Efficient Synthesis of 5-Demethyl-6-methylisoellipticine and Utilization of the Methodology to Prepare Angular and Linear Pyridocarbazoles

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5-Demethyl-6-methylisoellipticine and its analogue 7-methylpyrido[4,3-*c*]carbazole have been synthesized by thermal cyclization of *N*-methylcarbazoles having an active acid azide side-chain, followed by reduction.

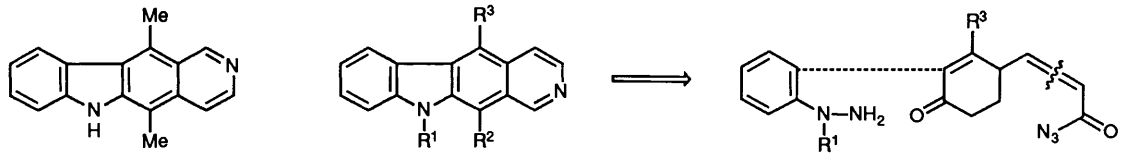
Pyridocarbazoles of both natural and unnatural origin have attracted synthetic organic chemists because of their wide variety of biological activities.[1] Ellipticine **1** has been synthesized by many groups (see ref. 1 and refs. therein). However, only a few syntheses of isoellipticine **2**[2–7] are known. Recently many new pyridocarbazoles have been synthesized and found to be potential antitumour agents.[3] In order to understand (at the molecular level) the mechanism of action of the antitumour activity and how DNA becomes alkylated by pyridocarbazoles, several analogues of ellipticine and isoellipticine are required. More recently[8] it has been reported that *N*-methyl derivatives of pyridocarbazoles are potent anticancer agents. To prepare a surrogate of ellipticine with the same molecular formula but with different positions of methyl groups and nitrogen atoms we have undertaken and completed the total synthesis of the hitherto unknown 5-demethyl-6-methylisoellipticine **3** (the title compound) and its angular analogue 7-methylpyrido[4,3-*c*]carbazole **20**, which are the main subjects of this paper.

Our approach to pyrridocarbazoles involves selective three-carbon annelation, in which an active acid azide group at the chain end is fused onto the carbazole moiety (shown retrosynthetically in Scheme 1). Carbazole derivative **7** was prepared from Hagemann's ester **5** and phenylhydrazine **4** by a modified method developed by Bergman and Pelcman,[9] followed by dehydrogenation with 10% Pd–C. Compound **7** on treatment with NaH/MeI produced the *N*-methylcarbazole derivative **8** in 76% yield. The ester group in compound **8** was converted into the aldehyde **10** by $LiAlH_4$ reduction to the alcohol **9** followed by oxidation with active MnO_2 in almost quantitative yield. Condensation of the aldehyde **10** with malonic acid produced the α,β-unsaturated *E*-acid **11**, which in turn was converted into the acid azide derivative **12** by treatment with $ClCO_2Et$/$-Et_3N$–NaN_3 in 80% yield. Following the method of Bisagni *et al.*,[10] the azide **12** on being heated with Bu_3N in boiling Ph_2O underwent smooth and selective cyclization to the δ-lactam **13** in very good yield. Compound **13**, when treated with $POCl_3$ at 120 °C, afforded 4-chloro-5-demethyl-6-methylisoellipticine **14** as a lemon yellow solid which, on reduction with Zn–AcOH, produced the title compound **3** in ~80% yield. The results are given in Table 1.

We then applied the above methodology to the synthesis of the angular pyridocarbazole derivative 7-methylpyrido[4,3-*c*]-carbazole **20** *via* the thermal cyclization of the azide **17** according to Scheme 2. Though it has been reported that 7*H*-pyrido[4,3-*c*]carbazoles in their dimeric form show enhanced activity against L1210 leukaemia compared with the ellipticine dimer[11,12] which was found to be completely inactive, but still only very few[13–15] syntheses of pyrido[4,3-*c*]carbazole and their derivatives have been published so far and in most cases they have led to the formation of a mixture of isomeric products.

The azide **17** required for the synthesis of the lactam **18** was prepared from the acid **16** which was, in turn, obtained by Knoevenagel condensation of *N*-methylcarbazole-3-carbaldehyde **15**[16] with malonic acid in excellent yield. Azide cyclization under similar conditions as described for the preparation of compound **13** produced 2,7-dihydro-7-methylpyrido[4,3-*c*]carbazol-1-one in high yield. In Scheme 1 we found that cyclization of the azide **12** produced the linear lactam **13** as the sole product; however, the azide having no methyl group at C-4 of the carbazole moiety (*i.e.*, azide **17**) gave, on thermal cyclization, the angular lactam **18** exclusively and no formation of linear product was observed, as evident by the high downfield shift of the proton (11-H) in ^1H NMR spectrum of the lactam **18** and that of the chloro derivative **19** which was obtained from the lactam **18** by treatment with $POCl_3$ at 120 °C. Subsequent reduction of the chloro derivative with Zn–AcOH produced the desired product, 7-methyl-7*H*-pyrido[4,3-*c*]carbazole **20** as a solid in ~90% yield. The overall results and spectral data are summarized in Table 2.

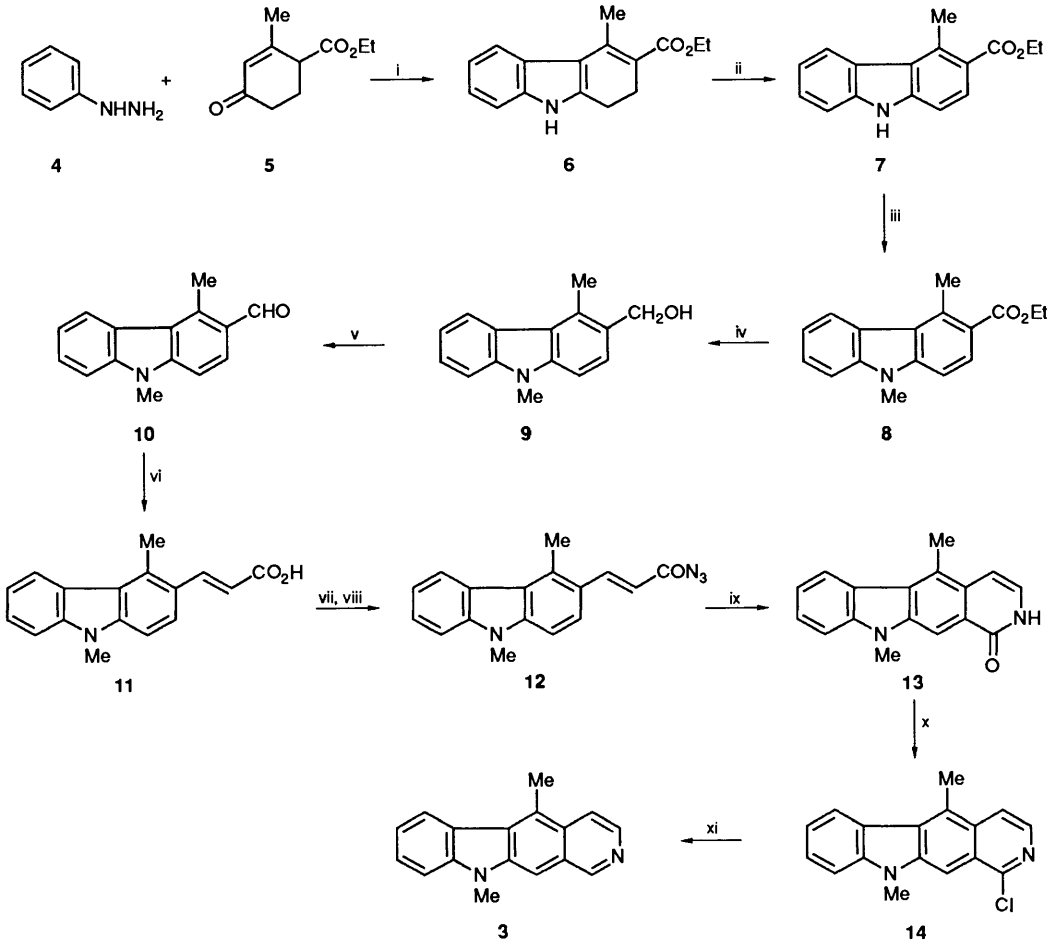
In an attempt to study the regioselectivity in the cyclization of a suitable isocyanate derivative (Scheme 3) with polyphosphoric acid (PPA) to produce the δ-lactam as the precursor of pyridocarbazole derivatives, it was found that the isocyanate **23** prepared from the corresponding dihydro azide **22** on treatment with PPA produced, in 71% yield, a mixture of the angular lactam 2,3,4,7-tetrahydro-7-methylpyrido[4,3-*c*]carbazol-1-one



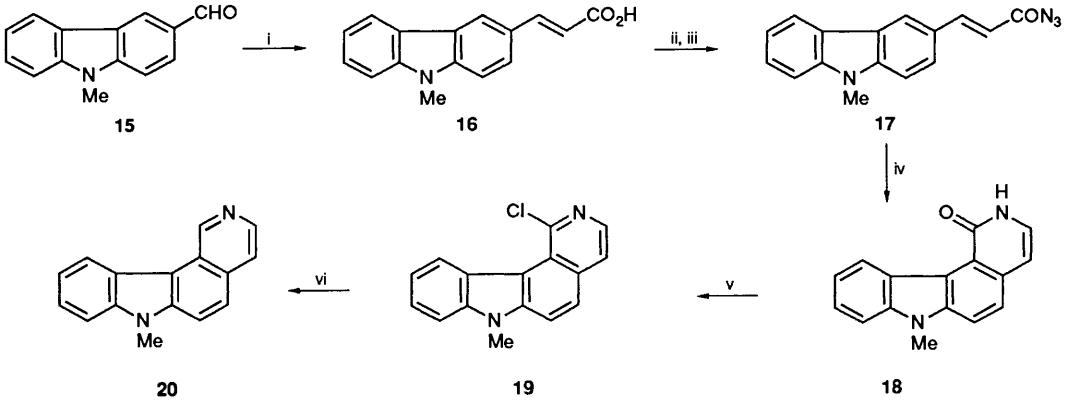
1 Ellipticine

2 Isoellipticine
(R^1 = H, R^2 = R^3 = Me)

3 5-demethyl-6-methyl isoellipticine
(R^1 = R^3 = Me, R^2 = H)



Scheme 1 *Reagents and conditions:* i, AcOH, reflux; ii, Pd–C (10%), *p*-cymene, reflux; iii, NaH, MeI, THF, 0 °C to room temperature; iv, LAH, THF, reflux; v, MnO_2, $CHCl_3$, 35 °C; vi, $CH_2(CO_2H)_2$, pyridine, piperidine, 80 °C; vii, $ClCO_2Et$, Et_3N, 0–5 °C; viii, NaN_3, 0–5 °C; ix, Ph_2O, Bu_3N, reflux; x, $POCl_3$, reflux; xi, Zn, AcOH, reflux



Scheme 2 *Reagents and conditions:* i, malonic acid, piperidine, pyridine, 80 °C; ii, $ClCO_2Et$, Et_3N, 0–5 °C; iii, NaN_3, 0–5 °C; iv, Bu_3N, Ph_2O, reflux; v, $POCl_3$, reflux; vi, Zn, AcOH, reflux

24 and the linear isomer 2,3,4,10-tetrahydro-10-methylpyrido[3,4-*b*]carbazol-1-one **25** in 3:1 ratio [as evident from ^1H NMR spectrometry (Fig. 1)] together with compound **26** in ~15% yield. However, we could not separate the lactams **24** and **25** at this stage by the usual chromatographic methods. The mixture of the above lactams, when treated with $POCl_3$ followed by the usual work-up, afforded the angular chloro derivative 1-chloro-3,6-dihydro-7-methyl-3*H*-pyrido[4,3-*c*]carbazole **27** and the linear lactam 2,3,4,10-tetrahydro-10-methylpyrido[3,4-*b*]carbazol-1-one **25**, which could easily be separated by chromatographic methods.

Conclusions.—Thermal cyclization of the azide *via* an intermediate nitrene usually takes place at the C-4 position of the carbazole moiety, leading to the angular isomer, *i.e.* compound **18**, exclusively whereas a methyl group at C-4 forces the cyclization to occur at the C-2 position of the carbazole moiety to produce the linear product **13** as the only product. However, in the case of cyclization of the isocyanate with PPA, cyclization occurs at C-2 as well as C-4 of the carbazole moiety, the major product being that formed by reaction at the C-4 position, *i.e.* the angular isomer.

The pyridocarbazoles thus prepared will be screened for

Table 1

Compound	Nature	M.p. (T/°C) (recryst. solvent)	Yield (%)	ν_{max}/cm^{-1}	δ_H	m/z
7	Solid	181–182 (EtOH)	90.6		1.45 (3 H, t), 3.2 (3 H, s), 4.42 (3 H, q), 7.2 (1 H, d), 7.15–7.5 (3 H, m), 8.0 (1 H, d), 8.3 (1 H, d), 8.4 (1 H, s)	
8	Solid	108–109 (light petroleum)	75.7	1700	1.4 (3 H, t), 3.1 (3 H, s), 3.7 (3 H, s), 4.4 (2 H, q), 7.1 (1 H, d), 7.15–7.5 (3 H, m), 7.95 (1 H, d), 8.2 (1 H, d)	
9	Solid	202–203	100	3400	2.8 (3 H, s), 3.7 (3 H, s), 4.4 (1 H, s), 4.7 (2 H, s), 7.0–7.6 (5 H, m), 8.0–8.2 (1 H, m)	
10	Solid	122–123	99	1700	3.0 (3 H, s), 3.6 (3 H, s), 7.0–7.5 (4 H, m), 7.9 (1 H, d), 8.1 (1 H, d), 10.3 (1 H, s)	
11	Solid	250–251	71.3	1610, 1675	(methyl ester) 3.0 (3 H, s), 3.2 (3 H, s), 3.8 (3 H, s), 6.4 (1 H, d), 7.2–7.8 (6 H, m), 8.2–8.5 (1 H, m)	
12	Yellow solid	146–147 (decomp.)	82.1	1610, 1660, 2050		
13	Light yellow solid	>280	71.4	1620, 1645		
14	Lemon yellow solid	188–189 ($CHCl_3$)	70.2		3.0 (3 H, s), 3.7 (3 H, s), 7.2–7.9 (5 H, m), 8.1–8.4 (4 H, m)	282 (M + 2), 281 (M + 1), 280 (M$^+$), 279 (M − 1), 267, 266, 265 (M − 15), 245, 244, 243, 242, 230, 229, 228, 217, 216, 215, 214, 203, 202, 201, 149, 141, 122
3	Yellow solid	168–170	79.7		3.1 (3 H, s), 3.8 (3 H, s), 7.2–7.7 (5 H, m), 7.9 (1 H, d), 8.3 (1 H, d), 9.3 (1 H, s)	247 (M + 1), 246 (M$^+$), 245 (M − 1), 231 (M − 15), 123

Table 2

Compound	Nature	M.p. (T/°C) (recryst. solvent)	Yield (%)	ν_{max}/cm^{-1}	δ_H	m/z
16	Solid	245–246	92.8	1615, 1670	(methyl ester) 3.6 (3 H, s), 3.7 (3 H, s), 6.3 (1 H, d), 7.0–8.1 (8 H, m)	
17	Yellow solid	124–125 (decomp.)	73.4	1588, 1674, 2133	3.8 (3 H, s), 6.5 (1 H, d), 7.2–8.3 (8 H, m)	
18	Light yellow solid	244–245	76.6	1586, 1642	4.0 (3 H, s), 6.72 (1 H, d), 7.04–7.92 (5 H, m), 8.12 (1 H, d), 9.84 (1 H, d), 11.32 (1 H, br s)	
19	Yellow solid	129–130	65.4		3.75 (3 H, s), 7.25–7.85 (6 H, m), 8.35 (1 H, d), 9.2 (1 H, d)	268 (M + 2), 267 (M + 1), 266 (M$^+$), 251, 231, 230, 229, 216, 215
20	Solid	164–165	90		3.92 (3 H, s), 7.2–8.08 (6 H, m), 8.6 (2 H, d), 10.24 (1 H, s)	

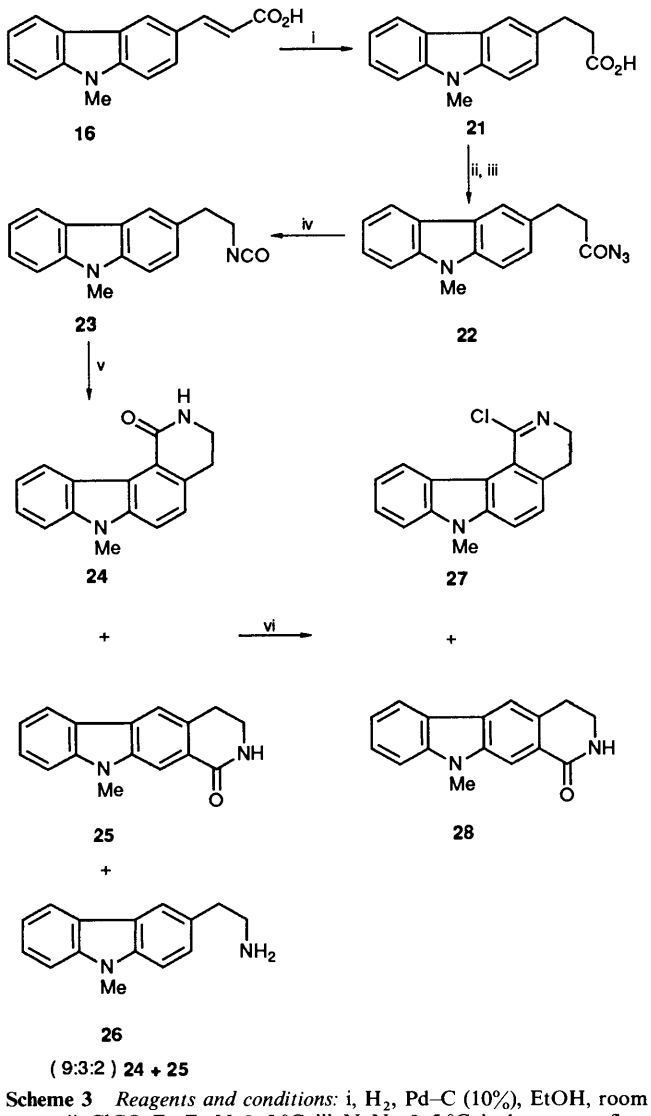
biological activity against leukaemia L1210 cells transplanted into mice.

Experimental

Unless otherwise stated ^{1}H NMR spectra were recorded at 90 MHz (Varian) and 100 MHz (Jeol) for solutions in [^{2}H]chloroform. J Values are given in Hz. IR spectra were recorded on a Perkin-Elmer 800 machine and mass spectral data were obtained from IICB, Calcutta.

Ethyl 4-Methylcarbazole-3-carboxylate **7**.—Ethyl 1,2-dihydro-4-methylcarbazole-3-carboxylate[9] **6** (3.0 g, 11.76 mmol) was refluxed with Pd–C (10%) (500 mg) *p*-cymene (25 cm^3) for 6 h. The catalyst was separated by filtration and the solvent was removed under reduced pressure. The crude product thus obtained was redissolved in benzene and filtered through a short column of neutral Al_2O_3. Removal of benzene afforded *compound* **7**, which on recrystallization from ethanol gave a shining solid (2.7 g, 90.6%), m.p. 181–182 °C; δ_H($CDCl_3$; 90 MHz) 1.45 (3 H, t), 3.2 (3 H, s), 4.42 (2 H, q), 7.2 (1 H, d), 7.15–7.5 (3 H, m), 8.0 (1 H, d), 8.3 (1 H, d), 8.3 (1 H, d) and 8.4 (1 H, s) (Found: C, 75.7; H, 5.75; N, 5.4. $C_{16}H_{15}NO_2$ requires C, 75.89; H, 5.93; N, 5.53%).

Ethyl 4,9-Dimethylcarbazole-3-carboxylate **8**.—To a suspension of 50% NaH (600 mg, 12.5 mmol) in anhydrous tetrahydrofuran (THF) (20 cm^3) at 0–5 °C was added dropwise a solution of compound **7** (3.0 g, 11.9 mmol) in THF (20 cm^3). The mixture was stirred under nitrogen at 0–5 °C for 45 min and then a solution of methyl iodide (2.13 g, 15.0 mmol) in THF (10 cm^3) was added dropwise. The reaction mixture was stirred for 1 h at 0–5 °C and then at room temperature overnight. THF was partly removed by distillation, and the



Scheme 3 *Reagents and conditions:* i, H_2, Pd–C (10%), EtOH, room temp.; ii, $ClCO_2Et$, Et_3N, 0–5 °C; iii, NaN_3, 0–5 °C; iv, benzene, reflux; v, PPA, 80–100 °C; vi, $POCl_3$, reflux

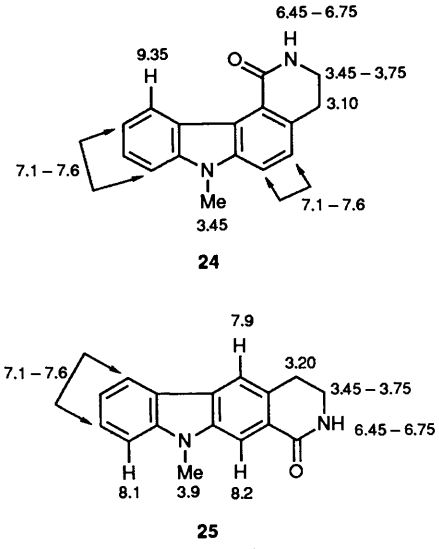


Fig. 1 ^1H NMR data for compounds **24** and **25**

product was decomposed with ice–water and extracted with chloroform. Usual work-up afforded the *title compound* as a solid (2.4 g, 75.7%), m.p. 108–109 °C [from light petroleum (60–80 °C)] ν_{max}(KBr)/cm^{-1} 1700; δ_H($CDCl_3$; 90 MHz) 1.4 (3 H, t), 3.1 (3 H, s), 3.7 (1 H, s), 4.4 (2 H, q), 7.1 (1 H, d), 7.15–7.5 (3 H, m), 7.95 (1 H, d) and 8.2 (1 H, d) (Found: C, 76.3; H, 6.2; N, 5.05. $C_{17}H_{17}NO_2$ requires C, 76.40; H, 6.37; N, 5.05%).

(4,9-*Dimethylcarbazol*-3-*yl*)*methanol* **9**.—A solution of compound **8** (2.0 g, 7.5 mmol) in anhydrous THF (10 cm^3) was added dropwise to a stirred solution of $LiAlH_4$ (595 mg, 15.6 mmol) in THF (15 cm^3) at room temperature. The mixture was refluxed and stirred under nitrogen for 4 h, cooled to 0–5 °C, decomposed with ice–water and extracted with CH_2Cl_2. Usual work-up afforded the alcohol **9** (1.69 g, 100%) as a solid, m.p. 202–203 °C; ν_{max}(KBr)/cm^{-1} 3400; δ_H($CDCl_3$; 90 MHz) 2.8 (3 H, s), 3.7 (3 H, s), 4.4 (1 H, s), 4.7 (2 H, s), 7.0–7.6 (5 H, m) and 8.0–8.2 (1 H, m). The compound was not purified further and was used directly for the next step.

4,9-*Dimethylcarbazole*-3-*carbaldehyde* **10**.—To a solution of the alcohol **9** (1.4 g) in chloroform (100 cm^3) was added an excess of active MnO_2 (10 g), and the mixture was stirred at 30–35 °C for 4.5 h and then filtered. The filtrate, on removal of solvent, afforded the *aldehyde* **10** which, on recrystallization from ethanol, gave shining needles (1.37 g, 99%), m.p. 122–123 °C; ν_{max}(Nujol)/cm^{-1} 1700; δ_H($CDCl_3$; 90 MHz) 3.0 (3 H, s), 3.6 (3 H, s), 7.0–7.5 (4 H, m), 7.9 (1 H, d), 8.1 (1 H, d) and 10.3 (1 H, s) (Found: C, 80.6; H, 5.65; N, 6.1. $C_{15}H_{13}NO$ requires C, 80.71; H, 5.83; N, 6.28%).

(E)-β-(4,9-*Dimethylcarbazol*-3-*yl*)*acrylic Acid* **11**.—A solution of malonic acid (1.0 g) and the aldehyde **10** (600 mg, 2.7 mmol) in pyridine (20 cm^3) containing 3–4 drops of piperidine was heated at 80 °C for 2 h and within this time an additional amount (1.0 g) of malonic acid was added in two batches. Finally the reaction mixture was refluxed for 1 h, cooled to room temperature and poured onto ice–water containing excess of hydrochloric acid. The solid was separated by filtration, washed well with water and dried (*in vacuo*) to give the *acid* **11** (770 mg, 71.3%), m.p. 250–251 °C; ν_{max}(Nujol)/cm^{-1} 1610 and 1675; ^1H NMR spectrum of the methyl ester: δ_H($CDCl_3$; 90 MHz) 3.0 (3 H, s), 3.2 (3 H, s), 3.8 (3 H, s), 6.4 (1 H, d, *J* 16), 7.2–7.8 (6 H, m) and 8.2–8.5 (1 H, m) (Found: C, 77.7; H, 5.45; N, 5.1. $C_{17}H_{15}NO_2$ requires C, 76.98; H, 5.66; N, 5.28%).

(E)-β-(4,9-*Dimethylcarbazol*-3-*yl*)*acryloyl Azide* **12**.—To a suspension of the acid **11** (420 mg, 1.6 mmol) in acetone (10 cm^3) at 0 °C, was added Et_3N (0.5 cm^3) followed by dropwise addition of a solution of ethyl chloroformate (200 mg, 1.8 mmol) in acetone (10 cm^3). The mixture was stirred at 0–5 °C for 45 min and then a solution of NaN_3 (200 mg, 3 mmol) in water (4–5 cm^3) was added. The mixture was stirred at 0–5 °C for 1 h more and was then poured into ice–water. The bright yellow solid which separated out was filtered off and dried (*in vacuo*) (390 mg, 82.1%), m.p. 146–147 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 1610, 1660 and 2050.

2,10-*Dihydro*-5,10-*dimethylpyrido*[3,4-b]*carbazol*-1-*one* **13**.—To a refluxing solution of diphenyl ether (10 cm^3) and Bu_3N (1.5 cm^3) under N_2 was added dropwise a solution of the azide **12** (155 mg, 0.53 mmol) in diphenyl ether (10 cm^3) during *ca.* 15 min. The solution was refluxed for 1 h. Diphenyl ether was removed as much as possible under reduced pressure and the residue was then diluted with light petroleum (40–60 °C). The dirty yellow solid was filtered off and washed with a little cold benzene to produce *lactam* **13** as a light yellow solid (100 mg, 71.4%), m.p. >280 °C; ν_{max}(Nujol)/cm^{-1} 1620 and 1645 (Found: C, 77.65; H, 5.15; N, 10.5. $C_{17}H_{14}N_2O$ requires C, 77.86; H, 5.34; N, 10.69%).

4-*Chloro*-5-*demethyl*-6,11-*dimethylisoellipticine* **14**.—The lactam **13** (80 mg, 0.30 mmol) and $POCl_3$ (2–3 cm^3) were refluxed and stirred at 120 °C for 3 h, cooled and poured into ice–water. The mixture was left overnight at 0–5 °C, basified with aq. Na_2CO_3 and extracted with chloroform. After the usual work-up a brown solid was obtained which, on purification by column chromatography [neutral Al_2O_3/benzene–light petroleum (3:7)] afforded *compound* **14** as a lemon yellow solid (60 mg, 70.2%), m.p. 188–189 °C δ_H($CDCl_3$; 90 MHz) 3.0 (3 H, s), 3.7 (3 H, s), 7.2–7.9 (5 H, m) and 8.1–8.4 (2 H, m); *m/z* 282 (M + 2), 281 (M + 1), 280 (M^+), 279 (M − 1), 267, 266, 265 (M − 15), 245, 244, 243, 242, 230, 229, 228, 217, 216, 215, 214, 203, 202, 201, 149, 141 and 122 (Found: C, 72.7; H, 4.6; N, 9.9. $C_{17}H_{13}ClN_2$ requires C, 72.72; H, 4.63; N, 9.98%).

5-*Demethyl*-6,11-*dimethylisoellipticine* **3**.—Compound **14** (50 mg, 0.18 mmol) was refluxed under nitrogen with Zn dust (150 mg) in acetic acid (3 cm^3) for 5.5 h. The mixture was then cooled, diluted with ice–water, made alkaline with aq. Na_2CO_3 and extracted with chloroform, and the extract was washed with brine and dried (Na_2SO_4). Removal of solvent afforded a very viscous oil, which was purified by column chromatography [neutral Al_2O_3/benzene–light petroleum (3:7)] to produce the title compound as a very viscous yellow oil (35 mg, 79.7%) which solidified to a yellow-brown solid on storage for some considerable time, m.p. 168–170 °C; δ_H($CDCl_3$; 100 MHz) 3.1 (3 H, s), 3.8 (3 H, s), 7.2–7.7 (5 H, m), 7.9 (1 H, d), 8.3 (1 H, d) and 9.3 (1 H, s) (Found: C, 82.9; H, 5.6; N, 11.3. $C_{17}H_{14}N_2$ requires C, 82.92; H, 5.69; N, 11.38%).

(E)-β-(9-*Methylcarbazol*-3-*yl*)*acrylic Acid* **16**.—9-Methylcarbazole-3-carbaldehyde[15] **15** (3.5 g, 16 mmol), malonic acid (3.8 g, excess), piperidine (0.2 cm^3) and dry pyridine (15 cm^3) on reaction under the similar conditions to those used for the preparation of compound **11** produced the *title acid* **16** as a solid (3.9 g, 92.8%), m.p. 245–246 °C; ν_{max}(Nujol)/cm^{-1} 1615 and 1670; ^{1}H NMR spectrum of the methyl ester: δ_H($CDCl_3$; 90 MHz) 3.6 (3 H, s), 3.7 (3 H, s), 6.3 (1 H, d, $J \sim 16$) and 7.0–8.1 (8 H, m) (Found: C, 76.3; H, 4.95; N, 5.4. $C_{16}H_{13}NO_2$ requires C, 76.49; H, 5.18; N, 5.58%).

(E)-β-(9-*Methylcarbazol*-3-*yl*)*acryloyl Azide* **17**.—The acid **16** (1.7 g, 6.8 mmol), Et_3N (0.86 g, 8.6 mmol), ethyl chloroformate (0.93 g, 8.6 mmol) and NaN_3 (2.7 g, excess) on reaction under the conditions as described for the preparation of compound **12** afforded the azide **17** as a yellow solid (1.36 g, 73.4%), m.p. 124–125 °C (decomp.); ν_{max}(KBr)/cm^{-1} 1588, 1674 and 2133; δ_H($CDCl_3$; 90 MHz) 3.8 (3 H, s), 6.5 (1 H, d) and 7.2–8.3 (8 H, m).

2,7-*Dihydro*-7-*methylpyrido*[4,3-c]*carbazol*-1-*one* **18**.—The azide **17** (0.64 g, 2.3 mmol), on being refluxed in diphenyl ether containing Bu_3N for 1 h under nitrogen, produced the title *compound* **18** as a light yellow solid (0.44 g, 76.6%), m.p. 244–245 °C (decomp.); ν_{max}(KBr)/cm^{-1} 1586 and 1642; δ_H[$(CD_3)_2SO$; 90 MHz] 4.0 (3 H, s), 6.72 (1 H, d), 7.04–7.92 (5 H, m), 8.12 (1 H, d), 9.84 (1 H, d) and 11.32 (1 H, br s) (Found: C, 77.2; H, 4.65; N, 11.1. $C_{16}H_{12}N_2O$ requires C, 77.42; H, 4.84; N, 11.29%).

1-*Chloro*-7-*methyl*-7H-*pyrido*[4,3-c]*carbazole* **19**.—The lactam **18** (0.4 g, 1.61 mmol) and $POCl_3$ (3 cm^3), on reaction under the conditions used for the preparation of compound **14**, produced, after the usual work-up, the title compound as a semi-solid mass, which was subjected to purification by column chromatography (neutral Al_2O_3). Elution with light petroleum (60–80 °C) gave *compound* **19** as a light yellow solid (0.27 g, 65.4%), m.p. 129–130 °C; δ_H($CDCl_3$; 100 MHz) 3.75 (3 H, s), 7.25–7.85 (6 H, m), 8.35 (1 H, d) and 9.2 (1 H, d); *m/z* 268 (M + 2), 267 (M + 1), 266 (M^+), 251, 231, 230, 229, 216 and 215 (Found: C, 71.9; H, 4.0; N, 10.4. $C_{16}H_{11}ClN_2$ requires C, 72.04; H, 4.13; N, 10.51%).

7-*Methyl*-7H-*pyrido*[4,3-c]*carbazole* **20**.—Compound **19** (0.128 g, 0.48 mmol) on reduction with Zn dust (0.35 g) in acetic acid under similar conditions to those described for the preparation of compound **3** produced *compound* **20** as a solid (0.1 g, 90%) after purification by column chromatography [Al_2O_3/light petroleum (60–80 °C)–benzene (9:1)], m.p. 164–165 °C; δ_H($CDCl_3$; 100 MHz) 3.92 (3 H, s), 7.2–8.08 (6 H, m), 8.6 (2 H, d) and 10.24 (1 H, s) (Found: C, 82.5; H, 4.9; N, 11.95. $C_{16}H_{12}N_2$ requires C, 82.76; H, 5.17; N, 12.07%).

β-(9-*Methylcarbazol*-3-*yl*)*propionic Acid* **21**.—A suspension of the acid **16** (1.0 g, 3 mmol) in anhydrous ethanol containing 10% Pd–C (0.4 g) was stirred under H_2 until the calculated amount of H_2 had been absorbed (*ca.* 7 h to complete the reaction) and after this time the whole acid became soluble in ethanol, resulting in a clear solution. The catalyst was removed by filtration, and then removal of solvent afforded the *acid* **21** as a solid (0.9 g, 89.3%), m.p. 118–120 °C; ν_{max}(KBr)/cm^{-1} 1690, 2920 and 3020; ^{1}H NMR spectrum of the methyl ester–δ_H($CDCl_3$; 90 MHz) 2.6 (2 H, t), 3.0 (2 H, t), 3.55 (3 H, s), 3.6 (3 H, s), 7.0–7.7 (5 H, m) and 7.8–8.1 (2 H, t) (Found: C, 75.6; H, 5.7; N, 5.4. $C_{16}H_{15}NO_2$ requires C, 75.89; H, 5.93; N, 5.53%).

β-(9-*Methylcarbazol*-3-*yl*)*propionyl Azide* **22**.—The acid **21** (0.4 g, 1.6 mmol), Et_3N (0.2 g, 2 mmol), ethyl chloroformate (0.22 g, 2 mmol) and NaN_3 (0.18 g, 2 mmol), on reaction under the conditions as described for the preparation of azide **12**, afforded compound **22** as a solid (0.37 g, 85%), m.p. 79–80 °C (decomp.); ν_{max}(KBr)/cm^{-1} 1600, 1610 and 2225.

2-(9-*Methylcarbazol*-3-*yl*)*ethyl Isocyanate* **23**.—The azide **22** (0.3 g, 1.07 mmol) was refluxed in anhydrous benzene (15 cm^3) for 3 h. Removal of solvent gave the isocyanate **23** as a viscous oil (0.24 g, 90%), ν_{max}($CHCl_3$)/cm^{-1} 2250. It was immediately used for the next step without further purification.

Cyclization of the Isocyanate **23**.—*Preparation of lactams* **24** *and* **25**. PPA (10 g) was added to the above isocyanate **23** (0.24 g) and the mixture was stirred at 125–130 °C for 2 h during which time it became deep green in colour. It was decomposed with ice–water, then extracted with ethyl acetate and the extract was washed successively with 5% aq. $NaHCO_3$ and water and dried (Na_2SO_4). Removal of solvent furnished a yellow brown solid, which was purified by preparative TLC (PLC) [neutral Al_2O_3/benzene–ethyl acetate (1:1)].

Compound **26** [2-*aminoethyl*-9-*methylcarbazole*] (relatively low polarity) was obtained as a solid (0.033 mg, 15.34%), m.p. 152–153 °C; δ_H($CDCl_3$; 90 MHz) 2.4 (2 H, br s), 2.9–3.1 (2 H, br t), 3.40–3.65 (2 H, br m), 3.7 (3 H, s), 7.0–8.2 (7 H, m); *m/z* 224 (M^+—not visible), 223 (M − 1), 209 (M − 15), 195, 194 (M − 30), 181, 180, 168, 167, 166, 157, 140, 139 and 137 (Found: C, 80.1; H, 6.9; N, 12.2. $C_{15}H_{16}N_2$ requires C, 80.36; H, 7.14; N, 12.5%).

From the relatively high polarity fraction a light yellow solid (154 mg, 71.62%) was obtained. It was identified as a mixture of lactams 2,3,4,7-tetrahydro-7-methylpyrido[4,3-*c*]carbazol-1-one **24** and 2,3,4,10-tetrahydro-10-methylpyrido[3,4-*b*]carbazol-1-one **25** in the ratio 3:1; ν_{max}(KBr)/cm^{-1} 1625, 1650 and 1655; ^{1}H NMR spectrum of the mixture of lactams **24** and **25**: δ_H($CDCl_3$; 90 MHz) 3.10 (t), 3.20 (t), 3.45–3.75 (br m), 3.85 (s), 3.9 (s), 6.45–6.75 (br), 7.1–7.6 (m), 7.9 (s), 8.1 (d), 8.2 (s) and 9.35 (d); *m/z* 251, 250 (M^+), 194 and 193. These two products could not be separated even by PLC at this stage.

1-*Chloro*-4,7-*dihydro*-7-*methyl*-3H-*pyrido*[4,3-c]*carbazole* **27** *and* 2,3,4,10-*Tetrahydro*-10-*methylpyrido*[3,4-b]*carbazol*-1-*one* **25**.—The mixture of lactams **24** and **25** (0.12 g) was refluxed with $POCl_3$ (3 cm^3) at 110–120 °C for 3 h under N_2. The mixture was poured into ice–water, left overnight at 0–5 °C, neutralized with aq. Na_2CO_3 and extracted with chloroform. After usual work-up the extract gave a brown viscous mass, which was purified by PLC [neutral Al_2O_3/benzene–ethyl acetate (1:1)].

Compound **27** (low polarity) was obtained as a solid (0.06 g), m.p. 55–56 °C; ν_{max}(KBr)/cm^{-1} 1525 and 1585; δ_H($CDCl_3$; 90 MHz) 3.1 (2 H, t), 3.45–3.7 (2 H, 2t), 3.8 (3 H, s), 7.1–7.6 (5 H, m) and 9.4 (1 H, d); *m/z* 269 (M + 1), 268 (M^+), 254, 253, 225, 224, 198, 197 and 196 (Found: C, 71.4; H, 4.5; N, 10.2. $C_{16}H_{13}ClN_2$ requires C, 71.51; H, 4.84; N, 10.43%).

Compound **25** (high polarity) was obtained as a solid (19 mg), m.p. 233–235 °C; ν_{max}(KBr)/cm^{-1} 1600 and 1655; δ_H($CDCl_3$; 90 MHz) 3.2 (2 H, t), 3.5–3.8 (2 H, br m), 3.9 (3 H, s), 6.4–6.75 (1 H, br), 7.1–7.6 (3 H, m), 7.9 (1 H, s), 8.1 (1 H, d) and 8.2 (1 H, s); *m/z* 250 (M^+), 221, 193, 125 and 111 (Found: C, 76.6; H, 5.5; N, 11.0. $C_{16}H_{14}N_2O$ requires C, 76.80; H, 5.60; N, 11.20%).

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