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CYCLISATION AND SUBSEQUENT REACTIONS OF 2'-HYDROXY-6'-METHOXYCHALCONE EPOXIDE AND RELATED COMPOUNDS

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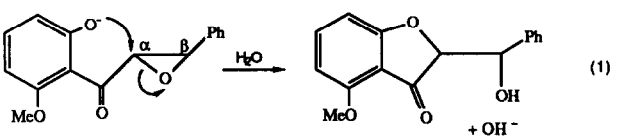
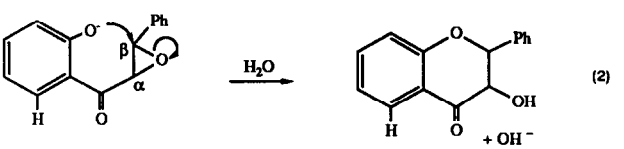
Abstract: 2'-Hydroxy-6'-methoxychalcone epoxide reacts in neutral aqueous acetonitrile solution to give a 6:1 ratio of the α- and β-cyclisation products, *erythro*-4-methoxyaurone hydrate [*erythro*-2-(α-hydroxybenzyl)-4-methoxycoumaran-3-one] and *trans*-3-hydroxy-5-methoxyflavanone; the dominance of α-cyclisation may be associated with a stereoelectronic preference for a conformation favourable for α- but not β-cyclisation when the carbonyl group is forced by the 6'-substituent to lie out-of-plane with the aromatic ring. In more basic solutions, *erythro-threo* isomerisation of aurone hydrate occurs, and 4-methoxycoumaran-3-one and 4-methoxyaurone are formed. Other 6'-substituted 2'-hydroxychalcone epoxides show a similar strong preference for α- over β-cyclisation.

Introduction

As outlined in the preceding paper, 2'-hydroxychalcone epoxides with 6'-substituents have historically been of considerable interest as possible precursors of aurones not only in biosynthesis[1] but also in a variety of laboratory preparations of aurones by reaction of 6'-substituted 2'-hydroxychalcone derivatives such as dibromides[2] and bromohydrins[3] with base, as well as in the oxidation of 6'-substituted 2'-hydroxychalcones themselves with alkaline H_2O_2 [Algar-Flynn-Oyamada (AFO) reaction].[4,5,6,7a] The formation of aurones in preference to 3-hydroxyflavanones in all these reactions has been accounted for by the 6'-substituent directing cyclisation by phenolate in the postulated epoxide intermediates to the α-position (eq. 1) rather than the β-position (*cf.* eq. 2).



(1)



(2)

Geissman and Fukushima[4] and Dean and Podimuang[5] accounted for this effect in relation to the AFO reaction. They suggested that in an epoxide intermediate there would be a steric interaction between the 6'-substituent and the C=O group which would force the latter out-of-plane with the aromatic ring. This would result, they suggested, in restricted access of the nucleophilic 2'-O^- function to the β-carbon (*cf.* eq. 2) such that α-cyclisation (eq. 1) becomes preferred. Such a steric restriction would diminish with increasing temperature so that β-cyclisation could become preferred and this would

account for[5] the finding that chalcones with 6'-substituents revert to 3-hydroxyflavanone formation (*cf.* eq. 2) at high temperatures. The latter explanation was contradicted, however, by the subsequent observation of Gormley and O'Sullivan[6] that 6'-methoxy-2'-tosyloxychalcone epoxide in strongly alkaline conditions, under which the protective group is removed, gives aurone at both room temperature and higher temperature. Assuming that the tosyl group is completely removed before cyclisation by 2'-O^- is initiated, this excludes chalcone epoxide involvement in the AFO reaction as conducted at higher temperatures. For the reaction at lower temperatures, however, epoxide involvement has still not been excluded although this seems to have passed unacknowledged.[7b] Independent of this uncertainty, the above steric explanation for the preferred α-cyclisation remains accepted for other aurone-forming reactions in which epoxide involvement is not under question, *i.e.* the reaction with base of 6'-substituted 2'-hydroxychalcone dibromides[2] and bromohydrins.[3]

Despite interest in the origin of this directive effect of a 6'-substituent, direct study of the reaction (*e.g.* eq. 1) has been impossible because of the unavailability of any 6'-substituted 2'-hydroxychalcone epoxide. Until now, 2'-hydroxychalcone epoxide itself was the only known[8] chalcone epoxide with a free 2'-hydroxy group and, lacking a 6'-substituent, it cyclises[8,9] to 3-hydroxyflavanone (eq. 2).

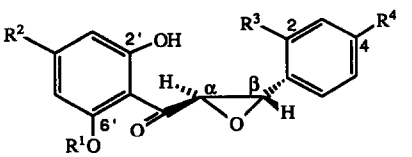
Given the availability now[10] of unprotected 2'-hydroxychalcone epoxides, one aim of the present study was to isolate and characterise the products of cyclisation of 6'-substituted 2'-hydroxychalcone epoxides under neutral or slightly basic conditions in which, unlike the situation for earlier indirect studies in strong base, there is reduced chance of interference from subsequent reactions. Study of the ongoing reactions of the primary cyclisation products under conditions made more basic can then also be carried out. The results should provide a basis for comparison with and understanding of those reactions in which, because of the strongly basic conditions, the existence of the epoxide or aurone hydrate intermediates can only be inferred.

Results and Discussion

(a) Outline

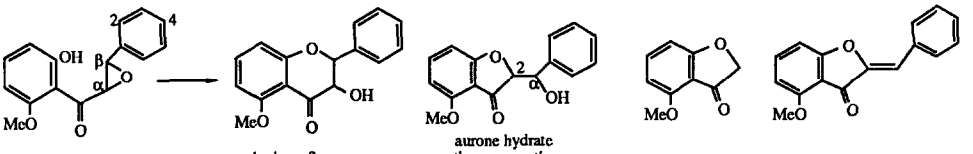
Most study was carried out with 2'-hydroxy-6'-methoxychalcone epoxide (**1**) but some results are reported also for other 6'-substituted epoxides (**2-5**), as well as for the parent epoxide itself (eq. 2).

So as to provide pH control by use of inorganic buffers, reactions were carried out in partly aqueous acetonitrile, initially 3:1 MeCN/H_2O and later, to provide a more aqueous medium for comparison, 1:1 MeCN/H_2O. The products obtained are recorded in Table 1. Details of buffers used and other reaction conditions are in the Experimental section. No studies of the effect of buffer species on product ratios have been made though it seems very likely that, particularly at low pH,



(1) R^1 = Me; R^2 = R^3 = R^4 = H
(2) R^1 = ^{i}Pr; R^2 = R^3 = R^4 = H
(3) R^1 = Me; R^2 = OMe; R^3 = R^4 = H
(4) R^1 = Me; R^2 = R^4 = H; R^3 = CF_3
(5) R^1 = Me; R^2 = R^3 = H; R^4 = Cl

Table 1 **Product Ratios[a] for 2'-Hydroxy-6'-methoxychalcone Epoxide (1)**



		hydroxyflavanone (6)	aurone hydrate *erythro* (7)	aurone hydrate *threo* (9)	coumaranone (12)	aurone (10)
Entry	Conditions[b]					
	3:1 MeCN/H2O					
1	pH 5 7, 13 days	14	86	-		
2	pH 7 6, 32 hours	16	42	42		
3	pH 12 0; 25 hours	18	~6	~9	13	16
	1:1 MeCN/H2O					
4	pH 6 9; 27 hours	15	85	-		
5	pH 6 6; 10 min reflux	17	83	-		
6	pH 6.9; 2 h reflux	18			46	36
7	pH 8 3; 1 hour	14	86	-		
8	pH 11 9; 20 min.	17	8	13	47	14

[a]Determined by quantitative n m r except for entry 3 which gives isolated yields of separated products
[b]Reactions at room temperature except for entries 5 and 6

buffer bases would be involved in place of OH^- in base-promoted reactions. Buffers can of course have no influence on product ratios of competing reactions at equilibrium (*cf.* Scheme) but in some of the discussion below, kinetic factors are considered and here buffer catalysis may occur in addition to that by hydroxide. Product ratios were determined by chromatographic separation in initial studies in which ^1H- and ^{13}C-n.m.r. characterisation of the purified *erythro* aurone hydrate (**7**) (Table 1; entry 2) and the other products (entry 3) was carried out. This then allowed in other cases that the product ratio could be established by quantitative n.m.r. spectroscopy on the reaction product mixture without chromatographic separation.

(b) 2'-Hydroxy-6'-methoxychalcone Epoxide (1) in MeCN/H2O Solvent: The Partitioning Ratio Between α- and β-Cyclisation.

Availability of the unprotected 2'-hydroxychalcone epoxides allowed the α/β cyclisation ratio to be studied starting even below neutral pH where secondary reactions did not intervene to complicate interpretation.

As consistent with the previous kinetic study[9] on 2'-hydroxychalcone epoxide, the 6'-methoxy derivative was found to be relatively stable at pH 4.4 being largely unreacted after 6 days at room temperature. As the pH is increased, the 2'-hydroxy group starts to ionise and the cyclisation rate increases accordingly, as the results indicate [Table 1].

At the lowest pH studied (5.7), there were after 13 days, apart from unreacted epoxide (**1**; *ca.* 30%), only two products, 3-hydroxy-5-methoxyflavanone (**6**) and *erythro*-4-methoxyaurone hydrate [2-(α-hydroxybenzyl)-4-methoxycoumaranone: (**7**)] in a ratio of *ca.* 1:6 (Table 1; entry 1). This ratio seems to be quite significant because even though at higher pH values, the *erythro* hydrate isomerises to the *threo* isomer (**9**) and undergoes elimination reactions as well [see Scheme and discussion in section (d)], the ratio of 3-hydroxyflavanone (**6**) to all other products (aurone hydrates **7** and **9** plus

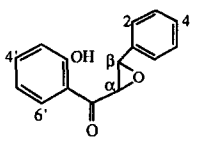
aurone-hydrate-derived products **10** and **12**; see Scheme) is maintained at 1 to *ca.* 5-6 (Table 1: entries 4,2,7,8,3 at increasing pH; entries 5,6 at higher temperature). The inference to be drawn is that the cyclisation reactions of the epoxide (eq. 1 and *cf.* eq. 2) are irreversible under the conditions and that the partitioning ratio of 1 to 5 or 6 between the β and α processes is kinetically controlled. There is no evidence of reversion of the 3-hydroxyflavanone to aurone products under these conditions; Litkei has suggested[7c] such reversed reactions account for aurone formation under AFO conditions though this seems to contradict earlier studies summarised by Dean[11] showing that 2-hydroxy-2-benzylcoumaranones are formed from 3-hydroxyflavanones and that these do not yield aurones under AFO conditions.

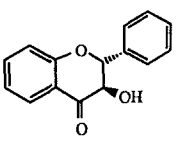
A similar partitioning ratio for the 6'-isopropoxy epoxide (**2**)(Table 2) reveals little influence of increasing the steric bulk of the *O*-alkyl group of the 6'-substituent indicating that a non-bonded interaction leading to twisting the C=O group out-of-plane with the ring, which (see Introduction and below) has been seen to limit β- at the expense of α-substitution of the epoxide, may have its origins mostly in lone pair/lone pair repulsion.

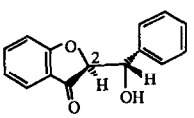
The β/α partitioning ratio is again about 1:6 for the 4,6-dimethoxy epoxide (**3**)(Table 2) indicating negligible influence of the electronic effect of the extra (4') methoxy group. Substituents in the other ring do, however, influence the ratio, most notably the 2-trifluoromethyl group which eliminates β-cyclisation altogether (compound **4**; Table 2), perhaps by a through-space electrostatic repulsion of 2'-O^- approach to the adjacent β-carbon. The more remote 4-chloro substituent has only a minor effect (compound **5**; Table 2).

By contrast, 2'-hydroxychalcone epoxide itself gives 100% β-cyclisation (Table 2; 1st line) indicating that the effect of the 6'-substituent in promoting α-cyclisation is really quite pronounced.

Table 2 **Ratio of β- to α-Cyclisation Products for Substituted 2'-Hydroxychalcone Epoxides**







Compound	Other substituents	*trans*-3-hydroxyflavanone	*erythro*-aurone hydrate
Parent epoxide[a]	None	100	-
(1)[b]	6'-OMe	14	86
(2)[b]	6'-O^{i}Pr	16	84
(3)[b]	4',6'-$(OMe)_2$	15	85
(5)[b]	4-Cl	10	90
(4)[c]	2-CF_3	-	100

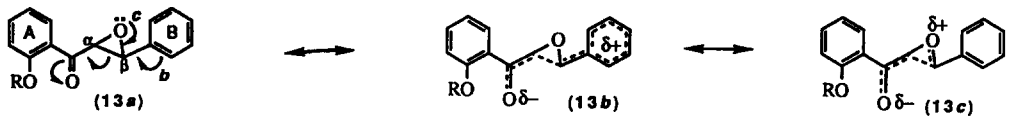
[a] pH 7 6 (phosphate buffer), 3 1 MeCN/H_2O
[b] pH 8.2-8 3 (TRIS buffer); 1·1 MeCN/H_2O
[c] pH 6.9 (phosphate buffer), 1 1 MeCN/H_2O

(c) An Explanation for the Preference for α- Rather Than β-Cyclisation of 2'-Hydroxychalcone Epoxides with 6'-Substituents

The original suggestion as outlined[5] by Dean was that a steric effect twists the C=O out-of-plane with the attached aromatic ring which also makes the epoxide β-carbon less accessible to the 2'-O-

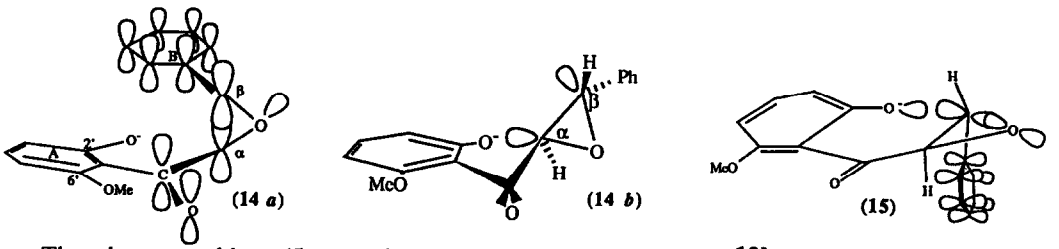
nucleophile so that α-substitution becomes preferable on proximity grounds. The fundamental basis of this suggestion is not disputed, but it can be put on a more acceptable footing by considering stereoelectronic effects on conformational preferences.

When a 6'-substituent forces the carbonyl group out-of-plane with the attached aromatic ring, delocalisation of negative charge from 2'-O⁻ is reduced and the C=O group will be more effectively electron-withdrawing from the remaining part of the system. It has been determined from i.r. studies[7d] of C=O stretching frequencies of chalcone epoxides that those with 2'-OR substituents to force the carbonyl group out-of-plane with the attached aromatic ring exist in a cisoid conformation (**13a**), as opposed to a gauche conformation normally observed in the absence of such a substituent. This conformational preference is deduced to arise from significant conjugation of the carbonyl group through the Cα-Cβ σ-bond with the B–ring (**13b**) as indicated by a LFER between C=O stretching frequency and σ* for 4-substituents in the B-ring; conjugation with the epoxide oxygen (**13c**) may



also occur. The stereoelectronic implications are that the Cα–Cβ bond of the epoxide should parallel the C=O π-system for maximum stabilisation and this requires this bond to be well out-of-plane with the A-ring to which the C=O (and the 2'-O⁻) are attached.

Such a conformation is depicted in the orbital overlap picture (**14a**) for the reactive 2'-O⁻ anion of 2'-hydroxy-6'-methoxychalcone epoxide (**1**), the species of central interest to the present study. This picture reveals (if not as clearly as models) that the 2'-O⁻ group is remote from the β-carbon in this ground-state conformation, and picture (**14b**) shows the unfavourable orientation of the antibonding Cβ-O orbital with which end-on overlap by a lone-pair orbital on 2'-O⁻ is required for optimal SN2 substitution. Clearly, rotation of the epoxide unit about the CO-Cα bond with loss of conjugation is required to achieve a conformation in which Cα-Cβ becomes more coplanar with the A-ring before 2'-O⁻ can approach Cβ with the appropriate orientation for SN2 substitution (*cf.* **15** below). For α-substitution, by contrast, the proximity of 2'-O⁻ and its orientation with respect to the epoxide Cα-O bond appear to be about as optimised for SN2 attack with inversion as is possible for 5-membered ring (5-exo-tet) formation.[12a]



Thus the reversal here (5-exo > 6-exo) of the normal (5 < 6) trend[12b] for intramolecular epoxide substitution reactions appears possibly to have a stereoelectronic origin associated with the out-of-plane C=O group imposing a stable conformation (**14a,b**) which happens to be geometrically highly favourable for α–attack but quite unfavourable for β-attack. De-conjugation of C=O from 2'-O⁻ as in (**14**) also increases both the nucleophilicity of the 2'-O⁻ nucleophile and, by increased inductive electron-withdrawal to C=O, the electrophilicity of the α-carbon, thereby promoting α-substitution.

Although there is also potential for a stereoelectronic effect to operate and stabilise the transition state for substitution α to the carbonyl group, as is thought[12c] to accelerate substitution of α-halocarbonyl compounds, the geometrical requirement for maximum such stabilisation, *i.e.* that the Cα-O bond be parallel to the C=O π-system, can scarcely be met by rotation along the CO-Cα bond in the present system given the constraints of near planarity in five-membered ring formation.

For epoxides without a 6'-substituent, maximum delocalisation from the 2'-O⁻ group to the carbonyl oxygen is possible since C=O coplanarity with the ring is now unrestricted. This would attenuate the electron-withdrawing capacity of the carbonyl group and delocalisation across the epoxide ring from the β-phenyl ring (*cf.* **14**), i.e. the benzylic epoxide centre may become deconjugated from the C=O and the conformational constraints implicit in (**14a**) removed. Rotation about the CO-Cα bond would now be freer to allow easier attainment of a conformation from which SN2 substitution, with normal[12b] benzylic transition state stabilisation (**15**), can proceed.

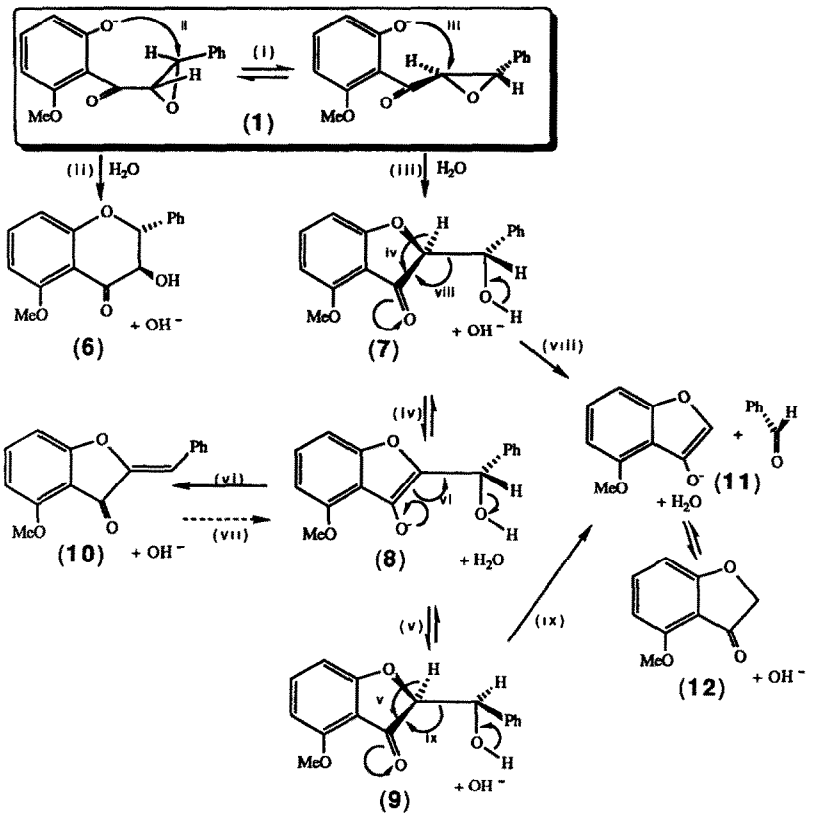
The reported observations[5,13] that some 6'-substituted 2'-hydroxychalcones in the AFO reaction revert at higher temperature to β-cyclisation (3-hydroxyflavanone formation) rather than α-cyclisation (aurone formation) could, if epoxide intermediates are involved, be accounted for by easier rotation away from conformation (**14**) to one (*cf.* **15**) in which β-substitution is available; however, as far as 6'-methoxychalcone epoxide is concerned, our results show that α-cyclisation is still preferred at reflux temperature (79 °C), as is consistent with the finding[6] of Gormley and O'Sullivan with the 6'-methoxy-2'-tosyloxychalcone epoxide. The electronic activation of α-substitution when the C=O is out-of-plane and de-conjugated from the 2'-O⁻ nucleophile as mentioned above may therefore be a dominant factor.

(d) **Mechanism of Aurone Hydrate Formation and Decomposition Reactions.**

Formation of the *erythro*-aurone hydrate (**7**) is consistent with SN2 substitution by 2'-O⁻ with inversion at the α-carbon (Scheme; step iii). The appearance of the *threo* isomer (**9**) at the higher pH of 7.6 (Table 1; entry 2) indicates base-promoted isomerisation through the enolate (**8**; steps iv and v), while the absence at this pH of aurone (**10**) indicates that the latter is formed by an E1cB(reversible) reaction, *i.e.* the enolate (**8**) reverts to "reactant" [either *erythro* (**7**) or *threo* (**9**) hydrate] faster than it eliminates hydroxide (step vi) to form the aurone (**10**), the latter becoming detectable at higher pH (Table 1; entries 3, 8) when the concentration of enolate is increased. It would be expected that at sufficiently high pH the reverse reaction (vii), conjugate addition of hydroxide to the aurone, would regenerate aurone hydrates. This may be the reason why aurone hydrate is present still at high pH after 20 min. at pH 11.9 (Table 1; entry 8) when kinetic measurements[14] show that at pH 11.8 in 1:1 MeCN/H2O, the measured half-life for decomposition of aurone hydrate at 30°C is about 50 seconds. Even after 25 h. at pH 12 in 3:1 MeCN/H2O (Table 1; entry 3), aurone hydrate is still present which is indicative of reversibility. By contrast, aurone is obtained in the absence of aurone hydrate by keeping to a low hydroxide concentration but high temperature (pH 6.9, 79°C; entry 6 in Table 1).

The coumaranone is presumably formed along with benzaldehyde from a retro-aldol reaction through the enolate (**11**) of the aurone hydrate (Scheme 1; viii and/or ix). There is evidence from u.v. spectral study under similar conditions (Fig. 1) for formation of a compound having the correct λmax (245 nm) for benzaldehyde in tandem with the formation of coumaranone. A coumaranone has not been mentioned to our knowledge as a product of chalcone oxidation or chalcone epoxide decomposition except[3] by Donnelly and coworkers as being implicit in the formation of a coumaranone-acetone aldol product formed with solvent acetone in a reaction of a 6'-substituted

chalcone dibromide with base.



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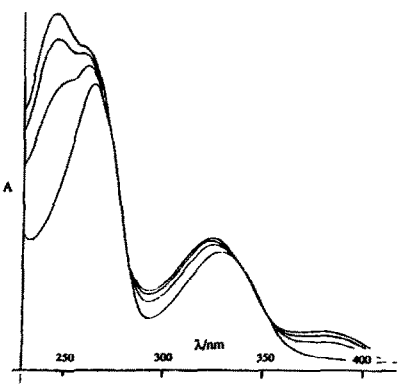
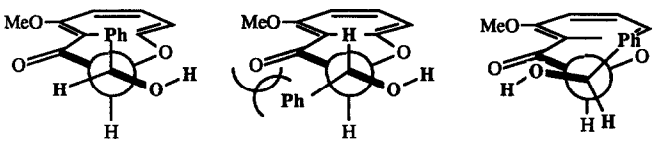


Figure: Repetitive scans at *ca.* 3 min. time intervals for the reactions subsequent to cyclisation of 2'-hydroxy-6'-methoxychalcone epoxide (**1**) at pH 10.07 and 30°C, indicating the formation of 4-methoxyaurone (385 nm) amd benzaldehyde (245 nm).

The stereoelectronic preference for aldol condensation reactions, *i.e.* an *anti* orientation of the enolate double bond and the carbonyl double bond,[12d,15] decrees in the present retro-aldol case that the ideal conformations for coumaranone formation would be (**16**) for *erythro-* and (**17**) for *threo-*aurone hydrate. The former seems likely to be the lowest-energy conformation for the *erythro* hydrate with the bulky phenyl group clear of steric interaction, but for the *threo* hydrate the *anti* conformation (**17**) suffers from steric crowding of the phenyl and C=O; it may even be that the retro-aldol reaction for the *threo* isomer would proceed faster from a conformation such as (**18**) in which a *syn* orientation of the C-OH and C-CO bonds can be approached. There is however no experimental evidence to suggest which stereoisomer leads to the coumaranone; *e.g. erythro-threo* isomerisation is already established (Table 1; entry 2) at a pH too low for formation of coumaranone (**12**) at room temperature, and repetitive scanning by u.v. spectroscopy to monitor the reaction of aurone hydrate at pH values above that for isomerisation shows tight isosbestic points (Fig. 1) indicating that, since depletion of the more reactive isomer would otherwise be observed, *erythro-threo* isomerisation is fast relative to the retro-aldol (and, for that matter, the aurone-forming) reaction of the aurone hydrate.



erythro (anti) (16) *threo (anti)* (17) *threo (syn)* (18)

Whether the retro-aldol reaction is significantly reversed under our conditions is not clear, but this offers another possible explanation for the presence of aurone hydrates amongst the products of reaction at higher pH. Certainly aurone hydrates can be synthesised[16] from coumaranones and aldehydes but the rather dilute solutions used in our work would make the bimolecular reaction less likely to contribute. Presumably under conditions of high concentration as normally used in synthetic work, any coumaranone formed reverts with aldehyde to aurone hydrate (and on to aurone), unless it is otherwise trapped, as for example by the solvent acetone as reported[3] in the case mentioned above.

Experimental

Preparations of the epoxides are described in the preceding paper[10] except for 2'-hydroxychalcone epoxide itself which was from an earlier study.[9]

P.l.c. refers to preparative layer chromatography on 1mm layers of silica gel (Merck 60 PF_{254} + 366).

U.v. spectra were recorded on a Uvikon 860 spectrophotometer, and n.m.r. spectra on a JEOL FX90Q FT spectrometer. The following internal standards were used: for $CDCl_3$ solvent, δC 77.06 and δH ($CHCl_3$) 7.26; for $(CD_3)_2CO$, δC 29.85 and δH (CD_3COCD_2H) 2.20. Multiplicities of ^{13}C signals were determined by standard techniques. For product analysis, ^{13}C-n.m.r. spectra of the reaction product mixtures were recorded with no nuclear overhauser enhancement and a long delay between pulses to allow complete relaxation of the C-nuclei so as to obtain sufficiently quantitative data for the purpose of this study.

Measurements of pH of reaction solutions were carried out prior to workup using a Radiometer Model PHM 84 meter fitted with a Radiometer GK2401B electrode and standardised with phthalate and borate buffer solutions.

Products from reactions carried out in water/acetonitrile mixtures were obtained by the addition of water to the reaction solution, multiple extraction with ether, washing and drying of the combined

ether layers, and solvent removal by evaporation under reduced pressure in a rotary evaporator. The term 'the usual workup' refers to this procedure and a typical example is that of the first reaction described below. In spite of the small quantities of reactants used, product recovery was greater than 80% for all reactions except those at high pH [Table 1, entry 3 (52% after p.l.c.) and entry 8 (65%)] or at high temperature [Table 1, entry 6 (65%)]. Presumably further product decomposition occurs under these more forcing conditions.

Reactions of 2'-Hydroxy-6'-methoxychalcone Epoxide (1) in Acetonitrile/Water Mixtures Buffered at Different pH Values

(a) 3:1 MeCN/H2O

(i) **pH 4.4** 2'-Hydroxy-6'-methoxychalcone epoxide (**1**; 86 mg, 0 32 mmol) was dissolved in MeCN (45 ml) to which was added aqueous acetic acid (12 ml; 0.02 mol l^{-1}) and aqueous sodium acetate (3 ml; 0.02 mol l^{-1}). The solution was stirred at room temperature for 6 days. Then water (100 ml) was added, and the resulting suspension was extacted with ether (3 x 30 ml). The combined ether fractions were washed with water (2 x 50 ml), dried ($MgSO_4$), and the solvent removed. The crude product (79 mg) was mainly starting material by ^{1}H-n.m.r. spectroscopy.

(ii) **pH 5.7** 2'-hydroxy-6'-methoxychalcone epoxide (**1**; 250 mg, 0.93 mmol) was dissolved in MeCN (60 ml) to which was added aqueous acetic acid (8 ml; 0.02 moll^{-1}) and aqueous sodium acetate (12 ml; 0.02 mol l^{-1}). After 13 days, the usual workup gave a product (216 mg) which the ^{13}C-n.m.r. spectrum showed to contain 2'-hydroxy-6'-methoxychalcone epoxide (**1**; 30 %), *erythro*-4-methoxyaurone hydrate (**7**; 60 %), and 3-hydroxy-5-methoxyflavanone (**6**; 10 %). Preparative layer chromatography on silica gel [3:1 petroleum spirit (b.p. 60-80°C):ethyl acetate] provided a pure sample of ***erythro-4-methoxyaurone hydrate*** (**7**, 76 mg; 30%), m.p. 125-130°C. Found C 70.90, H 5.14; $C_{16}H_{14}O_4$ requires C 71.10, H 5.22 %. δ_H (89.55 MHz; $CDCl_3$) 7.34 (6H, m, 2'-6',6-H), 6.57 (1H, d, $^{7,6}J$ = 8.3 Hz, 7-H), 6.35 (1H, d, $^{5,6}J$ = 8.1 Hz, 5-H), 4.96 (1H, d, ^{2,CH}OHJ = 6.3 Hz, 2-H), 4.65 (1H, d, CHOH,^2J = 6.3 Hz, CHOH), and 3.84 (3H, s, OCH_3). δ_C (22.49 MHz; $CDCl_3$) 197.3 (s, 3-C), 173.5 (s, 7a-C), 157.6 (s, 5-C), 139.4 (d, 6-C), 137.9 (s, 1'-C), 127.6 (d, 2',4',6'-C), 126.7 (d, 3',5'-C), 110.1 (s, 3a-C), 104.6 (d, 7-C), 102.9 (d, 5-C), 86.4 (d, 2-C), 73.3 [d, CH(OH)Ph], and 55.5 (q, OCH_3).

(iii) **pH 7.6** 2'-Hydroxy-6'-methoxychalcone epoxide (**1**; 99 mg, 0.37 mmol) was dissolved in MeCN (30 ml) to which was added aqueous K_2HPO_4 (6 ml; 0.02 mol l^{-1}) and aqueous KH_2PO_4 (4 ml; 0.02 mol l^{-1}). The solution was left for 32 h. After the usual workup, ^{13}C-n.m.r. of the separated product (88 mg) indicated the presence of three compounds; ***erythro-*** and ***threo-4-methoxyaurone hydrate*** (**7**,**9**; *ca.* 1:1, 84 %), and ***3-hydroxy-5-methoxyflavanone*** (**6**; 16 %) (see n.m.r. data below).

(iv) **pH 12.0** 2'-Hydroxy-6'-methoxychalcone epoxide (**1**; 100 mg, 0.37 mmol) was dissolved in MeCN (37.5 ml), then water (10.4 ml), aqueous K_2HPO_4 (1.25 ml; 0.2 mol l^{-1}) and aqueous KOH (0.88 ml; 0.2 mol l^{-1}) were added. After 25 h. at room temperature, the usual workup gave a product which was separated by rotating disc radial chromatography ('Chromatotron') on silica gel using hexane/CH_2Cl_2 (4:1). Products eluted in the following order were:

4-methoxyaurone (**10**; 15 mg; 16%), δ_C (22.49 MHz; $CDCl_3$) 182.1 (s, 3-C), 166.8 (s, 7a-C), 158.4 (s, 4-C), 146.7 (s, 2-C), 138.3 (d, 6-C), 132.3 (s, 1'-C), 131.1 (d, 4'-C), 129.4 (d, 2',6'-C), 128.7 (d, 3',5'-C), 111.6 (d, =CHPh), 110.6 (s, 3a-C), 105.1 (d, 7-C), 104.6 (d, 5-C), 56.1 (q, OCH_3);

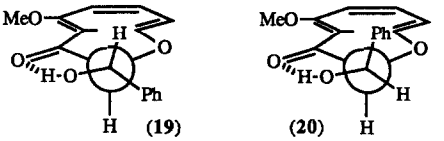
4-methoxycoumaran-3-one (**12**; 8 mg; 13%), δ_H (89.55 MHz; $CDCl_3$) 7.49 (1H, t, J = 8.2 Hz, 6-H), 6.65 (1H, d, $^{7,6}J$ = 8.2 Hz, 7-H), 6.44 (1H, d, $^{5,6}J$ = 8.2 Hz, 5-H), 4.56 (2H, s, CH_2), and 3.93 (3H, s, OCH_3); δ_C (22.49 MHz; $CDCl_3$) 197.2 (s, 3-C), 175.2 (s, 7a-C), 158.2 (s, 4-C), 139.4

(d, 6-C), 110.6 (s, 3a-C), 105.4 (d, 7-C), 103.2 (d, 5-C), 74.7 (t, 2-C), and 56.1 (q, OCH_3).

3-hydroxy-5-methoxyflavanone (**6**; 18 mg; 18%), δ_H (89.55 MHz; $CDCl_3$) 7.53-7.47 (6H, m, 2',3',4',5',6',7-H), 6.65 (1H, d, $^{8,7}J$ = 8.2 Hz, 8-H), 6.53 (1H, d, $^{6,7}J$ = 8.2 Hz, 6-H), 5.07 (1H, d, $^{2,3}J$ = 12.3 Hz, 2-H), 4.51 (1H, d, $^{3,2}J$ = 12.3 Hz, 3-H), and 3.95 (3H, s, OCH_3); δ_C (22.49 MHz; $CDCl_3$) 192.5 (s, 4-C), 163.1 (s, 8a-C), 160.7 (s, 5-C), 137.2 (d, 7-C), 136.5 (s, 1'-C), 129.2 (d, 4'-C), 128.6 (d, 2',6'-C), 127.5 (d, 3',5'-C), 110.1 (d, 8-C), 108.6 (s, 4a-C), 104.1 (d, 6-C), 83.2 (d, 2-C), 73.2 (d, 3-C), and 56.3 (q, OCH_3).

A mixture (15 mg; 15%) of ***erythro-4-methoxyaurone hydrate*** (**7**; *ca.* 2 parts) (n.m.r. data above) and ***threo-4-methoxyaurone hydrate*** (**9**; *ca.* 3 parts); n.m.r. data by subtracting where possible that for the *erythro* isomer: δ_H (89.55 MHz; $CDCl_3$) 5.32 (1H, d, ^{2,}CHOHJ = 2.4 Hz, 2-H), 4.65 (1H, d, CHOH, ^{2}J = 2.4 Hz, CHOH), 3.80, s, OCH_3); δ_C (22.49 MHz; $CDCl_3$) 197.4 (s, 3-C), 174.5 (s, 7a-C), 157.8 (s, 5-C), 139.9 (s, 1'-C), 139.5 (d, 6-C), 128.2 (d, 2',6'-C), 128.0 (d, 4'-C), 126.3 (d, 3',5'-C), 110.9 (s, 3a-C), 105.0 (d, 7-C), 103.0 (d, 5-C), 87.7 (d, 2-C), 72.6 (d, CH(OH)Ph), and 55.7 (q, OCH_3).

The *erythro* and *threo* assignments are based on an expected larger coupling constant between H-2 and the benzylic (CHOHPh) proton for the *erythro* compound in the hydrogen-bonded conformation (**19**) in the non-polar solvent $CDCl_3$. The dihedral angle for the corresponding protons in the *threo* isomer by comparison is expected to be much closer to 90° (**20**) and the coupling constant smaller.



erythro *threo*

H-bonded conformers of aurone hydrates

(b) 1:1 MeCN/H2O

(i) **pH 6.9** 2'-Hydroxy-6'-methoxychalcone epoxide (**1**; 74 mg, 0.27 mmol) was dissolved in acetonitrile (100 ml) to which was added an aqueous phosphate buffer solution [100 ml; containing KH_2PO_4 (0.016 mol l^{-1}), K_2HPO_4 (0.004 mol l^{-1}) and potassium chloride (0.2 mol l^{-1}). After 27.5 h. at ***room temperature***, water (150 ml) was added and the mixture was extracted with ether (3 x 40 ml). The combined extracts were washed with water (3 x 20 ml), dried ($MgSO_4$), and the ether removed to yield a mixture (63 mg) of ***erythro-4-methoxyaurone hydrate*** (**7**; 85 %) and ***3-hydroxy-5-methoxyflavanone*** (**6**; 15 %).

When this reaction was repeated but under ***reflux for 10 min***, the product (69 mg) comprised ***erythro-4-methoxyaurone hydrate*** (**7**; 83 %) and ***3-hydroxy-5-methoxyflavanone*** (**6**; 17 %).

The same reaction but using 82 mg of (**1**) under ***reflux for 2 h.*** gave a product mixture (55 mg) of ***4-methoxyaurone*** (**10**; 36 % by ^{13}C-n.m.r.), ***4-methoxycoumaran-3-one*** (**12**; 46 %), and ***3-hydroxy-5-methoxyflavanone*** (**6**; 18 %).

(ii) **pH 8.3** 2'-Hydroxy-6'-methoxychalcone epoxide (**1**; 75 mg, 0.28 mmol) was dissolved in acetonitrile (100 ml). An aqueous TRIS buffer solution [100 ml; containing tris(hydroxymethyl)aminomethane and its conjugate acid as the hydrochloride (each 0.01 mol l^{-1}) and KCl (0.2 mol l^{-1}] was added and the reaction left for 1 hour. The usual workup yielded a mixture (66 mg) of ***erythro-4-methoxyaurone hydrate*** (**7**; 86 % by ^{13}C-n.m.r.) and ***3-hydroxy-5-methoxyflavanone*** (**6**; 14 %).

(iii) **pH 11.9** 2'-Hydroxy-6'-methoxychalcone epoxide (**1**; 105 mg, 0.39 mmol) was dissolved in acetonitrile (100 ml). An aqueous phosphate buffer solution [100 ml; containing K_2HPO_4 and K_3PO_4 (each 0.01 mol l^{-1}) and KCl (0.2 mol l^{-1})] was added. After 20 min. the usual workup yielded a mixture (67 mg) of ***3-hydroxy-5-methoxyflavanone*** (**6**; 17 % by ^{13}C-n.m.r.), ***erythro-4-methoxyaurone hydrate*** (**7**; 8 %), ***threo-4-methoxyaurone hydrate*** (**9**; 13 %), ***4-methoxycoumaran-3-one*** (**12**; 47 %), and ***4-methoxyaurone*** (**10**; 14 %).

Reactions of Other Chalcone Epoxides in Buffered 1:1 MeCN/H_2O Solution

(i) 2'-Hydroxy-6'-isopropoxychalcone epoxide (2) at pH 8.3

The epoxide (**2**; 102 mg, 0.36 mmol) was dissolved in acetonitrile (100 ml). An aqueous TRIS buffer solution [100 ml; containing tris(hydroxymethyl)aminomethane and its conjugate acid as the hydrochloride (each 0.01 mol l^{-1}) and KCl (0.2 mol l^{-1})] was added and the reaction solution left for 5.3 h. The usual workup gave a mixture (96 mg) of ***3-hydroxy-5-isopropoxyflavanone*** (16 % by ^{13}C-n.m.r.) and ***erythro-4-isopropoxyaurone hydrate*** (84 %), δ_C (22.49 MHz; $CDCl_3$) 197.7 (s, C=O), 173.8 (s, 7a-C), 156.7 (s, 4-C), 139.4 (d, 6-C), 138.3 (s, 1'-C), 127.4 (d, 2',4',6'-C), 126.8 (d, 3',5'-C), 110.9 (s, 3a-C), 105.4 (d, 7-C), 104.2 (d, 5-C), 86.1 (d, 2-C), 73.4 [d, C<u>H</u>(OH)Ph], 71.4 [d, O<u>C</u>H(Me)2], and 21.5 [q, OCH(<u>C</u>H3)2].

(ii) 2'-Hydroxy-4',6'-dimethoxychalcone epoxide (3) at pH 8.2

The epoxide (**3**; 70 mg, 0.23 mmol) was reacted as described for (**2**) above except that the reaction was allowed to proceed for only 35 min. The usual workup gave a mixture (68 mg) of ***3-hydroxy-5,7-dimethoxyflavanone*** (15 %) and ***erythro-4,6-dimethoxyaurone hydrate*** (85 %), δ_H (89.55 MHz; $CDCl_3$) 7.32 (5H, m, 2'-5'-H), 6.05 (1H, d, $^{7,6}J$ = 1.8 Hz, 7-H), 5.91 (1H, d, $^{5,6}J$ =1.8 Hz, 5-H), 4.92 (1H, d, $^{2,C\underline{H}OH}J$ = 6.5 Hz, 2-H), 4.64 (1H, d, C<u>H</u>OH,^{2}J = 6.5 Hz, C<u>H</u>OH), 3.80 and 3.76 (each 3H, s, 4- and 6-OCH3); δ_C (22.49 MHz; $CDCl_3$) 195.8 (s, C=O), 175.8 (s, 7a-C), 170.1 (s, 6-C), 159.8 (s, 4-C), 138.5 (s, 1'-C), 128.4 (d, 4'-C), 128.0 (d, 2',6'-C), 126.9 (d, 3',5'-C), 104.4 (s, 3a-C), 93.0 (d, 7-C), 88.7 (d, 5-C), 86.8 (d, 2-C), 73.6 (d, CHOH), and 55.8 (two superimposed q's, 4- and 6-OCH3).

(iii) 4-Chloro-2'-hydroxy-6'-methoxychalcone epoxide (5) at pH 8.2

The epoxide (**5**; 64 mg, 0.21 mmol) was reacted as described for (**2**) and (**3**) above, except that the reaction was left to proceed for 30 min. The usual workup yielded a mixture (65 mg) of ***4'-chloro-3-hydroxy-5-methoxyflavanone*** (10 %) and ***erythro-4'-chloro-4-methoxyaurone hydrate*** (90 % by ^{13}C-n.m.r.), δ_H (89.55 MHz; $CDCl_3$) 7.47-7.28 (5H, m, 2',3',5',6,6'-H), 6.59 (1H, d, $^{5,6}J$ = 8.3 Hz, 5-H), 6.40 (1H, d, $^{7,6}J$ = 8.1 Hz, 7-H), 4.97 (1H, d, $^{2,C\underline{H}OH}J$ = 6.1 Hz, 2-H), 4.64 (1H, d, C<u>H</u>OH,^{2}J = 6.1 Hz, C<u>H</u>OH) and 3.89 (s, 3H, OCH3); δ_C (22.49 MHz; $CDCl_3$) 197.6 (s, C=O), 173.6 (s, 7a-C), 157.8 (s, 4-C), 139.8 (d, 6-C), 136.8 (s, 1'-C), 133.5 (s, 4'-C), 128.3 and 127.9 (each d, 2',6'-C and 3',5'-C), 110.1 (s, 3a-C), 104.7 (d, 5-C), 103.1 (d, 7-C), 86.5 (d, 2-C), 72.8 (d, CHOH), and 55.7 (q, OCH3).

(iv) 2-Trifluoromethyl-2'-hydroxy-6'-methoxychalcone epoxide (4) at pH 6.9

The epoxide (**4**; 92 mg, 0.27 mmol) was dissolved in acetonitrile (100 ml). An aqueous phosphate buffer solution [100 ml; containing KH_2PO_4 and K_2HPO_4 (each 0.01 mol l^{-1}) and KCl (0.20 mol l^{-1}) was added and the reaction left for 40 h. The usual workup gave as the only product ***erythro*-2'-trifluoromethyl-4-methoxyaurone hydrate** (85 mg; nett 92 %), δ_H (89.55 MHz; $CDCl_3$) 7.97-7.33 (5H, m, 3',4',5',6',6-H), 6.51 (1H, d, $^{5,6}J$ = 8.2 Hz, 5-H), 6.38 (1H, d, $^{7,6}J$ = 8.2 Hz, 7-H), 5.35 (1H, d, $^{2,C\underline{H}OH}J$ = 7.0 Hz, 2-H), 4.55 (d, C<u>H</u>OH,^{2}J = 7.0 Hz, C<u>H</u>OH), and 3.82 (3H, s, OCH3); δ_C (22.49 MHz; $CDCl_3$) 198.0 (s, C=O), 173.6 (s, 7a-C), 158.1 (s, 4-C), 139.9 (d, 6-C), 137.4 (s, 1'-C, q, J = 1.2 Hz), 131.9 (d, 5'-C), 129.0 and 128.1 (each d, 4'-C and 5'-C), 127.6 (s, 2'-C, q, J = 29.9 Hz), 125.3 (d, 3'-C, q, J = 5.5 Hz), 124.0 (s, CF_3, q, J = 273 Hz), 110.0 (s, 3a-C), 104.8 (d, 5-C), 103.3 (d, 7-C), 85.2 (d, 2-C), 68.3 [d, <u>C</u>HOH (q, 2.2 Hz)], and 55.6 (q, OCH3).

2'-Hydroxychalcone epoxide at pH 7.6 in 3:1 MeCN/H_2O

2'-Hydroxychalcone epoxide (30 mg, 0.13 mmol) was dissolved in acetonitrile (30 ml) and added to an aqueous phosphate buffer solution [10 ml; containing K_2HPO_4 (0.024 mol l^{-1}) and KH_2PO_4 (0.016 mol l^{-1})] and the solution left for 24 h. After the usual workup, ^{1}H-n.m.r. indicated the presence of only 3-hydroxyflavanone as consistent with the results of earlier studies.[8,9]

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