Synthesis of 11-Amino-substituted-9-methoxy-5-methyl-6*H*-pyrido[4,3-*b*]-carbazoles

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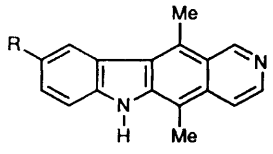
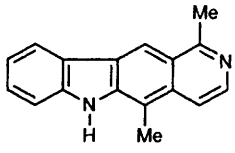
A route to 11-amino-substituted-6*H*-pyrido[4,3-*b*]carbazoles has been studied. Thus, condensation of 2-(4-lithiopyridine-3-yl)-4,4-dimethyloxazoline with 2-acetyl-5-methoxy-1-phenylsulphonylindole led to a low yield of the expected alcohol, which upon hydrolysis gave a complex mixture. A better starting building block was 4-acetyl-*N*,*N*-diisopropylnicotinamide obtained either from *N*,*N*-diisopropyl-4-lithionicotinamide (low yield) or from pyridine-3,4-dicarboxylic anhydride, using a 4-step sequence. This compound was treated with 2-lithio-5-methoxy-1-phenylsulphonylindole, affording *N*,*N*-diisopropyl-4-[1-(5-methoxy-1-phenylsulphonylindol-2-yl)-1-hydroxyethyl]nicotinamide. Hydrolysis and then reduction led to 4-[1-(5-methoxy-1-phenylsulphonylindol-2-yl)-ethyl]nicotinic acid whose amides were cyclized by phosphorus trichlorideoxide. Finally, the title compounds were obtained by Raney-nickel reduction–elimination of the 6-phenylsulphonyl protecting group.

The plant alkaloids ellipticine **1a** (5,11-dimethyl-6*H*-pyrido[4,-3-*b*]carbazole), 9-methoxyellipticine **1b** and olivacine **2** display significant antitumour activity in several experimental animal tumour systems.[1,2] A derivative of 9-hydroxyellipticine **1c**, 2-methyl-9-hydroxy elliptinium acetate **3** (elliptinium), was even commercialized for clinical use in human advanced breast cancer and other solid tumours.[3]



1a; R = H
b; R = OMe
c; R = OH



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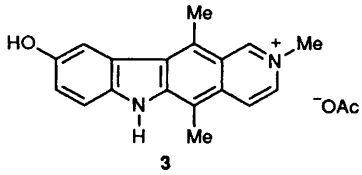

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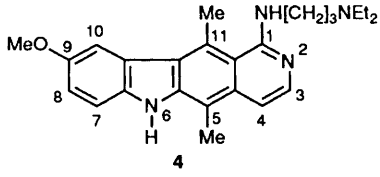

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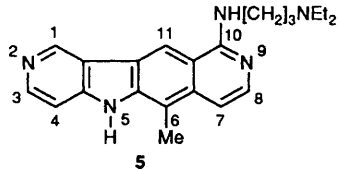

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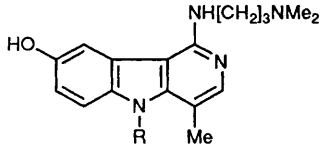
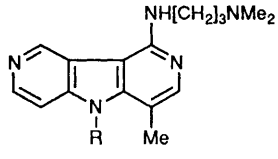


6a; R = H
b; R = Me



7a; R = H
b; R = Me

However, we have demonstrated, in various papers from our laboratory, that substitution at the 1-position of methoxy-ellipticine by a dialkylaminoalkylamino side chain markedly increased the biological properties in these series,[4] and in the 9-aza analogues series as well.[5,6]

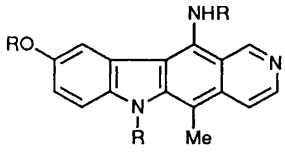
The biological results obtained with the selected compounds **4** (retelliptine) and **5** (pazelliptine), which display high anti-tumour activity against a large spectrum of experimental tumours in mice,[5] have prompted others to undertake clinical trials with these two new drugs.[7,8] Moreover, we have also described in more recent papers, the synthesis and antitumour properties of the tricyclic analogues **6** and **7**.[9,10] In particular, the γ-carboline derivatives **6a** and **6b** display potent biological activity in various animal systems, including against both experimental leukaemia and solid tumours.[10a]

This prompted us to investigate the as-yet unknown series of 11-amino-substituted-6*H*-pyrido[4,3-*b*]carbazole derivatives **8**, which appear to be closely related to compounds **4** and **6**.

The synthesis of ellipticine derivatives has been reviewed repeatedly.[11] Despite the various methods reported to date, none allowed the synthesis of such compounds as **8**. This report describes our results in this area.

At first, we tried to work out a scheme using the easily available 4,4-dimethyl-2-(pyridin-3-yl)oxazoline **9a**[12] and 2-acetyl-5-methoxy-1-phenylsulphonylindole **10a** as starting materials. Indeed, compound **10a** was obtained in 60% yield from 2-lithio-5-methoxy-1-phenylsulphonylindole **10b** and a large excess of acetic anhydride.

In this route, however, some difficulties were encountered: (i) when the oxazoline **9a** was lithiated to give derivative **9b** with



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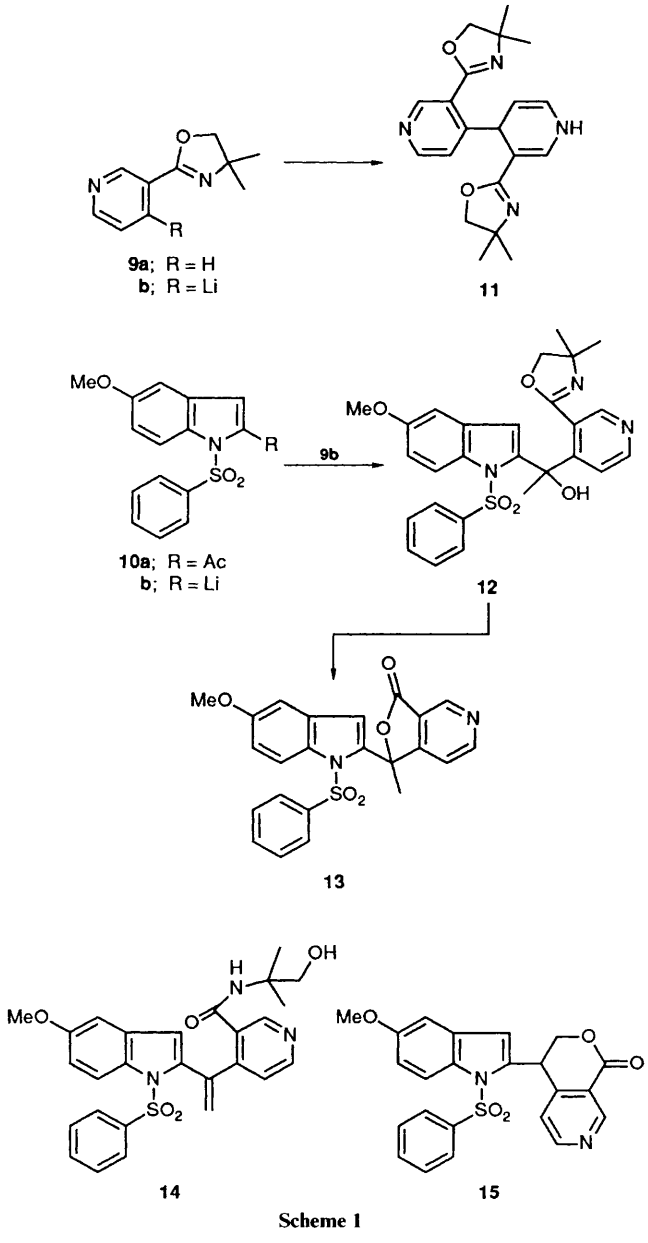
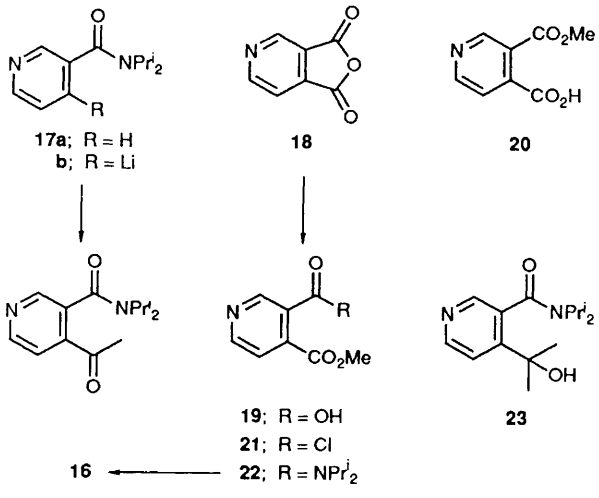
1.1 mol equiv. of *N*-lithio-2,2,6,6-tetramethylpiperidine (LiTMP) at 0 °C as described,[12] and the product was allowed to react with benzophenone, the product isolated was the unreported dimer **11**, resulting from addition of the salt **9b** to its parent **9a**; (ii) complete lithiation of compound **9a** was observed at −78 °C during 3 h with 3 mol equiv. of LiTMP but reaction with ketone **10a** led to the expected alcohol **12** with a yield limited to 40%; (iii) acidic hydrolysis of this last compound led to a mixture of lactone **13** (22% yield), ethylenic compound **14** (16.5%) and another product (~3%), probably the lactone **15**, which was not obtained in pure form (Scheme 1) (see Experimental section).



Scheme 1

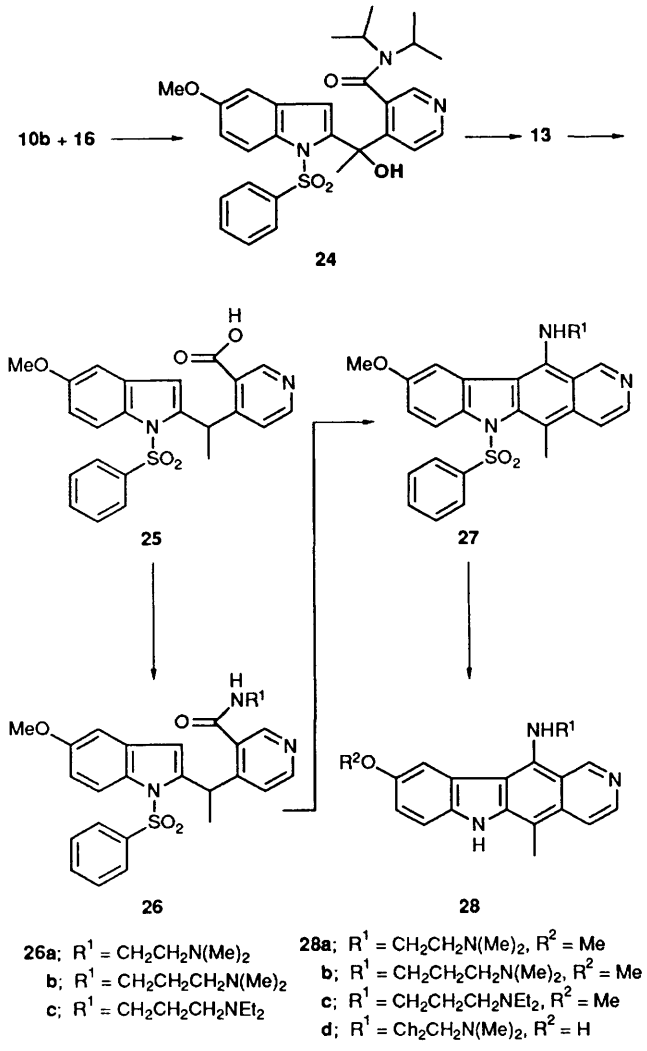
In view of these limitations to our original approach, we decided to use lithio derivative **10b** for the introduction of the indole part of the target structure and a new pyridine derivative as the complementary building block. 4-Acetyl-*N*,*N*-diisopropylnicotinamide seemed suitable for this purpose. It was first obtained by lithiation of *N*,*N*-diisopropylnicotinamide **17a** and reaction of the resulting lithio species **17b** with an excess of acetic anhydride. This reaction was performed under various conditions, but the best yield which was obtained for pure isolated ketone **16** did not exceed 15%. For satisfactory larger scale preparation of this key intermediate, we then chose pyridine-3,4-dicarboxylic anhydride **18** as a starting compound. Addition to a cooled −78 °C solution of methanol in dichloromethane gave 4-methoxycarbonylnicotinic acid **19** as the major product and a small amount of its isomer **20**. From half-ester **19**, the acid chloride **21** and *N*,*N*-diisopropyl-4-methoxycarbonylnicotinamide **22** were successively obtained under the usual conditions and this latter compound was then treated with methyllithium, giving 4-(1-hydroxy-1-methylethyl)-*N*,*N*-diisopropylnicotinamide **23** as a by-product and mainly the expected ketone **16** (23% overall yield from **18**) (Scheme 2).



Scheme 2

Condensation of the lithioindole **10b** with ketone **16** was then studied under various conditions. Whereas it failed when performed in diethyl ether, it gave a 55% yield of the alcohol **24** in tetrahydrofuran (THF). In contrast to the oxazoline **12**, this amide easily and cleanly led to the lactone **13** by acidic hydrolysis (80% yield). For reduction of the lactone **13** to the acid **25**, several attempts were first performed using Cu^{2+}-activated zinc, in basic medium. According to the literature,[13] these conditions usually work for similar lactones. However, in our hands the starting compound was totally recovered. The expected transformation was anyway obtained by the use of hydrochloric acid-activated zinc in boiling formic acid,[14] which provided 4-[1-(5-methoxy-1-phenylsulphonylindol-2-yl)ethyl]-nicotinic acid **25** in 62% yield. Amides **26a–c** were then prepared by reaction of the carbonyldiimidazole-activated acid with the required diamines. Subsequent cyclization in boiling phosphorus trichloride oxide gave the 11-amino-substituted-9-methoxy-5-methyl-6-phenylsulphonyl-6*H*-pyrido[4,3-*b*]carbazoles **27**, which were immediately treated by Raney-nickel in boiling ethanol to eliminate the 6-phenylsulphonyl protecting group. The target compounds, 11-(dialkylaminoalkyl)amino)-9-methoxy-5-methyl-6*H*-pyrido[4,3-*b*]carbazoles **28a–c** were thus obtained. Finally, boron tribromide demethylation of compound **28a** led to the corresponding phenolic derivative **28d** (Scheme 3).

Cytotoxicity and antitumour activity of these new 6*H*-



Scheme 3

pyrido[4,3-*b*]carbazole derivatives were determined under the usual conditions.[15] Results are given in Table 1.

Table 1 Cytotoxicity to L1210 cultured cells (compounds **28a–d**) and *in vivo* antitumour properties (compounds **28a** and **28d**) on L1210 leukaemia

Compound	ID_{50} [a] (10^{-6} mol dm^{-3}) (L1210 cells)	$T/C \times 100$,[b] L1210 ip (mg kg^{-1}, single dose at day 1, ip)
28a	0.22	100 (30)
28b	0.32	
28c	0.37	
28d	0.03	143 (30)
4	0.011	267 (40) [2/10][c]

[a] ID_{50}: the micromolar concentration of drug that, when added to cultures of L1210 cells for a period of 48 h, reduced the counted cells to 50% of the control value. [b] $T/C \times 100$: antitumour activity evaluated according to the formula $T/C \times 100$; median day of survival of treated animals at a given dose/median day of survival of control mice. [c] Ref. 8.[ ]: Long-term survivors.

When compared with reference compound **4**, it can be clearly seen that displacement of the side chain from the 1- to the 11-position induces a decrease in cytotoxicity. Complementary *in vivo* studies were performed with compounds **28a** and **28d** on L1210 leukaemia.[16] They confirmed the *in vitro* results since only the phenolic compound **28d** displays a positive (but borderline) activity in this system.

To sum up, the successful preparation of 4-[1-(5-methoxy-1-phenylsulphonylindol-2-yl)ethyl]nicotinic acid **25** allowed us to develop a route to the as yet unknown 11-amino-substituted-9-methoxy-5-methyl-6*H*-pyrido[4,3-*b*]carbazoles (ellipticines). Biological evaluation and comparison with their 1-amino-substituted analogues show that displacement of the dibasic side chains from the 1- to the 11-position leads to a loss of their antitumour properties.

Experimental

M.p.s (Kofler hot stage) are uncorrected. ^{1}H NMR spectra were obtained on a Varian XL 100 spectrometer, with tetramethylsilane as internal standard. *J*-Values are given in Hz. Purification of products was followed by TLC on silica gel and alumina. Homogeneity of non-crystalline compounds was established by TLC in at least three solvents of differing polarity. Elemental analyses were performed by Service Central de Microanalyses du CNRS, 91190 Gif-sur-Yvette, France.

2-Acetyl-5-methoxy-1-phenylsulphonylindole **10a**.—5-Methoxy-1-phenylsulphonylindole[16] (1.148 g, 4 mmol) was dissolved in freshly distilled, dry THF (25 cm^3) in a 100 cm^3, three-necked flask protected from moisture under argon. Butyllithium (3.2 cm^3 of the commercially available 1.6 mol dm^{-3} solution, 5 mmol) was added to the mixture at 0 °C, and the mixture was stirred for 2 h. The resulting solution of the lithio derivative **10b** was cooled to −10 °C and cautiously transferred into a stirred solution of acetic anhydride (4.4 cm^3, 40 mmol) in THF (10 cm^3) cooled at −10 °C and maintained under argon. The mixture was allowed to reach room temperature, was then stirred for 18 h, and poured into 3 mol dm^{-3} aq. ammonium chloride (50 cm^3). The organic phase and diethyl ether extracts (2 × 40 cm^3) were dried ($MgSO_4$). After the usual work-up, the residue was crystallized twice from ethyl acetate, to give compound **10a** as beige crystals (0.836 g, 63.5%), m.p. 161 °C (Found: C, 61.8; H, 4.8; N, 4.2; S, 9.9. $C_{17}H_{15}NO_4S$ requires C, 61.99; H, 4.59; N, 4.25; S, 9.73%).

Lithiation of the Oxazoline **9a** *at* 0 °C *and Reaction with Benzophenone.—Production of* 2-{4-[3-(4,5-*dihydro*-4,4-*dimethyloxazol*-2-*yl*)-1,4-*dihydropyridin*-4-*yl*]*pyridin*-3-*yl*}-4,5-*dihydro*-4,4-*dimethyloxazole* **11**. In a 250 cm^3, three-necked flask, dry THF (50 cm^3) was cooled to 0 °C and protected from moisture. Under argon, butyllithium (7 cm^3 of the 1.6 mol dm^{-3} solution, 11.2 mmol) and 2,2,6,6-tetramethylpiperidine (2.07 cm^3, 12.3 mmol) were successively added to the mixture at 0 °C which, after being stirred for 3 h at 0 °C, was treated with a solution of compound **9a** (1.76 g, 10 mmol) in dry THF (25 cm^3) added dropwise. The resulting mixture was left for 1 h, a solution of benzophenone (5.46 g, 30 mmol) in THF (25 cm^3) was added at 0 °C, and the mixture was stirred at room temperature for 18 h. After addition of water (150 cm^3) and extraction with diethyl ether (4 × 50 cm^3), the combined extract was dried ($MgSO_4$) and evaporated. The residue was washed with boiling pentane to eliminate the starting oxazoline **9a** and benzophenone. The resulting solid was recrystallized twice from toluene, to give crystals (430 mg, 24%), m.p. 230 °C. This compound was the *hydrogenated dimer* **11** (Found: C, 68.4; H, 6.9; N, 15.65. $C_{20}H_{24}N_4O_2$ requires C, 68.16; H, 6.86; N, 15.90%). It was a single new component, as shown by TLC of the crude mixture; $\delta_H(CDCl_3)$ 1.06 and 1.23 (2 × 3 H, 2 s), 1.49 (6 H, s), 3.84 and 4.19 (2 × 2 H, 2 s, CH_2O), 5.0 (1 H, dd, 5′-H), 5.59 (1 H, d, $J_{4',5'}$ 4.8, 4′-H), 6.09 (1 H, d, $J_{6',5'}$ 7.6, 6′-H), 7.26 (overlapped by $CDCl_3$, 1 H, 2′-H), 7.33 (1 H, br s, NH′), 7.47 (1 H, d, $J_{5,6}$ 5.2, 5-H), 8.63 (1 H, d, 6-H) and 8.93 (1 H, s, 2-H).

1-[3-(4,5-*Dihydro*-4,4-*dimethyloxazol*-2-*yl*)*pyridin*-4-*yl*]-1-(5-*methoxy*-1-*phenylsulphonylindol*-2-*yl*)*ethanol* **12**.—Under the usual conditions, butyllithium (18.75 cm^3 of 1.6 mol dm^{-3} solution, 30 mmol) and THF (100 cm^3) were added to a solution of 2,2,6,6-tetramethylpiperidine (5.6 cm^3, 33 mmol) in THF (50 cm^3) at 0 °C. The mixture was stirred for 3 h at this temperature, a solution of the oxazoline **9a** (2.68 g, 15.2 mmol) in THF (50 cm^3) was added dropwise, and the mixture was stirred for 2 h at 0 °C, then cooled to −78 °C. A sonicated suspension of 2-acetyl-5-methoxy-1-phenylsulphonylindole **10a** (5 g, 15.2 mmol) in THF (200 cm^3) was added all at once. The cooling bath was removed and the mixture was stirred for 18 h at room temperature. Addition of water (200 cm^3), subsequent extraction with diethyl ether (2 × 100 cm^3), and the usual work-up provided a residue, which was crystallized twice from ethanol to give *compound* **12** as crystals (3.02 g, 39%), m.p. 230 °C (corresponding to the hemihydrate) (Found: C, 62.9; H, 5.3; N, 8.3; S, 6.5. $C_{27}H_{27}N_3O_5S{\cdot}0.5\ H_2O$ requires C, 63.02; H, 5.48; N, 8.17; S, 6.23%); $\delta_H(CDCl_3)$ 1.34 and 1.38 (6 H, 2 s, MeOx), 2.05 [3 H, s, C(OH)Me], 3.84 (3 H, s, OMe), 4.06 (2 H, s, CH_2O), 6.88 (1 H, s, 3-H), 6.99 (2 H, m, 4- + 6-H), 7.45 (6 H, m, 5 × ArH + 5-H_{pyr}), 8.02 (1 H, d, $J_{7,6}$ 8.7, 7-H), 8.44 (1 H, d, $J_{6,5}$ 5.4, 6-H_{pyr}) and 8.90 (1 H, s, 2-H_{pyr}).

1-(5-*Methoxy*-1-*phenylsulphonylindol*-2-*yl*)-1-*methylfuro*[3,4-c]*pyridin*-3(1H)-*one* **13**.—*Method A*. Compound **12** (1 g, 1.98 mmol) was heated in 1 mol dm^{-3} hydrochloric acid (50 cm^3) at reflux for 5 h. The cooled mixture was filtered and the insoluble solid was recrystallized from ethanol to provide the *lactone* **13** as microcrystals (0.19 g, 22%), m.p. 207 °C (Found: C, 63.6; H, 4.0; N, 6.4; S, 7.3. $C_{23}H_{18}N_2O_5S$ requires C, 63.58; H, 4.18; N, 6.45; S, 7.38%); $\delta_H[(CD_3)_2SO]$ 2.18 (3 H, s, 1-Me), 3.8 (3 H, s, OMe), 7.07 (1 H, dd, $J_{6',7'}$ 9, $J_{6',4'}$ 2, 6′-H), 7.18 (1 H, d, 4′-H), 7.3 (1 H, d, $J_{3',7'}$ 0.4, 3′-H), 7.63 (6 H, m, 5 × ArH + 7-H), 8.03 (1 H, d, 7′-H), 8.94 (1 H, d, $J_{6,7}$ 5, 6-H) and 9.21 (1 H, d, $J_{4,7}$ 1, 4-H) (*Note*: ′ numbering for indole ring).

Method B. The amide **24** (1 g, 1.87 mmol) was heated in 1 mol dm^{-3} hydrochloric acid (45 cm^3) at reflux for 18 h (TLC monitoring, disappearance of starting compound **24**). After cooling, the solid was collected by filtration and recrystallized from ethanol, to give crystals (0.65 g, 80%), identical in all respects with the compound obtained by method A (m.p. 207 °C; δ_H).

N-(2-*Hydroxy*-1,1-*dimethylethyl*)-4-[1-(5-*methoxy*-1-*phenylsulphonylindol*-2-*yl*)*vinyl*]*nicotinamide* **14**.—The acid filtrate from the preparation of the preceding lactone (Method A) was evaporated to dryness under reduced pressure, the residue was taken up in water, and the mixture was neutralized to pH 7 with saturated aq. sodium hydrogen carbonate. The resulting solid was collected and chromatographed on a silica gel column. Elution with dichloromethane gave a first, homogeneous (TLC) fraction, which was collected and evaporated. The solid (77 mg) was an unresolved 2:1 mixture of the lactone **13** and (probably) its isomer **15**. Hence, in addition to the signals of lactone **13** and to those corresponding to the common structures, two peaks (δ 4.90, d and 5.32, t) characteristic of an $(Ar)_2CHCH_2O$ sequence, were observed.

With a 5% ethanol–dichloromethane mixture as eluent, a second, pure fraction was collected and evaporated. The solid was recrystallized from ethanol to give *compound* **14** as rosy crystals (165 mg, 16.5%), m.p. 228 °C (Found: C, 64.25; H, 5.5; N, 8.1; S, 6.6. $C_{27}H_{27}N_3O_5S$ requires C, 64.14; H, 5.38; N, 8.31; S, 6.34%); $\delta_H[(CD_3)_2SO]$ 1.14 (6 H, s, CMe_2), 3.41 (overlapped by HOD, CH_2OH), 3.79 (3 H, s, OMe), 4.82 (1 H, t, CH_2OH), 5.93 and 5.97 (2 × 1 H, 2 × s, CH_2), 7.02 (1 H, dd, 6′-H), 7.08 (1 H, d, $J_{4',6'}$ 3, 4′-H), 7.33 (1 H, s, 3′-H), 7.67 (6 H, m, 5 × ArH + 5-H), 7.91 (1 H, d, $J_{7',6'}$ 9, 7′-H), 8.55 (1 H, s, 2-H) and 8.57 (1 H, d, $J_{6,5}$ 5, 6-H) (′ numbering correspond to indole nucleus).

N,N-*Diisopropylnicotinamide* **17a**.—Nicotinic acid (10 g, 80 mmol) was stirred at room temperature in thionyl dichloride (30 cm^3, large excess) for 18 h. Excess of thionyl dichloride was evaporated off under reduced pressure and the solid residue was suspended in dichloromethane (150 cm^3). This mixture was progressively added to a cooled (0 °C) solution of diisopropylamine (31.4 cm^3, 0.24 mol) in dichloromethane (150 cm^3) and the mixture was stirred for a further 18 h at room temperature before being poured into water (300 cm^3) and extracted with dichloromethane (3 × 100 cm^3). Usual work-up afforded an oily residue, b.p. 147–150 °C/7 mmHg (12.6 g, 76.5%), which progressively became solid, m.p. 99 °C (Found: C, 69.9; H, 8.65; N, 13.3. $C_{12}H_{18}N_2O$ requires C, 69.87; H, 8.80; N, 13.58%); $\delta_H(CDCl_3)$ 1.34 (12 H, d, 4 × Me), 3.66 (2 H, m, 2 × $CHMe_2$), 7.29 (ddd, $J_{5,4}$ 8.2, $J_{5,6}$ 4.8, $J_{5,2}$ 1.1, 5-H), 7.62 (1 H, dt, 4-H), 8.55 (1 H, dd, $J_{2,4}$ 2.3, 2-H) and 8.58 (1 H, dd, 6-H, $J_{6,4}$ 2.3, 6-H).

4-*Methoxycarbonylnicotinic Acid* **19**.—A solution of pyridine-3,4-dicarboxylic (cinchomeronic) acid (50 g, 0.3 mol) in acetic anhydride (800 cm^3) was heated for 1 h at reflux and evaporated to dryness under reduced pressure. Cinchomeronic anhydride **18** was distilled off (b.p. 155–158 °C/19 mmHg) and immediately dissolved in dry dichloromethane under sonication. The resulting solution was added dropwise to methanol (170 cm^3) cooled and maintained at −70 °C. After the mixture had been stirred for 18 h at room temperature, the solid was collected (fraction **a**). Excess of methanol was evaporated off and the residue was weighed and dissolved in saturated aq. sodium hydrogen carbonate (1 mol equiv.), then neutralized with 1 mol dm^{-3} hydrochloric acid. This provided a second precipitate of the expected *compound* **19** (fraction **b**). The combined solid (**a** + **b**) was recrystallized from ethyl acetate, giving pale rosy crystals (37.3 g, 82%), m.p. 180–182 °C (Found: C, 53.2; H, 4.1; N, 7.8. $C_8H_7NO_4$ requires C, 53.04; H, 3.9; N, 7.73%); $\delta_H[(CD_3)_2SO]$ 3.88 (3 H, s, OMe), 7.67 (1 H, d, $J_{5,6}$ 5, 5-H), 8.91 (1 H, d, 6-H) and 9.06 (1 H, s, 2-H). The literature method [17] led to a mixture of compound **19** and its isomer **20**, m.p. 172 °C. This last compound was also present in the crude mixture (TLC), but the process described here gave compound **19** as the major product and purification was more easy.

Methyl 3-(*Diisopropylcarbamoyl*)*isonicotinate* **22**.—The acid ester **19** (30 g, 0.17 mol) was heated in thionyl dichloride (30 cm^3) at reflux for 1.5 h and excess of thionyl dichloride was evaporated off under reduced pressure. The solid residue (acid chloride **21**) was suspended in dry dichloromethane (200 cm^3) and the mixture was progressively added to a stirred solution of freshly distilled (CaH_2) diisopropylamine (70 cm^3, 0.53 mol) in dichloromethane (80 cm^3) cooled to −10 °C. After the addition was complete, the cooling bath was removed and the mixture was stirred for 18 h at room temperature. The heterogeneous mixture was then poured in water (300 cm^3) and the organic layer was washed successively with aq. sodium hydrogen carbonate and water. Usual work-up provided a solid residue, which was recrystallized twice from hexane to give *amido ester* **22** as crystals (39.6 g, 90%), m.p. 109 °C (Found: C, 63.5; H, 7.6; N, 10.8. $C_{14}H_{20}N_2O_3$ requires C, 63.62; H, 7.63; N, 10.60%); $\delta_H(CDCl_3)$ 1.14 and 1.59 [2 × 6 H, 2 d, $N(CHMe_2)_2$], 3.56 (2 H, m, $2CHMe_2$), 3.92 (3 H, s, OMe), 7.81 (1 H, dd, $J_{5,6}$ 5, $J_{5,2}$ 1, 5-H), 8.56 (1 H, s, 2-H) and 8.73 (1 H, d, 6-H).

4-*Acetyl*-N,N-*diisopropylnicotinamide* **16**.—*Method A*. Dry diethyl ether (30 cm^3), diisopropylamine (3.93 cm^3, 30 mmol), and butyllithium (18.7 cm^3 of the usual 1.6 mol dm^{-3} solution, 30 mmol) were put in a 250 cm^3, three-necked flask under argon

and cooled at 0 °C. The mixture was stirred 3 h at 0 °C, cooled to −70 °C, and a solution of *N,N*-diisopropylnicotinamide **17a** (2.06 g, 10 mmol) in dry diethyl ether (80 cm^3) was added all at once. The mixture was stirred for 2 h at −70 °C and the lithio derivative **17b** was then added *via* a flexible needle, under argon pressure, into an excess of acetic anhydride (15 cm^3) cooled to −50 °C. After 18 h at room temperature, the mixture was poured into saturated aq. ammonium chloride (150 cm^3) and extracted with dichloromethane; the extract was treated as usual, giving an oily residue, which was chromatographed on a silica gel column, with ethyl acetate as eluent. Three pure compounds were thus obtained, successively: (a) *N,N*-diisopropylacetamide, resulting from reaction of acetic anhydride with excess of diisopropylamine; (b) the starting *N,N*-diisopropylnicotinamide **17a** (8% recovery); (c) the expected *ketone* **16**, which was recrystallized from hexane to provide crystals (250 mg, 10%), m.p. 94 °C (Found: C, 67.6; H, 8.0; N, 11.0. $C_{14}H_{20}N_2O$ requires C, 67.71; H, 8.12; N, 11.28%); δ_H-($CDCl_3$) 1.27 and 1.67 [2 × 6 H, 2 d, N(CH*Me*$_2$)$_2$], 2.7 (3 H, s, Ac), 3.66 [2 H, m, N(CH=)$_2$], 7.64 (1 H, dd, 5-H), 8.65 (1 H, d, $J_{2,5}$ 0.8, 2-H) and 8.84 (1 H, d, $J_{6,5}$ 5, 6-H).

Method B. A solution of the amide ester **22** (20 g, 76 mmol) in dry diethyl ether (700 cm^3) was cooled to −10 °C and methyllithium (50 cm^3 of the commercially available 1.6 mol dm^{-3} solution, 80 mmol) was added dropwise, while the temperature was kept below −7 °C. The mixture was left for 18 h at room temperature and was then poured into saturated aq. ammonium chloride (500 cm^3). After extraction with diethyl ether (3 × 150 cm^3), the organic layer was treated as usual and evaporated. The residue was chromatographed on a silica gel column (1 m × 45 mm) and eluted with ethyl acetate. Four main fractions were thus collected: (a) the recovered amide ester **22** (4.31 g, 21.5% recovery); (b) 4-(1-*hydroxy*-1-*methylethyl*)-N,N-*diisopropylnicotinamide* **23** as crystals, m.p. 120 °C (from hexane) [total yield, after further chromatography of fraction c (see below): 1.31 g, 6.5%] (Found: C, 68.2; H, 9.25; N, 10.6. $C_{15}H_{24}N_2O_2$ requires C, 68.15; H, 9.15; N, 10.60%); δ_H($CDCl_3$) 1.25, 1.27, 1.64 and 1.65 [4 × 3 H, 4 d, *J* 6.8, N(CH*Me*)$_2$)$_2$], 1.64 and 1.73 (2 × 3 H, 2 s, C*Me*$_2$OH), 3.59 (1 H, s, OH), 3.72 [2 H, m, N(C*H*Me$_2$)$_2$], 7.31 (1 H, dd, 5-H), 8.42 (1 H, d, $J_{2,5}$ 0.5, 2-H) and 8.6 (1 H, d, $J_{6,5}$ 5.5, 6-H); (c) An unresolved mixture of the preceding compound **23** and ketone **16**, which was submitted to further chromatography, under the same conditions; (d) the pure ketone **16**. After the further chromatography, the total yield of pure compound **16** was 9.3 g (49.5%). It was completely identical with the compound obtained by method A (m.p., δ_H).

4-[1-*Hydroxy*-1-(5-*methoxy*-1-*phenylsulphonylindol*-2-*yl*)-*ethyl*]-N,N-*diisopropylnicotinamide* **24**.—To a solution of 5-methoxy-1-phenylsulphonyl indole (2.31 g, 8.07 mmol) in dry THF (100 cm^3) was added butyllithium (1.6 mol dm^{-3} solution; 5.05 cm^3, 8.08 mmol) all at once. The mixture was stirred for 2 h at room temperature, then cooled to −13 °C, and a solution of 4-acetyl-*N,N*-diisopropylnicotinamide **16** (2 g, 8.06 mmol) in THF (80 cm^3) was added dropwise. After being stirred for 18 h at room temperature the mixture was poured into saturated aq. ammonium chloride (200 cm^3) and extracted with dichloromethane (3 × 60 cm^3). The combined extract was dried ($MgSO_4$), filtered, and evaporated, to give a residue, which was taken up in ethyl acetate. Recrystallization from this solvent gave *compound* **24** as crystals (2.67 g, 62%), m.p. 253 °C (Found: C, 64.9; H, 6.1; N, 7.9; S, 6.2. $C_{29}H_{33}N_3O_5S$ requires C, 65.03; H, 6.21; N, 7.84; S, 5.98%); δ_H[2 D, 400 MHz; $(CD_3)_2SO$)] two rotamers (A + B), in the ratio 3:1, were observed, for indole nucleus, Ar for benzene ring of SO_2Ph). For A: 0.98, 1.10, 1.50 and 1.52 [4 × 3 H, 4 d, $(Me_2CH)_2$], 2.18 (3 H, s, *Me*COH), 3.55 and 4.04 [2 × 1 H, 2 m, (C*H*Me$_2$)$_2$], 3.89 (3 H, s, OMe), 6.14 (1 H, s, OH), 6.73 (1 H, d, $J_{5,6}$ 5.2, 5-H), 6.93 (1 H, dd, $J_{6',7'}$ 9.2, $J_{6',4'}$ 2.5, 6'-H), 7.13 (1 H, s, 3'-H), 7.19 (1 H, d, 4'-H), 7.6 (3 H, m, Ar 3-, 4-, 5-H), 7.78 (1 H, d, 7'-H), 8 (2 H, m, Ar 2-, 6-H), 8.32 (1 H, s, 2-H) and 8.39 (1 H, d, 6-H). For B: 1.03, 1.10 and 1.37 [2 × 3 H + 6 H, 3 d, $(Me_2CH)_2$], 2.05 (3 H, s, *Me*COH), 3.23 and 3.52 [2 H, 2 m, (C*H*Me$_2$)$_2$], 3.89 (3 H, s, OMe), 6.10 (1 H, s, OH), 6.80 (1 H, s, 3'-H), 6.98 (1 H, dd, $J_{6',7'}$ 9.2, $J_{6',4'}$ 2.6, 6'-H), 7.11 (1 H, d, 4'-H), 7.6 (3 H, m, Ar 3-, 4-, 5-H), 8 (3 H, m, Ar 2-, 6-H + 5-H), 8.26 (1 H, s, 2-H) and 8.59 (1 H, d, $J_{6,5}$ 5.4, 6-H).

4-[1-(5-*Methoxy*-1-*phenylsulphonylindol*-2-*yl*)*ethyl*]*nicotinic Acid* **25**.—A mixture of the lactone **13** (4 g, 9.2 mmol), activated zinc powder[14] (8 g), formic acid (54 cm^3), and water (14 cm^3) was heated at reflux for 12 h and evaporated to dryness. The solid residue was taken up in 1 mol dm^{-3} hydrochloric acid (80 cm^3) and the mixture was stirred for 4 h. The resulting solid was collected and treated with ammonia (1 mol dm^{-3}; 300 cm^3). Traces of insoluble material were filtered off and the filtrate was acidified with conc. hydrochloric acid to provide a solid, which was collected and recrystallized from ethanol to give *compound* **25** as crystals (2.48 g, 62%), m.p. >265 °C (Found: C, 63.0; H, 4.8; N, 6.4; S, 7.2. $C_{23}H_{20}N_2O_5S$ requires C, 63.29; H, 4.62; N, 6.42; S, 7.35%); δ_H[$(CD_3)_2SO$] 1.58 (3 H, d, *Me*CH), 3.82 (3 H, s, OMe), 5.76 (1 H, q, J_{CHMe} 7, C*H*Me), 6.96 (2 H, m, 5- + 6'-H), 7 (1 H, s, 3'-H), 7.17 (1 H, d, $J_{4',6'}$ 2.5, 4'-H), 7.57 (5 H, m, Ph), 7.93 (1 H, d, $J_{7',6'}$ 9, 7'-H), 8.49 (1 H, d, $J_{6,5}$ 5.5, 6-H) and 9.01 (1 H, s, 2-H).

N-[3-(*Dimethylamino*)*propyl*]-4-[1-(5-*methoxy*-1-*phenylsulphonylindol*-2-*yl*)*ethyl*]*nicotinamide* **26b**.—A mixture of the preceding acid **25** (200 mg, 0.45 mmol), dimethylformamide (DMF) (2 cm^3), and *N,N'*-carbonyldiimidazole (149 mg, 0.9 mmol) was stirred for 10 min at room temperature. To the resulting homogeneous solution was added 3-(dimethylamino)-propylamine (0.23 cm^3, 1.8 mmol) all at once. After the mixture had been stirred for 15 min, evaporation to dryness under reduced pressure (0.1 mmHg) provided an oily residue, which was taken up in water (15 cm^3) and extracted with dichloromethane (3 × 30 cm^3). The combined extracts were washed with water to neutrality (pH 7), dried ($MgSO_4$), and evaporated. The residue was recrystallized from toluene to afford *compound* **26b** as crystals (131 mg, 55%), m.p. 167 °C (Found: C, 64.75; H, 6.1; N, 10.9; S, 6.3. $C_{28}H_{32}N_4O_4S$ requires C, 64.59; H, 6.20; N, 10.76; S, 6.16%); δ_H[$(CD_3)_2SO$] 1.64 (3 H, d, *Me*CH), 1.71 (2 H, m, β-H_2), 2.05 (6 H, s, NMe_2), 2.26 (2 H, m, γ-H_2), 3.3 (overlapped by HOD signal, α-H_2), 3.76 (3 H, s, OMe), 5.22 (1 H, q, C*H*Me), 6.85 (1 H, s, 3'-H), 6.89 (1 H, d, $J_{5,6}$ 6, 5-H), 6.90 (1 H, dd, $J_{6',7'}$ 9, $J_{6',4'}$ 3, 6'-H), 7.11 (1 H, d, 4'-H), 7.56 (5 H, m, Ph), 7.88 (1 H, d, 7'-H), 8.42 (1 H, d, 6-H), 8.54 (1 H, br s, NH) and 8.61 (1 H, s, 2-H).

Amides **26a** and **26c** were prepared similarly. However, despite attempts in various solvents, they could not be crystallized. So, after ^1H NMR control, they were used as crude substrates (70–80% yields) in the subsequent transformations.

11-{[2-(*Dimethylamino*)*ethyl*]*amino*}-9-*methoxy*-5-*methyl*-6H-*pyrido*[4,3-b]*carbazole* **28a** *and Analogues* **28b** *and* **28c**.—The required amide **26** (200 mg) was dissolved in phosphorus trichloride oxide (10 cm^3) and the solution was heated for 2 h at reflux. The precipitate which soon appeared dissolved after this time. Excess of phosphorus trichloride oxide was evaporated off and cold water (50 cm^3) was added, giving a homogeneous solution, which was made alkaline with aq. sodium hydroxide. The pasty precipitate was extracted with dichloromethane (5 × 20 cm^3) and the extract was washed

Table 2 Physical data for compounds **28**

Compound (Formula)	Yield (%)	M.p./(°C)	Found (%) (Required) C	H	N	δ_H($CDCl_3$): **28a**, **28b** and **28c**; [$(CD_3)_2SO$]: **28d**	Mass spectra m/z [b]
28a ($C_{21}H_{24}N_4O$·0.5 H_2O·0.5 C_7H_8)	24.5[a]	227	72.95 (72.92)	7.4 7.24	13.9 13.88)	2.4 (6 H, s, NMe_2), 2.60 (2 H, m, β-H_2), 2.70 (3 H, s, 5-Me), 3.60 (2 H, m, α-H_2), 3.98 (3 H, s, OMe), 5.4 (1 H, br s, N*H*R), 7.12 (1 H, dd, $J_{8,7}$ 8.7, 8-H), 7.38 (1 H, d, 7-H), 7.78 (1 H, dd, $J_{4,3}$ 6.1, 4-H), 7.93 (1 H, br s, 6-H), 8.03 (1 H, d, $J_{10,8}$ 2.5, 10-H), 8.45 (1 H, d, 3-H), 9.74 (1 H, d, $J_{1,4}$ 1, 1-H)	349 (MH^+, 100%), 290 (22)
28b ($C_{22}H_{26}N_4O$·0.75 H_2O)	23.1[a]	218	70.5 (70.28)	7.2 7.37	14.5 14.90)	2.01 (2 H, q, β-H_2), 2.36 (6 H, s, NMe_2), 2.57 (2 H, t, γ-H_2), 2.7 (3 H, s, 5-Me), 3.53 (2 H, t, α-H_2), 3.97 (3 H, s, OMe), 5.2 (1 H, br s, N*H*R), 7.12 (1 H, dd, $J_{8,7}$ 8.5, $J_{8,10}$ 2.5, 8-H), 7.38 (1 H, dd, $J_{7,10}$ 0.5, 7-H), 7.79 (1 H, dd, $J_{4,3}$ 6, $J_{4,1}$ 1, 4-H), 7.9 (1 H, dd, 10-H), 8.01 (1 H, br s, 6-H), 8.46 (1 H, d, 3-H), 9.67 (1 H, d, 1-H)	363 (MH^+, 100%), 304 (16)
28c ($C_{24}H_{30}N_4O$·0.5 H_2O)	32.4[a]	218	72.1 (72.15)	7.7 7.82	13.95 14.02)	1.10 [6 H, t, ($MeCH_2$)$_2$N], 2.04 (2 H, m, β-H_2), 2.68 [6 H, q + d, N(CH_2Me)$_2$ + γ-H_2], 2.71 (3 H, s, 5-Me), 3.51 (2 H, t, α-H_2), 3.98 (3 H, s, OMe), 7.12 (1 H, dd, $J_{8,7}$ 8.7, $J_{8,10}$ 2.4, 8-H), 7.39 (1 H, d, 7-H), 7.79 (1 H, d, $J_{4,3}$ 6.2, 4-H), 7.87 (1 H, d, 10-H), 8.0 (1 H, br s, 6-H), 8.47 (1 H, d, 3-H), 9.69 (1 H, s, 1-H)	391 (MH^+, 100%), 304 (26)
28d ($C_{20}H_{22}N_4O$·H_2O·0.25 C_7H_8)	51	145	69.7 (69.58)	6.4 6.98	14.7 14.92)	2.20 (6 H, s, NMe_2), 2.45 (2 H, m, β-H_2), 2.65 (3 H, s, 5-Me), 3.39 (2 H, t, α-H_2), 5.47 (1 H, br s, N*H*R), 6.94 (1 H, dd, $J_{8,7}$ 8.5, $J_{8,10}$ 2.2, 8-H), 7.31 (1 H, d, 7-H), 7.72 (1 H, d, 10-H), 7.78 (1 H, d, $J_{4,3}$ 5.8, 4-H), 8.29 (1 H, d, 3-H), 8.96 (1 H, br s, 6-H), 9.62 (1 H, s, 1-H), 10.9 (1 H, br s, 9-OH)	335 (MH^+, 100%), 276 (31)

[a] Overall yield from the acid **25**. [b] Field desorption, chemical ionisation (NH_3).

with water. Evaporation of the solvent gave a pasty solid residue of intermediate compound **27** for which all attempts at crystallization in various solvents failed.

Compound **27** was taken up in ethanol (30 cm^3), W-2 commercially available Raney nickel (2 g) was added, and the mixture was heated at reflux until disappearance of compound **27** (TLC monitoring, alumina plates; 5% EtOH–CH_2Cl_2; 10–15 h). The mixture was filtered, the solid was washed with boiling ethanol (5 × 40 cm^3), and the filtrate was evaporated to dryness. The residue was recrystallized from cyclohexane (large volume required) or toluene to provide the expected tetracyclic compounds (**28**, Table 2). As mentioned in the formula entry in Table 2, these compounds are always associated with water of crystallization but toluene was also retained by the solid when this solvent was used for recrystallization. As can be seen from Table 2, however, ^1H NMR and mass-spectra are fully in agreement with the reported structures.

11-{[12-(*Dimethylamino*)*ethyl*]*amino*}-5-*methyl*-6H-*pyrido*-[4,3-b]*carbazol*-9-*ol* **28d**.—Compound **28a** (200 mg, 0.64 mmol) was dissolved in dry dichloromethane (30 cm^3) under nitrogen and the solution was cooled to −78 °C. A 1 mol dm^{-3} solution of boron tribromide (5 cm^3, 5 mmol) was added dropwise and the mixture was allowed to reach room temperature overnight, while being continuously stirred. It was then poured into water (50 cm^3), stirred for 1 h, and made alkaline with conc. ammonia, to afford a pasty precipitate, which was collected when it had solidified, and was dried under reduced pressure overnight and recrystallized from toluene to give pale yellow crystals (Table 2).

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