Electrochemical Oxidation of Aromatic Ethers. Part 7.[1] Oxidation of 4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,4-dihydro-3(2*H*)-isoquinolone and Related Compounds

Paul Bird, Mark Powell, and Malcolm Sainsbury
School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY
David I. C. Scopes
Glaxo Group Research Limited, Ware, Hertfordshire SG12 0DJ

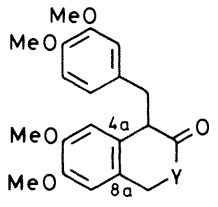
The electrochemical and chemical oxidations of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,4-dihydro-3(2*H*)-isoquinolone fail to yield an intramolecularly coupled product, yet the corresponding lactone 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochromanone affords both intramolecularly and intermolecularly coupled structures. Some aspects of the mechanism of these reactions are considered and attempts to synthesise isomorphinandienones are described.

We have reported earlier our failure to synthesise the lactam (1) which was required as the substrate for aryl–aryl coupling studies.[1] This compound has now been prepared by the catalytic reduction of the salt (3), but on chemical or electrochemical oxidation it does not provide an intramolecularly coupled product, giving instead a mixture of high molecular weight compounds.

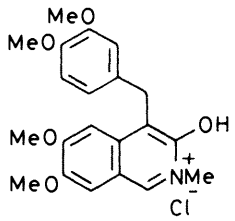
The *N*-formyl- and *N*-trifluoroacetyl-tetrahydroisoquinolines (4) and (5) behave similarly, but the *N*-methyl-analogue (6) affords the tetracyclic structure (7).† Interestingly, its higher homologue (8) yields the homoisoaporphine (9), and we suggest that the formation of these last two examples may be analysed in terms of the Baldwin rules for ring-closure.[2] Thus, in the first case, the formation of the salt (7) can be viewed in terms of an 'allowed' 6-*endo trig* cyclisation, whereas the homoisoaporphine (9) may arise either by a direct 7-*endo trig* ring closure or indirectly through initial cyclisation to C-4a, followed by ring expansion. Intramolecular carbon–carbon coupling to C-4a in the lower homologue leading eventually to an isoaporphine would require a 'disallowed' 5-*endo trig* transition state.

The factors which prevent the *N*-acyl compounds (1), (4), and (5) from undergoing intramolecular coupling are subtle. Thus an examination of molecular models indicates that despite some flattening of the heterocyclic ring, due to resonance within the amide units, the π-system of the 4-benzyl substituent may still approach either C-4a or C-8a quite closely in all three compounds. Furthermore, the isochromanone (2) on anodic oxidation affords the γ-lactone (10) in high yield. At one time we considered this product to have the alternative structure (11),[3,4] but differential nuclear Overhauser effect spectroscopy now leaves no doubt that the reformulation is correct.

Thus in the aromatic-olefinic region of the ^{1}H n.m.r. spectrum there are four one proton singlets at δ 6.98, 6.79, 6.51, and 6.00; these signals we assign to the resonances of 12-H, 9-H, 1-H, and 4-H respectively. Since on individual irradiation the singlets at δ 6.51 and 6.98 enhance one another (20—25%) these results rule out structure (11) unless the proton assignments in the dienone ring are reversed. This is untenable, however, since irradiation of the signal at δ 6.00 causes a 12% enhancement of a three-proton singlet at δ 3.76 due to the methoxy protons attached to the dienone ring (and *vice-versa*). In addition irradiation of the δ 6.00 resonance causes a 9% intensification of a methine resonance (7a-H) which occurs in the δ 3.2—3.0 region of the spectrum together with the resonances of the two benzylic protons. The resonance of the α-orientated proton of the bridging oxymethano unit (5α-H) at δ 4.24 is also enhanced by irradiation at δ 6.00 whereas the other signal of this AB system, at δ 3.98 (5β-H) is unchanged. Our complete results which are summarised in



(1) Y = NMe
(2) Y = O



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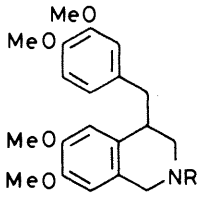
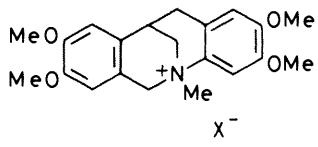
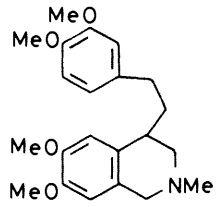


(4) R = CHO
(5) R = $COCF_3$
(6) R = Me



(7) X = ClO_4 or CF_3CO_2



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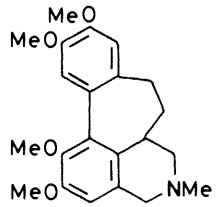
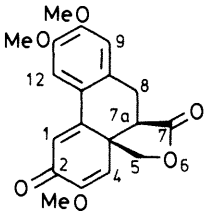


(9)

† In anodic reactions of this type carbon–carbon coupling *para-para* to existing methoxy groups is almost invariably observed, so that it is not surprising that an isoaporphine structure requiring *ortho-para* coupling was not formed even though this mode of cyclisation should proceed *via* a 6-*endo trig* transition state.



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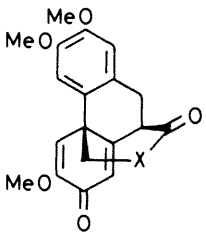


(11) X = O
(12) X = NMe

Table. Nuclear Overhauser enhancements for the γ-lactone (10) (spectra recorded in perdeuteriobenzene)

Signal irradiated (chemical shift δ)	Observed nuclear Overhauser enhancement
4-H (6.00)	3-OMe (12%), 7aα-H (9%), 5α-H (4%)
1-H (6.51)	12-H (23%)
12-H (6.98)	1-H (20—25%), 11-OMe (10%)
9H (6.79)	10-OMe (10%), 8β-H (4%), 8α-H (3%)
3-OMe (3.76)	4-H (12%)

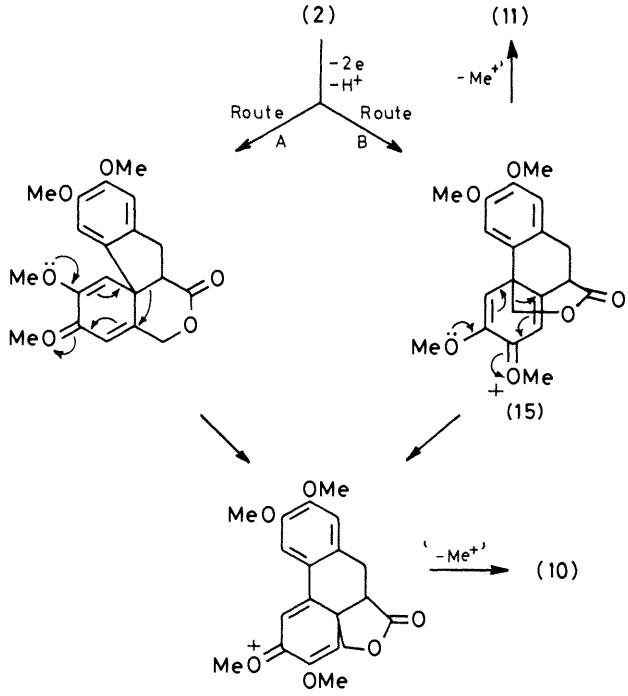
the Table uniquely define the structure of the lactone (10) and its relative stereochemistry.

Elliot has already shown [5] that the corresponding 1-benzylisochromanone (13) affords the γ-lactone (14), and so the two sets of results are now in accord, but either product could result from intermediate species in which coupling leads initially to five- or six-membered cyclic transition states. Thus the γ-lactone (10) may be formed from the isochromanone (2) in two ways indicated below as routes A and B (Scheme 1). In the first initial coupling occurs at C-4a, whereas in the second the primary event is attack at C-8a. Should the second route be followed it is difficult to understand why the δ-lactone (11) is not a major product since all that is required is *O*-demethylation of the initial reaction intermediate, shown here as the cation (15), whereas in order to form the γ-lactone (10) this species has to undergo ring-contraction, followed by *O*-demethylation.

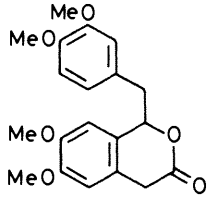
Recently Schäfer *et al.*[6] have shown that a change in solvent has a dramatic effect upon the course of related electrochemical reactions, but in our case, although we have varied the nature of the electrolyte system, so far we have been unable to determine the conditions under which the δ-lactone (11) becomes anything more than a very minor product. This problem is still under investigation.

It is usually assumed [7] that the mechanisms of chemical and electrochemical aryl-aryl coupling reactions are similar, if not the same, so at first we were surprised that vanadium oxytrifluoride oxidation of the isochromanone (2) afforded mainly the dehydro dimer (16) (as a mixture of diastereoisomerides) and only a very small quantity of the γ-lactone (10). A dilution of the substrate concentration had no effect on the ratio of products from the chemical oxidation, but when the electrolysis experiment was repeated at double the usual substrate concentration the dehydro dimer was produced in preference to the 'monomeric' lactone. Thus it seems that anodic coupling reactions of this type occur in the bulk phase of the electrolysis medium, but when certain chemical oxidants are used substrate–oxidant complexes are most probably involved, which in this case have an inhibitory effect upon intramolecular coupling.[8]

In an attempt to form the spirodienone (12), unobtainable by direct oxidation of the lactam (1), we decided to oxidise



Scheme. Alternative pathways to the γ-lactone (10) from the anodic oxidation of the isochromanone (2)



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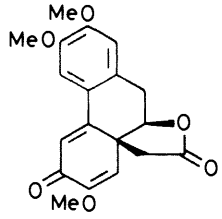
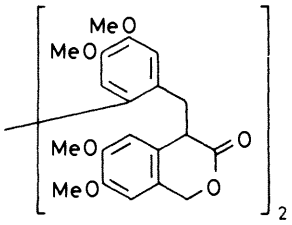


(14)

the amide acetate (16) hoping that we might be able to reconstitute the lactam ring after aryl-aryl coupling to the intermediate (20) had occurred. In practice, oxidation with vanadium oxytrifluoride yielded the tetracyclic product (21), which was also obtained when the *O*-benzyl ether (18) was oxidised. Electrochemical attempts at cyclisation gave only resins. We conclude that the first product in the chemical reaction is the tricyclic amide (22) (isolated in one case) formed by a non-oxidative ring-closure promoted by complexation of the ester or ether units with the reagent. This product is then oxidised to a carbocation (23), which is neutralised by the lone pair electrons in the nitrogen atom of the amide function. Unfortunately the yields obtained in these reactions were low and a repetition, now with the secondary amide (19), only afforded the phenanthrene (26). The formation of this last product indicates that our projected route to the spirodienone (12) had some merit for the acetoxymethylene side-chain of the substrate is most likely eliminated after aryl-aryl coupling has occurred, possibly as shown (24)→(25).

Experimental

U.v. spectra were recorded for solutions in 95% ethanol; i.r. spectra were measured at 100 and 250 MHz; differential n.O.e. experiments were conducted at 250 MHz; ^{13}C n.m.r. data were compiled at 22.6 MHz. All n.m.r. chemical shift



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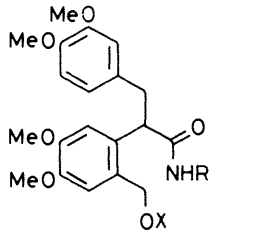
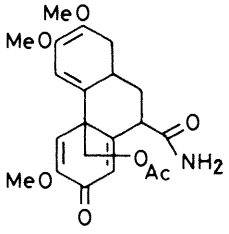


(17) R = H, X = COMe
(18) R = H, X = CH_2Ph
(19) R = Me, X = COMe



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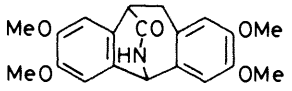

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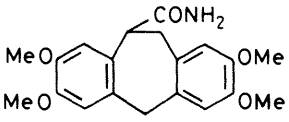

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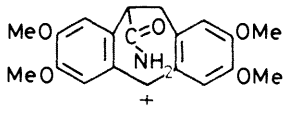


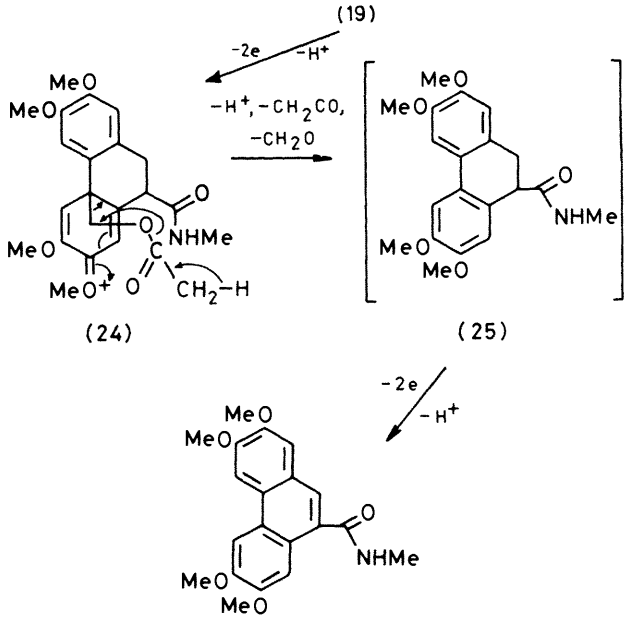
(23)

data are quoted in p.p.m. downfield from tetramethylsilane as internal standard.

Standard Electrochemical Oxidation Procedure.—The substrate (1 g) was dissolved in 0.1-M-sodium perchlorate in acetonitrile (250 cm^3), contained in a two-compartment cell with platinum electrodes, and electrolysed at an anode potential of *ca.* +1 V * until 2 F mol^{-1} of current had been consumed. The anolyte was partly evaporated under reduced pressure and then diluted with water (100 cm^3). The reaction mixture was then extracted with dichloromethane (3 × 50 cm^3), the combined, dry extracts evaporated, and the residue chromatographed on silica.

4-(3,4-*Dimethoxybenzyl*)-1,4-*dihydro*-6,7-*dimethoxy*-2-*methyl*-3(2H)-*isoquinolone* (1).—The isoquinolinium chloride (3) [1] (0.8 g, mmol) was suspended in acetone (200 cm^3) and hydrogenated at 100 lb in^{-2} in the presence of Adams' catalyst (0.1 g) for 3 days. The mixture was filtered through Kieselguhr and the solvent removed by evaporation to yield a green gum, which was chromatographed over silica using ethyl acetate as the eluant, to afford the title compound as a colourless gum (0.58 g, 80%), δ_H ($CDCl_3$) 6.66 (1 H, d, 5′-H, *J* 8 Hz), 6.45 (2 H, s, 5-, 8-H), 6.33 (1 H, dd, 6′-H, *J* 8, 2 Hz), 6.19 (1 H, d, 2′-H, *J* 2 Hz), 3.94—2.92 (3 H, ABX, CH_2CH), 3.8 (12 H, s, 4 × OCH_3), 3.6 (2 H, s, $ArCH_2N$), and 2.92 (3 H, s, NCH_3); $\nu_{max.}$ 1 640 and 1 600 cm^{-1}; $\lambda_{max.}$ 225 and 280 nm (Found: M^+, 371.1736. $C_{21}H_{25}NO_5$ requires M^+, 371.1739), *m/z* (%), 371 (M^+, 6), 220, (42), and 151 (100).

* The precise anode potential was determined by cyclic voltammetric analysis of the individual substrate.



(24) (25) (26)

2-*Benzyl*-4-(3,4-*dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinolone.*—2-Benzyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isoquinolinium bromide (3.2 g, 6.3 mmol) was dissolved in 95% ethanol (150 cm^3) and sodium borohydride (1.0 g, 26 mmol) was added portionwise. The mixture was stirred overnight and then 2M-hydrochloric acid (100 cm^3) was added cautiously; when the mixture had become homogenous 2M-sodium hydroxide solution was introduced until the solution became alkaline to litmus. After cooling, the solution was extracted with dichloromethane (3 × 50 cm^3) and the combined organic extracts were washed with water (2 × 50 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure to yield a colourless oil which was then dissolved in hot ethanol (10 cm^3). On cooling the solution the product separated as a white solid (2.2 g, 81%), m.p. 106—107 °C, δ_H ($CDCl_3$) 7.5—7.2 (5 H, m, 5 × Ar*H*, aryl protons of 2-benzyl substituent), 6.8—6.5 (5 H, m, 5 × ArH), 3.9—3.5 (12 H, 3s, 4 × OCH_3), 3.6 (2 H, bs, $ArCH_2N$), 3.7, 3.3 (2 H, d, *J* 18 Hz, $PhCH_2N$), 3.0—2.3 (5 H, m, $ArCH_2CHCH_2N$); $\nu_{max.}$ 1 605, 1 590, 1 510, and 1 135 cm^{-1}; $\lambda_{max.}$ (log ε) 239 (8 330) and 283 nm (6 710); *m/z* (%), 433 (12), 432 (21), 342 (100), 314 (10), 299 (16), 281 (62), and 151 (21) (Found: C, 74.9; H, 7.2; N, 3.4. $C_{27}H_{31}NO_4$ requires C, 74.8; H, 7.2; N, 3.2%).

The hydrochloride salt was prepared by adding a solution of hydrogen chloride in diethyl ether to a solution of the base (3.7 g, 8.5 mmol) dissolved in toluene (30 cm^3) until no further precipitate was observed and then recrystallising the product from methanol (10 cm^3). The salt was obtained as fine needles (3.28 g, 82%), m.p. 218—219 °C.

4-(3,4-*Dimethoxybenzyl*)-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline Hydrochloride.*—2-Benzyl-4-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride salt (0.40 g, mmol) was dissolved in absolute ethanol (200 cm^3) and hydrogenated at atmospheric pressure over 10% palladium on charcoal (0.05 g) for 3 h. The catalyst was then filtered off and the solvent removed by evaporation under reduced pressure to give a white solid which was recrystallised from ethanol (5 cm^3) to yield the product as prisms (0.31 g, 76%), m.p. 136—140 °C. On treatment with

sodium carbonate this gave the free base as a colourless oil; δ_H ($CDCl_3$) 6.9—6.6 (3 H, m, 3 × Ar*H*, aryl protons of 4-benzyl substituent), 6.50 (2 H, s, 2 × ArH), 3.9—3.7 (14 H, m, 4 × OCH_3 + $ArCH_2N$), and 3.0—2.8 (5 H, m, remaining protons); $\lambda_{max.}$ (log ε), 233 (15 350) and 282 nm (6 300); *m/z* (%), 343 (32), 192 (100), 161 (16), and 151 (16) (Found: C, 62.8; H, 7.2; N, 3.5. $C_{20}H_{25}NO_4HCl$ requires C, 63.2; H, 6.9; N, 3.7%).

1,2,3,4-*Tetrahydro*-6,7-*dimethoxy*-4-(3,4-*dimethoxybenzyl*)-2-*trifluoroacetylisoquinoline* (5).—4-(3,4-Dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride salt (1.60 g, 4.7 mmol) was dissolved in chloroform (50 cm^3) and washed with saturated sodium hydrogencarbonate solution until no further evolution of carbon dioxide was evident. The organic phase was washed with water (50 cm^3) and dried ($MgSO_4$).

To the solution of the free base was added anhydrous potassium carbonate (1.0 g) and trifluoroacetic anhydride (2.1 g, 10 mmol). The mixture was stirred at room temperature for 4 h protected by a calcium chloride drying tube. The chloroform solution was then washed with water (2 × 50 cm^3), dried ($MgSO_4$), and evaporated under reduced pressure to yield a white solid which was recrystallised from ethanol (10 cm^3) to yield the product as white prisms (1.4 g, 63%), m.p. 98.5—99.5 °C, δ_H ($CDCl_3$) 6.9—6.5 (3 H, m, 3 × ArH, 4-benzyl substituent), 6.35 (2 H, s, 2 × ArH), 4.85, 4.60 (2 H, d, $ArCH_2N$, *J* H), 4.55, and 4.0—2.7 (m, 17 H, remaining protons); $\nu_{max.}$ (0.5% $CHBr_3$) 1 690 cm^{-1}; $\lambda_{max.}$ 230sh and 283 nm (6 600); *m/z* (%), 439 (23), 288 (35), and 151 (100) (Found: C, 60.2; H, 5.6; N, 2.9. $C_{22}H_{24}F_3NO_5$ requires C, 60.1; H, 5.5; N, 3.2%).

4-(3,4-*Dimethoxybenzyl*)-2-*formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (4).—A solution of 4-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolinium hydrochloride [1] (0.7 g, 1.8 mmol) in formamide (30 cm^3) and formic acid (6 cm^3) was heated under reflux for 7 h. The cooled solution was poured into water (100 cm^3) and extracted with dichloromethane (4 × 30 cm^3); the combined extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4), and evaporated to give a yellow oil. The oil was chromatographed on silica using dichloromethane–ethyl acetate as eluant to afford a white solid (0.5 g, 75%), m.p. 115—117 °C; δ_H ($CDCl_3$) 8.36, 8.07 (1 H, 2s CHO), 6.9—6.5 (4 H, m, 5-, 2′-, 5′-, 6′-H), 6.44 (1 H, s, 8-H), 5.1, 4.21 (AB, 2 H, $ArCH_2N$, *J* 12 Hz), 4.0—3.54 (1 H, m, CH_2CHCH_2), 3.86, 3.78 (12 H, 2s, v × OCH_3), 3.78 (2 H, m, NCH_2CH), 3.2—2.46 (2 H, m, $ArCH_2CH$); $\nu_{max.}$ 1 660, 1 610, and 1 585 cm^{-1} (Found: M^+, 371.1736. $C_{21}H_{25}NO_5$ requires M^+, 371.1739); *m/z* (%), 371 (M^+, 21), 220 (74), and 151 (100) (Found: C, 67.8; H, 6.7; N, 3.7. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.8%).

5,6,11,12-*Tetrahydro*-2,3,8,9-*tetramethoxy*-5-*methyl*-5,11-*methanodibenz*[b,f]*azocinium Perchlorate* (7).—1,2,3,4-Tetrahydro-2-methyl-4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisoquinoline [1] (2 g) was dissolved in 0.1M-sodium perchlorate in dry acetonitrile (200 cm^3) and stirred over anhydrous sodium carbonate (0.5 g). The solution was electrolysed at a potential of +0.8 V until the current dropped below 10 mA, when the anolyte was filtered and partially evaporated under reduced pressure. The residue was treated with water (400 cm^3), extracted with dichloromethane (3 × 200 cm^3), and the combined extracts washed with water (200 cm^3) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a black solid which was added to acetone (50 cm^3). The insoluble material was collected by filtration and recrystallised from a large volume of methanol as white needles (0.28 g, 11%), m.p. 219 °C, δ_H [$(CD_3)_2SO$], 7.48 (1 H, s, 4-H), 7.04 (1 H, s, 1-H), 6.72 (1 H, s, 7-H), 6.58 (1 H, s, 10-H), 5.02 (1 H, d, *J* 14 Hz, 6*eq*-H), 4.76 (1 H, d, *J* 14 Hz, 6*ax*-H), 4.08 (1 H, 13*eq*-H), 3.9—3.6 (5 × 3 H, 5 × s, 4 × OCH_3, NCH_3), and 3.37—3.18 (4 H, m, 13*ax*-, 11-, 12*eq*-, 12*ax*-H); δ_C [$(CD_3)_2SO$], 149.79 (s), 149.09 (s), 148.42 (s), 148.38 (s), 133.05 (s), 126.33 (s), 122.22 (s), 119.07 (s), 112.09 (d), 111.65 (d), 109.00 (d), 104.56 (d), 68.04 (t), 61.92 (t), 56.34 (q), 55.64 (q), 55.56 (q), 55.53 (q), 48.54 (d), 35.48 (t), and 30.12 (q); $\lambda_{max.}$ (log ε) 231 (4.03) and 290 (3.70) nm (Found: C, 55.3; H, 5.7; Cl, 7.9; N, 3.05. $C_{21}H_{26}NO_4ClO_4$ requires C, 55.3; H, 5.7; N, 3.1; Cl, 7.8%).

4,5,6,6a,7,8-*Hexahydro*-1,2,10,11-*tetramethoxy*-5-*methylbenzo*[6,7]*cyclohept*[1,2,3-d,e]*isoquinoline* (9).—A solution of thallium(III) trifluoroacetate (0.75 g, 1.4 mmol) in dry acetonitrile (100 cm^3) and carbon tetrachloride (100 cm^3) was cooled to −40 °C under nitrogen in the absence of light. To this was added a solution of 2-methyl-4-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [1] (0.47 g, 1.27 mmol) in dry acetonitrile (15 cm^3) followed by boron trifluoride–diethyl ether (5 cm^3). The mixture was allowed to warm to room temperature and then stirred for 2 h. The solvent was partially evaporated under reduced pressure and the residue treated with 2M-ammonium hydroxide solution and extracted with chloroform (3 × 100 cm^3). The combined extracts phases were washed with water (100 cm^3) and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a brown oil which was subjected to column chromatography on basic alumina with diethyl ether as eluant. Evaporation of the eluate under reduced pressure afforded a colourless gum which crystallised in the form of white rods on trituration with ether (0.2 g, 43%), m.p. 109 °C, δ_H ($CDCl_3$), 7.14 (1 H, s, 12-H), 6.78 (1 H, s, 9-H), 6.62 (1 H, s, 3-H), 3.96 (3 H, s, 10-OCH_3), 3.90 (3 H, s, 2-OCH_3), 3.88 (3 H, s, 11-OCH_3), 3.86 (1 H, d, *J* 14 Hz, 5*eq*-H), 3.21 (1 H, d, *J* 14 Hz, 5*ax*-H), 3.46 (3 H, s, 1-OCH_3), 2.64 (1 H, d, *J* 12 Hz, 6*eq*-H), 2.5—2.0 (9 H, m, aliphatic H), and 2.44 (3 H, s, NCH_3). Strong n.O.e. enhancements <10% were noted: 12*-H–11-OCH_3 and 1-OCH_3 9*-H–10-OCH_3 and in the δ 2.5—2.0 region; 3*-H–2-OCH_3 (asterisk denotes signal irradiated); δ[$(CD_3)_2SO$] 151.04 (s), 148.11 (s), 146.59 (s), 143.78 (s), 132.57 (s), 132.29 (s), 129.75 (s), 127.20 (s), 127.09 (s), 114.58 (d), 112.03 (d), 109.54 (d), 59.75 (q), 57.97 (t), 57.48 (t), 55.76 (q), 55.69 (q), 55.58 (q), 45.88 (q), 38.73 (t), 34.18 (d), and 30.39 (t); $\lambda_{max.}$ (log ε) 270 (4.06) and 293 nm (3.95) (Found: C, 71.4; H, 7.3; N, 3.85. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.4; N, 2.8%).

7a,8-*Dihydro*-3,10,11-*trimethoxy*-2H-*phenanthro*[9,8a-b]*furan*-2,7(5H)-*dione* (10).—4-(3,4-Dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (2) (1.1 g, mmol) and 0.1 mol cm^{-3} anhydrous sodium perchlorate in dry acetonitrile (110 cm^3) were electrolysed at an anode potential of 1.22 V (*vs.* S.C.E.) at 0 °C using a platinum gauze electrode and a mercury pool cathode. After all the starting material had been oxidised (*ca.* 2 h), the anolyte was separated, water (10 cm^3) was added, and the mixture evaporated to near dryness. The dark residue was dissolved in chloroform (100 cm^3) and the solution washed with water (50 cm^3) and brine (40 cm^3) and finally dried ($MgSO_4$). After evaporation of the solvent, the resultant oil was chromatographed on silica using ethyl acetate as the eluant to yield an off-white solid. This was recrystallised from ethanol to furnish fine white needles (0.5 g, 48%), m.p. 252 °C (lit.,[4] 256—257 °C; † δ_H ($CDCl_3$),

† This compound appears to exist in polymorphic forms and samples with m.p. 238—239 °C (ethanol), may be produced.

6.98 (1 H, s, 12-H), 6.79 (1 H, s, 9-H), 6.51 (1 H, s, 1-H), 6.00 (1 H, s, 4-H), 4.24, 3.98 (2 H, AB, 2 × 5-H, *J* 12.5 Hz), 3.94, 3.92 (6 H, s, 2 × CH_3O), 3.76 (3 H, s, 3-CH_3O), 3.20—3.00 (3 H, m, 7a-H, 2 × 8-H). 180.2 (s, 2-C, C=O), 177.7 (s, 7-C), 155.2, 151.6, 151.0, 149.0 (4 × s, 3-C, 12b-C, 11-C, 10-C), 128.0 (s, 8a-C), 126.0 (s, 4a-C), 124.2 (d, 4-C), 116.7 (d, 9-C), 111.2 (d, 12-C), 108.7 (d, 1-C), 77.0 (t, 5-C), 47.0 (s, 12a-C), 43.1 (d, 7a-C), and 28.9 (t, 8-C); $\nu_{max.}$ 1 760 (δ-lactone), 1 660, 1 650 (dienone), and 1 610 cm^{-1}; $\lambda_{max.}$ (log ε) 265 (6 650), 290 (4 180), 360 nm (4 750); *m/z* (%), 342 (M^+, 100), 284 (28), 266 (15), and 253 (58) (Found: C, 66.3; H, 5.5%. M^+, 342.1102. Calc. for $C_{19}H_{18}O_6$: C, 66.7; H, 5.3%; *M* 342.1101.]

Repetition of the reaction now using acetonitrile–methanol (1 : 1, v/v) instead of acetonitrile alone as solvent gave a red oil which, after chromatography on silica with ethyl acetate–light petroleum (b.p. 60—80 °C) mixtures, afforded mainly the γ-lactone (10) contaminated with at least three other compounds. Further work is in progress to purify these minor products and to obtain unambiguous analytical and spectroscopic data. These results will be published later when we have studied the effects of different solvent systems upon the course of the electrochemical reaction.

6,6′-Bis(6,7-dimethoxy-3-oxoisochroman-4-ylmethyl)-3,3′,-4,4′-tetramethoxybiphenyl.—(16). A solution of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (2) (3.3 g, 9 mmol) in dry dichloromethane (12 cm^3) was cooled to −10 °C. Vanadium oxytrifluoride (3 g, 24 mmol) in dry acetonitrile (40 cm^3) was slowly added in portions and the mixture was stirred at −10 °C for 5.5 h. Citric acid (20 g) in water (200 cm^3) was added and the organic phase was separated; the aqueous phase was then extracted with dichloromethane (3 × 50 cm^3). The combined organic extracts were washed with brine (2 × 100 cm^3) and dried ($MgSO_4$). Removal of the solvent by evaporation left a black tar, which was chromatographed on silica using ethyl acetate/cyclohexane (9 : 1, v/v) as the eluant. This process gave the phenanthrofuran (10) (0.026 g, 1%) identical with a sample prepared by the electrochemical oxidation of the same substrate. The major product, however, was a white solid (0.48 g, 7%) which proved to be a mixture of diastereoisomers of the title compound. A partial separation was achieved by repeated recrystallisation of the mixture from ethyl acetate.

Diastereoisomer 1: δ_H ($CDCl_3$) 6.37, 6.56, 6.28 (8 H, 3s, 8 × ArH), 4.9 (4 H, s, 2 × $ArCH_2O$, 3.89, 3.85, 3.80, 3.72 (24 H,) 4s, 8 × OCH_3), 3.6 (2 H, m, 2 × $CHCH_2$), and 2.79 (4 H, d, 2 × CH_2–CH, *J* 12 Hz); $\nu_{max.}$ 1 740 cm^{-1}; *m/z* (%), 714 (M^+, 17), 507 (45), 46 (37), and 299 (100). *Diastereoisomer* 2: δ_H (90 MHz, $CDCl_3$) 6.8, 6.48, 5.8, 5.75 (8 H, 4 s, 8 × ArH), 4.9, 4.65 (4 H, AB, $ArCH_2O$, *J* 12 Hz), 3.9, 3.82, 3.68, 3.55 (24 H, 4s, 8 × OCH_3), 3.4 (2 H, m, 2 × CH-CH_2), and 3.0—2.7 (4 H, m, 2 × CH_2-CH); $\nu_{max.}$ 1 740 cm^{-1}; *m/z* (%), 714 (M^+, 13), 507 (37), 461 (31), and 299 (100). [Found: M^+ 714.2671. $C_{40}H_{42}O_{12}$ requires *M*, 714.2664 (measurement recorded on mixture of diastereoisomers].

3-(3,4-Dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)propionamide (17).—An ice-cold solution of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one (2) (3 g, 8 mmol) in absolute methanol (400 cm^3) was saturated with ammonia gas and left at room temperature for 24 h. Evaporation of the solvent left a yellow oil which was triturated with light petroleum to give a while solid. Recrystallisation from ethyl acetate–light petroleum produced a white solid (3.1 g, 95%), m.p. 108 °C, δ_H ($CDCl_3$), 7.06 (1 H, s, 6-H), 6.7—6.55 (4 H, m, 2′-, 5′-, 6′-H, and NH), 6.51 (1 H, s, 3-H), 5.3 (1 H, 6 s, NH), 4.5 (1 H, dd, C*H*OH *J* 11, 6 Hz), 4.3 (dd, 1 H, C*H*OH, *J* 11, 3 Hz), 4.04 (1 H, t, CH-CO, *J* 7 Hz), 3.88, 3.80, 3.79, 3.68 (12 H, 4 s, 4 × OCH_3), 3.38 (1 H, dd, ArC*H*-CH, *J* 13, 6 Hz), 3.14 (1 H, 6 s, OH), 2.94 (1 H, dd, ArC*H*-CH, *J* 13, 8.5 Hz); δ_C [$(CD_3)_2SO$] 174.7 (s, C=O), 148.3, 147.8, 147.1 (s, 4 × *C*OMe), 132.7 (s, Ar*C*CH_2-OH), 131.9, 131.2 (s, 1-, 1′-C), 120.8 (d, 6′-C), 113.0 (d, 3-C), 112.4, 111.7, 111.0 (d, 6-, 2′-, 5′-C), 61.2 (t, *C*H_2OH), 55.6, 55.4, 55.3 (q, 4 × CH_3O), 47.6 (d, CHCO), 38.46 (t, *C*H_2CH); $\nu_{max.}$ (0.5% $CHBr_3$), 3 580 (OH), 3 480, 3 380 (NH_2), and 1 675 cm^{-1} (C=O); $\lambda_{max.}$ (log ε) 232 (15 500) and 281.5 nm (5 700); *m/z* (%), 375 (M^+, 36%), 358 (100), 313 (20), 209 (16), and 151 (93) (Found: C, 63.85; H, 6.7; N, 3.6. $C_{20}H_{25}NO_6$ requires C, 64.0; H, 6.7; N, 3.7%).

2-(2-Benzyloxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (18).—Sodium hydride (0.16 g, 3 mmol) and dry 1,2-dimethoxyethane (DME) (15 cm^3) was stirred at 0 °C under a dry nitrogen atmosphere. 3-(3,4-Dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)propionamide (1.1 g, 0.003 mol) in the minimum volume of dry DME was added dropwise over 0.25 h. The mixture was stirred at 0 °C for 2 h, and then benzyl bromide (0.55 g, 3 mmol) in dry DME (5 cm^3) was added. The solution was stirred at room temperature for 3 days, filtered, and evaporated to yield a light brown oil, which was chromatographed over silica using dichloromethane–absolute ethanol (20 : 1) as the eluant. This procedure produced the title compound as a white solid (0.8 g, 59%), m.p. 102—104 °C, δ_H ($CDCl_3$), 7.3 (5 H, s, C_6H_5), 7.0, 6.6 (2 H, 2s, 3-H, 6-H), 6.62 (1 H, d, 5′-H), 6.45 (1 H, dd, 6′-H), 6.4 (1 H, d, 2′-H), 6.25, 5.0 (2 H, 2 × bs, NH_2), 4.45 (2 H, AB, O*C*H_2Ph, *J* 12 Hz), 4.15 (2 H, AB, *C*H_2O*C*H_2Ph, *J* 12 Hz), 3.87, 3.8, 3.77, 3.63 (12 H, 4s, 4 × O*C*H_3), 3.80, 3.35, 2.8 (3 H, ABX, CH_2-C*H*, *J* 14, 6 Hz); $\nu_{max.}$ (0.5% $CHBr_3$), 3 480, 3 340, and 1 680 cm^{-1}; *m/z* (%), 465 (M^+, 3), 358 (5), 313 (23), 179 (9), and 151 (100) (Found: C, 69.5; H, 6.7; N, 2.8. $C_{27}H_{31}NO_6$ requires C, 69.7; H, 6.7; N, 3.0%).

2-(2-Acetoxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-N-methylpropionamide (19).—2-(2-Hydroxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-*N*-methylpropionamide [1] (2.21 g, 6 mmol) and acetic anhydride (0.59 g, 6 mmol) in dry pyridine (30 cm^3) were left at room temperature for 3 days. Water (10 cm^3) was added and the solution evaporated to leave a yellow oil, which was dissolved in ethyl acetate (25 cm^3), and then washed with 1M-hydrochloric acid (2 × 50 cm^3) and water (50 cm^3), and finally dried (Na_2SO_4). Evaporation of the solvent left an off white solid which was crystallised from ethyl acetate–light petroleum to form colourless prisms (1.8 g, 73%), m.p. 125—127 °C; ^1H n.m.r. ($CDCl_3$), 7.1 (1 H, s, 6-H), 6.8—6.4 (4 H, m, 3-, 2′-, 5′-, 6′-H), 6.0 (1 H, bq, NH), 4.67 (2 H, AB, *C*H_2OAc, *J* 12 Hz), 3.9, 3.83, 3.80, 3.7 (12 H, 4s, 4 × O*C*H_3), 3.9, 3.5—2.8 (3 H, ABX, CH_2-C*H*), 2.7 (3 H, d, NCH_3, *J* 7 Hz), 2.0 (3 H, s, *C*H_3CO_2); δ_C ($CDCl_3$), 173.6 (s, NCO), 170.8 (s, $MeCO_2$), 149.8, 148.7, 147.9, 147.5 (s, 4 × MeO-*C*), 132.4, 132.2 (s, 1-, 1′-C), 126.0 (s, 2-C), 121.0 (d, 6′-C), 113.3 (d, 3-C), 112.6, 111.4, 110.4 (d, 6-, 2′-, 5′-C), 63.8 (t, *C*H_2OAc), 56.0, 55.8, 55.7 (q, 4 × OCH_3), 49.4 (d, *C*HCH_2), 39.7 (t, *C*HCH_2), 26.3 (q, NCH_3), 20.9 (q, *C*H_3CO_2); $\nu_{max.}$ (0.5% $CHBr_3$), 3 430, 3 400, 1 725, 1 665, and 1 510 cm^{-1} *m/z* (%) 431 (M^+, 2), 370 (28), 312 (90), and 151 (100) (Found: C, 64.15; H, 6.9; N, 3.4. $C_{23}H_{29}NO_7$ requires C, 64.0; H, 6.8; N, 3.25%).

10,11-Dihydro-5,11-iminomethano-2,3,7,8-tetramethoxy-5H-dibenzo[a,d]cyclohepten-12-one (21) *and* *11-Carboxamido-10,11-dihydro-2,3,7,8-tetramethoxy-5H-dibenzo[a,d]cyclo-*

heptene (22).—2-(2-Acetoxymethyl-3,4-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (17) (1.47 g, 3.5 mmol) in dry dichloromethane–acetonitrile (1 : 1, v/v; 10 cm^3) was cooled to −10 °C under a dry nitrogen atmosphere. Vanadium oxytrifluoride (0.5 g, 4 mmol) in dry acetonitrile (10 cm^3) was added and the mixture stirred at 0 °C for 6 h and at room temperature for 2.5 days. Citric acid (15 g) in water (100 cm^3) was added and the organic phase separated. The aqueous phase was extracted with dichloromethane (3 × 30 cm^3) and the combined organic extracts were washed with water (100 cm^3) and dried (Na_2SO_4). Removal of the solvents left a brown solid, which was chromatographed over silica, using light petroleum–dichloromethane–absolute ethanol (5 : 4 : 1) as the eluant, to give a white solid. This was further chromatographed over alumina using chloroform. The early fractions contained the amide (22) (0.092 g, 8%), m.p. 200—202 °C; δ_H [$CDCl_3$–$(CD_3)_2SO$], 6.75 (4 H, s, 1-, 4-, 6-, 9-H), 6.6 (2 H, bs, $CONH_2$), 4.4—3.0 (5 H, m, $ArCH_2Ar$, CH_2CH), 3.8—3.6 (12 H, 4s, 4 × CH_3O); $\nu_{max.}$ (0.5% $CHBr_3$), 3 510, 3 400, and 1 670 (Found: M^+, 357.1575. $C_{20}H_{23}NO_5$ requires 357.1576), *m/z* 313.1422 ($M^+ - CONH_2$).

Later fractions from the chromatography yielded the lactam (21) (0.135 g, 11%), m.p. 268—270 °C (decomp.), δ_H [$CDCl_3$–$(CD_3)_2SO$] 8.78 (1 H, d, CONH, removed by D_2O), 6.95, 6.88, 6.6 (4 H, 3 s, 1-, 4-, 6-, 9-H), 4.95 (1 H, d, NHC*H*), 3.9—3.8 (13 H, m, 4 × CH_3O, CHCO), 3.4, 2.95, (2 H, ABX, CH_2CH, J_{gem} 15 Hz); $\nu_{max.}$ (0.5% $CHBr_3$), 3 405 (NH) and 1 675 cm^{-1} (C=O) (Found: C, 67.5; H, 5.9; N, 4.0%; M^+, 355.1399. $C_{20}H_{21}NO_5$ requires C, 67.6; H, 6.0; N, 3.9%; *M*, 355.1420).

Alternatively, a solution of 2-(2-benzyloxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)propionamide (18) (0.18 g, 0.4 mmol) in dry dichloromethane (8 cm^3) was cooled to −10 °C, under a dry nitrogen atmosphere. Vanadium oxytrifluoride (0.12 g) in dry acetonitrile (30 cm^3) was added and the resultant mixture stirred for 2.5 days at a temperature of 0—2 °C. Citric acid (15 g) in water (100 cm^3) was added and the solution extracted with ethyl acetate (5 × 20 cm^3). The combined extracts were washed with brine (2 × 20 cm^3) and dried (Na_2SO_4). Evaporation of the solvent left a brown tar, which was chromatographed over silica with dichloromethane–absolute ethanol (10 : 1, v/v) as eluant. This produced the title compound (21) as an off-white solid identical with a sample prepared by the action of the same reagent on the acetate (17).

2,3,6,7-*Tetramethoxy*-N-*methylphenanthrene*-9-*carboxamide* (26).—A solution of 2-(2-acetoxymethyl-4,5-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-*N*-methylpropionamide (19) (1 g, 2.3 mmol) in dry dichloromethane–acetonitrile (1 : 1, v/v) (16 cm^3) was cooled under a dry atmosphere to −8 °C. Vanadium oxytrifluoride (1.2 g, 9 mmol) in dry acetonitrile (30 cm^3) was slowly added and the resultant mixture stirred for 3.5 h. Citric acid (7.5 g) in water (50 cm^3) was added, followed by water (200 cm^3); the organic phase was then separated. The aqueous phase was extracted with dichloromethane (4 × 25 cm^3) and the combined organic layers washed with water (20 cm^3) and dried (Na_2SO_4). Removal of the solvent left a brown tar which was chromatographed over silica using 1% absolute ethanol in dichloromethane as eluant. This process gave the title compound as an off-white solid after crystallisation from ethyl acetate–light petroleum (0.02 g, 2.5%), m.p. 126—129 °C; δ_H ($CDCl_3$), 8.0 (1 H, bq, CON*H*Me), 7.9—7.68 (4 H, 4 s, 1-, 4-, 5-, 8-H), 7.2 (1 H, s, 10-H), 4.1, 3.98 (12 H, 2 s, 4 × CH_3O), and 3.0 (3 H, s, $NHCH_3$), *J* 8 Hz); $\nu_{max.}$ 3 400, 1 650, and 1 610 cm^{-1}; $\lambda_{max.}$ 262 and 288 nm (Found: M^+, 355.1418. $C_{20}H_{21}NO_5$ requires *M*, 355.1420).

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