Tetrahedron, 1963, Vol. 19, pp. 499 to 512. Pergamon Press Ltd. Printed in Northern Ireland

OXIDATION OF CHALCONES (AFO REACTION)

B. CUMMINS, D. M. X. DONNELLY, J. F. EADES, H. FLETCHER,
F. O' CINNÉIDE, E. M. PHILBIN*, J. SWIRSKI,
T. S. WHEELER and R. K. WILSON
Department of Chemistry, University College, Dublin

(*Received* 20 *September* 1962)

Abstract—Discrepancies in published work on the alkaline peroxide oxidation of chalcones (AFO reaction) have been examined. It has been found that in addition to flavonols and aurones, 2-benzyl-2-hydroxydihydrobenzofuran-3-ones (IX), and 2-arylbenzofuran-3-carboxylic acids (XV), each new as regards this reaction, appear in the products. A mechanism for the production of these latter compounds is suggested.

INTRODUCTION

ALGAR and Flynn[1] and independently Oyamada[2] found that 2′-hydroxychalcones (I) with alkaline hydrogen peroxide give flavonols (V) in satisfactory yield; dihydroflavonols (III) are intermediate in this, the AFO, reaction.[3] It was later shown that if a methoxyl[4] or methyl[5] substituent is present in the 6′-position in the chalcone, aurones (VI) rather than flavonols are obtained, provided the 2-[6] or 4-position[7] does not carry a hydroxyl group.

Conflicting statements in the literature,[8–10] (discussed below) led to a re-investigation of the course of the reaction. Besides aurones and flavonols, 2-benzyl-2-hydroxydihydrobenzofuran-3-ones (IX) and 2-arylbenzofuran-3-carboxylic acids (XV) are sometimes formed.[11,12]

Reaction mechanism

The mechanism of production of flavonols (V) and aurones (VI) has been considered by a number of workers.[8,9] It involves (see reaction diagram) the production of a ketone-epoxide (II) from which (route i) a dihydroflavonol (*trans*-2,3-*H*) (III)[13,14] or (route ii) a "hydrated-aurone" (IV) is formed. The presence of a substituent (Me,

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* Communications to Dr. E. M. Philbin.

[1] J. Algar and J. P. Flynn, *Proc. Roy. Irish. Acad.* **42B**, 1 (1934).

[2] T. Oyamada, *J. Chem. Soc. Japan* **55**, 1256 (1934); *Bull. Chem. Soc. Japan* **10**, 182 (1935).

[3] M. Murakami and T. Irie, *Proc. Imp. Acad. Tokyo* **11**, 229 (1935); cf R. Bognár and J. Stefanovsky, *Tetrahedron* **18**, 143 (1962).

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

[5] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **30A** 216 (1949).

[6] T. H. Simpson and W. B. Whalley, *J. Chem. Soc.* 166 (1955).

[7] N. Anand, R. N. Iyer and K. Venkataraman, *Proc. Indian Acad. Sci.* **29A**, 203 (1949).

[8] T. S. Wheeler, *Record Chem. Progr. Kresge-Hooker Sci. Lib.* **18**, 133 (1957).

[9] J. E. Gowan, E. M. Philbin, and T. S. Wheeler, *Chemistry of Vegetable Tannins* p. 133. Soc. Leather Trades' Chemists (1956).

[10] E. M. Philbin, J. Swirski and T. S. Wheeler, *Chem. & Ind.* 1018 (1956).

[11] B. Cummins, D. M. X. Donnelly, E. M. Philbin, J. Swirski, T. S. Wheeler and R. K. Wilson, *Chem. & Ind.* 348 (1960).

[12] D. M. X. Donnelly, J. F. K. Eades, E. M. Philbin and T. S. Wheeler, *Chem. & Ind.* 1453 (1961).

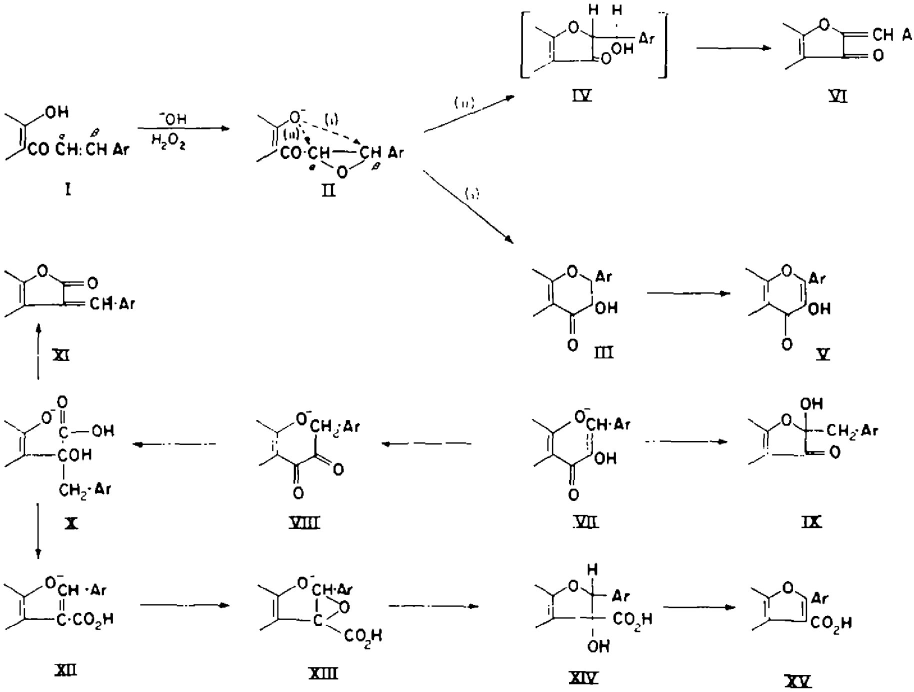
[13] V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.* **41A**, 210 (1955).

[14] E. J. Corey, E. M. Philbin and T. S. Wheeler, *Tetrahedron Letters* No. 13, 429 (1961).

OMe.) in the 6′-position of the chalcone displaces the keto-group from the plane of the nucleus. This produces steric inhibition of resonance from the 2′-O^- ion, and promotes activation of the α-carbon of the chalcone.[4,15] A hydroxyl group in the 2- or 4-position causes resonance expulsion of the β-epoxide bond with consequent dihydroflavonol formation.[7]

A route to the production of 2-benzyl-2-hydroxydihydrobenzofuran-3-ones (IX) and 2-arylbenzofuran-3-carboxylic acids (XV) in the AFO reaction is shown in the reaction diagram. It is based on a mechanism suggested for the production of compounds IX and XI by the action of alkali on dihydroflavonols.[15–17]

As the diagram shows the products of AFO oxidation of chalcones may be divided into two classes:



(i) Dihydroflavonols (III), flavonols (V), 2-benzyl-2-hydroxydihydrobenzofuran-3-ones (IX), and 2-arylbenzofuran-3-carboxylic acids (XV). Here attack of the O^- ion of compound II on the β-carbon atom of the propanone unit is involved.

(ii) Aurones (VI). The production of these compounds is related to attack of the O^- ion on the α-carbon atom of the epoxide (II).

It will be noted that as Gripenberg[15a] has pointed out the hypothetical "hydrated aurone" (IV) is unstable and immediately loses the elements of water to form the aurone (VI). On the other hand compound IX is stable and requires treatment with dehydrating agents to form VI. It is unlikely to be an intermediate in the AFO synthesis of aurone.

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[15] J. Gripenberg *a Acta. Chem. Scand.* 7, 1323 (1953); *b Les Hétérocycles Oxygénés, Colloq. Cent. Nat. de la Recher. Sci., Paris* **64**, 85 (1957); *c* T. Kubota, *J. Chem. Soc. Japan* **73**, 571 (1952).

[16] T. Oyamada, *J. Chem. Soc. Japan* **55**, 755, 785 (1934); **56**, 980 (1935); *Liebigs Ann.* **538**, 44 (1939).

[17] C. Enebäck and J. Gripenberg, *Acta Chem. Scand.* **11**, 866 (1957); J. Chopin and M. L. Bouillant, *C. R. Acad. Sci., Paris* **254**, 3699 (1962).

Discrepant results

Some discrepancies found in published work on the AFO reaction[8–10] may now be discussed. The numbers assigned to the chalcones concerned relate them to Tables 1, 2 and 3.

2′-Hydroxy-6′-methoxychalcone (5). Seshadri and Venkateswarlu[18] give m.p. 127–129° for this chalcone. Our m.p. 65° agrees with that of Oliverio and Schiavello[19] who consider that the chalcone is dimorphic. The latter authors by AFO oxidation of this chalcone without control of temperature obtained 5-methoxyflavonol, m.p. 172°.

Narasimhachari and his colleagues[20] prepared by oxidation in the cold, 4-methoxyaurone (1 mole H_2O), m.p. 189–190°, while Venturella and Bellino[21] working at about 60° isolated 4-methoxyaurone, m.p. 214–215° (see m.p. for dihydroflavonol below), and 5-methoxyflavonol m.p. 170–171°; no analytical results are provided for these compounds.

Our repetition of the work of the Indian authors[20] yielded 4-methoxyaurone, m.p. 155° (confirmed by an unambiguous synthesis) and 5-methoxydihydroflavonol, m.p. 224–226°; this compound was readily dehydrogenated to 5-methoxyflavonol, m.p. 173–175°.

2′-Hydroxy-3′,4′,6′-trimethoxychalcone (10). Balakrishna *et al.*[22] synthesized the aurone, m.p. 180–181° by AFO oxidation and we have confirmed this result. Oliverio *et al.*[23] who also carried out the reaction without cooling, isolated 5,7,8-trimethoxyflavonol, m.p. 179°, while Venturella and Bellino[21] obtained both flavonol and aurone. Chen *et al.*[24] also isolated the flavonol. In our hands oxidation at the boiling point[23] of the solvent (aqueous methanol) gave the aurone and in some runs a trace of a compound, m.p. 208–209°, which afforded the aurone on treatment with sulphuric acid and was possibly 2-benzyl-2-hydroxy-4,6,7-trimethoxydihydrobenzofuran-3-one. The U.V. spectrum supported this view.

2,2′-Dihydroxy-3′,4′,6′-trimethoxychalcone (11). Arcoleo *et al.*[25] examined the action of aqueous acetic acid containing sulphuric acid on 2′-hydroxy-3′,4′,6′-trimethoxy-2-methoxymethoxychalcone and isolated a product, m.p. 131–132°, which was not analysed but was regarded as 2,2′-dihydroxy-3′,4′,6′-trimethoxychalcone. The diacetate, m.p. 133–134°, obtained by the action of sodium acetate and acetic anhydride on this compound gave satisfactory analysis figures. Venturella and Bellino[26,28] state that the chalcone is dimorphic with m.p. 79–80° and 133–137°, and that AFO oxidation yields the flavonol, m.p. 202–204°.

We found the chalcone from the acetophenone and salicylaldehyde to have m.p. 163–164° (diacetate, m.p. 163–164°). AFO oxidation in the cold yielded 2-hydroxy-2-(*o*-hydroxybenzyl)-4,6,7-trimethoxydihydrobenzofuran-3-one (50% yield), which by

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[18] T. R. Seshadri and V. Venkateswarlu, *Proc. Indian Acad. Sci.* **26A**, 189 (1947).

[19] A. Oliverio and A. Schiavello, *Gazzetta* **80**, 788 (1950).

[20] N. Narasimhachari, S. Narayanaswami and T. R. Seshadri, *Proc. Indian Acad. Sci.* **37A**, 104 (1953).

[21] P. Venturella and A. Bellino, *Ann. Chim.. Italy* **50**, 202 (1960).

[22] K. J. Balakrishna, T. R. Seshadri and G. Viswanath, *Proc. Indian Acad. Sci.* **30**, 120 (1949).

[23] A. Oliverio, G. B. Marini-Bettòlo and G. Bargellini, *Gazzetta* **78**, 363 (1948).

[24] F. C. Chen, C. H. Yang, Y. S. Lin and T. K. Liau, *J. Taiwan Pharm. Assoc.* **4**, 48 (1952).

[25] A. Arcoleo, A. Bellino and P. Venturella, *Ann. Chim., Italy* **47**, 667 (1957).

[26] P. Venturella and A. Bellino, *Ann. Chim., Italy* **49**, 2023 (1959).

[27] T. Tsukamoto and T. Tominaga, *J. Pharm. Soc. Japan* **73**, 1179 (1953).

[28] P. Venturella and A. Bellino, *Ann. Chim., Italy* **50**, 1510 (1960).

treatment with acetic anhydride containing sulphuric acid[27] followed by deacetylation gave 2′-hydroxy-4,6,7-trimethoxyaurone, m.p. 250° (decomp). The lactone of the corresponding benzofuran-3-carboxylic acid was also prepared by AFO oxidation of this chalcone.

4,2′-*Dihydroxy*-3′,4′,6′-*trimethoxychalcone* (12). Our work on this chalcone was completed before publication of that of Venturella and Bellino.[28] These authors oxidized the chalcone (m.p. 234–236° decomp; our m.p. 207–208°) without control of temperature and obtained (yield not stated) the flavonol (m.p. 233–234°; our m.p. 281–283°).

In our experiments we isolated, in addition to the flavonol, the corresponding benzofurancarboxylic acid and the related 2-benzyl-2-hydroxydihydrobenzofuranone. We prepared the 4′-hydroxyaurone, m.p. 290–296° (decomp), by dehydration of the last compound and by an unambiguous synthesis from the dihydrobenzofuranone and aldehyde. Methylation of the aurone gave the known tetramethoxyaurone (see under chalcone 14). The Italian workers[28] synthesized the 4′-hydroxyaurone (m.p. 276–278° decomp) by hydrolysis of 4,6,7-trimethoxy-4′-methoxymethoxyaurone.

2′-*Hydroxy*-4,3′,4′,6′-*tetramethoxychalcone* (14). We have confirmed the result of Narasimhachari and Seshadri[5] who found that AFO oxidation in the cold gave the aurone, m.p. 200–201°, which they regarded as new. Shriner *et al.*[29] synthesized the aurone from the corresponding dihydrobenzofuranone and aldehyde and obtained m.p. 195–196°. Oliverio *et al.*[23] working at a higher temperature isolated the flavonol, m.p. 165°. Repetition of this experiment by Venturella and Bellino[21] yielded the aurone (m.p. 199–200°) and the flavonol, m.p. 186–187° (no analysis for either compound). Narasimhachari and Seshadri[5] who synthesized this flavonol from the flavanone by Kostanecki's isonitroso-method[30], report m.p. 198–200°.

In our hands AFO oxidation at the boiling point of the solvent mixture yielded aurone, m.p. 202°, and 4,6,7-trimethoxy-2-(*p*-methoxyphenyl)benzofuran-3-carboxylic acid (m.p. 193–194°); with increased concentration of hydrogen peroxide,[23] *p*-methoxycinnamic acid was formed.

2′-*Hydroxy*-4,4′,5′,6′-*tetramethoxychalcone* (18). Narasimhachari and Seshadri[5] by AFO oxidation in the cold obtained the aurone, m.p. 189–190°, which they regarded as new. At increased temperature Oliverio and Bargellini[31] isolated the flavonol, m.p. 185–186°. Venturella and Bellino[21] prepared both flavonol, m.p. 173–174°, and aurone, m.p. 189–190°, (no analysis for either compound) by oxidizing without control of temperature. Our repetition of Narasimhachari and Seshadri's experiment[5] gave aurone, m.p. 147–148°. Shriner *et al.*[29] give m.p. 148–149° for this compound, which they synthesized from *p*-methoxybenzaldehyde and the trimethoxydihydrobenzofuranone. A similar m.p. was exhibited by a specimen of the aurone prepared by us from the corresponding chalcone dibromide. At higher oxidation temperatures we obtained aurone, m.p. 147–148°, flavonol, m.p. 134–135°, and *p*-methoxybenzoic acid. The m.p. of an authentic sample of the flavonol (m.p. 134–135°) prepared by Kostanecki's method[30] from the isonitrosoflavanone was not depressed by addition of the AFO product.

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[29] R. L. Shriner, E. J. Matson and R. E. Damschroder, *J. Amer. Chem. Soc.* **61**, 2322 (1939).

[30] S. Kostanecki and V. Lampe, *Ber. Dtsch. Chem. Ges.* **37**, 773 (1904); S. Kostanecki and W. Szabrański, *Ibid*, 2819 (1904).

[31] A. Oliverio and G. Bargellini, *Gazzetta* **78**, 372 (1948).

Seshadri[5] using a modification of Kostanecki's method[30] synthesized flavonol, m.p. 171–173°. We found this method to yield a trace of flavonol, m.p. 134–135°, and mainly *p*-methoxybenzoic acid; the m.p. of the crude product (170–173°) was raised to 177–179° by addition of the acid, m.p. 180–182°. The indications are that the "flavonol" of the Indian[5] and Italian[21,31] workers contained *p*-methoxybenzoic acid; the analytical figures, for the acid and the flavonol do not differ greatly. On the other hand both sets of workers methylated their flavonols to 3,5,6,7,4′-pentamethoxyflavone. Their products had the same properties as the methylated compound obtained by us and by Goldsworthy and Robinson.[32]

A summary of the discrepancies discussed above is given below.

SUMMARY OF DISCREPANCIES IN M.P.S

Chalcone no.	Related compound	M.p.s °C
5	Chalcone	127–129[18]; 65[19,33]
	Aurone	189–190[20]; 214–215[21]; 155[33]
11	Chalcone	131–132[25]; 79–80; 133–137[26]; 163–164[33]
	O-Diacetylchalcone	133–134[25]; 163–164[33]
12	Chalcone	234–236 (decomp)[28]; 207–208[33]
	Aurone	276–278 (decomp)[28]; 290–296 (decomp)[33]
	Flavonol	233–234 (decomp)[28]; 281–283[33]
14	Flavonol	165[28]; 186–187[21]; 198–200[5]
18	Aurone	188–190[5,21]; 147–149[29,33]
	Flavonol	185–186[31]; 173–174[21]; 171–173[5]; 134–135[33]

Discussion of experimental results

Experimental results are summarized in Table 1. In Table 2 details of the experimental conditions employed in some of the runs are given.

Examination of the Tables indicates that:

(1) A chalcone which lacks a 6′-OMe or has a 2- or 4-OH group yields only Class (i) products.*

(2) Chalcones containing a 6′-OMe group and lacking a 2- or 4-OH group yield aurones generally accompanied by Class (i) products.*

(3) Satisfactory yields of 2-arylbenzofuran-3-carboxylic acids were obtained in some experiments. The AFO reaction provides a good route to some of these acids which normally are difficult to synthesize.

(4) The results with chalcones (11 and 12) are interesting in that little or no flavonol was obtained; the products were effectively the benzylhydroxydihydrobenzofuranones (50%) and the arylbenzofurancarboxylic acids (5%).

(5) The results with chalcones (7 and 18) indicate that the formation of flavonol is promoted by working at increased temperature,[10,21] The AFO reaction is, however, sensitive to external conditions, so that it is unsafe to generalize.

(6) The production of catechol in experiment 1*b* shows the trace occurrence of a Dakin hydroxylation reaction.

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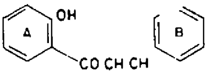
* As indicated in the introduction, conclusions (1) and (2) have already been stated in relation to the production of flavonols and aurones (references 4, 7, 21, 28).

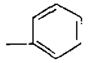
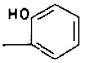
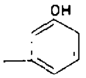
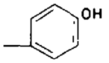
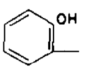
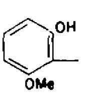
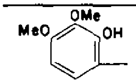
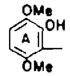
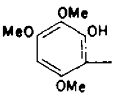
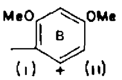
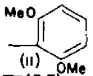
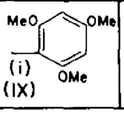
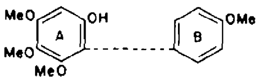
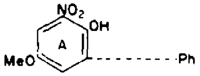
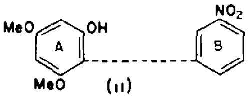
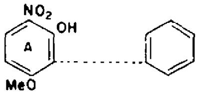
[32] L. J. Goldsworthy and R. Robinson, *J. Chem. Soc.* **46** (1937).

[33] Present research.

TABLE 1.



(Maximum percentage yields are shown)

Ring A	Ring B			
				
	1 (i) V(85), XV(46) IX (trace)	2 (i) V(30), XV(10) as lactone)	3 (i) V(10); XV(30)	4 (i) V(5), XV(15)
	5 (i) + (ii) III(15), VI(15)	6 (i) V(25) 7 (2-OMe) (i) + (ii) V(20), VI(40)		
	8 (i) V(20); XV(20)			9 (i) V(10), XV(20)
	10 (i) + (ii) VI(15); IX(trace)	11 (i) IX(50); XV(5, as lactone) 13 (2-OMe) (i) + (ii) V(20), VI(50)		12 (i) V(1), IX(50), XV(5) 14 (4-OMe) (i) + (ii) VI(30) XV(30)
	15  (i) + (ii) V(30), VI(15)	16  (ii) VI(25)	17  (i) (IX)	
18  (i) + (ii) V(25, as acetate), VI(25)		19  (i) V(30)		
20  (ii) VI(35)		21  (No useful result)		

EXPERIMENTAL

Crystallization was from ethanol unless otherwise stated.

Methylation was effected by the use of methyl sulphate, potassium carbonate, and acetone; for acetylation a mixture of acetic anhydride and sodium acetate was employed.

Chalcones. Particulars of the known chalcones used are given below. New chalcones are described in Table 3. The standard methods of preparation employed are described in the references cited for the known chalcones. M.p.s of known compounds are not recorded unless discrepant with the literature. The condensation of dihydrobenzofuran-3-ones and aldehydes to form aurones is described by Shriner *et al.*[34] and by Auwers and Pohl.[35]

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[34] A. Arcoleo, A. Bellino and P. Venturella, *Ann. Chim., Italy* **47**, 658 (1957).

[35] K. Auwers and P. Pohl. *Liebigs Ann.* **405**, 243 (1914).

TABLE 2. DETAILS OF SOME OXIDATION EXPERIMENTS

Chalcone and experiment nos.	Reagents (g) per 100 g of reaction mixture					Temp and time of		Crystallized products; (g) per g of chalcone taken
	Chalcone	H_2O_2	NaOH	EtOH	H_2O	mixing	keeping	
1*a*	3	1	5	20	71	0°; rapid	room temp; 24 hr	V (0·3); XV (0·15); PhCOOH (0·06); *o*-$(OH)C_6H_4Ac$ (0·1)
1*b*	1	1	5	10	83	0°; rapid	room temp; 1 hr	XV (0·4); PhCOOH (0·2); *o*-OHC_6H_4Ac (0·1)
1*c*	5	1	1 (KOH)	90	3	50°; rapid	room temp; 2 hr	V (0·25); IX (trace) *o*-$(OH)_2C_6H_4$ (0·05) *o*-OHC_6H_4COOH (0·1)
1*d*	4·5	1·5	2	40	52	0°; rapid	room temp; 24 hr	V (0·85) *o*-OHC_6H_4COOH (0·02)
5*a*	2·5	1	5	—	91·5	0°; 30 min	room temp; 24 hr	III (0·15); VI (0·15); recovered chalcone (0·1)
5*b*	2·5	1	5	56	35·5	b.p.; 30 min	room temp; 24 hr	VI (0·05); 2-(OH)-6-(OMe)C_6H_3COOH (0·3)
7*a*	3	2·5	3	27	64·5	0°; 15 min	room temp; 24 hr	VI (0·4)
7*b*	3	2·5	3	27	64·5	b.p.; 5 min	room temp; 24 hr	V (0·2); VI (0·1)
11	1·5	1	5	—	92·5	0°; rapid	0°; 24 hr	IX (0·5)
12	1·5	1	5	—	92·5	0°; rapid	0°; 24 hr	IX (0·5)
14	3	1	3	50	43	b.p.; 15 min	room temp; 2 hr	VI (0·25); XV (0·3)
16	2	0·5	0·5	72	25	room temp 15 min	room temp; 12 hr	VI (0·025)
18*a*	3	1	3	50	43	0°; 15 min	room temp; 2 hr	VI (0·25); recovered chalcone (0·25)
18*b*	3	1	3	50	43	b.p.; 15 min	room temp; 2 hr	V (0·25) as acetate. VI (0·15); *p*-OMe C_6H_4COOH (0·15)
20	2	3	5	35	55	30°; rapid	room temp; 4 hr	VI (0·35)

TABLE 3. NEW CHALCONES

Nos.	Chalcone	m.p.	Colour and crystalline form	Solvent	Mol formula	Analysis % F = Found; R = Required				
							C	H	OMe	N
9*	4,2′ Dihydroxy-3′,6′-dimethoxy	179	orange needles	MeOH	$C_{17}H_{16}O_5$	F:	67·7	5·2	20·8	
						R:	68·0	5·4	20·7	
13	2′-Hydroxy-2,3′,4′,6′-tetramethoxy	171–172	yellow plates	EtOH	$C_{19}H_{20}O_6$	F:	66·6	5·7	—	—
						R:	66·3	5·9	—	—
15	2′-Hydroxy-2,4,3′,4′,6′-pentamethoxy-	148	orange plates	EtOH	$C_{20}H_{22}O_7$	F:	63·9	6·0	40·8	—
						R:	64·2	5·9	41·7	—
16	2′-Hydroxy-2,6,3′,4′,6′-pentamethoxy-	160–161	red needles	MeOH	$C_{20}H_{22}O_7$	F:	64·5	6·0	41·4	—
						R:	64·2	5·9	41·7	—
17†	2′-Hydroxy-2,4,6,3′,4′,6′-hexamethoxy-	154	red needles	MeOH	$C_{21}H_{24}O_8$	F:	62·4	5·7	45·4	—
						R:	62·4	6·0	46·0	—
19‡	2′-Hydroxy-5′-methoxy-3′-nitro-	113	needles	MeOH	$C_{16}H_{13}NO_5$	F:	64·7	4·4	10·5	4·4
						R:	64·2	4·4	10·4	4·7
20	2′-Hydroxy-4′,6′-dimethoxy-3-nitro-	170	needles	AcOH	$C_{17}H_{15}NO_6$	F:	61·8	4·5	18·5	4·5
						R:	62·0	4·6	18·8	4·3
21§	2′-Hydroxy-6′-methoxy-3′-nitro-	179	yellow plates	EtOH	$C_{16}H_{13}NO_5$	F:	64·4	4·4	10·8	4·6
						R:	64·2	4·4	10·4	4·7

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* In the preparation of 2-hydroxy-3-6-dimethoxyacetophenone[44], the methylation of 2-benzyloxy-3,6-dihydroxyacetophenone was advantageously effected by the methyl sulphate-potassium carbonate-acetone method.

† For the preparation of 2,4,6-trimethoxybenzaldehyde see Kenyon and Mason.[45]

‡ *Preparation of 2-hydroxy-5-methoxy-3-nitroacetophenone*[46] A solution containing 2-hydroxy-5-methoxyacetophenone[44] (10 g), acetic acid (120 ml) and acetic anhydride (9ml) was cooled to solidification and treated, dropwise, under stirring with nitric acid (3 ml; *d* 1·5). After 1 hr the product was poured into excess of ice-water to precipitate the *ketone*, m.p. 110–112° (yellow plates from methanol) (Found: C, 50·9; H, 4·2; N, 6·7. $C_9H_9NO_5$ requires C, 51·2; H, 4·3; N, 6·6%). The structure of the ketone was confirmed by oxidation by aqueous sodium hypobromite.[47] The product was 2-hydroxy-5-methoxy-3-nitrobenzoic acid (mixed m.p. authentication).[48]

§ For the parent ketone see Naik *et al.*[49]

Chalcones previously prepared. (1) 2′-Hydroxy-;[36] (2) 2,2′-dihydroxy-;[37] (3) 3,2′-dihydroxy-. This chalcone, m.p. 165° (Found: C, 75·4; H, 5·0. Calc. for $C_{15}H_{12}O_3$: C, 75·6; H, 5·0%) was prepared by "cold condensation";[37] Schraufstätter and Deutsch[38] give m.p. 132°. The *diacetate* had m.p. 85° (light green needles from methanol) (Found: C, 70·4; H, 5·1. $C_{19}H_{16}O_5$ requires C, 70·4; H, 5·0%); (4) 4,2′-dihydroxy-;[37] (5) 2′-hydroxy-6′-methoxy-;[39a] (6) 2,2′-dihydroxy-6′-methoxy-;[6] (7) 2′-hydroxy-2,6′-dimethoxy-[40a] (8) 2′-hydroxy-3′,4′-dimethoxy-;[41] (10) 2′-hydroxy-3′,4,6′-trimethoxy[39a]; (11) 2,2′-dihydroxy-3′,4′,6′-trimethoxy-.[39a] This compound separated from methanol in orange needles, m.p. 163–164° (Found: C, 65·8; H, 5·6; OMe, 28·4. Calc. for $C_{18}H_{18}O_6$; C, 65·4; H, 5·5; OMe, 28·2%). The diacetate had m.p. 164° (yellow needles from methanol) (Found: C, 63·8; H, 5·4; OMe, 22·1. Calc. for $C_{22}H_{22}O_8$: C, 63·8; H, 5·4; OMe, 22·5%); (12) 4,2′-dihydroxy-3′,4′,6′-trimethoxy-.[39a] Our preparation had m.p. 207–208° (from methanol). (Found C, 65·3; H, 5·8; OMe, 28·2. Calc. for $C_{18}H_{18}O_6$: C, 65·4; H, 5·5; OMe, 28·2%). *The diacetate* had m.p. 117–118° (needles from methanol) (Found: C, 64·3; H, 5·5. $C_{22}H_{22}O_8$ requires C, 63·8; H, 5·4%); (14) 2′-hydroxy-4,3′,4′,6′-tetramethoxy-[39a]; (18) 2′-hydroxy-4,4′,5′,6′-tetramethoxy-.[39a]

For the preparation of 2-hydroxy-3,4,6-trimethoxyacetophenone, required in the synthesis of chalcones Nos. 10–17, see Baker,[42] and Sastri and Seshadri[43]

Details of oxidation experiments

Table 1 summarizes the results of the oxidation experiments; details of some are given in Table 2.

The usual reaction mixture (100 g) contained: chalcone (2 g), hydrogen peroxide (1·5 g), and sodium hydroxide (3 g) in aqueous ethanol or water.

Normally, solid formed (e.g., sodium peroxide or the sodium salt of a flavonol) was collected and the filtrate, if not strongly aqueous, was diluted with water; any further precipitate (e.g. aurone) was removed and the filtrate was acidified and shaken with ether. Acidic and phenolic compounds were extracted by aqueous sodium hydrogen carbonate (5%) and aqueous sodium hydroxide (10%) and recovered by acidification.

2′-Hydroxychalcone (1).[39b] In experiments 1*a* and 1*b* benzoic acid was removed by sublimation at 100° from the mixture of acids extracted by aqueous sodium hydrogen carbonate. 2-Phenylbenzofuran-3-carboxylic acid[50] (ν 1667 cm^{-1}; COOH) remained. The amide[51] was also prepared. Decarboxylation of the acid (Cu-quinoline) yielded 2-phenylbenzofuran[51]. *o*-Hydroxyacetophenone (extracted by aqueous sodium hydroxide) was identified as the benzoate.

In experiment 1*c* the sodium hydroxide extract afforded by acidification and extraction by ether a solid which separated from benzene in orange needles. Sublimation of these crystals at 100° under red press yielded catechol. The *di-p-toluenesulphonate* (Found: C, 57·1; H, 4·3; S, 15·6. $C_{20}H_{18}O_6S_2$ requires C, 57·4; H, 4·3; S, 15·3%) had m.p. 161–162° (prisms from methanol).

The unsublimed solid was separated by paper chromatography with aqueous acetic acid (5%) into

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[38] E. Schraufstätter and S. Deutsch, *Chem. Ber.* **81**, 489 (1948).

[39a] See Introduction, *Discrepant Results*; [b] see Table 2.

[40] N. Narasimhachari, D. Rajagopalan and T. R. Seshadri, *Proc. Indian Acad. Sci.* [a] **36A**, 231 (1952); [b] **37A**, 705 (1953).

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[51] J. N. Chatterjea, *J. Indian Chem. Soc.* **33**, 175 (1956).

catechol and 2-benzyl-2-hydroxydihydrobenzofuran-3-one. The phenol was removed by treatment with aqueous acetic acid (2%). The residue had m.p. 101–102°, not depressed by admixture with an authentic sample of the dihydrofuranone.[15a]

2,2′-Dihydroxychalcone (2). The reaction mixture (obtained at 0°) gave on acidification 2′-hydroxyflavonol identified by its properties and those of its diacetate.[8] Salicylic acid sublimed from the solid recovered from the sodium hydrogen carbonate extract. The residue yielded on crystallization from methanol the lactone of 2-(*o*-hydroxyphenyl) benzofuran-3-carboxylic acid[52,53] (ν, 1739 cm^{-1}; δ-lactone).

3,2′-Dihydroxychalcone (3). AFO oxidation gave 3′-hydroxyflavonol[54,55] and 2-(m-*hydroxyphenyl*) *benzofuran*-3-*carboxylic* acid (Found: C, 71·0; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%) which separated from benzene–light petroleum (b.p. 60–80°) in needles, m.p. 201–202° (ν 1681 cm^{-1}; COOH). The *amide* (prepared through the acid chloride) crystallized from dioxan–methanol in needles, m.p. 190–200° (decomp) (Found: C, 71·0; H, 4·4. $C_{15}H_{11}NO_3$ requires C, 71·1; H, 4·4%). 2-(*m-Hydroxyphenyl*)-*benzofuran* (decarboxylation by Cu–quinoline) was purified by sublimation. It formed needles, m.p. 133–134°. (Found: C, 80·4; H, 5·1. $C_{14}H_{10}O_2$ requires: C, 80·0; H, 4·8%).

4,2′-Dihydroxychalcone (4). 4′-Hydroxyflavonol and its acetate[56] gave acceptable analytical figures. 2-*Hydroxyphenylbenzofuran*-3-*carboxylic acid* had m.p. 221° (needles from benzene) (ν, 1686 cm^{-1}; COOH) (Found: C, 70·9; H, 4·0. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%). Decarboxylation (Cu–quinoline) yielded 2-(*p*-hydroxyphenyl)benzofuran which was crystallized from aqueous methanol and then sublimed at 200°/15 mm.[53]

2′-Hydroxy-6′-methoxychalcone (5).[39] The yellow precipitate collected from the AFO reaction mixture was treated with dil hydrochloric acid. The fraction of the resulting product soluble in ethanol yielded two compounds when chromatographed on magnesium trisilicate.

Product one was 4-methoxyaurone which crystallized from ethanol in yellow needles, m.p. 155°[39] (Found: C, 76·5; H, 4·7; OMe, 11·9. Calc. for $C_{16}H_{12}O_3$: C, 76·2; H, 4·8; OMe, 12·3%). For the unambiguous synthesis of the compound, 2-acetoxy-6-methoxyacetophenone (2 g)[57] was treated dropwise in chloroform (15 ml) solution at 0° with bromine (1·5 g) in the same solvent (10 ml). The oil remaining on removal of the solvent (red press) was heated at 100° for 10 min with a mixture of methanol (10 ml) and hydrochloric acid (3 ml conc). The precipitated bromoacetophenone separated from methanol in light green prisms (1·5 g), m.p. 78–79°. This compound (1 g) was treated with sodium acetate (2 g crystals) in ethanol (15 ml) on a steam-bath and after 1 hr the mixture was poured into a saturated solution of sodium chloride (200 ml).[58] The precipitate collected after 24 hr was treated with aqueous sodium hydroxide (2%). The undissolved solid was crystallized from methanol and then sublimed at 100°/10 mm to give 4-methoxydihydrobenzofuran-3-one in needles (0·1 g), m.p. 147–148° (Found: C, 65·7, H, 5·2. Calc. for $C_9H_8O_3$; C, 65·9; H, 4·9%). Farmer *et al.* give m.p. 151°[59] Condensation with benzaldehyde afforded 4-methoxyaurone. The red solution in sulphuric acid did not fluoresce in UV light and the ethanolic ferric test was negative.

The second product from the column, 5-*methoxydihydroflavonol*, crystallized from ethyl acetate in yellow needles, m.p. 224–226°. It was insoluble in alkali. (Found: C, 71·1; H, 5·5; OMe, 11·0. $C_{16}H_{14}O_4$ requires C, 71·1; H, 5·2; OMe, 11·5%). The Chadenson test[60] for dihydroflavonols was positive and the ethanolic ferric reaction was negative. Heated with glacial acetic acid for 45 min, the compound gave 5-methoxyflavonol, m.p. 173–175°.[18,19] Unreacted chalcone precipitated from the alkaline filtrate on acidification.

Oxidation at the b.p.[39b] The filtered reaction mixture was diluted with water. The yellow precipitate yielded 4-methoxyaurone (mixed m.p. confirmation). The filtrate was acidified and extracted *hydroxy*-5-*methoxyflavonol* which separated from methanol in yellow plates, m.p. 192–193°

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with ether. Aqueous sodium hydrogen carbonate removed from the solvent layer, 2-hydroxy-6-methoxybenzoic acid.[61]

2,2′-*Dihydroxy*-6′-*methoxychalcone* (6). Acidification of the reaction mixture precipitated 2′-(Found: C. 67·6; H, 4·3; OMe, 11·4. $C_{16}H_{12}O_5$ requires C, 67·6; H, 4·3; OMe, 10·9%). The ethanolic ferric colour was green and the U.V. fluorescence in sulphuric acid solution was yellow.

Demethylation (hydriodic acid–acetic anhydride) afforded 5,2′-*dihydroxyflavonol* which crystallized from methanol in yellow needles, m.p. 206–207° (Found: C, 66·7; H, 3·8. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%). The ethanolic ferric colour was brown and the U.V. fluorescence in sulphuric acid was yellow.

This compound (mixed m.p.) was also obtained by demethylation of 5,2′-dimethoxyflavonol (from chalcone (7), by aluminium chloride in dry benzene at the b.p.

Methylation of 5,2′-dihydroxyflavonol, of 2′-hydroxy-5-methoxyflavonol, or of 5,2′-dimethoxyflavonol afforded 3,5,2′-*trimethoxyflavone* which crystallized from methanol in needles, m.p. 142–143°; the U.V. fluorescence in sulphuric acid solution was yellow (Found: C, 69·6; H, 5·5; OMe, 29·5. $C_{18}H_{16}O_5$ requires C, 69·2; H, 5·2; OMe, 29·8%).

2′-*Hydroxy*-2,6′-*dimethoxychalcone* (7).[39b] Narasimhachari *et al.*[40b] obtained the aurone by AFO oxidation in the cold and their result has now been confirmed. By working at higher temperatures the flavonol is also formed. In one such experiment (7*b*) the reaction mixture was extracted with ether; the aurone (mixed m.p. with an authentic specimen)[40b] remained when the solvent was evaporated.

The alkali layer on acidification gave 5,2′-*dimethoxyflavonol* which crystallized in prisms, m.p. 197–199° (Found: C, 68·2; H, 4·9; OMe, 20·6. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7; OMe, 20·8%). The ethanolic ferric colour was blue–violet, and the solution in conc sulphuric acid exhibited a yellow–green fluorescence in U.V. light. (for demethylation see 6).

2′-*Hydroxy*-3′,4′-*dimethoxychalcone* (8). The fraction of the AFO product soluble in aqueous sodium hydrogen carbonate gave on crystallization from benzene, 6,7-*dimethoxy*-2-*phenylbenzofuran*-3-*carboxylic acid*, m.p. 226–228° (Found: C, 68·9; H, 4·8; OMe, 20·5. $C_{17}H_{14}O_5$ requires C, 68·5; H, 4·7; OMe, 20·8%), λ_{max}^{MeOH} 215, 235, 315 mμ.

The *amide* of the acid was prepared through the chloride. It separated from methanol in needles, m.p. 263° (Found: C, 69·3; H, 5·1; OMe, 21·4. $C_{17}H_{15}NO_4$ requires C, 68·7; H, 5·1; OMe, 20·9%).

7,8-Dimethoxyflavonol which was present in the aqueous sodium hydroxide extract was identified by its properties and by those of its acetate.[62]

4,2′-*Dihydroxy*-3′,6′-*dimethoxychalcone* (9). Oxidation by the AFO process[28] yielded no product soluble in aqueous sodium hydrogen carbonate. The solid obtained on acidification of the aqueous sodium hydroxide extract was separated by crystallization from methanol into the chalcone and 4′-*hydroxy*-5,8-*dimethoxyflavonol* (Found: C, 64·7; H, 4·7; OMe, 18·6. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5; OMe, 19·7%). This compound separated from methanol in green needles, m.p. 272–274° (decomp); λ_{max}^{EtOH} 270 (log ε 4·3); 340 (log ε 4·2); 375 mμ (log ε 4·36). When the ethanolic solution was treated with ethanolic aluminium chloride a shift (375–436; 61 mμ) characteristic of a flavonol was obtained.[63] The ethanolic ferric chloride colour was brown-green. The solution in concentrated sulphuric acid exhibited a faint orange fluorescence in U.V. light.

When oxidation was effected in aqueous solution[7] the aqueous sodium hydrogen carbonate extract yielded 4,7-*dimethoxy*-2-(p-*hydroxyphenyl*)*benzofuran*-3-*carboxylic acid*, m.p. 240° (needles on sublimation) (Found: C, 64·6; H, 5·2; OMe, 20·6. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5; OMe, 19·7%). The flavonol was present in the aqueous sodium hydroxide extract.

2′-*Hydroxy*-3′,4′,6′-*trimethoxychalcone* (10).[39a] Dilution of the reaction mixture by water precipitated 4,6,7-trimethoxyaurone with the properties described by Balakrishna *et al.*[22] The fraction of the product which was soluble in aqueous sodium hydroxide but not in aqueous sodium hydrogen carbonate yielded in some runs a trace of a compound (A), m.p. 208–209°, (needles from methanol). The ethanolic ferric reaction of (A) was negative. The U.V. spectrum (λ_{max}^{MeOH} 215, 295 mμ) was similar to that of the compounds of type IX from chalcones (11) and (12). All 3 compounds exhibited in the solid state an intense blue U.V. fluorescence.

A solution of (A) in conc sulphuric acid was poured into water and the mixture was extracted with ether. The ethereal layer was washed with water, shaken with charcoal, filtered and dried. The

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[61] H. W. B. Cleaver, S. J. Green and F. Tutin, *J. Chem. Soc.* **107**, 837 (1915).

[62] F. Dobrzyński and S. Kostanecki, *Ber. Dtsch. Chem. Ges.* **37**, 2807 (1904).

[63] T. Swain, *Chem. & Ind.* 1480 (1954).

residue from the removal of the solvent was run on paper using aqueous acetic acid (70%). 4,6,7-Trimethoxyaurone which was recovered was identified by its U.V. spectrum (λ_{max}^{MeOH}, 315, 390 mμ) (Venturella and Bellino[21] gave 315, 388 mμ).

4-*Hydroxy*-6,7-*dimethoxyaurone*. A mixture of 4,6,7-trimethoxyaurone (0·8 g), acetic acid (5 ml) and hydrobromic acid in acetic acid (60%; 5 ml) was heated on a steam-bath for 1 hr and diluted with water to precipitate 4-hydroxy-6,7-dimethoxyaurone (Found: C, 68·0; H, 4·7; OMe, 21·1. Calc. for $C_{17}H_{14}O_5$: C, 68·5; H, 4·7; OMe, 20·8%), which separated in yellow plates (0·4 g), m.p. 234–235°. Balakrishna *et al.*[22] give m.p. 177–178°. The ethanolic ferric colour was dark brown. Methylation of this aurone reformed the parent trimethoxyaurone.

4-*Acetoxy*-6,7-*dimethoxyaurone* had m.p. 158–160° (plates from ethanol) (Found: C, 67·1; H, 4·8; OMe, 18·8. $C_{19}H_{16}O_6$ requires C, 67·1; H, 4·8; OMe, 18·2%).

2,2′-*Dihydroxy*-3′,4′,6′-*trimethoxychalcone* (11)[39] Ethereal extraction of the acidified reaction product afforded 2-*hydroxy*-2-(o-*hydroxybenzyl*)-4,6,7-*trimethoxydihydrobenzofuran*-3-*one* which crystallized from ethyl acetate in needles (1·0 g), m.p. 199–200° (Found, C, 62·5; H, 5·3; OMe, 27·2. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2; OMe, 26·9%) λ_{max}^{MeOH} 295 mμ. The *diacetate* separated from aqueous methanol in needles, m.p. 140° (Found: C, 62·0; H, 5·3; OMe, 21·7. $C_{22}H_{22}O_9$ requires C, 61·4; H, 5·2; OMe, 21·6%).

Methylation of the dihydrobenzofuranone (m.p. 199–200°) yielded 2,4,6,7-*tetramethoxy*-2-(o-*methoxybenzyl*)*dihydrobenzofuran*-3-*one*, m.p. 127–128° (needles from light petroleum, b.p. 60–80°) (Found: C, 64·4; H, 6·0; OMe, 41·0. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9; OMe, 41·5%).

2′-*Hydroxy*-4,6,7-*trimethoxyaurone*. A mixture of 2-hydroxy-2-(*o*-hydroxybenzyl)-4,6,7-trimethoxydihydrobenzofuran-3-one (0·5 g), acetic anhydride (4 ml) and sulphuric acid (2 drops) was kept overnight at room temp and poured on ice (50·g). For deacetylation the precipitate was heated for 15 min with ethanol (6 ml) and conc hydrochloric acid (3 ml) and the reaction mixture was treated with hot water to incipient precipitation and allowed to cool. The resulting precipitate separated from methanol in yellow needles, m.p. (250° decomp). This m.p. was not depressed by addition of an authentic sample (Found: C, 65·4; H, 6·9; OMe, 28·3. Calc. for $C_{18}H_{16}O_6$: C, 65·9; H, 5·9; OMe, 28·4%) prepared by the condensation of the dihydrobenzofuranone[29] and salicylaldehyde in acidified ethanol. The U.V. spectra of both samples were identical (λ_{max}^{MeOH} 318, 407 mμ). Arcoleo *et al.*[25] prepared this aurone by the action of sulphuric acid in acetic acid solution on the 2′-methoxymethoxyderivative. Their product (no analysis) had m.p. 245° (λ_{max} 315, 406 mμ).[28]

No useful result was obtained when the benzylhydroxydihydrobenzofuranone was treated with sulphuric acid in the absence of acetic anhydride.

Oxidation of the chalcone at the b.p. of the solvent afforded the *lactone* of 2-(-o-*hydroxyphenyl*)-4,6,7-*trimethoxybenzofuran*-3-*carboxylic acid* (Found: C, 66·3; H, 4·5; OMe, 28·1. $C_{18}H_{14}O_6$ requires C, 66·3; H, 4·3; OMe, 28·5%) which separated on acidification of the aqueous sodium hydrogen carbonate extract. It crystallized from aqueous methanol in fine needles, m.p. 215–217°; λ_{max}^{MeOH} 218, 269, 350 mμ.

Unreacted chalcone (mixed m.p. confirmation) was present in the aqueous sodium hydroxide fraction.

4,2′-*Dihydroxy*-3′,4′,6′-*trimethoxychalcone* (12)[39]. Ethereal extraction of the acidified reaction mixture obtained by oxidation at 0° yielded 2-*hydroxy*-2-(p-*hydroxybenzyl*)-4,6,7-*trimethoxydihydrobenzofuran*-3-*one*. Found: C, 62·6; H, 5.2; OMe, 26·7. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2; OMe, 26·9%), m.p. 198–200° (needles from ethyl acetate) λ_{max}^{MeOH} 210, 296 mμ. This compound gave a red colour with sulphuric acid; in the solid state it exhibited a blue fluorescence. Methylation produced the pentamethyl ether (Found: C, 64·4; H, 5·9; OMe, 41·9. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9; OMe, 41·6%), m.p. 125–126° (needles from light petroleum, b.p. 60–80°).

2-*Acetoxy*-2-(p-*acetoxybenzyl*)-4,6,7-*trimethoxydihydrobenzofuran*-3-*one*. (Found: C, 61·0; H, 5·2; OMe, 21·5. $C_{22}H_{22}O_9$ requires C, 61·4; H, 5·2; OMe, 21·6%) separated from methanol in prisms, m.p. 139–140°. 4′-Hydroxy-4,6,7-trimethoxyaurone (Found: C, 66·0; H, 5·0; OMe, 28·2. Calc. for $C_{18}H_{16}O_6$. C, 65·9; H, 4·9; OMe, 28·4%), m.p. 290–296° (decomp) (yellow needles from methanol), λ_{max}^{MeOH} 335, 405 mμ (Venturella and Bellino[28] give m.p. 276–278° (decomp) and 333, 409 mμ) separated when a solution of the benzylhydroxydihydrobenzofuranone (m.p. 198–200°) in conc sulphuric acid which had been kept for 1 min was poured into water. An authentic sample prepared from the corresponding dihydrobenzofuranone[29] and *p*-hydroxybenzaldehyde had identical properties. Methylation gave the tetramethoxyaurone[5] (see under chalcone 14). Oxidation at the solvent b.p. yielded 2-p-*hydroxyphenyl*-4,6,7-*trimethoxybenzofuran*-3-*carboxylic acid* (Found: C, 62·0; H, 4·8; OMe, 26·5.

$C_{18}H_{16}O_7$ requires C, 62·8; H, 4·7; OMe, 26·9%), m.p. 222–225° (needles from aqueous methanol), λ_{max}^{MeOH} 215, 316 mμ, and *4′-hydroxy-5,7,8-trimethoxyflavonol* (Found: C, 62·6; H, 4·6; Calc. for $C_{18}H_{16}O_7$: C, 62·8; H, 4·7%), m.p. 281–283° (needles from methanol), λ_{max}^{MeOH} 370 mμ (+$AlCl_3$, 430 mμ[63]). The ethanolic ferric colour was green. Venturella and Bellino[28] give m.p. 233–234° and 256, 317, 360 mμ.

Oxidation in presence of conc alkali[6] yielded in the aqueous sodium hydrogen carbonate extract, *2-hydroxy-3,4,6-trimethoxybenzoic acid* (Found: C, 52·7; H, 5·2. $C_{10}H_{12}O_6$ requires C, 52·6; H. 5·3%), m.p. 146–147° (needles from methanol).

2′-Hydroxy-2,3′,4′,6′-tetramethoxychalcone (13). Addition of water to the oxidation mixture gave a solid which by fractional crystallization from methanol afforded *4,6,7,2′-tetramethoxyaurone* (plates) (Found: C, 67·1; H, 5·2; OMe, 36·4. $C_{19}H_{18}O_6$ requires C, 66·7; H, 5·3; OMe 36·3%), m.p. 198–200°, and unreacted chalcone. The aurone was also prepared from the corresponding dihydrobenzofuranone[29] and aldehyde. Acidification of the alkaline filtrate yielded 5,7,8,2′-*tetra*methoxyflavonol (Found: C, 63·8; H, 5·0; OMe, 35·0. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·1; OMe, 34·6%), m.p. 199–200° (needles from methanol). The ethanolic ferric colour was dark green, λ_{max}^{MeOH} 352 mμ (+$AlCl_3$ 409 mμ)[63].

2′-Hydroxy-4,3′,4′,6′-tetramethoxychalcone (14).[39] The aurone m.p. 202° precipitated on addition of water to the reaction mixture. The aqueous sodium hydrogen carbonate extract yielded *4,6,7-trimethoxy-2-(*p*-methoxyphenyl)benzofuran-3-carboxylic acid* which separated from ethanol in microcrystals, m.p. 193–194°. The ethanolic ferric reaction was negative. (Found: C, 63·9; H, 5·1; OMe, 34·3. M.Wt. (alkali titration) 353. $C_{19}H_{18}O_7$ requires: C, 63·7; H, 5·1; OMe, 34·6%. M.Wt. 358). I.R. spectrum cm^{-1} 3525 (OH associated), 1681 (COOH), 1285 (OMe). When oxidation was repeated under the conditions described by Oliverio *et al.*[23] the products were aurone and *p*-methoxycinnamic acid (mixed m.p. and analysis).

Demethylation of 4,6,7,4′-tetramethoxyaurone. A mixture of the aurone (1 g), acetic acid (5 ml) and hydrogen bromide in acetic acid (5 ml; 60% HBr) was heated on a steam bath for 1 hr and poured into water. The precipitate of *4-hydroxy-6,7,4′-trimethoxyaurone* separated from ethanol in microcrystals (0·5 g), m.p. 218° (Found: C, 65·8; H, 4·9; OMe, 28·4. $C_{18}H_{16}O_6$ requires: C, 65·9; H, 4·9; OMe, 28·4%).

2′-Hydroxy-2,4,3′,4′,6′-pentamethoxychalcone (15). Dilution of the AFO reaction mixture precipitated *4,6,7,2′,4′-pentamethoxyaurone*, m.p. 187° (plates from ethanol) (Found: C, 64·5; H, 5·4; OMe, 41·1. $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4; OMe, 41·6%).

Acidification of the filtrate gave *5,7,8,2′,4′-pentamethoxyflavonol*, m.p. 208–210° (prisms from methanol) (Found: C, 61·7; H, 5·2; OMe, 39·3. $C_{20}H_{20}O_8$ requires: C, 61·9; H, 5·2; OMe, 40·0%). The ethanolic ferric colour was green.

2′-Hydroxy-2,6,3′,4′,6′-pentamethoxychalcone (16).[39b] Addition of water to the AFO reaction mixture precipitated *4,6,7,2′,6′-pentamethoxyaurone*, m.p. 188° (yellow prisms from ethanol). (Found: C, 64·3; H, 5·3; OMe, 41·4. $C_{20}H_{20}O_7$ requires: C, 64·5; H, 5·4; OMe, 41·6%). It was purified prior to crystallization by elution from alumina by benzene.

2′-Hydroxy-2,4,6,3′,4′,6′-hexamethoxychalcone (17). Addition of water to the AFO product gave a solid from which by repeated crystallization from methanol a trace of a compound m.p. 204–205° was obtained. (Found: C, 60·2; H, 6·0; OMe, 43·9. $C_{21}H_{24}O_9$ requires: C, 60·0; H, 5·8; OMe, 44·4%). The crystals were coloured red by sulphuric acid and the ethanolic ferric reaction was negative. The compound was probably 2-hydroxy-2-(2,4,6-trimethoxybenzyl)-4,6,7-trimethoxydihydrobenzofuran-3-one.

2′-Hydroxy-4,4′,5′,6′-tetramethoxychalcone (18).[39] After AFO oxidation in the cold[5] the reaction mixture was diluted with water and extracted with ether. The extract contained 4,5,6,4′-tetramethoxyaurone, m.p. 147–148° (yellow needles from ethanol) (Found: C, 66·1; H, 5·3; OMe, 35·7. Calc. for $C_{19}H_{18}O_6$: C, 66·7; H, 5·3; OMe, 36·3%). The ethanolic ferric reaction was negative and the crystals were coloured red by treatment with sulphuric acid.

A solution of the chalcone (2·5 g) in chloroform (10 ml) was treated at 0° with bromine (1·6 g) in chloroform (10 ml) and after 24 hr the mixture was concentrated to 5 ml to precipitate *2,3-dibromo-1-(6-hydroxy-2,3,4-trimethoxyphenyl)-3-(*p*-methoxyphenyl)propan-1-one*, m.p. 149–150° (yellow needles from chloroform) (Found: C, 45·7; H, 4·2; OMe, 24·4. $C_{19}H_{20}Br_2O_6$ requires: C, 45·2; H, 4·0; OMe, 24·6%).

A boiling solution of the dibromide (2 g) in ethanol (10 ml) was treated with aqueous potassium hydroxide (3 ml; 20%). 4,5,6,4′-Tetramethoxyaurone, m.p. and mixed m.p. with the AFO product, 147–148°, separated on cooling. Shriner *et al.*[29] give m.p. 148–149°.

When oxidation was carried out at the b.p. of the solvent, ethereal extraction of the reaction product after dilution with water afforded the aurone as before. The diluted alkaline solution was treated with carbon dioxide to precipitate a yellow solid which was acetylated. The product, 3-*acetoxy-5,6,7,4′-tetramethoxyflavone*, separated from ethanol in needles, m.p. 90° and 150° after solidification. When crystallized from benzene the m.p. was 150° (Found: C, 63·0; H, 5·0. $C_{21}H_{20}O_8$ requires: C, 63·0; H, 5·0%).

The acetate when refluxed with ethanolic conc hydrochloric acid gave 5,6,7,4′-tetramethoxyflavonol, m.p. 134–135°; the ethanolic ferric colour was brown and the solution in conc sulphuric acid exhibited a yellowish green fluorescence in U.V. light. (Found: C, 64·0; H, 4·9; OMe, 34·3. Calc. for $C_{19}H_{18}O_7$: C, 63·7; H, 5·1; OMe, 34·6%). Methylation afforded 3,5,6,7,4′-pentamethoxyflavone, m.p. 153–154° cf. lit.[5,31,32] (plates from ethanol).

The alkaline layer after treatment with carbon dioxide gave on further acidification crude anisic acid, m.p. 169–172°; the mixed m.p. with an authentic sample (m.p. 180–182°) was 176–179°.

Repetition of the preparation of 5,6,7,4′-tetramethoxyflavonol from the flavanone through the isonitrosocompound[5] gave a solution which was diluted with water and extracted with ether. The extract was treated with aqueous sodium hydroxide (10%) and the alkaline layer acidified. The precipitate on fractional crystallization from ethanol gave anisic acid (5 pt.) and 5,6,7,4′-tetramethoxyflavonol (1 pt.); the structures were confirmed by the mixed m.p.'s with authentic specimens.

2′-Hydroxy-5′-methoxy-3′-nitrochalcone (19). The reaction mixture was acidified to precipitate *6-methoxy-8-nitroflavonol*, m.p. 225–227° (yellow needles from acetic acid) (Found: C, 60·7; H, 3·8; N, 4·7; OMe, 9·7. $C_{16}H_{11}NO_6$ requires: C, 61·3; H, 3·5; N, 4·5; OMe, 9·9%). The ethanolic ferric colour was reddish-brown. The *acetate* had m.p. 229° (needles from acetic acid) (Found: C, 60·9; H, 4·0; N, 4·3; OMe, 8·8; $C_{18}H_{13}NO_7$ requires: C, 60·9; H, 3·7; N, 3·9; OMe, 8·7%).

2′-Hydroxy-4′,6′-dimethoxy-3-nitrochalcone (20). Dilution of the reaction mixture with water gave *4,6-dimethoxy-3′-nitroaurone*, m.p. 231°, (needles from acetic acid). (Found: C, 62·4; H, 4·1; N, 3·8; OMe, 18·7. $C_{17}H_{13}NO_6$ requires: C, 62·4; H, 4·0; N, 4·3; OMe, 19·0%).