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STUDIES ON THE SYNTHESIS OF INDOLO[2,3-*a*]QUINOLIZIDIN-2-ONES. II[1]

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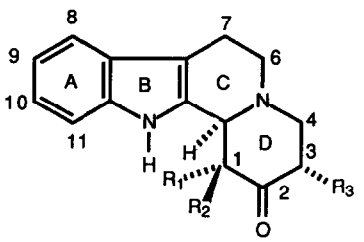
Abstract- The synthesis of indolo[2,3-*a*]quinolizidin-2-one (**1a**) has been accomplished by the direct cyclization of *N*-hydroxyethyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone ethylene acetal (**4**) with K^{t}BuO. Nevertheless, treatment of the 3-ethylpiperidine analogue **16** with K^{t}BuO only led to the corresponding hexahydro-4*H*-pyrido [1′,2′:1,2]pyrazino [4,3-*a*]indole (**23**), resulting from the cyclization upon the indole nitrogen.

The indolo[2,3-*a*]quinolizidin-2-one framework **1a**[2-9] is integrated in the structure of several key intermediates in the synthesis of pentacyclic indolo[2,3-*a*]quinolizidine alkaloids. The great majority of such compounds are substituted on position 3[8,10-14] and only two cases of C-1 substituted derivatives have been reported (see Figure 1).[15,16] Indolo[2,3-*a*]quinolizidin-2-one itself (**1a**) has been extensively studied and its synthesis has been carried out by two general synthetic strategies consisting in the elaboration of rings C or D in the key steps. Thus, elaboration of ring C has been carried out by formation of the C_{12a}-C_{12b} bond,[4] while ring D has been constructed by i) a Dieckmann cyclization of the appropriate diester,[3,6] ii) an hetero Diels-Alder or a Michael-Mannich tandem reaction applied on dihydrocarbolines,[7,8] iii) by formation of N-C_4 bond,[2] and iv) by application of the acid catalysed rearrangement of isoxazoline-5-spiro cyclopropanes.[9] These numerous synthetic studies arise from the application of **1a** in the synthesis of related compounds to Rauwolfia and Yohimbe alkaloids such as reserpine[17] and yohimbine[6]. Moreover, other important synthetic intermediates are 3- and 1-ethylindolo[2,3-*a*]quinolizidin-2-ones **1b** and **2**, respectively. In spite of the fact that 3-ethylderivative **1b** has been synthesized[10-12] and applied to the synthesis of dihydrocorynantheine,[18] corynantheidine[18,19] and flavopereirine[20] alkaloids , no synthesis has been described for its 1-ethyl analogue **2.** However, the 1-ethyl-1-methoxycarbonylmethyl derivative **1k** has been prepared and applied to the synthesis of eburnamonine.[15]

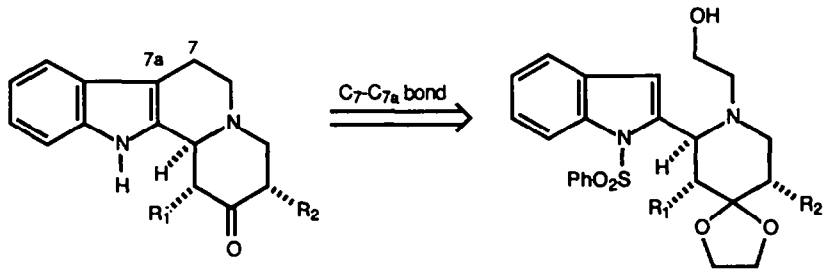


1a R_1=R_2=R_3=H (Ref. 2-9)
b R_1=R_2=H; R_3=C_2H_5 (Ref. 10-12)
c R_1-R_2=H; R_3=CH_3 (Ref. 10-12)
d R_1=R_2=H; R_3=*n*-C_3H_7 (Ref. 10,12)
e R_1=R_2=H; R_3=*i*-C_4H_9 (Ref. 10, 12)
f R_1=R_2=H; R_3=CH_2Ph (ref. 10, 12)
g R_1=R_2=H; R_3=$COCH_3$ (Ref. 13)
h R_1=R_2=H; R_3=$COOC_2H_5$ (Ref. 3,13)
I R_1=R_2=H; R_3=CH_2COOCH_3 (Ref. 8,12)
j R_1=R_2=H; $CH_2CH_2COOCH_3$ (Ref. 12,14
k R_1=C_2H_5; R_2=CH_2COOCH_3; R_3=H (Ref. 15)
l R_1=$CH_2CH_2COOCH_3$; R_2=R_3=H (Ref.16)

Figure 1

In a precedent paper we reported the synthesis of 3-ethylindolo[2,3-*a*]quinolizidin-2-one **1b** by a new methodology consisting in the elaboration of ring C by formation of C_7-C_{7a} bond by a potassium *tert*-butoxide one step cyclization of *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone ethylene acetal **3**,[1] as a synthetic application of protected 2-aryl-4-piperidones.[21-23]

In the present paper we report the use of this reaction on *N*-hydroxyethylpiperidines **4** and **16** in order to obtain a new synthesis of indolo[2,3-*a*]quinolizidin-2-one basic framework **1a** and the 1-ethyl derivative **2**.



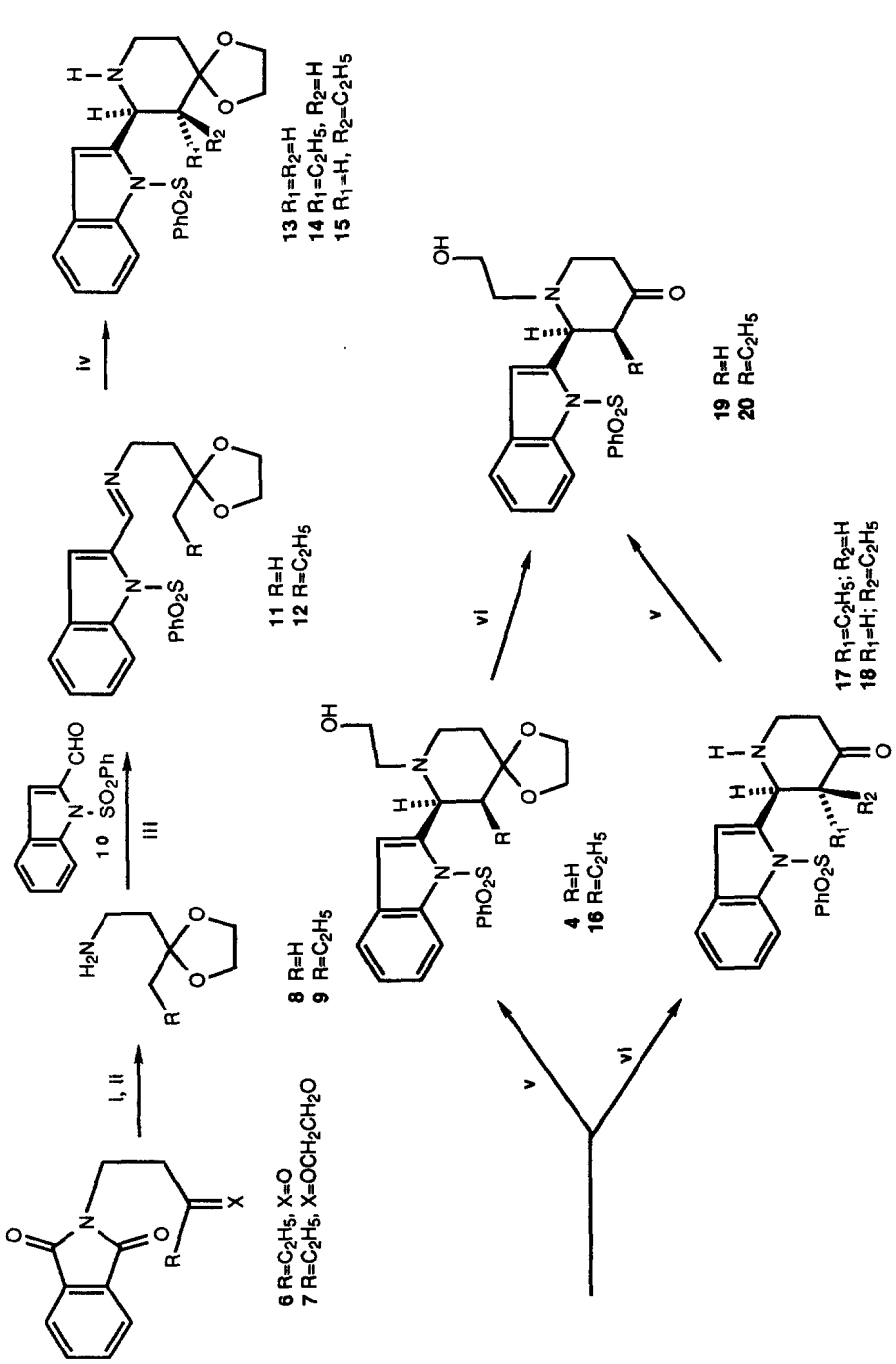
1a R_1=R_2=H
1b R_1=H; R_2=C_2H_5
2 R_1=C_2H_5; R_2=H

3 R_1=H; R_2=C_2H_5
4 R_1=R_2=H
5 R_1=C_2H_5; R_2=H

Figure 2

The starting *N*-hydroxyethylpiperidones ethylene acetals **4** and **16** were prepared by alkylation of piperidines **13** and **15** with 2-bromoethanol in the presence of anhydrous sodium carbonate. Secondary piperidines **13** and **15** were prepared according to our general procedure for the synthesis of 2-aryl-4-piperidones.[24-28] Thus, condensation between 1-phenylsulfonyl-2-indolylcarbaldehyde (**10**)[29,30] and the appropriate primary amines **8**[1] and **9**, furnished the corresponding imines **11** and **12**, as shown in figure 2. The acid cyclization of **11** and **12** led to the expected piperidines in very good yields. Furthermore, while **11** yielded **13**, compound **12** furnished a 2:1 C-3 epimeric mixture of **14** and **15**, in which the major compound was the thermodynamically more stable *trans* isomer **14**, as expected from our previous results.[1] Piperidines **14** (*trans* isomer) and **15** (*cis* isomer) were easily distinguished by the coupling constant between C-2 and C-3 protons (see Table 1). The following alkylation of **13** and **15** with 2-bromoethanol provided satisfactorily the *N*-hydroxyethylpiperidines **4** and **16**, required for our purposes. Rather surprisingly, isomer **14** did not undergo the *N*-alkylation, even in a variety of experimental conditions, including a NaH treatment followed by 2-bromoethanol addition. The lack of reactivity of piperidine **14** nitrogen atom was first accounted for by considering the steric hindrance that the cyclic acetal function could exert. However, when the corresponding unprotected piperidone **17**, obtained from **14** by acid treatment, was reacted with 2-bromoethanol in the same experimental conditions than **15**, no reaction occured either, the starting product being fully recovered.

Treatment of aminoalcohol **4** with potassium *tert*-butoxide was carried out in a variety of solvent conditions, which permitted a distinction between the reactivity of indole 1 and 3 positions. In all cases the reaction was complete, with good total yields. Thus, when **4** was reacted in ether, a 1:1 mixture of indoloquinolizidine **21** and hexahydro-4*H*-pyridopyrazinoindole **22** was obtained. The proportion moved towards the better cyclization upon the indole 3 position when the solvent used was less polar (hexane-ether)



Reagents: i) $HOCH_2CH_2OH$, benzene, *p*-TsOH, Dean-Stark, reflux 15 h. (ii) 1. H_2N-NH_2.H_2O, CH_3OH, reflux 15 h; 2. 2*N* KOH. iii) **Benzene**, 30 min at 0°C, 6 h at reflux, and 16 h Dean-Stark. iv) *p*-TsOH, benzene, reflux 1 h . v) $BrCH_2CH_2OH$, K_2CO_3, CH_3CH_2OH, reflux, 15 h. vi) 1:1 4*N* HCl-CH_3OH , reflux, 3h.

Scheme 1

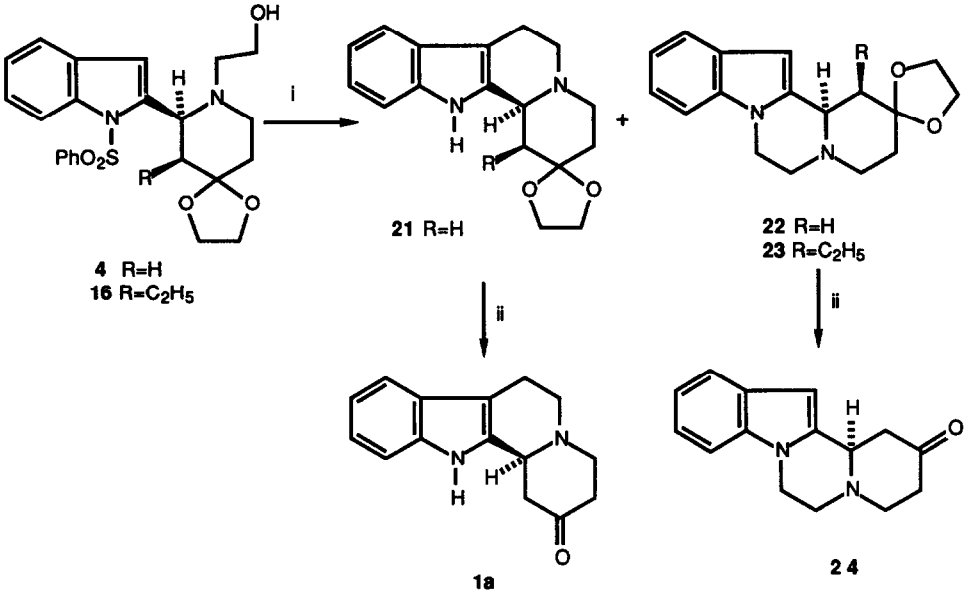
Table 1. ^{1}H-NMR Spectral Data[a] of 2-(2-Piperidyl)indoles

Proton n°	Compounds								
	4	4.HCl	13	13.HCl	14	15	16	17	18
2-H	4.45 dd (12, 4)	5.43 ddd (12, 11, 2)	4.50 dd (12, 3)	5.33 t (12)	4.42 d (12)	4.90 d (2)	4.55 d (3)	4.68 d (4.3)	5.12 d (7)
3-Ha	1.75 br t (12)	2.81 dd (13, 12)	1.6-1.9 m	2.13 dd (12, 11)	1.65 m	-----	-----	(b)	------
3-He	1.98 dd (12, 4)	1.92 ddd (12, 6, 2)	2.16 br d (12)	2.49 br d (12)	-----	2.27 m	1.55 br d (6)	-----	0.9-1.1 m
5-Ha	2.67 ddd (12, 10, 5)	2.97 td (13, 4)	1.6-1.9 m	2.38 td (12, 5)	1.9-2.0 m	1.8-2.0 m	2.05 td (13, 4)	2.5-2.7 m	2.57 ddd (11, 7, 2)
5-He	1.8-2.0 m	1.65 dt (13, 3)	1.6-1.9 m	1.68 br d (12)	1.80 dt (12, 2)	1.52 br d (10)	2.35 dd (13, 3)	2.2-2.4 m	2.39 dt (13, 6)
6-Ha	2.49 td (12, 3)	3.1-3.3 m	3.0-3.2 m	3.30 m	(b)	3.05 ddd (13, 10, 3)	2.90 m	3.0-3.2 m	2.7-2.9 m
6-He	3.17 ddd (12, 5, 3)	4.82 ddd (12, 4, 1)	3.0-3.2 m	3.55 br d (12)	2.97 dd (10, 4)	3.0-3.2 m	3.65 dd (14, 4)	2.9-3.1 m	3.0-3.2 m
OCH_2	3.8-4.5 m	3.9-4.1 m	3.9-4.1 m	3.9-4.2 m	3.9-4.2 m	3.9-4.2 m	3.9-4.1 m	-----	-----
CH_3CH_2	------	-----	-----	-----	0.74 br s	0.45 t (7)	0.32 t (7)	0.88 t (7)	0.58 t (7)
CH_3CH_2	------	-----	-----	-----	1.2-1.5 m	1.2-1.5 m	1.3-1.5 m	1.6-1.9 m	0.9-1.1m
	------	-----	-----	-----	------	1.8-2.0 m	-----	-----	1.7-2.0 m
NCH_2	2.67 m	2.8-3.0 m	-----	-----	-----	-----	3.13 ddd (11, 9, 2)	-----	-----
	3.56 td (10, 4)	3.6-3.8 m	-----	-----	-----	-----	3.45 ddd (10, 6, 3)	-----	-----
CH_2OH	3.2-3.4 m	3.8-4.0 m	-----	-----	-----	-----	4.0-4.3 m	-----	-----
In-3H	6.72 s	7.46 br s	6.65 s	6.76 br s	6.64 s	6.71 s	6.73 s	6.55 s	6.39 s
In-4H	7.81 dd (7, 1)	7.3-7.8 m	7.87 d (7)	7.94 dd (8, 0.7)	7.87 d (7)	7.70 d (7)	7.73 d (8)	7.72 d (7)	7.71 d (7)
In-5H	7.2-7.6 m	7.3-7.8 m	7.1-7.6 m	6.83 ddd (7, 6, 0.7)	7.2-7.6 m	7.2-7.6 m	7.2-7.6 m	7.2-7.6 m	7.2-7.6 m
In-6H	7.2-7.6 m	7.3-7.8 m	7.1-7.6 m	7.16 ddd (7, 6, 1.4)	7.2-7.6 m	7.2-7.6 m	7.3-7.8 m	7.2-7.6 m	7.2-7.6 m
In-7H	8.32 d (8)	8.21 d (8)	8.20 d (8)		8.30 d (8)	8.21 d (8)	8.32 d (8)	8.20 d (8)	8.23 d (8)
C_6H_5	7.2-7.6 m	7.3-7.8 m	7.1-7.6 m	7.3-7.4 m	7.2-7.6 m	7.2-7.6 m	7.2-7.6 m	7.2-7.6 m	7.2-7.6 m

a. ^{1}H-NMR spectra were recorded at 200 MHz in $CDCl_3$; *J* values in parentheses are reported in hertz and chemical shifts are given in δ units (downfield from TMS). b. Masked signal.

and was the best in a 1:1 hexane-ether mixture. These results were in accordance with those observed in our previous work for the cyclization of 3-ethylpiperidine **3**.[1]

The structure and stereochemistry of tetracyclic compound **21** were inferred from elemental analysis and spectroscopic data (see Tables 3 and 4). In the IR spectrum Bohlmann bands at 2800 cm^{-1}, characteristic of a *trans* B/C relationship, were observed. The ^{1}H-NMR spectrum of **21** (Table 3) showed, as the most significant signals a broad doublet (J=12 Hz) at δ 3.64 due to the methine proton at C-12b and a broad signal at δ 8.05 due to indole NH. As for the regioisomer **22**, the ^{1}H-NMR spectrum showed a doublet of doublets (J=1.3 and 0.5 Hz) at δ 6.19 assigned to the indole C-3 proton and no signal corresponding to indole NH



Reagents: (i) Potassium *tert*-butoxide, 1:1 hexane-ether, 0°C, 30 min. (ii) 4*N* 1:1 HCl-CH_3OH, reflux, 3 h.

Scheme 2

proton, which confirms that the cyclization occurs on the indole nitrogen atom. The most significant differences observed in the ^{13}C-NMR spectrum of **21** and **22** were the chemical shifts of C-7 (in **21**) and C-1 (in **22**) carbons at δ 21.6 and 42.0, respectively. The chemical shift difference (Δδ 20.4 ppm) is in accordance with the deshielding effect promoted by the indole nitrogen atom.

Table 2. ^{13}C-NMR Spectral Data[a] of 2-(2-Piperidyl)indoles

Carbon Nº	Compounds							
	4	**13**	**14**	**15**	**16**	**17**	**18**	**20**
C-2	59.6	53.3	56.5	56.1	61.1	56.4	55.8	61.5
C-3	40.9	40.3	51.6	47.4	47.2	56.3	55.5	40.6
C-4	104.4	105.0	110.9	110.0	211.1	108.0	210.4	211.9
C-5	32.1	31.7	36.2	31.5	30.6	28.9	30.2	29.5
C-6	53.9	43.6	44.2	43.9	49.8	41.9	40.9	41.8
OCH_2	64.8	64.7	64.9	64.0	63.8	-----	-----	-----
	65.1	65.1	65.5	64.2	64.3	-----	-----	-----
CH_3CH_2	-----	-----	14.8	14.5	14.9	12.1	11.6	13.8
CH_3CH2	-----	-----	19.1	17.6	18.8	22.9	19.0	22.0
NCH_2	56.7	-----	-----	-----	54.5	----	-----	56.3
CH_2OH	59.0	-----	-----	-----	58.1	-----	-----	60.7
In-C2	138.5	137.4	144.0	143.0	137.5	140.8	138.8	140.0
In-C3	114.9	112.0	109.4	110.5	112.5	112.1	112.8	112.1
In-C3a	128.8	129.4	130.0	128.9	129.1	128.9	128.6	128.9
In-C4	124.7	124.4	124.3	124.0	123.9	124.0	123.9	124.1
In-C5	122.6	122.1	121.5	120.7	120.8	121.0	121.1	121.2
In-C6	126.7	125.6	125.3	124.6	124.6	125.1	125.2	125.1
In-C7	116.1	114.8	115.6	115.4	115.3	115.1	114.9	115.1
In-C7a	132.9	136.9	138.5	139.0	137.0	137.5	133.9	137.0
C-*ipso*	137.2	136.2	140.0	138.0	139.0	138.7	137.4	138.0
C-*ortho*	126.2	127.1	127.9	126.4	126.6	126.0	126.0	126.2
C-*meta*	129.6	129.8	129.8	129.2	129.2	129.2	129.3	129.4
C-*para*	134.6	134.4	134.5	133.8	134.0	133.8	133.8	134.1

a. Recorded at 50.3 MHz in $CDCl_3$. Assignments were aided by DEPT sequence experiments. Chemical shifts are given in δ units (downfield from TMS).

On the other hand, treatment of piperidine **16** with potassium *tert*-butoxide only furnished, in any case, the pyridopyrazinoindole **23** resulting from the cyclization upon indole 1 position. The axial disposition of the C-7 ethyl group can be inferred from the deshielding effect (0.2 ppm) observed upon the axial proton on C-7a and by the existence of a small coupling constant between 7-H and 7a-H ($W_{1/2}$ 6 Hz) in the ^{1}H-NMR spectrum. Moreover, in the ^{13}C-NMR spectrum, the shielding effect observed for C-5 (Δδ -4.1 ppm) can be explained by the "γ-gauche" effect due to the axial ethyl group .

Finally, acid hydrolysis of the acetal function of quinolizidine **21** afforded indolo[2,3-*a*]quinolizidin-2-one **1a** in 68% yield which was identified by comparison of spectral data with the already reported.[9] Similarly, deprotection of keto groups of pyridopyrazinoindole **22** provided tetracyclic ketone **24**.

Table 3. ^{13}C-NMR Spectral Data[a] of Hexahydropyrido[1′,2′;1,2] pyrazino[4,3-*a*]indoles

Carbon Nº	Compounds		
	22	**23**	**24**
C-1	42.0	41.4	41.6
C-2	51.7	51.4	51.2
C-4	53.1	53.4	54.1
C-5	34.8	30.7	41.1
C-6	106.9	110.0	207.4
C-7	39.4	48.0	45.4
C-7a	57.7	62.4	59.0
C-7b	135.9	135.6	136.5
C-8	95.4	95.0	96.1
C-8a	128.2	128.2	128.5
C-9[b]	119.7	119.6	120.2
C-10[b]	120.1	120.0	120.5
C-11[b]	120.7	120.3	121.3
C-12	108.6	108.4	108.8
C-12a	138.0	137.0	138.0
OCH_2	64.4	64.1	-----
		64.2	
CH_3CH_2	-----	21.1	-----
CH_3CH_2	-----	15.6	-----

a. Recorded at 50.3 MHz in $CDCl_3$. Assignments were aided by DEPT sequence experiments. Chemical shifts are given in δ units (downfield from TMS); b. The assignment may be interchanged.

In summary, the obtention of **21** from **4** with a 48% yield and the effect of a nonpolar solvent to orientate the cyclization upon indole 3 position rather than upon the indole nitrogen atom, has once again been demonstrated. Nevertheless, the presence of a substituent on piperidine 3-position leads to the corresponding 1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1',2';1,2]pyrazino[4,3-*a*]indole **23** even in less polar solvent conditions, due to the steric hindrance. These results allow us to consider the K^{t}BuO cyclization method as a general one to prepare little hindered indolo[2,3-*a*]quinolizidines, and any hexahydropyrido[1,2':1,2]pyrazino[4,3-*a*]indole in a short and efficient way.

Table 4. ^{1}H-NMR Spectral Data[a] of Hexahydropyrido-[1′,2′:1,2]pyrazino[4,3-*a*]indoles

Proton Nº	Compounds		
	22	**23**	**24**
1-H	4.19 ddd (12, 4.5, 1.3)	3.8-4.1 m	4.0-4.3 m
1-Ha	3.95-4.10 m	3.8-4.1 m	4.0-4.3 m
2-He	3.19 ddd (12, 4.5, 1.3)	3.03 br d (11)	3.2-3.4 m
2-Ha	2.80 td (12, 4.5)	2.58 td (11, 6)	2.4-3.0 m
4-He	3.02 ddd (11.4, 4.5, 2.6)	2.92 ddd (11, 6, 2)	3.2-3.4 m
4-Ha	2.58 ddd (12.3, 11.4, 2.6)	2.45 td (11, 2)	2.4-3.0 m
5-He	1.80 dq (12.3, 2.6)	1.60 br d (11)	2.4-3.0 m
5-Ha	1.90-2.05 m	2.21 td (11, 6)	2.4-3.0 m
7-He	2.34 dt (12.3, 3)	2.00 dd (6, 2)	2.95 m
7-Ha	1.90-2.05 m	-----	2.4-3.0 m
7a-H	3.53 ddd (10, 3, 1.3)	3.75 br s ($W_{1/2}$=6 Hz)	3.65 dd (12, 3)
8-H	6.19 dd (1.3, 0.9)	6.15 s	6.20 s
9-H	7.55 ddd (7, 1.8, 0.9)	7.54 d (7)	7.55 d (7)
10-H	7.09 td (7, 1.8)	7.0-7.2 m	7.0-7.3 m
11-H	7.17 td (7, 1.8)	7.0-7.2 m	7.0-7.3 m
12-H	7.27 br d (7)	7.23 d (7)	7.0-7.3 m
OCH_2	3.9-4.1 m	3.8-4.1 m	------
CH_3CH_2	-------	1.3-1.5 m	------
CH_3CH_2	-------	0.94 t (7)	------

a. ^{1}H-NMR spectra were recorded at 200 MHz in $CDCl_3$; *J* values in parentheses are reported in hertz and chemical shifts are given in δ units (downfield from TMS).

Experimental

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded on a Varian XL-200 instrument or, when indicated, on a Perkin-Elmer R-24B (60 MHz) spectrometer. ^{13}C-NMR were recorded with a Varian XL-200 spectrometer. Unless otherwise noted, NMR spectra were measured in $CDCl_3$, and chemical shifts are expressed in parts per milion (δ) relative to internal Me_4Si. IR spectra were recorded on a Perkin-Elmer 1430 spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60,40-63 μm, Macherey-Nagel). TLC was performed on SiO_2 (silica gel 60 F254, Merck) using the same eluant than for the corresponding flash chromatography, and the spots were located with UV light or

iodoplatinate reagent. Purification of reagents and solvents was effected according to standart methods. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica Biològica. Barcelona.

1-Phthalimido-3-hexanone (6). A mixture of 1-chloro-3-hexanone[31] (70 g, 0.52 mol) and potassium phthalimide (96.2 g, 0.52 mol) in dry DMF (400 ml) was vigourously stirred at 100°C for 20 h. The reaction mixture was poured on ice-water and extracted with CH_2Cl_2. The organic extracts were washed with aqueous Na_2CO_3, dried and evaporated to obtain phthalimidoketone **6** (103 g, 81 %) after purification by flash chromatography (CH_2Cl_2): mp 63-64 °C (acetone) ; IR ($CHCl_3$) 1765, 1700 and 1610 cm^{-1}; ^{1}H-NMR (60 MHz) 0.90 (t, *J*=7 Hz, 3H, CH_3CH_2), 1.20-1.90 (m, 2H, CH_3CH_2), 2.40 (t, *J*=7 Hz, 2H, CH_3CH_2CO), 2.80 (t, *J*=7 Hz, 2H, CH_2CO), 3.80 (t, *J*=7 Hz, 2H, NCH_2), 7.40 (s, 4H, Ar-H). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.57; H, 6.12; N, 5.71. Found: C, 68.32; H, 6.11; N, 5.83.

1-Phathalimido-3-hexanone Ethylene Acetal (7). A mixture of phthalimidoketone **6** (79.1 g, 0.32 mol), *p*-toluenesulfonic acid monohydrate (30 g, 0.16 mol), ethylene glycol (53.6 ml, 0.96 mol), and benzene (500 ml) was refluxed for 15 h, with water removal by a Dean-Stark trap. The reaction mixture was poured into ice-water and extracted with benzene. The organic extracts were washed with aqueous $NaHCO_3$, dried and evaporated to provide phthalimido acetal **7** as a pale yellow oil (78.6 g, 85 %), after purification by flash chromatography (CH_2Cl_2); IR (NaCl) 1765, 1700, and 1610 cm^{-1}; ^{1}H-NMR (60 MHz) 0.90 (m, 3H, CH_3), 1.30-1.70 (m, 4H, $CH_3CH_2CH_2$), 1.90 (t, *J*=7 Hz, 2H, CH_2CH_2N), 3.50 (t, *J*=7 Hz, 2H, NCH_2), 3.60 (s, 4H, CH_2O), 7.41 and 7.42 (2 s, 4H, Ar-H). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.31; H, 6.56; N, 4.85.

3,3-(Ethylenedioxy)-*N*-{[1-(phenylsulfonyl)-2-indolyl]methylene}butylamine (11). A solution of aminoacetal **8**[23] (13.1 g, 0.1 mol) and aldehyde **10**[29] (28.1 g, 0.1 mol) in anhydrous benzene (350 ml) was stirred at 0 °C for 30 min, at room temperature overnight, and under reflux for 3 h. After 16 h of additional refluxing with removal of water by a Dean-Stark trap, the solvent was evaporated to give imine **11** which was purified by flash chromatography (39.5 g, 99%); IR ($CHCl_3$) 1630 (C=N), 1175 and 1370 cm^{-1} (SO_2); ^{1}H-NMR 1.39 (s, 3H, CH_3), 2.10 (t, *J*= 8 Hz, 2H, CH_2), 3.79 (td, *J*= 8 and 9 Hz, 2H, NCH_2), 3.97 (s, 4H, OCH_2), 7.1-8.2 (m, 10 H, Ar-H), 8.92 (s, 1H, HC=N); ^{13}C-NMR 24.3 (CH_3), 39.8 (CH_2), 57.24 (NCH_2), 64.64 (OCH_2), 109.17 (OCO), 113.28 (In-C3), 115.08 (In-C7), 121.9 (In-C5), 124.36 (In-C4), 126.3 (Ar-*o*), 126.48 (In-C6), 129.10 (Ar-*m*), 129.53 (In-C3a), 133.74 (Ar-*p*), 137.56 (In-C7a), 138.7 (Ar-*i*), 153.74 (HC=N); CIMS (m/z,%) 399 (M^++1, 100), 285 (2), 259 (32), 177 (46), 159 (16), 149 (5), 132 (6). Anal. Calcd for $C_{21}H_{22}N_2O_4S$: C, 63.29; H, 5.56; N, 7.03. Found: C, 62.92; H, 5.70; N, 7.05.

3,3-(Ethylenedioxy)-*N*-{[1-(phenylsulfonyl)-2-indolyl]methylene}hexylamine (12). A mixture of phthalimido acetal **7** (15 g, 51.8 mmol) and 80 % hydrazine hydrate (50 ml) in methanol (200 ml) was refluxed for 15 h. Methanol was distilled under atmospheric pressure, the residue was treated with 2*N*

aqueous KOH and extracted with CH_2Cl_2. The organic layers were dried and the solvent removed by distillation under atmospheric pressure to yield 1-amino-3-hexanone ethylene acetal (**9**) as a pale oil (6.47 g, 78 %) which was used without further purification; IR (NaCl) 3500-3200 cm^{-1} (NH_2); ^{1}H-NMR (60 MHz) 0.90 (m, 3H, CH_3), 1.40 (broad s, 2H, NH_2), 1.50 (broad s, 4H, $CH_3CH_2CH_2$), 1.70 (t, *J*=7Hz, 2H, CH_2CH_2N), 2.70 (t, *J*= 7Hz, 2H, NCH_2), 3.70 (s, 4H, OCH_2).

Operating as for compound **11**, from aminoacetal **9** (6.47 g, 40.7 mmol) and **10**[29] (12.75 g, 44.7 mmol) in dry benzene (200 ml), imine **12** was obtained (17.1 g, 97 %), which was used without further purification; IR (NaCl) 1620 (N=C), 1370 and 1170 cm^{-1} (SO_2); ^{1}H-NMR (60 MHz) 0.90 (m, 3H, CH_3), 1.30-1.60 (m, 4H, $CH_3CH_2CH_2$), 2.00 (t, *J*=7 Hz, 2H, CH_2CH_2N), 3.60 (t, *J*=7 Hz, 2H, NCH_2), 3.81 (s, 4H, OCH_2), 6.90-8.00 (m, 10 H, Ar-H), 8.60 (s, 1H, HC=N).

2-[1-(Phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (13). A stirred solution of the imino acetal **11** (17 g, 30 mmol) and anhydrous *p*-TsOH (10.32 g, 89 mmol) in dry benzene (300 ml) was refluxed under N_2 for 1 h. The cooled mixture was poured on ice-water and basified with Na_2CO_3. The organic layers were separated and the organic phase was washed with aqueous Na_2CO_3, dried and evaporated to give piperidine **13** (10.1 g, 84 %) after purification by flash chromatography (99:1 Et_2O-DEA); IR (NaCl) 3500-3200 (NH), 1370 and 1160 cm^{-1} (SO_2); MS (m/z, %) 398 (M^+, 2), 352 (30), 283 (13), 257 (58), 212 (19), 142 (41), 99 (47), 87 (69), 77 (100). The hydrochloride melted at 212-214 °C (acetone). Anal. Calcd for $C_{21}H_{23}ClN_2O_4S$: C,57.99; H, 5.33; N, 6.44; Cl, 8.15. Found: C, 57.87; H, 5.26; N, 6.54; Cl, 8.14.

3-Ethyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (14 and 15). Operating as above, from imine **12** (16.5 g, 38.7 mmol) and anhydrous *p*-TsOH (13.4 g, 60 mmol) a 2:1 mixture of piperidines **14** and **15** , respectively, was obtained, which was purified by flash chromathography (98:2 Et_2O-DEA). **14** (Lower Rf, *trans* isomer, 8.32 g, 51 %): IR ($CHCl_3$) 3300-3200 (NH), 1370 and 1170 cm^{-1} (SO_2); MS (m/z,%) 426 (M^+, 6), 381 (7), 285 (24), 283 (23), 228 (22), 185 (10), 171 (18), 157 (39), 130 (74), 115 (61), 99 (50), 77 (100). **15** (Higher Rf, *cis* isomer, 4.16 g, 25 %): IR ($CHCl_3$) 3300-3200 (NH), 1370 and 1170 cm^{-1} (SO_2); MS (m/z,%) 426 (M^+, 4), 381 (7), 285 (24), 283 (23), 228 (22), 185 (10), 171 (18), 157 (39), 130 (74), 115 (61), 99 (50), 77 (100). The hydrochloride melted at 209-210°C (acetone). Anal. Calcd for $C_{23}H_{27}ClN_2O_4S$: C, 59.67; H, 5.88; N, 6.05; Cl, 7.66. Found: C, 60.02; H, 6.32; N, 5.54; Cl, 7.41.

***N*-(2-Hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (4).** 2-Bromoethanol (1.61 ml, 23 mmol) was added dropwise to a mixture of piperidine **13** (9.2 g, 21 mmol) and anhydrous K_2CO_3 (10 g) in absolute ethanol (200 ml). The resulting mixture was refluxed under N_2 for 15 h. Ethanol was evaporated, the residue was dissolved in CH_2Cl_2 and washed with brine. The dried organic phase was evaporated and purified by flash chromatography (99.5:0.5 Et_2O-DEA) to give pure alcohol **4** (8 g, 86 %); IR (NaCl) 3500-3200 (OH), 1370 and 1170 cm^{-1} (SO_2); MS (m/z, %) 442 (M^+, 0.4), 411 (18), 410 (37), 296 (7), 215 (5), 156 (7), 142 (11), 128 (100), 115 (10), 99 (53), 87 (29), 77 (27). The hydrochloride melted at 187-190 °C (Et_2O-acetone). Anal. Calcd for $C_{23}H_{26}ClN_2O_5S$: C, 57.80; H, 5.44; N, 5.86; Cl, 7.43. Found: C, 57.75; H, 5.64; N, 5.83; Cl, 7.76.

***cis*-3-Ethyl-1-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (16).** Operating as above, from piperidine **15** (4.34 g, 10.2 mmol), 2-bromoethanol (1.1 ml, 15.3 mmol), K_2CO_3 (4 g) and absolute ethanol (100 ml), and after flash chromatography (95:5 CH_2Cl_2-CH_3OH), alcohol **16** was isolated (3.30 g, 63 %). IR ($CHCl_3$) 3300-3150 (OH), 1370 and 1170 cm^{-1} (SO_2); MS (m/z, %) 470 (M^+, 0.2), 439 (20), 329 (20), 329 (3), 298 (4), 215 (4), 156 (13), 128 (94), 115 (19), 99 (60), 77 (100). The hydrochloride melted at 194 °C (acetone). Anal. Calcd for $C_{25}H_{31}ClN_2O_5S$: C, 59.22; H, 6.16; N, 5.52; Cl, 6.99. Found: C, 59.29; H, 6.11; N, 5.52; Cl, 7.09.

***trans*-3-Ethyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone (17).** A solution of ethylene acetal **14** (370 mg, 0.8 mmol) in a 1:1 mixture of 4*N* hydrochloric acid and methanol (60 ml) was refluxed for 3 h. The reaction mixture was cooled, basified with Na_2CO_3 and extracted with CH_2Cl_2 to provide ketone **18** (243 mg, 80%), after purification by flash chromatography (98:2 Et_2O-DEA); IR (NaCl) 3450 (NH), 1730 cm^{-1} (C=O) ; MS (m/z, %) 382 (M^+, 55), 367 (71), 325 (21), 311 (14), 285 (3), 241 (48), 212 (14), 171 (70), 156 (43), 130 (64), 77 (100). The hydrochloride melted at 142-143°C (acetone-methanol). Anal. Calcd for $C_{21}H_{23}ClN_2O_3S$: C, 60.20; H, 5.53; N, 6.68; Cl, 8.46. Found: C, 60.23; H, 5.94; N, 6.65; Cl, 8.24.

***cis*-3-Ethyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone (18).** Operating as above from a 2:1 mixture of acetals **14** and **15** (200 mg, 0.47 mmol), 4*N* hydrochloric acid (20 ml) and methanol (20 ml) a 2:1 mixture of piperidones **18** was obtained which was separated by flash chromatography (98:2 ether-DEA). ***trans*-18** (Higher Rf, 53 mg, 30%) was identified by comparison of its spectral data with those of the sample previously obtained. ***cis*-18** (Lower Rf; 100 mg, 56%): IR (NaCl) 3450 (NH), 1730 cm^{-1} (C=O); MS (m/z, %) 382 (M^+, 6), 367 (9), 353 (1), 325 (2), 311 (2), 241 (9), 171 (17), 130 (21), 77 (100), 51 (25). Anal. Calcd for $C_{21}H_{23}ClN_2O_3S$: C, 60.20; H, 5.53; N, 6.68. Found: C, 60.34; H, 5.84; N, 6.63.

***N*-(Hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone (19).** Operating as above from acetal **4** (60 mg, 0.135 mmol), 4*N* hydrochloric acid (10 ml), and methanol (10 ml), piperidone **19** (45 mg, 83%) was obtained, after purification by flash chromatography (95:5 CH_2Cl_2-CH_3OH) ; IR ($CHCl_3$) 3500-3350 (OH), 1720 cm^{-1} (C=O); ^{1}H-NMR 3.00-3.90 (m, 6H), 4.10-4.40 (m, 2H, NCH_2), 4.50-4.60 (m, 1H, 6-He), 5.65 (t, *J*= 10 Hz, 1H, 2-H), 7.20 (s, 1H, In-3H), 7.70-8.20 (m, 7H, Ar-H), 8.32 (d, *J*=7 Hz, 1H, In-4H), 8.70 (d, *J*=7 Hz, 1H, In-7H); CIMS (m/z, %) 399 (M^++1, 3), 355 (1), 257 (73), 240 (100), 223 (6), 177 (3), 147 (8). Anal. Calcd for $C_{21}H_{22}N_2SO_4$.HCl: C, 57.99; H, 5.33; N, 6.44. Found: C, 58.23; H, 5.45; N, 6.34.

***cis*-3-Ethyl-*N*-(hydroxyethyl)-2-(1-phenylsulfonyl)-2-indolyl-4-piperidone (20).** Operating as above, from acetal **16** (1.4 g, 2.98 mmol) 4*N* hydrochloric acid (40 ml) and methanol (40 ml) piperidone **20** was obtained (0.65 g, 51%), after flash chromathography (93:7 CH_2Cl_2-CH_3OH); IR ($CHCl_3$) 3500-3350 (OH), 1730 cm^{-1} (C=O); ^{1}H-NMR 1.05 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.60-2.00 (m, 1H, CH_ACH_3), 5.12 (d, *J*=5 Hz, 1H, 2-H), 6.77 (s, 1H, In-3H), 7.20-7.50 (m, 7H, Ar-H), 7.62 (d, *J*=7 Hz, 1H, In-4H), 8.23

(d, *J*=7 Hz, 1H, In-7H); CIMS (m/z, %) 428 (M^+, 1), 383 (3), 260 (2), 240 (3), 203 (5), 147 (100), 130 (4). Anal. Calcd for $C_{22}H_{26}N_2O_4S$: C, 63.73; H, 6.32; N, 6.78. Found: C, 63.87; H, 6.43 ; N, 6.89.

K^{t}BuO Cyclization of *N*-Hydroxyethylpiperidine 4. To a solution of piperidine **4** (1.3 g, 2.9 mmol) in dry 1:1 hexane-Et_2O (40 ml) freshly sublimed K^{t}BuO (670 mg, 6 mmol) was added under N_2. After being stirred at 0°C for 30 min, the reaction mixture was poured into an aqueous NH_4Cl solution and extracted with Et_2O. Evaporation of the dried organic extracts gave a 1.5:1 mixture of compounds **21** and **22**, respectively, which were separated by flash chromatography (99:1 Et_2O-DEA).***trans*-6,6-(Ethylenedioxy)-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1',2':1,2]pyrazino[4,3-*a*]indole (22)** (Higher Rf, 264 mg, 32 %): MS (m/z, %) 284 (M^+, 100), 241 (30), 197 (51), 170 (30), 115 (13), 99 (26), 77 (6). The hydrochloride melted at 242-245°C (acetone). Anal. Calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.59; N, 8.73; Cl, 11.05. Found: C, 63.16; H, 6.51; N, 8.21; Cl, 11.13. ***trans*-2,2-(Ethylenedioxy)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizidine (21)** (Lower Rf; 396 mg, 48%): IR ($CHCl_3$) 3460, 2800 cm^{-1} (NH); ^{1}H-NMR 1.80 (dq, *J*=12 and 3 Hz, 1H, 3-He), 1.91 (t, *J*=12 Hz, 1H, 1-Ha), 2.04 (td, *J*=12 and 5 Hz, 1H, 3-Ha), 2.21 (dq, *J*=12 and 3 Hz, 1H, 1-He), 2.60-2.80 (m 2H, 6-Ha and 7-He), 2.72 (td, *J*=12, 4 Hz, 1H, 4-Ha), 3.02 (ddd, *J*=12, 6 and 2 Hz, 1H, 4-He), 3.05-3.25 (m, 1H, 6-He), 3.64 (br d, *J*=12 Hz, 1H, 12b-H), 3.90-4.10 (m, 4H, OCH_2), 7.00-7.30 (m, 2H, 9-H and 10-H) 7.35 (d, *J*=7 Hz, 1H, 8-H), 7.50 (d, *J*=7 Hz, 1H, 11-H), 8.05 (br, 1H, NH); ^{13}C-NMR 21.6 (C-7), 34.8 (C-3), 39.1 (C-1), 52.3 and 52.8 (C-4 and C-6), 57.0 (C-12b), 64.4 (OCH_2), 107.2 and 108.1 (C-2 and C-7a), 110.8 (C-11), 118.1, 119.4 and 121.4 (C-8, C-9, and C-10), 127.2 (C-7b), 134.1 (C-11a), 136.0 (C-12a); CIMS (m/z, %) 285 (M^++1, 100), 283 (2), 236 (1), 207 (3), 190 (2), 155 (1), 117 (1). The hydrochloride melted at 267-270°C (acetone). Anal. Calcd for $C_{17}H_{21}ClN_2O_2$: C, 63.65; H, 6.59; N, 8.73; Cl, 11.05. Found: C, 63.57; H, 6.64; N, 8.73: Cl, 11.05.

7-Ethyl-6,6-(ethylenedioxy)-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1',2':1,2]pyrazino[4,3-*a*]indole (23). Operating as above, from piperidine **16** (500 mg, 1.0 mmol), freshly sublimed K^{t}BuO (0.24 g, 2.0 mmol) and anhydrous 1:1 hexane-Et_2O (25 ml) compound **23** was obtained (237 mg, 76 %) after a flash chromatography (99:1 Et_2O-DEA) purification; CIMS (m/z, %) 313 (M^++1, 100), 267 (2), 152 (1), 108 (2). The hydrochloride melted at 248-251°C (acetone-methanol). Anal. Calcd for $C_{19}H_{25}ClN_2O_2.1/2H_2O$: C, 63.77; H, 7.32; N, 7.82. Found: C, 64.09; H, 7.31; N, 7.75.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizin-2-one (1a). Operating as above, from 1:1 mixture of acetals **21** and **22** (1.43 g, 5.9 mmol), 4*N* hydrochloric acid (34 ml) and methanol (34 ml), a 1:1 mixture of ketones **1a**[2-9] and 1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1',2';1,2]pyrazino[4,3-*a*]indole-6-one (**1a**) was obtained which was purified by flash chromatography (92:3 CH_2Cl_2-CH_3OH). **1a** (Higher Rf, 967 mg, 68%) mp: 180-182°C (lit.[2] 181-182 °C); IR ($CHCl_3$) 3460 (NH), 1720 cm^{-1} (CO); ^{1}H-NMR 1.69 (t, *J*=12 Hz, 1H, 1-Ha), 2.11 (dq, *J*=12 and 3 Hz, 1H, 3-He), 2.48 (dt, *J*=11 and 3 Hz, 1H, 1-He), 2.6-2.9 (m, 3H, 4-Ha, 6-Ha, 7-He), 3.0-3.1 (m, 2H, 4-He and 7-Ha), 3.32 (ddd, *J*=11, 6 and 3 Hz, 1H, 6-He), 3.66 (br d, *J*=11 Hz, 1H, 12b-H), 7.12 and 7.16 (2 br t, *J*=7 Hz, 1H each , In-9H and In-10H), 7.32 (dt, *J*=7 and 2 Hz, 1H, In-11H), 7.47 (dd, *J*=7 and 2 Hz, 1H, In-8H), 7,73 (br, 1H, In-NH); ^{13}C-NMR[9] 21.9

(C-7), 41.8 (C-3), 45.8 (C-1), 52.0 (C-6), 54.4 (C-4), 58.7 (C-12b), 108.7 (C-7a), 111.4 (C-11), 119.9 (C-8), 121.8 (C-9), 122.2 (C-10), 127.3 (C-7b), 133.6 (C-11a), 136.7 (C-11b), 208.8 (C-4); CIMS (m/z, %) 241 (M^++1, 100), 200 (5), 166 (4), 142 (10), 125 (70), 108 (24). The hydrochloride melted at 220-223°C (acetone). **24** (Lower Rf, 384 mg, 27%): IR ($CHCl_3$) 1720 (CO); CIMS (m/z, %) 241 (M^++1, 100), 191 (40), 127 (9), 110 (7), 107 (7). The hydrochloride melted at 219-221°C (acetone). Anal. Calcd for $C_{15}H_{17}ClN_2O.H_2O$: C, 61.12; H, 6.49; N, 9.50. Found: C, 61.05; H, 6.80; N, 9.21.

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