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CHALCONE DIHALIDES—II†
THE SIMILARITY OF THE EFFECTS OF 2-THIENYL AND 4-METHOXYPHENYL SUBSTITUENTS IN THE SIDE CHAIN

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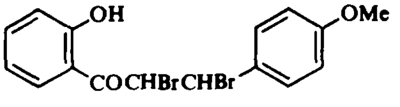
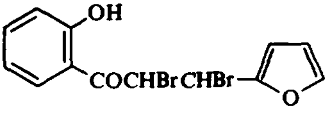
Abstract – 2,3-Dibromo-2'-hydroxy-3-(2-thienyl)propiophenones, with base, gave mixtures of the corresponding chromone and coumaranone and were readily converted into their 3-alkoxyl derivatives. Chromones were obtained by pyrolysing the dibromides and coumaranones by treatment of the 3-alkoxyl derivatives with aqueous ethanolic alkali.

THE effects of the five-membered heterocyclic systems, 2-thienyl and 2-furyl, on side-chain reactivity have been shown by Braude and Fawcett[1] to be intermediate between those of phenyl and 4-methoxy-phenyl. It seemed possible, therefore, that 2,3-dibromo-2'-hydroxy-3-(2-furyl)- and 3-(2-thienyl)- propiophenones (II and III) would react like their 3-(4-methoxyphenyl) analogues (e.g. I) and be convertible into heterocyclic-substituted chromones and coumaranones required[2] in another study.

2,3-Dibromo-2'-hydroxy-3-phenylpropiophenones (*i.e.* 2'-hydroxychalcone dibromides) with *ortho* or *para* alkoxyl substituents in the benzyl group (e.g. I) are converted into flavones and/or aurones by aqueous ethanolic alkali.[3] The product is determined[4] by the reaction conditions: flavone predominates if the reaction is carried out in an ethanolic suspension at room temperature but aurone if it is carried out in a warm ethanolic solution. The 3-(2-thienyl) analogues (III, a-e) synthesized are listed in Table 1 with the products of their reactions with aqueous ethanolic KOH at room



I



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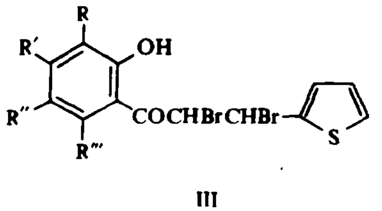

III

a: R = R' = R'' = R''' = H
b: R = R' = R''' = H: R'' = Cl
c: R = R' = OMe: R'' = R''' = H
d: R = R' = R''' = H: R'' = OMe
e: R = R''' = H: R' = OMe: R'' = Br

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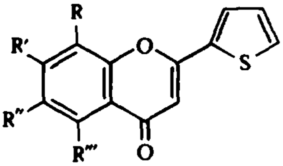
* Part I. D. J. Donnelly, J. A. Donnelly, J. J. Murphy, E. M. Philbin, and T. S. Wheeler, *Chem. Comm.* 351 (1966).

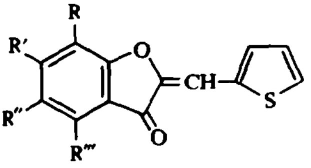
TABLE 1.

Chalcone dibromide	Aqueous alcoholic alkali reaction products	Alkoxyl derivatives
2,3-Dibromo-2′-hydroxy-3-(2-thienyl)propiophenone (IIIa)	2-(2-thienyl)chromone IVa) 2-(2-thenylidene)coumaranone (Va)	2-bromo-2′-hydroxy-3-methoxy-3-(2-thienyl)propiophenone (VIa)
2,3-Dibromo-5′-chloro-2′-hydroxy-3-(2-thienyl)propiophenone (IIIb)	6-chloro-2-(2-thienyl)chromone (IVb) 5-chloro-2-(2-thenylidene)coumaranone (Vb)	2-bromo-5′-chloro-2′-hydroxy-3-methoxy-3-(2-thienyl)propiophenone (VIb)
2,3-Dibromo-2′-hydroxy-3′,4′-dimethoxy-3-(2-thienyl)propiophenone (IIIc)	7,8-dimethoxy-2-(2-thienyl)chromone (IVc) 6,7-dimethoxy-2-(2-thenylidene)coumaranone (Vc)	2-bromo-2′-hydroxy-3,3′,4′-trimethoxy-3-(2-thienyl)propiophenone (VIc)
2,3-Dibromo-2′-hydroxy-5′-methoxy-3-(2-thienyl)propiophenone (IIId)	6-methoxy-2-(2-thienyl)chromone (IVd) 5-methoxy-2-(2-thenylidene)coumaranone (Vd)	2-bromo-2′-hydroxy-3,5′dimethoxy-3-(2-thienyl)propiophenone (VId)
2,3,5′-Tribromo-2′-hydroxy-4′-methoxy-3-(2-thienyl)propiophenone (IIIe)	6-bromo-7-methoxy-2-(2-thienyl)chromone (IVe) 5-bromo-6-methoxy-2-(2-thenylidene)coumaranone (Ve)	2,5′-dibromo-2′-hydroxy-3,4′-dimethoxy-3-(2-thienyl)propiophenone (VIe)

temperature. These products are analogous to those obtained[4] from 2′-hydroxy-4-methoxychalcone dibromides. 2,3-Dibromo-2′-hydroxy-3-(2-thienyl)propiophenone (IIIa), at room temperature gave 2-(2-thienyl)chromone (IVa) and 2-(2-thenylidene) coumaranone (Va) in the ratio 18 :1 while, from a warm solution, this ratio was 2 :7. Attempts to synthesize a 3-(2-furyl)dibromopropiophenone have, so far, failed.



IV



V

The synthesis of flavones by the pyrolysis of chalcone dibromides[5] has been extended to the preparation of 2-(2-thienyl)chromones from 2,3-dibromo-2′-hydroxy-3-(2-thienyl)propiophenones (III, a–e) and provided alternative syntheses of the chromones (IV, a–e).

TABLE 2. UV AND VISIBLE SPECTRA OF CHROMONES AND COUMARANONES

Compound	λ_{max}	log ε	Compound	λ_{max}	log ε
IVa	226(s)	3·93	IVb	222(s)	4·11
	257	4·13		260	4·15
	318	4·35		323	4·38
IVc	221(s)	4·27	IVd	227(s)	4·06
	261	4·29		270	4·16
	327	4·33		284(s)	4·10
				327	4·39
IVe	240	4·21	IXa	233(s)	4·30
	257	4·16		251(s)	4·26
	327	4·44		259	4·34
				327	4·42
IXb	258(s)	4·28	Va	223	4·08
	267	4·35		274	4·06
	309(s)	4·30		328(s)	4·09
	334	4·34		342	4·15
				409	4·22
Vb	229	4·16	Vc	218(s)	4·23
	264	4·06		283	3·78
	337(s)	4·14		348(s)	4·24
	350	4·20		391	4·39
	416	4·18			
Vd	228	4·07	Ve	235(s)	4·10
	250(s)	3·89		258	4·03
	270	4·04		334	4·31
	357	4·27		401	4·09
	407	4·12			
VIIIa	249	4·09	VIIIb	248	4·18
	344	4·30		330	4·23
	392	4·43		401	4·47

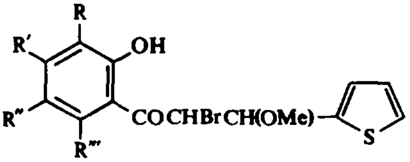
TABLE 3.

Reaction type	Products	M.p.	Solvent of crystallization	Yield	Formula or reference	Found Required C	(%) (%) H	Hal.	OMe	S
B	2,3-Dibromo-2'-hydroxy-3-(2-thienyl)propiophenone	124–125	C_6H_6	1·90	$C_{13}H_{10}Br_2O_2S$	40·3	2·2	40·7		8·4
						40·0	2·6	41·0		8·2
C	2-(2-Thienyl)chromone	101–102	MeOH	0·36	10					
	2-(2-Thenylidene)coumaranone	126–127	MeOH	0·02	$C_{13}H_8O_2S$	68·1	3·5			13·8
						68·4	3·5			14·0
D	2-(2-Thienyl)chromone	101–102	MeOH	0·08						
	2-(2-Thenylidene)coumaranone	126–127	MeOH	0·28						
E	2-Bromo-2'-hydroxy-3-methoxy-3-(2-thienyl)-propiophenone	102–103	MeOH	1·95	$C_{14}G_{13}BrO_3S$	49·7	4·1		9·2	9·9
						49·3	3·8		9·1	9·4
F	2-(2-Thenylidene)coumaranone	126–127	MeOH	0·14						
G	2-(2-Thienyl)chromone	101–102	ligroin							
B	2,3-Dibromo-5'-chloro-2'-hydroxy-3-(2-thienyl)-propiophenone	133–134	C_6H_6	3·07	$C_{13}H_9Br_2ClO_2S$	37·1	2·2	45·7		7·1
						36·8	2·1	46·0		7·55
C	6-Chloro-2-(2-thienyl)chromone	167–169	MeOH	0·42	2					
	5-Chloro-2-(2-thenylidene)courmaranone	180–181	MeOH	0·06	$C_{13}H_7ClO_2S$	59·0	2·9	13·4		12·4
						59·4	2·7	13·5		12·2
E	2-Bromo-5'-chloro-2'-hydroxy-3-methoxy-3-(2-thienyl)propiophenone	111–112	MeOH	2·20	$C_{14}H_{12}BrClO_3S$	44·7	3·6	30·3		
						44·8	3·2	30·7		
F	5-Chloro-2-(2-thenylidene)coumaranone	180–181	MeOH	0·26						
G	6-Chloro-2-(2-thienyl)chromone	165–167	MeOH							
A	2'-Hydroxy-3',4'-dimethoxy-3-(2-thienyl)acrylophenone	109–110	EtOH	1·34	$C_{15}H_{14}O_4S$	61·8	4·8			10·7
						62·05	4·9			11·0
B	2,3-Dibromo-2'-hvdroxy-3',4'dimethoxy-3-(2-thienyl)-propiophenone	130–131	C_6H_6	3·91	$C_{15}H_{14}Br_2O_4S$	40·1	3·1	35·1		6·8
						40·0	3·1	35·5		7·1
C	7,8-Dimethoxy-2-(2-thienyl)chromone	140–141	$EtOH-H_2O$	0·49	$C_{15}H_{12}O_4S$	62·0	4·2			11·2
						62·5	4·2			11·1
	6,7-Dimethoxy-2-(2-thenylidene)coumaranone	134–136	$EtOH-H_2O$	0·05	$C_{15}H_{12}O_4S$	62·1	4·4			10·9
						62·5	4·2			11·1
E	2-Bromo-2'-hydroxy-3,3',4'-trimethoxy-3-(2-thienyl)-propiophenone	156–157	MeOH	3·10	$C_{16}H_{17}BrO_5S$	47·6	4·2	20·2	23·3	7·3
						47·9	4·3	19·9	23·2	8·0
F	6,7-Dimethoxy-3-(2-thenylidene) coumaranone	136–137	$EtOH-H_2O$	0·48						
G	7,8-Dimethoxy-2-(2-thienyl)chromone	138–140	$EtOH-H_2O$							

	[illegible]	[illegible]	EtOH	1·00	$C_{14}H_{12}O_3S$	64·8	4·6			12·5
						64·6	4·6			12·3
B	2,3-Dibromo-2′-hydroxy-5′-methoxy-3-(2-thienyl)propiophenone	112–113	C_6H_6	2·46	$C_{14}H_{12}Br_2O_3S$	40·15	2·9	37·9		7·5
						40·05	2·9	38·05		7·6
C	6-Methoxy-2-(2-thienyl)chromone	127–128	MeOH-H_2O	0·33	$C_{14}H_{10}O_3S$	65·6	3·6			12·5
						65·1	3·9			12·4
	5-Methoxy-2-(2-thenylidene)coumaranone	137–138	MeOH-H_2O	0·15	$C_{14}H_{10}O_3S$	65·3	4·0			12·5
						65·1	3·9			12·4
E	2-Bromo-2′-hydroxy-3,5′-dimethoxy-3-(2-thienyl)-propiophenone	91–92	MeOH	1·64	$C_{15}H_{15}BrO_4S$	48·2	4·1	22·3		9·0
						48·5	4·1	21·5		8·6
F	5-Methoxy-2-(2-thenylidene)coumaranone	137–138	MeOH-H_2O	0·42						
G	6-Methoxy-2-(2-thienyl)chromone	127–128	MeOH-H_2O							
A	5′-Bromo-2′-hydroxy-4′-methoxy-3-(2-thienyl)-acrylophenone	178–179	EtOH-Me_2CO	1·28	$C_{14}H_{11}BrO_3S$	49·2	3·2	23·8		9·6
						49·5	3·3	23·6		9·45
B	2,3,5′-Tribromo-2′-hydroxy-4′-methoxy-3-(2-thienyl)propiophenone	144–145	C_6H_6	2·72	$C_{14}H_{11}Br_3O_3S$	33·5	2·0	48·0		6·6
						33·7	2·2	48·05		6·4
C	6-Bromo-7-methoxy-2-(2-thienyl)chromone	219–220	EtOH	0·56	$C_{14}H_9BrO_3S$	49·8	2·85	23·8		9·8
						49·9	2·7	23·7		9·5
	5-Bromo-6-methoxy-2-(2-thenylidene)coumaranone	195–196	MeOH	0·04	$C_{14}H_9BrO_3S$	50·2	3·0	23·8		9·6
						49·9	2·7	23·7		9·5
E	2,5′-Dibromo-2′-hydroxy-3,4′-dimethoxy-3-(2-thienyl)propiophenone	144–145	MeOH	2·32	$C_{15}H_{14}Br_2O_4S$	39·9	3·3	35·4		7·2
						40·0	3·1	35·5		7·1
F	5-Bromo-6-methoxy-2-(2-thenylidene)coumaranone	195–196	MeOH	0·55						
G	6-Bromo-7-methoxy-2-(2-thienyl)chromone	219–220	EtOH							
D	4′,6,7-trimethoxyaurone	157–158	AcOH-H_2O	3·10	$C_{18}H_{16}O_5$	69·0	5·3		29·5	
						69·2	5·2		29·8	
G	4′,7,8-Trimethoxyflavone	189–190	MeOH		8					
C	8-Bromo-4′,5,7-trimethoxyflavone	240–242	EtOH-Me_2CO	0·46	$C_{18}H_{15}BrO_5$	55·1	3·9	20·6	23·9	
						55·3	3·9	20·4	23·8	
	7-Bromo-4,4′,6-trimethoxyaurone	243–245	Me_2CO	0·29	$C_{18}H_{15}BrO_5$	55·4	3·9	20·7	23·7	
						55·3	3·9	20·4	23·8	
E	2,3′-Dibromo-2′-hydroxy-3,4′,6′-trimethoxy-3-(4-methoxyphenyl)propiophenone	161–162	MeOH	3·32	$C_{19}H_{20}Br_2O_6$	45·2	3·9	31·6	24·7	
						45·3	4·0	31·7	24·6	
F	7-Bromo-4,4′,6-trimethoxyaurone	242–244	Me_2CO	0·50						
G	8-Bromo-5-hydroxy-4′,7-dimethoxyflavone	249–250	Me_2CO		$C_{17}H_{13}BrO_5$	54·7	3·6	20·9	16·2	
						54·1	3·5	21·2	16·5	
A	3′-Bromo-2′-hydroxy-4,4′,6′-trimethoxychalcone	185–186	EtOH-Me_2CO	2·52	$C_{18}H_{17}BrO_5$	55·0	4·7	21·0	23·5	
						55·0	4·4	20·3	23·7	

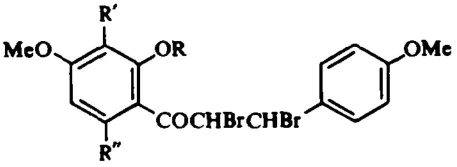
A characteristic of chalcone dibromides with *ortho* or *para* alkoxyl substituents in the benzyl group is the ease with which the β-bromine atom is solvolised[6] in refluxing alcohol. It has now been found that the 2,3-dibromo-3-(2-thienyl)propiophenones (III, a–e) behave similarly and are readily converted into their 2-bromo-3-methoxyl derivatives (VI a–e) (Table 1). Thus, 2,3-dibromo-2′-hydroxy-3-(2-thienyl)propiophenone (IIIa), on heating in MeOH, formed 2-bromo-2′-hydroxy-3-methoxy-3-(2-thienyl)propiophenone (VIa). These OMe derivatives (VI, a–e), with aqueous KOH in warm alcoholic solution, cyclized[7] to the corresponding 2-(2-thenylidene)coumaranones (V, a–e).

Two 2,3-dibromo-3-(4-methoxyphenyl)propiophenones were examined: 2′-acetoxy-3′,4,4′-trimethoxychalcone dibromide (VIIa) and 3′-bromo-2′-hydroxy-4,4′,6′-trimethoxychalcone dibromide (VIIb). The former (VIIa), when treated with aqueous KOH in hot ethanolic solution, gave 4′,6,7-trimethoxyaurone (VIIIa): its pyrolysis gave 4′,7,8-trimethoxyflavone (IXa) (Badhwar, Kang, and Venkataraman[8] have

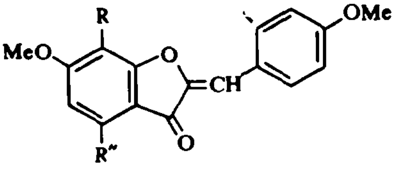


a: R = R′ = R″ = R‴ = H
b: R = R′ = R‴ = H; R″ = Cl
c: R = R′ = OMe; R″ = R''_1 = H
d: R = R′ = R''_1 = H; R″ = OMe
e: R = R''_1 = H; R′ = OMe; R″ = Br

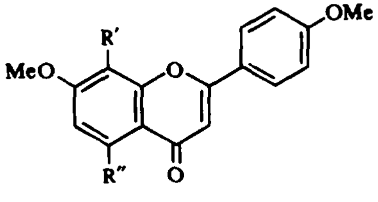
VI



VII

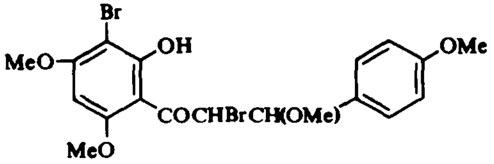


VIII

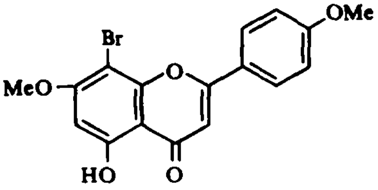


IX

a: R = OAc: R′ = OMe: R″ = H
b: R = H: R′ = Br: R″ = OMe



X



XI

reported its conversion into this flavone by aqueous ethanolic KOH at room temperature). The latter chalcone dibromide (VIIb), on treatment with aqueous ethanolic KOH, gave a mixture of 7-bromo-4,4',6-trimethoxyaurone (VIIIb) and 8-bromo-4',5,7-trimethoxyflavone (IXb) in the ratio 5:8 and, when refluxed in MeOH, gave 2,3'-dibromo-2'-hydroxy-3,4',6'-trimethoxy-3-(4-methoxyphenyl)propiophenone (X) which was converted into 7-bromo-4,4',6-trimethoxyaurone (VIIIb) by KOH aq in warm MeOH.

An unambiguous synthesis of 4',6,7-trimethoxyaurone (VIIIa) from 6,7-dimethoxycoumaranone was carried out. 7-Bromo-4,4',6-trimethoxyaurone (VIIIb) was otherwise synthesized by oxidative cyclization of 3'-bromo-2'-hydroxy-4,4',6'-trimethoxychalcone with alkaline H_2O_2. 8-Bromo-4',5,7-trimethoxyflavone (IXb) was prepared from 3'-bromo-2'-hydroxy-4',6'-dimethoxyacetophenone. The bromine, therefore, is in the 7-position of the latter aurone and in the 8-position of the flavone and not, as assumed,[9] in the 5- and 6- positions, respectively.

Pyrolysis of 3'-bromo-2',hydroxy-4,4',6'-trimethoxychalcone (VIIb) gave 8-bromo-5-hydroxy-4',7-dimethoxyflavone (XI). This result and that from the cyclization of the same chalcone dibromide with aqueous ethanolic alkali differ from those previously reported.[9] The pyrolysis reaction has been stated to yield 8-bromo-4',5,7-trimethoxyflavone (IXb) and the latter reaction to yield only 7-bromo-4,4',6-trimethoxyaurone (VIIIb).

The UV and visible spectra of the chromones and coumaranones in MeOH are given in Table 2.

EXPERIMENTAL

Reactions common to several products (Table 3) are classified as follows.

Type A: in which aqueous KOH (10 ml.: 60% w/v) was added to an ethanolic solution (approx. 25% w/v) of the acetophenone (0·01 mole) and the aldehyde (0·011 mole). After 24 hr the mixture was diluted with water, acidified with dilute HCl, and the precipitate collected.

Type B: in which bromine in $CHCl_3$ (10% w/v) was added dropwise to a similar solution of the chalcone (0·01 mole). The $CHCl_3$ was then allowed to evaporate.

Type C: in which aqueous (40% w/v) KOH (0·006 mole) was added to an ethanolic suspension (10% w/v) of the chalcone dibromide (0·002 mole). The mixture was diluted with water and the resulting precipitate chromatographed on a column of alumina.

Tyep D: as in Type C except that the dibromide was in refluxing EtOH.

Type E: in which the chalcone dibromide (0·10 mole) was dissolved in the minimum amount of boiling MeOH before allowing the product to crystallize.

Type F: in which a methanolic solution (5% w/v) of the α-bromo-β-methoxychalcone (0·002 mole) was treated with aqueous (40% w/v) KOH (0·006 mole) before being diluted with water and the precipitate collected.

Type G: in which the chalcone dibromide (5×10^{-4} mole) was heated under reduced pressure at 0–20° above its m.p. until effervescence was complete.

4',6,7-*Trimethoxyaurone* (VIIIa). HCl (5 ml) was added to a solution of 6,7-dimethoxycoumaranone[11] (0·3 g) and 4-methoxybenzaldehyde (0·25 g) in EtOH. The mixture was boiled and the aurone crystallized from the solution. It recrystallized from AcOH as yellow needles, m.p. 157–158°.

7-*Bromo*-4,4',6-*trimethoxyaurone* (VIIIb). H_2O_2 (15%: 8 ml) was added to an ice-cold solution of 3'-bromo-2'-hydroxy-4,4',6-trimethoxychalcone (3·9 g) in aqueous NaOH (16%: 20 ml) and MeOH (60 ml). The mixture was kept at 5° for 12 hr. The aurone separated and crystallized from acetone in yellow needles (2·8 g), m.p. 243–245°.

8-*Bromo*-4',5,7-*trimdthoxyflavone* (IXb). A mixture of 3'-bromo-2'-hydroxy-4',6'-dimethoxyacetophenone[12] (13·8 g), 4-methoxybenzoyl chloride (8·6 g), and pyridine (20 ml) was allowed to stand at room temp for 12 hr before being poured into dilute HCl. The precipitate, 3-*bromo*-4′,6′-*dimethoxy*-2′-(4-*methoxybenzoyloxy*)*acetophenone*, crystallized from acetone as platelets (14 g), m.p. 187–188°. (Found: C, 52·8: H, 4·3: Br, 19·7: OMe, 22·9. $C_{18}H_{17}BrO_6$ requires: C, 52·8: H, 4·2: Br. 19·5: OMe, 22·8%). A solution of the diketone (1 g) in AcOH (20 ml) and HCl (0·5 ml) was heated on a steambath for 5 min and poured into water. The product, 8-bromo-4′,5,7-trimethoxyflavone, crystallized from ethanolic acetone in needles (0·5 g), m.p. 240–242°.

All chromones gave a light yellow solution in H_2SO_4 which showed a bright blue fluorescence in UV light: the aurones gave dark red non-fluorescing solutions. 8-Bromo-5-hydroxy-4′,7-Dimethoxyflavone (XI) gave a deep brown colour with ethanolic $FeCl_3$.

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