The Synthesis of 2,3,4,6-Tetrahydro-5-hydroxy-2,6-dimethyl-1*H*-pyrido-[4,3-*b*]carbazole; Attempts to synthesise 2,3,4,10-Tetrahydro-5-hydroxy-2-methyl-1*H*-pyrido[3,4-*b*]carbazole

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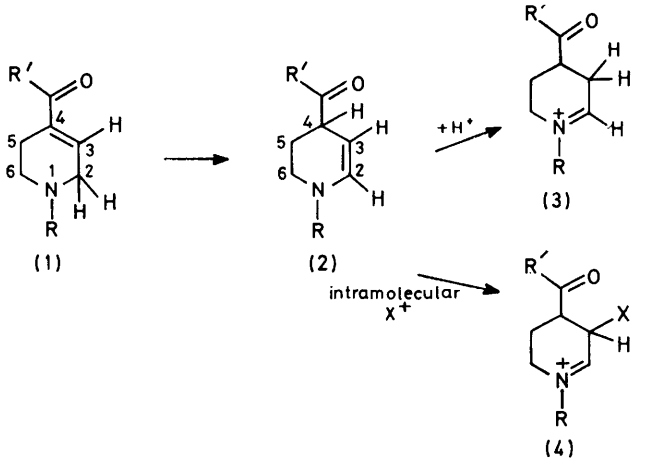
The synthesis of 1-methyl-3-(dimethylaminomethyl)indol-2-yl, 3-(dimethylaminomethyl)indol-2-yl, 2-(dimethylaminomethyl)indol-3-yl, and 2-methoxymethylindol-3-yl 1,2,5,6-tetrahydro-1-methylpyridin-4-yl ketones is described. Although each of these could be isomerised to the corresponding cyclic enamine (2-piperideine), only in the first case could the result of intramolecular β-alkylation of the enamine be obtained, *i.e.* 2,3,4,6-tetrahydro-5-hydroxy-2,6-dimethyl-1*H*-pyrido[4.3-*b*]carbazole (9a).

In previous papers [1,2] in this series we have demonstrated a means for generating six-membered cyclic enamines (2-piperideines) by isomerisation of 4-acyl-1,2,5,6-tetrahydropyridines (1) into 4-acyl-1,4,5,6-tetrahydropyridines † (2). The enamine (2) was then used by conversion into a β-protonated immonium form (3), which served as an intramolecular electrophile to achieve formation of the target cyclic system. Here we report [4] an extension of this theme, and the utilisation of cyclic enamine, generated in this way, as a nucleophile in the intramolecular β-alkylation [→(4)] to effect formation of the required ring system.

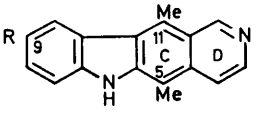


RESULTS AND DISCUSSION

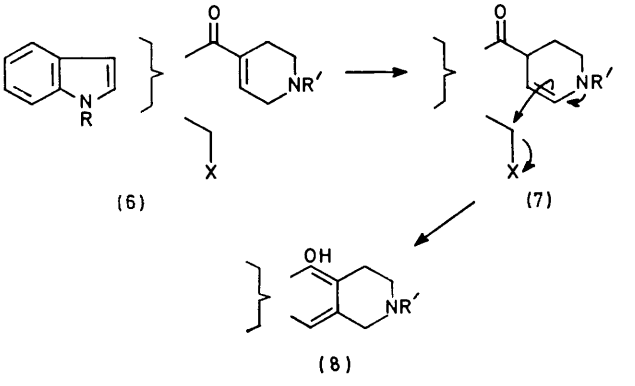
Considerable synthetic interest has been shown [5] in synthesis of the ellipticine (5a) system on account of its antineoplastic activity.[6] The phenolic 9-hydroxy-analogue (5b) is reported as being more active [7] than the parent. We set out, then, to synthesise ellipticine analogues with a phenolic hydroxy function elsewhere in the system, on ring C. Only one other group has described [8] the synthesis of ellipticine types with an alternatively placed hydroxy (on ring D).

The synthetic strategy envisioned was to generate from (6) an enamine (7) which, with a leaving-group-substituted one-carbon unit on the indole, might close [arrows on (7)] and tautomerise to a ring-C phenol (8). A closely similar synthetic strategy has been utilised [9] by French workers in parallel studies, in this case to produce ellipticine itself. Here we describe first the development of a successful route to the phenol (9a) and secondly our failure to bring about a parallel synthesis of an alternative ring-C phenolic system, as in (10).

Since the intermolecular nucleophilic displacement of amine from gramine systems by carbon nucleophiles is a very well established [10] process, this was the leaving group chosen [(6; X = NMe_2)] in the first instance for the present investigation. In the first attempt to prepare a suitable (6) the conjugated ketone (11a) was subjected to the usual Mannich conditions; however, either no reaction occurred or, under more vigorous conditions, only water-soluble products were obtained. This result was not surprising, since the substrate is an acylindole and is thus deactivated relative to a simple indole. However,

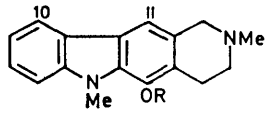


R
a; H
b; OH



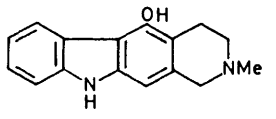
† Recently we have further shown [3] that the acyl group, which acidifies the C-2 protons and thus facilitates the isomerisation, is not a *necessary* condition for achieving isomerisation.

we were able to show that its dihydro-derivative (11b) underwent indole β-substitution with the Mannich reagent smoothly to give (11c).

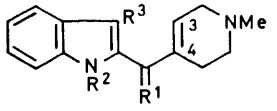


(9)

R
a; H
b; Ac



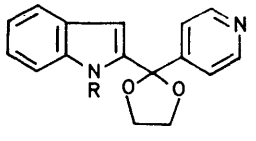
(10)



(11)

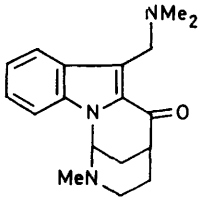
	R^1	R^2	R^3
a;	O	H	H
b;	O	H	H, 3, 4 - dihydro
c;	O	H	CH_2NMe_2, 3, 4 - dihydro
d;	H,OH	H	H
e;	H,OH	H	CH_2NMe_2
f;	OCH_2CH_2O	H	H
g;	OCH_2CH_2O	H	CH_2NMe_2
h;	O	H	CH_2NMe_2
i;	OCH_2CH_2O	Me	H
j;	OCH_2CH_2O	Me	CH_2NMe_2
k;	O	Me	CH_2NMe_2

The introduction of the required dimethylaminomethyl group was easily achieved using the alcohol (11d), but all the many efforts to oxidise the hydroxy group of the product (11e) met with failure, despite the known easy oxidative transformation of (11d) into (11a). A more roundabout route therefore had to be taken to the desired conjugated ketone. The ethylene acetal [11] (12a) was quaternised with methyl iodide, reduced with sodium borohydride, and the resulting acetal (11f) made to undergo the Mannich reaction. The product (11g) could be hydrolysed to the desired conjugated ketone (11h).



(12)

R
a; H
b; Me

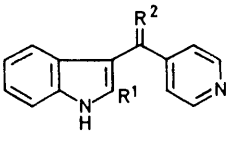


(13)

All attempts to achieve the desired C–C bond resulted only in the formation of the *N*-cyclised compound (13). Since this must have arisen *via* the desired enamine intermediate, it seemed that the problem to be overcome was the efficient competition by the alternative closure pathway. To prevent this, and thus test the synthetic strategy, the acetal (12a) was first N^a-methylated [to give (12b)], using sodium hydride as base and 1 mol of methyl iodide, and then carried through an exactly analogous sequence, (12b)→(11i)→(11j)→(11k).

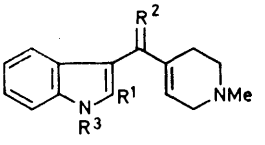
Treatment of the N^a-methyl conjugated ketone (11k) with de-oxygenated 50% aqueous acetic acid gave the desired, though somewhat unstable, phenol (9a), which was best handled and characterised as its stable *O*-acetate (9b). The key spectral features supporting the structure of the acetate are: a u.v. absorption very similar to that of 1-hydroxycarbazole (the absorption of the phenol showed a bathochromic shift in alkaline solution); a singlet at τ 2.40 for the C-11 proton (the C-10 hydrogen showed a doublet, *J* 6 Hz, at τ 2.05) and a singlet at τ 6.23 for the C-12 methylene; and the phenolic ester carbonyl at 1 770 cm^{-1}.

Although gramine-type displacements from the indole α-position are less favoured, nevertheless there are precedents for the displacement of both methoxy [12] and dimethylamino-groups,[13] both in protonated and quaternised forms. In planning a synthesis of (10) by an 'upside-down' version of the successful sequence described above, it was evident that one problem which could not present itself was competitive cyclisation onto N^a, and accordingly no N^a protection was undertaken in this series of reactions. Two possible leaving groups [X = OMe and NMe_2 in (6)] were examined: in the event neither was successful.



(14)

	R^1	R^2
a;	CH_2OMe	H,OH
b;	H	H,OH
c;	CH_2NMe_2	H,OH
d;	CH_2NMe_2	O



(15)

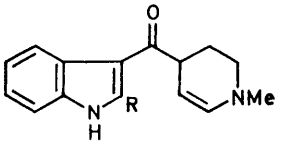
	R^1	R^2	R^3
a;	CH_2OMe	H,OH	H
b;	CH_2OMe	O	H
c;	H	H,OH	H
d;	H	H,OH	CH_2NMe_2
e;	CH_2NMe_2	O	H
f;	CH_2NMe_2	H,OH	H

2-Methoxymethylindole [14] was condensed * with pyridine-4-carbaldehyde in sodium hydroxide, the product (14a) was quaternised and reduced in the usual way and the resulting alcohol (15a) oxidised with manganese dioxide to the conjugated ketone (15b). Treatment with 50% aqueous acetic acid (see above), or successively with sodium methoxide in methanol and then acid, gave no phenolic product. It was established [3] that the base treatment did indeed isomerise (15b) into the enamine (16a).

In the first attempt to prepare a 2-dimethylamino-

* This extremely useful method, first reported [15] by French workers, is far superior to the alternative, *i.e.*, reacting the aldehyde with the indolyl Grignard reagent.

methylindole analogue, the alcohol (14b) was converted, in the usual way, to the piperideine (15c). However, as anticipated [10] Mannich condensation, which could not be carried out in the usual acidic conditions because of the sensitivity of the indol-3-ylmethanol group, occurred on the indolic nitrogen when milder conditions were employed, generating (15d). The synthesis clearly had to start with the α-substituent already present. Isogramine [16] was condensed with pyridine-4-carbaldehyde to give (14c); oxidation of the alcoholic product gave the ketone (14d). Selective quaternisation of the pyridine nitrogen was achieved by forming the mono-hydrochloride (at the more basic dimethylaminomethyl group) followed by reaction with methyl iodide. Borohydride reduction over a short period gave mainly the ketone (15e) together with some of the alcohol (15f).



(16)

R

a ; CH_2OMe

b ; CH_2NMe_2

The ketone (15e) could be isomerised [3] to the enamine (16b) by treatment with sodium methoxide in methanol, but neither the enamine (16b) nor the starting ketone (15e), on treatment with acetic acid, gave any phenolic product.

This failure must be attributed to the recognised [10] lower gramine-type reactivity at the indole α-position compared to the β-position. The effect in this case is aggravated by the greater conjugation of the indole nitrogen with the 3-acyl-carbonyl than with the 2-acyl-carbonyl; thus the electron release required for the amine elimination is even less for 3-acyl-α-gramine than in a simpler α-gramine.

EXPERIMENTAL

General.—Organic extracts were dried with anhydrous magnesium sulphate. Extracts and reaction mixtures were evaporated under reduced pressure (*ca.* 20 mmHg) using a rotary evaporator and a bath temperature of *ca.* 60 °C. Preparative layer chromatography (p.l.c.) was carried out using Merck silica gel 60 plates. Unless otherwise specified, u.v. spectra were measured in ethanol, i.r. spectra in chloroform, and n.m.r. spectra in deuteriochloroform solutions. Only clearly distinguished and unambiguously assignable absorptions are given for i.r. and n.m.r. spectra, in particular those which are of greatest importance for establishment of structure. Only ions of intensity >10% of base peak are given for mass spectra, except where a less intense ion is of particular importance for structure establishment.

3-(*Dimethylaminomethyl*)*indol*-2-*yl* 1-*Methylpiperidin*-4-*yl Ketone* (11c).—The ketone (11b) [1] (15 mg) was reacted with formaldehyde (0.09 ml, 36%), dimethylamine (0.15 ml, 30%), acetic acid (1 ml), and dioxan (1 ml) at reflux for 1 h. The cooled solution was basified and extracted with chloroform to give the crude product (14 mg), purified by p.l.c. [MeOH–NEt_3 (98 : 2)] to give the *Mannich product* (11c) (12 mg); $\lambda_{max.}$ 237 and 315 nm (log ε 4.15 and 4.3); $\nu_{max.}$ 3 450s and 1 645s cm^{-1}; τ 0.52 (1 H, br s, NH), 6.24 (2 H, s, CH_2NMe_2), 7.72 (3 H, s, piperidine-NMe), and 7.76 (6 H, s, NMe_2); *m/e* 299 (41%, M^+), 254 (16), 184 (12), 173 (13), 130 (10), 96 (100), 70 (14), and 58 (18) (Found: M^+, 299.2004. $C_{18}H_{25}N_3O$ requires *M*, 299.1997).

[3-(*Dimethylaminomethyl*)*indol*-2-*yl*]-1,2,5,6-*tetrahydro*-1-*methylpyridin*-4-*ylmethanol* (11e).—The alcohol (11d) [1] (900 mg) in dioxan (7 ml) was added to a mixture of formaldehyde (0.61 ml, 36%), dimethylamine (0.87 ml, 30%), acetic acid (7 ml), and dioxan (7 ml). After 2 h at room temperature the solvent was evaporated off and the residue basified and extracted with ethyl acetate to give the *Mannich alcohol* (11e) (700 mg) as a brown gum; $\lambda_{max.}$ 224, 276, 283, and 290 nm (log ε 4.26, 3.75, 3.78, and 3.72); $\nu_{max.}$ 3 420m cm^{-1}; τ 0.86 (1 H, br s, NH), 3.24 (1 H, br s, OH), 4.16 (1 H, m, HC=C), 4.78 (1 H, s, C*H*OH), 6.42 (2 H, s, CH_2NMe_2), 7.70 (3 H, s, piperideine-NMe), and 7.78 (6 H, s, NMe_2); *m/e* 299 (35%, M^+), 287 (15), 253 (100), 254 (84), 236 (51), 211 (24), 194 (62), 124 (42), 129 (37), 96 (57), and 58 (60) (Found: M^+, 299.1996. $C_{18}H_{25}N_3O$ requires *M*, 299.1997).

Indol-2-*yl* 1,2,5,6-*Tetrahydro*-1-*methylpyridin*-4-*yl Ketone Ethylene Acetal* (11f).—The acetal (12a) [11] (1.18 g) was reacted with methyl iodide (10 ml) in benzene (100 ml) at reflux overnight. The resulting solid methiodide (1.84 g) was reduced, without purification, with an excess of sodium borohydride in methanol (120 ml) for 20 min at room temperature. Evaporation, addition of water, and extraction with ethyl acetate gave the *piperideine acetal* (11f) (1.19 g), m.p. 171—172 °C (from EtOAc); $\lambda_{max.}$ 222, 281, and 290 nm (log ε 4.06, 3.93, and 3.81); $\nu_{max.}$ 3 460s cm^{-1}; τ 1.65 (1 H, br s, NH), 3.45 (1 H, br s, indole 3-H), 4.1 (1 H, m, HC=C), 5.95 (4 H, br s, OCH_2CH_2O), and 7.6 (3 H, s, NMe); *m/e* 284 (25%, M^+), 239 (10), 188 (100), 167 (63), 144 (33), 96 (67), 85 (25), 83 (33), and 70 (12) (Found: M^+, 284.1524; C, 71.8; H, 7.0; N, 9.9%. $C_{17}H_{20}N_2O_2$ requires *M*, 284.1524; C, 71.8; H, 7.0; N, 9.8%).

3-(*Dimethylaminomethyl*)*indol*-2-*yl* 1,2,5,6-*Tetrahydro*-1-*methylpyridin*-4-*yl Ketone Ethylene Acetal* (11g).—The acetal (11f) (873 mg) was treated with formaldehyde (0.52 ml, 30%), dimethylamine (0.75 ml, 30%), and acetic acid (6 ml) in dioxan (16 ml) for 1 d at 56 °C. The solvent was evaporated off and the residue basified and extracted with ethyl acetate to give the *Mannich acetal* (11g) (1.05 g) as crystals, m.p. 166—167 °C; $\lambda_{max.}$ 221, 274, 282, and 290 nm (log ε 4.45, 3.92, 3.94, and 3.86); $\nu_{max.}$ 3 460s cm^{-1}; τ 1.7 (1 H, br s, NH), 4.25 (1 H, m, HC=C), 6.0 (4 H, br s, OCH_2-CH_2O), 6.3 (2 H, s, CH_2NMe_2), 7.65 (3 H, s, piperideine NMe), and 7.70 (6 H, s, NMe_2); *m/e* 341 (28%, M^+), 297 (85), 296 (100), 295 (64), 255 (33), 254 (43), 253 (36), 252 (47), 251 (41), 224 (76), 223 (71), 211 (38), 210 (47), 209 (35), 203 (33), 202 (36), 96 (76), 94 (79), 58 (66), and 44 (92) (Found: M^+, 341.2102; C, 70.3; H, 7.9; N, 12.3%. $C_{20}H_{27}N_3O_2$ requires *M*, 341.2103; C, 70.4; H, 7.9; N, 12.3%).

3-(*Dimethylaminomethyl*)*indol*-2-*yl* 1,2,5,6-*Tetrahydro*-1-*methylpyridin*-4-*yl Ketone* (11h).—The acetal (11g) (459 mg) was hydrolysed with hydrochloric acid (2N, 8 ml) at 60 °C overnight. Basification and extraction with ethyl acetate gave the *ketone* (11h) (377 mg) as a solid, m.p. 135—136 °C (from EtOAc); $\lambda_{max.}$ 217, 243, and 321 nm (log ε 4.44, 4.19, and 4.15); $\nu_{max.}$ 3 460m and 1 630s cm^{-1}; τ 0.84 (1 H, br s,

NH), 3.48 (1 H, m, HC=C), 6.28 (2 H, s, CH_2NMe_2), 7.64 (3 H, s, NMe), and 7.86 (6 H, s, NMe_2); *m/e* 297 (13%, M^+), 252 (27), 251 (29), 210 (23), 96 (52), 94 (23), 91 (14), 81 (20), 71 (33), 58 (31), and 57 (42) (Found: M^+, 297.1847; C, 72.9; H, 7.8; N, 13.8%. $C_{18}H_{23}N_3O$ requires *M*, 297.1841; C, 72.7; H, 7.7; N, 14.1%).

7-(*Dimethylaminomethyl*)-1,5-*methano*-2-*methyl*-2,3,4,5-*tetrahydro*[1,3]*diazocino*[1,8-a]*indole*-6(1H)-*one* (13).—The ketone (11h) (108 mg) was treated with aqueous acetic acid (50%, 2 ml) at reflux for 1.5 h. The solution was made basic and extracted with ethyl acetate to give a gum (105 mg), which was purified by p.l.c. [$CHCl_3$–NEt_3 (96 : 4)] to give the *cyclic ketone* (13) (85 mg) as an amorphous solid; $\lambda_{max.}$ 212, 241, and 320 nm (log ε 4.45, 4.35, and 4.40); $\nu_{max.}$ 1 670s cm^{-1}; τ 4.5 (1 H, m, NCHN), 5.86, 5.94 (2 H, s × d, *J* 12 Hz, CH_2NMe_2), and 7.6 (9 H, s, piperidine NMe and CH_2NMe_2; *m/e* 297 (28%, M^+), 252 (43), 251 (40), 227 (24), 223 (10), 96 (100), 94 (28), and 44 (30) (Found: M^+ spectrometry, 297.1838; $C_{18}H_{23}N_3O$ requires *M*, 297.1841).

1-*Methylindol*-2-*yl Pyridin*-4-*yl Ketone Ethylene Acetal* (12b).—The acetal (12a) [11] (4.34 g) was deprotonated with sodium hydride (0.75 g) in DMF (60 ml) at room temperature for 0.5 h; a yellow solid precipitated. Methyl iodide (2.46 g) was added quickly and the solution stirred for 3 min. Dilution with water was followed by extraction with ether to give the N^a-*methyl acetal* (12b) (4.31 g) as brownish crystals, m.p. 136—137 °C (from EtOH); $\lambda_{max.}$ 225, 268, 285 (sh), and 285 (sh) nm; τ 1.35 (2 H, d, *J* 7 Hz, pyridine α-H), 3.40 (1 H, s, indole 3-H), 5.82 (4 H, br s, OCH_2CH_2O), and 6.40 (3 H, s, indole NMe); *m/e* 280 (35%, M^+), 202 (100), 158 (34), 150 (11), 106 (19), and 89 (22) (Found: M^+, 280.1212. $C_{17}H_{16}N_2O_2$ requires *M*, 280.1208).

1-*Methylindol*-2-*yl* 1,2,5,6-*Tetrahydro*-1-*methylpyridin*-4-*yl Ketone Ethylene Acetal* (11i).—The acetal (12b) (4.3 g) was reacted with excess of methyl iodide in toluene (100 ml) at reflux for 4 h. The methiodide precipitated and was filtered and used without further purification for the next step, which involved reduction with excess of sodium borohydride in methanol at room temperature for 1 h. The solvent was evaporated and the residue partitioned between water and chloroform to give the N^a-*methylpiperideine acetal* (11i) (4.49 g) as a gum; $\lambda_{max.}$ 224, 265, 282, and 290 (sh) nm; τ 3.35 (1 H, s, indole 3-H), 4.31 (1 H, m, HC=C), 5.95 (4 H, br s, OCH_2CH_2O), 6.27 (3 H, s, indole 1-Me), and 7.62 (3 H, s, piperideine NMe); *m/e* 298 (21%, M^+), 225 (10), 202 (100), 167 (54), 158 (35), 132 (19), and 96 (38) (Found: M^+, 298.1681. $C_{18}H_{22}N_2O_2$ requires *M*, 298.1684).

1-*Methyl*-3-(*dimethylaminomethyl*)*indol*-2-*yl* 1,2,5,6-*Tetrahydro*-1-*methylpyridin*-4-*yl Ketone Ethylene Acetal* (11j).—The acetal (11i) (3.7 g) was reacted with dimethylamine (30%, 30 ml) and formaldehyde (40%, 18 ml) in acetic acid (20 ml) at room temperature for 1 d. The solution was basified and extracted with ethyl acetate to give the *gramine acetal* (11j) (3.83 g) as a gum; $\lambda_{max.}$ 227, 278, 284 (sh), and 295 (sh) nm; τ 4.52 (1 H, m, HC=C), 6.00 (4 H, br s, OCH_2CH_2O), 6.19 (2 H, s, CH_2NMe_2), 6.30 (3 H, s, indole 1-Me), 6.68 (3 H, s, piperideine NMe), and 7.72 (6 H, CH_2NMe_2); *m/e* 355 (41%, M^+), 310 (100), 267 (35), 265 (35), 239 (62), 237 (50), 166 (64), and 94 (44) (Found: M^+, 355.2264. $C_{21}H_{29}N_3O_2$ requires *M*, 355.2260).

1-*Methyl*-3-(*dimethylaminomethyl*)*indol*-2-*yl* 1,2,5,6-*Tetrahydro*-1-*methylpyridin*-4-*yl Ketone* (11k).—The acetal (11j) (197 mg) was hydrolysed with hydrochloric acid (5N, 4 ml) at room temperature for 3 h. The product was extracted with ethyl acetate after basification, giving the *gramine ketone* (11k) (161 mg) as a pale yellow gum; $\tau_{max.}$ 243 (sh), 313, and 350 (sh) nm; $\nu_{max.}$ 1 635s, cm^{-1}; τ 3.50 (1 H, m, HC=C), 6.30 (3 H, s, indole 1-Me), 6.42 (2 H, s, CH_2NMe_2), 7.59 (3 H, s, piperideine NMe), and 7.85 (6 H, s, CH_2NMe_2); *m/e* 311 (1.5%, M^+), 310 (2.5), 267 (26), 249 (43), 224 (74), 209 (21), 144 (26), 96 (26), 94 (30), and 58 (100) (Found: M^+, 311.1992. $C_{19}H_{25}N_3O$ requires *M*, 311.1998).

2,3,4,6-*Tetrahydro*-5-*hydroxy*-2,6-*dimethyl*-1H-*pyrido*-[4,3-b]*carbazole* (9a) *and the* O-*Acetate* (9b).—The ketone (11k) (265 mg, freshly prepared) was reacted in thoroughly deoxygenated aqueous acetic acid (50%, 60 ml) at reflux for 20 h under nitrogen. Two routes could then be followed.

(*a*) The cooled solution was basified with potassium bicarbonate and extracted with ethyl acetate to give a black gum (130 mg) which was purified by p.l.c. [MeOH–EtOAc (7 : 3)] to give the *phenol* (9a) (27 mg) as white crystals, m.p. 67—70 °C [from EtOAc–MeOH (1 : 1)], $\lambda_{max.}$ 229, 248, 256, 264 (sh), 286 (sh), 297, 337, and 349 nm; $\tau_{max.}$ (EtOH–NaOH), 228, 269, 295 (sh), and 355 nm; $\nu_{max.}$ 3 580 cm^{-1}; τ 2.05 (1 H, d, 10-H), 2.5—2.93 (4 H, m, ArH), 5.88 (3 H, s, 6-Me), 6.26 (2 H, s, $ArCH_2N$), 6.95—7.30 (4 H, m, $ArCH_2CH_2N$), and 7.30 (3 H, s, 2-Me); *m/e* 266 (78%, M^+), 265 (83), 249 (24), and 223 (100) (Found: M^+, 266.1421. $C_{17}H_{18}N_2O$ requires *M*, 266.1419).

(*b*) The solvent was evaporated off and the residue reacted with acetic anhydride (20 ml) at room temperature for 0.5 h. The acetic anhydride was evaporated off and the residue partitioned between ethyl acetate and aqueous potassium bicarbonate to give, after p.l.c. [EtOAc–Me_2CO (1 : 1)] the *phenolic acetate* (66 mg), m.p. 166—167 °C (from EtOAc); $\lambda_{max.}$ 240, 250 (sh), 263, 286 (sh), 296, 317, 330, and 345 nm (log ε 4.52, 4.36, 4.25, 3.86, 4.16, 3.56, 3.60, and 3.56); $\nu_{max.}$ 1 770s cm^{-1}; τ 2.05 (1 H, d, *J* 6 Hz, ArH), 2.40 (1 H, s, 11-H), 2.45—3.00 (3 H, m, ArH), 6.11 (3 H, s, 6-Me), 6.23 (2 H, s, CH_2NMe), 7.00—7.30 (4 H, m, $ArCH_2CH_2N$), 7.50 (3 H, s, 2-Me), and 7.57 (3 H, s, OCOMe); *m/e* 308 (75%, M^+), 307 (70), 265 (66), 254 (65), 249 (33), 223 (100), 211 (41), 149) 30), and 96 (54) (Found: M^+, 308.1521. $C_{19}H_{20}N_2O_2$ requires *M*, 308.1525).

2-*Methoxymethylindol*-3-*yl*(*pyridin*-4-*yl*)*methanol* (14a).—2-Methoxymethylindole [14] (2.2 g) was reacted with pyridine-4-carbaldehyde (1.78 g) in methanol (11 ml) and aqueous sodium hydroxide (30%, 4.47 ml) at 0 °C, and then at room temperature for 1.5 h. A precipitate was formed, which was filtered and thoroughly washed with water to give the *alcohol* (14a) (3.6 g); $\lambda_{max.}$ 230, 267 (sh), 276 (sh), 283 and 291 (sh) nm; $\nu_{max.}$ 3 500—2 500 (br) cm^{-1}; τ [$(CD_3)_2SO$] —1.00 (1 H, br s, NH), 1.56 (2 H, d, *J* 7 Hz, pyridine α-H), 3.92 (1 H, d, *J* 3 Hz, CHOH), 4.31 (1 H, br s, OH), 5.27 and 5.38 (2 H, 2 × d, *J* 13 Hz, CH_2OMe), and 6.63 (3 H, s, OMe); *m/e* 268 (72%, M^+), 235 (15), 219 (60), 158 (100), 130 (40), 106 (20), and 78 (13) (Found: M^+, 268.1214. $C_{16}H_{16}N_2O_2$ requires *M*, 268.1211).

2-*Methoxymethylindol*-3-*yl*-(1,2,5,6-*tetrahydro*-1-*methylpyridin*-4-*yl*)*methanol* (15a).—The alcohol (14a) (1.0 g) was quaternised with methyl iodide (15 ml) in ethyl acetate (100 ml) at reflux for 4 h. The methiodide (1.5 g), m.p. 173—174 °C, was collected and reduced without purification, with an excess of sodium borohydride in methanol for 0.5 h. The solvent was evaporated off and the residue partitioned between ethyl acetate and water to give the *piperideine alcohol* (15a) (720 mg) as a foam; $\lambda_{max.}$ 276 (sh), 283, and 290 (sh) nm (log ε 3.84, 3.85, and 3.79); $\nu_{max.}$ 3 585m and 3 445m cm^{-1}; τ 1.36 (1 H, br s, NH), 4.10 (1 H, m, HC=C), 4.60 (1 H, s, CHOH), 4.39 (2 H, s, CH_2OMe), 6.62 (3 H, s,

OMe), and 7.67 (3 H, s, NMe); *m/e* 286 (10%, M^+), 268 (33), 253 (10), 235 (33), 194 (40), 193 (35), 161 (41), 158 (42), 130 (66), and 96 (100) (Found: M^+, 286.1677. $C_{17}H_{22}N_2O_2$ requires *M*, 286.1681).

2-Methoxymethylindol-3-yl 1,2,5,6-Tetrahydro-1-methylpyridin-4-yl Ketone (15b).—The alcohol (15a) (720 mg) was oxidised with manganese dioxide (3.6 g) in dry chloroform (100 ml) at room temperature with stirring for 4 h. The oxidant was filtered off, and the filtrate refiltered through magnesium sulphate and evaporated to give the ketone (660 mg) as a gum; $\lambda_{max.}$ 248, 270 (sh), and 315 nm; $\nu_{max.}$ 3 440s and 1 620 cm^{-1}; τ 0.88 (1 H, br s, NH), 3.50 (1 H, m, HC=C), 5.40 (2 H, s, CH_2OMe), 6.50 (3 H, s, OMe), and 7.53 (3 H, s, piperideine NMe); *m/e* 284 (13%, M^+), 253 (35), 210 (20), 195 (14), 156 (12), 128 (13), 96 (100), and 94 (60) (Found: M^+, 284.1530. $C_{17}H_{20}N_2O_2$ requires *M*, 284.1525).

Indol-3-yl(pyridin-4-yl)methanol (14b).—Indole (27 g) in methanol (100 ml) was treated with aqueous sodium hydroxide (10.8N, 25 ml) and then, at 0 °C, dropwise with pyridine-4-carbaldehyde (26 g). After 1 h at 0 °C and a further 3 h at room temperature, the precipitate was filtered off to afford the *alcohol* (14b) (52 g), m.p. 184—185 °C (from MeOH); $\lambda_{max.}$ 220, 265, 279, and 288 nm (log ε 4.32, 3.72, 3.73, and 3.65); $\nu_{max.}$ 3 440s and 3 400—2 800 (br) cm^{-1}; τ [$(CD_3)_2SO$] 0.93 (1 H, br s, NH), 1.50 (2 H, br s, pyridine α-H), 2.83 (1 H, s, indole 2-H), 4.00 (1 H, s, OH), and 4.20 (1 H, C*H*OH); *m/e* 224 (100%, M^+), 206 (54), 205 (50), 178 (10), 146 (63), 118 (54), 106 (18), and 79 (22) (Found: M^+, 224.0948. $C_{14}H_{12}N_2O$ requires *M*, 224.0950).

Indol-3-yl-(1,2,5,6-tetrahydro-1-methylpyridin-4-yl)-methanol (15c).—To the pyridyl alcohol (14b) [11] (7.15 g) suspended in ethyl acetate (150 ml) was added methyl iodide (37 g). After refluxing for 4 h, the solvent was decanted off and the residue crystallised from ethyl acetate to give the methiodide (9.7 g), m.p. 147—148 °C. The methiodide (6.5 g) was reduced with sodium borohydride (excess) in methanol (100 ml) at room temperature for 0.5 h. The solvent was evaporated off and the residue partitioned between water and ethyl acetate to give the *piperideine alcohol* (15c) (3.6 g), m.p. 133—135 °C (from EtOAc); $\lambda_{max.}$ 247 (sh), 280, and 289 nm; $\nu_{max.}$ 3 590 (br) and 3 480s cm^{-1}; τ 1.13 (1 H, s, NH), 2.91 (1 H, s, indole 2-H), 4.10 (1 H, m, HC=C), 4.60 (1 H, s, C*H*OH), and 7.68 (3 H, s, NMe); *m/e* 242 (M^+, 18%), 224 (58), and 96 (100) (Found: M^+, 242.1415. $C_{15}H_{18}N_2O$ requires *M*, 242.1419).

[1-(Dimethylaminomethyl)indol-3-yl]-1,2,5,6-tetrahydro-1-methylpyridin-4-ylmethanol (15d).—The alcohol (15c) (208 mg) was treated with aqueous formaldehyde (40%, 0.3 ml) dimethylamine (25%, 0.7 ml), and acetic acid (2.4 mg) in dioxan (5 ml) at room temperature for 2 d. The mixture was diluted with water and extracted with ethyl acetate after basification. The crude product (191 mg) was purified by p.l.c. [MeOH–$CHCl_3$–NEt_3 (10 : 90 : 4)]; $\lambda_{max.}$ 279 (sh), 282 (sh), and 293 (sh) nm; $\nu_{max.}$ 3 590 cm^{-1}; τ 2.89 (1 H, s, indole 2-H), 4.08 (1 H, m, HC=C), 5.32 (2 H, s, CH_2NMe_2), 7.62 (3 H, s, piperideine NMe), and 7.70 (6 H, s, CH_2NMe_2); *m/e* 299 (4%, M^+), 144 (16), 130 (23), and 96 (100) (Found: M^+, 299.1996. $C_{18}H_{25}N_3O$ requires *M*, 299.1998).

[2-(Dimethylaminomethyl)indol-3-yl]pyridin-4-ylmethanol (14c).—Isogramine [16] (550 mg) was treated with pyridine-4-carbaldehyde (370 mg) in methanol (3 ml) containing aqueous sodium hydroxide (30%, 0.1 ml) for 4 h at room temperature. Dilution with water and extraction with ethyl acetate gave the *pyridine alcohol* (14c) (800 mg) as an oil; $\lambda_{max.}$ 224, 267 (sh), 275 (sh), 282, and 291 nm (log ε 4.3, 3.74, 3.77, 3.78, and 3.70); $\nu_{max.}$ 3 450s and 3 500—2 600 (br) cm^{-1}; τ 1.28 (1 H, br s, NH), 1.50 (2 H, d, *J* 6 Hz, pyridine α-H), 3.83 (1 H, s, C*H*OH), 6.49 and 6.77 (2 H, s × d, *J* 14 Hz, CH_2NMe_2), and 7.72 (6 H, s, NMe_2); *m/e* 279 (50%, M^+), 265 (23), 264 (42), 263 (27), 250 (55), 249 (27), 233 (25), 207 (90), 193 (19), 158 (55), 130 (38), 106 (51), 103 (11), 78 (33), and 58 (100) (Found: M^+, 281.1522. $C_{17}H_{19}N_3O$ requires *M*, 281.1528).

2-(Dimethylaminomethyl)indol-3-yl Pyridin-4-yl Ketone (14d).—The alcohol (14c) (0.7 g) was oxidised with manganese dioxide (3.5 g) in chloroform (100 ml) at room temperature for 2.5 h. The oxidant was filtered off, and the filtrate passed through magnesium sulphate and then evaporated to give the *pyridyl ketone* (14d) (0.5 g), m.p. 199—200 °C (from MeOH); $\lambda_{max.}$ 269 and 325 nm (log ε 3.92 and 3.75); $\nu_{max.}$ 3 400s and 1 625s cm^{-1}; τ 1.18 (2 H, d, *J* 7 Hz, pyridine α-H), 2.41 (2 H, d, *J* 7 Hz, pyridine β-H), 6.10 (2 H, s, CH_2NMe_2), and 7.60 (6 H, s, NMe_2); *m/e* 279 (61%, M^+), 264 (39), 250 (22), 236 (51), 235 (100), 219 (22), 207 (41), 173 (21), 158 (35), 137 (34), 130 (35),123 (55), 122 (46), 108 (56), 106 (45), 78 (38), and 58 (67) (Found: M^+, 279.1370. $C_{17}H_{17}N_3O$ requires *M*, 279.1372).

2-(Dimethylaminomethyl)indol-3-yl 1,2,5,6-Tetrahydro-1-methylpyridin-4-yl Ketone (15e) *and* *[2-(Dimethylaminomethyl)indol-3-yl]-1,2,5,6-tetrahydro-1-methylpyridin-4-ylmethanol* (15f).—The ketone (14d) (325 mg) in methanolic hydrochloric acid (0.1N, 11.6 ml) was treated with methyl iodide (8.3 ml) and then refluxed for 5.5 h. The solvent was removed and the residue crystallised from methanol to give the hydrochloride methiodide (0.5 g), m.p. 235—236 °C.

The double salt (0.5 g) was reduced with sodium borohydride (excess) in methanol (50 ml) for 5 min at room temperature. The mixture was diluted with water and extracted with ethyl acetate to give a mixture (263 mg), of which a sample (30 mg) was separated by p.l.c. [MeOH–$CHCl_3$ (4 : 1)], to give the *alcohol* (15f) (6 mg) and the *ketone* (15e) (12 mg), both as gums.

The alcohol had $\lambda_{max.}$ 275 (sh), 282, and 291 nm; $\nu_{max.}$ 3 460s cm^{-1}; τ 1.25 (1 H, br s, NH), 4.10 (1 H, m, HC=C), 4.60 (1 H, br s, C*H*OH), 6.25 and 6.90 (2 H, 2 × d, *J* 12 Hz, CH_2NMe_2), 7.72 (3 H, s, piperideine NMe), and 7.80 (6 H, s, NMe_2); *m/e* 299 (3%, M^+), 281 (20), 254 (14), 253 (18), 236 (22), 210 (12), 195 (12), 194 (29), 193 (19), 180 (14), 167 (15), 158 (42), 144 (12), 130 (39), 96 (100), 94 (35), and 58 (99) (Found: M^+, 299.1996. $C_{18}H_{25}N_3O$ requires *M*, 299.1998).

The ketone had $\lambda_{max.}$ 250, 278 (sh), and 314 nm (log ε 3.88, 3.80 and 3.65); $\nu_{max.}$ 3 420s and 1 620s cm^{-1}; 0.56 (1 H, br s, NH), 3.50 (1 H, m, HC=C), 6.12 (s, CH_2NMe_2), 7.53 (3 H, s, piperideine NMe), and 7.64 (6 H, s, NMe_2); *m/e* 297 (4%, M^+), 279 (11), 265 (10), 264 (20), 253 (12), 236 (15), 235 (26), 210 (14), 173 (15), 158 (24), 130 (39), 96 (19), and 58 (100) (Found: M^+, 297.1841. $C_{18}H_{23}N_3O$ requires *M*, 297.1841).

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