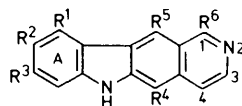


Synthesis of 8,9,10-Trimethoxyellipticine

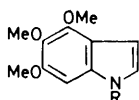
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4,5,6-Trimethoxyindole was synthesised by three independent routes and condensed with hexane-2,5-dione to give 1,4-dimethyl-5,6,7-trimethoxycarbazole. Formylation of the latter gave a mixture including the 3-formyl derivative which was converted into 8,9,10-trimethoxyellipticine by the modified Pomerantz-Fritsch annelation procedure.

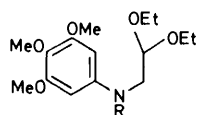
ELLIPTICINE (1) and 9-methoxyellipticine (2) were among four alkaloids first isolated from the plant *Ochrosia elliptica* Labill (family Apocynaceae), a tropical evergreen, in 1959.¹ After the discovery of anti-tumour activity in ellipticine and olivacine (3),² interest developed in the synthesis of ellipticine analogues and derivatives³ and the subject has received continuous attention for many years. In particular, the biological activity of 9-methoxy- and 9-hydroxy-ellipticines⁴ focused attention on ring-A oxygenated derivatives. There are



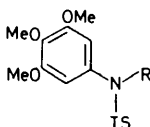
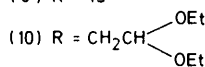
- (1) $R^1 = R^2 = R^3 = R^6 = H, R^4 = R^5 = Me$
 (2) $R^1 = R^3 = R^6 = H, R^2 = OMe, R^4 = R^5 = Me$
 (3) $R^1 = R^2 = R^3 = R^5 = H, R^4 = R^6 = Me$
 (4) $R^1 = R^2 = R^6 = H, R^3 = OMe, R^4 = R^5 = Me$
 (5) $R^1 = R^6 = H, R^2 R^3 = OCH_2O, R^4 = R^5 = Me$
 (6) $R^1 = R^2 = R^3 = OMe, R^4 = R^5 = Me, R^6 = H$



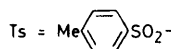
- (7) $R = H$
 (11) $R = Ts$



- (8) $R = H$
 (9) $R = Ts$



- (12) $R = H$
 (13) $R = CH_2CHO$



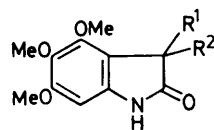
difficulties inherent in the synthesis of, for example, 8-methoxyellipticine (4)² or 8,9-methylenedioxyellipticine (5),⁵ but in this paper we describe the synthesis of the novel trimethoxyellipticine (6) by a conventional approach.⁶ The very low yield achieved and the problems encountered in obtaining a pure final product, however, re-emphasise the need for a genuinely successful general synthetic route.

Following earlier work^{2,7} we required 4,5,6-trimethoxyindole (7) as a starting material. In our first approach, 3,4,5-trimethoxyaniline was condensed with bromoacetaldehyde diethyl acetal to give the acetal (8). Earlier work⁷ had shown that even the 5-methoxyanalogue of (8) had largely decomposed during attempted cyclisation, so that the acetal (8) was converted directly into its *N*-tosyl derivative (9) in 20% overall yield from

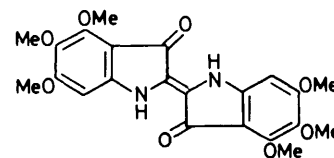
the aniline. A small amount of the disubstituted derivative (10) was also isolated from the condensation; its structure followed directly from its spectroscopic properties. By analogy with our modified isoquinoline synthesis,⁸ treatment of the *N*-tosyl derivative (9) with dilute hydrochloric acid in dioxan gave the *N*-tosylindole (11) (40%). In some preparations the sulphonamide (12)⁹ was a by-product; it was identical in all respects to a sample prepared directly from 3,4,5-trimethoxyaniline. T.l.c. analysis of the reaction mixture revealed a third component whose ¹H n.m.r. [broad singlets at τ 0.3 (CHO) and 5.8 (NCH₂CHO)] and i.r. [1733 cm⁻¹ (CHO)] spectra showed it to be the aldehyde (13). A sample of (13), isolated by preparative t.l.c., on treatment with dry HCl in ethanol was converted (t.l.c.) into a mixture of the indole (11), acetal (9), and the sulphonamide (12). Hence, as in the isoquinoline series,⁸ the aldehyde is an intermediate in the formation of both the cyclic nitrogen heterocycle and the sulphonamide.

Finally, base hydrolysis of the *N*-tosylindole (11) gave the required indole (7) (30%). The low overall yield in this procedure made an alternative synthesis desirable.

Condensation of 3,4,5-trimethoxyaniline with diethyl oxomalonate gives¹⁰ the hydroxy-ester (14) in high yield, and this can be oxidised to the isatin (15) in much lower yield.¹⁰ We found that the yield in the oxidation was improved to 60% by use of a longer heating period. Reduction of the isatin with lithium aluminium hydride in pyridine affords the indole (7) in 47% yield,¹¹ but in our hands, using tetrahydrofuran and an atmosphere of nitrogen or argon, this was improved to 86–92%. In the earlier preparation¹¹ and in the present work the formation of a blue contaminant was observed. This



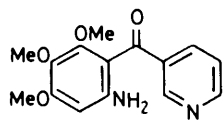
- (14) $R^1 = OH, R^2 = CO_2Et$
 (15) $R^1 R^2 = O$



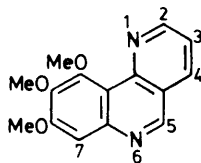
(16)

product, typically *ca.* 4% of the yield of indole, after separation by chromatography, was collected from several preparations and crystallised as the novel indigo (16); it presumably resulted from an intermediate trimethoxyindoxyl. The f.d. mass spectrum gave only two ions, the major one at m/z 442 (M^+) with a minor one (12%) at m/z 221. The ¹H n.m.r. spectrum showed only

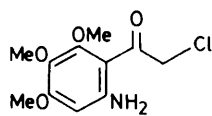
three OMe singlets (τ 5.89, 6.1, and 6.3) besides the NH and remaining aromatic hydrogen singlets at τ 0.06 (broad) and 3.38 respectively. Finally, in the i.r. spectrum the C=O stretching frequency ($1\ 610\ \text{cm}^{-1}$, KBr disc) was identical with that of an authentic sample of indigo itself, thus confirming the *trans* configuration shown.



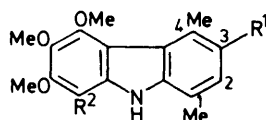
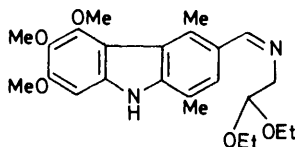
(17)



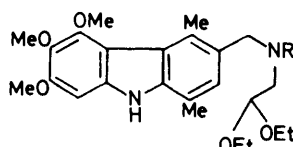
(18)



(19)

(20) $R^1 = R^2 = H$ (21) $R^1 = \text{CHO}, R^2 = H$ (22) $R^1 = H, R^2 = \text{CHO}$ (23) $R^1 = R^2 = \text{CHO}$ 

(24)

(25) $R = H$ (26) $R = \text{TS}$

In one of the less successful attempts to reduce the isatin (15) with lithium aluminium hydride in pyridine, a further contaminant (0.5%) was obtained together with the indole (13%) and the indigo (0.6%). This component was identified from its spectra as the ketone (17). The mechanism of its formation is unclear but its structure was confirmed by synthesis, using the procedure of Sugasawa *et al.*¹² for *ortho*-substitution of anilines. Thus, 3-cyanopyridine reacted with 3,4,5-trimethoxyanilino-dichloroborane (produced *in situ* from the aniline and boron trichloride) to give the ketone (17), in 42% yield, together with a by-product believed to be the 1,6-phenanthroline derivative (18). The mass spectrum of (18) showed only two major ions at m/z 270.1009 (M^+ , $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$ requires 270.1004, 35%) and 255 (100%) and the structure was consistent with the ^1H n.m.r. spectrum (τ 0.76, dd, J 2 and 5 Hz, 2-H; 0.84, s, 5-H; 1.72, dd, J 2 and 8 Hz, 4-H; 2.35–2.54, m, 3-H; 2.49, s, 7-H). These chemical shifts compared well with those for the corresponding protons in the unsubstituted 1,6-phenanthroline.¹³

The final preparation of the trimethoxyindole, based

on Sugasawa's work,¹⁴ proved to be easily the most efficient of those attempted. 3,4,5-Trimethoxyaniline was treated with boron trichloride followed by chloroacetonitrile to give the rather unstable intermediate (19). This was not fully characterised, but was reduced by sodium borohydride to the indole (7) in 62% overall yield.

The indole (7) was condensed with hexane-2,5-dione in the presence of *p*-toluenesulphonic acid to give the trimethoxycarbazole (20) (35%) as the only isolable product after preparative t.l.c. The mass spectrum (M^+ , 285) and the ^1H n.m.r. spectrum (see Experimental section) fully supported its structure. Formylation of the carbazole (20) with *N*-methylformanilide and phosphoryl chloride in trichloroethylene gave a mixture of the 3-formyl- (21), 8-formyl- (22), and 3,8-diformyl- (23) carbazoles. When the reaction was monitored by h.p.l.c. no obvious order of formylation was evident but, as expected, the diformyl derivative was always the minor product. The 3-formyl derivative (21), which showed the expected change in its ^1H n.m.r. spectrum compared with that of the parent carbazole (20), was obtained in 46% yield based on the carbazole.

Condensation of the 3-formyl derivative (21) with aminoacetaldehyde diethyl acetal in benzene afforded the oily Schiff's base (24) in quantitative yield, but because of its tendency to hydrolyse this was hydrogenated directly over platinum oxide to give the crystalline amine (25) (89%). The mass spectrum showed M^+ 430 and a base peak at m/z 298 corresponding to cleavage of the aminoacetal β to the aromatic system. The amine (25), on treatment with tosyl chloride in dry pyridine, gave the *N*-tosylaminoacetal (26) in virtually quantitative yield.

Treatment of the *N*-tosyl compound (26) with 6*N*-hydrochloric acid in dioxan under reflux for 6 h⁷ led to the crude product (6). Crystallisation from methanol-chloroform gave a very small yield of pure trimethoxyellipticine (6) which was characterised spectroscopically. The ultraviolet spectrum compared well with that of unsubstituted ellipticine allowing for the expected bathochromic shift of some peaks and the mass spectrum showed M^+ 336.1462 ($\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ requires 336.1474). In the ^1H n.m.r. spectrum, singlets (each 3H) at τ 7.28, 6.5, 6.03, 6.0, and 5.9 could be assigned to the 5- and 11-methyl and 8-, 9-, and 10-methoxy-groups respectively. The 1-, 6-, and 7-hydrogens gave singlets (each 1 H) at τ 0.32, 2.0 (broad), and 3.2, respectively, whilst the 3- and 4-hydrogens appeared as two doublets (J 9 Hz) at τ 2.16 and 1.45. Material obtained from the mother-liquors after this crystallisation contained predominantly (t.l.c.) the required product. This was subjected to preparative t.l.c. followed by h.p.l.c. in an attempt to obtain more pure product. Eventually a further sample of the alkaloid was obtained, chromatographically and spectroscopically similar to the first specimen, but showing a slight impurity (m/z 352 and 350, 4%). These ions, probably of composition $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4$ and $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_4$, might be due to the C-11 CH_2OH and CHO analogues.

In view of the heavy loss of material on crystallisation and chromatography, purification of the crude material by sublimation was also attempted. However, the sublimate again contained the impurity mentioned above and its ^1H n.m.r. spectrum showed contamination in the aromatic region.

We conclude that the purest material was the crystalline sample. This appears to be stable (over 6 months) as a crystalline solid. Solutions, however, tend to darken with time and we believe that the difficulties encountered during the attempted purification by chromatography are due, at least in part, to decomposition. Sublimation, although satisfactory for the unsubstituted ellipticine,⁷ is not suitable for the trimethoxy-derivative.

EXPERIMENTAL

U.v. (in ethanol), i.r. and n.m.r. (in CDCl_3), and mass spectra (electron impact) were measured as described previously⁸ unless stated otherwise. Light petroleum refers to a fraction of boiling range 40–60 °C unless described otherwise.

N-(3,4,5-Trimethoxyphenyl)aminoacetaldehyde Diethyl Acetal (8).—3,4,5-Trimethoxyaniline, (2.93 g, 0.016 mol), bromoacetaldehyde diethyl acetal (4.73 g, 0.048 mol), anhydrous sodium carbonate (1.7 g, 0.016 mol) and potassium iodide (0.49 g, 0.003 mol) in *n*-butanol (16 ml) were refluxed under nitrogen with vigorous stirring for 4 h. T.l.c. then indicated unchanged aniline and further bromoacetaldehyde diethyl acetal (1.58 g, 0.016 mol) was added and heating continued for a further 1.5 h. After cooling, inorganic salts were filtered off and removal of the solvent under reduced pressure afforded a dark brown oil (6.0 g). Extraction with light petroleum and then ether gave two fractions which, after washing with water and dilute sodium carbonate solution showed similar t.l.c. patterns. Removal of solvent afforded a brown oil (total 3.25 g) from the combined fractions. Part of the product was purified by preparative t.l.c.; elution with ether–light petroleum (1 : 1 v/v) gave (at R_F 0.2) the unstable acetal (8) (8%), τ 4.13 (2 H, s, 2 \times ArH), 5.35 [1 H, t, J 5.5 Hz, $\text{CH}(\text{OEt})_2$], 6.22 (6 H, s, 2 \times OMe), 6.28 (3 H, s, OMe), 6.00–6.71 (5 H, m, NH and 2 \times OCH_2CH_3), 6.82 (2 H, d, J 5.5 Hz, CH_2CH), and 8.80 (6 H, t, J 7 Hz, 2 \times CH_2CH_3), m/z 299 (M^+ , 100%), 196 (35), 103 (92), 75 (56), and 46 (77). Recovery of the material at R_F 0.4 gave the crude trisubstituted amine (10) as a yellow oil which solidified. Repetition of the preparative t.l.c. afforded *N*-(2,2-diethoxyethyl)-*N*-(3,4,5-trimethoxyphenyl)aminoacetaldehyde diethyl acetal (10) as a yellow solid, m.p. 67–70.5 °C, τ 3.93 (2 H, s, ArH), 5.34 [2 H, t, J 5 Hz, 2 \times $\text{CH}(\text{OEt})_2$], 6.18 (6 H, s, 3- and 5-OMe), 6.24 (3 H, s, 4-OMe), 6.0–6.6 (12 H, m, 4 \times OCH_2CH_3 and 2 \times CH_2CH), and 8.81 (12 H, t, J 7 Hz, 4 \times OCH_2CH_3), m/z 415 (M^+ , 38%), 312 (79), 299 (19), 266 (29), 248 (21), 220 (25), 196 (21), 195 (22), 180 (19), 103 (100), 75 (94), and 59 (23) (Found: M^+ , 415.2568. $\text{C}_{21}\text{H}_{37}\text{NO}_7$ requires M , 415.2570).

N-(*p*-Tolylsulphonyl)-*N*-(3,4,5-trimethoxyphenyl)aminoacetaldehyde Diethyl Acetal (9).—The above acetal (9) (6.0 g, 0.02 mol) and toluene-*p*-sulphonyl chloride (4.2 g, 0.025 mol, freshly crystallised) were stirred at 20 °C for 4.5 days in dry pyridine (30 ml). The mixture was poured into water and extracted with ether (\times 4). The ether solution

was washed with water, 0.2N-hydrochloric acid, and saturated sodium hydrogen carbonate solution before drying (K_2CO_3). Removal of the solvent under reduced pressure gave an oil (6.3 g) which was crystallised from light petroleum. Recrystallisation from ether afforded a pure sample of the *N*-tosyl acetal (9), m.p. 107.5–108 °C, τ 2.55 (4 H, ABq, J 9 Hz, 4 \times ArH of tosyl), 3.72 (2 H, s, 2 \times ArH), 5.33 (1 H, t, J 6 Hz, CHCH_2), 6.16 (3 H, s, OMe), 6.3 (6 H, s, 2 \times OMe), 6.0–6.8 (6 H, m, CHCH_2 and 2 \times OCH_2CH_3), 7.58 (3 H, s, ArMe), and 8.85 (6 H, t, J 7 Hz, 2 \times OCH_2CH_3), m/z 453 (M^+ , 5%), 408 (1), 362 (1.5), 298 (2), 202 (5), 200 (4), 195 (3), 180 (5), 152 (2), 104 (8), 103 (100), 91 (3), 75 (39), 59 (2), and 47 (27) (Found: C, 58.9; H, 6.8; N, 3.2. $\text{C}_{22}\text{H}_{31}\text{NO}_5\text{S}$ requires C, 58.3; H, 6.9; N, 3.1%).

Cyclisation of the N-Tosyl Acetal (9).—To the above acetal (9) (274 mg, 0.6 mmol) in dioxan (3 ml) was added 6N-hydrochloric acid (0.14 ml) and the mixture was heated under reflux for 1.5 h. After cooling, the mixture was poured into water (100 ml) and extracted with ether (100 ml + 4 \times 50 ml). After washing with saturated sodium hydrogencarbonate solution (2 \times 100 ml) and water (2 \times 100 ml) and drying (Na_2CO_3), removal of the solvent gave a light brown solid (181 mg) which on t.l.c. showed 3 components. The product of 2 preparations was purified by preparative t.l.c. using ether–light petroleum (1 : 1 v/v). The main component (R_F 0.7) gave, on extraction, an off-white solid (184.3 mg, 40%), m.p. 138–146 °C. Crystallisation from chloroform afforded 4,5,6-trimethoxy-*N*-(*p*-tolylsulphonyl)indole (11) as crystals, m.p. 139–141 °C, τ 2.54 (4 H, ABq, J 9 Hz, 4 \times ArH of tosyl group), 2.72 (1 H, s, 7-H), 2.66 (1 H, d, J 4 Hz, 2-H), 3.55 (1 H, d, J 4 Hz, 3-H), 6.03, 6.1, and 6.19 (9 H, 3s, 3 \times OMe), and 7.69 (3 H, s, ArMe), λ_{max} 222 (ϵ 54 480) and 257.5 nm (28 674), m/z 361 (M^+ , 42%), 346 (6), 207 (18), 206 (100), 191 (21), 176 (7), 148 (15), 133 (11), and 91 (9) (Found: C, 59.6; H, 5.3; N, 3.7. $\text{C}_{18}\text{H}_{19}\text{NO}_5\text{S}$ requires C, 59.8; H, 5.3; N, 3.9%). The second component of R_F 0.2 was isolated as an oil (37.3 mg, 9%) which later solidified. Crystallisation from chloroform–light petroleum gave the sulphonamide (12) as crystals, m.p. 141–142 °C (lit.,⁹ 132 °C), identical in its spectroscopic properties and by mixed m.p. 140.5–142.5 °C with the product from an unambiguous synthesis, m.p. 141.5–142.5 °C (see below). In a similar experiment, it was possible to isolate significant quantities of the third component, the aldehyde (13) of R_F 0.1. This was obtained as a solid τ 0.3 (1 H, t, J 1.5 Hz, CHO), 2.62 (4 H, ABq, J 9 Hz, 4 \times ArH of tosyl group), 3.73 (2 H, s, 2 \times ArH), 5.81 (2 H, d, J 1.5 Hz, NCH_2), 6.2 (3 H, s, OMe), 6.33 (6 H, s, 2 \times OMe), and 7.60 (3 H, s, ArMe), ν_{max} (CHCl_3) 1 733 cm^{-1} .

3,4,5-Trimethoxy-*N*-(*p*-tolylsulphonyl)aniline (12).—3,4,5-Trimethoxyaniline (0.5 g, 2.73 mmol) in dry pyridine (5 ml) was treated with toluene-*p*-sulphonyl chloride (0.57 g, 3 mmol) and the mixture stirred at 20 °C for 24 h. The mixture was poured into water (25 ml), extracted into ether (6 \times 10 ml) and the combined extracts were washed with 0.1N-hydrochloric acid (10 \times 5 ml), saturated sodium hydrogencarbonate (2 \times 5 ml) and water (2 \times 5 ml) before drying (K_2CO_3). Removal of the solvent gave the crude product (0.215 g, 24%) m.p. 128–141 °C. Crystallisation from chloroform–light petroleum (b.p. 30–40 °C) afforded the sulphonamide (12) m.p. 141.5–142.5 °C. Recrystallisation gave an analytical sample, m.p. 142–143 °C, τ 2.57 (4 H, ABq, J 9 Hz, 4 \times ArH of tosyl group), 3.02 (1 H, s, NH), 3.71 (2 H, s, 2 \times ArH), 6.28 (3 H, s, OMe), 6.33 (6 H,

s, 2 × OMe), and 7.67 (3 H, s, ArMe), m/z 338 ($M^+ + 1$, 5%), 337 (M^+ , 31), 322 (6), and 182 (100) (Found: C, 57.0; H, 5.7; N, 3.9. Calc. for $C_{16}H_{19}NO_5S$: C, 57.0; H, 5.7; N, 4.1%).

Hydrolysis of the *N*-Tolylsulphonylindole (11).—The above tosylindole (11) (31.7 mg, 6.088 mmol) in methanol (5.2 ml) was treated with 2*M*-sodium hydroxide (0.52 ml) and the mixture heated under reflux for 7 h. On cooling, the mixture was poured onto crushed ice. The aqueous solution was concentrated to small volume, made slightly acid with 1*M*-hydrochloric acid, and extracted with ether. The combined ether extracts were dried (K_2CO_3) and evaporation of the solvent gave 4,5,6-trimethoxyindole (7) (5.5 mg, 30%), m.p. 87–90.5 °C (lit.,¹¹ 101 °C), mixed m.p. 88.5–91.5 °C with an authentic sample prepared essentially as described in the literature¹¹ (m.p. 90–92 °C).

Reduction of 4,5,6-Trimethoxyisatin (15) with Lithium Aluminium Hydride.—The isatin (15) was synthesised from 3-ethoxycarbonyl-3-hydroxy-4,5,6-trimethoxyoxindole (8.3 g, 0.027 mol) essentially by the method of Benington¹⁰ except that the aeration was continued for 2.5 h. Precipitation with formic acid gave the crude isatin (5.58 g, m.p. 178–186 °C). This and a further crop (0.32 g, m.p. 215–224 °C) were combined and recrystallised twice from ethanol to give a total of 3.6 g (60%), m.p. 222–225.5 °C. Recrystallisation from 2-methoxyethanol gave the isatin (15), m.p. 221–225 °C (lit.,¹⁰ 194–195 °C) (Found: C, 55.8; H, 4.7; N, 5.9. Calc. for $C_{11}H_{11}NO_5$: C, 55.7; H, 4.7; N, 5.9%).

The isatin (15) was reduced with lithium aluminium hydride in several experiments essentially as described by Carlsson¹¹ giving after chromatography on basic alumina and crystallisation from benzene–cyclohexane, 4,5,6-trimethoxyindole (7), m.p. 92–93 °C, τ 1.74 br (1 H, s, NH), 3.0 (1 H, t, *J* 2 Hz, H-2), 3.4 (1 H, s, H-7), 3.3–3.5 (1 H, partially obscured m, H-3), and 5.92, 6.14, and 6.18 (9 H, 3 s, 3 × OMe), λ_{max} 221 (ϵ 8 580) and 270 (1 972), m/z 208 ($M^+ + 1$, 27%), 207 (M^+ , 100), 206 (12), 193 (16), 192 (99), 177 (8), 164 (27), 149 (47), 134 (42), 133 (12), 132 (13.5), 116 (6), 106 (8), 104 (18), 78 (12), and 63 (11) (Found: C, 64.0; H, 6.4; N, 6.6. Calc. for $C_{11}H_{13}NO_3$: C, 63.7; H, 6.3; N, 6.8%). If the temperature of the reaction was raised to 60–80 °C the yield of the indole increased to 50–55%. When pyridine was replaced by tetrahydrofuran at temperatures from 20 °C to reflux temperatures under nitrogen or argon, yields of 86–91% were achieved.

4,4',5,5',6,6'-Hexamethoxyindigo (16).—In all of the preparations of 4,5,6-trimethoxyindole from the isatin, after chromatographic separation of the indole, a more polar blue product was eluted in ether. Combination of the products of several preparations and crystallisation from chloroform afforded a pure sample of the indigo (16), m.p. 285–288 °C, τ (CDCl₃–[²H₆]DMSO) 0.06br (2 H, s, 2 × NH), 3.38 (2 H, s, 2 × ArH), 5.89, 6.1, and 6.3 (18 H, 3 s, 3 × 2 × OMe), λ_{max} 291.5 (ϵ 32 100), 374 (15 260), and 593 nm (14 740), ν_{max} (KBr) 3 300 (NH) and 1 610 cm⁻¹ (C=O), m/z (field desorption) 442 (M^+ , 100%) and 221 (12) (Found: C, 59.8; H, 5.1; N, 6.3. $C_{22}H_{22}N_2O_8$ requires C, 59.7; H, 5.0; N, 6.3%).

2-Amino-4,5,6-trimethoxyphenyl 3-Pyridyl Ketone (17).—In one of the reduction reactions of the isatin (15) the yield of indole (7) was very low. After destroying the excess of lithium aluminium hydride with water, and extraction with ether, the aqueous layer was evaporated to dryness and the residue was extracted with boiling ether and hot ethanol. The extracts were combined and the solvent was evaporated

to give a brown oil. This was subjected to preparative t.l.c. (5% v/v methanol–ether) and afforded a yellow oil (32 mg, 0.5%), R_F 0.7. After repeating the t.l.c. the ketone (17) was obtained as a yellow oil which solidified on standing, τ 1.21br (1 H, s, pyridyl 2-H) 1.32 (1 H, partially obscured d, pyridyl 6-H), 2.08 (1 H, dt, *J* 8 and 2 Hz, pyridyl 4-H), 2.66 (1 H, partially obscured m, pyridyl 5-H), 4.02 (1 H, s, 6-H), 4.62br (2 H, s, NH₂), and 6.17, 6.32, and 6.6 (9 H, 3 s, 3 × OMe), ν_{max} (CHCl₃) 3 500, 3 380 (NH₂), and 1 612 cm⁻¹ (C=O), m/z (field desorption) 288 (M^+ 100%), m/z (electron impact) 289 ($M^+ + 1$, 72%), 288 (M^+ , 100), 287 (55), 274 (46), 273 (95), 257 (15), 245 (38), 229 (11), 215 (17), 213 (11), 181 (13), 152 (14), 129 (14), 128 (10), 106 (55), 78 (54), and 51 (20) (Found: M^+ , 288.1101. $C_{15}H_{16}N_2O_4$ requires M , 288.1110).

Synthesis of the Ketone (17).—3,4,5-Trimethoxyaniline (1.8 g, 0.0098 mol) in dry 1,2-dichloroethane (60 ml) was added in portions with stirring to a 3.5% ice-cold solution of BCl₃ in dichloroethane (30 ml) under nitrogen; the aniline–BCl₃ complex separated. To the resultant yellow-green suspension was added a solution of 3-cyanopyridine (2.0 g, 0.0196 mol) in dichloroethylene (40 ml) and then aluminium chloride (1.6 g, 0.012 mol). The mixture was allowed to warm to 20 °C over 1 h during which time most of the complex dissolved, and then heated under reflux for 4 h under nitrogen. Dichloroethylene (20 ml) was added after 1 h. After cooling, ice-cold 2*M*-hydrochloric acid (100 ml) was added and the mixture heated to 80–95 °C for 1 h when all the solids dissolved. The cooled mixture was extracted with chloroform (8 × 100 ml + 20 × 50 ml). The aqueous layer was made alkaline (pH 8) with 2*M*-sodium hydroxide solution and re-extracted with chloroform (10 × 100 ml + 20 × 50 ml). The basic extracts were combined and dried (MgSO₄) and the solvent was evaporated to give a brown oil (2.84 g) which was chromatographed on a column of silica (220 g). The main component was eluted in chloroform–ether (3 : 17 v/v) as a yellow solid (1.19 g, 42%). Crystallisation from ethanol–water gave the ketone (17) as yellow needles; m.p. 114–115.5 °C, λ_{max} 242 (ϵ 15 540), 270sh (8 360), 291 (8 070), and 384 nm (4 918) (Found: C, 62.3; H, 5.6; N, 9.6. $C_{15}H_{16}N_2O_4$ requires C, 62.5; H, 5.6; N, 9.7%). The n.m.r. mass and i.r. spectra closely resembled those of the sample described above.

8,9,10-Trimethoxy-1,6-phenanthroline (18).—Later fractions from the above column chromatography afforded a brown oil (300 mg) which was subjected to preparative t.l.c. [ethanol–chloroform (1 : 50 v/v)]. In addition to the ketone (17) this mixture contained a component of R_F 0.45, obtained initially as a light brown oil. Re-chromatography gave the phenanthroline (18) as an off-white solid (10 mg), m.p. 109–114 °C, τ 0.76 (1 H, dd, *J* 5 and 2 Hz, 2-H), 0.84 (1 H, s, 5-H), 1.72 (1 H, dd, *J* 8, 2, 4-H), 2.35–2.54 (1 H, partially obscured dd, *J* 8 and 5 Hz, 3-H), 2.49 (1 H, s, 7-H), and 5.95 (9 H, s, 3 × OMe), λ_{max} 227 (ϵ 23 785), 235.5 (23 240), 274.5 (23 510), and 320.5 nm (3 510), m/z 270 (M^+ 35%), 256 (13), 255 (100), 241 (19), 227 (18), 225 (11), 224 (31), 212 (40), 197 (27), 184 (23), 167 (11), 156 (12), 155 (11), 154 (13), 141 (50), 128 (20), 105 (13), 90 (18), and 77 (15) (Found: M^+ , 270.1009. $C_{15}H_{14}N_2O_3$ requires M , 270.1004).

2-Amino-4,5,6-trimethoxy- α -chloroacetophenone (19).—A solution of 3,4,5-trimethoxyaniline (0.915 g, 5 mmol) in dry 1,2-dichloroethane (20 ml) was slowly added under nitrogen to a stirred ice-cold 3.5% (w/v) solution of boron trichloride in dry 1,2-dichloroethane (12.4 ml); the aniline–boron trichloride complex separated as a pale green solid.

Chloroacetonitrile (0.4 ml, 0.453 g, 6 mmol) was then added and the mixture was heated under reflux under nitrogen for 3 h. After cooling, ice-cold 2M-hydrochloric acid was added and the mixture was heated to 80–100 °C for 30 min before re-cooling. The pH was adjusted to 4 with 2M-sodium hydroxide solution and the mixture was extracted with chloroform (4 × 50 ml + 2 × 25 ml). The combined extracts were dried (MgSO₄) and the solvent was removed under reduced pressure to give the crude chloroacetophenone as a green oil (1.1 g, 85%) which then showed τ 4.0br (2 H, s, NH₂), 4.09 (1 H, s, ArH), 5.28 (2 H, s, COCH₂Cl), and 6.06, 6.2 and 6.29 (9 H, 3s, 3 × OMe). Preparative t.l.c. followed by crystallisation from chloroform afforded the chloroacetophenone (19), m.p. 85.5–87.5 °C (Found: C, 50.7; H, 5.5; N, 5.2. C₁₁H₁₄ClNO₄ requires C, 50.9; H, 5.4; N, 5.4%). The bulk of the product was used, without purification, for the indole preparation described below.

Cyclisation of the Chloroacetophenone (19) to 4,5,6-Trimethoxyindole (7).—To a stirred solution of the above ketone (19) (0.31 g, 1.2 mmol) in dioxan (5 ml) and water (0.5 ml) was added sodium borohydride (0.05 g, 1.3 mmol) and the mixture was heated under reflux for 1.5 h. After cooling and removal of the solvent under reduced pressure, water (10 ml) was added. The mixture was extracted with chloroform (4 × 15 ml) and the combined extracts were washed with 2M-hydrochloric acid (10 ml) and dried (Na₂SO₄). Removal of the solvent under reduced pressure gave the crude product as a violet oil (0.178 g, 72%). Part of this oil was subjected to preparative t.l.c. [ether–light petroleum (3 : 2 v/v)] and afforded the indole (7) as an off-white solid, m.p. 90.5–92.5 °C, mixed m.p. 89–94 °C with a sample, m.p. 92–93 °C, prepared by reduction of the isatin (15). The ¹H n.m.r. spectrum was identical with that of the earlier sample.

5,6,7-Trimethoxy-1,4-dimethylcarbazole (20).—4,5,6-Trimethoxyindole (0.768 g, 3.71 mmol) and hexane-2,5-dione (0.508 g, 4.45 mmol) were dissolved in ethanol (2.0 ml) containing toluene-*p*-sulphonic acid (0.374 g). The solution was heated under reflux for 1.5 h, cooled, concentrated to about one half of its original volume, diluted with ether (20 ml), and finally shaken with water (20 ml). The aqueous layer was extracted with ether (2 × 20 ml + 3 × 10 ml) and chloroform (20 ml + 3 × 10 ml). The combined ether extracts afforded a green solid (0.934 g) and the chloroform solution gave a green oil (0.555 g). Both samples gave identical t.l.c. patterns and so were combined before preparative t.l.c. (CHCl₃) which afforded a light brown solid (0.37 g, 35%), m.p. 166–174 °C. Two crystallisations from methanol gave the pure carbazole (20) as light brown platelets, m.p. 174.5–176 °C, τ 2.12br (1 H, s, NH) 3.05 (2 H, ABq, *J* 7 Hz, 2- and 3-H), 3.31 (1 H, s, 8-H), 5.99 (3 H, s, OMe), 6.13 (6 H, s, 2 × OMe), 7.12 (3 H, s, 4-Me), and 7.58 (3 H, s, 1-Me), λ_{max} 245 (ϵ 42 860), 254sh (31 550), 264sh (16 070), 287sh (10 120), 295.5 (15 330), 320 (3 720), and 333 nm (3 420), *m/z* 286 (*M* + 1, 32%), 285 (*M*⁺, 100), 284 (18), 271 (26), 270 (99), 227 (33), 212 (31), 143 (16), 135 (18), and 128 (27) (Found: C, 71.5; H, 6.8; N, 4.8. C₁₇H₁₉NO₃ requires C, 71.6; H, 6.7; N, 4.9%).

Formylation of the Carbazole (20).—To the above carbazole (20) (490 mg, 1.72 mmol) was added a solution of *N*-methylformanilide (279 mg, 2.06 mmol) and phosphoryl chloride (290 mg, 1.89 mmol) in trichloroethylene (1.2 ml) and the mixture was heated under reflux for 3.5 h before cooling. A solution of sodium acetate (580 mg) in water (3 ml) was added and the trichloroethylene and *N*-methyl-

aniline were removed by steam distillation. The brown oily residue was extracted into chloroform (10 ml) and the aqueous layer was extracted again (25 ml + 2 × 10 ml). The combined chloroform extracts were dried (K₂CO₃) and the solvent was removed under reduced pressure to give a brown oil (0.678 g). Preparative t.l.c. [ether–light petroleum (4 : 1 v/v)] gave three major components of *R_F* 0.95, 0.85, and 0.35. The first was obtained as a yellow solid (200 mg, 37%) which was crystallised twice from light petroleum to give 8-formyl-5,6,7-trimethoxy-1,4-dimethylcarbazole (22) as yellow needles, m.p. 94–95.5 °C, τ –0.49br (1 H, s, NH), –0.37 (1 H, s, CHO), 3.04 (2 H, ABq, *J* 7.5 Hz, 2- and 3-H), 5.92, 5.94, and 6.15 (9 H, 3s, 3 × OMe), 7.19 (3 H, s, 4-Me), and 7.53 (3 H, s, 1-Me), λ_{max} 233 (ϵ 88 400), 268 (38 900), 296 (29 830), 332 (13 260), and 385 nm (7 740), ν_{max} (CHCl₃) 3 416 (NH) and 1 652 cm^{–1} (CHO), *m/z* 314 (*M*⁺ + 1, 22%), 313 (*M*⁺, 100), 299 (9), 298 (49), 255 (6), 240 (6), and 157 (10) (Found: C, 68.9; H, 6.2; N, 4.5. C₁₈H₁₉NO₄ requires C, 69.0; H, 6.1; N, 4.5%).

The second component (*R_F* 0.85) was collected as a yellow solid (70 mg, 12%) which crystallised from chloroform–ether to afford 3,8-diformyl-5,6,7-trimethoxy-1,4-dimethylcarbazole (23) as yellow crystals, m.p. 175–176 °C, τ –0.75br (1 H, s, NH), –0.47 (1 H, s, CHO), –0.41 (1 H, s, CHO), 2.25 (1 H, s, 2-H), 5.87 (6 H, s, 2 × OMe), 6.1 (3 H, s, OMe), 6.77 (3 H, s, 4-Me), and 7.47 (3 H, s, 1-Me), λ_{max} 257 (ϵ 33 660), 308.5 (27 800), and 380 (11 710), ν_{max} (CHCl₃) 3 410 (NH) and 1 660 cm^{–1} (CHO), *m/z* 342 (*M*⁺ + 1, 33%), 341 (*M*⁺, 99), 327 (24), 326 (100), 283 (12), and 268 (14) (Found: C, 66.6; H, 5.7; N, 4.1. C₁₉H₁₉NO₅ requires C, 66.85; H, 5.6; N, 4.1%).

The third component (*R_F* 0.35) was isolated as a light brown solid (245 mg, 46%), m.p. 194–198.5 °C. Two crystallisations from chloroform gave 3-formyl-5,6,7-trimethoxy-1,4-dimethylcarbazole (21), m.p. 197–198 °C, τ –0.50 (1 H, s, CHO), 1.73br (1 H, s, NH), 2.3 (1 H, s, 2-H), 3.24 (1 H, s, 8-H), 6.0 (3 H, s, OMe), 6.1 (6 H, s, 2 × OMe), 6.7 (3 H, s, 4-Me), and 7.52 (3 H, s, 1-Me), λ_{max} 241 (ϵ 27 480), 256.5 (21 000), 284.5 (45 140), 293sh (39 150), and 337 nm (14 460), ν_{max} (CHCl₃) 3 470 (NH) and 1 663 cm^{–1} (CHO), *m/z* 314 (*M*⁺ + 1, 19%), 313 (*M*⁺, 100), 299 (13), 298 (62), 255 (18), 240 (6), and 149 (14) (Found: C, 69.1; H, 6.3; N, 4.5. C₁₈H₁₉NO₄ requires C, 69.0; H, 6.1; N, 4.5%).

3-(2,2-Diethoxyethyliminomethyl)-5,6,7-trimethoxy-1,4-dimethylcarbazole (24).—A mixture of the above carbazole (21) (190 mg, 0.61 mmol) and aminoacetaldehyde diethyl acetal (96 mg, 0.72 mmol) was heated on a steam-bath for 2 h. Dry benzene was added and water was removed by azeotropic distillation. Evaporation of solvent under vacuum gave the iminomethylcarbazole (24) as a yellow oil (301 mg, 100%) slightly contaminated by unchanged aminoacetaldehyde diethyl acetal, τ 1.17 (1 H, s, CH=N), 1.49br (1 H, s, NH), 2.23 (1 H, s, 2-H), 3.3 (1 H, s, 8-H), 5.17 [1 H, t, *J* 5 Hz, CH(OEt)₂], 6.02, 6.11, and 6.13 (9 H, 3 s, 3 × OMe), 6–6.6 (6 H, m, 2 × OCH₂CH₃ and CH₂CH), 6.94 (3 H, s, 4-Me), 7.58 (3 H, s, 1-Me), and 8.8 (6 H, t, *J* 7 Hz, 2 × OCH₂CH₃), ν_{max} (CHCl₃) 3 475 (NH) and 1 632 cm^{–1} (CH=N), *m/z* 429 (*M*⁺ + 1, 14%), 428 (*M*⁺, 55), 383 (8), 353 (16), 325 (14), 103 (100), 75 (73), and 47 (68). Attempts to purify the oil further led to hydrolysis and the material was used without further purification.

3-(2,2-Diethoxyethylaminomethyl)-5,6,7-trimethoxy-1,4-dimethylcarbazole (25).—The above imine (24) (249 mg, 0.58 mmol) in absolute ethanol (5 ml) was hydrogenated over platinum oxide (15 mg) at atmospheric pressure. The

solution was filtered through Celite and the solvent was evaporated under reduced pressure to give a brown oil (222 mg, 89%). This was extracted with light petroleum and the solution was concentrated to yield the *amino-methylcarbazole* as pale cream crystals, m.p. 112–116 °C, τ 2.12br (1 H, s, carbazole NH), 2.9 (1 H, s, 2-H), 3.3 (1 H, s, 8-H), 5.36 [1 H, t, J 6 Hz, $\text{CH}(\text{OEt})_2$], 6.02 and 6.12 (11 H, 2 s, 3 \times OMe and ArCH_2N), 6.2–6.7 (4 H, m, 2 \times OCH_2CH_3), 7.06 (3 H, s, 4-Me), 7.19 (2 H, d, J 6 Hz, CH_2CH), 7.59 (3 H, s, 1-Me), 8.49 (1 H, s, CH_2NH), and 8.83 (6 H, t, J 7 Hz, 2 \times OCH_2CH_3), λ_{max} 247.5 (ϵ 115 190), 225sh (94 940), 267 (52 790), 292sh (26 900), 299 (38 290), 323 (10 130), and 336.5 nm (8 990), ν_{max} (CHCl_3) 3 479 and 3 330 cm^{-1} (NH), m/z 430 (M^+ , 9%), 299 (25), 298 (100), 297 (87), 103 (25), 75 (17), and 47 (25) (Found: C, 67.0; H, 8.0; N, 6.5. $\text{C}_{24}\text{H}_{34}\text{N}_2\text{O}_5$ requires C, 67.0; H, 8.0; N, 6.5%).

3-(2,2-Diethoxyethyl-N-*p*-tolylsulphonyl)-5,6,7-trimethoxy-1,4-dimethylcarbazole (26).—The above amine (25) (244 mg, 0.567 mmol) was dissolved in dry pyridine (6 ml) and freshly crystallised toluene-*p*-sulphonyl chloride (130 mg, 0.681 mmol) was added. The solution was stirred at room temperature for 92 h, poured into water (20 ml), and extracted with ether (4 \times 25 ml + 6 \times 20 ml). The combined ether extracts were washed with 0.5M-HCl (25 ml and 10 ml), dried (MgSO_4), and evaporated to leave the crude product. Extraction with ether and evaporation gave a cream solid which was recrystallised from ethyl acetate–light petroleum, twice from ether, and then from ethyl acetate to afford the *N-p*-tolylsulphonyl compound (26), m.p. 154.5–158 °C, τ 2.1br (1 H, s, NH), 2.28 and 2.78 (4 H, ABq, J 8 Hz, 4 \times ArH of tosyl group), 3.11 (1 H, s, 2-H), 3.29 (1 H, s, 8-H), 5.38 (2 H, s, ArCH_2N), 5.6 [1 H, t, J 6 Hz, $\text{CH}(\text{OEt})_2$], 6.07 (3 H, s, OMe), 6.12 (6 H, s, 2 \times OMe), 6.2–6.95 (4 H, m, 2 \times OCH_2CH_3), 6.8 (2 H, d, J 6 Hz, CH_2CH), 7.13 (3 H, s, 4-Me), 7.64 and 7.68 (6 H, 2 s, 1-Me and MeC_6H_4), and 8.95 (6 H, t, J 7 Hz, 2 \times OCH_2CH_3), λ_{max} 248 (ϵ 59 360), 256sh (49 315), 267sh (30 685), 299 (17 350), 322 (5 710), and 336.5 nm (4 155), ν_{max} 3 470 (NH), m/z 584 (M^+ , 12%), 298 (27), 103 (100), 75 (31), and 47 (66) (Found: C, 63.9; H, 6.8; N, 4.8. $\text{C}_{31}\text{H}_{40}\text{N}_2\text{O}_7\text{S}$ requires C, 63.7; H, 6.9; N, 4.8%).

8,9,10-Trimethoxyellipticine (6).—Compound (26) (187 mg, 0.32 mmol) was dissolved in dioxan (4 ml) containing 6M-hydrochloric acid (0.3 ml). The mixture was heated under reflux for 6 h, cooled, poured into water (30 ml) and extracted with chloroform (4 \times 25 ml). The aqueous layer was made alkaline with aqueous ammonia and again extracted with chloroform (3 \times 50 ml + 4 \times 25 ml). The combined basic extracts were dried (MgSO_4) and evaporated to give the crude yellow trimethoxyellipticine (95 mg, 88%), m/z 337

($M^+ + 1$, 23%), 336 (100), 322 (18), 321 (86), 278 (27), and 263 (21).

The crude product was crystallised from methanol–chloroform as fine needles (4 mg), decomp. >198 °C, τ 0.3 (1 H, s, 1-H), 1.45 and 2.16 (2 H, ABq, J 6 Hz, 3- and 4-H), 1.98br (1 H, s, NH), 3.22 (1 H, s, 7-H), 5.94, 6.01, and 6.03 (9 H, 3 s, 3 \times OMe), 6.5 (3 H, s, 11-Me), and 7.28 (3 H, s, 5-Me), λ_{max} 234 (ϵ 19 190), 295sh (46 220), 301.5 (53 220), 339.5 (4 200), 383 (2 940), and 404 sh nm (2 800) (Found: M^+ , 336.1462. $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3$ requires M , 336.1474). The material from the mother-liquors was subjected to preparative t.l.c. on silica (EtOH; R_F 0.65) to recover 40 mg. An attempted sublimation then gave a less pure material. Preparative h.p.l.c. on Lichroprep (5–20 μ , 30 \times 0.5 cm) in cyclohexane–methanol–chloroform (1:1:8 v/v/v) gave a sample (5 mg), decomp. >155 °C, identical (^1H n.m.r. spectrum) to that described earlier, m/z 352 (4%), 350 (4), and ions as for the trimethoxyellipticine.

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