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CHALCONE DIHALIDES—VII

THE COURSE OF THE CYCLIZATION OF 2'-HYDROXY-6'-METHOXYL DERIVATIVES

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Abstract—2'-hydroxychalcone dibromides substituted by OMe in the 6'-position are found to yield little or no aurone in *dilute* aqueous ethanolic potassium hydroxide. The proportion of aurone to flavone in their products parallels increasing hydroxide concentration. It is proposed that the course of aurone formation is chalcone dibromide → α-bromochalcone → chalcone bromohydrin → chalcone epoxide → aurone hydrate → aurone and that the initial function of the nuclear substituent(s) is to sterically prevent deactivation of the carbonyl group by the phenoxide anion.

The cyclization of 2'-hydroxychalcone dihalides in aqueous alcoholic alkali (the Emilewicz-von Kostanecki reaction) is an important general synthesis[1] of naturally occurring flavones. Under certain conditions, some of these dihalides (Class[2] 2) yield[2,3] significant quantities of aurones. Described here is a study of the cyclization of one particular group of aurone-forming 2'-hydroxychalcone dibromides–Group 2A. These dihalides are characterised by a substituent, usually OMe, in the 6'-position of the A-ring. The course of their cyclization has been of continuing mechanistic interest for some time.[2-5]

The members of the group were 2'-hydroxy-6'-methoxychalcone dibromide (**1**), 3'-bromo-2'-hydroxy-6'-methoxychalcone dibromide (**2**), 2'-hydroxy-4',6'-dimethoxychalcone dibromide (**3**), and 3'-bromo-2'-hydroxy-4',6'-dimethoxychalcone dibromide (**4**). The reaction of 3'-bromo-4'-hydroxy-2',6'-dimethoxychalcone dibromide (**5**) in aqueous ethanolic potassium hydroxide was also examined.

RESULTS

Bromination of 3'-bromo-2'-hydroxy-6'-methoxychalcone and 2'-hydroxy-4', 6'-dimethoxychalcone gave the required nuclear halogenated compounds, 3'-bromo-2'-hydroxy-6'-methoxychalcone dibromide (**2**) and 3'-bromo-2'-hydroxy-4',6'-dimethoxychalcone dibromide[3b,11] (**4**), respectively. In the synthesis of the non-nuclear brominated dihalides (**1**, **3**), the corresponding chalcones had to be acetylated prior to bromination. After failing to remove the acetoxyl groups in basic media without otherwise altering the chalcone dibromides, the acetates, 2'-acetoxy-6'-methoxychalcone dibromide and 2'-acetoxy-4', 6'-dimethoxychalcone dibromide, were successfully hydrolysed by aqueous ethanolic hydrochloric acid to give 2'-hydroxy-6'-methoxychalcone dibromide (**1**) and 2'-hydroxy-4', 6'-dimethoxychalcone dibromide (**3**), respectively.

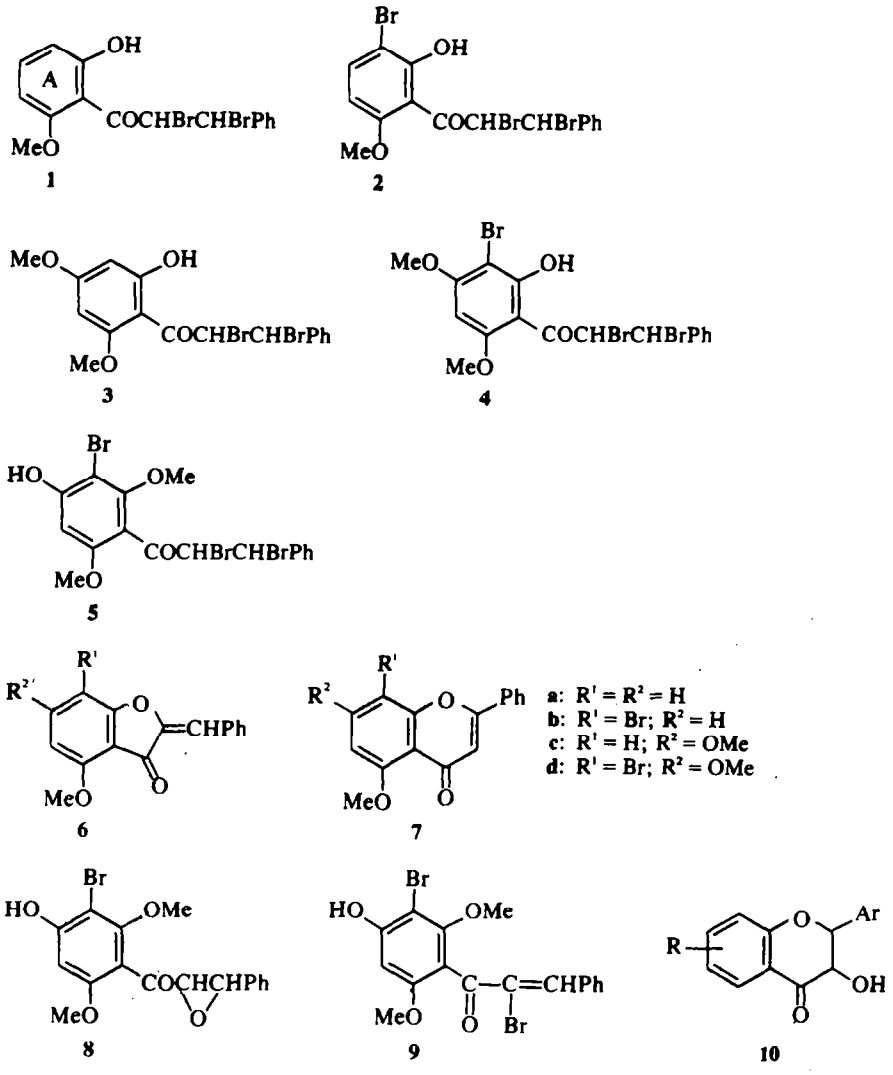
In the preparation of 3'-bromo-4'-hydroxy-2',6'-dimethoxychalcone dibromide (**5**), 4'-hydroxy-2',6'-dimethoxyacetophenone was brominated in a two-phase system of chloroform and aqueous sodium acetate to prevent demethylation by the liberated hydrogen bromide. The dibrominated product, 3',5'-dibromo-4'-hydroxy-2',6'-dimethoxyacetophenone, was isolated as well as the required 3'-bromo-4'-hydroxy-2',6'-dimethoxyacetophenone. The latter was condensed with benzaldehyde to give 3'-bromo-4'-hydroxy-2',6'-dimethoxychalcone which, when brominated, also yielded some nuclear dibrominated product, 3', 5' - dibromo - 4' - hydroxy - 2', 6' - dimethoxychalcone dibromide, together with the desired 3'-bromo-4'-hydroxy-2',6'-dimethoxychalcone dibromide (**5**).

The cyclization reactions were carried out by the addition of aqueous potassium hydroxide (1 ml) to a solution or suspension of the 2'-hydroxychalcone dibromide (*ca.* $6{\cdot}5 \times 10^{-5}$ mole) in ethanol (5 ml) maintained at 25°. The concentrations of the added potassium hydroxide solutions were: 0·2 M, 1·0 M, 4·0 M, 5·13 M, 8·33 M and 10·0 M. It was observed that the products of 3' - bromo - 2' - hydroxy - 6' - methoxychalcone dibromide (**2**) were more than usually decomposed by the higher base concentrations. In this case, therefore, the following concentrations were used: 0·2 M, 1·0 M, 2·0 M, 2·6 M and 4·0 M. The composition of the neutral products was established by UV spectroscopy.[6] The results are given in Table 1.

DISCUSSION

The cyclization of chalcone dihalides of Group 2A has been the subject of a previous study[2] aimed at determining the effects of different A-ring substitution patterns on product composition. It was carried out at a constant base concentration and the principal discovery was that these chalcone dihalides yield mainly flavones. Up to then, only aurones had been isolated.[3a,b,4b] As was mentioned at the time,[2] the work was impeded by the necessity of using 2'-*acetoxy*chalcone dihalides (to avoid nuclear halogenation during their preparation). Mechanistically, the acetates had the disadvantages of (a) having a key participating group masked and (b) not being completely soluble in the reaction medium. Another difficulty was the lack of a 2',4',6'-trisubstituted chalcone dihalide not also having a 3'-bromo substituent.

In the present work, it was found that the careful bromination of 2'-acetoxy-4',6'-dimethoxychalcone in carbon tetrachloride obviated nuclear halogenation[3a] and that the resulting 2'-acetoxy - 4',6' - dimethoxychalcone



dibromide (3, acetate), like 2' - acetoxy - 6' - methoxychalcone dibromide (1, acetate), could be cleanly hydrolysed to the corresponding 2' - hydroxychalcone dibromide.

Possibly the most important result, both practically and mechanistically, to emerge from the study (Table 1) of the effect of base concentration on the cyclization of these dibromides is that the proportion of aurone to flavone in the product decreases rapidly with decreasing base concentration. The applicability of this result to the synthesis of the many naturally occurring 5-oxy-substituted flavones has been pointed out[1] recently.

Several mechanisms have been suggested[2-5] to account for the production of aurones from this class of chalcone dibromide. None offers a role for the effect of base concentration.

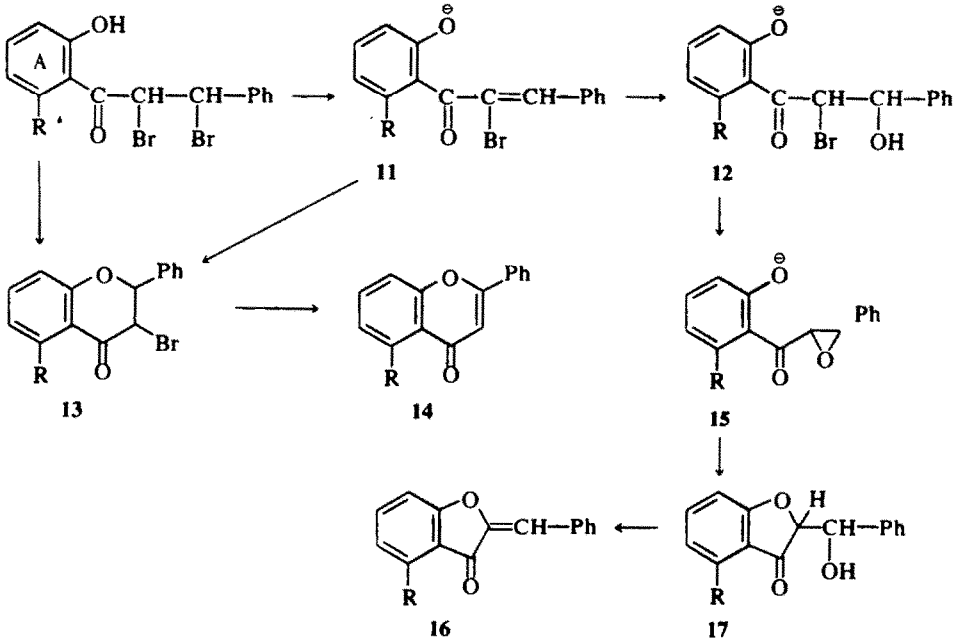
2',6' - Disubstituted chalcone dihalides readily eliminate[2] hydrogen halide from the side-chain. It is suggested (Scheme 1) that the enhancement of aurone (16) formation by increasing hydroxide concentration results from the increased effectiveness of *inter*molecular attack by hydroxide on the double bond of an α-bromochalcone intermediate[2-4] (11), relative to the corresponding *intra*molecular attack by phenoxide. A bromohydrin (12) is, therefore, formed at the expense of the flavone precursor, 3-bromoflavanone (13). Some of the latter (13) is probably also formed by direct substitution of the β-halogen atom of the chalcone dihalide itself.

It is proposed that the bromohydrin (12) cyclizes to an epoxide (15) before forming a hydrated aurone (17). It is conceivable that the bromohydrin could cyclize directly (Scheme 2; X = OH) to the aurone hydrate in a reaction analogous to the formation of coumaranones from *o*-hydroxyphenacyl bromides. The latter reaction is, however, in our experience an inefficient one—probably because the transition state for the displacement of the bromine atom by the phenoxide anion cannot approach the ideal conformation[7] for the substitution of a halogen atom in an α-halogenoketone. Also, a similar aurone-forming reaction might be expected to occur (Scheme 2; X = Br) in the chalcone dibromide itself at the more dilute base concentrations. That little or no aurone is then formed suggests that this type of reaction is not important.

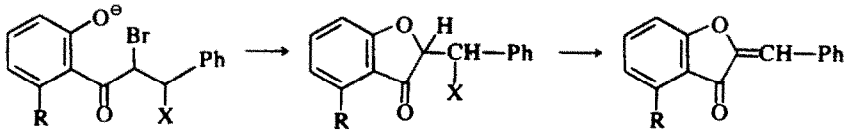
Support for the intermediacy of epoxides in aurone-formation and for their generation from Class 2A hydroxy -substituted α-bromochalcones, was obtained by examining the model compound, 3' - bromo - 4' - hydroxy - 2',6' - dimethoxychalcone dibromide (5), in which epoxide-formation could not be obscured by subsequent cyclization. This chalcone dibromide (5), on treatment with

Table 1. Composition of the neutral products from the cyclization of 2'-hydroxychalcone dibromides

	2'-Hydroxy-6'-methoxychalcone dibromide (1)			3'-Bromo-2'-hydroxy-6'-methoxychalcone dibromide (2)			2'-Hydroxy-4',6'-dimethoxychalcone dibromide (3)			3'-Bromo-2'-hydroxy-4',6'-dimethoxychalcone dibromide (4)		
Added base conc.	% Aurone (6a)	% Flavone (7a)	Aurone/Flavone	% Aurone (6b)	% Flavone (7b)	Aurone/Flavone	% Aurone (6c)	% Flavone (7c)	Aurone/Flavone	% Aurone (6d)	% Flavone (7d)	Aurone/Flavone
0.2M	0.0	100.0	0.00	6.7	100.0	0.06	5.7	96.4	0.06	0.0	100.0	0.00
	0.0	100.0		5.1	100.0		6.0	95.3		0.0	100.0	
1.0M	3.7	100.0	0.04	11.0	82.8	0.14	7.6	94.6	0.08	5.5	81.4	0.07
	4.7	100.0		13.3	88.9		7.4	93.5		6.8	84.7	
2.6M				12.6	79.3	0.17						
				14.4	80.5							
4.0M	6.5	79.0	0.08	11.5	59.1	0.19	12.0	91.4	0.13	22.5	66.4	0.34
	5.3	77.1		10.8	57.6		12.0	92.2		22.4	66.7	
5.15M	15.9	77.9	0.20				12.1	87.3	0.14	29.3	72.7	0.40
	14.7	75.0					12.1	87.3		28.1	71.6	
8.33M	15.4	65.5	0.26				21.1	75.7	0.27	52.5	36.2	1.45
	17.4	62.7					20.7	75.2		54.3	37.5	
10.0M	15.6	72.7	0.21				24.9	68.0	0.38	57.1	29.1	2.00
	15.6	75.1					26.1	68.0		54.2	27.6	



Scheme 1.



Scheme 2.

aqueous ethanolic potassium hydroxide gave the chalcone oxide (**8**) together with a mixture of the *cis* and *trans* isomers of α,3'-dibromo-4'-hydroxy-2',6'-dimethoxychalcone (**9**). This mixture was convertible into the epoxide (**8**) under similar conditions.

The initial function of the 6' - alkoxyl group in altering the normal flavone-forming course of the Emilewicz-von Kostanecki reaction appears to lie in preventing the deactivation of the CO group by the phenoxide anion so facilitating the elimination of hydrogen halide from, and the addition of hydroxide to, the side-chain. This it does by sterically inhibiting the coplanarity of the CO group and the adjacent aromatic ring. It must also play a major part in controlling the direction of ring-opening of the epoxide (**15**).

Normally, such epoxides would be expected to rearrange to a dihydroflavonol (**10**), as was found by Marathey[8] in a study of the Rasoda reaction. However, in supporting the intermediacy of these epoxides in the formation of aurones by the Algar-Flynn - Oyamada reaction of 6' - substituted 2' - hydroxychalcones with alkaline hydrogen peroxide, Dean and Podimuang[9] suggested that aurone-formation is favoured by the fact that rotation of the CO group out of the plane of the adjacent aromatic ring increases the distance of the phenolic O atom from the β-position more than from the α-position. And, as was pointed out by Geissman and Fukushima,[10] the non-bonded interaction between the 6' - substituent and the CO group also favours the product with the smaller heterocyclic ring.

It is obvious from the results recorded in Table 1 that substituents, other than the one in the 6' - position, contribute extensively to the formation of aurones. It has been suggested by Wheeler[11] that the effect of a 3' - bromo - substituent is a steric one operating on the phenoxide O atom and the developing heterocyclic ring. On the other hand, the effect of an alkoxyl substituent in the 4' - position must be electronic but how or at what stage of the reaction it occurs is unknown.

EXPERIMENTAL

UV spectra were taken in $CHCl_3$ using a Perkin-Elmer 124 spectrometer. NMR 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 chalcone dibromides were as follows. EtOH (5 ml) was added to the chalcone dibromide (*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 spectra of products, other than 5,7-dimethoxyflavone (λ_{max}262 and 301, log ε 4·43 and 4·19, respectively) and 4,6-dimethoxyaurone (λ_{max} 312 and 370, log ε 4·29 and 4·43, respectively) were given,[2] previously.

2'-Hydroxy-6'-methoxychalcone dibromide (**1**). A suspension of 2' - acetoxy - 6' - methoxychalcone dibromide[2] (4·7 g) in EtOH (400 ml), HCl (10%; 150 ml), and H_2O (200 ml) was heated on a steam-bath for 1 hr. Three 50 ml portions of H_2O were then added at *ca* 0·5 hr. intervals. Heating was continued for a further 3 hr. On cooling, 2' - hydroxy - 6'-methoxychalcone dibromide (2·6 g) precipitated, m.p. 150–151° (MeOH). (Found: C, 47·0; H, 3·5; Br, 38·6. $C_{16}H_{14}Br_2O_3$ requires; C, 46·4; H, 3·4; Br, 38·6%); NMR spectrum: 4·07 OMe, 5·74 β-H, 6·49 α-H, 12·6 OH, $J_{\alpha\beta}$ 12Hz.

3' - Bromo - 2' - hydroxy - 6' - methoxychalcone dibromide (**2**). Addition of Br_2 (2·1 g) in CCl_4 (50 ml) to 3' - bromo - 2' - hydroxy - 6' - methoxychalcone[12] (4·2 g) in CCl_4 (70 ml) gave, after removal of the solvent, the *dibromide* (3·7 g), m.p. 147–148° (EtOH). (Found: C, 39·2; H, 2·4; Br, 49·0. $C_{16}H_{13}Br_3O_3$ requires; C, 39·0; H, 2·7; Br, 48·6%); NMR spectrum: 4·07 OMe, 5·71 β-H, 6·45 α-H, 13·29 OH, $J_{\alpha\beta}$ 12 Hz.

2' - Hydroxy - 4',6' - dimethoxychalcone dibromide (**3**). Br_2 (2·75 g) in CCl_4 (20 ml) was added slowly to 2' - acetoxy - 4',6' - dimethoxychalcone[3a] (6·6 g) in CCl_4 (240 ml). Removal of the solvent gave *2' - acetoxy - 4',6' - dimethoxychalcone dibromide* (5·6 g) m.p. 180–181° (CCl_4). (Found: C, 46·4; H, 3·6; Br, 32·6. $C_{19}H_{18}Br_2O_5$ requires; C, 46·9; H, 3·7; Br 32·9%). NMR specrrum: 2·82 OAc, 3·88 4'-OMe, 3·98 6'-OMe, 5·56 β-H, 5·90 α-H, $J_{\alpha\beta}$ 12 Hz. A suspension of this 2'-acetoxychalcone dibromide (3·0 g) in EtOH (500 ml), H_2O (200 ml), and HCl (40 ml; 10%) was heated on a steam-bath until a clear soln was obtained (*ca* 0·5 hr). H_2O (280 ml) was slowly added and heating was continued for a further 3 hr. On cooling, *2' - hydroxy - 4',6' - dimethoxychalcone dibromide* (1·2 g) precipitated, m.p. 155–156° (CCl_4). (Found: C, 46·3; H, 3·6; Br, 36·2. $C_{17}H_{16}Br_2O_4$ requires: C, 46·0; H, 3·6; Br, 36·0%); NMR spectrum: 3·89 4' - OMe, 4·02 6' - OMe, 5·70 β-H, 6·45 α-H, 13·49 OH, $J_{\alpha\beta}$ 12 Hz.

3' - Bromo - 4' - hydroxy - 2',6'-dimethoxychalcone dibromide (**5**). Br_2 (6·2 g) in $CHCl_3$ (100 ml) was added slowly with vigorous stirring to a soln of 4' - hydroxy - 2',6' - dimethoxyacetophenone[13] (7·5 g) in $CHCl_3$ (250 ml) to which had been introduced NaOAc (5 g) in H_2O (200 ml). The $CHCl_3$ layer was washed and dried. Removal of the solvent, followed by crystallisation of the residue from benzene-light petroleum (b.p. 60–80°), gave *3' - bromo - 4' - hydroxy - 2',6' - dimethoxyacetophenone* (8·5 g), m.p. 156–157°. (Found: C, 43·5; H, 4·3; Br, 29·5. $C_{10}H_{11}BrO_4$ requires: C, 43·7; H, 4·0; Br, 29·0%); NMR spectrum: 2·54 Ac, 3·86 OMe, 3·90 OMe, 6·54 5' - H, 6·05 OH. Concentration of the mother liquor, followed by PLC on silica gel gave a further quantity (0·8 g) of the monobromacetophenone and some (0·6 g) *3',5' - dibromo - 4' - hydroxy - 2',6' - dimethoxyacetophenone*, m.p. 117–118° (benzene-light petroleum, b.p. 60–80°). (Found: C, 33·4; H, 2·6; Br, 45·0. $C_{10}H_{10}Br_2O_4$ requires: C, 33·9; H, 2·8; Br, 45·1%) NMR spectrum: 2·52 Ac, 3·85 2× OMe, 6·44 OH.

CO_2 was passed through a mixture of 3' - bromo - 4' - hydroxy - 2',6' - dimethoxyacetophenone (8·5 g), EtOH (200 ml), benzaldehyde (4·5 ml), and aq. KOH φ (50%; 85 ml) that had been standing for 4 days. *3' - bromo - 4' - hydroxy - 2',6' - dimethoxychalcone* (7·5 g), m.p. 113–114° (benzene-light petroleum, b.p. 60-80°), precipitated. (Found: C, 56·3; H, 4·1; Br, 21·9. $C_{17}H_{15}BrO_4$ requires: C, 56·2; H, 4·2; Br, 22·0%); NMR spectrum: 3·83 OMe, 3·89 Me, 6·10 OH, 6·58 5'–H.

Br_2 (1·3 g) in CCl_4 (10 ml) was added to the chalcone (2·6 g) in CCl_4 (60 ml). Removal of the solvent, followed by PLC on silica gel, gave *3' - bromo - 4' - hydroxy - 2',6' - dimethoxychalcone dibromide* (976 mg), a thermally unstable solid which was further purified by PLC; m.p. 139–140°. (Found: C, 39·4; H, 2·6; $C_{17}H_{15}Br_3O_4$ requires: C, 39·0; H, 2·9%). NMR spectrum: 3·91 OMe, 4·01 OMe, 5·56 β–H, 5·86 α–H, 6·18 OH, 6·57 5'–H, $J_{\alpha\beta}$ 12 Hz. Also obtained was *3',5' - dibromo - 4' - hydroxy - 2',6' - dimethoxychalcone dibromide* (504 mg), m.p. 113–114° (AcOEt). (Found: C, 34·4; H, 2·3; Br, 53·6. $C_{17}H_{14}Br_4O_4$ requires: C, 33·9; H, 2·3; Br, 53·1%); NMR spectrum : 4·05 2× OMe, 5·56 β–H, 5·90 α–H, $J_{\alpha\beta}$ 12 Hz.

3' - bromo - 4' - hydroxy - 2',6' - dimethoxychalcone oxide (**8**). Aq. KOH (6M; 8 ml) was added to a soln of 3'-bromo-4'-hydroxy - 2',6' - dimethoxychalcone dibromide (0·8 g) in EtOH (30 ml). The mixture was extracted with Et_2O after saturation with CO_2 and addition of H_2O (30 ml). The extract was washed, dried, and fractionated by PLC on silica gel. It gave *3' - bromo - 4' - hydroxy - 2',6' - dimethoxychalcone oxide* (180 mg), m.p. 173–175° (benzene-light petroleum, b.p. 60–80°). (Found: C, 54·2; H, 4·1; Br, 20·4. $C_{17}H_{15}BrO_5$ requires: C, 53·8; H, 4·0; Br, 21·1%); NMR spectrum: 3·81 OMe, 3·94 OMe, 3·94 OMe, 3·98 β–H, 4·09 α–H, 6·07 OH, 6·55 5'–H, $J_{\alpha\beta}$ 1·8 Hz. Also isolated was an oil (450 mg) which was shown by NMR[2] to be a mixture of the *cis* and *trans* isomers of α,3' - dibromo - 4' - hydroxy - 2',6' - dimethoxychalcone (**9**). This mixture was not further purified by PLC. It was dissolved in EtOH (30 ml) and treated with aqueous KOH (6M; 8 ml).

Saturation of the solution with CO_2 after 4 days, followed by the addition of H_2O (30 ml) and extraction with Et_2O, gave the chalcone oxide (**8**), (220 mg), m.p. 173–175°.

REFERENCES

[1]Part IV. J. A. Donnelly and H. J. Doran, *Tetrahedron Letters* 4083 (1974).

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

[3a]S. von Kostanecki and J. Tambor, Dtsch. Chem. Ber. **32**, 2260 (1899); [b]W. A. Hutchins and T. S. Wheeler, *J. Chem. Soc.* 91 (1939); [c]K. von Auwers and L. Anschutz, *Dtsch. Chem. Ber.* **54**, 1543 (1921).

[4a]E. M. Ryan and H. Ryan, *Proc. Roy. Irish Acad.* **39**, 425 (1930); [b]N. M. Cullinane and D. Philpott, *J. Chem. Soc.* 1761 (1929); [c]T. S. Wheeler, *Proc. Nat. Inst. Sci. India* **2**, 267 (1939).

[5]D. J. Donnelly, J. A. Donnelly and E. M. Philbin, *Tetrahedron* **28**, 1867 (1972).

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

[7]P. D. Bartlett and E. N. Trachtenberg, *J. Am. Chem. Soc.* **80**, 5808 (1958); and ref. therein.

[8]M. G. Marathey, *Sci. and Cult.* **20**, 135 (1954).

[9]F. M. Dean and V. Podimuang, *J. Chem. Soc.* 3978 (1965); see also T. R. Gormley and W. I. O'Sullivan, *Tetrahedron* **29**, 369 (1973).

[10]T. A. Geissman and D. K. Fukushima, *J. Am. Chem. Soc.* **70**, 1686 (1948).

[11]J. A. Donnelly, *Tetrahedron Letters* (19), 1 (1959).

[12]C. Chang, *Formosan Sci.* **16**, 127 (1963).

[13]F. W. Canter, F. H. Curd and A. Robertson, *J. Chem. Soc.* 1245 (1931).