737. *The Course of the Algar–Flynn–Oyamada (A.F.O.) Reaction*

By F. M. Dean and Verapong Podimuang

It is proposed that the course of the oxidation, by alkaline hydrogen peroxide, of derivatives of 2′-hydroxychalcone to flavonoids is a combination of cyclisation and oxidation not involving epoxides. For the alternative reaction leading to aurones the accepted route through epoxide intermediates is retained and supported. It is shown that the latter reaction can be diverted into a synthesis of isoflavones, and that 4′-hydroxyaurones are conveniently prepared by the ferricyanide oxidation of 2′,4-dihydroxychalcones.

Investigations by Oyamada,[1] Algar and Flynn,[2] and others [3,4] have demonstrated that alkaline hydrogen peroxide converts 2′-hydroxychalcone (I) firstly into 3-hydroxyflavanone (II) and then into flavonol (III). The reaction affords an important general synthesis of flavonoids.[5,6] It is widely believed [5-9] that an epoxide is formed initially and undergoes spontaneous internal substitution at the β-position giving the 3-hydroxyflavanone (route A), and that the presence in the chalcone of a 6′-substituent directs the substitution to the α-position (route B), thus accounting for the formation of derivatives of aurone (IV). While our evidence supports this view of the origin of aurones, it strongly indicates that epoxides are not intermediates in the formation of flavonoids. Instead, we suggest that the pyrone ring is produced either before oxidation (route C) or concurrently with it (route D).

The epoxidation of non-phenolic chalcones being well known,[10] it has been assumed

[1] T. Oyamada, *J. Chem. Soc. Japan*, 1934, **55**, 1256.
[2] J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad.*, 1934, **42***B*, 1.
[3] M. Murakami and T. Irie, *Proc. Imp. Acad.* (*Tokyo*), 1935, **11**, 229.
[4] L. Reichel and J. Steudel, *Annalen*, 1942, **553**, 83.
[5] (*a*) T. S. Wheeler, *Rec. Chem. Progr.*, 1957, **18**, 133; (*b*) E. M. Philbin and T. S. Wheeler, "Recent Progress in the Chemistry of Natural and Synthetic Colouring Matters," eds. T. S. Gore, B. S. Joshi, S. V. Suntharkar, and B. D. Tilak, Academic Press, New York, 1952, p. 167.
[6] T. R. Seshadri, "The Chemistry of Flavonoid Compounds," ed. T. A. Geissman, Pergamon Press, Oxford, 1962, p. 156; F. M. Dean, "Naturally Occurring Oxygen Ring Compounds," Butterworths, London, 1963, p. 337.
[7] G. B. Marini-Bettoló, *Gazzetta*, 1942, **72**, 201.
[8] T. A. Geissman and D. K. Fukushima, *J. Amer. Chem. Soc.*, 1948, **70**, 1686.
[9] M. G. Marathey, (*a*) *Science and Culture*, 1954, **20**, 135; (*b*) *J. Univ. Poona, Sci. Technol.*, 1954, No. 6, 87.
[10] E. Weitz and A. Scheffer, *Ber.*, 1921, **54***B*, 2327.

that phenolic chalcones would behave similarly, and failures [11] to isolate epoxides from A.F.O. reactions have been attributed to the relative rapidity of the subsequent cyclisations (routes A and B). According to Bunton and Minkoff,[12] however, the epoxidation of α,β-unsaturated ketones requires an attack at the β-position by hydroperoxide anion (route E), and this would be difficult in phenolic chalcones, such as (I), because the strongly alkaline conditions would convert them into anions and consequently there would be coulombic repulsion of the reagent as well as internal electronic inactivation as indicated in structure (V). To test this point we chose chalcone derivatives, *e.g.*, (VI; R = H or Me), in which epoxidation could not be obscured by subsequent cyclisation. The derivatives mentioned suffered only slow, general oxidation without giving epoxides, and phenolic chalcones (VII) and (VIII) behaved similarly showing that inactivation could be achieved from the other end of the molecule. Hence, epoxides can be intermediates in A.F.O. reactions only if, for some reason, the foregoing considerations are not applicable to 2′-hydroxychalcones. Even this remote possibility seems excluded by the ready conversion of dihydroxychalcones into hydroxyflavonoids; we have confirmed, for example, that despite its possession of two hydroxyl groups, either of which should be enough to prevent epoxidation, 2,2′-dihydroxychalcone (IX) smoothly affords 2′,3-dihydroxyflavone [13] (X). We conclude that epoxides normally play no part in the A.F.O. reaction.

Further evidence against epoxidation was obtained from the chalcone derivative (XI) in which approach to the β-position is hindered by methyl groups at positions 2 and 6, and which is correspondingly difficult to isomerise to the flavanone. In the derived epoxide (XII), steric hindrance to cyclisation (as in route A) should be still greater, since the transition state now requires the β-carbon atom to be surrounded by five atoms as opposed to four in the flavanone transition state. If formed, then, this epoxide should cyclise by α-substitution and yield an aurone derivative by route B despite the absence of a 6′-substituent. In fact, the slow oxidation of chalcone (XI) gave a flavonol.

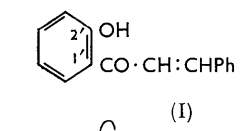
We suggest that, in normal A.F.O. reactions, cyclisation precedes oxidation as in route C or is synchronised with it as in route D. Such courses are a combination of the 2′-hydroxychalcone–flavanone interconversion [6] on the one hand, with nucleophilic substitution at peroxide oxygen [14] on the other. They make clear why only 2′-hydroxychalcones are attacked by the reagent in a specific fashion, and why the products have six- and not five-membered heterocyclic rings, even when obtained from compounds such as (IX) and (XI).

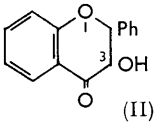
There is no plausible way of modifying the new routes so as to account for the behaviour of 6′-substituted chalcones in giving aurone derivatives.[8,15,16] However, the appropriate model chalcone is now compound (XIII) instead of those considered above, and it readily affords the epoxide (XIV) when treated with alkaline hydrogen peroxide. Although coulombic repulsion must still exist, the carbonyl group is protected from an inactivating interaction parallel to that in compound (V) because it is prevented for steric reasons from attaining coplanarity with the phenolic ring, thus permitting the Bunton–Minkoff mechanism to operate again.

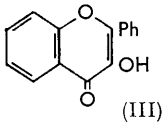
While this fact allows the retention of epoxide intermediates for aurone formation, it is still necessary to account for selective substitution at the α-position (route B). By an indirect method, Marathey [9a] prepared epoxide (XV) which, in basic media, was hydrolysed and cyclised to the 3-hydroxyflavanone (XVI) thus showing that, in the absence of special effects, β-substitution would predominate. Hence the 6′-substituent

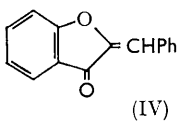
[11] H. Grisebach, " Recent Developments in the Chemistry of Natural Phenolic Compounds," ed. W. D. Ollis, Pergamon Press, London, 1961, p. 59.
[12] C. A. Bunton and G. J. Minkoff, *J.*, 1949, 665.
[13] T. H. Simpson and W. B. Whalley, *J.*, 1955, 166.
[14] J. O. Edwards, " Peroxide Reaction Mechanisms," ed. J. O. Edwards, Interscience, New York, 1962, p. 67.
[15] N. Narasimhachari, D. Rajagopalan, and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1953, **37**, 705, and other Papers in the Series.
[16] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1949, **30**, 216.

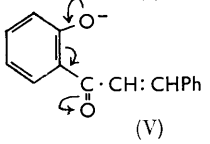
directs not only the initial production of an epoxide but also the subsequent ring-closure. One consideration is that the rotation of the carbonyl group out of the plane of the phenolic ring increases the distance of the phenolic oxygen atom from the β-position more than that from the α-position; another is the steric repulsion between the 6′-substituent and the

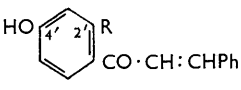

(I)

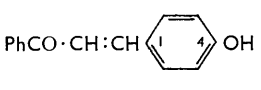

(II)

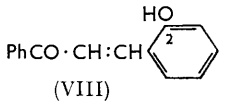

(III)

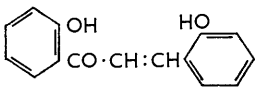

(IV)

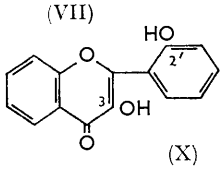

(V)

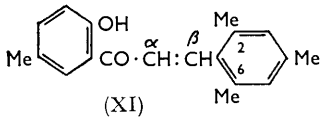

(VI)

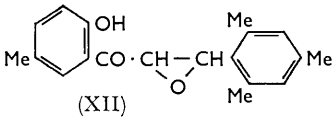

(VII)

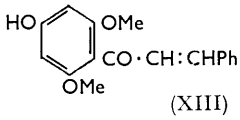

(VIII)

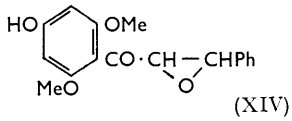

(IX)

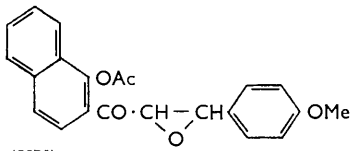

(X)

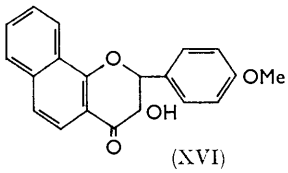

(XI)

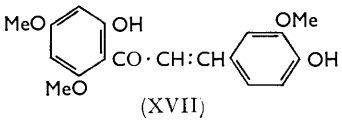

(XII)

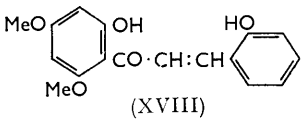

(XIII)

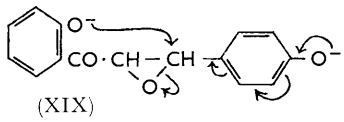

(XIV)


(XV)


(XVI)


(XVII)


(XVIII)


(XIX)

carbonyl oxygen, which favours the product with the smaller heterocyclic ring.[17] Such effects are not large and, even at the lower temperatures usually employed, aurones are accompanied by small amounts of the corresponding flavonoids. At temperatures about 20° higher, flavonoids are again the chief products,[18] as would be expected since the importance of small steric effects dwindles rapidly as the temperature rises. In certain limited circumstances, therefore, route A remains acceptable.

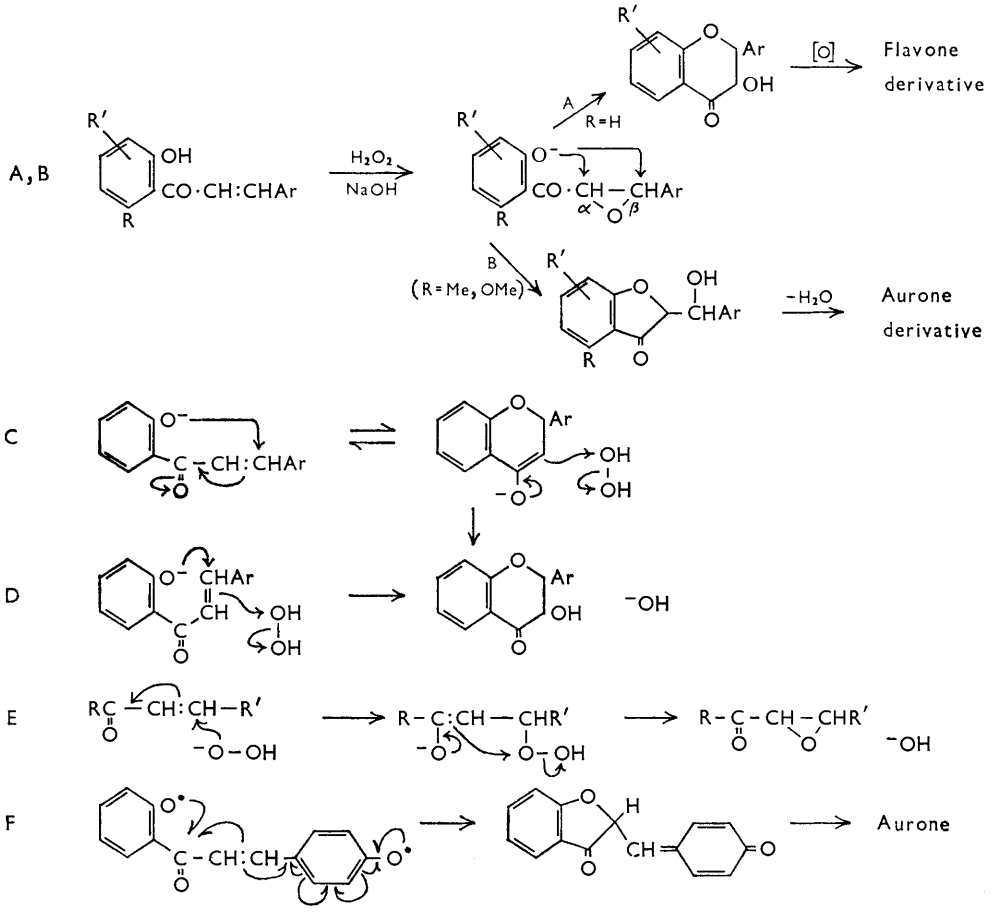
Flavonoids are the only products obtainable from 6′-substituted chalcones such as (XVII) and (XVIII), a reversion for which the free phenolic hydroxyl groups are responsible.[13,19] Epoxide intermediates being assumed, it has been suggested that electronic interactions of the type depicted in structure (XIX) might account for the phenomenon,[5b] but our finding that the 3-hydroxychalcone (XX) yields the flavone derivative (XXI) and not an aurone cannot be explained thus. Moreover, this observation indicates that the reversion is not primarily a result of internal electronic interactions. Instead, we regard coulombic repulsions as the decisive factor. These dihydroxychalcones would exist mainly as doubly charged anions, strongly repelling attack by hydroperoxide anions, and route B would be accordingly unfavourable. In contrast, routes C and D

[17] K. P. Barr, F. M. Dean, and H. D. Locksley, *J.*, 1959, 2425.
[18] E. M. Philbin, J. Swirski, and T. S. Wheeler, *Chem. and Ind.*, 1956, 1018.
[19] N. Anand, R. N. Iyer, and K. Venkataraman, *Proc. Indian Acad. Sci.*, 1949, **29***A*, 203.

necessitate only the approach of a neutral hydrogen peroxide molecule and, moreover, the dianion eliminates one of its charges as an integral part of the process (especially in route D) which should be promoted thereby.

According to route B, aurones are derived from β-hydroxy-ketones which undergo

Routes for oxidation of chalcones



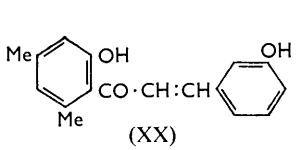
spontaneous dehydration. In support of this view, the α-methylchalcone (XXII) has been found to give the stable secondary alcohol (XXIII), which was differentiated from the isomeric tertiary alcohol (XXIV) by its absorption at 1715 cm.$^{-1}$, typical of β-coumaranones, and also by the ^{1}H resonance spectrum (in $CHCl_3$) which contained a one-proton singlet at τ 5·12, appearing in the acetate at τ 4·02.

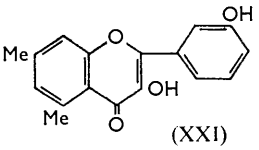
Sulphuric acid dehydrated the alcohol (XXIII), giving the isoflavone derivative (XXV) different from 3,5,7-trimethylflavone and further identified by an alternative synthesis. This transformation seems to involve the acyl migration shown in structure (XXVI), which is supported by tracer studies in related series;[20] and it offers a method of making isoflavones that is being examined further because it does not need the protecting groups essential in parallel techniques.[20,21]

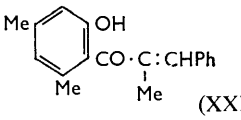
[20] H. O. House, D. J. Reif, and R. L. Wasson, *J. Amer. Chem. Soc.*, 1957, **79**, 2490, and other Papers in this Series.

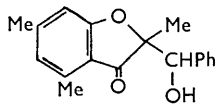
[21] J. Algar and J. McKenna, *Proc. Roy. Irish Acad.*, 1944, **49***B*, 15, 225.

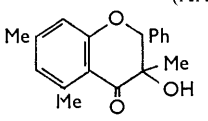
Following work by Marini-Bettoló,[7] we converted the chalcone vinylogue (XXVII) into the 3-hydroxychromone (XXVIII) by means of alkaline hydrogen peroxide. Our intention of extending the correspondence with the A.F.O. reaction by converting the homologue (XXIX) into the coumaranone derivative (XXX) could not be realised because

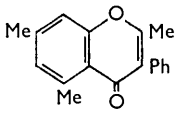

(XX)

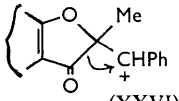

(XXI)

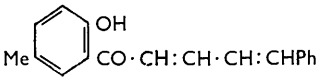

(XXII)

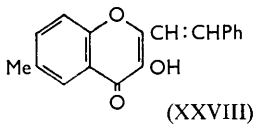

(XXIII)

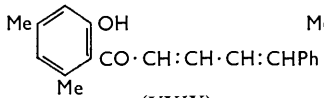

(XXIV)

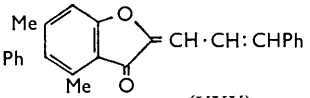

(XXV)

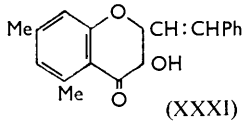

(XXVI)

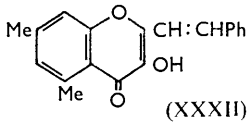

(XXVII)

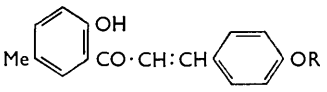

(XXVIII)

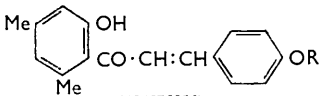

(XXIX)

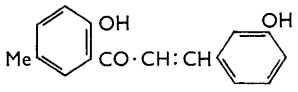

(XXX)

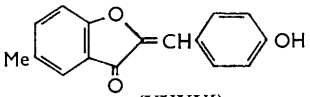

(XXXI)

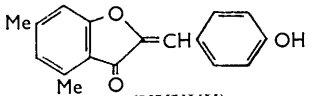

(XXXII)


(XXXIII)


(XXXIV)


(XXXV)


(XXXVI)


(XXXVII)

there was no reaction at the lower temperature needed for this result. At higher temperatures the products were the 3-hydroxychromanone (XXXI) and the derived chromone (XXXII).

Finally, we excluded the possibility that the above results could be related to radical reactions of the kind induced by alkaline ferricyanide. In contrast with alkaline hydrogen peroxide, this oxidant failed to attack the chalcone derivatives (XXXIII; R = Me), (XXXIV; R = Me), (XXXV), and (XX). However, it converted the derivatives (XXXIII; R = H) and (XXXIV; R = H) into the aurone derivatives (XXXVI) and (XXXVII), respectively, presumably through route F which is analogous to that assumed to underlie the conversion of polyhydroxybenzophenones into derivatives of grisan.[22] Thus, ferricyanide oxidations do not occur unless there is a free hydroxyl group at the 4-position in the 2′-hydroxychalcone, and the products are always aurones. The characteristics are completely different from those of the A.F.O. reaction which, in particular, never affords 4′-hydroxyaurones, and the new method is therefore a useful synthetical supplement to the old.

[22] C. H. Hassall and A. I. Scott, " Recent Developments in the Chemistry of Natural Phenolic Products," ed. W. D. Ollis, Pergamon Press, London, 1961, 119; J. R. Lewis, *Chem. and Ind.*, 1962, 159.

Experimental

Chalcones.—The chalcones (Table 1) were generally prepared by interaction of the acetophenone (0·02 mole) and the benzaldehyde (0·02 mole) in methanol (15 ml.) and 50% aqueous sodium hydroxide (12 ml.) at 0° for 10 hr. The products were isolated by acidification with ice and hydrochloric acid and purified from methanol or aqueous acetic acid. They were all yellow, and crystallised in needles, except for nos. 12 and 15, which formed plates, and no. 17, which formed rhombs. All the 2′-hydroxychalcones gave brown colours with ethanolic ferric chloride.

The condensation of 2-hydroxy-4,6-dimethylacetophenone and 3,4-dimethoxybenzaldehyde appeared to supply 2′-hydroxy-3,4-dimethoxy-4,6′-dimethylchalcone as the main product but this could not be separated from the isomeric 3′,4′-dimethoxy-5,7-dimethylflavanone formed simultaneously.

For chalcones nos. 3, 11, and 12 the condensation was allowed to continue for 3 days. For chalcones nos. 6 and 7 the condensation was effected at −10° and stopped after 6 hr.

Table 1

Chalcones

No.	Chalcone	Substituents in acetophenone	Substituents in benzaldehyde	M. p.	Yield (g.)
1	2′-Hydroxy-2,4,5′-trimethyl	2-Hydroxy-5-methyl	2,4-Dimethyl	107°	3·4
2	2′-Hydroxy-2,4,5′,6-tetramethyl	2-Hydroxy-5-methyl	2,4,6-Trimethyl	97	4·8
3	2′,4-Dihydroxy-5-methyl	2-Hydroxy-5-methyl	4-Hydroxy	172	2·1
4	2′-Hydroxy-2,4,6-trimethoxy-5′-methyl	2-Hydroxy-5-methyl	2,4,6-Trimethoxy	160	3·0
5	2′,3-Dihydroxy-5′-methyl	2-Hydroxy-5-methyl	3-Hydroxy	160	3·2
6	2′-Hydroxy-5′-methyl-4-nitro	2-Hydroxy-5-methyl	4-Nitro	205	2·3
7	2′-Hydroxy-5′-methyl-3-nitro	2-Hydroxy-5-methyl	3-Nitro	187	2·9
8	2′-Hydroxy-2,2′,4,6-tetramethyl	2-Hydroxy-4-methyl	2,4,6-Trimethyl	94	4·4
9	2′-Hydroxy-3,4-dimethoxy-4′-methyl	2-Hydroxy-4-methyl	3,4-Dimethoxy	138	4·3
10	2′-Hydroxy-2,4,4′,6,6′-pentamethyl	2-Hydroxy-4,6-dimethyl	2,4,6-Trimethyl	95	4·3
11	2′,4-Dihydroxy-4′,6′-dimethyl	2-Hydroxy-4,6-dimethyl	4-Hydroxy	135	4·1
12	2′,4′-Dihydroxy-3-methoxy-4,6-dimethyl	2-Hydroxy-4,6-dimethyl	4-Hydroxy-3-methoxy	148	3·9
13	2′,3-Dihydroxy-4′,6′-dimethyl	2-Hydroxy-4,6-dimethyl	3-Hydroxy	153	3·0
14	2′,3-Dihydroxy-4,4′-dimethoxy	2-Hydroxy-4-methoxy	3-Hydroxy-4-methoxy	168	3·4
15	2′-Hydroxy-3,4,4′-trimethoxy-6′-methyl	2-Hydroxy-4-methoxy-6-methyl	3,4-Dimethoxy	118	3·7
16	3-Hydroxy-4-methoxy-4′-methyl	4-Methyl	3-Hydroxy-4-methoxy	121	3·9
17	4′-Hydroxy-2′,6′-dimethoxy	4-Hydroxy-2,6-dimethoxy	None	152	

Analytical data

Chalcone no.	Found (%) C	H	Formula	Reqd. (%) C	H	Chalcone no.	Found (%) C	H	Formula	Reqd. (%) C	H
1	81·3	6·95	$C_{18}H_{18}O_2$	81·2	6·8	10	81·6	7·35	$C_{20}H_{22}O_2$	81·6	7·5
2	81·3	7·1	$C_{19}H_{20}O_2$	81·4	7·2	11	75·8	5·7	$C_{17}H_{16}O_3$	76·1	6·0
3	75·2	5·3	$C_{16}H_{14}O_3$	75·6	5·5	12	72·1	6·1	$C_{18}H_{18}O_4$	72·5	6·0
4	69·4	5·85	$C_{19}H_{20}O_5$	69·5	6·1	13	76·0	6·0	$C_{19}H_{16}O_3$	76·1	6·0
5	75·1	5·5	$C_{16}H_{14}O_3$	74·8	5·5	14	67·5	6·0	$C_{17}H_{16}O_5$	68·0	5·4
6	68·0	4·4	$C_{16}H_{13}NO_4$	67·8	4·6 [a]	15	69·3	6·1	$C_{19}H_{20}O_5$	69·5	6·1
7	68·0	4·7	$C_{16}H_{13}NO_4$	67·8	4·6 [b]	16	75·6	6·0	$C_{17}H_{16}O_3$	76·1	6·0
8	80·9	7·2	$C_{19}H_{20}O_2$	81·4	7·2	17	72·0	5·6	$C_{17}H_{16}O_4$	71·8	5·7
9	72·4	6·1	$C_{18}H_{18}O_4$	72·5	6·0						

[a] Found: N, 5·0. $C_{16}H_{13}NO_4$ requires N, 49%. [b] Found: N, 4·8. $C_{16}H_{13}NO_4$ requires N, 4·9%.

Aurones.—The aurones (Table 2) were prepared by condensing the appropriate coumaran-3-one (0·025 mole) with a benzaldehyde (0·025 mole) in acetic acid (25 ml.) containing concentrated hydrochloric acid (2 ml.). The reaction was usually complete in 5 hr. and the aurones were isolated by pouring the mixture into water and crystallising the precipitate from methanol or acetic acid. The yields exceeded 70%. Aurones nos. 2, 4, and 5 formed plates, the others formed needles; all were yellow.

TABLE 2

Aurones

No.	Aurone	Substituents in coumaran-3-one	Substituents in benzaldehyde	M. p.	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
1	2′,4′,5-Trimethyl	5-Methyl	2,4-Dimethyl	157°	81·7	6·1	$C_{18}H_{16}O_2$	81·8	6·1
2	2′,4′,5,6′-Tetramethyl	5-Methyl	2,4,6-Trimethyl	120	82·0	6·6	$C_{19}H_{18}O_2$	82·0	6·5
3	4′-Hydroxy-5-methyl	5-Methyl	4-Hydroxy	270	75·8	4·7	$C_{16}H_{12}O_3$	76·2	4·8
4	3′-Nitro-5-methyl	5-Methyl	3-Nitro	205	68·0	4·0	$C_{16}H_{11}O_4N$	68·3	4·0[a]
5	3′-Hydroxy-4,6-dimethyl	4,6-Dimethyl	3-Hydroxy	235	76·4	5·3	$C_{17}H_{14}O_3$	76·7	5·3
6	4′-Hydroxy-4,6-dimethyl	4,6-Dimethyl	4-Hydroxy	273	76·5	5·1	$C_{17}H_{14}O_3$	76·7	5·3
7	4′-Methoxy-4,6-dimethyl	4,6-Dimethyl	4-Methoxy	164	77·2	5·8	$C_{18}H_{16}O_3$	77·1	5·75
8	3′,4′-Dimethoxy-4,6-dimethyl	4,6-Dimethyl	3,4-Dimethoxy	165	73·5	5·8	$C_{19}H_{18}O_4$	73·6	5·8

[a] Found: N, 5·2. $C_{16}H_{11}O_4N$ requires N, 5·0%.

Flavanones.—The 2′-hydroxychalcone derivative (1·0 g.) in ethanol (50 ml.) was treated with 6N-aqueous hydrogen chloride (10 ml.) and kept at the b. p. for 6 hr. The flavanone separated on cooling and was purified from methanol or aqueous acetic acid. The flavanones listed (Table 3) all crystallised as needles.

TABLE 3

Flavanones

Chalcone no.	Flavanone	M. p.	Yield (g.)	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
1	2′,4′,6-Trimethyl	117°	0·60	81·3	6·8	$C_{18}H_{18}O_2$	81·2	6·8
2	2′,4′,6,6′-Tetramethyl	114	0·25	81·3	7·1	$C_{19}H_{20}O_2$	81·4	7·2
11	4′-Hydroxy-5,7-dimethyl	183	0·71	76·1	6·1	$C_{17}H_{16}O_3$	76·1	6·0
12	4′-Hydroxy-3′-methoxy-5,7-dimethyl	98	0·42	72·3	6·0	$C_{18}H_{18}O_4$	72·5	6·0

3′,4′-*Dimethoxy*-5,7-*dimethylflavanone.* The crude 2′-hydroxy-3,4-dimethoxy-5′,7′-dimethylchalcone (1·0 g.) mentioned above was treated as were the pure chalcones above. The *flavanone* crystallised from ethanol as needles (0·9 g.), m. p. 123° (Found: C, 73·1; H, 6·45%).

Ferricyanide Oxidations.—Solutions of 2′,4-dihydroxy-4′,6′-dimethylchalcone (3·0 g.) in 2N-aqueous sodium hydroxide (20 ml.) and of potassium ferricyanide (7·0 g.) in water (100 ml.) were stirred together and next day the mixture was acidified with acetic acid. The precipitate was washed with water until tests for ferricyanide ion were negative, and then purified from methanol and then acetic acid giving 4′-hydroxy-4,6-dimethylaurone as yellow needles (1·8 g.), m. p. 272°, identified spectroscopically.

Similarly 2′,4-dihydroxy-5-methylchalcone (3·0 g.) gave 4′-hydroxy-5-methylaurone, which crystallised from acetic acid as yellow needles (2·2 g.), m. p. 272°, identified spectroscopically. 2′-Hydroxy-4-methoxy-4′,6′-dimethylchalcone, 2′,3-dihydroxy-5′-methylchalcone, and 2′,3-dihydroxy-4′,6′-dimethylchalcone were recovered from parallel oxidations.

2-(4-*Hydroxy*-2,6-*dimethoxybenzoyl*)-3-*phenyloxiran* (XIV).—A solution of 4′-hydroxy-2,6-dimethoxychalcone (0·5 g.) in hot methanol (10 ml.) was cooled to about 20° and, before crystallisation began, 15% hydrogen peroxide (1·5 ml.) and 2N-aqueous sodium hydroxide (2 ml.) were added. After 20 min. the mixture was acidified with dilute nitric acid and the product was crystallised from methanol giving the *oxiran* as plates (0·3 g.), m. p. 201°, devoid

of a ferric reaction (Found: C, 68·0; H, 5·3. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%); $\nu_{max.}$ (Nujol) 1660 cm.$^{-1}$ and, in pyridine, τ 6·32 (singlet, relative intensity 6) assigned to methoxyl protons, and τ 5·61 (multiplet, relative intensity 2) assigned to oxiran protons, but no other aliphatic proton resonance.

Algar–Flynn–Oyamada Reactions.—In general, the 2′-hydroxychalcone (2·0 g.) in a mixture of methanol (20 ml.) and 20% aqueous sodium hydroxide (10 ml.) was kept at 0—5° while 30% hydrogen peroxide (4 ml.) was stirred in. After 8 hr. in ice, the product was liberated by ice-cold acetic acid, washed with water, and crystallised from methanol or dilute acetic acid. The 3-hydroxyflavones so made are listed in Table 4; those with hydroxyl groups at positions 3′ or 4′ were purified from acetic acid and formed plates, the others were purified from methanol or ethanol and formed needles. The nitro-compounds were yellow, otherwise these flavones were very faintly yellow. All gave violet colours with ethanolic ferric chloride and orange or brown colours in the Shinoda test.

In two instances the oxidation gave not a flavone but an aurone, which separated as the reaction proceeded and was purified from methanol. Thus, 2′-hydroxy-3,4,4′-trimethoxy-6′-methylchalcone afforded 3′,4′,6-*trimethoxy*-4-*methylaurone*, which formed yellow needles (0·8 g.), m. p. 185° (Found: C, 70·2; H, 5·2. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·6%). Since the appropriate chalcone was not available in a pure state, the isomeric flavanone was used for

TABLE 4

Flavones

Chalcone	Substituents in flavone	M. p.	Yield (g.)	Found (%) C	Found (%) H	Formula	Reqd. (%) C	Reqd. (%) H
1	3-Hydroxy-2′,4,6-trimethyl	167°	1·6	77·2	5·9	$C_{18}H_{16}O_3$	77·1	5·7
	acetate	121		74·8	5·5	$C_{20}H_{18}O_4$	74·5	5·6
2	3-Hydroxy-2′,4′,6,6′-tetramethyl	169	1·1	77·4	6·25	$C_{19}H_{18}O_3$	77·55	6·1
	acetate [a]	187		24·9	5·7	$C_{21}H_{20}O_4$	75·0	6·0
3	3,4′-Dihydroxy-6-methyl	291	1·5	71·5	4·4	$C_{16}H_{12}O_4$	71·6	4·5
	diacetate	166		68·2	4·45	$C_{20}H_{16}O_6$	68·2	4·5
4	3-Hydroxy-2′,4′,6′-trimethoxy-6-methyl	239	0·8	66·7	5·3	$C_{19}H_{18}O_6$	66·2	5·3
	acetate [b]	225		65·3	5·0	$C_{21}H_{20}O_7$	65·3	5·2
5	3,3′-Dihydroxy-6-methyl	235	1·6	71·3	4·5	$C_{16}H_{12}O_4$	71·6	4·5
	diacetate	149		68·3	4·6	$C_{20}H_{16}O_6$	68·2	4·5
6	3-Hydroxy-6-methyl-4′-nitro	207	0·4	64·4	3·4	$C_{16}H_{11}NO_5$ [c]	64·6	3·7
	acetate	215		63·8	3·9	$C_{18}H_{13}NO_6$ [d]	63·7	3·8
7	3-Hydroxy-6-methyl-3′-nitro	211	1·3	64·45	3·7	$C_{16}H_{11}NO_5$ [e]	64·6	3·7
	acetate	181		63·7	3·7	$C_{18}H_{13}NO_6$ [f]	63·7	3·8
8	3-Hydroxy-2′,4′,6′,7-tetramethyl	202	1·6	77·2	6·2	$C_{19}H_{18}O_3$	77·55	6·1
	acetate [b]	163		74·5	5·9	$C_{21}H_{20}O_4$	75·0	6·0
9	3-Hydroxy-3′,4′-dimethoxy-7-methyl	185	1·1	69·1	5·2	$C_{18}H_{16}O_5$	69·2	5·1
	acetate	185		67·6	5·05	$C_{20}H_{18}O_6$	67·8	5·1
11	3,4′-Dihydroxy-5,7-dimethyl [g]	274	1·4	72·1	4·9	$C_{17}H_{14}O_4$	72·3	5·0
	diacetate	159		68·6	4·9	$C_{21}H_{18}O_6$	68·5	4·9
12	3,4′-Dihydroxy-3′-methoxy-5,7-dimethyl [g]	214	1·0	69·2	5·0	$C_{18}H_{16}O_5$	69·2	5·1
	diacetate	180		66·2	5·1	$C_{22}H_{20}O_7$	66·7	5·05
13	3,3′-Dihydroxy-5,7-dimethyl [d]	210	1·4	72·4	5·0	$C_{17}H_{14}O_4$	72·3	5·0
	diacetate	132		68·9	5·1	$C_{21}H_{18}O_6$	68·85	4·9
14	3,3′-Dihydroxy-4′,7′-dimethoxy	188	1·1	65·0	4·5	$C_{17}H_{14}O_6$	65·0	4·45
	diacetate	187		63·8	4·65	$C_{21}H_{18}O_8$	63·8	4·5

[a] Neutralisation of the reaction mixture instead of acidification furnished the *sodium salt*, which crystallised from ethanol as yellow needles, m. p. 154—160° (decomp.) (Found: C, 72·2; H, 5·9. $C_{19}H_{17}O_3Na$ requires C, 72·2; H, 5·4%). [b] Rhombs from methanol. [c] Found: N, 4·75. $C_{16}H_{11}NO_5$ requires N, 4·7%. [d] Found: N, 4·0. $C_{18}H_{13}NO_6$ requires N, 4·1%. [e] Found: N, 4·6%. [f] Found: N, 4·1%. [g] Oxidation conducted for 12 hr. at 5° or 4 hr. at 20°.

the second oxidation; 3′,4′-dimethoxy-5,7-dimethylflavanone supplied 3′,4′-dimethoxy-4,6-dimethylaurone which formed yellow plates (1·5 g.), m. p. and mixed m. p. 165°, further identified spectroscopically. The acetates listed were prepared by the acetic anhydride–pyridine technique, and purified from methanol, from which most of them separated as needles.

2-α-*Hydroxybenzyl*-2,4,6-*trimethylcoumaran*-3-*one* (XXIII).—Aqueous sodium hydroxide (50%; 25 ml.) was added slowly to a stirred solution of 2-hydroxy-4,6-dimethylpropiophenone

(6·7 g.) and benzaldehyde (4·0 g.) in methanol (20 ml.) cooled in ice. After 10 hr. at 5°, the mixture was acidified with ice-cold 2N-hydrochloric acid and the precipitate was crystallised from methanol giving *2′-hydroxy-α,4′,6′-trimethylchalcone* (XXII) as pale yellow needles (6·2 g.), m. p. 122°, having a pale brown ferric reaction (Found: C, 81·1; H, 6·8. $C_{18}H_{18}O_2$ requires C, 81·2, 6·8%). This chalcone (1·0 g.) in methanol (10 ml.) and 20% aqueous sodium hydroxide (5 ml.) was cooled in ice and treated with 30% hydrogen peroxide during 1 hr. The mixture was kept for 8 hr. at 3° and acidified with acetic acid. When crystallised from benzene–light petroleum (b. p. 40—60°), the solid product afforded the *2-α-hydroxybenzylcoumaranone* as plates (0·48 g.), m. p. 109—111°, devoid of a ferric reaction (Found: C, 76·5; H, 6·35. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). The *acetate* (acetic anhydride–pyridine method) separated from methanol as plates, m. p. 89·5° (Found: C, 74·3; H, 6·1. $C_{20}H_{20}O_4$ requires C, 74·05; H, 6·2%).

2,5,7-Trimethylisoflavone (XXV).—(*a*) The foregoing 2-α-hydroxybenzylcoumaranone (0·3 g.) in acetic acid (2 ml.) was treated with sulphuric acid (0·5 ml.) and warmed on a steam-bath for 10 min. Poured on to ice (75 g.), the mixture gave a gum that was stirred with water until it solidified. The solid was washed with water, dried in air, and crystallised from benzene–light petroleum (b. p. 40—60°) giving the *isoflavone* as needles (0·21 g.), m. p. 124°, insoluble in alkali and having no ferric reaction (Found: C, 81·5; H, 6·0. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

(*b*) Benzyl 2-hydroxy-4,6-dimethylphenyl ketone (6 g.), acetic anhydride (6 g.), and sodium acetate (3 g.) were heated, under reflux, at 120—140° for 7 hr., cooled, and diluted with water (100 ml.). When purified from methanol, the precipitate supplied the isoflavone as needles (4·1 g.), m. p. and mixed m. p. 124°. Specimens prepared by the two methods had identical infrared spectra.

3,5,7-Trimethylflavone.—Benzoic anhydride (6 g.), sodium benzoate (3 g.), and 2-hydroxy-4,6-dimethylpropiophenone (4·0 g.) were heated at 120—140° under reflux for 6 hr. and the cooled product was mixed with water. The residual solid was clearly a mixture the spectroscopic properties of which indicated the presence of 2-benzoyloxy-4,6-dimethylpropiophenone. The mixture (2 g.) was treated with sodium hydride (1·5 g.) in boiling ether (75 ml.) for 1 hr., whereafter unchanged hydride was destroyed by addition of ethanol (3 ml.) followed 20 min. later by crushed ice (50 g.). The ether layer was separated, and the aqueous layer extracted with more ether (50 ml.); the ether solutions were combined, washed with water, dried (Na_2SO_4), and evaporated leaving a solid that crystallised from light petroleum (b. p. 40—60°) giving *3,5,7-trimethylflavone* as needles (1·1 g.), m. p. 89—91° (Found: C, 82·1; H, 6·0. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

1-(2-Hydroxy-4,6-dimethylphenyl)-5-phenylpenta-2,4-dien-1-one (XXIX).—Aqueous sodium hydroxide (60%; 25 ml.) was added slowly to a stirred solution of 2-hydroxy-4,6-dimethylacetophenone (8·2 g.) and cinnamaldehyde (6·7 g.) in methanol (5 ml.) cooled in ice. After 9 hr. at 0°, the mixture was acidified with ice-cold dilute hydrochloric acid. The yellow precipitate was collected, washed with water, and purified from aqueous ethanol giving the dienone as yellow plates (11·2 g.), m. p. 110—111°, having a reddish-brown ferric reaction (Found: C, 82·1; H, 6·5. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

3-Hydroxy-5,7-dimethyl-2-styrylchromone (XXXII).—Hydrogen peroxide (30%; 1 ml.) was added to a stirred solution of the foregoing dienone (1·0 g.) in 10% aqueous sodium hydroxide (15 ml.). After 4·5 hr. at 18°, the mixture was acidified with hydrochloric acid and the product separated into two fractions by crystallisation from 95% ethanol. The less soluble fraction consisted of *3-hydroxy-5,7-dimethyl-2-styrylchroman-4-one* (XXXI), which formed pale yellow leaflets (0·11 g.), m. p. 133—135° (from methanol) (Found: C, 77·3; H, 6·2. $C_{19}H_{18}O_3$ requires C, 77·55; H, 6·1%). This compound was not soluble in alkali and gave no ferric reaction, but formed an *acetate*, m. p. 105—107° (Found: C, 74·7; H, 5·9; OAc, 13·4. $C_{19}H_{17}O_2$,OAc requires C, 75·0; H, 5·95; OAc, 12·8%).

The more soluble fraction crystallised from dilute acetic acid yielding the *2-styrylchromone* as pale yellow plates, m. p. 193—194° (Found: C, 77·8; H, 5·5. $C_{19}H_{16}O_3$ requires C, 78·1; H, 5·5%). This compound was soluble in aqueous sodium hydroxide and gave a pale green Shinoda reaction, a brown-violet ferric reaction, and an *acetate*, m. p. 175° (Found: C, 75·4; H, 5·7. $C_{21}H_{18}O_4$ requires C, 75·4; H, 5·4%). This 3-hydroxychromone could also be obtained from the chromanone either by repeating the hydrogen peroxide oxidation or by heating an acetic acid solution of the chromanone in air.

2-Cinnamylidene-4,6-dimethylcoumaran-3-one (XXX).—4,6-Dimethylcoumaran-3-one (2·0 g.)

in acetic acid (8 ml.) was condensed with cinnamaldehyde (1·7 g.) by means of concentrated hydrochloric acid (0·5 ml.). Crystallised from methanol, the product afforded the *cinnamylidenecoumaranone* as yellow needles (2·7 g.), m. p. 132—135° (Found: C, 82·1; H, 5·8. $C_{19}H_{16}O_2$ requires C, 82·6; H, 5·8%).

1-(2-*Hydroxy*-5-*methylphenyl*)-5-*phenylpenta*-2,4-*dien*-1-*one* (XXVII).—This was made in the same way as was the homologue above but using 2-hydroxy-5-methylacetophenone (7·5 g.). The *dienone* separated from ethanol as yellow plates (7·8 g.), m. p. 136—138°, giving a dark brown ferric reaction (Found: C, 81·5; H, 6·3. $C_{18}H_{16}O_2$ requires C, 81·8; H, 6·1%).

3-*Hydroxy*-6-*methyl*-2-*styrylchromone* (XXVIII).—The foregoing dienone (0·6 g.) was oxidised by alkaline hydrogen peroxide as was the homologue, except that the reaction temperature was raised to 50° for the final hour. The *styrylchromone* separated from dilute acetic acid as yellow plates (0·32 g.), m. p. 229°, giving a pale green fluorescent colour in the Shinoda reaction and a red-brown ferric reaction (Found: C, 77·3; H, 5·4. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·0%). The *acetate* formed pale yellow plates, m. p. 170—172° (Found: C, 75·2; H, 5·0. $C_{20}H_{16}O_4$ requires C, 75·0; H, 5·0%).

THE ROBERT ROBINSON LABORATORIES,
UNIVERSITY OF LIVERPOOL.

[*Received, January 11th*, 1965.]