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3-(Tetrahydropyridinyl)indoles

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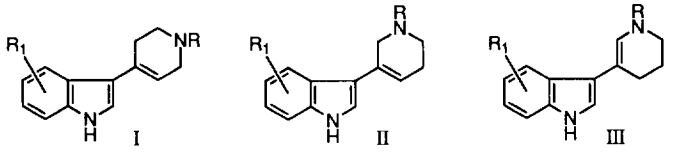
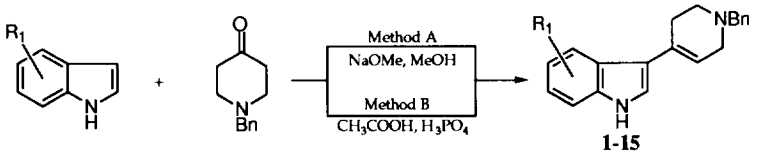
Abstract: Substituted indoles have been condensed with *N*-benzyl-4-piperidone to give 3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles. Under basic conditions, 5-, 6-, and 7- (but not 4-) substituted indoles give reasonable yields of the product. For condensation with 4-substituted indoles, acidic conditions and the presence of at least a 3-fold excess of *N*-benzyl-4-piperidone are beneficial. Under basic conditions, the condensation of indoles with *N*-substituted-3-piperidones is highly regioselective with the regioselectivity depending on the nature of the *N*-substituent. 4-Substituted indoles do not react with *N*-substituted-3-piperidones under basic conditions but give a single product under acidic conditions.

3-(Tetrahydropyridinyl)indoles are of interest because of their potent action at serotonin and dopamine receptors.[1-3] They can also serve as useful building blocks for the synthesis of more complicated molecules. For this latter reason we wished to synthesise a variety of tetrahydropyridinylindoles (THPI) of structures (I-III) shown below.



The general route for the preparation of THPI's is the condensation of an indole with the appropriate piperidone under either acidic or basic conditions. The synthesis of type I molecules has been investigated in some detail.[1, 3-7] Following this general approach, we prepared a number of novel THPI's with mono, di, tri-substituted indoles and excess *N*-benzyl-4-piperidone using sodium methoxide in methanol (Scheme 1, method A). This procedure proved to be efficient for 5-, 6-, and 7-substituted indoles and gave the corresponding THPI's in good yields (Table 1).

Scheme 1

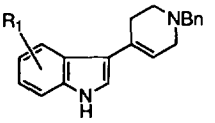


1-15

However, indoles with substituents in the 4-position appeared to be much less reactive under these conditions. They either failed to react or required much longer reaction times and only low yields of the products

were obtained. In view of this, the reaction of 4-substituted indoles and *N*-benzyl-4-piperidones was examined under acidic conditions, using different proportions of *N*-benzyl-4-piperidone (Scheme 1, method B).[7] We found the reaction to be rapid and high yielding when a three molar excess or more of *N*-benzyl-4-piperidone was used; with lower proportions, a mixture was usually obtained. One exception to this was 4,5,6-trimethoxyindole which gave a mixture of at least two products, the desired compound **17** and a considerable amount of the bisindolylpiperidine **17a**.[8]

Table 1. 3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)indoles

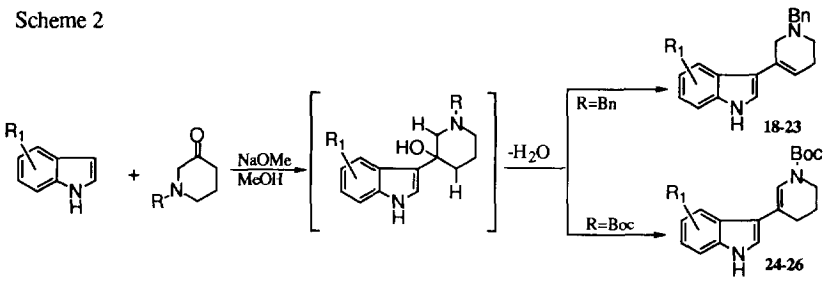


Compound [a]	R_1	Method [b]	Reaction time (hours)	%Yield [c]	M.P. °C
1	H	A	24	81	164-165
2	4-Cl	A	24	10	
		B	20	89	Oil
3	4-COOH	A	24	0	
		B	24	79 [d]	247-249
4	4-CH_3O	A	48	45	
		B	3	72	163-165
5	5-CH_3	A	6	85	159-161
6	5-CH_3O	A	20	85	170-172
7	5-BnO	A	3	97	110-111
8	5-COOH	A	8	95	194-197
9	5-morpholinocarbonyl	A	26	55	85(dec.)
10	6-Cl	A	6	79	208-210
11	6-CN	A	20	95	162-164
12	6-COOH	A	24	85 [e]	330(dec.)
13	6-CH_3O	A	5	95	216(dec.)
14	7-CH_3O	A	24	85	169-171
15	5,6-$(CH_3O)_2$	A	5	98	162-163
16	5,6-methylenedioxy	A	3	96	182-183
17	4,5,6-$(CH_3O)_3$	A	24	0	
		B	2	37 [f]	244-247

[a] ^1H NMR and MS analysis were consistent with the above structures, [b] Method A: $NaOCH_3$, CH_3OH, Method B: CH_3COOH, H_3PO_4, [c] Yields are based on the HPLC analysis of the reaction mixture at 254 nm, [d] K salt, [e] Na salt, [f] HCl salt.

The synthesis of compounds of type II and particularly its enamine isomer III has been less thoroughly investigated. The only reported route for the preparation of type III compounds involves a lengthy synthesis starting from 1-tosyl indole.[9] We therefore wished to develop a more suitable general synthesis of II and III. The mechanism for the reaction of *N*-substituted-3-piperidones under basic conditions is thought to proceed via the indolyl-3-piperidinol (Scheme 2).

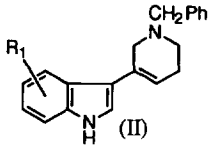
Scheme 2



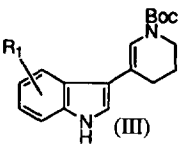
It is known that the regiochemistry of enolization of α-amino ketones depends on the nature of the nitrogen substituent.[9, 10] Enolization occurs towards the nitrogen atom with an electron withdrawing substituent and away from the nitrogen atom with an electron donating substituent. By analogy, it was envisaged that the regiochemistry of the dehydration step (Scheme 2) might also depend on the nature of the nitrogen substituent.

We accordingly condensed various indoles, under basic conditions, with *N*-substituted-3-piperidones, containing substituents with different electronic properties. As predicted, when the *N*-substituent was an electron donating group (e.g. CH_2Ph) only the allylamine isomer II (**18-23**) was produced while, with an electron withdrawing group (e.g. COOtBu), the enamine isomer III (**24-26**) was generated exclusively.

Table 2. Base-catalysed Formation of 3-(Tetrahydropyridinyl)indoles



(II)



(III)

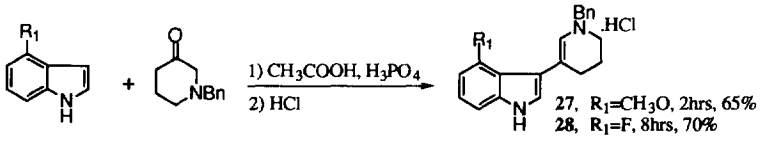
Compound [a]	R_1	Structure	Reaction time (hours)	Yield[b]	M.P. °C
18	H	II	20	73	127-128
19	5-CH_3O	II	20	80	141-142
20	5-BnO	II	20	78	oil
21	5-COOH	II	18	80	150-153
22	6-CH_3O	II	6	71	156-157
23	5,6-di-CH_3O	II	5	83	160-161
24	H	III	48	63	N.D.[c]
25	5-CH_3O	III	48	59	N.D.[c]
26	5-F	III	72	69	N.D.[c]

[a] ^1H NMR and MS analysis were consistent with the above structures, [b] Yields are based on the HPLC analysis of the reaction mixture at 254nm, [c] Not crystalline.

However, the reaction did not proceed with 4-fluoro, 4-chloro, 4-methoxy, 4-benzyloxy-indole or indole-4-carboxylic acid. It therefore appears that 4-substituted indoles, irrespective of the electronic nature of the substituents, are unreactive under basic conditions.

Under acidic conditions, 4-methoxyindole or 4-fluoroindole afforded single products in good yields, which were isolated and characterised as the enamine isomer III (**27, 28**, Scheme 3). This was unexpected, in view of the fact that condensation of other substituted indoles with *N*-substituted-3-piperidones under acidic conditions had

Scheme 3. Acid-catalysed Formation of 3-(1-Benzyl-1,2,3,4-tetrahydropyridin-5-yl)indoles



27, R_1=CH_3O, 2hrs, 65%
28, R_1=F, 8hrs, 70%

been reported to be nonregioselective [7] and also in our hands 5-methoxyindole and indole itself gave a complex mixture of products. The results could indicate that 4-substituents have an influence on the regioselectivity of this reaction, which appears to be independent of the electronic properties of the substituents.

In summary, a number of novel 3-(tetrahydropyridinyl)indoles with structures of types **I** and **II** have been prepared by two different methods depending on the position of the indole substituents. It has also been possible for the first time to synthesise enamines of type **III** structure in a single step. The reactions yielding the enamines

work efficiently and give moderate to high yields of the products. Unlike the existing method, our approach does not require air sensitive reagents and there is no necessity to protect and deprotect the indole nitrogen. Thus, the methods described here provide a simple and convenient approach to the synthesis of these molecules.

Experimental Section

All starting materials are available commercially and were used without further purification. Melting points (mp) were carried out in open capillaries on an Electrothermal digital melting point apparatus (IA9100) and are uncorrected. The ^{1}H NMR spectra were recorded on a Bruker AM 400 WB (400 MHz) and are reported in ppm downfield of internal tetramethylsilane (TMS) unless otherwise indicated. Mass spectra were run by Fast Atom Bombardment on a VG Analytical ZAB-SE double focussing magnetic sector mass spectrometer and are reported as a combination of high and low resolution data. Elemental analyses were performed by the microanalytical section of the Chemistry Department, University College London and were within ±0.4% of the calculated values. Analytical high pressure liquid chromatography (HPLC) was performed on a Beckman System Gold with UV detection at 254 nm and a Nacarai Cosmosil 5C18AR packed column (6 x 150 mm) with a flow rate of 1 ml/min. Column chromatography was carried out on Merck silica gel 60 (70-230 mesh ASTM).

General procedure for the condensation of indoles and piperidones under basic conditions (Method A): A solution of indole (0.26 mol), piperidone (0.77 mol, 3 equiv.) and sodium methoxide (1.54 mol, 6 equiv.) in anhydrous methanol (500 ml) was refluxed under argon for the time indicated. The reaction mixture was cooled and methanol evaporated under reduced pressure until precipitation occurred. The pure product was collected by filtration, washed with cold methanol and dried under vacuum. In cases where precipitation did not occur, the reaction mixture was taken to dryness, the inorganic materials were removed by aqueous extraction and the residue was purified by column chromatography. For compounds **24-26**, the reaction mixture was made slightly acidic with acetic acid, concentrated under reduced pressure and partitioned between water and ethyl acetate. The residue from the organic extract was purified by column chromatography (ethyl acetate:*n*-hexane, 1:4).

3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (1). ^{1}H NMR ($CDCl_3$): 2.60 (2H, br s), 2.78 (2H, t), 3.27 (2H, m), 3.68 (2H, s), 6.20 (1H, m), 7.13 (1H, t), 7.15 (1H, d), 7.19 (1H, t), 7.28 (1H, d), 7.33-7.40 (5H, m), 7.88 (1H, d), 8.16 (1H, br s). MS: 289.1700 (MH^+, $C_{20}H_{21}N_2$ requires 289.1705), 288, 287, 211,197, 182, 170. *Anal.* Calcd. for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.09; H, 6.97; N, 9.62.

5-Methyl-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (5). ^{1}H NMR ($CDCl_3$): 2.44 (3H, s), 2.56 (2H, br s), 2.73 (2H, t), 3.24 (2H, m), 3.67 (2H, s), 6.17 (1H, m), 7.00 (1H, m), 7.06 (1H, d), 7.21 (1H, d), 7.27-7.42 (5H, m), 7.66 (1H, s), 8.11 (1H, br s). MS: 302.1780 (MH^+, $C_{22}H_{22}N_2$ requires 302.1783), 301, 300, 287, 225, 211, 196. *Anal.* Calcd. for $C_{21}H_{22}N_2$: C, 83.40; H, 7.33; N, 9.26. Found: C, 83.31; H, 7.40; N, 9.26.

5-Methoxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (6). ^{1}H NMR ($CDCl_3$): 2.59 (2H, m), 2.75 (2H, t), 3.36 (2H, m), 3.67 (2H, s), 3.84 (3H, s), 6.12 (1H, m), 6.85 (1H, m), 7.12 (1H, d), 7.237.42 (7H, m), 8.01 (1H, br s). MS: 319.1816 (MH^+, $C_{21}H_{23}N_2O$ requires 319.1810), 318, 317, 303, 241, 227, 212, 146. *Anal.* Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.16; H, 6.96; N, 8.69.

5-Benzyloxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (7). ^{1}H NMR ($CDCl_3$): 2.58 (2H, m), 2.75 (2H, t), 3.24 (2H, m), 3.67 (2H, s), 5.09 (2H, s), 6.08 (1H, m), 6.93 (1H, m), 7.12 (1H, d),

7.23-7.48 (12H, m), 7.99 (1H, br s). MS: 395.2119 (MH^+, $C_{27}H_{27}N_2O$ requires 395.2123), 394, 393, 303, 211, 196. *Anal.* Calcd. for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 81.98; H, 6.62; N, 6.98.

3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-5-carboxylic acid (8). ^1H NMR (DMSO-d_6, D_2O): 2.66 (2H, br s), 3.02 (2H, br s), 3.45 (2H, br s), 3.95 (2H, s), 6.18 (1H, br s), 7.35 (1H, d), 7.43 (6H, s), 7.75 (1H, d), 8.45 (1H, s). MS: 333.1600 (MH^+, $C_{21}H_{21}N_2O_2$ requires 333.1603), 332, 331, 241, 196.

5-Morpholinocarbonyl-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (9). ^1H NMR ($CDCl_3$): 2.58 (2H, br s), 2.74 (2H, t), 3.24 (2H, m), 3.62-3.81 (10H, m), 6.18 (1H, m), 7.20 (1H, m), 7.25-7.45 (7H, m), 7.59 (1H, s), 8.23 (1H, br s). MS: 402.2188 (MH^+, $C_{25}H_{28}N_3O_2$ requires 402.2182), 401, 400, 329, 315, 212, 196.

6-Chloro-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (10). ^1H NMR (DMSO-d_6): 2.50 (2H, m), 2.64 (2H, t), 3.09 (2H, br s), 3.58 (2H, s), 6.10 (1H, m), 7.02 (1H, m), 7.26-7.37 (6H, m), 7.41 (1H, s), 7.79 (1H, d), 11.24 (1H, br s). MS: 323.1312 (MH^+, $C_{20}H_{20}ClN_2$ requires 323.1315), 322, 321. *Anal.* Calcd. for $C_{20}H_{19}ClN_2$: C, 74.41; H, 5.93; N, 8.68; Cl, 10.98. Found: C, 74.24; H, 5.87; N, 8.54; Cl, 11.26.

6-Cyano-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (11). Recrystallised from diethyl ether. ^1H NMR ($CDCl_3$): 2.55 (2H, m), 2.75 (2H, t), 3.24 (2H, m), 3.68 (2H, s), 6.15 (1H, m), 7.26-7.41 (7H, m), 7.65 (1H, s), 7.90 (1H, d), 8.77 (1H, br s). MS: 314.1653 (MH^+, $C_{21}H_{20}N_3$ requires 314.1657), 313, 312, 236, 222, 207, 195. *Anal.* Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.11; H, 5.98; N, 13.45.

3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-6-carboxylic acid, sodium salt (12). The reaction mixture was partitioned between aqueous Na_2CO_3 and ethyl acetate. The aqueous layer was concentrated in vacuo until crystallisation occurred. ^1H NMR [D_2O, 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt]: 2.47 (2H, br s), 2.63 (2H, t), 3.10 (2H, br s), 3.60 (2H, s), 6.13 (1H, m), 7.34-7.44 (6H, m), 7.70 (1H, d), 7.86 (1H, d), 8.02 (1H, s). MS: 354.1349 (MNa^+, $C_{21}H_{19}N_2O_2Na$ requires 354.1344), 353, 331, 329, 212.

6-Methoxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (13). ^1H NMR ($CDCl_3$): 2.58 (2H, m), 2.74 (2H, t), 3.23 (2H, m), 3.66 (2H, s), 3.84 (3H, s), 6.17 (1H, m), 6.79 (1H, m), 6.84 (1H, d), 7.05 (1H, d), 7.27-7.42 (5H, m),7.74 (1H, d), 7.91 (1H, br s). MS: 319.1815 (MH^+, $C_{21}H_{23}N_2O$ requires 319.1810), 318, 317, 289, 241, 227, 212, 184, 146. *Anal.* Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.06; H, 6.97; N, 8.67.

7-Methoxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (14). ^1H NMR ($CDCl_3$): 2.59 (2H, m), 2.74 (2H, t), 3.23 (2H, m), 3.66 (2H, s), 3.94 (3H, s), 6.18 (1H, m), 6.65 (1H, d), 7.04 (1H, t), 7.11 (1H, d), 7.26-7.42 (5H, m),7.47 (1H, d), 8.31 (1H, br s). MS: 319.1816 (MH^+, $C_{21}H_{23}N_2O$ requires 319.1810), 318, 317, 289, 241, 227, 212, 184, 146. *Anal.* Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.23; H, 6.96; N, 8.71.

5,6-Dimethoxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (15). ^1H NMR ($CDCl_3$): 2.59 (2H, m), 2.75 (2H, t), 3.24 (2H, m), 3.67 (2H, s), 3.90 (3H, s), 3.92 (3H, s), 6.11 (1H, m), 6.86 (1H, s),

7.03 (1H, d), 7.30 (1H, s), 7.27-7.42 (5H, m), 7.94 (1H, br s). MS: 349.1914 (MH^+, $C_{22}H_{25}N_2O_2$ requires 349.1916), 348, 347, 333, 271, 257, 242, 230, 198, 172.

5,6-Methylenedioxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (16). ^1H NMR ($CDCl_3$): 2.56 (2H, m), 2.73 (2H, t), 3.22 (2H, m), 3.66 (2H, s), 5.93 (2H, s), 6.06 (1H, m), 6.80 (1H, s), 7.02 (1H, d), 7.26 (1H, s), 7.27-7.42 (5H, m), 7.95 (1H, br s). MS: 333.1598 (MH^+, $C_{21}H_{21}N_2O_2$ requires 333.1603), 331, 241, 174, 161. *Anal.* Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.88; H, 6.06; N, 8.43. Found: C, 75.83; H, 6.03; N, 8.34.

3-(1-Benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (18). Recrystallised from ethyl acetate/n-hexane. ^1H NMR ($CDCl_3$): 2.40 (2H, m), 2.68 (2H, t), 3.38 (2H, d), 3.71 (2H, s), 6.25 (1H, m), 7.03 (1H, d), 7.13 (1H, t), 7.18 (1H, t), 7.27 (1H, d), 7.31-7.42 (5H, m), 7.85 (1H, d), 8.18 (1H, br s). MS: 289.1700 (MH^+, $C_{20}H_{21}N_2$ requires 289.1705 found), 288, 287, 211, 197, 169.

5-Methoxy-3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (19). ^1H NMR ($CDCl_3$): 2.41 (2H, m), 2.69 (2H, t), 3.37 (2H, d), 3.71 (2H, s), 3.84 (3H, s), 6.18 (1H, m), 6.85 (1H, m), 7.03 (1H, d), 7.21-7.42 (7H, m), 8.06 (1H, br s). MS: 319.1815 (MH^+, $C_{21}H_{23}N_2O$ requires 319.1810 found), 318, 317, 241, 226, 212, 184. *Anal.* Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.03; H, 6.88; N, 8.62.

5-Benzyloxy-3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (20). ^1H NMR ($CDCl_3$): 2.40 (2H, m), 2.69 (2H, t), 3.36 (2H, br s), 3.71 (2H, s), 5.08 (2H, s), 6.14 (1H, m), 6.93 (1H, m), 7.04 (1H, d), 7.17-7.51 (12H, m), 8.02 (1H, br s). MS: 395.2120 (MH^+, $C_{27}H_{27}N_2O$ requires 395.2123), 394, 393, 317, 303, 288, 211.

3-(1-Benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole-5-carboxylic acid (21). ^1H NMR [DMSO-d_6, D_2O, 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid, sodium salt]: 2.62 (2H, m), 3.30 (2H, t), 3.95 (2H, s), 4.35 (2H, s), 6.45 (1H, m), 7.38 (1H, s), 7.45 (1H, d), 7.51-7.59 (5H, m), 7.80 (1H, s), 8.46 (1H, s). MS: 333.1600 (MH^+, $C_{21}H_{21}N_2O_2$ requires 333.1603), 289, 255, 241, 226.

6-Methoxy-3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (22). ^1H NMR ($CDCl_3$): 2.40 (2H, m), 2.67 (2H, t), 3.36 (2H, m), 3.70 (2H, s), 3.83 (3H, s), 6.23 (1H, m), 6.80 (1H, m), 6.83 (1H, d), 6.96 (1H, d), 7.26-7.43 (5H, m), 7.72 (1H, d), 7.93 (1H, br s). MS: 319.1815 (MH^+, $C_{21}H_{23}N_2O$ requires 319.1810), 318, 317, 241, 226, 211, 184. *Anal.* Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.03; H, 6.97; N, 8.64.

5,6-Dimethoxy-3-(1-benzyl-1,2,5,6-tetrahydropyridin-3-yl)-1H-indole (23). ^1H NMR ($CDCl_3$): 2.42 (2H, m), 2.69 (2H, t), 3.36 (2H, m), 3.71 (2H, s), 3.90 (3H, s), 3.91 (3H, s), 6.17 (1H, m), 6.85 (1H, s), 6.95 (1H, d), 7.24 (1H, s), 7.26-7.43 (5H, m), 7.88 (1H, br s). MS: 349.1912 (MH^+, $C_{22}H_{25}N_2O_2$ requires 349.1916),348, 347, 333, 317, 302, 289, 255, 241, 229. *Anal.* Calcd. for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.64; H, 6.89; N, 7.86.

3-(1-t-Butoxycarbonyl-1,2,3,4-tetrahydropyridin-5-yl)-1H-indole (24). ^1H NMR ($CDCl_3$): 1.52 (9H, s), 1.99 (2H, m), 2.47 (2H, br s), 3.67 (2H, br s), 7.12-7.23 (3H, m), 7.33-7.36 (2H, m), 7.84 (1H, d), 8.19 (1H, m). MS: 298.1676 (M^+, $C_{18}H_{22}N_2O_2$ requires 298.1681), 242, 197.

5-Methoxy-3-(1-t-butoxycarbonyl-1,2,3,4-tetrahydropyridin-5-yl)-1H-indole (25). ^{1}H NMR ($CDCl_3$): 1.53 (9H, s), 2.01 (2H, m), 2.48 (2H, m), 3.67 (2H, br s), 3.87 (3H, s), 6.88 (1H, m), 7.08 (1H, d), 7.25 (1H, m), 7.33 (1H, d), 7.37 (1H, br s), 8.01 (1H, br s). MS: 328.1783 (M^+, $C_{19}H_{24}N_2O_3$ requires 328.1787), 272, 227, 196.

5-Fluoro-3-(1-t-butoxycarbonyl-1,2,3,4-tetrahydropyridin-5-yl)-1H-indole (26). ^{1}H NMR ($CDCl_3$): 1.54 (9H, s), 2.01 (2H, m), 2.46 (2H, m), 3.66 (2H, m), 6.95 (2H, m), 7.17 (1H, s), 7.24-7.32 (2H, m), 8.01 (1H, br s). MS: 316.1583 (M^+, $C_{18}H_{21}FN_2O_2$ requires 316.1587), 260, 215.

General procedure for the condensation of indoles and piperidones under acidic conditions (Method B): The appropriate indole (0.02 mol) was dissolved in acetic acid (60 ml) and heated to 90 °C. A solution of *N*-benzyl-4-piperidone (0.06 mol) in 2M phosphoric acid (20 ml) was added and the mixture maintained at 90 °C for three hours. The mixture was cooled to 0-5 °C and added dropwise with stirring to cold conc. ammonia (300 ml). The precipitate was collected by filtration and washed with cold water. The crude products **2, 17, 27, 28** were purified by column chromatography. Compounds **17, 27, 28** were converted to the corresponding hydrochloride salts on treatment with anhydrous hydrogen chloride in ether.

4-Chloro-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (2). ^{1}H NMR ($CDCl_3$): 2.46 (2H, t), 2.75 (2H, m), 3.19 (2H, m), 3.68 (2H, s), 5.70 (1H, m), 7.03-7.09 (3H, m), 7.22-7.44 (6H, m), 8.57 (1H, br s). MS: 323.1312 (MH^+, $C_{20}H_{20}ClN_2$ requires 323.1315), 322, 321, 287, 245, 231, 212.

3-(1-Benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole-4-carboxylic acid, potassium salt (3). The reaction mixture was partitioned between aqueous K_2CO_3 and ethyl acetate. The aqueous layer was concentrated in vacuo until crystallisation occurred. ^{1}H NMR (DMSO-d_6, D_2O, 3-[trimethylsilyl)prop-ionic-2,2,3,3-d_4 acid, sodium salt]: 2.64 (2H, m), 3.23 (2H, br s), 3.65 (2H, br s), 4.19 (2H, s), 5.61 (1H, m), 7.10-7.18 (2H, m), 7.40-7.53 (7H, m). MS: 370.1089 (MK^+, $C_{21}H_{19}N_2O_2K$ requires 370.1084), 333, 241.

4-Methoxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole (4). The product was obtained pure by stirring the crude residue in small amounts of methanol and collecting the white precipitate by filtration. ^{1}H NMR (DMSO-d_6): 2.63 (2H, t), 3.03 (2H, d), 3.34 (2H, m), 3.58 (2H, s), 3.80 (3H, s), 5.80 (1H, m), 6.47 (1H, d), 6.93-6.99 (2H, m), 7.09 (1H, d), 7.26-7.36 (5H, m), 9.05 (1H, br s). MS: 319.1815 (MH^+, $C_{21}H_{23}N_2O$ requires 319.1810), 318, 317, 289, 241, 227, 212, 184.

4,5,6-Trimethoxy-3-(1-benzyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indole hydrochloride (17). ^{1}H NMR ($CDCl_3$, free base): 2.71 (2H, m), 2.97 (2H, t), 3.39 (2H, m), 3.87 (9H, s), 3.91 (2H, s), 5.92 (1H, m), 6.64 (1H, s), 6.94 (1H, s), 7.26-7.45 (5H, m), 8.11 (1H, br s). MS: 379.2025 (MH^+, $C_{23}H_{27}N_2O_3$ requires 379.2022), 378, 287, 260. This reaction also furnished **17a** [8] as a light brown powder in 21% yield. mp 154-157 °C. ^{1}H NMR ($CDCl_3$, free base): 2.58 (4H, m), 2.70 (4H, m), 3.44 (3H, s), 3.53 (2H, s), 3.79 (6H, s), 3.83 (3H, s), 3.85 (3H, s), 4.06 (3H, s), 6.38 (1H, s), 6.44 (1H, s), 6.63 (1H, s), 6.91 (1H, s), 7.24-7.35 (5H, m), 8.13 (1H, br s), 8.22 (1H, br s). MS: 586.2917 (MH^+, $C_{34}H_{40}N_3O_6$ requires 586.2910), 585, 570, 379.

4-Methoxy-3-(1-benzyl-1,2,3,4-tetrahydropyridin-5-yl)-1H-indole hydrochloride (27). ^{1}H NMR ($CDCl_3$, free base): 1.99 (2H, m), 2.44 (2H, br s), 2.96 (2H, br s), 3.58 (3H, s), 4.11 (2H, br s), 6.47 (1H, d), 6.54 (1H, br s), 6.89 (1H, br s), 6.96 (1H, d), 7.08 (1H, t), 7.20-7.39 (5H, m), 7.92 (1H, br s). MS: 319.1815 (MH^+, $C_{21}H_{23}N_2O$ requires 319.1810), 227.

4-Fluoro-3-(1-benzyl-1,2,3,4-tetrahydropyridin-5-yl)-1H-indole hydrochloride (28). ^{1}H NMR ($CDCl_3$, free base): 2.00 (2H, m), 2.43 (2H, br s), 2.94 (2H, m), 4.11 (2H, m), 6.64 (1H, m), 6.74 (1H, m), 6.99 (1H, m), 7.11 (1H, m), 7.21-7.34 (6H, m), 8.01 (1H, br s). MS: 307.1615 (MH^+, $C_{20}H_{20}FN_2$ requires 307.1611), 306.

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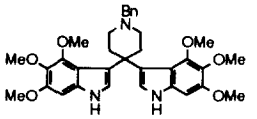
References and Notes

1. Taylor, W. T.; Nikam, S. S.; Lambert, G.; Martin, A. R. and Nelson, D. L., *Mol. Pharmacol.*, **1988**, 34: 42-53.
2. Agarwal, A.; Pearson, P. P.; Taylor, E. W.; Li, H. B.; Dahlgren, T.; Herslof, M.; Yang, Y.; Lambert, G.; Nelson, D. L.; Regan, J. W. and Martin A. R., *J. Med. Chem.*, **1993**, 36, 4006-4014.
3. Guillaume J.; Dumont, C.; Laurent, J. and Nedelec, L., *Eur. J. Med. Chem.*, **1987**, 22, 33-43.
4. Gasc, J-C.; Nedelec L.; Humbert, D. and Boaventura A-M., **1988**, *German Patent*, 3742124.
5. Oxford, A. W.; Coates, I. H. and Butina D., **1989**, *European Patent*, 0303 506.
6. Oxford, A. W.; Coates, I. H. and Butina D., **1989**, *European Patent*, 0303 507.
7. Freter, K., *J. Org. Chem.*, **1975**, 40, 2525-2529.
8. The bisindolylpiperidine,  **17a**, was isolated as a minor product.
9. Zheng, Q.; Yang, Y., and Martin A. R., *Tetrahedron Lett.*, **1993**, 34, 2235-2238.
10. Garst, M. E.; Bonfiglio, J. N.; Grudoski, D. A. and Marks, J., *Tetrahedron Lett.*, **1978**, 2671-2674.

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