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FLAVANOID EPOXIDES V[1]

Stereochemistry of Flavindogenide Epoxides

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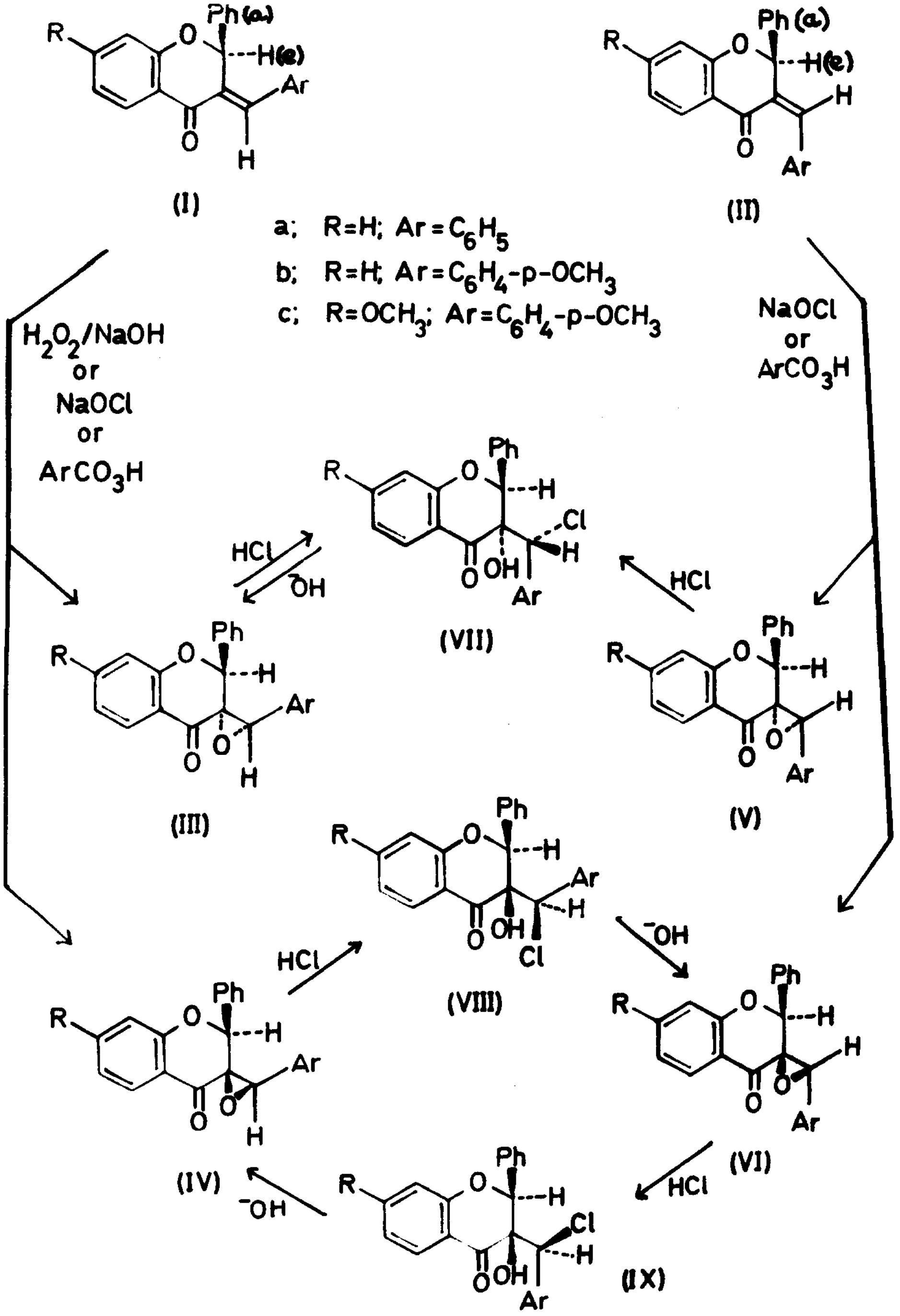
trans-3-Arylideneflavanones[2,3] (flavindogenides) (Ia,b,c) on epoxidation with alkaline hydrogen peroxide or with sodium hypochlorite gave in each case a mixture of two isomeric *trans*-flavindogenide epoxides (IIIa,b,c) and (IVa,b,c) in ratios of about one to three. Reaction of *cis*-flavindogenides (IIa,b,c) with alkaline hydrogen peroxide gave the same *trans*-epoxides (IIIa,b,c) and (IVa,b,c) in each instance in ratios of approximately one to seven. With sodium hypochlorite, however, *cis*-flavindogenides (IIa,b,c) gave the isomeric *cis*-epoxides (Va,b,c) and (VIa,b,c) in ratios of about five to one.

The configurations of the epoxides were correlated by the following reactions (Scheme I). *trans,trans*-Flavindogenide[3] epoxides (IIIb,c) on treatment with dry hydrogen chloride in benzene-ether caused the epoxide ring to open with inversion of configuration at the point of attack (*trans*-opening) to yield *erythro*-chlorohydrins (VIIb,c). Cyclisation of the latter compounds with base regenerated the original epoxides. On the other hand treatment of *trans,cis*-flavindogenide epoxides (IVb,c) and of *cis,trans*- and *cis,cis*-flavindogenide epoxides (Vb,c) and (VIb,c) with hydrogen chloride in benzene-ether caused the epoxide ring to open with retention of configuration (*cis*-opening) to give *threo*-chlorohydrins (VIIIb,c) and *erythro*-chlorohydrins (VIIb,c) and (IXb,c) respectively. Cyclisation of chlorohydrins (VIIIb,c) gave *cis,cis*-epoxides (IVb,c) and cyclisation of chlorohydrins (IXb,c) yielded *trans,cis*-epoxides (IVb,c).

Since treatment of the epoxides with hydrochloric acid followed by recyclisation of the chlorohydrins formed does not involve a change in stereochemistry at C-2 or C-3, the relative configurations at these positions must be the same in epoxides (IIIb,c) and Vb,c) and in epoxides (IVb,c) and (VIb,c).

SCHEME I



a; R=H; Ar=C_6H_5

b; R=H; Ar=C_6H_4-p-OCH_3

c; R=OCH_3; Ar=C_6H_4-p-OCH_3

That the epoxides have the structures and configurations shown in Scheme I was deduced by an examination of the products of *m*-chloro- or *p*-nitro- perbenzoic acid epoxidation of the flavindogenides. Epoxidation of *cis*-flavindogenides (IIa,b) with *m*-chloroperbenzoic acid gave in each case mixtures of epoxides (Va,b) and (VIa,b) in ratios of about 3.5 to 1. Since epoxidation of olefins by peracids is known to be stereospecific[4] these epoxides are *cis*-flavindogenide epoxides. Similarly epoxidation of *trans*-flavindogenide (Ib) with aromatic peracids gave *trans*-epoxide (IIIb) only, while *trans*-flavindogenide (Ia) gave predominantly *trans*-epoxide (IIIa) together with a trace of *trans*-epoxide (IVa).

In the oxidation of olefins by peracids attack by the reagent normally occurs[5] from the less hindered side of the molecule, which in flavindogenides is the side opposite to the axial[2] phenyl group at position 2. Thus it is concluded that epoxides (IIIa,b) and (Va,b) have the phenyl group at position 2 and the epoxidic oxygen at position 3 *trans* orientated. It follows that in epoxides (IVa,b) and (VIa,b) these groups have a 2,3-*cis* relationship.

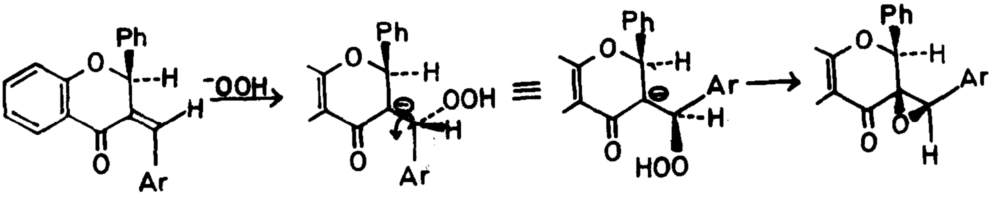
The N.M.R. spectra of the epoxides are consistent with the above assignments, and indicate that in isomers (IIIa,b,c), (IVa,b,c) and (VIa,b,c) the 2-phenyl group is axial, and equatorial in isomers (Va,b,c).

The epoxidic protons in isomers (Va,b,c) give signals considerably upfield and the protons on C-2 give signals downfield relative to the signals given by these protons in isomers (IIIa,b,c), (IVa,b,c) and (VIa,b,c). A comparison of these structures using Dreiding models shows that the epoxidic protons are closer to the shielding influence of the 2-phenyl (equatorial) group and that the protons at C-2 are further removed from the shielding influence of the epoxide ring in isomers (Va,b,c) relative to the positions of these protons to the same groups in isomers (IIIa,b,c), (IVa,b,c) and (VIa,b,c) where the 2-phenyl groups are axial.

If the ratio of products formed in the alkaline hydrogen peroxide epoxidation of *trans*-flavindogenides (Ia,b,c) were controlled by the steric approach of the reagent, *trans,trans*-epoxides (IIIa,b,c) should be the major products. This is not the case, and examination of models shows that, while initial attack of the double bond on the opposite side of the axial 2-phenyl group (*trans*-attack) would be favoured, in the resulting transition state the two aryl groups are forced closer to each other, whereas in the transition state resulting from *cis*-attack, the aryl groups are further apart. Consequently, *cis*-attack appears more energetically favoured and *trans,cis*-epoxides (IVa,b,c) resulting from *cis*-attack of the hydroperoxide ion are the major products.

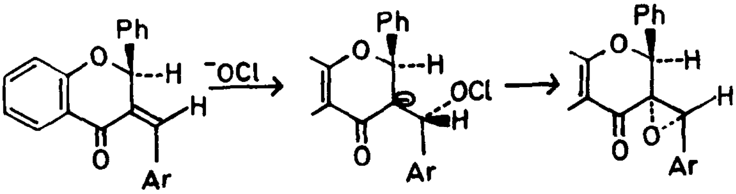
The ratio of products obtained from the alkaline hydrogen peroxide epoxidation of *cis*-flavindogenides (IIa,b,c) suggests that the reaction proceeds at least partially by the mechanism (for the major product) outlined in Scheme II. Some isomerisation to *trans*-flavindogenides (Ia,b,c) may precede epoxidation.

SCHEME II



For the hypochlorite epoxidation of *cis*-flavindogenides a nucleophilic stereospecific mechanism would account for the ratio of products found.

SCHEME III



(V)

cis,trans-Epoxide (V) is the major product expected by such a mechanism (outlined in Scheme III) involving hypochlorite attack of the olefin from the far side of the axial 2-phenyl group followed by fast elimination of the chloride ion with the formation of the epoxide ring. The minor product is formed by initial attack of the olefin from the more hindered side. A further study of the mechanism of this reaction is in progress.

Satisfactory analyses were obtained for all new compounds mentioned.

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References

1. Communication IV, B. Brady, M. Geoghegan, W. I. O'Sullivan and E. M. Philbin, *Chem. and Ind.,* in press.

2. J. R. Doherty, D. D. Keane, K. G. Marathe, W. I . O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Chem. and Ind.,* 1967, 1641.

3. The terms *cis*- and *trans*- prefixed to flavindogenides and their epoxides refer to the relative positions of the carbonyl and the side chain aryl groups; when a second term is prefixed it refers to the relative positions of the phenyl group at position 2 and the epoxidic oxygen at position 3. All flavindogenides and their epoxides and related compounds mentioned in this communication are racemates.

4. D. Swern, *J. Am. Chem. Soc.*70, 1235 (1948); H. H. Wasserman and N. E. Aubrey, *ibid.* 77, 590 (1955); H. E. Zimmerman, L. S. Singer and B. S. Thyagarajan, *ibid.* 81, 108 (1959).

5. The direction of attack may be influenced by nearby polar substituents, see H. O. House, *Modern Synthetic Reactions,* W. A. Benjamin, Inc., New York, 1965, p. 114.