Parameters regulating the α- and β-Cyclization of Chalcones

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Cyclizations of 2'-hydroxychalcones and their α-oxygenated counterparts (α-alkoxy- and peltogynoid chalcones) follow a logical sequence of α- or β-addition directed by the nature of the α-substituent and the pH of the reaction medium. For β-addition the reaction equilibrium and hence its course depends on the thermodynamic stability of, the presence of a 5-hydroxy function in, and the acidity of the 3-protons of the resulting flavanone. Cyclization of the chalcone is independent of possible α-directing steric effects introduced by 6'-methoxylation.

The latter reflects on similar cyclizations under oxidative conditions [alkaline ferricyanide, acidic lead tetra-acetate. and alkaline peroxide (Algar–Flynn–Oyamada reaction)]. where the directing effects of free radical and ionic mechanisms are invoked to rationalize their variable course.

THE cyclization of chalcones represents one of the most exhaustively studied reactions in heterocyclic chemistry, not only on account of its largely unexplained variability under oxidative conditions, but particularly because its fluctuating course may represent parallels amongst those biogenetic sequences which lead to the range of natural flavonoids.

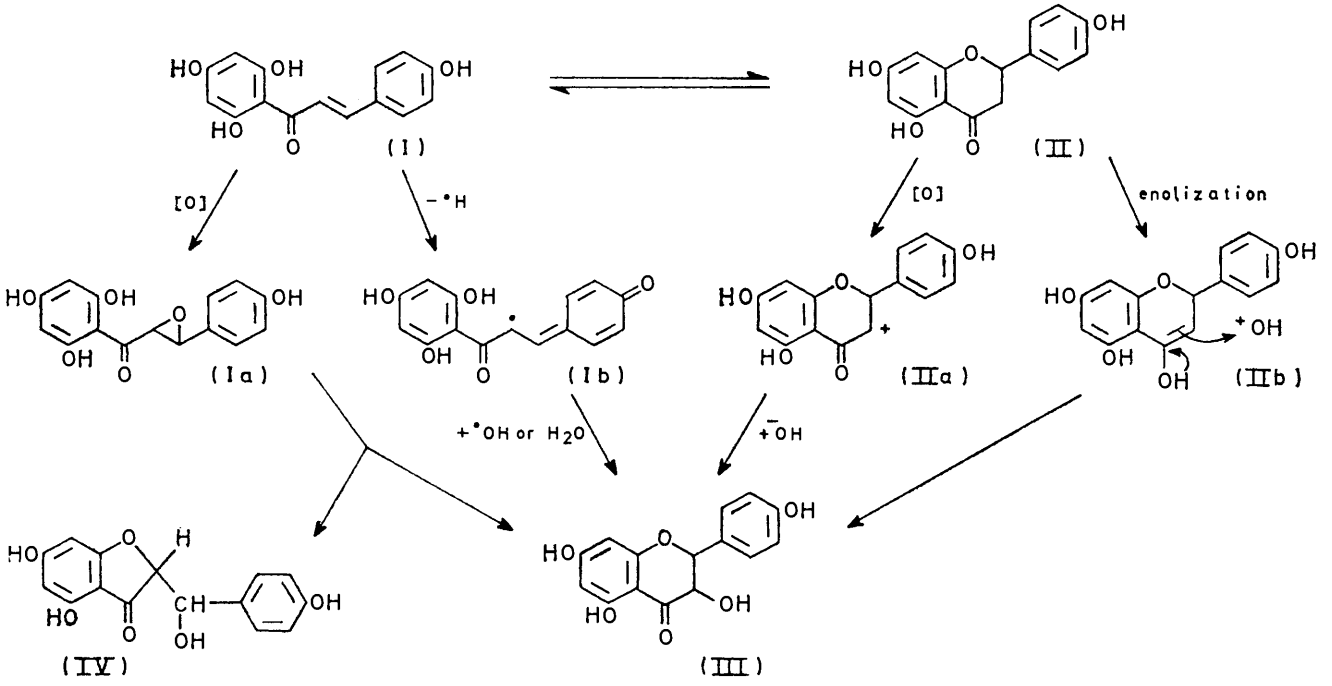
Thus, while conventional chalcones (I) have hitherto been considered [1-4] as key biogenetic intermediates, no unanimity exists regarding the introduction of oxygen to furnish 3-hydroxylation which is characteristic of most flavonoids. Amongst the proposals based on the chalcone–flavanone equilibrium (I) ⇌ (II) are: (i) direct oxidation of flavanones with formation of a 3-cation, followed by attack by ^{-}OH [5] [(II) ⟶ (IIa) ⟶ (III)]; (ii) enolization of the flavanone followed by direct reaction with the equivalent of ^{+}OH [2] [(II) ⟶ (IIb) ⟶ (III)]; (iii) attack by H_2O or $^{\cdot}OH$ at the α-position of a chalcone radical [2] formed by electron-transfer to an enzyme [(I) ⟶ (Ib) ⟶ (III)]; and (iv) epoxidation of a chalcone as proposed [6] for the Algar–Flynn–Oyamada (AFO) reaction [(I) ⟶ (Ia) ⟶ (III)].

However, considerations such as the dubious flavanone oxidation mechanisms proposed; the observation that natural chalcone epoxides have hitherto not been isolated; the strong alkaline conditions required for the AFO reaction; and the finding that epoxide-mediated conversion of chalcones does not lead to simultaneous

[1] E. Wong and H. Grisebach, *Phytochemistry*, 1967, **8**, 1419.
[2] A. Pelter, J. Bradshaw, and R. F. Warren, *Phytochemistry*, 1971, **10**, 835.
[3] H. Grisebach and W. D. Ollis, *Experientia*, 1961, **17**, 4.
[4] T. A. Geissman, 'Biogenesis of Natural Compounds,' 2nd edn., ed. P. Bernfeld, Pergamon, Oxford, 1967, p. 743.
[5] J. D. Bu'Lock, 'The Biosynthesis of Natural Products,' McGraw-Hill, New York, 1965, p. 86.
[6] T. A. Geissman and D. K. Fukushima, *J. Amer. Chem. Soc.*, 1948, **70**, 1686.

formation (together with flavanones) of 2-benzyl-2-hydroxybenzo[*b*]furan-3(2*H*)-ones (2-benzyl-2-hydroxycoumaranones) but rather to 2-(α-hydroxybenzyl) derivatives (IV) (unknown naturally)* and aurones, emphasize the tentative nature of these proposals.

By contrast cyclization of the recently isolated peltogynoid-type chalcones [8,9] (α-alkoxy) and especially α-hydroxychalcones [10,11] leads directly by β-addition to 3-hydroxyflavanones (dihydroflavanols) and *via* α-addition to 2-benzyl-2-hydroxycoumaranones—both known classes of natural compounds. In order to assess feasible chemical analogies for likely biogenetic steps, the above-mentioned types of chalcones were subjected to a series of corresponding cyclizations. Although some of these represent known reactions, their mechanistic aspects are almost as doubtful as some of the above proposals for oxygenation of flavanones.



SCHEME 1

β-*Cyclization*.—Ring closure to the β-position relative to the carbonyl proceeds with different types of chalcones under the conditions shown in Scheme 2.

β-Cyclization proceeds by a 1,4-Michael addition, which with conventional chalcones leads to the well-known chalcone–flavanone equilibrium [12] (V) ⇌ (VI) where the presence of a 6′-hydroxy-group (V; R = OH) pushes the equilibrium in favour of the flavanone (VI; R = OH).[13] In the case of 2′-hydroxy-α-methoxy-*trans*-chalcone (VII; R = H, R′ = OMe), weakly basic conditions (pH 8.4) result in the best yield of products, and lead to a mixture (2 : 1) of 3-*O*-methyl-2,3-*trans*- and 2,3-*cis*-fustin (VIII and IX; R = H, R′ = OMe) [10,14] in contrast with only the 2,3-*trans*-isomer obtained by Clark-Lewis, Jemison, and Nair [15] under similar conditions. This is in accord with the 1 : 2 *cis*–*trans*-equilibrium obtained by Clark-Lewis *et al.*[15] during acid-catalysed epimerization of 3-*O*-methyl-2,3-*cis*-dihydroflavonols, and also with the proportion in which they are present in the heartwood of *Trachylobium verrucosum*.[10,14] Since the last-mentioned ' equilibrium ' is irreversible,[15] the thermodynamically less stable 2,3-*cis*-isomer must originate simultaneously with the 2,3-*trans*-form during cyclization of the chalcone. The ease with which the reaction proceeds is of biogenetic significance as it furnishes the first chemical analogy for the natural origin of 2,3-*cis*- and 2,3-*trans*-dihydroflavonols.[15]

Since cyclization of α-methoxychalcones also occurs in ' neutral ' medium [EtOH–H_2O (1 : 1): weakly acid probably owing to atmospheric CO_2], and is totally absent

* Crombenin [7] (4,4′,6,6′7-pentahydroxyisochroman-3′-spiro-2-coumaran-3-one), a peltogynoid analogue, represents the only exception.

[7] E. V. Brandt, D. Ferreira, and D. G. Roux, *J.C.S. Chem. Comm.*, 1972, 392.

[8] O. R. Gottlieb and J. Rêgo de Sousa, *Phytochemistry*, 1972, **11**, 2841.

[9] E. V. Brandt and D. G. Roux, unpublished work on *Acacia carnei*, *A. crombei*, and *A. peuce* (*cf.* M. D. Tindale and D. G. Roux, *Phytochemistry*, 1974, **13**, 829).

[10] J. P. van der Merwe, D. Ferreira, E. V. Brandt, and D. G. Roux, *J.C.S. Chem. Comm.*, 1972, 521.

[11] F. du R. Volsteedt, G. J. H. Rall, and D. G. Roux, *Tetrahedron Letters*, 1973, 1001.

[12] S. von Konstanecki, V. Lampe, and J. Tambor, *Ber.*, 1904 **37**, 786.

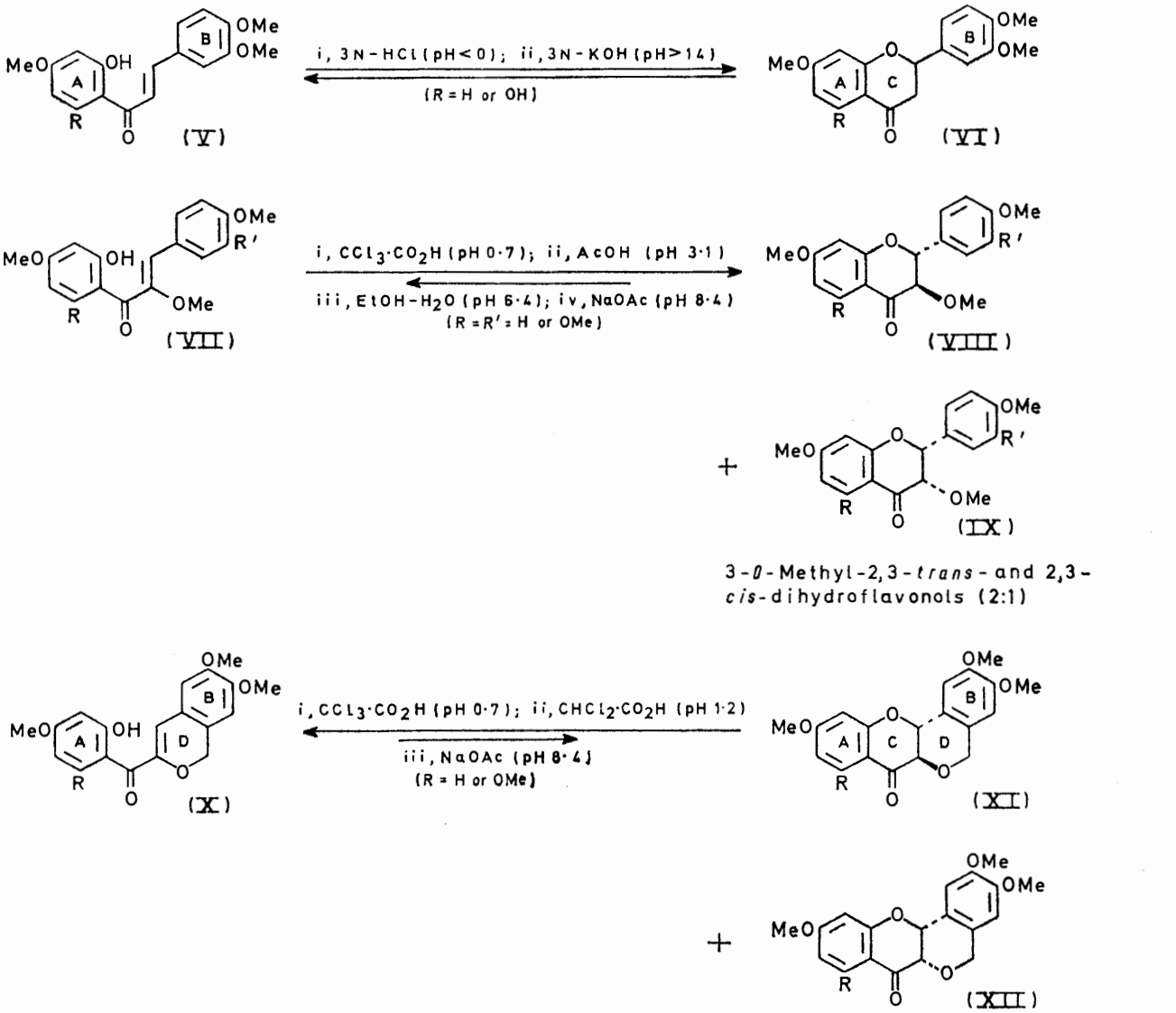
[13] U. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1948, **27A**, 223; T. R. Seshadri, *Sci. Proc. Roy. Dublin Soc.*, 1956, **27**, 77.

[14] D. Ferreira, J. P. van der Merwe, and D. G. Roux, *J.C.S. Perkin I*, 1974, 1492.

[15] J. W. Clark-Lewis, R. W. Jemison, and V. Nair, *Austral. J. Chem.*, 1968, **21**, 3015.

under alkaline conditions (10% KOH), the purpose of sodium acetate addition is not immediately apparent. Comparison of u.v. spectra of the chalcone under the above-mentioned conditions indicates that the 2′-hydroxy-group does not ionise in sodium acetate solution, and since the yield of dihydroflavonols under neutral shown by treating 3-*O*-methyldihydroflavonols under identical conditions with NaOAc to form 2′-hydroxy-α-methoxychalcones.

In contrast to its directing influence during presumed epoxidation of conventional chalcones [6,16–18] under oxidative conditions (see below), the 6′-methoxy-substituent

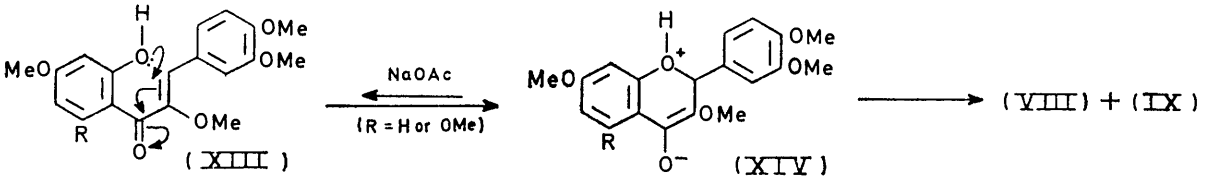


SCHEME 2

conditions is much lower, it appears that sodium acetate pushes the equilibrium (XIII) ⇌ (XIV) to the right by acting as buffer. That the reaction is indeed reversible is does not influence the direction of addition in sodium acetate, as illustrated by 2′-hydroxy-α,4,4′,6′-tetramethoxy-*trans*-chalcone (VII; R = OMe, R′ = H), which

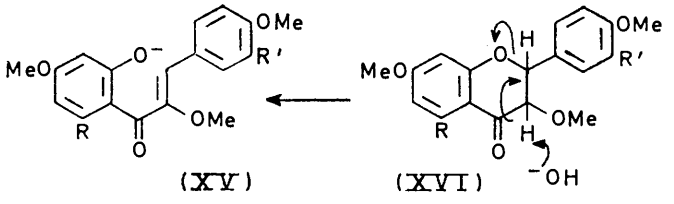
[16] F. M. Dean and V. Podimuang, *J. Chem. Soc.*, 1965, 3978.
[17] T. R. Gormley and W. I. O'Sullivan, *Tetrahedron*, 1973, **29**, 369.
[18] B. Cummins, D. M. X. Donnelly, J. F. Eades, H. Fletcher, F. O. Cinnéide, E. M. Philbin, J. Swirski, T. S. Wheeler, and R. K. Wilson, *Tetrahedron*, 1963, **19**, 499.

readily yields tetra-*O*-methyl-2,3-*trans*- and 2,3-*cis*-aromadendrin (VIII and IX; R = OMe, R′ = H, respectively). Accordingly the initial proposal by Geissman and Fukushima [6] as elaborated by Dean and Podimuang [16] that displacement of the carbonyl group out of the plane of the phenolic ring A through steric interaction with the 6′-methoxy-substituent, increases the distance of the phenolic oxygen from the β-position to a greater degree

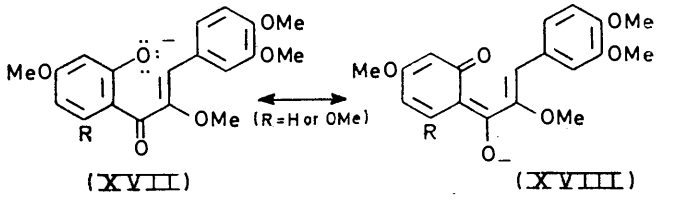


than from the α-position, thus favouring formation of the five-membered ring, cannot be accepted under these specified (NaOAc) reaction conditions. Although Dean and Podimuang [16] claimed that these steric effects are reduced under combined alkaline and oxidative conditions at higher temperatures, more recent work by Gormley and O'Sullivan [17] has shown that once an intermediate chalcone epoxide is formed, the 6′-methoxy-substituent directs cyclization exclusively to the α-position over a range of temperatures during the AFO reaction.

The ease with which cyclization proceeds in the case of α-methoxychalcones is in direct contrast with those of the



peltogynoid-type chalcones (X) where similar conditions yield 2,3-*trans*- and 2,3-*cis*-dihydroflavonol analogues, (XI) and (XII) respectively, in low yield. This phenomenon is attributable to internal D-ring stress, especially for the 2,3-*cis*-derivative (XII) with corresponding displacement of the equilibrium to the left.



Considered in the light of the known acid/base-catalysed chalcone–flavanone equilibrium [12] (V) ⇌ (VI) it is notable that strongly alkaline conditions do not promote cyclization of α-methoxy- and peltogynoid-type chalcones perceptibly. As both last-mentioned chalcones may be readily prepared from the corresponding 3-*O*-alkyl-dihydroflavonols,[19] this implies that alkaline conditions shift the equilibrium completely towards the chalcones, (XVI) ⟶ (XV). Such behaviour may be rationalized on the assumption that protons in the position α to the carbonyl in 3-*O*-methyl- and peltogynoid-type dihydroflavonols [(VIII), (IX); and (XI), (XII), respectively] are more strongly acidic than corresponding protons of flavanones (VI) owing to the presence of geminal 3-alkoxy-functions. Stabilization of the αβ-unsaturated ketone unit by resonance [6] (XVII) ⟷ (XVIII) is a factor which may favour the chalcone form in all the above equilibria.

Against this, the alkaline ring opening [20] of 3-hydroxyflavanones (XIX) (dihydroflavonols) yields 2-benzyl-2-hydroxybenzo[*b*]furan-3(2*H*)-ones (XXI) (2-benzyl-2-hydroxycoumaranones) very readily, probably *via* α-cyclization of the α-diketone tautomer of the α-hydroxychalcone (XX). This mechanism is in accord with the observation that α-methoxy- and α-alkoxychalcones, exclusively representing the enolic form of α-hydroxychalcones, fail to cyclize to benzofuranones under similar conditions.

α-*Cyclization*.—In contrast to observed β-addition (V) ⟶ (VI) of conventional chalcones with 3N-HCl, mineral acids direct cyclization with α-methoxy- and peltogynoid-chalcones [19] in an anti-Michael sense to the position α to the carbonyl group [(XXII) ⟶ (XXIII) and (XXIV) ⟶ (XXV)]. From this emerges that the nature of the α-substituent (H or OR) determines the direction of cyclization in acid medium.

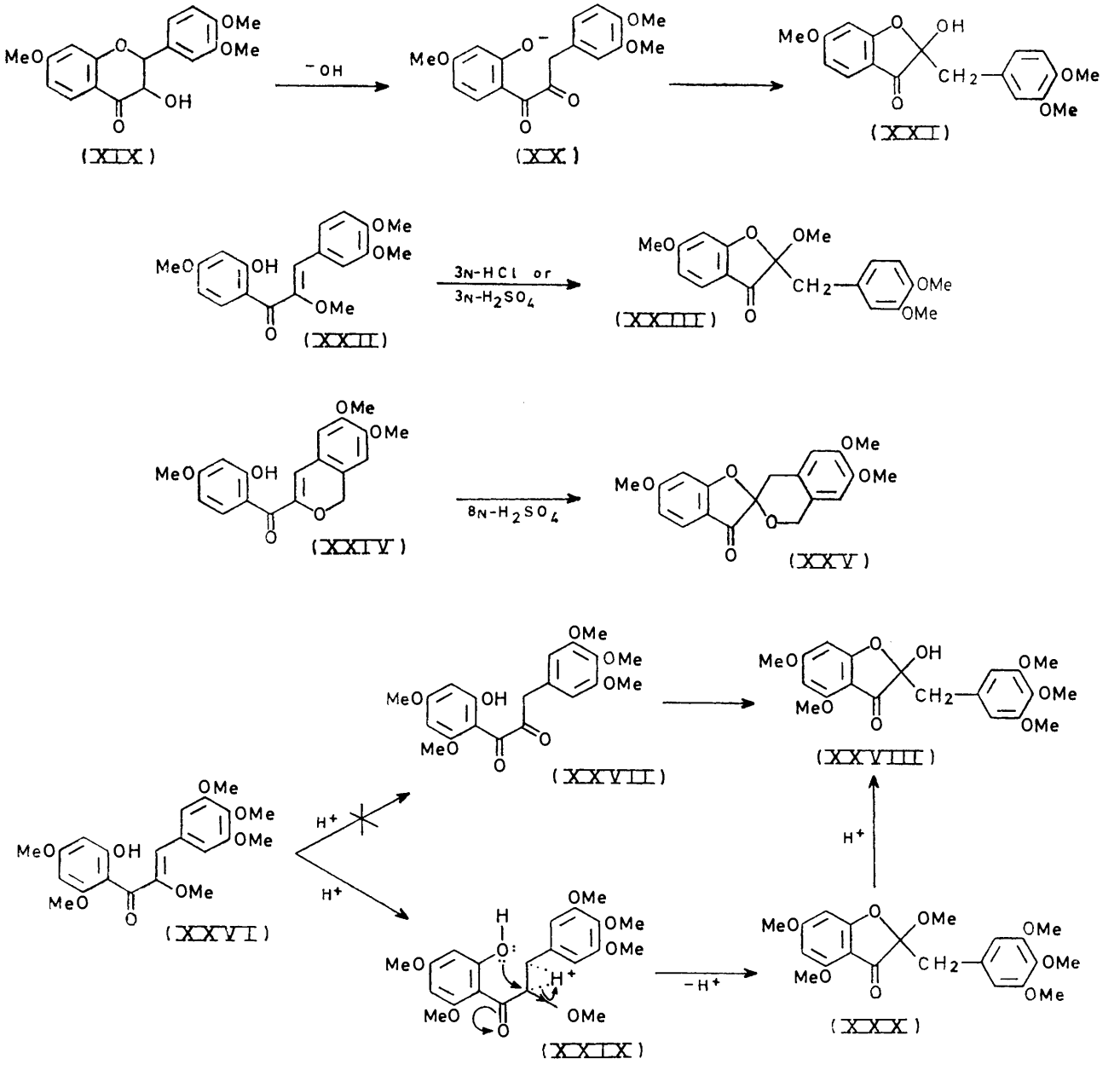
The mechanism previously proposed [21,22] for α-cyclization of α-methoxychalcone [(XXVI) ⟶ (XXVIII)] centres around initial hydrolysis of the α-enol ether group followed by α-cyclization of the resultant α-diketone (XXVII). This theory is, however, no longer acceptable as the present work illustrates that the same chalcone (XXVI) yields the 2-benzyl-2-methoxybenzo-[*b*]furan-3(2*H*)-one (XXX) as major product together with minor proportions of its 2-hydroxy-counterpart (XXVIII). This indicates that hydrolysis of the 2-methoxy-group follows cyclization (once it forms a portion of an acetal group).

The observation that an α-oxygen function is required for α-cyclization mediated by strong acid [*cf.* (V) ⟶ (VI) with (XXII) ⟶ (XXIII); (XXIV) ⟶ (XXV)] indicates that in addition to the effects of protonation of the αβ-double bond, the outweighing directing effect must be exercised by the inductive effect of the protonated α-methoxy-group, since protonation of the carbonyl

[19] W. R. Chan, W. G. C. Forsyth, and C. H. Hassall, *J. Chem. Soc.*, 1958, 3174.
[20] M. J. Chopin and M. L. Bouillant, *Compt. rend.*, 1962, **254**, 3699.
[21] M. Kotake and K. Kubota, *Annalen*, 1940, **544**, 253.
[22] J. Gripenberg, *Acta Chem. Scand.*, 1953, **7**, 1323.

and of the αβ-double bond is common to both conventional chalcones (V) and their α-alkoxy-counterparts under these conditions. The strong inductive effect of the α-methoxy-group is presumably also responsible for the reaction running to completion.

α- and β-Cyclization under Oxidative Conditions.—Compared with the largely predictable cyclizations of α-hydroxy-, α-methoxy-, and α-alkoxy-chalcones (the latter of the peltogynoid type) under acidic and alkaline conditions as outlined above, α- and β-cyclizations of these



Formation of 2,3-*trans*- and 2,3-*cis*-dihydroflavonol derivatives (β-cyclization) in addition to only trace amounts of benzylcoumaranones (α-cyclization) during the action of stronger organic acids such as di- and trichloroacetic acids on α-methoxy- and peltogynoid-type chalcones, may be rationalized on the premise that these acids are not strong enough to protonate both the αβ-double bond and the α-methoxy-function.

classes of compounds under the oxidative conditions (alkaline peroxide) of the Algar–Flynn–Oyamada (AFO) reaction, follow a varied course.[17,23] The AFO reaction leads to both dihydroflavonols, flavonols, and 2-arylbenzofuran-3-carboxylic acids (through rearrangement of the diketonic form of the flavonol) [23] representative of

[23] F. M. Dean, 'Naturally Occurring Oxygen Ring Compounds,' Butterworths, London, 1963, pp. 341—348.

β-cyclization, and often simultaneously to aurones, 2-benzyl-2-hydroxybenzofuranones, and 2-(α-hydroxybenzyl)benzofuranones [24,25] or their peltogynoid equivalent,[7] representative of α-cyclization.

New light is thrown on the possible origins of aurones in particular by the unique β-coupling of 2',4-dihydroxy-4',6'-dimethoxy-*trans*-chalcone (XXXI; R = H) with 3,5-dimethoxyphenol (XXXII) in the presence of alkaline potassium ferricyanide to form diastereoisomeric 2-[4-hydroxy-α-(4-hydroxy-2,6-dimethoxyphenyl)benzyl]-4,6-dimethoxybenzo[*b*]furan-3(2*H*)-ones (XXXIII) and 4'-hydroxy-4,6-dimethoxyaurone (XXXIV),[26] both in good yields. The suggested mechanism for both coupling and conversion is free radical formation at the 2'-hydroxy-group (XXXV), followed by attack of the latter on the αβ-double bond to give a resonance-stabilized benzylic β-radical (XXXVI). The latter undergoes oxidative loss of hydrogen at the 2-position of the benzofuranone to form the aurone, and simultaneously its direct coupling with a canonical form (XXXVII) of the phenoxyl radical (XXXVIII) gives the α-benzyl-substituted 2-benzylbenzofuranone. By contrast, attempts at similar reaction with 4-hydroxy-4',6'-dimethoxy-2'-methoxymethoxy-*trans*-chalcone (XXXI; R = CH_2O·CH_3) (aimed at α-coupling) gave no significant product, apparently confirming the role of the 2'-phenoxyl radical.

Similar free-radical mechanisms presumably operate also under acidic conditions where fully substituted 2'-hydroxychalcones are converted into *trans*- and *cis*-aurones by lead tetra-acetate or manganese(III) acetate.[27] This reaction is confirmed by our conversion of 2'-hydroxy-4,4',6'-trimethoxy-*trans*-chalcone into the *trans*-aurone analogue by lead tetra-acetate in acetic acid. The mechanism is considered similar to that outlined above for alkaline conditions [(XXXV) ⟶ (XXXVI) ⟶ aurone]. Application of the same reaction to the corresponding α-methoxychalcone (XXXIX) gave for the first time 2-(α-acetoxy-4-methoxybenzyl)-2,4,6-trimethoxy- and 2-acetoxy-2-(4-methoxybenzoyl)-4,6-dimethoxybenzo[*b*]furan-3(2*H*)-one [(XL) and (XLI) respectively] in the proportions of 15 : 1. The suggested course for this reaction* is again analogous to that proposed above for phenol coupling to the β-position of the chalcone with alkaline ferricyanide.

The free-radical concept enjoys independent support

* The alternative of an ionic mechanism as suggested by R. Criegee in 'Oxidation in Organic Chemistry,' ed. K. B. Wiberg, Academic Press, New York, 1965, pp. 288—291, is discounted in this case in view of the formation of aurones from 'conventional' 2'-hydroxychalcones (*cf.* above), as well as doubt regarding the proposed mechanism.

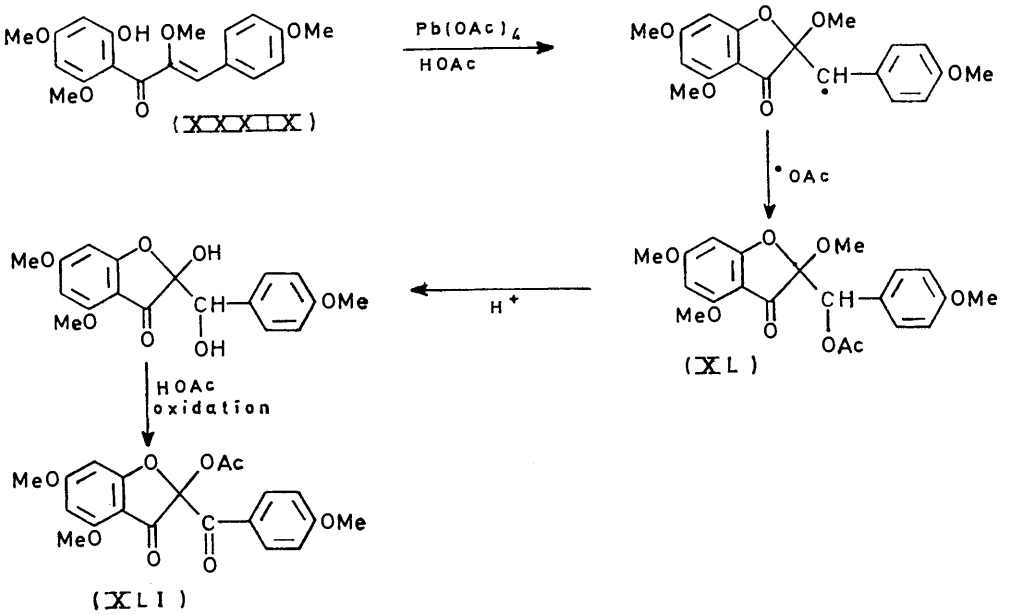
[24] E. Wong, *Phytochemistry*, 1967, **6**, 1227.
[25] D. M. X. Donnelly, T. P. Lavin, D. P. Melody, and E. M. Philbin, *Chem. Comm.*, 1965, 46; W. P. Cullen, D. M. X. Donnelly, A. K. Keenan, T. P. Lavin, D. P. Melody, and E. M. Philbin, *J. Chem. Soc.* (*C*), 1971, 2848; D. M. X. Donnelly, D. P. Melody, and E. M. Philbin, *Tetrahedron Letters*, 1967, 1023.
[26] F. du R. Volsteedt, D. Ferreira, and D. G. Roux, *J.C.S. Chem. Comm.*, 1975, 217.
[27] K. Kurosawa and J. Higuchi, *Bull. Chem. Soc. Japan*, 1972, **45**, 1132.

from the observation [28] that 7-glycosides of 5,7-dihydroxyflavanones in alkaline or neutral solution undergo autoxidation to aurones *via* 2′-hydroxychalcones, subject only to hydroxylation on ring B under neutral conditions.

Application of these results to the AFO reaction suggests that in general under alkaline oxidative conditions, two competing reactions participate: (i) ionic reactions which involve linking of the 2-phenoxide ion with either the α- or β-positions of chalcones or chalcone epoxides (or their α-methoxy- or peltogynoid analogues); and (ii) free-radical reactions resulting from attack by the 2′-phenoxyl radical on the αβ-double bond,[28] outlined in the sequence (XXXV) ⟶ (XXXVI) ⟶ aurone, as alternative to the well known epoxidation of αβ-unsaturated ketones with alkaline peroxide. The former leads to dihydroflavonols, flavonols, and 2-benzyl-2-hydroxycoumaranones, whereas the latter would lead to aurones only.

While the 6′-methoxy-substituent undoubtedly exercises a still largely unexplained (*cf.* ref. 17) directing effect towards α-cyclization with 2′-hydroxy-α-methoxychalcones [24,25] under conditions of the AFO reaction and also with stable 2′-substituted chalcone epoxides,[17,29] the steric effect attributed to interaction between the carbonyl and 6′-methoxy-groups must be small as judged from Catalin space-filling models, and plays no significant role in the absence of oxidizing reagents. The effect could also be rationalized on the premise that 6′-substitution stabilizes the 2′-phenoxyl radical. For example, in the coupling sequence (XXXI) + (XXXII) ⟶ (XXXIII) the stable free radical which results perhaps surprisingly from one of the participants [3,5-dimethoxyphenol (XXXII)], represents a canonical form of a phenoxyl radical (XXXVIII) which also corresponds, as regards oxygenated substitution, to ring A of the chalcone radical (XXXV) postulated for the cyclization step. Perhaps significantly the majority of those chalcones [6,23] and α-methoxychalcones [25] which readily participate in α-cyclization during the AFO reaction, possess the same 2′,4′,6′-trisubstitution pattern.

Ranged against the above are previous comment by Dean and Podimuang [16] that the characteristics of alkaline ferricyanide oxidations differ completely from those of the AFO reaction, and also comment by Pelter *et al.*[2] that oxidation of ring A, and therefore its participation as a free radical in cyclization of 2′-hydroxychalcones, has not been observed during the course of ferricyanide oxidations.



EXPERIMENTAL

N.m.r. spectra were recorded on a Varian T-60 spectrometer for solutions in $CDCl_3$ with Me_4Si as internal standard, and mass spectral data on a Varian CH-5 instrument. T.l.c. was performed on Kieselgel PF_{254} (0.25 mm); for preparative scale experiments (p.l.c.) the same material (1 mm) was used. Plates were air-dried and unactivated, and sprayed with H_2SO_4–40% HCHO (40 : 1). Evaporations were carried out under reduced pressure with water-bath temperature 60 °C.

Preparation of 2′-Hydroxychalcones and Cyclization Reactions.—*2′-Hydroxy-3,4,4′-trimethoxy-*trans*-chalcone* (V; R = H). The chalcone (10 mg) in ethanol (5 ml) was refluxed for 24 h on a water-bath after addition of 3N-HCl (1 ml), $CCl_3{\cdot}CO_2H$ (200 mg), NaOAc (100 mg), or 3N-KOH (1 ml) and the mixtures obtained were examined by t.l.c. in benzene–acetone (8 : 2 v/v), with both the chalcone and the isomerization product tri-*O*-methylbutin (VI; R = H) as reference compounds. These were the only compounds present after reaction. The stronger acids shifted the equilibrium (V) ⇌ (VI) to the right, strong bases to the left.

[28] G. Dellamonica and J. Chopin, *Bull. Soc. chim. France*, 1972, 2003.

[29] G. Litkei and R. Bognár, *Acta Chim. Acad. Sci. Hung.*, 1973, **77**, 93; J. P. Pineau, and J. Chopin, *Bull. Soc. chim. France*, 1971, 3678.

2'-Hydroxy-α,3,4,4'-tetramethoxy-trans-*chalcone* (VII; R = H, R' = OMe).[15] The chalcone, m.p. 98.4°, was prepared by methods detailed previously,[14] and its identity and purity were established by n.m.r. spectrometry.

The chalcone (10 mg) was treated with a variety of reagents (Table 1) in ethanol and 50% ethanol–water by refluxing for 24 h on a water-bath. The products were examined by t.l.c. developed with benzene–acetone (23 : 2 v/v).

Cyclization with sodium acetate in 50% *ethanol to* (±)-*3,3',4',7-tetra*-O-*methyl*-2,3-trans- *and* 2,3-cis-*fustin* (VIII and IX; R = H, R' = OMe). The 2'-hydroxychalcone (200 mg) was isomerized with NaOAc (500 mg) in 50% ethanol–water (30 ml) by refluxing for 24 h on a water-bath according to the method of Tominaga.[30] The products were separated by p.l.c. in benzene–acetone (23 : 2 v/v) to give the 2,3-*cis*- (R_F 0.57; 23.4 mg) and 2,3-*trans*-fustin racemates (R_F 0.51; 45 mg), together with unchanged 2'-hydroxychalcone (R_F 0.67; 52.6 mg).[14]

TABLE 1

Cyclization of 2'-hydroxy-α,3,4,4'-tetramethoxy-*trans*-chalcone (VII; R = H, R' = OMe)

Reagent	pH	% EtOH	Product †
KOH (200 mg)	>14	50	None
NaOAc,$3H_2O$ (100 mg)	8.4	50	(VIII), (IX)
AcOH (105 mg)	3.1	100	(VIII), (IX)
$CH_2Cl{\cdot}CO_2H$ (165 mg)	1.9	100	(VIII), (IX)
$CHCl_2{\cdot}CO_2H$ (225 mg)	1.2	100	(VIII), (IX), (XXIII) *
$CCl_3{\cdot}CO_2H$ (285 mg)	0.7	100	(VIII), (IX), (XXIII) *
H_2SO_4 (1 ml; 3N)	<0	100	(XXIII)

* Trace. † The formulae indicated correspond to (VIII; R = H, R' = OMe), (IX; R = H, R' = OMe), and (XXIII). Cyclization with NaOAc gave optimum yields of the former pair, and with H_2SO_4 a high yield of the last only.

Cyclization with 3N-*sulphuric acid in ethanol to 2-benzyl-2,3',4',6-tetramethoxybenzo*[b]*furan*-3(2H)-*one* (XXIII). The 2'-hydroxychalcone (50 mg) with 3N-H_2SO_4 (5 ml) in ethanol (5 ml) was refluxed on a water-bath (96 °C) for 24 h as described by Gripenberg.[22] The solution was neutralized with aqueous $NaHCO_3$, extracted with $CHCl_3$, and after drying (Na_2SO_4) the product was purified by p.l.c. in benzene–acetone (8 : 2 v/v). The band of R_F 0.60, violet with the spray reagent, gave a yellow oil (41 mg) which was shown by n.m.r. and mass spectroscopy to be the above compound.[14]

2'-Hydroxy-α,4,4',6'-tetramethoxy-trans-*chalcone* (VII; R = OMe, R' = H). The 2'-hydroxychalcone, m.p. 118.5°, was prepared as described by Cullen *et al.*[25] and the structure confirmed by n.m.r. and mass spectra.

Cyclization with sodium acetate in 50% *ethanol to* (±)-*3,4',5,7-tetra*-O-*methyl*-2,3-trans- *and* 2,3-cis-*aromadendrin*. The 2'-hydroxychalcone (100 mg) was treated with NaOAc (400 mg) in 50% EtOH (15 ml) as above and the products were separated by p.l.c. in benzene–acetone (9 : 1 v/v) to give the 2,3-*trans*- (R_F 0.26; 31 mg) and 2,3-*cis*-aromadendrin derivatives (R_F 0.32; 17 mg) together with unchanged chalcone (R_F 0.53; 34 mg).

(±)-3,4',5,7-Tetra-*O*-methyl-2,3-*cis*-aromadendrin (IX; R = OMe, R' = H), the fraction of R_F 0.32, brown with the spray reagent, gave a pale yellow oil, *m/e* 344(15%, M^+), 315(6.2), 314(33), 313(17), 207(8.4), 181(11.1), 180(27), 165(25), 164(100), 152(6.3), 150(3.6), 149(25), 137(7.0), 135(4.7), 134(20), 122(3.8), and 121(32); τ 2.47 (d, *J* 9.0 Hz, H-2' and -6'), 3.03 (d, *J* 9.0 Hz, H-3' and -5'), 3.77 (d, *J* 2.0 Hz, H-6), 3.85 (d, *J* 2.0 Hz, H-8), 4.65 (d, *J* 2.0 Hz, H-2), 6.33 (d, *J* 2.0 Hz, H-3), 6.08 (s, OMe), 6.17 (s, 2 × OMe), and 6.62 (s, 3-OMe) ($J_{2,3}$ 2.0 Hz confirms the 2,3-*cis*-configuration; *cf.* refs. 14 and 15).

(±)-3,4',5,7-*Tetra*-O-*methyl*-2,3-trans-*aromadendrin* (VIII; R = OMe, R' = H), the fraction of R_F 0.26, brown with the spray reagent, crystallized from ethanol as colourless needles, m.p. 141.4°, M^+ 344, τ 2.55 (d, *J* 8.4 Hz, H-2' and -6'), 3.05 (d, *J* 8.4 Hz, H-3' and -5'), 3.85 (s, H-6 and -8), 4.72 (d, *J* 9.0 Hz, H-2), 6.02 (d, *J* 9.0 Hz, H-3), 6.10 (s, OMe), 6.18 (s, 2 × OMe), and 6.52 (s, 3-OMe) ($J_{2,3}$ 9.0 Hz confirms the 2,3-*trans*-configuration; *cf.* refs. 14 and 15).

2'-Hydroxy-α,3,4,4',5,6'-hexamethoxy-trans-*chalcone* (XXVI). The 2'-hydroxychalcone, m.p. 146° (lit.,[21] 146—147°), was prepared from 2'-hydroxy-2,4',6'-trimethoxyacetophenone (281 mg) and 3,4,5-trimethoxybenzaldehyde (300 mg) in ethanol (15 ml) and 40% KOH (5 ml) according to the method of Kotake and Kubota [21] as pale yellow needles (350 mg) from ethanol.

Cyclization with hydrogen chloride in ethanol to 2,3',4,4',5',6-*hexamethoxy- and 2-hydroxy-3',4,4',5',6-pentamethoxybenzo*[b]*furan*-3(2H)-*one*. The 2'-hydroxychalcone in EtOH–10N-HCl–H_2O (20 : 3 : 5 v/v/v) was refluxed for 20 min and the products were worked up as for the related benzofuranone (XXIII) above. The mixture was separated by p.l.c. in benzene–acetone (7 : 3 v/v). 2,3',4,4',5',6-Hexamethoxybenzo[*b*]furan-3(2*H*)-one (XXX), the fraction from the band of R_F 0.47, gave white needles (48 mg) (from ethanol), m.p. 119.8° (lit.,[21] 119—120°). 2-Hydroxy-3',4,4',5',6-pentamethoxybenzo[*b*]furan-3(2*H*)-one (XXVIII), the fraction from the band of R_F 0.29, gave white needles (16 mg) (from ethanol), m.p. 168.6° (lit.,[21] 169—170°). These structures were both confirmed by n.m.r. and mass spectra.

3-(*2-Hydroxy-4-methoxybenzoyl*)-*6,7-dimethoxyisochromen* (X; R = H).[19] (+)-4',5',7-Tri-*O*-methylpeltogynone was isomerized to the chalcone by suspending the ketone (300 mg) in aqueous 10% KOH (72 ml) and heating for 1.25 h with agitation on a water-bath. The orange solution was filtered and the filtrate acidified to pH 2 with 2N-HCl; a fine precipitate formed. This was centrifuged off and crystallized as yellow plates (276 mg) from methanol, m.p. 125° (lit.,[19] 124—125°), M^+ 342.

Cyclizations of the peltogynoid chalcone (X; R = H). Isomerization of the isochromen was examined qualitatively as follows. The chalcone (10 mg, 2.9×10^{-5} mol) was dissolved in varying proportions of ethanol–water (5 ml), a quantity of catalytic reagent was added (*cf.* Table 2), and the mixture was heated under reflux for 24 h. The reaction was followed by t.l.c. with benzene–acetone (7 : 3 v/v) as developing medium. (+)-Tri-*O*-methyl-*trans*-peltogynone (XI; R = H), R_F 0.72, orange with the spray reagent, and 6,6',7-trimethoxyisochroman-3'-spiro-2-coumaran-3-one (XXV), R_F 0.81, violet with the spray reagent, were used as reference compounds. Formation of tri-*O*-methyl-*cis*-peltogynone (XII; R = H) was not observed.

(±)-4',5',7-*Tri*-O-*methyl*-2,3-trans-*peltogynone* (XI; R = H). The isochromen (100 mg) and dichloroacetic acid (2.25 g) dissolved in 96% ethanol (25 ml) were treated as immediately above. The products were separated on p.l.c. with benzene–acetone (7 : 3 v/v). Solids from the band of R_F 0.72 crystallized from ethanol as colourless needles (12.6 mg), m.p. 210° [lit.,[19] 213° for the (+)-isomer], $\nu_{max.}$ ($CHCl_3$) 1690 cm^{-1}, *m/e* 342(30%, M^+), 324(5.2), 310(4.9), 276(7.6), 193(11.7), 192(100), 191(13.2), 179(9.8), 177(21), 165(4.8),

[30] T. Tominaga, *J. Pharm. Soc. Japan*, 1960, **80**, 1202; 1962, **82**, 780.

164(8.2), 151(51), 150(4.6), 149(31), and 137(6.0); τ 2.04 (d, *J* 8.5 Hz, H-5), 2.83 (s, H-6'), 3.39 (dd, *J* 8.5 and 2.0 Hz, H-6), 3.42 (d, *J* 2.0 Hz, H-8), 3.57 (s, H-3'), 4.76 (d, *J* 12.0 Hz, H-2), 5.13br (s, CH_2), 5.75 (d, *J* 12.0 Hz, H-3), and 6.14 (s), 6.25 (s), and 6.30 (s) (3 × OMe). The n.m.r. and mass spectra were identical with those of the naturally derived (+)-enantiomer.[31]

TABLE 2

Cyclization of the peltogynoid chalcone (X; R = H)*

Reagent (mol)	pH	% EtOH	Product
KOH (2.1×10^{-5})	>14	10	None
KOH (2.1×10^{-5})	>14	95	None
K_2CO_3 (3.6×10^{-3})	*ca.* 12	50	None
NaOAc,$3H_2O$ (2.9×10^{-4})	8.4	50	(XI; R = H) †
NaOAc,$3H_2O$ (2.9×10^{-5})	8.4	50	(XI; R = H) †
No additive	6.4	10	None
No additive	6.4	96	None
AcOH (1.7×10^{-3})	3.1	96	(XI; R = H),† (XXV) †
$CH_2Cl{\cdot}CO_2H$ (1.7×10^{-3})	1.9	96	(XI; R = H), (XXV) †
$CHCl_2{\cdot}CO_2H$ (1.7×10^{-3})	1.2	96	(XI; R = H), (XXV) †
$CCl_3{\cdot}CO_2H$ (1.7×10^{-3})	0.7	96	(XI; R = H),† (XXV)
HCl (6.0×10^{-4})	<0	50	(XXV)
H_2SO_4 (6.0×10^{-4})	<0	50	(XXV)

* Optimum yields of tri-*O*-methyl-2,3-*trans*-peltogynone (XI; R = H) were obtained with $CHCl_2{\cdot}CO_2H$, and of the trimethoxyisochroman-3'-spiro-2-coumaran-3-one (XXV) with mineral acid (H_2SO_4). † Yield too low for preparative purposes.

(±)-6,6',7'-*Trimethoxyisochroman-3'-spiro-2-coumaran-3-one* (XXV).[19] The isochromen (XXIV or X; R = H) (50 mg) was refluxed (water-bath) for 24 h with 8N-H_2SO_4 (2.5 ml) in ethanol (5 ml). The ethanol was removed under reduced pressure, and the precipitate centrifuged off. The product (41.2 mg) crystallized from ethanol as white needles, m.p. 181° (lit.,[19] 183—185°).

3-(2-*Hydroxy*-4,6-*dimethoxybenzoyl*)-6,7-*dimethoxyisochromen* (X; R = OMe). The chalcone, prepared from either natural (+)-*trans*-[32] or synthetic (±)-*cis*-tetra-*O*-methylcrombeone [33] (10 mg) by treatment with alkali as described above for the 4-methoxybenzoyl analogue (X; R = H), crystallized as *yellow needles* (8.7 mg) (from ethanol), m.p. 93°, *m/e* 372 (19%, M^+), 284(5.0), 256(5.4), 198(15.1), 196(17.3), 192(8.5), 191(8.1), 182(20), 181(100), 180(77), 165(35), 164(8.8), 163(9.1), 152(20), 151(13.7), 150(10.0), 149(8.7), and 137(45) (Found: M^+, 372.120174. $C_{20}H_{20}O_7$ requires *M*, 372.120 892), τ −0.45 (s, 2'-OH), 3.26 (s, H-5), 3.35 (s, H-8), 3.43 (s, H-4), 3.83 (d, *J* 2.2 Hz, H-5'), 3.96 (d, *J* 2.2 Hz, H-3'), 4.82 (s, CH_2), 6.10 (s, 2 × OMe), and 6.15 (s) and 6.20 (s) (2 × OMe). The compound gave a pale violet colour with the spray reagent.

Cyclization with sodium acetate to (±)-4',5,5',7-*tetra*-*O*-*methyl*-2,3-trans- *and* 2,3-cis-*crombeone* (XI and XII; R = OMe). Isomerization of the chalcone (X; R = OMe) was investigated by methods outlined above for the 4-methoxybenzoyl analogue. This indicated that optimum conditions were achieved by refluxing (water-bath) the chalcone (55 mg) with NaOAc (220 mg) in 50% ethanol (5 ml). The ethanol was evaporated off, water was added, and the solution extracted with EtOAc (5 × 20 ml). Solids obtained after evaporation of the solvent were separated by p.l.c. in benzene–acetone (8 : 2 v/v) giving colourless needles (8.7 mg) of (±)-tetra-*O*-methyl-2,3-*trans*-crombeone (from ethanol), m.p. 184° [lit.,[32] 192° for (+)-enantiomer], R_F 0.32, yellow with the spray reagent, M^+ 372, n.m.r. and mass spectra identical with those of the (+)-enantiomer from *A. crombei*; [32,33] and also the (±)-2,3-*cis*-isomer as a pale yellow oil (2.4 mg), R_F 0.41, *m/e* 372(16.4%, M^+), 354(6.1), 341(5.3), 306(9.2), 207(3.9), 193(15.2), 192(100), 191(37), 182(6.5), 181(65), 180(10.2), 179(10.7), 178(11.3), 177(21), 165(4.9), 164(13.1), 163(7.3), 152(8.9), 151(6.5), 149(13.7), and 137 (7.8), τ 3.05 (s, H-6'), 3.35 (s, H-3'), 3.83 (d, *J* 2.0 Hz, H-6), 3.90 (d, *J* 2.0 Hz, H-8), 4.66 (d, *J* 5.8 Hz, H-2), 4.97 (s, CH_2), 5.83 (d, *J* 5.8 Hz, H-3), 6.05 (s, OMe), 6.10 (s, 2 × OMe), and 6.26 (s, OMe). The n.m.r. and mass spectra were identical with those of synthetic (±)-4',5,5',7-tetra-*O*-methyl-2,3-*cis*-crombeone obtained from 4',5,5',7-tetra-*O*-methyl-β-photomethylquercetin,[34] by catalytic hydrogenation under high pressure (100—110 atm) with nickel boride to (±)-4',5,5',7-tetra-*O*-methyl-2,3-*cis*-3,4-*cis*-crombeol,[33] followed by oxidation with MnO_2.

Coupling of 2',4-*Dihydroxy*-4',6'-*dimethoxy*-trans-*chalcone* (XXXI; R = H) *with* 3,5-*Dimethoxyphenol* (XXXII).—Details of this reaction are in the literature [26] and described below.

4-*Hydroxy*-4',6'-*dimethoxy*-2'-*methoxymethoxy*-trans-*chalcone* (XXXI; R = CH_2•OMe).—4,6-Dimethoxy-2-methoxymethoxyacetophenone was prepared by reaction of the sodium salt of 2-hydroxy-4,6-dimethoxyacetophenone with chloromethyl methyl ether according to the procedure of Eneback.[35] The solution of the acetophenone (1.28 g) and *p*-hydroxybenzaldehyde (0.8 g) in methanol (10 ml) and 50% KOH (3 ml) was stirred for 24 h at room temperature, poured into ice, and carefully acidified with 3N-HCl. Following ether extraction, the product was separated by p.l.c. with benzene–acetone (9 : 1 v/v) to give in addition to the starting materials, the desired chalcone as an oil (R_F 0.29; 537 mg), M^+ 344, τ 2.47 (d, *J* 16.0 Hz, H-β), 2.63 (d, *J* 8.5 Hz, H-2 and -6), 3.13 (d, *J* 8.5 Hz, H-3 and -5), 3.17 (d, *J* 16.0 Hz, H-α), 3.60 and 3.78 (d, *J* 2.0 Hz, H-3' and -5'), 4.88 (CH_2), 6.18 (s, OMe), 6.28 (s, OMe), and 6.62 (s, $CH_2{\cdot}OMe$).

Attempted coupling with 3,5-*dimethoxyphenol.* To the 2'-methoxymethoxychalcone (400 mg) and 3,5-dimethoxyphenol (400 mg) dissolved in 2N-NaOH (4.4 ml) was added $K_3Fe(CN)_6$ solution (880 mg in 20 ml water). After 10 min the mixture was diluted to 75 ml and acidified to pH 4 with HOAc. The yellow precipitate was filtered off, washed with water, and examined by t.l.c. in benzene–ethyl acetate (7 : 3 v/v). Starting materials only were recovered.

Oxidation of 2'-*Hydroxy*-α,4,4',6'-*tetramethoxy*- (XXXIX) and 2'-*Hydroxy*-4,4',6'-*trimethoxy*-trans-*chalcone with Lead Tetra-acetate in Glacial Acetic Acid.*—The 2'-hydroxy-α-methoxychalcone (344 mg), m.p. 119°, was heated with lead tetra-acetate (665 mg) in glacial acetic acid (15 ml) for 30 min at 96 °C. After evaporation of the acetic acid under reduced pressure, the mixture was taken up in chloroform (150 ml) and extracted (2 × 50 ml) with 10% (w/v) Na_2CO_3 solution. T.l.c. separation (benzene–acetone, 8 : 2 v/v) of

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the contents of the organic phase gave two products (R_F 0.41 and 0.46).

2-*Acetoxy*-2-(4-*methoxybenzoyl*)-4,6-*dimethoxybenzo*[b]-*furan*-3(2H)-*one* (XLI), the R_F 0.46 fraction, yellow-brown with the spray reagent, afforded a pale yellow amorphous solid (15 mg), $\nu_{max.}$ ($CHCl_3$) 1792 (benzoyl C=O), 1745 (acetyl C=O), and 1700 cm^{-1} (C=O in five-membered heterocycle) (Found: M^+, 386.101. $C_{20}H_{18}O_8$ requires M, 386.100); *m/e* 386 (8.2%, M^+), 223(32), 209(6.0), 206(23), 182(11), 180(10), 164(11), 152(10.3), 137(14), 136(10.1), and 135(50); τ 2.53 (d, J 8.5 Hz, H-2′ and -6′), 3.10 (d, J 8.5 Hz, H-3′ and -5′), 3.65 (d, J 2.0 Hz, H-7), 3.72 (d, J 2.0 Hz, H-5), 6.10 (s, 2 × OMe), 6.22 (s, OMe), and 7.73 (s, 2-OAc).

2-(α-*Acetoxy*-4-*methoxybenzyl*)-2,4,6-*trimethoxybenzo*[b]-*furan*-3(2H)-*one* (XL), the R_F 0.41 fraction, yellow-brown with the spray reagent, crystallized from ethanol in fine white needles (225 mg), m.p. 196°, $\nu_{max.}$ ($CHCl_3$) 1760 (acetyl C=O) and 1715 cm^{-1} (C=O in five-membered heterocyclic ring) [Found: (M^+ — 59), 343.118. $C_{21}H_{22}O_8$ requires *m/e* 343.118]; *m/e* 402 (<0.1%, M^+), 343(1.9), 329(3.1), 267(13), 266(78), 225(14), 224(99), 223(26), 210(16), 209(100), 181 (10.6), 180(9.4), 179(10), 152(6.9), 151(5.6), 149(6.9), 138(10), 137(89), and 135(13); τ 2.50 (d, J 8.2 Hz, H-2′ and -6′), 3.10 (d, J 8.2 Hz, H-3′ and -5′), 3.72 (d, J 2.0 Hz, H-7), 3.92 (d, J 2.0 Hz, H-5), 3.97 (s, H-α), 6.07 (s, 2 × OMe), 6.20 (s, OMe), 6.77 (s, OMe), and 8.15 (s, α-OAc).

4,4′,6′-*Trimethoxyaurone*.— 2′-Hydroxy-4,4′,6′-trimethoxy-*trans*-chalcone (314 mg), m.p. 110°, and lead tetra-acetate (660 mg), dissolved in acetic acid (10 ml), were heated for 40 min at 96 °C. The product, worked up as above and purified by t.l.c. (R_F 0.29 in benzene–ethyl acetate, 8 : 2; orange with the spray reagent) crystallized from acetone as orange-yellow needles (209 mg), m.p. 171° (lit.,[6] 166.5—167.5°), $\nu_{max.}$ ($CHCl_3$) 1700 cm^{-1} (C=O in five-membered ring), *m/e* 312(100%, M^+), 311(21), 297(4.2), 285(3.3), 284(17), 283(9.9), 282(36), 269(3.3), 267(2.7), 266(2.1), 253(2.5), 252(2.6), 205(2.1), 180(1.3), 156(6.9), 152(2.2), 151(2.4), 150(3.5), 134(4.5), 133(2.4), 132(3.3), 121(8.4), and 107(2.5); τ 2.17 (d, J 8.2 Hz, H-2′ and -6′), 3.03 (d, J 8.2 Hz, H-3′ and -5′), 3.27 (s, H_α), 3.65 (d, J 2.0 Hz, H-7), 3.88 (d, J 2.0 Hz, H-5), and 6.05 (s, 3 × OMe).

Financial assistance by the South African Council of Scientific and Industrial Research, the Leather Industries Research Institute, Grahamstown, the South African Wattle Growers' Union, and the Sentrale Navorsingsfonds of this University is gratefully acknowledged. Mass spectra were kindly recorded by Mr. H. K. L. Hundt and Dr. J. M. Steyn, Department of Pharmacology, Medical Faculty of this University.

[4/2617 *Received*, 16*th December*, 1974]