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The complete assignment of the  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra of some derivatives of both 4b,5-dihydro-4b-methyl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one **I** and 2,3,3a,4-tetrahydro-3a-methyl-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one **II** was herein reported by the combined use of one and two-dimensional nmr techniques. Eight compounds, three of which are novel, **2a**, **3**, **6**, were thus prepared. Their uv and ir spectra were also obtained. In addition, the mass spectra of compounds **1**, **2a**, **2b**, **3** and **6** are reported.

## Introduction.

The 4b,5-dihydro-4b-methyl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one derivatives **I** were first synthesized over twenty years ago [1,2]. They were claimed to possess interesting pharmacological activities and to be useful as sedatives and tranquilizers. Surprisingly, no systematic work has been carried out on these compounds, and neither have their spectroscopic characteristics been described.

More recently, some 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one derivatives **II** were shown to possess an anticonvulsant activity comparable to that of diphenylhydantoin in DBA/2 mice against sound-

size new compounds of these two classes (Scheme 1). In addition, their limited spectroscopic characterizations encouraged us to carry out more extensive studies on their spectral properties.

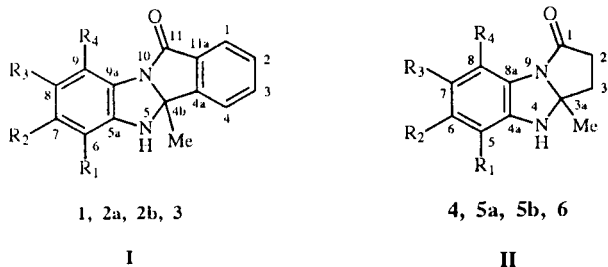
Since  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra are essential tools for the elucidation of the structures of certain organic compounds, we have carried out detailed  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra of some derivatives of **I** and **II** to provide a basis for future structural assignment of new compounds for these two general series. It has been accomplished by using information contained within the two dimensional  $^{13}\text{C}$ - $^1\text{H}$  direct (XHCORR) [6] and long range (COLOC) [7] correlation experiments together with the results of proton-coupled and single frequency decoupled  $^{13}\text{C}$  nmr spectra.

Eight compounds, three of which are novel, **2a**, **3** and **6**, were thus prepared and a full assignment of their  $^1\text{H}$  and  $^{13}\text{C}$  signals was achieved. Their uv and ir spectra were also obtained. In addition, the mass spectra of compounds **1**, **2a**, **2b**, **3** and **6** were recorded under electron ionization.

## Synthesis.

The compounds **1-6** were prepared by the condensation of the requisite *o*-phenylenediamine with either 2-acetylbenzoic acid [1,2] or 3-acylpropionic acid [5] in refluxing toluene with azeotropic removal of water. The products obtained were isolated by flash chromatography. The isomeric compounds were easily differentiated by Nuclear Overhauser Effect (NOE) difference spectroscopy [5]. Thus, the irradiation to the NH proton for **2a**, **2b**, **5a** and **5b** resulted in an enhancement of the signal for either H-6, **2a**, **2b** or H-5 **5a**, **5b**.

Scheme 1



induced seizures and in rats against maximal electroshock-induced seizures [3,4]. However, the  $^{13}\text{C}$  nmr spectra of these compounds have not, to our knowledge, been reported and there appears to be only few reports on their  $^1\text{H}$  nmr spectra [5].

The close correspondence in the structures **I** and **II** and their various pharmacological activities led us to synthe-

These reactions were carried out in the absence of light and with a slight excess of the appropriate acid, thus improving the originally recorded yields (Table 1).

For the synthesis of compounds **3** and **6**, the 3,5-dichloro-*o*-phenylenediamine was first prepared from the 2,4-dichloro-6-nitroaniline, as described in a previous communication [8]. The products of these reactions and their physical properties are summarized in Table 1.

Table 1

	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Yield (%) (lit)	mp (°) observed	lit
<b>1</b>	H	H	H	H	58 (52, [1])	186-187	183-184 [1] 172-174 [2]
<b>2a</b>	H	Cl	H	H	46	239-240	
<b>2b</b>	H	H	Cl	H	32 (30, [1])	219-221	233-235 [1]
<b>3</b>	Cl	H	Cl	H	55	223-224	
<b>4</b>	H	H	H	H	58	104-106	100-101 [9]
<b>5a</b>	H	Cl	H	H	50 (30, [5])	152-154	144-146 [5]
<b>5b</b>	H	H	Cl	H	24 (15, [5])	127-129	94-96 [5]
<b>6</b>	Cl	H	Cl	H	66	206-208	

A previous paper [5] reported the <sup>1</sup>H nmr spectral data for compounds **4**, **5a** and **5b** in deuteriochloroform. Since the solubility of most of these compounds in chloroform was very low, the spectra were measured in DMSO-d<sub>6</sub>. However, the results of this previous study [5], with the assignment strategy, were used in our work. The <sup>1</sup>H and <sup>13</sup>C nmr chemical shifts and signal assignments of all hitherto synthesized compounds are summarized in Tables 2 and 3.

The <sup>1</sup>H and <sup>13</sup>C signal assignments of these compounds are discussed here in detail for compound **1**.

The <sup>1</sup>H nmr spectrum contains one sharp singlet at 1.70 ppm for the methyl group and a broad resonance for NH at 6.85 ppm. The assignments of the protons in the aromatic moiety of the benzimidazole ring were based on the multiplicity of their signals. Thus, the *ortho* and *meta* couplings associated with the two peaks appearing at 6.64 and 7.28 ppm clearly allowed the assignment of these two resonances to H-6 and H-9 respectively. H-6 appears upfield as a consequence of the mesomeric effect of the

Table 2

<sup>1</sup>H NMR Chemical Shifts (δ, ppm) of Compounds 1-6 in DMSO-d<sub>6</sub>

	<b>1</b>	<b>2a</b>	<b>2b</b>	<b>3</b>	<b>4</b>	<b>5a</b>	<b>5b</b>	<b>6</b>
H-1	7.75	7.78	7.77	7.80				
H-2	7.57	7.58	7.58	7.58	2.80	2.80	2.80	2.90
						2.10 - 2.40		2.30 - 2.40
H-3	7.72	7.75	7.75	7.78		2.10 - 2.40		2.30 - 2.40
H-4	7.68	7.70	7.70	7.70	6.58	6.93	6.80	7.15
H-5	6.85	7.20	7.06	7.45	6.57	6.56	6.54	
H-6	6.64	6.65	6.62		6.86		6.90	7.04
H-7	6.92		6.96	7.13	6.61	6.62		
H-8	6.70	6.71			7.15	7.10	7.10	7.08
H-9	7.28	7.24	7.25	7.24				
Me	1.70	1.71	1.71	1.75	1.38	1.40	1.39	1.44

It was noteworthy that the reactions involving the 3,5-dichloro-*o*-phenylenediamine afforded just one isomeric derivative, even after a much longer reaction period. These compounds were shown by the NOE experiments to possess either the structure **3** or **6**. These results could be attributed to the additive electron withdrawing nature of the two chlorine atoms on the basis of the previously proposed mechanism for the formation of **II** [5].

Another striking feature is the melting point (219-221°) of **2b** obtained in our work which was significantly lower than that (233-235°) reported in a patent [1]. However, all the spectroscopic data confirm structure **2b**. In contrast, the melting point (127-129°) of **5b** obtained in our work was significantly higher than that (94-96°) reported [5]. All the spectroscopic data confirm again the structure **5b**.

Assignment of Proton and Carbon Resonances.

amino group and H-9 resonates at lower field for the deshielding effect of the amidic nitrogen at position 9 of the system. On irradiation of the signal at 7.28 ppm (H-9), the two double triplets at 6.70 ppm (H-8) and 6.92 ppm (H-7) collapsed respectively into a double doublet [due to removal of <sup>3</sup>J H-8 H-9] and a triplet [due to removal of <sup>4</sup>J H-7 H-9], thus confirming their assignments.

The assignments of the isoindole-ring protons in the aromatic moiety were more difficult. One of these protons resonates at 7.57 ppm as a broadened double triplet; it was thus attributed to either H-2 or H-3. The three other protons (H-1, H-4 and either H-2 or H-3) appear in a small shift range of 0.13 ppm (7.63-7.77 ppm). Their assignments could have been easily made by the use of HMQC-TOCSY spectra [10]. However, our instrument could not perform these experiments; data derived from

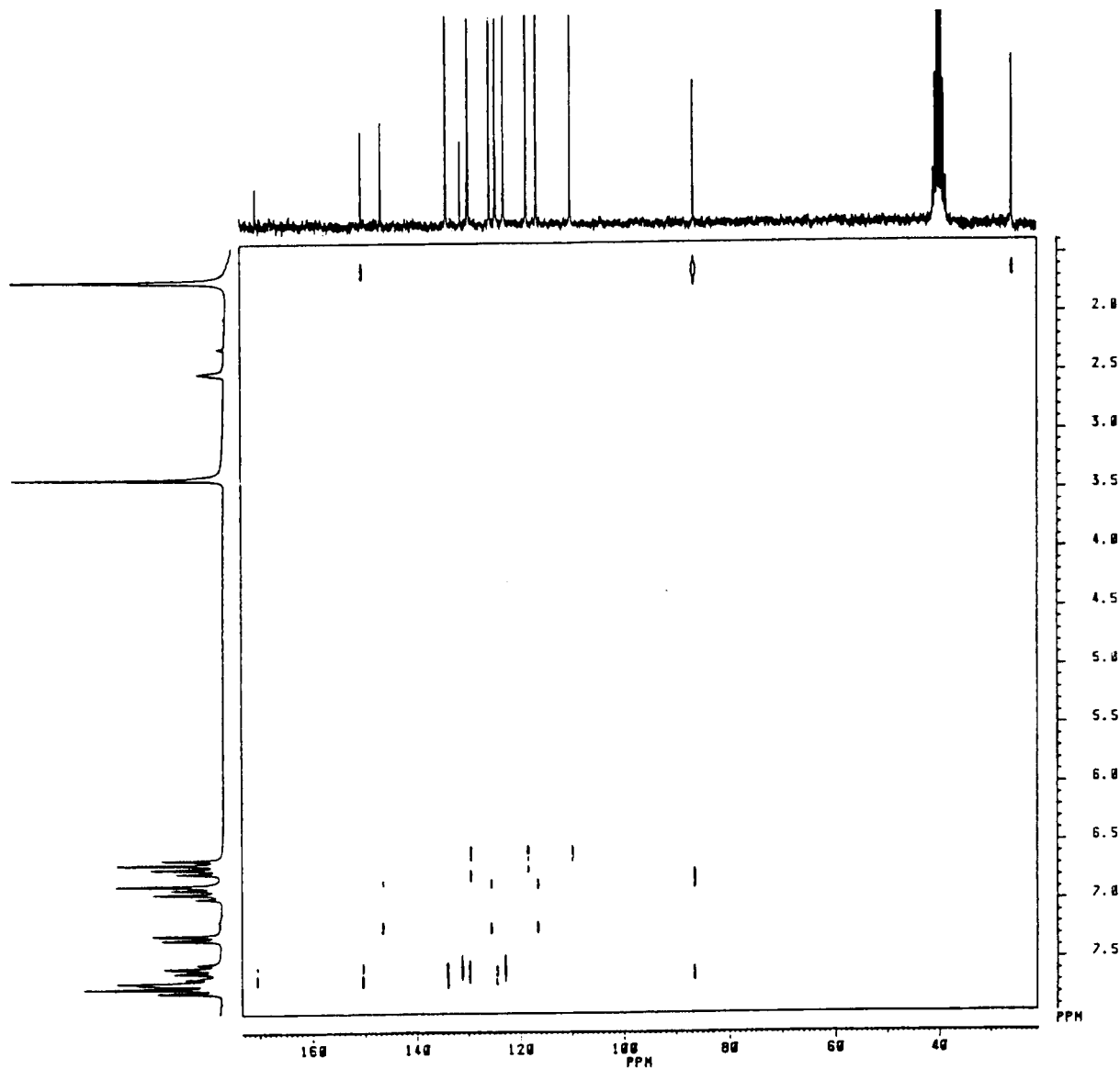


Figure 1. Two dimensional  $^{13}\text{C}$  -  $^1\text{H}$  long range correlation (COLOC) for compound 1.

$^{13}\text{C}$  signal assignments and XHCORR (discussed later) allowed these assignments to be made.

In the decoupled  $^{13}\text{C}$  spectrum, the peaks at 170.2, 86.2 and 25.5 ppm were assigned straightforward to C-11, C-4b and Me-4b, respectively, on the basis of their chemical shifts. The other values of the carbon chemical shifts did not allow unequivocal attributions.

To help the assignments, a direct (XHCORR) carbon-proton correlation experiment was obtained. It allowed correspondence to be established between the carbons and their directly bound protons. Thus, the peaks at 109.8, 125.3, 118.3 and 116.3 ppm were readily attributed respectively to C-6, C-7, C-8, and C-9. Data derived

from a 2D-COLOC experiment (Figure 1) confirmed the assignments of C-6 and C-9.

The coupled  $^{13}\text{C}$  spectrum was also informative since many carbons gave typical coupling patterns. Thus, the long range coupling interactions, especially the  $^3\text{J}(\text{CH})$  coupling constants, allowed some assignments to be made. On irradiation of the  $^1\text{H}$  signal at 6.70 ppm (H-8), the quaternary carbon signal at 129.4 ppm becomes slightly sharper due to the removal of three-bond  $^{13}\text{C}$ - $^1\text{H}$  coupling with H-8. This signal (129.4 ppm) was easily attributed to C-9a. Of course, the double doublet at 109.8 ppm (C-6) collapsed into a doublet [due to the removal of  $^3\text{J}(\text{C-6 H-8})$ ], thus confirming its assignment. In the same

way, the irradiation of the  $^1\text{H}$  signal at 7.28 ppm (H-9) allowed the assignment of C-5a at 146.3 ppm and confirmed the assignment of C-7 at 125.3 ppm.

Table 3

 $^{13}\text{C}$  NMR Chemical Shifts ( $\delta$ , ppm) of Compounds 1-6 in DMSO- $d_6$ 

	1	2a	2b	3	4	5a	5b	6
C-1	124.2	124.3	124.4	124.6	173.8	174.0	174.2	174.6
C-2	129.5	129.7	129.7	129.9	32.9	32.6	32.6	32.5
C-3	133.8	134.0	134.1	134.4	37.5	37.5	37.6	37.6
C-3a					85.3	86.0	86.1	86.4
C-4	122.6	122.7	122.7	122.9				
C-4a	150.2	150.0	150.0	149.8	144.0	145.4	142.9	140.0
C-4b	86.2	86.8	87.0	87.0				
C-5					109.3	108.7	109.8	112.7
C-5a	146.3	147.6	145.3	142.4				
C-6	109.8	109	110.3	113.0	124.9	128.7	124.3	123.7
C-7	125.3	129.5	124.9	124.3	117.7	116.7	120.6	121.0
C-8	118.3	117.5	121.3	121.6	114.2	114.8	114.0	112.8
C-8a					128.0	127.0	129.2	130.0
C-9	116.3	117	116.2	115.0				
C-9a	129.4	128.4	130.6 [b]	131.4				
C-11	170.2	170.3	170.3	170.3				
C-11a	131.0	130.6	130.4 [b]	130.0				
Me	25.5	25.6	25.6	25.6	25.3	25.4	25.4	25.7

[b] Assignments could be inverted.

The assignments of the remaining  $^1\text{H}$  and  $^{13}\text{C}$  signals required the use of a 2D-COLOC experiment (Figure 1). Thus, the quaternary carbon signal at 150.2 ppm was shown to be coupled to the methyl-protons, allowing it to be assigned to C-4a. C-4a was also coupled to the protons resonating at 7.72 and 7.75 ppm which were assigned to H-1 and H-3. The remaining quaternary carbon signal at 131 ppm could be assigned by default to C-11a. C-11a was coupled to the protons resonating at 7.57 and 7.68 ppm which were attributed to H-2 and H-4, respectively (it has already been shown that the signal at 7.57 ppm corresponds either to H-2 or H-3).

The XHCORR spectrum showed that the two protons (H-1 and H-3) corresponding to the signals at 7.72 and 7.75 ppm were directly bonded, respectively, to the carbons resonating at 133.8 and 124.2 ppm. On the basis of literature data on carbon resonances for related compounds such as indanones [11],  $\alpha$ -tetralones [12] and 1(2*H*)-isoquinolinones [13], the signals at 124.2 and 133.8 ppm were assigned to C-1 and C-3, respectively. Thus, the proton signals at 7.75 and 7.72 ppm were attributed to H-1 and H-3, respectively.

The remaining two carbon signals at 129.5 and 122.6 ppm were easily attributed to C-2 and C-4, respectively

(using the XHCORR spectrum).

The assignments of the  $^1\text{H}$  and  $^{13}\text{C}$  nmr resonances of compound 1 were thus completed. Some of its coupling constants are reported in table 4.

Table 4

Coupling Constants (in Hz) of Compound 1

$^1\text{H}$ $^1\text{H}$ coupling constants		$^{13}\text{C}$ $^1\text{H}$ coupling constants $^3J$ (C-H)	
H-1 H-2	7.1 [c]	C-1 H-3	6.7
H-2 H-3	6.9 [c]	C-2 H-4	5.9
H-6 H-7	7.8	C-3 H-1	7.5
H-7 H-8	7.6	C-4 H-2	7.7
H-8 H-9	7.7	C-6 H-8	8.7
H-6 H-8	1.0	C-7 H-9	7.5
H-7 H-9	1.2	C-8 H-6	7.2
H-2 H-4	1.5	C-9 H-7	8.9
		C-5a H-7	7.8
		C-5a H-9	7.8

[c] Constant values could be inverted.

Most of the  $^1\text{H}$  and  $^{13}\text{C}$  signals of the other compounds were similar to those in the  $^1\text{H}$  and  $^{13}\text{C}$  spectra of compound 1 and could be easily assigned on the basis of their chemical shift values. However, further experiments were required in some cases to ascertain the assignments and are here reported.

The coupled  $^{13}\text{C}$  spectrum of compound 2a allowed the assignments of the signals at 117 ppm (doublet) and 117.5 ppm (double doublet) to C-9 and C-8, respectively. The irradiation of the  $^1\text{H}$  signal at 7.24 ppm (H-9) resulted in collapse of the carbon signal at 129.5 ppm to a doublet [due to removal of  $^1J$  (CH)]. It allowed consequently the assignments of C-7 and C-2 at 129.5 and 129.7 ppm, respectively.

In the  $^1\text{H}$  nmr spectrum of compound 4, *ortho* coupling was evident between the signals at 7.15 and 6.61 ppm which were attributed to H-8 and H-7, respectively. The irradiation of the  $^1\text{H}$  signal at 7.15 ppm (H-8), in its  $^{13}\text{C}$  spectrum, revealed that the carbon signals at 114.2 and 124.9 ppm belonged to C-8 and C-6, respectively. On irradiation of the proton signal at 2.81 ppm, the triplet belonging to the carbon signal at 32.6 ppm collapsed into a doublet, thus showing this proton was bonded to this carbon. Since this irradiation also changed the signal pattern at 173.8 ppm (C-1), the proton signal at 2.81 ppm was attributed to H-2 as it was mentioned in the literature [5]. Thus, the carbon signals at 32.9 and 37.5 ppm were assigned to C-2 and C-3 respectively.

With the carbon signals assigned unambiguously for compounds 3 and 6, the proton signals at 7.13 and 7.24

ppm (3) and 7.04 and 7.08 ppm (6) were easily attributed by selective spin decoupling experiments in the  $^{13}\text{C}$  nmr spectrum.

The values of  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts obtained in our work agree with those given in literature data for related systems such as benzimidazoles [8,14,15] and those previously mentioned [11,12,13], and with the  $^1\text{H}$  nmr shift values of compounds 4, 5a and 5b obtained in deuteriochloroform [5].

Table 5

Principal Fragment Ions (intensity  $\geq 8\%$ ) in the Mass Spectra of Compounds 1, 2a, 2b, 3 and 6

	m/z (% relative intensities)
1	236 (18), 221 (100), 220 (8), 192 (22)
2a	270/272 (14), 255/257 (100), 256/258 (16), 220 (11), 192 (18)
2b	270/272 (16), 255/257 (100), 256/258 (18), 220 (8), 192 (16)
3	304/306/308 (13), 289/291/293 (100), 290/292/294 (18), 254/256 (11), 226/228 (8)
6	256/258/260 (41), 241/243/245 (88), 242/244/246 (12), 201/203/205 (100), 200/202/204 (60)

### Mass Spectroscopy

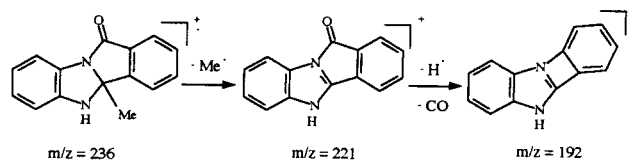
All compounds gave rise to only a few abundant fragmentations listed in Table 5. It is emphasized that the structures of the fragment ions are only assumed.

		1	2a	2b	3	4	5a	5b	6
ir (KBr)	N-H	3310	3305	3320	3300	3300	3250	3280	3280
	C=O	1695	1700	1705	1705	1690	1705	1700	1705
uv		204	205	205	204	220	225	223	228
		208	215	211	218	260	266	266	267
	$\lambda$ (nm) in EtOH	233	235	237	237	310	316	320	324
		250	248	250	250				
		300	310	312	316				

The mass spectra of the new compound 6 was similar to that reported in the literature for 5a and 5b [5], but with differences in the intensities of the various fragments. It gave, besides the molecular ion  $\text{M}^+$ , very strong ion peaks at  $m/z = 241$  and 201 which were attributed to the loss of a methyl radical and a  $(\text{HC}-\text{CH}=\text{CO})$  radical, from the molecular ion, respectively. Nevertheless, the base peak was at  $(\text{M}-55)$  and not at  $(\text{M}-15)$  (5a, 5b).

In the mass spectra of compounds 1-3, the molecular ion peak was also present, but with a lower intensity. The main fragmentation pathways for compound 1 are presented in Scheme 2. Its base peak was attributed to the loss of a methyl radical, from the molecular ion. This

Scheme 2  
Proposed pathways for the fragmentation of compound 1



reflected the stability of this fragment (strong stabilization by ring conjugation). Then, after the elimination of an hydrogen radical, a ring contraction reaction, with loss of a CO moiety, occurred. This led to the formation of a structure still stabilized by ring conjugation. Introduction of one (2a,2b) or two (3) chlorine atoms in the aromatic moiety of the benzimidazole ring caused an additional decomposition to become important. This was the formal elimination of chlorine radical from the fragment ( $\text{M}-\text{Me}$ ). Then the loss of carbon monoxide occurred.

### Ultraviolet Spectroscopy

The uv spectra (Table 6) demonstrated the bathochromic displacement of the absorption maxima of the mono and disubstituted compounds in comparison with the unsubstituted ones which has already been mentioned in other heterocyclic compounds [16]. The absorption bands of all these compounds are in agreement with those reported in the literature for related compounds [17,18].

### Infrared Spectroscopy (Table 6).

The N-H stretching absorption band of all hitherto synthesized compounds appeared in the 3250-3320  $\text{cm}^{-1}$  region. All the ir spectra showed also the characteristic band of the C=O stretching absorption in the 1690-1705  $\text{cm}^{-1}$  region.

### EXPERIMENTAL

Melting points were determined in a capillary tube using a Buchi 510 melting point apparatus and were uncorrected. The ir spectra were recorded on a Perkin Elmer spectrometer model 1310, using potassium bromide pellets. The  $^1\text{H}$  nmr

spectra were recorded at 293 K on a Bruker AC 200 instrument operating at 200 MHz using TMS as internal standard. The  $^{13}\text{C}$  nmr spectra were recorded on a Bruker AC 200 spectrometer operating at 50 MHz. For the 2D-experiments, the standard Bruker programs were used; for the COLOC spectra, an average  $J(\text{C},\text{C},\text{H})$  of 6 Hz was assumed. The digital resolutions of the  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectra were respectively 0.355 and 1.45 Hz per point. Mass spectroscopic analyses were carried out on a R-1010 C DELSI-NERMAG mass spectrometer. The uv spectra were obtained using a Perkin-Elmer 550 SE.

General Procedure for the Synthesis of 4b,5-Dihydro-4b-methyl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-ones **1-3** and 2,3,3a,4-Tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones **3-6**.

All of these reactions were carried out in the absence of light. To a stirred solution of either 2-acetylbenzoic acid or 3-acylpropionic acid (15 mmoles) in dry toluene (30 ml) was added the appropriate 1,2-phenylenediamine (12.5 mmoles). The reaction mixture was then refluxed for 6 hours using a Dean-Stark apparatus. After removal of the solvent under reduced pressure, the residue was subjected to flash chromatography on a silica gel column (3 x 45 cm), prepacked in toluene. Elution of the column with increasing amounts of ethyl acetate in toluene gave the isomeric products. Spectra data and physical properties are reported in Tables 1-6.

6,8-Dichloro-4b,5-dihydro-4b-methyl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one **3**.

This compound was obtained from 5,7-dichloro-*o*-phenylenediamine and 2-acetylbenzoic acid, as a whitish powder (ethyl acetate).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}$ : C, 59.04; H, 3.30; N, 9.18. Found: C, 58.91; H, 3.31; N, 9.23.

7-Chloro-4b,5-dihydro-4b-methyl-11*H*-isoindolo[2,1-*a*]benzimidazol-11-one **2a**.

This compound was obtained from 4-chloro-*o*-phenylenediamine and 2-acetylbenzoic acid as bright yellow needles (ethyl acetate).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{O}$ : C, 66.55; H, 4.09; N, 10.35. Found: C, 66.32; H, 4.06; N, 10.41.

5,7-Dichloro-3a-methyl-2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one **6**.

This compound was obtained from 5,7-dichloro-*o*-phenylenediamine and 3-acylpropionic acid as white needles (ethyl acetate).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}$ : C, 51.38; H, 3.92; Cl, 27.58. Found: C, 51.15; H, 3.90; Cl, 27.57.

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