A Flexible Approach to Pyrido[4,3-*b*]carbazoles. The Syntheses of 8,10-Dimethoxy-5-methyl-, 5,11-Dimethoxy-7,10-dimethyl- and 9-Fluoro-5,11-Dimethylpyrido[4,3-*b*]carbazoles by Variations of the 'Type D' Route

Robin J. Hall,[a] Priyanthi Dharmasena,[a] Jeremy Marchant,[a] Ana-M. F. Oliveira- Campos,[b] Maria-Joao R. P. Queiroz,[b] Manuela M. Raposo[b] and Patrick V. R. Shannon[a,*]

[a] *School of Chemistry and Applied Chemistry, University of Wales College of Cardiff, PO Box 912, Cardiff CF1 3TB, UK*

[b] *Centro de Quimica Pura e Aplicada (I.N.I.C.), Universidade do Minho, Avenida Joao XXI, 4700 Braga, Portugal*

Syntheses of three different pyridocarbazoles are described. Palladium acetate oxidation of 4-cyano-*N*-(3,5-dimethoxyphenyl)-2-methylaniline **19** and reduction of the resultant 3-cyano-4,6-dimethoxy-1-methylcarbazole **23** with diisobutylaluminium hydride gave the corresponding formylcarbazole **22**. Modified Pomeranz–Fritsch cyclisation then gave, as the major product, 8,10-dimethoxy-5-methylpyrido[4,3-*b*]carbazole **32**. Acid-catalysed condensation of 4,7-dimethoxyindole with hexane-2,5-dione gave 5,8-dimethoxy-1,4-dimethylcarbazole **37** which underwent an atypical regiospecific formylation to give 3-formyl-1,4-dimethoxy-5,8-dimethylcarbazole **39**. This was converted by standard methods into 5,11-dimethoxy-7,10-dimethylpyrido[4,3-*b*]carbazole **7**. The cyclisation reactions of the formylcarbazoles **26** and **43** were studied by ^{1}H NMR spectroscopy which enabled the isolation of intermediate *N*-tosyl-1,2-dihydropyridocarbazoles. An unambiguous synthesis of 9-fluoroellipticine **8** is described from 5-fluoroindole for the first time.

The actual and prospective anti-cancer activities of certain pyrido[4,3-*b*]carbazoles **1** are well known,[1] although knowledge of their mode of action is far from complete.[2] These structures, and especially the ellipticines **2** and olivacines **3** have been the targets for a plethora of synthetic programmes for over a quarter of a century.[1a,3,4] Despite this prolonged activity, it is still difficult to predict the ease of synthesis of a particular derivative or analogue—and specific examples can present a long-term problem. For some years we have explored in depth a comparatively straightforward synthetic route—the 'Type D' pathway[1a,3]—which, we believe, has proved more successful than any other, although we would not claim it as a completely general procedure. It has, nonetheless, including its modifications, provided viable syntheses of many different ellipticines and olivacines[5–15] *e.g.* **4a** ⟶ **4n**.

This approach, which proceeds *via* a suitably substituted carbazole intermediate **5**, has been improved and extended by several modifications of the original synthesis of ellipticine itself (**2**, R^1 = H) by Cranwell and Saxton.[5] These include:

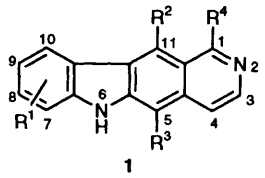
(a) The sulfonamide modification of the Pomeranz–Fritsch cyclisation.[7]

(b) A switch of regiospecificity from ring A to C in the electrophilic substitution of carbazoles by change of electrophile.[15]

(c) A new synthesis of 1,4-dimethylcarbazoles by photochemical deprotection and cyclisation of *N*-tosyldiphenylamines.[16]

(d) An alternative synthesis of 1-methyl-3-cyano-substituted carbazoles, precursors for pyridocarbazoles, from cyano diphenylamines.[17,18]

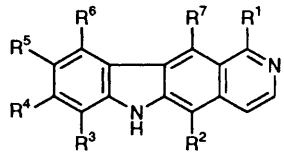
In this paper different aspects of the 'Type D' synthetic plan are illustrated by three new different pyrido[4,3-*b*]carbazoles **6**, **7** and **8**.



1

2 $R^2 = R^3 = Me$, $R^4 = H$

3 $R^2 = H$, $R^3 = R^4 = Me$



4

a $R^2 = R^7 = Me$

b $R^2 = R^7 = Me$, $R^5 = OMe$

c $R^2 = R^7 = Me$, $R^5 = Br$

d $R^2 = R^7 = Me$, $R^5 = NO_2$

e $R^2 = R^7 = Me$, $R^5 = OH$

f $R^2 = R^7 = Me$, $R^5 = Me$

g $R^2 = R^7 = Me$, $R^5 = NH_2$

h $R^2 = R^7 = Me$, R^4, $R^5 = OCH_2O$

i $R^2 = R^7 = Me$, $R^4 = R^5 = OMe$

j $R^2 = R^7 = Me$, $R^4 = R^5 = R^6 = OMe$

k $R^2 = R^7 = Me$, $R^3 = R^4 = R^5 = OMe$

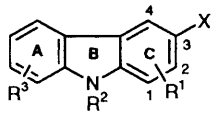
l $R^2 = R^7 = Me$, $R^3 = R^5 = OMe$

m $R^1 = R^2 = Me$

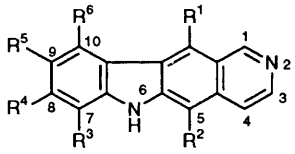
n $R^1 = R^2 = Me$, $R^5 = OMe$

R^n = H unless stated otherwise

The Synthesis of 8,10-*Dimethoxy*-5-*methylpyrido*[4,3-*b*]*carbazole* **6**.—The 8,10-dimethoxypyrido[4,3-*b*]carbazole system has been particularly elusive. Thus, exceptionally, our attempts to condense 4,6-dimethoxyindole with hexane-2,5-dione gave no corresponding carbazole **9a** despite persistent attempts to vary the conditions.[14] The simpler carbazole **9b**, however, proved easily accessible *via* Borsche cyclisation of the appropriate phenylhydrazone, but it underwent formylation and bromination in ring A.[15] It therefore seemed likely that even if



5

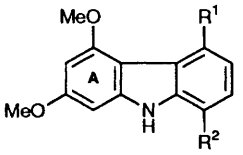


6 R^2 = Me, R^4 = R^6 = OMe
7 R^1 = R^2 = OMe, R^3 = R^6 = Me
8 R^1 = R^2 = Me, R^5 = F

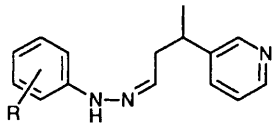
R^n = H unless stated otherwise

the dimethyl homologue **9a** were accessible, the required 3-substitution would be precluded.

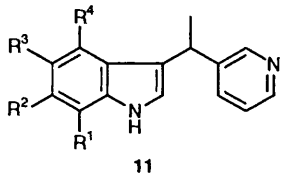
We therefore tried the alternative strategy[19,20] of Sainsbury and co-workers, whose indolisations of hydrazones of type **10** showed promise of a more general route to the pyridylethylindoles **11** and hence, *via* the established nitrile[21] route, to the corresponding pyrido[4,3-*b*]carbazoles. Initial attempts to form the pyridylbutenoate **13** by the literature procedure[20] failed, but addition of the ylide **17**, formed with lithium diisopropylamide at −10 °C in tetrahydrofuran, to 3-acetylpyridine, was successful. Chromatography of the crude products gave a mixture of *cis* and *trans* isomers of **13** (92%), the *cis* isomer predominating (4:1). All spectroscopic data were in agreement with those in the literature. A minor product was identified as the pyridylbutenoic acid **14**.



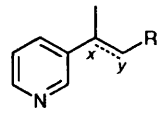
9a R^1 = R^2 = Me
b R^1 = R^2 = H



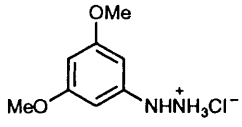
10



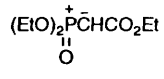
11
12 R^2 = R^4 = OMe



13 *xy* = C=CH, R = CO_2Et
14 *xy* = C=CH, R = CO_2H
15a *xy* = $CHCH_2$, R = CO_2Et
b *xy* = $CHCH_2$, R = CHO
c *xy* = $CHCH_2$, R = CH_2OH



16

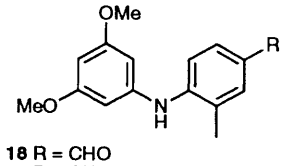


17

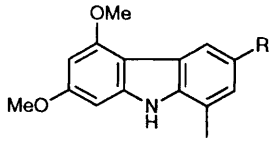
Hydrogenation of the ester **13** at 100 psi * over 10% palladium on charcoal gave the ester **15a** (92%). Attempts to reduce the latter to the aldehyde **15b** using diisobutylaluminium hydride, gave poor yields (5–13%)—but reduction of **15a** with lithium aluminium hydride to the alcohol **15c**[22] followed by Swern oxidation gave the aldehyde **15b** in 65% yield after chromatography. The dimethoxyhydrazine hydrochloride **16**, prepared by a literature method,[23] was heated at reflux in methanol with the aldehyde **15b**. Only trace amounts of products were isolated for which the spectra were inconsistent with the expected indole **12**.

Although many experimental conditions were tried, using hydrochloric acid, acetic acid, toluene-*p*-sulfonic acid, stannic chloride and trifluoroacetic acid for various times and in different solvents, no products corresponding to the required indole **12** were obtained and we reluctantly concluded that the 4,6-dimethoxyindole system was unobtainable *via* this route.

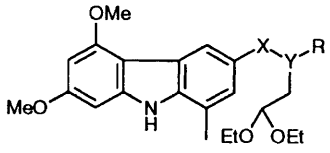
A different approach to structure **6** lay in our recent work on the palladium acetate ring closure of formyl and cyanodiphenylamines to carbazoles.[17,18,24] In principle, ring-closure of either of the diphenylamines **18** or **19** should give the carbazoles **22** or **23** which could then be annulated to the pyrido[4,3-*b*]carbazole **6**. The aldehyde **18**,[17] when heated at reflux in acetic acid with 2 mol equiv. of palladium(II) acetate for 1 h gave a complex mixture. Repeated chromatography enabled the isolation of three of the products, but the lability of the formyl group under the reaction conditions, as observed in some preliminary work,[24] made this step impracticable as a source of the 3-formylcarbazole **22**. Both the decarbonylated diphenylamine **20** (4%) and the carbazole **24** (1%) were isolated, but the formylcarbazole **22** was obtained in only 3% yield. This was improved to 11% by palladium(II) acetate treatment of the protected aldehyde **21**, but a much more efficient route to **22** was by reduction of the cyanodimethoxycarbazole **23**, also synthesised by the palladium(II) acetate route,[17] with diisobutylaluminium hydride in diglyme. The product **22** was obtained in 62% yield after careful acid hydrolysis of the intermediate imine. In one preparation a small amount (3%) of the corresponding alcohol **25** was isolated. The aldehyde **22** was



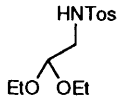
18 R = CHO
19 R = CN
20 R = H
21 R = —CH OCH_2CMe_2 CH_2O



22 R = CHO
23 R = CN
24 R = H
25 R = CH_2OH



26 X—Y = CH_2N, R = Tos
27 X—Y = CH=N
28 X—Y = CH_2N, R = H



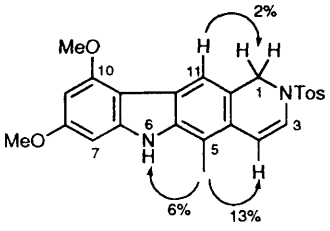
29

a key intermediate since experience has shown that in nearly every case tried, the acid-catalysed cyclisation of the derived sulfonamides, in the present case **26**, has successfully been accomplished to give the pyridocarbazole and usually in good yield. The construction of the *N*-tosylamino acetal side chain of **26** proved, however, to be only relatively straightforward. The Schiff's base **27** was obtained in 99% yield from the aldehyde **22** and aminoacetaldehyde diethyl acetal. Attempts to crystallise the product, led to its decomposition, but hydrogenation of **27** over Adam's catalyst gave the amine **28** (85%) characterised as its stable hydrochloride salt. Treatment of the crude amine **28** with toluene-*p*-sulfonyl chloride in pyridine for 4 days gave after chromatography, the sulfonamide **26**, but in only 40% yield. Also isolated was the *N*-tosylamino acetal **29** whose structure was confirmed by an independent preparation from aminoacetaldehyde diethyl acetal and toluene-*p*-sulfonyl chloride. It appears from results described below that this product arises from fragmentation of **26**, perhaps initiated by attack of pyridinium hydrochloride when the concentration of the latter is high, towards the end of the tosylation stage.

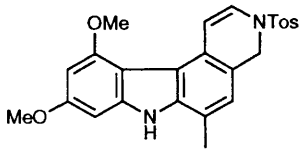
Our first attempt at cyclisation of the sulfonamide **26** was in dimethyl sulfoxide (DMSO) and hydrochloric acid at 60–64 °C for 2.5 h in the dark under nitrogen. Column chromatography

* 1 psi = 6.894×10^3 Pa.

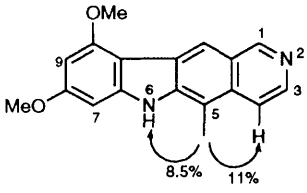
of the products caused extensive decomposition but preparative TLC gave two components. The first was identified as the *N*-tosyldihydropyridocarbazole **30** (39%). The ^{1}H NMR spectrum showed the 3- and 4-protons as doublets, *J* 6 Hz, at δ 6.82 and 6.17. The 1-H_2 signal had moved from δ 4.62 in the starting sulfonamide **26** to δ 4.70. That cyclisation had occurred to give the linear system of **30** rather than the alternative isomer **31** was evident from the NOE difference spectra shown. Thus, in particular, saturation of the 5-methyl protons at δ 2.39 enhanced the signals at δ 7.92 (NH) and 6.17 (4-H) by 6 and 13% respectively.



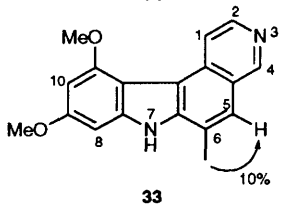
30



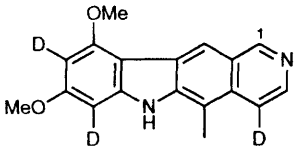
31



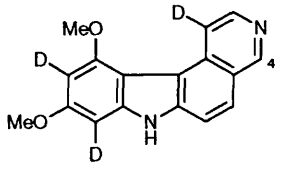
32



33



34



35

The second component appeared to be a mixture of the two unstable pyridocarbazoles **32** and **33**. In order to achieve complete conversion of the starting material to these pyridocarbazoles, the sulfonamide **26**, in DMSO containing hydrochloric acid (10 mol dm^{-3}), under a nitrogen atmosphere protected from light, was kept for 30 h at 66 °C. Aqueous alkaline work-up then gave an 89% yield of a mixture of the two pyridocarbazoles **32** and **33** in the ratio 83:17 respectively. The molecular formulae were confirmed by high resolution mass spectrometry. The ^{1}H NMR spectrum (in [$^2H_6$]DMSO) showed the aromatic methyl singlet from the linear isomer **32** at δ 2.80 and the corresponding signal from **33** at δ 2.71. For the predominant isomer **32** the 3- and 4-H signals appeared at δ 8.40 and 7.94 respectively and these assignments were confirmed by decoupling experiments and the NOE different spectra indicated. Irradiation of the broad 3-H singlet at δ 8.40 collapsed the broad 4-H doublet at δ 7.94 to a singlet. These results on the signals of the major component confirmed that it was the linear pyrido[4,3-*b*]carbazole **32**. Saturation of the lower intensity methyl proton singlet at δ 2.71 from isomer **33**, gave a 10% enhancement of the 5-H singlet signal and irradiation of the 1-H proton signal in **33** collapsed the 2-H doublet to a singlet.

The conversion of both the starting sulfonamide **26** and the linear *N*-tosyldihydropyridocarbazole **30** to the pyridocarbazoles **32** and **33** could be followed by ^{1}H NMR. Thus spectra of the dihydropyridocarbazole **30** in [$^2H_6$]DMSO containing a 20% solution of DCl in D_2O were recorded at ambient temperature and then on warming to 65 °C. After 5 h, by which time no tosyldihydro-compound **30** was visible from the spectrum, signals due to toluene-*p*-sulfinic acid and the pyridocarbazole mixture (ratio 85:15, **32**:**33**) were seen.

It is of interest that the spectrum of the mixture of **32** and **33** showed that as well as the NH signals, the aromatic signals from the ring A protons and one ring D proton (4-H in **32** and 1-H in **33**) were missing. When the reaction mixture was given an aqueous work-up, the EI mass spectrum of the product mixture gave a molecular ion at *m*/*z* 295 (100%) consistent with the specifically deuteriated structures **34** and **35** in which only the carbazole N–D deuterons had been predictably, rapidly re-exchanged to NH. 2,4-Dimethoxycarbazole **9b**[15] similarly exchanged the ring A protons in the DCl–DMSO–D_2O solvent system, ^{1}H NMR showing only a trace of these signals.

In a second ^{1}H NMR experiment, the conversion of the starting sulfonamide **26** through to the fully aromatic final products **34** and **35** was followed semi-quantitatively. The spectrum of a solution of **26** in the [$^2H_6$]DMSO–DCl–D_2O mixture was recorded at room temperature and the solution then kept at 66 °C for a period of 30 h.

Over the first 20 min of the reaction the signals from the sulfonamide **26** declined until they were no longer visible. Simultaneously ethanol (δ 1.00, triplet, δ 3.40, quartet) and the *N*-tosyldihydropyridocarbazole **30** were observed to be increasing in concentration from their uniquely assignable signals. After 120 min, the partially deuteriated pyridocarbazoles **34** and **35** (but with N–D) were visible from 1-H singlet of **34** at δ 9.80 and the weaker 4-H singlet from the isomer **35** at δ 9.56. During the period 165 to 720 min the signals of the tosyldihydro-compound **30** slowly disappeared and toluene-*p*-sulfinic acid was seen to build up in concentration. From 720 to 1890 min it appeared that the ratio of the isomers **34** and **35** remained constant within experimental error. No evidence for the intermediacy of the angular *N*-tosyldihydropyridocarbazole **31** was seen, but its presence could not be ruled out at a low concentration.

These semi-quantitative kinetic data are summarised in Fig. 1.

The isomers **32** and **33** proved impossible to separate by preparative TLC or HPLC although they were apparently successfully separated by TLC [diethyl ether–0.88 ammonia (98:2)] giving two spots, yellow and orange. The proportions of the two pyridocarbazoles remain essentially constant during the course of the cyclisation of the starting sulfonamide since equilibrating conditions exist throughout. It is worth noting that there are partially differing reports on the portions of linear and angular pyridocarbazoles formed as a result of ring D annulation in the methoxyolivacine[25] and olivacine[13a,26] series.

The Goldberg palladium acetate route to the 5-methyl-

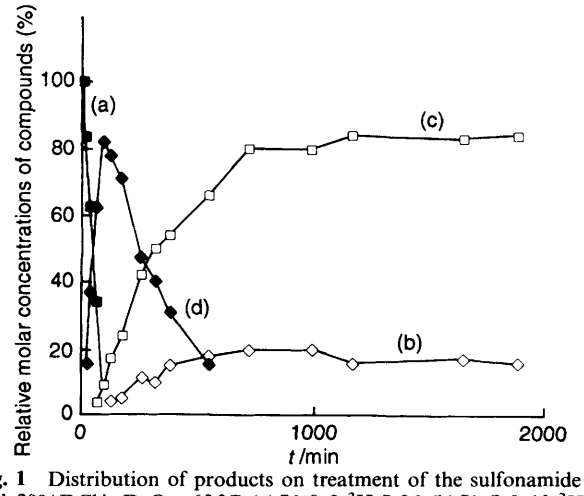
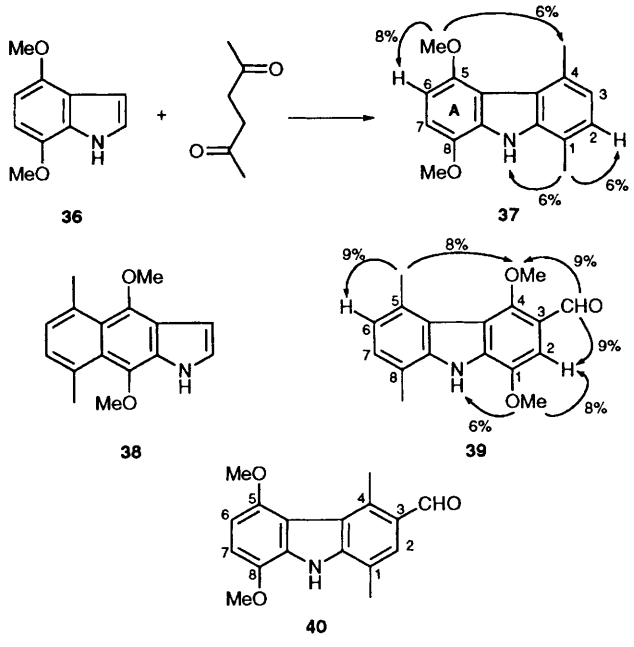


Fig. 1 Distribution of products on treatment of the sulfonamide **26** with 20% DCl in D_2O at 65 °C. (a) [6, 8, 9-$^2H_3$]-**26**; (b) [1, 7, 8, 10-$^2H_4$]-**33**; (c) [4, 6, 7, 9-$^2H_4$]-**6**; (d) [6, 7, 9-$^2H_3$]-**30**.

pyrido[4,3-*b*]carbazole system would appear to have considerable promise as a general synthetic route to olivacines **3** from simple benzene precursors. Addition of the 1-methyl group can be achieved either at the Schiff's base stage [14a] or by alkylation of the pyridocarbazole itself.[27,28]

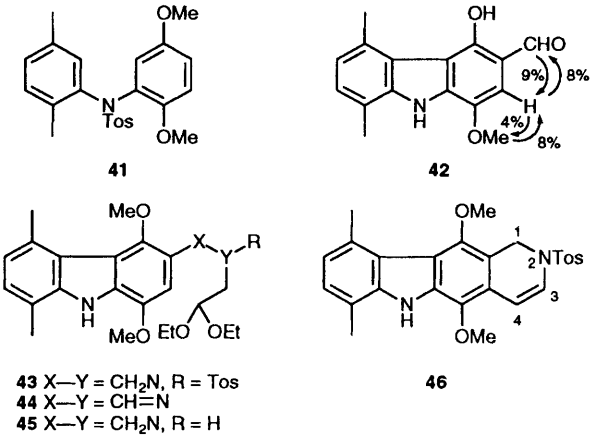
The Synthesis of 5,11-*Dimethoxy*-7,10-*dimethylpyrido*[4.3-b]*carbazole* **7**.—As stated above, the 'Type D' approach to ellipticines, based on the stepwise approach of Cranwell and Saxton, can be applied in a number of cases. When the indole is substituted by strongly electron donating groups in the 4-, 5-, 6- or 7-positions, however, the 1,4-dimethylcarbazole *e.g.* **37** which is formed as the first intermediate in the synthesis, can have enhanced nucleophilic activity in ring A. Formylation of such carbazoles can, and does [6,11,15] therefore often result in partial or complete attack in that ring. In the case of 4,7-dimethoxyindole [29] **36** it was, in principle, possible that condensation with hexane-2,5-dione could give either or both tricyclic systems **37** or **38**. We felt that on theoretical grounds,



the formation of the carbazole **37** would be preferred over the benzoindole **38**. In either event, however, we could envisage the potential synthesis of a novel example of a tetracyclic system. Formylation of the carbazole **37** could be predicted to afford the aldehyde **39** rather than the isomer **40**, and the formyl intermediate **39** should, by well-established annulation, enable the synthesis of the novel 5,11-dimethoxy-7,10-dimethylpyrido-[4,3-*b*]carbazole **7**.

4,7-Dimethoxyindole [29] was condensed with hexane-2,5-dione in the presence of toluene-*p*-sulfonic acid to give only the carbazole **37** (67%). That condensation had taken place at the 2- and 3-position of the indole was immediately evident from two distinct AB quartet systems centred on δ 7.02 (J 6 Hz, 6- and 7-H) and δ 6.66 (J 8 Hz, 2- and 3-H). The structure of this carbazole was confirmed by the NOE difference enhancements shown. Alternatively, this carbazole **37** was prepared by photochemical cyclisation and deprotection [17] of the sulfonamide **41**.

When formylated with refluxing *N*-methylformanilide and phosphorus oxychloride in trichloroethylene for 90 min, the carbazole **37** gave the formyl derivative **39** (84%). This showed the replacement of the 6- and 7-proton AB quartet in the ^{1}H NMR spectrum of **37** by a singlet at δ 7.37. The position of formylation was confirmed by the NOE difference spectra shown. When the reflux time for the formylation was increased to 3.5 h, the 3-formylcarbazole **39** was a minor product (8.5%) and 3-formyl-4-hydroxy-1-methoxy-5,8-dimethylcarbazole **42** was the major product isolated (40%). In the ^{1}H NMR spectrum, one of the OMe signals had been replaced by a 1 H signal at δ 11.05 corresponding to a hydroxy proton. Its position can be inferred from the NOE enhancements shown assuming that the formyl group remains intact under the reaction conditions.



The conversion of the aldehyde **39** into the sulfonamide precursor **43** was achieved, as in analogous cases [7,15] *via* the intermediate Schiff's base **44** (~ 100%) and amine **45** (95%). The last two precursors were not purified to an analytical standard because of their instability, but were used immediately for the succeeding stages. The amine **45** was converted with tosyl chloride in pyridine, into the sulfonamide **43** (M^+, 554) (86%) after chromatography. Its other spectroscopic properties confirmed its structure and purity.

The sulfonamide **43**, treated with hydrochloric acid in refluxing DMSO for 2.5 h under a nitrogen atmosphere protected from light, gave a mixture of two products, which were separated by preparative TLC. The higher R_F component was identified as the cyclic sulfonamide **46** (18%, M^+, 462.1613, $C_{26}H_{26}N_2SO_4$). The ^{1}H NMR spectrum showed the 3- and 4-H doublets at δ 7.12 and 6.96 characteristic of the *N*-tosyl-dihydroisoquinoline ring system.[7a] The second component was identified as the 5,11-dimethoxy-7,10-dimethylpyridocarbazole **7** (14%). The novel pyridocarbazole showed the expected long wavelength absorption (at 391 nm) in its UV spectrum and the ^{1}H NMR spectrum showed clearly the loss of all the signals from the tosyl group and the presence of a lowfield 1 H singlet at δ 9.64 due to the 1-H proton.

In order to optimise the yield of the pyridocarbazole **7** a kinetic study of the cyclisation and elimination sequence **43** → **46** → **7** was carried out in an NMR tube as previously for the cyclisation of the sulfonamide **26**. The spectra were run over a period of 500 min at 64 °C in [$^2H_6$]DMSO–DCl–D_2O. The results are shown in Fig. 2 from which it can be seen that, as with the previous example **26**, there was a relatively rapid conversion of the starting sulfonamide **43** into the tosyldihydropyridocarbazole **46**, complete in 90 min, which then eliminated toluenesulfinic acid more slowly to give the pyridocarbazole **7**.

On the basis of these results, a preparative scale reaction was carried out in which the sulfonamide **43** was kept in the same concentration of HCl in DMSO and water for 10 h at 60–64 °C. After aqueous alkaline work-up the pyridocarbazole **7** was obtained in 86% yield, identical with the sample obtained earlier. The pyrido[4,3-*b*]carbazole system with two alkoxy groups in ring C is novel, although the *p*-quinone **47** has been synthesised.[30,31]

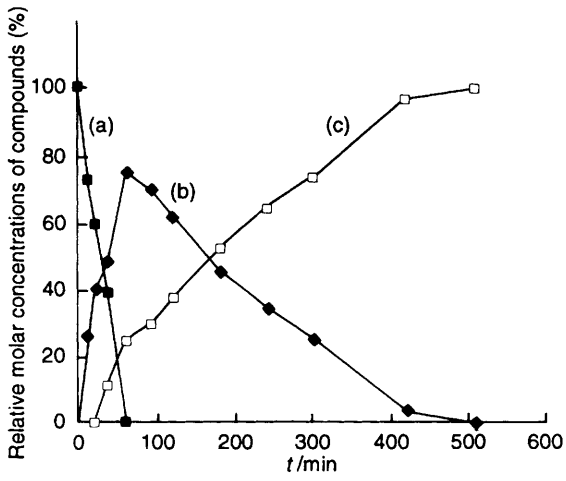
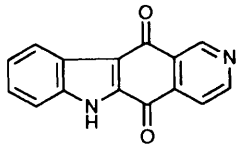


Fig. 2 Distribution of products on treatment of the sulfonamide **43** with 20% DCl in D_2O at 64 °C. (a) **43**; (b) **46**; (c) **7**.

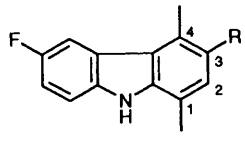
The third pyridocarbazole of interest was 9-fluoro-5,11-dimethylpyrido[4,3-*b*]carbazole **8** (9-fluoroellipticine). A sample was required for the study of its interactions with samples of DNA and lipids.

Examination of the literature indicates several references to 9-fluoroellipticine in papers dealing with measurements of its biological properties.[32–35] No data or indication of purity are given, however. In one case[33] it is claimed that Dalton's method[6] of synthesis was used, but of the expected intermediates in this route, *i.e.* the carbazole **48**, the formylcarbazole **49** and the imine **56**, only the carbazole **48** has been specifically mentioned in the literature,[36] but again no data at all is provided. We therefore carried out a systematic 'Type D' chemical synthesis. The essential carbazole **48** m.p. 91–92 °C, in fact, was synthesised in 83% yield from 5-fluoroindole and an excess of hexane-2,5-dione. On normal work-up, the product retained excess of hexane-2,5-dione, and even prolonged high vacuum conditions failed to remove a 2:1 excess of the diketone. Dalton[6] reports similar addition compounds formed with analogous carbazoles. In our case, chromatography on silica completely removed the excess of diketone. Although less satisfactory, it also proved possible to prepare the carbazole by our alternative route.[17] Although the diphenylamide **51** was hydrolysed quantitatively to the diphenylamine **52**, on treatment with 1.5 mol equiv. of palladium(II) acetate in refluxing trifluoroacetic acid, it failed to give the carbazole **48**. This was, however, obtained by photolysis of the *N*-tosyldiphenylamine **53**.

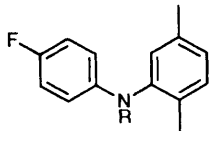
Vilsmeier formylation of the fluorocarbazole **48**, followed by chromatography, with difficulty, of the polar products, gave the formylcarbazole **49** (83%). The spectral properties of the aldehyde **49** confirmed its structure—and that formylation had occurred at the 3-position was shown by NOE difference spectra. Thus, saturation of the lower field 4-Me protons gave a 16.5% enhancement of the lowest-field aromatic doublet signal of the 5-H and a 10.5% enhancement of the formyl signal.



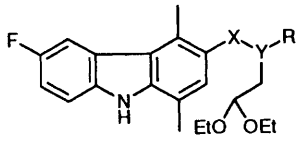
47



48 R = H
49 R = CHO
50 R = CH_2OH



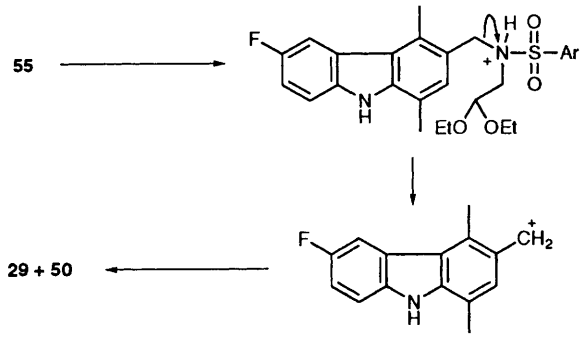
51 R = Ac
52 R = H
53 R = Tos



54 X—Y = CH_2N, R = H
55 X—Y = CH_2N, R = Tos
56 X—Y = CH=N

The formyl compound **49** was condensed with aminoacetaldehyde diethyl acetal and the mixture azeotroped with dry benzene. The resultant imine **56**, obtained in quantitative crude yield, was directly hydrogenated over platinum(II) oxide to give an almost quantitative yield of the amine **54** as an oil. Because of the tendency to oxidation, this product was treated immediately with toluene-*p*-sulfonyl chloride in dry pyridine. Aqueous work-up followed by column chromatography gave the sulfonamide **55** as a colourless solid, but contaminated with the *N*-tosylaminoacetal **29**. Fractional crystallisation, however, readily afforded a sample of the pure sulfonamide, m.p. 175–176 °C.

The column chromatography isolated a very small yield (*ca.* 2%) of a by-product showing a molecular ion, M^+, 243. This and the ^1H NMR spectrum, which, apart from the 1- and 4-methyl signals, showed a 2-proton $ArCH_2OH$ signal at δ 4.86, indicated that this sample was impure 3-hydroxymethylcarbazole **50**. The formation of the alcohol **50** suggests that the tosylamino acetal **29** is formed during the tosylation step by acid-catalysed fragmentation of the tosylamino-side chain of the main product **55**. Relatively very small amounts of water will be present to attack the resultant carbocation **50** (Scheme 1).



Scheme 1

The chromatographed sulfonamide **55** in a solution of hydrochloric acid (0.5 mol dm^{-3}) in dioxane, was heated at reflux for 7.25 h under an atmosphere of nitrogen. On aqueous, alkaline work-up the crude product was shown by its ^1H NMR spectrum to be essentially pure 9-fluoroellipticine formed in 80% yield. Chromatography of the original crude precipitated solid sample gave a sample of pure 9-fluoroellipticine **8**, m.p. 315 °C (decomp.) whose ^1H NMR spectrum, MS and UV spectra fully confirmed its structure.

Experimental

IR spectra were recorded on a Perkin-Elmer 257 grating spectrophotometer. UV Spectra were measured in methanol on a Unicam SP800 spectrophotometer; molar absorption coefficient (ε) values given in $dm^3\ mol^{-1}\ cm^{-1}$. ^1H NMR Spectra were obtained in $CDCl_3$ on a Bruker WM 360-NMR spectrometer at 360 MHz unless stated otherwise; *J*-values are given in Hz. EI mass spectra were run on a Varian CH 5D instrument. Flash column chromatography was performed on Kieselgel 60, 230–400 mesh Merck silica; light petroleum was of boiling range 40–60 °C. M.p.s were uncorrected.

Ethyl 3-(3-*Pyridyl*)*but*-2-*enoate* **13**.—Diisopropylamine (10 cm^3) in freshly distilled tetrahydrofuran (THF) (50 cm^3) was cooled to −70 °C under an atmosphere of nitrogen. Butyllithium (1.6 mol dm^{-4} solution in hexanes; 37.5 cm^3) was added dropwise. The mixture was allowed to warm to −10 °C and diethyl ethoxycarbonylmethylphosphonate (12.7 cm^3, 16.5 g, 0.074 mol) was added dropwise, the temperature being kept between −10 and −5 °C. The pale yellow solution was stirred at −10 °C for 0.5 h, and 3-acetylpyridine (5 g, 0.04 mol) was added dropwise to it at −5 °C. The mixture was allowed to warm slowly to room temp., at which temperature it was stirred for 20 h, and then poured onto ice (100 g). The pale orange two-phase system was extracted with dichloromethane (3 × 100 cm^3) and the combined extracts were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to give an orange oil (8.15 g). Flash chromatography of this, eluting with ethyl acetate, gave the *cis* and *trans* isomers of the ester **13** as a yellow oil (7 g, 92%), δ_H(60 MHz) 8.74 (1 H, d, *J* 2, 2′-H), 8.60 (1 H, dd, *J* 5, 2, 6′-H), 7.76 (1 H, dt, *J* 8, 5, 4′-H), 7.30 (1 H, dd, *J* 8, 5, 5′-H), 6.16 (0.8 H, q, *J* 1; *cis* CH_3C=C*H*), 6.00 (0.2 H, q, *J* 1, *trans* C=CH), 4.20 (2 H, m, CH_2CH_3), 2.60 (2.4 H, br s, *cis* CH_3C=CH), 2.20 (0.6 H, br s, *trans* CH_3C=CH) and 1.28 (3 H, t, *J* 7, CH_2CH_3). The NMR spectrum was identical with the literature values;[20] ν_{max}(liq. film)/cm^{-1} 1715, 1630, 1580 and 1560. Also eluted was a mixture of *cis* and *trans* 3-(3-pyridyl)-but-2-enoic acid **14** (0.5 g, 6.5%) as a pale orange oil, δ_H(60 MHz) 8.76 (1 H, d, *J* 2, 2′-H), 8.56 (1 H, dd, *J* 5, 2, 6′-H), 7.60 (1 H, dt, *J* 8, 5, 4′-H), 7.28 (1 H, dd, *J* 8, 5, 5′-H), 6.32 (0.75 H, br s, *cis* C=CH), 6.04 (0.25 H, br s, *trans* C=CH), 2.24 (2.25 H, br s, *cis* CH_3C=CH) and 2.04 (0.75 H, br s, *trans* CH_3C=CH); ν_{max}(liq. film)/cm^{-1} 3500, 1740, 1575 and 1560.

Ethyl 3-(3-*Pyridyl*)*butanoate* **15a**.—The unsaturated ester **13** (3 g, 0.02 mol) was hydrogenated at 100 psi * in ethanol (30 cm^3) over 10% Pd–C (300 mg) for 5 h. The reaction mixture was filtered through a bed of Celite and the residues washed with ethanol (2 × 50 cm^3). The combined ethanol solutions were evaporated to dryness to give the pure ester **15a** (2.8 g, 92%) as a pale yellow oil. The product was normally used without further purification, δ_H 8.62 (2 H, m, 2′- and 6′-H), 7.68 (1 H, dt, *J* 8, 5, 4′-H), 7.36 (1 H, dd, *J* 8, 5, 5′-H), 4.20 (2 H, m, CH_2CH_3), 3.40 (1 H, m, CH_3CHCH_2), 2.60 (2 H, d, *J* 7, $CHCH_2$), 1.40 (3 H, d, *J* 7, CH_3CH), and 1.20 (3 H, t, *J* 7, CH_2CH_3); ν_{max}(liq. film)/cm^{-1} 1740, 1590 and 1575.

3-(3-*Pyridyl*)*butanal* **15b**.—The ester **14** (3 g, 15 mmol) in dry diethyl ether (9 cm^3) and dry THF (9 cm^3) was added dropwise to a vigorously stirred suspension of lithium aluminium hydride (674 mg, 18 mmol) in dry diethyl ether (33 cm^3) under an atmosphere of nitrogen at room temp. After being stirred for 0.5 h, the mixture was cooled in ice and treated cautiously with aqueous sodium tartrate (33% w/w; 30 cm^3). The mixture was stirred for 15 min after which the layers were allowed to separate and the ether layer was removed. The aqueous layer was extracted with ethyl acetate (6 × 60 cm^3) and the combined organic solutions were dried (Na_2SO_4) and evaporated to yield the crude alcohol **15c** as a pale yellow oil (2.07 g, 88%). Bulb-to-bulb distillation under reduced pressure gave the pure alcohol **15c** as a colourless oil (1.8 g, 77%), b.p. 178–180 °C at 0.1 mmHg (lit.,[22] 180 °C/0.1 mmHg); δ_H(200 MHz) 8.50 (1 H, d, *J* 2, 2′-H), 8.45 (1 H, dd, *J* 8, 2, 6′-H), 7.55 (1 H, dt, *J* 8, 2, 4′-H), 7.25 (1 H, m, 5′-H), 3.55 (2 H, m, CH_2CH_2OH), 2.95 [1 H, m, $CH_3CH_2(CH_2)_2OH$], 2.60 (1 H, br s, OH) 1.85 (2 H, m, CH_2CH_2OH) and 1.30 (3 H, d, *J* 7, CH_3CHCH_2); ν_{max}(liq. film)/cm^{-1} 3300, 1590 and 1575.

Oxalyl chloride (1.3 cm^3, 0.015 mol) in dry dichloromethane (43 cm^3) was stirred and cooled to −70 °C under an atmosphere of dry nitrogen. Dry dimethyl sulfoxide (DMSO) (2.3 cm^3) in dichloromethane (8.6 cm^3) was added dropwise to it, the temperature being kept below −60 °C. The mixture was cooled over 10 min to −65 °C and a solution of the alcohol **15c** (1.0 g, 6.6 mmol) in dry dichloromethane (4 cm^3) was added dropwise to it at −65 °C over 0.5 h. Dry triethylamine (5 cm^3) was added dropwise to the mixture which was then allowed to warm to 20 °C over 2 h. It was then diluted with water (40 cm^3) and the organic layer was separated and the aqueous layer extracted with dichloromethane (5 × 20 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil (1.09 g). Flash chromatography of this, eluting with ethyl acetate gave the aldehyde **15b** (630 mg, 65%) as an orange oil. All spectra were identical with those previously reported.[20]

Oxidation of the Formyldiphenylamine **18**.—The diphenylamine **18** (197 mg, 0.73 mmol) and palladium(II) acetate (297.4 mg, 1.3 mmol) were heated at reflux in acetic acid (60 cm^3) under an atmosphere of nitrogen for 1 h. The mixture was cooled slightly and the solvent removed under reduced pressure. Extraction of the palladium residues with dichloromethane (2 × 40 cm^3) gave a brown solution. This was washed with water (100 cm^3), dried (Na_2SO_4) and evaporated to give an oily brown residue (120 mg). Flash chromatography of this, using diethyl ether–light petroleum [(1:9) → (7:3)] gave first *N*-(3,5-*dimethoxyphenyl*)-2-*methylaniline* **20** (7.3 mg, 4%) as a colourless oil, δ_H 7.28 (1 H, dd, *J* 6, 2, 6-H), 7.20 (1 H, dd, *J* 6, 2, 3-H), 7.18 (1 H, dt, *J* 6, 2, 5-H), 6.96 (1 H, dt, *J* 5, 2, 4-H), 6.10 (2 H, d, *J* 2, 2′- and 6′-H), 6.04 (1 H, t, *J* 2, 4′-H), 5.38 (1 H, br s, NH), 3.76 (6 H, s, 2 × OCH_3) and 2.26 (3 H, s, 1-CH_3); *m*/*z* (%) (EI) 244 (M + 1, 58), 243 (M^+, 100), 242 (57), 223 (68), 212 (62), 196 (38) and 184 (27); λ_{max}(EtOH)/nm 250 (ε 15 200) and 220 (21 500); ν_{max}(liq. film)/cm^{-1} 3300 (NH) (Found: M^+, 243.1241. $C_{15}H_{17}NO_2$ requires *M*, 243.1254). Next eluted was 5,7-*dimethoxy*-1-*methylcarbazole* **24**, (19.1 mg, 11%) as an oil, δ_H 8.04 (1 H, dd, *J* 4, 2, 4-H), 7.9 (1 H, br s, NH), 7.12 (2 H, m, *J* 4, 2, 2- and 3-H), 6.54 (1 H, d, *J* 2, 6-H), 6.31 (1 H, d, *J* 2, 8-H), 4.01 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3) and 2.53 (3 H, s, 1-CH_3); *m*/*z* (%) (EI) 242 (M + 1, 49), 241 (M^+, 100), 226 (52), 213 (44), 198 (66), 183 (70), 154 (40) and 121 (85); ν_{max}(Nujol)/cm^{-1} 3320 (NH) and 1600 (Found: M^+, 241.1090. $C_{15}H_{15}NO_2$ requires *M*, 241.1102).

Next eluted was an unidentified oil (2.7 mg) which was followed by 3-*formyl*-5,7-*dimethoxy*-1-*methylcarbazole* **22**, as an orange solid (5.8 mg, 3%), m.p. 220–230 °C, δ_H 10.06 (1 H, s, CHO), 8.54 (1 H, s, 4-H), 8.30 (1 H, br s, NH), 7.71 (1 H, s, 2-H), 6.61 (1 H, d, *J* 2, 6-H), 6.39 (1 H, d, *J* 2, 8-H), 4.09 (3 H, s, OCH_3), 3.90 (3 H, s, OCH_3) and 2.59 (3 H, s, 1-CH_3); *m*/*z* (%) (EI) 269 (M^+, 100), 254 (26), 226 (64) and 211 (39); λ_{max}/nm 326 (ε 2560), 310 (10 300), 274 (49 600), 255 (38 600) and 236 (40, 200); ν_{max}(Nujol)/cm^{-1} 3320 (NH), 1670 and 1580 (Found: M^+, 269.1060. $C_{16}H_{15}NO_3$ requires *M*, 269.1048).

Oxidation of the Diphenylamine **21** *with Palladium*(II) *Acetate*.—The diphenylamine **21** (118.9 mg, 0.35 mmol) was oxidised as in the above experiment with palladium(II) acetate (164 mg, 0.73 mmol) in acetic acid (20 cm^3) for 2 h under nitrogen. The product was extracted with chloroform (2 × 25 cm^3) and the combined extracts were washed with water, dried (K_2CO_3) and concentrated to give a brown oil (78.4 mg). The main product was isolated by flash chromatography which afforded the formylcarbazole **22** as a yellow powder (10 mg, 11%), m.p. 230–235 °C whose properties were identical with those described above.

Reduction of 3-*Cyano*-5,7-*dimethoxy*-1-*methylcarbazole* **23**.—The cyanocarbazole **23**[17] (329 mg, 1.2 mmol) in dry, freshly distilled diglyme (20 cm^3) was cooled to −70 °C under an

atmosphere of nitrogen and treated dropwise with a solution of diisobutylaluminium hydride (1 mol dm^{-3} solution in toluene; 2.4 cm^3). The mixture was maintained at −60–−70 °C for 0.5 h before being allowed to warm to 20 °C over 2 h. Methanol (6 cm^3) was added to the mixture with cooling and after the latter had been stirred for 0.5 h it was treated with hydrochloric acid (2 mol dm^{-3}; 50 cm^3), stirred for 1.5 h and then poured into water (200 cm^3). The resulting suspension was extracted with chloroform (4 × 100 cm^3) and the combined extracts were washed with water (200 cm^3), dried (Na_2SO_4) and evaporated to give a yellow solid (285 mg). Flash chromatography of this eluting with dichloromethane gave 3-formyl-5,7-dimethoxy-1-methylcarbazole **22** as an off-white powder (203.9 mg, 62%), m.p. 234–235 °C, whose spectra were identical with those described above (Found: C, 71.1; H, 5.8; N, 5.0. $C_{16}H_{15}NO_3$ requires C, 71.3; H, 5.61; N, 5.2%).

3-(2,2-*Diethoxyethyliminomethyl*)-5,7-*dimethoxy*-1-*methylcarbazole* **27**.—The formylcarbazole **22** (203.9 mg, 0.76 mmol) was heated on a steam-bath for 2 h with aminoacetaldehyde diethyl acetal (101 mg, 0.76 mmol). The mixture was azeotroped with toluene (2 × 10 cm^3) and any residual toluene removed at 20 °C under high vacuum. The resulting imine was a pale yellow gum (289.1 mg, 99%) which could not be crystallised; δ_H 8.41 (1 H, s, Ar C*H*=NCH$_2$), 8.31 (1 H, br s, NH), 8.28 (1 H, s, 4-H), 6.56 (1 H, d, *J* 2, 6-H), 6.33 (1 H, d, *J* 2, 8-H), 4.86 [1 H, t, *J* 3, –C*H*(OEt)$_2$], 4.06 (3 H, s, OCH$_3$), 3.85 (3 H, s, OCH$_3$), 3.82 (2 H, d, *J* 3, CHC*H*$_2$N), 3.75 (2 H, m, OC*H*$_2$CH$_3$), 3.60 (2 H, m, OC*H*$_2$CH$_3$), 2.48 (3 H, s, 1-CH$_3$) and 1.20 (6 H, t, *J* 7, 2 × OCH$_2$C*H*$_3$).

3-(2,2-*Diethoxyethylaminomethyl*)-5,7-*dimethoxy*-1-*methylcarbazole* **28**.—The above imine **27** (280 mg, 0.73 mmol) was hydrogenated in ethanol (5 cm^3) over platinium dioxide (22 mg) at 20 °C and atmospheric pressure until uptake of hydrogen ceased. The solution was filtered through Celite and the residues washed with ethanol (20 cm^3). Removal of the solvent under reduced pressure gave the amine **28** as a green gum (238.6 mg, 85%). A small sample was converted into the *hydrochloride salt*, m.p. >300 °C, δ_H 7.96 (1 H, s, 4-H), 7.20 (1 H, s, 2-H), 6.56 (1 H, d, *J* 2, 8-H), 6.32 (1 H, d, *J* 2, 6-H), 4.83 [1 H, t, *J* 2, C*H*(OEt)$_2$], 4.12 (2 H, s, ArC*H*$_2$NCH$_2$), 4.03 (3 H, s, OCH$_3$), 3.89 (3 H, s, OCH$_3$), 3.68 (2 H, m, CH$_3$C*H*$_2$O), 3.57 (2 H, m, CH$_3$C*H*$_2$O), 2.92 (2 H, d, *J* 7, CH$_2$NC*H*$_2$CH), 2.51 (3 H, s, 1-CH$_3$) and 1.12 (6 H, t, *J* 6, 2 × OCH$_2$C*H*$_3$); *m*/*z* (%) (EI) 386 (M$^+$ − HCl, 15), 270 (13), 254 (100) and 103 (35); λ_{max}(nm 322 (ε 6360), 309 (8080), 293 (18 530), 248 (76 750) and 217 (32 940) (Found: M$^+$, 386.2205. $C_{22}H_{30}N_2O_4$ requires 386.2197).

3-[N-(2,2-*Diethoxyethyl*)-N-p-*tosylaminomethyl*]-5,7-*dimethoxy*-1-*methylcarbazole* **26**.—The above amine (300 mg, 0.78 mmol) in dry pyridine (0.75 cm^3), containing freshly crystallised toluene-*p*-sulfonyl chloride (372 mg, 1.95 mmol) was kept for 4 days after which it was poured into water (10 cm^3). The resulting suspension was extracted with diethyl ether (4 × 10 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a brown oil (349.8 mg, 83%). Flash chromatography of this [elution with diethyl ether–light petroleum (1:1)] gave the product as a colourless solid (169.6 mg, 40%), m.p. 134–140 °C. Recrystallisation from diethyl ether–light petroleum gave the pure *sulfonamide* **26** as colourless needles, m.p. 140–141 °C, δ_H 7.95 (1 H, br s, NH), 7.84 (1 H, s, 2-H), 7.79 (2 H, d, *J* 8, 2 and 6-H of tosyl), 7.27 (2 H, d, *J* 8, 3 and 5-H of tosyl), 6.96 (1 H, s, 4-H), 6.55 (1 H, d, *J* 2, 8-H), 6.30 (1 H, d, *J* 2, 6-H), 4.62 (2 H, s, ArC*H*$_2$N), 4.57 (1 H, t, *J* 4, NCH$_2$C*H*), 4.00 (3 H, s, OCH$_3$), 3.88 (3 H, s, OCH$_3$), 3.60 (2 H, m, OC*H*$_2$CH$_3$), 3.39 (2 H, m, OC*H*$_2$CH$_3$), 3.29 [2 H, d, *J* 4, C*H*$_2$CH(OEt)$_2$], 2.43 (3 H, s, 1-CH$_3$), 2.42 (3 H, s, CH$_3$ of tosyl) and 1.16 (6 H, t, *J* 7, 2 × OCH$_2$C*H*$_3$); *m*/*z* (%) (EI) 540 (M$^+$, 16), 264 (43), 254 (90) and 103 (100); λ_{max}(nm 322 (ε 4380), 312 (5000), 294 (13 750), 282sh (12 500), 255 (32 500), 247 (50 600) and 218 (26 900); ν_{max}(Nujol)/cm^{-1} 3320, 1600, 1510 and 1335 (Found: M$^+$, 540.2294. $C_{29}H_{36}N_2SO_6$ requires *M*, 540.2285).

Elution with diethyl ether–light petroleum (3:2) gave a pale yellow oil (40.1 mg) which solidified with time. Recrystallisation of this from diethyl ether–light petroleum afforded N-p-*tosylaminoacetaldehyde diethyl acetal* **29**, δ_H 7.77 (2 H, d, *J* 8, 2- and 6-H of tosyl), 7.31 (2 H, d, *J* 8, 3- and 5-H of tosyl), 4.64 [1 H, t, *J* 4, SO$_2$N*H*CH$_2$CH(OEt)$_2$], 4.46 [1 H, t, *J* 4, CH$_2$C*H*(OEt)$_2$], 3.64 (2 H, m, OC*H*$_2$CH$_3$), 3.48 (2 H, m, OC*H*$_2$CH$_3$), 3.04 [2 H, t, *J* 4, C*H*$_2$CH(OEt)$_2$], 2.42 (3 H, s, CH$_3$ of tosyl) and 1.15 (6 H, t, *J* 7, 2 × OCH$_2$C*H*$_3$); *m*/*z* (%) (EI) 242 (2), 185 (9), 155 (18), 139 (15), 103 (100), 91 (44), 75 (81) and 47 (83) (Found: C, 54.3; H, 7.4; N, 5.0. $C_{13}H_{22}NSO_4$ requires C, 54.3; H, 3.37; N, 4.88%).

8,10-*Dimethoxy*-5-*methyl*-N-p-*tosyl*-1,2-*dihydropyrido*[4,3-b]*carbazole* **30**.—The sulfonamide **26** (46.6 mg, 0.086 mmol) in dimethyl sulfoxide (1.8 cm^3) containing hydrochloric acid solution (36%; 0.13 cm^3) was heated at 60–64 °C for 2.5 h under an atmosphere of nitrogen and protected from light. The cooled mixture was poured into water (20 cm^3) and the aqueous suspension basified with ammonia solution (*d* 0.88) to give an olive-green precipitate (25.7 mg). This, by preparative TLC (ethyl acetate), gave two products. The higher R_f band (0.89), after extraction with ethyl acetate, gave the cyclic *sulfonamide* **30**, as a yellow powder (15 mg, 39%), m.p. 118–120 °C, δ_H 7.92 (1 H, br s, NH), 7.76 (2 H, d, *J* 8, 2- and 6-H of tosyl), 7.69 (1 H, s, 11-H), 7.26 (2 H, d, *J* 8, 3- and 5-H of tosyl), 6.82 (1 H, d, *J* 6, 3-H), 6.52 (1 H, s, 9-H), 6.30 (1 H, s, 7-H), 6.17 (1 H, d, *J* 6, 4-H), 4.70 (2 H, s, 1-CH$_2$), 4.03 (3 H, s, OCH$_3$), 3.87 (3 H, s, OCH$_3$), 2.39 (3 H, s, 5-CH$_3$) and 2.37 (3 H, s, CH$_3$ of tosyl); *m*/*z* (%) (EI) 448 (M$^+$, 3), 338 (15), 326 (9) and 292 (100); λ_{max}/nm 334 (ε 42 500), 256 (69 200) and 224 (58 300) (Found: M$^+$, 448.1457. $C_{25}H_{24}N_2O_4S$ requires *M*, 448.1451).

The lower fluorescent band (R_f 0.16) was extracted with redistilled methanol to give a mixture of the pyridocarbazoles **32** and **33** (see below).

Preparation of the Pyridocarbazoles **32** *and* **33**.—The sulfonamide **26** (64 mg, 0.12 mmol) in dimethyl sulfoxide (2.5 cm^3) containing hydrochloric acid (10 mol dm^{-3}; 0.18 mol) was kept in the dark, at 66 °C for 30 h and then allowed to cool. It was diluted with water (50 cm^3) and the cloudy suspension basified with ammonia solution (*d* 0.880). The mixture was extracted with chloroform (8 × 10 cm^3) and the combined extracts were washed with water (10 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give a mixture of the linear and angular pyridocarbazoles **32** and **33** (83:17) as a yellow powder (31.2 mg, 89%), m.p. >300 °C. The isomer **32** showed δ_H-([$^2H_6$]DMSO) 11.38 (1 H, s, NH), 9.36 (1 H, br s, 1-H), 8.56 (1 H, s, 11-H), 8.40 (1 H, br s, 3-H), 7.94 (1 H, d, *J* 6, 4-H), 6.68 (1 H, d, *J* 1.5, 7-H), 6.45 (1 H, d, *J* 1.5, 9-H), 4.08 (3 H, s, OCH$_3$), 3.90 (3 H, s, OCH$_3$) and 2.80 (3 H, s, 5-Me). Signals from the isomer **33** (of much lower intensity) were observed at δ 11.99 (1 H, s, NH), 9.21 (1 H, d, *J* 5, 2-H), 9.17 (1 H, s, 4-H), 8.48 (1 H, s, 1-H), 7.77 (1 H, s, 5-H), 6.80 (1 H, d, *J* 1.5, 8-H), 6.48 (1 H, d, *J* 1.5, 10-H), 4.12 (3 H, s, OCH$_3$), 3.90 (3 H, s, OCH$_3$) and 2.71 (3 H, s, 6-Me); *m*/*z* (%) (EI) 292 (M$^+$, 100), 277 (15), 249 (22) and 234 (18); λ_{max}/nm 359 (ε 5580), 293 (57 050), 283sh (42 050) and 235 (25 050) (Found: M$^+$, 292.1181. $C_{18}H_{16}N_2O_2$ requires *M*, 292.1212). The mixture was only sparingly soluble in dichloromethane, chloroform, acetone and methanol. Attempts to separate the isomers by TLC using chloroform, dichloromethane, acetone, ethyl acetate and many mixed solvents failed.

However, separation was achieved with diethyl ether–ammonia solution (*d* 0.880) (98:2) into two components R_f 0.41 and 0.26.

^{1}H *NMR Experiments.*—(a) The dihydropyridocarbazole **30** (8.1 mg, 0.018 mmol) was dissolved in [$^2H_6$]DMSO (0.5 cm^3) containing DCl in D_2O (20%; 0.05 cm^3) and its spectrum was recorded at 20 °C; its temperature was then maintained at 65 °C. Spectra were recorded after 3 and 5 h by which time none of the starting material was visible, but signals for toluene-*p*-sulfinic acid [δ_H 7.73 (2 H, d, *J* 8), 7.39 (2 H, d, *J* 8) and 2.51 (3 H, s, Me)] and the mixture of the pyridocarbazoles **32** and **33** in the ratio 85:15 were visible. The signals from the NH and ring A aromatic protons in **32** and **33** were absent. The aromatic doublets from ring D were replaced by a singlet (1 H) in each isomer.

(b) The sulfonamide **26** (8 mg, 0.018 mmol) was dissolved in [$^2H_6$]DMSO (0.5 cm^3) containing DCl in D_2O (20%; 0.05 cm^3) and a spectrum was recorded at 20 °C. The solution was then warmed to 66 °C and spectra recorded after 10, 20, 35, 60, 90, 120, 165, 315, 375, 545, 720, 990, 1170, 1650 and 1890 min. The results of these spectra are shown in Figs. 1 and 2.

5,8-*Dimethoxy*-1,4-*dimethylcarbazole* **37**.—4,7-Dimethoxyindole[29] (903 mg, 5.1 mmol) and hexane-2,5-dione (1.62 g, 14.2 mmol) and toluene-*p*-sulfonic acid (540 mg, 2.8 mmol) were heated at reflux in ethanol (18 cm^3) for 5 h. The deep red mixture was cooled and poured into water (150 cm^3) and extracted with dichloromethane (8 × 20 cm^3). The extracts were washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to give a dark green solid (1.27 g). Flash chromatography of this eluting with dichloromethane–light petroleum (50:50 → 70:30) gave the product as colourless crystals (865 mg, 67%), m.p. 125–127 °C which upon recrystallisation (ethyl acetate–light petroleum) gave the pure *carbazole* **36**, m.p. 130–131 °C, δ_H 8.25 (1 H, s, NH), 7.10 (1 H, d, *J* 6, 3-H), 6.95 (1 H, d, *J* 6, 2-H), 6.80 (1 H, d, *J* 8, 7-H), 6.53 (1 H, d, *J* 8, 6-H), 4.00 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 2.96 (3 H, s, 4-Me) and 2.54 (3 H, s, 1-Me); *m*/*z* (%) (EI) 256 (M^+ + 1, 14), 255 (M^+, 85), 240 (100) and 225 (46); λ_{max}/nm 340 (ε 7600), 326 (6740), 285 (10 640), 275 (11 790), 269 (12 380), 249 (24 880) and 237 (25 090); ν_{max}(Nujol)/cm^{-1} 3525 and 1519 (Found: C, 75.05; H, 6.9; N, 5.4. $C_{16}H_{17}NO_2$ requires C, 75.3; H, 6.71; N, 5.49%).

Formylation of the Carbazole **37**.—(a) The above carbazole **37** (250.7 mg, 0.98 mmol), phosphorus oxychloride (redistilled) (0.14 cm^3, 1.5 mmol) and *N*-methylformanilide (0.13 cm^3, 1.05 mmol) were heated at reflux in trichloroethylene (1 cm^3) for 3.5 h. On cooling, the mixture was treated with sodium acetate (0.32 g) in water (1.6 cm^3) and steam distilled. The resulting dark red residue was extracted with chloroform (7 × 10 cm^3) and the extracts were dried (K_2CO_3) and evaporated under reduced pressure to give a brown solid (79 mg). Flash chromatography of this [elution with ethyl acetate–light petroleum (0:100 → 30:70)] separated two major products. The first eluted was 3-*formyl*-1,4-*dimethoxy*-5,8-*dimethylcarbazole* **39** (23.7 mg, 85%) as cream crystals, m.p. 186–188 °C, δ_H 10.49 (1 H, s, CHO), 8.58 (1 H, br s, NH), 7.37 (1 H, s, 2-H), 7.19 (1 H, d, *J* 7, 6-H), 7.05 (1 H, d, *J* 7, 7-H), 4.06 (3 H, s, OCH_3), 4.01 (3 H, s, OCH_3), 2.98 (3 H, s, 5-Me) and 2.56 (3 H, s, 8-Me); *m*/*z* (%) (EI) 284 (M^+ + 1, 5), 283 (M^+, 29), 268 (22), 225 (12) and 120 (100); λ_{max}/nm 352 (ε 4650), 286sh (5125), 272 (11 760), 265sh (9200), 236 (9015), 226 (9435) and 205 (8095); ν_{max}(Nujol)/cm^{-1} 3340, 1675, 1580 and 1500 (Found: C, 71.9; H, 6.0; N, 4.75. $C_{17}H_{17}NO_3$ requires C, 72.07; H, 6.05; N, 4.94%).

Second eluted was 3-*formyl*-4-*hydroxy*-1-*methoxy*-5,8-*dimethylcarbazole* **42** as a tan powder (35.5 mg), δ_H 11.05 (1 H, s, OH), 9.80 (1 H, s, CHO), 8.58 (1 H, br s, NH), 7.14 (1 H, d, *J* 7, 6-H), 7.02 (1 H, d, *J* 7, 7-H), 6.82 (1 H, s, 2-H), 4.04 (3 H, s, OCH_3), 3.05 (3 H, s, 5-Me) and 2.56 (3 H, s, 8-Me); *m*/*z* (%) (EI) 270 (M^+ + 1, 35), 269 (M^+, 100), 254 (51), 226 (15) and 198 (15); λ_{max}/nm 362 (ε 5958) 295sh (17 930), 264 (15 620), 237sh (15 060), 224 (26 690) and 204 (28 250) (Found: M^+, 269.1052. $C_{16}H_{15}NO_3$ requires *M*, 269.1052). The insoluble black powder left as a result of the chloroform extractions was further extracted with boiling dichloromethane (8 × 10 cm^3) to yield a cream powder (71 mg) identified as the carbazole **42** (total yield 40%) from its spectra.

(b) *N*-Methylformanilide (0.30 cm^3, 2.4 mmol) in trichloroethylene (10 cm^3) was cooled to 0 °C and phosphorus oxychloride (0.2 cm^3, 0.329 g, 2.145 mmol) in trichloroethylene (3 cm^3) was added slowly to it. The carbazole **37** (0.4058 g, 1.59 mmol) was then added to the mixture which after being heated at reflux for 90 min was cooled. After addition of sodium acetate (0.76 g) in water (4.1 cm^3) to it, the now red reaction mixture was steam distilled. The resulting red solid residue was extracted with dichloromethane (3 × 30 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a brown powder (0.521 g). Flash chromatography of this [elution with ethyl acetate–light petroleum (0:100 → 25:75)] gave, first some *N*-methylformanilide and then 3-formyl-1,4-dimethoxy-5,8-dimethylcarbazole **39** as colourless crystals (375.8 mg, 84%). All spectra were identical with those described above.

3-(2,2-*Diethoxyethyliminomethyl*)-1,4-*dimethoxy*-5,8-*dimethylcarbazole* **44**.—The formylcarbazole **39** (0.238 g, 0.84 mmol) and aminoacetaldehyde diethyl acetal (0.11 g, 0.84 mmol) were heated on a steam-bath for 2 h. The mixture was then azeotroped with benzene (5 cm^3) in a Dean–Stark apparatus for 2 h before the benzene was removed under reduced pressure to leave the imine **44** as an orange solid (314.3 mg, 94%), m.p. 115–118 °C, δ_H 8.84 (1 H, s, CH=N), 8.40 (1 H, br s, NH), 7.53 (1 H, s, 2-H), 7.15 (1 H, d, *J* 7, 6-H), 7.00 (1 H, d, *J* 7, 7-H), 4.85 [1 H, t, *J* 5, $CH_2CH(OEt)_2$], 4.07 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 3.86 (2 H, d, *J* 5, NCH_2CH), 3.77 (2 H, m, OCH_2), 3.63 (2 H, m, OCH_2), 2.99 (3 H, s, 5-Me), 2.55 (3 H, s, 8-Me) and 1.23 (6 H, t, *J* 5, 2 × OCH_2CH_3); *m*/*z* (%) (EI) 398 (M^+, 7), 353 (3), 295 (4), and 103 (100); λ_{max}/nm 348sh (ε 20 000), 334 (24 050), 325sh (23 100), 273 (43 930), 239 (41 670) and 227sh (37 020); ν_{max}(Nujol)/cm^{-1} 3320, 1645 and 1595. The imine failed to crystallise and so it was used directly without further purification.

3-(2,2-*Diethoxyethylaminomethyl*)-1,4-*dimethoxy*-5,8-*dimethylcarbazole* **45**.—The above imine **44** (314.3 mg) in ethanol (5 cm^3) was hydrogenated at 20 °C and atmospheric pressure over platinum(IV) oxide (25 mg). The dark green mixture was filtered through Celite and the latter washed with ethanol (10 cm^3). Evaporation of the filtrate under reduced pressure left the amine **45** as a tan solid (300 mg, 95%), m.p. 122–124 °C, δ_H 8.21 (1 H, br s, NH), 7.13 (1 H, d, *J* 7, 6-H), 6.97 (1 H, d, *J* 7, 7-H), 6.90 (1 H, s, 2-H), 4.66 (1 H, t, *J* 5, NCH_2CH), 4.02 (3 H, s, OCH_3), 4.00 (2 H, s, NCH_2Ar), 3.80 (3 H, s, OCH_3), 3.69 (2 H, m, OCH_2), 3.53 (2 H, m, OCH_2), 2.97 (3 H, s, 5-Me), 2.84 (2 H, d, *J* 5, NCH_2CH), 2.53 (3 H, s, 8-Me) and 1.21 (6 H, t, *J* 5, 2 × OCH_2CH_3); *m*/*z* (%) 400 (M^+, 11), 268 (100), 238 (13) and 103 (28); λ_{max}/nm 341, 327, 279, 256, 249 and 223. The amine was used immediately without purification.

3-[N-(2,2-*Diethoxyethyl*)-N-p-*tosylaminomethyl*]-5,8-*dimethoxy*-1,4-*dimethylcarbazole* **43**.—The amine **45** (300 mg, 0.75 mmol) was dissolved in dry pyridine (2 cm^3) containing freshly crystallised toluene-*p*-sulfonyl chloride (173.4 mg, 0.912 mmol) and the mixture stirred at 20 °C in the dark for 4 days. The mixture was diluted with water (10 cm^3) and extracted with dichloromethane (5 × 10 cm^3), and the combined extracts were

washed with water (10 cm^3), dried (Na_2SO_4) and evaporated to give a brown gum (392 mg). This was chromatographed with diethyl ether–light petroleum (50:50) as eluent to give the sulfonamide **43** as a foamy white solid (355 mg, 86%), m.p. 119–121 °C, δ_H 8.21 (1 H, br s, NH), 7.74 (2 H, d, *J* 8, 2 × ArH of tosyl), 7.23 (2 H, d, *J* 8, 2 × ArH of tosyl), 7.13 (2 H, d, *J* 7, 6-H), 6.96 (1 H, d, *J* 7, 7-H), 6.83 (1 H, s, 2-H), 4.74 (2 H, s, $ArCH_2N$), 4.61 (1 H, t, *J* 5, NCH_2CH), 3.90 (3 H, s, OCH_3), 3.70 (3 H, s, OCH_3), 3.59 (2 H, m, OCH_2), 3.38 (2 H, m, OCH_2), 3.34 (2 H, d, *J* 5, NCH_2CH), 2.91 (3 H, s, 5-Me), 2.53 (3 H, s, 5-Me), 2.35 (3 H, s, tosyl-Me) and 1.0 (6 H, t, *J* 6, 2 × OCH_2CH_3); *m/z* (%) (EI) 554 (M^+, 10), 268 (36) and 103 (100); λ_{max}/nm 341 (ε 4567), 327 (4067), 316sh (2667), 279 (12410), 254sh (42 000), 250 (48 270) and 22sh (39 300) (Found: M^+, 554.245. $C_{30}H_{38}N_2SO_6$ requires *M*, 554.2441).

Cyclisation of the Sulfonamide **43**.—(a) The sulfonamide **43** (52 mg, 9.4 mmol) was dissolved in dimethyl sulfoxide (5 cm^3) containing hydrochloric acid (10 mol dm^{-3}; 0.40 cm^3) and the solution heated at 60–64 °C for 2.5 h in the dark under an atmosphere of nitrogen. On cooling, the mixture was diluted with water (25 cm^3) and the cloudy mixture basified with ammonia solution (*d* 0.880) to give a cream precipitate which was extracted with chloroform (8 × 20 cm^3). The combined organic extracts were washed with water (20 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give an orange solid (27.8 mg) which was subjected to preparative TLC; elution with ethyl acetate–light petroleum (60:40) gave two major products. That at higher R_f (0.88) was 5,11-*dimethoxy*-7,10-*dimethyl*-N-*tosyl*-1,2-*dihydropyrido*[4,3-b]*carbazole* **46** obtained as a cream powder (8 mg, 18%), m.p. 137–140 °C, δ_H 8.10 (1 H, br s, NH), 7.75 (2 H, d, *J* 8, 2 × ArH of tosyl), 7.36 (2 H, d, *J* 8, 2 × ArH of tosyl), 7.12 (1 H, d, *J* 7, 3-H), 6.96 (1 H, d, *J* 7, 4-H), 6.90 (1 H, d, *J* 7, 8-H), 6.28 (1 H, d, *J* 7, 9-H), 4.77 (2 H, s, 1-CH_2), 3.88 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 2.92 (3 H, s, 10-Me), 2.52 (3 H, s, 7-Me) and 2.35 (3 H, s, tosyl-Me); *m/z* (%) 462 (M^+, 15), 307 (47), 291 (50), 276 (83), 261 (48) and 91 (100); λ_{max}/nm 327 (ε 11 990), 288 (96 100), 252 (19 160) and 226 (14 120) (Found: M^+, 462.1613. $C_{26}H_{26}N_2SO_4$ requires *M*, 462.1613).

The product at lower R_f (0.24) was 5,11-*dimethoxy*-7,10-*dimethylpyrido*[4,3-b]*carbazole* **7**, obtained as a yellow powder (4 mg, 14%), m.p. 225–228 °C, δ_H 9.64 (1 H, br s, 1-H), 8.52 (1 H, br s, NH), 8.24 (1 H, br s, 3-H), 7.92 (1 H, d, *J* 6, 4-H), 7.28 (1 H, d, *J* 7, 8-H), 7.06 (1 H, d, *J* 7, 9-H), 4.12 (3 H, s, OCH_3), 4.08 (3 H, s, OCH_3), 3.10 (3 H, s, 10-Me) and 2.58 (3 H, s, 7-Me); *m/z* (%) (EI) 307 (M + 1, 98), 306 (M^+, 100), 291 (52) and 276 (32); λ_{max}/nm 391 (ε 3252), 336 (3936), 292 (28 290) and 243 (21 210) (Found: M^+, 306.1368. $C_{19}H_{18}N_2O_2$ requires *M*, 306.1368).

(b) The sulfonamide **43** (51 mg, 0.092 mmol) in dimethyl sulfoxide (4 cm^3) containing hydrochloric acid solution (10 mol dm^{-3}; 0.4 cm^3) under an atmosphere of nitrogen and in the dark, was heated at 60–64 °C for 10 h. Work-up as in the previous experiment gave the crude pyridocarbazole **7** as a yellow solid (24.1 mg, 86%), m.p. 203–210 °C. Preparative TLC using ethyl acetate–light petroleum (60:40) gave a pure sample of **7**, m.p. 225–228 °C whose spectra were identical with those above.

(c) ^1H *NMR experiment*. The sulfonamide **43** in [$^2H_6$]DMSO (0.5 cm^3), containing a solution of DCl in D_2O (20%; 0.084 cm^3) was kept in an NMR tube. After an initial spectrum at 20 °C the reaction was run at 64 °C and spectra were recorded after 10, 20, 35, 60, 90, 120, 180, 240, 300, 420 and 510 min. The relative molar concentrations of components are shown in Fig. 2.

6-*Fluoro*-1,4-*dimethylcarbazole* **48**.—(a) 5-Fluoroindole (1 g, 7.4 mmol) in ethanol (20 cm^3) was heated at reflux with hexane-2,5-dione (6.9 cm^3, 59 mmol) and toluene-*p*-sulfonic acid (500 mg, 2.6 mmol) for 8 h. The red solution was poured into water (400 cm^3) and the aqueous layer extracted with dichloromethane (5 × 100 cm^3). The combined organic extracts were washed with aqueous sodium hydrogen carbonate (4 × 100 cm^3) and water (3 × 100 cm^3), dried (Na_2SO_4), and evaporated under reduced pressure to give a green-black product which was stored *in vacuo* to remove unchanged hexane-2,5-dione. Chromatography of the crude product eluting with light petroleum–ethyl acetate (8:2) gave the carbazole as a colourless solid (1.3 g, 83%). Recrystallisation of a small sample from methanol gave the pure *title compound* **48** as colourless crystals, m.p. 91–92 °C (lit.,[36] gives no m.p. or other data), δ_H 7.94 (1 H, br s, NH), 7.83 (1 H, dd, *J* 9, 2, 5-H), 7.38 (1 H, dd, *J* 9, 4, 8-H), 7.15 (1 H, dt, *J* 8, 2, 7-H), 7.14 (1 H, d, *J* 8, 2-H), 6.94 (1 H, d, *J* 8, 3-H), 2.82 (3 H, s, 4-CH_3) and 2.54 (3 H, s, 1-CH_3); *m/z* (%) 213 (M^+, 100) and 198 (52); λ_{max}/nm 345 (ε 5140), 332 (4955), 292 (16 320), 262 (11 000), 242 (32 490) and 225 (33 220); ν_{max}(Nujol)/cm^{-1} 3418 (Found: C, 78.8; H, 5.8; N, 6.8. $C_{14}H_{12}FN$ requires C, 78.85; H, 5.67; N, 6.57%).

(b) 5-Fluoroindole (193 mg, 1.4 mmol) in 1,2-dichloroethane (9.8 cm^3) was heated at reflux with hexane-2,5-dione (1.3 cm^3, 11.7 mmol) and K-10 clay (579 mg) for 8 h. After cooling, the clay was filtered off and washed with dichloromethane (200 cm^3). The organic extract was washed with water (3 × 30 cm^3), dried (Na_2SO_4) and evaporated to give a brown solid which was dried *in vacuo*. Chromatography of the solid, eluting with ethyl acetate–light petroleum (2:8), gave the carbazole **48** as a colourless solid (116 mg, 38%), m.p. 91–92 °C. All spectroscopic data were identical with those previously recorded.

(c) N-p-*Fluorophenyl*-2,5-*dimethyl*-N-p-*tosylaniline* **53**.—4-Fluoro-*N*-tosylaniline (m.p. 72–74 °C, 3 g, 12.9 mmol), 1-bromo-2,5-dimethylbenzene (2.9 g, 15.5 mmol) activated[17] copper bronze (1.05 g) and anhydrous potassium carbonate (0.45 g) were stirred for 19 h at 200 °C. The cooled mixture was diluted with chloroform (45 cm^3), stirred overnight, and then filtered to remove the insoluble material. Following this, vacuum filtration of the mixture through a silica column using diethyl ether–light petroleum 10:90 → 30:70 gave the product as a colourless solid (0.85 g, 30%), m.p. 130–132 °C. Recrystallisation of the latter from diethyl ether–light petroleum gave the *sulfonamide* **53** as colourless crystals, m.p. 132–133 °C, δ_H 7.56 (2 H, d, *J* 9, 2 and 6-H of tosyl), 7.29 (2 H, dd, *J* 8.5, 4, *o*-H), 7.27 (2 H, d, partially obscured, *J* 9, 3 and 5-H of tosyl), 7.11 (1 H, d, *J* 8, 3-H), 7.04 (1 H, dd, *J* 8, 1.5, 4-H), 6.96 (2 H, t, *J* 8.5, *m*-H), 6.87 (1 H, d, *J* 1.5, 6-H), 2.46 (3 H, s, tosyl Me) and 2.25 (6 H, s, 2 and 5-Me); *m/z* (%) (EI) 369 (M^+, 29), 215 (32), 214 (100), 200 (44), 198 (56) and 91 (23) (Found: C, 68.1; H, 5.5; N, 3.7. $C_{21}H_{20}NSO_2F$ requires C, 68.27; H, 5.46; , 3.79%).

6-*Fluoro*-1,4-*dimethylcarbazole* **48**.—The fluorosulfonamide **53** (300 mg, 1.25 × 10^{-4} mol) in ethanol (300 cm^3, degassed with nitrogen) was irradiated with a medium-pressure mercury lamp (400 W) for 26 h. The solvent was removed under reduced pressure to give a brown oil which upon preparative with TLC (diethyl ether–light petroleum) afforded the fluorocarbazole **48** (30 mg, 10%) as a pale brown solid, m.p. 91–92 °C, whose spectra were identical with the sample described above.

6-*Fluoro*-3-*formyl*-1,4-*dimethylcarbazole* **49**.—The fluorocarbazole **48** (100 mg, 0.47 mmol) was heated under reflux in 1,1,2-trichloroethylene (1.5 cm^3) containing phosphorus oxychloride (0.07 cm^3, 0.75 mmol) and *N*-methylformanilide (66.5 mg, 0.49 mmol) for 3.5 h. After cooling the mixture was treated with aqueous sodium acetate (0.15 g in 1.5 cm^3 of water). The mixture was steam distilled to remove the trichloroethylene and *N*-methylaniline and the remaining aqueous layer was extracted with chloroform (4 × 10 cm^3). The combined extracts were

dried (Na_2SO_4), and the black solid residue was extracted further with methanol (25 cm^3). Since TLC analysis of the two extracts showed similar patterns, after evaporation the crude products were combined and chromatographed. Elution with increasing concentrations of diethyl ether in light petroleum gave two products.

After unchanged fluorocarbazole (5 mg, 5%), next eluted was a colourless solid, which was identified as 6-*fluoro*-3-*formyl*-1,4-*dimethylcarbazole* **49** (94 mg, 83%), m.p. 232–233 °C. Recrystallisation from methanol gave colourless crystals, m.p. 234–235 °C, δ_H([$^2H_6$]DMSO) 11.84 (1 H, br s, NH), 10.42 (1 H, s, CHO), 8.04 (1 H, dd, *J* 9, 2, 5-H), 7.73 (1 H, s, 2-H), 7.60 (1 H, dd, *J* 9, 4, 8-H), 7.38 (1 H, dt, *J* 9, 2, 7-H), 3.13 (3 H, s, 4-CH_3) and 2.60 (3 H, s, 1-CH_3). Saturation of the 4-CH_3 protons at δ 3.13 enhanced signals due to 5-H at δ 8.04 (16.5%) and 3-CHO at δ 10.42 (10.5%); *m*/*z* (%) (EI) 241 (M^+, 100) and 212 (51); λ_{max}/nm 332 (ε 9290), 289 (27 390), 276 (27 120), 248 (14 890) and 238 (16 120); ν_{max}(Nujol)/cm^{-1} 3300 (NH) and 1649 (CHO) (Found: C, 74.5; H, 5.2; N, 5.7. $C_{15}H_{12}FNO$ requires C, 74.67; H, 5.01; N, 5.81%).

3-[N-(2,2-*Diethoxyethyl*)-N-*tosylaminomethyl*]-6-*fluoro*-1,4-*dimethylcarbazole* **55**.—The formylcarbazole **49** (258 mg, 1.08 mmol) and aminoacetaldehyde diethyl acetal (158 mg, 1.19 mmol) were heated on a steam-bath for 2 h after which dry benzene was added to the mixture and the water formed in the reaction removed by azeotropic distillation. Evaporation of the solvent gave an orange oil (422 mg) which showed signs of decomposition on TLC. Without purification, the crude product (422 mg) in ethanol (8 cm^3) was hydrogenated at room temperature and atmospheric pressure over Adams catalyst (50 mg). The solution was filtered and evaporated under reduced pressure to yield a dark brown oil (417 mg) which again showed signs of decomposition on TLC. The crude product (417 mg) was immediately dissolved in dry pyridine (4 cm^3) containing freshly crystallised toluene-*p*-sulfonyl chloride (244 mg, 1.27 mmol) and stirred under an atmosphere of nitrogen for 4 days at room temperature. The mixture was then poured into water (25 cm^3) and the aqueous suspension extracted with diethyl ether (4 × 15 cm^3) and methylene dichloride (4 × 15 cm^3). The extracts were washed with hydrochloric acid (0.5 mol dm^{-3}; 3 × 30 cm^3) and water (3 × 30 cm^3) dried (Na_2SO_4) and concentrated to give a brown oil. Chromatography of the latter, eluting with diethyl ether–light petroleum (8 : 2), gave a colourless solid (225 mg, m.p. 135–137 °C and 152–157 °C). The ^{1}H NMR spectrum indicated a mixture of the required sulfonamide **55** and the sulfonamide **29** in the ratio 3.4 : 1 respectively. The spectrum of the sulfonamide **29** was identical with an authentic specimen. Recrystallisation of the mixture from methanol gave the pure sulfonamide **55** as a colourless solid (124 mg, 23%), m.p. 175–176 °C, δ_H 7.94 (1 H, br s, NH), 7.82 dd, *J* 9, 2, 5-H), 7.72 (2 H, d, *J* 8, tosyl 2- + 6-H), 7.37 (1 H, dd, *J* 9, 4, 8-H), 7.27 (2 H, d, *J* 8, tosyl 3- + 5-H), 7.15 (1 H, dt, *J* 9, 2, 7-H), 6.98 (1 H, s, 2-H), 4.66 (2 H, s, ArCH_2N), 4.47 [1 H, t, *J* 5, $CH_2CH(OEt)_2$], 3.55 (2 H, m, *J* 7, OCH_2CH_3), 3.33 (2 H, m, *J* 7, OCH_2CH_3), 3.20 [2 H, d, *J* 5, $CH_2CH(OEt)_2$], 2.74 (3 H, s, 4-CH_3), 2.40 (6 H, s, tosyl-CH_3, 1-CH_3) and 1.08 (6 H, t, *J* 7, 2 × OCH_2CH_3); *m*/*z* (%) (EI) 512 (M^+, 1), 421 (4), 357 (3), 265 (3), 226 (46), 211 (6) and 103 (100); λ_{max}/nm 347 (ε 3912), 333 (3850), 295 (14 340), 285sh (9446), 263 (18 700), 253sh (32 490), 243 (38 070) and 235 (36 640); ν_{max}(Nujol)/cm^{-1} 3364, 1353, 1167, 1084, 1114 and 1055 (Found: C, 65.5; H, 6.6; N, 5.7. $C_{28}H_{33}FN_2O_4S$ requires C, 65.60; H, 6.49; N, 5.47%).

A further fraction from the column afforded the carbazole alcohol **50** obtained as a yellow solid (6 mg, 2%), m.p. 148–155 °C, δ_H 7.99 (1 H, br s, NH), 7.91 (1 H, dd, *J* 10, 2, 5-H), 7.42 (1 H, dd, *J* 9, 4, 8-H), 7.26 (1 H, s, 2-H), 7.18 (1 H, dt, *J* 9, 2, 7-H), 4.86 (2 H, s, CH_2OH), 2.88 (3 H, s, 4-CH_3) and 2.56 (3 H, s, 1-CH_3); *m*/*z* (%) (EI) 243 (M^+, 10), 226 (13), 212 (9), 205 (68), 177 (7) and 147 (13); ν_{max}(Nujol)/cm^{-1} 3434, 3327 and 1095. The crude solid showed signs of decomposition on TLC hence no attempts were made to purify it further.

9-*Fluoro*-5,11-*dimethylpyrido*[4,3-b]*carbazole* **8**.—The sulfonamide **55** (240 mg, 0.47 mmol) was heated to reflux in dioxane (6 cm^3) containing hydrochloric acid (6 mol dm^{-3}; 0.47 cm^3) under an atmosphere of nitrogen in the dark for 7.5 h. The resultant yellow solid and solution were poured into water (30 cm^3) and extracted with chloroform (3 × 12 cm^3). The yellow solid was incompletely soluble in water or chloroform. The aqueous solution was basified with dilute ammonia solution and re-extracted with chloroform (3 × 12 cm^3). The chloroform extracts were washed with water (2 × 12 cm^3) and dried (Na_2SO_4). The yellow insoluble solid was filtered off (35 mg). Evaporation of the chloroform extracts also gave a yellow solid (75 mg). The ^{1}H NMR spectrum of the crude insoluble solid and that from the chloroform extract showed them both to be essentially 9-fluoroellipticine (80% combined yield). Chromatography of the original solid (35 mg) eluting with increasing concentrations of ethyl acetate in light petroleum followed by increasing concentrations of methanol in ethyl acetate gave 9-fluoroellipticine **8** as a yellow powder (27 mg), m.p. 323–324 °C (decomp.), δ_H([$^2H_6$]DMSO) 11.42 (1 H, br s, NH), 9.73 (1 H, br, 1-H), 8.47 (1 H, d, *J* 5, 3-H), 8.17 (1 H, dd, *J* 10, 2, 10-H), 7.96 (1 H, d, *J* 5, 4-H), 7.58 (1 H, dd, *J* 10, 5, 7-H), 7.42 (1 H, dt, *J* 10, 2, 8-H), 3.27 (3 H, s, 11-Me) and 2.80 (3 H, s, 5-Me); *m*/*z* (%) (CI) 265 (M + 1, 100); λ_{max}/nm 407 (ε 2957), 389 (3023), 348 (2310), 332 (4171), 317 (2917), 298 (36 800), 287 (38 240), 276 (34 280), 238 (16 300), 214 (13 580) and 205 (14 490) (Found: M + 1, 265.114. $C_{17}H_{14}FN_2$ requires *M* + 1, 265.114).

Acknowledgements

We thank the Wellcome Research Laboratories, Beckenham, Kent for a CASE award (to R. J. H.), the SERC for a quota award (to J. M.), the Instituto National de Investigacao Cientifica, Portugal for support (to M. J. R. P. Q.), Amersham International plc and the Overseas Research Students Awards Scheme for scholarships (to P. M. D.) and the British Council (Treaty of Windsor Award).

References

1 (*a*) M. Sainsbury, *Synthesis*, 1977, 437; (*b*) A. Gouyette, R. Reynaud, J. Sadet, M. Baillarge, C. Gansser, S. Cros, F. Le Goffic, J.-B. Le Pecq, C. Paoletti and C. Viel, *Eur. J. Med. Chem.—Chim. Ther.*, 1980, **15**, 503.
2 C. Auclair, *Arch. Biochem. Biophys.*, 1987, **259**, 1.
3 M. J. E. Hewlins, A.-M. Oliveira-Campos and P. V. R. Shannon, *Synthesis*, 1984, **4**, 289.
4 G. W. Gribble and M. G. Saulnier, *Heterocycles*, 1985, **23**, 1277.
5 P. A. Cranwell and J. E. Saxton, *J. Chem. Soc.*, 1962, 3482.
6 L. K. Dalton, S. Demerac, B. C. Elmes, J. W. Loder, J. M. Swan and T. Teitei, *Aust. J. Chem.*, 1967, **20**, 2715.
7 (*a*) A. J. Birch, A. H. Jackson and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1974, 2185; (*b*) A. H. Jackson, P. R. Jenkins and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1698; (*c*) R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, R. W. Kierstead and E. Grunberg, *J. Med. Chem.*, 1975, **18**, 755.
8 J. Y. Lallemand, P. Lemaitre, L. Beeley, P. Lesca and D. Mansuy, *Tetrahedron Lett.*, 1978, **15**, 1261.
9 J. Gilbert, D. Rousselle, C. Gansser and C. Viel, *J. Heterocycl. Chem.*, 1979, **16**, 7.
10 D. A. Taylor, M. M. Baradarani, S. J. Martinez and J. A. Joule, *J. Chem. Res.*, 1979, (*S*) 387; (*M*) 4801.
11 M. J. E. Hewlins, A. H. Jackson, A.-M. F. Oliveira-Campos and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2906.
12 (*a*) C. Gansser, X. Leveque, M. Plat, C. Viel, C. Merienne, C. Malvy and S. Cros, *Farmaco. Ed. Sci.*, 1982, **37**, 283; (*b*) C. Gansser, C. Viel, C. Malvy and S. Cros, *Farmaco. Ed. Sci.*, 1980, **35**, 887.

13 (*a*) I. Hogan, P. D. Jenkins and M. Sainsbury, *Tetrahedron*, 1990, **46**, 2943; (*b*) I. Hogan, P. D. Jenkins and M. Sainsbury, *Tetrahedron Lett.*, 1988, **49**, 6505.
14 R. J. Hall, A. H. Jackson, A.-M. F. Oliveira-Campos and P. V. R. Shannon, *J. Chem. Res.*, 1990, (*S*) 314; (*M*) 2501.
15 R. J. Hall, A.-M. F. Oliveira-Campos, M.-J. R. P. Queiroz and P. V. R. Shannon, *J. Chem. Res.*, 1992, (*S*) 2; (*M*) 0114.
16 A.-M. Oliveira-Campos, M.-J. R. P. Queiroz and P. V. R. Shannon, *Chem. Ind.* (*London*), 1991, 352.
17 R. J. Hall, J. Marchant, A.-M. F. Oliveira-Campos, M.-J. R. P. Queiroz and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3439.
18 R. J. Hall, A. H. Jackson, A.-M. F. Oliveira-Campos, M.-J. R. P. Queiroz and P. V. R. Shannon, *Heterocycles*, 1990, **3** (3), 401.
19 M. Sainsbury and D. K. Weerasinghe, *J. Chem. Soc., Chem. Commun.*, 1981, 630.
20 M. Sainsbury, D. Weerasinghe and D. Dolman, *J. Chem. Soc., Perkin Trans. 1*, 1982, 587.
21 M. Sainsbury and R. F. Schinazi, *J. Chem. Soc., Perkin Trans. 1*, 1976, 1155.
22 D. Weerasinghe, Ph.D. Thesis, University of Bath, 1982.
23 A. I. Vogel, *Textbook of Practical Organic Chemistry*, Longman, London, 1986, 4th edn., p. 727.
24 M. J. E. Hewlins, A. H. Jackson, A. Long, A.-M. Oliveira-Campos and P. V. R. Shannon, *J. Chem. Res.*, 1986, (*S*) 292; (*M*) 2645.
25 (*a*) D. Rousselle, J. Gilbert and C. Viel, *CR Seances Acad. Sci.*, 1977, **284C**, 377; (*b*) J. Gilbert, D. Rousselle, C. Gansser and C. Viel, *J. Heterocycl. Chem.*, 1979, **16**, 7.
26 (*a*) Y. Murakami, Y. Yokoyama and N. Okuyama, *Tetrahedron Lett.*, 1983, **24**, 2189; (*b*) N. S. Narashimhan and S. M. Gokhale, *J. Chem. Soc., Chem. Commun.*, 1985, 86.
27 J. P. Kutney, M. Noda, N. G. Lewis, B. Monteiro, D. Mostowicz and B. R. Worth, *Can. J. Chem.*, 1982, **60**, 2426.
28 S. Veeraraghavan and F. D. Popp, *Synthesis*, 1980, 384.
29 G. Rodighiero, G. Malesani and U. Fornasiero, *Gazz. Chim. Ital.*, 1961, **91**, 742.
30 M. Watanabe and V. Snieckus, *J. Am. Chem. Soc.*, 1980, **102**, 1457.
31 D. A. Taylor and J. A. Joule, *J. Chem. Soc., Chem. Commun.*, 1979, 642.
32 C. Paoletti, P. Le Cointe, P. Lesca, S. Cros, D. Mansuy and N. Dat Xuong, *Biochimie*, 1978, **60**, 1003.
33 P. Lesca, P. LeCointe, D. Pelaprat, C. Paoletti and D. Mansuy, *Biochem. Pharmacol.*, 1980, **29**, 3231.
34 G. F. Alberici, J.-M. Bidart, P. Moingeon, J.-M. Mondesir, C. Bohuon and R. De Jager, *Biochem. Pharmacol.*, 1983, **32**, 2837.
35 C. Malvy and S. Cros, *Biochem. Pharmacol.*, 1986, **35**, 2264.
36 T. Tabka, B. Letois, J.-C. Lancelot, P. Gauduchon, J.-F. Heron, J.-Y. Le Talaer, S. Rault and M. Robba, *Eur. J. Med. Chem.*, 1989, **24**, 605.

Paper 3/01612I
Received 22*nd March* 1993
Accepted 29*th April* 1993