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CHALCONE DIHALIDES—VIII

SYNTHESIS AND CYCLIZATION OF THE STEREOISOMERS OF 2',6'-DISUBSTITUTED α-BROMOCHALCONES

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Abstract—2'-Acetoxy-6'-methoxychalcone dibromides reacted with ethanolic potassium acetate to form the *cis* and *trans* isomers of the corresponding 2'-acetoxy-α-bromochalcones. 2'-Hydroxychalcone dibromides reacted similarly but, in two cases, some ring closure also occurred. The stereoisomers of the α-bromo-2'-hydroxy-6'-methoxychalcones were cyclized with aqueous ethanolic potassium hydroxide. In keeping with their proposed intermediacy in the Emilewicz-von Kostanecki reaction, they yielded both flavone and aurone and aurone formation was related to the hydroxide concentration. The *trans* isomers more readily formed aurones.

α-Halogenochalcones (**4**) have often been considered[1-8] as intermediates in the cyclization of 2'-hydroxy (or acetoxy) chalcone dihalides (**1**) to flavones (**3**) or aurones (**8**) by aqueous alcoholic alkali (the Emilewicz-von Kostanecki reaction[9]). Support for their intermediacy in the cyclization of class 2A chalcone dihalides,[8] i.e. dihalides substituted in the 6'-position, was obtained[8] recently when it was found that the dibromide (**1a**) of 2' - acetoxy - 3' - bromo - 4',6' - dimethoxychalcone could be converted into the corresponding α-halogenochalcone (**4a**) by ethanolic potassium acetate and that this bromochalcone, when cyclized by aqueous ethanolic potassium hydroxide, yielded both a flavone (**3a**) and an aurone (**8a**) and in amounts comparable to those obtained from the corresponding chalcone dihalide (**1**). Previous attempts[4,10] to form an α-bromochalcone from a 2'-hydroxy or 2'-acetoxy chalcone dibromide yielded cyclized products.

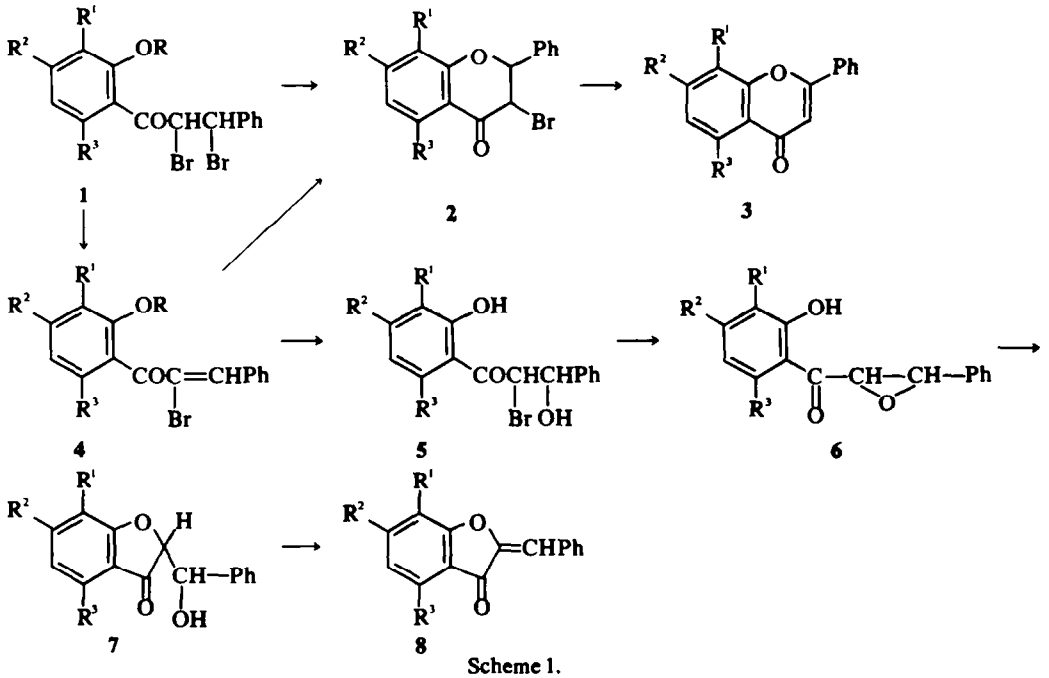
The conjecture of the role of α-halogenochalcones originated in the work of von Kostanecki and Tambor[2] who obtained the α-bromo chalcone, 2' - acetoxy - α,3' - dibromo - 4',6' - dimethoxy - 3,4 - methylenedioxy - chalcone, by brominating the corresponding chalcone (with spontaneous elimination of hydrogen bromide from the side-chain). On reaction with aqueous alcoholic alkali, it cyclized to an aurone. Another class 2AB α-bromochalcone, α - bromo - 2' - hydroxy - 4,6' - dimethoxychalcone was considered[11] to be the product, stable towards base, of the reaction of the corresponding chalcone dibromide with acetic acid. It has since been shown,[12] however, that this reaction takes an unusual course and that the product is the nuclear brominated chalcone, 3' - bromo - 2' - hydroxy - 4,6' - dimethoxychalcone. Reasonable doubt must exist as to the assumed α - halogenochalcone structure of products similarly produced[13] from class 2AB chalcone dihalides. An interesting group of α-bromochalcones, characterised by a nitro group in the 5'-position, has been systhesised by Jadhav *et al.*[14] These compounds have not been cyclized.

In the present work it was found that the 2'-acetoxychalcone dibromides (**1b, c**) react with ethanolic potassium acetate to form the *cis* (**9b, c**) and *trans* (**10b, c**) isomers of the corresponding 2' - acetoxy - α - bromo - chalcones. Similar treatment of the 2'-hydroxychalcone dibromides (**1d–h**) gave the isomers (**9d–h**; **10d–h**) of the corresponding 2' - hydroxy - α - bromochalcones. Only with 3' - bromo - 2' - hydroxychalcone dibromide (**1d**) and 3' - bromo - 2' - hydroxy - 4',6' - dimethoxychalcone dibromide (**1h**) were complications due to simultaneous cyclization observed. In these cases, a mixture of *cis*- (**11d**) and *trans*- (**12**) 3,8-dibromoflavanone and *cis* - 3,8 - dibromo - 5,7 - dimethoxyflavanone[15] (**11h**), respectively, were isolated in addition to the major products, the α-bromochalcone isomers.

In contrast to the stereoisomeric 2' - acetoxy - α - bromochalcones (**9b, c**; **10b, c**) which were inseparable by TLC and yielded only the *trans* isomers (**10b, c**) on crystallisation, the α - bromo - 2' - hydroxychalcone isomers (**9d–h**; **10d–h**) were readily separable by chromatography. Their stereochemical assignments were made initially by a study of their UV spectra, based on the work of Lutz *et al.*[16] It was latter found that PMR spectroscopy offered a more reliable and simpler method of distinguishing between the isomers. The proton signal of the unsubstituted aromatic ring of the *cis* isomers (**9d–h**) occurs as a singlet while that of the *trans* isomers (**10d–h**) occurs as a complex multiplet; the phenolic proton signal of the *cis* isomers occurs at lower field than that of the *trans* isomers; also, the signal of the β-H of the *cis* isomers is always clearly visible at *ca.* 7 ppm while that of the *trans* isomers is generally masked by the aromatic proton signals and is difficult to assign.

It has been reported[1] recently that the cyclization of class 2A 2'-hydroxychalcone dibromides (**1**) in basic conditions yields both flavone (**3**) and aurone (**8**) and that the proportions of these products are controlled by the base concentration—little or no aurone being formed in very dilute base. It was proposed (Scheme 1) that in dilute base these dibromides (**1**) cyclized to the flavone precursor, 3-bromoflavanone (**2**), either directly or via an α-bromochalcone (**4**) and that the enhanced aurone (**8**) formation with increasing hydroxide concentration was due to an increasingly competitive intermolecular reaction between the α-bromochalcone (**4**) and hydroxide resulting in the formation of a chalcone bromohydrin (**5**). It was assumed that aurone (**8**) formation from the bromohydrin (**5**) occurred via a chalcone epoxide (**6**) and an aurone hydrate (**7**).

A study was therefore made of the cyclization of the stereoisomers (**9, 10**) of the appropriate α - bromo - 2' - hydroxychalcones (**4e–h**) to determine whether or not they



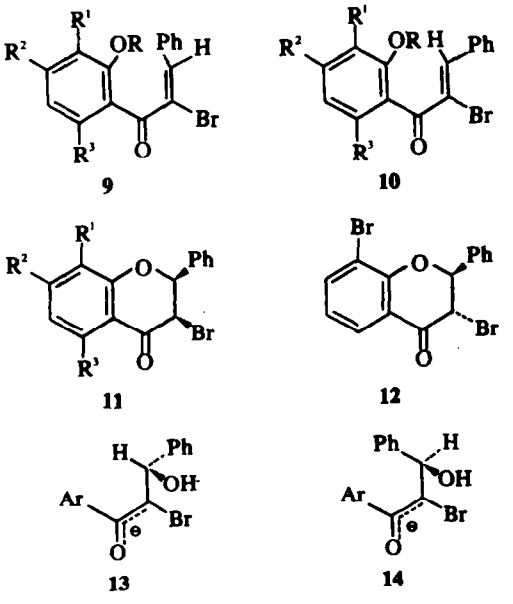
Scheme 1.

a: R = OAc, R' = Br, R² = R³ = OMe
b: R = OAc, R' = R² = H, R³ = OMe
c: R = OAc, R' = Br, R² = H, R³ = OMe
d: R = R² = R³ = H, R' = Br
e: R = R' = R² = H, R³ = OMe
f: R = R² = H, R' = Br, R³ = OMe
g: R = R' = H, R² = R³ = OMe
h: R = H, R' = Br, R² = R³ = OMe

yielded flavone and aurone and if the product composition was dependent on hydroxide concentration. The reactions were carried out by the addition of aqueous potassium hydroxide to a solution or suspension of the α-bromochalcone in ethanol maintained at 25°. The composition of the neutral products was established by UV spectroscopy.[17] The results are given in Table 1.

It can be seen that, in agreement with their proposed intermediacy in the Emilewicz-von Kostanecki reaction, the *cis* (**9e-h**) and the *trans* (**10e-h**) isomers, in general, yielded both flavone and aurone and that the proportion of aurone in the products was significantly greater at the higher base concentration.

It is also clear that the *cis*-α-bromochalcones (**9e-h**) more readily form flavone (**3e-h**) than the *trans* isomers (**10e-h**). This is, perhaps, surprising in view of the severe non-bonding interaction that must occur between the aromatic nuclei during the cyclization of a *cis*-α-bromochalcone (**9**) to a 3-bromoflavanone (**2**). The greater aurone-forming ability of *trans*-α-bromochalcones (**10e-h**) may be due to a faster rate of bromohydrin (**5**) formation. This rate would be expected to be subject to orbital overlap control as pointed out by Zimmerman, Singer and Thyagarajan[18] for the addition of hydroperoxide ion to α,β-unsaturated ketones; the anionic intermediate (**13**) from a *trans*-α-bromochalcone would be more stable than that (**14**) from its *cis* isomer because of the absence of non-bonding interaction between the aromatic nuclei.



EXPERIMENTAL

UV spectra were taken in $CHCl_3$ using a Perkin-Elmer 124 spectrometer. PMR spectra were obtained at 60 MHz with a Perkin-Elmer R12 spectrometer, in $CDCl_3$ with TMS as internal reference. Chemical shifts are given in ppm (δ). M.ps were taken with a Kofler hot-stage apparatus.

The standard conditions for the cyclization of α-bromochalcones were as follows. EtOH (5 ml) was added to the chalcone (*ca.* $6{\cdot}5 \times 10^{-5}$ mol) and the resulting soln or suspension was stirred in a closed tube at 25° for 15 min. Aqueous KOH (1 ml) of the stated concentration (Table 1) was added and the soln was stirred for 1 hr at 25°. Then, 5 min after the addition of H_2O (20 ml), the mixture

was extracted with five 10 ml portions of $CHCl_3$. The combined $CHCl_3$ extracts were washed once with H_2O (10 ml) before being diluted for the observation of their UV spectra. The UV spectra of the products have been recorded[1,8] previously.

α-Bromochalcones (**9**, **10**). These were generally prepared by stirring overnight at room temp a suspension of the corresponding 2'-hydroxychalcone dibromide and KOAc (1 molar equiv) in EtOH (100 ml). The mixture was then diluted with H_2O (150 ml) and extracted with $CHCl_3$. The extract was washed, dried, and fractionated by PLC on silica gel. The 2' - acetoxy - α - bromochalcones were similarly prepared except that they were refluxed with potassium acetate in ethanol for 1 hr.

3'-Bromo-2'-hydroxychalcone dibromide[1] (**1d**; 2 g) gave *cis-α,3'-dibromo - 2' - hydroxychalcone* (**9d**; 0·47 g) as an uncrystallisable oil. (Found: C, 47·4; H, 2·7; Br, 41·9. $C_{15}H_{10}Br_2O_2$ requires: C, 47·4; H, 2·6; Br, 41·8%). λ_{max} 263 nm (log ε 4·28) and 353 nm. (log ε 3·66). PMR spectrum: 7·21 Ph, 7·40 β-H, 12·26 OH. It also gave trans - α,3' - *dibromo - 2' - hydroxychalcone* (**10d**; 0·24 g) as an oil. (Found: C, 47·5; H, 2·8; Br, 41·9. $C_{15}H_{10}Br_2O_2$ requires: C, 47·2; H, 2·6; Br, 41·8%). λ_{max} 259 nm (log ε 4·09) and 323 nm (log ε 3·91). PMR spectrum: 11·9 OH. A mixture (0·43 g) of *cis* - **11d** and *trans* - **12** 3,8-dibromoflavanone was also obtained. Attempts to fractionate it by crystallisation led to partial decomposition. (Found: C, 46·5; H, 2·9. $C_{15}H_{10}Br_2O_2$ requires: C, 47·15; H, 2·6%). PMR spectrum: *cis*-isomer, 4·63 3-H, 5·52 2-H, J_{23} 2 Hz; *trans*-isomer, 5·03 3-H, 5·76 2-H, J_{23} 7 Hz.

2' - Hydroxy - 6' - methoxychalcone dibromide[1] (**1c**; 1·6 g) gave *cis - α - bromo - 2' - hydroxy - 6' - methoxychalcone* (**9e**; 0·25 g), m.p. 86–88°. (Found: C, 57·7; H, 3·9; Br, 24·4. $C_{16}H_{13}BrO_3$ requires: C, 57·7; H, 3·9; Br, 24·0%). λ_{max} 254 nm (log ε 4·23), 290 nm (log ε 4·12), and 347 nm (log ε 3·62). PMR spectrum: 3·89 OMe, 7·11 β-H, 7·32 Ph, 12·11 OH. Also obtained was trans - α - *bromo - 2' - hydroxy - 6' - methoxychalcone* (**10e**; 0·72 g), m.p. 120–121. (Found: C, 58·1; H, 4·2; Br, 23·8. $C_{16}H_{13}BrO_3$ requires: C, 57·7; H, 3·9; Br, 24·0%). λ_{max} 248 nm (log ε 3·97) and 304 nm (log ε 4·16). PMR spectrum: 3·82 OMe, 10·22 OH.

3' - Bromo - 2' - hydroxy - 6' - methoxychalcone dibromide[1] (**1f**; 2 g) gave *cis - α,3' - dibromo - 2' - hydroxy - 6' - methoxychalcone* (**9f**; 0·09 g), m.p. 93–94° (benzene/light petroleum, b.p. 60–80°). (Found: C, 46·4; H, 3·0; Br, 39·3. $C_{16}H_{12}Br_2O_3$ requires: C, 46·6; H, 2·9; Br, 38·8%). λ_{max} 254 nm (log ε 4·14), 291 nm (log ε 4·03) and 367 nm (log ε 3·56). PMR spectrum: 3·90 OMe, 7·15 β-H, 7·30 Ph, 12·76 OH. It also gave trans - α,3' - *dibromo - 2' - hydroxy - 6' - methoxychalcone* (**10f**; 0·65 g), m.p. 91–92° (benzene/light petroleum, b.p. 60–80°). (Found: C, 47·1; H, 3·2; Br, 38·5. $C_{16}H_{12}Br_2O_3$ requires: C, 46·6; H, 2·9; Br, 38·8%). λ_{max} 305 nm (log ε 4·14). PMR spectrum: 3·84 OMe, 11·0 OH.

2' - Hydroxy - 4',6' - dimethoxychalcone dibromide[1] (**1g**; 1·85 g) yielded *cis - α - bromo - 2' - hydroxy - 4',6', - dimethoxychalcone* (**9g**; 0·25 g), m.p. 91–92° (benzene/light petroleum, b.p. 60–80°). (Found: C, 56·8; H, 4·1; Br, 22·1. $C_{17}H_{15}BrO_4$ requires: C, 56·2; H, 4·2; Br, 22·0%). PMR spectrum: 3·79 OMe, 3·83 OMe, 7·02 β-H, 7·27 Ph, 12·99 OH. Also obtained was *trans - α - bromo - 2' - hydroxy - 4',6' - dimethoxychalcone* (**10g**; 0·53 g), m.p. 112–113° (benzene/light petroleum, b.p. 60–80°). (Found: C, 56·5; H, 4·0; Br, 21·8. $C_{17}H_{15}BrO_4$ requires: C, 56·2; H, 4·2; Br, 22·0%). PMR spectrum: 3·81 OMe, 3·89 OMe, 11·95 OH.

3' - Bromo - 2' - hydroxy - 4',6' - dimethoxychalcone dibromide[1] (**1h**; 2 g) gave *cis - α,3' - dibromo - 2' - hydroxy - 4',6' - dimethoxychalcone* (**9h**; 0·25 g), m.p. 146–148° (EtOH/Me_2CO). (Found: C, 46·1; H, 3·1; Br, 36·1. $C_{17}H_{14}Br_2O_4$ requires: C, 46·2; H, 3·2; Br, 36·2%). λ_{max} 247 nm (log ε 4·29) and 314 nm (log ε 4·23). PMR spectrum: 3·92 OMe, 4·01 OMe, 7·05 β-H, 7·28 Ph, 13·45 OH. It also gave *trans - α,3' - dibromo - 2' - hydroxy - 4',6' - dimethoxychalcone* (**10h**; 0·33 g), m.p. 168–170° (EtOH/Me_2CO). (Found: C, 45·7; H, 3·2; Br, 36·2. $C_{17}H_{14}Br_2O_4$ requires: C, 46·2; H, 3·2; Br, 36·2%). λ_{max} 242 nm (log ε 4·21) and 311 nm (log ε 4·22). PMR spectrum: 3·89 OMe, 4·03 OMe, 11·73 OH. Two other products were also obtained: **3h** (0·05 g), m.p. 255–256° (lit.[8] m.p. 256–257°) and *cis* - **11h**; (trace), m.p. 232–233°; PMR spectrum: 4·02 OMe, 4·07 OMe, 4·60 3-H, 5·64 2-H, 6·32 6'-H, J_{23} 2 Hz.

Compound[9] **1b** (0·51 g) gave trans - 2' - *acetoxy - α - bromo - 6' - methoxychalcone* (**10b**; 0·1 g), m.p. 95–97° (EtOH/H_2O). (Found: C, 57·7; H, 4·0; Br, 21·2. $C_{18}H_{15}BrO_4$ requires: C, 57·6; H, 4·0; Br, 21·3%). PMR spectrum: 2·17 OAc, 3·85 OMe. A mixture (0·04 g) of this product and its stereoisomer (**9b**) was also obtained.

Compound[9] **1c**; (0·5 g) yielded *trans - 2' - acetoxy - α,3' - dibromo - 6' - methoxychalcone* (**10c**; 0·05 g), m.p. 104–105° (EtOH/H_2O). (Found: C, 47·6; H, 2·8; Br, 35·1. $C_{18}H_{14}Br_2O_4$ requires: C, 47·6; H, 3·1; Br, 35·2%). PMR spectrum: 2·23 OAc, 3·85 OMe, 6·83 5'-H, $J_{4'5'}$ 9 Hz.

8-Bromoflavone (**3d**). 2' - Hydroxyacetophenone (5 g) was added to a mixture of Br_2 (6·4 g), CH_2Cl_2 (110 ml), and t-$BuNH_2$ (8 ml) at −70°. Cooling was stopped after 1 hr and 3 hr later the mixture was washed with H_2O and extracted with 10% NaOH aq. The acidified (HCl) extracts were washed, and then extracted with $CHCl_3$. Fractionation of this extract by PLC on silica gel gave 3' - bromo - 2' - hydroxyacetophenone[19] (0·95 g), 5' - bromo - 2' - hydroxyacetophenone (1·34 g), and substrate (2·1 g).

Benzaldehyde (4 g) and 50% KOH aq (26 ml) was added to a soln of 3' - bromo - 2' - hydroxyacetophenone (2 g) in EtOH. The mixture was acidified after 15 hr precipitating 3' - *bromo - 2' - hydroxychalcone* (1·6 g), m.p. 122–123° (EtOH). (Found: C, 59·0; H, 3·6; Br, 26·2. $C_{15}H_{11}BrO_2$ requires: C, 59·4; H, 3·7; Br, 26·4%).

The addition of Br_2 (1·2 g) to the chalcone (1·4 g) in CCl_4 (100 ml) gave 3' - *bromo - 2' - hydroxychalcone dibromide* (**1d**; 1·7 g), m.p. 187–188° (cyclohexane). (Found: C, 38·9; H, 2·4; Br, 51·7. $C_{15}H_{11}Br_3O_2$ requires: C, 38·9; H, 2·4; Br, 51·8%). PMR spectrum: 5·68 β-H, 5·98 α-H, 12·48 OH, $J_{\alpha\beta}$ 12 Hz. Treatment of the chalcone dibromide (**1d**; 0·37 g) in EtOH (40 ml) with KOH aq (0·2 M, 13 ml) gave, after dilution with H_2O (30 ml), **3d** (0·1 g), m.p. 178–180° (lit.[20] 178–179°). (Found: C, 59·5; H, 2·7; Br, 26·7. Calculated for $C_{15}H_9BrO_2$: C, 59·8; H, 3·0; Br, 26·5%). λ_{max} 257 nm (log ε 4·22) and 295 nm (log ε 4·29). PMR spectrum: 6·90 3-H.

REFERENCES

[1]Part VII: J. A. Donnelly and H. J. Doran, *Tetrahedron* **31**, 1565 (1975).

[2]S. von Kostanecki and J. Tambor, *Ber. Dtzch. Chem. Ges* **32**, 2260 (1899).

[3]W. A. Hutchins and T. S. Wheeler, *J. Chem. Soc.* 91 (1939).

[4]K. von Auwers and L. Anschutz, *Ber. Dtsch. Chem. Ges* **54**, 1543 (1921).

[5]E. M. Ryan and H. Ryan, *Proc. Roy. Irish Acad.* **39**, 425 (1930).

[6]N. M. Cullinane and D. Philpott, *J. Chem. Soc.* 1761 (1929).

[7]T. S. Wheeler, *Proc. Nat. Inst. Sci. India* **2**, 267 (1939).

[8]J. A. Donnelly, H. J. Doran, and J. J. Murphy, *Tetrahedron* **29**, 1037 (1973).

[9]T. Emilewicz and S. von Kostanecki, *Ber. Dtsch. Chem. Ges* **31**, 696 (1898).

[10]Unpublished work (J. A. D.).

[11]H. K. Pendse, *Rasayanam* **2**, 131 (1956).

[12]J. A. Donnelly, *Tetrahedron* **29**, 2585 (1973).

[13]P. Y. Mahajan, M. S. Kamat and A. B. Kulkarni, *Indian J. Chem.* **8**, 310 (1970); K. R. Chandorkar, D. M. Phatak and A. B. Kulkarni, *J. Sci. Ind. Res. India* **21**, 24 (1962); P. Y. Mahajan, M. S. Kamat and A. B. Kulkarni, *Indian J. Chem.* **6**, 55 (1968).

[14]V. G. Kulkarni and G. V. Jadhav, *J. Indian Chem. Soc.* **32**, 97 (1955); F. A. Atchabba, P. L. Trivedi and G. V. Jadhav, *J. Univ. Bombay* **27**, 8 (1958); G. S. Chhaya, P. L. Trivedi, and G. V. Jadhav, *Ibid.* **25**, 8 (1957); *Idem. Ibid.* **26**, 22 (1958), (*cf.* P. N. Wadodkar, *Indian J. Chem.* **1**, 163 (1963)); S. P. Wagh and G. V. Jadhav, *J. Univ. Bombay* **27**, 1 (1959).

[15]J. J. Beirne, A. M. Coyle and J. A. Donnelly, *Tetrahedron* **26**, 3809 (1970).

[16]R. E. Lutz, D. F. Hinkley and R. H. Jordan, *J. Am. Chem. Soc.* **73**, 4647 (1951).

[17]C. N. R. Rao, *Ultra-Violet and Visible Spectroscopy*, p. 102. Butterworths, London (1967).

[18]H. E. Zimmerman, L. Singer and B. S. Thyagarajan, *J. Am. Chem. Soc.* **81**, 108 (1959).

[19]J. A. Donnelly and J. J. Murphy, *J. Chem. Soc.* (C), 2596 (1970).

[20]F. C. Chen, C. T. Chang, C. Y. Chen, M. Hung and C. Lin, *J. Org. Chem.* **27**, 310 (1962).

Table 1. Composition of the neutral products from the cyclization of α-bromochalcones

Added Isomer base conc.	α,3'-Dibromo-2'-hydroxy-4'-6'-dimethoxychalcone			α-Bromo-2'-hydroxy-4',6'-dimethoxychalcone			α,3'-Dibromo-2'-hydroxy-6'-methoxychalcone			α-Bromo-2'-hydroxy-6'-methoxychalcone		
	% Aurone (8h)	% Flavone (3h)	Aurone / Flavone	% Aurone (8g)	% Flavone (3g)	Aurone / Flavone	% Aurone (8f)	% Flavone (3f)	Aurone / Flavone	% Aurone (8e)	% Flavone (3e)	Aurone / Flavone
	0·0	100·0		0·0	100·0							
0·2M *cis*			0·0			0·0	1·9	98·1	0·02	0·0	100·0	0·0
	0·0	100·0		0·0	100·0							
	0·3	99·7		1·9	98·1		5·2	84·0				
0·2M *trans*			0·003			0·02			0·06	0·0	100·0	0·0
	0·3	99·7		1·9	98·1		5·5	82·0				
	11·3	88·7		2·0	98·0							
4·0M *cis*			0·12			0·02	4·8	95·2	0·05	0·0	100·0	0·0
	10·7	89·3		2·0	98·0							
	43·9	56·1		6·7	93·3					7·5	92·5	
4·0M *trans*			0·78			0·08	7·9	79·3	0·10			0·09
	43·6	56·4		7·3	92·7					8·5	91·5	