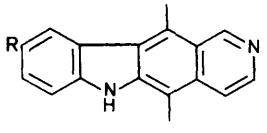
Chemistry of 6*H*-Pyrido[4,3-*b*]carbazoles. Part 12.[1] Synthesis of Potential Bisintercalating Drugs Bearing Two Ellipticine Units

Andrew J. Ratcliffe, Malcolm Sainsbury,* and Andrew D. Smith
University of Bath, Claverton Down, Bath BA2 7AY
David I. C. Scopes
Glaxo Group Research Ltd., Ware, Herts SG12 ODJ

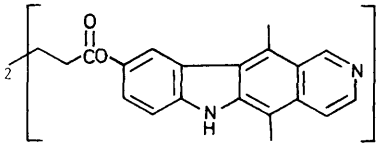
A number of bisellipticines have been synthesized in an attempt to increase the potency of the parent tetracycles as anti-cancer drugs through bis-intercalation into the same strand of DNA. The compounds described are structures in which two pyrido[4,3-*b*]carbazole units are joined at C-5 by an alkyl chain and two amide functions. The preparation of a number of new ellipticine 'monomers' is reported, as well as a synthesis of the alkaloid 5-formyl-11-methyl-6*H*-pyrido[4,3-*b*]carbazole. A novel oxidative coupling reaction of ellipticines has also been discovered.

5,11-Dimethylpyrido[4,3-*b*]carbazoles (ellipticines) have received much attention from organic chemists because of their anti-tumour activity,[2] and one derivative, 9-hydroxyellipticine (**1**; R = OH), in the form of its metho salts, is used in France for the treatment of human cancers.[3] Although the mode of action of the ellipticines is still uncertain, there is evidence that they intercalate between the base pairs of DNA[4] and interfere with the normal function of the enzyme topoisomerase II which is involved in the breaking and resealing of DNA strands.[5] In general, however, the promise of certain ellipticines against cancers in test systems in not fulfilled in mammals.

To overcome this problem we have sought to improve the activity of 'monomeric' ellipticines by coupling them together *via* a spacer unit so that *two* pyridocarbazole systems become available for intercalation into the same strand of DNA. The obvious anchor points for the spacer units for 'dimers' for the most potent drug 9-hydroxyellipticine are the hydroxy group and the pyridine nitrogen atom. Work on dimers joined through the N-2 positions has already been described,[6] but a significant increase in therapeutic effect was not observed. Similarly we find that the ester (**2**) shows activity comparable to that of 9-hydroxyellipticine itself. This is not surprising since there is evidence that a free hydroxy group at C-9 is a necessary adjunct to anti-cancer action,[7] and we speculate that our ester undergoes rapid hydrolysis *in vivo* to the parent phenol.[8]

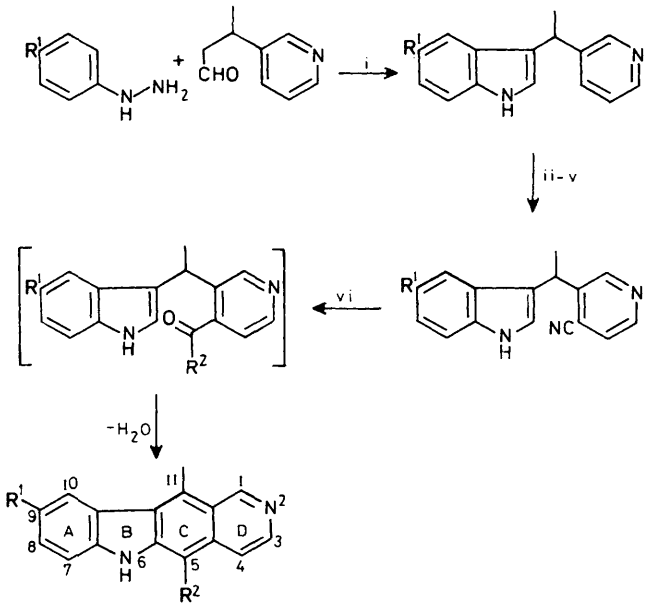


(1)



(2)

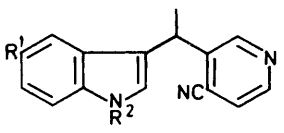
Where then to attach the spacer unit, and what should be its length and chemical constitution? To answer these questions we have carried out a number of computer graphics analyses[9] and conclude that substitution at any of the positions 5, 7, 8, 10, or 11 of the tetracycle would not adversely influence the intercalation of the chromophore between the base pairs of the nucleic acid. Since we have much experience in the synthesis of 5-substituted ellipticines through the implementation of the reactions shown in the Scheme[10,11] our initial interest is in compounds of this type, and here a spacer unit of 12—14 Å length is necessary, possibly in the form of a simple hydrocarbon chain linked through amide groups to the monomeric tetracycles.



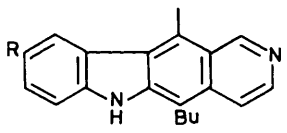
Scheme. Synthesis of 5- and 5,9-substituted ellipticines. *Reagents:* i, HOAC; ii, MSH; iii, Ac_2O; iv, MeI; v, KCN, *hν*; vi, R^2Li

In this paper we describe the syntheses of the 5-alkenyl analogues (**5**; R = H; *n* = 1) and (**5**; R = H; *n* = 2) which we sought to cleave into the corresponding aldehydes (**6**; R = H). From these aldehydes we hoped to obtain the corresponding bisellipticines (**8**; *n* = 2 or 4) by reductive amination followed by coupling of the product amines (**7**; R = H) with suitable dicarboxylic acids.

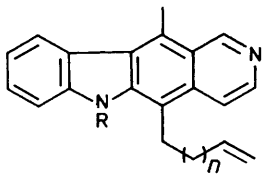
The two starting compounds were readily formed from the



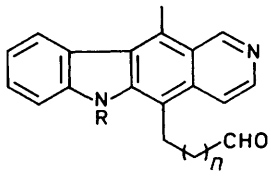
(3)



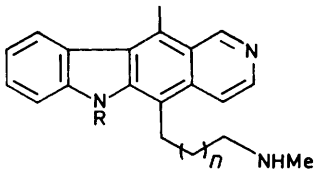
(4)



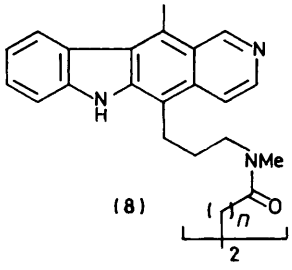
(5)



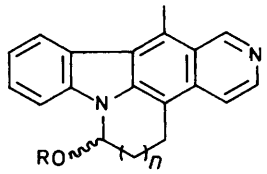
(6)



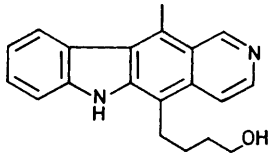
(7)



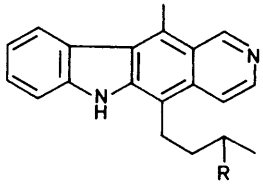
(8)



(9)



(10)



(11) R = NHCOMe
(12) R = SO_4H
(13) R = Br

nitrile (**3**; $R^1 = R^2 = H$) by reaction with but-3-enyl-lithium and pent-4-enyl-lithium respectively, but when these products were individually treated with sodium periodate and osmium tetraoxide the corresponding aldehydes were not obtained. Instead the amino alcohols (**9**; R = H; $n = 1$) and (**9**; R = H; $n = 2$) were isolated. These compounds do not show any tendency to exist in equilibrium with their ring-open forms. For example, they do not react with methylamine under reductive conditions to afford the desired amines (**7**; R = H), even in the presence of a range of different acid and base catalysts. However, when treated with sodium cyanoborohydride in methanolic hydrogen chloride the lower homologue (**9**; R = H; $n = 1$) gave the *O*-methyl ether (**9**; R = Me; $n = 1$), perhaps through an elimination/addition sequence. Numerous other attempts to convert the alkenylellipticines into suitably functionalised derivatives met with limited success. Thus, when compound (**5**; R = H, $n = 1$) was treated with diborane and then with hydrogen peroxide/ammonia only a very low yield of the alcohol (**10**) was obtained, whereas a Ritter reaction ($MeCN/H_2SO_4$) gave a 35% yield of the acetamidoellipticine (**11**), plus some of the hydrogen sulphate (**12**). Addition of hydrogen bromide similarly occurs by the Markownikoff mode to afford the bromide (**13**), but since we were forced, for reasons of substrate solubility, to conduct the reactions in polar media all attempts to reverse the regioselectivity by the addition of peroxides failed. Disappointingly the bromo compound did not react with alkylamines to form the corresponding aminoalkylellipticines, but underwent elimination of hydrogen bromide to form a mixture of 5-butenyl-5-demethylellipticines.

To circumvent these problems the butenylellipticine (**5**; R = H; $n = 1$) was treated with sodium hydride and benzyl bromide to yield the *N*-benzyl derivative (**5**; R = CH_2Ph; $n = 1$). Scission of the side-chain double bond in this compound with sodium periodate and a catalytic amount of osmium tetraoxide gave the aldehyde (**6**; R = CH_2Ph; $n = 1$).

Although we might have taken the aldehyde on to our target bisellipticines the extra steps and poor productivity of the route caused us to seek a more direct approach. Thus the nitrile (**3**; $R^1 = R^2 = H$) was treated with 2-lithio-1,3-dithiane to give the aminoketene thioacetal (**14**; R = H). None of the alternative imino tautomer (**15**) was isolated, and in this respect our results parallel those obtained by Page who worked with simpler systems.[12] The aminoketene dithioacetal (**14**; R = H) exists as a pair of diastereoisomers at room temperature since the large C-4 substituent of the pyridyl ring induces restricted rotation of the two heterocyclic units about each other (there is, of course, a chiral centre in the linking ethyl group). If the ^1H n.m.r. spectrum of this compound is re-recorded at 60—80 °C its form reverts to that expected of the racemic modification.

Hydrolysis of this product with dilute acetic acid gave rise to the ellipticine dithioacetal derivative (**16**; R = H) which has been previously synthesized by Gribble and his co-workers, but by a different route.[13] Gribble reported brief details concerning the conversion of the dithioacetal into 5-formyl-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**17**; R = H) by reaction with silver nitrate in aqueous acetone; however, in our hands this led only to the formation of the *N*-oxide (**18**). Interestingly, none of the corresponding *S*-oxide (**19**) was detected, but when we repeated the reaction, now with the addition of nitric acid to ensure protonation of the pyridine nitrogen atom, oxidative cleavage of the dithiane ring occurred smoothly to give the known alkaloid 5-formyl-11-methyl-6*H*-pyrido[4,3-*b*]pyridocarbazole (17-oxoellipticine[13] in 67% yield). Next this product was treated with methylamine in benzene solution to afford the imine (**20**; R = H) in 93% yield and this was then reduced with sodium borohydride in methanol to give the corresponding amine (**21**; R = H). Finally the amine was coupled with adipic acid in the presence of diphenylphosphoryl azide to give the bisellipticine (**22**; R = H) in 37% yield. We also attempted a more direct synthesis of the amine (**21**; R = H) by treatment of the aldehyde (**17**; R = H) with methylamine and sodium cyanoborohydride in methanolic hydrogen chloride. In this case, however, the major product was the methyl ether (**23**; R = H) together with the alcohol (**24**; R = H). The mechanism for the formation of the methyl ether is uncertain, and we note that the alcohol (**24**; R = H) is recovered unchanged after treatment with methanolic hydrogen chloride. This seems to rule out the participation of the methylene species (**25**), or its equivalent, in an elimination/methanol addition process.

Anti-cancer tests on the bisellipticine (see Table) showed that it retains a low level of activity against the experimental L1210 leukaemia system in cell culture, and we were encouraged to consider that oxygenated analogues might be much more effective. Thus the entire sequence was repeated with the methoxylated nitrile (**3**; R^1 = OMe, $R^2 = H$). All of the reactions worked well until the oxidative deprotection of the dithioacetal (**16**; R = OMe) was attempted. To our surprise this compound, on treatment with silver nitrate and nitric acid, failed to yield the corresponding aldehyde (**17**; R = OMe), but

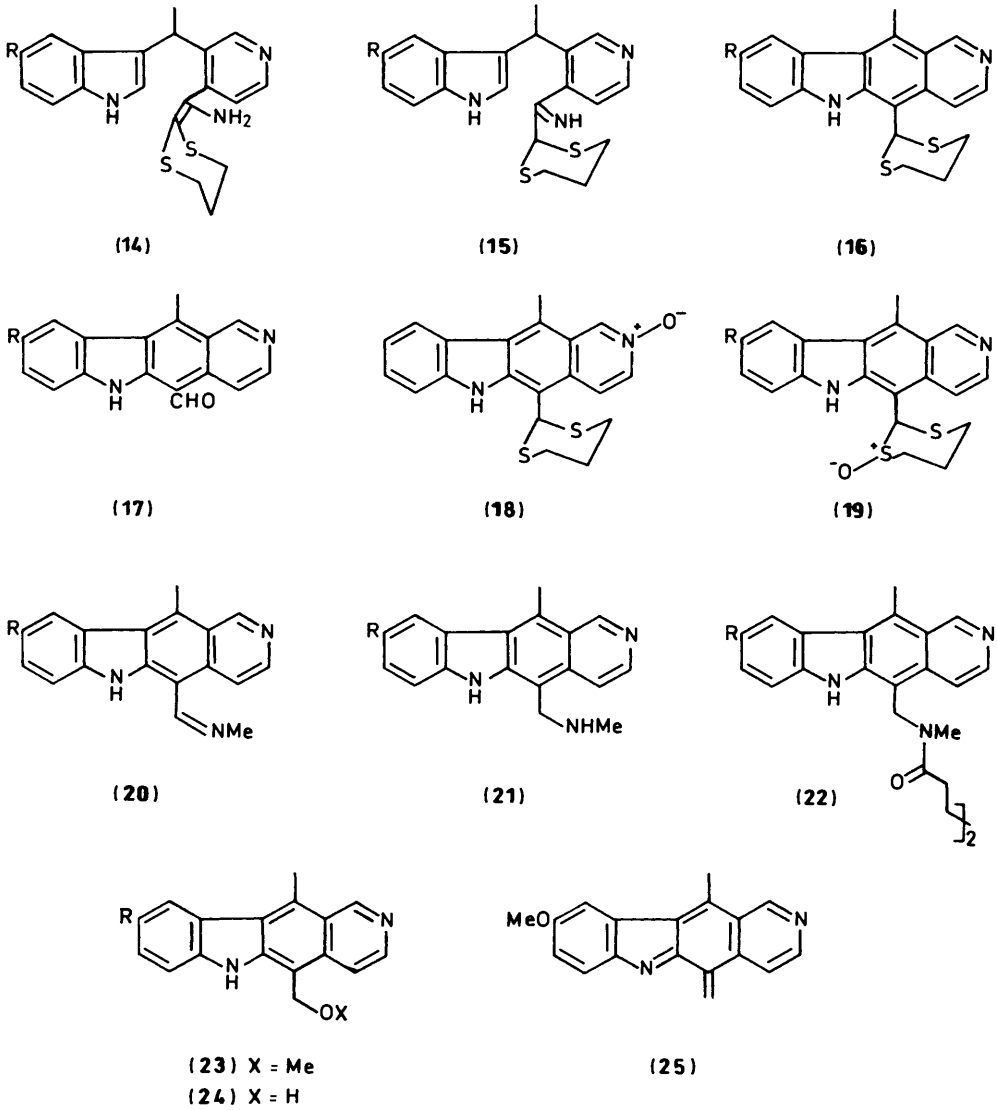


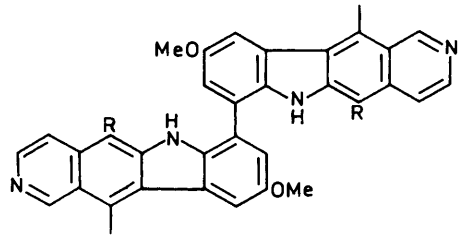
Table. Biological results for 5- and 9-substituted ellipticines

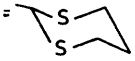
Compound	Tumour system (cell culture)[a]	
	Sarcoma 180	L1210/1C/50
(1; R = OH) as metholacetate		0.3μM
(2)		~2μM
(4; R = OMe)		>400μM
(5; R = H; *n* = 1)		4.6μM
(17; R = OMe)		6.5μM
(17; R = OH)		~10μM
(21; R = OMe)	80% inhibition at 3.7μM	
(22; R = H)	67% inhibition at 100μM	32% inhibition at >300μM
(22; R = OMe)		2.6μM

[a] Samples for testing against these tumours were administered as solutions in dimethyl sulphoxide.

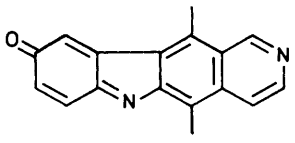
gave the dehydro dimer (**26**) instead. We assume that this is the result of single-electron oxidation, followed by coupling of the resultant radical cation and loss of protons, and we observe that 9-methoxyellipticine undergoes the same reaction to afford the dehydro dimer (**27**). The less-electron-rich parent ellipticine is unaffected by this treatment, whereas 9-hydroxyellipticines gives rise to a deep red coloured resin from which we were unable to isolate any pure components. It is known, however, that under more controlled conditions 9-hydroxyellipticine may be oxidised to the iminoquinone (**28**).[14] Deprotection of the dithioacetal (**16**; R = OMe) was eventually achieved by treatment with *N*-chlorosuccinimide (NCS) and silver nitrate.[15] In this way the aldehyde (**17**; R = OMe) was obtained in 71% yield, together with a 10% yield of the sulphone (**29**). The

aldehyde was converted through a similar series of reactions into those described above for the demethoxy analogue into the bisellipticine (**22**; R = OMe).

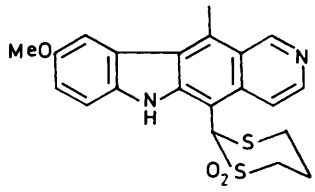


(**26**) R = 

(**27**) R = Me



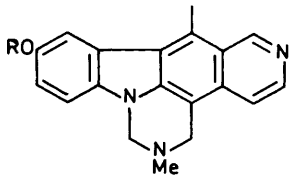
(**28**)



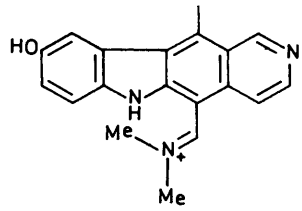
(**29**)

We expected to be able to *O*-demethylate this product by heating it with pyridinium chloride since this procedure has been often used successfully to *O*-dealkylate methoxyellipticines.[16] Unfortunately, in this case this procedure proved unsatisfactory and a good deal of our available material was lost, and thus we sought to evaluate other demethylating reagents in reactions with the more abundant aldehyde (**17**; R = OMe). The best results were obtained with boron tribromide,[17] and with this reagent the phenol (**17**; R = OH) was obtained in 90% yield. This compound is very insoluble in most organic solvents and we note that its reaction with methylamine in methanol solution proceeded at a much slower rate than the corresponding reactions of either ellipticine or 9-methoxyellipticine. Similarly the reduction of the derived imine (**20**; R = OH) with sodium borohydride in methanol was also very sluggish and we were forced to heat the solution at reflux for an hour until all the starting material had disappeared. For the other imines in this series the reduction is complete within 30 min at room temperature. Surprisingly, the product of the reduction was not the required amine (**21**; R = OH), but rather the pentacycle (**30**; R = H) which was fully characterised as its dimethyl-t-butylsilyl derivative (**30**; R = $SiMe_2Bu^t$). To account for this result we assume that the 'extra' carbon atom is donated from the solvent probably by means of methyl borate, or its equivalent. Once an intermediate of the type (**31**) is formed tautomerism to the iminium species (**32**) would facilitate the production of the pentacyclic product. It is interesting to compare this result with the formation of the methyl ether (**23**; R = H), under similar conditions, as described above.

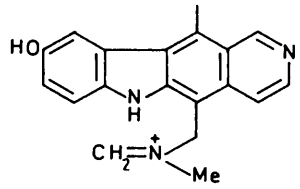
In the light of the difficulties described above we consider that the best route to the hydroxylated bisellipticine (**22**; R = OH) will involve *O*-demethylation of the methoxylated analogue, perhaps using boron tribromide rather than pyridinium chloride as reagent. Biological results for some of the compounds described in this paper are summarised in the Table, and it should be noted that the bisellipticine (**22**: R = OMe) exhibits activity against L1210 cells comparable to that shown by the clinically useful drug 9-hydroxyellipticine methoacetate. This activity is much reduced in the case of the demethoxy analogue



(**30**)



(**31**)



(**32**)

(**22**; R = H). It is known that 9-hydroxyellipticine is significantly more cytotoxic than 9-methoxyellipticine,[2] thus we are surprised to find that the formyl(methoxy)pyridocarbazole (**17**; R = OMe) is more active than the corresponding phenol (**17**; R = OH).

Experimental

U.v. spectra were recorded on a Perkin-Elmer 402 instrument for solutions in 95% aqueous ethanol. ^1H N.m.r. spectra were obtained at either 100 or 270 MHz and ^{13}C n.m.r. spectra were recorded at 67.8 MHz, with tetramethylsilane as internal reference using either JEOL PS 100 or JEOL JNM spectrometers. Mass spectra determined in the E1 mode refer to an ionising potential of 70 eV and data were recorded on a VG 7070E instrument. All solvents, other than ethanol and methanol, were redistilled prior to use. Light petroleum refers to that fraction boiling between 60—80 °C.

Bis-(5,11-*dimethyl*-6H-*pyrido*[4,3,-b]*carbazol*-9-*yl*) *Adipate* (**2**).—Dicyclohexylcarbodi-imide (0.2 g) was added to a stirred mixture of adipic acid (0.1 g) and 4-dimethylaminopyridine (DMAP) (0.02 g) in dichloromethane (10 cm^3) at room temperature. A solution of 9-hydroxyellipticine (**1**; R = OH) (0.13 g) in dry dimethylformamide (DMF) (2 cm^3) was added to this mixture after 1 h. After 2 h the mixture was evaporated under reduced pressure, and the orange residue was purified by flash chromatography (SiO_2; dichloromethane–methanol–triethylamine 90:9:1) to afford the *title compound* (**2**) as a bright yellow powder (0.02 g, 13%); a sharp m.p. was not observed (compound decomposed >310 °C); $\lambda_{max.}$(ε/l mol^{-1} cm^{-1}) 249 (24 950), 278 (39 500), 290 (48 500), 299 (51 050), 333 (5 450), 394 (3 100), and 403 nm (2 900); δ_H[$(CD_3)_2SO$] 11.44 (1 H, br s, NH), 9.65 (1 H, s, 1-H), 8.45 (1 H, d, *J* 6 Hz, 3-H), 8.1 (1 H, d, *J* 2 Hz, 10-H), 7.92 (1 H, d, *J* 6 Hz, 4-H), 7.6 (1 H, d, *J* 10 Hz, 7-H), 7.36 (1 H, dd, J_1 10, J_2 2 Hz, 8-H), 3.16 (3 H, s, 11-Me), 2.75 (3 H, s, 5-Me), 2.82 (2 H, m, $COCH_2CH_2$), and 1.92 (2 H, m, $COCH_2CH_2$) (Found: C, 75.5; H, 5.3; N, 8.9. $C_{40}H_{34}N_4O_4$ requires C, 75.7; H, 5.4; N, 8.8%).

5-(*But*-3-*enyl*)-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**5**; R = H, *n* = 1).—A solution of 3-[1-(4-cyano-3-pyridyl)ethyl]indole (1.0 g, 3.8 mmol) in dry tetrahydrofuran (THF) (7 cm^3) was added to a solution of but-3-enyl-lithium in THF (20 cm^3; 0.023M) at −78 °C under nitrogen, and the mixture was allowed to warm to room temperature during 2 h. T.l.c. analysis (SiO_2; ethyl acetate) revealed the total absence of starting material, and

a new component which appeared as an elongated spot at R_F 0.25. The mixture was poured into cold 20% aqueous acetic acid (200 cm^3), and warmed gently for 20 min. The yellow solution was cooled to room temperature, and made basic by the cautious addition of solid sodium carbonate. It was then extracted with dichloromethane (6 × 25 cm^3) and chloroform (3 × 25 cm^3). The combined extracts were washed with brine (50 cm^3), dried ($MgSO_4$), and evaporated to afford a yellow solid, which was washed with a little dichloromethane and recrystallised from methanol to give the *title compound* as bright yellow microcrystals (0.3 g, 28%), m.p. 281—284 °C (decomp.); $\lambda_{max.}$ 238 (19 200), 274 (44 000), 286 (46 700), 291 (44 350, and 332 nm (4 800); δ_H[$(CD_3)_2SO$] 11.48 (1 H, s, NH), 9.73 (1 H, s, 1-H), 8.45 (1 H, d, *J* 6 Hz, 3-H), 8.41 (2 H, d, *J* 6 Hz, 10-H), 7.95 (1 H, d, *J* 6 Hz, 4-H), 7.6—7.5 (2 H, m, 8- and 7-H), 7.29 (1 H, td, J_1 6 J_2 2 Hz, 9-H), 6.15—5.95 (1 H, m, C*H*=CH_2), 5.15—4.95 (2 H, m, CH=CH_2), 3.30 (3 H, s, Me), and 2.6—2.4 (m, CH_2CH_2 + solvent peak); *m/z* (e.i.) 286 (24%, M^+), 245 (100, $M^+ - C_3H_5$), and 149 (18) (Found: C, 84.0; H, 6.4; N, 9.6. $C_{20}H_{18}N_2$ requires C, 83.9; H, 6.3; N, 9.8%).

Pent-4-enyl-lithium.—A solution of 5-bromopent-1-ene (1.0 cm^3, 1.26 g, 8.5 mmol) in dry diethyl ether (3 cm^3) was added dropwise to a vigorously stirred suspension of lithium shot (0.25 g, 0.042 mol) in dry diethyl ether (4 cm^3) at 0 °C under dry nitrogen. The mixture was stirred at 0 °C for 2 h. Titration of the resulting solution against diphenylacetic acid indicated an alkenyl-lithium concentration of 1.15M (100%).

11-*Methyl*-5-(*pent*-4-*enyl*)-6H-*pyrido*[4,3-b]*carbazole* (**5**; R = H; *n* = 2).—A solution of 3-[1-(4-cyano-3-pyridyl)ethyl]indole (0.12 g, 0.5 mmol) in dry THF (5 cm^3) was added to a mixture of ethereal pent-4-enyl-lithium solution (1.5 cm^3; *ca.* 1.7 mmol) and dry THF (3 cm^3) at −78 °C under dry nitrogen. The mixture was stirred at −78 °C for 30 min, then warmed to room temperature overnight. A further portion of pent-4-enyl-lithium solution (0.6 cm^3) was added, and the mixture was kept at room temperature for 1 h, then poured into cold 20% aqueous acetic acid (25 cm^3), and heated under reflux for 20 min. The solution was cooled, neutralised with saturated aqueous sodium hydrogen carbonate, and extracted with ethyl acetate (4 × 10 cm^3). The combined, dried (Na_2SO_4) extracts were evaporated to afford a partially solid orange gum. Column chromatography (SiO_2; ethyl acetate) afforded the *title compound* as a bright yellow solid (0.06 g, 40%), m.p. 248—253 °C (decomp.); $\lambda_{max.}$ 240, 275, 286, 292, and 335 nm; δ_H[$(CD_3)_2SO$] 11.5 (1 H, br s, NH), 9.75 (1 H, s, 1-H), 8.5—8.4 (2 H, m, 3- and 10-H), 7.92 (1 H, d, *J* 6 Hz, 4-H), 7.6—7.5 (2 H, m, 8- and 7-H), 7.23 (1 H, td, J_1 6, J_2 2 Hz, 9-H), 6.0—5.8 (1 H, m, C*H*=CH_2), 5.1—4.9 (2 H, m, CH=CH_2), 3.27 (3 H, s, Me), and 2.1 (2 H, m, $CH_2CH_2CH_2$) (other aliphatic resonances were obscured by a large solvent impurity peak at δ 2.5); *m/z* (e.i.) 300 (38%, M^+) and 245 (80) (Found: C, 83.85; H, 6.8; N, 9.2. $C_{21}H_{20}N_2$ requires C, 84.0; H, 6.7; N, 9.3%).

9-*Methyl*-2,3-*dihydro*-1H-*indolo*[3,2,1-gh][3,7]*phenanthrolin*-3-*ol* (**9**; R = H; *n* = 1).—A solution of sodium periodate (0.2 g, 0.9 mmol) in water (1.5 cm^3) was added dropwise to a stirred solution of the ellipticine (**5**; R = H; *n* = 1) (0.1 g, 3.5 mmol) and osmium tetraoxide (1.5 mg) in 80% acetic acid (5 cm^3) under nitrogen. The solution was kept for 2 h at room temperature, then diluted with water (15 cm^3) and neutralised by cautious addition of sodium hydrogen carbonate. The precipated solids were collected by filtration, and extracted with hot methanol (3 × 20 cm^3). The resulting yellow solution was evaporated under reduced pressure, and the residue was purified by column chromatography (methanol–dichloromethane, 1:9) to afford the *title compound* as a yellow solid (0.05 g, 50%), m.p. 302—305 °C (decomp.); $\lambda_{max.}$ 238 (17 800), 274 (35 700), 285 (50 500), and 292 nm (42 700); $\nu_{max.}$($CHCl_3$) 3 690, 3 380, and 1 605 cm^{-1}; δ_H[$(CD_3)_2SO$] 10.14 (1 H, s, 10-H), 8.88 (1 H, d, *J* 6 Hz, 12-H), 8.84 (1 H, d, *J* 8 Hz, 8-H), 8.35 (1 H, d, *J* 6 Hz, 13-H), 8.16 (1 H, d, *J* 8 Hz, 5-H), 8.01 (1 H, td, J_1 8, J_2 1 Hz, 6-H), 7.74 (1 H, td, J_1 8, J_2 1 Hz, 7-H), 6.97 (1 H, d, *J* 6 Hz, peak exchanged on addition of D_2O, OH), 6.63 (1 H, m, which on addition of D_2O becomes t, *J* 3 Hz, C*H*OH), and 3.70 (3 H, s, Me); the resonances due to the protons of the CH_2CH_2 group were obscured by a solvent impurity peak at δ 2.5); *m/z* (e.i.) 288 (24%, M^+), 270 (55, $M^+ - H_2O$), 269 (100), and 245 (20) (Found: C, 79.0; H, 6.0; N, 9.5. $C_{19}H_{16}N_2O$ requires C, 79.1; H, 5.6; N, 9.2%).

3-*Methoxy*-9-*methyl*-2,3-*dihydroindolo*[3,2,1-gh][3,7]*phenanthroline* (**9**; R = Me; *n* = 1).—A saturated solution of hydrogen chloride in dry methanol was added dropwise to a solution of diethylamine (0.10 g) in methanol (5 cm^3) until a neutral (to pH 7) solution was obtained. To this the amino alcohol (**9**; R = H; *n* = 1) (0.05 g) was added, followed by sodium cyanoborohydride (0.01 g). The mixture was stirred overnight at room temperature, when a yellow solid had precipitated. T.l.c. analysis showed only unchanged starting materials. Sufficient methanolic hydrogen chloride solution was added to redissolve the precipitate, and the mixture was kept at room temperature for 4 h. The solvent was evaporated off under reduced pressure, and the residue was dissolved in chloroform (5 cm^3), and washed with saturated aqueous sodium hydrogen carbonate (3 × 3 cm^3). The dried (Na_2SO_4) organic phase was evaporated to afford a yellow solid, which was purified by preparative t.l.c. (p.l.c.) on silica gel with 10% methanol in dichloromethane as eluant to afford recovered starting material (0.02 g, 40%), and a fraction consisting of a new product (**9**; R = Me; *n* = 1) (0.03 g, 60%); $\lambda_{max.}$ 239, 276, 284, and 294 nm; δ_H($CDCl_3$) 9.73 (1 H, s, 10-H), 8.6—8.3 (2 H, m, 8- and 12-H), 7.9—7.25 (4 H, m, other aromatic protons), 5.78 (1 H, t, *J* 3 Hz, CH_2CH), 3.47 and 3.22 (2 × 3 H, 2 × s, MeO and Me), and 3.1—1.7 (4 H, m, CH_2CH_2); *m/z* (e.i.) 302, 271, 270, and 269 (Found: C, 79.6; H, 5.8; N, 9.5. $C_{20}H_{18}N_2O$ requires C, 79.4; H, 6.0; N, 9.3%).

6-*Benzyl*-5-(*but*-3-*enyl*)-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**5**; R = $CH_2C_6H_5$; *n* = 1).—Sodium hydride (50% dispersion in oil) (0.07 g, 1.5 mmol) was added to a suspension of the ellipticine (**5**; R = H; *n* = 1) (0.10 g, 0.35 mmol) in DMF (3 cm^3). The mixture was stirred at room temperature for 15 min to afford an orange solution. Benzyl bromide (0.08 g, 0.47 mmol) was added, and the mixture was stirred overnight at room temperature. The resulting dark solution was poured into water (10 cm^3) and extracted with dichloromethane (3 × 5 cm^3). The combined, dried (Na_2SO_4) extracts were evaporated, and the residue was purified by column chromatography (methanol–dichloromethane 1:17) to afford the *title compound* as a yellow solid (0.054 g, 41%), m.p. 284—290 °C (decomp.); $\lambda_{max.}$ 204, 275, 286, and 293 nm; δ_H[$(CD_3)_2SO$] 9.6 (1 H, s, 1-H), 8.25 (2 H, m, 3- and 10-H), 7.7 (1 H, d, *J* 6 Hz, 4-H), 7.4—6.9 (8 H, m, other aromatic protons), 6.0—5.5, 5.6 (4 H, m and s, C*H*=CH_2 and NCH_2Ph), 5.1—4.7 (2 H, m, CH_2=CH), 3.5—3.2, 3.3 (5 H, m and s, ArCH_2CH_2 and Me), and 2.7—2.2 (2 H, m, ArCH_2CH_2); *m/z* (e.i.) 376 (18%, M^+), 335 (78, $M^+ - C_3H_5$), and 91 (100, $C_7H_7^+$) (Found: C, 86.05; H, 6.4; N, 7.4. $C_{27}H_{24}N_2$ requires C, 86.1; H, 6.4; N, 7.4%).

3-(6-*Benzyl*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazol*-5-*yl*)*propanal* (**6**; R = $CH_2C_6H_5$; *n* = 1).—A solution of sodium periodate (0.06 g, 0.2 mmol) in water (0.5 cm^3) was added to a solution of the ellipticine (**5**; R = $CH_2C_6H_5$; *n* = 1) (0.05 g, 0.13 mmol) and a catalytic amount of osmium tetraoxide in 80% acetic acid (3 cm^3) under nitrogen. The solution was kept at room temperature for 2 days, then poured into water (10 cm^3)

and neutralised by cautious addition of sodium hydrogen carbonate. The resulting suspension was extracted with chloroform (5 × 5 cm^3), and the combined, dried (Na_2SO_4) extracts were evaporated under reduced pressure to afford an orange glass. Column chromatography (methanol–dichloromethane, 1:18) gave the *title aldehyde* as an orange glass (0.01 g, 20%); $\lambda_{max.}$ 238 (21 800), 247 (21 000), 275 (36 700), 296 (49 800), 303 (50 500), 342 (4 800), 359 (2 500), and 378 nm (3 700); $\nu_{max.}(CHCl_3)$ 1 730 and 1 605 cm^{-1}; *m/z* (e.i.) 378 (26%, M^+), 350 (4, $M^+ - CO$), 349 (5) 335 (32, $M^+ - CH_2CHO$), and 91 (100, $C_7H_7^+$) (Found: M^+, 378.1719. $C_{26}H_{22}N_2O$ requires *M*, 378.1732).

4-(11-*Methyl*-6H-*pyrido*[4,3-b]*carbazol*-5-*yl*)*butan*-1-*ol* (**10**).—A 1M solution of diborane in THF (0.5 cm^3) was added to dry diglyme (4.5 cm^3). A portion of the resulting solution (0.6 cm^3, 0.6 mmol) was added to a stirred suspension of the ellipticine (**5**; R = H; *n* = 1) (0.06 g, 2 mmol) in dry diglyme (8 cm^3) at room temperature to afford a clear yellow solution. The solution was kept at room temperature for 4 h, then a further portion of the diborane solution (0.9 cm^3) was added, and the mixture was kept overnight at room temperature. T.l.c. analysis showed only unchanged starting material. A further portion of 0.1M diborane solution (0.2 cm^3) was added, and the solution was kept at room temperature for 3 days, then poured into 2M aqueous ammonia (20 cm^3) containing 30% hydrogen peroxide (3 cm^3), and extracted with ethyl acetate (4 × 7 cm^3). The combined, dried ($MgSO_4$) extracts were evaporated under reduced pressure, and the yellow residue was purified by column chromatography (methanol–dichloromethane, 1:18), to afford recovered starting material (0.03 g, 60%), and the *title compound* (**10**) which was obtained as a yellow solid (5 mg, 8%), m.p. > 300 °C (decomp.); $\lambda_{max.}$ 250, 278, 290, 299, 395, and 400 nm; $\nu_{max.}(CHCl_3)$ 3 460, 3 380—3 100, 2 400, and 1 600 cm^{-1}; *m/z* (e.i.) 304 (5%, M^+), 303 (8), and 287 (100) (Found: M^+, 304.1580. $C_{20}H_{20}N_2O$ requires *M*, 304.1576; *m/z* 287.1548. $C_{20}H_{19}N_2$ requires *m/z* 287.1546).

N-[4-(11-*Methyl*-6H-*pyrido*[4,3-b]*carbazol*-5-*yl*)*butan*-2-*yl*]*acetamide* (**11**).—90% Sulphuric acid was added dropwise to a stirred suspension of 5-(but-3-enyl)-5-demethylellipticine (**5**; R = H; *n* = 1) (70 mg) in acetonitrile (2 cm^3) until complete dissolution was obtained. The solution was then stirred at room temperature overnight, by which time a yellow solid had precipitated. The mixture was poured into water (5 cm^3), made basic (2M aqueous ammonia), and extracted with chloroform (4 × 5 cm^3). Evaporation of the dried (Na_2SO_4) extracts gave the *title amide* as a yellow solid (30 mg, 35%), m.p. 262—270 °C (decomp.), $\nu_{max.}(CHCl_3)$ 3 680, 3 440, 1 705, and 1 605 cm^{-1}; $\lambda_{max.}$ 274, 286, and 292 nm; $\delta_H[(CD_3)_2SO]$ 11.42 (1 H, s, NH), 9.71 (1 H, s, 1-H), 8.43 (1 H, d, *J* 6 Hz, 3-H), 8.39 (1 H, d, *J* 8 Hz, 10-H), 7.94 (1 H, d, *J* 6 Hz, 4-H), 7.55 (2 H, m, 8- and 7-H), 7.26 (1 H, m, 9-H), 4.05 (1 H, m, AcNHC*H*), 3.3—3.2 (m, obscured by water in the solvent, $ArCH_2CH_2$), 3.27 (3 H, s, Ar*Me*), 1.90 (3 H, s, Ac), 1.89—1.69 (2 H, m, CH_2CH_2CH), and 1.13 (3 H, d, *J* 7 Hz, *Me*CH); *m/z* (e.i.) 345 (1%, M^+), 286 (31, $M^+ - CH_3CONH_2$), 271 (1), and 59 (100, CH_3CONH_2); *m/z* (isobutane CI) 346 (65%, $M^+ + 1$), 287 (23), and 214 (100) (Found: C, 76.5; H, 6.8; N, 12.0. $C_{22}H_{23}N_3O$ requires C, 76.5; H, 6.7; N, 12.2%).

Reacidification of the ammonium hydroxide solution, left after the extraction of the amide (**11**), gave a small amount (2—3 mg) of a hygroscopic yellow solid. This material was acidic in nature and exhibited the usual ellipticine-type electronic spectrum ($\lambda_{max.}$ 275, 285, and 292 nm). The i.r. spectrum was not clearly resolved, but exhibited a band $\nu_{max.}$ at 1 140—1 200 cm^{-1}. This suggests that a sulphate grouping is present in the molecule.

5-(3-*Bromobutyl*)-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**13**).—A suspension of 5-but-3-enyl-5-demethyl ellipticine (0.10 g, 3.5 × 10^{-4} mol) in glacial acetic acid (5 cm^3) containing 45% hydrogen bromide in acetic acid (1 cm^3; 5 mmol of HBr) was heated under reflux in nitrogen for 2 h. The resulting orange solution was poured into chloroform (50 cm^3), washed with saturated aqueous sodium hydrogen carbonate (4 × 30 cm^3), dried (Na_2SO_4), and evaporated to leave *compound* (**13**) as a yellow solid (0.12 g, 93%), m.p. 291—300 °C (with charring > 275 °C); $\lambda_{max.}$ 274, 286, and 291 nm; $\delta_H[(CD_3)_2SO]$ 11.42 (1 H, s, NH), 9.73 (1 H, s, 1-H), 8.46 (1 H, d, *J* 6 Hz, 3-H), 8.40 (1 H, d, *J* 8 Hz, 10-H), 7.95 (1 H, d, *J* 6 Hz, 4-H), 7.60—7.53 (2 H, m, 8- and 7-H), 7.28 (1 H, td, J_1 8, J_2 1.3 Hz, 9-H), 4.55—4.50 (1 H, m, CHBr), 3.52—3.40 (m, partially obscured by water in the solvent, $ArCH_2CH_2$), 3.28 (3 H, s, Ar*Me*), 2.17—2.12 (2 H, m, CH_2CHBr), and 1.81 (3 H, d, *J* 7 Hz, *Me*CH); *m/z* (e.i.) 368 (9%), 366 (9), 286 (18, $M - HBr$), 243 (100, 286 − C_3H_7), 185 (88), and 122 (44) (Found: C, 65.2; H, 5.3; Br, 21.7; N, 7.8. $C_{20}H_{19}BrN_2$ requires C, 65.4; H, 5.2; Br, 21.8; N, 7.6%).

5-(1′,3′-*Dithian*-2′-*yl*)-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**16**; R = H).—A dry THF solution (18 cm^3) containing freshly sublimed 1,3-dithiane (1.64 g, 13.7 mmol) was kept for 30 min in the presence of activated 4Å molecular sieves under nitrogen. The solution was cooled to −20 °C (tetrachloromethane–solid CO_2) and treated dropwise with 1.56M butyl-lithium in the same solvent (8.75 cm^3, 13.6 mmol). The resulting mixture was stirred for 3 h while the temperature was maintained between −20 and −15 °C (anion formation was judged >95% efficient after 3 h by addition of a small sample of the mixture to deuterium oxide and measurement of the deuterium incorporation at C-2 of the dithiane by ^1H n.m.r. spectroscopy). In a separate flask a solution of the carbonitrile (**3**; $R^1 = R^2 = H$) (506 mg, 2.15 mmol) in dry THF (6 cm^3) was kept for 30 min in the presence of activated 4Å molecular sieves under nitrogen. The pink solution was cooled to −78 °C (acetone–solid CO_2) and treated dropwise with the 2-lithio-1,3-dithiane solution (seven-fold excess). The resulting mixture, after being stirred for a further 30 min at this temperature, was sealed under nitrogen and kept at −20 °C for 15 h. It was then allowed to warm to room temperature during 30 min, saturated aqueous sodium chloride (15 cm^3) was added, and the resulting mixture was thoroughly stirred and filtered to remove the molecular sieves. The two layers remaining were separated and the aqueous layer was further extracted with chloroform (2 × 25 cm^3). The combined extracts were evaporated under reduced pressure to afford a yellow-brown oil, which was taken up in aqueous acetic acid (30%; 90 cm^3) and heated on a steam-bath for 2 h. On cooling, the mixture was basified with saturated aqueous sodium hydrogen carbonate and extracted with chloroform (3 × 100 cm^3). Evaporation under reduced pressure of the dry (Na_2SO_4) combined extracts gave a dark yellow oil which was purified by column chromatography (SiO_2; eluted initially with ethyl acetate–light petroleum, 2:1, and then neat ethyl acetate) to afford the title compound as a yellow solid (670 mg, 93%), which was crystallised from methanol–chloroform, m.p. 294—296 °C (lit.,[13] 236—240 °C) [R_F (SiO_2; ethyl acetate–light petroleum–triethylamine (10:5:1) 0.23]; $\lambda_{max.}$ 223 (19 500), 238sh (14 800), 279sh (36 600), 288 (55 800), and 322 nm (3 400); $\nu_{max.}$(Nujol) 3 380 (NH), 1 605, and 1 580 cm^{-1}; $\delta_H(CDCl_3)$ 9.71 (1 H, s, 1-H), 9.54 (1 H, br s, NH), 8.55 (1 H, d, *J* 6 Hz, 3-H), 8.34 (1 H, d, *J* 8 Hz, 10-H), 7.98 (1 H, br d, 4-H), 7.58—7.51 (2 H, m, 8- and 7-H), 7.31 (1 H, t, *J* 7.5 Hz, 9-H), 6.38 (1 H, s, 2′-H), 3.30 (3 H, s, Me), 3.26 (2 H, dd, J_1 14, J_2 12 Hz, 4′- and 6′-H_{ax}), 3.04 (2 H, br d, *J* 14 Hz, 4′- and 6′-H_{eq}), 2.31 (1 H, br d, *J* 14.5 Hz, 5′-H_{eq}), and 2.14 (1 H, m, 5′-H_{ax}); $\delta_C(CDCl_3)$ 150.0, 141.8, 141.4, 140.8, 132.3, 131.2, 127.4, 125.0, 123.8, 123.1, 122.5, 120.0, 114.7, 110.6, 107.9, 44.5, 32.2, 25.1, and 14.9; *m/z* (e.i.) 350 (100%, M^+), 276

(27), 260 (24), and 232 (31) (Found: C, 65.4; H, 5.5; N, 7.6. Calc. $C_{20}H_{18}N_2S_2 \cdot H_2O$: C, 65.2; H, 5.4; N, 7.6%).

A larger-scale reaction of the carbonitrile (**3**; $R^1 = R^2 = H$) (3.41 g, 13.8 mmol) with 2-lithio-1,3-dithiane under analogous conditions afforded a 64% yield of the thioacetal (3.08 g). Prior to acid hydrolysis a small amount of the intermediate was purified by column chromatography (SiO_2; eluted with ethyl acetate). The resulting yellow foam was shown to be the aminoketene thioacetal (**14**; R = H) which exists at room temperature as a mixture of diastereoisomers [R_F (SiO_2; ethyl acetate) 0.27], $\delta_H(CDCl_3)$ 8.69—8.42 (2 H, m), 8.30—8.16 (1 H, br d, exchanged with D_2O, indolic NH), 7.54—6.96 (6 H, m), 4.71—4.67 (1 H, m, MeC*H*), 4.26 (6/13 × 2 H, br s, exchanged with D_2O, NH_2), 4.10 (7/13 × 2 H, br s, exchanged with D_2O, NH_2), 2.90—2.05 (6 H, m), and 1.76 (3 H, d, *J* 7 Hz, *Me*CH); $\delta_C(CDCl_3)$ 150.0, 149.5, 147.3, 147.2, 146.4, 146.3, 144.4, 144.2, 139.4, 139.0, 136.6, 136.5, 126.6, 126.3, 123.8, 123.5, 122.2, 122.0, 121.8, 121.5, 120.9, 119.9, 119.4, 119.3, 119.1, 111.3, 110.9, 92.5, 92.3, 32.6, 32.3, 31.8, 31.6, 31.1, 26.6, 26.4, 22.9, and 22.1; *m/z* (e.i.) 367 (10%, M^+), 261 (11), 248 (17), 247 (22), and 222 (47).

5-(1′,3′-*Dithian*-2′-*yl*)-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* 2-*Oxide* (**18**).—To a solution of the thioacetal (55 mg, 0.16 mmol), from the previous experiment, in acetone (18 cm^3) was added a solution of silver nitrate (54 mg, 0.32 mmol) in water (1 cm^3) dropwise during 25 min. The resulting cloudy mixture was stirred for 2 days at room temperature under nitrogen. The mixture was filtered, and brine (15 cm^3) was added to the filtrate. The solid formed was collected and washed with chloroform (4 × 25 cm^3). The washings were subsequently used to extract the aqueous filtrate. The dried (Na_2SO_4) combined extracts were evaporated under reduced pressure to afford a yellow solid, which was purified by column chromatography (SiO_2; ethyl acetate) to give the *title compound* (**18**) as a yellow solid (25 mg, 44%), m.p. 254—260 °C; $\lambda_{max.}$ 289 nm; $\nu_{max.}$ ($CHCl_3$) 3 400 (NH) and 1 600 cm^{-1}; $\delta_H(CDCl_3)$ 9.41 (1 H, s, NH), 8.64 (1 H, br s, 1-H), 8.35 (1 H, d, *J* 8 Hz, 10-H), 8.00 (1 H, br d, 3-H), 7.65—7.45 (3 H, m, 4-, 7-, 8-H), 7.32 (1 H, ddd, J_1 8, J_2 6.5, J_3 1.5 Hz, 9-H), 6.37 (1 H, s, 2′-H), 3.31 (3 H, s, Me), 3.28 (2 H, ddd, J_1 14, J_2 13, J_3 2.5 Hz, 4′- and 6′-H_{ax}), 3.06 (2 H, ddd, J_1 14, J_2 4.5, J 3.0 Hz, 4′- and 6′-H_{eq}), 2.32 (1 H, dtt, J_1 14, J_2 4.5, J_3 2.5 Hz, 5′-H_{eq}), and 2.16 (1 H, dtt, J_1 14, J_2 13, J_3 3 Hz, 5′-H_{ax}); *m/z* (e.i.) 366 (36%, M^+), 350 (100), 276 (35), and 232 (24) (Found: C, 65.4; H, 5.1; N, 7.6. $C_{20}H_{18}N_2OS_2$ requires C, 65.5; H, 4.95; N, 7.65%).

5-(1′,3′-*Dithian*-2′-*yl*)-9-*methoxy*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**16**; R = OMe).—This compound was obtained from the appropriate carbonitrile in exactly the same way as described for the parent (**16**; R = H). However, the product was contaminated with a minor amount (5%) of 5-butyl-9-methoxy-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (**4**, R = OMe). This contaminant was separated from the desired product by column chromatography (SiO_2; ethyl acetate–light petroleum, 2:1). It is a *yellow solid*, m.p. 268—269 °C; $\lambda_{max.}$ 240, 276, 293, 336, and 354 nm; $\nu_{max.}$ (Nujol) 3 120 (NH) and 1 590 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 11.19 (1 H, s, NH), 9.69 (1 H, s, 1-H), 8.40 (1 H, d, *J* 6 Hz, 3-H), 7.91—7.87 (m, 2 H, H- and 10-H), 7.50 (1 H, d, *J* 9 Hz, 7-H), 7.20 (1 H, dd, J_1 9, J_2 2.5 Hz, 8-H), 3.91 (3 H, s, OMe), 3.30—3.26 (5 H, m, Ar*Me* and Me[CH_2]$_2$C*H*$_2$), 1.65 (2 H, m, MeCH_2CH$_2$-CH$_2$), 1.49 (2 H, m, MeCH_2[CH_2]$_2$), and 0.94 (3 H, t, *J* 7 Hz, *Me*[CH_2]$_3$); *m/z* (e.i.) 318 (100%, M^+) (Found: M^+, 318.1725. $C_{21}H_{22}N_2O$ requires *M*, 318.1730).

Further elution of the column now with ethyl acetate alone afforded the *title compound* as yellow prisms from ethyl acetate in 82% yield [R_F (SiO_2; ethyl acetate–light petroleum–triethylamine, 10:5:1) 0.3], m.p. 266—267 °C; $\lambda_{max.}$ 244 (25 650), 264sh (33 510), 275sh (40 380), 294 (64 450), and 337 nm (7 240); $\nu_{max.}$ (Nujol) 3 390 (NH), 1 615sh, 1 605, and 1 585 cm^{-1}; $\delta_H(CDCl_3)$ 9.71 (1 H, s, 1-H), 9.40 (1 H, br s, exchanged with D_2O, NH), 8.54 (1 H, d, *J* 6 Hz, 3-H), 7.97 (1 H, br d, *J* 6 Hz, 4-H), 7.87 (1 H, d, *J* 2.5 Hz, 10-H), 7.49 (1 H, d, *J* 9 Hz, 7-H), 7.19 (1 H, dd, J_1 9, J_2 2.5 Hz, 8-H), 6.38 (1 H, s, 2′-H), 3.29 (3 H, s, Me), 3.28 (2 H, ddd, J_1 14, J_2 12.5, J_3 2 Hz, 4′- and 6′-H_{ax}), 3.05 (2 H, ddd, J_1 14, J_2 4, J_3 3 Hz, 4′- and 6′-H_{eq}), 2.33 (1 H, dtt, J_1 14.5, J_2 4, J_3 2 Hz, 5′-H_{eq}), 2.14 (1 H, dtt, J_1 14.5, J_2 12.5, J_3 3 Hz, 5′-H_{ax}); $\delta_C(CF_3CO_2D)$ 144.8, 144.4, 139.6, 139.4, 136.0, 133.3, 130.6, 129.4, 124.8, 121.6, 120.3, 116.0, 114.7, 112.9, 112.7, 59.4 (MeO), 46.1 (SCS), 33.7 (SCC), 26.5 (SCC), and 15.9 (Me); *m/z* (e.i.) 382 (12%), 381 (28), 380 (100), and 306 (39) (Found: C, 66.1; H, 5.5; N, 7.2. $C_{21}H_{20}N_2OS_2$ requires C, 66.3; H, 5.3; N, 7.4%).

When the reaction was repeated using a slight excess of 1,3-dithane in proportion to butyl-lithium a 62% yield of the thioacetal (**16**; R = OMe) was obtained, but if, prior to hydrolysis, the reaction mixture is worked up the ketene thioacetal (**14**; R = OMe) may be isolated. After column chromatography (SiO_2; ethyl acetate), it was obtained as a yellow meringue [R_F(SiO_2; ethyl acetate–light petroleum, 1:1) 0.15], $\delta_H(CDCl_3)$ 8.7—8.40 (3 H, m, on addition of D_2O the integral of this signal decreased to that required of 2 H: indolic NH exchanged), 7.21—6.76 (5 H, m), 4.65—4.59 (1 H, m, MeC*H*), 4.32 ($\frac{13}{30}$ × 2 H, br s, exchanged with D_2O, NH_2), 4.13 ($\frac{17}{30}$ × 2 H, br s, exchanged with D_2O, NH_2), 3.80 ($\frac{22}{40}$ × 3 H, s, MeO), 3.67 ($\frac{18}{40}$ × 3 H, s, MeO), 2.90—2.02 (6 H, m), and 1.75—1.72 (3 H, m, *Me*CH); δ_H[$(CD_3)_2SO$; 127 °C]* 10.38 (1 H, br s, indolic NH), 8.44 (1 H, br s, 2′-H), 8.35 (1 H, d, *J* 5 Hz, 6′-H), 7.22 (1 H, d, *J* 9 Hz, 7-H), 7.14 (1 H, s, 2-H), 7.08 (1 H, d, *J* 5 Hz, 5′-H), 6.94 (1 H, d, *J* 2 Hz, 4-H), 6.68 (1 H, dd, J_1 9, J_2 2 Hz, 6-H), 5.04 (2 H, br s, NH_2), 4.54 (1 H, q, *J* 7 Hz, MeC*H*), 3.67 (3 H, s, MeO), 3.08—1.92 (6 H, m, $CH_2CH_2CH_2S$), and 1.67 (3 H, d, *J* 7 Hz, *Me*CH); $\delta_C(CDCl_3)$ 153.7, 149.8, 149.4, 147.1, 146.4, 144.7, 144.3, 139.3, 139.2, 131.6, 126.9, 126.6, 123.7, 123.4, 122.9, 122.3, 120.4, 119.0, 112.2, 111.9, 111.8, 111.7, 101.9, 101.2, 92.3, 56.0, 55.9, 32.5, 32.3, 31.8, 31.6, 30.9, 26.5, 26.4, 22.9, and 22.0; *m/z* (e.i.) 397 (100%), 291 (18), 278 (20), 277 (42), and 252 (35).

11-*Methyl*-6H-*pyrido*[4,3-b]*carbazole*-5-*carbaldehyde* (**17**; R = H).—Nitrogen was continually bubbled through a solution of the thioacetal (**16**; R = H) (457 mg, 1.3 mmol) in THF (175 cm^3) containing 2M nitric acid (150 cm^2). After 30 min a solution of silver nitrate (466 mg, 2.7 mmol) in 2M nitric acid (25 cm^2) was added and the resulting mixture was heated to 40—50 °C. After 20 h the mixture was allowed to cool, added to saturated aqueous sodium chloride (100 cm^3), and the mixture was basified with solid sodium hydrogen carbonate. Chloroform (200 cm^3) was added to the mixture, and the layers were thoroughly stirred, filtered, and separated; the solid collected was washed with chloroform (3 × 100 cm^3) and the dried (Na_2SO_4) washings further used to extract the aqueous phase. The dry (Na_2SO_4) combined extracts were evaporated under reduced pressure to afford a partially solid yellow material, which was purified by column chromatography (SiO_2; ethyl acetate in light petroleum–triethylamine, 20:15:1) to give the aldehyde (**17**; R = H) as a bright yellow solid (214 mg, 63%), m.p. 256—258 °C (lit.,[13] 266—268 °C) [R_F (SiO_2; ethyl acetate–light petroleum–triethylamine, 10:5:1) 0.4]; $\lambda_{max.}$ 231 (22 000), 238 (19 800), 290 (57 000), 357 (7 300), and 408 nm (6 450); $\nu_{max.}$ ($CHCl_3$) 3 400 (NH), 1 645 (C=O), 1 600, 1 590, and 1 570 cm^{-1}; $\delta_H(CDCl_3)$ 11.23 (1 H, br s, NH), 11.03 (1 H, s, CHO), 9.75 (1 H, s, 1-H), 8.66* (1 H, d, *J* 6 Hz, 3-H), 8.43* (1 H, d, *J* 6 Hz, 4-H), 8.34 (1 H, d, *J* 8 Hz, 10-H), 7.01—7.55 (2 H, m, 7- and 8-H), 7.41 (1 H, ddd, J_1 8, J_2 6, J_3 2 Hz, 9-H), and 3.35 (3 H, s, Me); *m/z*

* Unprimed refer to the indole nucleus, primed to the pyridine ring. Assignments may be interchanged.

(e.i.) 260 (100%, M^+) and 231 (7) (Found: M^+, 260.0913. Calc. for $C_{17}H_{12}N_2O$: M, 260.0950).

9-*Methoxy*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole*-5-*carbaldehyde* (**17**; R = OMe).—A suspension of the thioacetal (**16**; R = OMe) (283 mg, 0.7 mmol) in acetonitrile (150 cm^3) was warmed until dissolution was achieved and it was then placed under nitrogen in an ultrasonic bath and allowed to cool to room temperature. Nitrogen was continually bubbled through an ice-cold aqueous acetonitrile solution (60%; 100 cm^3) containing NCS (403 mg, 3.0 mmol) and silver nitrate (603 mg, 3.5 mmol). After 1 h the thioacetal solution was added to the stirred aqueous acetonitrile solution under nitrogen (*via* a cannula). A white precipitate separated as the liquid phase became yellow, and once the addition was complete the resulting mixture was stirred at 0 °C for 30 min. Ultrasonication was stopped, and the reaction mixture was then allowed to warm to room temperature and stirred for a further 30 min before being treated successively at 1 min intervals with saturated aqueous sodium sulphate (20 cm^3), saturated aqueous sodium hydrogen carbonate (20 cm^3), and saturated aqueous sodium chloride (20 cm^3). After being thoroughly stirred, the two resulting layers were filtered and separated. The solid collected was washed with chloroform (4 × 100 cm^3) which was further used to extract the aqueous phase. The combined dried ($MgSO_4$) extracts were evaporated under reduced pressure and column chromatography of the residue (SiO_2) gave two components. The first component was eluted from the column with ethyl acetate–light petroleum 2:1 and obtained as a yellow solid (153 mg, 71%). This compound was crystallised from ethyl acetate to give the *title aldehyde* as yellow microcrystals, m.p. 248—250 °C [R_F (SiO_2; ethyl acetate–light petroleum–triethylamine, 10:5:1) 0.34]; $\lambda_{max.}$ 234 (23 040), 261 (18 330), 297 (49 540), and 361 nm (4 900); $\nu_{max.}$(Nujol) 3 350 (NH), 1 640 (C=O), 1 595, and 1 570 cm^{-1}); δ_H[$(CD_3)_2SO$] 12.18 (1 H, s, NH), 11.03 (1 H, s, CHO), 9.74 (1 H, s, 1-H), 8.70* (1 H, d, *J* 6 Hz, 3-H), 8.58* (1 H, d, *J* 6 Hz, 4-H), 7.83 (1 H, d, *J* 2.5 Hz, 10-H), 7.76 (1 H, d, *J* 9 Hz, 7-H), 7.21 (1 H, dd, J_1 9, J_2 2.5 Hz, 8-H), 3.91 s, MeO), and 3.30 (3 H, s, Me); *m/z* (e.i.) 290 (100%, M^+) (Found: C, 74.3; H, 4.7; N, 9.4. $C_{18}H_{14}N_2O_2$ requires C, 74.5; H, 4.9; N, 9.65%).

A second component was eluted from the column with ethyl acetate–methanol (100:3) and was crystallised as yellow prisms from dichloromethane–light petroleum. This product (32 mg, 10%) was shown to be 5-(1′,1′-*dioxido*-1′,3′-*dithian*-2′-*yl*-9-*methoxy*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**29**), m.p. 304—305 °C [R_F (SiO_2; ethyl acetate–methanol, 25:1) 0.12]; $\lambda_{max.}$ 242, 275, 294, and 335 nm; $\nu_{max.}$(Nujol) 3 410 (NH), 1 610sh, 1 600, 1 590, 1 290 (SO_2), 1 135 (SO_2), and 1 110 cm^{-1} (SO_2); δ_H($CDCl_3$) 9.71 (2 H, s, NH and 1-H), 8.56 (1 H, d, *J* 6 Hz, 3-H), 7.90 (1 H, d, *J* 6 Hz, 4-H), 7.86 (1 H, d, *J* 2.5 Hz, 10-H), 7.48 (1 H, d, *J* 9 Hz, 7-H), 7.20 (1 H, dd, J_1 9, J_2 2.5 Hz, 8-H), 6.29 (1 H, s, SCHS), 3.96 (3 H, s, MeO), 3.52—3.41 (2 H, m), 3.31 (3 H, s, Me), 3.28—3.19 (1 H, m), 3.10—2.91 (2 H, m), and 2.81—2.68 (1 H, m); δ_C(CF_3CO_2D) 144.8, 144.5, 139.6, 139.2, 135.6, 133.2, 131.2, 130.6, 124.5, 121.0, 120.5, 117.8, 115.0, 113.7, 113.0, 64.8 (SO_2CS), 59.3 (MeO) 56.0 (SO_2CH_2), 31.7* ($SO_2CH_2CH_2$), 31.2* (SCH_2), and 16.2 (Me); *m/z* (e.i.) 412 (31%, M^+), 349 (31), 348 (100), and 290 (49) (Found: C, 61.4; H, 5.2; N, 6.5. $C_{21}H_{20}N_2O_3S_2$ requires C, 61.2; H, 4.85; N, 6.8%).

9-*Hydroxy*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole*-5-*carbaldehyde* (**17**; R = OH).—Boron tribromide (1.0M solution in dichloromethane; 8.4 cm^3, 8.4 mmol) was added to a solution of the aldehyde (**17**; R = OMe) (400 mg, 1.48 mmol) in dry dichloromethane. The resulting deep red solution was sealed under nitrogen and stirred at room temperature for 71 h, then the solvents were removed under reduced pressure. The residue was taken up in 2M hydrochloric acid (100 cm^3), then heated to gentle reflux for 30 min, and the hot mixture was basified by addition to saturated aqueous sodium hydrogen carbonate. The resulting precipitate was collected by filtration, washed with a little water (2 × 20 cm^3), and dried over phosphorus pentaoxide to afford the *hydroxy aldehyde* (**17**; R = OH) as a yellow solid (342 mg, 90%), which was used without further purification, m.p. >350 °C; $\lambda_{max.}$ 236, 243, 260, 299, and 364 nm (addition of 1% 2M aq. NaOH causes a change to $\lambda_{max.}$ 247 and 321 nm); $\nu_{max.}$(CH_3CN) 3 600 (OH), 3 525 (NH), and 1 620 cm^{-1} (C=O); δ_H[$(CD_3)_2SO$] 12.15 (1 H, br s, exchanged with D_2O, NH), 11.06 (1 H, s, CHO), 9.75 (1 H, s, 1-H), 9.42 (1 H, br s, exchanged with D_2O, OH), 8.73* (1 H, d, *J* 6 Hz, 3-H), 8.58* (1 H, d, *J* 6 Hz, 4-H), 7.79 (1 H, d, *J* 2.5 Hz, 10-H), 7.68 (1 H, d, *J* 9 Hz, 7-H), 7.07 (1 H, dd, J_1 9, J_2 2.5 Hz, 8-H), and 3.30 (3 H, s, Me) (Found: C, 71.3, H, 4.4; N, 9.4. $C_{17}H_{12}N_2O_2 \cdot \frac{1}{2}H_2O$ requires C, 71.6; H, 4.6; N, 9.8%).

11-*Methyl*-5-*methyliminomethyl*-6H-*pyrido*[4,3-b]*carbazole* (**20**; R = H).—Gaseous methylamine was bubbled through a cold (0 °C), stirred orange suspension of the aldehyde (**17**; R = H) (550 mg, 2.1 mmol) in dry benzene (150 cm^3) containing activated 3Å molecular sieves. After 90 min the flow of gaseous methylamine was stopped and the dark red solution was stirred for a further 1 h. The solution was filtered, to remove the molecular sieves, and the filtrate was evaporated under reduced pressure to give the imine (**20**; R = H) (535 mg, 93%) as a red gum. This was used directly in subsequent experiments; $\nu_{max.}$($CHCl_3$)1 630 (C=N), 1 600, and 1 575 cm^{-1}; δ_H($CDCl_3$) 11.87 (1 H, br s, NH), 9.71 (1 H, s, 1-H), 9.36 (1 H, q, *J* 1.5 Hz, MeN=C*H*), 8.56 (1 H, d, *J* 6 Hz, 3-H), 8.36 (1 H, d, *J* 8 Hz, 10-H), 8.16 (1 H, d, *J* 6 Hz, 4-H), 7.56 (2 H, d, *J* 4 Hz, 7- and 8-H), 7.36 (1 H, m, 9-H), 3.78 (3 H, d, *J* 1.5 Hz, MeN), and 3.31 (3 H, s, Me). Decoupling experiments: irradiation at δ 9.36 caused the doublet at δ 3.78 to collapse to a singlet. Similarly irradiation at δ 8.36 simplified the multiplet at δ 7.36 to a triplet (*J* 4 Hz), while irradiation at δ 7.56 reduced the same multiplet to a doublet (*J* 8 Hz).

9-*Methoxy*-11-*methyl*-5-*methyliminomethyl*-6H-*pyrido*[4,3-b]*carbazole* (**20**; R = OMe).—This compound was prepared from the aldehyde (**17**; R = OMe) in an exactly similar way to that described for the demethoxy compound (**20**; R = H). The yield was 99% for the crude red product, m.p. 161—163 °C, which was used directly in the subsequent experiment; $\nu_{max.}$(Nujol) 1 625 (C=N) and 1 600 cm^{-1}; δ_H($CDCl_3$) 11.65 (1 H, br s, NH), 9.56 (1 H, s, 1-H), 9.20 (1 H, m, MeN=C*H*), 8.43 (1 H, d, *J* 6 Hz, 3-H), 8.00 (1 H, d, *J* 6 Hz, 4-H), 7.71 (1 H, d, *J* 2.5 Hz, 10-H), 7.34 (1 H, d, *J* 9 Hz, 7-H), 7.08 (1 H, dd, J_1 9, J_2 2.5 Hz, 8-H), 3.88 (3 H, s, MeO), 3.64 (3 H, d, *J* 1 Hz, MeN), and 3.13 (3 H, s, Me). Decoupling experiments: irradiation of the multiplet at δ 9.2 changed the doublet at δ 3.64 into a singlet); *m/z* (e.i.) 303 (100%, M^+), 302 (10), and 288 (5).

11-*Methyl*-5-*methyliminomethyl*-6H-*pyrido*[4,3-b]*carbazol*-9-*ol* (**20**; R = OH).—Gaseous methylamine was bubbled through a stirred orange suspension of the hydroxy aldehyde (**17**; R = OH) (1.20 g, 4.3 mmol) in dry methanol (250 cm^3) containing activated 3Å molecular sieves. After 90 min the flow of gaseous methylamine was stopped and the resulting dark red solution was sealed under nitrogen and stirred for a further 17 h at room temperature. The solution was filtered, the 3Å molecular sieves were collected and washed with dry methanol (160 cm^3), and the combined washings and filtrate were evaporated under reduced pressure to afford the title compound (1.21 g, 96%) as a red solid, which was used without further

* Assignments may be interchanged.

purification, m.p. >350 °C; $\nu_{max.}$(Nujol) 1 625 (C=N), 1 595, and 1 580 cm^{-1}; δ_H[$(CD_3)_2SO$] 11.88 (1 H, br s, exchanged with D_2O, NH), 9.71 (1 H, s, 1-H), 9.53 (1 H, d, *J* 1 Hz, MeN=C*H*), 8.49—8.45 (3 H, m, 3- and 4-H, and OH; on addition of D_2O, the integral decreased to that corresponding to 2 H), 7.81 (1 H, d, *J* 2 Hz, 10-H), 7.65 (1 H, d, *J* 8.5 Hz, 7-H), 7.05 (1 H, dd, J_1 8.5, J_2 2 Hz, 8-H), 3.72 (3 H, d, *J* 1 Hz, MeN), and 3.27 (3 H, s, Me).

5-*Methylaminomethyl*-6H-*pyrido*[4,3-b]*carbazole* (**21**; R = H).—Sodium borohydride (114 mg, 3.0 mmol) was added portionwise to a cold (0 °C), stirred red solution of the imine (**20**; R = H) (535 mg, 2.0 mmol) in dry methanol (75 cm^3) under dry nitrogen. The resulting mixture was stirred for 3 h at 0 °C and then the solvent was evaporated off. The residue was partitioned between water (60 cm^3) and chloroform (60 cm^3), and the layers were thoroughly stirred and then separated. The aqueous phase was extracted with chloroform (6 × 60 cm^3) and the dry ($MgSO_4$) combined extracts were evaporated to give an orange gum, which was purified by column chromatography (SiO_2; eluted first with dichloromethane–methanol–ammonia, 100:5:1 and then with dichloromethane–methanol–ammonia, 100:10:1) to afford the title amine as an orange solid (322 mg, 60%), m.p. 190—191 °C [R_F (SiO_2; dichloromethane–methanol–ammonia, 125:8:1) 0.11]; $\lambda_{max.}$ 225 (15 300), 238 (16 000), 286 (47 100), 293 (39 600), 331 (4 200), 382 (3 400), and 395 nm (3 300); $\nu_{max.}$ 1 600 cm^{-1}; δ_H($CDCl_3$) 9.70 (1 H, s, 1-H), 8.46 (1 H, d, *J* 6 Hz, 3-H), 8.36 (1 H, d, *J* 8 Hz, 10-H), 7.88 (1 H, d, *J* 6 Hz, 4-H), 7.51—7.49 (2 H, m, 7- and 8-H), 7.31—7.27 (1 H, m, 9-H), 4.54 (2 H, s, MeNCH_2), 3.28 (3 H, s, 11-Me), and 2.58 (3 H, s, MeN) (indolic and secondary amino proton resonances not observed); *m/z* (e.i.) 275 (49%) and 244 (45).

9-*Methoxy*-11-*methyl*-5-*methylaminomethyl*-6H-*pyrido*[4,3-b]*carbazole* (**21**; R = OMe).—This compound was prepared from the imine (**20**; R = OMe) as described above for the demethoxy analogue (**21**; R = H). Yield, after column chromatography of the crude product (SiO_2; dichloromethane–methanol–triethylamine, 100:5:1) 49%; *yellow prisms*, m.p. 178–180 °C; [R_F (SiO_2; dichloromethane–methanol–ammonia, 125:8:1) 0.16]; $\lambda_{max.}$ 244 (23 450), 279 (36 300), 294 (48 800), and 335 nm (6 000); $\nu_{max.}$ 1 600 cm^{-1}; δ_H($CDCl_3$) 9.68 (1 H, s, 1-H), 8.44 (1 H, d, *J* 6 Hz, 3-H), 7.88 (1 H, d, *J* 2.5 Hz, 10-H), 7.86 (1 H, d, *J* 6 Hz, 4-H), 7.41 (1 H, d, *J* 9 Hz, 7-H), 7.16 (1 H, dd, J_1 9, J_2 2.5 Hz, H-8), 4.53 (2 H, s, MeNCH_2), 3.97 (3 H, s, MeO), 3.28 (3 H, s, 11-Me), and 2.58 (3 H, s, MeN) (indolic and secondary amino proton resonances not observed); *m/z* (e.i.) 305 (11%, M^+) and 274 (16) (Found: M^+, 305.1528. $C_{19}H_{19}N_3O$ requires *M*, 305.1528.

N,N′-*Bis*-(11-*methyl*-6H-*pyrido*[4,3-b]*carbazol*-5-*ylmethyl*)-N,N′-*dimethyladipamide* (**22**; R = H).—Freshly distilled diphenylphosphoryl azide (0.49 cm^3, 625 mg, 2.27 mmol) was added to a stirred solution of the amine (**21**; R = H) (312 mg, 1.1 mmol) and adipic acid (83 mg, 0.57 mmol) in dry DMF (25 cm^3) under nitrogen. The resulting mixture was cooled to 0 °C, dry triethylamine added dropwise (0.63 cm^3, 459 mg, 4.5 mmol), and then the reaction mixture was sealed under nitrogen and kept at −10 °C. After 1 h a dark red solution had formed, which after 22 h deposited a yellow precipitate. The mixture was allowed to warm to room temperature and was stirred for 2 h before the yellow solid was collected by filtration, washed with a little ethyl acetate, and dried under reduced pressure. Flash chromatography of the solid (SiO_2; ethyl acetate–methanol–ammonia, 100:8:3) afforded the *title compound* as a bright yellow solid (109 mg). The remaining filtrate was added to a mixture of dichloromethane (80 cm^3) and 2M hydrochloric acid (60 cm^3), and the layers were thoroughly stirred and then separated. The organic phase was further extracted with 2M hydrochloric acid (4 × 80 cm^3). The combined 2M hydrochloric extracts were basified with solid sodium hydrogen carbonate and extracted with dichloromethane (2 × 100 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent was removed. Purification of the resulting residue by flash chromatography (SiO_2; ethyl acetate–methanol–ammonia, 100:8:1) gave additional amounts of the *title compound* (31 mg) (total yield 140 mg, 37%), m.p. 305–308 °C [R_F (SiO_2; dichloromethane–methanol–triethylamine, 100:2:1) 0.4]; $\lambda_{max.}$ 225 (34 200), 238 (33 600), 285 (106 300), 292 (84 900), 317 (5 900), 330 (7 800), 380 (6 500), and 396 nm (6 400); $\nu_{max.}$ 1 620 and 1 600 cm^{-1}; δ_H($CDCl_3$) 10.63 (1 H, s, NH), 9.74 (1 H, s, 1-H), 8.53 (1 H, d, *J* 6 Hz, 3-H), 8.35 (1 H, d, *J* 8 Hz, 10-H), 7.98 (1 H, d, *J* 6 Hz, 4-H), 7.55—7.46 (2 H, m, 7- and 8-H), 7.29 (1 H, ddd, J_1 8, J_2 6, J_3 1.5 Hz, 9-H), 5.26 (2 H, s, MeNCH_2), 3.33 (3 H, s, 11-Me), 2.89 (3 H, s, MeN), 2.41 (1 H, m, COCH_2CH_2), and 1.75 (2 H, m, COCH_2CH_2); *m/z* (f.a.b. glycerol–thioglycerol–0.1M hydrochloric acid matrix) 661 (9%, M^+ + 1 (Found: C 76.0; H, 6.2; N, 12.55. $C_{42}H_{40}N_6O_2$ requires C, 76.3; H, 6.1; N, 12.7%).

N,N′-*Bis*-(9-*methoxy*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazol*-5-*ylmethyl*)-N,N′-*dimethyladipamide* (**22**; R = OMe) (**22**; R = OMe).—Freshly distilled diphenylphosphoryl azide (0.20 cm^3, 256 mg, 0.93 mmol) was added to a stirred orange solution of the amine (**21**; R = OMe) (142 mg, 0.47 mmol), adipic acid (34 mg, 0.23 mmol), DMAP (114 mg, 0.93 mmol), and 1-hydroxybenzotriazole (126 mg, 0.93 mmol) in dry DMF (20 cm^3) under nitrogen. The resulting mixture was cooled to 0 °C, dry triethylamine was added dropwise (0.26 cm^3, 188 mg, 1.9 mmol), and then the solution was sealed under nitrogen and kept at −10 °C for 41 h. After this time the solution was allowed to warm to room temperature and it was then stirred for 5 h before addition to a mixture of dichloromethane (80 cm^3) and 2M hydrochloric acid (60 cm^3). After thorough mixing, the layers were separated and the organic phase was further extracted with 2M hydrochloric acid (5 × 80 cm^3). The combined hydrochloric acid extracts were basified with solid sodium hydrogen carbonate and extracted with chloroform (3 × 100 cm^3). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure (50 °C/0.05 mmHg). Purification of the resulting residue by flash chromatography (SiO_2; ethyl acetate–methanol–triethylamine, 100:8:1 and then dichloromethane–methanol–triethylamine, 100:8:1) gave the *title compound* as a yellow solid (76 mg, 45%), which was crystallised from ethyl acetate–dichloromethane as yellow microcrystals, m.p. 207—209 °C [R_F (SiO_2; dichloromethane–methanol–triethylamine, 100:2:1) 0.4]; $\lambda_{max.}$ 243, 271, 292, and 334 nm; $\nu_{max.}$(Nujol) 3 180 (NH), 1 615sh (C=O), and 1 605 cm^{-1}; δ_H($CDCl_3$) 10.40 (1 H, br s, NH), 9.66 (1 H, s, 1-H), 8.44 (1 H, br d, *J* 6 Hz, 3-H), 7.89 (1 H, d, *J* 6 Hz, 4-H), 7.81 (1 H, d, *J* 2.5 Hz, 10-H), 7.37 (1 H, d, *J* 9 Hz, 7-H), 7.07 (1 H, dd, J_1 9, J_2 2.5 Hz, 8-H), 5.17 (2 H, s, MeNCH_2), 3.87 (3 H, s, MeO), 3.24 (3 H, s, 11-Me), 2.82 (3 H, s, MeN), 2.33 (2 H, m, COCH_2CH_2), and 1.67 (2 H, m, COCH_2CH_2); *m/z* (f.a.b. ethylene glycol–0.1M hydrochloric acid matrix) 721 (M^+ + 1) (Found: C, 73.0; H, 6.1; N, 11.4. $C_{44}H_{44}N_6O_4$ requires C, 73.3, H, 5.9; N, 11.7%).

5-*Methoxymethyl*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**23**; R = H).—Ethanolic methylamine (33% w/w; 0.7 cm^3, 5.8 mmol) was added to a stirred suspension of the aldehyde (**17**; R = H) (152 mg, 0.58 mmol) in dry methanol (25 cm^3) containing activated 3Å sieves. The mixture was adjusted to pH 6 with dry methanolic hydrogen chloride, and sodium cyanoborohydride (55 mg, 0.87 mmol) was added. The resulting orange solution was stirred at room temperature for 25 h, when further quantities of ethanolic methylamine (33% w/w; 0.7 cm^3, 5.8 mmol) and sodium cyanoborohydride (75 mg, 1.2 mmol) were added, the pH re-adjusted to ~6 with methanolic

hydrogen chloride, and the resulting solution stirred for a further 23 h. After this time the solution was filtered and the 3Å molecular sieves collected and washed with a little dry methanol. The acidity of the filtrate was increased to pH 2 with conc. hydrochloric acid and the methanol was removed by evaporation under reduced pressure. The resulting residue was basified with saturated aqueous sodium hydrogen carbonate, extracted with chloroform (6 × 25 cm^3), and the combined extracts were dried (Na_2SO_4). Removal of solvent under reduced pressure gave an off-yellow solid, which was purified by flash chromatography (SiO_2; ethyl acetate–hexane–triethylamine, 30:10:2 and then ethyl acetate–methanol, 50:1) to afford 5-*methoxymethyl*-11-*methyl*-6H-*pyrido*[4,3-b]*carbazole* (**23**; R = H) as a bright yellow solid (72 mg, 45%), m.p. 247—248 °C [R_F (SiO_2; ethyl acetate–hexane–triethylamine, 10:5:1) 0.16]; $\lambda_{max.}$ 224 (14 200), 238 (13 300), 285 (51 400), 292 (44 100), 317 (2 450), 330 (3 300), 382 (2 600), and 398 nm (2 500); $\nu_{max.}$(Nujol) 1 600 cm^{-1}; δ_H [$(CD_3)_2SO$] 11.17 (1 H, s, NH), 9.70 (1 H, s, 1-H), 8.44 (1 H, d, *J* 6 Hz, 3-H), 8.39 (1 H, d, *J* 8 Hz, 10-H), 8.01 (1 H, d, *J* 6 Hz, 4-H), 7.62—7.53 (2 H, m, 7- and 8-H), 7.29 (1 H, t, *J* 8 Hz, 9-H), 5.20 (2 H, s, $MeOCH_2$), 3.43 (3 H, s, MeO), and 3.31 (3 H, s, Me); *m/z* (e.i.) 276 (71%, M^+), 245 (70), and 244 (100) (Found: C, 78.1; H, 6.0; N, 10.3. $C_{18}H_{16}N_2O$ requires C, 78.2; H, 5.8; N, 10.1%).

11-*Methyl*-6H-*pyrido*[4,3-b]*carbazol*-5-*ylmethanol* (**24**; R = H).—Sodium cyanoborohydride (83 mg, 1.3 mmol) was added to a stirred suspension of the aldehyde (**17**; R = H) (170 mg, 0.65 mmol) in dry methanol (40 cm^3) containing activated 3Å sieves. The pH of the mixture was adjusted to ~3 with dry methanolic hydrogen chloride and the resulting solution was stirred at room temperature. After 5 days the solution was filtered and the molecular sieves were collected and washed with a little dry methanol. The combined methanol washings and filtrate were evaporated under reduced pressure and the resulting residue was basified with saturated aqueous sodium hydrogen carbonate and the mixture was extracted with dichloromethane (5 × 30 cm^3). The dry ($NaSO_4$), combined extracts were evaporated under reduced pressure to give a yellow solid. Column chromatography (SiO_2) gave two components. The first fraction (eluted with ethyl acetate–light petroleum–triethylamine, 30:10:1) was collected and evaporated to afford the same methoxy compound (**23**; R = H) as obtained in the previous experiment (41 mg, 23%) (^1H n.m.r., t.l.c. same as previous sample). The second component (eluted with ethyl acetate–methanol–triethylamine, 50:1:1), also a yellow solid corresponds to 11-methyl-6*H*-pyrido[4,3-*b*]carbazol-5-ylmethanol (**24**; R = H) (44 mg, 26%), m.p. 259—263 °C (lit.,[18] 257—258 °C); $\lambda_{max.}$ 226 (19 800), 239 (15 700), 276 (36 200), 286 (54 800), 293 (48 000), 331 (3 800), and 342 nm (2 300); $\nu_{max.}$(Nujol) 3 150br (NH, OH) and 1 600 cm^{-1}; δ_H[$(CD)_3SO$] 11.50 (1 H, s, exchanged with D_2O, NH), 9.72 (1 H, s, 1-H), 8.44 (1 H, d, *J* 6 Hz, 3-H), 8.39 (1 H, d, *J* 8 Hz, 10-H), 8.09 (1 H, d, *J* 6 Hz, 4-H), 7.63—7.49 (2 H, m, 7- and 8-H), 7.27 (1 H, t, *J* 8 Hz, 9-H), 5.25 (3 H, br s, CH_2OH; addition of D_2O to the sample caused the integral of this signal to decrease to that corresponding to 2 H), and 3.28 (3 H, s, Me); *m/z* (e.i.) 262 (24%, M^+) and 246 (15).

5,5′-*Bis*-(1″,3″-*dithian*-2″-*yl*)-9,9′-*dimethoxy*-11,11′-*dimethyl*-7,7′-*bi*-(6H-*pyrido*[4,3-b]*carbazole*) (**26**).—Nitrogen was continually bubbled through a solution of the thioacetal (**16**; R = OMe) (28 mg, 0.07 mmol) in THF (15 cm^3) and 2M nitric acid (10 cm^3). After a period of 45 min, a solution of silver nitrate (26 mg, 0.15 mmol) in 2M nitric acid (5 cm^3) was added and the resulting mixture was heated between 40—50 °C. After 16 h, the mixture was allowed to cool, added to saturated aqueous sodium chloride (10 cm^3), and basified with solid sodium hydrogen carbonate. The mixture was extracted with chloroform (5 × 40 cm^3) and the combined organic extracts dried ($MgSO_4$) and evaporated under reduced pressure. This gave a dark orange gum, which was purified by p.l.c. to afford the *title compound* as a rusty-red solid (19 mg, 68%), m.p. 279—283 °C [R_F (SiO_2; ethyl acetate–light petroleum–triethylamine, 15:5:1) 0.21]; $\lambda_{max.}$ 274 nm; $\nu_{max.}$ 3 380 (NH), 1 610sh, 1 600sh, and 1 575 cm^{-1}; $\delta_H(CDCl_3)$ 11.28 (2 H, br s, 2 × NH), 9.76 (2 H, s, 1- and 1′-H), 8.63 (2 H, d, *J* 6 Hz, 3- and 3′-H), 8.23 (2 H, d, *J* 2.5 Hz, 10- and 10′-H), 8.04 (2 H, d, *J* 6 Hz, 4- and 4′-H), 7.94 (2 H, d, *J* 2.5 Hz, 8- and 8′-H), 6.38 (2 H, s, 2 × SCHS), 4.02 (6 H, s, 2 × MeO), 3.29 (6 H, s, 2 × Me), 3.28 (4 H, ddd, J_1 14.5, J_2 12, J_3 2 Hz, 2 × 4″-H_{ax} and 2 × 6″-H_{ax}), 3.08 (4 H, ddd, J_1 14.5, J_2 4.5, J_3 3 Hz, 2 × 4″-H_{eq} and 2 × 6″-H_{eq}), 2.37 (2 H, dtt, J_1 14.5, J_2 4.5, J_3 2 Hz, 2 Hz, 2 × 5″-H_{eq}), and 2.23 (2 H, dtt, J_1 14.5, J_2 12, J_3 3 Hz, 2 × 5″-H_{ax}) (Found: C, 66.5; H, 5.2; N, 7.8. $C_{42}H_{38}N_4O_2S_4$ requires: C, 66.5; H, 5.05; N, 7.4%).

9,9′-*Dimethoxy*-5,5′,11,11′-*tetramethyl*-7,7′-*bi*-(6H-*pyrido*[4,3-b]*carbazole*) (**27**).—An identical reaction to that used above now with 9-methoxyellipticine as the substrate, gave the *title compound* as a red solid in 5% yield plus unchanged starting material and some resin. The product decomposes at >350 °C [R_F (SiO_2; ethyl acetate–light petroleum–triethylamine, 10:10:1) 0.27]; $\lambda_{max.}(CHCl_3)$ 3 370 (NH), 1 615, 1 600, and 1 580 cm^{-1}; $\delta_H(CDCl_3)$ 9.88 (2 H, br s, 2 × NH), 9.76 (2 H, s, 1- and 1′-H), 8.58 (2 H, d, *J* 6 Hz, 3- and 3′-H), 8.25 (1 H, d, *J* 2 Hz, 10- and 10′-H), 7.91—7.90 (4 H, m, 4-, 4′-, 8-, and 8′-H), 4.01 (6 H, s, 2 × MeO), 3.29 (6 H, s, 2 × 11-Me), and 2.84 (6 H, s, 2 × 5-Me) (Found: C, 78.8; H, 5.7; N, 10.0. $C_{36}H_{30}N_4O_2$ requires C, 78.5; H, 5.5; N, 10.2%).

2,9-*Dimethyl*-2,3-*dihydropyrido*[4,3-b]*pyrimido*[1,6,5-lm]*carbazol*-7-*ol* (**30**; R = H).—Sodium borohydride (0.51 g, 13.4 mmol) was added portionwise to a stirred solution of the imine (**20**; R = OH) (1.21 g, 4.2 mmol) in dry methanol at room temperature under dry nitrogen. The resulting mixture was further stirred for 1 h after which time t.l.c. analysis still revealed the presence of starting material. The solution was then heated to gentle reflux and further portions of sodium borohydride were added (2 g, 53 mmol). After 1 h the solution was allowed to cool, the solvent was removed under reduced pressure, and the residue was acidified with conc. hydrochloric acid. The mixture was then basified with saturated aqueous sodium hydrogen carbonate and exhaustively extracted with chloroform (7 × 35 cm^3). The combined dried (Na_2SO_4) extracts were evaporated under reduced pressure and column chromatography of the residue (SiO_2; dichloromethane–methanol, 150:9 and then dichloromethane–methanol–triethylamine, 100:8:1) gave the title compound as a light yellow gum (216 mg, 17%); [R_F (SiO_2; dichloromethane–methanol, 50:3) 0.11]; $\lambda_{max.}$ 252, 278, 297, 338, and 354 nm (changed by the addition of 1% 2M aq. NaOH to $\lambda_{max.}$ 259 and 309 nm); $\nu_{max.}$(Nujol) 1 600 cm^{-1}; $\delta_H[(CD_3)_2SO]$ 9.68 (1 H, s, 10-H), 9.26 (1 H, s, exchanged with D_2O, OH), 8.39 (1 H, d, *J* 6 Hz, 12-H), 7.81 (1 H, d, *J* 2.0 Hz, 8-H), 7.78 (1 H, d, *J* 6 Hz, 13-H), 7.44 (1 H, d, *J* 8.5 Hz, 5-H), 7.08 (1 H, dd, J_1 8.5, J_2 2.0 Hz, 6-H), 5.09 (2 H, s, NCH_2N), 4.40 (2 H, s, 1-H_2), 3.22 (3 H, s, 9-Me), and 2.51 (3 H, s, NMe).

7-(*Dimethyl*-t-*butylsiloxy*)-2,9-*dimethylpyrido*[4,3-6]*pyrimido*[1,6,5-lm]*carbazole* (**30**; R = $SiMe_2Bu^t$).—To a stirred solution of the pentacycle (**30**; R = H) (82 mg, 0.27 mmol) in dry DMF (5 cm^3) under dry nitrogen was added sodium hydride (60% dispersion in oil) (86 mg, 3.6 mmol). The mixture was stirred at room temperature for 30 min and then chlorodimethyl-t-butylsilane (606 mg, 4.0 mmol) was added. The resulting mixture was further stirred at room temperature for 5 h and was then added to water (30 cm^3) and extracted with chloroform (3 × 50 cm^3). The combined dried (Na_2SO_4)

extracts were evaporated under reduced pressure (50 °C/15 mmHg) to give a red gum, which was purified by column chromatography (SiO_2; dichloromethane–methanol, 25:1) to afford the title compound as a yellow gum (44 mg, 39%) [R_F (SiO_2; dichloromethane–methanol, 50:3) 0.32]; $\lambda_{max.}$ 277, 296, 336, and 352 nm; $\nu_{max.}(CHCl_3)$ 1 605 cm^{-1}; $\delta_H(CDCl_3)$ 9.65 (1 H, s, 10-H), 8.42 (1 H, d, *J* 6 Hz, 12-H), 7.80 (1 H, d, *J* 2 Hz, 8-H), 7.58 (1 H, d, *J* 6 Hz, 13-H), 7.18 (1 H, d, *J* 8.5 Hz, 5-H), 7.09 (1 H, dd, J_1 8.5, J_2 2 Hz, 6-H), 4.96 (2 H, s, NCH_2N), 4.35 (2 H, s, 1-H_2), 3.19 (3 H, s, 9-Me), 2.52 (3 H, s, MeN), 1.06 (9 H, s, Bu^t), and 0.27 (6 H, s, $SiMe_2$); $\delta_C(CDCl_3)$ 149.4 (SiOC), 149.2, 139.2, 130.5, 123.8, 120.0, 115.2, 115.0, 108.1, 105.5, 64.2 (C-3), 49.6 (C-1), 42.0 (MeN), 25.8 (CMe_3) 18.3 (CMe_3), 14.6 (9-Me and −4.3 ($SiMe_2$); *m/z* (e.i.) 417 (100%, M^+), 375 (34), and 374 (47) (Found: M^+, 417.2191. $C_{25}H_{31}N_3OSi$ requires M^+, 417.2234).

Acknowledgements

We thank the SERC and Glaxo Group Research Ltd for CASE studentships to A. J. Ratcliffe and A. D. Smith, and Mr. P. G. Green, Oncology Dept., Glaxo Group Research Ltd., for testing some of the compounds.

References

1 Part 11, A. Popplestone and M. Sainsbury, *Tetrahedron*, 1983, **39**, 4103.
2 For a recent review see M. Suffness and G. A. Cordell, 'Antitumour Alkaloids,' ch. 1, p. 1, in 'The Alkaloids,' ed. A. Brossi, Academic Press, London, 1985, vol. 25.
3 A. Brugarolas, M. Gracia, R. de Jager, M. Mallarme, and A. Clarysse, *Proc. Am. Soc. Clin. Oncol.*, 1979, **20**, 310; P. Juret, J. F. Heron, J. E. Couette, T. Delozier, and J. Y. Le Talaer, *Cancer Treat. Rep.*, 1982, **66**, 1909.
4 K. W. Kohn, M. J. Waring, D. Glaubiger, and C. A. Friedman, *Cancer Res.*, 1975, **35**, 71; J. Ashby, B. M. Elliott, and J. A. Styles, *Cancer Lett.*, 1980, **9**, 21.
5 W. E. Ross, *Biochem. Pharmacol.*, 1985, **34**, 4191.
6 A. Delbarre, B. P. Roques, and J.-B. Le Pecq, *C. R. Heb. Seances Acad. Sci. Ser. D*, 1977, **284**, 81; D. Pelaprat, A. Delbarre, I. Le Guen, and B. P. Roques, *J. Med. Chem.*, 1980, **23**, 1336.
7 Agence Nationale de Valorisation de la Recherche, Ger. Offen 2 451 360 (*Chem. Abstr.*, 1975, **83**, 126493v); A. Gouyette, R. Reynaud, J. Sadet, M. Baillarge, C. Ganasser, S. Gros, F. Le Goffic, J.-B. Le Pecq, C. Paoletti, and C. Viel, *Eur. J. Med. Chem.*, 1980, **15**, 503.
8 see R. W. Guthrie, A. Brossi, F. A. Mennona, J. G. Mullin, R. W. Kierstad, and E. Grunberg, *J. Med. Chem.*, 1975, **18**, 755.
9 A. Aggarwal, S. Neidle, and M. Sainsbury, *Acta Crystallogr., Sect. C*, 1983, **39**, 631; R. Kuroda and M. Sainsbury, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1751; P. D. Osguthorpe and M. Sainsbury, unpublished results.
10 see M. Sainsbury, D. K. Weeringshe, and D. Dolman, *J. Chem. Soc., Perkin Trans. 1*, 1982, 587, and papers cited therein.
11 M. Driver, I. T. Matthews, and M. Sainsbury, *J. Chem. Soc., Perkin Trans 1*, 1979, 2506.
12 P. C. B. Page, M. B. van Niel, and P. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 742.
13 M. G. Saulnier and G. W. Gribble, *Tetrahedron Lett.*, 1983, **24**, 3831; G. W. Gribble and J. A. Obaza-Nutaitus, *J. Nat. Prod.*, 1986, **49**, 449.
14 J. Moiroux and A. M. Armbruster, *J. Electroanal. Chem.*, 1984, **165**, 231.
15 E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1971, **36**, 3553.
16 see D. M. Dolman and M. Sainsbury, *Tetrahedron Lett.*, 1981, **22**, 2119.
17 J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron Lett.*, 1968, 2289.
18 S. Archer and B. S. Ross, *Tetrahedron Lett.*, 1986, **27**, 5343.

Received 21*st January* 1988; *Paper* 8/00238J