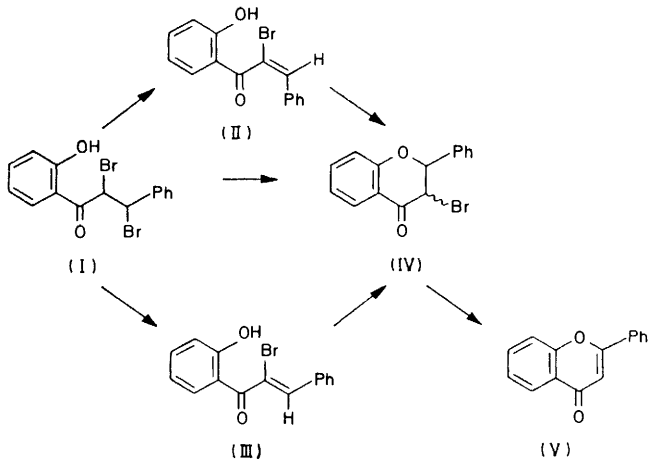
Routes to 3-Bromoflavanone from *erythro*-2'-Hydroxychalcone Dibromide: Spectral and Kinetic Evidence for the Dominating Role of Elimination–Addition Sequences *via* (*E*)- and (*Z*)-α-Bromo-2'-hydroxychalcones

By **Shantha K. David, Lyndsay Main,*** and **K. Barry Old,** Chemistry Department, University of Waikato, Hamilton, New Zealand

Rate coefficients for the formation from *erythro*-2'-hydroxychalcone dibromide of (*E*)- and (*Z*)-α-bromo-2'-hydroxychalcone and for their cyclisation to 3-bromoflavanone in 4 : 1 water–ethanol at pH 7.88 are established by a combination of kinetic and spectrophotometric measurements. The *E*-isomer is formed in a yield (%) of 35 ± 2 as opposed to 63 ± 8 for the *Z*-isomer. The *Z*-isomer cyclises over 20 times faster. Direct cyclisation of the dibromide, if any, is only a very minor route to 3-bromoflavanone. The implications for the elimination mechanism of the preference for *syn*- over *anti*-elimination, of the independence of rate of buffer (*N*-ethylmorpholine) concentration, and of the effect of pH change are briefly considered. Mechanisms discounted are *E*2 with *N*-ethylmorpholine or solvent molecules as base, and *E*1. No firm assignment is possible amongst a number of other mechanisms.

THOSE 2'-hydroxychalcone dibromides (I) which yield only flavones in aqueous alcoholic alkali (' class 1 ' 2'-hydroxychalcone dibromides [1a]) have been regarded for many years [2] as cyclising directly to 3-bromoflavanones (IV), the immediate precursors of flavones (V). The possible alternative routes to 3-bromoflavanones *via* the isomeric (*E*)- and (*Z*)-α-bromo-2'-hydroxychalcones (II) and (III), respectively, have been implicated [1b,c] only for some (' class 2 ' [1a]) 2'-hydroxychalcone dibromides which give aurones as well as flavones. However, the lack of previous detailed study of the course of reactions proceeding from any 2'-hydroxychalcone dibromide of class 1 raises the question of whether elimination–addition routes to 3-bromoflavanones were not prematurely dismissed solely on the basis of synthetic study. We were thus led to initiate a study on the parent 2'-hydroxychalcone dibromide (I) itself, our aim being to seek evidence for the formation of the α-bromochalcones (II) and (III) during the course of formation of 3-bromoflavanone (IV) and, if such evidence were found, to determine quantitatively how effectively the two elimination–addition routes compete with direct cyclisation (Scheme 1).



SCHEME 1

EXPERIMENTAL

^{1}H N.m.r. spectra (60 MHz; $CDCl_3$) were recorded on a JEOL C-60HL spectrometer, mass spectra on a Varian MAT CH5 spectrometer, and i.r. spectra on a Perkin-Elmer 180 spectrometer. U.v. spectral and kinetic measurements were carried out using a Cary 17 spectrophotometer, the cell block of which was maintained at constant temperature (30 °C) by circulation of water from an external thermostatted water-bath.

Materials.—Potassium chloride and hydrochloric acid used in the preparation of buffer solutions were of analytical grade. *N*-Ethylmorpholine was redistilled with collection of a middle fraction, b.p. 139 °C. (*E*)-2'-Hydroxychalcone was prepared by the standard method [3] of condensation of *o*-hydroxyacetophenone and benzaldehyde. It had m.p. 88 °C (lit.,[3] 89 °C).

erythro-2'-*Hydroxychalcone Dibromide.*—(*E*)-2'-Hydroxychalcone was dissolved in the minimum volume of cold acetic acid. An equimolar quantity of bromine was dissolved separately in a similar volume of acetic acid. The two solutions were mixed and left in the dark for 40 min. The precipitate was then collected and recrystallised three times from light petroleum (b.p. 60—80 °C) to give very pale cream crystals, m.p. 192 °C (lit.,[4] 192 °C).

(E)- *and* (Z)-α-*Bromo-2'-hydroxychalcone and* 3-*Bromoflavanone.*—Powdered *erythro*-2'-hydroxychalcone dibromide (1 g, 0.0026 mol) was dissolved with stirring in methanol (500 ml). *N*-Ethylmorpholine (2.63 ml, 0.0104 mol) was added and the solution was left in the dark at room temperature for 50 h. It was then added to diethyl ether (1 000 ml) and extracted with aqueous hydrochloric acid (1 000 ml; 0.1 mol l^{-1}) followed by water (3 × 500 ml). The ether layer was dried ($MgSO_4$) and the ether was removed (rotary evaporator; room temperature) to give the product mixture (0.75 g). Products were separated on silica gel plates (400 × 200 × 1.3 mm; Merck Kieselgel 60PF 254 + 366) using 30 : 70 chloroform–light petroleum (b.p. 60—80 °C) as eluting solvent. The product mixture was separated on five plates, using six successive full (200 mm) solvent developments for each plate. This gave, in addition to flavone, the following three major fractions (approximate weight, and relative R_F after six developments given): fraction 1 (0.20 g; 1.0); fraction 2 (0.13 g; 0.8); fraction 3 (0.10 g; 0.55).

Fraction 1 was further purified on a silica gel plate using

30 : 70 methanol–light petroleum (b.p. 60—80 °C) as eluting solvent, to give (E)-α-*bromo*-2′-*hydroxychalcone* (II) (0.18 g), a yellow oil, τ −1.55 (1 H, s, OH), *m/e* 304, 302, 227, 225, 223, 121, and 102; $\nu_{max.}$ (hexane) 1 630(s) and 1 613(m) cm^{-1}; $\lambda_{max.}$ (ethanol) 260 (log ε 4.3) and 346 nm (3.7) (Found: C, 59.7; H, 3.7; Br, 26.0. $C_{15}H_{11}BrO_2$ requires C, 59.4; H, 3.7; Br, 26.4%).

Fraction 2 was (Z)-α-*bromo*-2′-*hydroxychalcone* (III), a yellow oil, τ −1.35 (1 H, s, OH), *m/e* as for the *E*-isomer, $\nu_{max.}$ (hexane) 1 630(s) and 1 606(m) cm^{-1}; $\lambda_{max.}$ (ethanol) 258 (log ε 4.0) and 309 nm (4.1) (Found: C, 59.8; H, 3.6; Br, 26.2%). As in earlier [1c] studies, u.v. spectroscopy clearly distinguishes the *Z*- from the *E*-isomer. The chemical shift values of the hydrogen-bonded protons are also in accord with previous assignments.[1c] Confirmation based on β-proton chemical shifts,[1c] though unnecessary, was not possible here as these signals could not be assigned with certainty against the background of aromatic proton signals.

Fraction 3 was a mixture of *cis*- and *trans*-3-bromoflavanones (IV) in a ratio of *ca.* 3 : 1 as indicated by integration of the ^1H n.m.r. spectrum which showed τ 4.62 (1 H, d, *J* 2 Hz, α-H) and 5.47 (1 H, d, *J* 2 Hz, β-H) (*cis*-3-bromoflavanone), also τ 4.47 (1 H, d, *J* 8 Hz, 1 H, α-H) and 5.02 (1 H, d, *J* 8 Hz, β-H) (*trans*-3-bromoflavanone) (Found: C, 59.3; H, 4.0; Br, 26.2. Calc. for $C_{15}H_{11}BrO_2$: C, 59.4; H, 3.7; Br, 26.4%). Attempts to separate the isomers on silica gel plates were unsuccessful. They have previously been prepared [5] by bromination of flavanone. In ethanol they have identical u.v. spectra over the range 300—350 nm.[5]

All compounds were stored in the dark at −20 °C until required.

Solutions.—Stock solutions of reactants in dark containers were freshly prepared, in the case of the dibromide within 30 min of use during which time the compound was stable as indicated by spectral scans.

The ionic strength of aqueous buffer solutions was adjusted to 0.20 mol l^{-1} with potassium chloride. Owing to the subsequent addition of ethanol (20% by mixed volumes) when preparing reaction solutions, the ionic strength pertaining to kinetic data is 0.16 mol l^{-1}. Measurements of pH (7.88 ± 0.01 except where otherwise indicated) were made on individual reaction solutions after completion of runs.

General Kinetic Methods.—A silica cell containing the aqueous buffer solution and most of the required volume of ethanol was equilibrated at 30 °C in the cell block of the spectrophotometer. The reaction was started by syringing in the required additional volume of reactant solution. Normally the infinity absorbance reading was taken after ten half-lives and the first-order rate coefficient (k_{obs}) was calculated as the gradient of a plot of ln $(A_t - A_\infty)$ *versus* time. In cases where the infinity reading was affected by slow subsequent reactions, the Guggenheim [6a] method of analysis was used. Calculated rate coefficients were reproducible to within 3% or better. Checks showed that rates were unaffected by the u.v. radiation of the spectrophotometer.

METHODS AND RESULTS

In this section, for clarity of presentation the letters D [for the dibromide (I)], E [for the (*E*)-α-bromochalcone (II)], and Z [for the (*Z*)-α-bromochalcone (III)] are used as superscripts for absorbance and rate coefficient terms as appropriate, and also to denote concentrations of the corresponding compounds in rate equations.

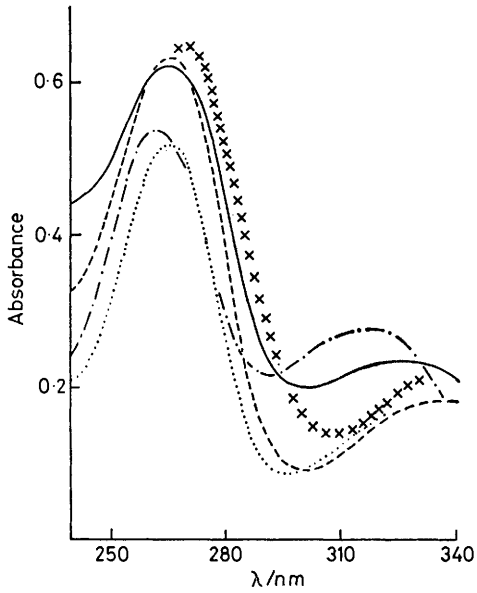


FIGURE 1 Spectral changes associated with reactions proceeding from the dibromide (I) (*ca.* 5 × 10^{-5} mol l^{-1}) at pH 7.88 ([*N*-ethylmorpholine] 8 × 10^{-3} mol l^{-1}). For clarity some scans are left incomplete. Times stated are those at which scans (4 nm s^{-1}) were commenced and are approximate. Zero time (×), unchanged dibromide (separately recorded at pH 2); 40 s (——), the strong absorbance at 310 nm, already decreasing, is due to the *Z*-α-bromochalcone (III); 160 s (– – –), the *Z*-α-bromochalcone has rapidly disappeared; 1 500 s (· · · ·), the decreased absorbance at 260 nm indicates the slower disappearance of the *E*-α-bromochalcone (II); 12 000 s (– · – · –), formation of flavone (V) ($\lambda_{max.}$ 304 nm), though far from complete, has now occurred

Evidence for the Formation of (E)- *and* (Z)-α-*Bromo*-2′-*hydroxychalcones from* erythro-2′-*Hydroxychalcone Dibromide in* 4 : 1 *Water–Ethanol at pH* 7.88.—For comparison, repeti-

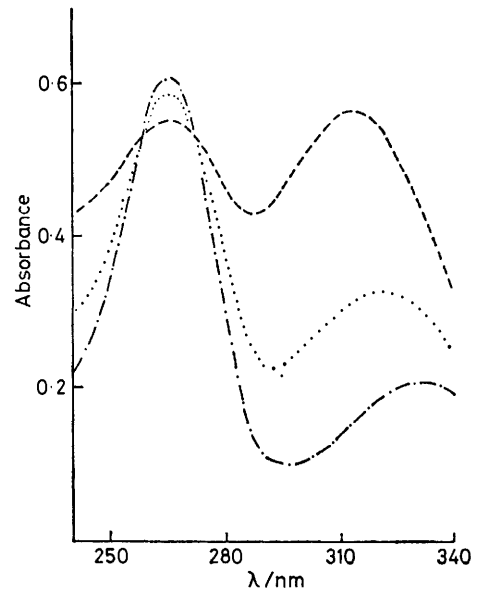


FIGURE 2 Spectral changes for the reaction of the (*Z*)-α-bromochalcone (III); (*ca.* 5 × 10^{-5} mol l^{-1}) at pH 7.88 ([*N*-ethylmorpholine] 8 × 10^{-3} mol l^{-1}) showing the isosbestic points at 258 and 272 nm. Scans (4 nm s^{-1}) were commenced after 10 (– – –); 55 (· · · ·); and 150 s (– · – · –)

tive scans were recorded on solutions of the dibromide (Figure 1) and the (*Z*)- and (*E*)-α-bromochalcones (Figures 2 and 3). The initial dibromide scans (at 40 and 160 s; Figure 1) showed clear evidence for the formation and subsequent disappearance of a compound absorbing strongly in the same wavelength region (310—320 nm) as the (*Z*)-α-bromochalcone (III) (Figure 2). Recording absorbance *versus* time on the dibromide at fixed wavelength (310 nm) showed that the absorbance increased rapidly to a maximum (*cf.* Figure 4) and then decreased again rapidly. Analysis of

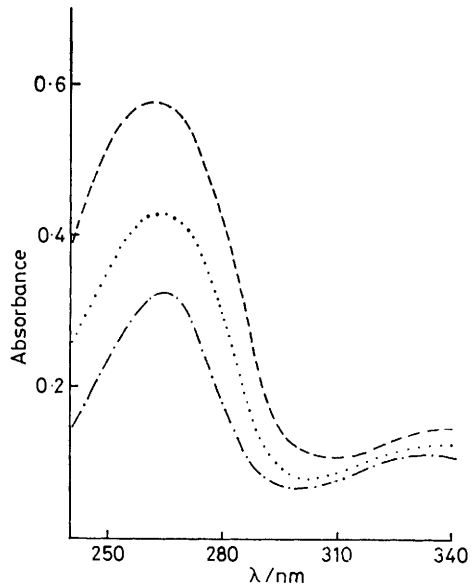


FIGURE 3 Spectral changes for the reaction of the (*E*)-α-bromochalcone (II) (*ca.* 3×10^{-5} mol l^{-1}) at pH 7.88 ([*N*-ethylmorpholine] 8×10^{-3} mol l^{-1}). Scans were recorded after 30 (– – –); 700 (· · · ·); and 3 500 s (— · — · —)

the absorbance decrease data allowed calculation of k_{obs} for the disappearance of the intermediate (0.02 s^{-1} at pH 7.88). At 260 nm [$\lambda_{max.}$ for the (*E*)-α-bromochalcone; *cf.* Figure 3], there was similar evidence for the formation and, in this case, much slower (k_{obs} 0.0010 s^{-1} at pH 7.88) disappearance of an intermediate.

Independently, rate coefficients for the reactions of (*E*)- and (*Z*)-α-bromo-2′-hydroxychalcone under the same conditions were determined. These values together with others established at a lower pH (7.21), are given in Table 1. None of the rate coefficients was affected by variation in the concentration of buffer.

TABLE 1

Rate coefficients for the cyclisation of (*E*)- and (*Z*)-α-bromo-2′-hydroxychalcones

pH	$10^3 k^Z_{obs}/s^{-1}$	$10^3 k^E_{obs}/s^{-1}$	k^Z_{obs}/k^E_{obs}
7.21	6.7 [a]	0.28 [a]	24
7.88	22.0 [b]	1.00 [b]	22

[a] Average of two measurements; *N*-ethylmorpholine 0.008 and 0.016 mol l^{-1}. [b] Average of six measurements; *N*-ethylmorpholine 0.008—0.080 mol l^{-1}.

The agreement between rate coefficients determined on solutions of the dibromide and solutions of the two α-bromochalcones was clear evidence that the latter are intermediates between the dibromide and 3-bromoflavanone. It remained to determine quantitatively the proportions in which the α-bromochalcones are formed, and the extent to which their formation competes with direct cyclisation of the dibromide to 3-bromoflavanone. In the face of low solubility of the dibromide, u.v. spectrophotometry provided the sensitivity required for analysis. The major difficulty is associated with the cyclisation of the α-bromochalcones, significant proportions of which, especially in the case of the *Z*-isomer, are already cyclised to 3-bromoflavanone before their formation is complete. A combination of spectrophotometric and kinetic measurements was used to circumvent this problem.

Yield of (E)-α-*Bromo-2′-hydroxychalcone.*—(a) *Choice of wavelength for analysis.* If it is determined for the reaction of the dibromide going to 3-bromoflavanone what contribution to absorbance change (at a particular wavelength) is made by the reaction of the (*E*)-α-bromochalcone initially formed, then this change, in relation to the final absorbance representing 3-bromoflavanone, can be used to estimate the fraction of dibromide leading to the (*E*)-α-bromochalcone: the absorbance change measures how much *E*-isomer is formed, while the final absorbance measures the total 3-bromoflavanone formed from all sources, *i.e.* the initial total dibromide. The requirements of the wavelength chosen for analysis are that the absorbance change for the reaction of the *E*-isomer going to 3-bromoflavanone should be large in comparison to changes for other reactions, and that, to ensure accuracy in the final absorbance value, the subsequent reaction of 3-bromoflavanone going to flavone, although slow, gives little or no absorbance change. From repetitive scans for the latter reaction, isosbestic points exist at 264 and 272.5 nm. At both these wavelengths, large absorbance changes occur for the reaction of the (*E*)-α-bromochalcone and, further, the reaction of the (*Z*)-α-bromochalcone shows isosbestic points at 258 and 272 nm (Figure 2). The wavelength 272.5 nm was therefore chosen for analysis as the sequence in which the *Z*-α-bromochalcone goes to 3-bromoflavanone and on to flavone gives a negligible absorbance change. For comparison measurements were made at 264 nm, at which in the very early stage of the reaction there is some interference from the rapid reaction of the *Z*-isomer.

(b) *Measurements.* The absorbance of pure (*E*)-α-bromo-2′-hydroxychalcone (A^E) was recorded until a constant infinity absorbance (A^E_∞) was obtained. The data were plotted to establish the first-order rate coefficient and extrapolation to zero (mixing) time gave zero-time absorbance (A^E_0). The ratio A^E_0/A^E_∞ equals the ratio of extinction coefficients of the (*E*)-α-bromochalcone and 3-bromoflavanone at the wavelength concerned.

The run was repeated using instead the dibromide. The absorbance (A^D) change, which is due mostly to the cyclisation of the *E*-α-bromochalcone at the wavelength used, is now smaller in relation to the infinity absorbance (A^D_∞) because the latter represents 3-bromoflavanone formed not only from the *E*-isomer but also from the *Z*-isomer and by direct cyclisation of the dibromide. From A^D_∞, the theoretical zero-time absorbance which would have applied if *all* the dibromide had been converted to the *E*-α-bromochalcone can be calculated as $A^D_\infty A^E_0/A^E_\infty$. To establish the experimental zero-time absorbance (A^D_0), absorbance data were plotted by the conventional infinity plot method for first-order kinetics and extrapolated. In this case, zero time is not mixing time because only the dibromide is then present. Clearly, before all the (*E*)-α-bromochalcone has been formed

some will have cyclised. We have chosen effective zero time somewhat arbitrarily as 30 s, at which time 77% of total (*E*)-α-bromochalcone will have been formed [see the rate coefficients below for the dibromide; the final calculated yield is little dependent on the chosen value of effective zero time, a value of 60 s (95% reaction) for instance, reducing the final calculated yields (Table 2) by only 1%]. Data for the initial stages deviated from the otherwise linear infinity plot because of interference from the reactions of the *Z*-α-bromochalcone (264 nm only) and residual dibromide. Extrapolation to effective zero time was made from the linear portion of the plot, a check for consistency always being made on the k_{obs} value calculated from the gradient.

Once the experimental effective zero-time absorbance (A^{D}_{0}) is established, the yield of the (*E*)-α-bromochalcone is calculated as the ratio of experimental absorbance change to theoretical absorbance change assuming 100% yield of the *E*-isomer:

$$\text{Yield (\%) E} = 100(A^{D}_{0} - A^{D}_{\infty})/[A^{D}_{\infty}(A^{E}_{0}/A^{E}_{\infty}) - A^{D}_{\infty}]$$
$$= 100[(A^{D}_{0}/A^{D}_{\infty}) - 1]/[(A^{E}_{0}/A^{E}_{\infty}) - 1]$$

(c) *Results.* Values of A_0 and A_∞ for various runs using (*E*)-α-bromo-2′-hydroxychalcone and *erythro*-2′-hydroxychalcone dibromide are recorded in Table 2 along with calculated yields of the former. The calculated yields are seen not to be affected by the wavelength used in the analysis or by the concentration of *N*-ethylmorpholine.

TABLE 2

Absorbance data and calculated yields of (*E*)-α-bromo-2′-hydroxychalcone from *erythro*-2′-hydroxychalcone dibromide

λ/nm	A^{E}_{0}	A^{E}_{∞}	A^{D}_{0}	A^{D}_{∞}	Yield (%) [a]
264	0.509	0.274	0.658	0.511	34 [b]
264	0.551	0.301	0.629	0.493	33 [b]
272.5	0.445	0.221	0.550	0.408	34 [b]
272.5	0.425	0.210	0.643	0.469	36 [b]
272.5	0.434	0.213	0.617	0.450	36 [c]
272.5	0.458	0.234	0.695	0.520	35 [d]

[a] Calculated using the mean value of A^{E}_{0}/A^{E}_{∞} for the conditions concerned and taking effective zero time for calculated A^{D}_{0} values as 30 s (see text). [b] Total *N*-ethylmorpholine 0.008 mol l^{-1}; pH 7.88. [c] Total *N*-ethylmorpholine 0.024 mol l^{-1}; pH 7.88. [d] Total *N*-ethylmorpholine 0.040 mol l^{-1}; pH 7.81.

The remaining 65% reaction of the dibromide represents the yield of the *Z*-α-bromochalcone plus the yield of 3-bromoflavanone formed by direct cyclisation. Measurement of the maximum absorbance attained at 310 nm suggested the presence of a *ca.* 30% yield of the *Z*-α-bromochalcone at this stage, but the total yield must be larger because rapid cyclisation of the compound occurs while it is still being formed.

Yield of (Z)-α-*Bromo*-2′-*hydroxychalcone.*—(a) *Kinetic theory.* A method based on the time taken for the *Z*-isomer to reach maximum concentration (measured at 310 nm) is used to determine its yield. The standard treatment [6b] for series first-order reaction kinetics relates to the following scheme:

$$D \xrightarrow{k_1} Z \xrightarrow{k_2} \text{3-bromoflavanone}$$

In the special case where D yields other products [(*E*)-α-bromo-2′-hydroxychalcone, and 3- bromoflavanone directly] in addition to Z, we have also:

$$D \xrightarrow{k_3} \text{all products}$$

The yield (%) of Z from D under conditions of kinetic control can be calculated, if rate coefficients are established, as $100k_1/k_3$. The differential equations are (1) and (2). From

$$dD/dt = -k_3D \quad (1)$$

$$dZ/dt = k_1D - k_2Z \quad (2)$$

(1) follows equation (3) so that equation (2), multiplying through by the factor e^{k_2t}, becomes equation (4). This

$$D = D_0e^{-k_3t} \quad (3)$$

$$e^{k_2t}dZ/dt + k_2Ze^{k_2t} = k_1D_0e^{(k_2-k_3)t} \quad (4)$$

$$d(e^{k_2t}Z)/dt = k_1D_0e^{(k_2-k_3)t} \quad (5)$$

can be rewritten as equation (5), integration of which leads to equation (6). Putting t and Z equal to zero in equation

$$Z = [k_1/(k_2 - k_3)]D_0e^{-k_3t} + Z_0e^{-k_2t} \quad (6)$$

(6) shows that Z_0 is given by $-D_0[k_1/(k_2 - k_3)]$ which, substituted into (6), leads to equation (7). If Z reaches a maximum ($Z_{max.}$) at time $t_{max.}$, substitution in (7) gives

$$Z = [k_1/(k_2 - k_3)]D_0(e^{-k_3t} - e^{-k_2t}) \quad (7)$$

$$Z_{max.}/D_0 = [k_1/(k_2 - k_3)](e^{-k_3t_{max.}} - e^{-k_2t_{max.}}) \quad (8)$$

equation (8). If $Z_{max.}/D_0$ and $t_{max.}$ can be measured and if k_2 is known from independent study of compound Z, k_1 and k_3 are left as the unknowns in equation (8). Further, k_3 can be determined from k_2 and $t_{max.}$ as can be seen by differentiating (7) to give equation (9) and by noting that Z

$$dZ/dt = [k_1/(k_2 - k_3)]D_0(k_2e^{-k_2t} - k_3e^{-k_3t}) \quad (9)$$

reaches a maximum when dZ/dt is zero. This leads to equation (10) which can be rewritten as (11). Given k_2, k_3

$$k_2e^{-k_2t_{max.}} = k_3e^{-k_3t_{max.}} \quad (10)$$

$$\ln k_3 - k_3t_{max.} = \ln k_2 - k_2t_{max.} \quad (11)$$

can be obtained as the non-trivial solution of equation (11). Then k_1 remains as the only unknown in equation (8). The yield (%) of Z, given by $100k_1/k_3$, can then be calculated.

(b) *Measurements and calculations.* (i) Determination of k_3. The value of k_2 in equation (11) is known (0.0220 s^{-1}; Table 1) for the conditions, while $t_{max.}$ was determined as the time after adding dibromide solution to start the reaction at which the absorbance reaches a maximum at 310 nm, a wavelength at which there is very little absorbance change due to reactions competing with the (*Z*)-α-bromochalcone formation.

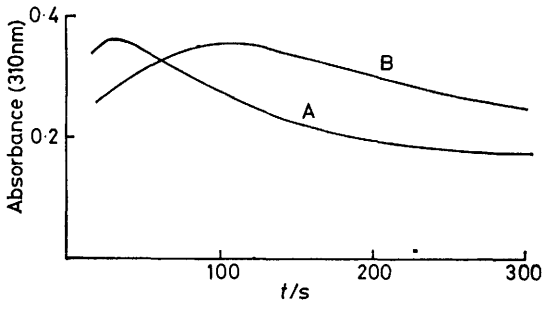


FIGURE 4 Monitoring the formation and disappearance of the (*Z*)-α-bromochalcone at 310 nm during the reaction of the dibromide (I) (*ca.* 7×10^{-5} mol l^{-1}) in *N*-ethylmorpholine (8×10^{-3} mol l^{-1}) solutions at pH 7.88 (curve A) and pH 7.21 (curve B)

For buffer solutions of total concentration in *N*-ethylmorpholine of 0.008, 0.016, 0.04, and 0.08 mol l^{-1}, values of $t_{max.}$ were determined (Figure 4) in duplicate runs all to be 30 ± 1 s. Substituting for k_2 (0.0220 ± 0.0005 s^{-1}) and $t_{max.}$ in equation (11) gives † k_3 as 0.048 ± 0.003 s^{-1}. Substituting values of k_2 and k_3 into equation (8) leads to equation (12).

$$Z_{max.}/D_0 = 10.77\ k_1 \qquad (12)$$

(ii) Determination of $Z_{max.}/D_0$. Measurement of the absorbance change due to Z between time $t_{max.}$ and the time (t_∞) at which all dibromide is converted to 3-bromoflavanone is required as a measure of $Z_{max.}$; the absorbance (A_∞) at t_∞ gives a measure of D_0. Although 310 nm is suitable for determining $t_{max.}$, it is not so for measuring A_∞ because the subsequent reaction of 3-bromoflavanone to form flavone (Figure 1) sets in before the cyclisation of the (*E*)-α-bromochalcone, initially formed from the dibromide, reaches its infinity stage. Measurements were made at 338.5 nm, another isosbestic point for the reaction of 3-bromoflavanone going to flavone. At this wavelength the absorbance of a dibromide solution decreased to an infinity value (A_∞) which remained constant even when significant flavone formation had set in, an essential condition for reliability of the value of A_∞.

At any wavelength, the total absorbance change between $t_{max.}$ and t_∞ (ΔA) will contain contributions from reactions of the (*Z*)- and (*E*)-α-bromochalcones and residual dibromide [equation (13)]. Values of ΔA for the three compounds

$$\Delta A = \Delta A^Z + \Delta A^E + \Delta A^D \qquad (13)$$

depend on their fractions at $t_{max.}$ (which can be calculated in the cases of E and D from earlier kinetic data) and their individual absorbance changes when they convert to 3-bromoflavanone (which must be independently determined with pure samples of the three compounds at the wavelength concerned).

To calculate the fraction ($D_{max.}/D_0$) of dibromide present at $t_{max.}$, values were substituted for k_3 (0.048 s^{-1}) and t (30 s) in equation (3). This gives $D_{max.}/D_0$ as 0.237. To calculate the amount of the (*E*)-α-bromochalcone present at $t_{max.}$ as a fraction of initial dibromide ($E_{max.}/D_0$), equation (7) is applied with E replacing Z. The values for k_3 (0.048 s^{-1}), k_2 (0.0010 s^{-1}; Table 1), and k_1 (0.0168 s^{-1}) are substituted. [The k_1 value is calculated as the product of k_3 and the fraction of the (*E*)-isomer (0.35) formed from the dibromide.] Taking t as 30 s, equation (7) gives $E_{max.}/D_0$ as 0.262.

Values of the ratio of initial to final absorbance (A_0/A_∞) for the formation of 3-bromoflavanone from pure samples of the (*E*)- and (*Z*)-α-bromochalcones were determined through extrapolation of linear first-order kinetic plots to zero (mixing) time as previously described for the *E*-isomer at 264 nm; k_{obs} values were checked for consistency. The resulting values were 1.56 (A^E_0/A^E_∞) and 2.34 (A^Z_0/A^Z_∞) at 338.5 nm. For the dibromide, because of the rapid series reactions occurring, A^D_0 could not be determined at this pH. Instead, it was determined in 4 : 1 water–ethanol containing hydrochloric acid (0.01 mol l^{-1}) and potassium chloride (0.15 mol l^{-1}) under which conditions the dibromide is stable. The corresponding value of A^D_∞ was established by adding the same amount of dibromide to *N*-ethylmorpholine buffer solution (pH 7.88) and recording the infinity absorbance. Three measurements each of A^D_0 and A^D_∞ led to a mean value for A^D_0/A^D_∞ of 1.34.

It remains to use the A_0/A_∞ values as well as $D_{max.}/D_0$ and $E_{max.}/D_0$ to calculate the ΔA values in equation (13). If after all the dibromide is converted to 3-bromoflavanone in a particular run the absorbance is A_∞, then the corresponding (initial) absorbance for the same concentration of dibromide would be $A_\infty A^D_0/A^D_\infty$ and the absorbance change as dibromide at this concentration converts to 3-bromoflavanone would be $A_\infty[(A^D_0/A^D_\infty) - 1]$. At time $t_{max.}$, however, the concentration of dibromide is not the same as that of final 3-bromoflavanone; only fraction $D_{max.}/D_0$ of dibromide remains, so that equation (14) results.

$$\Delta A^D = (D_{max.}/D_0)\ A_\infty[(A^D_0/A^D_\infty) - 1] \qquad (14)$$

Equivalent equations apply for the (*E*)- and (*Z*)-α-bromochalcones and so equation (13) becomes equation (15). Substituting known ratio values leads to equation (16).

$$\Delta A/A_\infty = (Z_{max.}/D_0)[(A^Z_0/A^Z_\infty) - 1] + (E_{max.}/D_0)[(A^E_0/A^E_\infty) - 1] + (D_{max.}/D_0)[(A^D_0/A^D_\infty) - 1] \qquad (15)$$

$$\Delta A/A_\infty = 1.34\ Z_{max.}/D_0 + 0.227 \qquad (16)$$

(iii) Calculation of the yield of (*Z*)-α-bromo-2′-hydrochalcone. Values of $\Delta A/A_\infty$ for various runs are recorded in Table 3 along with calculated values of $Z_{max.}/D_0$ [determined from equation (16)] and of k_1 [determined as 0.093 $Z_{max.}/D_0$ from equation (12)]. In the final column are given values of the yield (%) of the (*Z*)-α-bromochalcone calculated as $100k_1/k_3$, k_3 being 0.048 s^{-1}. The experimental error is no better than ±8, a value which would have been lower had it been possible to measure absorbance changes at 310 nm, where that due to the (*Z*)-α-bromochalcone is largest.

TABLE 3

Absorbance data and calculated yields of (*Z*)-α-bromo-2′-hydroxychalcone from *erythro*-2′-hydrochalcone dibromide

10^3 B [a]	$A_{t_{max.}}$	A_∞	$\Delta A/A_\infty$	$Z_{max.}/D_0$	$10^2\ k_1/s^{-1}$	Yield (%)
8	0.411	0.245	0.678	0.336	3.12	65
16	0.413	0.250	0.652	0.317	2.94	61
40	0.416	0.250	0.664	0.326	3.03	63
80	0.379	0.228	0.662	0.325	3.01	63

[a] B is total *N*-ethylmorpholine in mol l^{-1}.

DISCUSSION

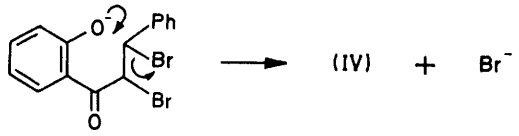
Products.—The major reaction of *erythro*-2′-hydroxychalcone dibromide in 4 : 1 water–ethanol at pH 7.88 is elimination to form (*E*)- and (*Z*)-α-bromo-2′-hydroxychalcone. The *Z* : *E* ratio (1.8) contrasts sharply with that (0.7) of the products obtained by synthesis in methanol as solvent, but the latter ratio is doubtless lower than that in which the isomers are initially formed because the *Z*-isomer is expected to cyclise faster than the *E*-isomer to 3-bromoflavanone which, with flavone, is a major byproduct in the synthesis.

Ratios of (*Z*)- and (*E*)-α-bromo-2′-hydroxychalcones synthesised from various 'class 2' 2′-hydroxychalcone dibromides using potassium acetate in ethanol have

† Independent measurements at pH 7.21 gave values of k_2 (0.0067 s^{-1}; Table 1) and $t_{max.}$ (104 s; Figure 4) which, as at pH 7.88, were independent of the concentration of *N*-ethylmorpholine up to 0.08 mol l^{-1}. Equation (11) in this case leads to a value of k_3 of 0.013 s^{-1}, which, as for k_2, is *ca.* 3.5 times smaller than the corresponding value at pH 7.88.

previously been established.[1c] In most, but not all cases, the *Z*-isomer predominates.

The Effect of pH on Routes to 3-Bromoflavanone.—The preference shown at pH 7.88 by the dibromide to undergo elimination rather than direct cyclisation to 3-bromoflavanone must be maintained also at higher pH, irrespective of the nature (see next section) of the elimination mechanism. Direct cyclisation (Scheme 2), the rate of



SCHEME 2

which is given by the product of a rate coefficient and the concentration of the conjugate base, is kinetically equivalent to the observed elimination, and if elimination, as we have shown, is the faster at pH 7.88 it must necessarily be so at any higher pH.

The proportion of dibromide giving direct cyclisation is calculated by difference to be 2 ± 12% which corresponds, given the rate coefficient (k_3) for overall dibromide reaction (0.048 s^{-1} at pH 7.88), to a maximum rate coefficient for direct cyclisation at this pH of 0.006 s^{-1}. This is somewhat larger than the rate coefficient for cyclisation of (*E*)-α-bromo-2′-hydroxychalcone (0.001 s^{-1}) but less than that for (*Z*)-α-bromo-2′-hydroxychalcone (0.022 s^{-1}) under the same conditions. However, the possibility that direct cyclisation of the dibromide is faster than that of one of the elimination products can not affect the proportions of 3-bromoflavanone formed through elimination–addition as opposed to direct cyclisation since the elimination reaction could not conceivably be reversible under basic conditions; once formed both α-bromochalcones must go on to 3-bromoflavanone.

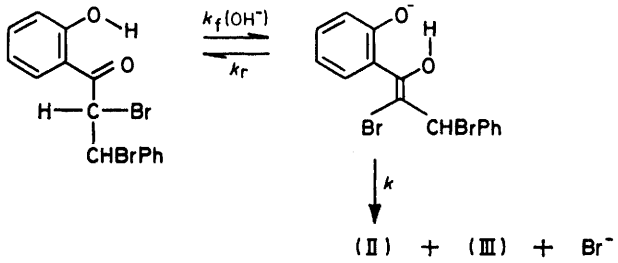
It is therefore reasonable to conclude that in the formation of 3-bromoflavanone from *erythro*-2′-hydroxychalcone dibromide, the preference shown for the elimination–addition route over direct cyclisation at pH 7.88 should apply equally in more strongly basic solutions. The previously held view,[2] unchallenged over many years, that ' class 1 ' 2′-hydroxychalcone dibromides [1a] cyclise directly to 3-bromoflavanone is clearly no longer tenable.

Relative rates of cyclisation of pairs of (*E*)- and (*Z*)-α-bromo-2′-hydroxychalcones have not previously been reported. If cyclisation rates are determined by degree of ionisation and if the pK_a values of the *E*- and *Z*-isomers are similar, the latter is expected to retain its (*ca.* 20-fold) higher reactivity at any pH above 7.88. We hope to confirm this when stopped-flow equipment becomes available to us.

Mechanism of Elimination.—Although the major purpose of the present study was to determine the degree of competition between direct cyclisation and elimination reactions of the dibromide, the implications for the elimination mechanism found in the lack of buffer catalysis, the proportions of *syn*- and *anti*-elimination, and the effect of pH merit brief comment.

The lack of catalysis by *N*-ethylmorpholine suggests that elimination is subject only to specific base catalysis but it is impossible to exclude with certainty general base catalysis in which *N*-ethylmorpholine happens not to be effective. An *E*2 mechanism [7] with *N*-ethylmorpholine as base is therefore excluded, but one involving the lyate bases HO^- and EtO^- is not . However, the preference for *syn*- over *anti*-elimination is unexpected for an *E*2 elimination of hydrogen bromide, particularly from a compound in which the departing bromide is strongly β-activated: [8] the effect of β-activation by halogeno and aryl substituents is such that significant *syn*-elimination is anticipated only with the most associated base–solvent systems.[8] 2′-Hydroxychalcone dibromide is activated by both a bromo and an acyl substituent and by analogy might therefore be expected to show a strong preference for *anti*-elimination if *E*2 applies, contrary to observation. We therefore consider that although it is not directly excluded by kinetic evidence, an *E*2 mechanism is unlikely.

*E*1cB Mechanisms [7] involving initial α-proton abstraction are likely alternatives. Owing to the presence of the phenolic OH group, the conjugate base would be expected to exist mostly as enol (Scheme 3) rather than enolate



SCHEME 3

ion. Reversible conjugate base formation [$(E1cB)_R$ mechanism [8]] requires $k_r \gg k$ and specific base catalysis. Such a mechanism is well established for some eliminations involving poor leaving groups, applying for example to eliminations from β-methoxyketones,[9a] though not [9b] to the corresponding acetoxyketones which have better leaving groups. Thus, $(E1cB)_R$ is not favoured by such a good leaving group as bromide, and to our knowledge it is unknown in dehydrobromination. We therefore consider it to be less likely in the present case than the corresponding mechanism with irreversible ($k \gg k_r$) conjugate base formation [$(E1cB)_I$ [8]]. The lack of detectable rate dependence on the concentration of *N*-ethylmorpholine must in this case be taken to indicate the ineffectiveness of this base in comparison with HO^- and EtO^-. It is noteworthy that in the related eliminations of β-acetoxyketones,[9b] *N*-methylmorpholine is only very weakly catalytic although it is not known in those cases whether $(E1cB)_I$ or *E*2 applies.

A set of alternative mechanisms which correspond with those just described but which apply to the pheno-

late ion species of the dibromide, which will be present at pH 7.88 as a very small fraction of the neutral species, are all consistent with specific base catalysis. In these mechanisms, the α-proton is abstracted intramolecularly by the phenolate oxygen instead of intermolecularly by external base. Formally, these are all unimolecular decompositions of the anion, but the concerted or stepwise nature of decomposition determines whether they are the intramolecular equivalents of *E*2 (Scheme 4, showing *anti*-elimination) or the *E*1cB mechanisms described above.

SCHEME 4

Finally, the *E*1 mechanism [7] involving a carbonium ion intermediate formed through rate-limiting ionisation of β-bromine can be excluded. It requires invariance with pH of the rate coefficient. In fact k_3 decreases from 0.048 at pH 7.88 to 0.013 s^{-1} at 7.21. A similar argument excludes also any elimination which is base-catalysed by solvent molecules.

Whichever of the acceptable alternative mechanisms applies remains to be determined by further study.

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