(357 mg, 0.67 mmol) in toluene (20 mL) afforded **8b** (257 mg, 57%): R_f 0.32 with ether-petroleum ether (1:1); mp 63-64 °C (methanol-ethyl acetate); $[\alpha]_D$ = +8.3° (*c* 1.4, $CHCl_3$); ^{13}C NMR ($CDCl_3$) 143.83, 138.84, 138.72, 138.53, 138.43, 130.81, 128.73, 128.29, 128.24, 128.09, 127.92, 127.85, 127.73, 127.44, 127.2 (C arom), 109.94 (C1'), 98.11 and 96.75 (OCH_3) 83.67 (C3'), 81.03 (C5'), 78.24 (C2'), 75.66, 74.84, 74.58, 73.08, 72.98 (-CH_2Ar), 73.29 (C4'), 68.76 (C6'). Anal. Calcd for $C_{43}H_{44}O_8$: C, 75.06; H, 6.45. Found: C, 74.49; H, 6.48.

1,1-Anhydro-1-*C*-[2-(hydroxymethyl)-4,6-dimethoxyphenyl]-β-D-glucopyranose (9b). Hydrogenolysis of **8b** (165 mg, 0.24 mmol) in methanol (1 mL) and ethyl acetate (1 mL) in the presence of 10% palladium on charcoal (20 mg) afforded **9b** in quantitative yield (83 mg), which was purified by preparative TLC (68 mg, 87%): R_f 0.40 with dichloromethane-methanol (80:20); mp 97-98 °C (ethyl acetate); $[\alpha]_D$ = +48.1° (*c* 0.43, $CHCl_3$); MS *m/z* 329 (M + 1). Anal. Calcd for $C_{15}H_{20}O_8$: C, 54.92; H, 6.15. Found: C, 54.89; H, 6.27.

1,1-Anhydro-1-*C*-[2-(hydroxymethyl)-4,6-dimethoxyphenyl]-β-D-glucopyranose Tetraacetate (10b).[2,3] Acetylation of **9b** (44 mg, 0.128 mmol) according to the procedure described for the preparation of **10a** [acetic anhydride (128 μL), pyridine (1 mL), and DMAP (1 crystal)] afforded **10b**, which was purified by preparative TLC (47 mg, 74%): R_f 0.41 with petroleum ether-ethyl acetate (1:1); mp 159-160 °C (petroleum ether) (lit.[3] mp 70-72 °C); $[\alpha]_D$ = +7° (*c* 1, $CHCl_3$) [lit.[3] $[\alpha]_D$ = +5° (*c* 1, $CHCl_3$)]; MS *m/z* 496 (M + 1); ^1H NMR ($CDCl_3$) δ 6.30-6.28 (2s, 2, H arom), 5.89 (d, 1, $J_{2',3'}$ = 9.98 Hz, H2'), 5.55 (t, 1, $J_{3',2'} = J_{3',4'}$ = 9.84 Hz, H3'), 5.30 (t, 1, $J_{4',3'} = J_{4',5'}$ = 9.9 Hz, H4'), 5.16 (d, 1, *J* = 12.7 Hz, ArCH_2O-), 5.03 (d, 1, *J* = 12.7 Hz, ArCH_2O-), 4.28-4.07 (2 m, 3, H5', H6', H6''), 3.82 (s, 3, -OCH_3), 3.78 (s, 3, CH_3CO-), 1.99 (s, 3, CH_3CO-), 1.73 (s, 3, CH_3CO-). Anal. Calcd for $C_{23}H_{28}O_{12}$: C, 55.69; H, 5.69. Found: C, 55.70; H, 5.74.

Acknowledgment. Dr. J. M. Valéry is acknowledged for recording the ^{13}C and ^1H NMR spectra and Dr. J. Vaissermanne (Laboratoire de Chimie des Métaux de Transition) for the structure determination of **10a** by X-ray diffraction.

Registry No. 1, 13096-62-3; **2a**, 132814-55-2; **2b**, 135877-95-1; **3a**, 135877-99-5; **3b**, 135878-00-1; **4a**, 5333-62-0; **4b**, 135877-96-2; **5a**, 132814-51-8; **5b**, 135877-97-3; **6**, 62641-00-3; **8a**, 132814-52-9; **8b**, 135877-98-4; **9a**, 132814-53-0; **9b**, 76843-39-5; **10a**, 132814-54-1; **10b**, 76843-40-8; 2-$BrC_6H_4CH_2OH$, 18982-54-2; 2-Br-3,5-$(MeO)_2C_6H_2CH_2OH$, 74726-76-4; papulacandin A, 61036-46-2; papulacandin B, 61032-80-2; papulacandin C, 61036-48-4; papulacandin D, 61036-49-5.

Supplementary Material Available: Crystallographic data for compound **10a** (6 pages). Ordering information is given on any current masthead page.

Synthetic Applications of Protected 2-Aryl-4-piperidones. 7.[1] Synthesis of 1-Ethylindolo[2,3-*a*]quinolizidin-2-one[§]

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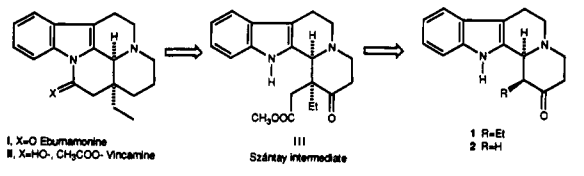
The synthesis of 1-ethylindolo[2,3-*a*]quinolizidin-2-one (1) by the intramolecular cyclization of protected *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone **15** by the action of K^{t}BuO and further acid treatment is reported. The methodology has been first carried out for its deethyl analogue **2** from (hydroxyethyl)piperidine **14** and has shown to be a good general method to reach indolo[2,3-*a*]quinolizidin-2-one systems. Compound **1** has also been obtained by an unusual rearrangement in acidic medium of 7-ethylhexahydropyrido[1',2':1,2]pyrazino[4,3-*a*]indole.

Introduction

In continuing our studies of the synthesis of the indolo[2,3-*a*]quinolizidin-2-one system[2] as a new synthetic application of easily accessible protected 2-aryl-4-piperidones,[3] we report now the synthesis of 1-ethylindolo[2,3-*a*]quinolizidin-2-one (**1**), which can be considered a key intermediate in the preparation of pentacyclic indole alkaloids of the vincamine type,[4] some of which, such as (-)-eburnamonine and (+)-vincamine,[5] are used in medicine for their vasodilator properties (Scheme I).

In previous work, we already reported the synthesis of the indolo[2,3-*a*]quinolizidin-2-one basic framework (**2**),[2b] as well as its 3-ethyl derivative,[2a] by the intramolecular cyclization of protected *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidones (**3** and **4**) by the initial action of potassium *tert*-butoxide.[6] However, the cyclization occurred as well, to some extent, upon the indole nitrogen atom, yielding the corresponding hexahydro-4*H*-

Scheme I



[†] Faculty of Pharmacy.

[‡] Faculty of Chemistry.

[§] This work is dedicated to Professor Fèlix Serratosa for his long and impressive years of research.

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Table I. ^{1}H NMR Spectra Data[a,b] of 3-(2-Piperidyl)indoles

proton	14	15	21	22	23
2-Ha	3.80 dd (12, 3)	3.44 d (11)	4.15 dd (12, 2)	3.86 d (12)	4.43 dd (12, 0.8)
3-He	1.76–1.89 m		1.75–1.85 m		masked
3-Ha	2.21 t (12)	masked	1.81 t (12)	1.60–1.80 m	
5-He	1.76–1.89 m	1.84 br d (12)	2.03 br d (12)	1.95 dt (11, 5)	1.56 ddd (12, 4, 1.7)
5-Ha	2.09 td (12, 3)	2.05 br t (12)	1.75–1.85 m	1.60–1.80 m	1.87 td (13, 5)
6-He	3.20–3.30 m	3.10–3.20 m	3.20 dt (12, 4)	2.97–3.09 m	3.12 br d (12)
6-Ha	2.45 td (12, 3)	2.37 m	3.02 ddd (13, 12, 5)	2.92 td (11, 5)	2.98 td (12, 3.5)
OCH_2CH_2O	3.90–4.00 m	3.90–4.00 m	3.90–4.00 m	3.90–4.10 m	3.90–4.00 m
CH_2CH_3		0.70–0.90 m		0.81–1.00 m	1.28–1.41 m
		1.20–1.40 m		1.20–1.40 m	
CH_2CH_3		0.21 t (7)		0.35 t (7)	0.17 t (7)
In-2H	7.54 s	7.52 s	7.55 s	7.55 s	7.55 s
In-4H	7.70 d (7)	7.75 d (7)	7.63 d (7)	7.80 d (7)	7.20–7.55 m
In-5H	7.20–7.50 m	7.20–7.50 m	7.30–7.50 m	7.20–7.45 m	7.20–7.50 m
In-6H	7.20–7.50 m	7.20–7.40 m	7.30–7.50 m	7.20–7.45 m	7.20–7.50 m
In-7H	7.97 d (7)	8.00 d (7)	8.00 d (7)	8.00 d (7)	8.00 d (7)
NCH_2CH_2	2.70 and 3.23 m	2.57 and 3.11 m			
OCH_2	3.56 td (11, 4)	3.42–3.53 m			

[a] Recorded at 200 MHz in $CDCl_3$. J values in brackets are reported in hertz and chemical shifts are given in δ units (downfield from Me_3Si). [b] Phenyl signals: 7.26 t (7), 7.45 t (7), 7.86 d (7) for **14**; 7.20–7.40 m, 7.85 d (7) for **15**; 7.26 t (7), 7.42 t (7), 7.88 d (7) for **21**; 7.21–7.49 m, 7.84 d (7) for **22**; 7.38 t (7), 7.48 t (7), 7.87 d (7) for **23**.

Table II. ^{13}C NMR Spectral Data[a] of 3-(2-Piperidyl)indoles

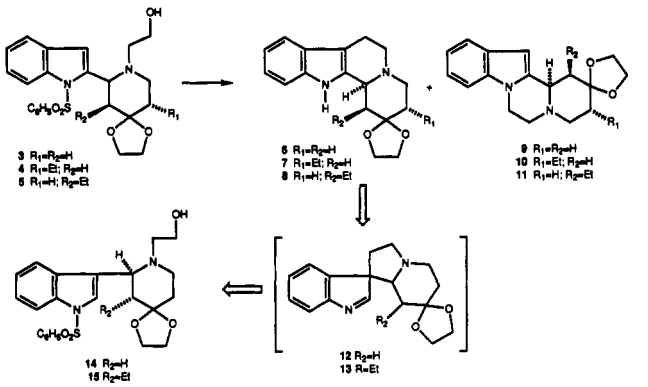
carbon	14	15	21	22	23
C-2	59.6	61.1	53.3	56.5	56.1
C-3	40.9	47.2	40.3	51.6	47.4
C-4	104.4		105.0	110.9	110.0
C-5	32.1	30.6	31.7	36.2	31.5
C-6	53.9	49.8	43.6	44.2	43.9
OCH_2	59.0	63.8	64.7	64.9	64.0
		64.3	65.1	65.5	64.2
CH_2CH_3		18.8		19.1	17.6
CH_2CH_3		14.9		14.8	14.5
In-C2	138.5	137.0	137.4	144.0	143.0
In-C3	114.9	112.5	112.0	109.4	110.5
In-C3a	128.8	129.1	129.4	130.0	128.9
In-C4	124.7	123.9	124.4	110.9	124.0
In-C5	122.6	120.8	122.1	121.5	120.7
In-C6	126.7	124.6	125.6	125.3	124.6
In-C7	116.1	115.3	114.8	115.6	115.4
In-C7a	132.9	137.0	136.9	138.5	139.0
$(C_6H_5)o$	126.2	126.6	127.1	127.9	126.4
$(C_6H_5)m$	129.6	129.2	129.8	129.8	129.2
$(C_6H_5)p$	134.6	134.0	134.4	134.5	133.8
$(C_6H_5)i$	137.2	139.0	136.2	140.0	138.0
NCH_2CH_2	56.7	54.5			
NCH_2CH_2	59.0	58.1			

[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 Me_4Si).

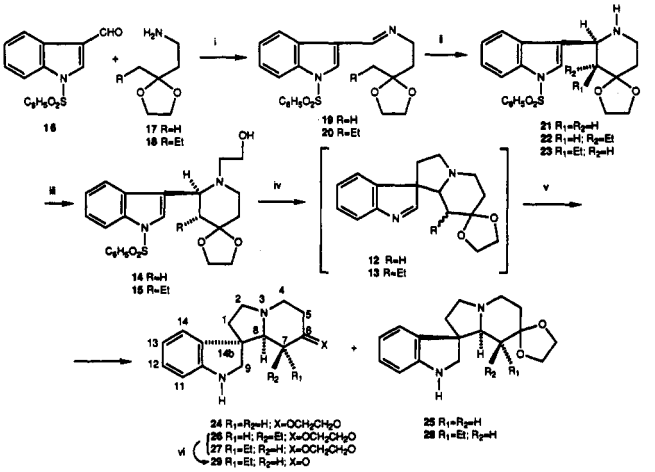
pyrido[1′,2′:1,2]pyrazino[4,3-*a*]indoles **9** and **10**, depending on the solvent and the substrate. Thus, when the synthesis of 1-ethylindoloquinolizidine **8** was envisaged by the same strategy, the K^{t}BuO reaction only provided the pyridopyrazinoindole regioisomer **11** in 76% yield (see Scheme II).

Such inconvenience has been successfully circumvented by taking advantage of the known capability of 3,3-disubstituted indolenines to rearrange into 2,3-disubstituted indoles.[7] Thus, the intramolecular cyclization of conveniently protected 2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidones **14** and **15** by the action of K^{t}BuO has been

Scheme II



Scheme III[a]



[a] Reagents and conditions: (i) benzene, Dean–Stark; (ii) *p*-TsOH, benzene, Dean–Stark; (iii) $BrCH_2CH_2OH$, EtOH, Na_2CO_3; (iv) Et_2O, 0 °C, ^{t}BuOK; (v) $LiAlH_4$, THF; (vi) 10% HCl, MeOH, Δ.

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Table III. ^{1}H NMR Spectral Data[a] of Spiroindolines 24–29

proton	24	25	26	27	28	29
1-Hα	1.98 dd (9, 5)	1.92 ddd (9, 5, 1)	1.93 ddd (11, 6, 1)	2.12 dd (9, 4)	2.07 dd (10, 4)	2.00–2.40 m
1-Hβ	2.2–2.3 m	2.16–2.20 m	2.30–2.40 m	2.30–2.40 m	2.18–2.26 m	2.00–2.40 m
2-Hα	2.36 dd (9, 5)	2.16–2.20 m	2.06 dd (11, 6)	2.39 dd (9, 3)	2.18–2.26 m	2.00–2.40 m
2-Hβ	3.18 td (9, 2)	3.12 td (9, 3)	3.00–3.30 m	3.19 td (9, 4)	3.06–3.13 m	3.30 td (10, 4)
4-He	3.08 ddd (12, 5, 2.5)	3.00 ddd (11, 5, 2)	3.00–3.30 m	3.04 ddd (11, 5, 3)	3.03 dt (11, 3)	3.26 br d (12)
4-Ha	2.28 td (12, 2.5)	2.16–2.20 m	2.40–2.50 m	2.52 t (11)		2.62 dd (13, 7)
5-He	1.67 dq (12, 2.5)	1.56 dq (13, 3)	1.50–1.60 m	1.70–1.80 m	1.66–1.75 m	2.00–2.40 m
5-Ha	1.88 td (12, 4.8)	1.72 td (13, 5)	1.50–1.60 m	1.89 ddd (13, 9, 2)	1.66–1.75 m	2.00–2.40 m
7-He	1.53 ddd (12, 3, 2.5)	1.46 dt (13, 3)	1.50–1.60 m			
7-Ha	1.68 t (12)	1.14 t (13)		1.10–1.25 m	1.10–1.30 m	2.22 d (12)
8-Ha	2.23 dd (12, 3)	2.16–2.20 m	2.24 d (6)	1.70–1.90 m		2.36 d (10)
9-H_A	3.24 d (9.5)	3.44 s	3.49 d (10)	3.36 d (10)	3.53 d (10)	3.42 d (10)
9-H_B	3.80 d (9.5)		3.67 d (10)	3.91 d (10)	3.65 d (10)	3.93 d (10)
11-H	6.62 dt (7, 0.8)	6.53 dt (7, 1)	6.67 ddd (7.5, 1, 0.6)	6.57 dd (7.5, 1.2)	6.58 dt (8, 0.5)	6.61 dt (7, 1)
12-H	7.04 td (7, 1.3)	6.66 td (7, 1)	6.76 td (7.5, 1)	6.99 td (7.5, 1.2)	6.71 td (7, 1)	7.06 dd (7, 1)
13-H	6.74 td (7, 1)	6.94 td (7, 1)	7.06 td (7.5, 1.5)	7.01 td (7.5, 1.2)	7.00 td (8, 1)	6.72 td (7, 1)
14-H	7.10 ddd (7, 1.3, 0.8)	7.28 dd (7, 1)	7.17 br d (7.5)	7.08 dd (7.5, 1.2)	7.33 br d (7)	7.04 d (7)
OCH_2	3.8–3.9 m	3.75–3.90 m	3.80–4.00 m	3.82–4.05 m	3.82–4.04 m	
CH_2CH_3			1.50–1.60 m	0.80–0.90 m	1.03–1.18 m	1.00–1.30 m
				1.20–1.30 m	1.64–1.76 m	
CH_2CH_3			1.01 t (7)	0.73 t (7)	0.43 t (7)	0.61 t (7)

[a] Recorded at 200 MHz in $CDCl_3$. J values in brackets are reported in hertz and chemical shifts are given in δ units (downfield from Me_4Si).

Table IV. ^{13}C NMR Spectral Data[a] of Spiroindolines 24–29

carbon	24	25	26	27	28	29
C-1	39.0	38.8	46.2	47.9	48.1	41.8[b]
C-2	49.8	49.9	50.4	49.4	49.3	50.7[b]
C-4	52.8	52.8	52.5	52.0	53.2	51.6[b]
C-5	34.4	34.4	31.1	34.3	34.6	40.7[b]
C-6	109.0	108.0	110.5	110.9	111.5	211.2
C-7	35.8	34.7	43.0	42.3	44.6	53.5
C-8	71.5	71.6	73.8	72.7	76.4	74.9
C-9	59.0	57.3	59.2	56.6	61.1	56.8
C-10a	151.0	151.5	149.5	150.7	150.9	151.2
C-11	109.4	109.4	109.4	109.2	109.3	109.6
C-12	125.1	123.0	122.7	122.9	125.2	123.9
C-13	118.9	118.7	118.9	118.5	118.7	118.9
C-14	127.6	127.8	127.6	127.7	127.6	128.5
C-14a	128.5	133.9	135.5	135.8	135.0	134.2
C-14b	54.0	53.5	53.1	54.2	54.1	54.7
OCH_2	64.1	64.2	64.2	64.3	64.2	
	64.2	64.3	64.4	64.8	64.8	
CH_2CH_3			21.9	17.2	17.3	17.7
CH_2CH_2			15.2	14.4	14.2	11.8

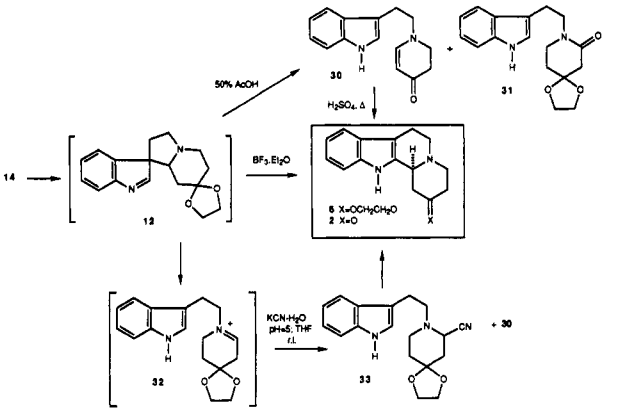
[a] ^{13}C NMR spectra were recorded at 50.3 MHz in $CDCl_3$. The assignments were aided by DEPT sequence experiments. Chemical shifts are given in δ units downfield from Me_4Si. [b] These signals can be interchanged.

applied to obtain the corresponding 3-spiroindolenines **12** and **13**, whose rearrangement would constitute a new way to prepare indolo[2,3-*a*]quinolizidin-2-one systems, and in particular, rearrangement of 3-spiroindolenine **13** would provide 1-ethylindolo[2,3-*a*]quinolizidin-2-one (**1**), our target compound.

Results and Discussion

The synthesis of *N*-(hydroxyethyl)piperidines **14** and **15** required for our purposes has been carried out by alkylation of the corresponding piperidines **21** and **22** with 2-bromoethanol following our usual procedure.[2a,8] In turn, the starting piperidines **21** and **22** were prepared by the *p*-TsOH cyclization of the iminoacetals **19** and **20**, resulting from the condensation of 1-(phenylsulfonyl)indole-3-carbaldehyde (**16**)[9] and the appropriate primary amines **17**[2b]

Scheme IV



and **18**,[2c] respectively. It is worth commenting that the cyclization of imine **20** furnished a 1:2 mixture of cis and trans isomers **22** and **23**, respectively, probably due to a minor difference of stability with respect to the 5-ethyl derivative isomers, whose trans form was the only one observed.[2a]

The K^{t}BuO treatment of alcohol **14** furnished the expected 3-spiroindolenine **12**,[10] the formation of which was monitored by TLC and demonstrated by $LiAlH_4$ reduction. Thus, a 1.2:1 mixture of 3-spiroindolines **24** and **25** was obtained.[17] They were separated by column chromatog-

(8) Alkylation of *cis*-piperidine **9** with 2-bromoethanol in several experimental conditions was unfruitful.

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(10) 3-Spiroindolenines are usually prepared by the following methods: (i) reduction of 2-oxindoles,[11] which in turn are majorly obtained from chloroindolenines derived from indolo[2,3-*a*]quinolizidine systems by ^{t}BuClO treatment;[7b,12] (ii) as a consequence of a retro-Mannich reaction in acid conditions on β-carbolines;[13,14] (iv) by alkylation of 3-substituted indoles[15] or reaction with *N*-acyliminium ions.[16]

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(16) Freund, R.; Mahboobi, S.; Noack, K.; Schönholzer, P.; Bernauer, K. *Helv. Chim. Acta* **1990**, *73*, 439–454.

(17) For a recent preparation of functionalized spiroindolines, see: (a) Zonjee, J. N.; Koning, H.; Speckamp, W. N. *Tetrahedron* **1989**, *45*, 7553–7564. (b) Mittendorf, J.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1990**, *46*, 4049–4062.

raphy and identified and differentiated by their spectroscopic data (see Tables III and IV). The most valuable information for identifying the spiroindolines was given by the presence of signals at ca. δ 54, due to the spiro carbon, a doublet at δ 71.5 corresponding to C-8, and the methylene carbon C-9 signal at δ 57–59 in the ^{13}C NMR spectra. In addition, the most characteristic data for differentiating the isomers was the chemical shift of 14-H in the ^1H NMR spectra, which appears at δ 7.28 when next to the piperidine nitrogen atom lone pair (in **25**) and at δ 7.10 when next to 8-H and far away from the influence of the nitrogen lone pair (in **24**).[18] Another distinctive signal corresponds to the AB system observable for C-9 methylene protons, which appears as two doublets at δ 3.24 and 3.80 in **24** and as a singlet at δ 3.44 in **25**. The complete signal assignment and the conformational study was accomplished on the basis of 2D NMR data (TOCSY and NOESY) and is shown in Tables III and IV.

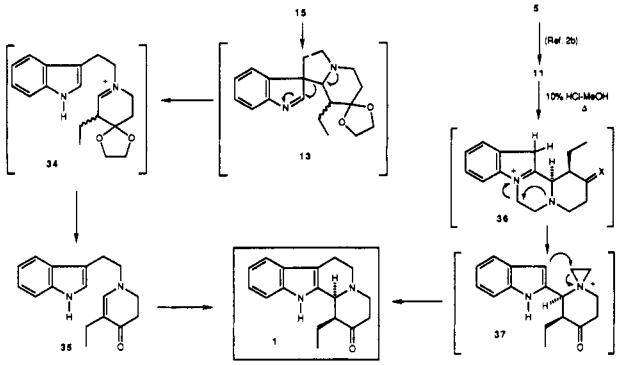
The rearrangement of indolenine **12** in BF_3·Et_2O led satisfactorily to the expected indolo[2,3-*a*]quinolizidine **6**,[19] which was identified by comparison of its spectral data to those previously obtained.[2b]

The reaction course in aqueous 50% AcOH implies the formation of an intermediate iminium salt **32**, which is converted into lactam **31**[21] or into enaminone **30**, when the acetal function is hydrolized. The formation of **32** in the aqueous acid medium was confirmed by its trapping with KCN to the corresponding α-aminonitrile **33**.[22] The conversion of **33** into the indolo[2,3-*a*]quinolizidin-2-one ethylene acetal **6** was accomplished by means of dry *p*-TsOH treatment.

Finally, the direct conversion of α-aminonitrile **33** into indolo[2,3-*a*]quinolizidin-2-one (**2**) was carried out by aqueous 50% AcOH treatment.[23,24]

In view of these satisfactory results, the application of this reaction sequence to preparation of 1-ethylindolo-[2,3-*a*]quinolizidin-2-one (**1**) from alcohol **15** was envisaged. The K^{t}BuO cyclization of alcohol **15** provided the corresponding 3-spiroindolenines **13**, which on $LiAlH_4$ reduction were converted into a 2.5:2:1 mixture of 3-spiroindolines **26–28** (Scheme III). Their structure and stereochemistry were once again determined from the spectral data.[25]

Scheme V



Thus, in the ^{13}C NMR spectra, the signals at ca. δ 54 characteristic of the spiro carbon C-14b, and at δ 42–45 and 72–76, corresponding to the ethyl-substituted C-7 and the angular C-8 carbons, respectively, together with the methylene carbon C-9 at δ 56–61, were important for determination of the structures (see Table IV). In the ^1H NMR spectra, the chemical shift of the signal corresponding to 14-H allowed the stereochemical assignment on the spiro carbon (see Table III). Thus, in spiroindolines **27** and **28** this proton appeared at δ ~7.1, while the third isomer **26** showed a deshielding to δ 7.33 due to the spatial proximity of this proton and the electron lone pair of the nitrogen atom. Furthermore, the disposition of the ethyl substituent was inferred from the ^{13}C NMR data, as isomer **28** showed an upfield shift for C-5 and C-14b, corresponding to a γ-gauche effect exerted by the ethyl group when axially disposed.

Treatment of C-7 epimeric acetals **26** and **27** with aqueous 10% HCl afforded in both cases the piperidone **29** in good yields, as a consequence of a C-7 epimerization in the acidic conditions.[27]

When 3-spiroindolenines **13** reacted with BF_3·Et_2O, only enaminone **35** was obtained, resulting from the aqueous workup of the intermediate iminium salt **34**, formed because the steric hindrance due to the ethyl group prevents the rearrangement to the corresponding indolo[2,3-*a*]-quinolizidine **8** and favors accumulation of the iminium salt. Enaminone **35** was identified by its very characteristic ^1H NMR spectrum, which presents a singlet at δ 6.65 for the olefinic proton, two signals at δ 0.83 and 2.00 corresponding to the ethyl substituent, and four triplets at δ 2.40, 3.02, 3.38, and 3.49 due to the methylene protons of the molecule assigned to 5-H, In-CH_2, 6-H, and NCH_2, respectively. Signals at δ 228.3, 153.0, and 110.9 in the ^{13}C NMR spectrum confirmed the presence of a conjugated carbonyl function.

Finally, aqueous acid treatment of enaminone **35** led to the expected 1-ethylindolo[2,3-*a*]quinolizidin-2-one (**1**) in 55% yield. The direct transformation of spiroindolenines **13** into our target molecule **1** was as well accomplished, in 60% yield, by heating in an aqueous 20% H_2SO_4 medium.

An alternative and rather surprising way to reach our goal was found to be the aqueous acid (4 N HCl or 20% H_2SO_4) treatment of 7-ethyl-6,6-(ethylenedioxy)-1,2,5,6,7,7a-hexahydropyrido[1′,2′:1,2]pyrazino[4,3-*a*]indole **11**, obtained by us in previous work,[2b] which implied a new kind of rearrangement, not observed in the case of unsubstituted systems. The formation of 1-ethylindolo[2,3-*a*]quinolizidin-2-one (**1**) can be accounted for by considering that in the acid medium the indole 3-position is

(18) The same ^1H NMR effect is characteristic in the case of 2-oxindoles: (a) Crabb, T. A. In *Annual Reports on NMR Spectroscopy*; Webb, G. A., Ed.; Academic Press: London, 1978. (b) Gaskell, A. J.; Randuz, H.-E.; Winterfeldt, E. *Tetrahedron* **1970**, *26*, 5353–5360.

(19) 3-Spiroindolenines has been observed as intermediates to 2,3-disubstituted indoles through a Wagner–Meerwein type rearrangement,[15] and the migratory aptitudes of diverse substituents has as well been established.[20]

(20) Jackson, A. H.; Naidoo, B. *Tetrahedron* **1968**, *24*, 6119–6129.

(21) For a related formation of lactams as byproducts in iminium salts cyclizations, see: (a) Rubiralta, M.; Torrens, A.; Palet, A.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 6761–6764. (b) Ponglux, D.; Wongseripipatana, S.; Aimi, N.; Nishimura, M.; Ishikawa, M.; Sada, H.; Haginiwa, J.; Sakai, S.-I. *Chem. Pharm. Bull.* **1990**, *38*, 573–575. (c) For a related formation of lactams in the mercuric acetate oxidation of piperidines, see: Fujii, T.; Ohba, M.; Sasaki, N. *Heterocycles* **1984**, *22*, 1805–1810.

(22) Grierson, D. S.; Vuilhorgne, M.; Husson, H.-P.; Lemoine, G. *J. Org. Chem.*, **1982**, *47*, 4439–4452.

(23) (a) Lounasmaa, M.; Jokela, R. *Tetrahedron* **1989**, *45*, 7449–7458. (b) Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Tamminen, T. *Tetrahedron* **1989**, *45*, 7615–7630.

(24) Indolo[2,3-*a*]quinolizidin-2-one **2** was also obtained from enaminone **30** (Winterfeldt, E. *Chem. Ber.* **1964**, 2463–2468) as well as from lactam **31**: Fujii, T.; Yoshifuji, S.; Ito, H. *Chem. Pharm. Bull.* **1988**, *36*, 3348–3353.

(25) The stereochemical assignment of the major spiroindoline **26**, in which the C-9 and C-14b bond is cis with respect to the nitrogen lone pair, corresponding to the "A series"[26] and the ethyl substituent is equatorial, was based on the ^{13}C NMR data, wherein C-9 is more deshielding in A series ($\Delta\delta$ 2.5) and C-5 c.a. 3 ppm shilded when the ethyl chain is axial due to a "γ-gauche" effect.

(26) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *34*, 3871–3877.

(27) For a related spiroindolizidin-7-one, see: Ban, Y.; Seto, M.; Oishi, T. *Chem. Pharm. Bull.* **1975**, *23*, 2605–2613.

protonated to give **36**. The hindrance due to the proximity of the ethyl substituent upon the N_b electron lone pair makes its protonation difficult and therefore the N_b nitrogen atom can act as a nucleophile upon C-7 with opening of ring C. The resulting aziridinium salt **37** is then opened by the indole from its most reactive 3-position (see Scheme V).

In conclusion, we can state that 1-ethylindolo[2,3-*a*]-quinolizidin-2-one (**1**) can be successfully prepared by an intramolecular cyclization of *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone **4** as well as from the 2-indolyl analogue[2b] by the action of K^{t}BuO, followed by acid treatment. However, the new strategy described in the present paper is a one-pot reaction that provides a superior global yield (60%) with respect to the previous one[2b] (38%), which proceeds in two steps. Furthermore, the reactivity of 3-spiroindolenines will be developed toward other potential biologically active families of indole alkaloids.

Experimental Section

General Methods. Melting points were determined in a capillary tube on a CTP-MP 300 hot-plate apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian XL-200 or a Varian Gemini-200 instrument. Unless otherwise noted, NMR spectra were registered 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 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40–63 μm, Macherey–Nagel) or Al_2O_3 (aluminum oxide 90 neutral, activity 1, 63–200 μM, Merck). TLC was performed on SiO_2 (silica gel 60 F254, Merck) and developed with the solvent described in each case for flash chromatography. The spots were located by UV light and iodoplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CSIC, Barcelona.

2-[1-(Phenylsulfonyl)-3-indolyl]-4-piperidone Ethylene Acetal (21). A solution of amino acetal **17**[2b] (5.92 g, 45.2 mmol) and 1-(phenylsulfonyl)indolyl-3-carbaldehyde[9] (14.17 g, 49.7 mmol) in anhydrous benzene (200 mL) was stirred at 0 °C for 30 min, at room temperature overnight, and at reflux for 3 h. After 16 h of additional reflux with water removal by a Dean–Stark trap, the solvent was evaporated to give imine **19** (17.5 g, 98%), which was used without further purification.

A stirred mixture of the imino acetal **19** (17.5 g, 44.5 mmol) and anhydrous *p*-TsOH (15.23 g, 88.6 mmol) in dry benzene (400 mL) was heated at reflux under N_2 for 1 h. The cooled mixture was washed with aqueous Na_2CO_3, dried, and evaporated to give a thick oil that was flash chromatographed (CH_2Cl_2–MeOH (95:5)) to yield piperidine **21** (12.63 g, 72%) as a yellow solid: mp 93–94 °C (acetone); IR (KBr) 3310, 1370, 1170 cm^{-1}; MS *m/e* (relative intensity) 398 (M$^+$, 15), 353 (21), 283 (20), 257 (24), 227 (11), 197 (16), 171 (30), 142 (36), 130 (19), 115 (37), 87 (64), 77 (100), 51 (22). Anal. Calcd for $C_{21}H_{22}N_2O_4S\cdot 1/2H_2O$: C, 61.90; H, 5.69; N, 6.87. Found: C, 61.78; H, 5.49; N, 6.85.

3-Ethyl-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone Ethylene Acetals (22 and 23). Operating as above, from 1-(phenylsulfonyl)indolyl-3-carbaldehyde[9] (14.51 g, 50.9 mmol) and amino acetal **18**[2b] (7.36 g, 46.29 mmol) in anhydrous benzene (200 mL) was obtained imine **20** (22.6 g, 98%), which, without further purification, was treated with anhydrous *p*-TsOH (15.6 g, 90.7 mmol), thus leading to a 1:2 mixture of *trans*- and *cis*-piperidines **22** and **23**, which were separated by flash chromatography (CH_2Cl_2–MeOH (95:5)). *cis*-Isomer **23** (higher R_f, 5.2 g, 24%): mp 79–82 °C (acetone); IR (NaCl) 3300, 1360, 1170 cm^{-1}; MS *m/e* (relative intensity) 426 (M$^+$, 1), 382 (2), 396 (1), 312 (1), 283 (4), 270 (1), 115 (15), 77 (100). Anal. Calcd for $C_{23}H_{26}N_2O_4S$: C, 64.77; H, 6.14; N, 6.57. Found: C, 64.50; H, 5.99; N, 6.48. *trans*-Isomer **22** (lower R_f, 9.93 g, 46%); mp 80–83 °C (acetone); IR (NaCl) 1340, 1150 cm^{-1}; CIMS *m/e* (relative intensity) 427 (M$^+$ + 1, 100), 304 (10), 287 (69), 213 (4), 177 (50), 125 (11). Anal. Calcd for $C_{23}H_{26}N_2O_4S$: C, 64.77; H, 6.14; N, 6.57. Found: C, 64.52; H, 6.33; N, 6.09.

***N*-(2-Hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone Ethylene Acetal (14).** 2-Bromoethanol (1.34 mL, 18.84 mmol) was added dropwise to a mixture of piperidine **21** (5 g, 12.56 mmol) and anhydrous K_2CO_3 (5 g) in absolute ethanol (150 mL). The resulting mixture was heated at reflux under N_2 for 15 h. The EtOH was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with H_2O. The dried organic phase was evaporated and purified by flash chromatography (Al_2O_3, CH_2Cl_2–MeOH (97:3)) to give pure alcohol **14** (3.44 g, 62%) as a yellow solid: 96–97 °C (acetone); IR (KBr) 3550–3300, 1370 and 1175 cm^{-1}; MS *m/e* (relative intensity) 442 (M$^+$, 0.1), 411 (15), 353 (3), 296 (4), 283 (3), 257 (4), 215 (4), 142 (21), 128 (91), 115 (24), 99 (64), 77 (100), 42 (86). Anal. Calcd for $C_{23}H_{26}N_2O_5S$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.49; H, 5.79; N, 6.46.

***trans*-3-Ethyl-1-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone Ethylene Acetal (15).** Operating as above, from *trans*-piperidine **22** (2.2 g, 5.16 mmol), anhydrous K_2CO_3 (2 g), absolute EtOH (200 mL), and 2-bromoethanol (0.55 mL, 7.74 mmol) was obtained alcohol **15** after flash chromatography (Al_2O_3, CH_2Cl_2–MeOH (97:3)) purification, together with the corresponding ***trans*-1-(2-hydroxyethyl)-2-(3-indolyl)-4-piperidone ethylene acetal** (lower R_f, 210 mg, 12%): mp 119–121 °C (acetone); IR (KBr) 3350–3200 cm^{-1}; CIMS *m/e* (relative intensity) 331 (M$^+$ + 1, 100), 287 (14), 207 (12), 180 (18), 163 (21). Anal. Calcd for $C_{19}H_{26}N_2O_3\cdot 1/2H_2O$: C, 67.84; H, 8.00; N, 8.33. Found: C, 67.89; H, 7.81; N, 8.12. Alcohol **15** (higher R_f, 1.69 g, 70%): IR (NaCl) 3300–3200, 1360, 1170 cm^{-1}; MS *m/e* (relative intensity) 470 (M$^+$, 1), 439 (10), 329 (1), 298 (1), 128 (63), 99 (46), 77 (100), 42 (33). Anal. Calcd for $C_{25}H_{30}N_2O_5S$: C, 63.80; H, 6.43; N, 5.95. Found: C, 63.53; H, 6.89; N, 5.64.

General Method To Prepare 3-Spiroindolenines. To a solution of the amino alcohols **14–15** (1 equiv) in anhydrous THF was added freshly sublimed K^{t}BuO (2 equiv) under a N_2 atmosphere, at 0 °C. The mixture was stirred for 30 min at 0 °C, and a TLC control of the indolenine formation was performed (SiO_2, CH_2Cl_2–MeOH (95:5)).

7-Oxoindolizidine-1-spiro-3′-indoline Ethylene Acetals (24 and 25). To a solution of spiroindolenine **12**, prepared as in the general method from alcohol **14** (300 mg, 0.68 mmol), in dry THF (30 mL) was added $LiAlH_4$ (51.5 mg, 1.46 mmol), and the mixture was heated at reflux for 15 min under a N_2 atmosphere. The reaction was quenched with saturated aqueous NH_4Cl (1 mL), and the reaction mixtures was poured into ice–water and Et_2O. The layers were separated, and the aqueous phase was extracted twice with Et_2O and one time with CH_2Cl_2. The mixed organic extracts were dried and evaporated to give a 1:1 epimeric mixture of 3-spiroindolenines **24** and **25**, which were separated by flash chromatography (CH_2Cl_2–MeOH (93:7)). Spiroindoline **24** (higher R_f, 48.6 mg, 25%): IR (NaCl) 3300–3400 cm^{-1}; MS *m/e* (relative intensity) 286 (M$^+$, 3), 156 (100), 144 (12), 130 (17). Spiroindoline **25** (lower R_f, 58.35 mg, 30%): IR ($CHCl_3$) 3400 cm^{-1} cm^{-1}; MS *m/e* (relative intensity (286 (M$^+$, 4), 156 (100), 144 (9), 130 (12). Anal. Calcd for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78. Found: C, 70.98; H, 7.87; N, 9.32.

8-Ethyl-7-oxoindolizidine-1-spiro-3′-indoline Ethylene Acetals (26–28). Operating as above, from a solution of spiroindolenine **13**, prepared following the general procedure from **15** (300 mg, 0.64 mmol) in dry THF (30 mL), and $LiAlH_4$ (49 mg, 1.28 mmol) was obtained a mixture of spiroindolines **26–28**, which was separated by flash chromatography (CH_2Cl_2–MeOH (95:5)). Spiroindoline **26** (R_f 0.54, 42 mg, 21%): IR (NaCl) 3350 cm^{-1}; MS *m/e* (relative intensity) 314 (M$^+$, 1), 227 (2), 184 (100), 168 (22), 130 (23), 117 (17), 98 (14). Spiroindoline **27** (R_f 0.25, 32 mg, 16%). Spiroindoline **28** (0.38, 16 mg, 8%): Anal. Calcd for $C_{19}H_{26}N_2O_2\cdot 1/4H_2O$: C, 71.49; H, 8.31; N, 8.78. Found: C, 71.72; H, 8.50; N, 8.83.

8-Ethyl-7-oxoindolizidine-1-spiro-3′-indoline (29). A solution of spiroindoline ethylene acetal **26** of **27** (50 mg, 0.16 mmol) in a 1:1 mixture of 4 N HCl and MeOH (40 mL) was heated at reflux for 24 h. The reaction mixture was cooled, basified with

Na_2CO_3 and extracted with CH_2Cl_2 to provide ketone **29** (36 mg, 89% from **26**) after flash chromatography (CH_2Cl_2–MeOH (95:5)): IR (NaCl) 1695 (CO) cm^{-1}; MS *m/e* (relative intensity) 270 (M^+, 34), 257 (4), 140 (100), 117 (14), 110 (12), 82 (19). Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.51; H, 8.20; N, 10.36. Found: C, 75.13; H, 8.08; N, 10.41.

***trans*-2,2-(Ethylenedioxy)-1,2,3,4,6,7,12,12b-octahydro[2,3-*a*]quinolizine (6). Method A.** To a solution of spiroindolenine **12**, prepared as in the general procedure from alcohol **14** (300 mg, 0.68 mmol), in dry THF (30 mL) was added freshly distilled BF_3·Et_2O (0.126 mL, 1.02 mmol), and the resulting mixture was treated at reflux for 2 h under N_2 atmosphere. The reaction mixture was poured into ice–water, basified with Na_2CO_3, and extracted twice with Et_2O and one time with CH_2Cl_2. The organic extracts were dried and evaporated to yield an oil that was purified by flash chromatography (CH_2Cl_2–MeOH (95:5)), thus isolating pure indolo[2,3-*a*]quinolizidin-2-one ethylene acetal **6**; 75 mg, 40%, which was identified by comparison of its spectral data to the described ones.[2b]

Method B. A solution of α-aminonitrile **33** (400 mg, 1.29 mmol) in dry benzene (25 mL) was added to a solution of anhydrous *p*-TsOH (47 mg, 2.6 mmol) in dry benzene (75 mL), and the mixture was treated at reflux for 1 h under a N_2 atmosphere. The reaction was poured into ice–water and basified with Na_2CO_3. The layers were separated, and the aqueous phase was extracted with benzene. The mixed organic layers were dried and evaporated to give an oil that was flash chromatographed (CH_2Cl_2–MeOH (95:5)) to yield pure indolo[2,3-*a*]quinolizidine **6** (147 mg, 40%), which was identified by comparison of its spectral data with those previously obtained.[2b]

Treatment of Spiroindolenine 12 with 50% Aqueous AcOH. To a solution of spiroindolenine **12** prepared as above was added 50% aqueous AcOH (30 mL), and the resulting mixture was stirred at room temperature for 30 min. The reaction mixtures was basified with Na_2CO_3, the layers were separated, and the aqueous phase was extracted twice with Et_2O and one time with CH_2Cl_2. The organic extracts were dried and evaporated to give an oil that was flash chromatographed (CH_2Cl_2–MeOH (95:5)), thus isolating **4,4-(ethylenedioxy)-1-tryptophyl-2-piperidone (31)** (higher R_f, 17 mg, 9%): IR ($CHCl_3$) 3440, 1650 cm^{-1}; ^1H RMN: 1.82 (m, 2 H, 5-H), 1.90–2.70 (m, 6 H, 3-H, 5-H and In-CH_2), 3.24 (dt, J = 6 and 2 Hz, 2 H, NCH_2), 3.56 (td, J = 10 and 4 Hz, 2 H, 6-Ha), 3.90 (br d, J = 10 Hz, 1 H, 6-He), 3.96–3.98 (m, 4 H, OCH_2), 7.10–7.50 (m, 2 H, In-5H and In-6H), 7.42 (s, 1 H, In-2H), 7.60–8.00 (m, 2 H, In-7H and In-4H), 9.20–9.30 (br s, 1 H, In-NH); ^{13}C NMR 24.1 (In-CH_2), 41.5 (C-5), 49.8 (C-3), 54.5 (C-6), 58.0 (NCH_2), 64.3 (OCH_2), 100.6 (C-4), 111.9 (In-C7), 114.0 (In-C3), 120.3 (In-C5), 121.8 (In-C6), 123.0 (In-C2), 129.3 (In-C3a), 136.5 (In-C7a), 185.7 (C=O); MS *m/e* (relative intensity) 300 (M^+, 25), 284 (100), 283 (75), 253 (1), 239 (15), 197 (57), 145 (57). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.59; H, 6.83; N, 9.01.

1-Triptophyl-2,3-dihydro-1*H*-pyridin-4-one (30) (lower R_f, 80 mg, 49%): IR ($CHCl_3$) 3480, 1640, 1600 cm^{-1}; ^1H NMR 2.38 (t, J = 8 Hz, 2 H, 3-H), 3.01 (t, J = 7 Hz, 2 H, In-CH_2), 3.46 (t, J = 8 Hz, 2 H, 2-H), 3.51 (t, J = 7 Hz, 2 H, In-CH_2CH_2), 4.77 (d, J = 7 Hz, 1 H, 5-H), 6.76 (d, J = 7 Hz, 6-H), 6.97 (s, 1 H, In-2H), 7.10 (t, J = 7 Hz, 1 H, In-5H), 7.19 (t, J = 7 Hz, 1 H, In-6H), 7.38 (d, J = 7 Hz, 1 H, In-7H), 7.53 (d, J = 7 Hz, 1 H, In-4H), 9.45–9.55 (br s, 1 H, In-NH); ^{13}C NMR δ 24.6 (In-CH_2), 34.5 (C-3), 46.4 (C-2), 56.2 (In-CH_2CH_2N), 96.2 (C-5), 110.5 (C-4), 111.6 (In-C7), 117.9 (In-C2), 119.1 (In-C5), 121.8 (In-C4), 122.9 (In-C6), 123.1 (In-C3), 126.6 (In-C3a), 136.4 (In-C7a), 155.5 (C-6), 192.1 (C=O); MS *m/e* (relative intensity) 240 (M^+, 25), 143 (6), 130 (100), 111 (55), 110 (41), 82 (23). The hydrochloride melted at 160–162 °C (acetone–MeOH) (lit.[21] mp 164 °C).

Treatment of Spiroindolenine 12 with Aqueous KCN. To a solution of spiroindolenine **12** prepared as above was added a solution of KCN (133 mg, 2.05 mmol) in an aqueous buffer solution (pH 4) of citric acid–sodium acetate (30 mL), and the mixture was vigorously stirred at room temperature for 30 min. The emulsion was basified with Na_2CO_3, the layers were separated, and the aqueous phase was extracted twice with Et_2O and one time with CH_2Cl_2. The mixed organic extracts were dried and evaporated to give an oil that was flash chromatographed (CH_2Cl_2–MeOH (95:5)), thus obtaining **α-aminonitrile 33** (110 mg, 69%): IR ($CHCl_3$) 3480, 2210 cm^{-1}; ^1H NMR δ 1.70–2.00 (m, 1 H, 5-H), 2.60–3.00 (m, 1 H, 5-H), 3.85–4.10 (m, 5 H, OCH_2 and 2-H), 7.01 (d, J = 1.5 Hz, 1 H, In-2H), 7.13 (br t, J = 7 Hz, 1 H, In-5H), 7.14 (br d, J = 7 Hz, 1 H, In-6 H), 7.32 (br d, J = 7 Hz, 1 H, In-4H), 7.62 (br d, J = 7 Hz, 1 H, In-7H), 8.30 (br s, 1 H, NH); ^{13}C NMR 22.9 (In-CH_2), 34.4 (C-5), 36.5 (C-3), 47.2 (C-6), 50.8 (C-2), 55.7 (In-CH_2CH_2), 64.2 and 64.5 (OCH_2), 105.3 (C-4), 111.2 (In-C7), 113.2 (In-C3), 117.0 (CN), 118.5 (In-C4), 119.2 (In-C5), 121.8 and 121.9 (In-C6 and In-C2), 127.3 (In-C3a), 136.2 (In-C7a); MS *m/e* (relative intensity) 311 (M^+, 12), 181 (100), 154 (62), 130 (38), 82 (10). Anal. Calcd for $C_{18}H_{21}N_3O_2$: C, 69.43; H, 6.83; N, 13.50. Found: C, 69.50; H, 7.04; N, 13.71.

***trans*-3,4,6,7,12,12b-Hexahydro[2,3-*a*]quinolizin-2(1*H*)-one (2).** A solution of α-aminonitrile **33** (100 mg, 0.32 mmol) in MeOH (3 mL) and aqueous 50% AcOH (50 mL) was stirred at room temperature for 15 h. The reaction mixtures was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and evaporated, and the oil thus obtained was flash chromatographed (CH_2Cl_2–MeOH (95:5)) yielding **2** (50 mg, 65%), which was identified by comparison of its spectral data to the previously obtained.[2b]

***trans*-1-Ethyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizin-2(1*H*)-one (1). Method A.** Operating as for the preparation of **6**, from a solution of spiroindolenine **13**, prepared as in the general method from alcohol **15** (300 mg, 0.64 mmol) in dry THF (30 mL), and freshly distilled BF_3·Et_2O (118 mL, 0.96 mmol) was obtained enaminone **35** (92 mg, 46%) after flash chromatography (CH_2Cl_2–MeOH (95:5)): IR ($CHCl_3$) 3460, 1590 cm^{-1}; ^1H NMR 0.83 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.00 (q, J = 7 Hz, 2 H, CH_2CH_3), 2.40 (t, J = 8 Hz, 2 H, 5-H), 3.02 (t, J = 7 Hz, 2 H, In-CH_2), 3.38 (t, J = 8 Hz, 2 H, 6-H), 3.49 (t, J = 7 Hz, 2 H, In-CH_2CH_2), 6.65 (s, 1 H, 2-H), 6.95 (s, 1 H, In-2H), 7.10 (t, J = 7 Hz, 1 H, In-4H), 7.18 (t, J = Hz, 1 H, In-5H), 7.35 (d, J = 7 Hz, 1 H, In-7H), 7.55 (d, J = 7 Hz, 1 H, In-4H), 8.70–8.90 (br s, 1 H, NH); ^{13}C NMR 14.3 (CH_3CH_2), 20.1 (CH_3CH_2), 24.1 (In-CH_2), 35.8 (C-5), 47.2 (InCH_2CH_2), 56.4 (C-6), 110.9 (C-3), 111.8 (In-C7), 118.4 (In-C2), 119.5 (In-C5), 122.3 (In-C4), 123.1 (In-C6), 127.1 (In-C3a), 128.6 (In-C3), 136.7 (In-C7a), 153.0 (C-2), 228.3 (C=O); MS *m/e* (relative intensity) 268 (M^+, 24), 184 (1), 139 (44), 138 (100), 130 (68), 110 (17), 55 (7). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.51; N, 10.44. Found: C, 76.35; H, 7.52; N, 10.79.

A solution of enaminone **35** (40 mg, 0.15 mmol) in MeOH (10 mL) and aqueous 10% H_2SO_4 (10 mL) was stirred at 90–95 °C for 6 h. The reaction mixture was poured into ice–water, basified with Na_2CO_3, and extracted with CH_2Cl_2. The organic extracts, dried and evaporated, furnished an oil that was purified by flash chromatography (CH_2Cl_2–MeOH (95:5)) to give quinolizidin-2-one **1** (22 mg, 55%): IR ($CHCl_3$) 3320, 2795, 2745, 1690 cm^{-1}; ^1H NMR 0.77 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.20–1.40 (m, 1 H, CH_ACH_3), 1.60–1.80 (m, 1 H, CH_BCH_3), 2.35 (br d, J = 12 Hz, 1 H, 3-He), 2.56 (m, 1 H, 1-He), 2.54–2.58 (m, 1 H, 6-Hα), 2.68 (br t, J = 12 Hz, 1 H, 3-Ha), 2.70–2.80 (m, 1 H, 4-Ha), 2.78 (br d, J = 12 Hz, 1 H, 7-Hα), 2.98 (t, J = 12 Hz, 1 H, 7-Hβ), 3.30 (br t, J = 6 Hz, 1 H, 4-He), 3.68 (br s, $W_{1/2}$ = 7 Hz, 1 H, 12b-H), 7.14 and 7.17 (2 t, J = 7 Hz, 1 H each, 9-H and 10-H), 7.35 (d, J = 7 Hz, 1 H, 11-H), 7.49 (dd, J = 7 Hz, 1 H, 8-H), 7.90 (br s, 1 H, NH); ^{13}C NMR 11.4 (CH_2CH_3), 20.3 (CH_2CH_3), 21.7 (C-7), 38.8 (C-3), 52.1 (C-6), 54.9 (C-4), 56.2 (C-1), 62.4 (C-12b), 108.0 (C-7a), 111.2 (C-11), 118.3 (C-9), 119.7 (C-8), 121.9 (C-10), 126.6 (C-7b), 131.5 (C-11a), 136.0 (C-12a), 211.2 (C=O); MS *m/e* (relative intensity) 268 M^+, 69), 267 (100), 253 (87), 197 (21), 169 (48), 115 (21), 55 (32). Anal. Calcd for $C_{17}H_{20}N_2O \cdot {}^1/_2H_2O$: C, 73.56; H, 7.63; N, 10.09. Found: C, 73.19; H, 7.36; N, 9.78.

Method B. To a solution of spiroindolenine **13**, prepared as in the general method from alcohol **15** (300 mg, 0.64 mmol) in anhydrous THF (30 mL), was added 20% aqueous H_2SO_4 (30 mL), and the mixture was heated at reflux for 15 h. The reaction mixture was poured into ice–water, basified with Na_2CO_3, and extracted with CH_2Cl_2. The organic layer, dried and evaporated, provided an oil which, after flash chromatography (CH_2Cl_2–MeOH (95:5)) gave indoloquinolizidinone **1** (103 mg, 60%), which was identified by comparison of its spectral data with those already obtained.

Method C. A solution of pyridopyrazinoindole **11**[2b] (50 mg, 0.16 mmol) in a 1:1 mixture of 4 N HCl (10 mL) and MeOH (10

mL) was heated at reflux for 4 h. The reaction mixtures was cooled, basified with Na_2CO_3, and extracted with CH_2Cl_2 to provide quinolizidinone 7 (38 mg, 95%) after flash chromatography (CH_2Cl_2–MeOH (95:5)), which was identified by comparison of its TLC and spectral data with those already obtained.

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Registry No. 1, 132113-29-2; 2, 55854-97-2; 6, 130179-28-1; 11, 130179-30-5; 12, 136061-54-6; 13, 136061-55-7; 14, 130627-35-9; 15, 132113-30-5; 15 (de-(phenylsulfonyl) derivative), 136061-57-9; 16, 80360-20-9; 17, 62240-37-3; 18, 130179-18-9; 19, 130627-33-7; 20, 132113-31-6; 21, 130627-34-8; 22, 132113-33-8; 23, 132113-32-7; 24, 130627-38-2; 25, 130627-37-1; 26, 132200-44-3; 27, 132200-45-4; 28, 132113-34-9; 29, 136061-56-8; 30, 92579-46-9; 31, 130627-39-3; 33, 130627-40-6; 35, 132113-35-0.

Supplementary Material Available: 2D NMR spectra of pertinent compounds (4 pages). Ordering information is given on any current masthead page.

Utilizing Acetyl Hypofluorite for Chlorination, Bromination, and Etherification of the Pyridine System

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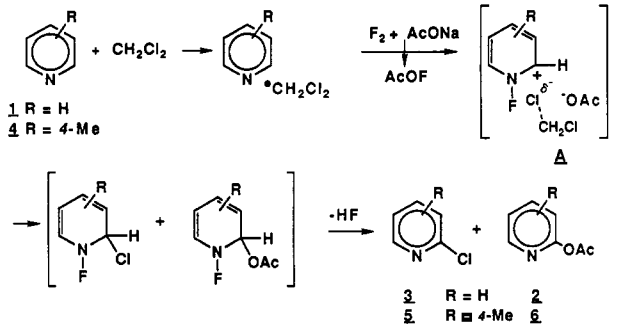
Acetyl hypofluorite, which is easily made from F_2, possesses a strong electrophilic fluorine. This electrophile is able to attach itself to the nitrogen atom of pyridine and activate the ring toward nucleophilic attacks. The ultimate elimination of HF results in an overall easy nucleophilic displacement of the hydrogen of the important 2-position. The nucleophiles used; $Cl^{\delta-}$, $Br^{\delta-}$, and $RO^{\delta-}$, originate from solvents such as CH_2Cl_2, CH_2Br_2, and various primary alcohols. Thus, 2-halo- or 2-alkoxypyridines were formed. The reaction conditions (room temperature, very short reaction times, and good yields) transform the task of direct substitution of the pyridine ring from an extremely difficult to a very easy procedure.

During the last few years we have demonstrated that, apart from its more obvious function as a fluorinating agent, F_2 can be used for an array of processes leading eventually to difficult to obtain, fluorine-free compounds. We have utilized reagents directly prepared from fluorine for introducing double bonds in deactivated saturated sites,[1] for bromination and iodination of aromatic compounds,[2,3] for hydroxylation of saturated tertiary C–H bonds,[4] and for efficient epoxidation of many types of olefins.[5]

The pyridine system is of course very important in organic and pharmaceutical chemistry. Despite numerous research reports dealing with this system, reactions aimed specifically at direct substitution of the parent hydrogen at the important 2-position are very rare. Hydroxylations through arrangements of the appropriate *N*-oxide[6] and Chichibabin's amination[7] are practically the only routes for activating this position. Direct regiospecific halogenation of the pyridine ring is extremely difficult and usually unsatisfactory, and yet, examination of the literature leads to the conclusion that halopyridines constitute a very large part of this heterocycle's chemistry.[8] Recently we have discovered that acetyl hypofluorite (AcOF), made from F_2,[9] can be used for direct acetoxylation of the pyridine ring by utilizing the strong electrophilicity of the oxygen-bound fluorine coupled with the formation of the very strong HF bond.[10] We present here a somewhat unexpected,[11] yet

Scheme I



general, reaction derived from the action of AcOF on the pyridine ring leading to chlorination, bromination, and alkoxylation of this relatively inactive heterocycle.[12] The mild conditions of this reaction and its efficiency (a few seconds at room temperature and usually high yields) are unparalleled for this type of chemistry.[13]

We found that the outcome of applying AcOF to pyridine (1) depends on the solvent system used. As we have already reported,[10] use of apolar solvents such as $CFCl_3$ resulted in 2-acetoxypyridine (2) in excellent yield. With CH_2Cl_2, however, the reaction course is altered and the major product, formed in 70% yield, is 2-chloropyridine

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