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FLAVANOID EPOXIDES—VI [1]

STEREOCHEMISTRY OF FLAVINDOGENIDE EPOXIDES

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Abstract—The four possible isomeric flavindogenide (3-arylideneflavanone) epoxides (type III, IV, V and VI) have been synthesized and their configurations assigned on the basis of chemical and spectroscopic data. Suggested mechanisms for the epoxidation reactions are discussed.

RESULTS

TREATMENT of *cis*- (IIa, b, c,) or *trans*- flavindogenides[2, 3a] (Ia, b, c) with alkaline hydrogen peroxide gave in each case a mixture of two isomeric *trans*-flavindogenide epoxides (IIIa, b, c) and (IVa, b, c) in the ratios shown in Table 1. The yields of

TABLE 1

Flavin-dogenide	Reagent	Ratio of epoxides in products			
		trans,cis- to *trans,trans*-		*cis,trans*- to *cis,cis*-	
trans Ia	H_2O_2/NaOH	3·2	1	—	—
	Peracid[a]	1	20	—	—
trans Ib	H_2O_2/NaOH	3·1	1	—	—
	peracid[a, b]	—	(100%)	—	—
trans Ic	H_2O_2/NaOH	3·3	1	—	—
cis IIa	H_2O_2/NaOH	7·4–8·0	1	—	—
	Peracid[a]	—	—	4·2	1
cis IIb	H_2O_2/NaOH	7·2	1	—	—
	peracid[a]	—	—	3·3	1
cis IIc	H_2O_2/NaOH	7·3	1	—	—

[a] *m*-chloropenbenzoic acid. [b] *p*-nitroperbenzoic acid

epoxides were almost quantitative and the NMR spectra of the reaction mixtures showed no other products. In each experiment it was possible to calculate the relative proportions of the two epoxides since each component had a singlet corresponding to a single proton and these singlets were well separated in the NMR spectrum. Although

* (a) The term *cis*- or *trans*- prefixed to flavindogenides and their epoxides refers 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 epoxide oxygen at position 3. All flavindogenides and their epoxides and related compounds mentioned in this communication are racemates; (b) the discussion will be based on the reactions of *trans*- and *cis*-flavindogenides Ib and IIb and their derivatives. The reactions of *trans*- and *cis*-flavindogenides (Ia, c) and (IIa, c) and their derivatives are analogous.

a *cis*- or *trans*- flavindogenide gave the same two epoxides, they were obtained in significantly different ratios (Table 1); the formation of epoxides from the *trans*-isomers were much faster than from the *cis*-compounds (Table 2).

TABLE 2. COMPARISON OF REACTIVITIES OF *cis*- AND *trans*-FLAVINDOGENIDES IN ALKALINE HYDROGEN PEROXIDE SOLUTIONS AT 50°

Flavindogenide	Time	% *Composition of reaction mixtures* Flavindogenides		Epoxides	
		cis-	*trans*-	*trans,cis*-	*trans,trans*-
cis- IIb	50 min	trace	0	89	11
trans- Ib	10 min	0	0	76	24
cis- IIc	4 hr*	0	0	73	10
trans- Ic	15 min	0	0	77	23

* The reaction was held at 50° for 15 min and then allowed to come to room temperature over a 4-hr period.

There was an appreciable difference in the stability of *cis*-flavindogenides (IIb and IIc) towards alkali of the concentration used in the alkaline hydrogen peroxide epoxidation reactions. For example, *cis*-flavindogenide (IIc) was isomerized into the *trans*-isomer (Ic) to the extent of only 5% after 24 hr, while *cis*-flavindogenide (IIb) was completely isomerized to Ib in 12 hr. However, the rate of isomerization of *cis*-isomer (IIb) by base was slower than its rate of epoxidation in alkaline hydrogen peroxide. Thus IIb was isomerized to Ib to the extent of 86% under conditions of time, temperature and initial sodium hydroxide concentration in which IIb was completely converted into epoxides when hydrogen peroxide was present.

Epoxidation of *trans*-flavindogenide (Ib) with *m*-chloro- or with *p*-nitro- perbenzoic acid gave only *trans,trans*-epoxide* (IIIb) while *trans*-flavindogenide (Ia) with *m*-chloroperbenzoic acid gave predominantly *trans,trans*-epoxide (IIIa) together with a small amount of *trans,cis*-epoxide (IVa). Epoxidation of *cis*-flavindogenides (IIa, b) with *m*-chloroperbenzoic acid gave mixtures of epoxides (Va, b and VIa, b), in the ratios shown in Table 1.

In order to differentiate between the signals of the β-and the C-2 protons in the NMR spectra of epoxides (IIIa, c and IVa, c) these compounds were prepared, with deuterium in the β-position, from the corresponding β-deuterated flavindogenides.[2]

When 2,2-diphenyl-3-benzylidene-4-chromanone (VII)[2] was treated under conditions which readily produce flavindogenide epoxides, only unchanged starting material was recovered. Under more vigorous conditions, although the chromanone disappeared from the reaction mixture, no epoxide was found.

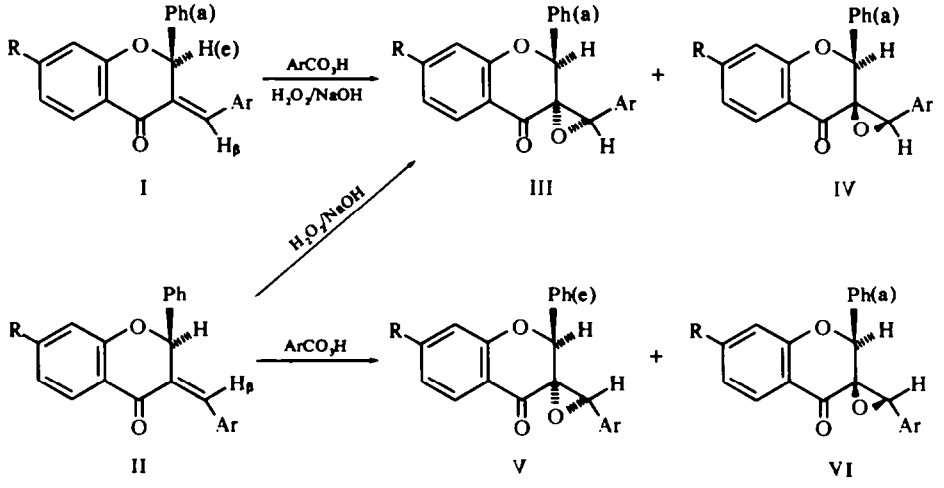
Attempts to prepare flavindogenide epoxides *via* flavan-4-ols (VIIIa, b; *cf.* Scheme 2) failed. Reduction of flavindogenides (Ib, c) with hydrides, depending on the reaction conditions, resulted in, either, the recovery of starting materials or formation of 3-anisylflavan-4-ol (IXa) or of 3-anisyl-7-methoxyflavan-4-ol (IXb).

DISCUSSION*

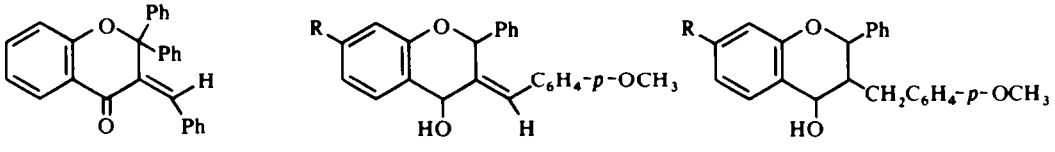
Stereochemistry. The gross structures of the flavindogenide epoxides were deduced from their formation by well established routes, satisfactory elemental analyses, characteristic ring opening reactions and spectral data. The configurations of the epoxides were assigned on the basis of the known stereospecificity of the peracid epoxidation reactions, the correlation of the epoxide structures through chlorohydrin derivatives[3] and on spectral data.

The usual method employed to prepare α-keto-epoxides is by reaction of α,β-unsaturated ketones with alkaline hydrogen peroxide. This reaction is stereoselective but not stereospecific.[4a] To obtain keto-epoxides stereospecifically the sequence of reactions shown in Scheme 2 has been used.[4a, b]

SCHEME 1



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



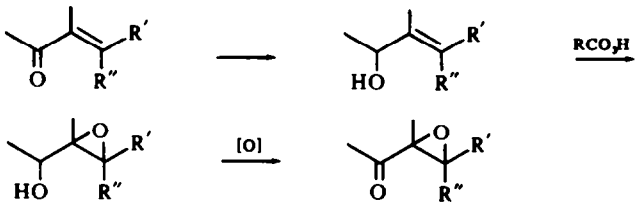
VII

VIII
a: R = H
b: R = OCH_3

IX
a: R = H
b: R = OCH_3

* (a) The term *cis-* or *trans-* prefixed to flavindogenides and their epoxides refers 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 epoxidic oxygen at position 3. All flavindogenides and their epoxides and related compounds mentioned in this communication are racemates; (b) the discussion will be based on the reactions of *trans-* and *cis*-flavindogenides Ib and IIb and their derivatives. The reactions of *trans-* and *cis*-flavindogenides (Ia, c) and (IIa, c) and their derivatives are analogous.

SCHEME 2



The double bond of an α,β-unsaturated carbonyl compound is generally unreactive[6] towards the electrophilic[7] peracid reagent and reaction at the CO group (Baeyer-Villiger reaction) predominates.[8] This difficulty was overcome in a number of cases[4a, b] by reduction of the CO group prior to the stereospecific[5] peracid epoxidation reaction. Application of this method to the flavindogenides proved unsuccessful.

trans-Flavindogenides failed to react with performic, peracetic and pertrifluoroacetic acids. Since *cis*-α,β-unsaturated ketones are known to be more reactive towards electrophilic reagents than are the *trans*-isomers,[9] epoxidation of *cis*-flavindogenide directly with aromatic peracids was attempted. *cis*-Flavindogenide (IIb) with *m*-chloroperbenzoic acid gave a mixture of the *cis*-epoxides (Vb and VIb). Unexpectedly, *trans*-flavindogenide (Ib) also reacted with aromatic peracids and formed the *trans*-epoxide (IIIb).

Studies on peracid epoxidation of olefins have shown that the reagent, if not influenced by a nearby polar substituent[10] such as hydroxyl, attacks the olefin predominantly from the less hindered side[11] of the molecule. In the epoxidation of *trans*-flavindogenides presumably the steric rather than the polar effect of the axial 2-Ph will influence the approach of the reagent and the olefinic bond will be attacked on the side of the molecule opposite that of this group (*trans*-attack).

Thus it is concluded that *trans*-epoxide (IIIb) has the Ph group at C-2 and the epoxide oxygen at C-3 *trans* orientated. Consequently, in the isomeric *trans*-epoxide (IVb) these groups have a *cis* relationship. This conclusion is supported by the NMR spectra (discussed later) of these compounds. It has been demonstrated,[3] through the intermediate formation of chlorohydrins, that the relative stereochemistry at C-2 and C-3 in *cis*-epoxide (Vb) and in *trans,trans*-epoxide (IIIb) is the same; hence epoxide Vb is the *cis,trans*-isomer. Similarly, the stereochemistry of the 2- and 3-positions of *cis*-epoxide (VIb) and *trans,cis*-epoxide (IVb) was related and showed the former to be the *cis,cis*-isomer.*

These findings are supported by results obtained from the *m*-chloroperbenzoic acid epoxidation of the *cis*-flavindogenide (IIb; in which the 2-Ph group is presumably mainly in the axial conformation[2]). The major product is the *cis,trans*-isomer (Vb) obtained by "*trans*-attack" of the double bond and the minor product is the *cis,cis*-isomer (VIb) which is obtained by "*cis*-attack" of the molecule (when the phenyl group is possibly in the equatorial position).

NMR spectra. The NMR spectral data (Table 3) of the four isomeric epoxides supports the structural assignments made above. It also enables assignments of conformation to be made to the 2-Ph groups.

* The epoxides IIIa, IVa, Va and VIa did not form chlorohydrins. Their structures were assigned by a comparison of their spectra with the known compounds IIIb, IVb, Vb and VIb, and by the methods used in their preparation.

It was expected that the β-protons in the *trans* pair of epoxides (IIIb and IVb) would absorb at lower field than the same protons in the *cis* pair (Vb and VIb) because of the deshielding influence of the CO group[12] in the former. The relatively high value (5·50τ) for the β-proton in the *trans,cis*-isomer (IVb) was unexpected. Inspection of Dreiding models of the *trans,trans*- (IIIb) and *trans,cis*- (IVb) isomers in which the CO groups are held in the same plane as the A rings, to take into account the conjugation between the fused benzene ring and the CO group, as shown by IR measurements, indicate that the β-hydrogen of the former is in the plane of the CO group (and thus in the deshielding region) while the β-hydrogen of the latter is 25–30° below the plane of the CO group. The β-proton of *trans,trans*-epoxide (IIIb; 4·82τ) is clearly more deshielded than the β-proton of *trans,cis*-epoxide (IVb; 5·60τ). A further significant difference between the NMR spectra of the two *trans*-isomers is that the 2-Ph protons of isomer IIIb are equivalent while those of isomer IVb are not. Dreiding models show that in each case the 2-Ph group must be axial to avoid severe steric interaction with the β-aryl group. In the case of the *trans,cis*-epoxide (IVb) the epoxidic oxygen is closer to the 2-Ph group, and presumably creates the magnetic non-equivalence of the 2-Ph protons.

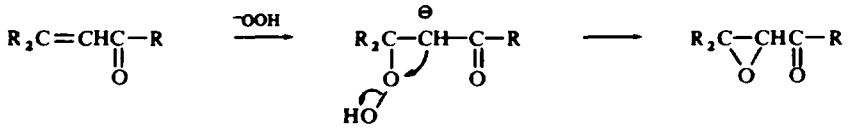
The NMR spectra of the *cis*-isomers indicates that the *cis,cis*-epoxide (VIb) also has an axial 2-Ph group since the β- and 2- proton signals are close to the field positions of the corresponding protons in epoxide (IVb) but different from those in *cis,trans*-epoxide (Vb) in which the 2-Ph group is considered to be in an equatorial conformation. The β-proton in the *cis,trans*-epoxide (Vb) gives a signal considerably upfield (6·23τ) and the protons at C-2 give a signal downfield (4·20τ) relative to those of the corresponding protons in the *cis,cis*-isomer (VIb).

This data is best explained by considering the 2-phenyl group in Vb as being in the equatorial conformation and that of VIb as being in the axial conformation. A comparison of structures Vb and VIb, using Dreiding models, shows that in isomer Vb relative to VIb the β-hydrogen is closer to the shielding influence of the 2-Ph group and the hydrogen at C-2 is further removed from the shielding effect of the epoxide ring. The magnetic non-equivalence of the protons of the 2-Ph group in *cis,trans*-epoxide (Vb) further supports the suggestion that this group is equatorial; were the 2-Ph axial, these protons should be equivalent by analogy with those in the *trans,trans*-epoxide (IIIb).

Mechanism of epoxidation. The establishment of the configurations of the flavindogenide epoxides has clarified the course of the alkaline hydrogen peroxide epoxidation reactions with *cis*- and *trans*- flavindogenides.

Alkaline hydrogen peroxide epoxidation of α,β-unsaturated ketones proceeds by attack on the olefin bond by hydroperoxide ion to produce an intermediate carbanion (or enolate ion) which collapses to a keto-epoxide (Scheme 3[4, 13]). The product formed, according to a general theory of "overlap control",[4a, 14] is that in which there is least

SCHEME 3



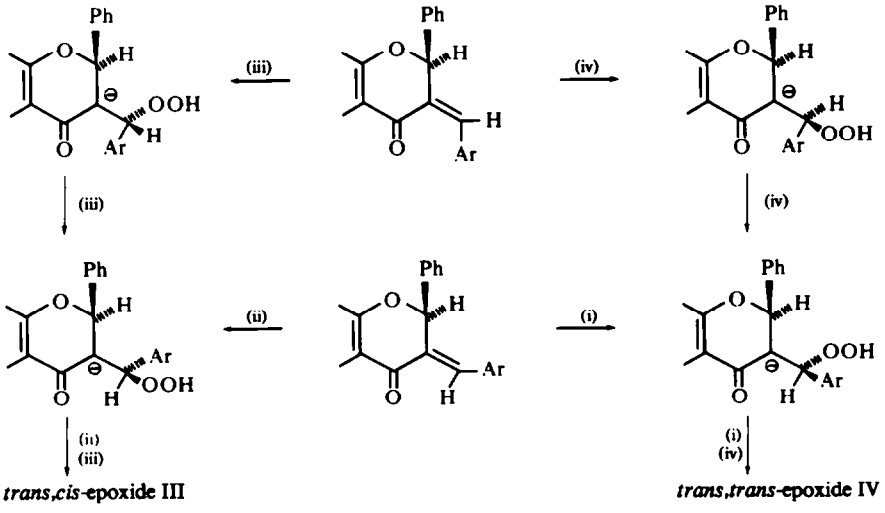
hindrance to electron delocalization in the transition state of the reaction. Overlap control favours the product with an unhindered CO group, which, in the case of keto-epoxides is the one in which the ketone function and the larger group on the β-C atom are *trans* to one another. The results of the present work on epoxidations are in accord with this accepted mechanism; however, several additional factors must be considered in the case of flavindogenide substrates.

Epoxidation both of *cis*- and *trans*- flavindogenide (IIb and Ib) gives in each case a mixture of *trans,cis*- (IVb) and *trans,trans*- flavindogenide epoxides (IIIb). Thus the alkaline hydrogen peroxide reaction results in products which have the larger group on the β-C atom *trans* to the CO group.

An inspection of models shows that when the 2-Ph group is in the axial conformation its steric interaction with the β-aryl group in the transition state leading to *trans* epoxides is less than that encountered between the β-aryl and the CO groups in the transition state leading to *cis* products. However, when the 2-Ph is in the equatorial conformation there is severe steric interaction in the transition state leading to the *trans* epoxides. Indeed, in the case of the 2,2-diphenylchromindogenide (X), where one of the 2-Ph groups must be in the equatorial conformation, the epoxidation reaction did not proceed.

That the *trans,cis*-epoxide was the major product from *trans*-flavindogenides was unexpected. One might anticipate that the major product would arise from attack by hydroperoxide ion from the least hindered side of the molecule, as in the case of attack by peracids, to give mainly the *trans,trans*-isomer. To understand the ratio of products obtained (Table 1), it is necessary to consider the steric effect of the 2-Ph group on the reaction.

SCHEME 4



Models show that while initial *trans*-attack of the double bond of *trans*-flavindogenides (Scheme 4; path i) would be favoured, in the resulting transition state the two aryl groups are forced closer together, whereas in the transition state resulting from *cis*-attack (Scheme 4; path ii) they are pushed further apart. Consequently, *cis*-attack appears more energetically favoured and *trans,cis*-epoxides are the major pro-

ducts. In epoxidation of *cis*-flavindogenides *trans* attack is favoured followed by rotation about the 3-β bond to produce the unhindered *trans,cis* enolate anion intermediate (Scheme 4; path iii). The ratio of *trans,cis*- to *trans,trans*-isomers obtained is higher than with the *trans*-flavindogenides.

There is the possibility that some of the *cis*-flavindogenide is isomerized by hydroxide or hydroperoxide ions into the *trans*-isomer before epoxidation takes place since it has been shown (Table 2) that such isomerization occurs under the alkaline conditions of epoxidation. However, since the ratio of isomers (*trans,cis*-; *trans,trans*-epoxide ca. 7:1) is considerably different from that (ca. 3:1) obtained from the *trans*-flavindogenide, it is evident that most of the *cis*-flavindogenide undergoes epoxidation by the mechanism shown in Scheme 4.*

The transition state in peracid epoxidations of olefins involves simultaneous attack at both carbon atoms of the olefin bond[7] (Fig. 1).†

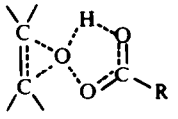


FIG 1

In the case of epoxidation of *trans*-flavindogenides by peracids the steric interaction between the β- and 2-aryl groups in the transition state resulting from *trans*-attack of the molecules is presumably not as great as that which results between the reagent and the 2-Ph group, in the transition state resulting from *cis*-attack of the molecule. *cis*-Attack of *trans*-flavindogenides by peracid presents a more serious steric problem than that involved in *cis*-attack by the smaller hydroperoxide ion.

EXPERIMENTAL

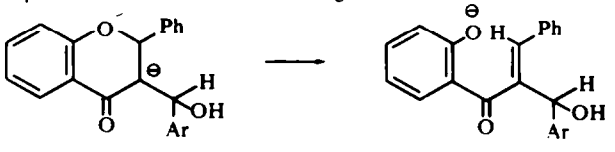
M.Ps are uncorrected. The NMR spectra of flavindogenide epoxides were taken at 60 Mc in $CDCl_3$ containing TMS as internal reference (Table 3). The ratio of epoxide isomers (Table 1) produced in each epoxidation reaction was obtained from integration of well separated singlets (β-H or 2-H) of each component in the NMR spectrum of the crude product.

Alkaline hydrogen peroxide epoxidation of 3-arylideneflavanones

Formation of trans,trans-3-*benzylideneflavanone epoxide* (IIIa) *and* trans,cis-3-*benzylideneflavanone epoxide* (IVa)

A. *From* trans-3-*benzylideneflavanone* (Ia). Aq NaOH (10%, 10 ml) and H_2O_2 (30%, 3·5 ml) were added

* An alternative mechanism involving ring opening of the carbanionic intermediates (Scheme 4), which in each case would give the same chalcone intermediate, was rejected since the same ratio of epoxides would be expected from *cis*- or *trans*-flavindogenides.



† More recently a 1,3-dipolar addition mechanism has been proposed by H. Kwart and D. M. Hoffman, *J. Org. Chem.* **31**, 419 (1966); H. Kwart, P. S. Starcher and S. W. Tinsley, *Chem. Comm.* 335 (1967) but it has not found general acceptance.[15]

TABLE 3. NMR DATA FOR 3-ARYLIDENEFLAVANONE EPOXIDES[a]

Isomer	β-H	2-H	5-H (m)[b]	*J*	2-Ph	β-Ar (m)[b]	*J*
trans,trans-IIIa	4·81	4·64	2·17 (q)	8·2	2·92 (s)	2·7 (s)	
trans,trans-IIIb	4·82	4·61	2·16 (q)	8·2	2·90 (s)	2·63 (d), 3·20 (d)	8·8
trans,trans-IIIc	4·82	4·63	2·2 (d)	9·5	2·91 (s)	2·84 (d), 2·91 (d)	9
trans,cis- IVa	5·54	4·82	2·17 (q)	8·2	(m)	2·63 (s)	
trans,cis- IVb	5·60	4·81	2·17 (q)	8·2	(m)	2·67 (d), 3·06 (d)	8
trans,cis- IVc	5·58	4·80	2·21 (d)	8·5	(m)	2·64 (d), 3·08 (d)	9
cis,trans- Va	6·20	4·11	2·26 (q)	8·2	(m)	(m)	
cis,trans- Vb	6·23	4·20	2·4 (q)	8·2	(m)	(m)	
cis,cis- VIa	5·48	4·57	~2·6 (q)[c]		(m)	(m)	
cis,cis- VIb	5·57	4·69	~2·6 (q)[c]		(m)	(m)	

[a] Chemical shifts are in τ values. *J* values are in c/s

[b] m = multiplet, s = singlet, d = doublet, q = quartet

[c] doublet appears at 2·52 τ ($J = 2$); the second doublet of the quartet is buried in the aromatic multiplet. The value of 2·6 τ is obtained assuming that *ortho* coupling has a value of 8 c/s.

to a suspension of Ia (10 g) in EtOH (95%, 200 ml), the mixture was stirred for 4 hr and allowed to stand for 16 hr. The crude product (10·4 g) which separated was collected washed with water and chromatographed over 500 g of standard alumina (benzene-light petroleum, (b.p. 40–60°); 20:80). The first fraction was an oil (1·2 g) which crystallized from light petroleum (b.p. 80–100°) in needles of *epoxide* IIIa, m.p. 149–149·5°. (Found: C, 80·5; H, 5·1. $C_{22}H_{16}O_3$ requires: C, 80·47; H, 4·91%), ν_{max}(KBr) 1686 cm^{-1}, λ_{max} (in MeOH) 261 mμ, 334 mμ. The second fraction was a yellow oil which crystallized from light petroleum in cubes of *epoxide* IVa (3·6 g), m.p. 121–122°. (Found: C, 80·4; H, 4·9. $C_{22}H_{16}O_3$ requires: C, 80·47; H, 4·91%); ν_{max}(KBr) 1689 cm^{-1}, λ_{max}(MeOH) 262 mμ, 332 mμ.

B. *From* cis-3-*benzylideneflavanone* (IIa). Oxidation of IIa (0·5 g) gave a solid (0·39 g) which on fractional crystallization from light petroleum gave IIIa (42 mg) and IVa (290 mg). Mixture m.p. determinations in each case with authentic samples showed no depression.

Formation of trans,trans-3-*benzylideneflavanone*-β-*d epoxide* (III'a) *and* trans,cis-3-*benzylideneflavanone*-β-*d epoxide* (IV'a)

Alkaline H_2O_2 epoxidation of *trans*-3-benzylideneflavanone-β-d (0·5 g) gave a solid which on fractional crystallization from light petroleum gave *epoxide* III'a (92 mg), 149–150° and *epoxide* IV'a (230 mg), m.p. 120–122°, Identical (Mixture m.p.s, NMR spectra) with undeuterated analogues IIIa and IVa except for the absence of signals at 4·81τ (β-H in IIIa) and 5·54τ (β-H in IVa) in the NMR spectra.

Formation of trans,trans-3-*anisylideneflavanone epoxide* (IIIb) *and* trans,cis-3-*anisylideneflavanone epoxide* (IVb).

A. *From* trans-3-*anisylideneflavanone* (Ib). Alkaline H_2O_2 epoxidation of Ib (20 g) gave a solid (18·5 g) (on dilution of the reaction mixture with water) which crystallized from benzene (35 ml) to give *epoxide* IIIb (3·2 g), m.p. 176–176·5°. (Found: C, 77·2; H, 5·0, CH_3O, 9·2. $C_{23}H_{18}O_4$ requires: C, 77·08; H, 5·06; CH_3O, 8·66%). ν_{max}(KBr) 1681 cm^{-1}, λ_{max} 262 mμ, 334 mμ. The solid obtained on removal of the

127°. (Found: C, 77·4; H, 5·0; OCH_3, 9·3. $C_{23}H_{18}O_4$ requires: C, 77·08; H, 5·06; OCH_3, 8·66%); ν_{max}(KBr) 1689 cm^{-1}, λ_{max}(EtOH) 267 mμ, 332 mμ.

B. *From* cis-3-*anisylideneflavone* (IIb). Alkaline H_2O_2 epoxidation of IIb (2·0 g), gave a solid (1·8 g) which on fractional crystallization from EtOH gave epoxide IIIb (96 mg), m.p. 176–177° and IVb (1·2 g), m.p. 126–127°, identical (mixture m.ps and NMR spectra) with authentic samples.
solvent from the mother liquor crystallized from 95% EtOH in cubes of *epoxide* IVb (10·3 g), m.p. 126–

Formation of trans,trans-3-*anisylidene*-7-*methoxyflavanone epoxide* (IIIc) *and* trans,cis-3-*anisylidene*-7-*methoxyflavanone epoxide* (IVc)

A. *From* trans-3-*anisylidene*-7-*methoxyflavanone* (Ic). Alkaline H_2O_2 epoxidation of Ic (2 g) was carried out as for Ia except that the reaction mixture was stirred at 50° for 3 hr and then allowed to stand for 16 hr. Fractional crystallization of the product from aq EtOH gave *epoxide* IVc (1·0 g), m.p. 165–166°. (Found: C, 74·3; H, 5·25. $C_{24}H_{20}O_5$ requires: C, 74·20; H, 5·16%); ν_{max}($CHCl_3$) 1685 cm^{-1}, λ_{max}(EtOH) 283 mμ (ε 17,600), 322 mμ (ε 9,170) and *epoxide* IIIc (0·3 g), m.p. 147·5–148·5°. (Found: C, 74·4; H, 5·5. $C_{24}H_{20}O_5$ requires: C, 74·20; H, 5·16%). ν_{max}($CHCl_3$) 1680 cm^{-1}, λ_{max}(EtOH) 285 mμ (ε 16,000), 318 mμ (ε 8,000).

In subsequent preparations epoxide IVc was obtained as either fine needles, m.p. 165·6°, or as fine needles, m.p. 145–147°. The spectral properties of the two crystalline modifications were identical. Either form can be converted into the other by seeding a sat soln of one with the other modification.

B. *From* cis-3-*anisylidene*-7-*methoxyflavanone* (IIc). Alkaline H_2O_2 epoxidation of IIc (0·5 g) was carried out as in the preceding experiment. Crystallization of the product from EtOH gave epoxide IVc (0·31 g), m.p. 145–147°. The filtrate was diluted with water. The NMR spectrum of the solid (0·18 g), m.p. 119–130°, obtained showed it to be a mixture (70:30) of epoxides IVc and IIIc. Repeated crystallizations gave a small quantity of IIIc, m.p. 147–148°. The compounds were identical (m.ps, IR and NMR spectra) in each case with authentic samples.

Formation of trans,trans-3-*anisylidene*-7-*methoxyflavanone*-β-*d epoxide* (III'c) *and* trans,cis-3-*anisylidene*-7-*methoxyflavanone*-β-*d epoxide* (IV'c)

Alkaline H_2O_2 epoxidation of *trans*-3-anisylidene-7-methoxyflavanone-β-d (5 g) was carried out essentially as for Ic. Fine white needles of epoxide IV'c (2·7 g), m.p. 145–147° separated from the reaction mixture. The IR ($CHCl_3$) and NMR ($CDCl_3$) spectra of (IV'c) were essentially identical to those of IVc except for the presence of bands at 1510, 998 cm^{-1}, and the absence of a band at 1083 cm^{-1} in the IR

spectrum, and the absence of a signal at 5·58 τ (β-H) in the NMR spectrum. The NMR spectrum of the solid (2·25 g) obtained on dilution with water of the reaction mixture, after separation of IV'c, showed that it was mixture (56:44) of III'c and IV'c isomers. The spectrum was essentially identical to spectra of mixtures of undeuterated isomers except for the absence of the β-proton signals. The overall isomer composition of isolated product was thus IV'c (75%) and III'c (25%).

Peracid epoxidation of arylideneflavanones

trans-3-*Benzylideneflavanone* (Ia). A soln of Ia (0·5 g) and *m*-chloroperbenzoic acid (0·5 g; 85% assay) in benzene (10 ml) was heated under reflux for 8 hr and then allowed to stand at room temp for 12 hr. The needles of *m*-chlorobenzoic acid which separated were removed by filtration. The filtrate was washed with $NaHCO_3$aq (5%), with water and dried ((Na_2SO_4)). The yellow oil obtained on removal of the solvent was dissolved in benzene (1 ml) and chromatographed on two silica gel (100 μ) TLC plates (20 × 20 cm) (Eluent 1:4, Benzene-light petroleum). The upper of three bands formed, gave an oil (242 mg) which crystallized from light petroleum (60–80°) in prisms of epoxide IIIa, m.p. 149–150°. The middle band yielded an oil (150 mg) which crystallized from EtOH in rhombs of Ia, m.p. 101–102°. These products were indentical (mixed m.ps and NMR spectra) with the epoxides obtained on alkaline hydrogen peroxide epoxidation of Ia. The lower band gave a trace of oil which had the same R_f value as epoxide IIIa on TLC (silica gel; eluent 1:3 benzene-light petroleum).

Subsequent peracid epoxidation reactions were carried out as in the above experiment except where indicated.

trans-3-*Anisylideneflavanone* (Ib). A. *m*-Chloroperbenzoic acid epoxidation of Ib (·05 g) gave an oil which separated into two bands on preparative silica gel TLC plates (eluent 1:4 benzene-light petroleum). The lower band gave a yellow oil which crystallised from EtOH (95%) in needles of epoxide IIIb (327 mg), m.p. 176–177°; identical (mixed m.p., NMR spectra) with a sample of IIIa obtained from alkaline hydrogen peroxide epoxidation of Ib. The lower band also gave an oil which crystallized from EtOH (95%) in prisms of Ib, m.p. and mixed m.p. 145–146·5°. The NMR spectrum of the product showed no trace of isomer IVb.

B. When the epoxidation was carried out with *p*-nitroperbenzoic acid in $CHCl_3$ at 35° for 24 hr epoxide IIIa (85%) and unchanged Ib (15%) were obtained (NMR analysis). The epoxide, isolated by crystallization from EtOH, was identical (m.p. and NMR spectrum) with a sample of epoxide IIIa obtained above.

Formation of cis,trans-3-*benzylideneflavanone epoxide* (Va) *and* cis,cis-3-*benzylideneflavanone epoxide* (VIa)

m-Chloroperbenzoic acid epoxidation of IIa (0·5 g) gave a mixture which separated into three bands on preparative silica gel TLC plates (eluent 1:4 benzene-light petroleum). The lower band gave an oil which crystallized from light petroleum in fine needles of *epoxide* Va (235 mg), m.p. 167–168·5. (Found: C, 80·4; H, 4·95. $C_{22}H_{16}O_3$ requires: C, 80·47; H, 4·91%); ν_{max}(KBr) 1698 cm^{-1}, λ_{max}(MeOH) 268 mμ, 337 mμ. The upper band gave an oil which separated from light petroleum in needles of *epoxide* VIa (52 mg), m.p. 141–142°. (Found: C, 80·5; H, 5·3. $C_{22}H_{16}O_3$ requires: C, 80·47; H, 4·91%); ν_{max}(KBr) 1684 cm^{-1} λ_{max}(MeOH) 262 mμ, 334 mμ. The middle band gave unchanged IIa (140 mg) m.p. and m.m.p. 94–95°.

Formation of cis,trans-3-*anisylideneflavanone epoxide* (Vb) *and* cis,cis-3-*anisylideneflavanone epoxide* VIb)

m-Chloroperbenzoic acid epoxidation of IIb (0·5 g) gave a yellow oil which separated into three bands on silica gel preparative TLC plates (eluent 1:4 benzene-light petroleum). Crystallization of the oil obtained from the lower band from light petroleum gave *epoxide* Vb (180 mg), m.p. 128–129°. (Found: C, 76·9; H, 5·1; OMe, 8·9. $C_{23}H_{18}O_4$ requires: C, 77·08; H, 5·06; OMe, 8·66%); ν_{max}(KBr) 1695 cm^{-1}, λ_{max}(MeOH) 262 mμ, 336 mμ. The upper band gave an oil which crystallized from EtOH in fine needles of *epoxide* VIb (42 mg), m.p. 145–146°. (Found: C, 76·7; H, 4·9; CH_3O, 8·5.$C_{23}H_{18}O_4$ requires: C, 77·1; H, 5·1; CH_3O, 8·7%); ν_{max}(KBr) 1698 cm^{-1}. The middle band gave an oil which had the same R_f on TLC as starting IIb.

Stability of flavindogenides under alkaline conditions of epoxidation

cis-3-*Anisylideneflavanone* (IIb). To a soln of IIb (0·25 g) in EtOH (25 ml) was added NaOH (0·25 ml;

10%) and the resulting soln was kept at 50° (const temp bath) for 50 min and then poured into water (150 ml) and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water and dried (Na_2SO_4). The $CHCl_3$ was removed and the residual oil was dissolved in $CDCl_3$. Analysis by NMR showed the mixture to consist of 84% *trans*-isomer (Ib) and 16% of *cis*-isomer (IIb).

cis-3-*Anisylidene*-7-*methoxyflavanone* (IIc). A similar experiment was carried out with IIc except that after addition of the reagents to the reaction mixture at 50° the resulting soln was allowed to stand at room temp for 24 hr. The NMR spectrum of the product was essentially identical with a spectrum of the *cis*-isomer (IIc). A very weak signal at 1·98 τ (β-H in Ic) indicated that less than 5% isomerisation had occurred.

Comparison of rates of epoxidation of Ib *and* IIb

To a soln of Ib (0·5 g) in EtOH (50 ml) was added H_2O_2 (0·5 ml; 30%) and NaOH (0·5 ml; 10%) and the resulting mixture was kept at 50° for 10 min and then poured into 500 ml of ice-water mixture and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried (Na_2SO_4) and the solvent removed. NMR analysis of the residual oil in $CDCl_3$ showed it to consist of IIIb (24%) and IVb (76%). No Ib was detected.

A similar expt was run with IIb except that the quantities were reduced by half and the reaction period at 50° was 50 min. NMR analysis of the product in $CDCl_3$ showed it to consist of a mixture of epoxides IIIb (11%) and IVb (89%). A trace of IIb but no Ib was detected.

Comparison of rates of epoxidation of Ic *and* IIc

The expts were carried out essentially as in the preceding examples except that the reaction mixtures were kept at 50° for 10 min and then allowed to stand at room temp for 4 hr. Almost quantitative recoveries were realised in each case. NMR analysis of the crude product from Ic showed it was a mixture of epoxides IIIc (23%) and IVc (77%); Ic was not detected. Similar analysis of the product from IIc gave IIIc (10%), IVc (73%) and unchanged IIc (17%).

An identical expt was repeated with Ic except that the reaction period was 15 min. Only the epoxides, in the same ratio as found in the 4 hr period, were found; no Ic was detected in the crude product.

Formation of 3-*anisylflavan*-4-*ol* (IXb)

Sodium borohydride (1·0 g) was added to a stirred suspension of *trans*-3-anisylideneflavanone (2·0 g) in MeOH (40 ml). A soln was obtained and after 0·5 hr a solid separated out which was recrystallized from chloroform to give 3-*anisylflavan*-4-*ol* (1·8 g), m.p. 199–200°. (Found: C, 79·9; H, 6·6; OMe, 8·5. $C_{23}H_{22}O_3$ requires: C, 79·7; H, 6·4; OMe, 8·96%); ν_{max}(Nujol) 3354 cm^{-1}. Acetyl derivative, m.p. 148·5–149°. (Found: C, 77·6; H, 6·2, OMe, 7·7. Requires: C, 77·3; H, 6·23, OMe, 8·0%); ν_{max}(KBr) 1727 cm^{-1}.

Formation of 3-*anisyl*-7-*methoxyflavan*-4-*ol* (IXc)

In a similar experiment *trans*-3-anisylidene-7-methoxyflavone (1·0 g) gave 3-*anisyl*-7-*methoxyflavan*-4-*ol*, m.p. 146·5–147·5. (Found: C, 76·4; H, 6·4. $C_{24}H_{24}O_4$ requires: C, 76·57; H, 6·43%); ν_{max}($CHCl_3$) 3580 (OH), 2830 (OCH_3), 1239, 1035 (=C—O—C) cm^{-2} τ 2·69 (S, 5H, 2-Ph), 3·54 (broad multiplet (1H, 4H) becomes less complex when sample is acidified, 624 (S, 6H, OCH_3) 7·4 (narrow multiplet, 2H, CH_2), 8·58 (d, 1H, OH); collapses to a singlet upon acidification; exchanges with D_2O.

REFERENCES

[1] Communication V (preliminary communication to the present paper), 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] D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *J. Org. Chem.* In press (1970)

[3] J. R. Doherty, D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philbin, R. M. Simons and P. C. Teague, *Tetrahedron* **26**, 2545 (1970)

[4] [a] H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *J. Am. Chem. Soc.* **81**, 108 (1959); [b] H. H. Wasserman and N. E. Aubrey, *ibid.* **77**, 590 (1955)

[5] L. P. Witnauer and D. Swern, *Ibid.* **72**, 3364 (1950); B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.* 1525 (1955); V. Prelog, V. Boarland, *Helv. Chem. Acta* **38**, 1776 (1955); A. C. Cope, S. W. Fenton and C. F. Spencer, *J. Am. Chem. Soc.* **74**, 5884 (1952); A. C. Cope, A. Fournier and H. E. Simmons, *Ibid.* **79**, 3905 (1957)

[6] D. Swern, *Chem. Revs.* **45**, 1 (1949)

[7] [a] P. D. Bartlett, *Rec. Chem. Progr.* **11**, 51 (1950);
[b] B. M. Lynch and K. H. Pausacker, *J. Chem. Soc.* 1525 (1955);
[c] D. R. Campbell, J. O. Edwards, J. MacLachan and K. Polgar, *J. Am. Chem. Soc.* **80**, 5308 (1958;
[d] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.* 3293 (1958);
[e] M. L. Sassiver and J. English, *J. Am. Chem. Soc.* **82**, 4891 (1960).

[8] H. M. Walton, *J. Org. Chem.* **22**, 1161 (1957); G. B. Payne and P. H. Williams, *Ibid.* **24**, 284 (1959).

[9] W. B. Black and R. E. Lutz, *J. Am. Chem. Soc.* **75**, 5990 (1953)

[10] H. B. Henbest, *Proc. Chem. Soc.* 159 (1963); H. B. Henbest, *Chem. Soc. Special Publ.* No. **19**, 85 (1965)

[11] H. Kwart and W. G. Vosburgh, *J. Am. Chem. Soc.* **76**, 5400 (1954); D. H. R. Barton and R. C. Cookson, *Quart. Revs* **10**, 44 (1956); L. F. Fieser, *Experientia* **6**, 312 (1950); J. Meinwald and Cadoff, *J. Org. Chem.* **27**, 1539 (1962); J. C. Leffingwell and E. E. Royals, *Tetrahedron Letters* No **21**, 3829 (1965); B. Rickborn and Shiow-Yueh Lwo, *J. Org. Chem.* **30**, 2212 (1965); E. J. Corey and E. L. Dawson, *J. Am. Chem. Soc.* **85**, 1782 (1963)

[12] L. J. Jackman, *Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* Chap. 7, Pergamon Press, (1959).

[13] C. A. Burton and G. J. Minkoff, *J. Chem. Soc.* 665 (1953); W. G. Black and R. E. Lutz, *J. Am. Chem. Soc.* **75**, 5990 (1953); H. O. House and R. S. Ro, *Ibid.* **80**, 2428 (1958).

[14] H. E. Zimmerman, L. Ahramjian, *Ibid.* **81**, 2086 (1959) and *Ibid.* **82**, 5459 (1960).

[15] K. D. Bingham, G. D. Meakins and G. H. Whitham, *Chem. Com.* 445 (1966); J. B. Lee and B. C. Uff, *Quart. Revs* **21**, 432 (1967)