Tetrahedron Vol. 27, pp. 3535 to 3539 Pergamon Press 1971. Printed in Great Britain

FLAVANOID EPOXIDES—XI[1]

THE STEREOSPECIFIC EPOXIDATION OF 3-ARYLIDENEFLAVANONES BY SODIUM HYPOCHLORITE

D. D. KEANE, W. I. O'SULLIVAN* and E. M. PHILBIN
Department of Chemistry, University College, Belfield, Dublin 4, Ireland

and

R. M. SIMONS and P. C. TEAGUE*
Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

(*Received in the UK* 16 *March* 1971; *Accepted for publication* 1 *April* 1971)

Abstract—The sodium hypochlorite epoxidation of 3-arylideneflavanones (flavindogenides) is shown to be stereospecific. The results and mechanism of the hypochlorite and of the alkaline hydrogen peroxide epoxidations of flavindogenides are compared.

EPOXIDATION of α,β-unsaturated ketones by hypochlorite ion was first reported by Zinke[2] who used calcium hypochlorite to expoxidize 1,4-napthoquinone. Sodium hypochlorite was used subsequently to epoxidize α,β-unsaturated aldehydes,[3] ketones[4,5] and nitriles.[6,7a,b] While the work now described was in progress the stereospecific epoxidation of a series of β,β-disubstituted α-cyanoacrylates by means of sodium hypochlorite was reported.[7a]

Recently[8] we described the preparation and defined the stereochemistry of the four isomeric epoxides derived from *trans*- and *cis*-flavindogenides.* Treatment of *trans*-(**1a**, **b**, **c**) or *cis*-flavindogenides (**2a**, **b**, **c**) with alkaline hydrogen peroxide gave in each case a mixture of the two isomeric *trans*-flavindogenide epoxides (**3a**, **b**, **c** and **4a**, **b**, **c**), the reagent proving to be stereoselective, while *m*-chloroperbenzoic acid stereospecifically produced the *trans*- epoxides (**3a**, **b** and **4a**) from **1a**, **b** and *cis*-epoxides (**5a**, **b** and **6a**, **b**) from **2a**, **b**. We now report a study on the epoxidation of *trans*- and *cis*-flavindogenides by sodium hypochlorite in which the reagent is shown to be stereospecific for these compounds.

Treatment of a pyridine solution of **1a**, **b**, **c** with an aqueous solution of sodium hypochlorite gave the *trans*-epoxides **3a**, **b**, **c** and **4a**, **b**, **c** while the *cis*-epoxides **5a**, **b**, **c** and **6a**, **b**, **c** were produced from **2a**, **b**, **c** (Scheme 1). Sodium hypobromite produced flavindogenide epoxides **3c** and **4c** from **1c** in approximately the same proportion (Table 1) as did sodium hypochlorite. The yields of epoxides were almost quantitative and the relative proportions of the two epoxides produced in each reaction could be determined from the NMR spectrum of the product as each component has a well separated singlet corresponding to a single proton. The ratios of the respective epoxides obtained by use of sodium hypochlorite are shown in Table 1.

* The terms *cis* and *trans* prefixed to flavindogenides and their epoxides refer to the relative positions of the carbonyl and side chain aryl groups; when a second term is prefixed it refers to the relative position of the phenyl group at position 2 and epoxide oxygen at position 3.

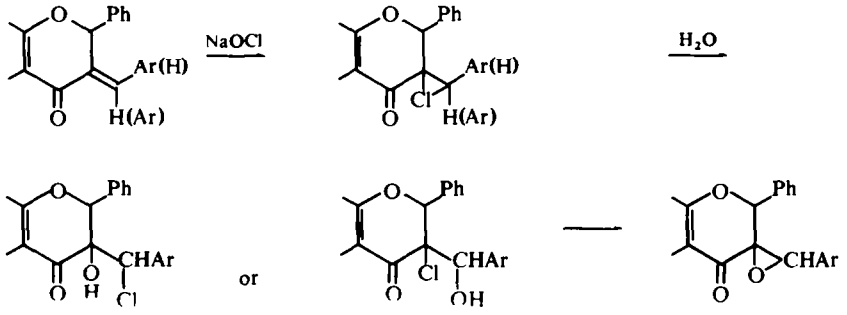
SCHEME 1

TABLE 1. RATIOS OF FLAVINDOGENIDE EPOXIDES FROM NaOCl

Flavindogenide	% Epoxides	Flavindogenide	% Epoxides
1a	21 **3a** 79 **4a**	**2a**	85 **5a** 15 **6a**
1b	23 **3b** 77 **4b**	**2b**	85 **5b** 15 **6b**
1c	22 **3c** 78 **4c**	**2c**	81 **5c** 19 **6c**

The stereospecificity of the sodium hypochlorite epoxidation could be accounted for by attack of the olefin bond of the flavindogenide by hypochlorous acid, present to some extent in aqueous hypohalite solution, to form an intermediate chlorinium ion (Scheme 2). However, there are objections to this pathway. If a chloronium ion were an intermediate the flavindogenides would be expected to react with other sources of positive halogen such as N-bromosuccinimide or hypochlorous acid itself. However, both *cis*, and *trans*-flavindogenides were inert to these reagents. In addition, alkenes (in which the double bond is not conjugated to a carbonyl group) would be expected to form epoxides; however, only starting material was recovered when a solution of *trans*-1,2-diphenylethylene in pyridine was treated with aqueous sodium hypochlorite.[9] Furthermore, a mechanism involving a chloronium ion intermediate (Scheme 2) does not account for the ratio of epoxides formed from

SCHEME 2



cis-flavindogenides; if the reaction took place by such a mechanism the *cis,cis*-epoxides (**6a, b, c**) should be the major products with initial attack by the chloronium ion *trans* to the 2-phenyl group as in the peracid epoxidations.[8]

A possible mechanism for the sodium hypochlorite epoxidation reaction is attack on the flavindogenide olefinic bond by hypochlorite ion, followed by ring closure with elimination of the chloride ion (Scheme 1). On the basis of kinetic studies with *o*-chlorobenzylidenemalononitrile Rosenblatt and Broome[6] suggested such a nucleophilic mechanism for the sodium hypochlorite epoxidation of negatively substituted olefins.

This mechanism is analogous to that of alkaline hydrogen peroxide epoxidation[8] and is supported by the fact that the ratio of *trans*-epoxides (**3a, b, c** and **4a, b, d**) obtained from *trans*-flavindogenides (**1a, b, c**) are almost the same for both reagents. Two *trans*-epoxides result from *trans*-flavindogenides since the hypochlorite ion attacks the double bond *cis* and *trans* to the axial 2-phenyl group.

In the case of the hypochlorite epoxidations of *cis*-flavindogenides (**2a, b, c**) the same mechanism accounts for the product distribution and the stereochemical course of the reaction (Scheme 1) A preferential attack by hypochlorite ion on the least hindered side[10,*] of the molecule will produce the *cis,trans*-epoxide (**5a. b. c**) as the major product (Table 1). The stereospecificity of the reaction may be attributed to the fact that ring closure, by cyclisation of the enolate anions to form epoxides, occurs more rapidly than rotation about the C3-Cβ bond. This is in contrast to the alkaline hydrogen peroxide epoxidation mechanism where the lifetime of the enolate anion is sufficiently long for such rotation to occur. This finding is in keeping with the chloride being a better leaving group than the hydroxide ion.

Robert and Foucaud[7b] suggested a mechanism involving a concerted *trans* attack of the olefin bond by OH^- and HOCl to form an intermediate chlorohydrin in a stereospecific sodium hypochlorite epoxidation of ethyl α-cyanoacrylates. If this mechanism were operating in the hypochlorite epoxidation of *cis*-flavindogenides the *cis.cis*-epoxide should be the major product through a preferential attack by the bulkier HOCl molecule on the side of the flavindogenide molecule away from the 2-phenyl group. However, the *cis,trans*-isomer is the major product. It is possible that the epoxidations of the two classes of compounds takes place by different mechanisms. The epoxidations of ethyl α-cyanoacrylates were carried out in ethanol at pH 7 while the epoxidations of flavindogenides were carried out in pyridine* at pH 12 to 13. In test runs using sodium hypochlorite (12%) in pyridine at pH 13·6 epoxidations of *cis*- and *trans*-flavindogenides were complete in about 0·5 min. The relatively high speeds of the reactions at this pH value suggest that the rates are not dependent on the concentration of HOCl.

To date the most plausible mechanism for the hypochlorite epoxidation of flavindogenides is that outlined in Scheme 1 but further investigations of this reaction are in progress.

EXPERIMENTAL

Materials. Freshly prepared NaOCl aq[12] or 5–6% stabilized commercial solns (Baker and Adamson or Clorox) were equally effective in the epoxidation reactions. Reagent grade pyridine (Baker and Adamson) was used without further treatment. *cis*-(**2a, b, c**) and *trans*-Flavindogenides (**1a, b, c**) were prepared as described previously.[10]

Epoxidation of flavindogenides by sodium hypochlorite. The flavindogenide epoxides, except **5c** and **5'c** (see below) have been characterized previously.[8] In initial NaOCl experiments the individual epoxides were isolated and purified. Physical and spectral properties were identical with authentic samples. In subsequent experiments the reaction products were isolated, weighed, and analyzed by NMR (Table 1). The yields of the epoxides were essentially quantitative. The following experiment illustrates the general procedure for the sodium hypochlorite epoxidations.

(1) To a stirred soln of *trans*-**1b** (1 g) in 25 ml pyridine at room temp was added 5 ml of 5% NaOCl aq. After 30 min the mixture was cooled to 0° and diluted with water. The white ppt was dissolved in 10 ml EtOH. The solid (0·9 g) which separated on cooling the resulting soln to −5° was shown by NMR analysis to contain 77% *trans,cis*-**4b** and 23% *trans,trans*-**3b**. These ratios were determined by integration of the signals at 5·60 τ and 4·61 τ in the NMR spectrum of the product.

* Although NMR studies of the *cis*-flavindogenide **2a** indicated there was little energy difference between its two conformers.[10] the results of the peracid and hydrogen peroxide epoxidations appear to indicate[8] that an axial 2-phenyl group is the preferred conformation.

* The percentage of HOCl present as such in sodium hypochlorite solution at pH 7 is 72% and at pH 12 is 0·003%.[11]

The same results were obtained when a freshly prepared NaOBraq was used instead of the NaOClaq.

(2) The following experiment was carried out separately on *trans*-**1a** and *cis*-**2a** and *trans*-**1b**.

Aqueous sodium hypochlorite (5 ml; ~12%) was added to a stirred soln of the flavindogenide (0·5 g) in pyridine (25 ml) at room temp. After 0·5 min the mixture was poured onto a mixture of crushed ice and 10% HCl and the resulting ppt was extracted with ether. The residual oil obtained on removal of the dried ethereal soln was analysed by NMR spectroscopy. In each case the NMR spectrum of the product was that of a mixture of the expected epoxides and the reaction was shown to be complete by the absence of the β-proton signal expected for the starting flavindogenide.

A soln obtained by mixing 5 ml NaOClaq used in the above experiment with 25 ml pyridine recorded a pH of 13·6 on a pH meter (Model 38A, Electronic Instrument).

cis,trans-3-*Anisylidene-7-methoxyflavone epoxide* (**5c**). In a similar experiment *cis*-**2c** (1 g) gave a solid which was dissolved in ether (20 ml) at reflux and hot hexane (75 ml) was added. When the soln was cooled, needles of *cis,cis*-**6c** (0·1 g), separated, mp and mmp 185–189°.

An amorphous solid was isolated from the filtrate which on repeated crystallisations from hexane–ether and hexane-chloroform gave *cis,trans*-**5c**; mp 161–163° (dec); IR ($CHCl_3$) 2840 cm^{-1} (OCH_3) and 1696 cm^{-1} (C=O); NMR ($CDCl_3$) τ 2·36 (perturbed doublet, J = 10 c/s, 1, 5-H), 2·45–3·6 (complex multiplet, 11, Ar-H), 4·19 (s, 1, 2-H), 6·22 (s, 3, OCH_3), and 6·33 (s, 4, OCH_3, β-H). (Found: C, 73·85; H, 5·22. Calcd. for $C_{24}H_{20}O_5$: C, 74·21; H, 5·19%).

cis,trans-3-*Anisylidene-7-methoxyflavanone epoxide*-β-d (**5'c**). The deuterated *cis,trans*-**5'c**, mp 160–162° (dec) was prepared from *cis*-3-anisylidene-7-methoxyflavanone-β-d[10] and NaOClaq under conditions similar to those described in the previous experiment. The IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of the compound were essentially identical with those of the nondeuterated isomer except for the absence of a small band at 968 cm^{-1} in the IR spectrum, and the signal at τ 6·33 in the NMR spectrum integrated for 3 instead of 4 protons and allows assignment of the β-H to this field position.

Treatment of flavindogenides with N-*bromosuccinimide*. N-Bromosuccinimide (0·15 g; 95%) was added to a suspension of *trans*-**1a** (0·25 g) in 10 ml water. The mixture was stirred for 12 hr at 25° and then extracted with ether. The yellow oil obtained on removal of the solvent from the ethereal soln crystallized from EtOH in yellow rhombs of **1a** (0·2 g). A mixture m.p. with the starting material showed no depression. There was no evidence by TLC of a second product in the mixture.

Similar results were obtained when water–DMSO, dioxan–diglyme and acetone (with additiion of dil H_2SO_4) were substituted for water as the solvent.

REFERENCES

[1] [a] Communication X, B. A. Brady, W. I. O'Sullivan and E. M. Philbin, *Chem. Comm.* 1435 (1970); [b] preliminary communication, J. R. Doherty, D. D. Keane, K. G. Marathe, W. I. O.Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Tetrahedron Letters* 441 (1968)

[2] T. Zincke, *Ber. Dtsch. Chem. Ges.* **25**, 3599 (1892)

[3] C. Schaer, *Hel. Chim. Acta* **41**, 560 (1958); **41**, 614 (1958)

[4] R. C. Fuson and R. Johnson, *J. Am. Chem. Soc.* **68**, 1668 (1946)

[5] S. Marmor, *J. Org. Chem.* **28**, 250 (1963); **30**, 3556 (1965)

[6] D. H. Rosenblatt and G. H. Broome, *Ibid.* **28**, 1290 (1963)

[7] [a] A. Robert, *C. R. Acad. Sci., Paris* Ser. C. **263**, 1439 (1966); [b] A. Robert and A. Foucaud, *Bull. Soc. Chim. Fr.* 2531 (1969)

[8] D. D. Keane, W. I. O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Tetrahedron* **26**, 2533 (1970)

[9] H. J. Leighton and W. O. Lever, University of South Carolina, personal communication

[10] D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *J. Org. Chem.* **35**, 2286 (1970)

[11] J. A. Horton, M. A. Laura, S. M. Kalbag and R. C. Petterson, *J. Org. Chem.* **34**, 3366 (1969)

[12] F. B. Mallory, *Organic Synthesis*, Coll. Vol. IV, p. 74. Wiley, New York, N.Y. (1963)