Mechanism of the Conversion of Flavan-3,4-diols into Dihydroflavonols and Flavanones in Acid Medium

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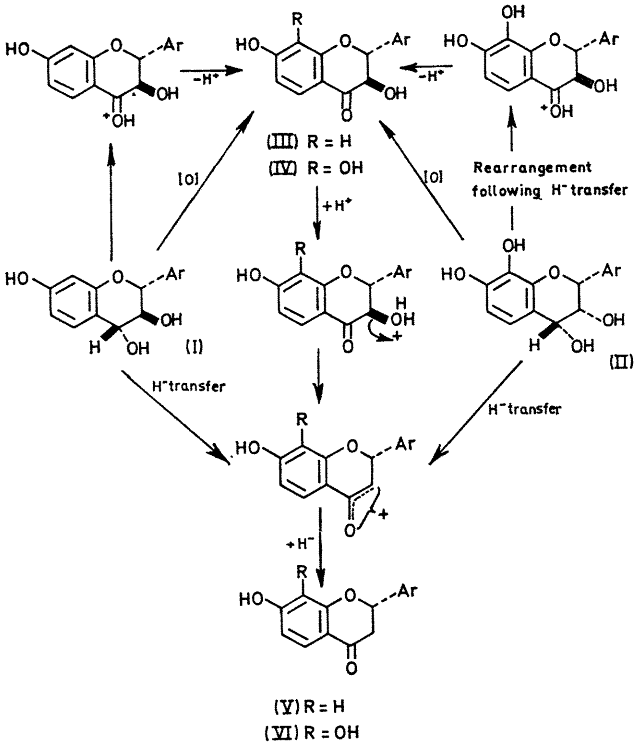
Summary Substitution reactions of mercaptoacetic acid with 2,3-*trans*- and 2,3-*cis*-flavan-3,4-diols and 2,3-*trans*-flavan-[4-^{2}H]-3,4-diols illustrate the mechanism of their conversion into dihydroflavonol and flavanone analogues as side-reactions.

READY conversion of (+)-2,3-*trans*-3,4-*trans*-flavan-3,3′,4,4′,7-pentaol (I) into the 2,3-*trans*-dihydroflavonol analogue, (+)-fustin (III), and the stereochemically analogous flavanone, (—)-butin (V), occurs as side reactions to the substitution (S_N1) at C-4 of the flavan-3,4-diol with mercaptoacetic acid.[1] Compound (III) is formed at least partly by autoxidation of the flavan-3,4-diol, since the side reactions are eliminated in the absence of oxygen. We have confirmed the suggested mechanism[1] of reduction of the dihydroflavonol to the flavanone (Scheme) by applying the same reaction to (—)-2,3-*cis*-3,4-*cis*-flavan-3,3′,4,4′,7,8-hexaol (II) [(—)-melacacidin]. The expected 4-*axial* substitution product, identified after methylation as methyl (—)-[2,3-*cis*-3,4-*trans*-3-hydroxy-3′,4′,7,8-tetramethoxyflavan-4-ylthio]acetate, $[\alpha]_D^{22}$ —56° in acetone–water (9 : 1 v/v), predominates. This is accompanied, as before,[1] by the methyl ether, m.p. 163°, $[\alpha]_D^{25}$ +12·0°, of compound (IV) and by the corresponding methyl ether, m.p. 133°, $[\alpha]_D^{25}$ $-43{\cdot}7°$ of compound (VI). The absolute configurations (IV) and (VI) were confirmed by c.d. comparisons.



Ar = 3,4-dihydroxyphenyl.

Initial oxidation of the 2,3-*cis*-flavan-3,4-diol at the benzylic position gave the 2,3-*cis*-dihydroflavonol (*cf.* ref. 2) followed by selective and complete inversion at C-3 into the (+)-2,3-*trans*-dihydroflavonol analogue of (−)-melacacidin. Such inversion implies the formation of a carbonium ion at C-3; the mutual repulsion of charges between the C-3 carbonium ion and the C-4 carbonyl position makes this unlikely except when the carbonium ion is stabilized by resonance. Such evidence supports the suggestion[1] that the flavanones in the above reactions originate from dihydroflavonol analogues by removal of the 3-hydroxy-group after its initial protonation (*cf.* Scheme), followed by abstraction by the resultant unstable C-3 carbonium ion of a hydride ion from the benzylic position of the flavan-3,4-diol in an oxidation–reduction mechanism.

The hydride ion transfer was accordingly examined by the reaction of the mercaptoacetic acid with synthetic (±)-3′,4′,7-trimethoxyflavan-[4-^{2}H]-3,4-diol, m.p. 136°, $J_{2,3}$ 10·0 Hz (AB-quartet). In contrast with the free phenolic or methylated flavan-3,4-diols which readily yield both dihydroflavonol and flavanone analogues, the 4-deuterium derivative gives only the former in the side-reaction and no significant yield of flavanone, even after doubling of the reaction time. Such inhibition of flavanone formation is indicative of the higher energy requirement for removal of deuteride as compared with hydride ions from the 4-position in this reaction, and as indirect proof of hydride ion transfer where the flavanone is formed. Positive evidence of hydride ion transfer under acid conditions has been obtained from the reduction of diaryl- and triaryl-methanols by alcohols, where deuterium-labelling has shown that the α-hydrogen appears at the point of reduction of the newly formed hydrocarbon.[3]

The "difficult" conversion of dihydroflavonols into flavanones has possible biosynthetic implications since the oxidative–reductive transformation could contribute to the association of almost all types of flavanoid analogues based on finite phenolic hydroxylation patterns common amongst almost all South African and Australian *Acacia* spp.[4] Birch[5] has suggested the reverse, *i.e.* oxygenation of flavanones at C-3 as the probable origin of 3-hydroxyflavanoids from chalcones (*cf.* ref. 6).

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