Electrochemical Oxidation of Aromatic Ethers. Part 11.[1] The Synthesis of Phenanthropyrrolidines

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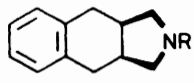
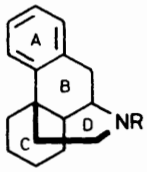
7a,8-Dihydro-3,10,11-trimethoxyphenanthro[8a,9-*c*]furan-2,7(5*H*)dione (**5**), obtained by electrochemical oxidation of 6,7-dimethoxy-4-(3,4-dimethoxybenzyl)isochroman-3-one, has been converted by reduction, treatment with propylamine, and further reduction into 2,3,4,5,6,7a,8,12b-octahydro-3,10,11-trimethoxy-6-propyl-1*H*-phenanthro[8a,9-*c*]pyrrol-2-ol (**12**). Anodic oxidation of 6,7-dimethoxy-4-(3,4-dimethoxyphenethyl)isochroman-3-one (**18**) affords 8,9-dihydro-2,11,12-trimethoxybenzo[*c*]naphtho[1,2-*d*]pyran-3,7(5*H*,7a*H*)dione (**26**) which on reaction with methylamine yields 4a,5,7,8-tetrahydro-4a-hydroxymethyl-2,10,11-trimethoxy-5-methylnaphth[2,1-*c*]indole-3,6(4*H*,6a*H*)dione.

Since their introduction as analgesics benz[*f*]indoles, *e.g.* AH 8649 (**1**; R = alkyl),[2] have not received much attention and no attempts have been made to incorporate an additional ring, analogous to the C-ring of the morphinans (**2**), into the system

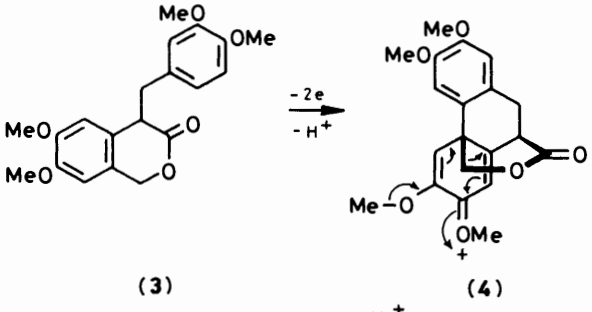


(**1**)



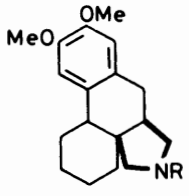
(**2**)

which might then serve to increase their potency. We, however, have demonstrated recently[3] that anodic oxidation of the 4-benzylisochroman-3-one (**3**) yields the cation (**4**) which rearranges and *O*-demethylates to afford the γ-lactone (**5**). From this compound routes to novel phenanthropyrrolidines (**6**), can be devised.

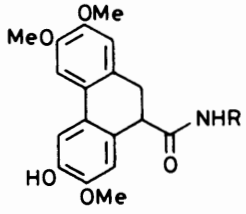


(**3**) (**4**) (**5**)

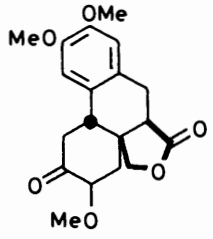
In order to implement such a conversion, however, it is mandatory first to prevent the degradation of the starting material, for if the spirodienone (**5**) is treated with primary amines, dihydrophenanthrenes (**7**) are produced with concomitant loss of formaldehyde, or its equivalent. Thus the dienone system was eliminated by hydrogenation of the γ-lactone over a catalyst yielding first the keto lactone (**8**) and then the hydroxy lactone (**9**).



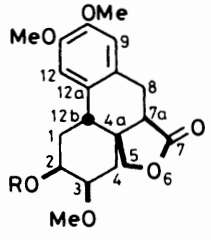
(**6**)



(**7**)



(**8**)

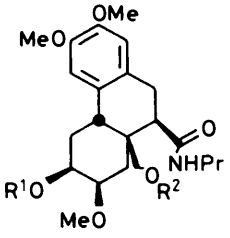


(**9**) R = H
(**13**) R = $Bu^t(Me)_2Si$

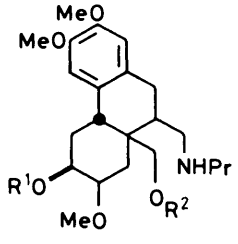
The relative stereochemistry of the last product is evident from an analysis of its ^1H n.m.r. spectrum; in particular the resonance of the axial proton at C-1 (δ 1.75) is coupled to that of 12b-H (δ 2.54) and also to that of 2-H (δ 3.85), with coupling constants (*J*) the magnitudes of which (both 12 Hz) signify *trans*-diaxial relationships for the two sets of protons. The signal of the equatorial proton at C-1 (δ 2.37) is geminally coupled to the 1-H axial resonance (*J* 13 Hz) and, through a W-effect (*J* 2 Hz), to the signal of the C-3 (δ 3.70) proton, which must therefore be equatorially orientated. An AMX spin system arises from the

interaction of the resonances of the proton at C-3 and those of the C-4 methylene unit (4-H_α, δ 2.56; 4-H_β, δ 1.64; J_{AX} 3, J_{AM} 3, J_{MX} 15 Hz). A second AMX spin system is formed by the signals of the protons at C-7a (δ 2.67) and at C-8 (H_α, δ 2.86; H_β, δ 3.05; J_{AX} 2, J_{AM} 8, J_{MX} 15 Hz).

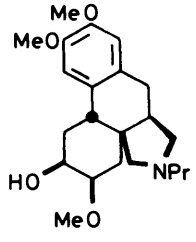
The hydroxylactone (**9**) when treated with *N*-lithiopropylamine gave the dihydroxy amide (**10**) and this was then reduced with diborane to yield the corresponding amine (**11**). Attempts to cyclise this product to the pyrrolidine (**12**) under a variety of conditions were unsuccessful, mainly because of alternative reactions involving the secondary hydroxy group. To succeed this function must be protected; thus the hydroxy lactone was treated with dimethyl-t-butylsilyl chloride and imidazole to afford the *O*-silyl derivative (**13**), which was converted into the hydroxy amide (**14**) as before. The *O*-mesylate (**15**) of this compound was then cyclised to the lactam (**16**) in the presence of sodium hydride. Finally, reduction with diborane gave the required tetracycle (**12**), deprotection taking place during the work-up procedure. A reversal of this sequence of reactions is unsatisfactory since when the amide (**15**) is treated with diborane the product acyclic amine complexes strongly with the reagent. Attempts to decompose this complex led to its resinification.



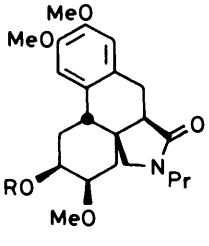
(**10**) $R^1 = R^2 = H$
(**14**) $R^1 = Bu^t(Me)_2Si$; $R^2 = H$
(**15**) $R^1 = Bu^t(Me)_2Si$; $R^2 = SO_2Me$



(**11**) $R^1 = R^2 = H$
(**17**) $R^1 = Bu^t(Me)_2Si$; $R^2 = SO_2Me$



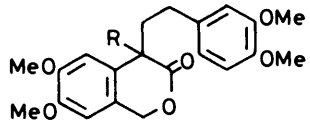
(**12**)



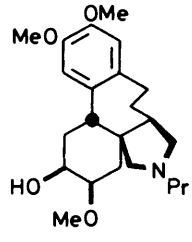
(**16**) $R = Bu^t(Me)_2Si$

We expected that a similar series of reactions, now with the 4-phenethylisochromanone (**18**), would generate the analogous structure (**19**) which represents a new tetracyclic system, but in order to test this projection it was first necessary to prepare the starting material, itself unknown. Although the 4-benzylisochroman-3-one (**3**) can be obtained by heating the parent isochromanone (**20**) with veratraldehyde and pyrrolidine, followed by hydrogenation of the 4-benzylidene derivative (**21**), this method is not applicable to the synthesis of the homologue (**18**). Treatment of the lithium salt of the isochromanone (**20**) with 3,4-dimethoxyphenylacetyl chloride gives the ester (**22**), and it might be supposed that a reversal of the *O*-acylation step could be effected by hydrolysis. In practice, however, both *O*- and *C*-acylation processes are reversed and the parent isochromanone is returned. Similarly base-catalysed alkylation of the isochromanone (**20**) with 3,4-dimethoxyphenylethyl bromide is impracticable, due to competitive elimination of hydrogen bromide from the alkyl halide. Recently a number of authors have demonstrated that a benzylic proton of the tricarbonylchromium complexes of, for example, tetrahydroisoquinolines[4] and tetralones[5] may be removed by base. The reaction is quantitative and the anions so formed may then be alkylated or acylated. From our viewpoint this technique applied to the isochromanone (**20**) would enable strict control of the amount of base used and in fact when the tricarbonylisochromanone chromium complex was made and treated first with one equivalent of lithium di-isopropylamide and then with the alkyl halide the required substrate (**18**) for electrolysis was obtained in good yield, together with a small amount of its 4-hydroxylated derivative (**23**).

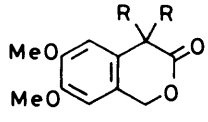
These products were separated by h.p.l.c. and the first compound (**18**) then oxidised in a non-divided cell, using a platinum anode maintained at 1.1 V. This gave a single product,



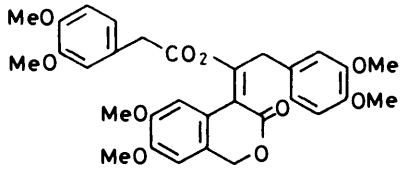
(**18**) R = H
(**23**) R = OH



(**19**)



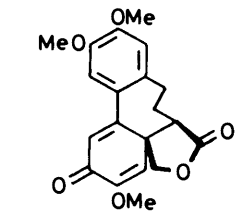
(**20**) R,R = H_2
(**21**) R,R = $CHC_6H_3(OMe)_2$-3,4



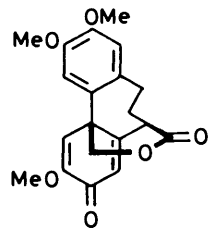
(**22**)

$C_{21}H_{24}O_6$, which shows a carbonyl band at 1 740 cm^{-1} in the infra-red spectrum. This fact indicates the presence of a six- rather than a five-membered lactone ring and thus favours either structure (**25**) or (**26**) as opposed to the γ-lactone (**24**). A decision between the two alternatives is not easy on the basis of the ^1H and ^{13}C n.m.r. spectral data (see the Experimental section), but if the first structure is correct, then treatment of it with methylamine should yield the dihydro-homophenanthrene (**27**) through ring-opening, and a dienone-phenol rearrangement with concomitant loss of formaldehyde. In contrast a likely product from the structure (**26**) would be the spirodienone (**28**). In practice, however, a reaction between the electrolysis product and methylamine gave the oxindole (**30**) (the most stable ring-fusion for the lactam system is assumed). This result does, in fact, clearly identify the δ-lactone (**26**) as the correct formulation since lactonic ring-opening with methylamine is accompanied (perhaps preceded) by attack of the reagent at the most electrophilic enone position. Although no intermediates in this process were isolated, it is now reasonable to conclude that the amino amide (**29**) is produced and that this species, or its equivalent, then recyclises to generate the oxoindole (**30**) with loss of methylamine.

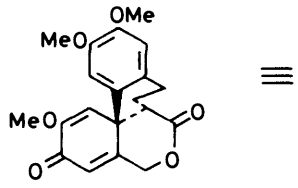
The constitution (**26**) of the spiro lactone is interesting for once again it illustrates the strong preference in anodic coupling reactions of this type for six-membered ring forming processes over other alternative modes of cyclisation.



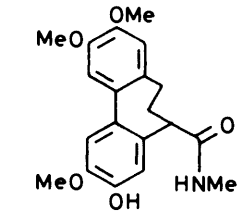
(**24**)



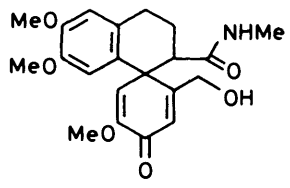
(**25**)



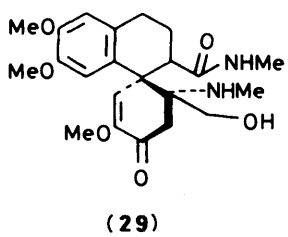
(**26**)



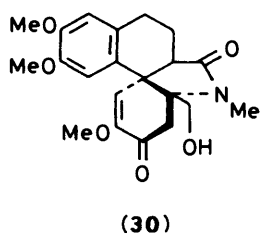
(**27**)



(**28**)



(**29**)



(**30**)

Experimental

U.v. spectra were recorded as solutions in 98% ethanol. I.r. data refer to Nujol mulls unless stated otherwise. ^1H 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 undivided cell using 0.1M-sodium perchlorate in acetonitrile as the electrolyte unless stated otherwise. Platinum gauze electrodes (dimensions 2 × 2 in) were used throughout. Chemical ionization (c.i.) mass spectrometric analyses were determined using isobutane as the ionozing medium.

1,3,4,7a,8,12b-*Hexahydro*-3,10,11-*trimethoxyphenanthro*-[8a,9-c]*furan*-2,7-(5H)-*dione* (**8**) *and* 1,2,3,4,5,7a,8,12b-*Octahydro*-2-*hydroxy*-3,10,11-*trimethoxyphenanthro*[8a,9-c]*furan*-7-*one* (**9**).—A suspension of the lactone (**5**) (0.5 g) in AnalaR acetone (200 cm^3) was hydrogenated at a pressure of 100 p.s.i. in the presence of 10% palladium-on-charcoal (0.5 g) for a period of 20 h. After filtration of the reaction mixture through Kieselguhr, the filtrate was evaporated to a colourless gum which was chromatographed over silica using ethyl acetate as the eluant. The early fractions contained the dione (**8**) (0.12 g, 25%), which was crystallised from ethyl acetate as colourless prisms, m.p. 175—177 °C, δ_H (250 MHz; $CDCl_3$), 6.79, 6.61 (2 × s, 2 H, 9-H, 12-H), 4.80, 3.72 (dd, 2 H, J_1 10 Hz, 5-H_2), 3.90, 3.88 (2 × s, 6 H, 10-MeO, 11-MeO), 3.68 (dd, 1 H, J_1 4, J_2 2.5 Hz, 3-H), 3.35 (s, 3 H, 3-MeO), 3.2—2.7 (m, 6 H aliphatic H), and 2.62 and 2.09 (part of ABX spin system, 2 H, J_1 4.75, J_2 4.0, J_3 2.5 Hz, 4-H_{eq}, 4-H_{ax}); $\nu_{max.}$($CHBr_3$) 1 760 and 1 720 cm^{-1}; *m/z* 346 (M^+, 100%), 227 (6), 201 (8), and 177 (12) (Found: C, 65.8; H, 6.4. $C_{19}H_{22}O_6$ requires C, 65.9; H, 6.4%).

The later fractions contained the hydroxy lactone (**9**) (0.36, 72%), which crystallised from ethyl acetate–light petroleum (b.p. 60—80 °C) as colourless prisms, m.p. 157—159 °C, δ_H (250 MHz; $CDCl_3$) 6.77, 6.72 (2 × s, 2 H, 9-H, 12-H), 4.36 (dd, 1 H, J_1 10, J_2 0.5 Hz, 5-H_{eq}), 3.50 (dd, 1 H, J_1 10, J_2 1 Hz, 5-H_{ax}), 3.90, 3.88 (2 × s, 6 H, 10-MeO, 11-MeO), 3.85 (m, 1 H, 2-H_{ax}), 3.70 (m, 1 H, J_1 3.3, J_2 3.0 Hz, 3-H_{eq}), 3.48 (s, 3 H, 3-OMe), 3.05 (*A*BC, 1 H, J_1 15, J_2 2 Hz, 8-H_{eq}), 2.86 (A*M*X, 1 H, J_1 15, J_2 8 Hz, 8-H_{ax}), 2.67 (AM*X*, 1 H, J_2 8, J_3 2 Hz, 7a-H), 2.65 (s, 1 H, 2-OH), 2.56 (m, 1 H, J_1 15, J_2 3 Hz, 4-H_{eq}), 2.54 (m, 1 H, J_1 12, J_2 3 Hz, 12b-H), 2.37 (m, 1 H, J_1 13, J_2 4, J_3 3 Hz, 1-H_{eq}), 1.75 (m, 1 H, J_1 13, J_2 = J_3 = 12 Hz, 1-H_{ax}), and 1.64 (m, 1 H, J_1 15, J_2 3, J_3 1 Hz, 4-H_{ax}); δ_C($CDCl_3$) 179.5 (s, C-7), 148.4, 147.9 (2 × s, C-10, C-11), 130.8, 127.9 (2 × s, C-8a, C-12a), 111.9, 108.6 (2 × d, C-9, C-12), 79.6 (t, C-5), 73.6, 71.1 (2 × d, C-2, C-3), 57.4, 56.2, 56.0 (3 × q, 3 × MeO), 48.1 (d, C-12b), 42.3 (s, C-4a), 40.8 (d, C-7a), 36.8 (t, C-8), 30.0 (t, 4-C), and 28.7 (t, C-1); $\nu_{max.}$($CHBr_3$) 3 550 and 1 762 cm^{-1}; $\lambda_{max.}$ 228, 278, and 282 nm; *m/z* 248 (M^+, 100%), 201 (6) and 177 (6) (Found: C, 65.3; H, 6.8. $C_{19}H_{24}O_6$ requires C, 65.5; H, 6.9%).

2-*Dimethyl-t-butylsilyloxy*-1,2,3,4,5,7a,8,12a-*octahydro*-3,10,11-*trimethoxyphenanthro*[8a,9-c]*furan*-7-*one* (**13**).—A solution of dimethyl-t-butylsilyl chloride (3.46 g, 0.023 mol) in dry *N,N*-dimethylformamide (15 cm^3) was added in portions to a solution of the hydroxy lactone (**9**) (4 g, 0.012 mol) and imidazole (3.13 g, 0.046 mol) in dry *N,N*-dimethylformamide (40 cm^3), with stirring, under an atmosphere of dry nitrogen at

room temperature. After stirring overnight the solution was diluted with diethyl ether (200 cm^3), washed with water (3 × 100 cm^3) and dilute hydrochloric acid (100 cm^3), and dried (anhydrous $MgSO_4$). The solvents were evaporated off to leave a white solid which was purified by chromatography over silica eluting with ethyl acetate to give the product as a white solid. This was recrystallised from ethyl acetate to yield white prisms (4.81 g, 91%), m.p. 169—171 °C; ^1H n.m.r. ($CDCl_3$; 250 MHz), 6.76, 6.72 (2 × s, m, 2 H, 9-H, 12-H), 4.58 (d, 1 H, *J* 10 Hz, 5-H_{eq}), 3.90 (m, 7 H, 2 × OMe, 2-H), 3.61 (m, 1 H, 3-H), 3.51 (s, 3 H, 3-OMe), 3.46 (d, 1 H, *J* 10 Hz, 5-H_{ax}), 3.04 (br d, 1 H, *J* 15 Hz, 8-H_{eq}), 2.84 (dd, 1 H, J_1 15, J_2 8 Hz, 8-H_{ax}), 2.64 (d, *J* 8 Hz, 7a-H), 2.52 (dd, 1 H, J_1 15, J_2 3 Hz, 4-H_{eq}), 2.40 (dd, 1 H, J_1 12, J_2 3 Hz, 12b-H), 2.09 (m, 1 H, 1-H_{eq}), 2.01 (m, 1 H, 1-H_{ax}), 1.65 (br d, 1 H, *J* 15 Hz, 4-H_{ax}), 0.96 (s, 6 H, $SiMe_2$), and 0.16 (s, 9 H, $SiCMe_3$); ν($CHBr_3$) 2 830, 1 760, and 1 250 cm^{-1}; *m/z* 462 (M^+, 23%), 405 (91), 299 (83), and 89 (100) (Found: C, 65.2; H, 8.35. $C_{25}H_{38}O_6Si$ requires C, 64.9; H, 8.3%).

The O-*methanesulphonyl derivative* (**15**). This had m.p. 132—134 °C; $\nu_{max.}$($CHBr_3$) 3 445, 1 660, and 1 350 cm^{-1}; *m/z* 599 (M^+, 2%) and 503 (100) (Found: C, 58.3; H, 8.1; N, 2.4. $C_{29}H_{49}NO_8SSi$ requires C, 58.1; H, 8.2; N, 2.3%).

4b,5,6,7,8,8a,9,10-*Octahydro*-6-*hydroxy*-8a-*hydroxymethyl*-2,3,7-*trimethoxy*-9-(N-*propylaminocarbonyl*)*phenanthrene* (**10**).—Freshly distilled dry propylamine (1.42 g, 0.024 mol) in dry tetrahydrofuran (16 cm^3) was cooled to 0 °C under a dry nitrogen atmosphere. Butyl-lithium in hexane (1.5 cm^3; 1.6 mmol cm^{-3}; 0.0024 mol) was added dropwise and, after the reaction had been stirred for 0.25 h, the hydroxy lactone (**9**) (0.24 g) in dry THF (40 cm^3) was added in portions over a period of 0.25 h. The mixture was stirred overnight, then ammonium chloride (2.2 g) in water (10 cm^3) was introduced and the organic phase separated. The aqueous phase was extracted with ether (3 × 20 cm^3) and the combined organic layers were washed with dilute hydrochloric acid (50 cm^3), water (50 cm^3), and then dried (Na_2SO_4). Removal of the solvent left a colourless gum which was chromatographed over silica using dichloromethane–ethyl acetate as the eluant to yield the title compound as a colourless solid which was crystallised from ethyl acetate (0.15 g, 51%), m.p. 154—155 °C, δ_H (250 MHz; $CDCl_3$) 6.66 (s, 1 H, 4-H), 6.54 (s, 1 H, 1-H), 6.30 (t, 1 H, *J* 7 Hz, NH), 4.92 (dd, 1 H, J_1 10, J_2 3 Hz, OH), 3.83 (s, 6 H, 2-MeO), 3.8—3.55 (m, 4 H, 6-H_{ax}, 7-H_{eq}, CH_2OH), 3.52 (s, 3 H, 7-MeO), 3.4—3.2 (m, 3 H, $NHCH_2$, 10-H_{ax}), 2.90 (dd, 1 H, J_1 17.0, J_2 6.5 Hz, 10-H_{eq}), 2.76 (dd + d, 2 H, 6-OH, 8-H_{eq}), 2.58 (br d, 1 H, J_1 13.0, J_2 3.0 Hz, 4b-H), 2.40 (dd, 1 H, J_1 12.5, J_2 6.5 Hz, 9-H), 2.34 (dt, 1 H, J_1 13.0, J_2 3.0 Hz, 5-H_{eq}), 1.65 (m, 3 H, CH_2CH_2Me, 5-H_{ax}), and 0.92 (m, 4 H, CH_2Me, 8-H_{ax}); n.O.e. experiments: irradiation at δ 6.66 (4-H) caused a 9% enhancement of the signal at δ 2.34 (4a-H); irradiation at δ 6.54 (1-H) caused enhancements at δ 83.4 (10-H_{ax}), 6% and at δ 2.90 (10-H_{eq}), 5%; $\nu_{max.}$ 3 440, 3 250, and 1 640 cm^{-1}; *m/z* 407 (M^+, 13%), 389 (18), 348 (100), and 239 (15) (Found: M^+ 407.2308. $C_{22}H_{33}NO_6$ requires 407.2309).

The 6-O-*dimethyl-t-butylsilyl derivative* (**14**). This had m.p. 221—222 °C; $\nu_{max.}$ 3 440, 3 290, and 1 640 cm^{-1}; *m/z* 521 (92%), 503 (100), and 462 (65) (Found: C, 64.4; H, 9.4; N, 2.6. $C_{28}H_{47}NO_6Si$ requires C, 64.45; H, 9.1; N, 2.69%).

2-*Dimethyl-t-butylsilyloxy*-1,2,3,4,5,6,7,7a,8,12b-*decahydro*-3,10,11-*trimethoxy*-6-*propylphenanthro*[8a,9-c]*pyrrol*-7-*one* (**16**).—Dry, distilled dimethyl sulphoxide (25 cm^3) and sodium hydride (50% dispersion in oil; 0.3 g, 6.25 mmol) under an atmosphere of dry nitrogen were warmed at 70 °C for 1 h, until hydrogen evolution had ceased and the solution had turned pale brown. The methanesulphonate (**15**) (1.5 g, 2.5 mmol) in dry dimethyl sulphoxide (35 cm^3) was then added dropwise to the cooled solution and stirring was continued for 2 h. The solution was partitioned between ethyl acetate (100 cm^3) and water (100 cm^3) and the aqueous layer was separated and washed with ethyl acetate (3 × 100 cm^3). The combined organic extracts were washed with saturated brine (2 × 75 cm^3), and dried (anhydrous $MgSO_4$), and the solvents evaporated to leave an oil. This was chromatographed over silica eluting with ethyl acetate to give a white foam, which crystallised from diethyl ether–hexane (1:1) to yield the *title product* as colourless prisms (0.85 g; 67%), m.p. 121 °C: δ_H (250 MHz; $CDCl_3$) 6.71, 6.78 (2 × s, 2 H, 9-H, 12-H), 3.92 (m, 1 H, 3-H), 3.91 3.84 (2 × s, 6 H, 2 × OMe), 3.57 (dd, 1 H, J_1 7, J_2 2 Hz, 2-H), 3.52 (d, 1 H, *J* 12 Hz, 5-H_{eq}), 3.48 (s, 3 H, 3-OMe), 3.12, 2.78 (2 × dt, 2 H, J_1 12, J_2 8 Hz, NCH_2), 3.03 (d, 1 H, *J* 14 Hz, 8-H_{eq}), 2.74 (dd, 1 H, J_1 14, J_2 7 Hz, 8-H_{ax}), *ca.* 2.5 (m, 3 H, 5-H_{eq}, 7a-H, 12b-H), 2.34 (dd, 1 H, J_1 14, J_2 3 Hz, 4-H_{eq}), *ca.* 2.1 (m, 2 H, 1-H_2), 1.56 (dd, 1 H, J_1 14, J_2 4 Hz, 4-H_{ax}), 1.11 (m, 2 H, NCH_2CH_2), 0.96 (s, 9 H, $SiCMe_3$), 0.45 (t, 3 H, *J* 7 Hz, NCH_2CH_2Me), and 0.13 (2 × s, 6 H, $SiMe_2$); δ_C($CDCl_3$) 175.1 (s, C-7), 148.0, 147.8 (2 × s, C-10, C-11), 131.7, 129.1 (2 × s, C-8a, C-12a), 112.0, 108.4 (2 × d, C-9, C-12), 80.9 (d, C-3), 72.0 (d, C-2), 59.1, 56.4, 56.1 (3 × q, 3 × OMe), 52.9 (t, NCH_2), 51.7 (d, C-7a), 43.7 (t, NCH_2CH_2), 41.8 (d, C-12b), 39.5 (t, NCH_2CH_2), 38.7, 38.0 (2 × t, C-4, C-8), 26.0 (q, NCH_2CH_2Me), 19.8 (t, C-1), 10.5 (q, $SiCMe_3$), and −4.6 (q, $SiMe_2$); $\nu_{max.}$($CHBr_3$) 2 830 and 1 670 cm^{-1}; *m/z* 503 (M^+, 30%), 446 (62), and 241 (100) (Found: C, 66.7; H, 9.3; N, 2.7. $C_{28}H_{45}NO_5Si$ requires C, 66.8; H, 9.0; N, 2.8%).

This silyloxy derivative was converted into the corresponding *alcohol* (in 58% yield) by treatment with tetrabutylammonium fluoride in tetrahydrofuran. The product, an oil, was purified by chromatography over silica using ethyl acetate–ethanol (4:1) as the eluant, δ_H (250 MHz; $CDCl_3$) 6.74, 6.68 (2 × s, 2 H), 3.86 (m, 7 H), 3.68 (dd, 1 H), 3.45 (s, 3 H), 3.30 (d, 1 H), 3.10 (m, 1 H), 3.05 (d, 1 H), 2.9—2.7 (m, 2 H), 2.68 (d, 1 H), 2.5 (m, 4 H), 2.35 (dt, 1 H), 1.77 (dd, 1 H), 1.55 (dd, 1 H), 1.18 (m, 2 H), and 0.5 (t, 3 H); $\nu_{max.}$($CHBr_3$) 3 330 and 1 670 cm^{-1}; *m/z* 389 (M^+, 100%) and 142 (57) (Found: 389.2195. $C_{22}H_{31}NO_5$ requires 389.2199).

2,3,4,5,7,7a,8,12b-*Octahydro*-3,10,11-*trimethoxy*-6-*propyl*-1H-*phenanthro*[8a,9-c]*pyrrol*-2-*ol* (**12**).—The protected lactam (**16**) (0.8 g, 1.59 mmol) in dry tetrahydrofuran (40 cm^3) was cooled to 0 °C under an atmosphere of dry nitrogen. A solution of diborane in tetrahydrofuran (3.18 cm^3; 1M; 3.18 mmol) was added dropwise with stirring. The solution was heated at reflux for 2.5 h, then cooled, and treated carefully with 5M-hydrochloric acid (15 cm^3) before the heating was continued for a further 1.5 h. The tetrahydrofuran was removed by distillation at atmospheric pressure and the residue basified with aqueous 5M-sodium hydroxide, then extracted with ethyl acetate (3 × 75 cm^3). The combined organic layers were washed with saturated brine (100 cm^3) and dried (anhydrous Na_2SO_4). Removal of the solvents left an oil which was purified by chromatography over neutral alumina with ethyl acetate as the eluant to yield the *title compound* as a colourless gum (0.51 g) 85%; m.p. (maleate salt) 166—169 °C, δ_C(250 MHz; $CDCl_3$) 6.68 (s, 2 H, 9-H, 12-H), 3.9 (s, 6 H, 2 × OMe), 3.82 (ddd, after D_2O shake, 1 H, J_1 12, J_2 4, J_3 4 Hz, 2-H_{ax}), 3.65 (dd, 1 H, J_1 15, J_2 7 Hz, 8-H_{eq}), 3.63 (ddd, 1 H, J_1 4, J_2 2.5, J_3 2.5 Hz, 3-H_{eq}), 3.33 (s, 3 H, 3-OMe), 3.25 (d, 1 H, *J* 9 Hz, 5-H_{eq}), 3.07 (dd, 1 H, J_{gem} 12, J_{vic} 8.5 Hz, 7-H_{eq}), 2.60 (dd, 1 H, J_1 14.5, J_2 2.5 Hz, 4-H_{eq}), 2.38 (m, 1 H, J_1 12.5, J_2 2.5 Hz, 12b-H), 2.33 (br d, 1 H, *J* 15 Hz, 8-H_{ax}), 2.23 (dd, 1 H, $J_{7eq,7a}$ 8.5, $J_{7ax,7a}$ 7 Hz, 7a-H), 2.40, 1.83 (2 × m, 2 H, NCH_2), 2.30 (m, 1 H, 1-H_{eq}), 1.67 (dd, 1 H, J_1 10, J_2 4 Hz, 1-H_{ax}), 1.38 (dd, 1 H, J_{gem} 12, J_{vic} 7 Hz, 7-H_{ax}), 1.33 (m, 1 H, 4-H_{ax}), 1.36 (m, 2 H, NCH_2CH_2), 1.01 (d, 1 H, *J* 9 Hz, 5-H_{ax}), 0.83 (t, 3 H, *J* 6 Hz, NCH_2CH_2Me); $\nu_{max.}$(Nujol) 3 450 and 1 710 cm^{-1}; *m/z* 375 (M^+, 12%), and 349

(100) (Found: C, 63.35; H, 7.75; N, 2.7%; M^+, 375.2403. $C_{22}H_{33}NO_4$ requires C, 63.5; H, 7.6; N, 2.85%; M, 375.2410).

6,7-*Dimethoxy*-4-(3,4-*dimethoxyphenethyl*)*isochroman*-3-*one* (**18**).—A solution of 6,7-dimethoxyisochroman-3-one (1.05 g) and hexacarbonylchromium (1.35 g) in dry THF (50 cm^3) under dry nitrogen, was heated at reflux overnight. The mixture was then cooled to 0 °C and a solution of lithium di-isopropylamide (1.1 mol. equiv.) and HMPT (1 cm^3) in THF (5 cm^3) was added dropwise. After 1 h, a solution of 3,4-dimethoxyphenethyl bromide (2.5 g) in THF (3 cm^3) was added quickly. The reaction mixture was allowed to warm to room temperature overnight, and then opened to the air and stirred for a further 4 h. The resulting dark green product was poured into 2M-hydrochloric acid (200 cm^3) and the aqueous phase separated and extracted with ethyl acetate (3 × 100 cm^3). The combined extracts were washed with water (25 cm^3) and brine (2 × 25 cm^3), dried and evaporated to give a dark coloured oil which was subjected to short path chromatography on silica eluting with ethyl acetate–light petroleum, b.p. 60—80 °C (1:5). The first fractions yielded 6,7-dimethoxyisochroman-3-one (0.35 g, 33% recovery) and later fractions a mixture of two components of closely similar R_F value. Separation of this mixture into the title compound (0.87 g, 47%; 70% corrected) and its 4-hydroxy derivative (**23**) (0.39 g, 20%; 30% corrected) was achieved by preparative h.p.l.c. using a Waters 500A system utilising one C18 reverse phase cartridge. The hydroxy compound was the first product off the column; both were obtained as colourless gums.

Compound (**18**) showed $\nu_{max.}$ 2 980 and 1 740 cm^{-1}; $\delta_H(CDCl_3)$ δ 6.78 (m, 3 H, 2′-H, 5′-H, 6′-H), 6.72, 6.66 (2 × s, 2 × 1 H, 5-H, 8-H), 5.28 (AB dd, 2 H, J 14 Hz, 1-H_2), 3.88 (s, 12 H, 4 × OMe), 3.60 (t, 1 H, J 7 Hz, 4-H), 2.76 (t, 2 H, J 7 Hz, ArCH_2CH_2), and 2.20 (q, 2 H, J 7 Hz, ArCH_2CH_2); δ_C 172.5 (s, C-3), 149.5, 149.2, 148.4, 147.7 (4 × s, C-3′, C-4′, C-6, C-7), 126.9, 123.4, 120.4 (3 × s, C-1′, C-4a, C-8a), 120.4, 112.2, 111.7, 110.0, 108.4 (5 × d, C-2′, C-5, C-5′, C-6′, C-8), 69.4 (t, C-1), 55.9 (q, 4 × OMe), 44.9 (d, C-4), 32.8 (t, ArCH_2CH_2), and 32.5 (t, ArCH_2CH_2); m/z 372 (M^+, 100%) and 208 (50) (Found: C, 67.8; H, 6.75. $C_{21}H_{24}O_6$ requires C, 67.7; H, 6.45%).

Compound (**23**) showed $\nu_{max.}$ 3 500 and 1 750 cm^{-1}; $\delta_H(CDCl_3)$ 7.24 (s, 1 H, 5-H), 6.84—6.60 (m, 4 H, 2′-H, 5′-H, 6′-H, 8-H), 5.40 (AB dd, 2 H, J 14 Hz, 1-H_2), 3.96, 3.88, 3.86 (3 × s, 12 H, 4 × OMe), 2.68 (t, 2 H, J 8 Hz, ArCH_2CH_2), and 2.04 (t, 2 H, J 8 Hz, ArCH_2CH_2); δ_C 175 (s, C-3), 149.8, 149.0, 148.9, 147.6 (4 × s, C-3′, C-4′, C-6, C-7), 133.4, 129.5, 120.9 (3 × s, C-1′, C-4a, C-8a), 120.2, 112.0, 111.7, 108.0, 107.5 (5 × d, C-2′, C-5, C-5′, C-6′, C-8), 72.9 (s, C-4), 70.0 (t, C-1), 56.2 (q, 4 × OMe), 40.2 (t, ArCH_2CH_2), and 29.4 (t, ArCH_2CH_2); m/z 388 (M^+, 100), 224 (80), and 208 (18).

8,9-*Dihydro*-2,11,12-*trimethoxybenzo*[c]*naphtho*[1,2-d]-*pyran*-3,7(5H,7aH)-*dione* (**26**).—A solution of the isochromanone (**18**) (0.93 g) in dry acetonitrile (500 cm^3) containing anhydrous sodium perchlorate (6.5 g) protected under a nitrogen atmosphere was oxidised at a platinum anode until 2 F mol^{-1} of current had been consumed. Water was then added, the acetonitrile removed under reduced pressure and the residual aqueous phase extracted with dichloromethane (3 × 100 cm^3). The combined extracts were dried and evaporated to yield a red gum which was chromatographed on silica eluting with dichloromethane to afford the *title compound* as a colourless solid (0.54 g) 61%, m.p. 210—212 °C; $\nu_{max.}$($CHCl_3$) 1 730, 1 665, and 1 640 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 6.65, 6.60 (2 × s, 10-H, 13-H), 6.20 (s, 1 H, 1-H), 6.05 (s, 1 H, 4-H), 4.73 (AB dd, 2 H, J 13 Hz, 5-H_2), 3.87, 3.70 (2 × s, 2 × 3 H, 11-OMe, 12-OMe), 3.65 (s, 3 H, 2-OMe), 3.05 (dd, 1 H, J_1 17, J_2 7 Hz, 9-H_β), 2.96 (t, 1 H, J 4 Hz, 7a-H), 2.80 (m, 1 H, 9-H_α), 2.71 (m, 1 H, 8-H_β), and 2.18 (m, 1 H, 8-H_α); δ_C 180.1 (s, C-3), 169.1 (s, C-7), 154.4, 149.4, 148.6 (3 × s, C-2, C-11, C-12), 128.6, 124.1 (2 × s, C-9a, C-13a), 127.8, 120.5 (2 × d, C-1, C-4), 112.6, 108.9 (2 × d, C-10, C-13), 69.3 (t, C-5), 56.1, 55.8, 55.1 (3 × q, 3 × OMe), 46.9 (d, C-7a), 44.7 (s, 13b-C), and 25.0, 21.8 (2 × t, C-9, C-8); m/z 356 (M^+, 100%) (Found: C, 67.7; H, 5.7. $C_{20}H_{20}O_6$ requires: C, 67.8; H, 5.65%).

4a,5,7,8-*Tetrahydro*-4a-*hydroxymethyl*-2,10,11-*trimethoxy*-5-*methylnaphth*[2,1-c]*indole*-3,6(4H,6aH)-*dione* (**30**).—The dione (**26**) (0.15 g) in ethanol (10 cm^3) containing 33% methylamine was heated under reflux for 3 h, then cooled and evaporated under reduced pressure. The residue was subjected to chromatography on silica eluting with ethyl acetate to yield the title compound as colourless prisms (0.16 g, 100%), m.p. 252—254 °C, $\nu_{max.}$ 3 350 and 1 650 cm^{-1}; δ_H [400 MHz; $(CD_3)_2SO$] 6.89, 6.75 (2 × s, 2 H, 9-H, 12-H), 5.46 (s, 1 H, 1-H), 4.94 (t, 1 H, J 5 Hz, exchanged with D_2O, CH_2OH), 3.80, 3.71 (2 × s, 2 × 3 H, 10-OMe, 11-OMe), 3.44 (s, 3 H, 2-OMe), 3.33, 3.15 (2 × dd, 2 H, J_1 12, J_2 5 Hz, CH_2OH), 3.15, 2.95 (2 × d, 2 H, J 17 Hz, 4-H_2), 2.73 (m, 2 H, 8-H_2), 2.70 (s, 3 H, NMe), 2.59 (dd, 1 H, J_1 12, J_2 6 Hz, 6a-H), and 2.00 (m, 2 H, 7-H_2); δ_C 190.8 (s, C-3), 173.5 (s, C-6), 148.0, 147.6, 147.3 (3 × s, C-2, C-10, C-11), 129.6, 123.5 (2 × s, C-8a, C-12a), 125.7 (d, C-1), 113.2, 112.0 (2 × d, C-9, C-12), 67.3 (s, C-4a), 65.4 (t, CH_2OH), 56.1, 55.3, 54.6 (3 × q, 3 × OMe), 49.7 (d, C-6a), 46.3 (s, C-12b), 41.3 (t, C-4), 27.2, 23.3 (2 × t, C-7, C-8), and 25.7 (q, NMe); m/z (c.i.) 388 (M^+ + 1, 100%) (Found: C, 67.1; H, 6.4; N, 4.0. $C_{20}H_{23}NO_5$ requires: C, 67.2; H, 6.4; N, 3.9%).

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