Electrochemical Oxidation of Aromatic Ethers. Part 10.[1] Regioselectivity in the Aryl–Aryl Coupling Reactions of some 4-Benzylisochroman-3-ones and Benzyl-1,2,3,4-tetrahydroisoquinolines.

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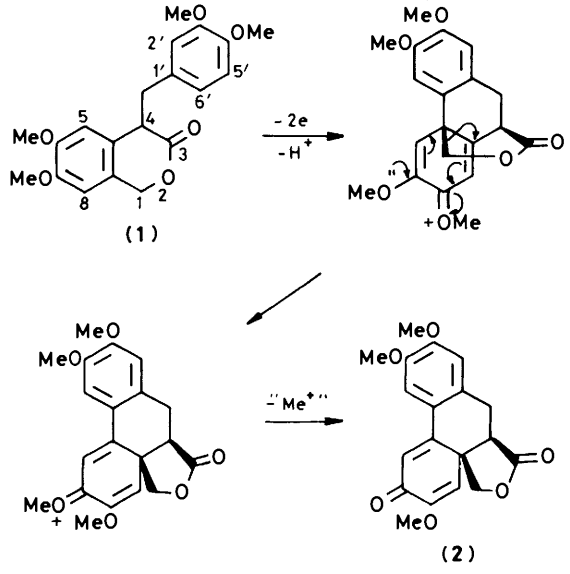
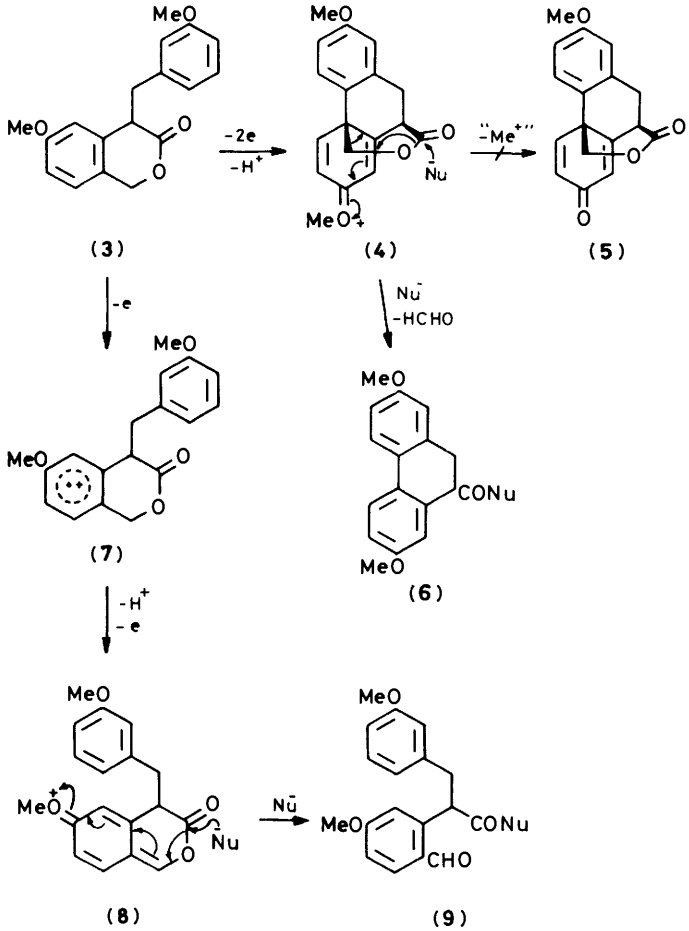
The anodic coupling reactions of 4-benzylisochroman-3-ones, 1- and 4-benzyl-1,2,3,4-tetrahydroisoquinolines are compared and analysed. In neutral media 4-benzyltetrahydroisoquinolines may afford products resulting from coupling to C-1 and/or to N-2 depending on the ring substituents. In acidic solution 4-benzyltetrahydroisoquinolines yield isoaporphines whereas their 1-benzyl analogues couple at C-8a to give morphindienones. This difference may be explained by considering the inductive effects inherent in the protonated forms of the bases. 4-Benzylisochroman-3-ones also couple at C-8a, but the intermediates thus produced are unstable and either rearrange or react with available nucleophiles.

Previously we have demonstrated that anodic oxidation of the isochromanone (**1**) affords the spirodienone lactone (**2**), through aryl–aryl coupling to C-8a, followed by rearrangement.[1] A key feature in the latter process is the availability of the lone pair of electrons on the methoxy group located at C-7 in the substrate (see Scheme 1). In the less substituted analogue (**3**) no such



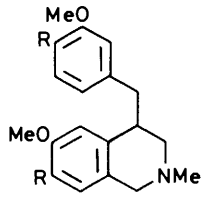
Scheme 1. The anodic coupling and rearrangement of 4-(3,4-dimethoxybenzyl)-6,7-dimethoxyisochroman-3-one

alkoxy group exists and now the rearrangement cannot occur. Thus we expected that oxidation of this compound should give the intermediate (**4**), which on O-demethylation would yield the lactone (**5**). In practice this is partly correct, but the intermediate appears to be 'long lived' and when chloroform containing ethanol is added at the end of the electrolysis the dihydrophenanthrene ester (**6**; Nu = OEt) is produced by degradative aromatisation, probably as shown (4 ⟶ 6). A competitive process occurs when alcohols are deliberately added to the electrolysis medium prior to the oxidation and this then leads to aldehyde esters (**9**). Here we assume that the initially formed radical cation (**7**) undergoes oxidative deprotonation (perhaps

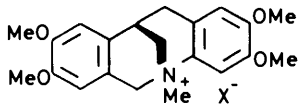


Scheme 2. Competitive oxidative reactions of 4-(3-methoxybenzyl)-6-methoxyisochroman-3-one in the presence of nucleophiles

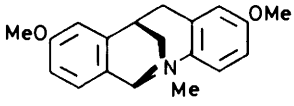
mediated by the alcohol acting as a latent base) to give the cation (**8**). This species then reacts with the alcohol with concomitant ring-opening and restoration of aromaticity to the ring fused to the heterocycle (Scheme 2). The lability of the intermediate (**4**) is due to the presence of a lactonic group and initially we speculated that the corresponding structures derived



(10) R = OMe
(11) R = H



(12)
X = ClO_4 or CF_3CO_2

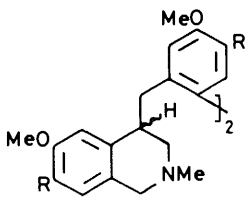


(13)

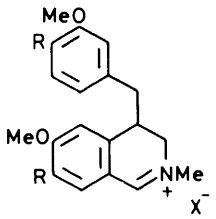
from the secondary amines (**10**) or (**11**) should be more stable. However, we have now shown that in acetonitrile solution anodic oxidation of the isoquinoline (**10**) leads predominantly to the salt (**12**).[2] Surprisingly oxidation of the analogue (**11**) in acetonitrile/methanol (3:1) gives the tetracyclic structure (**13**).

Hence to effect a successful aryl–aryl coupling we considered that the oxidation should be carried out in an acidic solution where N-protonation might inhibit these types of cyclisations, but when such an experiment was conducted upon the isoquinoline (**11**) only a small amount of the dehydrodimer (**14**) was obtained. This product, a mixture of diastereoisomers (see below), arises through radical cation formation in the nucleus of the 4-benzyl substituent group. We did not isolate the 3,4-dihydroisoquinolinium salt (**15**) which might originate from initial oxidation of the benzenoid ring fused to the heterocycle, followed by deprotonation at C-1 and further oxidation. However, it is possible that this compound is 'lost' in the considerable amount of tar which is produced in this electrolysis for in the oxidation of the hydrochloride salt of the tetramethoxyisoquinoline (**10**) the corresponding salt (**16**) is a major product.[3]

Next the anodic oxidation of the tetramethoxyisoquinoline (**10**) in acetonitrile containing fluoroboric acid was examined. Three compounds were isolated: one was the dehydro dimer (**17**)



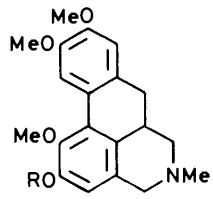
(14) R = H
(17) R = OMe



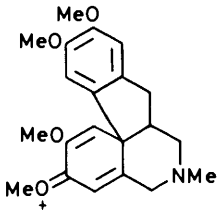
(15) R = H
(16) R = OMe

and the other two were the isoaporphines (**18**) and (**19**). The ^1H n.m.r. spectrum of the dehydro dimer, like that of its lower homologue (**14**), is poorly resolved but it is not temperature dependent. Both compounds give rise to diffuse spots on t.l.c. analysis and thus it is likely that they are present as mixtures of (±)- and *meso*-isomers.

The structures of the isoaporphines are interesting, and, for example, the tetramethoxy compound[4] may form either directly through *ortho–para* coupling (C-5, C-6′), or by *para–para* union (C-4a, C-6′), followed by rearrangement. The first pathway may be regarded as a favoured 6-*endo-trig* reaction,



(18) R = Me
(19) R = H



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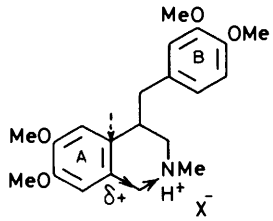

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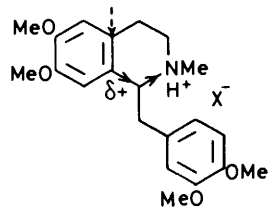
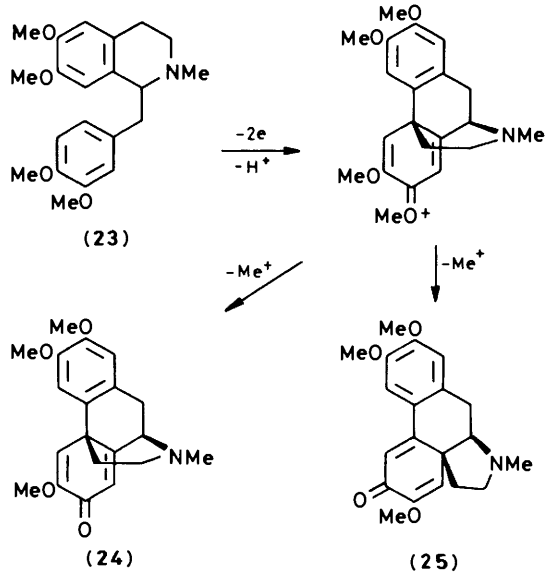


(22)

but anodic *ortho-para* coupling with respect to aryl methoxy groups is a rare event. Equally the alternative route requires an initial 5-*endo-trig* cyclisation which is also uncommon.[5] Strong circumstantial evidence in favour of the latter process is provided by the fact that the isoaporphine (**19**) is phenolic. Thus it is reasonable to suggest that both structures (**18**) and (**19**) derive from a common intermediate (**20**), and in the formation of the hydroxylated product, *o*-demethylation precedes dienone–phenol rearrangement. From these results it seems probable that N-protonation of 4-benzyltetrahydroisoquinolines sets up an inductive effect which inhibits intramolecular coupling to C-8a, but allows attack at C-4a and the formation of 'unusual' structures such as the isoaporphines (**18**) and (**19**). The same effect in 1-benzyltetrahydroisoquinolines [see structures (**21**) and (**22**)] such as laudanosine (**23**), complements the kinetically favoured 6-*endo trig* process leading from coupling at C-4a on to morphindienones exemplified by *O*-methylflavinantine (**24**).[6] However, when 1-benzyltetrahydroisoquinolines are oxidised in neutral media they also yield neospirodienones (**25**) (see Scheme

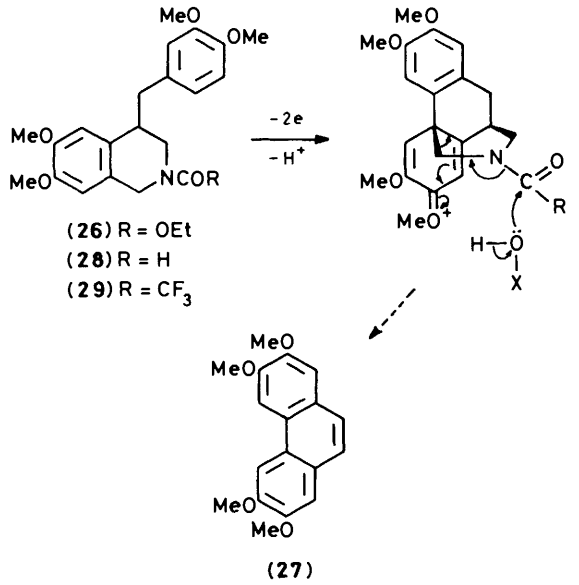


Scheme 3. Alternative products formed from the anodic oxidation of laudanosine

3), but it has been shown that this rearrangement reaction is repressed if methanol is present in the electrolyte.[7]

In a further attempt to effect intramolecular coupling to C-8a in our substrates, and to inhibit any possible rearrangement of the intermediate cation, we have prepared and oxidised the *N*-ethoxycarbonyl compound (**26**) in acetonitrile–methanol solution. By reducing the concentration of the isoquinoline in this experiment, dehydro dimer formation was avoided but the only product isolated (35% yield) was the tetramethoxyphenanthrene (**27**). This structure is also formed when the oxidation is carried out in acetonitrile alone, and again when similar electrolyses are carried out on the *N*-formyl (**28**) and *N*-trifluoroacetyl (**29**) derivatives.

These results indicate that coupling does indeed take place between C-6′ and C-8a, but the intermediate is degraded in the presence of methanol, or when water is added during the work-up procedure (see Scheme 4). We are working actively to circumvent this problem.



Scheme 4. Coupling and degradation of *N*-acyl-4-benzyl-1,2,3,4-tetrahydroisoquinolines

Experimental

U.v. spectra were recorded as solutions in 98% ethanol. I.r. data refer to Nujol mulls unless stated otherwise. ^{1}H N.m.r. spectra were recorded at 100 and at 400 MHz using tetramethylsilane as an internal standard. Anode potentials were measured relative to a standard calomel electrode, and electrolyses were conducted in an H-type cell using 0.1M-sodium perchlorate in acetonitrile as electrolyte unless stated otherwise. The capacity of the anode compartment was 50 cm^3 and platinum electrodes were used throughout. Chemical ionisation (CI) mass spectrometric analyses were determined using isobutane as the ionising medium.

6-Methoxy-4-(3-methoxybenzylidene)isochroman-3-one.—6-Methoxyisochroman-3-one[8] (0.6 g), 3-methoxybenzaldehyde (0.38 g) and piperidine (0.1 g) were heated together at 140 °C under an atmosphere of nitrogen. After 2 h the mixture was allowed to cool and then it was treated with 40% acetic acid in methanol (15 cm^3). A yellow solid which formed was collected and purified by column chromatography ($CHCl_3$–SiO_2) and crystallisation from ethanol to give the title compound as prisms (0.8 g, 83%), m.p. 140—141 °C. $\lambda_{max.}$ 245 and 323 nm; $\nu_{max.}$ 1 720 and 1 610 cm^{-1}; δ_H ($CDCl_3$), 7.81 (s, 1 H), 7.23—6.90 (m, 7 H), 5.28 (s, 2 H, ArC*H*$_2$), 3.72, 3.52 (2 × s, 2 × 3 H, 2 × OCH_3); δ_C ($CDCl_3$) 168.4 (s, CO), 152.8, 152.6 (2 × s, C-2′, C-6), 138.7, 129.7, 126.3, 121.9, 115.7, 115.5, 114.6, 111.9 (8 × d, 7 × aromatic CH and 1 × CH=), 135.7, 125.6, 125.0 (3 × s, C-1′, C-4a, *C*-8a) and 69.0 (t, C-1), 55.2 (2 × q, 2 × OCH_3); *m/z* (%) 296 (M^+, 100), 251(36), 237(25) and 177(18) (Found: C, 72.8; H 5.6. $C_{18}H_{16}O_4$ requires: C, 73.0; H, 5.4%).

6-Methoxy-4-(3-methoxybenzyl)isochroman-3-one (**3**).—The product from the previous reaction (0.6 g) in ethyl acetate (200 cm^3) was hydrogenated for 10 h at atmospheric pressure over 10% palladium in charcoal catalyst (0.12 g). The catalyst and solvent were removed and the colourless oil which remained was allowed to crystallize. This product was quite pure (0.55 g, 92%), m.p. 79.5—81 °C, $\nu_{max.}$ 1 722, 1595, and 1 585 cm^{-1}; δ_H ($CDCl_3$) 7.15—6.97 (m, 3 H), 6.8—6.5 (m, 4 H), 5.10, 4.25 (2 × d, 2 H, J_{gem} 12 Hz, H_2-1), 3.90 (br t, 1 H, H-4), 3.69 (s, 6 H, 2 × OCH_3), 3.11—3.90 (m, 3 H); δ_C($CDCl_3$) 172 (s, CO), 159.6 (s, 2 × *C*-OMe), 138.7, 135.2, 123.4 (3 × s, C-1, C-4a, C-8a), 129.4, 125.5, 121.6, 111.7, 113.3, 112.8, 112.4 (7 × d, 7 × aromatic CH), 69.3 (t, C-1), 55.3, 55.1 (2 × q, 2 × OCH_3), 47.6 (d, C-4), and 38.1 (t, Ar*C*H$_2$); *m/z* (%), 298 (M^+, 15), 177 (85), and 121 (100) (Found: C, 72.4; H, 6.2. $C_{18}H_{18}O_4$ requires: C, 72.5; H, 6.1%).

Anodic Oxidation of 6-Methoxy-4-(3-methoxybenzyl)isochroman-3-one (**3**).—The substrate (1.5 g) was electrolysed at a reference anode potential of 1.2 V until 2 F mol^{-1} of current had been consumed. The electrolyte system in this case was 0.1M-sodium perchlorate in acetonitrile–methanol (5:1). After this time the anolyte was collected, water (20 cm^3) was added and the volume reduced to near dryness under reduced pressure. The residue was then mixed with chloroform (40 cm^3) and water (40 cm^3), and the organic phase separated, dried ($MgSO_4$), and evaporated to leave a brown oil. This material was chromatographed on silica eluting with 20% ethyl acetate in light petroleum (b.p. 60—80 °C) Two products were obtained; these were (in order of elution from the column): (a) *methyl 2-formyl-5-methoxyphenyl-3′-methoxybenzyl acetate* (**9**; Nu = OMe), a colourless oil (0.4 g, 24%), $\lambda_{max.}$ 222 and 237 nm; $\nu_{max.}$ 1 730, 1 680 and 1 595 cm^{-1}; δ_H($CDCl_3$) 9.96 (s, 1 H, CHO), 7.80 (d, 1 H, *J* 8.5 Hz, 3-H), 7.22—6.76 (m, 6 H, ArH), 5.16 (br t, 1 H, *J* 7 Hz, α-CH), 3.82, 3.75 (2 × s, 2 × 3 H, 2 × OCH_3), 3.61 (s, 3 H, CO_2CH_3), 3.50, 2.87 (2 × d, d, 2 × 1 H, J_1 16 Hz, J_2 7 Hz, ArC*H*$_2$); δ_C($CDCl_3$), 191.0 (s, CHO), 173.4 (s, *C*O_2Me), 166.0, 163.9 (2 × s, 2 × *C*-OCH_3), 142.7, 139.2 (2 × s, C-1, C-1′), 137.0, 129.3, 121.5, 114.9, 114.6, 112.5, 112.2 (7 × d, 7 × CH), 127.2 (s, C-2), 55.5, 55.1 (2 × q, 2 × OCH_3), 52.0 (q, CO_2CH_3), 47.4 (d, α-CH), and 47.1 (t, Ar*C*H$_2$); *m/z* 328.1309 (M^+, 10%) $C_{19}H_{20}O_5$ requires *M* 328.1311; and (b) *9-ethoxycarbonyl-9,10-dihydro-2,7-dimethoxyphenanthrene* (**6**; Nu = OEt) a viscous oil (0.1 g, 6.3%), $\nu_{max.}$ 1 733 and 1 600 cm^{-1}; δ_H($CDCl_3$) 7.15—6.95 (m, 2 H, 4-H, 5-H), 6.75—6.59 (m, 4 H, 1-H, 3-H, 6-H, 7-H), 3.75 (q, 2 H, *J* 7 Hz, O*C*H$_2$CH$_3$), 3.71, 3.65 (2 × s, 2 × 3 H, 2 × OCH_3), 3.60—3.05 (m, 3 H, ArC*H*$_2$CH), and 1.24 (q, 3 H *J* 7 Hz, OCH_2CH_3); δ_C($CDCl_3$) 174.4 (*C*O_2Et), 158.4, 158.3 (2 × s, 2 × *C*OMe), 137.7, 136.4, 132.6, 131.5 (4 × s, C-4a, C-4b, C-8a, C-10a), 130.7, 129.1 (2 × d, C-4, C-5), 115.6, 115.3, 112.3, 111.7 (4 × d, C-1, C-3, C-6, C-8), 55.2 (q, 2 × OCH_3), 52.1 (q, OCH_2CH_3), 48.8 (d, $ArCH_2CH$), 39.0 (t, O*C*H$_2$CH$_3$), and 35.1 (t, Ar*C*H$_2$CH); *m/z* (%) 312.1362 (M^+, 22) ($C_{19}H_{20}O_4$ requires 312.1362), 272(14), 252(100), 253(34), and 223(32).

2-(2-Hydroxymethyl-5-methoxyphenyl)-3-(3-methoxyphenyl)-N-methylpropionamide.—6-Methoxy-4-(3-methoxybenzyl)isochroman-3-one (**3**) (1.2 g) in 33% methylamine in ethanol (80 cm^3) was heated at reflux for 5 h. Removal of

reagent and solvent gave a yellow oil which was chromatographed on silica eluting with 5% methanol in dichloromethane to yield the title compound as a colourless oil (0.83 g, 71%), $\lambda_{max.}$ 221 and 274 nm; $\nu_{max.}$ 3 500, 3 250, 1 667, and 1 610 cm^{-1}; $\delta_H(CDCl_3)$ 7.1—7.0 (m, 4 H, ArH), 6.61 (br m, 1 H, NH), 6.70—6.52 (m, 3 H ArH), 4.42 (dd, 2 H, J_{gem} 10 Hz, CH_2OH), 4.15, 3.40, 2.95 (AMX spin system, 3 H, $CHCH_2$), 3.70, 3.61 (2 × s, 2 × 3 H, 2 × OCH_3), 3.3 (br s, 1 H, OH), and 2.56 (d, 3 H, *J* 4 Hz, $NHCH_3$); *m/z* (%) 329.1627 (M^+, 4), ($C_{19}H_{23}NO_4$ requires 329.1627), 253(100), 121(56).

2-(2-*Hydroxymethyl*-5-*methoxyphenyl*)-3-(3-*methoxyphenyl*)-N-*methylpropylamine*.—The amide (1.8 g) from the previous experiment in tetrahydrofuran (30 cm^3) was added dropwise to a well stirred slurry of lithium aluminium hydride (0.27 g) in the same solvent (90 cm^3) and the mixture was heated at reflux for 11 h. It was then cooled and treated with 30% sodium potassium tartrate in water (60 cm^3). The organic layer was decanted off and the aqueous phase extracted with ethyl acetate (3 × 30 cm^3). The combined organic layer and extracts were then washed with water (2 × 20 cm^3), dried ($MgSO_4$) and evaporated to give a yellow oil. This material was chromatographed on basic alumina eluting with 3% methanol in dichloromethane to yield the title amine as a colourless oil (1.6 g, 93%); $\lambda_{max.}$ 215 and 250 nm; $\nu_{max.}$ 3 670, 3 500, 1 600, and 1 590 cm^{-1}; δ_H ($CDCl_3$) 7.25—6.60 (m, 7-H, ArH), 4.65, 4.22 (2 × d, 2 H, J_{gem} 11.5 Hz, CH_2OH), 4.20 (br s, 2 H, OH, NH), 3.81, 3.75 (2 × s, 2 × 3 H, 2 × OCH_3), 2.95—2.59 (m, 5 H, $ArCH_2CHCH_2$) 2.18 (s, 3 H, NCH_3) (this signal was eliminated when D_2O was added); $\delta_C(CDCl_3)$ 159.8, 159.5 (2 × s, 2 × $COCH_3$), 143.6 141.3 (2 × s, C-3′, C-5), 133.0 (s, C-2), 131.4, 129.3 (×2), 121.2, 114.6, 112.2, 111.4, 111.1 (7 × d, aromatic methine carbon atoms), 121.7, 108.7 (2 × s, C-1, C-1′), 62.4 (t, CH_2OH), 56.8 (t, CH_2N), 55.2, 55.0 (2 × q, 2 × OCH_3), 42.7 (d, CH-CH_2), 40.4 (t, CH-CH_2), 36.1 (q, NCH_3); *m/z* 315 (M^+, 5%), 254(12), 175(8) and 121(40%).

1,2,3,4-*Tetrahydro*-6-*methoxy*-4-(3-*methoxybenzyl*)-2-*methylisoquinoline* (**11**).—The propylamine (1 g) from the previous experiment and toluene-*p*-sulphonic acid (0.6 g) were heated in benzene (100 cm^3) in a Dean-Stark apparatus for 9 h. The mixture was then cooled and agitated with aqueous 2M-sodium bicarbonate solution (50 cm^3). The organic phase was then separated and the aqueous layer extracted with benzene (2 × 25 cm^3). The combined organic layer and extracts were then dried ($MgSO_4$) and evaporated to afford a gum which gave the title compound as a colourless oil after chromatography on basic alumina, with 5% methanol in dichloromethane as eluant; yield 0.85 g (90%); $\nu_{max.}$ 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 7.20—6.95 (m, 3 H) and 6.81—6.59 (m, 4 H, ArH), 4.00 (dd, 2 H, J_{gem} 8 Hz, 1 H_2), 3.70 (s, 6 H, 2 × OCH_3), 3.22—2.72 (m, 5 H, $ArCH_2CHCH_2$) and 2.42 (s, 3 H, NCH_3); $\delta_C(CDCl_3)$ 158.2 (s, 2 × *C*-OMe), 141.4, 139.0 (2 × s, C-1′, C-8a), 132.1 (s, C-4a), 130.2, 129.0, 115.9, 115.5, 115.2, 111.1, 110.9 (7 × d, aromatic carbons), 58.1 (t, C-1), 55.2 (q, 2 × OCH_3), 46.1 (d, C-4), 41.3 (t, C-3), 39.3 (q, NCH_3) and 36.5 (t, $ArCH_2$); *m/z* (%), 297.1741 (M^+, 60). ($C_{19}H_{23}NO_2$ requires M297.1729), 254(17) and 101(100).

Electrochemical Oxidation of 1,2,3,4-*Tetrahydro*-6-*methoxy*-4-(3-*methoxybenzyl*)-2-*methylisoquinoline*.—(*a*) The isoquinoline (**11**) (1 g) was dissolved in a 0.1M-solution of sodium perchlorate in acetonitrile–methanol (3:1) and electrolysed at an anode potential of +1.2—1.3 V and a cell current of 200 mA until 2 F mol^{-1} had been consumed. The anolyte was then diluted with water (10 cm^3) and evaporated to low bulk. Dichloromethane (20 cm^3) was added and the mixture washed with water (2 × 5 cm^3). After drying the organic phase was added to a column of silica suspended in dichloromethane and eluted with 5% methanol in this solvent. This treatment afforded 10,11-dihydro-2,8-dimethoxy-5,10-(*N*-methylazaethano)-5*H*-dibenzo[*a*,*d*]cycloheptene (**13**) as a pale yellow oil (6.5 g, 50%); $\nu_{max.}$ 1 600 and 1 590 cm^{-1}; $\delta(CDCl_3)$ 7.05—6.49 (2 × ABC spin systems, 6H, ArH), 4.25 (s, 1 H, 10-H), 3.75, 3.68 (2 × s, 2 × 3 H, 2 × OCH_3), 3.4—2.8 (m, 5 H, 5-H, 11-H_2, CH_2NMe) and 2.4 (s, 3 H, NCH_3); $\delta_C(CDCl_3)$, 159.2, 159.0 (2 × s, 2 × *C*-OMe), 139.1, 137.0, 135.5 (3 × s, C-4a, C-5a, C-9a), 130.6 (s, C-11a), 130.2, 125.4, 116.6, 112.5, 111.1, 111.0 (6 × d, aromatic methine carbons), 68.3 (d, C-10), 55.5 (t, CH_2NMe), 55.0 (2 × q, 2 × OCH_3), 43.6 (q, NCH_3), 41.2 (t, C-11) and 37.4 (d, C-5); *m/z* (%) 295.1570 (M^+, 22, $C_{19}H_{21}NO_2$ requires 295.1572) 252(100), 209(15) and 174.1(31). (*b*) The tetrahydroisoquinoline (**11**) (1 g) in acetonitrile (400 cm^3) and hydrofluorboric acid (2 cm^3) containing tetrabutylammonium fluoroborate was oxidised at a potential of +1.5 V until 2 F mol^{-1} of current had been consumed. Water (10 cm^3) was then added and the organic solvent evaporated, sodium carbonate added in small portions to the aqueous residue until no more carbon dioxide was evolved, followed by chloroform (50 cm^3). After a period of stirring, the chloroform layer was collected, dried and evaporated to afford a gum; this was added to a column of silica–dichloromethane and eluted with the same solvent and then with 1% methanol in dichloromethane. From the final fractions, a pale yellow gum (0.2 g) was obtained. T.l.c. analysis indicated that this material contained two components of very closely similar R_F in several solvent systems. Some data were obtained for the mixture: $\nu_{max.}$ 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 7.20—6.59 (m, 6 H), 4.00 (dd, 2 H) 3.75, 3.70, 3.66 (3 × s, 6 H) and 3.40—2.65 (m, 5 H) and 2.45 (m, 3 H); *m/z* (EI) (%) 296(20), 295(80), 294(50); *m/z* (CI) (%) 593(M + 1). The similarity between the ^1H n.m.r. spectrum and that of the tetrahydroisoquinoline (**11**) is striking and in conjunction with the remaining evidence indicates that this product is a diastereoisomeric mixture of the dehydro dimers (**14**).

Electro-oxidation of 1,2,3,4-*Tetrahydro*-4-(3,4-*dimethoxybenzyl*)-6,7-*dimethoxy*-2-*methylisoquinoline* (**10**).—The tetrahydroisoquinoline [3] (0.5 g) in acetonitrile (150 cm^3) containing hydrofluoroboric acid (1 cm^3) and tetraethylammonium tetrafluoroborate (1 g) was electrolysed in a simple one compartment cell at a constant current of 200 mA, until 4 F mol^{-1} had been consumed (45 min). Water was added and the solvent evaporated under reduced pressure until crystals of electrolyte began to separate from the aqueous phase. Methanol (2 cm^3) was then introduced, the crystals were filtered off and the mother-liquor was diluted with chloroform (20 cm^3) and washed with 2M-aqueous ammonia (2 × 10 cm^3). The organic phase was dried and evaporated to give an oil which was chromatographed on silica using ethyl acetate—methanol (3:1) as eluant. The first fractions contained electrolyte and some starting material, later fractions gave a gum. This was subjected to flash chromatography using the same solvent conditions. Three components of the gum were isolated, the first of which (R_F 0.20, 2:1 EtOAc—MeOH) was the phenolic isoaporphine (**19**) (0.15 g, 31%), m.p. 208—210 °C (ethanol); $\lambda_{max.}$ 280 and 302 nm; $\nu_{max.}$ 3 400—3 150 (br) and 1 595 cm^{-1}; $\delta_H(CDCl_3$, 400 MHz) 7.90 (s, 1 H, 11-H), 6.71 (s, 1 H, 8-H), 6.54 (s, 1 H, 3-H), 3.86 (s, 3 H, 10-OCH_3), 3.85 (s, 3 H, 9-OCH_3), 3.54 (s, 3 H, 10-OCH_3), 3.78 (d, 1 H, *J* 15 Hz, 4β-H), 3.39 (dd, 1 H, J_1 12, J_2 5 Hz, 7β-H), 3.25 (d, 1 H, *J* 15 Hz, 3α-H), 3.06 (dd, 1 H, *J* 10, J_2 5 Hz, 6β-H), 2.86 (m, 1 H, 6a-H), 2.50 (dd, 1 H, J_1 12, J_2 5 Hz, 7α-H), 2.43 (s, 3 H, NCH_3) and 2.08 (dd, 1 H, J_1 10, J_2 5 Hz, 6α-H); $\delta_C(CDCl_3)$ 148.1, 147.8, 147.5 (3 × s, C-1, C-9, C-10), 142.4 (s, C-2), 130.8, 130.0, 126.4, 125.9, 124.3 (5 × s, C-3a, C-3b, C-7a, C-11a, C-11b), 110.9, 110.8, 109.5 (3 × d, C-3, C-8, C-11), 60.2 (q, 1-OCH_3), 58.6 (t, C-4), 57.8 (t, C-6), 56.0, 55.8 (2 × q, 9-OCH_3, 10-OCH_3), 45.9 (q, NCH_3), 34.4 (d, C-6a) and 33.7 (t, C-7); *m/z*

Nuclear Overhauser experiments

Signal irradiated	Observed enhancements
OCH_3-10 (3.86 p.p.m.)	11-H (7.90 p.p.m.) 5%
11-H (7.90 p.p.m.)	1-OCH_3 (3.54 p.p.m.) 10%
1-OCH_3 (3.54 p.p.m.	1-H (7.90 p.p.m.) 8%
3-H (6.54 p.p.m.)	4β-H (3.78 p.p.m.) 2%
4β-H (3.78 p.p.m.)	4α-H (3.25 p.p.m.) 12%
	3-H (6.54 p.p.m.) 2%

(%) 341 (M^+, 80) and 298(30) (Found: C, 70.2; H, 6.8; N, 3.9. $C_{20}H_{23}NO_4$ requires C, 70.4; H, 6.8; N 4.1%).

The second component of this gum (R_F 0.33, 3:2 EtOAc–MeOH) was the tetramethoxyisoaphorine (**18**) which was obtained as a colourless solid (0.03 g, 6%), m.p. 113—114 °C (ethanol) (lit.,[4] 112—114 °C); $\lambda_{max.}$ 235, 281, and 305 nm; $\nu_{max.}$ 1 590 cm^{-1}; $\delta_H(CDCl_3)$ 8.14 (s, 1 H, 11-H), 6.73 (s, 1 H, 8-H) 6.53 (s, 1 H, 3-H), 3.91 (s, 3 H, 9-OCH_3), 3.90 (s, 3 H, 10-OCH_3), 3.87 (s, 3 H, 2-OCH_3), 3.66 (s, 3 H, 1-OCH_3), 3.2—2.0 (m, 7 H, aliphatic protons), and 2.46 (s, 3 H, NCH_3); *m/z* (%) 355(16), 312(41), 297(44), 281(69), and 243(100) (Found: C, 69.8; H, 6.7; N, 3.7. Calc. for $C_{21}H_{25}NO_4$: C, 71.0; H, 7.1; N, 3.9%).

The third compound isolated from the gum was a mixture of (±)- and *meso*-isomers of the dehydro dimer (**17**). T.l.c. analysis (SiO_2, 3:2 EtOAc–MeOH) showed this as a diffuse spot R_F 0.28 which exhibits blue fluorescence under the u.v. lamp (low pressure); yield 0.12 g (12.5%), m.p. *ca.* 90 °C; $\lambda_{max.}$ 284 nm; $\nu_{max.}$ 1 605 cm^{-1}; $\delta_H(CDCl_3)$, 6.8, 6.5, 6.1, 5.9, 5.7 (4 × m, 8 H, ArH), 4.0—3.0 (m, 24 H, aliphatic protons and methoxy protons), and 2.2 (2 × s, 6 H, 2 × NCH_3); $\delta_C(CDCl_3)$ 147.8, 147.5, 147.2 (3 × s, *C*-OMe), 133.4, 131.8, 130.1, 129.8, 126.4 (5 × s, quaternary aromatic carbons), 113.9, 110.6, 109 (3 × d, aromatic methine carbons), 58.1, 58.0 (2 × q, OCH_3), 55.9, 55.5 (2 × q, OCH_3), 46.4 (q, NCH_3), 40.1, 38.9 (2 × t, CH_2N), 29.7 (d, CH_2CHCH_2N) and 22.6 (t, CH_2CH); *m/z* (%) 712 (M^+, 1), 357(35), 358(6), 356(28), and 355(71); [+] ion FAB (xenon) 713 (M^+, 1) [Found: C, 71.0; H, 7.5; N, 3.8; $(C_{21}H_{26}NO_4)_2$ requires C, 70.8; H, 7.3; N, 3.9%].

4-(3,4-*Dimethoxybenzyl*)-2-*ethoxycarbonyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**26**).—4-(3,4-Dimethoxybenzyl)-1,2,3-4-tetrahydro-6,7-dimethoxyisoquinoline hydrochloride (0.5 g) was treated with a mixture of chloroform (25 cm^3), water (3 cm^3) and sodium carbonate (0.3 g). After the mixture had been stirred for 1 h ethyl chloroformate (0.15 g) was introduced and the whole agitated for another 3 h, before more chloroform (50 cm^3) and water (25 cm^3) were added. The organic phase was separated, washed with water (2 × 25 cm^3), dried and evaporated to give a gum which after elution through a column of silica with ethyl acetate yielded a colourless solid (0.52 g, 90%), m.p. 153—154 °C; $\lambda_{max.}$ 240 and 290 nm; $\nu_{max.}$ 1 690, 1 610 and 1 590 cm^{-1}; $\delta_H(CDCl_3)$ 6.70 (m, 3 H, 2′-H, 5′-H, 6′-H), 6.51, 6.30 (2 × s, 4-H, 8-H), 4.75, 4.26 (dd, 2 H, J_{gem} 10 Hz, 1-H_2), 4.20 (q, 2 H, *J* 7 Hz, OCH_2CH_3), 3.87, 3.85 (2 × s, 12 H, 4 × OCH_3), 3.80, 3.4—2.7 (m, 5 H, CH_2CHCH_2N) and 1.31 (t, 3 H, *J* 7 Hz, OCH_2CH_3); $\delta_C(CDCl_3)$ 156.2 (s, C=O), 148.9, 148.1, 147.7, 147.5 (4 × s, 4 × *C*-OMe), 132.7, 130.8, 124.7 (3 × s, C-1′, C-4a, C-8a), 121.7, 113.2, 112.1, 111.4, 109.0 (5 × d, aromatic methine carbons), 61.4 (d, OCH_2), 55.9 (q, 4 × OCH_3), 45.6 (d, C-1), 44.8 (d, C-3), 41.0 (d, s, C-4, CH_2Ar) and 14.8 (q, CH_2CH_3); *m/z* (%) 415.2000 (M^+, 8) ($C_{23}H_{29}NO_6$ requires: 415.1995), 264(100) and 151(23) (Found: C, 66.4, H, 7.1; N, 3.5. $C_{23}H_{29}NO_6$ requires: C, 66.5; H, 7.0; N, 3.4%).

Electrochemical Oxidation of 4-(3,4-*Dimethoxybenzyl*)-2-*formyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**28**).—The *N*-formylisoquinoline[3] (1.1 g) in 0.1M-sodium perchlorate in acetonitrile solution (300 cm^3) was oxidised at an anode potential of +1.0—1.1 V until 2 F mol^{-1} of current had been consumed. Water (10 cm^3) was added to the anolyte which was then evaporated to near dryness. The residue was mixed with chloroform (55 cm^3), the organic phase separated, washed with water (2 × 20 cm^3), dried and evaporated to afford a brown gum. This material was chromatographed on silica using chloroform as eluant to give a colourless crystalline solid (0.44 g, 50%), m.p. 178—180 °C. This compound was 2,3,6,7-tetramethoxyphenanthrene (**27**) (lit.,[9] m.p. 178 °C); $\lambda_{max.}$ 251, 282 and 306 nm; $\nu_{max.}$ 1 660 cm^{-1}; $\delta_H(CDCl_3)$ 7.76, 7.52, 7.20 (3 × s, 6 H, ArH), 4.08 and 3.98 (2 × s, 2 × 6 H, 4 × OCH_3); $\delta_C(CDCl_3)$ 149.5, 149.0 (2 × s, 4 × *C*-OMe), 129.0, 127.1 (2 × s, C-4a, C-4b, C-8a, C-10a), 124.3, 108.6 (2 × d, C-1, C-4, C-5, C-8), 103.3 (d, C-9, C-10), and 56.2, 55.9 (2 × q, 4 × OCH_3); *m/z* (%) 298.1202 (M^+, 40. Calc. for $C_{18}H_{18}O_4$: *M* 298.1205), 169(49), and 166(100) (Found: C, 72.3; H, 6.0. Calc. for $C_{18}H_{18}O_4$: C, 72.5; H, 6.1%).

Electrochemical Oxidations of 4-(3,4-*Dimethoxybenzyl*)-2-*ethoxycarbonyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (**26**).—(*a*) The isoquinoline (1.2 g) in 0.1M-sodium perchlorate in acetonitrile solution (250 cm^3) was electrolysed at an anode potential of +0.95 V and a cell current of 100 mA until 2 F mol^{-1} had been consumed. The anolyte was then separated, diluted with water (10 cm^3) and the mixture evaporated under reduced pressure to near dryness. The residue was extracted with dichloromethane (3 × 25 cm^3) and the combined extracts were washed with water (2 × 10 cm^3), dried and evaporated to give a dark brown gum which after chromatography (as in the previous experiment) gave the tetramethoxyphenanthrene (**27**); yield 0.30 g (35%).

(*b*) A similar experiment was carried out in which the electrolyte was 0.1M-sodium perchlorate in acetonitrile–methanol (5:1). The only product isolated was the tetramethoxyphenanthrene (**27**) in 28% yield.

Oxidations of the *N*-trifluoroacetylisoquinoline[3] (**29**) under identical conditions were relatively unproductive, much tar was formed and the yields of the tetramethoxyphenanthrene were only 8—15%.

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