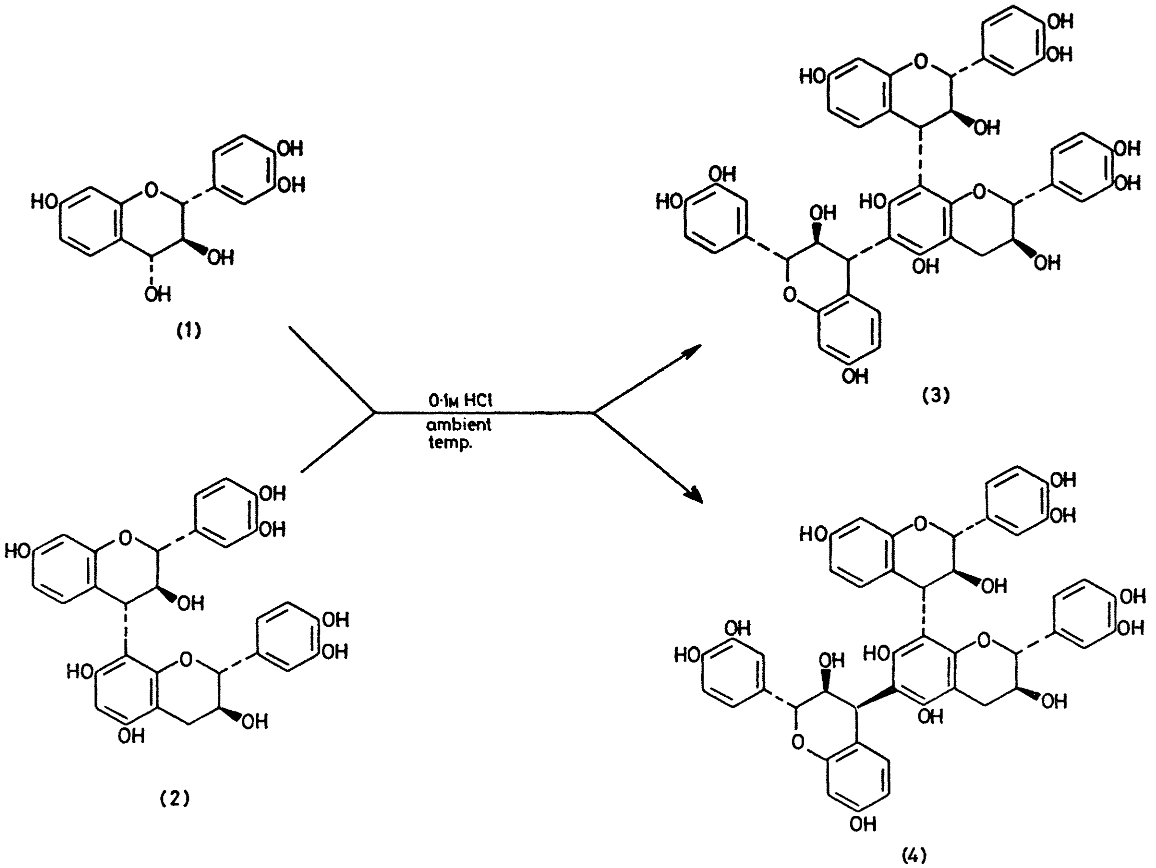
† $J_{2,3} = J_{3,4} = 9·5$ for all triplets where $\Sigma|J_S| = 19·0$.

4·07 (t, $\Sigma|J_s|$ 19·0) and 4·57 (dd, $\Sigma|J_s|$ 14·5, $J_{2,3}$ 8·0, $J_{3,4}$ 6·5) for the same derivative of (**4**) reflect the above relative stereochemistry (*cf.* refs 1, 4), and hence their absolute stereochemistry as 2*R*,3*S*,4*S*-2′*R*,3′*S*-2″*R*,3″*S*,4″*S* and -2″*R*,3″*S*,4″*R*, respectively, from the method of synthesis. These assignments are supported by diagnostic multiple Cotton-effects in the low-wavelength region in the c.d. spectra of (**3**) and (**4**) when compared with that of the biflavonoid starting compound (**2**).[1,4]



(1)

(2)

(3)

(4)

N.m.r. spectra at lower temperatures [80 MHz, 37 °C] indicate the phenomenon of rotational isomerism[5] about the interflavonoid bonds for the methyl ether acetates of both triflavonoids (**3**) and (**4**), with the two rotameric forms (duplication of n.m.r. signals) equally populated in each instance.‡ Barriers to rotation (free energy of activation[6]) in Me_2SO were found by dynamic n.m.r. studies [$\Delta G^{\ddagger}$ 19·3 and 18·3 kcal mol^{-1}, respectively] to be well in excess of that of the biflavonoid (**2**) [$\Delta G^{\ddagger}$ 16·01 kcal mol^{-1}], thus reflecting a significant increase in overcoming the energy barrier to 'fast' rotation about both interflavonoid bonds. At the related tetraflavonoid[7] level the free energy of activation has presumably increased even further to a level [$\Delta G^{\ddagger} \geqslant 27$ kcal mol^{-1}] which permits separation of atropisomers as previously demonstrated.[7]

The identical triflavonoids (**3**) and (**4**), accompanied by the 4,8-linked biflavonoid (**2**) and flavan-3,4-diol (**1**), were isolated in the proportions of 3 : 2 from the heartwood of the mopane tree (*Colophospermum mopane*) some seven years ago[5,8] and the phenomenon of rotational isomerism for the all-*trans* bi- (shown to be 4,8-linked[1]) and triflavonoids§ (**2**) and (**3**) demonstrated at that time.[5] The identity of the natural and synthetic triflavonoids is now confirmed by n.m.r. spectrometry at progressively increasing temperatures (37—167 °C) at 80 MHz, and by comparison of c.d. spectra. Identical structural and stereochemical relationships also exist between the natural mono-, 4,8-linked bi-,[1,3] and 4,8 : 4,6-linked triflavonoids¶ of commercial wattle bark ('Mimosa') extract (*Acacia mearnsii*), and will be the subject of full publication.

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‡ *Added in proof:* Gaussian enhancement of signals in the acetoxy (methyl) region of the 400 MHz spectrum of the corresponding derivative of an all-*trans*-triflavonoid analogue has subsequently shown the existence at 27 °C of the four theoretically possible rotameric forms (in the ratio *ca.* 8 : 4 : 2 : 1) about its two interflavonoid bonds.

§ The points of linkage of these units (**2**) and (**3**) as previously indicated (ref. 5) must now be revised.

¶ Triflavonoids E_2 and C_2 from the bark of *Acacia mearnsii* were kindly supplied by Dr. H. M. Saayman, Leather Industries Research Institute, Grahamstown.

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