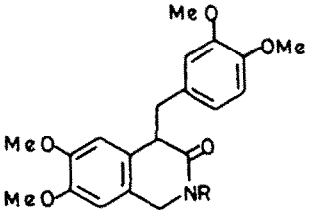
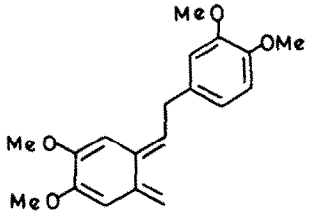
As part of another programme[4] we require the 4-benzyl-1,2,3,4-tetrahydroisoquinolin-3-one (7,R=Me) and we have already commented on the difficulties encountered in preparing this structure by conventional methods,[5] thus despite the uncertainty surrounding the conversion (5 → 2) described above we considered that the compound should be available by heating the 4-benzylisochromanone (6) with N,N[1]-dimethylurea at 200°C. In practice the desired product was not formed, instead the stilbene (9) was obtained in good yield, and it is clear that this compound arises from thermally induced extrusion of carbon dioxide from the isochromanone (6), followed by a 1,5-prototropic shift within the intermediate quinone methide (8), or its equivalent.

There are a number of precedents for the generation of quinone methides by the thermolysis of isochromanones[6] and we suggest that the formation of the simple isoquinolinone (2) may proceed through a cycloaddition reaction between the quinone methide (10) and a pyrolysis product of urea, possibly cyanuric acid, or cyanic acid.



(7)



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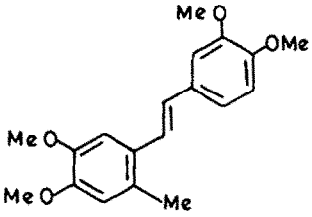
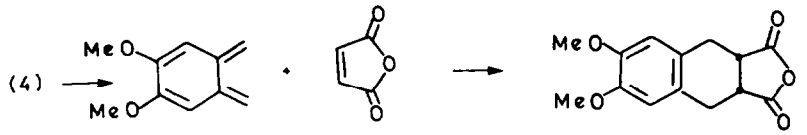


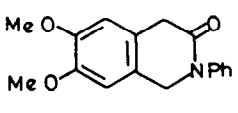
(9)

In support of the view we have shown that when the isochromanone (4) is heated with maleic anhydride the adduct (11) is produced. We also note that urea can be replaced by some of its derivatives and, for example, when the isochromanone is heated with N-phenylurea the N-phenylisoquinolinone (12) is formed.

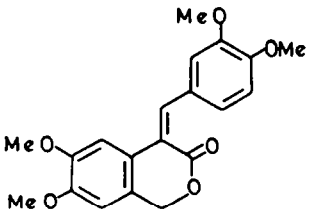
For the quinone methide (8) the availability of benzylic hydrogen atoms facilitates isomerization to the stilbene (9), but should these atoms be absent then it follows that the life time of the thermolysis product will be enhanced. Thus the probability of an intermolecular cycloaddition reaction with a suitable addend is improved, and when the benzylidene derivative (13) is heated with N,N[1]-dimethylurea the corresponding isoquinolinone (14,R=Me) is obtained. Catalytic hydrogenation of this compound affords the desired 4-benzylisoquinolinone (7,R=Me), but unfortunately the yield in the first reaction is poor (8%). Better results are obtained with urea, and the product (14,R=H) may then be N-methylated and reduced to give the isoquinolinone (7,R=Me) in 22% overall yield. Even though this is still a modest performance the route does provide almost direct access to the lactam since the starting material (13) is made in one step from the simple isochromanone (4) thus circumventing all the problems previously encountered during other attempts to make 4-benzyl-1,2,3,4-tetrahydroisoquinolin-3-ones.[5]



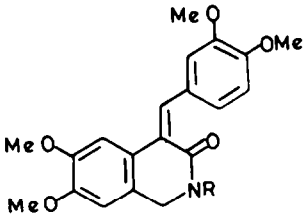
(10) (11)



(12)



(13)



(14)

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Experimental Yields are not optimised and m.p. are uncorrected. N.M.R. data refer to solutions in $CDCl_3$ or $(CD_3)_2SO$ containing T.M.S. as internal standard. Electronic absorption spectra were recorded for 98% ethanol solutions and infra red spectra were recorded as Nujol mulls.

2-Hydroxymethyl-4,5-dimethoxyphenylacetylurea (5) To sodium hydride (0.24g) suspended in dry dimethylformamide (20cm^3) was added urea (0.3g) in the same solvent (4cm^3). After 30 minutes, 6,7-dimethoxyisochroman-3-one (1g) in dimethylformamide (2cm^3) was introduced and the reaction mixture stirred for 1 hour. Removal of the solvent gave a gum which on chromatography on silica eluting with ethyl acetate gave the title compound as colourless prisms (0.39g, 30%), m.p. 124-127°C; ν_{max}3470, 3400-3200, 1670, 1640cm^{-1}; $\delta_H[(CD_3)_2SO]$ 6.98(s,1H,H-6, 6.80(s,1H, H-3), 5.6-5.25 (bs,4H, removed by addition of D_2O, 4.41(s,2H,Ar$\underline{CH}_2$O), 3.78(s,6H,2xO$\underline{CH}_3$), 3.58(s,2H,Ar$\underline{CH}_2$CO); $\delta_C[(CD_3)_2SO]$, 172.9(s), 159.7(s), 147.2(s,2x$\underline{C}$-OCH$_3$), 133.0(s,C-2), 124.8(s,C-1), 114.6(d,C-6), 111.8(d,C-3), 60.6(t,Ar$\underline{CH}_2$O), 55.6, 55.5(2xq,2xO$\underline{CH}_3$), 37.6(t,Ar$\underline{CH}_2$CO [Found: C,53.5; H,5.8; N,10.2 $C_{12}H_{16}N_2O_5$ requires: C,53.7, H,6.0; N, 10.45%].

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolin-3-one (7,R=Me) The benzylidene derivative (14,R=Me) (0.8g) in ethyl acetate (20cm^3) and 10% palladium on carbon (10mg) were hydrogenated at atmospheric pressure during 3 hours. Removal of the catalyst and the solvent afforded the title compound as a colourless gum which was purified by chromatography on a short path column of silica eluting with ethyl acetate. Yield, 0.75g, 91%. This compound is identical in every respect with a sample prepared by an alternative route:[4] ν_{max}1640, 1600cm^{-1}; λ_{max}225, 280(weak)nm, $\delta_H(CDCl_3)$, 6.62(d,1H,$\underline{J}$=8Hz, 5-H), 6.42(s,2H, 5-H, 8-H), 6.30(dd,1H,$\underline{J}$=8Hz, $\underline{J}$=2Hz, 6'-H), 6.21(d,1H,$\underline{J}$=2Hz, 2'-H), 3.82(bs,2H,4xO$\underline{CH}_3$), 3.62(s,2H,1-H$_2$), 2.98(s,3H,N$\underline{CH}_3$), 3.0-4.0 (m,3H,4-H,$\underline{CH}_2$Ar); $\underline{m/z}$ 371.1738, calculated for $C_{21}H_{25}NO_5$ 371.1739.

E-1-(3,4-Dimethoxyphenyl)-2-(3,4-dimethoxy-5-methylphenyl)-ethene(9). The isochromanone (6) (3g) was intimately mixed with N,N^1-dimethylurea (0.7g) and heated at 200°C for 3 hours. The residue was then dissolved in chloroform (10cm^3) and filtered through a column of silica (50g). Evaporation of the solvent afforded an oil which slowly crystallised and was recrystallised from methanol to give the title compound as colourless prisms (1.8g, 68%), m.p. 115-116°C λ_{max} 300 inf., 337nm; ν_{max}1610, 1605cm^{-1}; δ_H($CDCl_3$) 2.38(s,3H,C-CH_3), 3.81(3.84(2xs, 2x6H,4xOCH_3), 6.6-7.25(m,7H,olefinic and aromatic protons); δ_C($CDCl_3$/D_2O) 19.3(q,C-CH_3), 55.9(bq 4xOCH_3), 109.2, 111.5, 113.6, 119.4, 124.6, 127.8, 128.4 (7xd), 128.6, 128.8, 131.1 (3xs), 147.4, 148.4, 148.6, 149.1 (4xs); m/z (EI) 314(100%M), 299(24%) [Found: C,72.7; H,6.7 $C_{19}H_{22}O_4$ requires c,72.6; H,7.05.

6,7-Dimethoxy-3a,4,9,9a-tetrahydronaphtho[2,3-c]furan-1,3-dione(11). 6,7-Dimethoxyisochroman-3-one (1.04g) was mixed with maleic anhydride (0.49g) and heated at 200°C for 5 hours. The resultant dark red gum was chromatographed on silica eluting with dichloromethane to afford the title compound (0.2g, 16%) as colourless prisms, m.p. 203-205°C (lit.,[7] 204-205°C); ν_{max}1840, 1780cm^{-1}; δ_H[$(CD_3)_2SO$] 6.54(s,2H,H-5,H-8), 3.60(s,6H,2xOCH_3), 3.20(m,4H,H_2-4, H_2-9), 2.81(m,2H,H_2-3a,H_2-9a); m/z (EI %) 262(M,100), 234(43),189(94), 164(16) [Found: C,64.0;H, 5.5 Calculated for $C_{14}H_{14}O_5$ C,64.1; H,5.4%].

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-phenylisoquinolin-3-one (12). 6,7-Dimethoxyisochroman-3-one (1g) and N-phenylurea (3.3g) were mixed and fused at 200°C. After 2 hours the mixture was cooled and chromatographed on silica, eluting with ethyl acetate, to give the title compound as a colourless solid (0.35g, 26%), m.p. 160-162°C, ν_{max}1660cm^{-1}; δ_H($CDCl_3$), 7.30(bs,5H,C_6H_5), 6.95(s, 1H,H-8), 6.85(s,1H,H-5), 4.81(s,2H,1-H_2), 3.81, 3.79(2xs, 2x3H, 2xOCH_3), 3.45(s,2H,H_2-4) [Found: C, 72.0, H,6.2; N,4.8 $C_{17}H_{17}NO_3$ requires: C,72.1; H,6.05; N,4.9%].

1,2,3,4-Tetrahydro-6,7-dimethoxy-4-(3,4-dimethoxybenzylidene)isoquinolin-3-one (14,R=H) 6,7-Dimeth oxy-4-(3,4-dimethoxybenzylidene)isochroman-3-one (1.2g) was mixed with urea (1.2g) and heated at 210°C for 2 hours. The product was then cooled dissolved in dichloromethane (70cm^3) and washed with water (3x10cm^3). After drying ($MgSO_4$) the solvent layer was evaporated to give a red gum which after chromatography on silica eluting firstly with dichloromethane, to remove less polar components, and then with ethyl acetate afforded the title compound as pale yellow prisms (0.3g, 24%), m.p. 210-212°C; ν_{max}3200, 1680cm^{-1}; δ_H($CDCl_3$) 7.75(s,1H,vinyl H); 7.06(d,1H,J=8Hz,5^1-H), 7.03, 7.00(2xs, 2x1H, 8-H,5-H), 6.80(bd,1H,6^1-H), 6.64(bs,1H,2^1-H), 4.50(bd,2H,1-H_2), 3.93(s, 6H,2xOCH_3), 3.80, 3.50 (2xs, 2x3H, 2xOCH_3), 1.95(t,1H,NH) [Found: C, 67.5; H,5.95; N,4.0 $C_{20}H_{21}NO_5$ requires: C, 67.6; H,6.0; N,3.9%].

4-(3,4-Dimethoxybenzylidene)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-3-one (14,R=Me) The desmethyl compound (14,R=H) (0.1g) in acetone (4.5cm^3) was treated first with potassium hydroxide (0.45g) in water (1.7cm^3) and then after 30 minutes, with dimethyl sulphate (0.26cm^3). Three days later the mixture was partitioned between ethylacetate and water, the organic phase collected, dried and evaporated to yield a gum which was chromatographed on silica (20g) eluting with ethyl acetate to give the title compound as colourless crystals (0.8g, 80%), m.p. 178-179°C; ν_{max}1640cm^{-1}; m/z (CI, isobutane, %) 370(11), 344(39), 206(13), 188(13); δ_H[$(CD_3)_2SO$], 7.46(s,1H vinyl-H), 7.04-6.94 (ABX system, 3H,2^1-H, 5^1-H, 6^1-H), 6.89(s,1H,5-H), 6.80(s,1H,8-H), 4.48(s,2H,1-H_2), 3.76(s,6H, 2xOCH_3), 3.64, 3.35(2xs,2x3H, 2xOCH_3), 3.05(s,3H, NMe). [Found: C,68.1 H, 6.2 N, 3.6 $C_{21}H_{23}NO_5$ requires C, 68.3; H, 6.3; N, 3.8%].

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