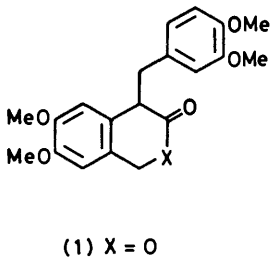
Electrochemical Oxidation of Aromatic Ethers. Part 6.[1] Oxidation of 4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline and Attempted Synthesis of 4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,4-dihydro-3(2*H*)-isoquinolone

By **Maurice P. Carmody** and **Malcolm Sainsbury,*** School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY
Roger F. Newton,* Glaxo Group Research Limited, Ware, Hertfordshire SG12 0DJ

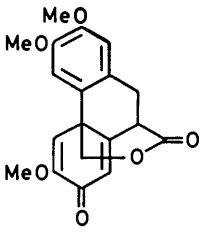
The cyclisation of 3-(3,4-dimethoxyphenyl)-2-(2-hydroxymethyl-4,5-dimethoxyphenyl)-*N*-methylpropionamide (5) and related compounds does not yield 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1,4-dihydro-3(2*H*)-isoquinolone, but gives instead dibenzo[*b*,*f*]cycloheptane derivatives. Anodic oxidation of 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline affords the corresponding 3,4-dihydroisoquinolinium and 4-(3,4-dimethoxybenzylidene)-6,7-dimethoxy-2-methyl-1,4-dihydroisoquinolinium salts. No intramolecularly aryl–aryl coupled products are isolated and the implication of this result on the design of substrates for the synthesis of biphenyl derivatives is discussed.

WHILE much effort has been directed towards the anodic coupling of 1-benzyl-1,2,3,4-tetrahydroisoquinolines [2a-d] the behaviour of the 4-benzyl analogues has received little attention and intramolecularly cyclised products equivalent to morphinandienones are unknown.

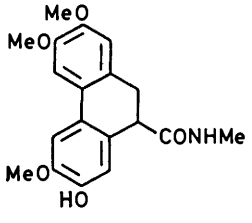
Previously [3] we have reported that electrochemical oxidation of the isochromanone (1) gives the spirodienone (2) but attempts to convert this product into the corresponding nitrogen-containing compound by reaction with methylamine causes rearrangement with the elimination of formaldehyde and leads to the dihydrophenanthrene (3). The obvious solution to this problem is to prepare the tetrahydroisoquinolone (4) and to electrolyse it, but this derivative is not easily synthesised. Thus, treatment of the isochromanone with methylamine affords the acyclic alcohol (5), which although it does not cyclise on heating alone, or in benzene solution containing toluene-*p*-sulphonic acid, yields the dibenzo[*b*,*f*]cycloheptene (6) with polyphosphoric ester or phosphorus pentaoxide. No reaction occurs between the alcohol (5) and toluene-*p*-sulphonic acid in pyridine at room temperature; however, on heating, the isochromanone (1) is reformed, showing that the oxygen rather than the nitrogen atom of the amide function displaces toluene-*p*-sulphonate ion from the intermediate ester (7). Attempts to convert the alcohol (5) into the acetal (8) were unsuccessful and a reaction with thionyl chloride, followed by the addition of silver tosylate once more gave the dibenzocycloheptene (6).



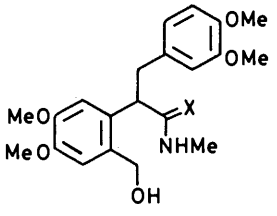
(1) X = O
(4) X = NMe



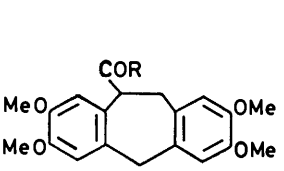
(2)



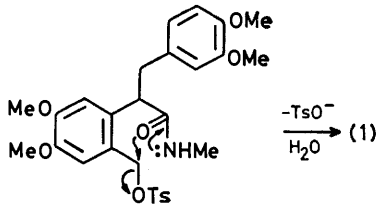
(3)



(5) X = O
(8) X = $(OMe)_2$



(6) R = NHMe
(22) R = OEt
(26) R = OH



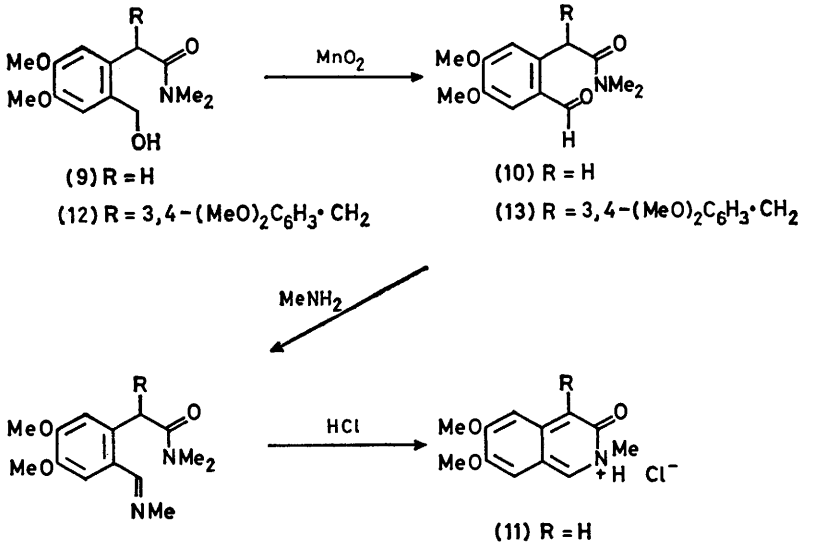
(7)

Some years ago McCorkindale and McCulloch described [4] the synthesis of 6,7-dimethoxy-2-methyl-3-oxo-2*H*-isoquinolinium chloride (11) *via* oxidative cyclisation of the amido-alcohol (9) (Scheme 1). We have repeated this sequence now with the veratryl analogue (12) and obtained the salt (14) in good yield. Disappointingly, however, all attempts to reduce this to the isoquinolone (4) lead to multicomponent mixtures.

An alternative route to the desired tetrahydroisoquinolone (4), would be the alkylation of 6,7-dimethoxy-2-methyl-1,4-dihydro-3(2*H*)-isoquinolone (15). This compound has been made previously by Finkelstein and Brossi,[5] albeit in modest yield; we have now modified this synthesis (Scheme 2) so that the major by-product

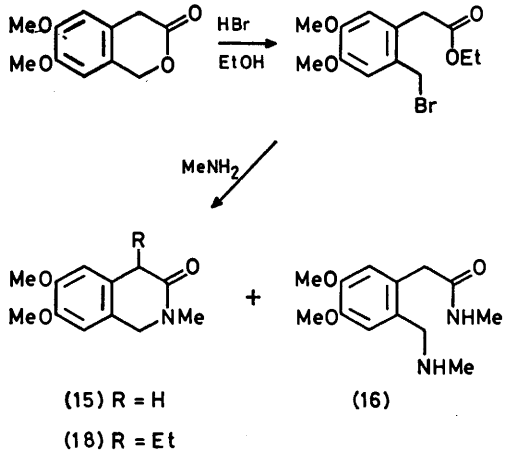
(16) is eliminated and an improved yield (70%) of the tetrahydroisoquinolone (15) is obtained.

Reaction of the tetrahydroisoquinolone (15) with veratraldehyde under a variety of basic conditions failed the isochromanone (1) was treated with hydrogen bromide, but when this compound was treated with methylamine in an attempt to replicate Finkelstein and Brossi's procedure the dibenzocycloheptane (22) was obtained.



SCHEME 1

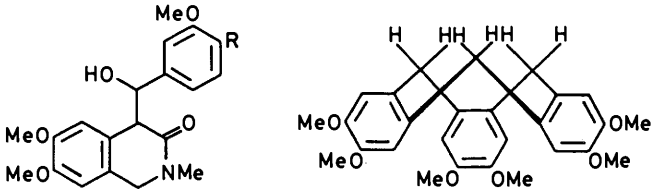
and we conclude that this is due to the unreactivity of this particular aldehyde rather than the non-availability of the anion of the isoquinolone, since 3-methoxybenzaldehyde yields the alcohol (17), and ethyl bromide in the presence of lithium isopropylamide affords the 4-ethyltetrahydroisoquinolone (18). Interestingly, when the last reaction is repeated, with veratryl chloride instead of ethyl bromide, cyclotriveratrylene (19) and cyclotetraveratrylene (20) are formed. There is no



SCHEME 2

evidence of the required 4-alkylated tetrahydroisoquinolone (4), and we note that these compounds are formed by the action of the base on veratryl chloride alone. The unstable bromo-ester (21) was formed when

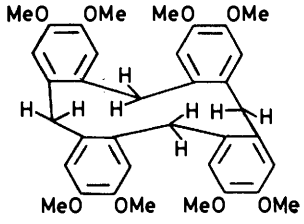
The same product results from the action of sodium carbonate and ethanol upon the bromo-ester. Rosen and Popp [6] describe the synthesis of the *N*-demethyltetrahydroisoquinolone (24) *via* the acid-catalysed



cyclisation of the hydrazide (23), but similar treatment of the veratryl analogue (25) simply yields the acid (26). Veratroyl chloride and the tetrahydroisoquinolone in the presence of base yield the enol ester (27). Presumably this product arises through the further acylation of the ketone (28) or its tautomer (29), although attempts to restrict the reaction to these compounds are unsuccessful. Hydrolysis of the enol ester does, however, afford the ketone (28), but this is unstable and readily decomposes. Reduction with sodium borohydride, for example, yields the phthalonimide (30) probably through oxidation of the corresponding alcohol (31) during work-up. This conclusion is supported by the fact that the trimethoxylated alcohol (17) rapidly forms the same phthalonimide during attempts at recrystallisation.

Furthermore McCorkindale and McCulloch [4] note that

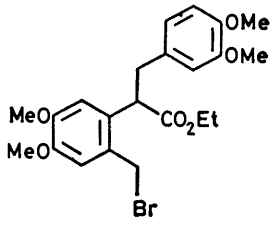
unsubstituted tetrahydroisoquinolones, for example (15), also decompose to phthalonimides and present evidence that 3(2*H*)-isoquinolones are intermediates in this reaction. We favour this proposal since chro-



(20)

mium trioxide oxidation of the amide-alcohol (5) gives the phthalonimide (30), probably *via* the 3(2*H*)-isoquinolone (33), or a tautomer formed in turn from the aldehyde (32).

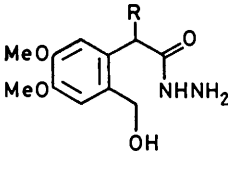
The selection of the tetrahydroisoquinolone (4) as a candidate for electro-oxidation rests upon the results obtained with the isochromanone (1). However, the ease with which secondary lactams of this type oxidise to phthalonimides caused us to question this choice and to



(21)

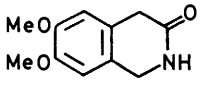
wonder if 4-(3,4-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (34) might not be a better substrate, expecially since Miller *et al.*[2b,c] have shown that anodic oxidation of laudanosine (35) readily affords (±)-*O*-methylflavinantine (36).

Miller and his co-workers [7] suggest that oxidation of the nitrogen atom in laudanosine at a potential of *ca.* +0.6 V leads to an aziridinium species (37), or its equivalent, which then undergoes further oxidation to the dication (38). Cyclisation then occurs with the loss of protons and methanol. An aziridinium radical cation favourable to isomophinandienone is unlikely with the



(23) R = H

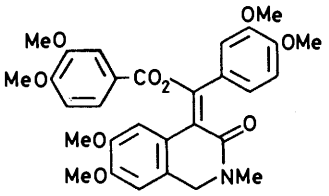
(25) R = 3,4-$(MeO)_2C_6H_3 \cdot CH_2$



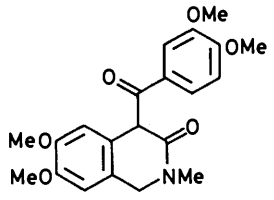
(24)

4-substituted tetrahydroisoquinoline (34) and instead of a well defined cyclic voltammogram this compound shows a broad anodic peak extending from +0.5 to +1.2 V.

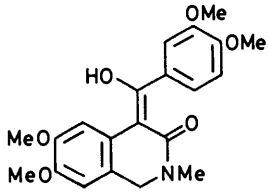
Preparative electrolyses using platinum or carbon electrodes were difficult to control and had to be terminated prematurely because of electrode filming. This type of behaviour is commonly encountered with benzylamines [1] and we have proposed that initial oxidation at the nitrogen atom is followed rapidly by monodeprotonation of the benzylic methylene function, further oxidation, and decomposition. By changing the electrolyte from acetonitrile to dichloromethane and trifluoroacetic acid we expected to eliminate this problem



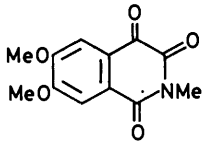
(27)



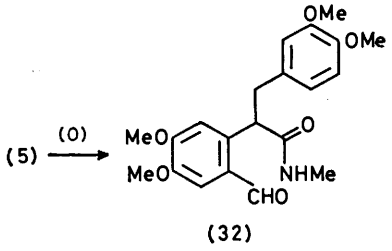
(28)



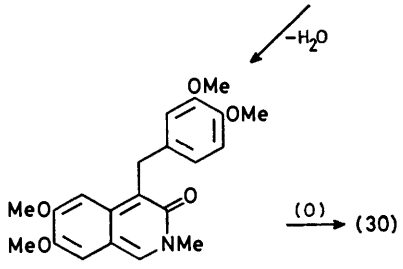
(29)



(30)

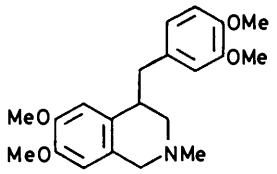


(32)

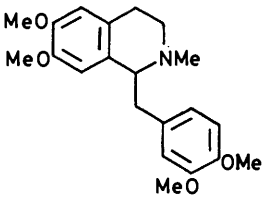


(33)

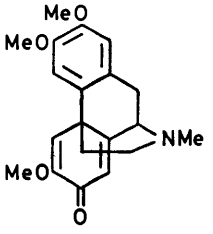
since now the substrate will exist principally as the isoquinolinium salt (39). Indeed the cyclic voltammogram now shows the first oxidation peak as a broad band centred at +1.4 V, followed by a further electron loss at +1.9 V. A preparative electrolysis at the lower potential did not, however, lead to aryl–aryl coupling but gave instead the 3,4-dihydroisoquinolinium salt (40), whereas an oxidation at the higher value afforded the benzylidene derivative (41). Scheme 3 rationalises the formation of these two products. They are, however,



(34)

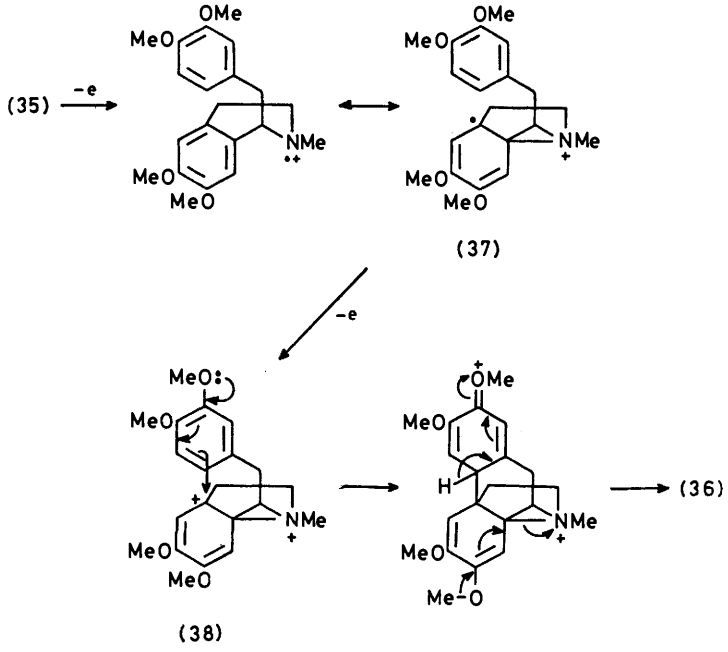


(35)

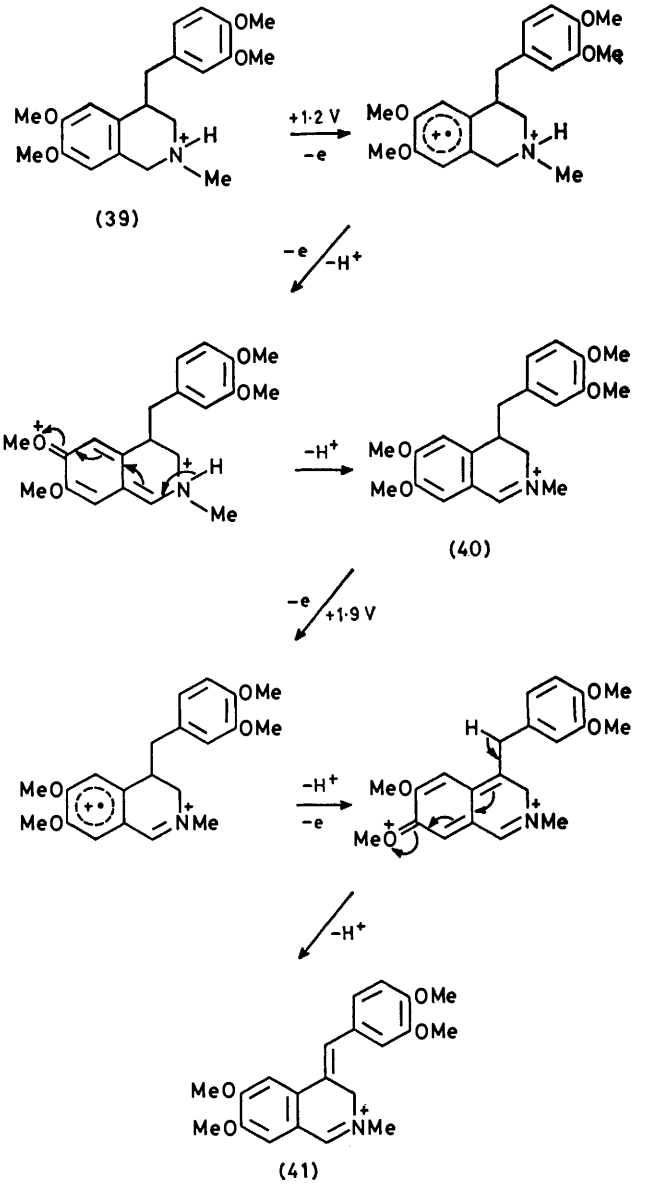


(36)

accompanied by much resinous material and it is most probable that other compounds produced, for example, by intermolecular coupling reactions of the veratryl ring system, are destroyed by the severity of the electrolysis conditions. It seems therefore that in order to achieve the desired intramolecular union between the two methoxylated rings their oxidation potentials should be very closely similar.[8] In the isochromanone (1), for example, both aromatic rings lose an electron to a platinum anode at *ca.* 1.1 V, but the effect of protonation on the nitrogen atom of the tetrahydroisoquinoline (34) is to raise the oxidation potential of the benzenoid ring fused to the heterocycle to *ca.* +1.4 V and thus facilitate formation of a 3,4-dihydroisoquinolinium salt. The presence of a basic nitrogen atom is equally undesirable. We now intend to study the electrochemistry of the appropriate *N*-acyl-1,2,3,4-tetrahydroisoquinolines in an attempt to solve this problem.



(38)



(41)

SCHEME 3

EXPERIMENTAL

All preparative electrolyses were conducted in a H-type cell of 200 cm³ total capacity. Current was provided by a Farnell stabilised power supply and the potential of the anode was monitored with a digital voltmeter *via* an agar bridge and a standard calomel electrode (SCE). U.v. spectra were recorded for solutions in 95% ethanol, unless otherwise stated; i.r. spectra refer to Nujol nulls; ^{1}H n.m.r. spectra were recorded at 100 MHz with tetramethylsilane as internal standard.

3-(3,4-*Dimethoxyphenyl*)-2-(2-*hydroxymethyl*-4,5-*dimethoxyphenyl*)-N-*methylpropionamide* (5).—6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isochroman-3-one (6 g) was heated

under reflux for 1 h with methylamine–ethanol (1 : 3 v/v) (50 cm³). The excess of solvent and reagent was removed by evaporation under reduced pressure and the residual oil triturated with ethanol to give a white *solid* (4.05 g, 61%), m.p. 146—148 °C (from EtOH), δ ($CDCl_3$) 7.15 (s, 1 H, ArH), 6.7—6.3 (m, 4 H, 4 × ArH), 4.42 (br q, 2 H, *J* 12 Hz, CH_2OH), 3.91, 3.82, and 3.72 (3 s, 4 × 3 H, 4 × OMe), 3.63—2.9 (m, 3 H, $ArCH_2CH$), 2.67 (d, 3 H, *J* 4.5 Hz, NH*Me*), and 2.41 (br s, 1 H, OH), $\nu_{max.}$ 3 370 and 1 655 cm⁻¹, $\lambda_{max.}$ 285 nm (ε 3 815), *m/e* 289 (10%), 371 (15), and 313 (100). (Found: C, 64.6; H, 7.1; N, 3.6. $C_{21}H_{27}NO_6$ requires C, 64.8; H, 7.0; N, 3.6%).

2,3,7,8-*Tetramethoxy*-N-*methyl*-10,11-*dihydro*-5H-*dibenzo*-[a,d]*cycloheptene*-10-*carboxamide* (6).—Ethyl polyphosphoric ester (5 g) was added to the amide (6) (1.0 g) in chloroform (25 cm³). The solvent was then distilled off and the residue heated at 140 °C for 15 min. When cool the reaction mixture was poured into water (100 cm³) and extracted with chloroform (3 × 70 cm³). The combined solvent layers were washed with saturated sodium chloride solution (20 cm³) and water (20 cm³), decolourised over charcoal, filtered, and dried (Na_2SO_4). Removal of the solvent gave a colourless residue which crystallised from ethanol as *needles* (0.71 g, 71%), m.p. 199—199.5 °C, δ ($CDCl_3$) 6.76—6.58 (m, 3 H, 3 + ArH), 6.5 (s, 1 H, H-5), 4.96 (q, 1 H, *J* 5 Hz, N*H*Me), 4.0 [t, 1 H, *J* 9 Hz, Ar C*H*(CONMe)CH_2–], 3.96 (q, 2 H, *J* 9 Hz, Ar, CH_2Ar), 3.88, 3.84, 3.80, 3.75 (4 s, 4 × 3 H, 4 × OMe), 3.40 and 3.33 [8 lines, 2 H, ArCH(CONMe)CH_2–], and 2.54 (d, 3 H, *J* 5 Hz, NH*Me*), $\nu_{max.}$ 3 300(NH) and 1 640 cm⁻¹ (CONHMe), $\lambda_{max.}$ 237 (ε 5 910) and 287 nm (5 230), *m/e* 371 (49%; M^+), 313 (100), and 282 (15) (Found: C, 67.9; H, 6.8; N, 3.8. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.8; N, 3.8%).

Reaction of the Alcohol (5) *with Toluene*-4-*sulphonyl Chloride and Pyridine*.—The alcohol (1 g) and toluene-4-sulphonyl chloride (0.65 g) were dissolved in pyridine (50 cm³) and heated to reflux for 5 h. The solvent was removed and the residue in dichloromethane (50 cm³) was washed with 10% brine (2 × 50 cm³) and water (50 cm³). The dried organic phase was finally evaporated to yield a gum which when triturated with ethanol afforded the isochromanone (1) (0.73 g, 68%) m.p. and mixed m.p.[3] 83—84 °C.

Reaction of the Alcohol (5) *with Thionyl Chloride and Silver Tosylate*.—The alcohol (1 g) in dry tetrahydrofuran (100 cm³) was treated with thionyl chloride (5 g). The solution was then heated to reflux for 20 min and then evaporated under reduced pressure to leave an oil (0.97 g). This was taken up in acetonitrile (50 cm³) and treated with silver tosylate (0.9 g) in acetonitrile (50 cm³). The precipitated silver chloride was removed and the solvents evaporated off. The residue was dissolved in dichloromethane (20 cm³) and diethyl ether (20 cm³), filtered, and the solvents removed to give the cycloheptene (6) (0.68 g, 67%).

3-(3,4-*Dimethoxyphenyl*)-2-(2-*hydroxymethyl*-4,5-*dimethoxyphenyl*)-NN-*dimethylpropionamide* (12).—6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isochroman-3-one (6.0 g) in dimethylamine–ethanol (1 : 3 v/v) (50 cm³) was heated at reflux for 5 h. Solvent and reagent were then removed *in vacuo*, and the residual oil dissolved in ethanol, boiled with charcoal, filtered, and evaporated to give a colourless solid (4.85 g, 71%), m.p. 134—135 °C (from EtOH), δ ($CDCl_3$) 7.06, 6.78 (2 s, 2 × 1 H, 2 × Ar*H*), 6.75—6.48 (m, 3 × ArH), 4.42 (q, 2 H, CH_2OH), 4.24 (t, 1 H, *J* 7 Hz, C*H*CON), 3.87, 3.84, 3.80, and 3.71 (4 s, 4 × 3 H, 4 × OMe), and 3.02—2.68 (m, 7 H, 2 × NCH_3, OH), $\nu_{max.}$ 3 380 and 1 620 cm⁻¹, $\lambda_{max.}$ 242 (ε 8 460) and 281 nm (5 860), *m/e* 403 (37%, M^+), 385(16), 313(99), 179(98), and 151(100) (Found: C, 66.0; H, 6.9; N, 3.7. $C_{22}H_{29}NO_6$ requires: C, 65.5; H, 7.2; N, 3.5%).

3-(3,4-*Dimethoxyphenyl*)-2-(2-*formyl*-4,5-*dimethoxyphenyl*)-NN-*dimethylpropionamide* (13).—The amide (12) (3.0 g) in chloroform (100 cm³) was shaken with manganese dioxide (25 g) for 48 h. Reagent and solvent were then removed to leave a pale yellow oil which crystallised from ethanol as almost colourless *prisms* (2.1 g, 70%), m.p. 104—105 °C, (from EtOH), δ ($CDCl_3$) 9.83 (s, 1 H, –CHO), 7.23 and 7.17 (2 s, 2 × 1 H, 2 × ArH), 6.75—6.65 (m, 3 H, 3 × ArH), 5.4 (t, 1 H, *J* 7 Hz, CHCON), 3.96, 3.92, 3.82, and 3.80 (4 s, 4 × 3 H, 4 × OMe), 3.45—3.22 (m, 2 H, $-CH_2-CH-$), and 2.90 and 2.78 (2 s, 2 × 3 H, 2 × NMe), $\nu_{max.}$ 1 680 and 1 625 cm⁻¹, $\lambda_{max.}$ 243 (ε 11 600), 283 (9 960), and 310 nm (5 780), *m/e* 401 (0.8%, M^+), 383(41), and 151(100) (Found: C, 66.0; H, 6.6; N, 3.7. $C_{22}H_{27}NO_6$ requires C, 65.8; H, 6.8; N, 3.5%).

4-(3,4-*Dimethoxybenzyl*)-6,7-*dimethoxy*-2-*methyl*-3-*oxo*-2H-*isoquinolinium Chloride* (14).—A solution of the amide (13) (3 g) in ethanol–methylamine (3 : 1 v/v) (50 cm³) was heated under reflux for 3 h. Ethanol and the excess of methylamine were then removed to yield a green gum which was dissolved in 6M-hydrochloric acid (80 cm³) and warmed to 60 °C. On cooling the product, the isoquinolinium salt (14) separated as white *needles* (2.3 g, 81%), m.p. 140—150 °C (decomp.) δ (CF_3CO_2H) 7.46, 7.32 (2 s, 2 × 1 H, 5- and 8-H), 7.0 and 6.9 (m, 2 H, 2 × ArH), 6.9 (s, 1 H, 1-H), 6.71 (d, 1 H, *J* 9 Hz, ArH), 4.66 (s, 2 H, $ArCH_2$), 4.4 (s, 3 H, $\overset{+}{N}Me$), and 4.20, 4.12, 4.00, and 3.94 (4 s, 4 × 3 H, 4 × OMe), $\nu_{max.}$ 1 640 and 1 600 cm⁻¹, $\lambda_{max.}$ 256 nm (ε 53 500) (Found: C, 62.0; H, 5.8; N, 3.2. $C_{21}H_{24}NO_5Cl$ requires C, 62.1; H, 6.0; N, 3.45%). This product is light sensitive and decomposes rapidly when exposed to base.

6,7-*Dimethoxy*-2-*methyl*-1,4-*dihydro*-3(2H)-*isoquinolone* (15).—6,7-Dimethoxy-3-isochroman-3-one (5 g) was added in portions to a solution of hydrogen bromide (20 g) in ethanol (300 cm³). After 24 h, the solvent was removed *in vacuo* at 20 °C, to leave ethyl 2-bromomethyl-4,5-dimethoxyphenylacetate as a colourless oil which solidified on trituration with diethyl ether (7 g), m.p. 55—57 °C, δ ($CDCl_3$) 6.88 and 6.78 (2 s, 2 × 1 H), 4.16 (q, 2 H, *J* 7 Hz), 3.86 (s, 6 H, 2 × OMe), 3.70 (s, 2 H), and 1.25 (t, 3 H, *J* 7 Hz), $\nu_{max.}$ 1 717 and 1 602 cm⁻¹, *m/e* 318, 316(10%), M^+), 238(100), and 192 (30). This ester (2 g) was dissolved in dry diethyl ether (50 cm³) containing methylamine (1.2 g) and heated in a stainless steel bomb (capacity 60 cm³) at 100 °C for 2 h. The reaction mixture was then cooled, washed with water (2 × 25 cm³), dried, and evaporated to yield the title compound as a pale yellow solid (1.0 g, 70%) which was recrystallised from diethyl ether, m.p. 118—119 °C (lit.,[5] 119.5—121.5 °C, δ ($CDCl_3$) 6.80 (s, 2 H, 2 × ArH), 4.60 (s, 2 H, $ArCH_2N$), 4.0 (s, 6 H, 2 × OMe), 3.7 (s, 2 H, $ArCH_2CO$), and 3.22 (s, 3 H, NMe), $\nu_{max.}$ 1 630 cm⁻¹, *m/e* 221 (10%, M^+), 206(20), 192(30), and 164(100).

4-*Ethyl*-6,7-*dimethoxy*-2-*methyl*-1,4-*dihydro*-3(2H)-*isoquinolone* (18).[9]—*N*-Butyl-lithium (0.28 g) in tetrahydrofuran (3.6 cm³) was added to di-isopropylamine (0.36 g) in the same solvent (5 cm³). After stirring for 1 h the isoquinolone (15) (0.4 g) in tetrahydrofuran (5 cm³) was added and the resulting mixture stirred for a further 2 h. Ethyl bromide (0.51 g) was then introduced and the reaction mixture again stirred for 2 h. Finally it was poured onto ice

(*ca.* 50 g) and eventually extracted with dichloromethane (3 × 25 cm³). The combined extracts were washed with water (2 × 10 cm³), dried, and evaporated to give the title compound as a pale yellow oil (0.37 g, 83%), δ ($CDCl_3$) 6.68 and 6.58 (2 s, 2 × 1 H, 2 × ArH), 4.50 (s, 2 H, $ArCH_2N$), 3.85 (m, 7 H, ArCHCO, 2 × OMe), 3.14 and 3.09 (2 s, 3 H, ratio 1 : 2, NMe), 2.50 and 1.20 (m, 2 H, CH_2CH_3), and 0.80 and 0.62 (2 t, 3 H, ratio 2 : 1, CH_2CH_3),* $\nu_{max.}$ 1 640 and 1 522 cm^{-1}, *m/e* 249(100%, M^+) (Found: C, 67.3; H, 7.8; N, 5.4. $C_{14}H_{19}NO_3$ requires C, 67.4; H, 7.7; N, 5.6%).

4-(α-*Hydroxy*-3-*methoxybenzyl*)-6,7-*dimethoxy*-2-*methyl*-1,4-*dihydro*-3(2H)-*isoquinolone* (17).—(The whole of the following reaction sequence was carried out under an atmosphere of dry nitrogen and the reagents were introduced *via* a septum cap by means of glass syringes. The temperature was maintained at 0 °C throughout until 1 h after the final addition, when the temperature was allowed to rise to that of the laboratory.) n-Butyl-lithium (0.42 g ≡ 2.5 cm³ of a 15% solution in n-hexane) was added dropwise to a stirred solution of di-isopropylamine (0.72 g) in dry tetrahydrofuran (5.0 cm³). After 30 min, hexamethylphosphoric triamide (0.5 g) in dry tetrahydrofuran (5.0 cm³) was added and after another 90 min, the isoquinolone (15) (1.5 g) in the same solvent (25 cm³) was slowly introduced. After 1 h, 3-methoxybenzaldehyde (0.95 g) in dry tetrahydrofuran (20 cm³) was added over a further 1 h. Next day the reaction mixture was filtered to afford the title compound (17) as a colourless solid (1.85 g, 78%), m.p. 98—101 °C, δ [$(CD_3)_2SO$–$CDCl_3$] 7.56—6.95 (m, 4 H, 4 × ArH), 6.9 and 6.84 (2 s, 2 × 1 H, 2 × ArH), 4.42 (br s, 2 H, $ArCH_2N$), *ca.* 3.9 (3 s, 3 × 3 H, 3 × OMe), 3.85—3.6 [m, 2 H, ArCHCH(OH)], 3.0 (s, 3 H, NMe), and 2.75 (br s, 1 H, OH), $\nu_{max.}$ 3 375 and 1 630 cm^{-1}. All attempts to recrystallize this product led to 6,7-*dimethoxy*-2-*methylisoquinoline*-1,3,4(2H)-*trione* (2-methyl-6,7-dimethoxyphthalonimide) (30) as yellow needles, m.p. 256—257 °C, δ [$(CD_3)_2SO$] 7.59 and 7.47 (2 s, 2 × 1 H, 2 × ArH), 3.95 and 3.91 (2 s, 2 × 3 H, 2 × OMe), and 3.32 (s, 3 H, NMe), $\nu_{max.}$ 1 725, 1 695, and 1 670 cm^{-1}, $\lambda_{max.}$ (MeOH) 233 (ε 7 710), 267(17 800), 340(2 850), and 364 nm (2 820), *m/e* 249(100%, M^+), 221(90), 177(86), 164(90), and 136(69) (Found: C, 57.7; H, 4.7; N, 5.7. $C_{12}H_{11}NO_2$ requires C, 57.8; H, 4.5; N, 5.6%).

Oxidation of 3-(3,4-*Dimethoxyphenyl*)-2-(2-*hydroxymethyl*-4,5-*dimethoxyphenyl*)-N-*methylpropionamide* (5).—The amide (2.0 g) in glacial acetic acid (30 cm³) was treated with 10% chromium trioxide in glacial acetic acid (20 cm³) dropwise over 1 h and allowed to stand with agitation for a further 4 h. Water (150 cm³) was then added and a yellow precipitate which formed was filtered off. Crystallisation from ethanol gave 2-methyl-6,7-dimethoxyphthalonimide (30) as yellow needles (0.96, 64%), m.p. 256—257 °C.

Attempted Alkylation of 6,7-*Dimethoxy*-2-*methyl*-1,4-*dihydro*-3(2H)-*isoquinolone with* 3,4-*Dimethoxybenzyl Chloride*.[10]—Di-isopropylamine (0.23 g) in dry tetrahydrofuran (3 cm³) was added to n-butyl-lithium (15% solution in hexane, 1.4 cm³) in tetrahydrofuran (4 cm³) under nitrogen and maintained at 0 °C. After 1 h, the dihydroisoquinolone (15) (0.5 g) in tetrahydrofuran (15 cm³) was introduced and after another 1 h, 3,4-dimethoxybenzyl chloride (0.42 g) in tetrahydrofuran (5 cm³); the reaction mixture was stirred for a further 2 h and then 0.2M-hydrochloric acid (100 cm³) was added and the reaction mixture extracted with chloroform (3 × 25 cm³). The combined extracts were washed with water, dried, and evaporated to give a pale yellow solid. This was triturated with ethanol to yield 10,15-dihydro-2,3,7,8,12,13-hexamethoxy-5*H*-tribenzo[*a,d,g*]-cyclononene (19) (cyclotriveratrylene) † (60 mg), m.p. and mixed m.p. with authentic specimen 233—234 °C (lit.,[11] 234 °C). Evaporation of the mother-liquor and fractional recrystallisation from chloroform–benzene afforded the isoquinolone (15) (0.35 g) and cyclotetraveratrylene (20) (10 mg), m.p. 313—314 °C (decomp.) (lit.,[12] 319—322 °C) δ ($CDCl_3$) 6.62 (s, 8 H), 3.68 (s, 24 H), and 4.0—3.4 (m, 8 H), *m/e* 600(M^+), 449, 312, and 151 (Found: C, 71.85; H, 6.8. Calc. for $C_{36}H_{40}O_8$: C, 72.0; H, 6.7%).

Ethyl 2-(2-*Bromomethyl*-4,5-*dimethoxyphenyl*)-3-(3,4-*dimethoxyphenyl*)*propionate* (21).—6,7-Dimethoxy-4-(3,4-dimethoxybenzyl)isochroman-3-one (2.0 g) was added to a stirred solution of hydrogen bromide (10 g) in anhydrous ethanol (100 cm³). The mixture was left stirring for 24 h, during which time the isochromanone slowly dissolved affording an orange solution. Removal of the solvents at 25 °C under reduced pressure gave a yellow oil which gradually solidified over several weeks (2.32 g, 70%), m.p. 82—84 °C. This product is unstable when exposed to light or air and was used directly in subsequent experiments. It had δ ($CDCl_3$) 7.02 (s, 1 H, ArH), 6.78 (m, 3 H, 3 × ArH), 4.8—3.85 (m, 5 H, $ArCH_2Br$, $ArCHCH_2OCH_2CH_3$), 3.85—3.80 (4 s, 4 × 3 H, 4 × OCH_3), 3.6—2.8 (m, 2 H, ArCHCH-CH_2), and 1.1 (t, 3 H, *J* 6 Hz, OCH_2CH_3), $\nu_{max.}$ 1 725 and 1 600 cm^{-1}.

Ethyl 2,3,7,8-*Tetramethoxy*-10,11-*dihydro*-5H-*dibenzo*[b,f]-*cycloheptene*-10-*carboxylate* (22).—The ester (21) (2.5 g) in dry toluene–ethanol (90 cm³; 7 : 2 v/v) was added slowly to a stirred suspension of anhydrous potassium carbonate (15 g) in ethanol (50 cm³). After 24 h, filtration and evaporation yielded a pale yellow oil which was taken up in chloroform (50 cm³), washed with water (2 × 20 cm³), dried, and evaporated to give a pale yellow solid. This product in ethanol (30 cm³) was decolourised with charcoal to afford, after removal of the solvent, colourless plates of the *ester* (22) (1.4 g, 72%), m.p. 108—110 °C (from EtOH), δ ($CDCl_3$) 6.80—6.72 (m, 3 H, 3 × ArH), 6.65 (s, 1 H, ArH), 4.14 (q, 2 H, *J* 7 Hz, OCH_2CH_3), 4.04 (t, *J* 5 Hz, 1 H, $ArCH_2CHAr$), 3.86, 3.84, 3.81, and 3.78 (4 s, 4 × 3 H, 4 × OMe), 3.80—3.60 (m, 2 H, $ArCH_2Ar$), 3.26 and 3.28 (8 lines, 2 H, $ArCH_2CHAr$), and 1.22 (t, 3 H, *J* 7 Hz, OCH_2CH_3), $\nu_{max.}$ 1 715 and 1 610 cm^{-1}, *m/e* 385(55%; *M* − 1), 312(100), 165(95), 152(85), and 151(42) (Found: C, 68.3; H, 6.7. $C_{22}H_{26}O_6$ requires C, 68.4; H, 6.8%).

3-(3,4-*Dimethoxyphenyl*)-2-(2-*hydroxymethyl*-4,5-*dimethoxyphenyl*)*propionohydrazide* (25).—Hydrazine hydrate (0.25 g) was added to 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isochroman-3-one (1.5 g) in ethanol (50 cm³) and the mixture then heated under reflux for 6 h. Approximately half the solvent was removed and the residual solution allowed to cool overnight. The solid which formed was then collected and crystallised from ethanol (15 cm³) as colourless needles (1.35 g, 82%), m.p. 159—160 °C, δ ($CDCl_3$) 8.92 (br s, 1 H, OH), 7.63 and 6.88 (2 s, 2 × 1 H, 2 × ArH), 6.82—6.60 (m, 3 H, 3 × ArH), 5.08 (br s, 1 H, $NHNH_2$), 4.4 (s, 2 H, CH_2OH), 4.4—3.8 (m, 2 H, $NHNH_2$), 3.70 and 3.68 (2 s, 2 × 3 H, 2 × OMe), 3.64 (s, 6 H, 2 × OMe), 3.95—3.4 (m, 1 H, $ArCH_2CH$), and 2.96 (dd, 2 H, $J_1 = J_2$ = 7 Hz, $ArCH_2CH$), $\nu_{max.}$ 3 330, 3 230, 3 130, 3 070, and 1 690

* The ^1H n.m.r. spectrum shows the presence of diastereoisomers.

† Compounds (19) and (20) can be made directly by the reaction of 3,4-dimethoxybenzyl chloride and lithium di-isopropylamide under anhydrous conditions.

cm^{-1}, $\lambda_{max.}$ 238 (ε 10 500) and 281 nm (5 460), *m/e* 390 (90%; M^+) and 151 (100) (Found: C, 61.2; H, 6.6; N, 7.3. $C_{20}H_{26}N_2O_6$ requires C, 61.5; H, 6.7; N, 7.2%).

2,3,7,8-*Tetramethoxy*-10,11-*dihydro*-5H-*dibenzo*[b,f]*cycloheptene*-10-*carboxylic Acid* (26).—The hydrazide (25) (0.6 g) in 2M-hydrochloric acid (20 cm^3) was heated under reflux for 2 h. After cooling, the solution was poured into water and extracted with dichloromethane (3 × 30 cm^3). The combined extracts were washed with water (2 × 20 cm^3), dried, and evaporated to yield the colourless *acid* (26) (0.44 g, 82%), m.p. 132—135 °C (from EtOH), δ [$(CD_3)_2SO$–$CDCl_3$] 11.5 (br s, 1 H, CO_2H), 6.80 (s, 1 H, ArH), 6.75 (s, 3 H, 3 × ArH), 4.1 (t, 1 H, *J* 9 Hz, $ArCH_2CH$), *ca.* 3.75 (4 s + m, 4 × 3 H + 2 H, 4 × OMe + $ArCH_2Ar$), and 3.6—2.9 (8 lines, 2 H, $ArCH_2CHAr$), $\nu_{max.}$ 3 550, 1 650, and 1 610 cm^{-1}, *m/e* 358 (100%; M^+), 327 (45), 313 (100), and 282 (24) (Found: C, 66.9; H, 6.3. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%).

α-(6,7-*Dimethoxy*-2-*methyl*-3-*oxo*-1,2,3,4-*tetrahydroisoquinolin*-4-*ylidene*)-3,4-*dimethoxybenzyl* 3,4-*Dimethoxybenzoate* (27).—Di-isopropylamine (0.72 g) in dry tetrahydrofuran (5 cm^3) was added to n-butyl-lithium (15% solution in hexane, 2.5 cm^3) in tetrahydrofuran (5 cm^3) under dry nitrogen and maintained at 0 °C. After 30 min, hexamethylphosphoric triamide (2 cm^3) in dry tetrahydrofuran (5 cm^3) was introduced and in a further 30 min the isoquinolone (15) (1.5 g) in dry tetrahydrofuran (25 cm^3). After 1 h, 3,4-dimethoxybenzoyl chloride (3.0 g) in dry tetrahydrofuran (20 cm^3) was admitted dropwise and, after 1 h, the temperature of the reaction mixture was allowed to rise to that of the laboratory. Next day the product was filtered off and recrystallised from dimethyl sulphoxide to give pale yellow *needles* (2.7 g, 72%), m.p. 207—209 °C, δ (CF_3CO_2H) 8.24—6.90 (2 × AMX pattern + 2 s, 8 H, 8 × ArH), 4.96 (q, 2 H, *J* 16 Hz, $ArCH^2$), 4.15, 4.0, 3.95, and 3.85 (4 s, 18 H, 6 × OMe), and 3.5 (s, 3 H, NMe), $\nu_{max.}$ 1 740 and 1 645 cm^{-1}, $\lambda_{max.}$ 223 (ε 26 400), 260 (22 800), 300 (19 400), and 330 nm (11 800), *m/e* 549 (42%; M^+), 385 (15), 247 (10), and 165 (100) (Found: C, 65.7; H, 2.5; N, 2.65. $C_{30}H_{31}NO_9$ requires C, 65.6; H, 5.7; N, 2.55%).

4-(3,4-*Dimethoxybenzoyl*)-6,7-*dimethoxy*-2-*methyl*-1,4-*dihydro*-3(2H)-*isoquinolone* (28).—The enol ester (27) (3.3 g) in glacial acetic acid (50 cm^3) was heated under reflux for 8 h. The reaction mixture was then cooled and added to water (150 cm^3). Extraction with dichloromethane (3 × 50 cm^3) gave, after removal of the solvent, a colourless oil which crystallised from ethanol as *plates* (1.65 g, 71%), m.p. 149—150 °C, δ [$(CD_3)_2SO$] 8.0 (dd, 1 H, J_1 9 Hz, J_2 3 Hz, 6′-H), 7.62 (d, 1 H, *J* 3 Hz, 2′-H), 7.08 (d, 1 H, *J* 9 Hz, 5′-H), 6.93 and 6.68 (2 s, 2 H, 5-H, 8-H), 5.46 (s, 1 H, 4-H), 4.53 (q, 2 H, *J* 1.6 Hz, $ArCH_2$), 3.9, 3.85, 3.78, and 3.68 (4 s, 4 × 3 H, 4 × OMe), and 3.02 (s, 3 H, NMe), $\nu_{max.}$ 1 650, 1 620, and 1 610 cm^{-1}, $\lambda_{max.}$ 241 (ε 8 520), 280 (9 570), and 307 nm (8 080), *m/e* 385 (36%; M^+), 247 (19), 220 (16), and 165 (100) (Found: C, 65.3; H, 6.0; N, 3.2. $C_{21}H_{23}NO_6$ requires C, 65.4; H, 6.0; N, 3.6%).

4-(α-*Hydroxy*-3,4-*dimethoxybenzyl*)-6,7-*dimethoxy*-2-*methyl*-1,4-*dihydro*-3(2H)-*isoquinolone* (31).—The anion from the isoquinolone (15) (1.5 g) was prepared in tetrahydrofuran solution by the action of lithium isopropylamide as previously described, and treated at 5—10 °C with 3-methoxybenzaldehyde (0.9 g) in the same solvent (15 cm^3). The reaction mixture was allowed to reach room temperature overnight, and the pale yellow crystalline product (2.3 g, 96%) was then filtered off, m.p. 95—98 °C (decomp.), δ [$(CD_3)_2SO$–$CDCl_3$] 8.4 (s, 1 H, OH), 7.5—6.8 (m, 4 H, 4 × ArH), 6.79 and 6.68 (2 s, 2 H, 2 × ArH), 5.18 [br s, 1 H, $ArCH(OH)CH$], 4.22 (br s, 2 H, $ArCH_2N$), 3.80 (s, 9 H, 3 × OMe), 3.45 [br s, 1 H, $ArCH(OH)CH$], and 3.05 (s, 3 H, NMe), $\nu_{max.}$ 3 380, 1 635, and 1 600 cm^{-1}, $\lambda_{max.}$ 232 (ε 5 500) and 278 nm (4 500), *m/e* 339 (73%; $M^+ - 18$), 234 (82), 220 (100), and 136 (55).

All attempts to recrystallise this material resulted in extensive decomposition with the formation of the phthalonimide (30). The ^1H n.m.r. spectrum quoted above shows some extra peaks which correspond to resonances of this last compound and possibly also the corresponding benzylidene derivative formed from the alcohol (31) by dehydration.

4-(3,4-*Dimethoxybenzyl*)-6,7-*dimethoxy*-2-*methyl*-3,4-*dihydroisoquinolinium Trifluoroacetate* (40).—4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline [13] (1.0 g) was electrolysed in 0.001 4M-tetra-n-butylammonium tetrafluoroborate in trifluoroacetic acid–dichloromethane (1 : 3 v/v) (60 cm^3) using a carbon-felt anode maintained at 1.15 V (*versus* SCE). After 3 h (utilisation of 4.5 F mol^{-1}) the anolyte was poured into water (100 cm^3), rendered basic with ammonium hydroxide, and extracted with dichloromethane (3 × 50 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried, and evaporated to give a colourless oil, which was dissolved in hot ethanol (10 cm^3) containing a few drops of trifluoroacetic acid. On cooling, the trifluoroacetate salt (40) was obtained as colourless *prisms* (0.65 g, 49%), m.p. 204—205 °C, δ [$(CD_3)_2SO$–$CDCl_3$] 9.2 (s, 1 H, 1-H), 7.55 and 7.43 (2 s, 2 × H, 5-H, 8-H), 7.25, 6.7, and 6.6 (AMX, 3 H, 3 × ArH), 3.95 (s, 3 H, $\overset{+}{N}Me$), 3.86 and 3.75 (2 s, 12 H, 4 × OMe), 4.0—3.6 (m, 3 H, $\overset{+}{N}CH_2CHCH_2Ar$), 2.92 (br d, 2 H, $\overset{+}{N}CH_2CHCH_2Ar$), $\nu_{max.}$ 1 640 and 1 610 cm^{-1}, $\lambda_{max.}$ 247 (ε 13 000), 295 (5 100), 312 (5 400), and 355 nm (5 800) (Found: C, 58.6; H, 5.8; N, 3.1. $C_{23}H_{26}NO_5F_3$ requires C, 58.8; H, 5.6; N, 3.0%).

4-(3,4-*Dimethoxybenzylidene*)-6,7-*dimethoxy*-2-*methyl*-3,4-*dihydroisoquinolinium Trifluoroacetate* (41).—4-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (1.0 g) was oxidised under the same conditions as in the previous experiment except that, as the anode potential was difficult to control above +1.8 V, the electrolysis was continued at a constant current of 100 mA until the u.v. spectrum of the reaction mixture showed no further change (*ca.* 3 h). Work-up as in the previous experiment gave a colourless solid which crystallised from ethanol–trifluoroacetic acid as needles, m.p. 195—196 °C, δ ($CDCl_3$) 9.3 (s, 1 H, 1-H), 7.63, 7.57 (2 s, 2 × 1 H, 5-H, 8-H), 7.18 (m, 3 H, 3 × ArH), 6.6 (1 H, s, $ArCH$=), 4.35 (s, 2 H, $\overset{+}{N}CH_2$), 4.27 (s, 3 H, $\overset{+}{N}Me$), and 3.99, 3.95, 3.78, and 3.65 (4 s, 4 × 3 H, 4 × OMe), $\nu_{max.}$ 1 635 and 1 605 cm^{-1}, $\lambda_{max.}$ 259 (ε 14 500) and 313 nm (12 300) (Found: C, 58.65; H, 5.0; N, 3.1. $C_{23}H_{24}NO_6F_3$ requires C, 59.0; H, 5.2; N, 3.0%). This compound is formulated as a 3,4- rather than a 1,4-dihydroisoquinolinium salt on the basis of its ^1H n.m.r. spectrum; for reference compounds see Brown, Dyke, and Sainsbury.[14]

M. P. C. is the recipient of an S.R.C. CASE studentship in conjunction with Glaxo Group Research Limited.

[9/1660 *Received*, 19*th October*, 1979]

REFERENCES

[1] M. Sainsbury and J. Wyatt, *J.C.S. Perkin I*, 1979, 108.
[2] (*a*) J. M. Bobbitt and R. C. Hallcher, *Chem. Comm.*, 1971, 543; (*b*) L. L. Miller, F. R. Stermitz, and J. R. Falck, *J. Amer. Chem. Soc.*, 1973, **95**, 2651; *Tetrahedron*, 1974, **30**, 931; (*c*) L. L. Miller and R. F. Stewart, *J. Org. Chem.*, 1978, **43**, 1580; (*d*) I. W. Elliott, jun., *J. Org. Chem.*, 1977, **42**, 1091.
[3] M. Sainsbury and R. F. Schinazi, *J.C.S. Chem. Comm.*, 1972, 718.
[4] N. J. McCorkindale and A. W. McCulloch, *Tetrahedron*, 1971, **27**, 4653.
[5] J. Finkelstein and A. Brossi, *J. Heterocyclic Chem.*, 1967, **4**, 315.
[6] G. Rosen and F. Popp, *Canad. J. Chem.*, 1969, **47**, 864.
[7] L. L. Miller, F. R. Stermitz, J. Y. Becker, and V. Ramachandran, *J. Amer. Chem. Soc.*, 1975, **97**, 2922.
[8] U. Palmquist, A. Nilsson, T. Pettersson, A. Ronlán, and V. D. Parker, *J. Org. Chem.*, 1979, **44**, 196.
[9] J. Wyatt, Ph.D. Thesis, University of Bath, 1978.
[10] R. K. Maskell, B.Sc. Project Report, University of Bath, 1977.
[11] A. S. Lindsey, *J. Chem. Soc.* (*C*), 1965, 1685.
[12] J. D. White and B. D. Gesner, *Tetrahedron Letters*, 1968, 1591.
[13] P. Warren, Ph.D. Thesis, University of Bath, 1978.
[14] D. W. Brown, S. F. Dyke, and M. Sainsbury, *Tetrahedron*, 1969, **25**, 101.