Isomeric Ellipticines. Part 1. Synthesis of two Linear Isomers of the Antitumour Alkaloid Ellipticine

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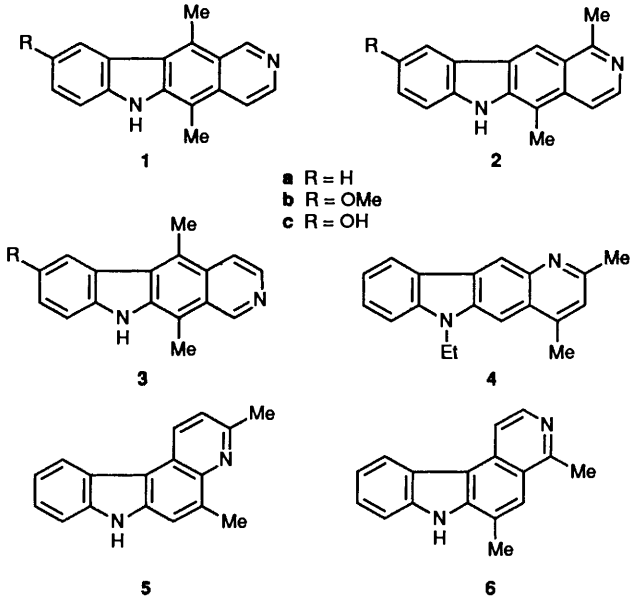
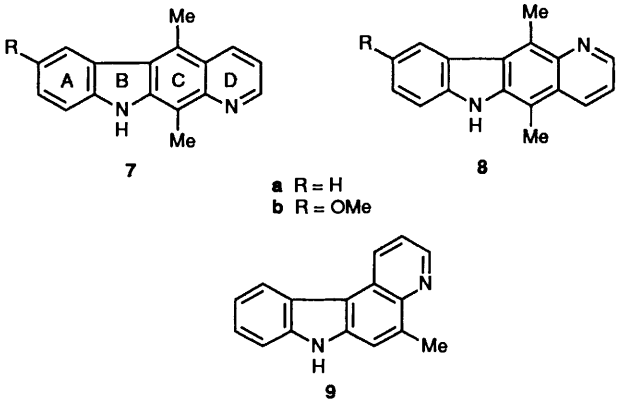
Two linear isomers of the parent 5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole ellipticine **1a**, belonging to the 6*H*- and 10*H*-pyridocarbazoles series and their methoxylated derivatives, have been synthesized by three different methods using the Skraup reaction and the Fischer–Borsche cyclization. One of these (method A) afforded an angular monomethyl-7*H*-pyridocarbazole **9** instead of the expected linear 6*H*-isomer **8a** on cyclisation of 5,8-dimethyl-6-hydrazinoquinoline **21** with cyclohexanone *via* the Fischer–Borsche indole synthesis. The two other methods (B and C) afforded the desired linear isomers **7** and **8** when the Skraup reaction was performed with aminocarbazoles **26** or with tetrahydroaminocarbazoles **17** and **27** respectively, followed by aromatization of the A ring. Oxidized species were isolated after the aromatization step in method C and were tentatively assigned structures **30–33**.

Ellipticine **1a** and olivacine **2a** are two naturally occurring isomeric alkaloids belonging to the 6*H*-pyridocarbazole family. 9-Methoxyellipticine **1b** and 9-hydroxyellipticine **1c** are endowed with antitumour properties.[1–3] They are DNA intercalating compounds and their high DNA binding affinity is thought to be responsible, in part, for such pharmacological properties.[4] However, at present, it seems that the intercalating mode governs the cytotoxic potency of these drugs rather than the strength of binding.[5,6] Olivacine **2a** shows significant differences in *in vitro* cytotoxicity and *in vivo* toxicity compared to ellipticine itself[7] and this in spite of their great structural similarity. Nevertheless, a hydroxy group at its 9-position (compound **2c**), increases the *in vitro* cytotoxicity against leukemia L1210 cells.[8] Olivacine and some of its derivatives seem to belong to a class of compounds potentially active against leukemia L1210 cells transplanted in mice.[9]



Despite the great interest that has given rise to much synthetic work on ellipticine and derivatives,[10–23] very little attention has been focused on the synthesis of its isomers, olivacine apart.

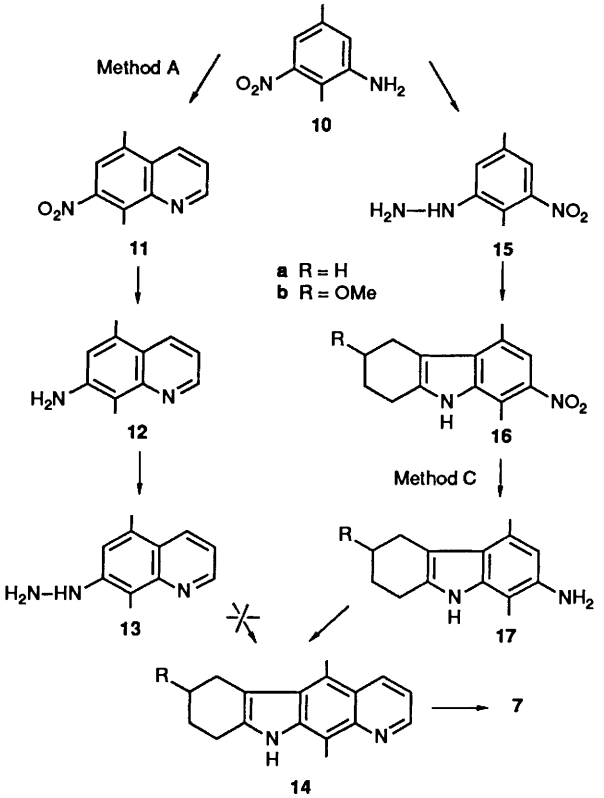
Fujiwara *et al.* have reported the synthesis of isoellipticine **3a**, a 10*H*-pyridocarbazole isomer,[24] as also have Moody and May.[25] This compound was shown to be inactive against L1210 cells transplanted in mice. More recently, Saulnier and Gribble prepared 7-methoxyisoellipticine **3b**.[26] The 6-ethyl derivative of another isomer **4** of ellipticine in the 6*H*-pyridocarbazole series has been synthesized by Buu-Hoï *et al.*[27] Dalton and his group reported the synthesis of **5** an isomer in the 7*H*-pyridocarbazole series.[28] Very recently, Yokohama *et al.* obtained a further isomeric 7*H*-pyridocarbazole **6**.[20] Bergman and Carlson,[29] then Gribble *et al.*[30] synthesized 5,11-dimethyl-10*H*-pyrido[2,3-*b*]-carbazole **7a** and 5,11-dimethyl-7-methoxy-10*H*-pyrido[2,3-*b*]-carbazole **7b** respectively, by routes other than those described here. While synthetizing ellipticine, Kano *et al.*[31] also obtained **7a**, as a by-product. These are the only examples, to our knowledge, describing the synthesis of isomeric ellipticines.



With the aim of investigating further isomers of ellipticine and their corresponding methoxylated derivatives as potential antitumour drugs we have prepared two isomeric ellipticines, and their methoxylated derivatives, belonging to the 6*H*- and 10*H*-

pyridocarbazoles series. The isomeric change concerns only the pyridine moiety. With respect to ellipticine, in the 6*H*-isomer the nitrogen atom shifts from position 2 to position 1, and in the 10*H*-isomer it shifts from position 2 to position 4.

Such compounds were synthesized by three different methods which are outlined in Scheme 1 (Methods A and C) and in Scheme 2 (Methods A, B and C).



Scheme 1

Method A. This method consisted of first preparing the hydrazinodimethylquinolines **13** and **21**[32] by a Skraup reaction with 2,5-dimethyl-3-nitroaniline **10**[33,34] and 2,5-dimethyl-4-nitroaniline **18**[32] using acrolein and arsenic pentoxide as oxidizing agent.[35] The nitroquinolines thus obtained were reduced to the corresponding aminoquinolines **12** and **20**[32] which were then transformed into the desired hydrazinoquinolines by diazotization followed by a stannous chloride reduction according to Wieland and Horner's procedure.[36] In the case of the hydrazinoquinoline **13**, reaction with cyclohexanone or with 4-methoxycyclohexanone failed to afford the linear tetrahydropyridocarbazole **14** upon the Fischer–Borsche cyclization under classical conditions, whereas the hydrazinoquinoline **21**[32] afforded the angular monomethyltetrahydro-7*H*-pyridocarbazole **22** instead of the expected linear dimethyltetrahydro-6*H*-pyridocarbazole **28**. This angular cyclization, which took place along with a monodemethylation, confirms Huisgen's finding[32] who first observed this phenomenon. The angular structure of **22** was confirmed by UV spectroscopy by comparing the spectrum of the fully aromatized compound **9** with that of 7*H*-pyrido[4,3-*c*] carbazole **29** which was available to us.[37–39] UV spectra of angular and linear pyridocarbazoles display quite different patterns (see Fig. 1). The general tendency of such a cyclization to yield more or less easily angular aromatic polycyclic compounds rather than linear ones has been widely discussed by Kulka and Mansk.[40,41] In connnection with the synthesis of angular monomethyl-7*H*-pyridocarbazoles other synthetic routes have been developed to obtain such monomethylated compounds.[39,42]

Method B and Method C. The Fischer–Borsche cyclization was performed first on 2-hydrazino-6-nitro-*p*-xylene **15** and on 2-hydrazino-5-nitro-*p*-xylene **23** with cyclohexanone or/and with 4-methoxycyclohexanone, thus giving the dimethyltetrahydronitrocarbazoles **16** and **24** respectively, as starting materials for these two methods.

Method B. Compound **24** was aromatized to the corresponding nitrocarbazole **25** which subsequently, on reduction, afforded the aminocarbazole **26**. Compounds **26a** and **26b** have been obtained by other authors[43,44] using routes different from ours. Finally, 6*H*-pyridocarbazole **8** was obtained when **26** was subjected to a Skraup reaction under the same experimental conditions as in Method A (see Experimental section).

Method C. The tetrahydronitrocarbazoles **16** and **24** were reduced to the corresponding tetrahydroaminocarbazoles **17** and **27**, respectively. A Skraup reaction with the latter afforded **7** and **8** after aromatization of **14** and **28** with 10% palladium on activated carbon in boiling mesitylene. During the aromatization of **14b** and **28b** a partial demethoxylation took place which lowered the yield of final products even when lower boiling solvents such as xylene or toluene were used. This phenomenon has already been observed previously by one of us.[45]

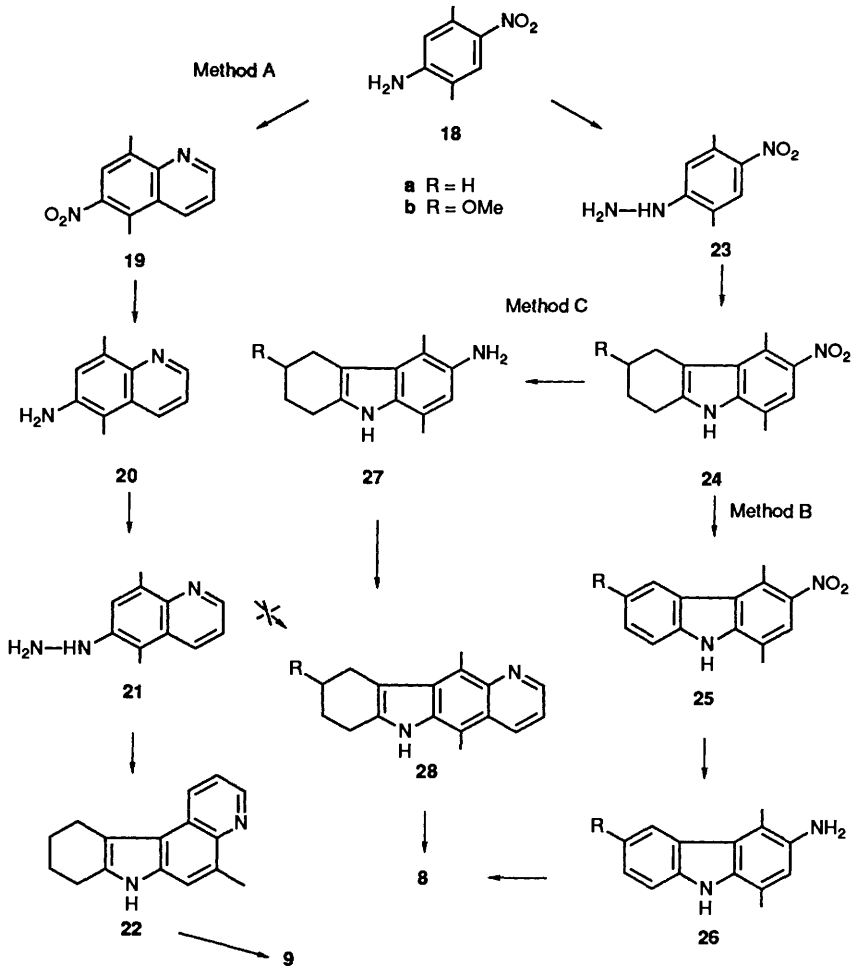
A further observation was made using method C. On purification of **7a**, **7b**, **8a** and **8b**, an unknown fraction was isolated by flash chromatography from each of these four pyridocarbazoles. ^{1}H NMR analysis showed that each of these fractions consisted, in fact, of a mixture of two products which could not be separated by the usual chromatographic techniques. ^{13}C NMR spectrometry, however, showed chemical shifts at 187–189 ppm indicative of carbonyl groups, probably due to the presence of quinone compounds in the mixtures studied. These by-products could not be obtained pure, although by a gas chromatography/mass spectrometry technique (GC/MS) they were tentatively assigned structures **30–33** as shown in Scheme 3 for **7a** and **7b**. In the case of **8a** and **8b** similar oxidized by-products were also isolated.

To conclude, the linear pyridocarbazoles **7** and **8** are obtained only when ring D was constructed in the final stage by employing the corresponding aminocarbazoles in a Skraup reaction (Methods B and C). An attempted synthesis in which the CD rings were formed first followed by a Fischer–Borsche reaction to give a linear, ABCD, system failed (Method A).

In the course of this work, no attempt has been made to synthesize isomers of ellipticine belonging to the 11*H*-pyridocarbazoles series because it has been shown that in those series substitution on the pyridocarbazole ring system by a methyl, methoxy or hydroxy group prevents DNA intercalation.[45] This was explained in terms of geometry, *i.e.* the size of the 11*H*-pyrido[2,3-*a*]-, [3,4-*a*]-, [4,3-*a*]- and [3,2-*a*]-carbazole molecules being slightly larger than that of 6*H*- and 7*H*-pyridocarbazole molecules, prohibits intercalation, despite their good DNA affinity.

Experimental

M.p.s (Kofler hot stage or Büchi 520) are uncorrected. ^{1}H NMR spectra were recorded on a Brüker MLS 300 (300 MHz) spectrometer, with tetramethylsilane as internal standard and ^{13}C NMR spectra on a Brüker AM 500 (125 MHz) also with tetramethylsilane as internal standard. Chemical shifts are given in ppm and *J*-values in Hz ± 0.5. UV absorption spectra were recorded with a Uvikon 860 spectrophotometer. The GC/MS analyses were performed on a HP 5890 series II gas chromatograph and on a HP 5971 A mass selective detector controlled by a Vectra QS-20 microcomputer using the DOS chemstation software (Hewlett-Packard, Les Ulis, France). A WCOT fused-silica capillary column (25 mm × 0.25 mm i.d.) coated with a



Scheme 2

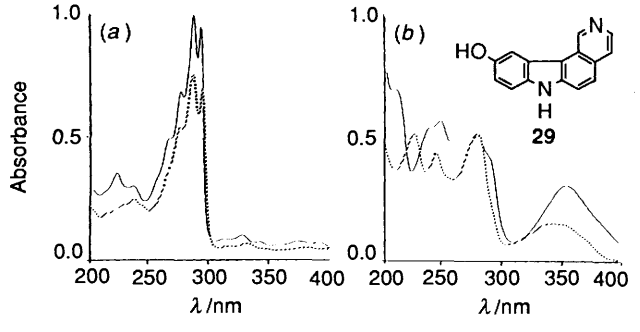


Fig. 1 UV spectral comparison between linear and angular pyridocarbazoles in ethanol (a) ellipticine **1a** (– – –) and olivacine **2a** (—); (b) compound **9** (– – –) and compound **29** (——)

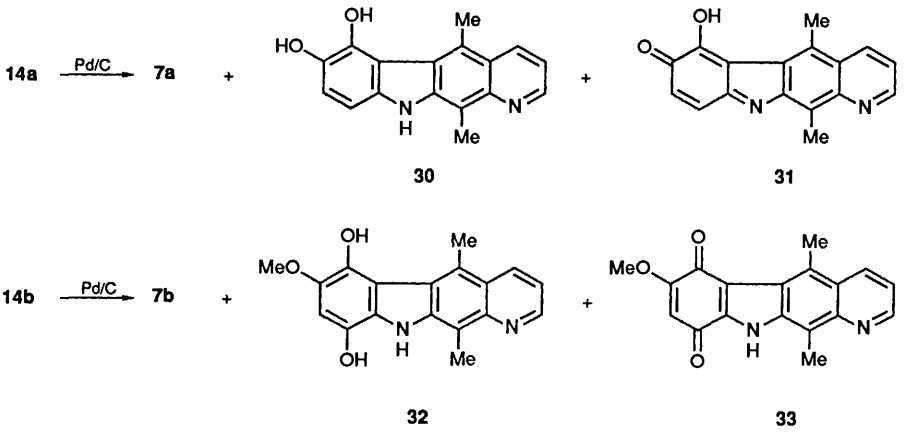
0.12 μm film of CP-Sil 5CB (Chrompack, Les Ulis, France) was used under helium gas with a 250 °C splitless injection and a temperature gradient of 5 °C min^{-1} in the range 150–300 °C. The 70 eV electron impact (EI) mass spectra were obtained using the MSD 5971 A detector heated at 200 °C and calibrated over the 40–450 D mass range with unit mass calibration. Purifications were performed on preparative thin layer chromatography (TLC) plates (Stratocrom SIF, 2 mm, Carlo Erba, Milano, Italy). For column chromatography, Carlo Erba silica gel was used.

Method A

5,8-*Dimethyl*-7-*nitroquinoline* **11**.—In a three-necked flask equipped with a water condenser a dropping funnel and a thermometer, 2,5-dimethyl-3-nitroaniline **10** (5 g, 30 mmol)[33,34] was dissolved in orthophosphoric acid (85%; 75 cm^3) and then arsenic pentoxide dihydrate (5 g, 18.5 mmol) was added. The mixture was magnetically stirred and heated in an oil-bath and the temperature raised gradually to 105 °C. Acrolein (3.1 cm^3, 55 mmol) was added dropwise over a period of 45 min. The reaction mixture was kept at 105 °C for a further 45 min and, after cooling to room temperature, was made basic (pH 8–9) with a 20% aqueous sodium hydroxide. The resulting brown precipitate was extracted with dichloromethane (3 × 50 cm^3) and the combined extracts, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with chloroform–hexane (1 : 3) as eluent to give a homogeneous yellow solid (1.58 g, 26%). A similar reaction for 3 h at 95 °C gave a yield of 33%. Recrystallization from ethanol afforded microcrystals, m.p. 125–126 °C (Found: C, 65.2; H, 5.1; N, 14.2. $C_{11}H_{10}N_2O_2$ requires C, 65.33; H, 4.98; N, 13.90%).

5,8-*Dimethyl*-6-*nitroquinoline* **19**.—This compound was prepared from **18** (5 g, 30 mmol) as described in ref. 32; the pure material (1.58 g, 26%) had m.p. 117 °C (lit.,[32] 118 °C) (Found: C, 65.1; H, 5.1; N, 14.2. $C_{11}H_{10}N_2O_2$ requires C, 65.33; H, 4.98; N, 13.90%).

7-*Amino*-5,8-*dimethylquinoline* **12**.—To a stirred solution of hydrochloric acid (5 mol dm^{-3}; 10 cm^3) containing stannous chloride (8 g) was added **11** (2 g, 9.8 mmol). The suspension obtained was refluxed for 3 h and, after cooling, the reaction mixture was made basic with a 40% aqueous potassium hydrox-



Scheme 3

ide to give a white precipitate; this was extracted with dichloromethane (3 × 50 cm^3). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give a white solid (84%) pure enough for the next step. A sample was crystallized from ethanol giving colourless microcrystals, m.p. 128–129 °C (Found: C, 76.55; H, 7.0; N, 16.1. $C_{11}H_{12}N_2$ requires C, 76.80; H, 7.02; N, 16.18%).

6-*Amino*-5,8-*dimethylquinoline* **20**.—Following the above procedure **19** (2 g, 9.8 mmol) afforded the title compound (1.7 g, 92%). Recrystallization from ethanol gave colourless microcrystals, m.p. 175 °C (lit.,[32] 185 °C) (Found: C, 76.5; H, 7.0; N, 16.1. $C_{11}H_{12}N_2$ requires C, 76.80; H, 7.02; N, 16.28%).

7-*Hydrazino*-5,8-*dimethylquinoline* **13** *and* 6-*Hydrazino*-5,8-*dimethylquinoline* **21**.—These two hydrazines were prepared following the procedure described in ref. 32, with **12** (1 g, 5.7 mmol) and **20** (1 g, 5.7 mmol) respectively as starting material. The hydrazinoquinoline **13** was obtained as white microcrystals (68%, 0.68 g) from ethanol–water (1:1), m.p. 162–164 °C (Found: C, 70.4; H, 6.8; N, 22.2. $C_{11}H_{13}N_3$ requires C, 70.57; H, 6.83; N, 22.44%). The hydrazinoquinoline **21** was obtained as yellow microcrystals (66%, 0.66 g) from ethanol–water (1:1), m.p. 184–185 °C (lit.,[32] 185 °C) (Found: C, 70.4; H, 6.9; N, 22.35. $C_{11}H_{13}N_3$ requires C, 70.57; H, 6.83; N, 22.44%).

5-*Methyl*-8,9,10,11-*tetrahydro*-7H-*pyrido*[2,3-c]*carbazole* **22**.—This compound was prepared as described in ref. 32, **21** (1 g) affording colourless microcrystals (0.2g, 15.9%), m.p. 225 °C (lit.,[32] 225 °C) (Found: C, 81.4; H, 6.8; N, 11.8. $C_{16}H_{16}N_2$ requires C, 81.36; H, 6.78; N, 11.86%); δ_H[$(CD_3)_2SO$] 1.90 (4 H, m, 9-CH_2, 10-CH_2), 2.70 (3 H, s, 5-CH_3), 2.84 (2 H, m, 8-CH_2), 2.98 (2 H, m, 11-CH_2), 5.52 (1 H, s, 6-H), 7.45 (1 H, q, $J_{2,3}$ 4.1, $J_{2,1}$ 8.1, 2-H), 8.74 (1 H, d, $J_{3,2}$ 3.9, 3-H) and 11.13 (1 H, s, 7-NH).

5-*Methyl*-7H-*pyrido*[2,3-c]*carbazole* **9**.—Tetrahydro-7*H*-pyridocarbazole **22** (1 g, 4 mmol) and 10% palladium on activated carbon (2 g) were refluxed during 18 h in mesitylene (40 cm^3), the end of the reaction being checked by TLC. After cooling, a mixture of dichloromethane–methanol (50 ml, 1:1) was added to dissolve any precipitated material. The Pd/C was filtered off and the filtrate evaporated. The mesitylene left was eliminated by a silica gel column chromatography using light petroleum as eluent, and the reaction product then being eluted with a mixture of dichloromethane–methanol (95:5). The resulting solution was evaporated to dryness and the residue flash chromatographed with dichloromethane–methanol (0.1–0.5%) as eluent to give **9** as yellow microcrystals (0.17 g, 18%), m.p. 200 °C (Found: C, 76.8; H, 5.6; N, 11.3. $C_{16}H_{12}N_2$·H_2O requires C, 76.80; H, 5.60; N, 11.20%); δ_H[$(CD_3)_2SO$] 2.87 (3 H, s, 5-CH_3), 7.30 (1 H, t, $J_{10,9}$ ~ 8, $J_{10,11}$ ~ 8, 10-H), 7.42 (1 H, t, $J_{9,8}$ ~ 8, 9-H), 7.65 (1 H, d, $J_{8,9}$ 8.9, 8-H), 7.71 (1 H, q, $J_{2,3}$ 4.2, $J_{2,1}$ 8.2, 2-H), 7.89 (1 H, s, 6-H), 8.53 (1 H, d, $J_{1,2}$ 7.9, 1-H), 8.87 (1 H, d, $J_{3,2}$ 4.2, $J_{3,1}$ 1.4, 3-H), 9.2 (1 H, d, $J_{11,10}$ 8.2, 11-H), 11.92 (1 H, s, 7-NH); λ_{max}(EtOH)/nm 225, 244 and 280; *m/z* 232 (M^+, 100%).

Starting Material for Methods B and C.

2,5-*Dimethyl*-3-*nitrophenylhydrazine* **15**.—In a warm solution of hydrochloric acid–water (3:2; 10 cm^3), **10** (1 g, 6 mmol)[33,34] was dissolved and then cooled to −5 °C. Diazotization was carried out in the usual manner by adding portionwise, to the cold, stirred mixture, a cold solution of sodium nitrite (0.8 g, 11.6 mmol) in water (4.5 cm^3). After 10 min at −5 °C, a solution of stannous chloride (5.2 g, 23 mmol) was then added with vigorous stirring. The reaction mixture was brought to room temperature over 2 h and the precipitate was filtered off. The solid was resuspended in water and made basic (pH 9) by adding concentrated aqueous sodium hydroxide. The yellow solid obtained was extracted with dichloromethane (× 3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The title compound was obtained as yellow crystals (62%, 0.6 g) from ethanol–water (1:1), m.p. 162–165 °C (Found: C, 53.0; H, 6.1; N, 23.0. $C_8H_{11}N_3O_2$ requires C, 53.02; H, 6.11; N, 23.19%).

2,5-*Dimethyl*-4-*nitrophenylhydrazine* **23**.—This compound, prepared as above with **18** (1 g),[32] was obtained as yellow crystals (0.35 g, 34%) from ethanol–water (1:1), m.p. 177–178 °C (Found: C, 53.0; H, 6.1; N, 23.1. $C_8H_{11}N_3O_2$ requires C, 53.02; H, 6.11; N, 23.19%).

1,4-*Dimethyl*-2-*nitro*-5,6,7,8-*tetrahydrocarbazole* **16a**.—To a suspension of **15** hydrochloride (1 g, 4.6 mmol) in ethanol (10 cm^3) a solution of sodium acetate (1 g, 12 mmol) in water (10 cm^3) was added and then heated until complete dissolution. Cyclohexanone (0.62 g, 6.3 mmol) was added to the reaction mixture which was then refluxed for 2 h and subsequently evaporated to dryness. The resulting solid was taken up with acetic acid (10 cm^3) saturated with hydrogen chloride and refluxed for 10 min. The reaction mixture was poured onto ice and the resulting yellow precipitate was extracted with dichloromethane (× 3). The combined extracts were washed with 30% aqueous sodium hydrogen carbonate until neutral and then with water and finally dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on a silica gel chromatographic column with dichloromethane as eluent to

give **16a** as orange microcrystals (0.6 g, 56%) which was recrystallized from ethanol, m.p. 208 °C (Found: C, 68.6; H, 6.6; N, 11.4. $C_{14}H_{16}N_2O_2$ requires C, 68.90; H, 6.61; N, 11.48%); $\delta_H[(CD_3)_2SO]$, 1.80 (4 H, m, 6-CH_2, 7-CH_2), 2.56 (3 H, s, 4-CH_3), 2.64 (3 H, s, 1-CH_3), 2.74 (2 H, m, 8-CH_2), 2.90 (2 H, m, 5-CH_2) and 7.40 (1 H, s, 3-H); λ_{max}(EtOH)/nm 220 and 255; *m/z* 244 (M^+, 100%).

6-*Methoxy*-1,4-*dimethyl*-2-*nitro*-5,6,7,8-*tetrahydrocarbazole* **16b**.—This compound was prepared as described above, the hydrochloride **15** (1 g, 4.6 mmol) and 4-methoxycyclohexanone (0.62 g, 6.3 mmol) affording yellow microcrystals (0.4 g, 39%) which were recrystallized from ethanol, m.p. 167 °C (Found: C, 68.7; H, 6.6; N, 11.4. $C_{15}H_{18}N_2O_3$ requires C, 68.90; H, 6.61; N, 11.48%); $\delta_H[(CD_3)SO]$ 1.75 (1 H, m, 7-CH_β), 1.93 (1 H, m, 7-CH_α), 2.58 (3 H, s, 4-CH_3), 2.64 (3 H, s, 1-CH_3), 2.86 (1 H, m, 5-CH_β), 3.25 (1 H, 5-CH_α), 3.34 (3 H, s, 6-OCH_3) and 3.68 (1 H, m, 6-H); λ_{max}(EtOH)/nm 220 and 257; *m/z* 274 (M^+, 72%).

1,4-*Dimethyl*-3-*nitro*-5,6,7,8-*tetrahydrocarbazole* **24a**.—As described above, compound **23**·HCl (1 g) and cyclohexanone (0.62 g) afforded the title compound as orange microcrystals (0.3 g, 28%) which were recrystallized from ethanol, m.p. 177–178 °C (Found: C, 68.8; H, 6.6; N, 11.4. $C_{14}H_{16}N_2O_2$ requires C, 68.90; H, 6.6; N, 11.48%); $\delta_H[(CD_3)_2SO]$ 1.15 (4 H, m, 6-CH_2, 7-CH_2), 2.40 (3 H, s, 1-CH_3), 2.65 (3 H, s, 4-CH_3), 2.70 (2 H, m, 8-CH_2), 2.90 (2 H, m, 5-CH_2), 7.04 (1 H, s, 2-H) and 11.30 (s, 9-NH); λ_{max}(EtOH)/nm 215 and 273; *m/z* 244 (M^+, 100%).

6-*Methoxy*-1,4-*dimethyl*-3-*nitro*-5,6,7,8-*tetrahydrocarbazole* **24b**.—As described above compound **23**·HCl (1 g) and 4-methoxycyclohexanone (1 g) afforded **24b** as yellow microcrystals (0.22 g, 22%) which were recrystallized from ethanol, m.p. 173 °C (Found: C, 68.65; H, 6.5; N, 11.4. $C_{15}H_{18}N_2O_3$ requires C, 68.90; H, 6.61; N, 11.48%); $\delta_H[(CD_3)_2SO]$ 1.83 (1 H, m, 7-CH_β), 2.02 (1 H, m, 7-CH_α), 2.38 (3 H, s, 1-CH_3), 2.70 (3 H, s, 4-CH_3), 2.74 (2 H, m, 8-CH_2), 2.82 (1 H, dd, 5-CH_β), 3.25 (1 H, dd, 5-CH_α), 3.34 (3 H, s, 6-OCH_3), 3.65 (1 H, m, 6-CH), 7.41 (1 H, s, 2-H) and 11.23 (1 H, s, 9-NH); λ_{max}(EtOH)/nm 216 and 270; *m/z* 274 (M^+, 92%).

Method B

1,4-*Dimethyl*-3-*nitrocarbazole* **25a**.—Compound **24a** (1 g, 4 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (2 g, 8 mmol) were refluxed in xylene (40 cm^3) for 3 h. The reaction mixture was filtered whilst still hot and the brown precipitate was washed with hot xylene. The filtrate and washings were evaporated under reduced pressure and the residue was purified by silica gel column chromatography using chloroform–methanol (95:5) as eluent to afford yellow microcrystals (0.43 g, 43%), m.p. 215–216 °C (Found: C, 70.1; H, 5.0; N, 11.7. $C_{14}H_{12}N_2O_2$ requires C, 70.00; H, 5.00; N, 11.67%); $\delta_H[(CD_3)_2SO]$ 2.58 (3 H, s, 1-CH_3), 2.97 (3 H, s, 4-CH_3), 7.28 (1 H, m, $J_{6,8} \sim 0.8$, $J_{6,7} \sim 7.2$, $J_{6,5} \sim 7.2$, 6-H), 7.50 (1 H, m, $J_{7,5} \sim 0.8$, $J_{7,6} \sim 7.7$, $J_{7,8} \sim 7.7$, 7-H), 7.52 (1 H, d, $J_{8,7}$ 8.1, 8-H), 7.86 (1 H, s, 2-H), 8.27 (1 H, d, $J_{5,6}$ 8, 5-H) and 11.88 (1 H, s, 9-H); *m/z* 240 (M^+, 100%).

6-*Methoxy*-1,4-*dimethyl*-3-*nitrocarbazole* **25b**.—As described above, compound **24b** (1 g) and DDQ (2g) in xylene (40 cm^3) afforded orange-yellow microcrystals (0.32 g, 31%), m.p. 222–225 °C (lit.,[44] 260 °C) (Found: C, 66.8; H, 5.2; N, 10.4. $C_{15}H_{14}N_2O_3$ requires C, 66.67; H, 5.15; N, 10.37%); $\delta_H[(CD_3)_2SO]$ 2.50 (3 H, s, 1-CH_3), 2.94 (3 H, s, 4-CH_3), 3.87 (3 H, s, 6-OCH_3), 7.14 (1 H, dd, $J_{7,5}$ 2.3, $J_{7,8}$ 8.8, 7-H), 7.51 (1 H, d, $J_{8,7}$ 8.8, 8-H), 7.66 (1 H, d, $J_{5,7}$ 1.8, 5-H), 7.78 (1 H, s, 2-H) and 11.68 (1 H, s, 9-NH).

3-*Amino*-1,4-*dimethylcarbazole* **26a**.—To a suspension of compound **25a** (1 g, 4 mmol) in ethanol (30 cm^3), hydrazine hydrate ((1 cm^3, 20 mmol) and Raney nickel (0.1 g) were added and refluxed for 30 min. At the end of the reaction, checked by TLC, the nickel was filtered off and the filtrate evaporated to dryness. The solid was recrystallized from toluene to give colourless needles (0.56 g, 65%), m.p. 210 °C (lit.,[43] 198 °C) (Found: C, 80.15; H, 6.7; N, 13.4. $C_{14}H_{14}N_2$ requires C, 80.00; H, 6.66; N, 13.34%); $\delta_H[(CD_3)_2SO]$ 2.43 (3 H, s, 1-CH_3), 2.46 (3 H, s, 4-CH_3), 4.38 (2 H, br, 3-NH_2), 6.68 (1 H, s, 2-H), 7.07 (1 H, t, $J_{6,7}$ 8.0, $J_{4,5}$ 8.0, 6-H), 7.28 (1 H, t, $J_{7,6}$ 8.1, 7-H), 7.44 (1 H, d, $J_{8,7}$ 8.0, 8-H), 8.12 (1 H, d, $J_{5,6}$ 8.0, 5-H) and 10.68 (1 H, s, 9-NH).

3-*Amino*-6-*methoxy*-1,4-*dimethylcarbazole* **26b**.—Following the same procedure as for **26a**, compound **25b** (1 g, 4 mmol) afforded orange-ochre microcrystals (0.45, 50.6%), m.p. 201 °C (lit.,[44] 200 °C) (Found: C, 74.9; H, 6.7; N, 11.8. $C_{15}H_{16}N_2O$ requires C, 75.00; H, 6.66; N, 11.67%); $\delta_H[(CD_3)_2SO]$ 2.53 (3 H, s, CH_3), 2.54 (3 H, s, CH_3), 3.88 (3 H, s, 6-OCH_3), 4.33 (2 H, br, 3-NH_2), 6.65 (1 H, s, 2-H), 7.15 (1 H, dd, $J_{7,5}$ 2.5, $J_{7,8}$ 8.8, 7-H), 7.52 (1 H, d, $J_{8,7}$ 8.8, 8-H), 7.68 (1 H, d, $J_{5,7}$ 2.3, 5-H) and 10.44 (1 H, s, 9-H).

Method C

2-*Amino*-1,4-*dimethyl*-5,6,7,8-*tetrahydrocarbazole* **17a**.—Hydrazine hydrate (1 cm^3, 20 mmol) and Raney nickel (0.1 g) were added to a suspension of compound **16a** (1 g, 4 mmol) in ethanol (30 cm^3) and the mixture warmed gradually to reflux for 30 min. At the end of the reaction, monitored by TLC, the nickel was filtered off and the filtrate evaporated under reduced pressure. The residue was recrystallized to afford yellow–ochre microcrystals (0.7 g, 84%) from benzene–light petroleum, m.p. 168–170 °C (Found: C, 78.3; H, 8.4; N, 12.9. $C_{14}H_{18}N_2$ requires C, 78.46; H, 8.46; N, 13.07%); $\delta_H[(CD_3)_2SO]$ 1.74 (4 H, m, 6-CH_2, 7-CH_2), 2.07 (3 H, s, 1-CH_3), 2.29 (3 H, s, 4-CH_3), 2.71 (2 H, m, 8-CH_2), 2.77 (2 H, m, 5-CH_2), 4.24 (2 H, br, 2-NH_2), 6.12 (1 H, s, 3-H) and 9.82 (1 H, s, 9-H); λ_{max}(EtOH)/nm 230; *m/z* 214 (M^+, 59%).

2-*Amino*-6-*methoxy*-1,4-*dimethyl*-5,6,7,8-*tetrahydrocarbazole* **17b**.—Following the above procedure, **16b** (1 g) afforded beige microcrystals (0.7 g, 84%) from silica gel preparative TLC using as eluent chloroform–methanol (98:2), m.p. 149 °C. (Found: C, 73.5; H, 8.2; N, 11.3.$C_{15}H_{20}N_2O$ requires C, 73.73; H, 8.25; N, 11.46%); $\delta_H[(CD_3)_2SO]$ 1.69 (4 H, m, 6-CH_2, 7-CH_2), 1.70 (1 H, m, 7-CH_β), 1.90 (1 H, m, 7-CH_α), 2.10 (3 H, s, 1-CH_3), 2.38 (3 H, s, 4-CH_3), 2.68 (2 H, m, 8-CH_2), 2.80 (1 H, m, 5-CH_β), 3.20 (1 H, m, 5-CH_α), 3.32 (3 H, s, 6-OCH_3), 4.30 (2 H, br, 2-NH_2), 6.12 (1 H, s, 3-H) and 9.88 (1 H, s, 9-NH); λ_{max}(EtOH)/nm 232 and 279; *m/z* 24 (M^+, 55%).

3-*Amino*-1,4-*dimethyl*-5,6,7,8-*tetrahydrocarbazole* **27a**.—With compound **24a** (1 g, 4 mmol) the above procedure afforded yellow–ochre microcrystals (0.47, g, 56%) from silica gel column chromatography using chloroform–methanol (95:5) as eluent, m.p. 176 °C (Found: C, 78.3; H, 8.4; N, 13.0. $C_{14}H_{18}N_2$ requires C, 78.46; H, 8.46; N, 13.07%); $\delta_H[(CD_3)_2SO]$ 1.75 (4 H, m, 6-, 7-CH_2), 2.21–2.22 (6 H, s, 1-, 4-CH_3), 2.52 (2 H, m, 8-CH_2), 2.84 (2 H, m, 5-CH_2), 3.98 (2 H, br, 3-NH_2), 6.20 (1 H, s, 2-H) and 9.89 (1 H, s, 9-NH); λ_{max}(EtOH)/nm 230 and 279; *m/z* 214 (M^+, 92%).

3-*Amino*-6-*methoxy*-1,4-*dimethyl*-5,6,7,8-*tetrahydrocarbazole* **27b**.—As described above, compound **24b** (1 g, 3.65 mmol) afforded red–ochre microcrystals (0.56 g, 65%) from silica gel column chromatography using as eluent chloroform–methanol (95:5), m.p. 142–143 °C (Found: C, 73.5; H, 8.2; N, 11.3.

$C_{15}H_{20}N_2O$ requires C, 73.73; H, 8.25; N, 11.46%); δ_H-[$(CD_3)_2SO$] 1.73 (1 H, m, 7-CH_β), 2.02 (1 H, m, 7-CH_α), 2.69 (2 H, m, 8-CH_2), 2.74 (1 H, m, 5-CH_β), 3.25 (1 H, m, 5-CH_α), 3.34 (3 H, s, 6-OCH_3), 3.6 (1 H, m, 6-CH), 4.48 (2 H, br, 3-NH_2), 7.28 (1 H, s, 2-H) and 10.0 (1 H, s, 9-NH); λ_{max}(EtOH)/nm 227 and 277; *m/z* 244 (M^+, 98%).

5,11-*Dimethyl*-6,7,8,9-*tetrahydro*-10H-*pyrido*[2,3-b]*carbazole* **14a**.—Compound **17a** (1 g, 4.67 mmol) and 85% orthophosphoric acid (12 cm^3) were heated and stirred at 95 °C in a three-necked flask equipped with a water condenser, a dropping funnel and a thermometer. Arsenic pentoxide dihydrate (0.77 g, 2.9 mmol) was then added and after the mixture had been heated for 10 min at 95 °C acrolein (570 mm^3, 8.5 mmol) was added dropwise over a period of 0.75 h. Heating and stirring were continued for a further 1 h. The reaction mixture was then poured onto ice and made basic (pH 9) with 20% aqueous potassium hydroxide. The brown precipitate was extracted with dichloromethane (3 × 50 cm^3) and the combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The resulting solid was purified by preparative silica gel TLC using chloroform–methanol (9:1) as eluent to afford yellow microcrystals (0.37 g, 32%), m.p. 193–195 °C (Found: C, 76.2; H, 7.5; N, 10.5. $C_{17}H_{18}N_2$. $1H_2O$ requires C, 76.12; H, 7.46; N, 10.44%); $\delta_H[(CD_3)_2SO]$ 2.07 (4 H, m, 7-CH_2, 8-CH_2), 2.63 (3 H, s, 5-CH_3), 2.71 (2 H, m, 9-CH_2), 2.84 (3 H, s, 11-CH_3), 3.10 (2 H, m, 6-CH_2), 7.48 (1 H, dd, $J_{3,2}$ 4.1, $J_{3,4}$ 8.5, 3-H), 8.42 (1 H, dd, $J_{4,2}$ 1.6, $J_{4,3}$ 8.4, 4-H) and 8.87 (1 H, dd, $J_{2,3}$ 4.1, $J_{2,4}$ 1.5); λ_{max}(EtOH)/nm 255 and 265; *m/z* 250 (M^+, 100%).

7-*Methoxy*-5,11-*dimethyl*-6,7,8,9-*tetrahydro*-10H-*pyrido*-[2,3-b]*carbazole* **14b**.—Following the above procedure compound **17b** (1 g, 4 mmol) afforded yellow microcrystals of **14b** (0.26g, 22%), m.p. 165–167 °C (Found: C, 72.5; H, 7.4; N, 9.4. $C_{18}H_{20}N_2O{\cdot}1H_2O$ requires C, 72.48; H, 7.38; N, 9.39%); $\delta_H[(CD_3)_2SO]$ 2.62 (3-H, s, 5-CH_3), 2.82 (3 H, s, 11-CH_3), 2.95 (2 H, m, 9-CH_2), 3.17 (3 H, s, 7-OCH_3), 3.80 (2 H, m, 6-CH_2), 4.20 (1 H, m, 7-CH), 7.50 (1 H, q, $J_{3,2}$ 4.0, $J_{3,4}$ 8.4, 3-H), 8.45 (1 H, d, $J_{4,3}$ 8.4, 4-H), 8.81 (1 H, d, $J_{2,3}$ 4.0, 2-H) and 11.66 (1 H, s, 10-NH); λ_{max}(EtOH)/nm 257 and 264; *m/z* 280 (M^+, 68%).

5,11-*Dimethyl*-7,8,9,10-*tetrahydro*-6H-*pyrido*[3,2-b]*carbazole* **28a**.—Following the above procedure, compound **27a** (1 g, 4.67 mmol) afforded **28a** as yellow crystals (0.23, 20%) by preparative silica gel TLC with chloroform–methanol (95:5) as eluent, m.p. 199–200 °C (Found: C, 78.8; H, 7.35; N, 11.0. $C_{17}H_{18}N_2{\cdot}1/2H_2O$ requires C, 78.76; H, 7.33; N, 10.81%); $\delta_H[(CD_3)_2SO]$ 2.05 (4 H, m, 8-CH_2, 9-CH_2), 2.70 (3 H, s, 5-CH_3), 2.72 (2 H, m, 7-CH_2), 2.80 (3 H, s, 11-CH_3), 3.07 (2 H, m, 10-CH_2), 7.51 (1 H, q, $J_{3,2}$ 4.1, $J_{3,4}$ 8.5, 3-H), 8.45 (1 H, d, $J_{4,3}$ 8.4, 4-H), 8.78 (1 H, d, $J_{2,3}$ 4.2, 2-H); λ_{max}(EtOH)/nm 256 and 264; m/z 250 (M^+, 100%).

9-*Methoxy*-5,11-*dimethyl*-7,8,9,10-*tetrahydro*-6H-*pyrido*-[3,2-b]*carbazole* **28b**.—Following the same procedure as above, compound **27b** (1 g, 4 mmol) afforded **28b** as yellow-ochre crystals (0.31 g, 26%) by preparative silica gel TLC with chloroform–methanol (95:5) as eluent, m.p. 210–212 °C (Found: C, 72.5; H, 7.4; N, 9.4. $C_{18}H_{20}N_2O{\cdot}1/2H_2O$ requires C, 72.48; H, 7.38; N, 9.39%); $\delta_H[(CD_3)_2SO]$ 1.55 (1 H, m, 8-CH_β), 1.80 (1 H, m, 10-CH_β), 2.35 (1 H, m, 8-CH_α), 2.70 (3 H, s, 5-CH_3), 2.77 (3 H, s, 11-CH_3), 3.10 (1 H, m, 10-CH_α), 3.15 (3 H, s, 9-OCH_3), 4.2 (1 H, m, 9-CH), 7.52 (1 H, q, $J_{3,2}$ 4.1, $J_{3,4}$ 8.4, 3-H), 8.45 (1 H, d, $J_{4,3}$ 8.4, 4-H), 8.85 (1 H, d, $J_{2,3}$ 4.2, 2-H) and 10.20 (1 H, s, 6-NH); λ_{max}(EtOH)/nm 257 and 267; *m/z* 280 (M^+, 70%).

5,11-*Dimethyl*-10H-*pyrido*[2,3-b]*carbazole* **7a**: *Method C*.—Aromatization was performed with compound **14a** (1 g, 4 mmol) as for **9** (Scheme 2, Method A). Flash chromatography afforded in a ratio of 40:60, two different fractions which were collected and repurified separately on preparative silica gel TLC plates using dichloromethane–methanol (95:5) as eluent. After evaporation, the first fraction corresponded to the title compound giving **7a** as yellow microcrystals (0.15 g, 16%), m.p. 213–215 °C (lit.,[29,30] 212–213 °C and 217–221 °C respectively) (Found: C, 77.3; H, 6.1; N, 10.6. $C_{17}H_{14}N_2{\cdot}1H_2O$ requires C, 77.28; H, 6.06; N, 10.60%); $\delta_H[(CD_3)_2SO]$ 2.90 (3 H, s, 11-CH_3), 3.17 (3 H, s, 5-CH_3), 7.41 (1 H, q, $J_{3,2}$ 4, $J_{3,4}$ 8.5, 3-H), 7.50 (1 H, t, $J_{8,9}$ ~ 7.6, $J_{8,7}$ ~ 7.2, 8-H), 8.35 (1 H, d, $J_{6,7}$ 7.9, 6-H), 8.72 (1 H, dd, $J_{4,2}$ 1.6, $J_{4,3}$ 8.5, 4-H), 8.90 (1 H, dd, $J_{2,3}$ 4, $J_{2,4}$ 1.5, 2-H), 11.36 (1 H, s, 10-NH); *m/z* 246 (M^+, 100%), 231 (M^+ − 15) and 217 (M^+ − 29); λ_{max}(EtOH)/nm 232, 280 and 302.

The other fraction afforded, after evaporation, a solid which was a mixture of two by-products (24%). After GC/MS the first by-product displayed: *m/z* 278 (M^+, 100%), 263 (M^+ − 15), 249 (M^+ − 29), 234 (M^+ − 44), 219 (M^+ − 59) and 205 (M^+ − 73); the second one: *m/z* 276 (M^+, 91%), 261 (M^+ − 15), 247 (M^+ − 29), 233 (M^+ − 43) and 219 (M^+ − 57).

7-*Methoxy*-5,11-*dimethyl*-10H-*pyrido*[2,3-b]*carbazole* **7b**.—The compound was synthesized as above from compound **14b** (1 g) as yellow microcrystals (0.17 g, 18%), m.p. 158–160 °C (lit.,[30] 197–199 °C) (Found: C, 73.5; H, 6.1; N, 9.8. $C_{18}H_{16}N_2O{\cdot}1H_2O$ requires C, 73.47; H, 6.12; N, 9.52%); $\delta_H[(CD_3)SO]$ 2.87 (3 H, s, 5-CH_3), 3.17 (3 H, s, 11-CH_3), 3.90 (3 H, s, 7-OCH_3), 7.17 (1 H, dd, $J_{8,6}$ 2.4, $J_{8,9}$ 8.5, 8-H), 7.39 (1 H, q, $J_{3,2}$ 4, $J_{3,4}$ 8.2, 3-H), 7.47 (1 H, d, $J_{9,8}$ 8.6, 9-H), 7.86 (1 H, d, $J_{6,8}$ 2.3, 6-H), 8.00 (1 H, dd, $J_{4,2}$ 1.6, $J_{4,3}$ 8.6, 4-H), 8.90 (1 H, dd, $J_{2.4}$ 1.4, $J_{2,3}$ 4.6, 2-H) and 11.05 (1 H, s, 10-NH); *m/z* 276 (M^+, 99.39%), 261 (M^+ − 15), 245 (M^+ − 31) and 231 (M^+ − 45); λ_{max}(EtOH)/nm 236, 278 and 303.

The other fraction isolated, was a mixture of two by-products (27%) as for **7a** above. After GC/MS the first by-product displayed: *m/z* 308 (M^+, 100%), 293 (M^+ − 15), 279 (M^+ − 29), 247 (M^+ − 61), 221 (M^+ − 87) and 219 (M^+ − 89); the second one: *m/z* 306 (M^+, 100%), 291 (M^+ − 15), 275 (M^+ − 31), 247 (M^+ − 59), 235 (M^+ − 71) and 219 (M^+ − 87).

5,11-*Dimethyl*-6H-*pyrido*[3,2-b]*carbazole* **8a**.—*Method B*. The Skraup reaction performed with compound **26a** (3 g, 12 mmol) as for the preparation of **11** and **19** afforded **8a** as yellow microcrystals (0.42 g, 15%) after purification by preparative silica gel TLC, m.p. 213 °C (Found: C, 77.3; H, 6.1; N, 10.8. $C_{17}H_{14}N_2{\cdot}1H_2O$ requires C, 77.28; H, 6.06; N, 10.60%); $\delta_H[(CD_3)_2SO]$ 2.82 (3 H, s, 5-CH_3), 3.30 (3 H, s, 11-CH_3), 7.22 (1 H, t, $J_{9,8}$ ~ 7.5, $J_{9,10}$ ~ 7.5, 9-H), 7.48 (1 H, d, 7-H), 7.50 (1 H, ddr, $J_{3,2}$ 3.4, $J_{3,2}$ 8.7, 3-H), 7.55 (1 H, t, $J_{8,9}$ ~ 7.8, $J_{8,7}$ ~ 7.8, 8-H), 8.35 (1 H, d, $J_{10,9}$ 7.8, 10-H), 8.54 (1 H, d, $J_{4,3}$ 8.7, 4-H), 8.85 (1 H, d, $J_{2,3}$ 3.8, 2-H) and 11.34 (1 H, s, 6-NH); *m/z* 246 (M^+, 100%) and 231 (M^+ − 15); λ_{max}(EtOH)/nm 238, 277 and 302.

Method C. Aromatization was carried out with compound **28a** (1 g, 4 mmol) as for **7a** to afford two fractions in a ratio of 40:60 after flash chromatography: repurification of each fraction separately on preparative silica gel TLC plates with dichloromethane–methanol (95:5) as eluent gave for the first fraction yellow microcrystals (0.15 g, 16%) having physical constants identical with those found with method B. The second fraction isolated, as for **7a** in Method C, was also a mixture of two by-products (22%).

9-*Methoxy*-5,11-*dimethyl*-6H-*pyrido*[3,2-b]*carbazole* **8b**.—*Method B*. As for compound **8a** the Skraup reaction performed with compound **26b** (1 g, 4 mmol) afforded yellow microcrystals (0.13 g, 15%), m.p. 221–223 °C (Found: C, 73.5; H, 6.15; N, 9.4.

$C_{18}H_{16}N_2O \cdot 1H_2O$ requires C, 73.47; H, 6.12; N, 9.52%); δ_H[$(CD_3)SO$] 2.82 (3 H, s, 5-CH_3), 3.32 (3 H, s, 11-CH_3), 3.90 (3 H, s, 9-OCH_3), 7.15 (1 H, d, $J_{7,8}$ 8.8, 7-H), 7.19 (1 H, dd, $J_{8,10}$ 2.7, $J_{8,7}$ 8.8, 8-H), 7.47 (1 H, q, $J_{3,2}$ 3.8, $J_{3,4}$ 8.8, 3-H), 7.85 (1 H, dd, $J_{10,8}$ 2.7, 10-H), 8.52 (1 H, dd, $J_{4,2}$ 1.6, $J_{4,3}$ 8.82, 4-H), 8.84 (1 H, dd, $J_{2,4}$ 1.6, $J_{2,3}$ 3.8, $J_{2,4}$ 1.6, 2-H) and 11.30 (1 H, s, 6-NH); *m/z* 276 (M^+, 100%) and 261 ($M^+ - 15$); λ_{max}(EtOH)/nm 240, 278 and 304.

Method C. Following the same procedure as for compound **7a**, aromatization of compound **28b** (1 g, 4 mmol) afforded yellow microcrystals (0.15 g, 16%) having physical constants identical with those found above with Method B. As for compound **7a** the other fraction isolated also was a mixture of two oxidized by-products obtained in 23% yield.

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