Epimerization Mechanism of (+)-Mollisacacidin, its Diastereoisomers, and Related Flavan-3,4-diols

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EPIMERIZATION of (+)-mollisacacidin [(+)-3′,4′,7-trihydroxy-2,3-*trans*-flavan-3,4-*trans*-diol] by autoclaving leads to the (+)-forms of the 2,3-*trans*-3,4-*cis*-, 2,3-*cis*-3,4-*trans*-, and 2,3-*cis*-3,4-*cis*-diastereoisomers.[1,2] Under optimum conditions (2 hr. at 15 lb./sq. in.) these were recovered from the reaction mixture in 28, 12, 11, and 2·8% yields respectively, an apparent equilibrium being established.[2] The mechanism of the inversions at C-2 and C-4 is now examined by following the extent and direction of the epimerization of each diastereoisomer by means of two-dimensional paper chromatography, using water-saturated phenol and then 2% acetic acid. These conditions permit the separation of the mixture of four (+)-diastereoisomers.

In each instance a mixture of either three or four diastereoisomers results after autoclaving for 15 minutes and 2 hours (Table 1). The composition of the mixtures varied according to the starting material used, showing that true equilibria are not established after 2 hours, and that inversions occur with varying facility.

Thus, the 2,3-*cis*-3,4-*cis*-diastereoisomer is present in lowest concentration in each mixture after 2 hours irrespective of starting material, signifying that it has the energetically least-favoured configuration under these conditions. This contrasts with the relatively slow epimerizations of the 2,3-*cis*-3,4-*trans*- and 2,3-*trans*-3,4-*trans*-diols due, presumably, to their energetically more-favoured configurations. These observations are in apparent accord with the natural abundance of their enantiomers in *Guibourtia coleosperma* heartwood where the (−)-2,3-*cis*-3,4-*trans*-form predominates, with the (−)-2,3-*cis*-3,4-*cis*-isomer present in lowest concentration,[3,4] and also with the high natural abundance of (+)-2,3-*trans*-3,4-*trans*-forms in those *Acacia* spp. which are related to the black wattle (*A. mearnsii*).[5]

[1] S. E. Drewes and D. G. Roux, *Chem. and Ind.*, 1964, 1555.
[2] S. E. Drewes and D. G. Roux, *Biochem. J.*, 1965, **94**, 482.
[3] S. E. Drewes and D. G. Roux, *Chem. and Ind.*, 1964, 1799.
[4] S. E. Drewes and D. G. Roux, *Biochem. J.*, 1965 (in press).
[5] D. G. Roux, E. A. Maihs, and E. Paulus, *Biochem. J.*, 1961, **78**, 843.

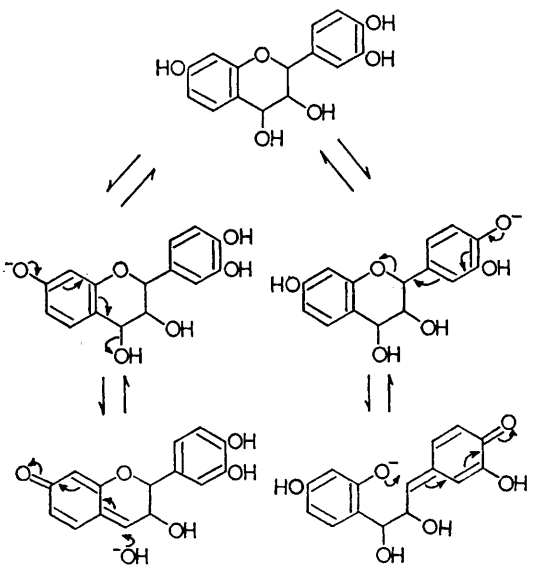
During the course of these epimerizations two diastereoisomers may result from inversion of the starting material at C-2 and C-4, respectively, whereas the third product must be formed by inversion at the remaining of these two asymmetric centres of one or both of these intermediates. Inversions at C-2 and C-4 occur seemingly with varying rapidity. For example, the 2,3-*cis*-3,4-*cis* → 2,3-*trans*-3,4-*cis* epimerization is rapid compared with the similar 2,3-*cis*-3,4-*trans* → 2,3-*trans*-3,4-*trans* conversion. This implies that the 4*ax*-OH of the latter (2,3-*cis*-3,4-*trans*) has a greater inhibiting effect on the inversion of the 2-phenyl group than the 4*eq*-OH of the former. The ready interconversion of the 2,3-*trans*-3,4-*cis*- and 2,3-*cis*-3,4-*cis*-diastereoisomers is indicative of an equilibrium between these forms in which the former predominates. This is in agreement with the recognised ease of inversion of 2,3-*cis*- to 2,3-*trans*-catechins, *e.g.* (−)-*epi*-catechin → (−)-catechin, and the corresponding difficulty of the reverse transformation, *e.g.* (+)-catechin → (+)-*epi*catechin.[6] Epimerization of the 2,3-*cis*-3,4-*trans*-diol gives low yields of the 2,3-*cis*-3,4-*cis*-diol signifying that inversion of 4*ax*-OH → 4*eq*-OH occurs with difficulty in this instance, and that during the epimerization of (+)-mollisacacidin (2,3-*trans*-3,4-*trans*) the route to the (+)-*cis*-*cis*-diol will be mainly through the (+)-*trans*-*cis*-intermediate according to the scheme A:

When a parallel series of epimerizations were attempted under similar conditions on the trimethyl ethers of the four diastereoisomeric (+)-leucofisetinidins, no inversions could be detected by the ionophoretic method[7]* for the 2,3-*trans*-3,4-*cis*- and 2,3-*cis*-3,4-*trans*-forms. However, a very low order of the inversions 2,3-*trans*-3,4-*trans* → 2,3-*trans*-3,4-*cis* and 2,3-*cis*-3,4-*cis* → 2,3-*cis*-3,4-*trans*, both of which occur

TABLE 1. *Percentages of (+)-diastereoisomeric flavan-3,4-diols present in the reaction mixture after autoclaving for 15 min. and 2 hr.*

Starting material	Leucofisetinidins (%) *trans-trans*	*trans-cis*	*cis-trans*	*cis-cis*
trans-trans	70 (60)†	15 (18)	15 (18)	0 (4)
trans-cis	15 (25)	50 (25)	20 (35)	15 (15)
cis-trans	14 (18)	6 (18)	80 (60)	0 (4)
cis-cis	6 (27)	44 (27)	6 (35)	44 (11)

† Values in parentheses are for the 2 hr. period.



(+)-2,3-*trans*-3,4-*trans*

(+)-2,3-*trans*-3,4-*cis* (+)-2,3-*cis*-3,4-*trans*

(+)-2,3-*cis*-3,4-*cis*

Scheme A

* The ionophoretic method has the limitation that no distinction between 2,3-*trans*-3,4-*trans* and 2,3-*cis*-3,4-*trans* forms is possible.

[6] E. A. H. Roberts and D. J. Wood, *Biochem. J.*, 1953, **53**, 332.
[7] S. E. Drewes and D. G. Roux, *Biochem. J.*, 1964, **92**, 555.

at C-4, was found. Methylation of the free phenolic hydroxyl groups clearly inhibits epimerizations, particularly of the 2-phenyl group.

Epimerizations at C-2 and C-4 of the free phenolic forms proceed, presumably, according to the following mechanisms, with retention of configuration at C-3. The mechanisms are based on the presumed partial dissociation of the 4′- and 7-hydroxyl groups, those involving the 2-phenyl group being similar to that invoked by Whalley[8] to explain the epimerizations of catechins. Methylation of the phenolic hydroxyl groups should, therefore, inhibit the epimerizations of diastereoisomeric flavan-3,4-diols.

Other natural flavan-3,4-diols, *e.g.* (−)-leucofisetinidin (2,3-*trans*-3,4-*trans*-configuration) and (−)-melacacidin and (−)-teracacidin (both 2,3-*cis*-3,4-*cis*) undergo epimerizations similar to those of the corresponding configurations in Table 1.

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[8] P. P. Mehta and W. B. Whalley, *J. Chem. Soc.*, 1963, 5327.