Some Notes on the Chlorogenic Acids.
2. NMR Characterisation
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Referees

The following chlorogenic acid researchers are thanked for taking the time to read and comment upon the content of this document before its uploading to Researchgate

Professor Gary Williamson	**University of Leeds, UK**
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Dr Dimitrina Zheleva-Dimitrova	**Medical University of Sofia, Bulgaria**
Professor Andrea Motta	**ICB, CNR, Pozzuoli, Italy**
Dr Edwin Madala	**University of Johannesburg, South Africa**

Objectives

These notes are designed to draw attention to the complexity of the chlorogenic acids and confusion surrounding their naming, characterisation and identification. They have been placed on Researchgate to make them freely available, and have been reviewed by the undermentioned chlorogenic acid researchers in an attempt to ensure that no errors of fact have crept through, and that the information is presented clearly. Please use them in conjunction with Part 1 that covers the complications of nomenclature. Please notify me of any errors that are found and these notes will be updated as necessary.

Summary

Based on this examination of the literature the recommendation of Pauli *et al*. and Könczöl *et al*. to use d_4-MeOH as the solvent of choice for ^{1}H-NMR characterisation of acyl quinic and acyl shikimic acids is endorsed. Similarly, a full assignment of all seven quinic acid and all five shikimic acid ring protons is essential if errors are to be avoided in defining the quinic acid or shikimic acid configuration and hence which isomer is present.

In any situation in which the data obtained for the ^3J H–H coupling constants suggest that the quinic acid or shikimic acid moiety might be anything other than (–)-quinic acid (L-quinic acid) or (–)-shikimic acid (L-shikimic acid) IUPAC, it is desirable that the isolate is hydrolysed or saponified to release the quinic acid or shikimic acid moiety, and that it is compared chromatographically and spectrally with (–)-quinic acid or (–)-shikimic acid, the latter step necessary to determine its optical rotation.

If these procedures confirm that the isolate is other than (–)-quinic acid or (–)-shikimic acid IUPAC it is further recommended that it and the acyl-quinic acid or acyl-shikimic acid from which it was released are characterised by LC–ion trap-MS so as to establish a fragmentation fingerprint that potentially can be used to locate such derivatives in complex extracts without the need for the time-consuming isolation and characterisation.

If possible, it is also recommended that the acyl-quinic acid or acyl-shikimic acid is subjected to acyl migration and the products analysed by LC–MS to obtain the equivalent fingerprints for associated regio-isomers.

1. Characterisation of Chlorogenic Acids by ^{1}H-NMR

For many years ^{1}H-NMR was the routine method for characterising the structure of a putative chlorogenic acid that had been extracted from plant material or synthesised in the laboratory, and determining the configuration of its quinic acid moiety. The basic approach was to determine the vicinal and geminal H–H coupling constants attributable to the quinic acid moiety, deduce the dihedral angles from the Karplus relationship, and hence the average conformation in solution and the configuration. The configuration then defined which quinic acid diastereomer was present.

The cyclohexane ring of quinic acid has rapid conformational instability on the ^{1}H-NMR timescale, each conformer having its own set of dihedral angles. The measured vicinal (^{3}J) H–H-coupling constants are an average of whatever conformations exist during data acquisition. Two chairs, and one or more intermediate skewed or boat forms, can be expected, proportions varying with the configuration. Because the observed values are an average, they will never correspond to any idealised chair or boat form, although they might approach the ideal if one conformer is dominant.

A significant disadvantage of this approach in the early days of NMR when instruments did not exceed 100 MHz was the need to purify sufficient of the substance(s) of interest, and in the case of the acyl quinic acids, of finding a solvent in which the material was sufficiently soluble to give good signals in a reasonable time. Often d_5-pyridine, d_6-acetone or d_6-DMSO were required at elevated temperature, for example Corse (1966).*(1)*

It was through such NMR investigations that the earliest reports of *muco*-quinic acid,*(2, 3) cis*-quinic acid,*(4)* and *epi*-quinic acid *(5)* derivatives were obtained, albeit with more powerful instruments.

Even with the advent of more powerful instruments these solvents were often retained, probably for reasons of consistency and facilitating comparison of data.

However, incomplete resolution of triplet or double doublet of doublets signals precluded precise calculation of the coupling constants, especially when these multiplets overlapped, as was often the case for H2 and H6 methylenes and H3 and H5 methines. Moreover it was often difficult to discriminate H2 from H6, and H3 from H5. Given sufficient resolution the H2 and H6 signals can be fully assigned by 2D NMR or coupling constant considerations.

For these reasons DQF–COSY spectra were often used to derive the (^{3}J) H–H-coupling constants, but this does not *per se* prevent confusion as to which is H3 (double triplet or double doublet of doublets) and which is H5 (double doublet of doublets) when they overlap in (–)-quinic acid or a 3,5-diacyl-quinic acid.*(6)* In contrast, the double doublet of H4 is usually distinct. In principle ^{1}H–^{13}C-HMBC will establish the carbon(s) to which esters are attached but this may not be possible when

multiple aliphatic and aromatic proton overlaps occur as is the case in more complex chlorogenic acids, such tri- or tetra-acyl-quinic acids, especially those with aliphatic substituents. If there is any error in assigning H2 and H6, and / or H3 and H5 then ROESY spectra which detect bonded atoms which are in close proximity but not directly bonded will also result in mis-interpretation.

The definitive studies by Pauli and colleagues *(6, 7)* demonstrated for a range of chlorogenic acids that the choice of solvent not only influenced the chemical shift of the quinic acid protons and the order in which the shifts occurred, but also the conformation of the quinic acid moiety and hence the coupling constants for those protons. There were also effects of temperature and concentration on these parameters. They concluded that d_4-MeOH was the preferred solvent for routine use, to which if essential a small amount of D_2O or d_6-DMSO (not exceeding 10%) could be added. d_6-DMSO and d_5-pyridine were shown to be problematic and better avoided because of distortion of the chair conformation suggested by altered coupling constants and spectral simulation, and a risk of hydrolysis and overlap of aromatic signals, respectively.

An extreme example of solvent effects is provided by Armesto *et al*. who demonstrated that methyl *cis*-quinate adopted a carboxy axial conformation in d_4-MeOH but a carboxy equatorial conformation $CDCl_3$.*(8)*

Fortunately, H6 can be recognised from spectra in d_4-MeOH or D_2O by two large di-axial coupling constants $^2J_{6ax,6eq}$ and $^3J_{6ax,5ax}$, provided that sufficient resolution is available either experimentally or through the use of spectral analysis software.*(7, 9)* Pauli *et al*. stress the need for considerable precision.*(10)*

Once H_{6ax} has been identified, H_{6eq} can be identified from its correlation in a TOCSY or COSY spectrum, and then H_{2ax} and H_{2eq} can be identified. H3 and H5 can then be defined by TOCSY or COSY correlations with H2 and H6, respectively.

However, the solvent effects are such that the order in which the H2 and H6 protons appear in the spectrum changes, as illustrated below with data from Pauli *et al*. for d_4-MeOH and d_6-DMSO.*(7)*

	d_4-MeOH	d_6-DMSO
	δ ppm	
H_{2ax} dd	2.175	2.023
H_{2eq} ddd	2.047	1.778
H_{6ax} dd	2.078	2.010
H_{6eq} ddd	2.227	1.950

Accordingly, unless there is full resolution, and in most studies so far reported this has not been achieved, correctly assigning these protons by comparison of spectra in one solvent with those in another is virtually impossible and likely to result in errors. This problem becomes more acute when one or more aliphatic acid moieties are present because of additional methyl, methylene and methine signals overlying those from the quinic acid moiety.

Pauli *et al*.*(6)* present data for the $^{3}J_{5ax,6ax}$ and $^{3}J_{4ax,5ax}$ couplings in a range of mono- and di-acyl-quinic acids. These values in combination with spectral simulation suggest that, with the exception of 3,5-diCQA and 1,3-diCQA, there is some flattening of the cyclohexane chair with a diaxial dihedral angle in most cases of nearer 140° than 180°. Such flattening can make it difficult to distinguish di-equatorial couplings from equatorial-axial couplings, although it has been noted that an equatorial oxygen substituent at C3 or C5 leads to a somewhat larger *gauche* coupling (4.5 ± 1 Hz) with the equatorial proton at C2 or C6 as appropriate, whereas for an axial oxygen substituent the coupling falls in the range 2.5–3.2 Hz.*(11)*

The table below presents ^{1}H-NMR data for the quinic acid moiety of a range of caffeoylquinic acids, obtained in the preferred solvent, d_4-MeOH, by several independent groups. An additional set of data including 1,5-diCQA, obtained in D_2O, have been recorded and are presented by Tolonen *et al*.*(9)*

It is clear from these data that if best operating practice is pursued, as described by Pauli *et al*., then identification by ^{1}H-NMR of mono- and di-acyl-quinic acids is possible. If these occur as major components in an extract, and are chromatographically resolved, it is possible, albeit tedious and time consuming, to isolate sufficient material in sufficient purity to achieve identification. If the compound of interest is a minor component, and especially if poorly resolved from similar compounds, this task becomes much more difficult.

These problems associated with mono-acyl-quinic acids and diacyl-quinic acids become more acute in tri-acyl and tetra-acyl-quinic acids, especially when two or more different acyl residues are present. Signal overlap is inevitable and full assignment required for structure elucidation becomes impossible, even if relatively large quantities of pure material are available.

	Table 1. H–H coupling constants obtained in d_4-MeOH for a range of naturally-occurring and synthetic acyl-quinic acids																
	5-CQA	5-CQA	5-CQA	5-CQA	5-CQA	3-F, 5-CQA	3,5-diCQA	4,5-diCQA	3,4,5-triCQA	1,3,4,5-tetra-CQA	4,5-diCQA	3,5-diCQA	5-C-*epi*-QA	3,5-diC-*epi*-QA	1,3-diC-*epi*-QA	4,5-diC-*epi*-QA	4,5-diC-*epi*-QA	Me-4-acetyl-*epi*-Q
	600 MHz		300 MHz		500 MHz	400 MHz	500 MHz	500 MHz	500 MHz	500 MHz	300 MHz	300 MHz		300 MHz	300 MHz	500 MHz	500 MHz	300 MHz
Ref	*(6)*	*(12)*	*(13)*	*(14)*	*(15)*	*(16)*	*(17)*	*(17)*	*(17)*	*(17)*	*(13)*	*(13)*	*(12)*	*(18, 19)*	*(18)*	*(20)*	*(21)*	*(8)*
H2	14.2, 5.1, 2.3	14.1, 4.9, 3.1				14.8, 5.2, 4.0	m	16.0, 5.0	13.5, 3.8	16.0, 10.3, 3.6, 2.0			13.8, 8.8, 4.1	m	13.6, 9.0, 3.4	13.1, 5.3, m*	13.4	13.8, 6.6, m*
H3 ddd or dt	5.1, 3.2	4.9, 3.3, 3.1	3.0	5.4, 3.3, 3.4,	4.44, 9.28, 9.27	4.8, 3.6	m	m	m	m	4.4, 4.4, 3.0	7.0	8.8, 4.1	10.0, 5.8	m	5.6, 5.4, 5.3	5.5, 5.5, 5.5	m
H4 dd	3.2, 8.6	3.3, 8.5	3.0, 10.0	3.3, 8.4	3.14, 8.58	3.2, 9.2	3.5, 7.4	3.2, 8.2	3.0, 7.6	3.6, 10.3	3.0, 9.1	3.96	3.7, 8.8,	3.4, 9.9	3.2, 8.0	3.0, 6.1	4.5, 5.5	2.9, 6.4
H5 ddd	9.7, 8.6, 4.5	9.1, 8.5, 4.2	10.0, 10.0, 4.2	9.3, 8.4, 4.4	m	m	m	13.0, 8.2, 4.0	m	11.5, 10.3, 4.5	9.1, 9.1, 5.3	7.1, 7.0, 3.3	4.3, 3.7, 3.3	m	7.4, 3.8	8.6, 4.1, 3.3	8.3, 4.5, 4.5	6.4, 6.4, 4.1
H6	13.3, 9.7, 4.5	14.0, 9.1, 4.2				m	m	m	m	13.0			13.9, 4.3, 3.3	15.2, 3.4	m	13.2, 4.1 m*		13.3, 3.4. m*

- multiplet observed for H_{2ax} and H_{6ax}

The data from Pauli *et al*.,*(6)* Forino *et al*.,*(12)* Batista *et al*.*(13)* and Kuczkowiak *et al*. *(14)* for 5-CQA are very similar, but that from Okonkwo *et al*. *(15)* for the same compound is markedly different. Okonkwo *et al*. show a IUPAC-numbered structure, but the assignment of two large diaxial couplings to H3 strongly suggests that H3 and H5 have been wrongly assigned in the text, but it is clear that acylation is on C5 IUPAC (H5 δ = 5.34 ppm) and this isolate, as claimed, appears to be 5-CQA IUPAC.

The next seven sets of data for di-, tri and tetra-acyl-(–)-quinic acids show subtle differences, which must arise either from errors in calculating the coupling constants, differences in conformation as a consequence of different patterns of substitution, or both. The values for H4 show least variation, but the difficulty of assigning H2 and H6, H3 and H5, and distinguishing between them is clearly illustrated by the lack of data or merely assigning an incompletely resolved multiplet.

The remaining six sets of data are for putative acyl-*epi*-quinic acids.

The set of data form Forino *et al*.*(12)* is for the putative 5-caffeoyl-*epi*-quinic acid. As presented, there is on first sight considerable difference between the coupling constants for this putative acyl-*epi*-quinic acid and the acyl-(–)-quinic acids, but note that H6 has only one large di-axial coupling and H2 has two, strongly suggesting that these have been reversed. If H3 and H5 as presented are also reversed, this putative *epi*-quinic acid looks very like a (–)-quinic acid, specifically 3-CQA IUPAC. *Sorbus* species are usually considered to contain both 3-CQA IUPAC and 5-CQA IUPAC,*(22-26)* and while this does not in any way make it impossible for them also to contain *epi*-quinic acid derivatives, the apparent absence of 3-CQA IUPAC in this sample as reported by Forino *et al*., is unexpected.

The next two columns are data from Kim and Lee *(18, 19)* for two putative di-acyl-*epi*-quinic acids from *Chrysanthemum morifolium* and one from *Ipomoea batatas*. Neither has a full set of coupling constants, and such as are available, are not greatly different from those for the acyl-(–)-quinic acids. 1,3-DiCQA IUPAC (Cynarin) and 3,5-diCQA IUPAC have with other diCQA been reported in *Chrysanthemum* and related species,*(27)* including analyses by LC–ion trap-MS *(28)* that would have detected the presence of an unusual quinic acid moiety by its distinctive fragmentation had such been present.*(29-31)* Note, as discussed in Part 1, Lin and Harnly describe the quinic acid diastereomer reported by Kim and Lee as '1-*epi*-quinic acid, (i.e 1 D-OH)',*(32)* presumably meaning D-quinic acid or (+)-quinic acid IUPAC, but it cannot be the carboxy-axial conformer of D-quinic acid (or L-quinic acid) because in both of those diastereomers the C4-OH must be axial in the carboxy-axial conformer — see Table 5 in Part 1.

The ante-penultimate data set from Wang *et al*. *(20)* is for a chlorogenic acid isolated from *Scorzonera radiata*, previously obtained by them from *Psiadia trinerva (5)* when more limited NMR data in d_6-DMSO were published (see below). The absence of a large diaxial coupling for H4, the presence of a single large diaxial coupling for H5, and no large diaxial couplings for H3, are consistent with their assignment. Even reversing H3 and H5 would not suggest that this might be a derivative of the usual (–)-quinic acid, and more importantly, as discussed below for the data in d_6-DMSO, the quinic acid moiety obtained by saponification did not chromatograph with authentic (–)-quinic acid in the two chromatographic systems employed, important evidence that seems to have been overlooked by Könczöl *et al*. *(33)* who were unconvinced by Wang's assignment. In the penultimate column are essentially identical ^{1}H-NMR data reported by Ono *et al*.*(21)* for the same compound isolated from *Tessaria integrifolia*. The final data set from Armesto *et al*. *(8)* provides analogous data for synthetic methyl-4-acetyl-*epi*-quinate which is a very good match for Wang *et al*.'s isolate. Kang *et al*. have reported the same compound in the buds of *Tussilago farfara*.*(34)* Interestingly, Ono *et al*. reported the specific rotation as [+19.2} at 25°C in MeOH (c = 0.1) *(21)* consistent with the value of [+33] in MeOH (c = 0.6) reported by Wang *et al*.*(5)* very different from the commoner diCQA which all show substantial negative values — for example see Corse *et al*.*(35)* but note that these are presented using non-IUPAC numbering.

In contrast, an isolate from *Ainsliaea acerifolia* described as (–)-3,5-dicaffeoyl-*epi*-quinic acid Is less convincing, with a prominent diaxial coupling for H4 (9.0 Hz, 3.0 Hz) and only multiplets reported for H3 and H5.*(36)* Although ROESY data are presented and interpreted to support the assignment, but the data presented for H2 (13.6, 9.0, 3.0 Hz) more closely resemble that expected for H6 and this appears to be the same compound as reported by Kim and Lee.*(18, 19)* ROESY data establish the close spatial proximity of atoms that are not directly bonded, but the spatial

arrangement of atoms in the average conformers of (–)-quinic acid and (–)-*epi*-quinic acid are not greatly different, and confusion is easy especially if H6 and H2 have been confused.

Data from Pauli *et al*. are presented below for 5-CQA in d_4-MeOH and d_6-DMSO to illustrate the effect of solvent, along with further data for various acyl-quinic acids obtained in d_6-DMSO.

Table 2. The effect of solvent on δ and *J* with data for various naturally-occurring acyl-quinic acids obtained in d_6-DMSO																		
Ref	*(7)*				*(2)*		*(7)*		*(3)*				*(5)*		*(37)*		*(38)*	
	5-CQA				3C-*muco*-QA		3-CQA		3,5-diC-*muco*-QA		3,5-diCQA		4,5-diC-*epi*-QA		4,5-diC-*epi*-QA		5-caffeoyl-*epi*-quinic acid	
	δ ppm	*J* Hz	δ ppm	*J* Hz	δ ppm	*J* Hz	δ ppm	*J* Hz	δ ppm	*J* Hz	δ ppm	*J* Hz	δ ppm	*J* Hz	δ ppm	*J* Hz	δ ppm	*J* Hz
	d_4-MeOH		d_6-DMSO		d_6-DMSO		d_6-DMSO		d_6-DMSO		d_6-DMSO		d_6-DMSO		d_6-DMSO		d_6-DMSO	
$H2_{ax}$	2.175	14.2, 3.4	2.023	13.2, 3.0	1.89	13.1, 4.6	1.992		2.11	13.0, 14.0	2.13	15.0, 9.0			1.95	m	1.79	m
$H2_{eq}$	2.047	14.2, 5.4, 2.2	1.788	13.2, 8.0, 0	1.98	13.1, 7.5	1.893	13.4, 7.6	1.96	13.0	1.86	15.0, 6.0						
H3	4.168	5.4, 3.4, 3.3	3.931	8.0, 3.0, 2.9	3.86	9.2, 7.5, 4.6	5.179	3.8, 3.3	5.13	11.0, 14.0	5.21	9.0, 8.0, 6.0	3.75	3.1	3.82	m	3.80	8.0, 8.0, 3.0
H4	3.726	3.3, 8.6	3.568	2.9, 6.8	3.52	9.2, 6.1	3.547	6.4, 3.3	3.83	16.0, 11.0	3.73	15.0, 8.0	5.05	3.1, 3.1			3.53	8.0
H5	5.334	9.3, 8.6, 4.4	5.072	6.8, 6.8, 4.5	5.17	6.1	3.851	7.5, 6.4, 3.3	5.19	16.0, 15.0, 10.0	5.30	17.0, 15.0, 8.0	5.52	10.1, 3.1, 3.1	5.32	5.0	5.17	8.0, 3.0, 3.0
$H6_{ax}$	2.078	13.5, 9.3	2.010	13.0, 6.8	1.8	13.6, 4.2	1.846	13.5, 7.5	2.14	12.0, 15.0	1.91	17.0, 14.0			2.09	15.3, 3.7		
$H6_{eq}$	2.227	13.5, 4.4, 2.2	1.950	13.0, 4.5, 0	2.58	13.6, 5.7	1.851	13.5, 3.3	1.96	12.0, 10.0	1.91	14.0, 8.0					1.90	m

The data from Kwon *et al*. *(3)* for the putative 3,5-dicaffeoyl-*muco*-quinic acid are striking — all coupling constants are large falling in the range 10 to 16 Hz, suggesting at first sight that all hydrogens are axial, which is not possible for C2 and C6, each of which has one equatorial hydrogen. The strong negative specific rotation [–183.6°} also indicates that this is not a *meso* form, and hence cannot be a symmetrical diacyl-*muco*-quinic acid. This does not necessarily eliminate a diacyl-*epi*-quinic acid, but the large coupling constants for H4 are not compatible with such a structure, and very different from those reported for 4,5-dicaffeoyl-*iso*-quinic acid (= 4,5-dicaffeoyl-*epi*-quinic acid) by Wang *et al*.*(5)*

The data from Haribal *et al*. *(2)* for the putative 3-caffeoyl-*muco*-quinic acid fall in the range 4.2 to 13.6 Hz, but the data set is clearly incomplete, or imperfect, with for some carbon atoms two couplings failing to resolve and appearing as one value. Pauli *et al*. suggest that this incomplete resolution accounts for the relatively large 9.2 Hz coupling observed for H4 and H3 and casts doubt on the authors' understandable interpretation of a diaxial arrangement for H3 and H4.*(7)* As mentioned previously doubt is cast on the validity of the assignment also by the authors stating that the putative 3-caffeoyl-*muco*-quinic acid can be produced from 5-caffeoyl-(–)-quinic acid by acyl migration.

Wang *et al*. isolated a novel chlorogenic acid from *Psiadia trinerva* and named it 3,4-dicaffeoyl-*iso*-quinic acid (= 4,5-dicaffeoyl-*iso*-quinic acid IUPAC).*(5)* NMR data obtained in d_6-DMSO are incomplete, but the coupling constants for H3, H4 and H5 are very different to those obtained for 3-caffeoylquinic acid IUPAC and 5-caffeoylquinic acid IUPAC in this solvent by Pauli *et al*.*(7)* The structure assigned by Wang *et al*. corresponds to 4,5-dicaffeoyl-*epi*-quinic acid IUPAC, and the absence of a large diaxial coupling for H4, the presence of a single large diaxial coupling for H5, and no large diaxial couplings for H3, are consistent with this assignment. More importantly, the quinic acid moiety obtained by saponification did not chromatograph with authentic (–)-quinic acid in the two chromatographic systems employed, important evidence that seems to have been overlooked by Könczöl *et al*. *(33)* who were unconvinced by Wang's assignment. Data for the same compound in d_4-MeOH are consistent as discussed above.

Lee *et al*. reported 4,5-dicaffeoyl-*epi*-quinic acid IUPAC in *Gymnaster koraiensis* but in the original publication used non-IUPAC numbering. This structure was assigned from a far from complete NMR data set and reference to the earlier data of Kim and Lee,*(19)* and Peng *et al*.*(39)* Peng *et al*. did not refer to any *epi*-quinic acid derivatives, but did report incomplete data for 3,5-dicaffeoylquinic acid IUPAC.*(39)* Kim and Lee presented NMR data for a putative 4,5-dicaffeoyl-*epi*-quinic acid in d_4-MeOH, which as discussed above are not complete and not convincing.

Furbacher's data for a chlorogenic acid isolated from *Phoradendron juniperinum (38)* was interpreted as 5-caffeoyl-*epi*-quinic acid IUPAC after comparison with previously published data for 3-caffeoylquinic acid obtained in d_4-MeOH *(40)* and 5-caffeoylquinic acid obtained in d_6-DMSO.*(41)* These data are cited faithfully by Furbacher, but are misleading. Nakatani *et al*. clearly used IUPAC numbering for the assignment of a putative 3-CQA IUPAC, but the NMR data for H3 (J = 3, 3, 4 Hz), H4 (J = 3, 9 Hz) and H5 (J = 3, 9, 9 Hz) clearly establish that this was 5-CQA IUPAC. Nakatani's assignment is based partly on data from Morishita *et al*.,*(42)* and partly on data from Tatefuji *et al*.,*(43)* both of whom used non-IUPAC numbering and neither of whom reported coupling constants. Tatefuji *et al*. merely cite another publication that cannot be traced.

Azuma also clearly used non-IUPAC numbering but the NMR spectrum used for assignment was so poorly resolved that it did not yield coupling constants,*(41)* and it is impossible to judge whether this is 3-CQA IUPAC or 5-CQA IUPAC.

Although Furbacher's data at first sight seem very different from the previously published data with which it is compared, once a revision is made for the use of non-IUPAC numbering in the earlier data, and some allowance is made for the use of different solvents, Furbacher's isolate looks remarkably like 3-caffeoylquinic acid IUPAC.

Zhou *et al*. present only limited NMR data, obtained in d_6-acetone and D_2O, for the putative 4-caffeoyl-*cis*-quinic acid isolated from fermented tea.*(4)* The protons at H3, H4 and H5 are shown as multiplets and no further interpretation is possible. This product is supposedly present also in *Camellia crassicolumna*, but no further spectral data were provided.*(44)*

Zahoor *et al*. reported the presence of 1,4-dicaffeoyl-*neo*-quinic acid in *Erigeron bonariense* L. on the basis of HRMS and NMR (d_6-MeOH) characterisation.*(45)* The assignment must be considered as highly tentative because the C4 and C5 methines are recorded at δ_H = 5.11 and 5.63 ppm respectively, the behaviour of C5 being attributed to hydrogen bonding to the carboxyl, and the detection of only one HMBC correlation, assigned to C4. The ^{1}H-NMR data are incomplete with H3 (4.37 ppm) and H5 (5.63 ppm) recorded as broad singlets but without couplings, and H4 being recorded as a doublet (5.11 ppm and J =7.1 Hz) from which two synchronous axial-equatorial couplings were apparently deduced. This observation along with a NOESY plot showing correlations between H3 and H4, and H4 and H5, led to the conclusion that these three H atoms were in the same plane (i.e. *cis* to each other) and all three had a β-configuration (i.e. were *cis* to the carboxyl). However, a specific rotation of $[\alpha]_D$ = –22° casts some doubt on the assignment of this compound as a 1,4-diacyl-*meso*-quinic acid derivative unless the suggested hydrogen bonding is sufficient to distort the molecule.

Table 3. H–H coupling constants in various solvents for various synthetic acyl-*muco*-, acyl-*cis*- and acyl-*scyllo*-quinic acid methyl esters											
Ref	*(46)*	*(46)*	*(46)*	*(46)*	*(46)*	*(46)*	*(8)*	*(8)*	*(47)*	*(48)*	*(48)*
	Methyl-3-caffeoyl-*muco*-quinate	Methyl-3-feruloyl-*muco*-quinate	Methyl-1,3-dicaffeoyl-*muco*-quinate	Methyl 1,3-diferuloyl-*muco*-quinate	Methyl 1-feruloyl-3-caffeoyl-*muco*-quinate	Methyl 1-caffeoyl-3-feruloyl-*muco*-quinate	Methyl 3-acetyl-*muco*-quinate	Methyl 4-acetyl-*cis*-quinate	(–)-Methyl-*cis*-quinate	Methyl *scyllo*-quinate	Methyl 5-benzoyl-*scyllo*-quinate
	J Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz
	d_4-MeOH	d_4-MeOH	d_4-MeOH	d_6-acetone	d_6-acetone	d_6-acetone	d_6-acetone	d_6-acetone	d_4-MeOH	d_4-MeOH	$CDCl_3$
H2	m	12.0, and m	m	15.1, 11.5	13.5, 4.6, 4.6	13.5, 11.7, and 11.0, 4.6, 4.6	12.9, 11.7, 5.7	12.0, 11.9, 4.6	12.1, 3.3	12.7, 12.2, 2.4	13.7, 11.2, 4.4
H3	m	?	m	m	m	m	11.6, 9.6, 4.8	m	m	9.8, 9.8, 2.9	10.8, 8.3, 4.4
H4	8.7	8.7	9.17	9.2	?	9.2	9.2, 9.2	≈2.4, ≈2.4	Broad singlet	9.3, 9.3	8.3, 8.3
H5	10.5, 4.6	11.4, 5.0, 1.8	14.21, 4.58	m	11.7, 4.6, 4.6	m	11.6, 9.0, 4.6	m	m	9.8, 9.8, 2.9	10.8, 8.8, 4.9
H6	m	12.0, and m	m	14.0, 10.5	13.75, 4.6, 4.6, and m	13.5, 11.9, and 11.0, 4.6, 4.6	12.9, 11.7, 5.7	12.0, 11.9, 4.6	12.1, 3.3	12.7, 12.2, 2.4	13.2, 10.8, 4.9

These data in Table 3 above, obtained in a range of solvents, are for methyl esters of the less common quinic acid diastereomers, where the synthetic pathway effectively defines the structure obtained, supported in many cases by X-ray diffraction data after crystallisation. Accordingly, the NMR data are not essential for identification, and the incomplete nature in this situation is not a problem. However, in most cases such data in isolation would not have been sufficient fully to define the diastereomer had they been obtained on an isolate. Where the fuller data sets are available, the symmetrical nature of the data is apparent, consistent with the meso character of the quinic acid moiety.

There are no certain records of these quinic acids, or their acyl derivatives in unprocessed plant material, but 3-caffeoyl-*muco*-quinic acid and 3-feruloyl-*muco*-quinic acid have been reported in roasted coffee.*(49)*

(±)-*Epi*-quinic acid and *scyllo*-quinic acid have also been found in roasted coffee,*(31, 50-52)* accompanied by acyl-γ-quinides, acyl-γ-*muco*-quinides and acyl-γ-*epi*-quinides in roasted coffee,*(53-58)* and acyl-γ-quinides in roasted maté.*(59)*

Distinguishing acyl-quinic acid methyl ethers from acyl-quinic acid methyl esters

There have been several reports of hydroxycinnamoyl esters of quinic acid methyl ethers,*(60-64)* based primarily on ^{1}H- and ^{13}C- NMR data with the methyl ether in the range δ = 3.70 to 3.75 ppm and δ = 52.9, 53.0 or 57 ppm, respectively.*(60, 63)*. Synthesis by Zeller *et al.* of authentic quinic acid methyl ethers establishes the alicyclic methyl ether as having chemical shifts of δ = 3.31 and 53 and these authors concluded that previous reports referred to methyl caffeoylquinates.*(65)*

Aryl methyl ethers, as seen in feruloylquinic acid for example, and methyl esters (ether δ_H ≈3.72 and ester δ_H ≈3.85) can be distinguished unequivocally by HMBC.

Note also, that Simões-Pires *et al*. isolated from *Baccharis* a component which they named as 4-caffeoyl-1-methyl-quinic acid, thus implying a methyl ether, but actually show the structure of this compound as methyl 4-caffeoylquinate,*(66)* which assignment is consistent with their reported NMR data.

Some less common quinic acid derivatives

In addition to the acyl-quinic acids discussed above there is good evidence for the occurrence in unprocessed plant material of acyl derivatives also of 2-hydroxyquinic acid,*(67)* 4-deoxy-quinic acid *(68)* and 1,2,4,5-tetrahydroxy-6-methyl-1,6-dicarboxylic acid *(69)* for which the configurations are not fully determined.

In the case of 2-hydroxyquinic acid, the ^{3}J values for H4 (3.4 and 9.8 Hz) *(67)* suggest one di-axial and one axial–equatorial coupling and that C3, C4 and C5 have either the same configuration as (–)-quinic acid (L-quinic acid) IUPAC in its preferred carboxy-equatorial conformation, or (–)-*epi*-quinic acid in its preferred carboxy-equatorial configuration — see Part 1 Table 5 and Part 2 Table 1.

In the case of 1,2,4,5-tetrahydroxy-6-methyl-1,6-dicarboxylic acid *(69)* the ^{2}J coupling constant (13.2 Hz) and the ^{3}J coupling constants (8.4 and 9.9 Hz) for the C4 methylene initially suggest two diaxial couplings, but the absence of any obvious di-equatorial or equatorial–axial coupling associated with H_{4eq} suggests that two coupling constants have merged, and it is thus impossible to assign the configuration. Note that the numbering for this compound has been altered from that originally reported, where the methylene in question is shown as H5, so as better to allow comparison with (–)-quinic acid.

In the case of 4-deoxyquinic acid the overlap of three methylene signals (C2, C4 and C6) prevents assignment of the configuration.

However, these observations do not necessarily rule out a configuration of these two derivatives at C3 and C5 that matches both (–)-quinic acid and (–)-*epi*-quinic acid.

Acyl-shikimic Acids

There are fewer data available for the shikimic and acyl-shikimic acids, with the majority of data being for synthetic products, but it has been noted that the conformation, and hence ^{3}J values are very solvent dependent.*(70)* The data below for (–)-shikimic acid, (–)-3-*epi*-shikimic acid, (–)-5-galloylshikimic acid, methyl-5-galloyl-4-*epi*-shikimate and 5-galloylshikimic acid are for natural isolates. The data from Geiger *et al*. for (–)-3-*epi*-shikimic acid isolated from *Sequoiadendron* is convincingly different to that for the better known (–)-shikimic acid,*(71)* but that for methyl-5-galloyl-4-*epi*-shikimate isolated from *Euphorbia* by Yang *et al*. is not greatly different from that reported for (–)-5-galloylshikimic acid. One incompletely characterised caffeoyl-*epi*-shikimic acid has been reported in *Rudbeckia* based on a distinctive mass fragmentation.*(30)*

Table 4. ^2J, ^3J and ^4J H–H coupling constants in various solvents for various acyl-shikimic acids, shikimic acids and associated methyl esters										
	(72)	*(48)*	*(73)*	*(74)*	*(75)*	*(71)*	*(48)*	*(48)*	*(74)*	*(47)*
	(–)-shikimic	Methyl shikimate	(–)-5-galloyl-shikimic acid	5-galloyl-shikimate	5-caffeoyl shikimate	(–)-3-*epi*-shikimic	(+)-methyl-3-*epi*-shikimate	(–)-methyl-4-*epi*-shikimate	Methyl (–)-5-galloyl-4-*epi*-shikimate	Methyl 5-*epi*-shikimate
	J Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz	*J* Hz
	d_4-MeOH	d_4-MeOH	d_6-acetone + D_2O	d_6-acetone	d_4-MeOH	d_4-MeOH	d_4-MeOH	d_4-MeOH	d_6-acetone	d_4-MeOH
H2	multiplet $W_{½}$ = 9 Hz	multiplet	1.6	Singlet		3, 1.9	multiplet	3.3, 2.2, 2.2	Broad singlet	Broad singlet
H3	4, 4	singlet	Broad singlet	Multiplet	Multiplet	7.8, 3.8, 1.9, 1.4	multiplet	6.6, 1.9, 1.9, 1.9	Broad singlet	Broad singlet
H4	8, 4	7.1, 3.8	7.2, 4.2	Multiplet	4.1	9.8, 7.8	9.6, 7.9	6.6, 2.2	6, 4.8	Broad singlet
H5	multiplet $W_{½}$ = 20 Hz	7.1, 4.9, 4.9	multiplet	multiplet	7.5, 5.3, 5.1	9.8, 9.8, 5.9	10.1, 10.1, 6.1	4.8, 4.8, 2.2	11.2, 4.8	9.6, 6.0, 1.8
$H6_{ax}$ and H_{6eq}	18.5, 7, 5	18.7, 3.8, 1.6, 1.6 and 18.1, 4.9, 2.2, 2.2	18.5, 4.2	18.4, 4.6 and 18.4, 2.4	18.4	17.5, 9.8, 5.9, 3.8, 1.4	17.5, 9.6, 3.9, 3.9 and 17.1, 4.4, 1.8	18.3, 5.1, 1.8, 1.8 and 18.3, 4.8, 2.2, 2.2,	18.4, 4.0 and 18.4, 2.4	17.2, 9.6, 6.0, 2.9 and 17.2, 6.0

There are several further sets of data for the ^{1}H NMR of caffeoylshikimic acids, but these are presented as fingerprints and were not fully assigned in the original studies. In both of these the double doublet associated with H4 is easily located with ^3J values of ≈8 and ≈4 Hz consistent with the assignment as acyl-shikimic acids,*(76, 77)* rather than as derivatives of an *epi*-shikimic acid. However, just as for quinic acid, full assignment of all protons is essential for reliable assignment of the configuration.

2. Conclusions

A thorough examination of published NMR data for acyl-quinic acids and related compounds suggests that most claims of chlorogenic acids containing a quinic acid moiety other than (–)-quinic acid (L-quinic acid) IUPAC are unlikely to be reliable. The only exception with reference to isolates from unprocessed plant material are the limited reports of diacyl-*epi*-quinic acids where, not only have convincing NMR data been obtained, but also the quinic acid moiety released by saponification did not chromatograph with authentic (–)-quinic acid IUPAC in two different chromatographic systems.

Mono-acyl *muco*-quinic acids have been observed in roasted coffee and there is evidence also for the presence of *epi*-quinic acid, acyl-*epi*-quinides, acyl-*muco*-quinides and *scyllo*-quinic acid in this product, making it an interesting subject for further study, and an excellent, readily available and cheap surrogate standard for use in LC–ion trap-MS studies, and against which potentially novel isolates can be compared.

There is, however, good evidence for quinic acid derivatives having an additional hydroxyl at C2, and / or lacking a hydroxyl at C4.

There is also good evidence for the natural occurrence of (–)-3-*epi*-shikimic acid and at least one incompletely characterised caffeoyl-*epi*-shikimic acid has been reported in *Rudbeckia.*

3. Recommendations

Based on this examination of the literature the recommendations of Pauli *et al*. and Könczöl *et al*. to use d_4-MeOH as the solvent of choice to characterise acyl quinic and acyl shikimic acids are endorsed. Similarly, a full assignment of all seven quinic acid ring protons or all five shikimic acid ring protons is essential if errors are to be avoided in defining the quinic acid or shikimic acid configuration.

In any situation in which the data obtained for the ^3J H–H coupling constants suggest that the quinic acid or shikimic acid moiety might be anything other than (–)-quinic acid (L-quinic acid) IUPAC or (–)-shikimic acid (L-shikimic acid) IUPAC it is desirable that the isolate is hydrolysed or saponified to release the quinic acid or shikimic acid moiety and that it is compared chromatographically and spectrally with (–)-quinic acid or (–)-shikimic acid IUPAC, the latter necessary to determine its optical rotation.

If these procedures confirm that the isolate is other than (–)-quinic acid or (–)-shikimic acid IUPAC it is further recommended that it and the acyl-quinic acid or acyl-shikimic acid from which it was released are characterised by LC–ion trap-MS so as to establish a fragmentation fingerprint that potentially can be used to locate such derivatives in complex extracts without the need for the time-consuming isolation and characterisation.

If possible, it is also recommended that the acyl-quinic acid or acyl-shikimic acid is subjected to acyl migration and the products analysed by LC–MS to obtain the equivalent fingerprints for associated regio-isomers

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