A New Approach to the Synthesis of Ellipticines

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1,4-Dimethylcarbazole-3-carbaldehyde (2a) was condensed with aminoacetaldehyde diethyl acetal, and the Schiff's base was hydrogenated before conversion into the *N*-tosyl derivative (3a). The latter was cyclised in boiling dilute hydrochloric acid in dioxan to ellipticine [5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) (1a) (87%). *N*-Tosyl-3,4-dihydroellipticine (4) was shown to be an intermediate. Under the same conditions, *m*-methoxyanilinoacetaldehyde diethyl acetal (6a) gave a low yield (5%) of 6-methoxyindole, but its *N*-methyl derivative (6b) gave 4- and 6-methoxy-*N*-methylindoles in 11 and 32% yields, respectively.

Condensation of 6-methoxy-1-methylindole with hexane-2,5-dione in ethanol containing toluene-*p*-sulphonic acid gave 7-methoxy-1,4,9-trimethylcarbazole (9a) (58%) and 1,2,3,4-tetrahydro-7-methoxy-1,4-bis-(6-methoxy-1-methylindol-3-yl)-1,4,9-trimethylcarbazole (10), which on heating with toluene-*p*-sulphonic acid in boiling chloroform gave the carbazole (9a). Treatment of the latter (9a) with pyridinium bromide perbromide gave 6-bromo-7-methoxy-1,4,9-trimethylcarbazole (9b). Formylation of (9b) with *N*-methylformanilide and phosphoryl chloride gave a complex mixture of *N*-methylcarbazoles resulting in part from *ipso*-attack of the Vilsmeier electrophile at C-6.

2,5-Dimethyl-4-acetamidobenzaldehyde (13) was condensed with aminoacetaldehyde diethyl acetal, and the Schiff's base (14) formed was hydrogenated to 4'-(2,2-diethoxyethylaminomethyl)-2',5'-dimethylacetanilide (15a). The *N*-tosyl derivative (15b) on boiling with dilute hydrochloric acid in dioxan gave only the corresponding aldehyde (16), but coupling of (15b) with *p*-bromoanisole under Goldberg conditions gave 4'-[*N*-(2,2-diethoxyethyl)tosylaminomethyl]-*N*-(4-methoxyphenyl)-2',5'-dimethylacetanilide (17a) (75%). Similarly, (15b) coupled with *m*-bromoanisole gave 4'-[*N*-(2,2-diethoxyethyl)tosylaminomethyl]-*N*-(3-methoxyphenyl)-2',5'-dimethylacetanilide (17b) (66%). Goldberg coupling of *p*-bromoanisole and 2,5-dimethylacetanilide gave *N*-(4-methoxyphenyl)-2',5'-dimethylacetanilide (18a), which on irradiation afforded 4-acetyl-*N*-(4-methoxyphenyl)-2,5-dimethylaniline (18b), 2-acetyl-*N*-(2,5-dimethylphenyl)-4-methoxyaniline (18c), and 6-methoxy-1,4-dimethylcarbazole (2b).

RECOGNITION of the anti-tumour and antileukaemic activity [1] of ellipticine (1a) has stimulated widespread interest in its synthesis,[2-8] and in that of related compounds.[9-13] The pharmacological activity of ellipticines substituted in ring A has been of particular interest; for example 9-methoxyellipticine (1c) was reported to be active against lymphoid leukaemia L1210 in mice.[5] A key intermediate in the synthesis of the latter was the 6-methoxycarbazole-3-carbaldehyde (2f), prepared [5] by formylation of the 6-methoxycarbazole (2b); however, attempts to prepare 8-methoxyellipticine (1b) by a similar route were unsuccessful because formylation of 7-methoxycarbazole afforded the 6-carbaldehyde (9e) as the major product together with a smaller amount of the 8-carbaldehyde, but none of the required 3-carbaldehyde (2d).

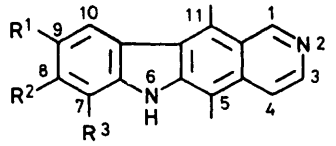
In these syntheses, as well as all the other syntheses of ellipticines so far described, a pre-formed indole or carbazole derivative has been used as starting material, although a variety of routes to the isoquinoline moiety have been employed. We now describe a new approach to the ellipticine ring system, and the synthesis, in high yields, of intermediates of potentially general usefulness in this field. Our initial studies were concerned with extending the application of our improved version [14] of the Pomeranz–Fritsch isoquinoline synthesis by carrying out ring closure reactions of carbazolecarbaldehydes (2; $R^3 = CHO$); the conventional Pomeranz cyclisation is known to be very dependent on conditions, and even when improved by the Bobbitt [15] modification a dehydrogenation step is required.

The aminoacetaldehyde diethyl acetal (3b) was converted into the tosylate (3a) in 93% yield; cyclisation of the latter in dioxan and dilute hydrochloric acid (*cf.* ref. 14) gave ellipticine (1a) in 90% yield. A small amount of *N*-tosyl-3,4-dihydroellipticine (4) was also obtained; this was easily separated by chromatography and converted into ellipticine by boiling with hydrochloric acid in dioxan. This yield of ellipticine compares very favourably with those of earlier syntheses.[2,3,5] Since our original work,[14c] Brossi [16] has applied the same isoquinoline annelation to the synthesis of other ellipticines, unobtainable by the original Pomeranz–Fritsch process, and has similarly obtained high yields

[1] G. H. Svoboda, G. A. Poore, and M. L. Montfort, *J. Pharm. Sci.*, 1968, **57**, 1720.
[2] R. B. Woodward, G. A. Iacobucci, and F. A. Hochstein, *J. Amer. Chem. Soc.*, 1959, **81**, 4434.
[3] P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 1962, 3482.
[4] T. R. Govindachari, S. Rajappa, and V. Sudarsanam, *Indian J. Chem.*, 1963, **1**, 247.
[5] L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan, and T. Teitei, *Austral. J. Chem.*, 1967, **20**, 2715.
[6] K. N. Kilminster and M. Sainsbury, *J.C.S. Perkin I*, 1972, 2264.
[7] F. Le Goffic, A. Gouyette, and A. Ahond, *Tetrahedron*, 1973, **21**, 3357.
[8] Y. Oikawa and O. Yonemitsu, *J.C.S. Perkin I*, 1976, 1479.
[9] A. N. Fujiwara, E. M. Acton, and L. Goodman, *J. Heterocyclic Chem.*, 1969, **6**, 379.
[10] A. N. Fujiwara, E. M. Acton, and L. Goodman, 1968, **5**, 853.
[11] E. Campaigne and J. Ashby, *J. Heterocyclic Chem.*, 1969, **6**, 875.
[12] J. C. Perche, G. Saint-Ruf, and N. P. Buu-Hoï, *J.C.S. Perkin I*, 1972, 260.
[13] L. K. Dalton, S. Demerac, and T. Teitei, *Austral. J. Chem.*, 1969, **22**, 185.
[14] (*a*) A. J. Birch, A. H. Jackson, P. V. R. Shannon, and P. S. P. Varma, *Tetrahedron Letters*, 1972, **47**, 4789; (*b*) A. J. Birch, A. H. Jackson, and P. V. R. Shannon, *J.C.S. Perkin I*, 1974, 2185; (*c*) A. J. Birch, Ph.D. Thesis, University of Wales, 1974.
[15] J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, 1965, **30**, 2247.
[16] R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullen, R. W. Kierstead, and E. G. Grunberg, *J. Medicin. Chem.*, 1975, **18**, 755.

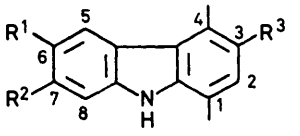
under mild conditions. Hence it was anticipated that no difficulties would be encountered in the formation of the isoquinoline ring system from a series of carbazoles of general structure (3).

Our next objective was the 6-bromo-7-methoxycarbazole (2e), which it was hoped could be formylated at the 3-position and converted into 8-methoxyellipticine, the bromo-group being removed during hydrogenation of the intermediate Schiff's base (5).



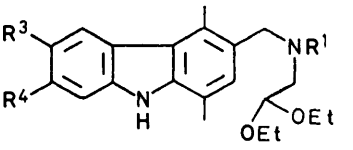
(1)

a; $R^1 = R^2 = R^3 = H$
b; $R^1 = R^3 = H, R^2 = OMe$
c; $R^1 = OMe, R^2 = R^3 = H$



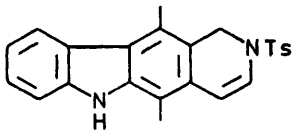
(2)

a; $R^1 = R^2 = H, R^3 = CHO$
b; $R^2 = R^3 = H, R^1 = OMe$
c; $R^1 = R^3 = H, R^2 = OMe$
d; $R^1 = H, R^2 = OMe, R^3 = CHO$
e; $R^1 = Br, R^2 = OMe, R^3 = H$
f; $R^1 = OMe, R^2 = H, R^3 = CHO$

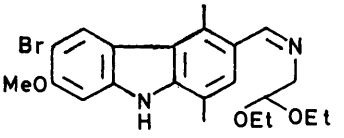


(3)

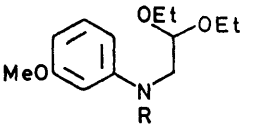
a; $R^1 = Ts, R^2 = R^3 = H$
b; $R^1 = R^2 = R^3 = H$



(4)

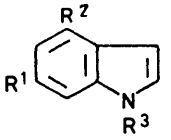


(5)



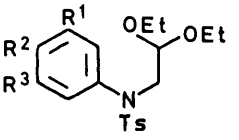
(6)

a; R = H
b; R = Me



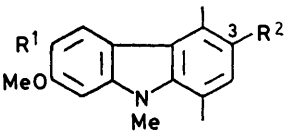
(7)

a; $R^1 = OMe, R^2 = R^3 = H$
b; $R^1 = H, R^2 = OMe, R^3 = Me$
c; $R^1 = OMe, R^2 = H, R^3 = Me$



(8)

a; $R^1 = R^3 = OMe, R^2 = H$
b; $R^1 = R^2 = R^3 = OMe$



(9)

a; $R^1 = R^2 = H$
b; $R^1 = Br, R^2 = H$
c; $R^1 = R^2 = Br$
d; $R^1 = Br, R^2 = CHO$
e; $R^1 = CHO, R^2 = H$

By analogy with our isoquinoline synthesis,[14] *m*-methoxyanilinoacetaldehyde diethyl acetal (6a) (from *m*-anisidine and bromoacetaldehyde diethyl acetal) was treated with dilute hydrochloric acid in boiling dioxan, but the yield (5%) of isolated 6-methoxyindole (7a) was poor. A considerable amount of polymerisation took place during the reaction, and since for the bromination and formylation of the 7-methoxycarbazole (2c) the *N*-methyl derivative should be an adequate model, we repeated the cyclisation with the *N*-methyl analogue (6b). Cyclisation of the latter had been achieved previously[17] with boron trifluoride–acetic acid in trifluoroacetic anhydride, but in our hands this reagent was unsuccessful. By contrast, under optimum conditions, dilute hydrochloric acid in boiling dioxan afforded a mixture of 4- and 6-methoxy-*N*-methylindoles (7b) (11%) and (7c) (32%), which could be separated by column chromatography. Subsequent work[18] has shown that protection of the N–H group as in the analogues (8a and b) with the tosyl group and cyclisation with acid as described above gives the corresponding *N*-tosylindoles in good yields.

Condensation of 6-methoxy-1-methylindole (7c) with hexane-2,5-dione in ethanol containing toluene-*p*-sulphonic acid gave two products which were readily separated by column chromatography. The first eluted was the desired 7-methoxy-1,4,9-trimethylcarbazole (9a) (55%); the second showed a molecular ion at *m/e* 561 and analytical figures consistent with the formula

[17] M. J. Bevis, E. J. Forbes, N. N. Naik, and B. C. Uff, *Tetrahedron*, 1971, **27**, 1253.

[18] A. H. Jackson, P. V. R. Shannon, A. Tinker, and N. Waite, unpublished results.

$C_{36}H_{39}N_3O_3$. These facts pointed to a structure resulting from three indole units and one hexanedione molecule. The ^1H n.m.r. spectrum showed eleven aromatic protons divided into two groups of three (τ 2.70—2.95, indolyl 4-protons) and eight (τ 3.12—3.56, indolyl 2-, 5-, and 7-protons), and the aromatic methoxy-groups resonated as two singlets [τ 6.18 (6 H) and 6.21 (3 H)]. The three NMe signals were also grouped in the ratio 2 : 1 (τ 6.21, 6.29, and 6.33). No carbazole 1- and 4-methyl signals were evident, but instead two methyl singlets at τ 8.02 and 8.07 and two methylene multiplets (τ 7.55 and 8.17) indicated a substituted tetrahydrocarbazole structure. This gained support from the u.v. spectrum [$\lambda_{max.}$ 297 (log ε 4.24) and 290sh nm (4.23)], which lacked carbazole bands above 300 nm. The quasisymmetrical structure (10) fitted all the above facts and was supported by the mass spectral base peak at *m/e* 385 (loss of methyl and 6-methoxy-1-methylindolyl groups). Finally, heating with a trace of toluene-*p*-sulphonic acid in refluxing chloroform gave (t.l.c.) the carbazole (9a).

Treatment of the carbazole (9a) with pyridinium bromide perbromide (*cf.* ref. 19) afforded the crude 6-bromo-derivative (9b) in 74% yield. The identification followed from elemental analysis and spectral properties—in particular the 5-H doublet (τ 1.96, *J* 9 Hz) in the n.m.r. spectrum of the carbazole (9a) was replaced in that of (9b) by a singlet at τ 1.78. The expectation that formylation of (9b) by the Vilsmeier procedure would be directed to the 3-position was encouraged, since Kametani,[20] in the isoquinoline series, had successfully used a bromo-substituent to block Bischler–Napieralski cyclisation of the phenylethylamide (11) *para* to the activating OH group.

In the event, although formylation of the bromocarbazole (9b) was attempted with *N*-methylformanilide and phosphoryl chloride in several different solvents, in none of the cases tried was a clean product obtained. However, in dibromoethane, the mixture of products showed *two* aldehydic proton signals in the n.m.r. spectrum. After partial separation on t.l.c. into three fractions, field desorption mass spectrometry showed molecular ions corresponding to four different *N*-methylcarbazoles with the following substituents; (*a*) Br, Br, OMe, (*b*) Br, OMe, (*c*) Br, OMe, CHO, and (*d*) OMe, CHO. The yields were too low to enable useful n.m.r. spectra to be run on the individual fractions and for synthetic purposes the reaction was abandoned.

The complexity and distribution of the products can be explained by *ipso*-attack by the Vilsmeier electrophile at the brominated 6-carbon atom in (9b). Displacement of Br^+ during nitration of *p*-bromoanisole and attack by the bromine on starting material has been claimed recently,[21] and substitution of the product of *ipso*-attack (a Reverdin-type ' rearrangement ') [22] is also possible. The observed molecular weights and multiple aldehyde signals may therefore be assigned to the mixture of products (9b—e).

In view of the difficulties in the preparation of suitably substituted carbazoles, a new approach to ellipticines (1) was sought. In the light of (*a*) the requirement for different substituents in the indole ring and (*b*) the expense of substituted indoles, a pathway avoiding pre-formed indoles was desirable. Since the isoquinoline ring system can be formed in high yield *after* the completion of the carbazole moiety (see above) we selected routes summarised by diagram (12). The order of carbon–carbon bond forming reactions is arguable; in this paper we describe the route to a synthon leaving bonds *a* and *c* unformed since this approach provides the greatest flexibility in the preparation of a variety of ellipticines.

2,5-Dimethylacetanilide was formylated to give the aldehyde (13) [10] (87% yield), which was converted into the Schiff's base (14) (75%). Hydrogenation (Adams catalyst) gave the corresponding amine, which with toluene-*p*-sulphonyl chloride in pyridine afforded the tosylate (15b) (84%). The latter, on treatment with dilute hydrochloric acid in boiling dioxan gave only the aldehyde (16), indicating that the aromatic ring was insufficiently reactive for isoquinoline formation (*cf.* ref. 14). 5,8-Dimethylisoquinoline, although known,[23] is accessible in very low yield *via* a Bischler–Napieralski reaction.

However, coupling of the tosylate (15b) with *p*-bromoanisole under the improved [24b] Goldberg [24a] conditions gave a 75% yield of the *N*-acetyldiphenylamine (17a).

Compound (17a) could not be obtained solid, but after column chromatography its spectroscopic and other properties indicated the presence of a single component. The field desorption mass spectrum showed the molecular ion (100%) at *m/e* 568 and only one major fragment ion at *m/e* 103 [$CH(OEt)_2^+$]. In the n.m.r. spectrum, at 35 °C, three of the aromatic protons and the NAc and aromatic CMe groups gave broad overlapping signals (which became well resolved on raising the temperature to 55 °C). This was considered to be due to hindered rotation about the *N*–Ac bond, which was investigated more fully in the model compound (18a).

Similarly *m*-bromoanisole gave, in 95% yield, the analogue (17b).

The substituted diphenylamines (17a and b) can be obtained in high overall yield from readily available materials, and in principle they can be converted into *N*-acetylellipticines by one-step thermal dehydrogenation (*cf.* ref. 25) or into ellipticines by photocyclisation of either the free amines [26] or their *N*-acetyl derivatives (see below).

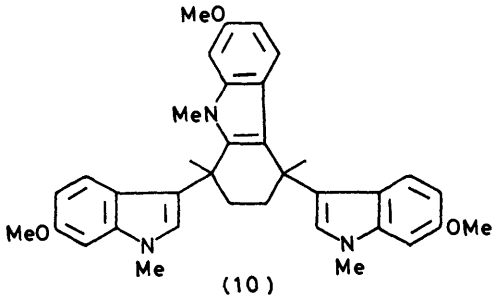
[19] K. Piers, C. Meimaroglou, R. V. Jardine, and R. K. Brown, *Canad. J. Chem.*, 1963, **41**, 2399.
[20] T. Kametani, T. Nakano, K. Shishido, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1971, 3350.
[21] C. L. Perrin and G. A. Skinner, *J. Amer. Chem. Soc.*, 1971, **93**, 3389.
[22] F. Reverdin and F. During, *Ber.*, 1899, **32**, 152.
[23] M. S. Gibson, *J. Chem. Soc.*, 1956, 808.
[24] (*a*) I. Goldberg, *Ber.*, 1907, **40**, 4541; (*b*) P. E. Weston and H. Adkins, *J. Amer. Chem. Soc.*, 1928, **50**, 859.

Thus in the case of the model compound (18a) prepared from *p*-bromoanisole and 2,5-dimethylacetanilide, direct irradiation in ethanol with a medium-pressure mercury lamp gave three components separable by p.l.c. The first (8%) showed a molecular weight (mass spectrum) unchanged from that of the starting material, and its other spectroscopic properties were in accord with the diphenylamine (18b). The structure was established by synthesis through Goldberg-type coupling of 4′-acetyl-2′,5′-dimethylacetanilide with *p*-bromoanisole, followed by hydrolysis; the photochemical and synthetic products had identical t.l.c. and spectroscopic properties.

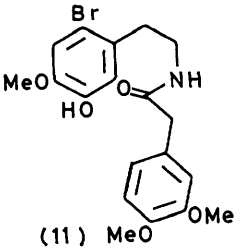
The second component in the photolysis mixture (15%), also isomeric with starting material (18a), showed similar spectroscopic properties to the first (18b), but displayed an additional long wavelength band ($\lambda_{max.}$ 404 nm) in its u.v. spectrum and evidence of hydrogen bonding between the acetyl carbonyl ($\nu_{max.}$ 1 640) and NH (3 300 cm^{-1}) groups in the i.r. These and other spectroscopic data lead to assignment of the structure (18c).

The final product (12%), M^+ 225, exhibited a carbazole u.v. spectrum; its spectral and other properties were identical with those reported for 6-methoxy-1,4-dimethylcarbazole.[5]

The products obtained from the photolysis of the model compound (18a) indicate that cyclisation to ellipticine and its analogues is feasible through intermediates of type (17). In the case of (18a) the course of the photoreaction is diverted through the involvement of a photo-Fries [27] rearrangement to give the *C*-acetyl by-products which are precluded in the case of the free amines of type (18; R = H).



(10)



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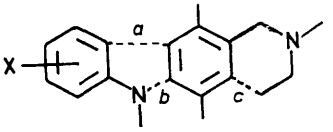

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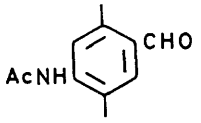
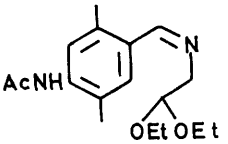
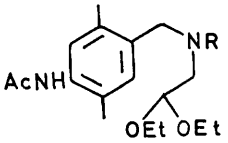


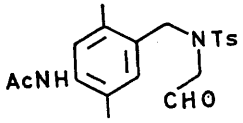
(13)



(14)



(15) a; R = H
b; R = Ts



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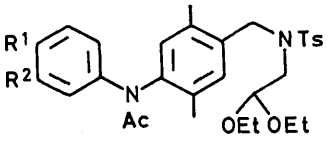
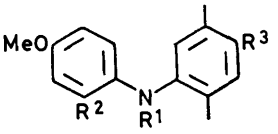


(17)

a; R^1 = OMe, R^2 = H
b; R^1 = H, R^2 = OMe



(18)

a; R^1 = Ac, R^2 = R^3 = H
b; R^1 = R^2 = H, R^3 = Ac
c; R^1 = R^3 = H, R^2 = Ac
d; R^1 = R^2 = R^3 = H
e; R^1 = R^3 = Ac, R^2 = H

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EXPERIMENTAL

M.p.s were corrected u.v. (in ethanol), i.r., n.m.r. (in $CDCl_3$), and mass spectra (electron impact) were measured as described previously,[14b] unless described otherwise. ' Petroleum ' refers to a fraction of boiling range 60—80 °C unless stated otherwise. Spectroscopic data for compounds designated with an asterisk are available as Supplementary Publication No. SUP 22063 (17 pp.).*

Ellipticine.— 3-(2,2-Diethoxyethylaminomethyl)-1,4-dimethylcarbazole (3b) [3] (4.0 g) in dry pyridine (20 ml) was stirred with toluene-*p*-sulphonyl chloride (2.5 g; freshly crystallised) at 20 °C for 3 days; plates of pyridine hydrochloride separated. The mixture was poured into water (100 ml) and extracted with ether (3 × 50 ml). The extract was washed with dilute (< 1M) hydrochloric acid (2 × 50 ml) and water (2 × 50 ml) and dried ($MgSO_4$; washed subsequently with chloroform). The organic solvents were removed under reduced pressure leaving crystals of 3-[N-(2,2-*diethoxyethyl*)*tosylaminomethyl*]-1,4-*dimethylcarbazole* (3a) * (5.4 g, 96%). A sample recrystallised from petroleum (b.p. 40—60 °C)–chloroform gave crystals, m.p. 183.5—185° (Found: C, 68.2; H, 6.75; N, 6.1. $C_{28}H_{34}N_2O_4S$ requires C, 68.0; H, 6.9; N, 5.7%).

The tosylate (3a) (1 g) in dry dioxan (25 ml) containing 6M-hydrochloric acid (1.9 ml) was heated to reflux under nitrogen for 6 h. After cooling, the solution was poured into water (100 ml) and extracted with chloroform (3 × 50 ml); the aqueous layer was made alkaline to litmus with dilute ammonium hydroxide, then re-extracted with chloroform (3 × 50 ml). The combined second extracts were washed with water (2 × 50 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a yellow-green solid (0.65 g) which showed two spots on t.l.c. (ethanol). The lower spot (R_F 0.3) was separated by p.l.c. and the product identified as ellipticine (1a) from its u.v. spectrum; the upper spot had R_F 0.7. The mixture was chromatographed on silica (100 g; washed with methanol). The column was prepared in and eluted with ether until all the component of R_F 0.7 had been removed. Removal of the ether under reduced pressure gave N-*tosyl*-3,4-*dihydroellipticine* (4) * as a cream solid (0.11 g, 13%), m.p. 178—182° (Found: *m/e* 402.1387 and 246.1141. $C_{24}H_{22}N_2O_2S$ requires *M*, 402.1408; *M* − Ts, 246.1157). Elution of the column with mixtures of ether, ethyl acetate, and methanol, and finally with methanol afforded methanolic fractions which yielded a yellow solid (0.55 g). Part of this (0.41 g) was recrystallised from acetone then chloroform to give ellipticine (1a) * as a yellow solid (0.31 g, 62%; grossed up yield 87%), m.p. 306—309°. Vacuum sublimation (200—220 °C; 0.5 Torr) gave yellow needles, m.p. 310—312° (decomp.), m.p. (7 Torr) 318—322° (decomp.) (lit.,[5] 315—317°).

6-*Methoxyindole* (7a).—3-Methoxyanilinoacetaldehyde diethyl acetal [17] (1 g) in dry dioxan (12 ml) was treated with 6M-hydrochloric acid (1 ml). The solution was heated under reflux for 10 min then poured into water (100 ml) and extracted with ether (5 × 50 ml). The extract was dried ($MgSO_4$) and evaporated under reduced pressure to give an oil (0.4 g). T.l.c. showed two products with some starting material and polymer. The mixture was chromatographed on a column of silica (35 g) prepared in petroleum. Elution with ether–petroleum (1 : 1) gave mainly starting material (100 mg); later fractions gave 6-methoxyindole (7a) * as a gummy solid (28 mg, 5%), n.m.r.[28] and u.v.[29] data identical with those reported.

4-*Methoxy-* (7b) *and* 6-*Methoxy*-1-*methylindole* (7c).—3-Methoxy-*N*-methylanilinoacetaldehyde diethyl acetal (6b) [17] (10 g) in dry dioxan (120 ml) was treated with 6M-hydrochloric acid (10 ml) and the mixture was heated under reflux for 15 min. The deep red solution obtained was poured into water (200 ml) and extracted with ether (9 × 50 ml). The extract, after washing with water (4 × 50 ml) and drying ($MgSO_4$), was evaporated under reduced pressure to give a yellow oil (6.0 g), which was chromatographed on silica (150 g). Elution with ether–petroleum (1 : 9) gave 4-methoxy-1-methylindole (7b) * (0.7 g, 11%), m.p. 87—88° (lit.,[17] 89—90°). Later fractions afforded 6-methoxy-1-methylindole (7c) * as a pale yellow oil (2.0 g, 32%). The picrate crystallised from benzene–petroleum as red needles, m.p. 121—122° (lit.,[17] 123°).

Condensation of 6-*Methoxy*-1-*methylindole* (7c) *with Hexane*-2,5-*dione*.—6-Methoxy-*N*-methylindole (6.05 g, 0.37 mol), toluene-*p*-sulphonic acid (3.6 g), and hexane-2,5-dione (4.3 g) in ethanol (reagent grade; 100 ml) were heated under reflux with stirring for 2 h and then kept at 20 °C overnight. A grey precipitate (5.5 g), m.p. 137—155°, was recrystallised from ether–petroleum (b.p. 40—60 °C) to give material (2 g) of m.p. 138—160°. T.l.c. showed the presence of two components, and chromatography on silica (160 g; Grace) and elution with ether–petroleum (1 : 1) gave 7-*methoxy*-1,4,9-*trimethylcarbazole* (9a) * (1.1 g, 55%) as needles, m.p. 133—134° [142—142.5° (from chloroform–petroleum)] (Found: C, 80.4; H, 7.3; N, 6.0. $C_{16}H_{17}NO$ requires C, 80.3; H, 7.2; N, 5.9%). Elution with ethyl acetate–acetone (1 : 1) gave 1,2,3,4-*tetrahydro*-1,4-*bis*-(6-*methoxy*-1-*methylindol*-3-*yl*)-1,4,9-*trimethylcarbazole* (10) * as a cream solid (0.8 g, 40%), m.p. 260—272°, which gave crystals, m.p. 268—272° (from chloroform–petroleum) (Found: C, 76.7; H, 7.0; N, 7.6. $C_{36}H_{39}N_3O_3$ requires C, 77.0; H, 7.0; N, 7.5%).

6-*Bromo*-7-*methoxy*-1,4,9-*trimethylcarbazole* (9b).—To a solution of 7-methoxy-1,4,9-trimethylcarbazole (9a) (1.9 g) in pyridine (20 ml) was added pyridinium bromide perbromide (2.6 g) in pyridine (10 ml) with stirring and warming. After stirring for 1 h a precipitate had formed and the mixture was poured into ether (200 ml) and filtered. The precipitate was washed with ether (200 ml) and the combined ether layers were washed with hydrochloric acid (4M; 200 ml), sodium hydroxide solution (2M; 100 ml), and water (50 ml) before drying ($MgSO_4$). Concentration of the extract, and extraction of the initial precipitate and drying agent with ether and chloroform afforded 6-*bromo*-7-*methoxy*-1,4,9-*trimethylcarbazole* (9b) * as crystals (1.85 g, 75%), m.p. 189—202° {m.p. 200—203° [from ether–petroleum (b.p. 40—60 °C), acetone–petroleum, and chloroform–petroleum]} (Found: C, 60.1; H, 5.1; Br, 21.8; N, 4.2. $C_{16}H_{16}BrNO$ requires C, 60.3; H, 5.1; Br, 25.1; N, 4.4%).

Formylation of 6-*Bromo*-7-*methoxy*-1,4,9-*trimethylcarbazole* (9b).—(a) *Dibromoethane as solvent.* To the bromocarbazole (150 mg) in dibromoethane (3 ml; dried and redistilled), *N*-methylformanilide (100 mg) and then phosphoryl chloride (150 mg), each in dibromoethane (total 3 ml), were added separately. The dark green solution was

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

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heated on an oil-bath to 100 °C and the reaction followed by t.l.c.; after 4 h no starting material remained. Sodium acetate (0.4 g) in water (30 ml) was added and the mixture was steam distilled to remove solvents and *N*-methylaniline. A grey-brown solid was filtered from the aqueous mixture, then dried and continuously extracted with toluene (50 ml) (Soxhlet). The toluene solution was treated with charcoal and evaporated under reduced pressure to give a cream solid (62 mg). The complex ^{1}H n.m.r. spectrum showed two signals at τ −0.3 and −0.4. Recrystallisation from chloroform–petroleum ether gave a first crop of cream-coloured crystals (0.6 mg), m.p. 253—257°, *m/e* 399 (37%), 397 (78), 395 (39), 347 (100), 345 (91), 318 (9), 316 (10), and 267 (9). A second crop (5.5 mg) had m.p. 220—225°. Removal of solvent under reduced pressure from the mother liquors left a yellow solid (55.9 mg), which was separated into three components by p.l.c. The field-desorption mass spectra were as follows: component (a) *m/e* 395 (57%), 397 (100), 399 (42), 317 (44), and 319 (47); component (b) *m/e* 345 (8), 347 (10), and 267 (95); component (c) *m/e* 345 (24), 347 (30), and 267 (100). The structures of these components are discussed in the main text.

4′-(2,2-Diethoxyethyliminomethyl)-2′,5′-dimethylacetanilide (14).—4′-Formyl-2′,5′-dimethylacetanilide [10] (1 g) and 2,2-diethoxyethylamine (0.7 g) were boiled with toluene (sodium-dried; 60 ml) in a Dean–Stark apparatus. After 3½ h the toluene solution (20 ml) was removed and on cooling *4′-(2,2-diethoxyethyliminomethyl)-2′,5′-dimethylacetanilide* * was deposited as a solid (1.2 g, 75%), m.p. 142—147°. Two recrystallisations from toluene gave crystals (0.7 g, 44%), m.p. 145—149° (Found: C, 66.8; H, 8.2; N, 9.3. $C_{17}H_{34}N_2O_3$ requires C, 66.6; H, 8.5; N, 9.1%).

4′-(2,2-Diethoxyethylaminomethyl)-2′,5′-dimethylacetanilide (15a).—The anilide (14) (0.4 g) was hydrogenated under atmospheric pressure in ethanol (30 ml) over platinum dioxide (12 mg). The mixture was filtered through Celite and the solvent removed under reduced pressure to leave an oil which crystallised on tritration with petroleum, affording *4′-(2,2-diethoxyethylaminomethyl)-2′,5′-dimethylacetanilide* (15a) * (0.25 g, 63%), m.p. 101—102° (Found: C, 66.5; H. 8.7; N, 9.1. $C_{17}H_{28}N_2O$ requires C, 66.3; H, 9.1; N, 9.1%).

4′-[N-(2,2-Diethoxyethyl)tosylaminomethyl]-2′,5′-dimethylacetanilide (15b).—The amine (15a) (1.5 g) in pyridine (5 ml) was treated with toluene-*p*-sulphonyl chloride (1 g; freshly crystallised) in pyridine (5 ml). The mixture was stirred at 20 °C for 3 days and then poured into water (100 ml) and extracted with chloroform (3 × 50 ml). The extract was washed with hydrochloric acid (1M; 6 × 50 ml) then water (2 × 50 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure gave the crude tosylate as a faintly pink solid (1.9 g, 84%), m.p. 125—128°. Three recrystallisations from chloroform–petroleum gave the *tosyl derivative* (15b) * as needles, m.p. 134—136°, *m/e* (field desorption) 462 (M^+, 100%) (Found: C, 62.6; H, 7.3; N, 6.0. $C_{24}H_{34}N_2O_5$ requires C, 62.3; H, 7.4; N, 6.1%).

Attempted Cyclisation of the Tosylate (15b).—The tosylate (15b) (150 mg) in dioxan (12 ml) was treated with 6M-hydrochloric acid (0.5 ml). The solution was heated under reflux for 30 min, poured into water (60 ml), and extracted with ether (3 × 25 ml). The extract was dried ($MgSO_4$) and evaporated under reduced pressure leaving *N*-(4-acetamido-2,5-dimethylbenzyl)tosylaminoacetaldehyde (16) as a yellow oil (88 mg, 70%), τ 0.79 (1 H, s, CHO), 2.25 and 2.63 (4 H, 2d, each *J* 9 Hz, $SO_2C_6H_4Me$), 2.37 (1 H, s, H-3), 2.92 (1 H, s, NH), 3.11 (1 H, s, H-6), 5.74 (2 H, s, $ArCH_2NTs$), 6.30 (2 H, d, *J* 3 Hz, CH_2·CHO), 7.56 and 7.58 (3 H, 2s, 2-Me), 7.62 (3 H, s, SO_2·C_6H_4Me), and 7.89br (6 H, s, Ac and 5-Me).

4′-[N-(2,2-Diethoxyethyl)tosylaminomethyl]-N-(4-methoxyphenyl)-2′,5′-dimethylacetanilide (17a).—The tosylate (15b) (1.1 g), *p*-bromoanisole (redistilled; 5 ml), potassium carbonate (dried at >100 °C; 0.5 g), and copper foil (washed with water, dilute hydrochloric acid, and acetone; 1.4 g) were heated to reflux under nitrogen for 2¼ h. The reaction was followed by t.l.c., which showed disappearance of starting material and the formation of a single product. The mixture, without the copper, was transferred to a round-bottomed flask. Water (50 ml) and potassium carbonate (5 g) were added and the mixture was steam distilled for 3 h to remove the excess of *p*-bromoanisole. Water was added to keep the volume constant. The aqueous residue was extracted with ether (4 × 50 ml) and the extract was dried ($MgSO_4$) and evaporated under reduced pressure to give the crude acetanilide (17a) as an orange oil (1.28 g, 96%). The material gave a single spot on t.l.c. but would not crystallise. Chromatography on a silica (130 g) column made up in ether–petroleum (1 : 1) gave the *acetanilide* (17a) * (1.0 g; 75%), *m/e* (field desorption) 568 (M^+, 100%) and 103 (14) (Found: C, 65.1; H, 7.35%; M^+, 568.2607. $C_{31}H_{40}N_2O_6S$ requires C, 65.45; H, 7.1%; *M*, 568.2607).

4′-[N-(2,2-Diethoxyethyl)tosylaminomethyl]-N-(3-methoxyphenyl)-2′,5′-dimethylacetanilide (17b).—The tosylate (15b) (0.2 g), *m*-bromoanisole (redistilled and dried; 3 ml), potassium carbonate (dried at 100 °C; 0.2 g), and copper foil (washed with water, dilute hydrochloric acid, and acetone; 0.7 g) were heated to reflux under nitrogen for 8 h. T.l.c. then showed the disappearance of starting material. Work-up as for (17a) gave an orange oil (0.23 g, 95%). P.l.c. [ethyl acetate–petroleum (b.p. 40—60 °C) (2 : 3)] gave a band of R_F 0.23, which, on removal of solvent under reduced pressure yielded the *acetanilide* (17b) * as a colourless oil (0.16 g, 66%), *m/e* (field desorption) 568 (M^+, 100%) (Found: *m/e* 568.2586 and 413.2441. $C_{31}H_{40}N_2O_6S$ requires *M*, 568.2607; *M* − Ts, 413.2440).

N-(4-Methoxyphenyl)-2′,5′-dimethylacetanilide (18a).—2′,5′-Dimethylacetanilide (1.6 g), *p*-bromoanisole (3 g), potassium carbonate (0.5 g), and copper foil (washed with ether, dilute hydrochloric acid, water, and acetone and dried at >100 °C; 1.4 g) were heated under reflux for 12 h. The reaction was followed by t.l.c. Water (50 ml) was added to the cooled mixture (after removal of copper), which was then distilled for 4 h to remove the excess of *p*-bromoanisole, water being added to keep a constant volume. The cooled aqueous residue was extracted with ether (4 × 50 ml) and the extracts dried ($MgSO_4$) and evaporated under reduced pressure to give an oil (2.6 g) containing three components (t.l.c.). Chromatography on silica [150 g; made up in ether–petroleum (1 : 1); elution with ethyl acetate–ether (1 : 9)] gave an oil (50 mg) identified as *N-(4-methoxyphenyl)-2,5-dimethylaniline* (18d),* *m/e* (field desorption) 227 (100%) (Found: M^+, 227.1310. $C_{15}H_{17}NO$ requires *M*, 227.1310). The second product from the column was an oil which crystallised to a brown solid. Recrystallisation from ethyl acetate and then petroleum gave cubic crystals of *N′-(4-methoxyphenyl)-2′,5′-dimethylacetanilide* (18a) * (0.9 g, 35%), m.p. 91—96°,

m/e (field desorption) 269 (M^+, 100%) (Found: C, 76.2; H, 6.7; N, 5.5. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%). Further recrystallisations from petroleum gave crystals of m.p. 91—93° and finally 90.5—94°.

Irradiation of N-(4-*Methoxyphenyl*)-2′,5′-*dimethylacetanilide* (18a).—The amide (102 mg) in AnalaR ethanol (50 ml) in a quartz vessel was irradiated with a medium-pressure mercury lamp. Dry nitrogen was drawn through the solution at hourly intervals. The reaction was terminated when t.l.c. indicated the disappearance of starting material and the formation of three products. The solvent was removed under reduced pressure to give an oil (102 mg).

This oil, in dry toluene (25 ml) was unaffected (t.l.c.) when heated to reflux with palladium–charcoal (5%; 100 mg) under nitrogen. Filtration and removal of the toluene under reduced pressure gave again an oil (80 mg). Separation of the three components was achieved by p.l.c. in ethyl acetate–petroleum (1 : 4) to give (highest R_F) 2-*acetyl*-N-(2,5-*dimethylphenyl*)-4-*methoxyaniline* (18c) * as a yellow oil which slowly crystallised (15 mg, 15%), *m/e* 269 (M^+, 100%), 254 (64), and 226 (11) (Found: M^+, 269.1414. $C_{17}H_{19}NO_2$ requires M, 269.1416).

The component of lowest R_F was 4-acetyl-*N*-(4-methoxyphenyl)-2,5-dimethylaniline (18b),* obtained as an oil (8 mg, 8%) (Found: M^+, 269.1414. Calc. for $C_{17}H_{19}NO_2$: M, 269.1416), identical with a synthetic sample (see below).

The component of intermediate R_F was 6-methoxy-1,4-dimethylcarbazole (2b),[5,*] obtained as an oil (10 mg, 12%) which crystallised; m.p. 112—130° (lit.,[5] 136.5°) (Found: M^+, 225.1148. Calc. for $C_{15}H_{15}NO$: M, 225.1154). The spectroscopic data were very similar to those reported.[5]

4-*Acetyl*-N-(4-*methoxyphenyl*)-2,5-*dimethylaniline* (18b).—4′-*Acetyl*-2′,5′-*dimethylacetanilide*. Acetyl chloride (7.0 g) was added to a stirred suspension of 2′,5′-dimethylacetanilide (9.3 g) and dry carbon disulphide (60 ml). Aluminium chloride (23 g; anhydrous) was added with cooling (ice) and stirring, and the mixture was then heated under reflux with stirring for 2 h. The mixture became dark red and formed an insoluble mass; it was kept overnight at 20 °C. The carbon disulphide solution was then decanted and the residual complex decomposed with 4M-hydrochloric acid and ice. The white precipitate obtained was mixed with concentrated hydrochloric acid (50 ml) and water (600 ml) and filtered to give the crude product (11.1 g), m.p. 190.5—192°. Recrystallisation from ethanol gave 4′-*acetyl*-2′,5′-*dimethylacetanilide* * (8.3 g, 71%), m.p. 191—192° (Found: C, 70.6; H, 7.4; N, 7.2. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%).

4′-*Acetyl*-N-(4-*methoxyphenyl*)-2′,5′-*dimethylacetanilide* (18e). The foregoing anilide (1 g), *p*-bromoanisole (5 ml), potassium carbonate (0.5 g; anhydrous), and copper foil (1.4 g; washed with dilute hydrochloric acid and dried) were heated under reflux in nitrogen for 7 h. The mixture was then poured into water and the excess of *p*-bromoanisole was removed by steam distillation. The cooled aqueous residue was extracted with chloroform (3 × 50 ml) and the extracts were dried ($MgSO_4$) and evaporated to leave an oil (2 g). Chromatography on silica (130 g) and elution with ethyl acetate–ether (3 : 7) gave the *acetanilide* (18e) * as an orange oil (1.2 g, 75%) (Found: M^+, 311.1510. $C_{19}H_{21}NO_3$ requires M, 311.1521).

The aniline (18b). The anilide (18e) (1.0 g) was heated under reflux with ethanol (25 ml), water (5 ml), and sodium hydroxide (2 g). The mixture was poured into water (100 ml) after 70 min. The precipitate of the crude amine (18b) (1 g; m.p. 120—125.5°) was crystallised from ethanol–water to give orange crystals (0.75 g, 86%), m.p. 124.5—129.5°. Treatment with charcoal and further recrystallisations afforded the *aniline* (18b) * as colourless needles, m.p. 127.5—129.5° (Found: C, 75.5; H, 7.2; N, 5.4. $C_{17}H_{19}NO_2$ requires C, 75.8; H, 7.1; N, 5.2%), identical with that obtained from irradiation of (18a).

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