Synthesis of Tachrosin, (±)-Stachyoidin, and (±)-Tephrodin, Prenylflavonoids of Novel Type from *Tephrosia polystachyoides*[1]

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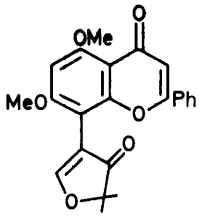
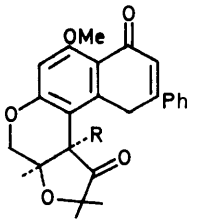
Tachrosin [8-(2,3-dihydro-2,2-dimethyl-3-oxo-4-furyl)-5,7-dimethoxyflavone] (1) has been synthesized by oxidative rearrangement of a 1-aryl-4-hydroxypent-1-en-3-one with thallium(III) nitrate followed by cyclisation to a 4-aryl-2,2-dimethylfuran-3(2*H*)-one as the key step. A multi-stage transformation of the flavone (1) gave 8-(3-hydroxy-3-methyl-2-oxobutyl)-5-methoxy-7-methoxycarbonylmethoxyflavone (29), which afforded in one step the furo[2,3-*c*]pyran (30). Reduction of (30) with borohydride and reoxidation yielded (±)-stachyoidin (2), and treatment of (2) with lead tetra-acetate gave (±)-tephrodin (3). Sodium alkoxides are shown to catalyse the transacetalisation of α-aryl-α-aroylacetaldehyde acetals.

TACHROSIN (1),[2] stachyoidin (2), and tephrodin (3),[3] isolated from *Tephrosia polystachyoides*, represent novel types of flavonoids and also novel patterns of incorporation of an isoprenoid unit into heterocyclic systems. In this paper we report the first synthesis of compounds (1), (±)-(2), and (±)-(3).

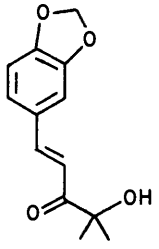
The synthesis of tachrosin (1) required the construction



(1)



(2) R = H
(3) R = OAc



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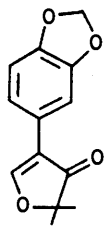

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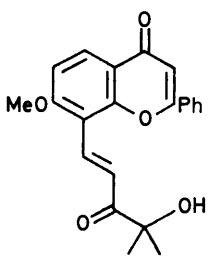


(6)

of a 4-arylfuran-3(2*H*)-one ring, for which there was no precedent in the literature. This ring contains a masked β-oxo-aldehyde function, suggesting that we should apply the oxidative rearrangement of chalcones by thallium(III) nitrate (TTN) in methanol to 1,2-diaryl-3,3-dimethoxypropan-1-ones[4] [reaction (i)]. In practice a model compound, the α-ketol (4),[5] underwent rapid oxidation with concomitant cyclisation, and furnished directly the desired 4-aryl-2,2-dimethylfuran-3(2*H*)-one (5). Next, 8-formyl-7-hydroxyflavone [6],† was transformed into 8-formyl-7-methoxyflavone and condensed with 3-hydroxy-3-methylbutan-2-one[7] to give the flavone (6). Oxidation of this model compound however was not successful owing to the formation of an insoluble precipitate, presumably a thallium complex, on addition of TTN.

$$\mathrm{ArCH{=}CH{\cdot}COAr' \xrightarrow[MeOH]{TTN} (MeO)_2CH{\cdot}CHAr{\cdot}COAr'} \quad \text{(i)}$$

The alternative route, *i.e.* to build up the furanoid ring before the flavone system, proved more useful. Accordingly the ketone (7) was prepared from 2-hydroxy-4,6-dimethoxybenzaldehyde.[8] Oxidation of (7) at room temperature followed by heating with acid gave directly the furanone (8). At lower temperature (−20 to 0 °C) the precursors of (8), the dimethyl acetal (9) and the cyclic acetal (10), were formed. Treatment with acid converted both into (8). From the diastereoisomeric mixture of cyclic acetals (10) the major *trans*-isomer could be obtained pure. Assignment of configuration was based on the shielding effect of the aromatic ring on the acetal methoxy-protons, which was operative in the *cis*- (δ 3.33) but not in the *trans*-epimer (δ 3.48). Whereas the acid-catalysed transformation of (9) or (10) required refluxing for several hours, treatment with sodium methoxide effected the same cyclisation within a few minutes at room temperature. With acetals incapable of cyclisation sodium alkoxides catalyse rapid transacetalisation and/or alcohol elimination. Thus upon treatment with sodium ethoxide the dimethyl acetal (11) was converted first into the diethyl acetal (12); this upon further treatment slowly changed into the vinyl ether (13), which was precipitated. This novel alkali-catalysed reaction of acetals can be interpreted as a reversion of the well known addition of a

† An improved preparation of this compound, obtained previously as a mixture with the 6-formyl derivative,[6] is described in the Experimental section.

[1] For a preliminary report on the synthesis of tachrosin see S. Antus, L. Farkas, M. Nógrádi, and P. Sohár, *J.C.S. Chem. Comm.*, 1974, 799.
[2] T. M. Smalberger, R. Vleggaar, and H. L. de Waal, *J. S. African Chem. Inst.*, 1971, **24**, 1.
[3] R. Vleggaar, T. M. Smalberger, and H. L. de Waal, *Tetrahedron Letters*, 1972, 703; *J. S. African Chem. Inst.*, 1973, **26**, 53.
[4] (*a*) A. McKillop, B. P. Swann, M. E. Ford, and E. C. Taylor, *J. Amer. Chem. Soc.*, 1973, **95**, 3641; (*b*) L. Farkas, Á. Gottsegen, M. Nógrádi, and S. Antus, *J.C.S. Perkin I*, 1974, 305.
[5] H. Scheibler and A. Fischer, *Ber.*, 1922, **55**, 915.
[6] S. Rangeswami and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 1939, **9A**, 7.
[7] H. Scheibler and A. Fischer, *Ber.*, 1922, **55**, 2903.
[8] D. D. Pratt and R. Robinson, *J. Chem. Soc.*, 1924, **125**, 195.

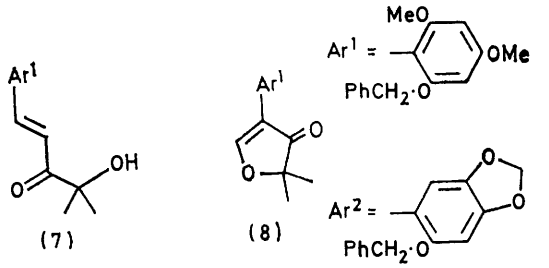
nucleophile at the β-carbon atom of an αβ-unsaturated carbonyl compound and proceeds by initial formation of an α-carbanion, stabilised by the adjacent aryl and carbonyl groups.

The furanone (8) was debenzylated to give the phenol (14), which reacted with acetonitrile (Houben–Hoesch) to afford the acetophenone (15). Benzoylation gave the ester (16), which underwent a Baker–Venkataraman transformation [9] by potassium hydroxide in pyridine to yield the diketone (17) (in the enol form); this was dehydrated to afford tachrosin (1).

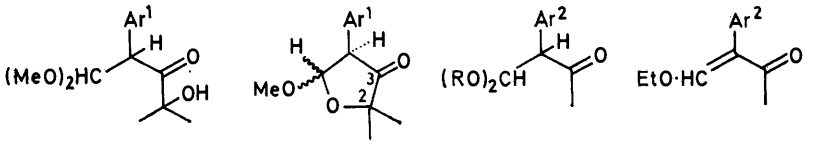
In view of the acceptable overall yield of this sequence (10.9% over ten steps from phloroglucinol) a scheme was devised for the transformation of tachrosin into stachyoidin, and tested on a model system. This involved the preparation of the furanone (18) in two steps from 2-benzyloxy-4-methoxybenzaldehyde,[10] debenzylation of (18) to give the phenol (19), and ethoxycarbonylmethylation to yield the ester (20), which was degraded with alkali to the acid (21). On treatment with sodium methoxide the corresponding ester (22) underwent double cyclisation and furnished directly the furopyran (23) as well as some hydrolysis product (21). This reaction is considered to proceed by an initial Dieckman-type condensation to give the hydroxy-ketone (24), one of the tautomers of which is the hemiacetal (25). Like the acetals discussed above this has a dissociable α-proton and can thus undergo alkali catalysed elimination of water to form (23).* Catalytic hydrogenation of (23) afforded (26) [an analogue of stachyoidin (2)], which was then oxidised with lead tetra-acetate to (27) containing the α-acetoxy-ketone unit of tephrodin (3).

Difficulties with the synthesis of the natural products motivated an alternative approach to (26) *via* reduction of (23) with sodium borohydride to the alcohol (28) followed by oxidation with chromic acid. Assignments of configuration to (26) and (28) were supported by the similarity of their n.m.r. spectra to those of the natural products of known relative configuration.[3] There is no such evidence for the acetate (27) but it is reasonable to suppose that attack of the oxidant takes place predominantly from the less-hindered ' convex ' face of the molecule.

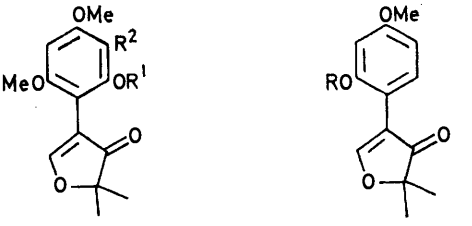
Transformation of tachrosin (1) into the ester (29) in five steps has already been reported,[3] and proceeded in our hands with an overall yield of 52%. Cyclisation of



(7) (8)



(9) (10) (11) R = Me (12) R = Et (13)



(14) $R^1 = R^2 = H$
(15) $R^1 = H$, $R^2 = CO \cdot CH_3$
(16) $R^1 = COPh$, $R^2 = CO \cdot CH_3$
(17) $R^1 = H$, $R^2 = CO \cdot CH_2 \cdot COPh$

(18) $R = CH_2Ph$
(19) R = H
(20) $R = CH_2 \cdot CO_2Et$

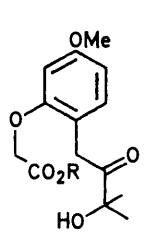
* A similar explanation for the dehydration of 2-hydroxyisoflavan-4-ones to isoflavones has been proposed independently.[11]

[9] H. Wagner and L. Farkas, in ' The Flavonoids,' ed. J. B. Harborne, T. J. Mabry, and H. Mabry, Chapman and Hall, London, 1975, p. 138.

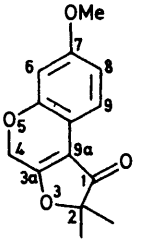
[10] L. Farkas, Á. Gottsegen, M. Nógrádi, and S. Antus, *J. Chem. Soc.* (*C*), 1971, 1994.

[11] V. Szabó and M. Zsuga, *Acta Chim. Acad. Sci. Hung.*, 1975, **85**, 179 and 191.

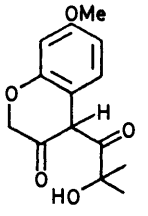
(29) with sodium methoxide in benzene gave didehydrostachyoidin (30). Treatment with 0.1M-sodium methoxide, satisfactory with the model (23) gave only traces of (30). Unlike the tetrasubstituted double bond in the model (23), that of didehydrostachyoidin (30) could not be saturated selectively by catalytic hydrogenation. The enone (30) was therefore reduced first with sodium borohydride to the (±)-alcohol (31), which was then oxidised with chromium trioxide in acetic acid to (±)-stachyoidin (2). Oxidation of (2) with lead tetra-acetate gave (±)-tephrodin (3).



(21) R = H
(22) R = Me



(23)



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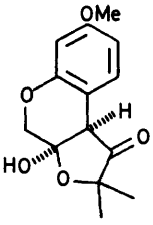

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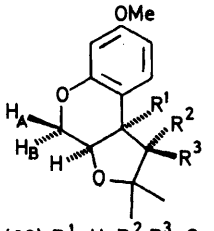
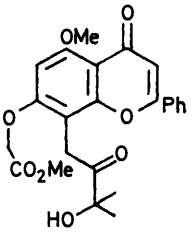


(26) R^1=H, R^2 R^3=O
(27) R^1=OAc, R^2 R^3=O
(28) R^1=R^2=H, R^3=OH



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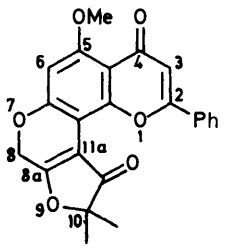

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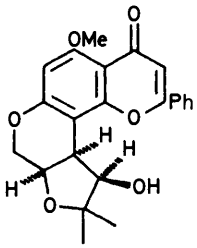

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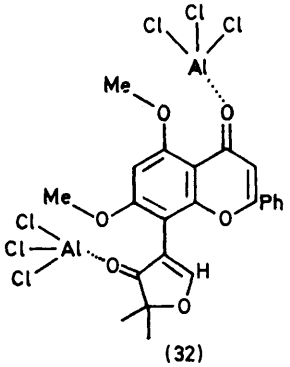

(32)

Synthetic tachrosin (1) was identified by direct comparison with the natural material, and racemic stachyoidin and tephrodin were compared with the optically active natural compounds; they showed identical n.m.r. and solution i.r. spectra.

The interaction between the furanone carbonyl group and the neighbouring oxygen atom in the pyrone ring deserves some comment. Demethylation of tachrosin to 5,7-di-*O*-demethyltachrosin was carried out with aluminium chloride in benzene at room temperature.[3] Under such conditions only partial 5-*O*-demethylation usually takes place, since this reaction is promoted by complexation of the aluminium chloride with the flavone carbonyl group.[12] A similar participation of the furanone carbonyl group may operate in the ready removal of the 7-*O*-methyl group of tachrosin (1), though in this case a less favoured seven-membered chelate ring has to be postulated (32). The viability of such a chelate ring was substantiated by comparison of the i.r. and n.m.r. spectra of the phenol (14), in which this type of chelation is conceivable, with analogues in which such chelation is prevented either by alkylation (8) or by a combined effect involving both the possibility of formation of a more stable six-membered chelate ring [(15) and (17)] and the disturbance of coplanarity of the two rings by *ortho*-disubstitution of the phenyl group. Diagnostic for the coplanarity of the aromatic nucleus and the furanoid ring in (14) was a decrease in the i.r. carbonyl frequency and a marked downfield shift of the furan H-5 signal [ν_{CO} (14) 1 645; *cf.* (8) 1 695, (15) 1 685, and (17) 1 695 cm^{-1}; δ(H-5) (14) 8.95; *cf.* (8) 8.15, (15) 8.18, and (17) 8.04].

EXPERIMENTAL

The purity of products was checked by t.l.c. and their structures were confirmed by i.r. and n.m.r. spectroscopy; here only relevant data are quoted, and such data are not

[12] Ref. 9, p. 157.

duplicated for analogous compounds. ^{1}H N.m.r. spectra were recorded with a Perkin-Elmer R12 (60 MHz) or a Varian XL 100 spectrometer (100 MHz) for solutions in $CDCl_3$; i.r. spectra were determined, unless otherwise stated, for KBr discs with a Zeiss UR10 spectrometer. Mass spectra were recorded with an A.E.I. MS9 instrument. M.p.s were determined with a Kofler hot-stage apparatus. Evaporations were carried out *in vacuo*. Acetylations were performed by heating the hydroxy-compound with acetic anhydride–pyridine on a steam-bath for 2 h. Catalytic hydrogenation over 10% palladium–charcoal was used for debenzylations.

2,2-*Dimethyl*-4-(3,4-*methylenedioxyphenyl*)*furan*-3(2H)-*one* (5).—A solution of 3-hydroxy-3-methyl-4-(3,4-methylenedioxyphenyl)but-3-en-2-one [5] (3.0 g) in methanol (120 ml) was treated with thallium(III) nitrate trihydrate (TTN) (6.4 g) at room temperature for 30 min. Filtration, neutralisation with N-sodium methoxide, evaporation, chromatography on silica gel ($CHCl_3$) and crystallisation from light petroleum gave the *furanone* (5) (1.0 g, 33%), m.p. 94—95 °C (Found: C, 67.1; H, 5.5. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%), $\nu_{max.}$ 1 700 (CO) and 1 610 cm^{-1} (C=C), δ 1.45 (s, Me) and 8.42 (s, =CHO).

8-*Formyl*-7-*methoxyflavone*.—The reaction of 7-hydroxyflavone [13] with hexamethylenetetramine yielded not as claimed [6] pure 8-formyl-7-hydroxyflavone, but a mixture with the 6-formyl isomer. The mixture (1.1 g) was acetylated and the product crystallised from methanol to give 7-*acetoxy*-8-*diacetoxymethylflavone* (0.65 g), m.p. 150—152 °C (Found: C, 64.4; H, 4.5. $C_{22}H_{18}O_8$ requires C, 64.4; H, 4.4%), $\nu_{max.}$ 1 780 and 1 760 (ester CO) and 1 660 cm^{-1} (CO); δ 2.82 [s, CH(O*Ac*)$_2$], 2.82 (s, ArO*Ac*), and 9.92 [s, C*H*(OAc)$_2$]. 8-Formyl-7-hydroxyflavone, m.p. 220—221 °C (lit.,[6] 223—224 °C) was recovered from this acetal in 92% yield by boiling for 2 h with 1 : 20 methanol–aqueous 10% hydrochloric acid.

Methylation of the hydroxyflavone gave the 7-*methyl ether* (62%), m.p. 210—211 °C (from Me_2CO) (Found: C, 72.8; H, 4.4. $C_{17}H_{12}O_4$ requires C, 72.9; H, 4.3%).

8-(4-*Hydroxy*-4-*methyl*-3-*oxopent*-1-*enyl*)-7-*methoxyflavone* (6).—To an ice-cold solution of 8-formyl-7-methoxyflavone (0.50 g) and 3-hydroxy-3-methylbutan-2-one [7] (0.20 g), powdered potassium hydroxide (0.11 g) was added, and stirring was continued for 30 min at 0 °C. The product was precipitated with dilute hydrochloric acid and recrystallised from methanol to give *needles* (0.17 g, 26%), m.p. 181—182 °C (Found: C, 72.7; H, 5.4. $C_{22}H_{20}O_5$ requires C, 72.5; H, 5.5%), $\nu_{max.}$ 3 400 (OH), 1 680 (CO), and 1 630 cm^{-1} (flavone CO); δ 1.46 (s, Me_2C), 7.20 (d, *J* 16 Hz, ArC*H*=), and 8.40 (d, *J* 16 Hz, CO·C*H*=).

2-*Benzyloxy*-4,6-*dimethoxybenzaldehyde*.—2-Hydroxy-4,6-dimethoxybenzaldehyde (2.73 g),[8] benzyl chloride (19.8 ml), and potassium carbonate (30 g) in dimethylformamide (100 ml) were stirred under reflux for 25 min. Dilution with water and crystallisation from methanol gave the *product* (34 g, 83%), m.p. 97—100 °C (Found: C, 70.2; H, 5.8. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%).

1-(2-*Benzyloxy*-4,6-*dimethoxyphenyl*)-4-*hydroxy*-4-*methylpent*-1-*en*-3-*one* (7).—2-Benzyloxy-4,6-dimethoxybenzaldehyde (16.3 g) was condensed, as described for (6), with 3-hydroxy-3-methylbutan-2-one (0.67 g) to afford, after recrystallisation from methanol, the *product* (7) (17.7 g, 83%), m.p. 131—133 °C (Found: C, 69.9; H, 6.6. $C_{21}H_{24}O_5$ requires C, 70.8; H, 6.8%); $\nu_{max.}$ 1 660 (CO) and 3 450 cm^{-1} (OH).

Oxidation of the Enone (7) *with TTN in Methanol*.—The ketone (7) (4.0 g) was dissolved in hot methanol (240 ml). The solution was chilled quickly in an ice-bath and as soon as crystallisation began TTN (6.0 g) was added. After stirring for 1 h at 0 °C the solution was filtered, neutralised with N-sodium methoxide, and evaporated to about 40 ml. After dilution with water the organic material was extracted ($CHCl_3$) and chromatographed on silica with benzene–acetone (8 : 1). First a mixture of cis- and trans-4-(2-*benzyloxy*-4,6-*dimethoxyphenyl*)-2,2-*dimethyl*-5-*methoxyfuran*-3(2H)-*one* (10) (*ca.* 1 : 4 by n.m.r.) was eluted (0.28 g); $\nu_{max.}$ 1 760 cm^{-1} (CO), δ (for *cis* only) 1.35 (s, Me_2C), 3.33 (s, CHO*Me*), 3.74 and 3.76 (s, ArOMe), 4.31 (d, *J* 6 Hz, ArC*H*), 5.26 (d, *J* 6 Hz, MeO·C*H*), and 5.01 (s, O·CH$_2$*Ph*). Repeated crystallisation from benzene–light petroleum afforded pure trans-*isomer* (10), m.p. 84—86 °C (Found: C, 68.2; H, 6.9. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.8%), δ 1.28 and 1.43 (s, Me_2C), 3.48 (s, CH·O*Me*), 4.35 (d, *J* 5 Hz, ArC*H*), and 5.05 (d, *J* 5 Hz, MeO·C*H*). Subsequent fractions yielded 2-(2-*benzyloxy*-4,6-*dimethoxyphenyl*)-4-*hydroxy*-1,1-*dimethoxy*-4-*methylpentan*-3-*one* (9) (1.06 g), m.p. 105—106 °C (from light petroleum) (Found: C, 64.7; H, 7.1. $C_{23}H_{30}O_7$ requires C, 65.0; H, 7.4%), $\nu_{max.}$ 3 470 (OH) and 1 698 cm^{-1} (CO); δ 1.05 and 1.27 (s, CMe_2), 3.10 and 3.40 [s, CH(O*Me*)$_2$], 4.85 (d, *J* 7.5, ArC*H*), and 5.35 [d, *J* 7.5 (MeO)$_2$C*H*].

4-(2-*Benzyloxy*-4,6-*dimethoxyphenyl*)-2,2-*dimethylfuran*-3(2H)-*one* (8).—To the crude reaction mixture from the oxidation of (7) (35.6 g), N-sodium methoxide (600 ml) was added. After 15 min the mixture was acidified with concentrated hydrochloric acid (5 ml), filtered, and evaporated, and the residue was recrystallised from methanol (280 ml) to give the *product* (8) (32.0 g, 87%), m.p. 109—110 °C (Found: C, 70.5; H, 6.0. $C_{21}H_{22}O_5$ requires C, 71.2; H, 6.3%), $\nu_{max.}$ 1 695 cm^{-1} (CO), δ 1.40 (s, CMe_2) and 8.15 (s, =CH–O).

2,2-*Dimethyl*-4-(4,6-*dimethoxy*-2-*hydroxyphenyl*)-2,3-*dihydrofuran*-3-*one* (14).—Debenzylation of the furanone (8) (0.53 g) gave the *product* (14) (0.35 g, 90%), m.p. 69—71 °C (from light petroleum) (Found: C, 63.25; H, 5.7. $C_{14}H_{16}O_5$ requires C, 63.6; H, 6.1%), $\nu_{max.}$ 1 645 cm^{-1} (CO), δ 8.95 (s, =CH–O) and 9.78 (s, OH). The *acetate* had m.p. 87—88 °C (Found: C, 62.2; H, 5.8. $C_{16}H_{18}O_6$ requires C, 62.7; H, 5.9%), $\nu_{max.}$ 1 768 (CO of ester) and 1 690 cm^{-1} (CO), δ 8.20 (s, =CH–O).

4-(3-*Acetyl*-2-*hydroxy*-4,6-*dimethoxyphenyl*)-2,2-*dimethylfuran*-3(2H)-*one* (15).—A solution of compound (14) (16.0 g) in dry ether (850 ml) and acetonitrile (85 ml) was saturated with hydrogen chloride gas in the presence of powdered zinc chloride (50 g). Next day more acetonitrile (50 ml) and zinc chloride (30 g) were added and the mixture was re-saturated with hydrogen chloride. The solvent was decanted and the gummy residue treated with hot water (1 000 ml) for 30 min. The oily product was chromatographed on silica with benzene–acetone (8 : 1) to remove unchanged (14) (8.3 g). Crystallisation from methanol gave the *product* (15) (7.7 g; conversion 42%; yield 87%), m.p. 142—144 °C (Found: C, 63.0; H, 5.9. $C_{16}H_{18}O_6$ requires C, 62.7; H, 5.9%), $\nu_{max.}$ 1 695 (furan CO) and 1 625 cm^{-1} (CO), δ 2.60 (s, $COCH_3$), 8.18 (s, =CH–O), and 14.05 (s, OH).

4-(3-*Acetyl*-2-*benzoyloxy*-4,6-*dimethoxyphenyl*)-2,2-*dimethylfuran*-3(2H)-*one* (16).—The acetophenone (15) (7.0 g)

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was treated with benzoyl chloride (3.0 ml) in pyridine (60 ml) for 40 min on a steam-bath. Dilution with water afforded the *product* (16) (8.0 g, 85%), m.p. 144—145 °C (from methanol) (Found: C, 67.4; H, 5.4. $C_{23}H_{22}O_7$ requires C, 67.3; H, 5.4%).

4-[3-(2-*Benzoylacetyl*)-4,6-*dimethoxy*-2-*hydroxyphenyl*]-2,2-*dimethylfuran*-3(2H)-*one* (17).—A solution of benzoate (16) (2.2 g) in pyridine (5.0 ml) was shaken with powdered potassium hydroxide (0.84 g) on a steam-bath for 15 min. Dilution with aqueous 3% acetic acid afforded the *diketone* (17) (2.0 g, 90%) as yellow prisms (from methanol), m.p. 174—175 °C (Found: C, 67.0; H, 5.3. $C_{23}H_{22}O_7$ requires C, 67.3; H, 5.4%), $\nu_{max.}$ 1 695 (CO) and 1 650—1 500 cm^{-1} (CO and C=C) (no OH absorption), δ 5.92 [s, 1 H, COC*H*C(OH)=], 8.04 (s, =CH–O), 13.03 (s, 2-OH), and 15.10 (s, enol OH).

8-[4-(2,2-*Dimethyl*-2,3-*dihydro*-3-*oxofuryl*)]-5,7-*dimethoxyflavone* (*Tachrosin*) (1).—The diketone (17) (0.36 g) in acetic acid (5 ml) was refluxed with sodium acetate (0.1 g) for 4 h. Dilution with water and recrystallisation of the precipitate from benzene yielded the flavone (0.29 g, 85%), m.p. 224—225 °C (lit.,[2] 226—227 °C; mixed m.p. 224—226 °C).

3-(2-*Benzyloxy*-4,5-*methylenedioxyphenyl*)*but*-3-*en*-2-*one*.—To a solution of 2-benzyloxy-4,5-methylenedioxybenzaldehyde [10] (9.0 g) in acetone (80 ml), aqueous 4% sodium hydroxide (15 ml) was added dropwise at room temperature with stirring. After 20 h the precipitated product was separated and recrystallised from methanol (400 ml) to give yellow *needles* (7.0 g, 67%), m.p. 154—155 °C (Found: C, 72.9; H, 5.5. $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.4%), δ 2.33 (s, CH_3·CO), 6.63 (d, *J* 16 Hz, =C*H*Ar), and 8.00 (d, *J* 16 Hz, CO CH=).

3-(2-*Benzyloxy*-4,5-*methylenedioxyphenyl*)-4,4-*dimethoxybutan*-2-*one* (11).—A solution of the foregoing ketone (2.7 g) in methanol (180 ml) was treated with TTN (4.5 g). After 30 min the pH was adjusted to 5 with N sodium methoxide, the solution was evaporated, and the residue was treated with water and extracted with chloroform. The extract was evaporated; crystallisation of the residue from benzene–light petroleum gave the *acetal* (11) (2.2 g, 67%), m.p. 86—87 °C (Found: C, 66.8; H, 6.1. $C_{22}H_{22}O_6$ requires C, 67.0; H, 6.2%), $\nu_{max.}$ 1 720 cm^{-1} (CO), δ 2.1 (s, CO·CH_3), 3.12 and 3.45 (s, OMe), 4.66 [d, *J* 8.0 Hz, C*H*$(OMe)_2$], and 5.05 (d, *J* 8.0 Hz, COC*H*).

3-(2-*Benzyloxy*-4,5-*methylenedioxyphenyl*)-4,4-*diethoxybutan*-2-*one* (12).—(a) *By oxidation with TTN*. 3-(2-Benzyloxy-4,5-methylenedioxyphenyl)but-3-en-2-one (0.30 g) was oxidised as described for (11) but in ethanol to give (12) as an oil (0.30 g, 77%), M^+ 386, δ 1.01 and 1.17 (t, *J* 7.5 Hz, CH_3·CH_2) and 3.15—3.85 (m, 4 H, CH_2·CH_3) (no OMe peaks).

(b) *By transacetalisation*. When dissolved in 0.1N-sodium ethoxide (2.0 ml) compound (11) (0.18 g) was transformed quantitatively within 1 h at room temperature into the acetal (12) contaminated with some vinyl ether (13).

3-(2-*Benzyloxy*-4,5-*methylenedioxyphenyl*)-4-*ethoxybut*-3-*en*-2-*one* (13).—When a solution of either of the acetals (11) (0.36 g) and (12) (0.39 g) in 0.5N-sodium ethoxide (5.0 ml) was left at room temperature for 3 h, the *vinyl ether* (13) was precipitated (0.22 and 0.24 g, respectively, 65 and 70%), m.p. 131—132 °C (from ethanol) (Found: C, 70.6; H, 6.1. $C_{20}H_{20}O_5$ requires C, 70.6; H, 5.9%), $\nu_{max.}$ 1 615 cm^{-1} (CO), δ 1.28 (t, *J* 7.5 Hz, CH_3·CH_2), 2.11 (s, CH_3·CO), 4.09 (q, *J* 7.5 Hz, CH_2·CH_3), and 7.52 (s, EtO·C*H*=).

1-(2-*Benzoyloxy*-4-*methoxyphenyl*)-4-*hydroxy*-4-*methylpent*-1-*en*-3-*one*.—Condensation of 2-benzyloxybenzaldehyde [10] with 3-hydroxy-3-methylbutan-2-one as described for (6) gave the *enone* (50%), m.p. 112—113 °C (from methanol) (Found: C, 73.2; H, 6.8. $C_{20}H_{22}O_4$ requires C, 73.6; H, 6.8%).

1-(2-*Benzyloxy*-4-*methoxyphenyl*)-2,2-*dimethylfuran*-3(2H)-*one* (18).—Oxidation of the foregoing ketone (10.5 g) in methanol (300 ml) with TTN (15.0 g) as described for (5) followed by cyclisation with sodium methoxide gave the *furanone* (18) (7.0 g, 67%), m.p. 85—86 °C (from methanol) (Found: C, 73.8; H, 6.2. $C_{20}H_{20}O_4$ requires C, 74.1; H, 6.2%), $\nu_{max.}$ 1 675 cm^{-1} (CO), δ 1.40 (s, CMe_2) and 8.82 (s, =CH–O).

4-(2-*Hydroxy*-4-*methoxyphenyl*)-2,2-*dimethylfuran*-3(2H)-*one* (19).—Debenzylation of (18) gave the *product* (19), m.p. 122—123 °C (from methanol) (Found: C, 66.6; H, 6.0. $C_{13}H_{14}O_4$ requires C, 66.7; H, 6.0%), $\nu_{max.}$ 1 650 cm^{-1} (CO), δ 8.43 (s, =CH–O) and 9.6br (s, OH).

4-(2-*Ethoxycarbonylmethoxy*-4-*methoxyphenyl*)-2,2-*dimethylfuran*-3(2H)-*one* (20).—The furanone (19) (2.0 g), ethyl chloroacetate (1.0 ml), potassium carbonate (2.0 g), and potassium iodide (0.2 g) in acetone (50 ml) were refluxed with stirring for 5 h. Filtration, evaporation, and crystallisation from methanol afforded the *ester* (20) (2.1 g, 93%), m.p. 109—110 °C (Found: C, 63.5; H, 6.2. $C_{17}H_{20}O_6$ requires C, 63.7; H, 6.3%), $\nu_{max.}$ 1 730 (ester CO) and 1 670 cm^{-1} (CO), δ 4.54 (s, O·CH_2·CO_2) and 9.15 (s, =CH·O–).

1-(2-*Carboxymethoxy*-4-*methoxyphenyl*)-3-*hydroxy*-3-*methylbutan*-2-*one* (21).—The ester (20) (1.5 g) with methanol (300 ml) and 3% potassium hydroxide (300 ml) was refluxed for 4 h. Evaporation, addition of dilute hydrochloric acid, saturation with sodium chloride, extraction with chloroform, evaporation, and crystallisation from benzene gave the *acid* (21) (0.75 g, 55%), m.p. 134—135 °C (Found: C, 59.2; H, 6.5. $C_{14}H_{18}O_6$ requires C, 69.6; H, 6.4%), $\nu_{max.}$ 3 300 (tert. OH) and 1 720 cm^{-1} (carboxy and ketone CO), δ 3.90 (s, ArCH_2) and 4.55 (s, O·CH_2·CO_2).

3-*Hydroxy*-1-(4-*methoxy*-2-*methoxycarbonylmethoxyphenyl*)-3-*methylbutan*-2-*one* (22).—The acid (21) (1.0 g) was esterified with diazomethane in chloroform to give the *ester* (22) (0.85 g, 81%), m.p. 85—87 °C (from methanol) (Found: C, 60.9; H, 6.8. $C_{15}H_{20}O_6$ requires C, 60.8; H, 6.8%).

7-*Methoxy*-2,2-*dimethyl*-2H-*furo*[2,3-c][1]*benzopyran*-1(4H)-*one* (23).—To a boiling solution of the ester (22) (1.0 g) in ethanol (30 ml), boiling 0.2M-sodium ethoxide (17 ml) was added. After 4 min the reaction was quenched by addition of acetic acid (0.7 ml) and the solution chilled rapidly and evaporated. A solution of the residue in chloroform was extracted twice with water (20 ml) to remove the acid (21). Evaporation gave pure product (23) as a yellow oil (0.6 g, 58%), M^+ 246, $\nu_{max.}$ 1 700 cm^{-1} (CO), δ 1.51 (s, CMe_2), 3.72 (s, OMe), 5.00 (s, CH_2), and 6.20, 6.50, and 7.20 (3 H, m, 6-, 8-, and 9-H).

cis-2,2-*Dimethyl*-3a,9a-*dihydro*-7-*methoxy*-2H-*furo*[2,3-c]-[1]*benzopyran*-1(4H)-*one* (26).—A freshly prepared neutralised solution of compound (24) [from 3.0 g of (22)] in ethanol (70 ml) was added to palladium–charcoal (10%; 2.0 g) prehydrogenated in acetic acid (30 ml). After uptake of *ca.* 0.75 mol. equiv. of hydrogen (*ca.* 50 min) the rate of hydrogenation dropped sharply. Evaporation, extraction of the acid (21) with water from chloroform solution, and chromatography on silica (C_6H_6–EtOAc, 8 : 1)

gave, after recrystallisation from light petroleum, the *product* (26) (0.44 g), m.p. 78—79 °C (Found: C, 68.3; H, 6.5. $C_{14}H_{16}O_4$ requires C, 67.7; H, 6.5%), $\nu_{max.}$ 1 760 cm^{-1} (CO), δ 1.17 and 1.32 (s, CMe_2), 3.72 (d, *J* 6.5 Hz, 9a-H), 4.13 (q, $^3J_{trans}$ 2, ^2J 12 Hz, 4-H_A), 4.35 (q, $^3J_{cis}$ 2.7, ^2J 12 Hz, 4-H_B), and (1 H, m, 3a-H).

cis-9a-*Acetoxy*-3a,9a-*dihydro*-7-*methoxy*-2,2-*dimethyl*-2H-*furo*[2,3-c][1]*benzopyran*-1(4H)-*one* (27).—A solution of the ketone (26) (100 mg) was treated in acetic acid (2 ml) at 80 °C for 6 h with lead tetra-acetate (100 mg). Dilution with water, extraction, and chromatography on silica (C_6H_6–Me_2CO, 8 : 1) gave an oil (43 mg, 35%), M^+ 306, $\nu_{max.}$ 1 760 (ester CO), 1 730 (furan CO), 1 610, and 1 570 cm^{-1} (C=C), δ 1.02 and 1.52 (s, CMe_2), 2.14 (s, $CO{\cdot}CH_3$), 4.08 (q, $^3J_{trans}$ 1.2, ^2J 12 Hz, 4-H_B), 4.52 (q, $^3J_{cis}$ 2.2, ^2J 12 Hz, 4-H_A), and 4.83 (q, $^3J_{trans}$ 1.2, $^3J_{cis}$ 2.2 Hz, 3a-H).

1, t-3a, 4, t-9a-*Tetrahydro*-7-*methoxy*-2,2-*dimethyl*-2H-*furo*[2,3-c][1]*benzopyran*-r-1-*ol* (28).—To a solution of the furanone (23) (100 mg) in ethanol (2.0 ml), sodium borohydride (20 mg) was added. After 20 min the reaction was complete. The usual work-up gave an oil (80 mg, 79%), M^+ 250, $\nu_{max.}$ 3 430 cm^{-1} (OH) (no CO band), δ 1.09 and 1.34 (s, CMe_2), 3.30 (q, $^3J_{1,9a}$ 5.5, $^3J_{9a,3a}$ 8 Hz, 9a-H), 3.72 (d, $^3J_{3a,9a}$ 8 Hz, 1-H), and 3.94—4.26 (3 H, m, 3a-H, CH_2).

10,10-*Dimethyl*-5-*methoxy*-2-*phenyl*-4H,8H-*furo*[3,2-d]-*benzo*[1,2-b:3,4-b′]*dipyran*-4,11(10H)-*dione* (*Didehydrostachyoidin*) (30).—To a boiling solution of the ester (29) [12] (0.63 g) in benzene (36 ml) a solution of sodium methoxide (0.36 g) in methanol (48 ml) was added. After boiling for 25 min the solution was neutralised with acetic acid and evaporated, and the residue was chromatographed on silica (C_6H_6–Me_2CO, 2 : 1) to afford (30) (0.21 g, 38%), m.p. 252—256 °C (from methanol) (lit.,[13] 253—255 °C).

r-8a,c-11a-*Dihydro*-t-11-*hydroxy*-5-*methoxy*-10,10-*dimethyl*-2-*phenyl*-4H,8H-*furo*[3,2-d]*benzo*[1,2-b:3,4-b′]*dipyran*-4(10H)-*one* [(±)-*Stachyoidinol*] (31).—To a solution of the ketone (30) (0.28 g) in ethanol (30 ml), sodium borohydride (120 mg) was added. After 1 h the mixture was diluted with 10% hydrochloric acid. Extraction with dichloromethane, evaporation, and crystallisation from methanol–chloroform yielded the *racemic alcohol* (31) (0.27 g, 85%), m.p. 311—313 °C [lit.,[13] for (−)-(32), 324—327 °C] (Found: C, 69.9; H, 5.7. $C_{23}H_{22}O_6$ requires C, 70.0; H, 5.6%), $\nu_{max.}$ 3 380 (OH) and 1 655 cm^{-1} (CO); δ 1.48 and 1.50 (s, CMe_2), 4.00 (m, 11a-H), 4.24—4.48 (3 H, m, CH_2 and 8a-H), 4.68 (d, *J* 4.5 Hz, 11-H).

cis-8a,11a-*Dihydro*-5-*methoxy*-10,10-*dimethyl*-2-*phenyl*-4H,8H-*furo*[3,2-d]*benzo*[1,2-b:3,4-b′]*dipyran*-4,11(10H)-*dione* [(±)-*Stachyoidin*] (2).—To a solution of the alcohol (31) in acetic acid (2.0 ml) chromium trioxide in acetic acid (2.0 ml) was added and the mixture was kept at 50 °C for 30 min. Dilution with water, extraction with dichloromethane, evaporation, and recrystallisation from benzene–light petroleum gave *racemic stachyoidin* (2) (12 mg, 48%), m.p. 240—242 °C.*

cis-11a-*Acetoxy*-8a,11a-*dihydro*-5-*methoxy*-10,10-*dimethyl*-2-*phenyl*-4H,8H-*furo*[3,2-d]*benzo*[1,2-b:3,4-b′]*dipyran*-4,11(10H)-*dione* [(±)-*Tephrodin*] (3).—(±)-Stachyoidin (2) (120 mg) in acetic acid (12 ml) was oxidised at 80 °C with lead tetra-acetate (200 mg) for 4 h. The usual work-up followed by preparative t.l.c. ($CHCl_3$–MeOH, 100 : 1) and crystallisation from benzene–light petroleum gave racemic *tephrodin* (3) (26 mg), m.p. 233—235 °C [lit.,[3] of (−)-(3), 236—237 °C].

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* (−)-Stachyoidin crystallised with one mole of methanol (m.p. 113—114 °C) that was slowly released. The sample provided by Dr. Smalberger had m.p. 207—208 °C.