APPLICATION OF THE MERCURIC ACETATE-EDETIC ACID OXIDATION METHOD TO THE SYNTHESIS OF 11-AZA-1,2,3,4,5,6,7,12b-OCTAHYDROINDOLO[2,3-*a*]QUINOLIZINES

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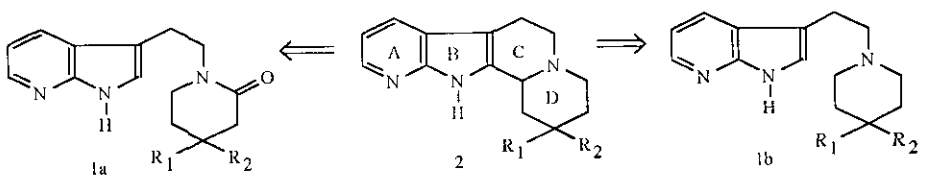
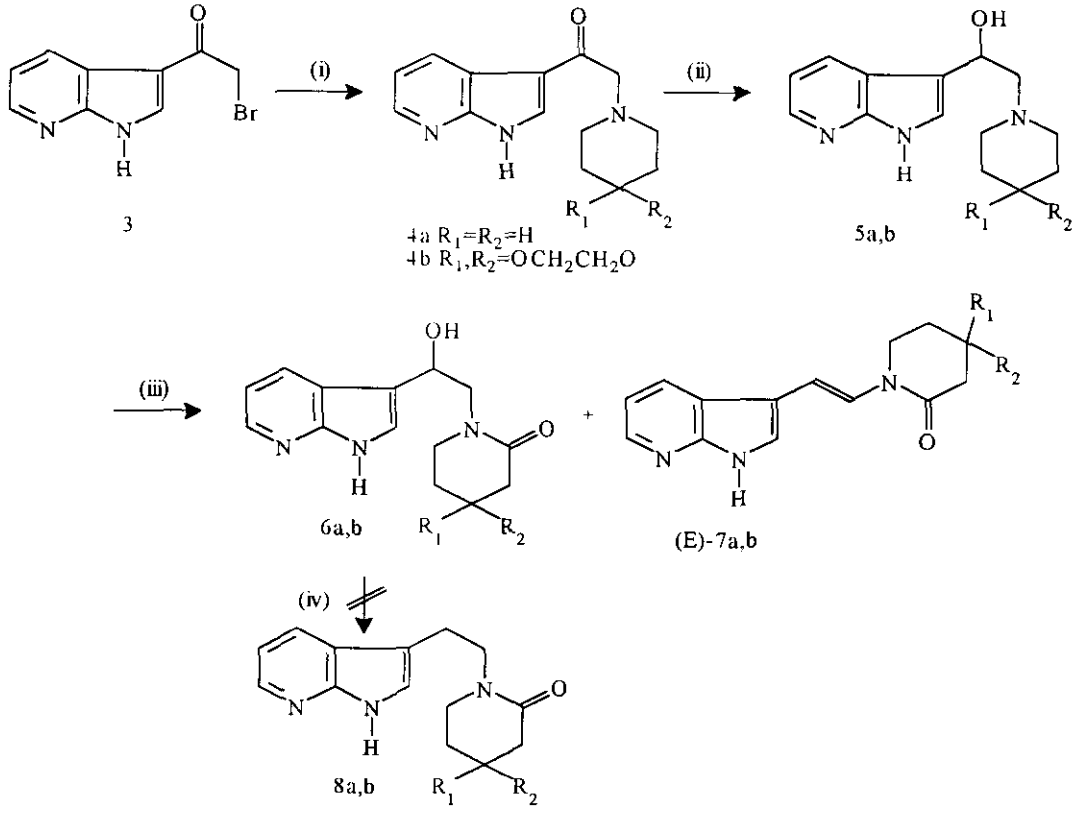
Abstract- The synthesis of 11-*azaindolo*[2,3-*a*]*quinolizidines* such as **2** is reported by cyclisation of lactams (**1a**) or piperidines (**1b**).

Interest in the indolo[2,3-*a*]quinolizidine ring system has increased these last years since this tetracycle is implicated in the synthesis of biological active compounds belonging to the *Yohimban* and *Eburnan* families of indole alkaloids.[1] In addition, number of 2-substituted indoloquinolizidines have been found to be some potent and selective antagonists of α_2-adrenoreceptors.[2] As a part of our studies concerning the chemistry of azaindolic structures,[3] we developed now a program for the preparation of azaindoloquinolizidine system such as **2**. In this optic, key step was the formation of the C12a-C12b bond. For this purpose two "routes" were investigated: preparation and cyclization of lactams types (**1a**) through a Bischler-Napieralski reaction,[4] or preparation and cyclization of piperidines types (**1b**) through a "mercuric acetate-edetic acid" procedure.[5]



1a 2 1b

Our first investigation was to prepare the lactams (**8a,b**). Synthesis of starting 3-bromoacetylazaindole (**3**) was achieved according published methods.[6] Treatment of **3** with appropriate piperidines yielded the ketones (**4a,b**) which upon a lithium aluminium hydride reduction gave the corresponding alcohols (**5a,b**). Treatment of these two alcohols with mercuric acetate to generate the lactams (**6a,b**) according the Fujii procedure[7] led to the expected compounds. Presence of the lactam function was made evident by ^{13}C-nmr with a carbonyl group at δ 172.1 for **6a** and at δ 169.4 for **6b**. In contrast with previous results obtained by Fujii,[4,7] no oxazolidine formation was found, but the unsaturated lactams (**7a,b**) were respectively obtained with appreciable amounts. The E-configuration was found in respect to their coupling constant ($J_{1'-2'}$ = 15.4 Hz for **7a**, and 15.3 Hz for **7b**). Surprisingly, all attempts to reduce the alcohols (**6a,b**) to give **8a,b** failed under various conditions of catalytic hydrogenation (Scheme 1).

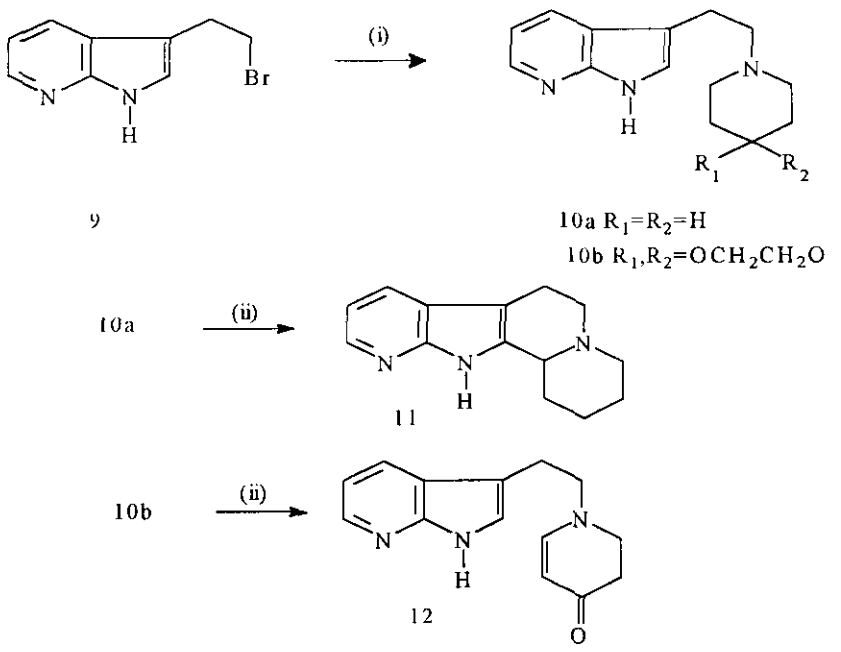


reagents and conditions: (i) piperidines/MeCN/Et_3N/reflux (ii)$LiAlH_4$/THF/O°C 30 min, 20°C, 2 h (iii) $Hg(OAc)_2$/EDTA/2N NaOH/reflux (iv) H_2, Pd-C

Scheme 1

This disappointing result led us to investigate the second route starting from 3-bromoethylazaindole (**9**) obtained by reduction of **3**.[6] Treatment of **9** with appropriate piperidines gave the derivatives (**10a,b**) in good yield. The expected azaindoloquinolizidine (**11**) was obtained when **10a** was treated by mercuric

acetate. Structural determination of **11** was based on ^{1}H and ^{13}C spectra, ^{1}H-^{1}H, and ^{1}H-^{13}C correlations. The *trans* relationship between C and D rings was made evident by the presence of a double doublet in the ^{1}H-nmr spectra at δ 3.30 for H-12b ($J_{12b\text{-}1ax}$ = 10.7 Hz and $J_{12b\text{-}1eq}$ = 1.7 Hz) and by the signals of C-6 and C-4 at δ 53.4 and 55.9 respectively.[8] Bolhmann bands at ν = 2760 and 2800 cm^{-1} in the infrared spectrum confirmed this analysis.[9] In contrast, compound (**10b**) treated in the same conditions gave the 2,3-dihydropyridone (**12**). The structure of **12** was easily determined by ^{1}H and ^{13}C-nmr: ^{1}H spectra showed two doublets (J = 7.3 Hz) at δ 4.81 and 6.80 corresponding to H-5 and H-6, while the ^{13}C-nmr spectrum showed characteristic resonances of such pyridone with δ 97.6 for C-6, δ 154.1 for C-5 and δ 191.2 for the carbonyl group. In attempt the cyclization of **12** into corresponding azaindoloquinolizidinone, we tried diverses acidic conditions described for the indolic structure[10] (sulfuric, hydrobromic or trifluoroacetic acids) : in all cases, starting material was recovered (Scheme 2).

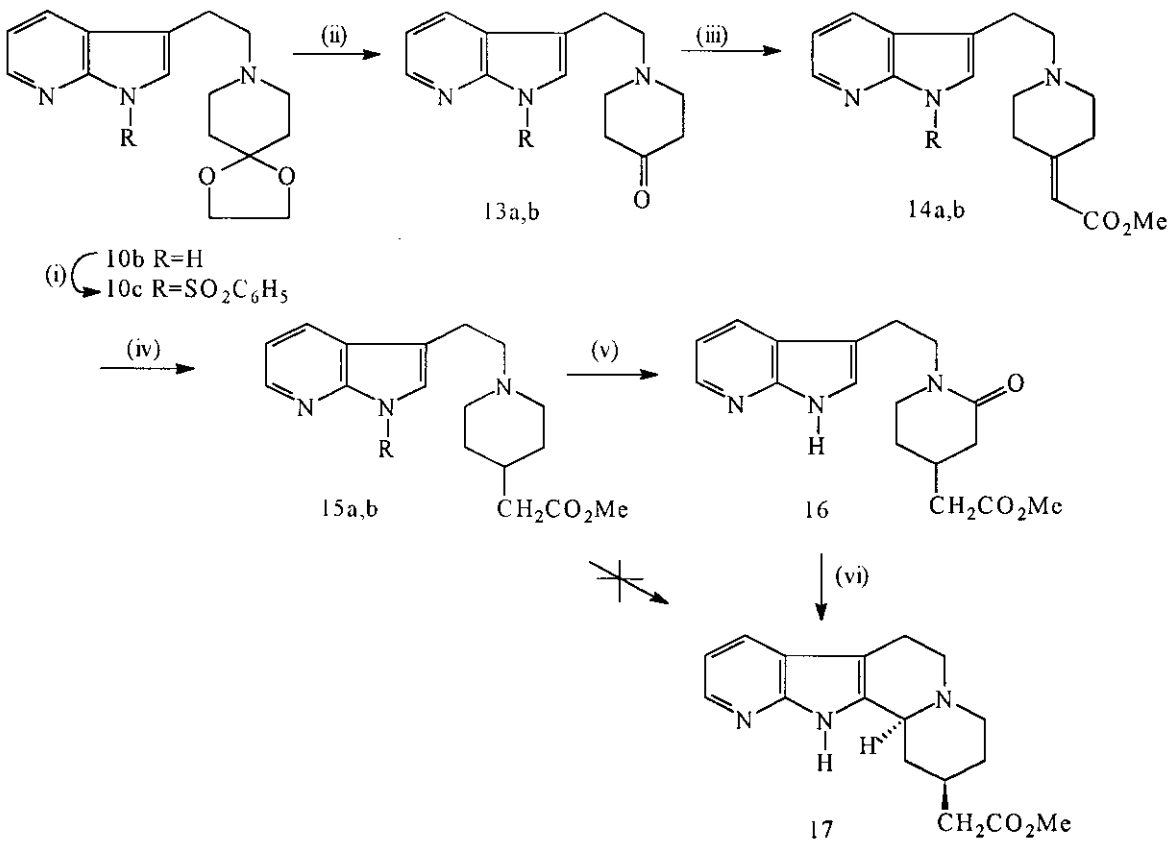


reagents and conditions: (i) piperidines/MeCN/$NaHCO_3$/reflux
(ii) a: $Hg(OAc)_2$/EDTA/H_2O,EtOH (2/1)reflux, b: $NaBH_4$

Scheme 2

From these results, and in our course for the obtention of 2-substituted azaindoloquinolizidines, we have turned our interest to the intramolecular cyclisation of piperidine (**15a,b**). Deprotection of the dioxolane (**10b,c**) under acidic conditions gave the piperidones (**13a,b**) in 95% and 45% yields, respectively. Subsequent Wittig reaction gave **14a,b** in 61% and 39% yields.[11] Structural determination of these two last was made by ^{13}C-nmr spectrum with δ_{C_4} 159.3 for **14a** and 159.2 for **14b**, $\delta_{C\alpha}$ 113.3 for **14a** and

113.6 for **14b** and by ^{1}H-nmr with the exocyclic ethylene proton at δ 5.71 for **14a** and δ 5.68 for **14b**. Catalytic hydrogenation of **14a,b** gave quantitatively the expected piperidines (**15a,b**). The piperidine (**15a**) was unreactive in the conditions cited above ($Hg(OAc)_2$, 3 eq.), and starting material was recovered, while **15b** led to tar formation. Using 5 equivalent of mercuric acetate, we were able to isolate the lactam (**16**) in 42% yield from **15a**. Structure of **16** was made evident by ^{13}C-nmr with δ 172.1 for the lactam function. Further treatment of **16** with phosphorus oxychloride in refluxed toluene followed by sodium borohydride gave the expected 2-substituted azaindoloquinolizidine (**17**) (Scheme 3).

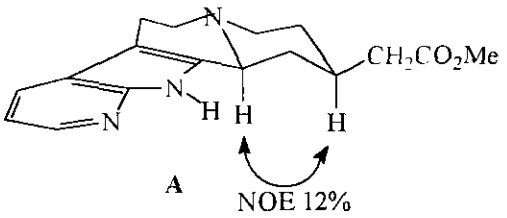


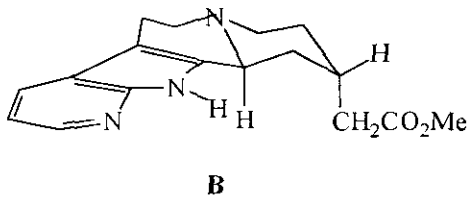
reagents and conditions: (i) a: BuLi/THF/-78°C, b: $C_6H_5SO_2Cl$, 2 h, 20°C (ii) 6N HCl/reflux,6 h (iii) $(C_6H_5)_3P{=}CHCO_2Me/C_6H_6$/reflux (iv) H_2/10% Pd-C/MeOH/1 atm (v) $Hg(OAc)_2$/EDTA/ H_2O,EtOH(2/1) (vi) a: $POCl_3$/toluene/reflux b: $NaBH_4$

Scheme 3

Compound (**17**) was isolated as a single diastereoisomer. Determination of the stereochemistry to the C-D *trans*, H12b-H2 *cis* isomer (**A**) was based on its spectral data (ir, ^{1}H, ^{13}C, ^{1}H-^{1}H and ^{1}H-^{13}C correlations). From the ir spectrum, the *trans* relationship between the C and D rings was found by the

presence of the Bolhmann bands at υ = 2800 and 2760 cm^{-1}, and by ^{1}H-nmr with H-12b at δ 3.39 as a double doublet. The axial position of H-2 was determined by examination of the ^{1}H-^{1}H COSY spectrum which showed H-3ax as a double quadruplet with $J_{3ax\text{-}2ax}$ = 12.5 Hz. Examination of the ^{13}C-nmr spectrum confirmed this elucidation with C-2 at δ 33.2 as a tertiary carbon. This value is in good agreement with those observed in the 2-substituted octahydroindolo[2,3-*a*]quinolizidines ($\delta_{C\text{-}2}$ (H-2/H-12b *cis*) 31.1 > $\delta_{C\text{-}2}$ (H-2/H-12b *trans*) 25.8 when R = methyl).[12] In addition, a NOE experiment clearly indicated this *cis* relationship with a NOE effect of 12% between H-12b$_{ax}$ and H-2$_{ax}$.





In conclusion, we have described a usefull synthesis of 2-substituted azaindoloquinolizidine (**17**). Influence of the 7-azaindolyl on the reactivity of starting piperidines (**9,10,12,15**) and lactams (**6,7**) is found to be quite different from those observed for indolyl or phenyl substrates.

EXPERIMENTAL

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. *Spectral measurements were taken using the following instruments:* ^{1}H and ^{13}C-nmr spectrum were taken on a Brüker AC-100 or a Brüker AC-400; chemical shifts are expressed in ppm downfield δ from TMS. Coupling constants, J, are given in Hz. Mass spectroscopy were recorded on a LKB 2091 spectrometer at 15eV [(θ_{source})=180°C] or JEOL DX 300 (FAB). Elemental analyses were performed by Microanalytical Center, ENSCM, Montpellier. Possible inversion of two values in the ^{13}C-nmr spectra is expressed by an asterisk.

Procedure for condensations of piperidines with 3-bromoacetylindole (**3**). A mixture of 5.05 mmol of the appropriate piperidine, 4 mmol of the halogeno derivative, 1.4 g (10.1 mmol) of potassium carbonate in 100 ml of toluene was stirred at reflux for 2 h under a nitrogen stream. After cooling, water (100 ml) was added and the mixture extracted with dichloromethane. Organic layers were dried over sodium sulfate and evaporated *under vacuo*. All compounds were purified by column chromatography on silica gel eluted with dichloromethane.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl]piperidine (**4a**). Obtained from piperidine and **3**; yield

90%; mp 157-159°C (recrystallization solvent: ether); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.51 (m, 6H, H-3,4,5), 2.46 (m,4H, H-2,6), 3.52 (s,H-1'), 7.18 (dd, $J_{4''-5''}$ = 7.4, $J_{5''-6''}$ = 4.8, H-5''), 8.32 (d, $J_{5''-6''}$ = 4.8, H-6''), 8.50 (s, H-2''), 8.66 (d, $J_{4''-5''}$ = 7.4, H-4''), 12.76 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 24.0 (C-4), 26.9 (C-3,5), 55.0 (C-2,6), 67.5 (C-1'), 115.0 (C-3''), 118.4 (C-5''), 119.4 (C-3a''), 131.8 (C-2''*), 133.4 (C-4''*), 143.5 (C-6''), 148.9 (C-7a''), 193.8 (CO); *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17,27. Found : C, 69.02; H 4.16; N, 17.19.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxoethyl]piperidine-4-ethylene ketal (**4b**). obtained from 1,4-dioxa-8-azaspiro[4,5]decane and **3**; yield 95%; mp 180-182°C (recrystallization solvent: ether); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.83 (m, H-3,5), 2.68 (m, H-2,6), 3.69 (s, 2H, H-1'), 3.95 (s, 4H, -OCH_2CH_2O-), 7.27 (dd, $J_{5''-6''}$ = 4.1, $J_{4''-5''}$ = 6.9, H-5''), 8.41 (d, $J_{5''-6''}$ = 4.1, H-6''), 8.44 (s, H-2''), 8.72 (d, $J_{4''-5''}$ = 6.9, H-4'') 13.11 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 35.2 (C-3,5), 52.5 (C-2,6), 64.8 (-OCH_2CH_2O-), 66.6 (C-1'), 107.7 (C-4), 115.9 (C-3''), 119.4 (C-5''), 120.4 (C-3a''), 132.8 (C-4''), 134.1 (C-2''), 144.7 (C-6''), 148.8 (C-7a''), 195.5 (CO); *Anal.* Calcd for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found : C, 63.68; H 6.31; N, 13.99.

Procedure for the reduction of **4a,b.** To a cooled solution of lithium aluminium hydride (0.55 g, 14.4 mmol) in 10 ml of THF was slowly added a solution of ketone (2 mmol) in 30 ml of THF. The resulting mixture was stirred at 0°C for 30 min, then at room temperature for 2 h. The mixture was diluted with 5 ml of water and made basic with 15% NaOH. After extraction with dichloromethane and evaporation of solvents, the compounds were chromatographied on neutral alumina eluted with dichloromethane.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]piperidine (**5a**). Yield 82%; mp 140-142°C (recrystallization solvent: dichloromethane); ms (m/z, relative intensity) 245 (7), 227 (44), 147 (12), 98 (100); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.49 (m, 6H, H-3,4,5), 2.28-2.86 (m, 6H, H-2,6,1'), 5.02 (dd, J =10.0 and 3.6, H-2'), 5.49 (s, OH), 6.92 (dd, $J_{4''-5''}$ = 7.8, $J_{5''-6''}$ = 4.7, H-5''), 7.22 (s, H-2''), 7.99 (d, $J_{4''-5''}$ = 7.8, H-4''), 8.16 (d, $J_{5''-6''}$ = 4.7, H-6''), 11.89 (s, NH); *Anal.* Calcd for $C_{14}H_{19}N_3O$: C, 68.54; H, 7.81; N, 17.13. Found : C, 68.49; H 7.76; N, 17.04.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]piperidine-4-ethylene ketal (**5b**). Yield 97%; mp 150-152°C (recrystallization solvent: dichloromethane); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.80 (m, 4H, H-3,5), 2.59-3.10 (m, 6H, H-2,6, H-1'), 5.04 (dd, J = 9.5 and 2.7 Hz, H-2'), 7.07 (dd, $J_{4''-5''}$ = 6.9, $J_{5''-6''}$ = 4.2, H-5''), 7.32 (s, H-2''), 8.07 (d, $J_{4''-5''}$ = 6.9, H-4''), 8.30 (d, $J_{5''-6''}$ = 4.2, H-6''), 10.86 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 34.9 (C-3,5), 51.4 (C-2,6), 63.8 (C-2'), 64.3 (C-1',

OCH_2CH_2O), 107.0 (C-4), 115.2 (C-3''), 115.5 (C-5''), 118.9 (C-3a''), 122.5 (C-2''), 128.4 (C-4''), 142.6 (C-6"), 149.2 (C-7a''); *Anal.* Calcd for $C_{16}H_{21}N_3O_3$: C, 63.35; H, 6.98; N, 13.85. Found : C, 63.23; H 7.12; N, 13.78.

Mercuric acetate/EDTA oxidation of **5a,b.** A solution of alcohol (**5a,b**) (2 mmol), EDTA,$2H_2O$ (1.9 g, 5 mmol), $Hg(OAc)_2$ (1.6 g, 5 mmol), in 12 ml of 1N NaOH was refluxed for 3 h. After beeing cooled and basified (pH=11), the mixture was extracted with dichloromethane. Organic layers were washed with 10% HCl, dried over sodium sulfate and concentrated *under vacuo*.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]-2-piperidone (**6a**) and 1-[2-(1*H*-pyrrolo[2,3-*b*]-pyridin-3-yl)vinyl]-2-piperidone (**7a**). Purification of the crude product on silica gel eluted with dichloromethane gave first **6a** as an oil; yield 53%; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.58 (m; 4H, H-4,5), 2.33 (m, 2H, H-3), 3.10 (m, 2H, H-6), 3.47-3.93 (m, 2H, H-1'), 4.81 (s, OH), 5.27 (m, H-2'), 6.95 (dd, $J_{4''-5''}$ = 7.9, $J_{5''-6''}$ = 4.2, H-5''), 7.25 (s, H-2''), 8.03 (d, $J_{4''-5''}$ = 7.9, H-4''), 8.16 (d, $J_{5''-6''}$ = 4.2, H-6''), 11.31 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 20.9 (C-4), 23.0 (C-5), 32.1 (C-3), 50.2 (C-6), 55.9 (C-1'), 67.2 (C-2'), 115.5 (C-3''), 116.0 (C-5''), 118.6 (C-3a''), 122.5 (C-2''), 128.3 (C-4''), 142.5 (C-6''), 148.8 (C-7a''), 172.1 (CO). *Anal.* Calcd for $C_{14}H_{17}N_3O_2$: C, 64.85; H, 6.61; N, 16.20. Found : C, 64.92; H 6.59; N, 16.11. Further elution gave **7a** as an oil; yield 12%; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.89 (m, H-4,5), 2.54 (t, J= 6.2, H-6), 3.57 (t, J = 5.2, H-3), 6.11 (d, $J_{1'-2'}$ = 15.4, H-2'), 7.12 (dd, $J_{4''-5''}$ = 7.6, $J_{5''-6''}$ = 4.7, H-5''), 7.32 (s, H-2''), 8.09-8.32 (m, 3H, H-1',4'',6''), 10.05 (s, NH); *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found : C, 69.80; H 6.14; N, 17.36.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2-hydroxyethyl]-2-piperidone-4-ethylene ketal (**6b**) and 1-[2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)vinyl]-2-piperidone-4-ethylene ketal (**7b**). Purification of the crude product on silica gel eluted with dichloromethane gave first **6b**; 25%; mp 91-93°C (recrystallization solvent: dichloromethane); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.72 (m, 2H, H-5), 2.57 (br s, 2H, H-3), 3.23 (m, 2H, H-6), 3.50-4.00 (m, 6H, H-1', OCH_2CH_2O), 5.24 (m, H-2'), 6.94 (dd, $J_{4''-5''}$ = 6.9, $J_{5''-6''}$ = 4.7, H-5''), 7.22 (s, H-2''), 7.92-8.16 (m, 2H, H-4'',6''), 11.13 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 31.9 (C-5), 42.4 (C-3), 46.5 (C-6), 55.0 (C-1'), 64.6 (OCH_2CH_2O), 66.9 (C-2'), 105.8 (C-4), 115.5 (C-3''), 115.8 (C-5''), 118.6 (C-3a''), 122.5 (C-2''), 128.3 (C-4''), 142.5 (C-6''), 148.7 (C-7a''), 169.4 (CO); *Anal.* Calcd for $C_{16}H_{19}N_3O_4$: C, 60.56; H, 6.03; N, 13.24. Found: C, 60.49; H 6.17; N,

13.26. Further elution gave **7b** as an oil; 5%; ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 2.15 (m, 2H, H-5), 2.78 (s, 2H, H-3), 3.69 (m, H-6), 4.02 (s, 4H, OCH_2CH_2O), 6.20 (d, $J_{1'-2'}$ = 15.3, H-2'), 7.14 (dd, $J_{4''-5''}$ = 7.3, $J_{5''-6''}$ = 4.8, H-5''), 7.34 (s, H-2''), 8.02-8.30 (m, 3H, H-1',4'',6''); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 31.5 (C-5), 41.8 (C-3), 42.9 (C-6), 64.9 (OCH_2CH_2O), 104.6 (C-1'*), 105.5 C-4*), 112.3 (C-2'), 116.1 (C-5''), 118.2 (C-3a''), 122.9 (C-2''), 124.8 (C-3''), 128.9 (C-4''), 142.9 (C-6''), 149.1 (C-7a''), 166.3 (CO); *Anal.* Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found : C, 64.12; H 5.87; N, 14.06.

Procedure for condensation of piperidines with 3-bromoethylazaindole (**9**). A mixture of 8.4 mmol of the appropriate piperidine, 4.2 mmol of **9**, 1.35 g (16.0 mmol) of sodium hydrogenocarbonate in 25 ml of acetonitrile was refluxed under a nitrogen stream for 4 h. After cooling, 100 ml of water was added and the solution was extracted with dichloromethane. Organic layers were dried over sodium sulfate and solvents were removed *under vacuo*. All coumponds were purified by chromatography on silica gel eluted with dichloromethane.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]piperidine (**10a**). Yield 72%; mp 113-115°C (recrystallization solvent: ether); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.48 (m, 2H, H-4), 1.65 (m, 4H, H-3,5), 2.52 (m, 2H, H-2,6), 2.67 (t, $J_{1'-2'}$ = 7.7, H-1'), 2.97 (t, $J_{1'-2'}$ = 7.7, H-2'), 7.06 (dd, $J_{4''-5''}$ = 7.8, $J_{5''-6''}$ = 4.2, H-5''), 7.16 (s, H-2''), 7.94 (dd, $J_{4''-5''}$ = 7.8, $J_{4''-6''}$ = 1.3, H-4''), 8.30 (d, $J_{5''-6''}$ = 4.2, H-6''), 10.67 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 22.9 (C-2'), 24.4 (C-4), 25.9 (C-3,5), 54.5 (C-2,6), 59.9 (C-1'), 112.6 (C-3''), 114.9 (C-5''), 120.3 (C-3a''), 122.4 (C-2''), 127.3(C-4''), 142.1 (C-6''), 148.9 (C-7a''); *Anal.* Calcd for $C_{14}H_{19}N_3$: C, 73.33; H, 8.35; N, 18.32. Found : C, 73.22; H 8.47; N, 18.31.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)ethyl]piperidine-4-ethylene ketal (**10b**). Yield 94%; mp 145-147°C (recrystallization solvent: hexane); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ: 1.81 (t, J_{2-3}=J_{5-6} = 5.6, H-3,5), 2.70 (m, H-1',2,6), 2.97 (t, $J_{1'-2'}$ = 7.1, H-2'), 4.00 (s, OCH_2CH_2O), 7.06 (dd, $J_{4''-5''}$ = 7.8, $J_{5''-6''}$ = 4.5, H-5''), 7.16 (s, H-2''), 7.93 (d, $J_{4''-5''}$ = 7.8, H-4''), 8.28 (d, $J_{5''-6''}$ = 4.5, H-6''), 9.80 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 23.3 (C-2'), 34.7 (C-3,5), 51.3 (C-2,6), 58.7 (C-1'), 64.1 (OCH_2CH_2O), 107.1 (C-4), 112.4 (C-3''), 114.8 (C-5''), 120.2 (C-3a''), 122.4 (C-2''), 127.2 (C-4''), 142.0 (C-6''), 148.9 (C-7a''); *Anal.* Calcd for $C_{16}H_{21}N_3O_2$: C, 66.88; H, 7.37; N, 14.62. Found : C, 66.72; H 7.41; N, 14.60.

Mercuric acetate/EDTA oxidation of **10a,b**. A solution of mercuric acetate (2.2 g, 6.9 mmol), EDTA

(2.57 g, 6.9 mmol) in 60 ml of water was added to a solution of starting heterocycle (2.27 mmol) in 30 ml of ethanol. The whole mixture was refluxed for 4 h. After beeing cooled and basified with aqueous 30% ammonia (pH=9), sodium borohydride (0.87g, 22.8 mmol) was added and the solution was then stirred for 18 h more. The resulting mixture was acidified with 10% HCl, the precipitate formed was filtered off, the filtrate was basified with 10% NaOH (pH=10) and extracted with dichloromethane. Organic layers were dried over sodium sulfate and evaporated *under vacuo*. All compounds were purified by column chromatography on silica gel eluted with dichloromethane.

1,2,3,4,6,7,12b-Octahydropyrido[2',3';2,3]pyrrolo[4,5-*a*]quinolizine (**11**). lit.,[13] Yield 30%, mp 202-204°C (recrystallization solvent: dichloromethane).

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-2,3-dihydro-4-pyridone (**12**). Yield 29%; mp 170-172°C (recrystallization solvent: hexane); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 2.40 (t, J = 7.5 Hz, 2H, H-3), 3.03 (t, $J_{1'-2'}$ = 6.7, H-2'), 3.50 (m, 4H, H-1',2), 4.81 (d, J_{5-6} = 7.3 Hz, H-5), 6.80 (d, J_{5-6} = 7.3 Hz, H-6), 7.15 (dd, $J_{4''-5''}$ = 7.1, $J_{5''-6''}$ = 3.8, H-5''), 7.24 (s, H-2''), 7.98 (d, $J_{4''-5''}$ = 7.1, H-4''), 8.30 (d, $J_{5''-6''}$ = 3.8, H-6''), 11.90 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 25.1 (C-2'), 35.5 (C-3), 47.0 (C-2), 56.5 (C-1'), 97.6 (C-6), 109.8 (C-3''), 115.4 (C-5''), 119.6 (C-2''), 123.5 (C-3a''), 126.7 (C-4''), 142.7 (C-6''), 149.0 (C-7a''), 154.1 (C-5), 191.2 (CO); *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found : C, 69.75; H 6.13; N, 17.38.

1-[2-(1-Phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]piperidine-4-ethylene ketal (**10c**). To a stirred solution of **10b** (1.3 g, 4.5 mmol) in THF (40 ml) at -78°C, was added 3 ml of BuLi (6 mmol) (2M in cyclohexane). After beeing stirred at 0°C for 15 min, the mixture was cooled again at -78°C and phenylsulfonyl chloride (0.8 ml, 6.2 mmol) was slowly added. After stirring 3 h more at room temperature, the reaction mixture was washed with a 2% solution of sodium carbonate, extracted with ether. Organic layers were dried over sodium sulfate, and solvents removed *under vacuo*. The crude product was chromatographed on silica gel eluted with dichoromethane to give 2.05 g of **10c**; yield 94%; mp 129-131°C (recrystallization solvent: ether); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 1.74 (m, 4H, H-3,5), 2.48-2.95 (m, 8H, H-1',2',2,6), 3.91 (s, 4H, OCH_2CH_2O), 7.12 (dd, $J_{4''-5''}$ = 7.9, $J_{5''-6''}$ = 4.5, H-5''), 7.35 (s, H-2''), 7.44-7.61 (m; 4H, H-2'', H-ar), 8.1-8.25 (m, 3H, H-4'', H-ar), 8.37 (d, $J_{5''-6''}$ = 4.5, H-6''); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 23.2 (C-2'), 34.9 (C-3,5), 51.4 (C-2,6), 57.4 (C-1'), 64.3 (OCH_2CH_2O), 107.1 (C-4), 117.9 (C-3''), 118.6 (C-5''), 122.9 (C-8''), 123.3 (C-3a''), 127.8 (C-ar), 127.9 (C-4''), 128.9 (C-ar), 133.8 (C-ar), 138.6 (C-ar), 144.9 (C-6''), 147.5 (C-7a''); *Anal.*

Calcd for $C_{22}H_{25}N_3O_4S$: C, 61.81; H, 5.89; N, 9.83. Found : C, 61.75; H 6.03; N, 9.78.

Deprotection of **10b,c**. To a solution of ketal (2 g for **10b**, 2.9 g for **10c**, 6.9 mmol) in 50 ml of acetone was added 20 ml of 6N HCl. The mixture was refluxed for 6 h. After beeing cooled, the solution was diluted with 50 ml of water, basified with Na_2CO_3 (powder) and extracted with dichloromethane. The solvents were removed *under vacuo*. The compounds were purified by chromatography on neutral alumina eluted with dichloromethane.

1-[2-(1*H*-Pyrrolo[2,3-*b*]pyridin-3-yl)-4-piperidone (**13a**). Yield 95%; mp 125-127°C (recrystallization solvent: cyclohexane); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 2.51 (t, J = 5.8 , 4H, H-3,5), 2.88 (m, 8H, H-2,6, H-1',2'), 7.09 (m, H-5''), 7.25 (s, H-2''), 7.96 (dd, $J_{4''-5''}$ = 7.8, $J_{4''-6''}$ = 1.4, H-4''), 8.34 (dd, $J_{5''-6''}$ = 4.7, $J_{4''-6''}$ = 1.4, H-6''), 10.38 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 23.7 (C-2'), 41.2 (C-3,5), 53.1 (C-2,6), 58.0 (C-1'), 112.3 (C-3''), 115.1 (C-5''), 120.2 (C-3a''), 122.5 (C-2''), 127.2 (C-4''), 142.4 (C-6''), 149.0 (C-7a''), 209.1 (CO); *Anal.* Calcd for $C_{14}H_{17}N_3O$: C, 69.11; H, 7.04; N, 17.27. Found : C, 69.25; H 7.03; N, 17.38.

1-[2-(1-Phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-4-piperidone (**13b**). Yield 45%; mp 103-105°C (recrystallization solvent: dichloromethane); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 2.40 (t, 4H, J = 5.7, H-3,5), 2.77 (m, 8H, H-2,6, H-1',2'), 7.15 (m, H-5''), 7.33 (s, H-2''), 7.35-7.60 (m, 3H, H-ar), 7.77 (dd, $J_{4''-5''}$ = 7.8, $J_{4''-6''}$ = 1.3, H-4''), 8.00-8.20 (m, 2H, H-ar), 8.37 (dd, $J_{4''-6''}$ = 1.3, $J_{5''-6''}$ = 4.8, H-6''); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 23.3 (C-2'), 41.1 (C-3,5), 52.9 (C-2,6), 56.5 (C-1'), 117.4 (C-3''), 118.6 (C-5''), 122.9 (C-2''), 123.1 (C-3a), 127.7 (C-4", C-ar), 128.9 (C-ar), 133.8 (C-ar), 144.9 (C-6''), 147.4 (C-7a''), 208.6 (CO); *Anal.* Calcd for $C_{20}H_{21}N_3O_3S$: C, 62.64; H, 5.52; N, 10.96. Found : C, 62.52; H 5.61; N, 10.88.

Procedure for preparation of **14a,b**. A solution of **13a,b** (1.8 mmol) and (carbomethoxymethylene)triphenylphosphine (0.62 g, 1.8 mmol) in 15 ml of benzene was refluxed for 7 h. After cooling, solvent was removed *under vacuo*. The residual oil was dissolved in dichloromethane and chromatographed on neutral alumina eluted with dichloromethane.

Methyl 1-[2-(1*H*-Pyrrolo[2,3-b]pyridin-3-yl)piperidine-$\Delta^{4,\alpha}$-acetate (**14a**). Yiled 61%; mp 104-106°C (recrystallization solvent: ether); ^{1}H-nmr ($CDCl_3$, 100 MHz) δ 2.00-3.40 (m, 12H), 3.74 (s, 3H, CH_3), 5.71 (s, 1H, C<u>H</u>CO_2CH_3), 7.09 (dd, $J_{4''-5''}$ = 7.3, $J_{5''-6''}$ = 4.2, H-5''), 7.22 (s, H-2''), 7.95 (d, $J_{4''-5''}$ =7.3, H-4''), 8.36 (d, $J_{5''-6''}$ = 4.2, H-6''), 12.10 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 22.9 (C-2'),

29.0 (C-3), 36.2 (C-5), 50.6 (CH_3), 53.7 (C-2*), 54.4 (C-6*), 58.3 (C-1'), 111.9 (C-3''), 113.3 ($\underline{C}HCO_2CH_3$), 114.6 (C-5''), 120.0 (C-3a''), 122.4 (C-2''), 126.9 (C-4''), 141.7 (C-6''), 148.7 (C-7a''), 159.3 (C-4), 166.6 (CO); *Anal.* Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found : C, 68.01; H 7.14; N, 14.21.

Methyl 1-[2-(1-phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]piperidine-$\Delta^{4,\alpha}$-acetate **(14b).** Yield 39%; oil; ms (FAB+); 440 (100), 438 (51), 285 (10), 168 (40), 131 (20); ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 2.40 (m, 2H, H-3*), 2.65 (m, 4H, H-2,6*), 2.72 (t, J = 7.6, H-1'*), 2.92 (t, J = 7.6, H-2'*), 3.07 (m, H-5*), 3.69 (s, CH_3), 7.18 (dd, $J_{4''-5''}$ = 7.8, $J_{5''-6''}$ = 4.7, H-5''), 7.46 (m, 2H, H-2'', H-ar), 7.55 (m, 2H, H-ar), 7.85 (dd, $J_{4''-5''}$ = 7.8. $J_{4''-6''}$ =1.2, H-4''), 8.16 (m, 2H, H-ar), 8.42 (dd, $J_{5''-6''}$ = 4.7, $J_{4''-6''}$ = 1.2,, H-6''); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ 22.9 (C-2'), 29.2 (C-3), 36.5 (C-5), 50.7 (CH_3), 53.9 (C-2*), 54.5 (C-6*), 57.1 (C-1'), 113.6 ($\underline{C}HCO_2CH_3$), 117.6 (C-3''), 118.4 (C-5''), 122.8 (C-2''), 123.1 (C-3a''), 127.6 (C-ar), 127.8 (C-4''), 128.8 (C-ar), 133.7 (C-ar), 138.3 (C-ar), 144.7 (C-6''), 147.4 (C-7a''), 159.2 (C-4), 166.7 (CO); *Anal.* Calcd for $C_{23}H_{25}N_3O_4S$: C, 62.85; H, 5.73; N, 9.59. Found : C, 62.76; H, 5.82; N, 9.51.

Procedure for reduction of **14a,b.** A mixture of **14a,b** (0.36 mmol), 150 mg of 10% Pd-C, in 10 ml of methanol was hydrogenated at atmospheric pressure during 3 h. After filtration, the solvent was evaporated, and the crude products were used without further purification.

Methyl 1-[2-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)-4-piperidineacetate **(15a).** Yield 97%; mp 85-87°C (recrystallization solvent: ether); ms (FAB+) 302 (100), 170 (73), 145 (53); ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 1.70-2.10 (m, 5H, H-3,4,5), 2.34 (d, 2H, J = 6.8, $C\underline{H}_2CO_2CH_3$), 2.51 (m, 2H, H-2,6), 3.00 (m, 2H, H-2'), 3.26 (m, 2H, H-1'), 3.42 (m, 2H, H-2,6), 3.70 (s, CH_3), 7.10 (dd, $J_{4''-5''}$ = 7.6, $J_{5''-6''}$ = 4.0, H-5''), 7.19 (s, H-2'), 8.04 (d, $J_{4''-5''}$ = 7.6, H-4''), 8.31 (d, $J_{5''-6''}$ = 4.0, H-6''), 9.61 (s, NH); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ 22.6 (C-2'), 31.4 (C-3,5), 32.5 (C-4), 40.6 ($\underline{C}H_2CH_3$), 51.3 (CH_3), 53.3 (C-2,6), 59.1 (C-1'), 111.9 (C-3'), 114.9 (C-5''), 120.1 (C-3a''), 122.5 (C-2''), 127.1 (C-4''), 142.0 (C-6''), 148.8 (C-7a''), 172.9 (CO); *Anal.* Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.76; H, 7.82; N, 13.91.

Methyl 1-[2-(1-phenylsulfonylpyrrolo[2,3-*b*]pyridin-3-yl)ethyl]-4-piperidineacetate **(15b).** Yield 97%; mp 140-142°C (recrystallization solvent: ether); ms (FAB+): 442 (100), 302 (15), 170 (83), 154 (70), 136 (60); ^{1}H-nmr ($CDCl_3$, 250 MHz) δ: 1.90-2.09 (m, 5H, H-3,4,5), 2.38 (d, J = 4.7, 2H, $C\underline{H}_2CO_2CH_3$), 2.73 (m, 2H, H-3,5), 3.18 (m, 2H, H-2'), 3.42 (m, 2H, H-1'), 3.69 (m, 5H, H-

2,6,CH_3), 7.23 (dd, $J_{4''-5''}$ = 7.8, $J_{5''-6''}$ = 4.7, H-5''), 7.49 (m, 2H, H-ar), 7.59 (m, 2H, H-ar), 8.18 (m, 2H, H-ar, H-2''), 8.23 (dd, $J_{4''-5''}$ =7.8, $J_{4''-6''}$ = 1.4, H-4''), 8.45 (dd, $J_{5''-6''}$ = 4.7, $J_{4''-6''}$ = 1.4, H-6''); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ: 20.2 (C-2'), 28.6 (C-3,5), 30.7 (C-4), 39.2 ($\underline{C}H_2CO_2CH_3$), 51.6 (CH_3), 52.3 (C-2,6), 55.9 (C-1'), 114.4 (C-3''), 118.9 (C-5''), 122.2 (C-3a''), 123.3 (C-2''), 127.6 (C-ar), 128.5 (C-4''), 128.9 (C-ar), 134.1 (C-ar), 137.8 (C-ar), 145.2 (C-6''), 147.0 (C-7a''), 172.1 (CO); *Anal.* Calcd for $C_{23}H_{27}N_3O_4S$: C, 62.57; H, 6.16; N, 9.52. Found: C, 62.66; H, 6.22; N, 9.47.

Methyl 1-[2-(1*H*pyrrolo[2,3-*b*]pyridin-3-yl)-2-oxo-4-piperidineacetate (**16**). This coumpond is obtained following the procedure used for the preparation of **11,12** using 5 equivalent of $Hg(OAc)_2$; yield 42%; mp 112-114°C (recrystallization solvent: cyclohexane); ^{1}H-nmr ($CDCl_3$, 250 MHz) δ 1.23-1.41 (m, 1H, H-4), 1.78 (m, 1H, H-5), 1.93-2.27 (m, 4H, H-3, $C\underline{H}_2CO_2CH_3$), 2.50 (m, H-5), 2.96 (t, J = 7.4, H-2'), 3.02-3.20 (m, 2H, H-6), 3.60 (m, 5H, H-1', CH_3), 7.02 (dd, $J_{4''-5''}$ = 7.9, $J_{5''-6''}$ = 4.8, H-5''), 7.13 (s, H-2''), 7.94 (dd, $J_{4''-5''}$ = 7.9, $J_{4''-6''}$ = 1.5, H-4''), 8.25 (dd, $J_{5''-6''}$ = 4.8, $J_{4''-6''}$ = 1.5, H-6''), 10.49 (s, NH); ^{13}C-nmr ($CDCl_3$, 25 MHz) δ 23.2 (C-2'), 28.7 (C-4*), 29.8 (C-5*), 38.2 (C-3), 39.6 ($\underline{C}H_2CO_2CH_3$), 47.5 (C-6), 48.1 (C-1'), 51.7 (CH_3), 111.5 (C-3''), 115.3 (C-5''), 120.2 (C-3a''), 122.7 (C-2''), 127.4 (C-4''), 142.6 (C-6''), 148.9 (C-7a''), 168.6 (CO), 172.1 (CO); *Anal.* Calcd for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found : C, 64.67; H, 6.82; N, 13.47.

Methyl 1,2,3,4,6,7,12,12b-octahydropyrido[2'3':2,3]pyrrolo[4,5-*a*]quinolizine-4-acetate (**17**). A solution of **16** (50 mg, 0.16 mmol), phosphorus oxychloride (1.7 g, 11 mmol) in toluene (5 ml) is refluxed for 2 h. After evaporation of solvent, the residual oil is dissolved in 7 ml of methanol, cooled at 0°C, and $NaBH_4$ (90 mg, 2.3 mmol) is slowly added. The resulting mixture is then stirred at room temperature for 1.5 h, and 3 ml of acetone are added. After evaporation of the solvents, the crude product was dissolved in water and extracted with dichloromethane. The solvents were removed *under vacuo*. Chromatography on silica gel eluted with dichloromethane/methanol (98/2) gave **17** (45 mg) as a white solid; 95%; mp 158-160°C (recrystallization solvent: ether); ir (KBr); Bolhmann bands 2800 and 2760 cm^{-1}; ms (FAB$^+$): 300 (M^++1, 46%), 154 (100%); ^{1}H-nmr ($CDCl_3$, 400 MHz) δ 1.35 (q, J = 12.5, H-1ax), 1.55 (qd, J = 12.5, J = 5, H-3a), 1.85, (dm, J = 12.5, H-3eq), 2.18 (m, H-2ax), 2.36 (d, J = 7.5, CH_3), 2.39 (m, H-1eq), 2.5 (td, J = 12.5, J = 2.5, H-4a), 2.60-2.77 (m, 2H, H-6, H-7), 2.95-3.15 (m, 3H, H-4eq, H-6', H-7'), 3.39 (dd, $J_{12bax-1eq}$ = 5, $J_{12bax-1ax}$ = 1.7, H-12bax), 3.70 (s, CH_3), 7.05 (dd, J_{8-9} = 6.0, J_{9-10} = 4.8, H-9), 7.77 (dd, J_{8-9} = 6.0, J_{8-10} = 1.1, H-8), 8.21 (dd, J_{9-10} = 4.8, J_{8-10} = 1.1, H-10), 10.7 (s, NH); ^{13}C-nmr ($CDCl_3$, 100 MHz) δ 21.7 (C-7), 32.1 (C-3), 33.2 (C-

2), 36.2 (C-1), 41.1 ($\underline{C}H_2C0_2CH_3$), 51.7 (CH_3), 53.0 (C-6), 55.4 (C-4), 59.6 (C-12b), 106.4 (C-7a), 115.4 (C-9), 120.4 (C-7b), 126.3 (C-8), 136.0 (C-12a), 141.5 (C-10), 149.3 (C-11a), 173.0 (CO); *Anal.* Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found : C, 68.37; H, 7.08; N, 13.98.

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Received, 2nd August, 1996