Studies on the Synthesis of the Indolo[2,3-*a*]quinolizidine System[1]

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A new route to the indolo[2,3-*a*]quinolizidin-2-one ring system is reported. It is based on the elaboration of the C ring in the key step by cyclization upon the indole 3-position of an N-substituted 2-(2-indolyl)-4-piperidone derivative. This cyclization was efficiently accomplished by treatment of the sulfonylated indole alcohol **6** with potassium *tert*-butoxide.

The indolo[2,3-*a*]quinolizidine ring system has received great attention from a synthetic standpoint because it is present in a large number of indole alkaloids.[2] In particular, the indolo[2,3-*a*]quinolizidin-2-ones,[3] including the 3-ethyl derivative **1**,[4] are known intermediates in the synthesis of indole alkaloids. Previous approaches to the indolo[2,3-*a*]quinolizidin-2-one ring system involve either closure of ring C by formation of the C_{12a}–C_{12b} bond[5] or construction of ring D[6] in the key steps of the synthesis.

In the context of our studies about the use of 2-aryl-4-piperidones as synthetic intermediates,[7] we report here a new synthetic entry to the indolo[2,3-*a*]quinolizidin-2-one system based on the elaboration of ring C in the crucial synthetic step by cyclization upon the indole 3-position using an appropriately substituted 2-(2-indolyl)-4-piperidone derivative.[8] By a similar strategy, we recently reported[7c] a new synthesis of benzo[*a*]quinolizidin-2-ones which constitutes a formal synthesis of the alkaloid emetine.

The starting 2-(2-indolyl)piperidone derivative **5** was prepared according to our general procedure for the synthesis of 2-aryl-4-piperidones,[9] consisting in the condensation between an aromatic aldehyde (**2** in this case) and a β-amino ketone ethylene acetal (**3** in this case) followed by a Mannich-type cyclization of the resulting imino acetal (Scheme I). The expected,[9b] more stable trans relationship between indolyl and ethyl substituents was confirmed by the coupling constants of the axial piperidine protons at C(2) and C(6) (see Table I).

Initially, the closure of ring C according to our strategy was planned as in the benzene series,[7c] by cyclization of piperidine-1-acetaldehyde **7**. This aldehyde was prepared by alkylation of **5** with 2-bromoethanol followed by a Swern[10] oxidation of the resulting amino alcohol **6**. However, in spite of some precedents about related cyclizations upon the indole 3-position in *N*-(phenylsulfonyl)indoles,[11] treatment of aldehyde **7** under a variety of acidic conditions (4 N HCl, $TiCl_4$, $BF_3{\cdot}Et_2O$) gave only negligible or poor yields of the desired tetracyclic system **8**. For this reason we decided to try a similar cyclization from an indole derivative lacking the deactivating sulfonyl substituent. However, when amino alcohol **10**, which was prepared either by alkaline hydrolysis of **6** or by deprotection of **5** followed by alkylation, was subjected to the Swern oxidation, the unexpected tetracyclic alcohol **11** was obtained in 80% yield. Under the reaction conditions, not only had the initially formed aldehyde undergone cyclization upon the indole nitrogen[12] but also chlorination at the indole 3-position had occurred. The chlorination of nucleophilic carbon centers under Swern oxidation conditions has recently been reported[13] and can be accounted for by considering that the intermediate chlorodimethylsulfonium salt[14] acts as a source of chloronium ion instead of undergoing substitution at the sulfur atom by the alcohol hydroxy group as in the normal Swern oxidation mechanism. In fact, treatment of 2-(1-methylpiperidyl)-

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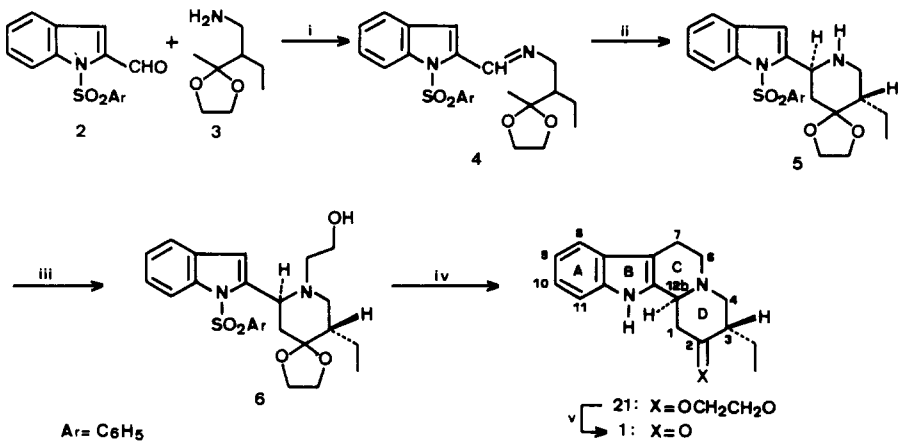
Scheme I[a]

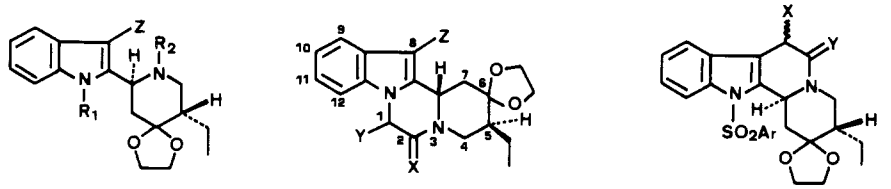


[a] Reagents: (i) benzene, Dean–Stark; (ii) *p*-TsOH, benzene, Dean–Stark; (iii) $BrCH_2CH_2OH$, EtOH, Na_2CO_3; (iv) Et_2O, 0 °C, *t*-BuOK; (v) 4 N HCl, MeOH.

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

	compound						
proton	5	6	9	10	12	13	14
2-H_a	4.54 dd (12, 2.4)	4.36 dd (12, 2.4)	4.10 dd (12, 2.4)	3.77 dd (10.8, 4.8)	3.92 dd (12.9, 2.7)	3.40 dd (10.4, 4.6)	3.74 dd (11, 3.5)
3-H_e	2.25 dd (12, 2.4)	1.96 dd (12, 2.4)	2.12 dd (12, 2.4)	1.8–1.9 m	2.08 dd (12.9, 2.7)	1.9–2.0 m	1.94 dd (11, 3.5)
3-H_a	1.63 t (12)	1.66 t (12)	1.72 t (12)	1.95 m	1.58 dd (12.9, 11.5)	1.9 m	1.8 t (11)
5-H_a	1.5–1.8 m	1.8–1.9 m	1.5–1.8 m	1.8–1.9 m	1.85–2.0 m	1.9–2.0 m	1.9–2.0 m
6-H_e	3.26 dd (12, 4.8)	3.22 dd (12, 4)	3.24 dd (12, 2.4)	3.20 dd (12, 4.2)	3.02 dd (11.5, 4)	3.04 dd (11.6, 4.3)	3.08 dd (12, 4)
6-H_a	2.76 t (12)	2.16 t (12)	2.86 t (12)	2.19 t (12)	2.20 t (11.5)	2.18 t (11.6)	2.28 t (12)
OCH_2CH_2O	3.9–4.1 m	3.9–4.0 m	4.0 br s	3.95 br s	3.8–4.1 m	3.9–4.0 m	3.9–4.1 m
CH_2CH_3	0.9–1.3 m	0.9–1.3 m	0.9–1.2 m	0.96–1.3 m	1.0–1.2 m	1.0–1.2 m	1.0–1.2 m
	1.5–1.9 m	1.5–1.8 m	1.5–1.8 m	1.6–1.8 m	1.6–1.8 m	1.6–1.8 m	1.6–1.8 m
CH_2CH_3	0.93 t (8)	0.93 t (7)	0.93 t (7)	0.93 t (7)	0.92 t (7)	0.94 t (7)	0.96 t (7)
In-3H	6.65 s	6.71 s	6.32 d (2)	6.34 d (2)	6.71 s	6.35 s	–
In-4H	7.76 dt (7, 1.5)	7.78 dt (7, 1.5)	7.32 br d (7)	7.28 dd (7.2, 1.5)	7.80 d (8)	7.32 d (8)	7.56 dd (7, 1)
In-5H	7.2–7.5 m	7.2–7.6 m	7.08 td (7, 1.2)	7.0 td (7, 2)	7.2–7.6 m	7.06 t (8)	7.1–7.3 m
In-6H	7.2–7.5 m	7.2–7.6 m	7.16 td (7, 1.2)	7.12 td (7, 2)	7.2–7.6 m	7.14 t (8)	7.1–7.3 m
In-7H	8.2 dd (7, 1.5)	8.3 dd (7, 1.5)	7.54 br d (7)	7.50 dd (7.2, 1.5)	8.30 d (8)	7.54 d (8)	7.31 d (7)
C_6H_5	7.2–7.5 m	7.2–7.6 m	–	–	7.2–7.6 m	–	–
NCH_3	–	–	–	–	1.92 s	2.09 s	2.12 s
NCH_2CH_2	–	2.70 m	–	3.38 ddd (11.4, 10.8, 4.2)	–	–	–
		3.28 m		2.76 ddd (13.2, 9, 4.2)			
OCH_2	–	3.55 td (10, 3.5)	–	3.64 ddd (11.4, 9, 3.6)	–	–	–

[a] 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 Me_4Si).



	R_1	R_2	Z
5	$SO_2C_6H_5$	H	H
6	$SO_2C_6H_5$	CH_2CH_2OH	H
7	$SO_2C_6H_5$	CH_2CHO	H
9	H	H	H
10	H	CH_2CH_2OH	H
12	$SO_2C_6H_5$	CH_3	H
13	H	CH_3	H
14	H	CH_3	Cl
15	H	$(CH_2)_2OCH_2SCH_3$	H
17	$SO_2C_6H_5$	$COCH_2Cl$	H
18	H	$COCH_2Cl$	H

	X	Y	Z
11	H,H	α-OH	Cl
16	H,H	β-OH	H
20	O	H	H
22	H,H	H	H
23	H,H	H	Cl

	X	Y
8	OH	H,H
19	H	O

Figure 1.

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

carbon	compound 5	6	9	10	12	13	14	17[b,c]	18[c]
C-2	52.5	58.0	53.0	59.7	59.4	60.9	58.6	48.3[d]	47.4
C-3	42.3	43.4	42.2	42.7	43.1	43.4	41.0	42.2	41.3
C-4	109.2	108.3	109.2	108.6	108.4	108.6	108.0	107.4	108.3
C-5	46.6	44.9	47.1	45.3	45.2	45.7	43.0	43.5	45.0
C-6	49.1	54.4	48.6	55.1	59.2	58.7	58.0	43.8[d]	42.1
OCH_2	64.8	64.8	65.0	64.9	64.7	65.0	65.1	63.7	64.5
	64.9	64.9	65.2	65.1	64.9	65.1	65.2	63.8	64.6
CH_2CH_3	18.2	18.4	18.2	18.5	18.3	18.3	18.3	19.2	19.2
CH_2CH_3	12.0	12.1	12.0	12.1	12.0	12.0	11.9	12.4	12.7
In-C2	143.8	142.7	140.8	139.4	142.9	139.9	121.8	141.7	136.0
In-C3	108.7	109.98	98.5	101.0	109.2	100.5	134.4	110.2[d]	101.9
In-C3a	129.5	129.3	128.1	127.9	129.6	128.1	127.9	129.8	127.7
In-C4	123.7	123.7	120.2	120.1	120.7	120.2	120.3	124.1	120.5
In-C5	120.7	120.8	119.5	119.6	123.6	119.6	118.0	120.7	119.7
In-C6	124.5	124.5	121.6	121.6	124.3	121.6	123.0	124.2	122.0
In-C7	115.0	114.9	110.7	110.0	114.9	110.8	111.5	114.9	111.1
In-C7a	137.3	137.1	135.8	136.3	137.2	136.0	131.6	136.1	137.4
$(C_6H_5)_o$	126.3	126.5	–	–	126.5	–	–	126.5	–
$(C_6H_5)_m$	129.1	129.2	–	–	12.91	–	–	129.3	–
$(C_6H_5)_p$	133.6	133.8	–	–	133.7	–	–	134.3	–
$(C_6H_5)_i$	138.7	139.7	–	–	139.8	–	–	136.9	–
C=O	–	–	–	–	–	–	–	166.3	166.5
NCH_3	–	–	–	–	42.8	42.8	45.3	–	–
NCH_2CH_2	–	54.7	–	54.6	–	–	–	–	–
NCH_2CH_2	–	58.3	–	58.8	–	–	–	–	–
$ClCH_2$	–	–	–	–	–	–	–	35.2	32.7

[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). [b] Recorded in DMSO-d_6. [d] Only one rotamer was detected. [d] Broad signal.

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

proton	compound 11	16	22	23
1-H_e	5.7 br s ($W_{1/2}$ = 10)	–	3.8–4.2 m	3.9–4.2 m
1-H_a	–	5.6 dd (8, 5)	3.8–4.2 m	3.9–4.2 m
2-H_e	3.96 dd (12.8, 1.6)	3.16 dd (12, 5)	3.19 ddd (11.7, 4.5, 1)	3.2 dt (11, 3.4)
2-H_a	2.86 dd (12.8, 3)	2.26 dd (12, 8)	2.78 td (11.7, 4.5)	2.80 ddd (11, 9, 5.5)
4-H_e	3.56 dd (12, 1.5)	2.84 dd (12, 2.5)	3.11 dd (11.7, 4.5)	3.11 dd (11, 4.3)
4-H_a	3.0 t (12)	2.16 t (11.7)	2.30 t (11.7)	2.48 t (11)
5-H_a	1.5–1.9 m	1.7–1.9 m	1.8–2.0 m	1.8–2.0 m
7-H_e	2.12 dd (12.8, 3.2)	2.14 dd (13, 3)	2.35 dd (13, 3)	3.04 dd (13.5, 2.5)
7-H_a	1.74 t (12)	1.67 dd (13, 11)	1.80 dd (12, 11)	1.71 dd (13.5, 12)
7a-H	4.46 dd (12, 3)	3.4 dd (11, 3)	3.50 ddd (12, 3, 0.7)	3.82 dd (11, 2.5)
8-H	–	6.08 s	6.18 br t (0.7)	–
9-H	7.4–7.6 m	7.62 m	7.55 dt (7, 0.7)	7.54 dt (7, 0.7)
10-H	7.0–7.3 m	7.0–7.4 m	7.0–7.3 m	7.0–7.3 m
11-H	7.0–7.3 m	7.0–7.4 m	7.0–7.3 m	7.0–7.3 m
12-H	7.0–7.3 m	7.48 m	7.0–7.3 m	7.0–7.3 m
OCH_2	3.8–4.2 m	3.8–4.0 m	3.8–4.2 m	3.9–4.2 m
CH_2CH_3	0.8–1.2 m	0.9–1.3 m	1.0–1.3 m	1.0–1.3 m
	1.5–1.9 m	1.5–1.7 m	1.6–1.8 m	1.6–1.8 m
CH_2CH_3	0.92 t (7)	0.88 t (7)	0.95 t (7)	0.96 t (7)

[a] ^1H 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 Me_4Si).

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

carbon	compound 11	16	22	23
C-1	74.0	76.1	41.4	42.6
C-2	53.8	56.6	51.1	50.0
C-4	56.2	57.0	57.1	57.7
C-5	41.6	44.5	45.3	45.1
C-6	108.4	108.8	108.2	10,.8
C-7	33.8	38.8	39.1	37.1
C-7a	54.0	58.9	57.2	57.0
C-7b	130.7	136.0	135.4	131.3
C-8	99.9	96.9	94.7	99.3
C-8a	126.0	128.8	127.6	126.1
C-9	120.4	120.4	119.5	120.2
C-10	116.9	120.1	119.1	117.6
C-11	121.9	121.4	120.1	121.9
C-12	110.4	111.4	107.9	108.7
C-12a	133.5	138.2	137.5	134.3
OCH_2	64.6	65.1	64.6	65.0
	64.7	65.3	64.7	65.1
CH_3CH_2	17.7	18.2	17.7	18.3
CH_3CH_2	11.3	11.9	11.3	12.0

[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.

indole **13** with DMSO/$(COCl)_2$ under Swern conditions afforded the 3-chlorinated indole **14** in 43% yield, whereas, under the same reaction conditions, the deactivated *N*-(phenylsulfonyl)indole **12** was recovered unchanged. In order to avoid the undesired chlorination which could be responsible for the regioselectivity of the cyclization, oxidation of alcohol **10** was performed with DMSO activated with DCC.[15] However, the initially formed aldehyde again underwent cyclization upon the indole nitrogen, rather than upon the indole 3-position, giving pyridopyrazinoindole **16** in 42% yield. Thioether **15** was isolated in 18% yield as a minor byproduct.[16] The structural and stereochemical assignment of tetracycles **11** and **16**, as well as of **22** and **23** (see later), was deduced from their spec-

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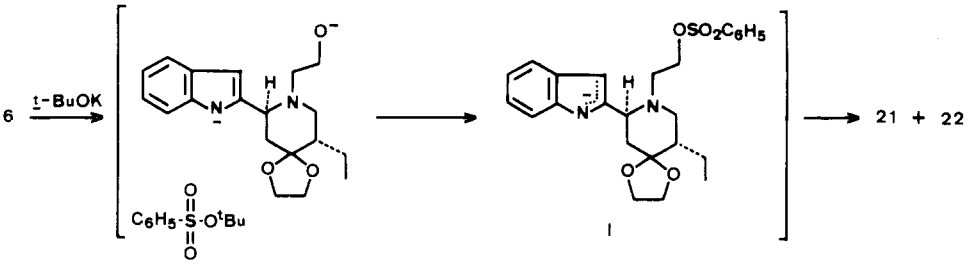
(16) The formation of alkyl (methylthio)methyl ethers as byproducts in the oxidation of alcohols with DMSO/DCC is a known process: Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.

Scheme II



troscopic data (see Tables III and IV, and the Experimental Section).

An alternative way to incorporate the two-carbon unit necessary for completion of the indoloquinolizidine C ring and to induce the desired cyclization was the tandem chloroacetylation–photocyclization.[17] The required chloroacetamides **17** and **18** were prepared by reaction of the corresponding N-unsubstituted piperidines, **5** and **9**, respectively, with chloroacetyl chloride. As expected, photocyclization of **17** took place upon the indole 3-position, giving the desired indolo[2,3-*a*]quinolizidine derivative **19**. However, the yield of the process was low (11%), so further elaboration of **19** into the target molecule **1** was not attempted. On the other hand, rather unexpectedly,[18] irradiation of the indole-deprotected chloroacetamide **18** gave tetracycle **20**, resulting again from cyclization upon the indole nitrogen, as the only isolable product. Our synthetic goal was accomplished in a rather unforeseen manner. When, in a routine deprotection of the indole nitrogen of **6**, potassium *tert*-butoxide in THF[19] was used instead of aqueous sodium hydroxide, a nearly equimolecular mixture of indoloquinolizidine **21** and its regioisomer **22** was obtained in 88% yield. The identity of these compounds was established by their elemental analysis and spectroscopic data (see Tables III and IV, and the Experimental Section). Furthermore, tetracycle **22** was identical with that obtained by reduction of **16** with triethylsilane.[20]

Scheme II shows a possible pathway to rationalize the formation of tetracycles **21** and **22**. *tert*-Butyl benzenesulfonate, formed in the deprotection of the indole nitrogen by *t*-BuOK, can act as a sulfonylating agent upon the piperidine ethoxy substituent to give the intermediate I. Further deplacement of the sulfonate group by the ambident indolyl anion, either by C(3) or by the nitrogen, would lead to compounds **21** and **22**. In accordance with the above interpretation involving an intermolecular rather than an intramolecular sulfonylation of the alkoxy group, alcohol **6** was recovered unchanged after treatment with either *n*-butyllithium (1.5 equiv, THF, −30 °C, 30 min; then room temperature, 2 h) or sodium hydride[21] (2 equiv, THF, room temperature, 2 h). Under the latter reaction conditions, the deprotected indole derivative **10** was also formed to a considerable extent. Additional evidence for the operation of an intermolecular mechanism was obtained when alcohol **10** was treated with potassium hydride (2 equiv, THF, 0 °C, 10 min) and then with *tert*-butyl benzenesulfonate[22,23] (1.1 equiv, room temperature, 2 h); a mixture of the cyclized products **21** and **22** was formed.[24]

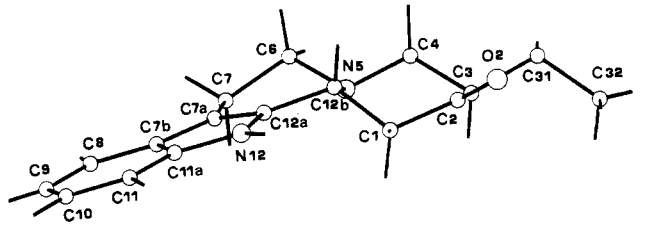


Figure 2.

In order to increase the regioselectivity of the cyclization step toward the formation of the desired indoloquinolizidine system, we performed the reaction of **6** with *t*-BuOK in a less polar solvent,[25] either Et_2O or a 4:1 Et_2O–hexane mixture. In the first case, an approximately 4:1 mixture of indoloquinolizidine **21** and its regioisomer **22** was obtained in 77% yield, whereas in the latter, indoloquinolizidine **21** was isolated in 63% yield as the only cyclized product, the starting alcohol **6** being recovered to some extent probably as a consequence of the low solubility in the solvent employed.

Finally, acid hydrolysis of the acetal function present in **21** afforded the target indolo[2,3-*a*]quinolizidin-2-one **1**. The accessibility of 2-aryl-4-piperidones, the low number of synthetic steps, and the acceptable overall yield (35% from **2** and **3**) make the herein described procedure a valuable route for the synthesis of indoloquinolizidin-2-one **1**.

The crystal structure of **1** was solved by direct methods.[26] Full-matrix least-squares refinement of atomic positional and thermal parameters[27] converged at R = 0.049 (R_w = 0.052, 1156 reflections).[28] A view of the solid-state conformation of one enantiomer is presented in Figure 2. The benzene ring and the double-bond character of the C(12a)–C(7a) bond cause C(12b) to C(7) to be in a plane (largest deviation from the mean plane is 0.027 (7) Å in C(7b)). Moreover, N(5) and C(6) deviate

(17) Sundberg, R. J. *Org. Photochem.* **1983**, *6*, 121.

(18) There are few examples about photocyclization of chloroacetamides upon the indole nitrogen: (a) Bennasar, M.-L.; Zulaica, E.; Vila, R.; Bosch, J. *Heterocycles* **1989**, *29*, 381. (b) See also ref 11a.

(19) For the use of this method for the deprotection of indoles, see: Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 4836.

(20) Similarly, tetracyclic alcohol **11** was reduced to **23** (see the Experimental Section).

(21) The same result was obtained by using potassium hydride.

(22) Plisko, E. A.; Topunova, I. G.; Danilov, S. N. *Zh. Prikl. Khim.* **1963**, *36*, 1303; *Chem. Abstr.* **1963**, *59*, 11747*b*.

(23) The crude reaction mixture prepared as indicated in ref 22 was transferred into a THF solution of the dianion derived from **10**. We were not able to isolate *tert*-butyl benzenesulfonate following the general experimental procedure described in this reference. However, the procedure gave an excellent yield of isopropyl benzenesulfonate.

(24) We acknowledge the suggestion of one reviewer about this experiment.

(25) It is well-known that the use of nonpolar solvents favors 3- vs N-alkylation of indole: (a) Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, 1970; pp 19–31. (b) Powers, J. C. In *Indoles. Part II*; Houlihan, W. J., Ed.; Wiley: New York, 1972; pp 149–151.

(26) Main, P.; Fiske, S. E.; Hull, S. L.; Lessinger, L.; Germain, G.; Leclercq, J. P.; Woolfson, M. M. MULTAN/84. A system of Computer Programs for Crystal Structure Determination from X-Ray Diffraction Data; University of York, England, and University of Louvain, Belgium, 1984.

(27) Supplementary material, see the paragraph at the end of the paper.

(28) $R = \sum w||F_o| - |F_c||^2$; $w = (\sigma^2 + 0.0013|F_o|^2)^{-1}$.

0.402 (7) and −0.403 (7) Å from this plane, while the N(5), C(4), C(3), C(2), C(1), and C(12b) ring has a chair conformation with N(5) and C(2) atoms 0.715 (7) and −0.619 (7) Å, respectively, out of the plane defined by the remaining four atoms. Bond lengths and angles[26] are generally close to normal values. Every two molecules are hydrogen bonded by N(12)–H(N12)···O(2) bond.[29]

Experimental Section

General Methods. Melting points were determined in a capillary tube on a Büchi or a CTP-MP 300 hot plate 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 spectra were recorded with a Varian XL-200 spectrometer. Unless otherwise noted, NMR spectra were taken in $CDCl_3$, and chemical shifts are expressed in parts per million (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. Column chromatography was carried out on SiO_2 (silica gel 60, 63–200 μm, Merck) or Al_2O_3 (aluminum oxide 90, neutral, activity I, 63–200 μm, Merck). 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 F_{254}, Merck) using 99:1 Et_2O–DEA as developing solvent, and the spots were located with UV light or iodoplatinate reagent. Purification of reagents and solvents was effected according to standard 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.

2-Ethyl-3,3-(ethylenedioxy)-*N*-[[1-(phenylsulfonyl)-2-indolyl]methylene]butylamine (4). A solution of the amino acetal 3[7c] (7.28 g, 46 mmol) and aldehyde 2[30] (13.04 g, 46 mmol) in anhydrous C_6H_6 (200 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 H_2O by a Dean–Stark trap, the solvent was evaporated to give imine 4 (19.3 g, 99%). An analytical sample of 4 was obtained by column chromatography (Al_2O_3, 3:7 hexane–Et_2O): IR (NaCl) 1630, 1370, 1175 cm^{-1}; ^{1}H NMR (60 MHz) δ 0.96 (t, J = 6 Hz, 3 H, CH_3CH_2), 1.3 (s, 3 H, CH_3C), 3.7 (d, J = 7 Hz, NCH_2), 3.8 (s, 4 H, OCH_2), 6.9–8.1 (m, 10 H, Ar H), 8.7 (s, 1 H, =CH). Anal. Calcd for $C_{23}H_{26}N_2O_4S$: C, 64.71; H, 6.09; N, 6.50. Found: C, 64.75; H, 5.91; N, 6.20.

***trans*-5-Ethyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (5).** A stirred mixture of the imino acetal 4 (3.67 g, 8.6 mmol) and anhydrous *p*-TsOH (3.50 g, 20.3 mmol) in anhydrous C_6H_6 (100 mL) was refluxed under N_2 for 1 h. The cooled mixture was washed with aqueous Na_2CO_3 and extracted with CH_2Cl_2. The extract was dried and evaporated to give piperidine 5 (2.9 g, 80%): mp 136–138 °C (hexane–EtOAc); IR (KBr) 3280, 1370, 1165 cm^{-1}; MS (*m/e*, relative intensity) 426 (M^+, 0.1), 381 (1), 285 (3), 219 (2), 170 (3), 150 (3), 142 (10), 115 (15), 84 (45), 49 (100), 43 (65). Anal. Calcd for $C_{23}H_{26}N_2O_4S \cdot {}^1/_2H_2O$: C, 63.43; H, 6.25; N, 6.43; S, 7.34. Found: C, 63.54; H, 6.27; N, 6.24; S, 7.47.

***trans*-5-Ethyl-2-[1-(phenylsulfonyl)-2-indolyl]-1-(2-hydroxyethyl)-4-piperidone Ethylene Acetal (6).** 2-Bromoethanol (1.67 mL, 23.4 mmol) was added dropwise to a mixture of piperidine 5 (5 g, 11.7 mmol) and anhydrous Na_2CO_3 (5 g) in absolute EtOH (100 mL). The resulting mixture was refluxed 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 (99.5:0.5 Et_2O–DEA) to give pure alcohol 6 (4.7 g, 85%): IR ($CHCl_3$) 3500–3200, 1360, 1170 cm^{-1}; MS (*m/e*, relative intensity) 470 (M^+, 1), 439 (12), 184 (2), 170 (8), 168 (5), 156 (77), 127 (74), 115 (79), 77 (100), 55 (41), 42 (70). Anal. Calcd for $C_{25}H_{30}N_2O_5S$: C, 63.82; H, 6.42; N, 5.95. Found: C, 64.03; H, 6.80; N, 5.55.

***trans*-5-Ethyl-4,4-(ethylenedioxy)-2-[1-(phenylsulfonyl)-2-indolyl]-1-piperidineacetaldehyde (7).** DMSO (0.88 mL, 12.6 mmol) was slowly added under N_2 to a solution of oxalyl chloride (0.5 mL, 5.84 mmol) in anhydrous CH_2Cl_2 (10 mL) maintained at −70 °C. After stirring at −70 °C for 30 min, a solution of alcohol 6 (2.5 g, 5.3 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise, and the mixture was stirred at −70 °C for 1 h. Then, Et_3N (3.68 mL, 26.4 mmol) was slowly added (0.2 mL/min), the cooling bath was removed, and the reaction was quenched by addition of H_2O (20 mL). After stirring for 10 min, the organic phase was washed with H_2O, dried, and evaporated to give aldehyde 7 (2.3 g, 92%) as an unstable yellow foam: IR ($CHCl_3$) 1720, 1365, and 1170 cm^{-1}; ^{1}H NMR (60 MHz) δ 0.9 (t, J = 7 Hz, 3 H, CH_3), 3.8 (br s, 4 H, OCH_2), 4.2 (dd, J = 12 and 3 Hz, 1 H, 2-Ha), 6.5 (s, 1 H, In-3H), 7.0–7.7 (m, 8 H, Ar H), 8.0–8.2 (m, 1 H, In-7H), 9.2 (br s, 1 H, CHO).

3-Ethyl-2,2-(ethylenedioxy)-7-hydroxy-12-(phenylsulfonyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (8). To a solution of aldehyde 7 (380 mg, 0.81 mmol) in CH_2Cl_2 (40 mL) was added a solution of $TiCl_4$ (0.39 mL, 3.6 mmol). The mixture was stirred under N_2 at room temperature for 6 h and then poured into aqueous Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2, and the combined organic extracts were washed with brine, dried, and filtered through Celite. Evaporation under reduced pressure followed by flash chromatography (98:2 Et_2O–DEA) afforded 30 mg of an unstable mixture of alcohols 8: IR ($CHCl_3$) 3200–3600, 1450, 1570, and 1170 cm^{-1}; ^{1}H NMR δ 0.92 (t, J = 7 Hz, 3 H, CH_3), 3.85–4.15 (m, 4 H, OCH_2), 4.76 (br s, 1 H, 7-H), 7.2–7.8 (m, 8 H, Ar H), 8.06 (m, 1 H, In-7H); ^{13}C δ NMR 12.1 (CH_3), 18.1 (CH_2CH_3), 40.2 (C-1), 52.4 (C-3), 55.2 (C-4), 56.9 (C-6), 61.9 (C-12b), 64.8 (C-7), 106.8 (C-2), 109.6 (C-7a), 115.2 (C-11), 118.9 (C-9), 124.2 (C-10), 124.8 (C-8), 126.4 (*o*-C_6H_5), 129.2 (*m*-C_6H_5), 129.4 (C-7b), 133.8 (*p*-C_6H_5), 137.0 (C-12a), 137.8 (C-11b), 139.0 (*i*-C_6H_5); MS (*m/e*, relative intensity) 468 (M^+, 2), 451 (M^+ − OH, 4), 439 (4), 424 (2), 423 (7), 327 ($M^+ - SO_2C_6H_5$, 100), 309 (8), 265 (7), 213 (15), 185 (25), 127 (32), 115 (25), 77 (37).

***trans*-5-Ethyl-2-(2-indolyl)-4-piperidone Ethylene Acetal (9).** A solution of piperidine 5 (2 g, 4.6 mmol) in EtOH (200 mL) and 10% aqueous NaOH (20 mL) was refluxed for 12 h. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with H_2O. Evaporation of the dried organic phase afforded piperidine 9 (0.8 g, 62%) as a solid. An analytical sample was obtained by flash chromatography (98:2 Et_2O–DEA): mp 210–212 °C (Et_2O–acetone); IR ($CHCl_3$) 3445, 3300 cm^{-1}; MS (*m/e*, relative intensity) 286 (M^+, 71), 285 (10), 241 (70), 158 (29), 157 (59), 144 (79), 143 (91), 142 (45), 130 (65), 115 (57), 87 (39), 86 (63), 84 (74) 49 (100). Anal. Calcd for $C_{17}H_{22}N_2O_2 \cdot H_2O$: C, 67.08; H,7.94; N, 9.20. Found: C, 67.03; H, 7.59; N, 9.11.

***trans*-5-Ethyl-1-(2-hydroxyethyl)-2-(2-indolyl)-4-piperidone Ethylene Acetal (10). Method A.** Operating as above, from 6 (1 g, 2.1 mmol), EtOH (150 mL), and 10% aqueous NaOH (20 mL) was obtained alcohol 10 (0.6 g, 86%) as a yellow solid after flash chromatography (99:1 Et_2O–DEA): mp 128–130 °C (Et_2O–acetone); IR (KBr) 3500–3200 cm^{-1}; MS (*m/e*, relative intensity) 330 (M^+, 11), 299 (19), 185 (7), 156 (100), 143 (27), 115 (88), 99 (16), 83 (19), 69 (34), 55 (36). Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.47. Found: C, 68.98; H, 7.96; N, 8.22.

Method B. Operating as in the preparation of 6, from piperidine 9 (1.7 g, 5.9 mmol), 2-bromoethanol (0.9 mL, 12 mmol), and anhydrous Na_2CO_3 (2 g) in absolute EtOH (50 mL) was obtained pure alcohol 10 (1.7 g, 88%) after flash chromatography.

Oxidation of Alcohol 10 with DMSO-$(COCl)_2$. Operating as in the above oxidation of alcohol 6, from oxalyl chloride (0.23 mL, 2.73 mmol) in anhydrous CH_2Cl_2 (10 mL), DMSO (0.35 mL, 4.9 mmol), alcohol 10 (820 mg, 2.48 mmol) in CH_2Cl_2 (20 mL), and then Et_3N (1.7 mL, 12.4 mmol) was obtained ***trans*-8-chloro-5-ethyl-6,6-(ethylenedioxy)-1-hydroxy-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*a*]indole (11)** (730 mg, 89%): mp 202–204 °C (acetone); IR (KBr) 3100–3000 cm^{-1}; MS (*m/e*, relative intensity) 364 (M^+ + 2, 12), 362 (M^+, 35), 333 (42), 317 (54), 234 (15), 220 (18), 164 (27), 156 (98), 127 (53), 115 (100), 87 (62), 69 (29), 55 (41). Anal. Calcd for $C_{19}H_{23}ClN_2O_3$: C, 62.88; H, 6.38; Cl, 9.78; N, 7.72. Found: C, 62.69; H, 6.18; Cl, 9.60; N, 7.50.

***trans*-5-Ethyl-1-methyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (12).** To a solution of piperidine 5 (21.5 g, 50.5 mmol) in anhydrous acetone (250 mL) containing anhydrous K_2CO_3 (15 g) was slowly added CH_3I (3.1

(29) Hydrogen-bonded distances (Å) follow: N...O (at $i = -x, -y, -z$) 2.954 (7), H...O 1.95 (4). Angle N–H...O 170 (3) °.

(30) Saulnier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.

mL, 50.5 mmol). The mixture was stirred at 0 °C under N_2 for 3 h and filtered. Evaporation of the solvent followed by flash chromatography (98:2, Et_2O–DEA) gave **12** as a yellow foam (16.7 g, 75%): mp 108–110 °C (hexane–Et_2O); IR (KBr) 1370 and 1170 cm^{-1}; MS (*m/e*, relative intensity) 440 (M^+, 27), 395 (25), 394 (100), 299 (64), 283 (51), 254 (14), 213 (16), 185 (43), 171 (18), 156 (25), 142 (44), 130 (42), 115 (45), 99 (30), 77 (57), 70 (19), 42 (13). Anal. Calcd for $C_{24}H_{28}N_2O_4S$: C, 65.43; H, 6.40; N, 6.36; S, 7.28. Found: C, 65.42; H, 6.27; N, 6.08; S, 7.21.

***trans*-5-Ethyl-2-(2-indolyl)-1-methyl-4-piperidone Ethylene Acetal (13).** Via the usual procedure, from piperidine **12** (2.8 g, 6.4 mmol), EtOH (250 mL), and 10% aqueous NaOH (28 mL) was obtained piperidine **13** (1.0 g, 83%) after flash chromatography (8:2 hexane–EtOAc); IR (KBr) 3330 cm^{-1}; MS (*m/e*, relative intensity) 300 (M^+, 26), 241 (13), 184 (12), 171 (45), 143 (100), 130 (54), 115 (48), 99 (35), 70 (16), 42 (22). The hydrochloride melted at 226–227 °C (Et_2O–acetone). Anal. Calcd for $C_{18}H_{25}ClN_2O_2 \cdot {}^1/_2H_2O$: C, 62.50; H, 7.52; N, 8.10. Found: C, 62.58; H, 7.57; N, 8.02.

***trans*-2-(3-Chloro-2-indolyl)-5-ethyl-1-methyl-4-piperidone Ethylene Acetal (14).** Via the Swern procedure used above, from oxalyl chloride (0.13 mL, 1.46 mmol), DMSO (0.18 mL, 2.66 mmol), piperidine **13** (0.4 g, 1.33 mmol), Et_3N (0.9 mL, 6.65 mmol), and anhydrous CH_2Cl_2 (20 mL) was obtained piperidine **14** (190 mg, 43%) after flash chromatography (85:15 Et_2O–CH_2Cl_2): IR ($CHCl_3$) 3450 cm^{-1}; MS (*m/e*, relative intensity) 336 ($M^+ + 2$, 17), 334 (M^+, 53), 289 (10), 273 (7), 204 (100), 183 (26), 177 (43), 140 (14), 115 (24), 99 (31), 70 (29), 42 (23). Anal. Calcd for $C_{18}H_{23}ClN_2O_2$: C, 64.55; H, 6.87; N, 8.36. Found: C, 64.83; H, 6.68; N, 8.39.

Oxidation of Alcohol 10 with DMSO-DCC. Anhydrous orthophosphoric acid (122 mg, 1.25 mmol) was added to a mixture of alcohol **10** (1.24 g, 3.75 mmol) and DCC (2.38 g, 11.6 mmol) in DMSO (33 mL). The mixture was stirred at room temperature under N_2 for 4 h 30 min. The precipitate was removed by filtration and washed with CCl_4. The combined filtrate and washings were basified with aqueous Na_2CO_3 and extracted with CH_2Cl_2. The extracts were dried and evaporated to give, after flash chromatography (99:1 Et_2O–DEA), ***trans*-5-ethyl-2-(2-indolyl)-1-[2-[(methylthio)methoxy]ethyl]-4-piperidone Ethylene Acetal (15)** (260 mg, 18%) and ***trans*-5-ethyl-6,6-(ethylenedioxy)-1-hydroxy-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*a*]indole (16)** (520 mg, 42%).

Compound **15**: IR (NaCl) 3400 cm^{-1}; ^1H NMR (60 MHz) δ 0.9 (t, J = 7 Hz, 3 H, CH_3CH_2), 2.0 (s, 3 H, SCH_3), 3.8 (s, 4 H, OCH_2), 4.4 (s, 2 H, SCH_2O), 6.1 (br s, 1 H, In-3H), 6.6–7.5 (m, 4 H, indole), 8.6 (br, 1 H, NH).

Compound **16**: IR ($CHCl_3$) 3450–3300 cm^{-1}; MS (*m/e*, relative intensity) 328 (M^+, 60), 311 (100), 283 (37), 241 (14), 204 (11), 185 (13), 156 (44), 127 (37), 99 (20), 55 (20), 43 (13). Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.48; H, 7.36; N, 8.53. Found: C, 69.79; H, 7.01; N, 8.21.

***trans*-1-(Chloroacetyl)-5-ethyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone Ethylene Acetal (17).** A solution of chloroacetyl chloride (0.8 mL, 10.5 mmol) in anhydrous $CHCl_3$ (10 mL) was added dropwise to a solution of piperidine **5** (3 g, 7 mmol) in anhydrous $CHCl_3$ (90 mL) containing anhydrous Na_2CO_3 (3 g). The mixture was stirred at room temperature under N_2 for 1 h 30 min, and then H_2O (50 mL) was added. After being stirred for 10 min, the phases were separated. The organic layer was washed with aqueous $NaHCO_3$, dried, and evaporated. The residue was chromatographed (flash, 8:2 C_6H_6–$CHCl_3$) to give chloroacetamide **17** (2.76 g, 78%): mp 190–192 °C (MeOH); IR (KBr) 1670, 1365, and 1170 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.97 (t, J = 7 Hz, 3 H, CH_3), 1.2–1.7 (m, 2 H, CH_2CH_3), 2.1–2.6 (m, 3 H, 3-H and 5-Ha), 3.1–3.4 (m, 1 H, 6-Ha), 3.6–3.9 (m, 4 H, OCH_2), 4.5–4.6 (m, 2 H, CH_2Cl), 6.12 (br, $W_{1/2}$ = 16 Hz, 1 H, 2-H), 6.68 (s, 1 H, In-3H), 7.1–7.4 (m, 7 H, C_6H_5 and In-H), 7.8–8.0 (m, 2 H, In-4H and In-7H); MS (*m/e*, relative intensity) 502 (M^+, 1), 214 (2), 184 (1), 183 (1), 170 (5), 142 (10), 128 (9), 127 (100), 115 (8), 77 (23), 55 (4); Anal. Calcd for $C_{25}H_{27}ClN_2O_5S$: C, 59.69; H, 5.41; Cl, 7.05; N, 5.57; S, 6.37. Found: C, 59.90; H, 5.08; Cl, 7.03; N, 5.76; S, 5.99.

***trans*-1-(Chloroacetyl)-2-(2-indolyl)-4-piperidone Ethylene Acetal (18).** Operating as above, from piperidine **9** (1 g, 3.5 mmol), chloroacetyl chloride (0.4 mL, 5.25 mmol), and anhydrous Na_2CO_3 (1 g) in anhydrous CH_2Cl_2 (50 mL) was obtained chloroacetamide **18** (1.0 g, 80%) after purification by flash chromatography (6:4 C_6H_6–$CHCl_3$): mp 172–173 °C (MeOH); IR (KBr) 3450–3300, 1650 cm^{-1}; ^1H NMR δ 0.98 (t, J = 7 Hz, 3 H, CH_3), 0.9–1.3 (m, 2 H, CH_2CH_3), 1.5–1.7 (m, 2 H, 3-Ha and 5-Ha), 2.10 (t, J = 14 Hz, 1 H, 6-Ha), 2.2–2.3 (m, 1 H, 3-He), 3.32 (br, $W_{1/2}$ = 32 Hz, 1 H, 6-He), 3.9–4.2 (m, 6 H, OCH_2 and CH_2Cl), 5.78 (br, $W_{1/2}$ = 28 Hz, 1 H, 2-H), 6.20 (br, 1 H, In-3H), 6.70 and 6.78 (2 t, J = 7 Hz, 1 H each, In-5H and In-6H), 7.05 (d, J = 7 Hz, 1 H, In-7H), 7.20 (d, J = 7 Hz, 1 H, In-4H); MS (*m/e*, relative intensity) 364 ($M^+ + 2$, 7), 362 (M^+, 20), 313 (44), 281 (4), 213 (6), 171 (40), 127 (100), 115 (53), 89 (32), 77 (40), 55 (69), 43 (43). Anal. Calcd for $C_{19}H_{23}ClN_2O_3$: C, 62.89; H, 6.34; Cl, 9.77; N, 7.72. Found: C, 62.85; H, 6.67; Cl, 9.70; N, 7.67.

***trans*-3-Ethyl-2,2-(ethylenedioxy)-12-(phenylsulfonyl)-1,2,3,4,12,12b-hexahydro-7*H*-indolo[2,3-*a*]quinolizin-6-one (19).** A solution of chloroacetamide **17** (1 g, 2.0 mmol) in CH_3CN (200 mL) containing anhydrous Na_2CO_3 (1 g) was irradiated under N_2 at room temperature for 3 h using a 125-W medium-pressure mercury lamp in a quartz immersion well reactor. The mixture was evaporated to dryness and the residue was dissolved in H_2O and extracted with CH_2Cl_2. Evaporation of the dried extracts followed by flash chromatography (first with 99:1 Et_2O–DEA and then with 3:2 C_6H_6–$CHCl_3$) furnished quinolizidine **19** (100 mg, 11%): mp 241–242 °C (Et_2O); IR ($CHCl_3$) 1690, 1650, 1360, and 1170 cm^{-1}; MS (*m/e*, relative intensity) 466 (M^+, 37), 449 (4), 421 (12), 380 (25), 325 (98), 296 (18), 252 (11), 223 (14), 183 (9), 154 (23), 127 (100), 99 (19), 77 (30), 55 (58). Anal. Calcd for $C_{25}H_{26}N_2O_5S \cdot H_2O$: C, 61.97; H, 5.82; N, 5.78; S, 6.61. Found: C, 61.85; H, 5.68; N, 5.57; S, 6.91.

***trans*-5-Ethyl-6,6-(ethylenedioxy)-2-oxo-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*a*]indole (20).** Operating as above, from chloroacetamide **18** (0.4 g, 1.1 mmol), CH_3CN (100 mL), and anhydrous Na_2CO_3 (0.5 g) was obtained compound **20** (40 mg, 11%) after flash chromatography (99:1 Et_2O–DEA): ^1H NMR δ 0.99 (t, 3 H, CCH_3), 0.9–1.1 (m, 1 H, $CHCH_3$), 1.1–1.3 (m, 1 H, $CHCH_3$), 1.6–1.9 (m, 1 H, 5-Ha), 2.3–2.9 (m, 6 H), 3.5–4.3 (m, 7 H, 1-H, 7a-H, and OCH_2), 6.74 (s, 1 H, 8-H), 7.10 (t, J = 7 Hz, 1 H, 10-H), 7.20 (t, J = 7 Hz, 1 H, 11-H), 7.34 (dt, J = 7 and 1 Hz, 1 H, 12-H), 7.56 (dt, J = 7 and 1 Hz, 1 H, 9-H); IR ($CHCl_3$) 1620 cm^{-1}; MS (*m/e*, relative intensity) 326 (M^+, 23), 325 (3), 284 (77), 253 (10), 225 (18), 211 (40), 183 (60), 170 (63), 142 (72), 127 (100), 115 (64), 99 (55), 69 (44), 55 (98). Anal. Calcd for $C_{19}H_{22}N_2O_3 \cdot H_2O$: C, 66.26; H, 7.02; N, 8.13. Found: C, 66.44; H, 7.32; N, 7.89.

***trans*-3-Ethyl-2,2-(ethylenedioxy)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (21).** To a solution of piperidine **6** (0.5 g, 1.1 mmol) in anhydrous Et_2O (30 mL) was added under N_2 freshly sublimed *t*-BuOK (0.24 g, 2.2 mmol). 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 mixture of two compounds which were separated by flash chromatography (7:3 Et_2O–hexane). Higher R_f, ***trans*-5-ethyl-6,6-(ethylenedioxy)-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*a*]indole (22)** (60 mg, 17%): mp 166–167 °C (acetone); MS (*m/e*, relative intensity) 312 (M^+, 100), 281 (2), 267 (52), 225 (36), 197 (41), 184 (33), 170 (61), 156 (35), 127 (27), 115 (24), 86 (27), 55 (27). Anal. Calcd for $C_{19}H_{24}N_2O_2 \cdot {}^1/_2H_2O$: C, 70.99; H, 7.52; N, 8.71. Found: C, 71.03; H, 7.57; N, 8.55. Lower R_f, quinolizidine **21** (0.2 g, 60%): IR (KBr) 2860–2750 cm^{-1}; ^1H NMR δ 0.95 (t, J = 7 Hz, 3 H, CH_3), 1.0–1.3 (m, 1 H, CH_ACH_3), 1.5–1.8 (m, 1 H, CH_BCH_3), 1.74 (t, J = 12 Hz, 1 H, 1-H_a), 1.8–2.1 (m, 1 H, 3-H_a), 2.15 (dd, J = 12 and 2.4 Hz, 1 H, 1-H_e), 2.36 (t, J = 12 Hz, 1 H, 4-H_a), 2.63 (td, J = 11 and 4 Hz, 1 H, 6-H_a), 2.74 (br d, J = 14 Hz, 1 H, 7-H_e), 2.9–3.0 (m, 1 H, 7-H_a), 3.0–3.2 (m, 1 H, 6-H_e), 3.12 (dd, J = 12 and 4.5 Hz, 1 H, 4-H_e), 3.5 (dd, J = 12 and 2.4 Hz, 1 H, 12b-H), 3.9–4.1 (m, 4 H, OCH_2), 7.0–7.2 (m, 2 H, 9-H and 10-H), 7.28 (dd, J = 7 and 1.4 Hz, 1 H, 11-H), 7.46 (dd, J = 7 and 1.4 Hz, 1 H, 8-H), 7.76 (br, 1 H, NH); ^{13}C NMR δ 11.9 (CH_3), 18.4 (CH_3CH_2), 21.8 (7-C), 39.5 (1-C), 46.2 (3-C), 52.3 (6-C), 57.0 (4-C), 57.7 (12b-C), 65.1 and 65.3 (OCH_2), 108.2 (7a-C), 109.3 (2-C), 110.7 (11-C), 118.1 (9-C), 119.3 (8-C), 121.3 (10-C), 127.4 (7b-C), 134.5 (11a-C), 136.0 (12a-C); MS (*m/e*, relative intensity) 313 ($M^+ + 1$, 1), 312 (M^+, 9), 311 (9), 197 (4), 184 (2), 170 (5), 169 (7), 156 (7), 127 (9), 84 (83), 69 (29), 55 (25), 51 (35), 49 (100), 43 (25), 41 (25). For the

hydrochloride: mp 288-290 °C (acetone-MeOH). Anal. Calcd for $C_{19}H_{25}ClN_2O_2$: C, 65.40; H, 7.22; Cl, 10.17; N, 8.03. Found: C, 65.34; H, 7.20; Cl, 10.12; N, 8.00.

***trans*-3-Ethyl-3,4,6,7,12,12b-hexahydroindolo[2,3-*a*]-quinolizin-2(1*H*)-one (1).** A solution of acetal **21** (0.2 g, 0.6 mmol) in MeOH (20 mL) and 4 N aqueous HCl (20 mL) was refluxed for 24 h. The mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried, and the solvent was removed to leave an oil, which was purified by flash chromatography (99:1 Et_2O-DEA) to give **1** (160 mg, 86%): mp 208-209 °C (acetone) [lit.[6a] mp 208 °C (EtOH)]; IR (KBr) 3320, 1690 cm^{-1}; ^1H NMR δ 0.98 (t, J = 7 Hz, 3 H, CH_3), 1.2-1.4 (m, 1 H, CH_ACH_3), 1.8-2.0 (m, 1 H, CH_BCH_3), 2.46 (t, J = 11 Hz, 1 H, 1-H_a), 2.6-2.8 (m, 1 H, 3-H_a), 2.64 (br t, J = 11 Hz, 1 H, 6-H_a), 2.72 (t, J = 11 Hz, 1 H, 4-H_a), 2.82 (ddd, J = 14, 5, and 2 Hz, 1 H, 7-H_e), 3.0 (dd, J = 11 and 2.3 Hz, 1 H, 1-H_e), 3.05 (m, 1 H, 7-H_a), 3.27 (ddd, J = 11, 5, and 2 Hz, 1 H, 6-H_e), 3.4 (dd, J = 11 and 5 Hz, 1 H, 4-H_e), 3.64 (br d, J = 11 Hz, 1 H, 12b-H_a), 7.0-7.2 (m, 2 H, 9-H and 10-H), 7.3 (dt, J = 7 and 1.4 Hz, 1 H, 11-H), 7.48 (dd, J = 7 and 1.4 Hz, 1 H, 8-H), 7.74 (br s, 1 H, NH); ^{13}C NMR δ 11.7 (CH_3), 19.4 (CH_3CH_2), 21.9 (7-C), 45.9 (1-C), 51.6 (6-C), 51.7 (3-C), 59.4 (12b-C), 60.4 (4-C), 108.6 (7a-C), 111.0 (11-C), 118.3 (C-9), 119.7 (8-C), 121.9 (10-C), 127.0 (7b-C), 133.2 (11a-C), 136.2 (12a-C), 208.9 (2-C); MS (m/e, relative intensity) 268 (M^+, 60), 267 (79), 225 (18), 213 (8), 184 (20), 169 (40), 129 (33), 97 (42), 69 (100), 60 (86). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.09; H, 7.56; N, 10.44. Found: C, 76.35; H, 7.54; N, 10.71.

***trans*-5-Ethyl-6,6-(ethylenedioxy)-1,2,5,6,7,7a-hexahydro-4*H*-pyrido[1′,2′:1,2]pyrazino[4,3-*a*]indole (22).** To a solution of alcohol **16** (160 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (10 mL) were successively added dropwise TFA (0.39 mL, 5.28 mmol) and Et_3SiH (0.27 mL, 1.68 mmol). The mixture was refluxed under N_2 for 24 h, cooled, basified with anhydrous Na_2CO_3, poured into ice-water, and extracted with CH_2Cl_2. The extract was washed with aqueous $NaHCO_3$, dried, and evaporated. The residue was purified by flash chromatography (99:1 Et_2O-DEA) to give **22** (70 mg, 47%). This material was identical with that obtained by cyclization of **6**.

***trans*-8-Chloro-5-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 alcohol **11** (730 mg, 2 mmol), CH_2Cl_2 (20 mL), TFA (1.82 mL, 24 mmol), and Et_3SiH (1.22 mL, 7.7 mmol) was obtained compound **23** (200 mg, 29%) after flash chromatography (99:1 Et_2O-DEA): mp 144-146 °C (Et_2O); MS (m/e, relative intensity) 348 (M^+ + 2, 4), 346 (M^+, 13), 301 (40), 285 (3), 259 (15), 231 (13), 204 (33), 178 (13), 149 (29), 127 (26), 97 (37), 69 (96), 55 (100), 43 (84). Anal. Calcd for $C_{19}H_{23}ClN_2O_2$: C, 65.89; H, 6.65; Cl, 10.11; N, 8.09. Found: C, 65.75; H, 6.71; Cl, 9.80; N, 7.89.

X-ray crystal structure analysis of indoloquinolizidin-2-one (1): $C_{17}H_{20}N_2O$, F_w = 268.36, monoclinic, a = 14.855 (3) Å, b = 8.217 (1) Å, β = 114.53 (2) °, V = 1469.8 (7) Å^3, $P2_1/a$, D_x = 1.212 g cm^{-3}, Z = 4, F(000) = 576, λ(Mo Kα) = 0.710 69 Å, μ = 0.82 cm^{-1}, 188 K.

A prismatic crystal (0.1 × 0.1 × 0.15 mm) was selected and mounted on a Philips PW-1100 four circle diffractometer. Unit-cell parameters were determined from 25 reflections ($4 \le \theta \le 12°$) and refined by least-squares method. Intensities were collected with graphite monochromatized Mo Kα radiation, using the ω-scan technique, with scan width 0.8° and scan speed 0.03° s^{-1}; 1156 independent reflections were measured in the range $2 \le \theta \le 25°$, 1034 of which were assumed as observed applying the conditions $I \ge 2.5\sigma(I)$. Three reflections were measured every 2 h as orientation and intensity control, significant intensity decay was not observed. Lorentz-polarization, but no absorption, corrections were made.

The structure was solved by direct methods, using the MULTAN84[26] system of computer programs and refined by full-matrix least-squares method, using the SHELX76 program.[31] The function minimized was $\sum w||F_o| - |F_c||^2$, where $w = (\sigma^2(F_o) + 0.0013|F_o|^2)^{-1}$. A total of 19 hydrogen atoms were located from a difference synthesis and refined with an overall isotropic temperature factor and anisotropically the remaining atoms. The final R value was 0.049 (R_w = 0.052) for all observed reflections.

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Supplementary Material Available: Tables of non-hydrogen atom positional and anisotropic thermal parameters, hydrogen atom positional, interatomic distances, and bond angles (7 pages). Ordering information is given on any current masthead page.

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Successive Michael Reaction-Sigmatropic Rearrangement of Polyquinones with Silyl Ketene Acetals†

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Michael-type additions of polyquinones such as quinizarinquinone (1) and naphthodiquinone (2) with various *O*-silylated ketene acetals followed by successive sigmatropic rearrangements of the adducts are described. The Michael-type additions of the *O*-silylated ketene acetals with the highly electrophilic polyquinones took place exclusively at the internal double bond without any catalysts. Some of the resultant adducts performed interesting rearrangements under thermal or Lewis acid conditions to give external adducts that are obtained formally by the addition to polyquinones at the less reactive external double bond.

Polyquinones such as quinizarinquinone (1, Chart I) and naphthodiquinone (2) are activated *p*-benzoquinone derivatives[1,2] and are expected to react not only as dienophiles but also as electrophiles. Despite their enhanced electrophilicity due to markedly lowered LUMO energy levels,[1,2] little attention has been paid to electrophilic reactions of polyquinones.

Because of their cyclic tetraone structures, polyquinones are utilized in Diels-Alder reactions to construct tetracyclic

† This paper is dedicated to Professor Haruaki Yajima on the occasion of his retirement from Kyoto University in March, 1989.

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