An Investigation into the Unusual Formation of an Isocoumarin by Acylation of 2,3,6-Trimethoxytoluene with (*E*)-2-Methylbut-2-enoic Acid and Trifluoroacetic Anhydride

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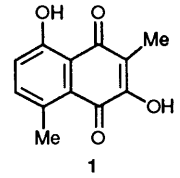
Prolonged reaction of 2,3,6-trimethoxytoluene with an excess of premixed (*E*)-2-methylbut-2-enoic acid and trifluoroacetic anhydride in air affords 5,6,8-trimethoxy-3,4,7-trimethylisocoumarin **11** in 66% yield as the sole product isolated, the structure of which was confirmed by X-ray crystallography. Shorter reaction times afford products which enable the identification of the reaction mechanism. This involves initial regioselective acylation, cyclisation of the derived α,β-unsaturated aryl ketone **5** to the *cis/trans* mixture of indanones **18** and **19** and *O*-acylation of these indanones to yield the indenyl ester **17**. The indanones and compound **17** can all react with trifluoroacetic acid in the presence of atmospheric oxygen to afford the isocoumarin by a mechanism which requires the intermediacy of an α-keto indanyl hydroperoxide, which in turn undergoes an acid-catalysed Baeyer–Villiger-type rearrangement to incorporate oxygen, thereby giving the isocoumarin.

While investigating potential syntheses of the naturally occurring naphthoquinone aristolindiquinone **1**[1] isolated by Cordell[2] from the roots of *Aristolochia indica* (Indian birthwort), we studied the acylation of 2,3,6-trimethoxytoluene **2** with a number of carboxylic acids in the presence of trifluoroacetic anhydride (TFAA). With (*E*)-2-methylbut-2-enoic acid, the major product obtained after prolonged stirring at room temperature was not the anticipated 5-acyl derivative **5**, but rather the isocoumarin **11** in 66% yield. This paper describes the identification of a number of intermediates in this unusual reaction, which enables a mechanism to be put forward for the formation of the observed product.



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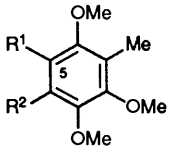
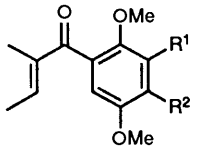
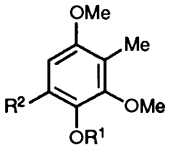


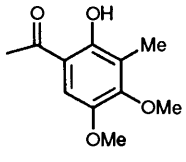
2 $R^1 = R^2 = H$
3 R^1 = COMe, $R^2 = H$
4 $R^1 = H$, R^2 = COMe



5 R^1 = Me, R^2 = OMe
6 R^1 = OMe, R^2 = Me



7 $R^1 = R^2 = H$
8 R^1 = COMe, $R^2 = H$
9 $R^1 = H$, R^2 = COMe



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Results and Discussion

Electrophilic substitution of 2,3,6-trimethoxytoluene **2** would be expected to occur preferentially at C-5, for which the transition state would be stabilised by the two methoxy substituents at C-2 and C-6. Thus, with acetic acid and TFAA, the 5-acetyl derivative **3** would be expected. A search of the literature established, however, that neither 4- nor 5-acetyl-2,3,6-trimethoxytoluene has been reported. As a preliminary study, this reaction was investigated.

Reaction of toluene **2**[3,4] with premixed acetic acid and TFAA afforded the 5-acetyl derivative **3** as the sole product. Its spectroscopic properties, particularly its ^{1}H NMR spectrum, showed it to be different from the 4-acetyl isomer **4**, obtained as follows. The phenol **7**[4] was acetylated to form the acetate **8**. This ester was treated with boron trifluoride–diethyl ether in a Fries rearrangement to yield the *ortho*-acetylphenol **9**, which was characterised by a low-field hydrogen-bonded phenolic proton in its ^{1}H NMR spectrum at δ 12.22. This confirmed that the acetyl group was attached to C-4. This phenol was methylated with dimethyl sulphate to afford 4-acetyl-2,3,6-trimethoxytoluene **4**.

The acetyl derivative **3** was selectively demethylated with boron trichloride to afford 6-acetyl-3,4-dimethoxy-2-methylphenol **10**, different from and isomeric with compound **9**.

Reaction of the toluene **2** with an excess of (*E*)-2-methylbut-2-enoic acid and TFAA afforded a crystalline product, the best yield (66%) being obtained when the reaction was carried out for 64 h at room temperature in the presence of air. Elemental analysis showed that it possessed the molecular formula $C_{15}H_{18}O_5$ rather than $C_{15}H_{20}O_4$ expected for the acyl derivative **5**. The mass spectrum of the compound supported this formulation, with a molecular ion as base peak at *m/z* 278. The ^{1}H NMR spectrum showed three methyl and three *O*-methyl singlets. The IR spectrum showed a carbonyl stretching

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‡ For crystallography.

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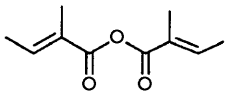
frequency at 1722 cm^{-1}, which must be part of an ester function since the ^{13}C NMR spectrum showed no absorption below δ_C 160. These spectral characteristics supported four possible structures, these being the isocoumarin **11** or the coumarin **13**, or their regioisomers **12** or **14**. An X-ray crystallographic study (below) confirmed the structure as **11**.

Staunton has reported[5] the syntheses of a number of isocoumarins by a multistep sequence involving initial acylation of aromatic species, followed by cyclisation, enol ester formation, ozonolysis and finally cyclisation. The facility with which the current reaction occurred was remarkable and the mechanism for the formation of the isocoumarin was investigated.

It was first established that atmospheric oxygen was the source of the additional oxygen in the isocoumarin product. This was shown by the fact that when two parallel reactions were undertaken, one under air, and the other under nitrogen, negligible quantities of the isocoumarin were observed in the latter.

11 R^1 = Me, R^2 = OMe **13**
12 R^1 = OMe, R^2 = Me **14**



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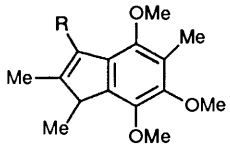
TLC of the mixture of products in the latter reaction showed the presence of a number of different compounds, which were separated by careful column chromatography. The first product to elute was (*E*)-2-methylbut-2-enoic anhydride **15** as an oil; this was identified by a ^1H NMR spectrum which was very similar to that of the corresponding acid, but which lacked the carboxylic acid proton signal. The IR spectrum showed two carbonyl stretches, at 1772 and 1712 cm^{-1}, typical of anhydrides. The presence of this anhydride caused difficulty with subsequent chromatographic fractions since it was partly hydrolysed to the corresponding acid which caused contamination of the fractions. The difficulty was overcome by flash chromatography of the crude residue, which removed the anhydride. The remaining fractions were combined and worked up by treatment with aqueous sodium hydrogen carbonate, and the non-acidic products were extracted into diethyl ether. The residue obtained from this fraction was carefully chromatographed and individual products were found to be free of (*E*)-2-methylbut-2-enoic acid and its anhydride.

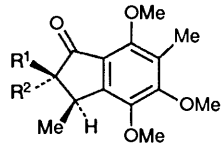
The first compound to be isolated through further chromatography proved to be the chloroindene **16** in 2% yield. Since commercially available TFAA has been used without further purification, it was assumed that this artefact had arisen through chlorination of the mixture of indanones **18** and **19**; the chlorinating agent is assumed to be thionyl chloride used in the commercial synthesis of TFAA. The chloroindene was identified by its mass spectrum which showed two molecular ions at *m/z* 282 and 284 observed in the ratio 3:1. Chlorine was lost from the molecular ion to give the base peak at *m/z* 247 as a single signal. The ^1H and ^{13}C NMR spectra were straightforward and consistent with this assignment.

The next compound to be isolated from the reaction under nitrogen was obtained in 9% yield. This product was formulated as the indenyl methylbutenoate **17** since its ^1H NMR spectrum closely resembled that of the chloro compound **16** except that it showed signals due to an additional methylbutenoyl group, namely a methyl doublet, a methyl singlet and an olefinic proton. Other spectral evidence and elemental analysis supported this assignment.

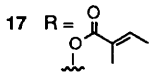
Next to be eluted was a colourless oil whose spectral characteristics indicated it to be a mixture of the isomeric *cis*- and *trans*-dimethylindanones **18** and **19**. Thus the ^{13}C NMR spectrum showed two signals, at δ_C 204.58 and 204.67, while the ^1H NMR spectrum showed four different methyl doublets and four different methine protons. The mass spectrum showed a molecular ion at *m/z* 264.

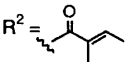
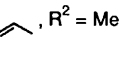
A further compound was then eluted, and which was once again a mixture of two isomers as evidenced by the duplication of signals in the ^1H and ^{13}C NMR spectra of the sample. These proved to be the two isomers **20** and **21** obtained in the ratio 5:3 by *C*-acylation of the indanones **18** and **19**. The mass spectrum closely resembled that of the indenyl ester **17**, with a molecular ion at *m/z* 346, and the base peak at *m/z* 263, which arose through loss of the acyl group.





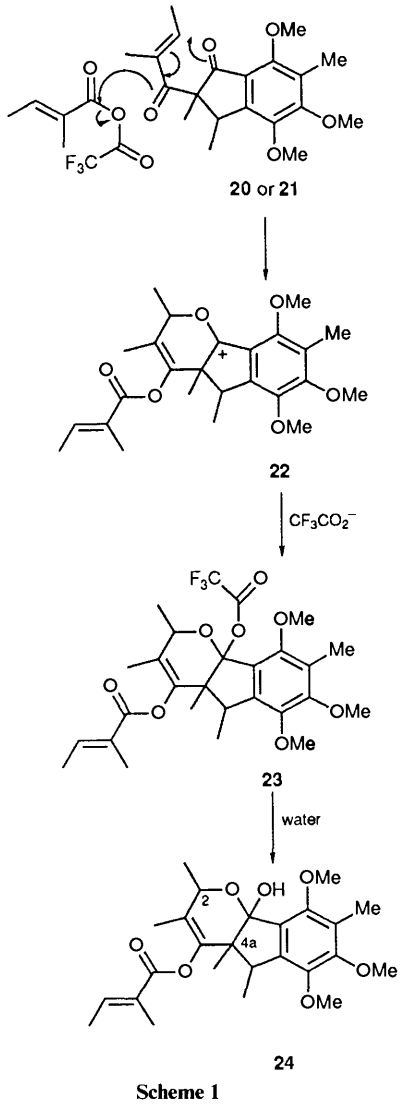
16 R = Cl

17 R = 

18 R^1 = Me, R^2 = H
19 R^1 = H, R^2 = Me
20 R^1 = Me, R^2 = 
21 R^1 =  , R^2 = Me

The final product eluted was crystalline and its mass spectrum showed a molecular ion at *m/z* 446; the only other major signals were those at *m/z* 263 and 83, as found in the fragmentation patterns of the indenyl methylbutenoate **17** and its *C*-acyl isomers, the diketones **20** and **21**. The ^1H NMR spectrum showed signals very similar to those of the indenyl ester **17** with an additional methyl doublet, methyl singlet, a one-proton quartet at δ 4.69, and a hydroxy-group proton (D_2O-exchangeable) at δ 4.95. The IR spectrum confirmed the presence of an O–H group by a sharp signal at 3493 cm^{-1}. These spectral observations pointed to a product in which the elements of 2-methylbutenoic acid had been added to either the diketones **20** and **21**, or the indenyl ester **17**, and this was confirmed by elemental analysis, which supported the molecular formula $C_{25}H_{34}O_7$. The ^{13}C NMR spectrum was highly instructive. It showed an ester carbonyl carbon at δ_C 165.21, ten olefinic and aromatic carbons in the region δ_C 120–154, only one of which carried a proton as determined by an attached proton-test (APT) experiment, a very significant quaternary carbon at δ_C 105.32 suggestive of a benzylic carbon carrying two oxygens, two methine carbons, at δ_C 67.88 and 45.64, a quaternary carbon at δ_C 52.11 and three *O*-methyl and seven methyl signals. This information suggested the product to have structure **24** whose assembly can be rationalised in terms of the formation of the enol methylbutenoate of the diketones **20** and/or **21**, followed by cyclisation by attack of the carbonyl oxygen on the derived carbocation as shown in Scheme 1. This affords a second carbocation **22**, well stabilised through resonance with both the adjacent oxygen atom, the phenyl ring,

and two of the three oxygen atoms on the ring. This carbocation **22** is quenched by the only nucleophile present in the reaction, trifluoroacetate and the ester **23** is readily hydrolysed on aqueous work-up to afford compound **24**.



Scheme 1

A further interesting observation was that certain signals in both the ^1H and ^{13}C NMR spectra of compound **24** when measured at ambient temperature (24 °C) showed significant broadening. On raising of the temperature to +50 °C these signals sharpened, while at −40 °C they (and others) separated into two peaks. In particular, at the lower temperature, two hemiacetal carbon atoms were observed, but no ketone carbonyl carbons were found at any temperature, which excluded the presence of significant amounts of the indanone derived by ring opening of the hemiacetal.

These observations were consistent with either conformational mobility within the molecule at higher temperatures and which was frozen at lower temperatures, or the existence of two different stereoisomers which equilibrated at higher temperatures. The latter may arise either by a process analogous to mutarotation in pyranoses, or by protonation of the hydroxy-group oxygen of compound **24**; this would lead to dissociation of **24** into the highly stabilised carbocation **22** and water, which could reunite to afford the alternative stereochemistry at the hemiacetal carbon.

No attempt was undertaken to define the relative stereochemistry at the chiral centres within compound **24**.

An effort *was* made to isolate the acyl derivative **5** which had hitherto not been found on chromatography of the reaction mixture. This was achieved by performing the reaction for only 2.5 h in air. Chromatography afforded the two isomeric monoacyl compounds **5** and **6** in the ratio 9:1 and 14% yield. Starting material **2** and compounds **15** and **17** were also obtained. The ^1H NMR spectrum of the acyl derivatives **5** and **6** in deuteriochloroform indicated the presence of the two isomers. When a few drops of trifluoroacetic acid (TFA) were added to this NMR sample, the minor isomer was converted during 15 min into the major isomer **5**. This rearrangement no doubt occurs by protonation of the aromatic carbon attached to the carbonyl group, deacylation, and reacylation to afford the thermodynamically favoured regioisomer. This observation explains why all other products obtained were single regioisomers with respect to the adjacent methyl and methoxy substituents on the aromatic ring. Further support for the structure of compound **5** was obtained from its mass spectrum, in which the molecular ion (*m/z* 264) fragments with the loss of the but-2-enyl group to yield the stabilised benzoyl ion (*m/z* 209) as the base peak.

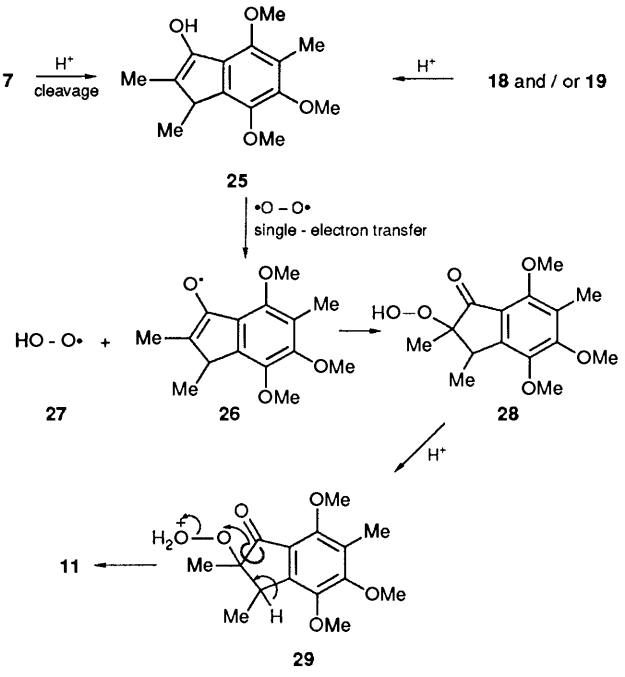
A mechanism for the formation of the isocoumarin could be established in part from the compounds identified from the reaction mixture. Initial acylation affords the preferred acyl compound **5**, which undergoes cyclisation under the acidic conditions to give the mixture of indanones **18** and **19**. These indanones could be further *C*-acylated to form the mixture of indanones **20** and **21**, or *O*-acylated to yield the indenyl ester **17**. However, further experiments were necessary to establish which of these products reacted with oxygen gave rise to the isocoumarin, and by what mechanism.

It was found that when either the indanone mixture **18** and **19** or the indenyl ester **17** in air was stirred with a mixture of (*E*)-2-methylbut-2-enoic acid and TFAA, the isocoumarin was obtained in 34 and 38% yield, respectively, together with other compounds previously described. Similar reactions in which (*E*)-2-methylbut-2-enoic acid was replaced by TFA (together with TFAA) also gave the isocoumarin. Reaction of each with TFAA alone, however, gave no isocoumarin, while reaction of the indenyl 2-methylbutenoate with TFA alone also gave the isocoumarin.

A final experiment was undertaken in which the reaction between (*E*)-2-methylbut-2-enoic acid, TFAA, and the trimethoxytoluene **2** took place under an atmosphere of isotopically labelled oxygen ($^{18}O_2$). The isocoumarin isolated showed the molecular ion and base peak at *m/z* 280, with fragment ions at *m/z* 265 and 249, whereas the corresponding peaks in the unlabelled isocoumarin were observed at *m/z* 278, 263 and 247. The high-resolution mass spectrum confirmed a molecular formula of $C_{15}H_{18}{}^{16}O_4{}^{18}O$, showing that a single oxygen atom had been incorporated from atmospheric molecular oxygen.

These experiments enabled the mechanism shown in Scheme 2 to be proposed for the conversion of the indanones or the indenyl methylbutenoate into the isocoumarin. Protonation of the former or acid-catalysed cleavage of the enol ester function of the latter would provide the enol **25** of the indanone. Reaction of this with oxygen may well occur by single-electron transfer to give the enolate radical **26** and hydroperoxyl radical **27**. Combination of these two radicals affords the organic hydroperoxide **28**; protonation of this to give the intermediate **29** promotes migration of the acyl carbon to oxygen in a Baeyer–Villiger-type rearrangement to give the isocoumarin **11**.

Crystal Structure of the Isocoumarin **11**.—The results of the structure determination are consistent with the above stoicheiometry and connectivity; one molecule comprises the asymmetric unit of the structure. Because of substituent



Scheme 2

crowding, the methoxy substituents are not coplanar with the aromatic ring, as is usual, but are twisted about the C_{ar}–O bond towards the normal. The six carbon atoms of the aromatic ring are significantly but trivially non-planar [χ^2 (plane) 105]; peripheral atom deviations are C(1,3,4), O(2): 0.080, 0.026, −0.043, 1.216 Å (for the other ring), and O(5,6,8), C(51,61,71,81): 0.043, 0.031, 0.057, 1.320, −0.938, 0.037, −1.208 Å. Substituent crowding also appears to account for substantial angular asymmetries about the attachment of the substituents at C(1,3,4).

Experimental

All ^{1}H NMR spectra were measured for solutions in [^{2}H]chloroform with tetramethylsilane as internal reference using either a Varian XL-100 or a Bruker WH-90 spectrometer; IR spectra were measured for Nujol mulls using a Perkin-Elmer 983 spectrophotometer, unless otherwise stated. Preparative layer chromatography (PLC) was performed on glass plates coated with Merck Kieselgel 60 F_{254}; column chromatography refers to dry-packed columns of the same gel (70–230 mesh). Light petroleum refers to the fraction boiling in the range 60–80 °C, and 'ether' to diethyl ether. The phrase 'residue obtained upon work-up' refers to the material remaining when an organic extract was separated, dried ($MgSO_4$) and evaporated under reduced pressure.

*3-Acetyl-2,5,6-trimethoxytoluene** **3**.—Compound **2** (90 mg, 0.49 mmol) was added to a mixture of acetic acid (44 mg, 0.74 mmol) and TFAA (206 mg, 0.98 mmol) and the solution was stirred at 25 °C for 24 h. Aq. sodium hydrogen carbonate was added and the mixture was extracted with methylene dichloride. The residue obtained upon work-up was chromatographed (PLC, eluant 15% ethyl acetate–light petroleum) to afford the *title product* **3** (77 mg, 70%) as a pale yellow oil (Found: C, 64.2; H, 7.2. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.1%); ν_{max}(film)/cm^{-1} 1671 (C=O); δ 2.25 (3 H, s, ArMe), 2.64 (3 H, s, COMe), 3.72 (3 H, s, OMe), 3.86 (6 H, s, 2 × OMe) and 7.14 (1 H, s, ArH); *m/z* 224 (M^+, 62%), 209 (100) and 181 (12).

* Non-systematic name.

*4-Acetyl-3-hydroxy-2,6-dimethoxytoluene** **9**.—The phenol **7**[4] (422 mg, 2.51 mmol) was dissolved in acetic anhydride (14 cm^3) and pyridine (3.5 cm^3) was added. The mixture was stirred at room temperature for 3 h. Methanol was then added and the mixture was stirred for a further 20 min. The solvents were removed under reduced pressure at 40 °C. The residue was chromatographed (eluant 20% ethyl acetate–light petroleum) to afford 3-acetoxy-2,6-dimethoxytoluene* **8** (495 mg, 94%) as an oil; ν_{max}(film)/cm^{-1} 1767 (C=O); δ 2.15 (3 H, s, ArMe), 2.29 (3 H, s, OAc), 3.72 and 3.78 (each 3 H, s, OMe), 6.48 (1 H, d, *J* 9 Hz, 5-H) and 6.79 (1 H, d, *J* 9 Hz, 4-H); *m/z* 210 (M^+, 15%), 168 (100) and 153 (40).

The acetate **8** (495 mg) and freshly distilled boron trifluoride–diethyl ether (1.5 cm^3) were heated in an oil-bath maintained at 95 °C for 3 h. The reaction mixture was then thrown into ice (20 g), and extracted with methylene dichloride, the organic layer was separated, and the solvent was removed under reduced pressure. The residue was dissolved in 3% sodium hydroxide in methanol (25 cm^3) and the mixture was stirred at room temperature for 30 min to hydrolyse any existing starting material **8** to enable its separation from the product **9** which had the same R_f-value on TLC. The solution was then diluted with water (200 cm^3), acidified and the mixture was exhaustively extracted with methylene dichloride. The residue obtained upon work-up of the extract was chromatographed (eluant 30% ethyl acetate–light petroleum) to afford the *title product* **9** (312 mg, 63%) as crystals, m.p. 73.5–75 °C (from isopropyl alcohol) (Found: C, 62.8; H, 6.6. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7%); ν_{max}/cm^{-1} 1635 (C=O) and 1614 (C=C); δ 2.16 (3 H, s, ArMe), 2.57 (3 H, s, COMe), 3.77 and 3.83 (each 3 H, s, OMe), 6.77 (1 H, s, 5-H) and 12.22 (1 H, s, OH); *m/z* 210 (M^+, 100%), 196 (20), 195 (86), 181 (15), 167 (43), 149 (27) and 121 (19). Later fractions gave the starting phenol **7** (36 mg, 9%).

*4-Acetyl-2,3,6-trimethoxytoluene** **4**.—The phenol **9** (191 mg, 0.91 mmol) was dissolved in dry acetone (5 cm^3) and dimethyl sulphate (286 mg, 2.27 mmol) and potassium carbonate (32 mg, 2.4 mmol) were added. The mixture was stirred at room temperature for 24 h, after which it was filtered, and was then evaporated under reduced pressure. Ether was added to the residue and the solution was washed successively with ammonia (25%), water, dil. hydrochloric acid and brine. The residue obtained upon work-up was chromatographed (eluant 10% ethyl acetate–light petroleum) to yield the *title product* **4** (200 mg, 98%) as pale yellow needles, m.p. 28–30 °C (from light petroleum) (Found: C, 64.5; H, 7.2. $C_{12}H_{16}O_4$ requires C, 64.3; H, 7.1%); ν_{max}/cm^{-1} 1678 (C=O); δ 2.18 (3 H, s, ArMe), 2.65 (3 H, s, COMe), 3.83 (3 H, s, OMe), 3.88 (6 H, s, OMe) and 6.99 (1 H, s, 5-H); *m/z* 224 (M^+, 88%), 209 (100), 181 (20), 166 (12) and 149 (25).

*6-Acetyl-3,4-dimethoxy-2-methylphenol** **10**.—Compound **3** (132 mg, 0.59 mmol) was dissolved in anhydrous methylene dichloride (10 cm^3), and a solution of boron trichloride (0.271 g, 2.31 mmol) in anhydrous methylene dichloride (2.5 cm^3) was added at 0 °C. The reaction mixture was stirred at this temperature for 80 min, whereupon the derived red complex was decomposed by the addition of water to the stirred mixture (5 min). The organic material was extracted into methylene dichloride. The usual work-up afforded the crystalline *title product* **10** (105 mg, 85%) as needles, m.p. 86–87 °C (from methylene dichloride–light petroleum) (Found: C, 62.8; H, 6.7. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7%); δ 2.17 (3 H, s, ArMe), 2.58 (3 H, s, COMe), 3.83 and 3.86 (each 3 H, s, OMe), 6.99 (1 H, s, 4-H) and 12.59 (1 H, s, OH, D_2O-exchangeable); *m/z* 210 (M^+, 85%), 195 (100), 167 (11), 149 (14) and 121 (11).

5,6,8-Trimethoxy-3,4,7-trimethylisocoumarin **11**.—(*a*) Compound **2** (600 mg, 3.29 mmol) was stirred with a premixed

solution of (*E*)-2-methylbut-2-enoic acid (1.300 g, 1.3 mmol) and TFAA (1.8 ml, 2.68 g, 1.28 mmol) in air at room temperature for 64 h. Dry sodium hydrogen carbonate was added followed, after 5 min, by the cautious addition of water. The mixture was extracted with ether and the residue obtained upon work-up was chromatographed (eluant 10% ether–light petroleum) to afford anhydride **15** (see below) (310 mg, 26%). Increase of the eluant polarity to 30% ether–light petroleum afforded the *title isocoumarin* **11** (610 mg, 66%) as needles, m.p. 103–105 °C (from chloroform–light petroleum) (Found: C, 64.9; H, 6.6%; M^+, 278.115 079. $C_{15}H_{18}O_5$ requires C, 64.7; H, 6.5; M, 278.115 402); ν_{max}/cm^{-1} 1722 (C=O), 1641 and 1571 (C=C); δ_H 2.25 (6 H, s, Me), 2.32 (3 H, s, Me), and 3.75, 3.83 and 3.92 (each 3 H, s, OMe); δ_C 9.28, 15.03, and 17.49 (Me), 60.26, 61.11, and 61.31 (OMe), 106.44 and 110.89 (C-4 and -4a), 126.36 and 132.38 (C-7 and -8a), 145.17, 149.35, 157.51, 158.44, and 158.92 (C-3, -5, -6, -8 and -1).

(*b*) When the reaction was performed under an atmosphere of $^{18}O_2$, the molecular ion was observed at *m/z* 280.119 969, while the mass calculated for $C_{15}H_{18}{}^{16}O_4{}^{18}O$ is 280.119 649. The observed mass difference for labelled and unlabelled isocoumarin is 2.004 89 amu, while the calculated mass difference between ^{18}O and ^{16}O is 2.004 25 amu.

Reaction of 2,3,6-*Trimethoxytoluene* **2** *with Premixed* (E)-2-*Methylbut-2-enoic acid and TFAA under Nitrogen.*—2,3,6-Trimethoxytoluene **2** (750 mg, 4.12 mmol) was stirred with a premixed solution of the methylbutenoic acid (1.65 g, 1.65 mmol) and TFAA (2.3 ml, 3.43 g, 1.63 mmol) under nitrogen at room temperature for 24 h. Solid sodium hydrogen carbonate was added to the reaction mixture followed, after 10 min, by the cautious addition of water (100 cm^3). The mixture was extracted with ether (4 × 50 cm^3) and the residue obtained upon work-up was flash chromatographed (eluant 10% ether–light petroleum) to remove the *anhydride* **15** in early fractions (0.25 g) as an oil, b.p. 65–70 °C (Kugelrohr) at 0.02 mmHg (Found: C, 65.75; H, 7.7. $C_{10}H_{14}O_3$ requires C, 65.9; H, 7.75%); ν_{max}(film)/cm^{-1} 1772 and 1712 (anhydride C=O) and 1647 cm^{-1} (C=C); δ_H 1.86 (6 H, d, *J* 6.7 Hz, *Me*CH), 1.89 (6 H, s, MeCC=O) and 6.99 (2 H, q, *J* 6.7 Hz, MeC*H*); δ_C 11.84 (2-Me), 14.72 (4-Me), 128.67 (C-2), 141.59 (C-3) and 164.05 (C=O); *m/z* 154 (3%), 83 (95) and 55 (100).

Subsequent fractions were evaporated to dryness and dry sodium hydrogen carbonate was again added, followed by water. The remaining products were extracted into ether, and the residue obtained upon work-up was slowly rechromatographed (eluant 8% ether–light petroleum) to afford the following compounds in chromatographic order.

3-*Chloro*-4,6,7-*trimethoxy*-1,2,5-*trimethyl*-1H-*indene* **16**. (30 mg, 3%) as an *unstable, pale yellow oil*, b.p. 130 °C/0.02 mmHg (Kugelrohr) (Found: C, 63.5; H, 7.2. $C_{15}H_{19}ClO_3$ requires C, 63.7; H, 6.8%); δ_H 1.35 (3 H, d, *J* 7.4 Hz, 1-Me), 2.00 (3 H, s, 2-Me), 2.22 (3 H, s, 5-Me), 3.36 (1 H, q, *J* 7.4 Hz, 1-H), and 3.78, 3.82, and 3.89 (each 3 H, s, OMe); δ_C 9.09, 11.92 and 14.77 (Me), 44.90 (C-7), 60.20 (× 2) and 62.36 (OMe), 123.05, 125.13, 128.88, 136.62 and 142.77 (C-2, -3, -3a, -5 and -7a), and 145.64, 147.01, and 149.49 (C-4, -6 and -7); *m/z* 284 (M^+, 15%), 282 (M^+, 45%), 247 (100), 232 (18) and 216 (15).

4,6,7-*Trimethoxy*-1,2,5-*trimethyl*-1H-*inden*-3-*yl* (E)-2′-*methylbut*-2′-*enoate* **17**. (130 mg, 9%) as a *yellow oil*, b.p. 125–130 °C/0.015 mmHg (Kugelrohr) (Found: C, 69.45; H, 7.6. $C_{20}H_{26}O_5$ requires C, 69.3; H, 7.6%); ν_{max}(film)/cm^{-1} 1731 (C=O) and 1648, 1584 and 1471 (C=C); δ_H 1.38 (3 H, d, *J* 7 Hz, 1-Me), 1.83 (3 H, s, 2-Me), 1.88 (3 H, d, *J* 6.5 Hz, 4′-H_3), 1.99 (3 H, d, *J* 1 Hz, 2′-Me), 2.14 (3 H, s, 5-Me), 3.38 (1 H, q, *J* 7 Hz, 1-H), 3.62, 3.79 and 3.90 (each 3 H, s, OMe), and 7.14 (1 H, dq, *J*/Hz 1 and 6.5, 3′-H); δ_C 9.25 (5-Me), 10.01 (1-Me), 12.26, 14.61 and 14.76 (2-, 2′- and 3′-Me), 42.43 (C-1), 60.25 (× 2) and 61.81 (OMe), 124.47 (C-5), 126.84 (C-3a), 127.86 (C-2′), 132.30 (C-7a), 136.25 (C-2), 138.87 (C-3′), 141.58 (C-3), 145.98, 146.23 and 149.39 (C-4, -6 and -7) and 165.69 (C=O); *m/z* 346 (M^+, 14%), 264 (20), 263 (52), 83 (100) and 55 (65).

cis- **18** *and* trans-4,5,7-*Trimethoxy*-2,3,6-*trimethylindan*-1-*one* **19**. (300 mg, 27.5%) as an oily mixture, b.p. 105 °C/0.2 mmHg (Kugelrohr) (Found: C, 68.4; H, 7.75. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%); ν_{max}(film)/cm^{-1} 1710 (C=O) and 1585 (C=C); δ_H (*cis*) 1.19 and 1.20 (each 3 H, d, *J* 7.5 Hz, 2- and 3-Me), 2.17 (3 H, s, 6-Me), 2.75 (1 H, quintet, *J* 7.5 Hz, 3-H), 3.56 (1 H, quintet, *J* 7.5 Hz, 2-H), and 3.90, 3.91 and 3.92 (each 3 H, s, OMe); δ_H (*trans*) 1.27 (3 H, d, *J* 7.4 Hz, 3-Me), 1.47 (3 H, d, *J* 6.9 Hz, 2-Me), 2.17 (3 H, s, 6-Me), 2.20 (1 H, dq, *J*/Hz 7.4 and 3.5, 3-H), 2.97 (1 H, dq, *J*/Hz 6.9 and 3.5, 2-H), and 3.87, 3.90 and 3.91 (each 3 H, s, OMe); δ_C (*cis*) 10.48 (6-Me), 17.02 (2- and 3-Me), 34.53 (C-3), 47.20 (C-2), 59.70 (× 2) and 60.17 (OMe), 123.12 and 124.91 (C-6 and -7a), 145.41, 150.26, 152.34 and 157.26 (C-3a, -4, -5 and -7), and 204.58 (C=O); δ_C (*trans*) 8.95 (6-Me), 15.43 (3-Me), 19.80 (2-Me), 39.87 (C-3), 51.81 (C-2), 60.03 (× 2) and 60.17 (OMe), 123.58 and 125.16 (C-6 and -7a), 146.04, 148.80, 152.57 and 157.77 (C-3a, -4, -5 and -7), and 202.22 (C=O); 264 (M^+, 100%), 249 (35), 235 (85), 131 (19), 119 (11), 105 (21), 91 (22) and 77 (19).

4,5,7-*Trimethoxy*-2,3,6-*trimethyl*-2(2-*methylbut*-2-*enoyl*)-*indan*-1-*one as a mixture of the stereoisomers* **20** *and* **21**. (60 mg, 4%) as an oil (Found: C, 69.3; H, 7.6. $C_{20}H_{26}O_5$ requires C, 69.3; H, 7.6%); ν_{max}(film)/cm^{-1} 1709, 1680 and 1660 (C=O), 1645sh, 1582 and 1472 (C=C); δ_H (minor isomer) 1.30 (3 H, d, *J* 7 Hz, 3-Me), 1.42 (3 H, s, 2-Me), 1.48 (3 H, dq, *J*/Hz 7 and 1.8, 4′-H_3), 1.73 (3 H, s, 2′-Me), 2.17 (3 H, s, 6-Me), 3.79 (1 H, q, *J* 7 Hz, 3-H), 3.87, 3.90 and 3.94 (each 3 H, s, OMe), 5.42 (1 H, qq, *J*/Hz 7 and 1.8, 3′-H); (major isomer) 1.35 (3 H, d, *J* 7 Hz, 3-Me), 1.36 (3 H, s, 2-Me), 1.72 (3 H, dq, *J*/Hz 7 and 1.3, 4′-H_3), 1.74 (3 H, s, 2′-Me), 2.19 (3 H, s, 6-Me), 3.87, 3.90 and 3.94 (each 3 H, s, OMe), 3.90 (1 H, q, *J* 7 Hz, 3-H, partly obscured by OMe) and 6.19 (1 H, qq, *J*/Hz 7 and 1.3, 3′-H); δ_C (both isomers) 9.02, 9.04, 12.53, 14.69, 14.80, 15.16, 16.27, 16.47, 18.22 and 20.59 (Me), 39.11 and 40.50 (C-3), 60.24 (× 2), 60.46, 60.50, 61.45 and 61.51 (OMe), 65.52 and 67.72 (C-2), 126.61 and 136.54 (vinyl CH), 122.62, 122.72, 125.65 and 125.87 (C-3a and -6), 135.21 and 137.88 (C-7a), 145.64, 146.38, 147.39, 147.41, 149.52, 153.32, 153.56, 158.31 and 158.44 (C-4, -5, -7 and -2′) and 199.78, 200.29, 201.89 and 207.56 (C=O); *m/z* 346 (M^+, 2%) 283 (100), 249 (5), 233 (5), 83 (45) and 55 (47).

2,4a,5,9b-*Tetrahydro*-9b-*hydroxy*-6,7,9-*trimethoxy*-2,3,4a,5,8-*pentamethylindeno*[1,2-b]*pyran*-4-*yl* (E)-2-*methylbut*-2-*enoate* **24**. Elution with 20% ether–light petroleum as eluant afforded *title compound* **24** (280 mg, 15%) as a crystalline powder, m.p. 97–100.5 °C (from light petroleum) (Found: C, 67.35; H, 7.3. $C_{25}H_{34}O_7$ requires C, 67.25; H, 7.65%); ν_{max}/cm^{-1} 3493 (OH), 1724 (C=O) and 1687, 1648 and 1611 (C=C); δ_H 0.99br (3 H, s, 4a-Me), 1.33 (6 H, d, *J* 7 Hz, 2- and 5-Me), 1.46 (3 H, s, 3-Me), 1.85 (3 H, dq, *J*/Hz 1 and 7, 4′-H_3), 1.94 (3 H, sharp m, 2′-Me), 2.18 (3 H, s, 8-Me), 3.48 (1 H, q, *J* 7 Hz, 5-H), 3.71, 3.77 and 3.85 (each 3 H, s, OMe), 4.69 (1 H, br q, *J* 7 Hz, 2-H), 4.95 (1 H, s, OH, D_2O-exchangeable) and 6.98 (1 H, qq, *J*/Hz 7 and 2, 3′-H); δ_C 9.07, 12.10, 12.24, 13.59, 13.72, 14.59 and 19.66 (Me), 45.64 (C-5), 52.11 (C-4a), 60.18, 60.46 and 61.98 (OMe), 67.88 (C-2), 105.32 (OCOH), 121.36, 124.27, 128.26, 129.59, 135.39 and 142.8 (vinyl- and Ar-C), 138.56 (C-3′), 147.78, 150.43 and 153.23 (Ar-O) and 165.21 (C=O); *m/z* 446 (M^+, 6%), 346 (5), 264 (19), 263 (91), 83 (100) and 55 (33).

(E)-2-*Methyl*-1-(2,4,5-*trimethoxy*-3-*methylphenyl*)*but*-2-*en*-1-*one* **5**.—2,3,6-Trimethoxytoluene (750 mg) was treated with (*E*)-2-methylbut-2-enoic acid and TFAA as described above, but in air for 2.5 h. As before, the anhydride **15** was removed by initial flash chromatography, and subsequent fractions afforded a

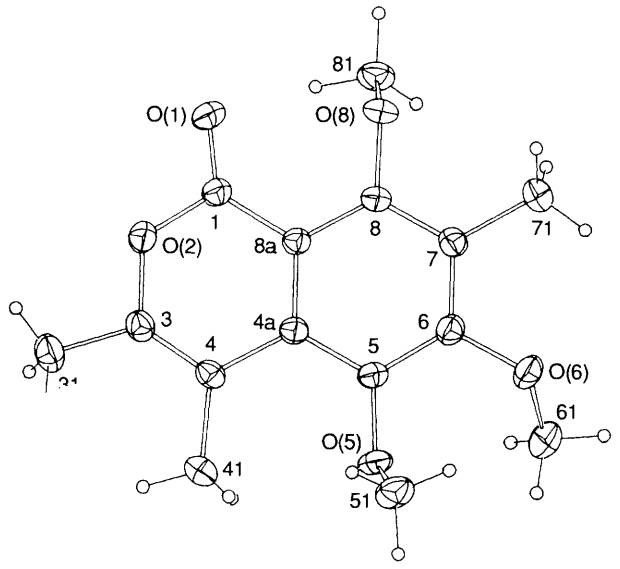


Fig. 1 A single molecule projected normal to the aromatic ring plane. 20% Thermal ellipsoids are shown for the non-hydrogen atoms, together with the atomic numbering scheme. Hydrogen atoms have an arbitrary radius of 0.1 Å.

Table 1 Non-hydrogen atom fractional co-ordinates

Atom	*x*	*y*	*z*
C(1)	0.847 3(4)	0.016 4(2)	0.120 3(2)
O(1)	0.901 6(3)	0.004 2(2)	0.192 9(1)
O(2)	0.815 3(3)	−0.084 7(1)	0.076 3(1)
C(3)	0.745 3(3)	−0.087 7(2)	−0.007 5(2)
C(31)	0.718 1(4)	−0.211 5(3)	−0.032 6(2)
C(4)	0.712 4(3)	0.008 3(2)	−0.052 5(1)
C(41)	0.629 1(4)	−0.003 8(3)	−0.141 8(2)
C(4a)	0.753 3(3)	0.121 1(2)	−0.012 1(1)
C(5)	0.736 9(3)	0.227 9(2)	−0.055 5(1)
O(5)	0.683 4(2)	0.231 6(2)	−0.139 2(1)
C(51)	0.823 4(5)	0.252 0(3)	−0.189 0(2)
C(6)	0.769 3(3)	0.333 0(2)	−0.012 3(2)
O(6)	0.755 8(3)	0.437 5(2)	−0.053 8(1)
C(61)	0.593 8(5)	0.464 7(3)	−0.103 0(2)
C(7)	0.829 1(3)	0.336 3(2)	0.071 9(1)
C(71)	0.873 0(4)	0.450 3(2)	0.116 6(2)
C(8)	0.850 0(3)	0.232 1(2)	0.114 3(1)
O(8)	0.913 9(2)	0.237 1(2)	0.197 5(1)
C(81)	0.780 1(4)	0.236 1(2)	0.252 0(2)
C(8a)	0.813 6(3)	0.124 5(2)	0.073 6(1)

Table 2 Non-hydrogen interatomic distances (Å)

C(1)–O(1)	1.204(3)	C(5)–O(5)	1.365(3)
C(1)–O(2)	1.369(3)	O(5)–C(51)	1.421(4)
C(1)–C(8a)	1.461(3)	C(6)–C(7)	1.381(3)
O(2)–C(3)	1.394(3)	C(6)–O(6)	1.374(3)
C(3)–C(4)	1.330(3)	O(6)–C(61)	1.420(4)
C(3)–C(31)	1.490(4)	C(7)–C(8)	1.381(3)
C(4)–C(4a)	1.469(3)	C(7)–C(71)	1.516(4)
C(4)–C(41)	1.512(3)	C(8)–C(8a)	1.414(3)
C(4a)–C(5)	1.413(3)	C(8)–O(8)	1.375(3)
C(4a)–C(8a)	1.405(3)	O(8)–O(81)	1.415(4)
C(5)–C(6)	1.403(3)		

residue which was slowly rechromatographed (eluant 10% ether–light petroleum) to afford compound **17** (230 mg, 16%), followed by a mixture of compounds **5** and **6** in the ratio 9:1 (150 mg, 14%). Earlier fractions were richer in compound **6** for which were obtained δ 1.66 (3 H, dq, *J*/Hz 7 and 1, 4′-H_3), 1.95 (3 H, q, *J* 1 Hz, 2′-Me), 2.21 (3 H, s, 3-Me), 3.66, 3.82 and 3.86 (each 3 H, s, OMe), 5.82 (1 H, qq, *J*/Hz 7 and 1, 3′-H), and 6.95 (1 H, s, 6-H). When this solution was treated with an equal volume of TFA, it was found that compound **6** was converted into its isomer **5** over a period of 15 min at 30 °C. Distillation of the mixture at 100 °C (0.02 mmHg) achieved the same result to afford the *title product* **5** (Found: C, 68.1; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.15; H, 7.65%); δ 1.87 (3 H, dq, *J*/Hz 7 and 1, 4′-H_3), 1.94 (3 H, q, *J* 1 Hz, 2′-Me), 2.21 (3 H, s, 3-Me), 3.62, 3.82 and 3.86 (each 3 H, s, OMe), 6.45 (1 H, qq, *J*/Hz 7 and 1, 3′-H), and 6.57 (1 H, s, 6-H); *m*/*z* 264 (M^+, 73%), 249 (15), 233 (29), 209 (100), and 55 (56).

Table 3 Non-hydrogen interbond angles (°)

O(2)–C(1)–O(1)	115.1(2)	C(5)–O(5)–C(51)	114.0(2)
C(8a)–C(1)–O(1)	128.3(2)	C(5)–C(6)–C(7)	122.0(2)
O(2)–C(1)–C(8a)	116.6(2)	C(5)–C(6)–O(6)	121.0(2)
C(1)–O(2)–C(3)	123.2(2)	C(7)–C(6)–O(6)	116.8(2)
O(2)–C(3)–C(4)	122.3(2)	C(6)–O(6)–C(61)	118.5(2)
O(2)–C(3)–C(31)	108.2(2)	C(6)–C(7)–C(8)	117.9(2)
C(4)–C(3)–C(31)	129.4(2)	C(6)–C(7)–C(71)	121.4(2)
C(3)–C(4)–C(4a)	118.4(2)	C(8)–C(7)–C(71)	120.6(2)
C(3)–C(4)–C(41)	118.4(2)	C(7)–C(8)–C(8a)	121.7(2)
C(4a)–C(4)–C(41)	123.2(2)	C(7)–C(8)–O(8)	117.0(2)
C(4)–C(4a)–C(5)	123.2(2)	C(8a)–C(8)–O(8)	121.2(2)
C(4)–C(4a)–C(8a)	119.2(2)	C(8)–O(8)–C(81)	114.0(2)
C(5)–C(4a)–C(8a)	117.5(2)	C(1)–C(8a)–C(4a)	120.0(2)
C(4a)–C(5)–C(6)	120.3(2)	C(8)–C(8a)–C(4a)	120.3(2)
C(4a)–C(5)–O(5)	121.0(2)	C(1)–C(8a)–C(8)	119.6(2)
C(6)–C(5)–O(5)	118.6(2)		

Structure Determination of the Isocoumarin **11**.—A unique data set was measured within the limit $2\theta_{max} = 50°$, using an ENRAF-Nonius CAD-4 four-circle diffractometer in conventional 2θ/θ scan mode. 2521 Independent reflections were obtained, 1897 with $I > 3\sigma(I)$ being considered 'observed' and used in the full-matrix least-squares refinement without absorption correction after solution of the structure by direct methods. Anisotropic thermal parameters were refined for the non-hydrogen atoms; (x, y, z, U_{iso})$_H$ were constrained at estimated values after location of the atoms in difference maps. Residuals at convergence on $|F|$ were $R = 0.060$, $R' = 0.087$ with statistical reflection weights derived from $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0005\sigma^4(I_{diff})$. The data were seriously affected by extinction and the model was improved considerably by refinement of the Larson extinction parameter ($g = 0.0013$). Neutral atom complex scattering factors were employed;[6] computation used the XTAL program system[7] implemented by Dr. S. R. Hall on a Perkin-Elmer 3240 computer. The non-hydrogen atom numbering is shown in the molecular projection (Fig. 1); the more significant results (non-H co-ordinates, bond lengths and angles); are given in Tables 1–3.*

Crystal Data.—$C_{15}H_{18}O_5$, $M = 278.3$, Monoclinic, space group $P2_1/n$ (C_{2h}^5, No. 14), $a = 7.580(3)$, $b = 11.510(5)$, $c = 16.114(5)$ Å, $\beta = 96.52(3)°$, $V = 1397$ Å^3, D_c (Z 4) = 1.32 g cm^{-3}; $F(000)$ 592. Monochromatic Mo-Kα radiation, $\lambda = 0.7106_9$ Å, μMo = 1.1 cm^{-1}. $T \sim 295$ K.

Acknowledgements

Skilled technical assistance in determining NMR spectra is gratefully acknowledged from Dr. L. Byrne, University of Western Australia (compound **24**) and from Dr. H. S. C. Spies,

* *Supplementary data* (see section 5.6.3 of Instructions for Authors, January issue): thermal and H-atom parameters have been deposited at the Cambridge Crystallographic Data Centre.

Stellenbosch University (compounds **20** and **21**). Useful discussions were held with Mr. W. E. Campbell, University of Cape Town, and Professor I. R. Green, University of the Western Cape. Financial support from the Council for Scientific and Industrial Research, the Council of the University of Cape Town, and the Australian Research Council is gratefully acknowledged.

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Paper 0/02213F
Received 18*th May* 1990
Accepted 24*th July* 1990