

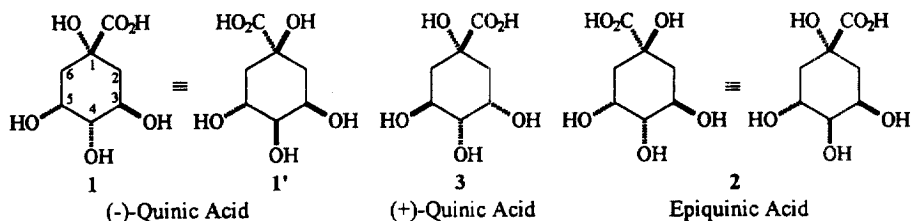
## (–)-Quinic acid: configurational (stereochemical) descriptors

 Ernest L. Eliel<sup>a,\*</sup> and Mara Bello Ramirez<sup>b</sup>
<sup>a</sup> W. R. Kenan Jr. Laboratories, Department of Chemistry, University of North Carolina, Chapel Hill, NC 27599-3290, USA

<sup>b</sup> Centro de Investigaciones Químicas, Universidad Autónoma del Estado de Morelos, Av. Universidad 1001, Cuernavaca, Mor, 62210, Mexico

**Abstract:** The configurational descriptors at C(1) and C(4) of (–)-quinic acid are given incorrectly in at least four reference compendia. The stereogenic centers C(1) and C(4) as a pair are reflection invariant and are thus not chiral centers. The correct name, according to the 1982 amendment to the CIP system, is (1*s*,3*R*,4*s*,5*R*)-tetrahydroxycyclohexanecarboxylic acid. © 1997 Elsevier Science Ltd

(–)-Quinic acid (**1**, Scheme 1) is found in a variety of plant materials ranging from Cinchona bark to tobacco leaves to cranberries. It was first isolated in 1790<sup>1</sup> and its empirical formula was established in 1838,<sup>2</sup> but nearly 100 years passed until its correct constitution — first suggested by Emde<sup>3</sup> but not initially accepted — was established by Fischer and Dangschat.<sup>4</sup> The same investigators proved the relative configuration<sup>4</sup> and a few years later<sup>5</sup> the absolute configuration of the (–) acid — the latter by correlation with shikimic acid and thence D-glucose.



Scheme 1.

Examination of the planar formula (**1**) according to the Cahn–Ingold–Prelog (CIP) system<sup>6</sup> immediately establishes the configuration at C(3) and C(5) as *R*. It is also evident that neither C(1) nor C(4) are chiral centers, since two of the branches attached to either of these carbon atoms are identical. Thus no *R/S* chirality descriptor can be assigned to these atoms.<sup>7,10,11</sup>

Before addressing the confusion in this regard that has arisen in a variety of reference compendia<sup>12–15</sup> we need to decide how to number compound **1**. Even on this point there is no unanimity in the literature, even though, constitutionally, the compound is universally named as a 1,3,4,5-tetrahydroxycyclohexanecarboxylic acid. If one then uses the  $\alpha,\beta$  system<sup>8b</sup> to denote configuration of the hydroxyl groups relative to CO<sub>2</sub>H, with ligands *cis* to that group being denoted  $\beta$  and those *trans*  $\alpha$ ,<sup>16</sup> one can either denote the configuration as 1 $\alpha$ ,3 $\alpha$ ,4 $\alpha$ ,5 $\beta$  or 1 $\alpha$ ,3 $\beta$ ,4 $\alpha$ ,5 $\alpha$ . According to the *Dictionary of Organic Compounds*<sup>12</sup> ‘...the C atom carrying the OH which is *cis* to the CO<sub>2</sub>H is normally numbered 3...’. This is also in accord with the Beilstein convention,<sup>8c,17</sup> but if one makes the equivalency  $\beta$ =*cis* (*c*),  $\alpha$ =*trans* (*t*) and notes that *c* precedes *t* in the numbering one would use the descriptors 1 $\alpha$ ,3 $\beta$ ,4 $\alpha$ ,5 $\alpha$  (cf. **1**). The fact that two of the above compendia<sup>12,13</sup> as well as

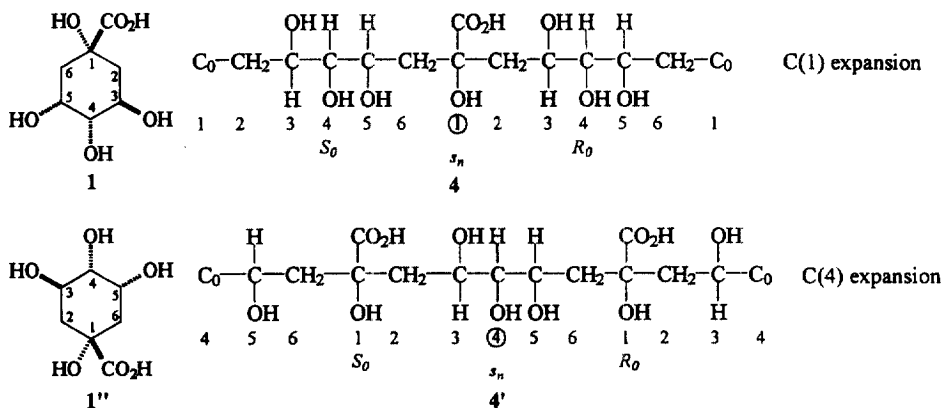
\* Corresponding author.

Chemical Abstracts<sup>15</sup> use the opposite ( $1\alpha,3\alpha,4\alpha,5\beta$ ) notation, suggests however that in them, the  $\alpha/\beta$  designation is opposite to that defined above, which is in itself a source of confusion.

We have already noted that C(1) and C(4) are not chiral centers, even though, in the terminology of Mislow and Siegel<sup>18</sup> they are both chirotopic and stereogenic. The chirotopicity results from the chirality of the molecule as a whole; it is similar to that of C(1) in, say, *trans*-3,5-dimethylcyclohexanone. The stereogenicity of C(1) and C(4) results from the possibility of having two relative configurations: the OH(4) can be *cis* or *trans* to the CO<sub>2</sub>H(1). We note that change of configuration of *either* C(1) or C(4) leads to the (known)<sup>9</sup> epiquinic acid (2, Scheme 1) but *simultaneous change at both of these centers leads back to the original (-)-quinic acid*, as shown by formula 1' which is superimposed with 1 by a 180° rotation around an axis passing through C(1) and C(4). Also, if (-)-quinic acid is mirror-imaged to (+)-quinic acid (3, Scheme 1), the configuration at C(1) and C(4) remains the same. In other words, C(1) and C(4) are reflection-invariant, they are *not* chiral centers. In fact, the situation with respect to C(1) and C(4) is analogous to that in 1,4-dihydroxycyclohexanecarboxylic acid which is achiral but displays *cis-trans* isomerism.<sup>19</sup>

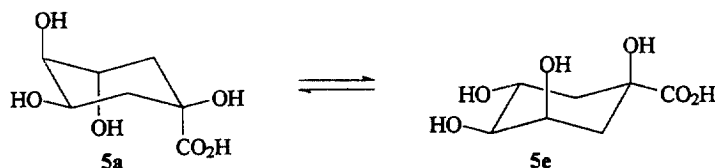
Since C(1) and C(4) are not chiral centers we must reject all names that assign capital-*R/S* descriptors to these atoms:  $1R-(1\alpha,3\alpha,4\alpha,5\beta)$ ,<sup>13,15</sup>  $(1R)-1,3c,4t,5t$ <sup>20a</sup> (note that locant 3 is here given to the OH *cis* to CO<sub>2</sub>H),  $1R,3R,4S,5R$ ,<sup>21</sup> and  $1R,3R,4R,5R$ <sup>14</sup> (note the inconsistency between the last two designations!). The 4th (latest printed) supplement of Beilstein's Handbuch<sup>20b</sup> gives the name as  $(3R)-1,3r,4t,5t$ -tetrahydroxycyclohexane-*c*-carboxylic acid. This name would appear correct if somewhat unconventional in that the reference (*r*) atom is C(3) rather than C(1) and the CIP symbol for C(5) is not explicitly indicated. We would have preferred the name to be  $(3R,5R)1,3c,4c,5t$ -tetrahydroxycyclohexane-*r*-carboxylic acid.

It is preferable, however, to name the compound entirely according to the CIP system as extended by Prelog and Helmchen.<sup>22,8d</sup> To apply their procedure to C(1), we expand 1 into a Fischer projection formula (4, Scheme 2) and note the hypothetical priority of the two branches ( $R_0$ ,  $S_0$ ) thereby induced. The symbol for C(1) thus becomes  $s_n$  (the subscript *n* standing for the fact that this is novel nomenclature as compared to the original CIP system). If we turn formula 1 180° (1'') we can then expand it into Fischer formula 4' (Scheme 2) which, in the same manner, leads to the descriptor  $s_n$  for C(4). Thus the complete name is  $(1s_n,3R,4s_n,5R)$ -tetrahydroxycyclohexanecarboxylic acid. In this system the question as to which carbon is C(3) and which C(5) is immaterial (the same descriptor would have been obtained if we had numbered counter-clockwise) and the carbon bearing the functional (carboxylic acid) group not only is C(1) but comes first in the descriptor.



Finally, we note that quinic acid can exist in two equilibrating chair conformations (Scheme 3); this does not affect the descriptors, however. It was postulated quite some time ago<sup>23</sup> that conformer 5e

would predominate and this was the only conformer detected in an early  $^{13}\text{C}$  NMR investigation.<sup>10</sup> However, a later more detailed study<sup>24</sup> involving proton–proton coupling constants disclosed that quinic acid actually exists as two conformers in rapid equilibrium, in a ratio **5e:5a** of 73:27, as might perhaps have been predicted from the fact that the syn-axial interactions in the two conformers are not energetically greatly different, if one assumes that a  $\text{CO}_2\text{H}/\text{OH}$  syn-axial interaction is somewhat smaller than the known  $\text{CH}_3/\text{OH}$  one.<sup>8e</sup>



Scheme 3.

### Acknowledgements

We are indebted to Dr E. M. Olefirowicz for the drawings and to Prof. J. Siegel for helpful discussions.

### References

- Hofmann, F. C. *Crell's Chemische Annalen* **1790**, 2, 314.
- Woskresensky, A. *Ann. Pharm.* **1838**, 27, 257.
- Emde, H. *Apotheker Ztg.* **1917**, 32, 601.
- Fischer, H. O. L.; Dangschat, G. *Ber. Dtsch. Chem. Ges.* **1932**, 65, 1009.
- Fischer, H. O. L.; Dangschat, G. *Helv. Chim. Acta* **1937**, 20, 705.
- Cahn, R. S., Ingold Sir C.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 385.
- It is, however, true that C(1) and C(4) are prochiral<sup>8a</sup> and the branches C(2)–C(3) and C(6)–C(5)—including the chiral centers at C(3) and C(5)—are diastereotopic.<sup>8a</sup> Accordingly quinic acid displays seven signals in its  $^{13}\text{C}$  NMR spectrum<sup>9,10</sup> and the OH groups at C(3) and C(5) are chemically distinct in that only the one *cis* to C(4) can be bridged to C(4) by formation of an acetonide.<sup>11</sup>
- ElieI, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*, Wiley: New York, 1994 (a) Chapter 8; (b) p. 750; (c) p. 666; (d) p. 667; (e) pp. 696, 707.
- Scholz-Böttcher, B. M.; Ludger, E.; Maier, H. G. *Justus Liebigs Ann. Chem.* **1991**, 1029.
- Kelley, C. J.; Harruff, R. C.; Carmack, M. *J. Org. Chem.* **1976**, 41, 449.
- Fischer, H. O. L. *Ber. Dtsch. Chem. Ges.* **1921**, 54, 775.
- Dictionary of Organic Compounds*, 6th Ed. Chapman and Hall: New York, 1996, Vol. 6, p. 5577.
- Budavari, S., Ed. *The Merck Index*, 12th Ed. Merck and Co., Inc.: Whitehouse Station, NJ 1996, p. 1385
- Catalog—Handbook of Fine Chemicals*, Aldrich Chemical Co.: Milwaukee, WI, 1996/97, p. 1291.
- Chemical Abstracts Index Guide 1992–1996. After this paper was accepted for publication, Dr James E. Blackwood of Chemical Abstracts (CA) informed the authors that CA has consistently named (-)-quinic acid **1R** on the basis of ref. 6 (rather than ref. 22), using the rule *seqcis>seqtrans* in going around the ring (OHs at positions 3,4 or 5,4 being fiduciary). Also, since the C(2,3,4) and C(6,5,4) branches are diastereomeric, it is his view that C(1) and C(4) should receive upper-case descriptors, even though he agrees that C(1) and C(4) are not chiral centers. It must be conceded that on the basis of ref. 6 (-)- and (+)-quinic acid and (-)- and (+)-epiquinic acid all differ in descriptors at C(1) and C(4).
- This would be analogous to the descriptors in aldohexoses [ $\beta$  at C(1) on the side of the  $\text{CH}_2\text{OH}$  group at C(6)] and of steroids [ $\beta$  on the side of the angular methyl groups].

17. Also indicated at the beginning of each volume of Beilsteins Handbuch; see ref. 20.
18. Mislow, K.; Siegel J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.
19. The situation is different in the (achiral) 3,5-*cis* stereoisomers since here OH(1) and OH(4) can be *independently cis* or *trans* to OH(3,5) thus generating a total of four *meso* isomers, all of which have been prepared.<sup>9</sup>
20. (a) Beilsteins Handbuch der Organischen Chemie, 3rd Supplement, Boit, H.-G., Ed. Springer Verlag: New York, Vol. 10, 1971, p. 2407. (b) *ibid.*, 4th Supplement, Lukenbach, R., Ed., Vol. 10, 1983, p. 2257.
21. Corse, J.; Lundin, R. E. *J. Org. Chem.* **1970**, *35*, 1904.
22. Prelog, V.; Helmchen, G. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 567.
23. Hanson, K. R. *J. Chem. Educ.* **1962**, *39*, 419.
24. Flores-Parra, A.; Gutiérrez-Avella, D. M.; Contreras, R.; Khuong-Huu, F. *Magn. Reson. Chem.* **1989**, *27*, 544.

(Received in USA 8 August 1997; accepted 9 September 1997)