SYNTHESIS AND CHARACTERIZATION OF ISOMERIC 2,3,3a,4-TETRAHYDRO-1H-PYRROLO[1,2-a]BENZIMIDAZOL-1-ONES FROM 1,2-PHENYLENEDIAMINES AND 3-ACYLPROPIONIC ACIDS

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Abstract - Synthesis and identification of isomeric 2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-ones are described. A mechanism for their formation is suggested by evaluating the effects of substituents on the phenylenediamine ring in the reaction of 1,2-phenylenediamines and 3-acylpropionic acids. The structures of obtained adducts have been assigned by means of ^{1}H nmr spectra assisted by NOE measurements.

In a previous paper[1] we have ascertained that the reaction between o-phenylenediamine and 3-benzoylpropionic acid affords a pyrrolobenzimidazolone adduct, to which the structure of 5-phenyl-3,4-dihydro-1,6-benzodiazocin-2(1H)-one had been previously attributed[2]. This compound exhibits interesting effects in mammals and on central nervous system (CNS) in particular[2].

To our knowledge very limited data concerning derivatives of the 1H-pyrrolo[1,2-a]benzimidazol-1-one system have appeared in literature[3]; in particular the presence of substituents on the phenylenediamine ring in the reaction of 1,2-phenylenediamines and 3-acylpropionic acids has not been investigated. In fact, the condensation of an unsymmetrical aromatic diamine with a γ-keto acid is inherently complicated due to the formation of possible isomeric products, whose differentiation and separation can be a difficult and time consuming task. However, the presence of electron-withdrawing groups such as chloro and nitro in the system can be important for the pharmacodynamic activities on CNS.

As part of our program on the chemistry of heteropolycyclic systems as potential pharmacological agents[4], we have extended the investigation to the reaction of variously substituted aromatic diamines with 3-acylpropionic acids, with the aim of clarifying the influence of added substituents on the reaction course. We report here the synthesis, the spectroscopic characterization and the separation of some isomeric pyrrolobenzimidazolones. The obtained derivatives have been characterized on the basis of spectroscopic data; in particular NOE measurements gave a very valuable aid in the unambiguous assignment of the structures.

RESULTS AND DISCUSSION

Syntheses were carried out by the reaction of 1,2-phenylenediamines 1 with 3-acylpropionic acids 2, as shown in Scheme 1.

The reaction of 4-chloro-1,2-phenylenediamine with 3-acylpropionic acids in boiling toluene with azeotropic removal of water afforded a yellow crude product which, after flash chromatography[5], was separated in two isomers a and b in the approximative 2:1 ratio. Similar results were obtained from 4-methyl-1,2-phenylenediamine and 3-acetylpropionic acid.

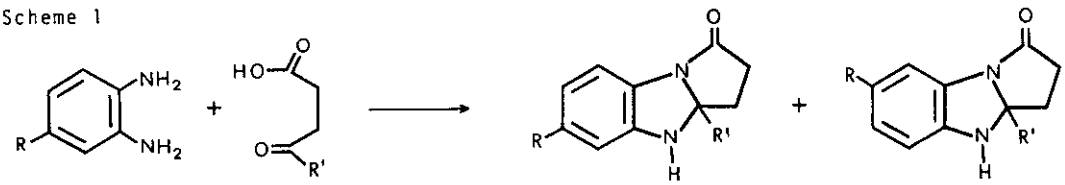
On the contrary, the reaction between 4-nitro-1,2-phenylenediamine and 3-acetylpropionic acid led to a mixture of the two isomeric adducts (8a and 8b) in the reversed ratio 1:3.

The structures of adducts were deduced from spectroscopic data (ir, ^{1}H-nmr, ms) and supported by satisfactory elemental analysis.

The ir spectra of all the synthesized compounds show the carbonyl absorption in the range of 1686-1730 cm^{-1} and the NH band in the range of 3240-3370 cm^{-1} (vide infra).

The ^{1}H-nmr parameters are reported in Table I. In particular the characterization of isomers a and b for each pair of adducts was obtained by a careful examination of the resonance pattern of the aromatic moiety.

Scheme 1



1 2 3a-8a 3b-8b

Compd	R	R'	Total Yield (%)	Rel. Ratio (%)
3a / 3b	Cl	CH_3	45	63 / 37
4a / 4b	Cl	C_6H_5	50	68 / 32
5a / 5b	Cl	4-Cl-C_6H_4	58	66 / 34
6a / 6b	Cl	4-F-C_6H_4	70	62 / 38
7a / 7b	CH_3	CH_3	75	61 / 39
8a / 8b	NO_2	CH_3	45	24 / 76

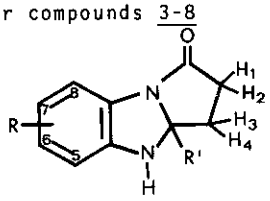
For compounds 3-7, the signals of the hydrogen atoms in ortho to the NH appeared upfield in both isomers as a consequence of the mesomeric effect of the amino group. On this basis and by consideration of the coupling pattern, the attribution of other aromatic protons was straightforward, with the 8-H resonating at lower fields for the deshielding effects of the amidic nitrogen at position 9 of the system. In compounds 8a-b, the nitro group shifts downfield the resonances of the adjacent protons: in fact the proton at C-5 in 8a appeared at 7.46δ as a doublet of doublets (J=2.0 and 0.4 Hz) while the proton at the same position in 8b resonated at 6.59δ as a doublet of doublets (J=8.5 and 0.36 Hz).

On the other hand, the application of nuclear Overhauser effect difference spectroscopy (NOEDS)[6] in combination with analysis of proton coupling constants allowed a facile determination of the structure of these 2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-ones. In fact, the irradiation to the NH proton in both isomers for all the synthesized compounds resulted in an enhancement (23%) of the signals for 5-H. These results are indicative of its close proximity to the aminic proton; the examination of related coupling pattern supported unambiguously the assigned structure.

In the ^{1}H nmr spectra of compounds 4-6 the alicyclic region was characterized by an ABCD-like spin system, while a substantial difference was observed in the case of compounds 3, 7 and 8: their spectra exhibited an ABCM system for the four hydrogen atoms. These resonance patterns were analyzed by means of LAOCN3 program[7]. For compounds 3, 7 and 8, protons H_1 and H_2 (see Table 1) can be assigned as the methylene protons next to the carbonyl group, on the basis of their smaller geminal coupling and of their having the highest value of the chemical shift. Moreover, the consequent assignment of high field resonances to protons H_3 and H_4 was consistent with the broader half-height widths of the peaks, because H_3 and H_4 have a small unresolved coupling constant with the methyl group.

In order to assign the methylene protons of 3a-aryl substituted compounds 4-6, experiments using lanthanide complex Eu(fod)$_3$ were also performed. In fact, the addition of a small quantity of the lanthanide ion induced a considerable downfield shift for the methylene protons H_1 and H_2 (upfield in undoped spectra) as a consequence of the complexation at the carbonyl group. The upfield chemical shifts of proton H_1 in compounds 4-6, compared with the analogous shifts in compounds 3a-methyl substituted (3, 7 and 8) can be explained as being due to its position into the shielding cone of the aryl substituent, while the downfield shifts of the protons H_3 and H_4 can be attributed to the deshielding effects of the same group. These attributions were confirmed by NOE measurements. In fact, the irradiation to NH gave a positive NOE for the signals corresponding to the methylene protons at C-3: these results indicated that the aminic NH is close enough to induce enhancements in their respective resonances.

Table 1 - 'H nmr spectral data for compounds 3-8

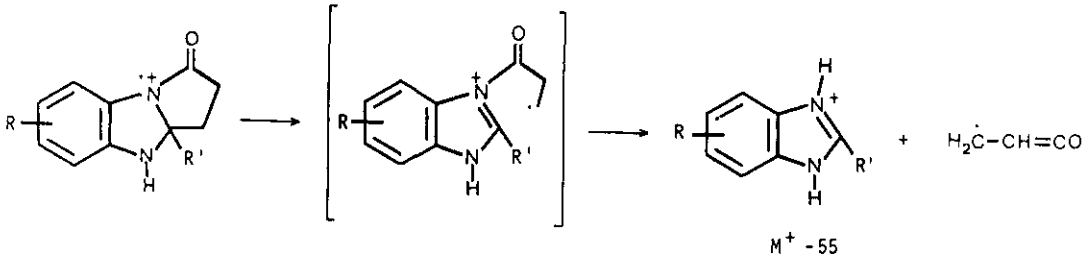


Compd.	ν_1	ν_2	ν_3	ν_4	ν_5	ν_6	ν_7	ν_8	NH	R'
3a	2.77	2.53	2.40	2.37	6.63		6.76	7.30	4.23	1.52
	$J_{1,2}$-17.0 $J_{1,3}$ 12.4 $J_{1,4}$ 8 0	$J_{2,3}$9.0 $J_{2,4}$1.2	$J_{3,4}$-13.5		$J_{5,7}$2.0 $J_{5,8}$0.4		$J_{7,8}$8.0			
3b	2.78	2.54	2.39	2.35	6.57	6.91		7.40	4.23	1.52
	$J_{1,2}$-17.0 $J_{1,3}$ 12.4 $J_{1,4}$ 8.0	$J_{2,3}$9.0 $J_{2,4}$1.2	$J_{3,4}$-13.5		$J_{5,6}$8.0 $J_{5,8}$0.4	$J_{6,8}$2.0				
4a	2.57	2.48	2.75	2.79	6.56		6.78	7.45	4.79	7.33
	$J_{1,2}$-17.0 $J_{1,3}$ 12.0 $J_{1,4}$ 8.3	$J_{2,3}$8.2 $J_{2,4}$1.3	$J_{3,4}$-13.0		$J_{5,7}$2.0 $J_{5,8}$0.4		$J_{7,8}$8.5			
4b	2.56	2.47	2.74	2.80	6.49	6.88		7.55	4.46	7.34
	$J_{1,2}$-17.0 $J_{1,3}$ 12.0 $J_{1,4}$ 8.3	$J_{2,3}$8.2 $J_{2,4}$1.3	$J_{3,4}$-13.0		$J_{5,6}$8.0 $J_{5,8}$0.4	$J_{5,8}$2.0				
5a	2.55	2.47	2.73	2.78	6.58		6.79	7.41	4.55	7.35
	$J_{1,2}$-17.0 $J_{1,3}$ 11.8 $J_{1,4}$ 8.0	$J_{2,3}$8.1 $J_{2,4}$1.2	$J_{3,4}$-13.0		$J_{5,7}$2.0 $J_{5,8}$0.4		$J_{7,8}$8.5			
5b	2.56	2.50	2.73	2.79	6 51	6.92		7.54	4.58	7.36
	$J_{1,2}$-17.0 $J_{1,3}$ 11.8 $J_{1,4}$ 8.0	$J_{2,3}$8.1 $J_{2,4}$1.2	$J_{3,4}$-13.0		$J_{5,6}$8.0 $J_{5,8}$0.4	$J_{5,8}$2.0				
6a	2.55	2.47	2.72	2.76	6 58		6.79	7.45	4.73	6.9-7.4
	$J_{1,2}$-17.1 $J_{1,3}$ 12.1 $J_{1,4}$ 8.2	$J_{2,3}$8.2 $J_{2,4}$1.3	$J_{3,4}$-13.2		$J_{5,7}$2.0 $J_{5,8}$0.4		$J_{7,8}$8.0			
6b	2.55	2.47	2.72	2.76	6.49	6.90		7.53	4.08	6.9-7.5
	$J_{1,2}$-17.1 $J_{1,3}$ 12.1 $J_{1,4}$ 8.2	$J_{2,3}$8.2 $J_{2,4}$1.3	$J_{3,4}$-13.2		$J_{5,6}$8.0 $J_{5,8}$0.4	$J_{6,8}$2.0				
7a	2.71	2.47	2.30	2.26	6.33		6.40	7.11	4.60	1.41
	$J_{1,2}$-17.0 $J_{1,3}$ 12.0 $J_{1,4}$ 8.0	$J_{2,3}$9.0 $J_{2,4}$1.2	$J_{3,4}$-13.5		$J_{5,7}$2.0 $J_{5,8}$0.4		$J_{7,8}$8.0			
7b	2.72	2.46	2.30	2.24	6.35	6.62		7.10	4.31	1.41
	$J_{1,2}$-17.0 $J_{1,3}$ 12.2 $J_{1,4}$ 8.0	$J_{2,3}$9.0 $J_{2,4}$1.2	$J_{3,4}$-13.5		$J_{5,6}$8.0 $J_{5,8}$0.4	$J_{6,8}$2.0				
8a	2.83	2.63	2.51	2.47	7.46		7.81	7.48	4.53	1.58
	$J_{1,2}$-17.0 $J_{1,3}$ 12.6 $J_{1,4}$ 8.0	$J_{2,3}$9.0 $J_{2,4}$1.3	$J_{3,4}$-13.6		$J_{5,7}$2.0 $J_{5,8}$0.4		$J_{7,8}$8.5			
8b	2.82	2.59	2.44	2.39	6.59	7 97		8.21	5.14	1.58
	$J_{1,2}$-17.0 $J_{1,3}$ 12.6 $J_{1,4}$ 8.0	$J_{2,3}$9.0 $J_{2,4}$1.3	$J_{3,4}$-13.6		$J_{5,6}$8.5 $J_{5,8}$0.36	$J_{6,8}$2.3				

In the mass spectra of all the synthesized compounds the molecular ion peak was always present. For compounds 3, 7 and 8, the base peak was at M^+-15, corresponding to the loss of the methyl group.

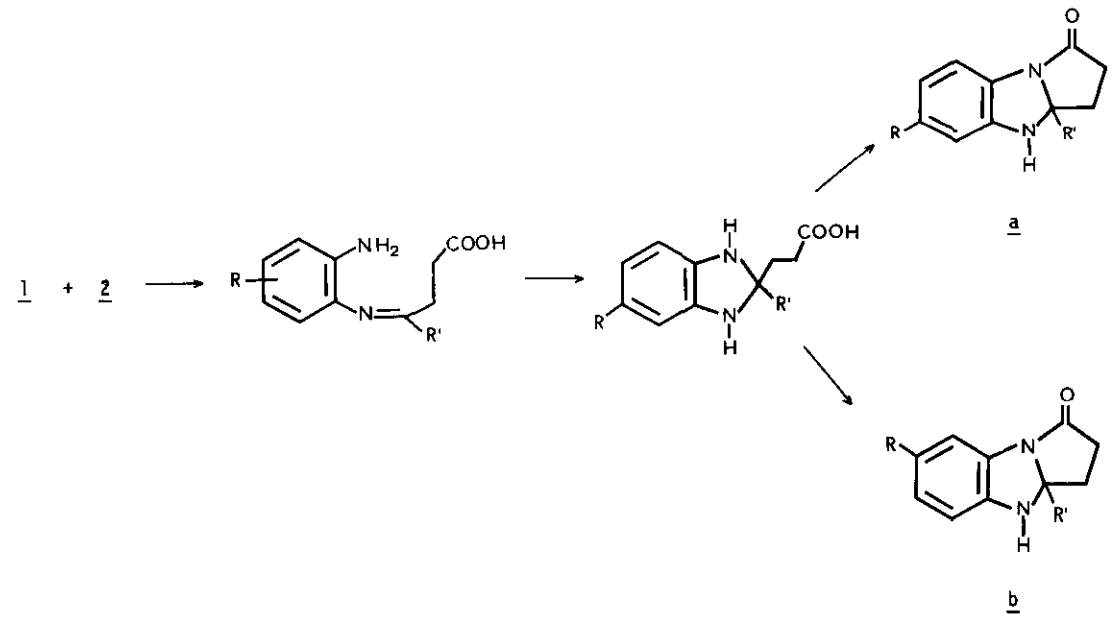
The fragmentation shown in Scheme 2 accounts for the peak at M^+-55 which is the base peak for compounds 4-6.

Scheme 2



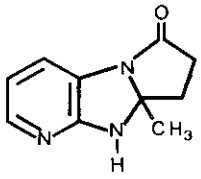
Regardless of the exact mechanism by which these adducts are formed during the condensation reaction, the assignment of the structures implies that the first step involves the condensation of the keto-carbonyl function of the γ-keto acid with the amino group of the o-phenylenediamine. In the second step, the nucleophilic attack of NH_2 to the C=N double bond leads to an intermediate benzimidazole derivative, not isolated, which undergoes successively ring closure to 2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (Scheme 3)

Scheme 3

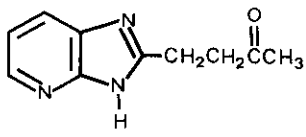


The results obtained clearly point out that the last step must be the isomer formation determining one: in fact, the presence of electron-withdrawing substituent as NO_2 populates the reaction channel which leads to isomer b as the major product, according to a reaction pathway which involves the more nucleophilic NH_2 in meta with respect to the NO_2 group. Conversely, in the same step, the chloro and the methyl as substituents increase, by mesomeric and inductive effect respectively, the nucleophilicity of NH_2 in para to the substituent so giving a major percentage of isomer a in the final mixture.

As a further support to this hypothesis, we have reacted in similar conditions the 2,3-diaminopyridine with 3-acetylpropionic acid[8]. The 2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]imidazo[4,5-b]pyridin-1-one 9 was the only isomer detected in the reaction mixture, together with a little amount of compound 10.



9



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Even if the more nucleophilic amino group at position 3 is the one favoured in the first step of the reaction, the formation of 9 is explainable only on the basis of its involvement in the second step of the reaction which, then, must control the overall process. Moreover, the minor reactivity experienced with the heterocyclic diamine agrees with this reaction pathway, with a first step controlled by the slightly nucleophilic NH_2 at position 2.

In conclusion this novel heterocyclic system has been characterized on the basis of analytical and spectroscopic data. The presence of substituents on the aromatic substrate allows the elucidation of the reaction pathway: on this basis the electronic effects have been found to influence predominantly the distribution pattern of the possible isomers.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Microanalyses were carried out on a C. Erba Elemental Analyzer mod. 1106. Analytical thin-layer chromatography was run on Merck silica gel 60 F_{254} plates. Flash chromatography was performed with thick-walled glass column on silica gel (Merck, 32-63 mμ) according to the method of Still et al[5].

Infrared spectra were recorded in hexachlorobutadiene on a Perkin-Elmer mod. 257 spectrophotometer. ^{1}H nmr spectra were obtained with Brüker WP 200 and AM 400 spectrometers in $CDCl_3$ (internal lock) with TMS as internal standard. The proton NOE measurements were performed by the FT difference method on carefully degassed $CDCl_3$ solutions of all compounds. The data were obtained by the PAPS sequence. Four FID's were acquired with the decoupler set exactly on a given resonance; four FID's with the decoupler off-resonance were then substracted. This procedure was repeated until an adequate signal to noise ratio was achieved.

General Procedure for the Synthesis of 2,3,3a,4-Tetrahydro-1H-pyrrolo[1,2-a]-benzimidazol-1-ones, 3a-8a and 3b-8b

A solution of the appropriate 1,2-phenylenediamine (1) (0.025 moles) in anhydrous toluene (40 ml) was added, under stirring at room temperature, to a solution of the 3-acylpropionic acid (2) (0.025 moles) in 20 ml of the same solvent. The reaction mixture was refluxed for 6 h 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, using as eluant CCl_4 with increasing amounts of ethyl acetate to give the isomeric products as stable adducts.

6-Chloro-3a-methyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (3a)
Mp 144-146°C (from ethyl acetate). Ir: 3262, 1704 cm^{-1}. Anal. calcd. for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.42; H, 5.18; N, 12.42. Ms m/z (%): 222 (M^+, 31), 221 (4), 207 (100), 167 (46), 166 (46), 165 (53), 126 (7).

7-Chloro-3a-methyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (3b)
Mp 94-96°C (from light petroleum). Ir: 3300, 1710 cm^{-1}. Anal. calcd. for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.47; H, 5.21; N, 12.36. Ms m/z (%): 222 (M^+, 34), 221 (8), 207 (100), 167 (56), 166 (45), 165 (53), 126 (10).

6-Chloro-3a-phenyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (4a)
Mp 179-181°C (from ethyl acetate). Ir: 3264, 1704 cm^{-1}. Anal. calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.42; H, 4.46; N, 9.88. Ms m/z (%): 284 (M^+, 36), 283 (16), 229 (100), 228 (68), 207 (98), 165 (28), 126 (13), 77 (18), 63 (19).

7-Chloro-3a-phenyl-2,3,3a,4 tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (4b)
Mp 157-159°C (from ethyl acetate). Ir: 3248, 1686 cm^{-1}. Anal. calcd. for $C_{16}H_{13}ClN_2O$: C, 67.49; H, 4.60; N, 9.84. Found: C, 67.57; H, 4.72; N, 9.93. Ms m/z (%): 284 (M^+, 35), 283 (19), 229 (100), 228 (51), 207 (74), 165 (20), 126 (12), 77 (13), 63 (14).

6-Chloro-3a-(4-chlorophenyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (5a)
Mp 176-178°C (from ethyl acetate). Ir: 3366, 1696 cm^{-1}. Anal. calcd. for $C_{16}H_{12}Cl_2N_2O$: C, 60.20; H, 3,79; N, 8,78. Found: C, 60.31; H, 3.92; N, 9.13. Ms m/z (%): 318 (M^+, 36), 317 (16), 263 (100), 262 (63), 207 (98), 192 (18), 165 (34), 126 (15), 111 (12), 75 (16), 63 (27).

7-Chloro-3a-(4-chlorophenyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (5b)
Mp 105-107°C (from light petroleum). Ir: 3250, 1692 cm^{-1}. Anal. calcd. for $C_{16}H_{12}Cl_2N_2O$: C, 60.20; H, 3.79; N, 8.78. Found: C, 60.12; H, 3.86; N, 8.91. Ms m/z (%): 318 (M^+, 31), 317 (15), 263 (100), 262 (42), 207 (76), 192 (18), 165 (30), 126 (22), 111 (15), 75 (14), 63 (21).

6-Chloro-3a-(4-fluorophenyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (6a)
Mp 160-162°C (from ethyl acetate). Ir: 3244, 1695 cm^{-1}. Anal. calcd. for $C_{16}H_{12}ClFN_2O$: C, 63.48; H, 4.00, N, 9.25. Found: C, 63.42; H, 4.15; N, 9.27. Ms m/z (%): 302 (M^+, 34), 301 (14), 247 (100), 246 (60), 207 (63), 165 (22), 126 (13), 95 (11), 75 (9).

7-Chloro-3a-(4-fluorophenyl)-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (6b)
Mp 135-138°C (from light petroleum). Ir: 3320, 3278, 1692 cm^{-1}. Anal. calcd. for $C_{16}H_{12}ClFN_2O$: C, 63.48; H, 4.00; N, 9.25. Found: C, 63.72; H, 4.21; N, 9.18. Ms m/z (%): 302 (M^+, 27), 301 (15), 247 (100), 246 (46), 207 (44), 165 (17), 126 (13), 95 (8), 75 (8), 63 (16).

3a,6-Dimethyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (7a)
Oil (from light petroleum). Ir: 3300, 1698 cm^{-1}. Anal. calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.43; H, 6.79; N, 13.67. Ms m/z (%): 202 (M^+, 35), 201 (6), 187 (100), 159 (15), 147 (34), 146 (60), 145 (77).

3a,7-Dimethyl-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (7b)
Oil (from light petroleum). Ir: 3350, 1710 cm^{-1}. Anal. calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.12; H, 6.83; N, 13.75. Ms m/z (%): 202 (M^+, 33), 201 (8), 187 (100), 159 (14), 147 (33), 146 (58), 145 (78).

3a-Methyl-6-nitro-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1-one (8a)
Mp 183-185°C (from chloroform). Ir: 3340, 1750 cm^{-1}. Anal. calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.52; H, 4.79; N, 18.25. Ms m/z (%): 233 (M^+, 35), 232 (6), 218 (100), 178 (27), 177 (27), 176 (11), 172 (41), 147 (17), 132 (29), 63 (20).

3a-Methyl-7-nitro-2,3,3a,4-tetrahydro-1H-pyrrolo[1,2-a]benzimidazol-1 one (8b)
Mp 179-181°C (from chloroform). Ir: 3260, 1710 cm^{-1}. Anal. calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.87; H, 4.55; N, 18.15. Ms m/z (%): 233 (M^+, 32), 232 (5), 218 (100), 178 (42), 177 (24), 172 (48), 147 (20), 132 (38).

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