Conformational Analysis of Oligomeric Flavanoids. Part 1. 4-Arylflavan-3-ols

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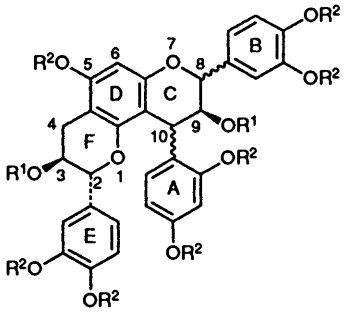
4-(2,4-Dihydroxyphenyl)-5-oxyflavan-3-ols, which incorporate structural features compatible with those of tetrahydropyrano[2,3-*h*]chromenes, are adopted as models for the conformational demeanour of related phlobatannins. The anomalous behaviour, culminating in atypical Cotton effects (CD) and $^3J_{HH}$-coupling constants (^{1}H NMR) for the C-ring of analogues with a 2,4-*cis*-arrangement of the phenyl substituents, is attributed to major contributions by A- as opposed to E-conformers for the pyran heterocycle. This is concluded from the persistent geometries generated respectively by three variants of the MM2 force-field for preferred E- and A-conformers, hence allowing calculation of $^3J_{HH}$-values for these conformations and consequent estimation of E:A-ratios in conjuction with observed $^3J_{HH}$-values. The phenomenon presumably originates from 1,3-allylic strain and concomitant stabilization by π-stacking of the B- and D-rings, and by π-alkyl-interaction between 3-OMe(B) and the π-system of the A-ring.

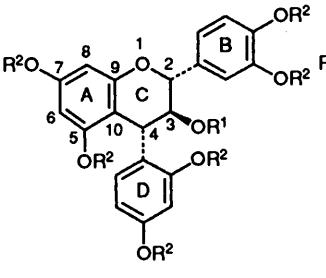
The natural occurrence and synthesis of a novel class of oligoflavanoids based on a tetrahydropyranochromene functionality (phlobatannins) **1** have recently been demonstrated.[1–4] Definition of configuration of the pyran ring (C-ring) of derivatives **2**, however, remains ambiguous, presumably as a result of unconventional conformational behaviour culminating in unexpected Cotton effects (CD) and $^3J_{HH}$-coupling constants for the C-ring. A series of 4-(2,4-dihydroxyphenyl)-5-oxyflavan-3-ols (4-resorcyl-5-oxyflavan-3-ols) **3**, **5**, **7** and **9**,[5–7] which incorporate strategic structural and functional features displayed by the tetrahydropyrano[2,3-*h*]chromenes **1**, have consequently been adopted as models in appraisal of the conformational demeanour of phlobatannin-derivatives of type **2**.

Whereas derivatives of 4-resorcyl-5-oxyflavan-3-ols with a 2,4-*trans*-arrangement of the B- and D-rings,† 2,3-*trans*-3,4-*cis*-**8** and 2,3-*cis*-3,4-*trans*-**10**, display ^{1}H $^3J_{2,3}$ and $^3J_{3,4}$-values expected for the relative stereochemistry of the C-ring, coupling constants for analogues with a 2,4-*cis*-arrangement, all-*trans*- **4** and all-*cis*- **6**, are less diagnostic (Table 1).[5,7,8] The all-*trans*-isomer **4**, for example, exhibits conspicuously small *J*-values ($J_{2,3}$ 6.5 and $J_{3,4}$ 5.5 Hz), characteristic of 5-oxygenated analogues with 4-resorcinol-type substituents,[3,5,7,8] and similar to those observed for derivatives of 5-oxygenated all-*trans*-flavan-3,4-diols.[9] Such behaviour also results in reversal of the Cotton effects in the 230–240 nm region, *i.e.* positive and negative, respectively, *vs.* the expected negative and positive effects predicted by the aromatic quadrant rule[7,10] (assuming half-chair/sofa conformations for the C-ring) (Table 1). These exceptions to the otherwise simple rule have initially been attributed to boat conformations for the C-rings,[7] thereby 'explaining' both the observed ^3J-values and the signs of the Cotton effects.

The high strain-energy associated with a boat conformation,[11] however, compels consideration of significant contributions by an A-conformer for the C-ring. First proposed by Brown,[12] recognized by us and others on several occasions,[3,6,13,14] and formally designated the A-conformer by Porter,[11] this represents a half-chair/sofa conformation for the pyran ring in which the 2-aryl group (B-ring) occupies an axial (**15**–**18**) as opposed to the 'customary' equatorial orientation



1 $R^1 = R^2 = H$
2 $R^1 = Ac, R^2 = Me$



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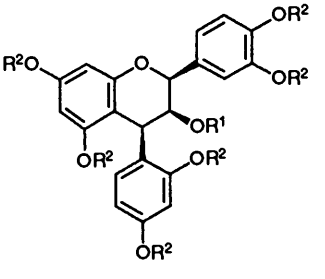
4 $R^1 = Ac, R^2 = Me$



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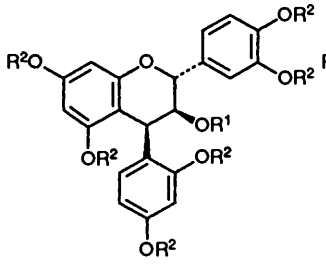
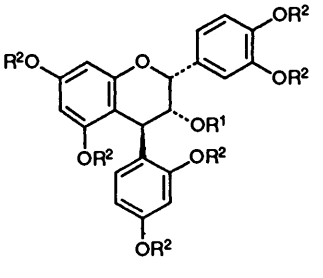
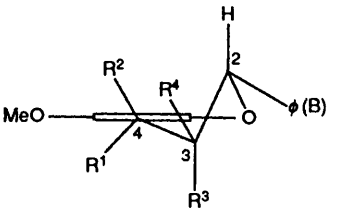


7 $R^1 = R^2 = H$
8 $R^1 = Ac, R^2 = Me$

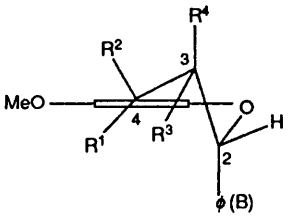


9 $R^1 = R^2 = H$
10 $R^1 = Ac, R^2 = Me$

† Designation of the A- and D-rings is reversed for the 4-arylflavan-3-ols relative to the phlobatannins, *e.g.* compound **1**.



E-Conformers



A-Conformers

	E-Conformers	A-Conformers
2,3-*trans*-3,4-*trans*	**11** $R^1 = \phi(D), R^2 = R^3 = H, R^4 = OAc$	**15** $R^1 = \phi(D), R^2 = R^3 = H, R^4 = OAc$
2,3-*cis*-3,4-*cis*	**12** $R^1 = \phi(D), R^2 = R^4 = H, R^3 = OAc$	**16** $R^1 = \phi(D), R^2 = R^4 = H, R^3 = OAc$
2,3-*trans*-3,4-*cis*	**13** $R^1 = R^3 = H, R^2 = \phi(D), R^4 = OAc$	**17** $R^1 = R^3 = H, R^2 = \phi(D), R^4 = OAc$
2,3-*cis*-3,4-*trans*	**14** $R^1 = R^4 = H, R^2 = \phi(D), R^3 = OAc$	**18** $R^1 = R^4 = H, R^2 = \phi(D), R^3 = OAc$

Structures **11**–**18** represent a view along the C(4)–C(10) axis with the plane of the aromatic A-ring in a horizontal orientation and depict the conformation of the C-ring relative to the plane of the A-ring

(E-conformer; **11**–**14**), thus mutating the dihedral angle between the heterocyclic protons and consequently the observed physical data. Knowledge of C-ring conformations and equilibria therefore appear to be a prerequisite for unequivocal assessment of the absolute stereochemistry by means of physical methods. This argument initiated a systematic study of preferred conformations (E and A) of the diastereoisomeric 4-resorcyl-5-oxyflavan-3-ols **4**, **6**, **8** and **10** by molecular mechanics (MM), both in appreciation of the exposition of such conformations by different versions of MM, as well as correlation of the results with the observed NMR and CD data.

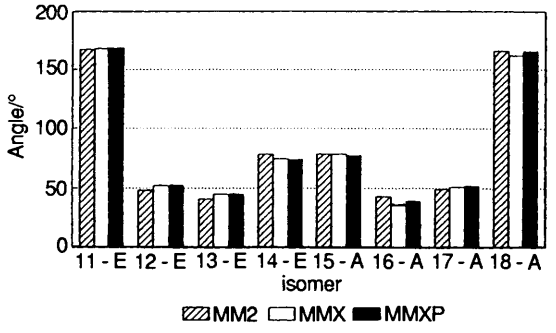


Fig. 1 H(3)–C(3)–C(4)–H(4) torsion angles, respectively minimized by MM2, MMX and MMXP for the E- (**11**–**14**) and A-conformers (**15**–**18**)

Results and Discussion

Three variants of the MM2 force-field,[15] MM2[16] and MMX[17] without pi-VESCF routines, and MMXP which includes pi-VESCF routines,[18] were respectively exploited in assessment of the ability to predict preferred low-energy conformational geometries for these 4-arylflavan-3-ol structures. The geometries accordingly obtained from the various methods for specific conformers disclose a remarkable correspondence which is manifested by the equity of the H(3)–C(3)–C(4)–H(4) torsion angles (Fig. 1) and clearly reflect the consistency of the results.

Although the H(2)–C(2)–C(3)–H(3) torsion angles displayed similar uniformity to those of H(3)–C(3)–C(4)–H(4), the latter were preferred as conformational pointers on the rationale of their greater sensitivity towards conformational changes of the pyran ring.[19] H(3)–C(3)–C(4)–H(4) torsion angles (Table 1) therefore allow the use of ^1H NMR $^3J_{3,4}$ (C-ring) data, *via* the Karplus equation, as a conformational probe both in the discrimination between E- and A-conformers, as well as the observation of C(2)-sofa ↔ half-chair ↔ C(3)-sofa preferences[19] for the pyran ring.

^1H $^3J_{3,4}$-values expected from these torsion angles were calculated by a refinement[20] of the Karplus equation,[21,22] which includes the complex electronegativity effects of both α- and β-substituents on $^3J_{HH}$-values [see Experimental section, eqns. (1)–(3)]. Two parameter sets[20] deduced, respectively, for a generalized approach and for four non-hydrogen substituents, both with β-effect, were applied with very little difference between the ensuing $^3J_{3,4}$-values and consequent trend of conformational equilibria (Table 1). Assumption that E- and A-conformations adopted in solution are similar to those predicted by MM-calculations, and $^3J_{3,4}$ to be a measure thereof, allows estimation of the E:A-conformer ratios for the different isomers **4**, **6**, **8** and **10** by way of eqn. (4). This depends on $^3J_{3,4}$-observed to be representative of the biased equilibrium (on the NMR time-scale) between E- and A-conformers in solution, and yields the E:A ratios summarized in the Table.

The results conspicuously favour pronounced contributions by A-conformers **15** and **16** for isomers with a 2,4-*cis*-relative configuration (all-*trans*- **4** and all-*cis*-isomers **6**), as opposed to isomers with a 2,4-*trans*-configuration (2,3-*trans*-3,4-*cis*- **8** and 2,3-*cis*-3,4-*trans*-isomers **10**) for which the phenomenon is less profound. Such a preference is presumably the result of several conducive factors including major contributions by 1,3-allylic strain (A-strain)[23] between 5-OMe(A) and the 4-resorcyl group (the D-ring) in the E-conformers **11** and **12**.

A half-chair conformation for the C-ring of all E-conformers **11**–**14** signifies quasi-equatorial, 4α- or quasi-axial, 4β-substituents for the C-ring relative to the plane of the aromatic A-ring, accommodating the 5-OMe. 2,4-*cis*-Isomers, with 4α-resorcyl units in a quasi-equatorial orientation (**11** and **12**) will therefore expectedly experience greater A-strain than their 2,4-*trans* counterparts, with the 4β-resorcyl moiety in a quasi-axial position (**13** and **14**).

Fig. 2 represents a schematic synopsis of the geometries minimized by MMXP for E-conformers of the isomeric 4-resorcyl-5-oxyflavan-3-ols **4**, **6**, **8** and **10**. These are defined by the out-of-plane distance (Å), respectively, of C-(2) and C(3) above (+) or below (−) the mean plane of the aromatic A-ring. The effect of A-strain on the 2,4-*cis* E-conformers **11** and **12** is reflected in a tendency of the pyran ring in these isomers towards a C(2)-sofa, hence decreasing both the C(3)–C(4)–C(10)–C(9) torsion angle and the out-of-plane distance of C(3) (see Fig. 2). The latter represents an effective increase in the torsion angle between 5-OMe(A) and the 4-resorcyl group and therefore alleviation of the A-strain. The effect is, as expected, absent for the 2,4-*trans* E-conformers **13** and **14**, which in fact display an increased out-of-plane distance for C(3), culminating in a tendency toward a C(3)-sofa for the C-ring (see Fig. 2). These findings are affirmed by the absence of irregularities regarding ^1H NMR and CD data among the 5-deoxy analogues,[7] indicative of the predominance of E-conformers and the absence of A-strain for both their 2,4-*trans*- and 2,4-*cis*-isomers.

Table 1 Observed and calculated physical data for 4-resorcyl-5-oxyflavan-3-ols

Isomer	CD 10^4 $[\theta]$[a]	$J_{2,3}$/Hz Observed[a]	$J_{3,4}$/Hz Observed[a]	Conformer	(φ/°) H(2)–C(2)–C(3)–H(3)	(φ/°) H(3)–C(3)–C(4)–H(4)	$J_{3,4}$/Hz Calc.[b]	$J_{3,4}$/Hz Calc.[c]	Mol. fraction[b]	Mol. fraction[c]	MMXP Energy (E)[d]	ΔE
2,3-*cis*-3,4-*cis*	239/−2.14	1.20	4.75	A	52.66	38.77	6.97	6.61	45	51	52.32	3.56
	266/+0.82			E	62.60	51.82	2.95	2.84	55	49	48.76	
	281/−0.19											
2,3-*cis*-3,4-*trans*	231/+0.56	0.90	2.00	A	47.69	166.64	10.06	10.15	4	6	50.60	0.80
	241/−2.34			E	63.45	74.78	1.69	1.51	96	94	49.80	
	262/−2.84											
2,3-*trans*-3,4-*cis*	235/+11.55	10.00	5.80	A	62.28	52.01	2.92	2.81	7	0	50.20	0.90
	260/−3.78			E	176.51	44.99	6.01	5.67	93	100	49.30	
	278/+3.95											
2,3-*trans*-3,4-*trans*	240/−54.64	6.50	5.50	A	63.79	78.16	1.36	1.21	54	53	50.54	2.43
	265/+13.11			E	178.66	169.06	10.31	10.39	46	47	48.11	
	284/+21.86											

[a] Average observed for E ↔ A. [b] Calculated *via* generalized constants (P_1–P_7) for eqns. (2) and (3). [c] Calculated *via* four-substituent constants (P_1–P_7) for eqns. (2) and (3). [d] kcal/mol^{-1} (1 cal = 4.184 J).

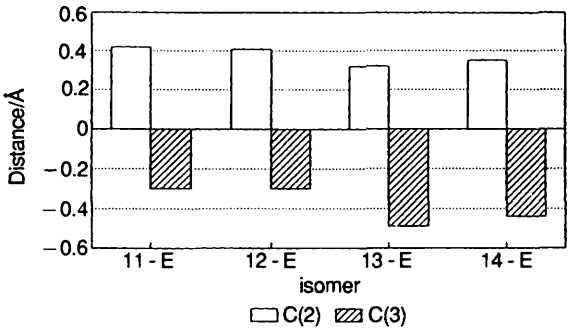


Fig. 2 Out-of-plane distances of C(2)/C(3) of the C-ring, minimized by MMXP for E-conformers **11**–**14**

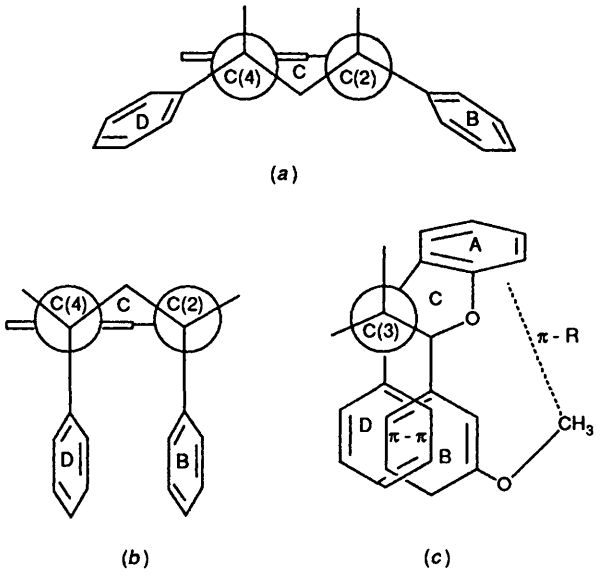
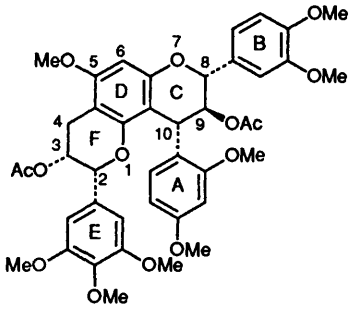


Fig. 3 Newman projections of the 2,4-*cis*-4-resorcyl-5-oxyflavan-4-ols, illustrating (*a*) an E-conformer viewed along the C(2)–O(1)/C(4)–C(10) bonds with the A-ring depicted horizontally; (*b*) the analogous A-conformer; and (*c*) the A-conformer viewed along the C-(3)–C(4) bond, showing the offset face-to-face arrangement of the B- and D-ring and the π–π and π–alkyl interactions. Substituents have been omitted for clarity.

Maximum relief from A-strain, however, is achieved for the 2,4-*cis*-isomers by inversion of the pyran ring to an A-conformer (half-chair), hence locating the 4α-resorcyl moiety in a quasi-axial orientation relative to the A-ring (structures **15** and **16**), similar to that experienced by the 4β-substituents in the E-conformers of the 2,4-*trans*-isomers **13** and **14**. By contrast, A-conformers for the 2,4-*trans*-isomers **17** and **18** possess a 4β-resorcyl group in a quasi-equatorial orientation, resulting in greater A-strain and less stability.

While 1,3-diaxial arrangements are commonly avoided on energetic grounds in terms of a classical stereochemical approach, A- [Fig. 3(*b*)] as opposed to E-conformers [Fig. 3(*a*)] for the 2,4-*cis*-isomers appear to be an exception by virtue of the aromaticity and associated geometry of the diaxial 2,4-biphenyl substituents, which are stacked parallel to the O(1)–C(2) bond at an interplanar distance of ~3.5 Å by MMXP [Fig. 3(*b*)]. Even though this geometry is achieved by MMXP, principally *via* van der Waal's and electrostatic interactions, it also conforms with an offset face-to-face arrangement [Fig. 3(*c*)] required for π-stacking (stabilizing π–σ-attraction).[24] This is probably further reinforced by a π-CH-interaction[25] between 3-OMe(B) and the π-system of the A-ring [Fig. 3(*c*)].

The first unambiguous evidence for such conformational behaviour in 2,4-*cis*-4-arylflavan-3-ol-type structures has recently been obtained[26] for phlobatannin **19** (2,3-*trans*-3,4-*trans* for ring C) which displays strong NOE associations between 2-OMe(A) and 2-H(B) and between 3-OMe(B) and 3-H(A). These dipole relaxations are possible only for a structure with an appreciable contribution by an A-conformer for the C-ring and the concomitant stacking of the B- and D-rings [see Fig. 3(*c*)]. This is supported by X-ray evidence for the existence of an A-conformer for penta-*O*-acetylcatechin.[27]



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Viability of the exposition of π-systems by MMXP is, however, ambiguous and predictions regarding their contributions, unreliable. This inadequacy to assert the role of π-systems is probably responsible for the anomaly of high ΔE-values (difference in energy between E- and A-conformers) calculated for 2,4-*cis*-isomers and the associated low E:A-ratios (E- and A-concentration similar), predicted by observed $^3J_{HH}$-couplings, the reverse being found for 2,4-*trans*-isomers (see Table 1).

'Abnormal' coupling constants of the 2,4-*cis*-4-resorcylflavan-3-ols **4** and **6** are therefore the manifestation of significant contributions by A-conformers **15** and **16**, resulting largely from A-strain in the E-conformers **11** and **12**. The ensuing low E:A-ratios cause major deviations in orientation in the vicinity of the C(4)-chiral centre, involving above all the swing of the D-ring to and from the lower right quadrant[10] by E–A conformational inversion. This will crucially influence the amplitude and sign of the Cotton effect, thus rendering the CD-method of assessing the absolute configuration at C(4) of 4-resorcyl-5-oxyflavan-3-ols dubious, unless the conformations of their heterocycles and the major contributors to the Cotton effect are established. However, the observed deviations from the general rule do coincide with low E:A ratios, with appreciable contributions by A-conformers, and may find future application for species at the phlobatannin level which suffer from similar irregularities.

In a bid towards a better understanding of the contribution by different factors to the stability of specific conformers, we have of late resorted to a molecular orbital approach (MNDO, AM1, MNDO/PM3) supported by extensive NMR analyses of a series of analogous compounds. Results of relevance to such analyses of the above phenomena, pertaining to underivatized oligoflavanoids, will be the subject of future communications.

Experimental

Compounds **3**–**10**, together with their characterization data, were available from synthetic sequences reported earlier.[5–7] ^{1}H NMR data were obtained in $CDCl_3$ with $SiMe_4$ as internal reference with Bruker WP80 and/or AM300 instruments, while CD curves were acquired with a JASCO J20 spectropolarimeter for solutions in MeOH.

Three variants of the MM2 force-field were respectively employed for the optimization of conformational geometries. MM2 was applied as QCPM004 for IBM PC without pi-VESCF routines (the MMI portion of QCPE318 for non-conjugated systems)[16] and required several added parameters to express the nature of the aromatic rings:[11]

C(Ar)–C(Ar)–C(Ar)–C(Ar): V1 −0.93, V2 9.0, V3 0.0
H–C(Ar)–C(Ar)–H: V1 −0.93, V2 9.0, V3 0.0
C(Ar)–C(Ar)–C(Ar)–H: V1 −0.93, V2 9.0, V3 −1.06
H–C(Ar)–C(Ar)–O: V1 −0.93, V2 9.0, V3 0.0
C(Ar)–C(Ar)–C(Ar)–O: V1 −0.93, V2 9.0, V3 0.0
C(Ar)–O–C(sp3)–C(Ar): V1 0.0, V2 0.0, V3 0.403

MMX, an elaboration on MM2 by Gilbert and Gajewski,[17] was utilized with both features, *i.e.* an empiric approach to aromaticity by definition of 'aromatic carbons' as well as a full pi-VESCF routine.[18] The results were examined and evaluated by PCMODEL (version 3.3).[17]

$^3J_{HH}$-values were calculated from the optimized torsion angles (φ) by way of the Altona refinement[20] of the Karplus equation [eqns. (1)–(3)] [where $X_{(subst)}$ and $X_{(H)}$ represent

$$\Delta X = X_{(subst)} - X_{(H)} \quad (1)$$

$$\Delta X_{(grp)} = \Delta X_{(\alpha)} - P7\Delta X_{(\beta)} \quad (2)$$

$$^3J_{HH} = P_1\cos^2\varphi + P_2\cos\varphi + P_3 + \Sigma\Delta X_{(grp)}[P_4 + P_5\cos^2(\varepsilon_i\varphi + P_6\Delta X_{(grp)})] \quad (3)$$

Huggins electronegativities for, respectively, the substituent atom and hydrogen, and ΔX their difference; $\Delta X(\alpha)$ and $\Delta X(\beta)$ refer to α-and β-substituents and ε_i to the orientation of the substituents as defined by Altona[20]. Two sets of constants (P_1–P_7) (see ref. 20), a generalized set and one optimized for four non-hydrogen substituents, were compared. $^3J_{HH}$-values thus obtained in combination with $^3J_{HH}$ observed gave mole fractions for a specific isomer *via* eqn. (4) [where x represents the

$$^3J_{HH(obs)} = {}^3J_{HH(eq)}x + {}^3J_{HH(ax)}(1 - x) \quad (4)$$

mole fraction for the equatorial-(E) and $1 - x$ that for the axial-conformer (A)].

Acknowledgements

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