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SYNTHETIC APPLICATIONS OF 2-ARYL-4-PIPERIDONES. VI.[1]

SYNTHESIS OF THE FUNDAMENTAL TETRACYCLIC SKELETON OF ERVITSINE AND ITS 20-DEETHYLIDENE-6,16-DIHYDRO ANALOGUE

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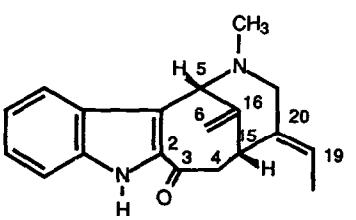
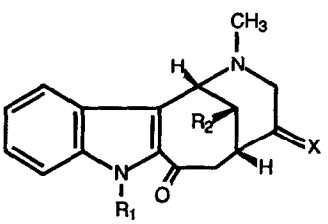
Abstract- The synthesis of the basic tetracyclic skeleton **2** of ervitsine and its 20-deethylidene-6,16-dihydro analogue **4** is reported *via* 2-aryl-*N*-methyl- and 2-aryl-*N*-formylpiperidines which are easily accessible from *N*-formyl- and *N*-methyl-2-(3-indolyl)-4-piperidones **5** , **6**, and **14**.

Ervitsine is a minor indole alkaloid isolated in 1977 from *Pandaca boiteaui*,[2] lacking the characteristic tryptamine bridge present in the greater part of the indole alkaloids but presenting a 2-acylindole unit[3] and two exocyclic ene substituents (C-20 (*E*)-ethylidene and C-16 methylene). The synthetic problems associated with the simultaneous elaboration of a seven membered ring, an (*E*)-ethylidene[4] and a methylene side chain have not been solved to date and no synthesis for ervitsine has yet been described. However, two synthetic approaches to ervitsine analogues (**1-3**) have been reported which involve either intramolecular cyclization of an appropriate 2-cyanopiperidine[5] or the use of 2-cyano-1,2,3,6-tetrahydropyridine chemistry[6,7].



ERVITSINE

(Biogenetic numbering)



1 R_1=CH_3; R_2=CH_3, X=H, H (Ref. 5a)
2 R_1=R_2=H; X=H, H (Ref. 6a)
3 R_1=R_2=H; X=(*Z*)-$CHCH_3$ (Ref. 6b)
4 R_1=H; R_2=CH_3; X=H, H

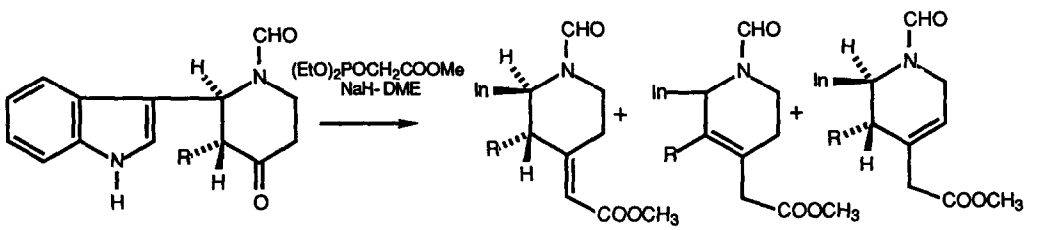
Scheme 1

In the context of our studies on 2-aryl-4-piperidones[8] as potential synthetic intermediates in polycyclic compounds presenting a 2-arylpiperidine moiety[9], we planned to evaluate the effectiveness of these compounds in the synthesis of simplified ervitsine analogues.

In this paper we report a new synthetic entry to the ervitsine skeleton **2** and its 20-deethylidene-6,16-dihydro analogue **4**[10] involving closure of ring C by formation of the C2-C3 bond from appropriate 2-aryl-*N*-methyl- and 2-aryl-*N*-formylpiperidines, having a C-4 methoxycarbonylmethyl substituent, which were prepared, from a convenient 2-(3-indolyl)-4-piperidone previously synthesized.[11]

In order to control the stereochemistry of the catalytic hydrogenation step of the olefins obtained by Wadsworth-Emmons condensation, we turned our attention to piperidones **5**[11] and **6**[11] The *N*-formyl substituent was expected to exert a favorable conformational effect since it is known that the α-substituents in *N*-acylpiperidines are axially oriented to relieve the steric crowding with the amide carbonyl group.[12]

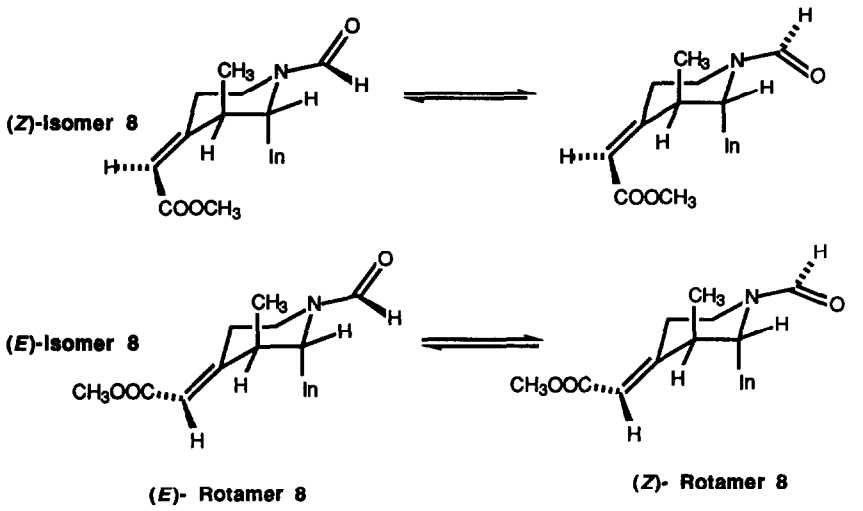
Transformation of *N*-formyl-4-piperidone **5** into tetrahydropyridine **9** was carried out in 45% yield by means of a Wadsworth-Emmons condensation[13] with diethyl methoxycarbonylmethylphosphonate prepared by an Arbuzov reaction,[14] using an excess of sodium hydride as the base.[15] Under these conditions, only the endocyclic olefin **9** was obtained by isomerization of the initially formed exocyclic olefin **7**.[16] The assignment of the position of the double bond for the endocyclic isomer **9** was inferred from the absorption at 1740 cm^{-1} in its IR spectrum, and the presence of two signals at δ 3.12 and 3.15 corresponding to the exocyclic methylene protons of each rotamer. The Δ^3-double bond was unequivocally assigned by a 2D nOe experiment. Thus, nOe signals were observed between the vinylic proton at δ 5.85 and the two signals at δ 6.29 and 5.43, assigned to the C-2 equatorial proton of the major (*Z*)- and the minor (*E*)-rotamers, respectively.



R=H	**5**	**7**	**9**	**11**
$R=CH_3$	**6**	**8**	**10**	**12**

Scheme 2

Alternatively, reaction of piperidine **6** with the corresponding phosphonate gave a mixture of olefins **8**, **10**, and **12** in 9%, 27%, and 63% yields, respectively. The structure of isomer **8** presenting the exocyclic double bond was established by its absorption at 1715 cm^{-1} in the IR spectrum due to the α,β-unsaturated carbonyl group. The ^{1}H-NMR spectrum shows the signals of both (*E*)- and (*Z*)-isomers of C-4 exocyclic double bond, each one split into two signals due to the presence of (*E*)- and (*Z*)-amide rotamers (see Scheme 3). The olefinic proton corresponding to each rotamer of the (*Z*)-isomer **8** was assigned to the doublets at δ 5.86 and 5.87, in the ^{1}H-NMR spectrum, by means of the greater magnitude of the cisoid allylic coupling constant (J= 4 Hz) in comparison with the value of the transoid allylic coupling constant of the doublets at δ 5.90 and 5 96 corresponding to both rotamers of the (*E*)-isomer.[17]



Scheme 3

Moreover, these NMR data imply a preferred conformation with the methyl substituent in a pseudoaxial disposition to avoid the $A^{(1,3)}$ strain.[18] The assignement of the ^{1}H-NMR spectroscopic data of the (*Z*)- and (*E*)-isomers was confirmed by the bidimensional ^{1}H-^{1}H homonuclear correlated spectrum and by 2D nOe spectroscopy (NOESY)

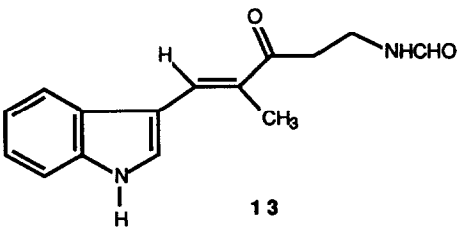
The major products of the Wadsworth-Emmons reaction of piperidone **6** were the endocyclic isomers **10** and **12** derived from the isomerization of the initially obtained isomer **8** In this case, the presence of a methyl substituent at the C-3 position promotes the formation of the Δ^4-tetrahydropyridine, kinetically the more favoured, as the major product

The structural assignments of **10** and **12** were based upon the absortion at 1730 and 1740 cm^{-1}, respectively, in their IR spectra. The major isomer **12** presents two signals at δ 5 46 and 5.86 for the vinylic proton of both rotamers, and a doublet at δ 2.21 for the pseudoaxial C-3 methyl substituent in its ^{1}H-NMR spectrum and two signals at δ 19 0 and 19 9 corresponding to the C-3 methyl group for each rotamer in the ^{13}C-NMR spectrum.

The assignment of (*E*)- and (*Z*)-rotamers were carried out by considering the deshielding effect of the carbonyl group *syn* to an equatorial proton at the α position.[19] Thus, values of δ 4.50 and 3.34 for the C-6 equatorial proton and δ 4.82 and 5.86 for the C-2 equatorial proton were assigned to the (*E*)- and (*Z*)-rotamers, respectively. The pseudoaxial disposition of the indole group was also evidenced by the chemical shift and the coupling constant of protons attached to C-2 and C-3.

When the condensation of **6** with phosphonoacetate took place under a long reaction time, only a 3:7 mixture of endocyclic olefins **10** and **12** was obtained. Moreover, when an excess of sodium hydride was used, the fragmentation product **13** was obtained in 44% yield. The formation of **13** was explained by initial abstraction of the indole NH proton followed by opening of the C2-N bond.

Our next goal was to study the Wadsworth-Emmons condensation with the previously prepared *N*-methyl-4-piperidone **14**[8b], using an excess of phosphonacetate under the conditions described above as being the most suitable for avoiding the isomerization of the double bond. In this case, only products with an exocyclic double bond were obtained in an 8:3 C-3 epimeric mixture due to epimerization of the conjugate enolate of the ester function favoured by the allylic interaction of the exocyclic double bond and the equatorial C-3 methyl substituent

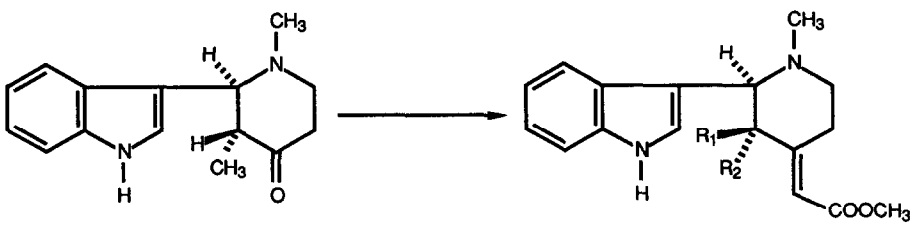


13

Figure 1

The major *trans*-isomer **15** presents the C-3 methyl and indole substituents in an equatorial orientation as has been confirmed by the chemical shift of the methyl group, at δ 0.79 in the ^{1}H-NMR spectrum and by the signal at δ 14.9 in the ^{13}C-NMR spectrum. Also the chemical shift of the doublet at δ 2.94, assigned to the proton at the C-2 position with a coupling constant of 14 Hz is in agreement with a *trans*-diaxial C2-C3 disposition

The minor *cis*-isomer **16** exhibits the methyl group in an axial orientation as evidenced by the magnitude of the chemical shift (δ 0.99), more deshielded than in the equatorial disposition due to the effect of the nitrogen lone pair in a *syn* relationship.[20]



14

15 R_1=H; R_2=CH_3
16 R_1=CH_3; R_2=H

Scheme 4

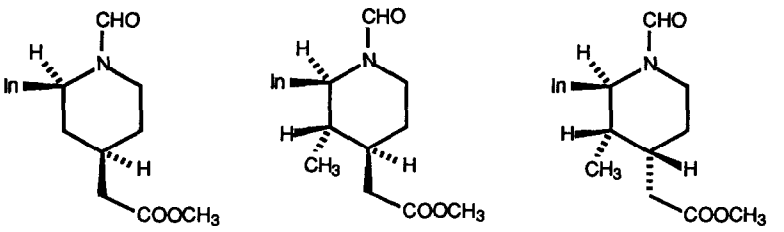
The next step in our synthetic plan was the catalytic hydrogenation of the double bond of olefins **9**, **8**, and **12** to give piperidine-4-acetates **17**, **18**, and **19**, respectively The high stereoselectivity observed was possibly due to the axial disposition of the indole group promoting hydrogen delivery from the less hindered side. As expected, hydrogenation of *N*-formyltetrahydropyridine **9** with Adam's catalyst, in methanol, afforded stereoselectively *N*-formylpiperidine **17** in 95% yield. The preferred conformation of **17**, with two substituents in an equatorial disposition despite the $A^{(1,3)}$ strain of the indole group, was confirmed by NMR spectroscopy. Thus, the chemical shift of the proton at the C-2 position (δ 4.60) and the magnitude of the coupling constants (*J*=12 and 2 4 Hz) are in accordance with an axial orientation.

The equatorial disposition of the (methoxycarbonyl)methyl substituent was evidenced by the chemical shift of the exocyclic methylene at δ 2.32 and 40 7 in its ^{1}H- and ^{13}C-NMR spectra, respectively, and these data are in accordance with those for other piperidine-4-acetates.[6a] The equatorial arrangement of the indole group give rise to the existence of only the (*E*)- rotamer, which was established by the chemical shift at δ 4 66 for the C-6 equatorial proton.

Moreover, catalytic hydrogenation of **8**, having an exocyclic double bond, occurred in high stereoselectivity to give the *cis*-2,4-disubstituted piperidine **18**, due to the large steric effect of the axial indole group. This result contrasts

with those previously described for ethyl *N*-benzyl-3-ethylpiperidine-$\Delta^{4,\alpha}$-acetate and related compounds in which the *cis*-3,4-disubstituted isomer was obtained.[15]

The preferred conformation of piperidine **18** disposes all piperidine substituents in the equatorial position. Thus, the equatorial indole group give rise to the existence of only one (*E*)-rotamer easily identified by the chemical shift of the equatorial C-6 proton. As observed in piperidine **17**, the chemical shifts of the exocyclic methylene carbon (δ 38 9) and methylene protons (δ 2.40) confirm the assigned stereochemistry.



17 **18** **19**

In=3-Indolyl

Scheme 5

When the same hydrogenation process was carried out with the major tetrahydropyridine **12**, a 5:2 epimenc mixture of *cis*- and *trans*-2,4-disubstituted piperidines **18** and **19** was obtained. Both isomers were separated by column chromatography and the *trans*-isomer **19** presents a piperidine conformation with the C-2 and C-3 substituents axially disposed and the acetate chain in an equatorial disposition. The axial indole group gives rise to the existence of two rotamers clearly observed by NMR spectroscopy.

In the *cis*-isomer **18**, suitable for the next cyclization step, three C-substituents are in an equatorial orientation and the C-methyl carbon appears at δ 16.5, more deshielded than the same methyl in **19** (Δδ 4 5 ppm) due to the non-existence of the "γ-gauche" effect.

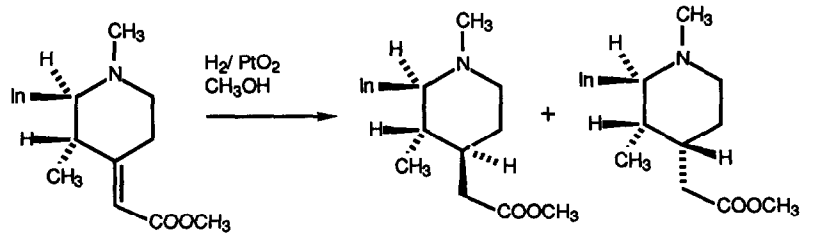
The attempted hydrogenation of the tetrasubstituted olefin **10** under drastic experimental conditions (70 atm, 80°C, 60 h) in dioxane or glacial acetic acid gave the starting material **10** or the *N*-acetyl derivative, respectively.

Catalytic hydrogenation of the *N*-methylpiperidines **15** and **16**, which have the indole group in an equatorial disposition, is mainly influenced by the C-3 methyl substituent. For compound **16**, having the C-3 methyl group in an axial disposition, piperidine **22** was stereoselectively obtained, while the hydrogenation of **15** an equimolecular mixture of C-4 epimers **20** and **21** was obtained.

The *trans* relationship of the C-2 and C-3 substituents in both isomers **20** and **21** was corroborated by the chemical shift of the axial C-2 proton (δ ~3.1) and by the coupling constant of 10 Hz, which it is characteristic of a *trans* diaxial orientation between the C-2 and C-3 protons. The axial disposition of the acetate chain of piperidine **21** was inferred by ^{1}H-NMR spectroscopy and showed signals at δ 2.20 and 2.60 for the two protons of the exocyclic methylene group. In contrast, piperidine **20** showed only one signal at δ~2.4 for the methylene protons

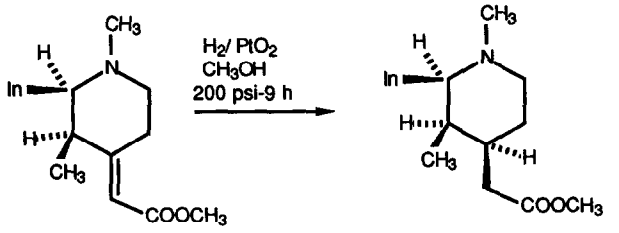
Catalytic hydrogenation of the *cis*-isomer **16** was effected in the presence of Adam's catalyst at 200 psi to afford the piperidine **22** stereoselectively, which presents the C-2, C-3 and C-4 substituents in a syn relationship. In this case,

the C-2 methine proton (δ 3.46) appears as a broad signal in accordance with a virtual coupling promoted by the axial methyl group. The ^{13}C-NMR spectrum shows a chemical shift (δ~8.1) for this carbon at a higher field than for the one of the piperidine **20** as expected for a "γ-gauche" effect. The side chain methylene group presents a chemical shift (δ 2.13) characteristic of an equatorial orientation in accordance with the shielding effect observed for an axial methyl group in the α-position compared to the 3-demethyl analogue (δ 2.55).



15 **20** **21**

In= 3-Indolyl



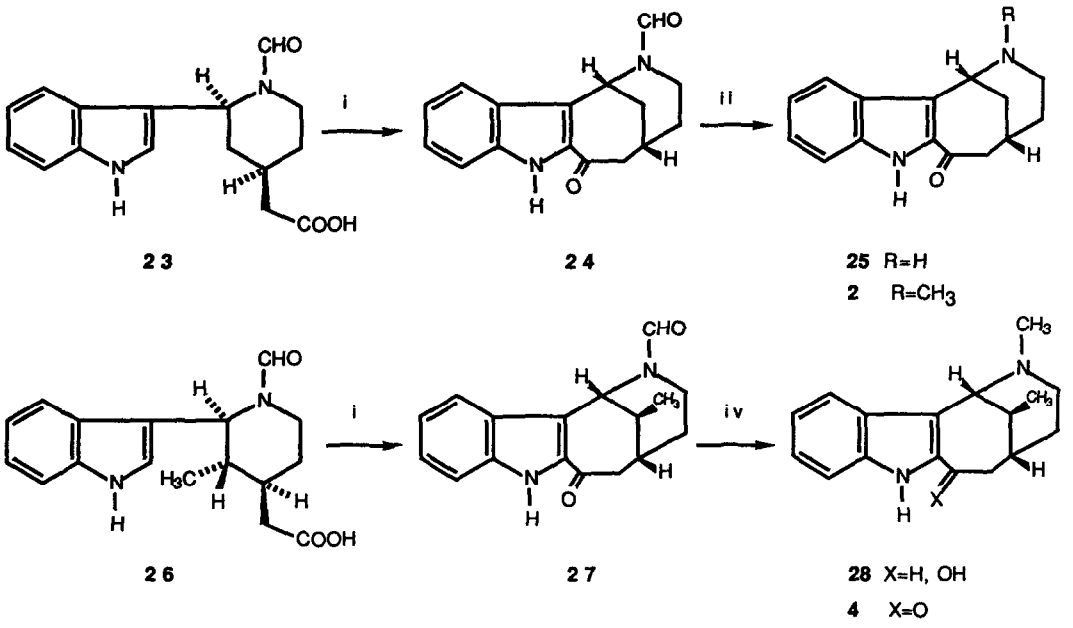
16 **22**

Scheme 6

Finally, hydrolysis of the *N*-methylpiperidines **20** and **21** was carried out with barium hydroxide solution in dioxane-water and the resulting aminoacids were used directly , without purification, in the cyclisation step. Moreover, *N*-formyl substituted esters **17** and **18** were transformed into acids **23** and **26**, respectively, by treatment with 1*N* sodium hydroxide-dioxane at room temperature.

The Friedel-Crafts cyclisation of *N*-formylpiperidine **23** with PPA afforded the *N*-formylderivative **24** as a 3 1 mixture of (*Z*)- and (*E*)-rotamers in low yield. Hydrolysis of the amide function with sodium hydroxide in water-methanol followed by alkylation with methyl iodide gave the basic tetracyclic framework of ervitsine.

The ^{13}C- and ^{1}H-NMR spectra of the tetracyclic compound **24** clearly differentiate the two rotamers. Thus, in the major (*Z*)-rotamer the signal of the equatorial methine proton adjacent to the indole nucleus (δ 6 35) appears at a lower field with respect to that of the (*E*)-rotamer (δ 5.40) Those data reflect the deshielding effect promoted by the amide carbonyl group. In the compound **25** the C-1 methine proton appeared as a doublet of doublets (*J*=6 and 2 Hz) shielded (δ 4 86) due to the absence of the amide function and in the *N*-methyl analogue **2** as a doublet of doublets at δ 4.77.



Reagents: i) PPA, 100 °C, 15 min. ii) 30% NaOH, EtOH, Δ, 2 h. iii) CH_3I, acetone, dry K_2CO_3, r.t., 15 min. iv) $LiAlH_4$, THF, Δ, 6 h. v) MnO_2, $CHCl_3$, r.t., 2 h.

Scheme 7

Similarly, cyclisation of the *N*-formyl derivative **26** with PPA afforded the tetracyclic compound **27**, in 16% yield, and also unexpected fragmentation products **29** and **30** (see Figure 2) in 20% and 12% yield, respectively.

Formation of the enamine **29** *can be explained by considering the initial protonation of the indole 3-position in* compound **26** with the subsequent opening of the C1-C12b bond and isomerisation of the resulting iminium salt to the stabilised enamine **29**. Alternatively, the fragmentation of the C1-N bond afforded the tricyclic compound **30**. The structures of both fragmentation products has been confirmed by elemental analysis and by spectroscopic data

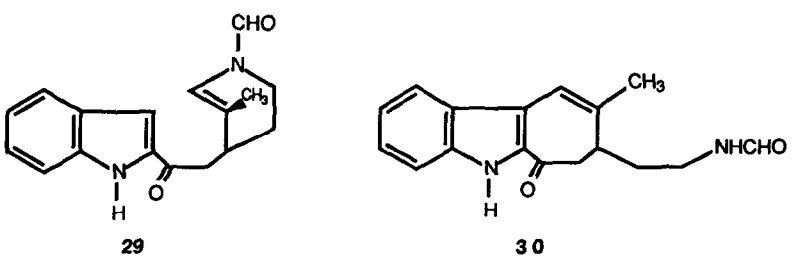
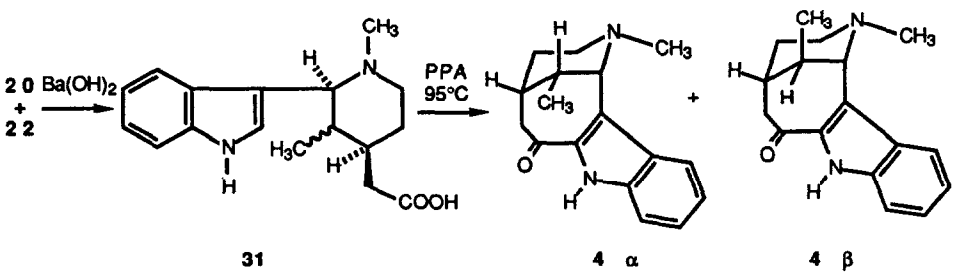


Figure 2

Tetracyclic ketone **27** shows characteristic absorptions at 1625 and 1655 cm^{-1} for the carbonyl groups of amide and 2-acylindole functions. The methyl group on C-13 is disposed axially as may be deduced by the chemical shift of δ 1.34 and 1.37 for each rotamers and by the magnitude of the coupling constant of C-1 and C-13 methine protons. The ^{13}C-NMR spectrum shows a signal at δ 19.8 for this methyl group , which promotes a "γ-gauche" effect upon the carbon at the 4-position (Δδ 4.9 ppm) with respect to the demethyl analogue **24**. Finally, the transformation of the *N*-formyl derivative **27** into *N*-methyl analogue **4** was carried out by initial reduction of **27** with lithium aluminium hydride followed by reoxidation of the resulting carbinol **28** using MnO_2.

Alternatively, Friedel-Crafts cyclisation of the mixture of aminoacids **31** by treatment with PPA at 95°C for 30 min. gave in this case, a mixture of tetracyclic epimeric compounds **4α** and **4β** which were separated by column chromatography. The axial orientation of the C-13 methyl group in **4β** was clearly evidenced by the chemical shift of δ 1 51, in its ^1H-NMR spectrum, more deshielded than in **4α** (δ 1.00) as a consequence of the *syn* nitrogen lone pair. Similarly, a clear difference of chemical shift for this methyl carbon in the ^{13}C-NMR spectrum, due to the shielding effect of the two *syn* C-2 and C-4 substituents, was observed (axial methyl group: δ 21.3; equatorial methyl group: δ 16.9). This shielding effect was also evidenced for the C-6 methylene group in **4β** in which appeared at higher field than in **4α** (Δδ ~6 ppm).



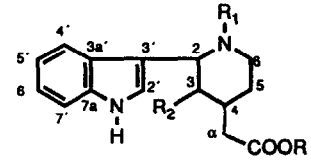
31 **4 α** **4 β**

Scheme 8

EXPERIMENTAL

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H- And ^{13}C-NMR spectra were recorded in $CDCl_3$ (unless otherwise indicated) on a Varian XL-200 spectrometer using TMS as an internal standard. Chemical shifts are reported in ppm downfield (δ) from TMS. In the 2D NOE experiment the sample was degassed by a nitrogen stream and was performed using the standard sequence.[21] The mixing time was 0.150 ms, and 32 transients were accumulated for 256 values of evolution period with an spectral width of 1315 Hz in both dimensions, and a delay of 2 s was employed. A 512x512 data matrix was used with pseudoecho and triangular folding.[22] Ir spectra were registered on 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 was carried out on SiO_2 (silica gel 60, Merck 0.0063-0.200 mm), and the spots were visualised with uv light or iodoplatinate reagent. Flash column chromatography was carried out on SiO_2 (silica gel 60, 0 040-0.063 mm, Macherey Nagel). Drying of organic

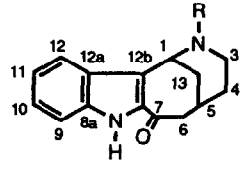
Table 1. ^{13}C-NMR Data of 4-Substituted *N*-Formyl- and *N*-Methyl-2-(3-indolyl)piperidines [a]



Compound	Carbon																	
	C-2	C-3	C-4	C-5	C-6	C-α	C-Me	N-Me	CHO	COO	OMe	In-C2	In-C3	In-C3a	In-C4[b]	In-C5[b]	In-C6	In-C7	In-C7a
8	49.9	34.4	c	31.4	35 9	113.2	18.7	—	161.4	166.6	51.2	122 4	113.2	126.1	119.0	116 2	119.9	111.0	136 9
	58.0	34.5		33.1	41.8	114 2	18.9	—	161.6	166.7	51 3	122.5	114.2	127.2	119.7	116.5	120.1	111 4	136.5
9	44.5	124.9	129.9	29.4	39.3	42 2	—	—	160.7	171.7	52.0	125.2	114.4	126.1	119.9	119.8	122 2	111.3	136.7
	50.8	124.8	131.2	27.9	33.7		—	—	161 1			125.6	113.5		118.5	119.6		111.8	136.9
10	48 7	c	c	30.7	39.5	38.1	17.4	—	160 0	171.5	52.0	125.1	114.4	126.5	120.1	119.9	122.3	111.1	136.8
	54.6			28.8	32.2		17.3	—					118.5					111.5	136 9
12	48.2	36.1	133 3	123.1	42.2	40.2	19.0	—	161.6	171 9	51.8	122.2	113.1	123.1	118.3	119.8	121.5	111.0	136.1
	55.9	36.3	134.8	123.5	37.3	40.5	19.2	—	161.3	172.1	51.9	122 3	113 2	126.6	119.5	119 9	121.6	111.5	136.2
15	65.0	45.3	163.0	27.6	54.1	112.9	15.5	43.6	—	167.2	50.9	122 6	113.1	126.5	119.0	119.6	122.0	111.1	136.1
16	69.9	44.0	163.3	30.1	57.2	111.3	14 9	43.7	—	167.2	51.0	122 9	114.0	126.8	119.8	119.4	122.1	111.5	136.5
17	54.4	38.8	33.8	31.5	40.8[b]	41.0[b]	—	—	161.6	172.5	51.6	123 4	111.5	125.8	120.2	119.2	122.7	111.8	136.6
18[e]	61.3	40.6	40.2	30.9	41.0	38.9	16.5	—	162.7	173.7	51.7	123.6	109.6	125.5	120.1	119.3	122.5	112.2	137.3
19	59.5	33.3	31.7	25.2	43.0	36.8	12.0	—	162.0	173.0	51.6	123.2	112.9	126.0	119.1	119.7	122.2	111.2	136.6
	51.3	33.9	32.0	27.3	37.9	37.9	12.2	—	162.2	173.1	51.7	123.4	113.2	126.4	119.6	119.8		111.6	136.8
21	d	39.9	d	31.3	56.7	39.0	16.3	44.3	—	173.9	51.4	121.5	116.1	122.9	118.9	119.0	121.5	111.2	136.0
22	67.4	37.6	38.2	26.3	58.2	38.8	8.1	44.6	—	173.7	51.5	123.2	114.8	126.9	121.5	119.0	123.0	111.3	135.9
23	55.3	39.1	34.1	31.9	41.7	41.2	—	—	162.4	175.9	—	124.5	110.7	126.3	120.3	119.1	122.3	112.4	137.4
26[f]	62.6	42.0[b]	42.1[b]	32.1	42.8	41.8	16.8	—	163.6	178.9	—	123.1	110.7	123.5	120.0	120.7	120.8	113.0	137.9

a. Recorded at 50.3 MHz in $CDCl_3$. Assignments were aided by DEPT sequence. Chemical shifts are given in δ units (downfield from TMS). b. These values may be interchanged.
c Masked by the CHO signal. d. Broad bands. e. Recorded in $CDCl_3$-CD_3OD. f. Recorded in CD_3OD.

Table 2 ^{13}C-NMR Data of 2,3,4,5,6,7-Hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indoles [a]



Compound	Carbon																	
	C-1	C-3	C-4	C-5	C-6	C-7	C-7a	C-8a	C-9	C-10	C-11[b]	C-12[b]	C-12a	C-12b	C-13	N-Me	C-Me	CHO
1[c]	58.9	45.9	26.1	34.4	53.6	198.3	135.2	138.2	110.2	127.4	120.2	120.1	125.2	121.1	32.0	44 2	21.0	—
2[d,e]	55.2	46.6	31 1	27 6	50.0	199 5	136.9	137 7	113.9	127.4	122.2	122.2	127.0	121 7	34.1	44.4	—	—
3	54.8	47.3	f	38 6	52.9	196.8	137 1	138.0	113.5	127.0	122 4	122.7	127.2	121.6	35.3	43.7	12.7	—
4α[g]	59.5	44.5	31.8	32.8	44.4	196.6	134.3	136 4	112.3	126.0	120.8	121.2	129.5	113.8	35.7	43.4	16.9	—
4β[g]	59.1	45.3	26.8	33.3	50.6	195.0	f	f	112.0	126.1	120.4	121.7	f	f	f	44.3	21.3	—
24	41.9	38.9	31.6	27.9	49.2	194 2	134.2	136.4	111.6	127.0	121.0	122.5	120 4	126.9	32.3	—	—	160.0
25[g]	46.8	36.9	30.3	27.2	49.7	194.9	134 7	137.1	112.5	126.8	120.5	120.8	120.9	126.1	32.1	—	—	—
27	47.3 40 9	38 9 36.2	26.7 24.9	34.3 32.6	50.0 54.8	194.2	133.9	134.1	111.8	127.1	120.9	122.4	126.0	121.7	35.8 34.4	—	19.8 20.1	161.0
28	59.3 59.8	45.9 45.7	25.3	35.5	48 8	68.3 66.9	133.7	139.3	110.7 110.9	121.3 121.9	118.5	119.5 119.4	f	f	40.1 41.3	44.6 44 8	21.3 21.1	— —

a. Recorded at 50.3 MHz in $CDCl_3$. Assignments were aided by DEPT sequence. Chemical shifts are given in δ units (downfield from TMS). b. These values may be interchanged.
c. Reported in ref. 5a. d Reported in ref. 6a. e. Recorded in CD_3OD. f Signal not clearly observed. g Recorded in $CDCl_3$-CD_3OD.

extracts during the workup of reactions was performed over anhydrous sodium sulphate. Microanalyses were performed on a Carlo-Erba 1106 analyser by Departament de Química Orgànica Biològica, Barcelona.

Methyl 1-Formyl-2-(3-indolyl)-1,2,5,6-tetrahydropyridine-4-acetate (9). Methyl diethyl phosphonacetate[14] (9.45 g, 45 mmol) was added under N_2 to a suspension of NaH (2.4 g, 55 mmol) in anhydrous DME (50 ml). The resulting suspension was stirred at room temperature for 5 min, and then a solution of piperidone 5[11] (9 6 g, 40 mmol) in anhydrous DME (250 ml) was added dropwise. The mixture was heated at 70°C for 3 h, cooled, poured into ice-water and extracted with CH_2Cl_2. The organic extracts were washed with aqueous K_2CO_3, dried and evaporated to obtain **9** (4 7 g, 45%) after purification by flash chromatography (CH_2Cl_2); mp. 124-126 °C (acetone), IR (KBr) 3200 (NH), 1740 (C=O), 1650 cm^{-1} (NCHO); ^{1}H-NMR 2.00* (major rotamer) and 2.30 (m, 2H, 5-H), 3.12* and 3.15 (br s, 2H, CH_2CO), 3.73* and 3.75 (s, 3H, OCH_3), 3.38* and 4.20 (dd, *J*=10.5 , 4.5 Hz and dd, *J*=13 0 , 6 5 Hz, 1H, 6-He), 6.29* and 5.43 (br s, 1H, 2-He), 5.86 (br, 1H, =CH), 7.05-7.26 (m, 3H, In-H), 7.35* and 7.38 (ddd, *J*=7.5, 1.5 and 0.9 Hz, 1H, In-7H), 7.97* and 7.56 (ddd, *J*=7.5, 1.5 and 0.9 Hz, 1H, In-4H), 8.64 (br , 1H , NH), 8.07* and 8.50 (s, 1H, CHO); MS (m/z, %) 298 (M^+, 100), 281 (30), 269 (50), 225 (32), 211 (28), 197 (25), 180 (28) 130 (25), 59 (13), 43 (15). Anal. Calcd for $C_{17}H_{18}N_2O_3$. C, 66.00; H, 6.70; N, 9.00. Found: C, 66.09; H, 6.58; N, 8.96.

Methyl 1-Formyl-2-(3-indolyl)-3-methylpiperideine-4-acetates (8), (10), and (12). Following a similar procedure to that described above, starting from piperidone 6[11] (14.3 g, 55 mmol) in dry DME (200 ml) , NaH (2 5 g, 55 mmol) and methyl diethylphosphonacetate (12.7 ml, 70 mmol) in DME (50 ml) an oil was obtained. The excess of methyl phosphonacetate was removed by distillation (0.01 mmHg, 120°C, 30 min) to obtain 17.2 g of the isomeric mixture Purification by column chromatography (9 1 benzene-$CHCl_3$ as eluent) afforded **methyl 1-formyl-2-(3-indolyl)-3-methyl-4-piperidein-$\Delta^{4,\alpha}$-acetate (8)** (1.54 g, 9%) as a 1 3 mixture of *E* and *Z* isomers which was separated by preparative tlc (SiO_2, Et_2O as eluent). *Z* Isomer of **8**: (Rf 0.40) mp 167-168°C (Et_2O); ^{1}H-NMR 1 25* and 1.29 (d, *J*=7 Hz, 3H, CCH_3), 2.05* and 2 11 (d, *J*=13.5 Hz, 1H, 5-He), 2.50-2.80 (m, 2H, 6-Ha *E*-rotamer and 5-He), 3.03 (td, *J*=13 and 4 Hz, 6-Ha *Z*-rotamer*), 3.38* and 4.32 (dd, *J*=13 and 6 Hz, 1H, 6-He), 3.76* and 3.78 (s, 3H, OCH_3), 4.77* and 4.86 (q, *J*=7 Hz, 1H, 3-H), 5.97* and 4.90 (br, 1H, 2-He), 5.86* and 5.87 (d, *J*=1.8 Hz, 1H, =CH), 6.90-7.30 (m, 3H, InH), 7 45 (d, *J*=8 Hz, 1H, In-7H), 7.79* and 7.59 (d, *J*=8 Hz, 1H, In-4H), 8.43* and 8 55 (s, 1H, CHO); MS (m/z, %) 312 (M^+, 70), 253 (55), 224 (46) , 208 (29), 157 (40), 130 (100), 115 (20). *E* Isomer of **8**: (Rf 0.45)· IR (KBr) 3230 (NH), 1715 (COO), 1640 cm^{-1} (CHO); ^{1}H-NMR 1.32* and 1.35 (d, *J*=7 Hz, 3H, CCH_3), 2 36* and 2 44 (tdd, *J*=13.5, 6.6, and 2.0 Hz, 1H, 5-Ha), 3.00* and 2.78 (td, *J*=13.5 and 3.6 Hz, 1H, 6-Ha), 3.36* and 4.20 (dd, *J*= 13 and 6 Hz, 1H, 6-He), 3 82* and 3.60 (dt, *J*=13 and 2.4 Hz, 1H, 5-He), 3.71* and 3.74 (s, 3H, OCH_3), 5 86* and 4 80 (br s, 1H, 2-He), 5 90 and 5 96 (d, *J*=1 8 Hz, 1H, =CH), 7.00-7.20 (m, 3H, InH), 7.32* and 7 36 (d, *J*=8 Hz, 1H, In-7H), 7 72* and 7 46 (d, *J*=8 Hz, 1H, In-4H), 8.31* and 8 47 (s, 1H, CHO), 8.42* and 8.56 (br, 1H, NH). Anal. Calcd for $C_{18}H_{20}N_2O_3.H_2O$. C, 65 40; H, 6.70; N, 8 40. Found: C, 65.45; H, 6.37; N, 8.04. On elution with 7:3 benzene-$CHCl_3$ **methyl 1-formyl-2-(3-indolyl)-3-methyl-1,2,3,6-tetrahydropyridine-4-acetate (12)** (10.8 g, 63%) was obtained: mp 115-117 °C (acetone-Et_2O); IR (KBr) 3230 (NH), 1730 (COO), 1650 cm^{-1} (CHO); ^{1}H-NMR 1.21 (d, *J*=7 Hz, 3H, CCH_3), 2.83* and 2.88 (q, *J*=7 Hz, 1H, 3-H), 3.12* and 3.14 (br s, 2H, CH_2CO), 3 34* and 4.50 (br d, *J*=15 Hz, 1H, 6-He), 3 61* and 3.73 (s, 3H, OCH_3), 5 86* and 4.82 (br s, 1H, 2-He), 5.46 (br s, 1H, =CH), 7.01-7.24 (m, 3H, InH), 7.32* and 7.35 (d, *J*=8 Hz, 1H, In-7H), 7.47* and 7.71 (d, *J*=8 Hz, 1H, In-4H), 8.27* and 8.47 (s, 1H, CHO), 8 37* and 8.50 (sa, 1H, NH); MS (m/z, %) 312 (M^+, 23), 172 (46), 163 (62), 149 (92), 143 (38), 130 (100), 117 (58), 91 (47), 77 (46), 55 (42). Anal. Calcd for $C_{18}H_{20}N_2O_3$. C, 69.20; H, 6 45; N, 8.96. Found· C, 68.92; H, 6.68; N, 8.68. On elution with 6:4 benzene-$CHCl_3$ **methyl 1-formyl-2-(3-indolyl)-3-methyl-1,2,5,6-tetrahydropyridine-4-acetate (10)** (4.8 g, 27%) was obtained: IR ($CHCl_3$) 3460 (NH), 1730 (COO), 1655 cm-1

(CHO); ^{1}H-NMR 1.73 (br s, 3H, CCH_3), 2.08-2.73 (m, 2H, 5-H), 2.94* and 3.00 (br s , 2H, CH_2CO), 3.35* and 4.16 (dd, J=9.6 , 4.0 Hz and dd, J=12.8, 7.2 Hz, 1H, 6-He), 3.76* and 3.77 (s, 3H, OCH_3), 6.03* and 5.20 (s, 1H, 2-He), 7.00-7.20 (m, 3H, InH), 7.38* and 7.40 (d, J=8 Hz, 1H, In-7H), 8.00* and 7.65 (d, J=8 Hz, 1H, In-4H), MS (m/z, %) 312 (M^+, 1), 183 (46), 179 (21), 166 (34), 151 (35), 123 (100) , 109 (38), 95 (35).

Methyl 2-(3-Indolyl)-1,3-dimethyl-$\Delta^{4,\alpha}$-piperideine-4-acetates (15) and (16). Following a similar procedure to that described above, starting from piperidone **14**[8b] (15.4 g, 63 mmol) in anhydrous DME (250 ml), NaH (2.96 g, 68 mmol) and methyl diethylphosphonacetate (17.06 g, 81 mmol), a mixture of epimers **15** and **16** was obtained. Purification by flash chromatography, using 1:1 Et_2O-acetone as eluent, afforded 3α-epimer **16**: IR ($CHCl_3$) 3470 (NH), 1710 (COO), 1645 cm^{-1} (=C); ^{1}H-NMR 0.79 (d, J=6.5 Hz, 3H, CCH_3); 2.05 (s, 3H, NCH_3), 2.20 (ddd, J= 12.8, 11 and 2.8 Hz, 1H, 5-Ha), 2.50 (td, J=12.8 and 4 6 Hz, 1H, 6-Ha), 2.84 (dq, J=9.6 and 6.5 Hz, 1H, 3-Ha), 2.94 (d, J=0.6 Hz, 1H, 2-H), 3.20 (ddd, J=11, 4.6, and 3.2 Hz, 1H, 5-He), 3.74(s, 3H, OCH_3), 3.98 (dt, J=12.8 and 2.8 Hz, 1H, 6-He), 5.72 (br s, 1H, =CH), 7.10-7.20 (m, 3H, InH), 7.40 (d, J=8 Hz, 1H, In-7H), 7 85 (d, J=8 Hz, 1H, In-4H), 8.20 (br, 1H, NH), MS (m/z, %) 298 (M^+, 4), 284 (21), 270 (17), 226 (56), 197 (65), 173 (30), 158 (52), 131 (91), 43 (30). The hydrochloride melted at 226-227 °C (acetone). Anal. Calcd for $C_{18}H_{22}N_2O_2$.HCl: C, 64 57; H, 6 90; N, 8.50, Cl, 10.50 Found· C, 64.20; H,6.80; N, 8.21; Cl, 10.55. 3β-Epimer **15** (Lower Rf, 3.2 g, 17%) . IR ($CHCl_3$) 3480 (NH), 1710 (COO), 1645 cm^{-1} (C=C); ^{1}H-NMR 0.93 (d, J=6.6 Hz, 3H, CCH_3), 2.08 (s, 3H, NCH_3), 2.44 (ddd, J=12, 7.2 and 4.8 Hz, 1H, 5-Ha), 2.74 (dt, J=11.2 and 6 4 Hz, 1H, 6-Ha), 2.91 (dq, J=6.5 and 5.6 Hz, 1H, 3-He), 3.10-3.20 (m, 2H, 5-He and 6-He), 3.68 (s, 3H, OCH_3), 4.02 (d, J=4.8 Hz, 1H, 2-H), 5.65 (br s, 1H, =CH), 7.00-7.20 (m, 3H, InH), 7.32 (d, J=7 Hz, 1H, In-7H), 7.63 (d, J=7 Hz, 1H, In-4H), 8.47 (br, 1H, NH); MS (m/z, %) 298 (M^+, 1), 243 (11), 225 (20), 172 (22), 158 (35), 157 (59), 144 (25), 130 (79), 83 (60), 48 (100), 43 (26).

***N*-[5-(3-Indolyl)-4-methyl-3-oxo-4-pentenyl]formamide (13).** To a suspension of NaH (2.14 g, 48 mmol) in anhydrous DME (20 ml) , methyl diethylphosphonoacetate (0.85 ml, 4.69 mmol) was added under N_2. The resulting mixture was stirred at room temperature for 1 h and then a solution of piperidone **6**[11] (1.0 g, 4 mmol) in DME (15 ml) was added dropwise. The mixture was stirred at room temperature for 1 h, cooled, poured into ice-water, acidified with aqueous hydrochloric acid to pH 6 and extracted with $CHCl_3$. The organic layer was dried and evaporated to give **13** as a solid (0.43 g, 44%) after purification by flash chromatography (99:1 $CHCl_3$-CH_3OH): mp 177-180 °C (acetone); IR (KBr) 3340 (NH), 1670 (CHO), 1640 cm^{-1} (C=C); ^{1}H-NMR 2.06 (s, 3H, CCH_3), 3.06 (t, J=6 Hz, 2H, 2-H), 3.50 (ta, J=6 Hz, 2H, 1-H), 7.00-7.50 (m, 4H, InH), 7.53 (s, 1H, =CH), 7.93 (d, J=5 Hz, 1H, In-4H); MS (m/z, %) 256 (M^+, 23), 211 (37), 210 (21), 198 (41), 184 (100), 183 (22), 184 (100), 182 (31), 168 (31), 155 (31), 154 (78), 130 (82), 129 (96), 128 (87), 117 (66). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.50, H, 5 92, N, 10.97 Found· C, 70 88, H, 6 32; N, 10 96.

Methyl 1-Formyl-2-(3-Indolyl)piperidine-4-acetate (17). A solution of tetrahydropyridine **9** (5.20 g, 17 mmol) in methanol (100 ml) was hydrogenated at room temperature and atmospheric pressure in the presence of PtO_2 (260 mg). When the absorption ceased the catalyst was filtered off and the solution was evaporated to give**17** as an oil (5 g, 95%) : mp 142-143 °C (acetone-ether): IR (KBr) 3260 (NH), 1735 (COO), 1640 cm^{-1} (CHO); ^{1}H-NMR 1 20-1.40 (m, 1H, 4-Ha), 2.12 (br d, J=13.6 Hz, 1H, 3-He), 2.32 (s, 2H, CH_2CO), 2.79 (td, J=13 6 and 3 3 Hz, 1H, 6-Ha), 3.67 (s, 3H, OCH_3), 4.60 (dd, J=12 and 2.4 Hz, 1H, 2-Ha), 4.66 (dq, J=13.6 and 2.4 Hz, 1H, 6-He), 7 00-7.20 (m, 3H, InH), 7.30 (d, J=8 Hz, 1H, In-7H), 7.52 (d, J=8 Hz, 1H, In-4H), 7.77 (s, 1H, CHO), 8.66 (br, 1H, NH); MS (m/z, %) 300 (M^+, 100), 283 (98), 271

(69), 206 (49), 189 (42), 182 (71), 143 (50), 130 (45), 118 (40), 93(45), 43 (36). Anal. Calcd for $C_{17}H_{20}N_2O_3.H_2O$: C, 65.95; H, 6.78; N, 9.05. Found: C, 65.90; H, 6.58; N, 8.96.

Methyl 1-Formyl-2-(3-indolyl)-3-methylpiperidine-4-acetate (18) and (19). A solution of tetrahydropyridine **12** (11.6 g, 37 mmol) in methanol (150 ml) was hydrogenated at room temperature and 300 psi for 48 h in the presence of PtO_2 (300 mg). The solution was filtered and evaporated to obtain an isomeric mixture of **18** and **19** (10.8 g) which was purified by flash chromatography (6:4 $CHCl_3$-Et_2O). **Methyl 1-formyl-*t*-2-(3-indolyl)-*c*-3-methylpiperidine-*r*-4-acetate (19)** (Higher Rf, 3.10 g, 27%): mp 139-140 °C (acetone-Et_2O); IR ($CHCl_3$) 3460 (NH), 1725 (COO), 1650 cm-1 (CHO); ^{1}H-NMR 1 05* and 1 06 (d, *J*=7 Hz, 3H, CCH_3), 3.37* and 4.31 (br d, J=12 Hz, 1H, 6-He), 3.69* and 3.72 (s, 3H, OCH_3), 5.81* and 4 77 (s, 1H, 2-He), 7 00-7 40 (m, 4H, InH), 7 66* and 4.77 (s, 1H, 2-He), 7.00-7.40 (m, 4H, InH), 7.66* and 7.49 (d, *J*=8 Hz, 1H, In-4H), 8.32* and 8.49 (s, 1H, CHO); MS (m/z, %) 314 (M^+, 55), 297 (49), 285 (31), 171 (28), 130 (100), 117 (41), 83 (33), 43 (25). Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 67 98; H, 6.71; N, 9.32. Found: C, 67.76; H, 7.04; N, 8.96. **Methyl 1-formyl-*c*-2-(3-indolyl)-*t*-3-methylpiperidine-*r*-4-acetate (18)** (Lower Rf, 7.70 g, 66 %): mp 167-168 °C (acetone-Et_2O); IR (KBr) 3460 (NH), 1725 (COO), 1650 cm^{-1} (CHO); ^{1}H-NMR 0.74 (d, *J*=5.8 Hz, 3H, CCH_3), 2.21 (dd, *J*=15.8 and 4 Hz, 1H, CH_2CO), 2.64 (dd, *J*=15.8 and 3 4 Hz, 1H, CH_2CO), 2.79 (td, *J*=11.7 and 3.4 Hz, 1H, 6-Ha), 4.15 (d, *J*=10.1 Hz, 1H, 2-Ha), 4 62 (dt, *J*=13.4 and 3.4 Hz, 1H, 6-He), 6.90-7.40 (m, 4H, InH), 7.53 (d, *J*=7.9 Hz, 1H, In-7H), 7.84 (s, 1H, CHO), 9.22 (s, 1H, NH); MS (m/z, %) 314 (M^+, 1), 167 (10), 149 (26), 130 (29), 97 (36), 73 (45), 69 (88), 43(100). Anal. Calcd for $C_{18}H_{22}N_2O_3$· C, 65.90; H, 6.70, N, 8.90. Found. C, 65.70; H, 7.07; N, 8.93

Methyl 2-(3-indolyl)-1,3-dimethylpiperidine-4-acetate (20) and (21). A solution of piperidine **15** (6.37 g, 21 mmol) and PtO_2 (320 mg) in MeOH (100 ml) was hydrogenated at room temperature and 200 psi for 9h The solution was filtered and evaporated to give a 1:1 isomeric mixture of **20** and **21** (5.1 g) which was separated by flash chromatography (1:1 acetone-Et_2O). **Methyl *c*-2-(3-indolyl)-1,*t*-3-dimethylpiperidine-*r*-4-acetate (21)** (Higher Rf): IR (NaCl) 3400 (NH), 1730 cm^{-1} (COO); ^{1}H-NMR (60 MHz) 0.82 (d, *J*=7 Hz, 3H, CCH_3), 2.08 (s, 3H, NCH_3), 3.08 (da, *J*=10 Hz, 1H, 2-Ha), 3.58 (s, 3H, OCH_3), 7.00-7.20 (m, 4H InH), 7.60 (m, 1H, In-4H), 8.67 (br, 1H, NH). **Methyl *t*-2-(3-indolyl)-1,*c*-3-dimethylpiperidine-*r*-4-acetate (20)** (Lower Rf) · IR (NaCl) 3450 (NH), 1730 cm-1 (COO); ^{1}H-NMR 0.67 (d, J=6 Hz, 3H, CCH_3), 2.04 (s, 3H, NCH_3), 2.18 (m, 1H, CH_2CO), 2.61 (br d, *J*=16 Hz, 1H, CH_2CO), 3.09 (br d, *J*=10 Hz, 1H, 2-Ha), 3.70 (s, 3H, OCH_3), 7.00-7.20 (m, 3H, InH), 7.34 (d, *J*=7 Hz, 1H, In-7H), 7.72 (m, 1H, In-4H); MS (m/z, %) 300 (M^+, 9), 227 (18) 185 (22), 172 (35), 157 (63), 143 (28), 130 (100), 117 (22), 83 (24), 69 (24), 55 (25), 43 (30) The hydrochlonde melted at 236-238°C (acetone-Et_2O). Anal. Calcd for $C_{18}H_{24}N_2O_2$ HCl: C, 64.19, H, 7.30; N, 8.30; Cl, 10 50. Found C, 63.91; H, 7.40; N, 8.21; Cl, 10.45.

Methyl *c*-2-(3-indolyl)-1,*c*-3-dimethylpiperidine-*r*-4-acetate (22). Following a similar procedure to that above, starting from piperidine **16** (2 38 g, 8 mmol) and PtO_2 (120 mg) in MeOH (50 ml), 1 9 g (80%) of piperidine **22** was obtained after purification by flash chromatography (1:1 acetone-Et_2O); IR ($CHCl_3$) 2950 (NH), 1730 cm^{-1} (COO), ^{1}H-NMR 0.75 (d, *J*=7 Hz, 3H, CCH_3), 2.07 (s, 3H, NCH_3), 2.13 (m, 2H, CH_2CO), 3.06 (dt, *J*=11 2 and 3.2 Hz, 1H, 6-He), 3 46 (br, 1H, 2-H), 3 57 (s, 3H, OCH_3), 6.00-7.20 (m, 3H, InH), 7.25 (d, *J*= 7 Hz, 1H, In-7H), 7.56 (d, *J*=7 Hz, 1H, In-4H), 8.90 (br, 1H, NH); MS (m/z, %) 336 (M^+, 2) , 300 (54), 285 (10), 228 (22), 227 (100), 157 (32). The hydrochloride melted at 194-196 °C. Anal. Calcd for $C_{18}H_{24}N_2O_2$.HCl: C, 64 19; H, 7.30; N, 8.30; Cl, 10.50. Found 64 12; H, 7.57, N, 8 11, Cl, 10 51.

1-Formyl-2-(3-indolyl)piperidine-4-acetic Acid (23). To a solution of methyl piperidineacetate **17** (5 g, 16 mmol) in dioxane (100 ml), 1*N* aqueous NaOH (20 ml) was slowly added. After being stirred at room temperature for 12 h, the mixture was acidified with 1*N* aqueous HCl to pH 6-7 and evaporated to dryness. The residue was dissolved in MeOH, filtered and evaporated to give **23** as a solid (4 g, 84%): mp 137-140 °C (acetone-Et_2O); IR (KBr) 3360 (OH), 1710 (COO), 1620 cm^{-1} (CHO); ^{1}H-NMR 1.30 (m, 1H, 4-Ha), 1.85 (q, J=11.5 Hz, 1H, 5-Ha), 1.95 (br d, J=11.7 Hz, 1H, 5-He), 2.10 (br d, J=12 Hz, 1H, 3-He), 2.32 (br s, 2H, CH_2CO), 2.82 (td, J=11.5 and 2.8 Hz, 1H, 6-Ha), 4.30 (d, J=11.5 Hz, 1H, 6-He), 4.64 (br d, J=12 Hz, 1H, 2-Ha), 7.00-7.30 (s, 3H, InH), 7.42 (d, J=8 Hz, 1H, In-7H), 7.51 (d, J=8 Hz, 1H, In-4H), 7.72 (s, 1H, CHO); MS (m/z, %) 286 (M^+, 1), 268 (3), 169 (15), 117 (100), 110 (32), 90 (34), 82 (43), 63 (20). Anal. Calcd for $C_{16}H_{18}N_2O_3.H_2O$: C, 63.19; H, 6.57; N, 9 27. Found: C, 63.38; H, 6.58; N, 9.27.

1-Formyl-2-(3-indolyl)-3-methylpiperidine-4-acetic Acid (26). Following a similar procedure to the above, from starting piperidine **20** (7.7 g, 24 mmol) and 1*N* aqueous NaOH (30 ml) in dioxane (100 ml), pipendineacetic acid **26** was obtained as a solid (7.18 g): mp 232-234 °C (MeOH-acetone); IR (KBr) 3310 (OH), 1710 (COO), 1620 cm^{-1} (CHO); ^{1}H-NMR (CD_3OD) 0.87 (d, J=6 Hz, 3H, CCH_3), 1.54 (dq, J=11.2 and 4.8 Hz, 1H, 5-Ha), 2.00 (m, 3H, 3-H, 4-H, and 5-He), 2.20 (dd, J=14.4 and 4.0 Hz, 1H, CH_2CO), 2.70 (dd, J=14.4 and 3.2 Hz, 1H, CH_2CO), 2 91 (td, J=12.8, 4.8 and 1.6 Hz, 1H, 6-He), 7.15 (td, J=8 and 1.3 Hz, 1H, In-5H), 7 26 (td, J=8 and 1 3 Hz, 1H, In-6H), 7.29 (d, J=1.3 Hz, 1H, In-2H), 7 50 (dd, J=8 and 1.3 Hz, 1H, In-7H), 7.62 (dd, J=8 and 1.3 Hz, 1H, In-4H), 7.80 (s, 1H, CHO), MS (m/z, %) 300 (M^+, 1), 254 (4), 182 (7), 117 (100), 89 (37), 90 (53), 44 (17). Anal. Calcd for $C_{17}H_{20}N_2O_3$ 1/2H_2O: C, 66.00; H, 6.84; N, 9.05. Found: C, 65.66; H, 6.90; N, 8.72.

2-Formyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (24). The acid **23** (1.20 g, 4 mmol) was stirred vigorously in the presence of PPA (60 g) under nitrogen at 100°C for 25 min. The mixture was cooled, poured into ice-water, made alkaline with concentrated NH_4OH, and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by column chromatography of the residue (SiO_2, $CHCl_3$ as eluent) gave the tetracyclic compound **24** (0.1 g, 10%): mp 198-200 °C (MeOH); IR (KBr) 1620-1660 cm^{-1} (InCO and CHO); ^{1}H-NMR 3.28* and 4 18 (dd, J=14.4 and 5.6 Hz, 1H, 3-He), 6.35* and 5.38 (dd, J=4 2 ,1.4 Hz and br d, J= 4 2 Hz, 1H, 1-He), 7.10-7.40 (m, 3H, InH), 8.09* and 7 62 (d, J=8 Hz, 1H, 12-H), 7 98* and 8.47 (s, 1H, CHO), 9.05* and 9.10 (sa, 1H, 8-H); MS (m/z, %) 268 (M^+, 100), 240 (5), 197 (23), 196 (36), 195 (32), 182 (21), 169 (43), 168 (70), 155 (40). Anal. Calcd for $C_{16}H_{16}N_2O_2.H_2O$ C, 67.06; H, 6.28; N, 9.77. Found: C, 67.31; H, 5.97; N, 9 69.

2-Formyl-13-methyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (27). Method A. Following a similar procedure to that described above, starting from piperidine **26** (5.6 g, 19 mmol) and PPA (300 g), a solid was obtained which was purified by column chromatography (SiO_2) Elution with 7 3 $CHCl_3$-benzene gave 13α-epimer **27** (0 84 g, 16%): mp 234-236 °C (acetone); IR ($CHCl_3$) 3430 (NH), 1655 (CHO), 1625 cm^{-1} (InCO), ^{1}H-NMR 1 34* and 1.37 (d, J=7 Hz, 3H, CCH_3), 3.18* and 4.20 (dd, J= 14 and 4 Hz, 1H, 3-He), 6 06* and 5.02 (br s, 1H, 1-He), 7 00-7 50 (m, 3H, InH), 8 06* and 7.64 (d, J=8 Hz, 1H, 12-H), 8 09* and 8.40 (s, 1H, CHO), 9.20* and 9.30 (sa, 1H, NH), MS (m/z, %) 282 (M^+, 77), 196 (36), 183 (62), 182 (87), 168 (53), 167 (67), 149 (67), 144 (100), 143 (36), 139 (41), 124 (73), 83 (77), 57 (30). Anal. Calcd for $C_{17}H_{18}N_2O_2$ C, 72 30, H, 6 40; N, 9 90 Found C, 71 96; H, 6 30; N, 9 80

Elution with 98:2 $CHCl_3$-MeOH gave **2-[(1-formyl-3-methyl-1,4,5,6-tetrahydro-4-pyridyl)acetyl]indole (29)** (1.10 g, 20%): IR ($CHCl_3$) 3445 (NH), 1670-1630 cm-1 (C=O and C=C); ^{1}H-NMR 1.75 (br s, 3H, =CCH3), 2.79 (dd, J=17 and 14 Hz, 1H, CH_2CO), 3.09 (dd, J=17 and 4 Hz, 1H, CH_2CO), 2.95* and 3.82 (dt, J=14 and 5 hz, 1H, 6-He), 6.28* and 6.88 (br s, 1H, 2-H), 7.10-7.50 (m, 3H, In-3H, In-5H, and In-6H), 7.73 (br d, J=8 Hz, 1H, In-7H), 8.35 (m, 1H, In-4H), 8.19* and 7.96 (s, 1H, CHO), 9.93 (br s, 1H, NH); ^{13}C-NMR (CD_3OD-$CDCl_3$) 19.1* and 19.2 (CH_3), 25.8* and 27.3 (C-5), 33.5* and 34.0 (C-4), 36.0* and 41.3 (C-6), 42.3* and 42.6 (*C*H2CO), 117.9 (In-C7), 120.7 , 122.2, 122.7, and 123.4 (C-2, In-C4, In-C5, and In-C6), 132.3 (In-C3a), 136.9 (In-C7a), 159.7 (C-3), 161.2 (CHO), 195.0 (CO); MS (m/z, %) 282 (M^+, 100), 256 (22), 159 (24), 144 (84), 138 (46), 124 (78), 117 (48), 111 (50), 44 (22). Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72 30; H, 6.40; H, 9.90. Found: C, 72.15; H, 6.38; N, 9.65. Elution with 95:5 $CHCl_3$-MeOH afforded **8-(2-formamidoethyl-9-methyl-6-oxo-7,8-dihydrocyclohepta[*b*]indole (30)** (0.62 g, 12%): IR (CHCl3) 3440 (NH), 1675 (CHO), 1640 cm-1 (InCO); ^{1}H-NMR 2.10 (br s, 3H, =CCH_3), 2.84 (dd, J=16 and 6 Hz, 1H, CH_2CO), 3.18 (dd, J=16 and 2.5 Hz, 1H, CH_2CO), 3.34 (m, 2H, CH_2NH), 5.60 (br, 1H, NHCO), 6.69 (d, J=1.5 Hz, 1H, =CH), 7.10-7.25 (m, 2H, 2-H and 3-H), 7.34 (m, 1H, 4-H), 7.74 (d, J=8 Hz, 1H, 1-H), 8.12 (s, 1H, CHO), 9.22 (br s, 1H, NH); ^{13}C-NMR (CD_3OD-$CDCl_3$) 26.6 (CH_3), 27.5 (CH_2), 36.5 (NCH_2), 37.0 (CH), 43.3 ($COCH_2$), 112.4 (C-4), 116.7 (C-10), 120.7 and 121.0 (C-1 and C-2), 127.2 (C-3), 144.2 (C-9), 162.3 (CHO), 197.8 (C-6); MS (m/z, %) 282 (M^+, 12), 224 (12), 210 (100), 194 (11), 180 (21), 167 (26), 124 (27), 96 (11), 91 (14). Anal. Calcd for $C_{17}H_{18}N_2O_2$. C, 72.30; H, 6.40; N, 9.90. Found: C, 72.23; H, 6.28; N, 9 68

Method B. A solution of acid **26** (1.5 g, 5 mmol) and methanosulphonic acid (25 ml) saturated with P_2O_5 was stirred under N_2 at 70 °C for 2 h. The cooled mixture was poured into ice-water, extracted with $CHCl_3$ and washed with aqueous 10% K_2CO_3 solution. The organic layer was evaporated to give **27** (0.16 g,11%), **29** (0.1 g, 7%), and **30** (0.31 g, 22%) after column chromatography .

7-Oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (25). A solution of **24** (0.79 g, 3 mmol) in aqueous 30% NaOH solution (35 ml) and EtOH (20 ml) was refluxed for 2 h, cooled and extracted with $CHCl_3$. Drying and evaporation of the extracts gave the tetracyclic compound **25** (0 16 g, 23%) as a solid which was chromatographed by preparative tlc (SiO_2, 95:5 Et_2O-acetone as eluent)· IR ($CHCl_3$) 3440 (NH), 1630 cm^{-1} (C=O); ^{1}H-NMR (60 MHz) 2.98 (m, 1H, 3-He), 4.87 (dd, J=6 and 2 Hz, 1H, 1-He), 7.00-7.50 (m, 3H, InH), 7.70 (d, J=8 Hz, 1H, 12-H), 9.10 (br, 1H, NH). The picrate melted at 248-249 °C (EtOH). Anal. Calcd for $C_{21}H_{19}N_5O_8$. C, 53.74; H, 4.08, N, 14.92 Found: 53.68; H, 4.14; N, 14.57.

2-Methyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (2). A suspension of **25** (0.06 g, 0.25 mmol) and MeI (0.035 g, 0.25 mmol) in anhydrous acetone (20 ml) and dry K_2CO_3 (0.2 g) was stirred at room temperature for 15 min. The mixture was filtered and evaporated to obtain 2^{6a} (45 mg, 71 %).

2,13-Dimethyl-7-hydroxy-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (28). To a solution of **27** (300 mg, 1 mmol) in THF (20 ml) , $LiAlH_4$ (400 mg, 11 mmol) was added slowly. After being stirring at reflux for 6 h and cooled, water (6 ml) was added dropwise. The resulting suspension was filtered and the aluminium salts were di ssolved with boiling $CHCl_3$. The whole organic layers were dried and evaporated to give a solid which was purified by preparative tlc (SiO_2, Et_2O as eluent) to obtain a C-7 epimeric mixture of alcohols **28** (0.1 g, 35%). A pure sample of the 7α–epimer of **28** (lower Rf) melted at 218-220 °C (Et_2O-acetone); IR ($CHCl_3$), 3430 (NH), 3400-3200 cm^{-1} (OH); ^{1}H-NMR (CD_3OD) 1.44 (d, J=7 Hz, 3H, CCH_3), 2.22 (s, 3H, NCH3), 2.10-2.22 (m, 2H, 6-H), 4.45 (br s, 1H, NCH), 5.39 (dd, J=12 and 6 Hz, 1H, 7-H), 7 10-7.20 (m, 2H, 10-H and 11-H), 7.40 (dd, J=8 and 1.5 Hz, 1H, 9-H), 7.59 (dd, J=8 and 1.5 Hz,

1H, 12-H); MS (m/z, %) 270 (M^+, 8), 252 (7), 221 (10), 211 (10), 196 (16), 183 (19), 110 919), 69 (66), 57 (79), 44 (100). Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.17; H, 8.36; N, 10.40.

2,3-Dimethyl-7-oxo-2,3,4,5,6,7-hexahydro-1,5-methano-1*H*-azonino[4,3-*b*]indole (4α) and (4β). Method A. A solution of a C-3 epimeric mixture of piperidine-4-acetates **20** and **22** (6.9 g, 23 mmol) in dioxane (200 ml) and aqueous saturated $Ba(OH)_2$ solution (200 ml), was stirred at 80°C for 5 h. The mixture was cooled, acidified to pH 6-7 with solid CO_2, filtered, and evaporated to give a mixture of aminoacids (6.5 g) which was treated with PPA (420 g) as described previously, to obtain a 1:1 epimeric mixture (13α- and 13β-epimer) of **4** (0.6 g, 10%). Purification by column chromatography (SiO_2) using $CHCl_3$ as eluent 13β- epimer (4β) was obtained; IR ($CHCl_3$) 3420 (NH), 1630 cm^{-1} (CO); ^{1}H-NMR 1.51 (d, J=7 Hz, 3H, CCH_3), 2.00 (s, 3H, NCH_3), 2.84 (dd, J=17.6 and 4 Hz, 1H, 6-H), 2.98 (dd, J=17.6 and 4.8 Hz, 1H, 6-H), 3.30 (dt, J=10 and 3 Hz, 1H, 3-He), 4.34 (sa, 1H, 1-H), 7.16 (td, J=8 and 1.4 Hz, 1H, 11-H), 7.34 (td, J=8 and 1.4 Hz, 1H, 10-H), 7.42 (d, J=8 Hz, 1H, 9-H), 7.75 (d, J=8 Hz, 1H, 12-H), 9.26 (br, 1H, NH).

4α (13α-epimer) was obtained using 2:98 MeOH-$CHCl_3$ as eluent: mp 244-246 °C (MeOH); IR ($CHCl_3$) 3340 (OH), 1630 cm-1 (C=O); ^{1}H-NMR 1.07 (d, J=7 Hz, 3H, CCH_3), 2.00 (s, 3H, NCH_3), 2.72 (dd, J=17 and 3.2 Hz, 1H, 6-H), 3.06 (dd, J=17 and 4.8 Hz, 1H, 6-H), 4.53 (d, J= 4Hz, 1H, 1-H), 7 17 (td, J=8 and 1.4 Hz, 1H, 11-H), 7.35 (td, J=8 and 1 4 Hz, 1H, 10-H), 7.43 (d, J= 8 Hz, 1H, 9-H), 7.75 (d, J= 8 Hz,1H, 12-H), 9.37 (br, 1H, NH); MS (m/z, %) 269 (M^++1, 20), 268 (M^+, 49), 211 (46), 196 (40), 168 (23), 130 (20), 110 (50), 85 (63), 83 (100), 59 (54) 44 (54). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75 81, H, 7.60, N, 10 28.

Method B. A suspension of **28** (20 mg, 0.1 mmol) and MnO_2 (180 mg, 2 mmol) in $CHCl_3$ (10 ml) was stirred at room temperature for 2 h. The mixture was filtered and evaporated to obtain 13β-epimer **4β** (14 mg, 70%).

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