The Stereochemistry of 2-α-Hydroxybenzyl-2,4,6-trimethoxycoumaran-3-one. Mechanism of the Algar–Flynn–Oyamada Reaction

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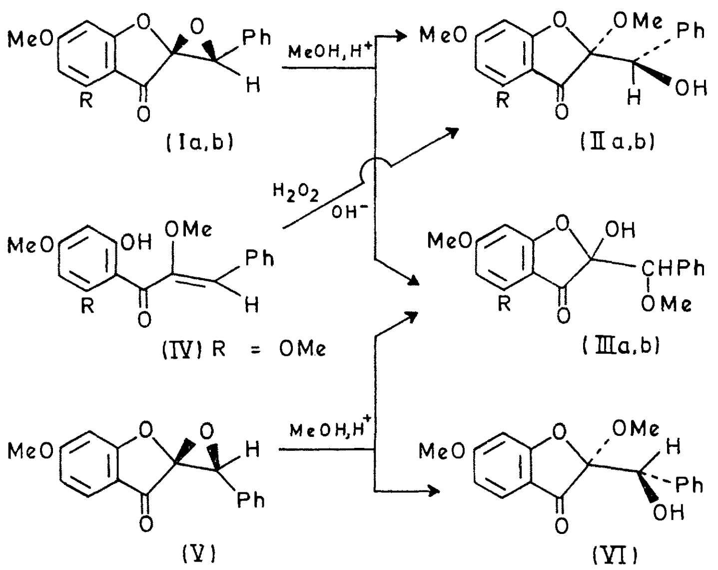
Summary Stereochemistry is assigned to the 2-α-hydroxy-2,4,6-trimethoxycoumaran-3-one obtained by alkaline hydrogen peroxide oxidation of 2′-hydroxy-α,4′,6′-trimethoxychalcone.

4,6-*trans*-DIMETHOXYAURONE EPOXIDE (Ib), synthesised by condensation of 4,6-dimethoxycoumaran-3-one and benzaldehyde followed by epoxidation with alkaline hydrogen peroxide, afforded on treatment with hot methanol containing a trace of concentrated sulphuric acid a mixture of two isomeric aurone derivatives (IIb) and (IIIb) in the ratio of 2 : 7. The minor isomer (IIb) was identical with the product obtained[2] from the reaction of 2′-hydroxy-α,4′,6′-trimethoxychalcone (IV) with alkaline hydrogen peroxide (Algar–Flynn–Oyamada reaction) (Scheme 1).

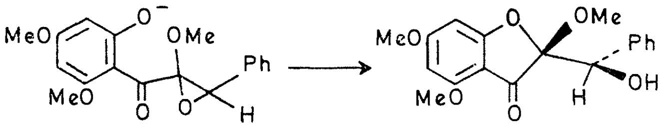
Coumaranone (IIb) was assigned the *erythro*-configuration on the basis of the known stereochemistry of the aurone epoxide and on the mode of opening of the oxiran ring. Aurones obtained by the condensation of coumaranones with aromatic aldehydes have the *trans*-configuration[1] as have the epoxides derived from them on alkaline hydrogen peroxide epoxidation.[1]. Attack by methanol on the α-carbon of *trans*-aurone epoxide (Ib) with attendant inversion of configuration at that site (S_N2 process) produces the *erythro*-diastereomer (IIb). The operation of an S_N1 mechanism was considered improbable, as such a process would entail formation of a carbonium ion at a position α to the carbonyl group. This conclusion was supported by the facts that both *cis*- and *trans*[3]-6-methoxyaurone epoxides (V and Ia) on acid-catalysed methanolysis gave as minor product only one α-methoxy-derivative in each case, and that these derivatives (VI and IIa) were diastereomeric.



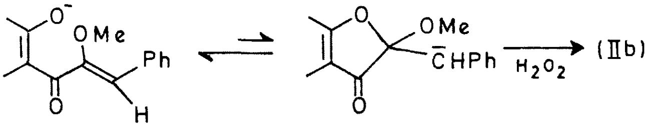
SCHEME 1. a; R = H, b; R = OMe.

The structure of coumarone (IIb) is of interest from the viewpoint of the mechanism of the Algar–Flynn–Oyamada reaction. Dean and Podimuang concluded[4] from an investigation of the mechanism of this reaction that, contrary to earlier postulates, epoxides did not participate in the alkaline hydrogen peroxide oxidation of 2′-hydroxychalcones to flavonols, but accepted the earlier suggestion that epoxides were intermediates in the formation of aurones from 6′-substituted-2′-hydroxychalcones. These authors did not discuss the stereochemical structures of the products of the reaction.

From a consideration of the concept of "overlap control"[5,6] it is reasonable to assume that chalcone (IV), which was prepared by the condensation of 2′-hydroxy-α,4′,6′-trimethoxyacetophenone and benzaldehyde, and the suggested epoxide intermediate (VII) in the Algar–Flynn–Oyamada reaction would have *trans* (phenyl/carbonyl groups) configurations. Attack by the phenoxide anion on the oxiran ring in intermediate (VII) would be expected to proceed with inversion of configuration at the point of attack (α-carbon) to give an aurone derivative with the *threo*-configuration (VIII). However, as reported above, the *erythro*-diastereomer was obtained in the Algar–Flynn–Oyamada reaction, and consequently, if the above assumptions are correct and equilibration through a reverse aldol reaction has not taken place, a *trans*-chalcone epoxide is not an intermediate in the reaction. A further indication of the non-participation of an epoxide intermediate was the failure of the *O*-tosyl derivative of chalcone (IV) to epoxidise under Algar–Flynn–Oyamada reaction conditions.[7] An alternative mechanism, analogous to the non-concerted mechanism suggested by Dean and Podimuang[4] for flavonol production, leading to the formation of aurone derivatives is outlined in Scheme 2. However, the mechanistic course of the Algar–Flynn–Oyamada synthesis of aurone derivatives remains uncertain.



(VII) (VIII)



SCHEME 2

Analytical and spectroscopic data of all new compounds mentioned are consistent with the structures assigned to them.

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[1] Preceding communication.

[2] D. M. X. Donnelly, T. P. Lavin, D. P. Melody, and E. M. Philbin, *Chem. Comm.*, 1965, 460.

[3] B. A. Brady, M. Geoghegan, W. I. O'Sullivan, and E. M. Philbin, *Chem. and Ind.*, 1967, 2004.

[4] F. M. Dean and V. Podimuang, *J. Chem. Soc.*, 1965, 3978.

[5] H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, 1959, **81**, 2086.

[6] H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Amer. Chem. Soc.*, 1959, **81**, 108.

[7] J. A. Kennedy, Ph.D. Thesis, National University of Ireland, 1969.