Total Synthesis of Pulvinones, 4-Benzylidene-2-phenyltetronic Acid Pigments of Fungi

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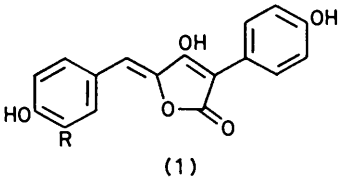
The application of 2-aryl *O*-methyltetronic acids (9) and (31) in the total synthesis of pulvinone pigments found in *Aspergillus terreus* and *Suillus grevillei* is described. Regioselective reductions of the corresponding maleic anhydride derivatives (8) and (30) with lithium aluminium hydride provide (9) and (31) respectively. Metallation of the tetronic acid (9) using lithium *N*-cyclohexyl-*N*-isopropylamide, followed by treatment with *p*-anisaldehyde and dehydration of the intermediate carbinol led to pulvinone (14). In a similar manner, condensations between (9), and 3,4- and 2,4-dimethoxybenzaldehydes produced pulvinones (17) and (18) respectively. The pulvinone (17) was identical with that obtained from the larch mushroom *S. grevillei*, but the isomeric pulvinone (18) was not identical with that purported to have this constitution and isolated from *A. terreus*.

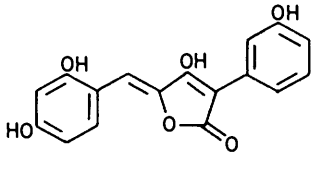
Unambiguous syntheses of the prenylated pulvinones (23) and (24) from *O*-methyltetronic acids (9) and (31) respectively, and the appropriate aryl aldehydes, suggest that the biosynthesis of the bis-chromanated metabolite (22), from (1a) *via* (20) in *A. terreus*, proceeds by selective monoprenylation of (1a) leading to intermediate (4a), and by selective chromanation of (20) leading to intermediate (21).

'PULVINONE' is the generic name used to designate the new family of substituted 4-benzylidene-2-phenyltetronic acid pigments isolated recently from the common larch mushroom *Suillus grevillei* (Klotsch) Sing, and from cultures of *Aspergillus terreus*.[1] The isolation

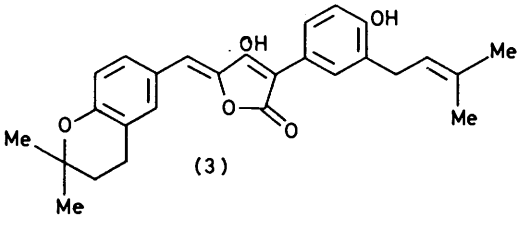


(1)

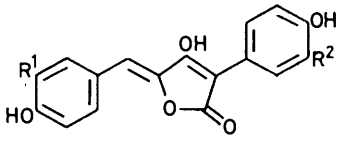
a R = H; *b* R = OH



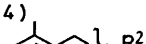
(2)

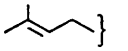


(3)



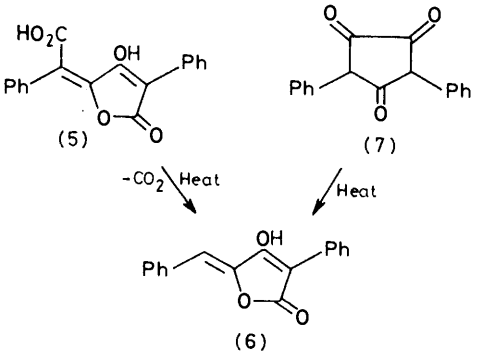
(4)

a R^1 =  ; R^2 = H

b R^1 = H; R^2 = 

of the relatively simple di- and tri-hydroxylated derivatives (1a) and (1b) was reported simultaneously in 1973 from *A. terreus* [2] and *S. grevillei* [3] respectively. Two years later Seto and his co-workers reported the isolation of six additional pulvinones † from *A. terreus*,[4] which included (2), and several novel 'prenylated' derivatives [*e.g.* (3)]; more recent studies have resulted in the isolation of a biosynthetically significant monoprenylated pulvinone [(4a) or (4b)] from a cell-free preparation of the fungus.[5]

The fundamental pulvinone carbon skeleton has been recognised for a number of years as a product of thermal decarboxylation of lichen pulvinic acids (5), themselves known for almost a century.[8] In addition, pulvinone itself (6) was prepared by Claisen as early as 1895 by thermal rearrangement of 2,5-diphenylcyclopentane-1,3,4-trione (7).[9] The uncertainties inherent in assigning structures to *unsymmetrically* substituted pulvinones,‡ necessitated the development of an unambiguous synthetic route to this new class of natural compound. In the preceding paper [11] we described the application of 2-methoxy-3-aryl, and other unsymmetrically substituted, maleic anhydrides to the synthesis of *O*-methyltetronic acid and 4-ylidenetetronic acid derivatives. We now report the development of



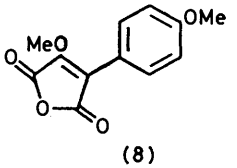
(5) (7) (6)

† The names 'aspulvinone'[6] and 'aspergillide'[7] have also been suggested to designate the family of pulvinone metabolites from *A. terreus*.

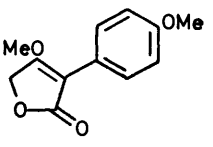
‡ See following paper, and ref. 10.

these studies to the total synthesis of pulvinone pigments found in *A. terreus* and *S. grevillei*. These studies have not only resolved a number of structural uncertainties amongst this class of compound, but also provided a basis for consideration of the biosynthesis of the intriguing 'prenylated' pulvinones in *A. terreus*.[12]

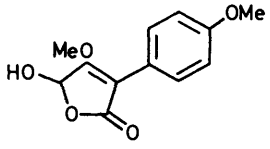
We first examined synthetic routes to permethylated



(8)



(9)



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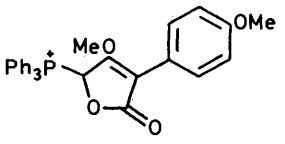
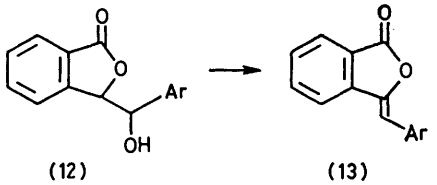


(11)

derivatives of the hydroxypulvinones [(1a), (2)] (ex. *A. terreus*) and (1b) (ex. *S. grevillei*), utilising the maleic anhydride (8) as the common starting material. The maleic anhydride (8) is easily available from 4-methoxyphenylacetonitrile by the methods outlined previously,[11] and the reduction of (8) with lithium aluminium hydride has been shown to lead to a mixture of the *O*-methyltetronic acid (9) and the corresponding 4-hydroxy-derivative (10).[11] Allylic bromination of (9), with *N*-bromosuccinimide, and bromination of the hydroxy-derivative (10) with phosphorus tribromide led to the same bromide, which was converted into the phosphonium salt (11) with triphenylphosphine. Although we have successfully applied ylides produced from salts of type (11) in Wittig synthesis during earlier work,[13] attempts to utilise the ylide from (11) in a synthesis of pulvinones, *via* condensation with aryl aldehydes, met with limited success, and only low yields of pulvinones were secured. We ultimately abandoned this approach to the pulvinone carbon skeleton in favour of one based on aldol-type condensations involving the *O*-methyltetronic acid (9) and appropriate aryl aldehydes.

The feasibility of the aldol-type condensation approach to pulvinones *via* the *O*-methyltetronic acid carbanions, was first investigated using phthalide as a model substrate. Reaction of phthalide with lithium *N*-cyclohexyl-*N*-isopropylamide (LCPA), at −70 °C, produced the corresponding carbanion which with *p*-anisaldehyde gave (>90%) the carbinol (12). Dehydration of (12) in an acetic acid–sulphuric acid–acetic anhydride mixture then led to the orange crystalline *Z*-benzylidenephthalide (13) (60%) identical with a sample prepared by an alternative (Perkin-type) method starting from phthalic anhydride.[14]

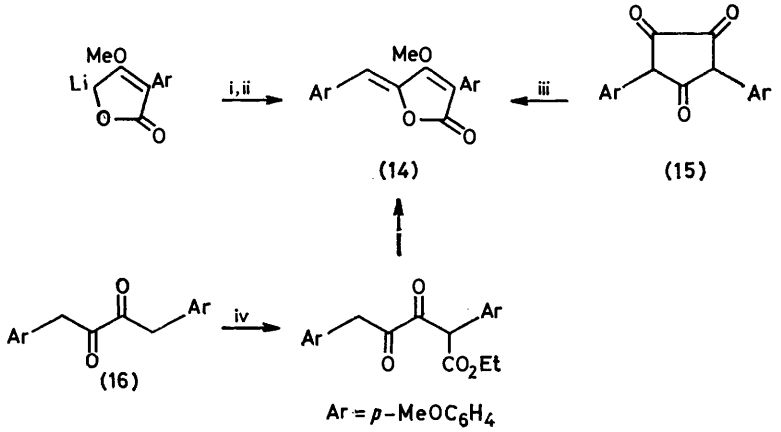
We next turned to the application of the *O*-methyltetronic acid (9) as precursor for the aldol synthesis of pulvinones. Metallation of the tetronic acid at −78 °C in tetrahydrofuran using lithium *N*-cyclohexyl-*N*-isopropylamide (LCPA), followed by treatment with *p*-anisaldehyde and dehydration of the intermediate



(12) (13)

Ar = *p*-MeOC$_6$H$_4$

carbinol gave *O*-methyl-4,4′-dimethoxypulvinone (14) as golden needles, which was identical in every respect



(14) (15) (16)

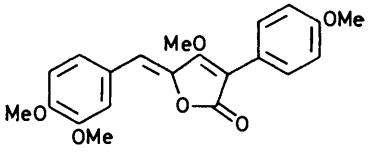
Ar = *p*-MeOC$_6$H$_4$

SCHEME 1 *Reagents:* i, 4-MeOC$_6$H$_4$CHO; ii, 4-MeC$_6$H$_4$SO$_3$H; iii, heat; iv, K$_2$CO$_3$–ClCO$_2$Et

(m.p. and mixed m.p., i.r., ^{1}H n.m.r., and mass spec.) with a natural sample obtained from *A. terreus*.[2] During the course of our studies, two alternative routes to the symmetrically substituted pulvinone were described. In one approach, the pulvinone carbon skeleton was generated by the familiar (Claisen) thermal rearrangement of dimethoxycyclopentanetrione (15),[2] and in the second approach, use was made of the acylation of 1,4-diphenylbutane-2,3-dione (16), by methyl chloro-

formate, as a key stage (Scheme 1).[7] It is significant that neither of these alternative approaches is adaptable to the unambiguous synthesis of unsymmetrically substituted pulvinones.

In a manner similar to that described for pulvinone (14), the *O*-methyltetronic acid (9) with 3,4-dimethoxybenzaldehyde gave the pulvinone (17) identical with that obtained from the larch mushroom *S. grevillei*.[3] The isomeric *O*-methyl-2,4,4′-trimethoxypulvinone (18) was also synthesised; this pulvinone was not identical (m.p., spectral, and chromatography data) with that purported to have this constitution and isolated from *A. terreus*.[4] Inspection of the ^{1}H n.m.r. spectral data for the trihydroxypulvinone metabolite from *A. terreus*, defines clearly a 2,4-dihydroxy aryl-substitution pattern, which, taken together with our present synthetic work, supports the revised structure (19) for the pigment. This observation later led us to question several of the structures proposed by Seto *et al.* for the unsymmetrically substituted pulvinone metabolites from *A. terreus*. The outcome of a re-examination of these structures, using n.m.r., mass spectral, and *X*-ray measurements, in addition to synthetic studies is described in an accompanying paper.



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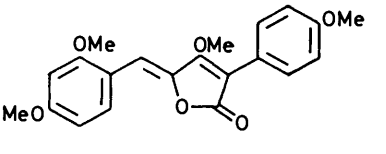
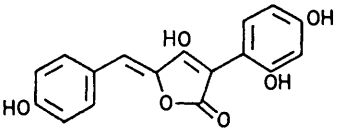
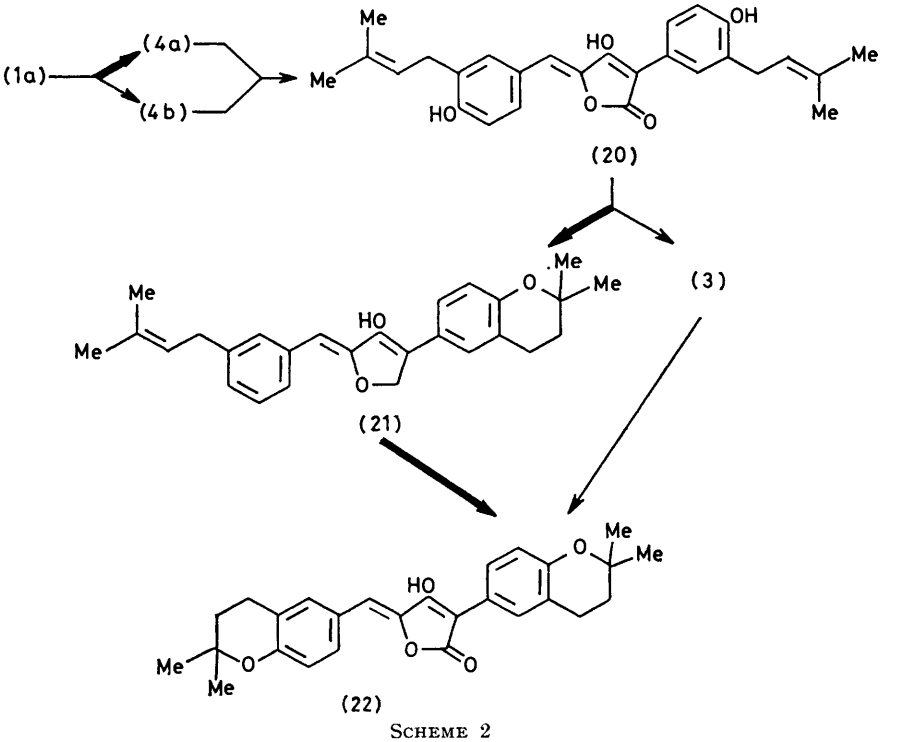


(18)



(19)

In contemporaneous studies of the biosynthesis of pulvinones in *A. terreus*, Seto and his co-workers suggested that the bischromanated metabolite (22) originates from the 4,4′-dihydroxy-compound (1a) by step-wise enzymatic 'prenylation' of the aryl rings leading to (20) followed by step-wise cyclisation ('chromanation').[5,6] This scheme (Scheme 2) posed two interesting and fundamental questions: (*a*) which ring in (1a) is first prenylated and (*b*) is chroman (3) or chroman (21) an intermediate between (20) and (22)? As a contribution to this problem we extended our synthetic work, and developed unambiguous syntheses

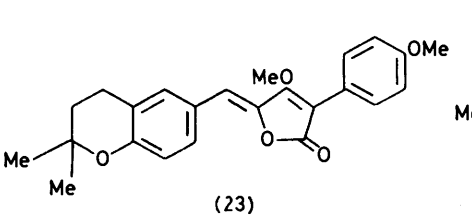


SCHEME 2

of the unsymmetrically substituted prenylated pulvinone derivatives (23) and (24).

4-Hydroxybenzaldehyde was first converted into the 3-prenylated derivative (26a) following conversion into the allyl ether (25) and Claisen rearrangement.[15] Treatment of the prenylated phenol with acid then led to the chroman (27) which was smoothly converted into the nitrile (28b) *via* the corresponding benzyl alcohol (28a) and benzyl chloride. Condensation between the anion produced from (28b) and diethyl oxalate then gave the pyruvate (29) which by methylation followed by acid hydrolysis and cyclisation led to the maleic anhydride derivative (30). The reduction of the anhydride with lithium aluminium hydride was totally regioselective, and gave rise to the key intermediate *O*-methyltetronic acid (31).

Metallation of (9) with LCPA, followed by treatment with the chroman-aldehyde (27) and dehydration of the intermediate carbinol then led to the pulvinone (23). The pulvinone was found to be identical with the compound derived from the monoprenylated metabolite, m.p. 183—185 °C, found in young cultures of *A. terreus*,[6] following acid cyclisation to the corresponding chroman and methylation. In a similar sequence the *O*-methylchromantetronic acid (31) and the aryl aldehyde (26b) led to the pulvinone (24) which was found to be identical with the dimethyl derivative of the monochromanated intermediate [earlier assigned the incorrect structure (3) by Seto *et al.*[4]] between (20) and (22).* Our synthetic investigations thus suggested that the initially produced prenylated metabolite in the biosynthesis of (22) from (1a) is (4a), and that chroman (21) rather than (3) is the more likely immediate precursor of (22).



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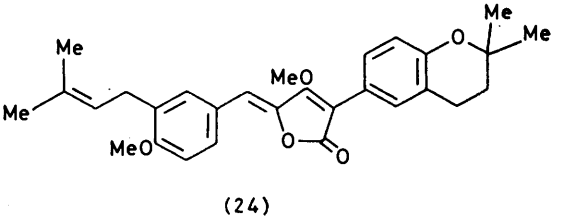

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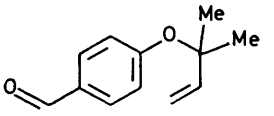

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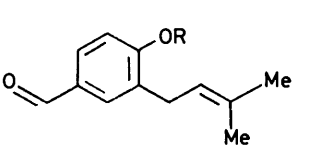
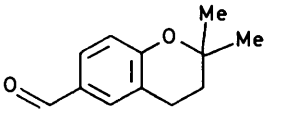


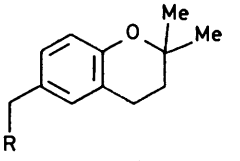
(26)

a; R = H

b; R = Me



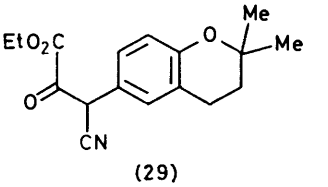
(27)



(28)

a; R = OH

b; R = CN



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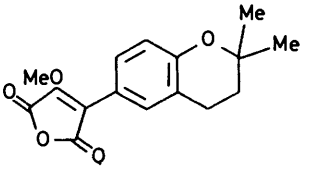

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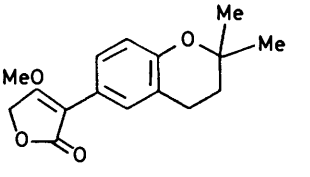

(31)

EXPERIMENTAL

For general experimental details see preceding paper.

(Z)-3-(4-*Methoxybenzylidene*)*phthalide* (13).—A solution of n-butyl-lithium (2.1M) in hexane (10 ml) was added to *N*-cyclohexyl-*N*-isopropylamine (2.8 g) at 0 °C under argon, and the mixture was then cooled to −70 °C and diluted with dry tetrahydrofuran (10 ml). A solution of phthalide (2.7 g) and 4-methoxybenzaldehyde (2.7 g) in tetrahydrofuran (40 ml) was added during 5 min, and the mixture was then allowed to warm to −50 °C at which point it was diluted with dilute hydrochloric acid and extracted with ether. Evaporation of the washed (H_2O) and dried ether

* A similar condensation between (31) and (27) led to the methyl derivative of bischroman (22).

extracts left the intermediate secondary carbinol (5.5 g) as an oil τ 2.1—3.5 (m, 8 H), 4.46 (d, *J* 6, 1 H), 5.03 (d, *J* 6, 1 H), 5.5 (OH), and 6.3 (OMe) which was not further purified. A mixture of the carbinol (1 g) in acetic acid (400 ml), acetic anhydride (200 ml), and concentrated sulphuric acid (10 ml) was heated at 100 °C for 5 min, then cooled and poured onto iced water (2 l) and extracted with ether. Evaporation of the dried ether extracts and crystallisation of the residue from benzene gave the benzylidenephthalide (0.55 g, 60%) as orange needles, m.p. 147—147.5 °C (lit.,[14] m.p. 147.5—148 °C), $\lambda_{max.}$(CHCl$_3$) 358, 323, and 311 nm; $\nu_{max.}$(KBr) 1 790 and 1 607 cm^{-1}; τ 2.05—2.8 (m, 4 H), 2.27 (d, *J* 9, 2 H), 3.12 (d, *J* 9, 2 H), 3.7 (ArC*H*), and 6.2 (OMe); *m/e* 252; $C_{16}H_{12}O_3$ requires *M* 252.

Preparation of Pulvinones: General Procedure.—A solution of the 2-aryl-3-methoxybut-2-enolide [3-aryl-4-methoxyfuran-2(5*H*)-one] (1 equiv.) and the aryl aldehyde (1 equiv.) in dry tetrahydrofuran (*ca.* 5 ml per mmol reactant) was added, during 5 min, to a stirred solution of lithium *N*-cyclohexyl-*N*-isopropylamide (1 equiv.) [prepared from Bu^{n}Li (2 mol in hexane) and *N*-cyclohexyl-*N*-isopropylamine at 0 °C] in dry tetrahydrofuran (*ca.* 3 ml per mmol reagent) at −78 °C under argon. The mixture was stirred at −78 °C for 20 min, and then allowed to warm to −50 °C during 0.25 h. Water was added to the mixture at −50 °C which was then acidified (dilute HCl) and extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts left the intermediate secondary carbinol (>90%) which was dehydrated without further purification. A solution of the secondary carbinol in dry benzene (*ca.* 0.1% solution) containing toluene-*p*-sulphonic acid (*ca.* 0.1% solution) was heated under reflux for 0.5 h, and then evaporated to dryness. Chromatography on silica gel, followed by crystallisation then gave the pulvinones.

4,4′-*Dimethoxypulvinone* O-*Methyl Ether* [4-*Methoxy*-3-p-*methoxyphenyl*-5-p-*methoxybenzylidenefuran*-2(5H)-*one*] (14).—By the general procedure, the butenolide (9) (0.44 g) and 4-methoxybenzaldehyde (0.27 g) gave an intermediate secondary carbinol (0.68 g), a yellow oil, τ 2.0—3.3 (m, 8 H), 4.92 (m, 2 H), 5.4 (m, 1 H), and 6.2—6.3 (3 × O*Me*). Dehydration, followed by chromatography in chloroform and crystallisation from methanol–chloroform (95 : 5) gave the *pulvinone* (0.46 g, 70%) as golden needles, m.p. 137—138.5 °C (lit.,[2,7] m.p. 137—139 °C), $\lambda_{max.}$(EtOH) 361, 292infl., 280, and 274 nm; $\nu_{max.}$(KBr) 1 765, 1 630, and 1 601 cm^{-1}; τ 2.47 (d, *J* 9, 2 H), 2.73 (d, *J* 9, 2 H), 3.26 (d, *J* 9, 2 H), 3.29 (d, *J* 9, 2 H), 3.93 (ArC*H*:), and 6.32 (3 × O*Me*). The pulvinone was identical (m.p. and mixed m.p., ^{1}H n.m.r. and i.r. spectra and t.l.c. behaviour) with a sample derived from natural 4,4′-dihydroxypulvinone (from *Aspergillus terreus*) by methylation with diazomethane.

3′,4,4′-*Trimethoxypulvinone* O-*Methyl Ether* [5-(3,4-*Dimethoxybenzylidene*)-4-*methoxy*-3-p-*methoxyphenylfuran*-2(5H)-*one*] (17).—By the general procedure, the butenolide (9) (0.44 g) and 3,4-dimethoxybenzaldehyde (0.29 g) gave an intermediate secondary alcohol showing τ 2.2—3.5 (m, 7 H), 4.95 (m, 2 H), 5.95 (OH), 6.1—6.3 (4 × O*Me*). Dehydration, followed by chromatography in chloroform and crystallisation from ethyl acetate gave the *pulvinone* (0.41 g, 60%) as green-yellow plates, m.p. 153.5—154 °C, $\lambda_{max.}$(MeOH) 367.5 (4.51), 258 (4.1), and 239 (4.24) nm; $\nu_{max.}$(KBr) 1 744 and 1 657 cm^{-1}; τ 2.5—3.3 (m, 7 H), 3.86 (ArC*H*:), 6.12 (OMe), 6.17 (OMe), and 6.23 (OMe) (Found: C, 68.4; H, 5.4. $C_{21}H_{20}O_6$ requires C, 68.5; H, 5.5%). The pulvinone was identical (m.p. and mixed m.p., ^{1}H n.m.r. and i.r. spectra, t.l.c. behaviour) with a sample derived from natural 3′,4,4′-trihydroxypulvinone (from *Suillus grevillei*) by methylation with diazomethane.

2′,4,4′-*Trimethoxypulvinone* O-*Methyl Ether* [5-(2,4-*Dimethoxybenzylidene*)-4-*methoxy*-3-p-*methoxyphenylfuran*-2(5H)-*one*] (18).—By the general procedure, the butenolide (9) (0.44 g) and 2,4-dimethoxybenzaldehyde (0.29 g) gave an intermediate secondary alcohol showing τ 2.5—3.7 (m, 7 H), 4.61 (d, *J* 2, 1 H), 4.86 (d, *J* 2, 1 H), 5.9 (O*H*), and 6.3 (3 × OMe). Dehydration, followed by chromatography in chloroform–methanol (99 : 1), and crystallisation from methanol–ethyl acetate gave the *pulvinone* (0.49 g, 70%) as yellow needles, m.p. 167—167.5 °C, $\lambda_{max.}$(MeOH) 373.5 (4.47), 322.5infl. (4.01), 248.5infl. (4.18), and 240.5 (4.19) nm; $\nu_{max.}$(KBr) 1 750 and 1 626 cm^{-1}; τ 1.9 (d, *J* 9, 6′-H), 2.57 (d, *J* 9, 2- and 6-H), 3.13 (d, *J* 9, 3- and 5-H), 3.32 (ArC*H*:), 3.51 (dd, *J* 9 and 2, 5′-H), 3.66 (3′-H), and 6.19—6.22 (4 × O*Me*) (Found: C, 68.5; H, 5.7. $C_{21}H_{20}O_6$ requires C, 68.5; H, 5.5%).

4-*Hydroxy*-3-(3-*methylbut*-2-*enyl*)*benzaldehyde* (26a).—Reaction between the potassium salt of 4-hydroxybenzaldehyde and 3-chloro-3-methylbut-1-yne led to the corresponding dimethylprop-2-ynyl ether (30%), b.p. 104 °C/1 mmHg (lit.,[15] b.p. 107—109 °C/3 mmHg), $\nu_{max.}$(film) 3 300, 2 126, and 1 695 cm^{-1}; τ 0.2 (C*H*O), 2.26 (d, *J* 9, 2 H), 2.77 (d, *J* 9, 2 H), 7.2 (:C*H*), and 8.32 (*Me*$_2$), which was treated with hydrogen in hexane in the presence of Lindlar's catalyst to give 4-(1,1-dimethylprop-2-enoxy)benzaldehyde (25) (95%), b.p. 86—100 °C/0.1 mmHg (lit.,[15] b.p. 96—97 °C/0.4 mmHg), $\nu_{max.}$ 1 795 and 1 604 cm^{-1}; τ 0.24 (C*H*O), 2.33 (d, *J* 9, 2 H), 3.01 (d, *J* 9, 2 H), 3.92 (m, C*H*:CH$_2$), 4.86 (m, CH:C*H*$_2$), and 8.49 (Me$_2$); *m/e* 190.096 0 (Calc. for $C_{12}H_{14}O_2$: *M* 190.099 4). Claisen rearrangement of the allyl ether in diethylaniline at 165 °C for 2 h, then gave the phenol (26a) (78%), b.p. 138—142 °C/0.05 mmHg (lit.,[15] b.p. 138—140 °C/0.3 mmHg), $\lambda_{max.}$(EtOH) 226 and 286 nm; $\nu_{max.}$ 3 280, 1 670, and 1 590 cm^{-1}; τ 0.3 (C*H*O), 1.78 (O*H*), 2.15—2.5 (m, 2 H), 3.02 (d, *J* 9, 1 H), 4.7 (t, *J* *ca.* 7, CH$_2$C*H*), 6.65 (d, *J* 7, C*H*$_2$CH), and 8.28 (Me$_2$); *m/e* 190.100 1 (Calc. for $C_{12}H_{14}O_2$: *M* 190.099 4).

4-*Methoxy*-3-(3-*methylbut*-2-*enyl*)*benzaldehyde* (26b).—The ether was prepared from the corresponding phenol (26a) using dimethyl sulphate in acetone in the presence of anhydrous potassium carbonate. It had b.p. 90—96 °C/0.3 mmHg, $\nu_{max.}$ 1 692 and 1 590 cm^{-1}; τ 0.14 (C*H*O), 2.1—2.4 (m, 2 H), 3.06 (d, *J* 9, 1 H), 4.7 (t, *J* 7, CH$_2$C*H*:), 6.12 (OMe), 6.68 (d, *J* 7, C*H*$_2$CH:), and 8.28 (Me$_2$); *m/e* 204.116 9 ($C_{13}H_{16}O_2$ requires *M* 204.115 0).

6-*Formyl*-2,2-*dimethylchroman* (27).—A solution of 4-hydroxy-3-(3-methylbut-2-enyl)benzaldehyde (22 g) in ethanol (720 ml) and 10% sulphuric acid (1 320 ml) was heated under reflux in a nitrogen atmosphere for 4 h, and then cooled. The solution was diluted with water and then extracted with ether. Evaporation of the washed (H_2O) and dried ether extracts, followed by distillation of the residue gave the *chroman* (20.4 g, 93%) as a colourless oil, b.p. 97—98 °C/0.2 mmHg, $\nu_{max.}$(film) 1 692 cm^{-1}; τ 0.26 (C*H*O), 2.3—2.5 (m, 2 H), 3.18 (d, *J* 8, 1 H), 7.18 (t, *J* 7, ArC*H*$_2$CH$_2$), 8.17 (t, *J* 7, ArCH$_2$C*H*$_2$), and 8.62 (Me$_2$); *m/e* 190.100 ($C_{12}H_{14}O_2$ requires *M* 190.099).

6-*Hydroxymethyl*-2,2-*dimethylchroman* (28a).—Reduction of 6-formyl-2,2-dimethylchroman (25.5 g) with lithium

aluminium hydride (1.4 g) in ether (500 ml) in the usual manner, gave the *alcohol* (23.7 g, 92%) as a colourless oil, b.p. 108—110 °C/0.2 mmHg, $\nu_{max.}$(film) 3 350, 1 617, and 1 591 cm^{-1}; τ 3.1 (m, 2 H), 3.4 (d, *J* 8, 1 H), 5.57 (CH_2O), 7.28 (t, *J* 7, $ArCH_2{\cdot}CH_2$), 8.16 (OH), 8.26 (t, *J* 7, $ArCH_2CH_2$), and 8.7 (Me_2); *m/e* 192.115 ($C_{12}H_{16}O_2$ requires *M* 192.115 0).

6-*Cyanomethyl*-2,2-*dimethylchroman* (28b).—A solution of thionyl chloride (11 ml) in dry benzene (30 ml) was added dropwise during 0.5 h, to a stirred solution of 6-hydroxymethyl-2,2-dimethylchroman (22.7 g) in pyridine (11 g) and benzene (200 ml) at 0—2 °C. The mixture was heated at 60 °C for 1 h, then cooled and poured into water (500 ml) and extracted with ether. The combined ether extracts were washed with water, then dried, and evaporated to leave the corresponding chloride (24 g, 90%) as a solid, m.p. 57—59 °C, $\nu_{max.}$ 1 620, 1 588, and 1 504 cm^{-1}; τ 3.04 (m, 2 H), 3.36 (d, *J* 8, 1 H), 5.54 (CH_2Cl), 7.29 (t, *J* 7, $ArCH_2{\cdot}CH_2$), 8.27 (t, *J* 7, $ArCH_2CH_2$), and 8.7 (Me_2) which was used without further purification.

A solution of the chloride (24 g) (from above) in dimethyl sulphoxide (50 ml) was added to a stirred solution of dry sodium cyanide (9.1 g) in dimethyl sulphoxide at 50 °C, at such a rate that the temperature did not exceed 50 °C. The mixture was heated at 60 °C for 0.5 h, then cooled and diluted with water and extracted with ether. The combined ether extracts were washed successively with water, 4M-hydrochloric acid and water, and then dried and evaporated. Distillation of the residue gave the *nitrile* (20 g, 84%), b.p. 110—111 °C/0.5 mmHg, which crystallised; this was recrystallised from light petroleum (b.p. 40—60 °C) to give colourless needles, m.p. 55 °C, $\nu_{max.}$ 2 280, 1 618, and 1 582 cm^{-1}; τ 3.05 (m, 2 H), 3.32 (d, *J* 8, 1 H), 6.44 (CH_2CN), 7.25 (t, *J* 7, $ArCH_2CH_2$), 8.22 (t, *J* 7, $ArCH_2CH_2$), and 8.7 (Me_2) (Found: C, 77.6; H, 7.7; N, 6.8. $C_{13}H_{15}NO$ requires C, 77.6; H, 7.5; N, 7.0%).

Ethyl 3-*Cyano*-3-(2,2-*dimethylchroman*-6-*yl*)*pyruvate* (29).—A mixture of 6-cyanomethyl-2,2-dimethylchroman (23 g), diethyl oxalate (35 g), and sodium hydride (5.8 g) in ether (600 ml) containing ethanol (0.5 ml) was heated under gentle reflux for 16 h and then cooled. The mixture was diluted with ethanol (*ca.* 2 ml) followed by water (4 000 ml), and the aqueous layer was then separated, acidified with hydrochloric acid, and extracted with ether. Evaporation of the dried ether extracts and crystallisation of the residue from n-hexane gave the *pyruvate* (27 g, 80%) as pale yellow needles, m.p. 108—109 °C, $\lambda_{max.}$(EtOH) 236, 251infl., and 329 nm; $\nu_{max.}$(KBr) 3 290, 2 230, and 1 706 cm^{-1}; τ 2.38—2.48 (m, 2 H), 2.82 (OH), 3.27 (d, *J* 8, 1 H), 5.52 (q, *J* 7.5, OCH_2Me), 7.21 (t, *J* 7, $ArCH_2CH_2$), 8.18 (t, *J* 7, $ArCH_2CH_2$), 8.53 (t, *J* 7.5, OCH_2CH_3), and 8.67 (Me_2) (Found: C, 67.4; H, 6.4; N, 4.5. $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.3; N, 4.6%).

2-(2,2-*Dimethylchroman*-6-*yl*)-3-*methoxymaleic Anhydride* (30).—Methylation of ethyl 3-cyano-3-(2,2-dimethylchroman-6-yl)pyruvate (23 g) with dimethyl sulphate (7.7 ml) in dry acetone (500 ml) in the presence of anhydrous potassium carbonate (11.7 g), in the usual manner, gave *ethyl* 3-*cyano*-3(2,2-*dimethylchroman*-6-*yl*)-2-*methoxyacrylate* (22.7 g, 94%) as pale yellow needles, m.p. 63—63.5 °C, $\lambda_{max.}$(EtOH) 232, 247, and 320 nm; $\nu_{max.}$(KBr) 2 270 and 1 720 cm^{-1}; τ 2.45—2.65 (m, 2 H), 3.29 (d, *J* 8, 1 H), 5.56 (q, *J* 7.5, OCH_2CH_3), 6.17 (OMe), 7.18 (t, *J* 7, $ArCH_2CH_2$), 8.14 (t, *J* 7, $ArCH_2CH_2$), 8.49 (t, *J* 7.5, OCH_2CH_3), and 8.62 (Me_2) (Found: N, 4.4. $C_{18}H_{21}NO_4$ requires N, 4.4%).

A solution of the acrylate (5 g) (from above) in acetic acid (60 ml) and water (36 ml) was treated dropwise with concentrated sulphuric acid (60 ml) at such a rate that the temperature did not exceed 110 °C. The mixture was cooled, then poured onto ice–water and extracted with ethyl acetate. The combined organic extracts were washed with water and then with 2M-potassium hydroxide solution. The aqueous layer was acidified with dilute hydrochloric acid and then extracted with ethyl acetate. Evaporation of the washed (H_2O) and dried ethyl acetate extracts left a residue which crystallised from benzene to give the *anhydride* (2.3 g, 50%) as yellow needles, m.p. 141.5—142.5 °C, $\lambda_{max.}$($CHCl_3$) 397 nm; $\nu_{max.}$(KBr) 1 836, 1 761, 1 642, and 1 618 cm^{-1}; τ 2.4 (m, 2 H), 3.34 (d, *J* 8, 1 H), 5.75 (OMe), 7.25 (t, *J* 7, $ArCH_2CH_2$), 8.24 (t, *J* 7, $ArCH_2CH_2$), and 8.71 (Me_2) (Found: C, 66.4; H, 5.5. $C_{16}H_{16}O_5$ requires C, 66.6; H, 5.6%).

2-(2,2-*Dimethylchroman*-6-*yl*)-3-*methoxybut*-2-*enolide* [3-(2,2-*Dimethylchroman*-6-*yl*)-4-*methoxyfuran*-2(5H)-*one*] (31).—By the general procedure described in the preceding paper, reduction of 3-methoxy-2-(2,2-dimethylchroman-6-yl)maleic anhydride (0.6 g) with lithium aluminium hydride (0.04 g), followed by chromatography using chloroform–methanol (50 : 1) as eluant led to (*a*) the *butenolide* (0.18 g) (eluted first) which crystallised from benzene–hexane as colourless prisms, m.p. 142—143 °C, $\lambda_{max.}$(EtOH) 278 nm; $\nu_{max.}$(KBr) 1 722 and 1 645 cm^{-1}; τ 2.42 (m, 2 H), 3.2 (d, *J* 8, 1 H), 5.18 (CH_2O), 6.04 (OMe), 7.19 (t, *J* 8, $ArCH_2CH_2$), 8.19 (t, *J* 8, $ArCH_2CH_2$), and 8.66 (Me_2) (Found: C, 70.4; H, 6.9. $C_{16}H_{18}O_4$ requires C, 70.1; H, 6.6%); and (*b*) 2-(2,2-*dimethylchroman*-6-*yl*)-4-*hydroxy*-3-*methoxybut*-2-*enolide* [3-(2,2-*dimethylchroman*-6-*yl*)-5-*hydroxy*-4-*methoxyfuran*-2(5H)-*one*] (0.23 g) (eluted second) which crystallised from benzene as colourless plates, m.p. 160—161 °C, $\lambda_{max.}$(EtOH) 229 and 287 nm; $\nu_{max.}$(KBr) 3 280, 1 704, and 1 649 cm^{-1}; τ 2.48 (m, 2 H), 3.25 (d, *J* 8, 1 H), 3.4 (OH), 3.9 (CHOH), 5.99 (OMe), 7.28 (t, *J* 8, $ArCH_2CH_2$), 8.27 (t, *J* 8, $ArCH_2CH_2$), and 8.71 (Me_2) (Found: C, 66.2; H, 6.4. $C_{16}H_{18}O_5$ requires C, 66.2; H, 6.2%).

2-(2,2-*Dimethylchroman*-6-*yl*)*but*-2-*enolide* [3-(2,2-*dimethylchroman*-6-*yl*)*furan*-2(5H)-*one*] (18 mg) was also separated by chromatography [eluted before butenolide (31)]; it crystallised from methanol as needles, m.p. 143—144 °C, $\lambda_{max.}$ 285 nm; $\nu_{max.}$(KBr) 1 732 cm^{-1}; τ 2.28 (HC:C·CO), 2.44 (m, 2 H), 3.18 (d, *J* 8, 1 H), 5.08 ($H_2C{\cdot}OCO$), 7.17 (t, *J* 8, $ArCH_2CH_2$), 8.18 (t, *J* 8, $ArCH_2CH_2$), and 8.66 (Me_2); *m/e* 244.114 4 ($C_{15}H_{16}O_3$ requires *M* 244.110).

2-(2,2-*Dimethylchroman*-6-*yl*)-4-(2,2-*dimethylchroman*-6-*ylidene*)-3-*methoxybut*-2-*enolide* [*O*-Methyl- (22)] [3-(2,2-*Dimethylchroman*-6-*yl*)-5-(2,2-*dimethylchroman*-6-*ylidene*)-4-*methoxyfuran*-2(5H)-*one*].—By the general procedure, the butenolide (31) (0.11 g) and chromancarbaldehyde (27) (0.09 g) gave the *butenolide* (0.1 g) which was purified by chromatography in chloroform, and crystallised from methanol as yellow prisms, m.p. 133—135 °C (Seto *et al.* report m.p. 154—157 °C for the naturally derived metabolite), $\lambda_{max.}$(EtOH) 236 and 366 nm; $\nu_{max.}$(KBr) 1 750, 1 601, and 1 496 cm^{-1}; τ 2.4—2.95 (m, 4 H), 3.28 (2 H), 3.89 (ArCH:), 6.21 (OMe), 7.23 (t, *J* 7, $ArCH_2CH_2$), 8.71 (t, *J* 7, $ArCH_2CH_2$), and 8.66 (Me_2) (Found: C, 75.1; H, 6.9. $C_{28}H_{30}O_5$ requires C, 75.3; H, 6.8%).

4-(2,2-*Dimethylchroman*-6-*ylidene*)-2-(4-*methoxyphenyl*)-3-*methoxybut*-2-*enolide* [3-p-*Methoxyphenyl*-4-*methoxy*-5-(2,2-*dimethylchroman*-6-*ylidene*)*furan*-2(5H)-*one*] (23).—By the

general procedure the butenolide (9) (0.29 g) and the chromancarbaldehyde (27) (0.25 g) gave the *butenolide* (0.4 g, 78%) which was purified by chromatography in chloroform and crystallised from methanol–ethyl acetate as yellow-green plates, m.p. 168.5—169 °C, $\lambda_{max.}$(EtOH) 240 and 364 nm; $\nu_{max.}$(KBr) 1 748, 1 602, 1 516, and 1 498 cm^{-1}; τ 2.48—2.74 (m, 4 H), 3.15 (d, *J* 9, 2 H), 3.31 (d, *J* 9, 1 H), 3.88 (ArC*H*:), 6.2 (2 × O*Me*), 7.21 (t, *J* 7, ArCH_2CH_2), 8.19 (t, *J* 7, ArCH_2CH_2), and 8.66 (Me_2) (Found: C, 73.1; H, 6.4. $C_{24}H_{24}O_5$ requires C, 73.4; H, 6.2%). The butenolide was identical with a sample derived from natural pulvinone (4a) (from *A. terreus*) following acid cyclisation to the corresponding dimethyl chroman and methylation with diazomethane.

2-(2,2-*Dimethylchroman*-6-*yl*)-4-[4-*methoxy*-3-(3-*methylbut*-2-*enyl*)]*benzylidene*-3-*methoxybut*-2-*enolide* [3-(2,2-*Dimethylchroman*-6-*yl*)-5-p-*methoxyphenyl*-3-*methylbut*-2-*enylbenzylidene*-4-*methoxyfuran*-2(5H)-*one*] (24).—By the general procedure, the butenolide (31) (0.11 g) and aryl aldehyde (26b) (0.096 g) gave the *butenolide* which was purified by chromatography in ether–pentane (1 : 1), and crystallised from ethanol as yellow needles, m.p. 106—108 °C, $\nu_{max.}$ 1 775 cm^{-1}; τ 2.27 (dd, *J* 9 and 2, 1 H), 2.51 (d, *J* 2, 1 H), 2.73 (d, *J* 2, 1 H), 2.8 (dd, *J* 9 and 2, 1 H), 3.13 (d, *J* 9, 1 H), 3.21 (d, *J* 9, 1 H), 3.79 (1 H), 4.7 (t, *J* 6.5, 1 H), 6.14 (3 H), 6.16 (3 H), 6.67 (d, *J* 6.5, 2 H), 7.19 (t, *J* 7, 2 H), and 8.18 (t, *J* 7, 2 H) (Found: C, 75.5; H, 6.8. $C_{29}H_{32}O_5$ requires C, 75.6; H, 7.0%).

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REFERENCES

[1] G. Pattenden, *Fortschr Chem. org. Naturstoffe*, 1978, **35**, 133.
[2] N. Ojima, S. Takenaka, and S. Seto, *Phytochemistry*, 1973, **12**, 2527.
[3] R. L. Edwards and M. Gill, *J.C.S. Perkin I*, 1973, 1921.
[4] N. Ojima, S. Takenaka, and S. Seto, *Phytochemistry*, 1975, **14**, 573.
[5] N. Ojima, K. Ogura, and S. Seto, *J.C.S. Chem. Comm.*, 1975, 717.
[6] N. Ojima, I. Takahashi, K. Ogura, and S. Seto, *Tetrahedron Letters*, 1976, 1013.
[7] B. T. Golding, R. W. Rickards, and Z. Vanek, *J.C.S. Perkin I*, 1975, 1961.
[8] *Cf.* A. Schonberg and A. Sina, *J. Chem. Soc.*, 1946, 601, and ref. 3.
[9] L. Claisen and T. Ewan, *Annalen*, 1895, **284**, 245.
[10] M. J. Begley, D. W. Knight, and G. Pattenden, *Tetrahedron Letters*, 1976, 131.
[11] D. W. Knight and G. Pattenden, preceding paper.
[12] Preliminary communications, D. W. Knight and G. Pattenden, *J.C.S. Chem. Comm.*, 1975, 876; 1976, 635.
[13] D. W. Knight and G. Pattenden, *J.C.S. Perkin I*, 1975, 635, 641.
[14] A. Horeau and J. Jacques, *Bull. Soc. chim. France*, 1948, 53; J. Rigaudy and P. Derible, *ibid.*, 1965, 3047.
[15] *Cf.* K. Kyogoku, K. Hatayama, S. Yokomori, T. Seki, and I. Tanaka, *Agric. Biol. Chem.*, 1975, **39**, 133, 667.