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Studies on the Synthesis of the Indole Alkaloids Ngouniensine and Epingouniensine

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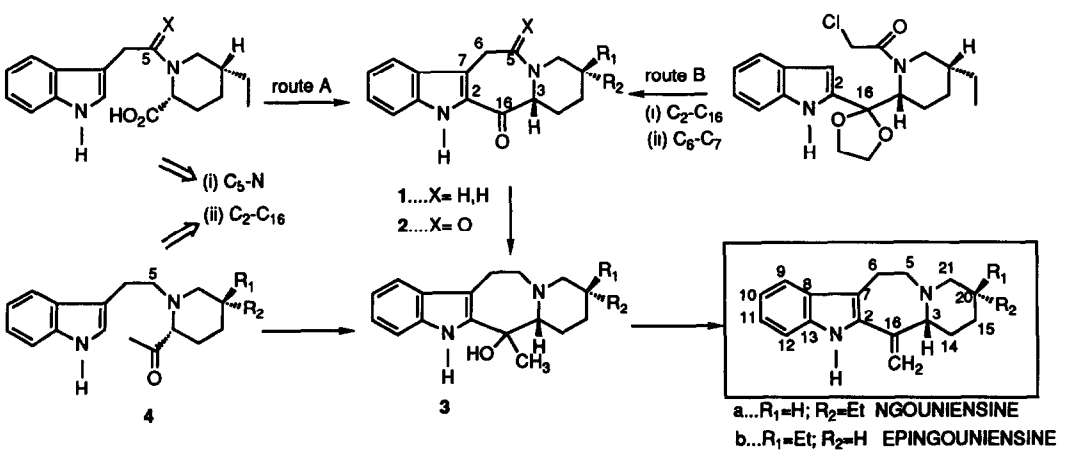
Abstract: Tetracyclic keto lactam **2a** has been synthesized by acylation of a mixture of esters **5**, followed by saponification and further cyclization. Due to the presence of an exocyclic amide carbonyl group, epimerization at C-3 occurs to give the most stable *cis* relative configuration. *Trans* acetylpiperidine **4b** has been prepared in five steps from pyridinium salt **9**. Attempted direct cyclization of **4b** to epingouniensine failed.

We have previously reported[1,2] two synthetic routes to ngouniensine and epingouniensine, two indole alkaloids isolated from *Strychnos ngouniensis* [3] having a rather unusual structure.[4] Both syntheses converge to the tetracyclic ketones **1**, from which the introduction of the exocyclic methylene substituent was effected by way of the tertiary alcohols **3**, either directly by drastic treatment with $POCl_3$ (very low yield) or by base-promoted elimination of the corresponding mesylate (45% yield).

The two routes developed for the preparation of the key 2-acylindole intermediates **1** involve the successive formation of either C_5-N^5 and C_2-C_{16} (route A)[1] or C_2-C_{16} and C_6-C_7 bonds (route B,[2] Scheme 1). In both cases, nearly equimolecular diastereomeric mixtures (series a and b) were obtained because of the easy epimerization at C-3.



SCHEME 1

Two points of the former approach merit further study: i) the effect of an exocyclic amide carbonyl group at C-5 upon the stereochemistry of the resulting cyclized product **2**, and ii) an alternative mode of forming the C_2-C_{16} bond, by acid cyclization of an appropriate 2-acetylpiperidine **4**, so that, under the acidic reaction conditions, the initially formed alcohol **3** might undergo dehydration to the target alkaloids.

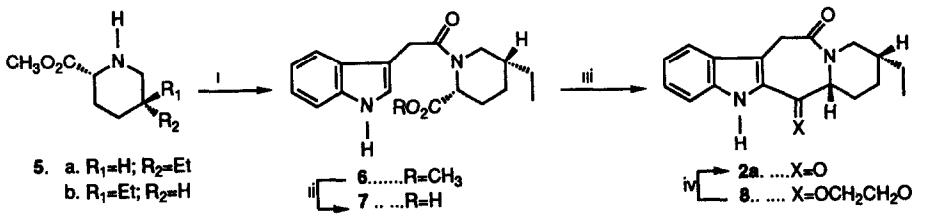
RESULTS AND DISCUSSION

The effect of an exocyclic amide carbonyl group.

Condensation of a *cis-trans* mixture of piperidines **5** with 3-indolylacetyl chloride afforded ester **6** (stereochemistry not determined) in 83% yield. Further alkaline hydrolysis of **6** gave the required amido acid **7**[6] in 70 % yield. Only the *cis* isomer was obtained, thus pointing out that, under the basic conditions, an epimerization at the stereocenter α to the carbonyl group had occurred. The *cis* relationship between the substituents at the piperidine 2- and 5-positions was evident from the multiplicity and coupling constants of 2-H (d, J = 4 Hz) and 6-Hax (dd, J = 12 and 12 Hz). These data also indicated the axial disposition of the carboxy substituent at C-2. Finally, PPA cyclization of **7** led to the expected *cis* keto lactam **2a**, but in only 17% yield. The *cis* relative configuration of tetracycle **2a** and the axial disposition of the bulkier piperidine α–substituent (C-16) was again deduced from the multiplicity and coupling constants of piperidine 2-H and 6-Hax.

This stereochemical result contrasts with the observed epimerization at C-3 during the formation of the related tetracyclic ketones **1**, which lack the lactam carbonyl group, by a similar cyclization (route A, Scheme 1).[1] However, due to the lower yield of the cyclization here reported (17%) as compared with the yield of **1** (53%), the present route was not further explored.

The same *cis* keto lactam **2a** was obtained by hydrolysis of *cis* acetal lactam **8**, which had been previously obtained by chloroacetamide cyclization (route B, Scheme 1).[2] The stereoselective preparation of *cis* **2a** by two alternative procedures indicates that the presence of an exocyclic *N*-acyl group favours the *cis* configuration in 2,5-disubstituted piperidines.[7]



Reagents and Conditions: (i) 3-indolylacetyl chloride, Et_3N, $CHCl_3$, rt, 5 h; (ii) 5% NaOH, MeOH, reflux, 2 h: (iii) PPA, 80°C, 30 min; (iv) 1% HCl, MeOH, reflux, 4 h.

SCHEME 2

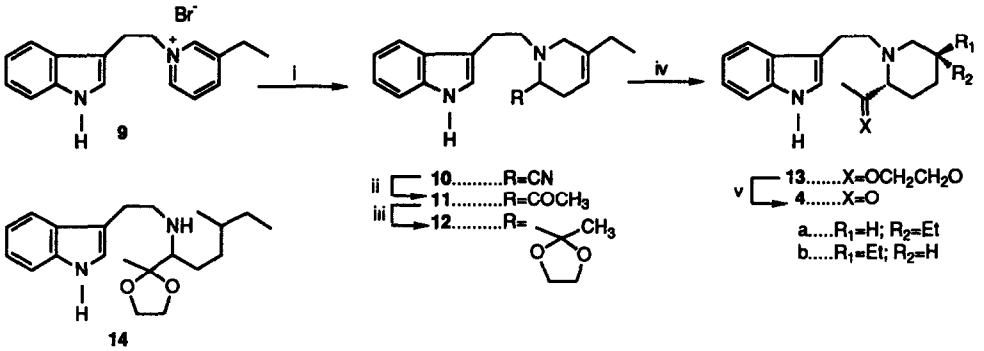
Attempted cyclization of acetylpiperidine 4.

The required 2-acetylpiperidine **4** was prepared from the pyridinium salt **9** through the reaction sequence depicted in Scheme 3. Reductive cyanation[8] of **9** by means of sodium borohydride in the presence of an excess of

cyanide ions gave 2-cyanotetrahydropyridine **10**, which was converted to acetyltetrahydropyridine **11** by treatment with methyl-lithium followed by acid hydrolysis .[9]

Previous attempts indicated that the carbonyl group had to be protected before the hydrogenation step. Thus, **11** was converted to the corresponding ethylene acetal **12** and then hydrogenated to give (47% yield) a 4:1 diastereomeric mixture of piperidines **13a** and **13b**. The secondary amine **14** was obtained as by product. Its formation can be rationalized by considering that hydrogenolysis of the allylic carbon-nitrogen bond occurs prior to the hydrogenation of the carbon-carbon double bond.[10] Finally, acid hydrolysis of piperidines **13a,b** afforded the required 2-acetylpiperidine **4b** in 74% yield. Clearly under the acidic conditions epimerization at the ketone α–position, to give the most stable *trans* 2,5-relationship, had occurred.

Cis-trans isomers **13a** and **13b** were easily distinguishable by ^{13}C-NMR. Thus, all piperidine carbons in the *cis* isomer **13a** are shifted upfield, as compared with **13b**, due to the existence of an axial substituent, either at C-2 or at C-5. On the other hand, the *trans* diequatorial disposition of the piperidine substituents in **13b** and **4b** was confirmed from the multiplicity and coupling constants of 2-H and 6-Hax in the ^{1}H-NMR spectra.



Reagents and Conditions: (i) $NaBH_4$; NaCN, ether-H_2O, rt, 3 h; (ii) CH_3Li, THF, rt, 30 min; then 1 N H_2SO_4, rt, 7 h; (iii) $(CH_2OH)_2$, TsOH, benzene, reflux, 20 h; (iv) H_2-PtO_2, EtOH, rt, 24 h; (v) 10% HCl, THF, 60 °C, 8 h.

SCHEME 3

Unfortunately, attempts (*p*-toluenesulfonic acid, chloroform, reflux or boron trifluoride-etherate, 65 °C) to cyclize acetylpiperidine **4b** resulted in failure, and only polymeric materials were recovered. Probably, under the acidic reaction conditions, the initially formed alcohol **3** (Scheme 1) undergoes dehydration to give an unstable aminovinylindole instead of the exocyclic methylene substituent. The same reason could account for the low yield in the $POCl_3$ promoted dehydration of **3**[1] This result is in contrast with the success of similar acid-induced cyclizations in the context of the synthesis of uleine-type systems,[11] in which the endocyclic dehydration does not occur on structural grounds.

EXPERIMENTAL PART

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Perkin-Elmer R-24B (60 MHz) instrument or on a Varian XL-200 spectrometer. ^{13}C-NMR spectra were measured with a Varian XL-200 spectrometer. Unless otherwise noted NMR spectra were recorded in $CDCl_3$, and chemical shifts are expressed in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer and only noteworthy absorptions (reciprocal centimeters) are listed. Mass spectra were determined on

a Hewlett-Packard 5930A mass spectrometer. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm), and the spots were located with UV light or iodoplatinate reagent. Prior concentration under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate powder. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Centro de Investigación y Desarrollo (C.S.I.C.), Barcelona.

Methyl 5-Ethyl-1-(3-indolylacetyl)-2-piperidinecarboxylate (6). A solution of 3-indolylacetyl chloride[12] (1.7 g, 8 mmol) in anhydrous chloroform (50 ml) was added dropwise to a stirred solution of piperidines **5a,b**[1] (1.5 g, 8 mmol) and triethylamine (2.2 ml, 16 mmol) in anhydrous chloroform (25 ml). The resulting solution was stirred at room temperature for 5 h and successively washed with 5% hydrochloric acid and 10% aqueous sodium carbonate. The organic extracts were evaporated to give amido ester **6** (2.2 g, 83%). An analytical sample was obtained by column chromatography (AcOEt): IR (NaCl) 3280 (NH), 1730, 1625 (CO); ^{1}H-NMR (60 MHz) 0.6-3.0 (m, 11 H), 3.5 (s, 3 H, OCH_3), 3 7 (s, 2 H, $IndCH_2$), 5.35 (br, 1 H, 2-H), 6.7-7.1 (m, 4 H, indole), 7.4 (m, 1 H, indole 4-H), 8.4 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{24}N_2O_3.2/3H_2O$: C, 67.01; H, 7.50; N, 8.23. Found: C, 67.08; H, 7.66; N, 8.28.

***Cis*-5-Ethyl-1-(3-indolylacetyl)-2-piperidinecarboxylic Acid (7).** A solution of ester **6** (2 g, 6 mmol) in methanol (70 ml) and 5% aqueous sodium hydroxide was refluxed for 2 h. The methanol was removed, and the resulting basic aqueous solution was washed with ether, acidified with 10% hydrochloric acid, and extracted with dichloromethane Evaporation of the dried organic extracts gave a solid residue, which was crystallized from acetone-dichloromethane to give acid **7** (1.3 g, 70%): mp 78-80°C (acetone-dichloromethane); IR (KBr) 3200-3500 (NH, OH), 1580,1720 (CO); ^{1}H-NMR (major rotamer, DMSO-d_6, 200 MHz) 0.67 (t, J = 7 Hz, 3 H, CH_2CH_3), 0.71-1.70 (m, 6 H), 2.10 (dm, J = 12 Hz, 1 H, 3-Heq), 2.70 (dd, J = 12 and 12 Hz, 1 H, 6-Hax), 3.26-3.97 (m, 3 H, $IndCH_2$ and 6-Heq), 5.14 (d, J = 4 Hz, 1 H, 2-H), 6.80-7 38 (m, 4 H, indole), 7.50 (d, J = 7 Hz, 1 H, indole 4-H), 10.80 (br s, 1 H, NH); ^{13}C-NMR ($CDCl_3$-CD_3OD) 10.9 (CH_3CH_2), 26.6 (CH_2CH_3), 26.7 and 27.6 (C-3 and C-4), 31.7 (CH_2CO), 37.9 (C-5), 49.7 (C-6), 52.1 (C-2), 108.1 (indole C-3), 111.5 (indole C-7), 118.4 (indole C-4), 119.3 (indole C-5), 121.9 (indole C-6), 123 0 (indole C-2), 127.1 (indole C-3a), 136 5 (indole C-7a), 172.7 and 173.5 (CO). Anal. Calcd for $C_{18}H_{22}N_2O_3.H_2O$: C, 65.04; H, 7.27; N, 8.42. Found: C, 64.64; H, 7.15; N, 8.61.

***Cis*-9-Ethyl-6,12-dioxo-6,6a,7,8,9,10,12,13-octahydropyrido[1′,2′:1,2]azepino[4,5-*b*]indole (2a). Method A.** A mixture of acid **7** (0.5 g, 1.59 mmol) and excess of PPA was vigorously stirred under nitrogen at 80°C for 30 min. The mixture was cooled, poured into ice-water, basified with concentrated ammonium hydroxide, and extracted with dichloromethane. Evaporation of the organic extracts gave a residue, which was chromatographed (7:3 hexane-chloroform) to give keto lactam **2a** (0.08 g, 17%): mp 207-209°C (acetone-ether); IR (KBr) 3300 (NH), 1650 (CO), ^{1}H-NMR ($CDCl_3$-CD_3OD, 200 MHz) 0.92 (t, J = 7 Hz, 3 H, 18-H), 1.20-1.94 (m, 6 H), 2.12 (dd, J = 13.2 and 11.2 Hz, 1 H, 21-Hax), 2.45 (dm, J = 13 Hz, 1 H, 14-Heq), 4.15 (s, 2 H, 6-H), 4.46 (dd, J = 13 2 and 3.2 Hz, 1 H, 21-Heq), 4.80 (d, J = 5 Hz, 1 H, 3-H), 7.08-7.48 (m, 3 H, indole), 7.62 (d, J = 7 Hz, 1 H, 9-H); ^{13}C-NMR 11.1 (C-18), 22.9 (C-19), 26.7 and 26.9 (C-14 and C-15), 34.8 (C-20), 36.6 (C-6), 46.5 (C-21), 58.5 (C-3), 112.3 (C-12), 119.4 (C-7), 121.0 (C-9 and C-10), 126.6 (C-8), 127.3 (C-11), 130.9 (C-2), 136.9 (C-13), 172.6 (C-5), 187.5 (C-16). Anal. Calcd for $C_{18}H_{20}N_2O_2.1/4C_3H_6O$. C,72 44; H, 6.89; N, 9.01. Found: C, 72.21; H, 6.49; N, 8.70.

Method B. A solution of *cis* acetal **8** (0.1 g, 0.29 mmol) in methanol (20 ml) and 1% hydrochloric acid (10 ml) was refluxed for 4 h. The solvent was removed, and the residue was diluted with water and extracted with dichloromethane. Evaporation of the dried organic extracts gave essentially pure **2a** (40 mg, 46%).

5-Ethyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine-2-carbonitrile (10). Hydrochloric acid (6 N, 2.8 ml) was added dropwise to a stirred solution of sodium cyanide (2 g, 40 mmol) in water (33 ml), layered with ether (66 ml), and kept below 15°C. To the resulting mixture were added the pyridinium bromide **9**[13] (4 g, 12 mmol) and then sodium borohydride (0.54 g, 14.4 mmol) portionwise. The mixture was stirred at room temperature for 13 h, the ether was decanted, and the aqueous layer was extracted with ether. The combined ethereal solutions were washed with 5% aqueous hydrochloric acid, dried, and evaporated to give an oil which was chromatographed. Elution with 8:2 hexane-ethyl acetate gave nitrile **10** (1.5 g, 44%): IR ($CHCl_3$) 3480-3250 (NH), 2220 (CN), 1620 (C=C); ^{1}H-NMR (60 MHz) 1.1 (t, J

= 7 Hz, 3 H, CH_3), 2.0 (c, J = 7 Hz, 2 H, CH_2CH_3), 2.3 and 2.8 (2 m, 8 H, $IndCH_2CH_2N$, pyridine 3- and 6-H), 3.8 (dd, 1 H, pyridine 2-H), 5.35 (br s, 1H, pyridine 4-H), 6.8 (d, J = 2 Hz, 1 H, indole 2-H), 6.9-7.3 (m, 3 H, indole), 7.5 (m, 1 H, indole 4-H), 8.0 (br s, 1 H, NH). The hydrochloride melted at 120-121°C (acetone-ether). Anal. Calcd for $C_{18}H_{22}ClN_3$: C, 68.43; H, 7.02; Cl, 11.23; N, 13.31. Found: C, 68.40; H, 7.22; Cl, 11.39; N, 13.13.

2-Acetyl-5-ethyl-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine (11). A solution of nitrile **10** (1.8 g, 6.4 mmol) in anhydrous THF (20 ml) was slowly added to a solution of methyl-lithium (1.6 M, 11.1 ml, 17.9 mmol) in anhydrous THF (5 ml), and the resulting solution was stirred for 30 min. Subsequently, 1 N aqueous sulfuric acid (23 ml) was added, and the mixture was stirred at room temperature for 7 h. The reaction mixture was poured into a saturated aqueous potassium carbonate solution and extracted with chloroform. Evaporation of the organic extracts afforded an oil, which was chromatographed. Elution with 8:2 hexane-ethyl acetate gave ketone **11** (0.8 g, 46%): mp 98-99°C (ethanol-ether); IR ($CHCl_3$) 3490 (NH), 1710 (CO), 1620 (C=C); ^{1}H-NMR (60 MHz) 0.9 (t, J = 7 Hz, 3H, CH_2CH_3), 1.9 (c, J = 7 Hz, 2 H, CH_2CH_3), 2.1 (s, 3 H, CH_3CO), 2.3 and 2.8 (2 m, 8 H, $IndCH_2CH_2N$, pyridine 3- and 6-H), 3.2 (t, 1 H, pyridine 2-H), 5 3 (br, 1 H, pyridine 4-H), 6.7 (d, J = 2 Hz, 1 H, indole 2-H), 6.8-7.1 (m, 3 H, indole), 7.3 (m, 1 H, indole 4-H), 8.5 (br s, 1 H, NH); ^{13}C-NMR 12.0 (CH_3CH_2), 23.6 (Indole CH_2), 25.6 (CH_2CH_3), 26.5 (CH_3CO), 27.6 (C-3), 52.6 (C-6), 55.5 (NCH_2), 67.6 (C-2), 111.1 (indole C-7), 113.9 (indole C-3), 115.2 (C-4), 118.6 (indole C-4), 119.1 (indole C-5), 121.6 (indole C-6), 121.8 (indole C-2), 127.4 (indole C-3a), 136.2 (indole C-7a), 137.4 (C-5), 210.8 (CO). Anal. Calcd for $C_{19}H_{24}N_2O$: C, 77.00; H, 8.16; N, 9.46. Found: C, 77.03; H, 8.55; N, 9.24.

5-Ethyl-2-(1,1-ethylenedioxyethyl)-1-[2-(3-indolyl)ethyl]-1,2,3,6-tetrahydropyridine (12). A stirred solution of ketone **11** hydrochloride (1.4 g, 4.1 mmol), *p*-toluenesulfonic acid (0.39 g, 2 mmol), and ethylene glycol (12.4 ml) in anhydrous benzene (200 ml) was refluxed for 20 h with removal of water by a Dean-Stark trap. The reaction mixture was poured into aqueous sodium carbonate and extracted with ether. The organic extracts were washed several times with water, dried, and evaporated. The residue was chromatographed (8:2 hexane-ethyl acetate) to give acetal **12** (0.9 g, 64%): IR ($CHCl_3$) 3480 (NH), 1620 (C=C); ^{1}H-NMR (60 MHz) 0.9 (t, J = 7 Hz, 3 H, CH_2CH_3), 1 4 (s, 3 H, CH_3), 1.8 (c, J = 7 Hz, 2 H, CH_2CH_3), 2.0 (m, 2 H, CH_2CH_2N), 2.9 (m, 5 H, Pyridine 2-, 3-, and 6-H), 3.2 (m, 2 H, CH_2CH_2N), 3.8 (s, 4 H, CH_2O), 5.4 (br, 1 H, pyridine 4-H), 6.8 (d, J = 2 Hz, 1 H, indole 2-H), 6.9-7.2 (m, 3 H, indole), 7.4 (m, 1 H, indole 4-H), , 8.1 (br s, 1 H, NH). The hydrochloride melted at 205-207°C (acetone-methanol). Anal. Calcd for $C_{21}H_{29}ClN_2O_2$: C, 66.91, H, 7.75; Cl, 9.40; N, 7.43. Found: C, 66.58; H, 7.67; Cl, 9.41; N, 7.48.

Catalytic Hydrogenation of Acetal 12. A solution of acetal **12** (2.2 g, 6.4 mmol) in absolute ethanol (50 ml) was hydrogenated over PtO_2 (110 mg) at atmospheric pressure for 24 h. The catalyst was filtered off, and the filtrate was evaporated to give an oil, which was chromatographed. Elution with 9:1 hexane-ethyl acetate gave ***cis*-5-ethyl-2-(1,1-ethylenedioxyethyl)-1-[2-(3-indolyl)ethyl]piperidine (13a**, 0.8 g, 37%): IR ($CHCl_3$) 3480 (NH); ^{1}H-NMR (200 MHz) 0.89 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.39 (s, 3 H, CH_3), 1.00-1.80 (m, 7 H), 2.50-3.20 (m, 7 H), 3.97 (s, 4 H, CH_2O), 6 94 (br s, 1 H, indole 2-H), 7.05-7.30 (m, 3 H, indole), 7.60 (d, J = 7 Hz, 1 H, indole 4-H), 8.03 (br s, 1 H, NH); ^{13}C-NMR 11.5 (CH_3CH_2), 20.8 ($IndCH_2$), 22.2 (CH_3C), 24.0 (CH_2CH_3), 26.5 and 27.2 (C-3 and C-4), 32.7 (C-5), 54.6 (NCH_2), 56.5 (C-6), 62.8 (C-2), 64.3 and 66.4 (CH_2O), 111.2 (indole C-7), 111 9 (CH_3C), 114.4 (indole C-3), 118.9 (indole C-4), 119 1 (indole C-5), 121.8 (indole C-6 and C-2), 127.7 (Indole C-3a), 136.4 (indole C-7a); MS, m/e (rel intensity) 341 (M^+, 0.2), 253 (100). The hydrochloride melted at 150-151°C (acetone). Anal. Calcd for $C_{21}H_{31}ClN_2O_2.1/2H_2O$: C, 65.01; H, 8.31; Cl, 9.15; N, 7.22. Found:C, 65.13; H, 8.20; Cl, 8.68; N, 6.97. Further elution with 8:2 hexane-ethyl acetate gave ***trans*-5-ethyl-2-(1,1-ethylenedioxyethyl)-1-[2-(3-indolyl)ethyl]piperidine (13b,** 0.2 g, 10%): ^{1}H-NMR (200 MHz) 0.92 (t, J = 7 Hz, 3 H, CH_3CH_2), 1.00 (m, 4 H), 1.22 (m, 1 H, 4-Hax), 1.38 (s, 3 H, CH_3), 1.90 (m, 2 H), 2.10 (dd, J = 12 and 12 Hz, 1 H, 6-Hax), 2.46 (dd, J = 12 and 3 Hz, 1 H, 2-H), 3.03 (dd, J = 12 and 4 Hz, 1 H, 6-Heq), 2.95-3.16 (2 m, 4 H, $IndCH_2CH_2N$), 3 90 (m, 4 H, CH_2O), 6.92 (d, J = 1.8 Hz, 1 H, indole 2-H), 7.02-7.34 (m, 3 H, indole), 7 60 (dd, J=7 and 1 Hz, 1 H, indole 4-H), 8 05 (br s, 1 H, NH); ^{13}C-NMR 11.4 (CH_3CH_2), 19.8 (CH_3C), 20.5 ($IndCH_2$), 27.0 (CH_2CH_3), 27.4 and 30.9 (C-3 and C-4), 36.8 (C-5), 54.2 (NCH_2), 59.3 (C-6), 63.8 and 64.5 (CH_2O), 66.0 (C-2), 111.1 (indole C-7), 111.9 (CH_3C), 114.9 (indole C-3), 118 9 (indole C-4), 119.0 (indole C-5), 121.6 (indole C-2 and C-6), 127.1 (indole C-3a), 136.3 (indole C-7a). MS, m/e (rel intensity) 341 (M^+, 0.3), 255 (100). Finally, elution with 7:3 hexane-ethyl acetate gave **3-[4-(1,1-**

ethylenedioxyethyl)-7-methyl-3-azanonyl]indole (14, 0.7 g, 33%): IR ($CHCl_3$) 3480 (NH); ^{1}H-NMR (200 MHz) 0 80 (m, 6 H, C*H*$_3$CH and 9-H), 1.29 (s, 3 H, C*H*$_3$C), 0.90-2.00 (m, 8 H), 2.44 (m, 1 H), 2.98 (m, 4 H, 1- and 2-H), 3.80 (m, 4 H, CH_2O), 7.00 (d, J = 2 Hz, 1 H, indole 2-H), 7.06-7.38 (m, 3 H, indole), 7.60 (d, J = 7 Hz, 1 H, indole 4-H), 8.20 (br s, 1 H, NH); ^{13}C-NMR 11.2 (C-9), 19.1 (*C*H$_3$CH), 20.3 (*C*H$_3$C), 25.9 (C-1), 28.2, 29.4, and 34.6 (C-5, C-6, and C-8), 33.8 (C-7), 49.2 (C-2), 64.1 (C-4), 64.5 and 64.4 (CH_2O), 111.2 (indole C-7), 111.9 (CH$_3$*C*), 113.3 (indole C-3), 118.7 (indole C-4), 118.9 (indole C-5), 121.7 (indole C-6), 122.3 (indole C-2), 127.4 (indole C-3a), 136.5 (indole C-7a); MS, m/e (rel intensity) 343 (M^+, 0.3), 257 (100). The hydrochloride melted at 155-156ºC (acetone). Anal. Cacd for $C_{21}H_{33}ClN_2O_2$: C, 66.44; H, 8.23; Cl, 9.49; N, 7.38. Found: C, 66.33; H, 8.38; Cl, 9.40; N, 7.25.

***Trans*-2-Acetyl-5-ethyl-1-[2-(3-indolyl)ethyl]piperidine (4b)**. A solution of acetals **13a,b** (0.8 g, 2 3 mmol) in THF (40 ml) and 10% hydrochloric acid (17 ml) was heated at 60ºC for 8 h. The solvent was removed, and the residue was diluted with water, basified with solid sodium carbonate, and extracted with dichloromethane. Evaporation of the dried organic extracts gave a residue, which was chromatographed. Elution with 2:8 hexane-chloroform gave ketone **4b** (0.52 g, 74%): IR ($CHCl_3$) 3480 (NH), 1720 (CO); ^{1}H-NMR (200 MHz) 0.93 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.20-1.80 (m, 7 H), 1.73 (dd, J = 12 and 11 Hz, 1 H, 6-Hax), 2.10 (s, 3 H, CH_3CO), 2.50 and 2.56 (2 m, 2 H, NCH_2), 2.82 (dd, J = 12 and 3 Hz, 1 H, 6-Heq), 2.97 (m, 2 H, IndCH_2), 3.30 (dm, J = 11 Hz, 1 H, 2-H), 6.93 (d, J = 1.8 Hz, 1 H, indole 2-H), 7.05-7.35 (m, 3 H, indole), 7.56 (dd, J = 7 and 1.8 Hz, 1 H, indole 4-H), 8.35 (br s, 1 H, NH); ^{13}C-NMR 11.4 (*C*H$_3$CH$_2$), 22.3 (Ind*C*H$_2$), 25.6 (CH$_3$*C*O), 27.3 (*C*H$_2$CH$_3$), 29.2 and 30.1 (C-3 and C-4), 37.4 (C-5), 57.7 (C-6 and NCH_2), 74.2 (C-2), 111.3 (indole C-7), 113.6 (indole C-3), 118.6 (indole C-4), 119.0 (indole C-5), 121.7 (indole C-6), 121.9 (indole C-2), 127.5 (indole C-3a), 136.3 (indole C-7a), 212.3 (CO). The picrate melted at 72-73ºC (acetone-ether) Anal. Calcd for $C_{25}H_{29}N_5O_8$: C, 56 90; H, 5.54; N, 13.28. Found: C, 56.75; H, 5.37; N, 13.01.

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