Alkylation of 5- and 6-Methylindolo[2,3-*b*]quinoxalines: Revised Structures of the *N*,*N*′-Dimethylated Salts

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N,*N*′-Dialkylation of indolo[2,3-*b*]quinoxaline could theoretically furnish three isomers, that is, salts dialkylated at the 5,6-, the 6,11-, and the 5,11-positions. By using the 2,3-dimethylated derivatives as models, the regioisomeric salts were selectively synthesized either by alkylation of the tetracycle or by cyclization of 1-methylisatin with *N*,4,5-trimethylbenzene-1,2-diamine. The structure of the *N*,*N*′-dimethyl salts were unambiguously determined by NMR correlation sequences (^{1}H-^{1}H NOESY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC). The results of these studies show that the previous findings from the dialkylation of indoloquinoxaline need revision.

Introduction

Indolo[2,3-*b*]quinoxalines are important DNA intercalating agents with antiviral and cytotoxic activities.[1] In the course of our search for antitumoral drugs, we have become interested in the selective preparation of the three regioisomers of the *N*,*N*′-disubstituted indolo[2,3-*b*]quinoxaline series, that is, salts **4**, **5**, and **6** dialkylated at the 5,6-, the 6,11-, and the 5,11-positions, respectively (Figure 1).

Several 5- or 6-substituted indolo[2,3-*b*]quinoxalines have been synthesized either by condensation of an isatin with a benzene-1,2-diamine or by alkylation of an indoloquinoxaline. Alkylation in neutral conditions usually gives an N^5-alkylated product, but the same reaction in an alkaline medium results in N^6-alkylation. Under the latter conditions, a small amount of the N^5-substituted derivative may also be formed.[2]

To the best of our knowledge, only two publications relate the synthesis of *N*,*N*′-disubstituted indoloquinoxalines. In 1925, Armit and Robinson reported that two successive alkylations of 2,3-dimethoxyindolo[2,3-*b*]quinoxaline (**1b**) with dimethyl sulfate in nitrobenzene probably led to the N^6,N^{11}-dimethylated derivative **5b** as an orange-yellow salt.[3] The scarlet product of the first alkylation was regarded as the 11-methyl derivative but there is no direct proof of this. Forty years later, the above structures were revised by Badger and Nelson who worked on unsubstituted indolo[2,3-*b*]quinoxaline (**1a**) presuming that the two methoxy groups would not affect the position of alkylation.[2] According to these authors, treatment of 6-methylindoloquinoxaline (**2a**) with methyl toluene-*p*-sulfonate in ethanol gave the N^5,N^6-dimethylated red product **4a** and, under the same conditions, the orange-yellow N^5,N^{11}-dimethylated isomer **6a** was obtained starting from the 5-methylindoloquinoxaline (**3a**). The structures of **4a** and **6a** were established by comparing their UV spectra with those of the mono-*N*-methyl starting materials in an acidic medium.

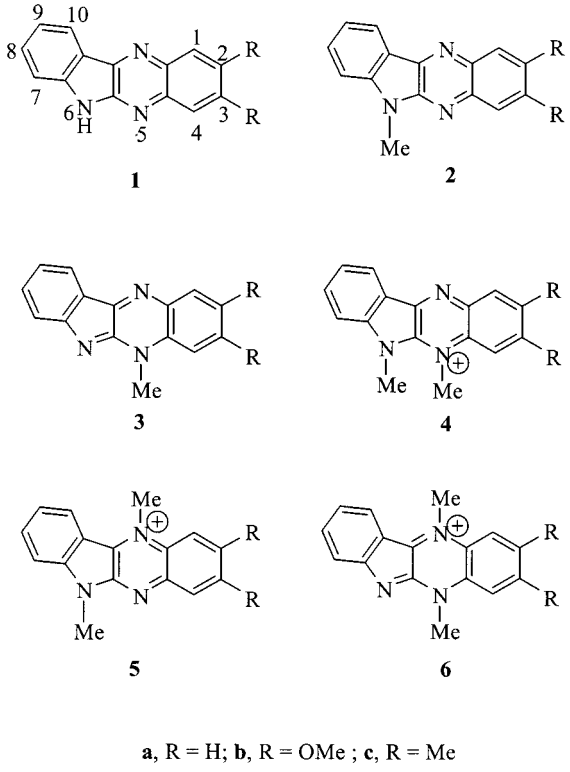

Figure 1. Structures of *N*-methyl- and *N*,*N*′-dimethylindolo[2,3-*b*]-quinoxalines

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In view of these contradictory results we report herein the selective synthesis of all three *N*,*N*′-dimethyl regioisomeric salts and their structural elucidation by 2D NMR studies. In order to facilitate the structural assignment, the 2,3-dimethylindolo[2,3-*b*]quinoxaline (**1c**) was chosen as the starting material.

Results and Discussion

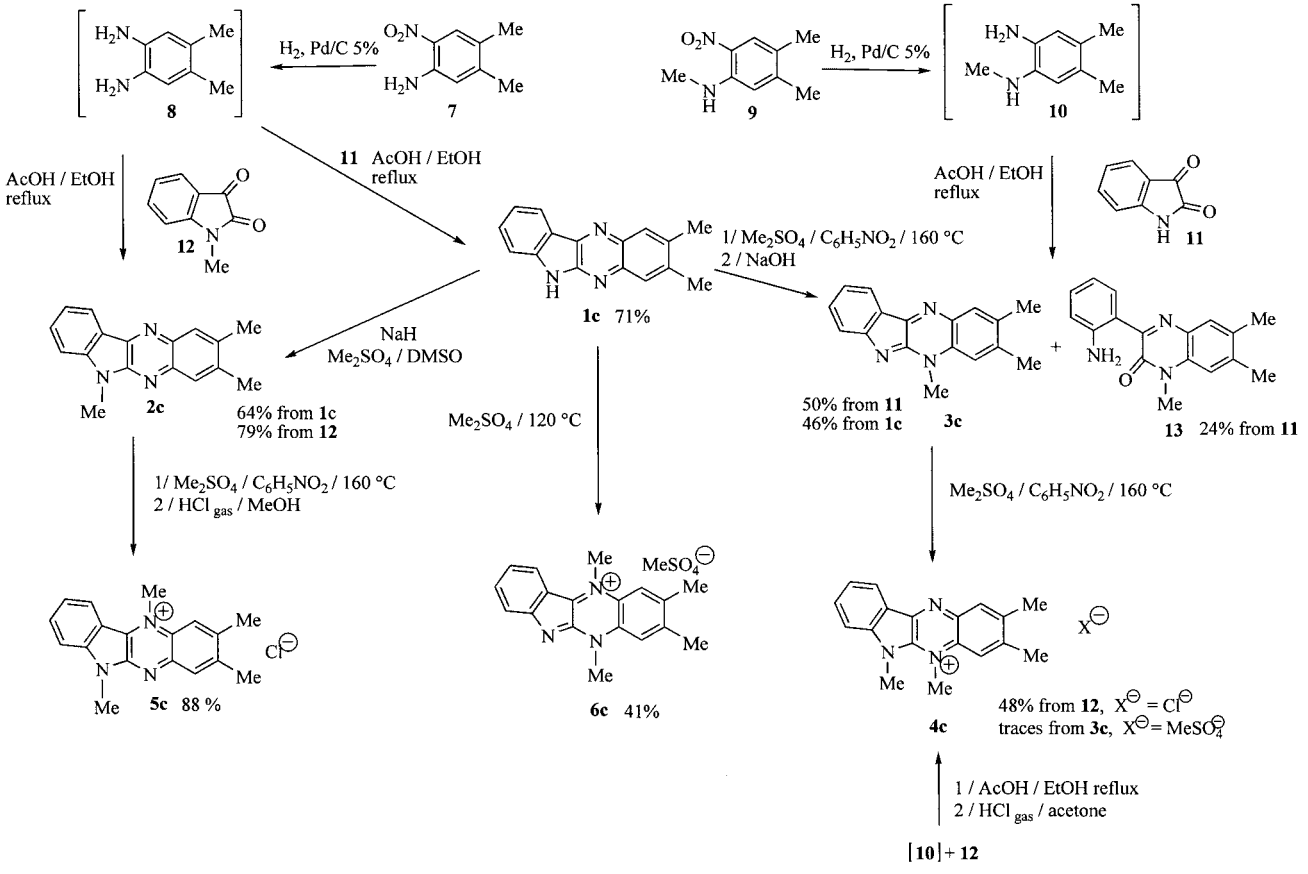
Synthesis of the *N*,*N*′-Dimethylindolo[2,3-*b*]quinoxalines

2,3-Dimethylindolo[2,3-*b*]quinoxaline (**1c**) was prepared by the condensation of 1*H*-indole-2,3-dione (isatin) (**11**) with 4,5-dimethylbenzene-1,2-diamine (**8**) (Scheme 1).[4]

Similarly, condensation of 1-methylisatin (**12**) with the diamine **8** and of isatin (**11**) with *N*,4,5-trimethylbenzene-1,2-diamine (**10**) led to the formation of 6-methyl- and 5-methyl derivatives **2c** and **3c**, respectively. In the latter reaction, the quinoxaline **13** was isolated as a by-product (24%). Derivatives **2c** and **3c** could also be obtained with similar yields by the alkylation of **1c**. In agreement with the results described in the literature for other indoloquinoxalines,[2,3] methylation of compound **1c** in a neutral medium (dimethyl sulfate in nitrobenzene) and subsequent alkaline treatment furnished the anhydrobase **3c**. In contrast, in our case, alkylation in an alkaline medium (NaH and then dimethyl sulfate in DMSO), gave only the N^6 derivative **2c**; the 5-isomer **3c** was not detected. As previously mentioned by Badger and Nelson,[2] the synthesis of **3c** by cyclization is not unambiguous. Indeed, formation of the 11-methyl regioisomer by the reaction of the secondary amino group of **10** with the ketone function of isatin cannot be excluded. The NMR spectral analysis is in agreement with the structures **2c** and **3c**.

In order to obtain the dimethylated salts, a second reaction was performed with the two *N*-methyl derivatives. Thus, 2,3,6,11-tetramethylindolo[2,3-*b*]quinoxalinium chloride (**5c**) was obtained in good yield from the 6-methyl compound **2c** by treatment with dimethyl sulfate in nitrobenzene at a high temperature and subsequent replacement of the anion with chloride. The structure of **5c** was established by NMR spectroscopy and, in particular, by the absence of a NOESY correlation between the two *N*-methyl groups and the presence of a NOESY effect between the N^{11}-methyl group and the 10-H atom. Under similar conditions, the reaction of the N^5-methyl isomer gave a tar with only traces of a salt which was identical to the product obtained by the condensation of 1-methylisatin (**12**) with diamine **10**. The NOESY correlation between the two *N*-methyl groups confirmed the 2,3,5,6-tetramethylindoloquinoxalinium structure (**4c**).

Interestingly, the third isomer **6c** (the N^5,N^{11}-dimethyl salt) was obtained in 41% yield by heating the *N*-unsubstituted indoloquinoxaline **1c** in dimethyl sulfate at 120 °C in



Scheme 1

the absence of a solvent. The poor solubility of the salt **6c** did not allow a complete NMR study to be performed. However, its physical characteristics, ^{1}H NMR and IR spectra are significantly different from those of salts **4c** and **5c**.

Structural Determinations

The assignment of the ^{1}H and ^{13}C NMR spectra of compounds **2c**−**5c** was based on the analysis of coupling patterns and 2D NMR (^{1}H-^{1}H NOESY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC) experiments.

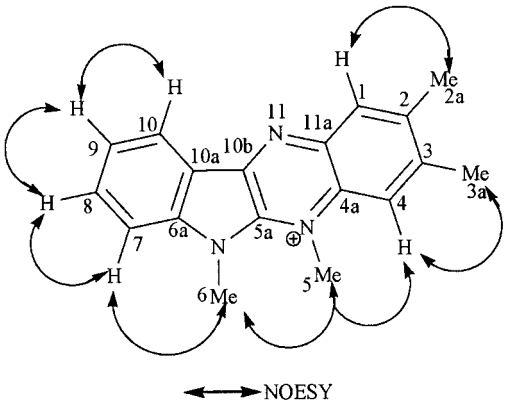
In order to illustrate the typical procedure, the structural assignment of compound **4c** is described here. The first significant structural information was gained from the 2D NOESY spectrum which shows a correlation spot between the two *N*-methyl groups (singlets at δ = 4.36 and 4.74 ppm). The spatial proximity of the methyl groups is then proved and confirms the chemical hypothesis of a 5,6-dimethylation. Furthermore, support for their localization was provided by correlations between the singlet aromatic proton at δ = 8.40 ppm and the *N*−Me at δ = 4.74 ppm and between the aromatic proton, which appears as a doublet at δ = 8.05 ppm, and the *N*−Me at δ = 4.36 ppm. Consequently, the former signals can be attributed to 4-H and N^5-Me and the latter ones to 7-H and N^6-Me. A whole series of NOESY correlations, on one hand, between 4-H and 3a-H (δ = 2.66 ppm), 2a-H (δ = 2.57 ppm) and 1-H (δ = 8.30 ppm), and, on the other hand, between 7-H and 8-H (δ = 7.98 ppm), 8-H and 9-H (δ = 7.67 ppm), and 9-H and 10H (δ = 8.45 ppm) allow the assignment of all the ^{1}H signals.

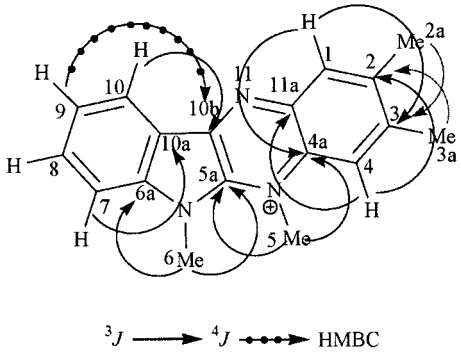
The ^{13}C NMR signals were identified by HMQC analysis of the protonated carbon atoms (Table 1) and by HMBC correlations of the quaternary carbon atoms. The HMBC spectrum shows long-range ^3J couplings from 1-H (δ = 8.30 ppm) to C-3 (δ = 144.9 ppm) and C-4a (δ = 127.9 ppm), which in turn is coupled to the N^5-Me protons. Analysis of the remaining data − ^3J connectivities from N^5−Me protons to C-5a (δ = 139.7 ppm), from N^6-Me protons to C-5a and C-6a (δ = 145.7 ppm), from 4-H to C-11a (δ = 136.5 ppm) and C-2 (δ = 138.9 ppm), and from 10-H to C-10b (δ = 145.3 ppm) and ^4J connectivity from 9-H to C-10b − allow the assignment of these carbon atoms. Consequently, the signal at δ = 119.1 ppm can be attributed to C-10a, which has long-range ^3J couplings with 7-H.

The ^{1}H and ^{13}C NMR spectra of compounds **2c**, **3c**, and **5c** were assigned (Table 2−4) in the same manner. The quinoxaline moiety of compound **2c** could not be totally assigned, but there is no chemical ambiguity concerning the position of the *N*-methyl group. The structure was corroborated by a whole series of NOESY and HMBC correlations and, in particular, by a NOESY correlation spot between the *N*-Me (singlet at δ = 3.88 ppm) and 7-H (doublet at δ = 7.36 ppm) (Table 2).

Attempts to assign the structure of compound **5c** (Table 3) were based on the two NOESY correlations between the N^6-Me (singlet at δ = 4.10 ppm) and 7-H (doublet at δ = 8.06 ppm) and between the N^{11}-Me (singlet at δ = 5.05 ppm) and both the singlet at δ = 8.65 ppm (1-H) and the doublet at δ = 8.87 ppm (10-H).

Table 1. ^{1}H and ^{13}C chemical shifts, 2D ^{1}H-^{13}C HMQC and HMBC correlations, and ^{1}H-^{1}H NOESY correlations for compound **4c**

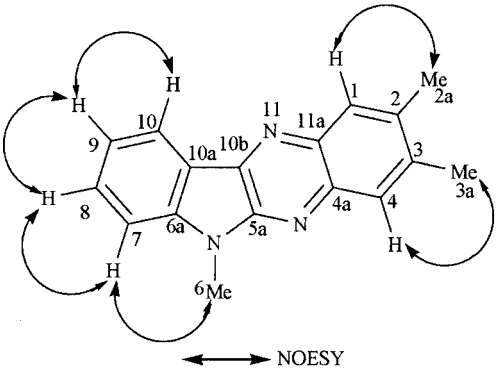


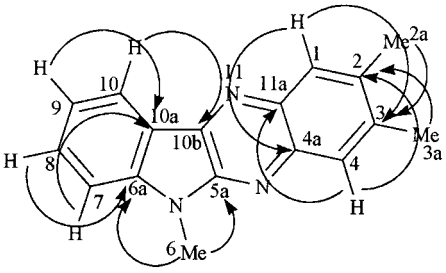


Position	δ (^{13}C) [ppm]	δ (^{1}H) [ppm]	HMQC [$J_{C,H}$] ^1J	HMBC [$J_{C,H}$] ^3J	^4J	NOESY
1	130.0	8.30 (s)	1-H			2a-H
2	138.9			3a-H, 4-H		
2a	19.5	2.57 (s)	2a-H			1-H
3	144.9			1-H, 2a-H		
3a	20.9	2.66 (s)	3a-H			4-H
4	117.2	8.40 (s)	4-H			3a-H, 5-H
4a	127.9			1-H, 5-H		
5	38.5	4.74 (s)	5-H			4-H, 6-H
5a	139.7			5-H, 6-H		
6	34.8	4.36 (s)	6-H			5-H, 7-H
6a	145.7			6-H		
7	113.2	8.05 (d)	7-H			6-H, 8-H
8	133.6	7.98 (t)	8-H			7-H, 9-H
9	125.1	7.67 (t)	9-H			8-H, 10-H
10	122.7	8.45 (d)	10-H			9-H
10a	119.1			7-H		
10b	145.3			10-H	9-H	
11a	136.5			4-H		

As in the carbazole series,[5] the most deshielded aromatic proton is the angular one, that is, the 10-H atom of the indoloquinoxalines. Such chemical shifts were also found for the 10-H atoms of salt **4c** (δ = 8.45 ppm) and derivative **3c** (doublet at δ = 8.19 ppm) in which 10-H also has two

Table 2. ^{1}H and ^{13}C chemical shifts, 2D ^{1}H-^{13}C HMQC and HMBC correlations, and ^{1}H-^{1}H NOESY correlations for compound **2c**

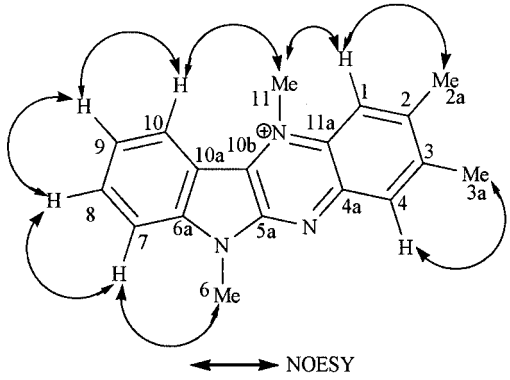


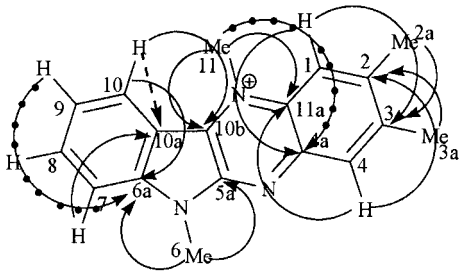


Position	δ (^{13}C) [ppm]	δ (^{1}H) [ppm]	HMQC [$J_{C,H}$] ^1J	HMBC [$J_{C,H}$] ^3J	NOESY
1	126.8 or 128.3	7.82 or 7.97 (s)	1-H		2a-H
2	135.8 or 139.1			3a-H, 4-H	
2a	20.1 or 20.4	2.46 (s)	2a-H		1-H
3	135.8 or 139.1			1-H, 2a-H	
3a	20.1 or 20.4	2.46 (s)	3a-H		4-H
4	126.8 or 128.3	7.82 or 7.97 (s)	4-H		3a-H
4a	138.0 or 139.1			1-H	
5a	145.5			6-H	
6	27.3	3.88 (s)	6-H		7-H
6a	144.4			6-H, 8-H	
7	108.9	7.36 (d)	7-H		6-H, 8-H
8	130.3	7.60 (t)	8-H		7-H, 9-H
9	120.5	7.30 (t)	9-H		8-H, 10-H
10	122.2	8.38 (d)	10-H		9-H
10a	119.5			7-H, 9-H	
10b	139.1			10-H	
11a	138.0 or 139.1			4-H	

^3J long-range couplings with C-6a (δ = 158.3 ppm) and C-10b (δ = 152.0 ppm). The other correlations are consistent with the structure **3c** (Table 4).

Table 3. ^{1}H and ^{13}C chemical shifts, 2D ^{1}H-^{13}C HMQC and HMBC correlations, and ^{1}H-^{1}H NOESY correlations for compound **5c**



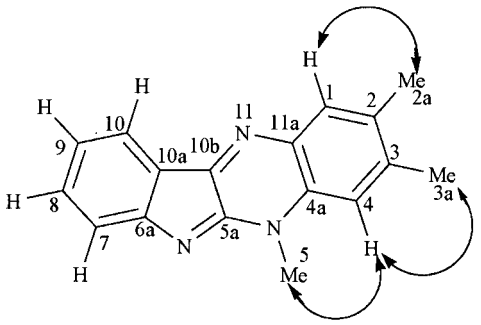


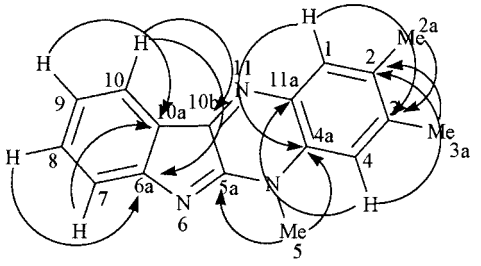
Position	δ (^{13}C) [ppm]	δ (^{1}H) [ppm]	HMQC [$J_{C,H}$] ^1J	HMBC [$J_{C,H}$] ^2J	^3J	^4J	NOESY
1	118.3	8.65 (s)	1-H				2a-H, 11-H
2	143.6				3a-H, 4-H		
2a	21.4	2.53 (s)	2a-H				1-H
3	143.6				1-H, 2a-H		
3a	20.6	2.64 (s)	3a-H				4-H
4	128.9	8.26 (s)	4-H				3a-H
4a	140.6				1-H	11-H	
5a	147.6				6-H		
6	29.4	4.10 (s)	6-H				7-H
6a	147.6				6-H,10-H	9-H	
7	112.8	8.06 (d)	7-H				6-H, 8-H
8	136.8	8.12 (t)	8-H				7-H, 9-H
9	123.6	7.64 (t)	9-H				8-H, 10-H
10	128.5	8.87 (d)	10-H				9-H, 11-H
10a	113.2			10-H	7-H		
10b	130.6				10-H, 11-H		
11	41.4	5.05 (s)	11-H				1-H, 10-H
11a	127.9				4-H, 11-H		

Conclusion

The *N*,*N*′-dialkylation of indolo[2,3-*b*]quinoxaline could theoretically furnish three salts. In this work, using the 2,3-dimethylated derivatives as models, we have shown that all three possible regioisomers can be selectively synthesized either by alkylation of the corresponding tetracycle **1c** (salts

Table 4. ^{1}H and ^{13}C chemical shifts, 2D ^{1}H-^{13}C HMQC and HMBC correlations, and ^{1}H-^{1}H NOESY correlations for compound **3c**





Position	δ (^{13}C) [ppm]	δ (^{1}H) [ppm]	HMQC [$J_{C,H}$] ^1J	HMBC [$J_{C,H}$] ^3J	NOESY
1	130.6	7.96 (s)	1-H		2a-H
2	133.3			3a-H, 4-H	
2a	19.4	2.39 (s)	2a-H		1-H
3	140.3			1-H, 2a-H	
3a	20.8	2.45 (s)	3a-H		4-H
4	114.0	7.41 (s)	4-H		3a-H, 5-H
4a	127.9			1-H, 5-H	
5	32.2	4.25 (s)	5-H		4-H
5a	146.6			5-H	
6a	158.3			8-H, 10-H	
7	118.2	7.63 (d)	7-H		
8	132.3	7.58 (t)	8-H		
9	120.8	7.23 (t)	9-H		
10	122.4	8.19 (d)	10-H		
10a	123.1			7-H, 9-H	
10b	152.0			10-H	
11a	133.0			4-H	

6c and **5c**) or by the cyclization of 1-methylisatin (**12**) with the *N*-methylbenzenediamine **10** (salt **4c**). Their structures were unambiguously determined by NMR correlation sequences (^{1}H-^{1}H NOESY, ^{1}H-^{13}C HMQC, and ^{1}H-^{13}C HMBC). This work presents evidence that the previously reported structures[2,3] need revision. The synthesis of analogues with potential antitumoral activity can now be considered.

Experimental Section

General Remarks: Thin-layer chromatography was carried out on Merck GF 254 silica gel plates. Flash chromatography was performed on Merck silica gel 70 (30−70 μm). Melting points were determined with a Maquenne apparatus and are uncorrected. Elemental analyses were performed at the CNRS Analysis Laboratory, Gif-sur-Yvette. ESI/HRMS spectra were acquired with a QTOF/Micromass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 300 and AC 400 spectrometers. Multiplicities are listed as s (singlet), d (doublet), t (triplet), and m (multiplet). IR spectra were recorded with a Perkin−Elmer 1600 spectrometer.

2,3-Dimethyl-6*H*-indolo[2,3-*b*]quinoxaline (1c): A suspension of 4,5-dimethyl-2-nitroaniline (**7**) (1.66 g, 10 mmol) in ethanol (60 mL) was hydrogenated for 12 h at room temperature under a pressure of 5 bar in the presence of 5% palladium on activated charcoal (0.25 g). After filtration, the catalyst was washed with ethanol (10 mL). Isatin (**11**) (0.735 g, 5 mmol) in acetic acid (60 mL) was added to the resulting solution and the mixture was refluxed for 12 h. After elimination of the solvents under reduced pressure, ethanol (50 mL) was added and the resulting precipitate was filtered off then washed with ethanol to give pure quinoxaline **1c** (0.88 g, 71%) as a yellow powder. M.p. 352−354 °C [ref.[4] 69%, m.p. 352−353 °C (acetic acid)]. IR (KBr): $\tilde{\nu}$ = 3113, 3071, 1622, 1595, 1483, 1451, 1408, 1387, 1328, 1243, 1216, 1162, 1107, 1039, 1010, 861, 746 cm^{-1}. ^{1}H NMR ([D$_6$]DMSO, 400 MHz): δ = 2.47 (s, 6 H, 2 × CH$_3$), 7.32 (t, J = 8 Hz, 1 H, 9-H), 7.54 (d, J = 8 Hz, 1 H, 7-H), 7.65 (t, J = 8 Hz, 1 H, 8-H), 7.81 (s, 1 H, 1-H or 4-H), 7.98 (s, 1 H, 1-H or 4-H), 8.29 (d, J = 8 Hz, 1 H, 10-H), 11.89 (s, 1 H, NH) ppm. ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 20.7 (C-2a or C-3a), 21.0 (C-2a or C-3a), 112.9 (C-7), 120.2 (C-10a), 121.5 (C-9), 122.9 (C-10), 127.6 (C-1 or C-4), 129.1 (C-1 or C-4), 131.8 (C-8), 136.7 (C-2 or C-3), 138.6 (C-4a or C-11a), 139.7 (C10b), 139.9 (C-2 or C-3 and C-4a or C-11a), 144.5 (C-6a), 146.7 (C-5a) ppm.

2,3,6-Trimethyl-6*H*-indolo[2,3-*b*]quinoxaline (2c). Method A: Compound **2c** was obtained by using the same procedure as described above for the preparation of **1c** starting from the nitro derivative **7** (1.66 g, 10 mmol) and 1-methylisatin (**12**) (0.735 g, 5 mmol) to give pure compound **2c** as a yellow solid (1.03 g, 79%). **Method B:** Sodium hydride (60% oil dispersion, 0.21 g, 5.25 nmol) and then dimethyl sulfate (0.5 mL, 5.25 mmol) were added, whilst stirring, to a solution of compound **1c** (0.865 g, 3.5 mmol) in dry DMSO (40 mL). After stirring the reaction mixture at room temperature for 12 h, water (160 mL) was added and the resulting precipitate was filtered off. The crude product was purified by flash chromatography (CH_2Cl_2/methanol, 100:0 to 98:2) to yield compound **2c** as a yellow solid (0.59 g, 64%). M.p. 194 °C. IR (KBr): $\tilde{\nu}$ = 3028, 2921, 1611, 1579, 1483, 1429, 1392, 1323, 1242, 1209, 1115, 745 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.46 (s, 6 H, 2a-H and 3a-H), 3.88 (s, 3 H, 6-H), 7.30 (t, J = 10 Hz, 1 H, 9-H), 7.36 (d, J = 10 Hz, 1 H, 7-H), 7.60 (t, J = 10 Hz, 1 H, 8-H), 7.82 (s, 1 H, 1-H or 4-H), 7.97 (s, 1 H, 1-H or 4-H), 8.38 (d, J = 10 Hz, 1 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.1 (C-2a or C-3a), 20.4 (C-2a or C-3a), 27.3 (C-6), 108.9 (C-7), 119.5 (C-10a), 120.5 (C-9), 122.2 (C-10), 126.8 (C-1 or C-4), 128.3 (C-1 or C-4), 130.3 (C-8), 135.8 (C-2 or C-3), 138.0 (C-4a or C-11a), 139.1 (C-2 or C-3 and C-4a or C-11a and C-10b), 144.4 (C-6a), 145.5 (C-5a) ppm. $C_{17}H_{15}N_3$: calcd. C 78.13, H 5.79, N 16.08; found C 77.73, H 5.64, N 16.09.

2,3,5-Trimethyl-5*H*-indolo[2,3-*b*]quinoxaline (3c) and 3-(2-Aminophenyl)-1,6,7-trimethylquinoxalin-2(1*H*)-one (13). Method A: Com-

pounds **3c** and **13** were obtained by using the same procedure as described above for the preparation of **1c** starting from the nitro derivative **9** (1.80 g, 10 mmol) and isatin (**11**) (0.735 g, 5 mmol). After refluxing for 12 h, the reaction mixture was cooled to room temperature. The solid was collected, washed with ethanol and dried to give compound **13** (0.32 g, 24%). An analytical sample was prepared by recrystallization from methanol. The mother liquor was evaporated in vacuo, the resulting residue was taken up in a 50:50 ethanol/diethyl ether mixture which was then filtered. The crude product was purified by flash chromatography (CH_2Cl_2/methanol, 99:1 to 90:10) to give compound **3c** as a red solid (0.65 g, 50%). **Method B:** A mixture of compound **1c** (0.37 g, 1.5 mmol) and dimethyl sulfate (0.43 mL, 4.5 mmol) in nitrobenzene (10 mL) was heated at 160 °C for 2 h. The reaction mixture was cooled to room temperature and then diethyl ether (15 mL) was added. The resulting precipitate was filtered off, suspended in a 10% aqueous sodium hydroxide solution (15 mL), and then extracted with CH_2Cl_2 (3 × 15 mL). After elimination of the solvent, the crude product was purified by flash chromatography (CH_2Cl_2/methanol, 99:1 to 95:5) to give pure compound **3c** (0.18 g, 46%).

Compound 3c: M.p. 280−282 °C. IR (KBr): $\tilde{\nu}$ = 3042, 2912, 1582, 1558, 1487, 1446, 1410, 1328, 1221, 1186, 1127, 1038, 743 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.39 (s, 3 H, 2a-H), 2.45 (s, 3 H, 3a-H), 4.25 (s, 3 H, 5-H), 7.23 (t, J = 10 Hz, 1 H, 9-H), 7.41 (s, 1 H, 4-H), 7.58 (t, J = 10 Hz, 1 H, 8-H), 7.63 (d, J = 10 Hz, 1 H, 7-H), 7.96 (s, 1 H, 1-H), 8.19 (d, J = 10 Hz, 1 H, 10-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.4 (C-2a), 20.8 (C-3a), 32.2 (C-5), 114.0 (C-4), 118.2 (C-7), 120.8 (C-9), 122.4 (C-10), 123.1 (C-10a), 127.9 (C-4a), 130.6 (C-1), 132.3 (C-8), 133.0 (C-11a), 133.3 (C-2), 140.3 (C-3), 146.6 (C-5a), 152.0 (C-10b), 158.3 (C-6a) ppm. $C_{17}H_{15}N_3 \cdot 0.25H_2O$: calcd. C 76.81, H 5.88, N 15.81; found C 76.74, H 5.61, N 15.61.

Compound 13: M.p. 250−252 °C (methanol). IR (KBr): $\tilde{\nu}$ = 3414, 3309, 1647, 1615, 1573, 1462, 1441, 1239, 1154, 1001, 842, 736, 609 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.30 (s, 3 H, 6a-H), 2.37 (s, 3 H, 7a-H), 3.68 (s, 3 H, N-CH_3), 5.26 (s, 2 H, NH_2), 6.72 (d, J = 8 Hz, 1 H, 3′-H), 6.80 (t, J = 8 Hz, 1 H, 5′-H), 7.03 (s, 1 H, 8-H), 7.14 (t, J = 8 Hz, 1 H, 4′-H), 7.53 (s, 1 H, 5-H), 8.00 (d, J = 8 Hz, 1 H, 6′-H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 19.2 (C-6a), 20.6 (C-7a), 29.4 (C-1a), 114.1 (C-8), 117.2 (C-3′), 117.3 (C-5′), 120.0 (C-1′), 129.7 (C-5), 130.9 (C-4a and C-4′), 131.1 (C-8a), 131.8 (C-6′), 132.6 (C-6), 140.0 (C-7), 147.2 (C-2′), 154.2 (C-3), 154.8 (C-2) ppm. $C_{17}H_{17}N_3O \cdot H_2O$: calcd. C 68.67, H 6.44, N 14.13; found C 69.03, H 6.23, N 14.48.

2,3,5,6-Tetramethylindolo[2,3-*b*]quinoxalinium Chloride (4c): Compound **4c** was obtained by using the same procedure as described above for the preparation of **1c** starting from the nitro derivative **9** (0.72 g, 4 mmol) in ethanol (30 mL) and 1-methylisatin (**12**) (0.23 g, 2 mmol) in acetic acid (30 mL). At the end of the reaction (12 h), the solvents were eliminated under reduced pressure. Dry acetone (30 mL) was added to the residue and hydrochloric gas was condensed into the vessel at 0 °C for 0.5 min. After stirring for 1 h at 0 °C, the precipitate was filtered off and purified by flash chromatography (CH_2Cl_2/methanol, 95:5 to 70:30) to afford salt **4c** as an orange-yellow solid (0.30 g, 48%). M.p. 277−279 °C. IR (KBr): $\tilde{\nu}$ = 3499, 3408, 3006, 1632, 1601, 1496, 1470, 1406, 1343, 1312, 1259, 1223, 1118, 1013, 932, 892, 784, 761, 729 cm^{-1}. ^1H NMR ([D_6]DMSO, 400 MHz, 25 °C): δ = 2.57 (s, 3 H, 2a-H), 2.66 (s, 3 H, 3a-H), 4.36 (s, 3 H, 6-H), 4.74 (s, 3 H, 5-H), 7.67 (t, J = 8 Hz, 1 H, 9-H), 7.98 (t, J = 8, Hz, 1 H, 8-H), 8.05 (d, J = 8 Hz, 1 H, 7-H), 8.30 (s, 1 H, 1-H), 8.40 (s, 1 H, 4-H), 8.45 (d, J = 8 Hz, 1 H, 10-H) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 19.5 (C-2a), 20.9 (C-3a), 34.8 (C-6), 38.5 (C-5), 113.2 (C-7), 117.2 (C-4), 119.1 (C-10a), 122.7 (C-10), 125.1 (C-9), 127.9 (C-4a), 130.0 (C-1), 133.6 (C-8), 136.5 (C-11a), 138.9 (C-2), 139.7 (C-5a), 144.9 (C-3), 145.3 (C-10b), 145.7 (C-6a) ppm. $C_{18}H_{18}ClN_3 \cdot 2H_2O$: calcd. C 62.15, H 6.37, N 12.08; found C 61.83, H 6.06, N 11.84.

2,3,6,11-Tetramethylindolo[2,3-*b*]quinoxalinium Chloride (5c): Dimethyl sulfate (0.95 mL, 10 mmol) was added to a solution of derivative **2c** (0.653 g, 2.5 mmol) in nitrobenzene (15 mL) maintained at 160 °C. After 0.75 h at 160 °C, the reaction mixture was cooled to room temperature and addition of diethyl ether (30 mL) led to the formation of a precipitate. The precipitate was filtered off and washed with dry diethyl ether, anhydrous methanol (15 mL) was added, and hydrochloric gas was condensed into the vessel for 0.5 min at 0 °C. After stirring for 0.5 h at 0 °C the solvent was removed in vacuo. The residue was triturated with diethyl ether (15 mL) and the mixture filtered. The crude product was purified by flash chromatography (CH_2Cl_2/methanol, 95:5 to 85:15) to give salt **5c** as a brick-red solid (0.69 g, 88%). M.p 257−259 °C. IR (KBr): $\tilde{\nu}$ = 3452, 3087, 2931, 1612, 1573, 1514, 1488, 1475, 1430, 1375, 1339, 1254, 1215, 1156, 1153, 1140, 1070, 1013, 970, 900, 875, 752, 726 cm^{-1}. ^1H NMR ([D_6]DMSO, 400 MHz): δ = 2.53 (s, 3 H, 2a-H), 2.64 (s, 3 H, 3a-H), 4.10 (s, 3 H, 6-H), 5.05 (s, 3 H, 11-H), 7.64 (t, J = 8 Hz, 1 H, 9-H), 8.06 (d, J = 8 Hz, 1 H, 7-H), 8.12 (t, J = 8 Hz, 1 H, 8-H), 8.26 (s, 1 H, 4-H), 8.65 (s, 1 H, 1-H), 8.87 (d, J = 8 Hz, 1 H, 10-H) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 20.6 (C-3a), 21.4 (C-2a), 29.4 (C-6), 41.4 (C-11), 112.8 (C-7), 113.2 (C-10a), 118.3 (C-1), 123.6 (C-9), 127.9 (C-11a), 128.5 (C-10), 128.9 (C-4), 130.6 (C-10b), 136.8 (C-8), 140.6 (C-4a), 143.6 (C-2 and C-3), 147.6 (C-5a and C-6a) ppm. $C_{18}H_{18}ClN_3 \cdot 0.5H_2O$: calcd. C 67.39, H 5.97, N 13.10; found C 67.20, H 6.26, N 13.26.

2,3,5,11-Tetramethylindolo[2,3-*b*]quinoxalinium Methyl Sulfate (6c): A mixture of compound **1c** (0.494 g, 2 mmol) and dimethyl sulfate (3 mL) was heated at 120 °C for 1.75 h and then cooled to room temperature. After addition of a 50:50 ethyl acetate/diethyl ether mixture (25 mL) the resulting residue was collected and then purified by flash chromatography (CH_2Cl_2/methanol, 95:5 to 70:30) to afford salt **6c** as a dark purple solid (0.32 g, 41%). M.p. 266−268 °C. IR (KBr): $\tilde{\nu}$ = 3452, 3348, 2983, 2722, 1658, 1612, 1514, 1456, 1358, 1280, 1247, 1208, 1059, 1020, 772, 753 cm^{-1}. ^1H NMR (CD_3OD, 300 MHz): δ = 2.59 (s, 3 H, 2a-H or 3a-H), 2.62 (s, 3 H, 2a-H or 3a-H), 3.17 (s, 3 H, $MeSO_4^-$), 4.58 (s, 3 H, 5-H), 5.04 (s, 3 H, 11-H), 7.53 (t, J = 8 Hz, 1 H, 9-H), 7.74 (d, J = 8 Hz, 1 H, 7-H), 7.97 (t, J = 8 Hz, 1 H, 8-H), 8.31 (s, 1 H, 1-H or 4-H), 8.55 (s, 1 H, 1-H or 4-H), 8.62 (d, J = 8 Hz, 1 H, 10-H) ppm. HRMS: m/z calcd. for $[M - MeSO_4]^+$: 276.1501; found 276.1500.

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