REACTIVITY OF 6,7,8,9-TETRAHYDROPYRIDO[1,2-*a*]BENZIMIDAZOL-9-ONE : SYNTHESIS OF PYRROLOPYRIDOBENZIMIDAZOLES

Marianne DUPUY[a b], Frédéric PINGUET[b], Olivier CHAVIGNON[c], Jean-Claude TEULADE[c], Jean-Pierre CHAPAT[a], Yves BLACHE[a]*.

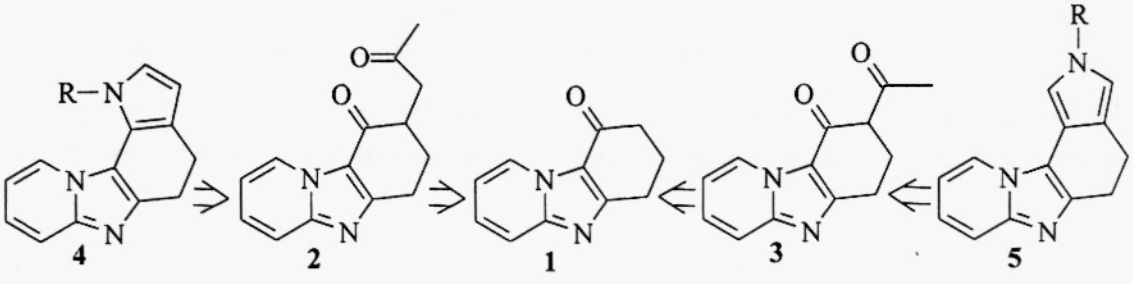
Laboratoire de Chimie Organique Pharmaceutique, E.A. 2414 Pharmacochimie et Biomolécules,[a] 15 Avenue Charles Flahault, Faculté de Pharmacie, 34060 Montpellier, Laboratoire d'oncopharmacologie, Centre Regional de Lutte contre le Cancer, [b] Val d'Aurelle, 34298 Montpellier Cedex 05, and Laboratoire de Chimie Organique Pharmaceutique, Groupe de Recherche en Pharmacochimie, UFR de Pharmacie, [c] 28 Place Henry Dunant, B.P. 38, 63001 Clermont-Ferrand, France.

Abstract : reactivity of 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-ones **1** to give the 1,4 and 1,3-dicarbonyl compounds **2** and **3** is reported Further heterocyclisation of these derivatives is investigated in view of the obtention of the tetracyclic pyrrolic frameworks **4** and **5**.

Introduction

As part of studies related to the biological activities of tri- and tetracyclic heterocycles with a bridghead nitrogen (1), we initiated a program aimed at examining the synthesis and cytotoxicity against resistant tumor cells of new tetracyclic derivatives of azacarbazoles. Since the pyrido[1,2-*a*]benzimidazole ring system has been found to exhibit anticancer properties by Badaway and co-workers (2), a number of studies have been directed toward this heterocycle. These investigations showed good activities for compounds substituted on ring A. As a first approach of modifications which should be integrated into ring C, we reported the regioselective synthesis of some pyrazolo derivatives and and their antitumor activities *in vitro* against some resistant cell lines (MDR+) (3).

In order to determine the effect of the position of nitrogen atoms on such heterocyclic compounds, we describe now our investigations concerning the reactivity of the 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one **1** system in view of the synthesis of pyrrolo derivatives **4** and **5**.

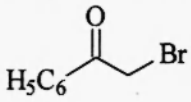
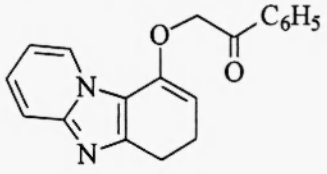
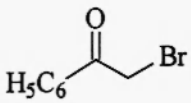
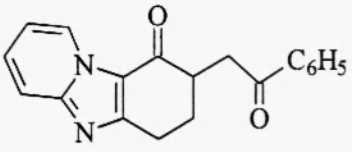
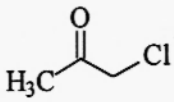
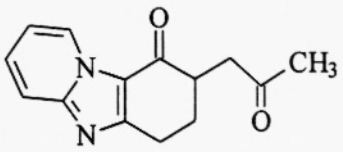
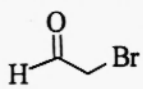


Results and discussion

In a first approach, we anticipated that the two pyrrolo derivatives **4** and **5** could be obtained from 6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one **1** respectively *via* the 1,4-dicarbonyl intermediate **2** through a Paal-Knorr reaction for **4** and *via* the 1,3-dicarbonyl intermediate **3** by using a glycinate salt for **5**.

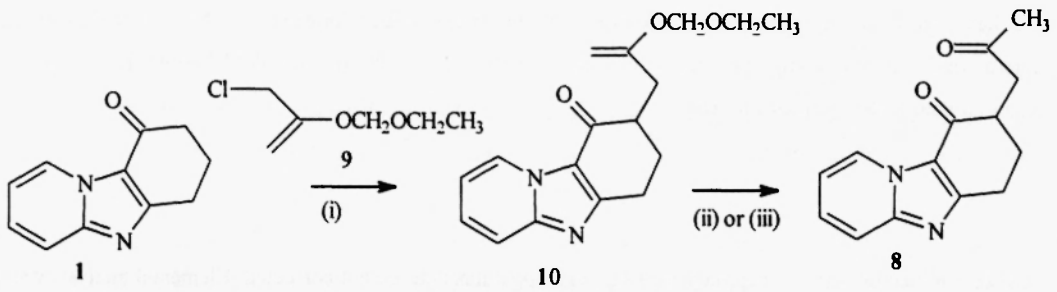
Preparation and reactivity of 1,4-dicarbonyl compounds : Compound **1** was obtained according to previous reports (4). Direct treatment of enolates salts of **1** with α-halogenoketones was investigated under various conditions. The results are summarized in table 1. Enol ether **6** was obtained by using bromoacetophenone and LiHMDS at -100°C, while the expected 1,4-dicarbonyl derivative **7** was obtained by increasing the temperature to -70°C. When the reaction was carried out at room temperature, no reaction occured with sodium hydride, while the use of LiHMDS only led to a degradation mixture. By using chloroacetone, the 1,4-dicarbonyl derivative **8** was obtained in only 5% yield while bromoacataldehyde did not react in these conditions.

Table 1 : preparation of 1,4-dicarbonyl compounds by direct alkylation of 1

α-halogenocarbonyl compounds	base/solvent	T	products/yields
	LiHMDS/THF	-100°C	 **6** (61%)
	NaH/THF LiHMDS/THF LiHMDS/THF	0°C RT -70°C	 **7** (7%) degradation **7** (57%)
	NaH/THF NaH/toluene LiHMDS/THF	RT reflux -70°C	no reaction no reaction  **8** (5%)
	LiHMDS/THF	-70°C	no reaction

A convenient synthesis of **8** was finally assumed by treatment of **1** with 2-(chloromethyl)-3,5-dioxahept-1-ene **9** (5) to give the enolether **10**, which upon aqueous acidic conditions or SiO_2/CH_2Cl_2 treatment, was hydrolysed to expected diketone **8** in 30% yield (scheme 1).

Scheme 1



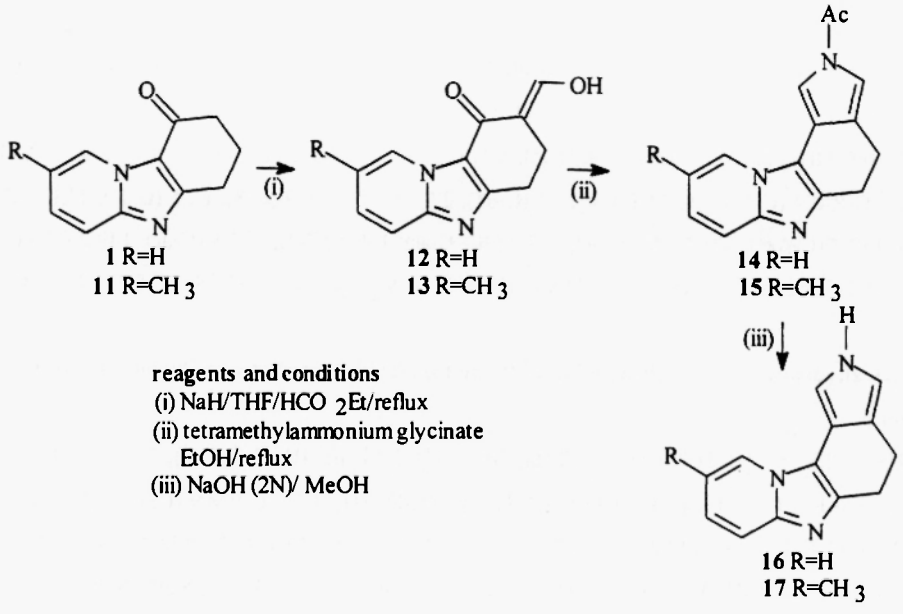
reagents and conditions (i) LiHMDS/toluene, -70°C then reflux
(ii) H_2SO_4/dioxane
(iii) SiO_2/CH_2Cl_2

Compound **7**, **8** were then submitted to a Paal-Knorr reaction under various conditions (NH_3/EtOH/100°C, $(NH_4)_2CO_3$/toluene/reflux (**6**)). However no clear results were obtained for these cyclizations exept for **7** when treated by ammoniac in ethanol at 100°C. In this case, the pyrrolo derivative was only detected as a minor product by mass spectrometry, and by ^{1}H-nmr spectra of the crude mixture.

Reactivity of 1,3-dicarbonyl compound : preparation of pyrrolo[3,4-*g*]pyrido[1,2-*a*]benzimidazoles. The 8-hydroxymethylene derivatives **12, 13** were obtained from **1, 11** according to our previous methodology (3). Subsequent treatment of **12, 13** by tetramethylammonium glycinate (7) in refluxing ethanol affored the intermediary enamines which upon treament by acetic anhydride at 150°C gave the expected N-acetylpyrroloderivatives **14, 15** in 37,5% and 41% yield respectively. Further N-deacetylation of **14, 15** was finally carried out by treatment with a 2N NaOH methanolic solution (scheme 2).

Structural determinations of compound **16, 17** were made by nmr experiment. In particular, discrimination of the signals of H-1 and H-3 was done on the basis of a selective INEPT NMR technique and ^{1}H-^{13}C two-dimensional chemical shift correlation.

Scheme 2



reagents and conditions
(i) NaH/THF/HCO_2Et/reflux
(ii) tetramethylammonium glycinate EtOH/reflux
(iii) NaOH (2N)/ MeOH

Cytotoxicity of compound **16, 17** was evaluated against HL 60 and K 562 cell lines showing lower activities than the pyrrazolo derivatives previously described (3).

In conclusion, we have reported our efforts to synthetize some pyrrolopyridobenzimidazoles. The pyrrolo[3,4-*g*]pyrido[1,2-*a*] benzimidazole derivatives were efficiently obtained while our attempts to obtain the pyrrolo[2,3-*g*]pyrido[1,2-*a*]benzimidazole derivatives by mean of a Paal-Knorr synthesis failed.

Experimental

Melting points were determined on a Büchi capillary melting point apparatus and are not corrected. Elemental analysis was perfomed by Microanalytical Center, ENSCM, Montpellier. Spectral measurements were taken using the following instruments: ^{1}H-NMR spectra were taken on Brüker AC 100 or EM 400WB; ^{13}C-NMR spectra were obtained at 26°C with proton noise decoupling at 25 MHz with a Brüker AC 100 instrument. Chemical shifts are expressed relative to residual chloroform. Mass spectra were recorded on a LKB 2091 spectrometer at 15eV [θ(source)=180°C]. Dichloromethane was dried over activated alumina and distilled from calcium hydride.

9-[(2-phenyl-2-oxo)ethoxy]-6,7-dihydrohydropyrido[1,2-*a*]benzimidazole (6) : a solution of LiHMDS (3 ml, 1M in hexane/THF) in 10 ml of anhydrous THF was cooled at –100°C. 500 mg (2.7 mmol) of compound **1** was added, and the mixture was stirred 15 min. 2-bromoacetophenone (0,53 g, 2.7 mmol) was then added, and the resulting mixture was stirred for 2 hours at –100°C and then 2 h at 0°C. After neutralisation with a saturated solution of ammonium chloride and extraction with dichloromethane, the crude product was purifiied by chromatography eluted with ethyl acetate to give 6 (61%). MS (m/z) : 304 (15), 303 (21.6), 286 (30), 273 (100), 257 (27), 245 (25). ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2.90 (m, 4H, H-6, H-7), 5.05 (s, 2H, CH_2CO), 7.03 (t, 1H, H-2, J_{1-2}= J_{1-3}= 7.0 Hz), 7.36 (m, 7H, Ph, H-3, H-8), 7.69 (d, 1H, H-4, J_{3-4}=11.0 Hz), 9.46 (d, 1H, H-1). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ: 26.9 (C-7*), 31.5 (C-6*), 62.8 (C-1'), 115.1 (C-2), 117.4 (C-4), 121.5 (C-9a), 127.0 (C-1), 128.0-129.0 (C-8, C-ar), 130.3 (C-3), 133.0 (C-ar), 147.8 (C-9*), 149.6 (C-4a*), 159.0 (C-5a), 180.5 (C-2'). Anal.Calcd.for $C_{19}H_{16}N_2O_2$; C, 74.98 ; H, 5.30 ; N, 9.20. Found C, 74.77 ; H, 5.41 ; N, 9.42.

8-(2-oxo-2-phenyl-ethyl)-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one (7) : This compound was obtained as a brown oil in 57% yield at –70°C using the procedure used for 6. MS (m/z) : 305 (47), 304 (52), 275 (79), 273 (100), 255 (22), 245 (50), 199 (21), 185 (54). ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2.0-2.8 (3H, H-8, H-1'), 3.07 (m, 4H, H_6, H_7), 6.90-7.70 (m, 8H, H-ar, H-2, H-3, H-4), 9.29 (d, 1H, H-1, J_{1-2}= 8.8 Hz). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ: 25.3 (C-6*), 27.2 (C-7*), 50.9 (C-8), 60,5 (C-1'), 115.1 (C_2), 117.4 (C_4), 121.0 (C-9a), 126.6 (C1*), 127.7 (C-Ar*), 128.5 (2C, C-ar), 128.9 (2C, C-ar), 130.3 (C-3), 138.5 (C-ar), 149.2 (C-4a), 160.8 (C-5a), 186.8 (C-2'), 194.0 (C-9). Anal.Calcd.for $C_{19}H_{16}N_2O_2$; C, 74.98 ; H, 5.30 ; N, 9.20. Found C, 75.18 ; H, 5.22 ; N, 9.40.

8-(2-oxo-propyl)-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one (8) : This compound was obtained at –70°C with chloroaceton using the procedure used for 6.

^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2.29 (s, 4H, H-8, CH_3), 2.52 (m, 2H, H-1'), 3.14 (m, 4H, H-6, H-7), 7.03 (t, 1H, H_2, J_{1-2}= J_{2-3}= 6.0 Hz), 7.48 (dt, 1H, H-3, J_{3-4}= 6.0 Hz, J_{1-3} = 1.2 Hz), 7.68 (d, 1H, H_4), 9.24 (dd, 1H, H_1). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ: 25.2 (C-7), 29.6 (C-6), 30.1 (CH_3), 43.2 (2C, C-1', C-8), 114.4 (C-2), 116.8 (C-4), 128.1 (C-1), 129.4 (C-3), 148.2 (C-4a), 160.0 (C-5a), 188.7 (C-9), 206.9 (C-2'). Anal.Calcd.for $C_{14}H_{14}N_2O_2$; C, 69.41 ; H, 5.82 ; N, 11.56. Found C, 69.45 ; H, 5.29 ; N, 9.30.

8-[2-(2-ethoxymethoxy)allyl]-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one (10) : A solution of **1** (0.6 g, 3.2 mmol), NaH (60% dispersion in oil, 140 mg, 3.5 mmol) in 5 ml of xylene was stirred at 40°C for 3 hours. Compound 9 (0.52 g, 3.5 mmol) was then added, and the resulting mixture was heated at reflux for 1 hour. After cooling, methanol was added, and the mixture washed with water. After extraction with dichloromethane and evaporation of solvents, the residual oil was chromatographed on silica gel eluted with dichloromethane to give **10** in 30% yieldas a brown oil. ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 1.02 (t, J = 9.0 Hz, 3H, CH_3), 1.90-2.20 (m, 2H), 2.40-2.90 (m, 4H), 3.00-3.50 (m, 3H), 3.98 (s, 2H, O-CH_2-O), 4.93 (s,2H, H-3'), 7.17 (t, 1H, J_{1-2}= J_{2-3}=7.0 Hz, H-2), 7.59 (t, 1H, J_{3-4}= 7.0 Hz, H-3), 7.81 (d, 1H, H-4), 9.46 (d, 1H, H-1). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ: 15.1 (CH_3), 28.5 (C-7), 30.5 (C-6), 44.5 (C-8), 48.5 (C-1'), 65.1 (O-CH_2CH_3), 88.0 (C-3'), 92.5 (O-CH_2-O), 115.0 (C-2), 117.5 (C-4), 119.0 (C-9a), 128.4 (C-1), 129.5 (C-3), 148.0 (C-4a), 157.5 (-C=CH_2), 158.5 (C-5a), 190.6 (C-9).

2-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one (11) : This compound was obtained in 61% yield according to the procedure previously published (4). Mp 93-95°C. ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2.19 (t, 2H, J_{6-7}= J_{7-8}= 6.0 Hz, H_7), 2.34 (s, 3H, CH_3), 2.6 (t, 2H, H_8), 2.98 (t, 2H, H_6), 7.25 (d, 1H, H_3, J_{3-4}= 9Hz), 7.48 (d, 1H, H_4), 8.97 (s, 1H, H_1). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ: 17.7 (CH_3), 23.4 (C_6), 25.1 (C_7), 37.9 (C_8), 115.5 (C_4), 118.8 (C_{9a}), 123.9 (C_2), 125.8 (C_1), 131.7 (C_3), 146.3 (C_{4a}), 159.6 (C_{5a}), 187.5 (CO).

8-hydroxymethylene-2-methyl-6,7,8,9-tetrahydropyrido[1,2-*a*]benzimidazol-9-one (13) : This compound was obtained in 65% yield according to the procedure previously published (3). Mp 208-210°C. MS (m/z) : 229 (33); 228 (56); 200 (51); 199 (90). ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2.42 (s, CH_3), 2.69 (t, 2H, J_{6-7}= 7.0Hz, H_7), 3.03 (t, 2H, H_6), 7.27 (s, CHOH), 7.30-7.45 (m, 2H, H-3, H-2), 7.58 (d, 1H, J_{3-4} = 8.5 Hz, H-4), 9.03 (s, 1H, $J_{1,2}$ = 5.4 Hz, H-1), 10.03 (s, CHO), 13.17 (s, OH). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ_{CH}: 18.4 (CH_3); 24.9 (C-6); 25.2 (C-7); 116.5 (C-4); 126.6 (C-1); 132.6 (C-3)

2-acetyl-4,5-dihydropyrrolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole (14) : a solution of 15 (0.5 g, 2.34 mmol), tetramethylammonium glycinate (6) (0.4 g, 2.7 mmol) in 8 ml of EtOH is refluxed under a nitrogen atmosphere for 2 hours. After evaporation of solvents, 6.2 ml of acetic anhydride was added, and the mixture stirred for 2 hours at 150°C. after evaporation of solvents, water was added, and the mixture extracted with dichloromethane, evaporated under vacuo, and chromatographed on silica gel eluted with dichloromethane to give **14** with 37.5% yield. Mp 138-140°C. MS (m/z) 251 (24); 209 (40); 49 (100). ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2,55 (s, 3H, CH_3), 3.05 (m, 4H, H_4, H_5), 6.91 (dt, 1H, J_{9-10}= J_{9-8}= 6.8 Hz, J_{9-7}= 1.1 Hz, H_9), 7.09-7.30 (m, 2H), 7.49 (s, 1H, H-1 or H-3), 7.62 (d, 1H, H-7), 8.06 (d, 1H, H_{10}). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ_{CH}: 20.8 (C-4), 22.3 (CH3), 24.3 (C-5), 107.7 (C-1), 112.9 (C-9), 115.9 (C-3), 117.3 (C-7), 123.7(C-8*), 124.1 (C-10*). Anal.Calcd.for $C_{15}H_{13}N_3O$; C, 71.70 ; H, 5.21 ; N, 16.72. Found C, 71.59 ; H, 5.32 ; N, 16.61.

2*H*-2-acetyl-9-methyl-4,5-dihydropyrrolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole 15 : this compound was prepared with 41% yield according the method given for **17**. Mp 109-111°C. MS (m/z) : 265 (97); 223 (100); 222 (84); 195 (15). ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2.40 (CH_3), 2.56 (C_2), 3.00 (m, 4H, H_4, H_5), 7.03 (d, 1H, H_8, J_{7-8}= 9.0 Hz), 7.08 (s, 1H, H_1), 7.51 (d, 1H, H_7), 7.84 (s, 1H, H_3), 9.18 (s, 1H, H_{10}). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ_{CH}: 18.3 (CH_3) 20.9 (C-4), 22.3 (CH3), 24.3 (C-5), 107.4 (C-1), 115.8 (C-3*), 116.6 (C-7*), 121.9 (C-8), 126.7 (C-10). Anal.Calcd.for $C_{16}H_{15}N_3O$; C, 72.43 ; H, 5.70 ; N, 15.84. Found C, 72.34 ; H, 5.56 ; N, 16.01.

2*H*-4,5-dihydropyrrolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole 16. A solution of **14** (260 mg, 1.2 mmol), NaOH (4.7 ml of a 2N solution) in 21 ml of MeOH was stirred for 20 min and then diluted in water. After extraction with dichloromethane and evaporation, the crude product was chromatographed on silica gel eluted with dichloromethane to give **16** with 60% yield. Mp 197-199°C. MS (m/z) : 209 (100), 208 (61), 181 (11), 104 (11). ^{1}H-RMN ($CDCl_3$, 400 MHz) δ: 3.03 (t, 2H, J_{4-5}= 7.2 Hz, H-4), 3.19 (t, 2H, H-5), 6.77 (s, 1H, H-3), 6.93 (t, 1H, J_{9-10}= J_{9-8}= 8.0 Hz, H-9), 7.06 (s, 1H, H-1), 7.17 (t, 1H, J_{7-8}= 8.0 Hz, H-8), 7,66 (d, 1H, H-7), 8.08 (d, 1H, H-10), 8,49 (s, NH). ^{13}C-RMN ($CDCl_3$, 100 MHz) δ: 21.2 (C-4), 24.8 (C-5), 108.4 (C-1), 112.5 (C-9), 112.8 (C-11b), 114.8 (C-3), 117.1 (C-7), 117.7 (C-11a), 118.8 (C-3a), 122.3 (C-8), 123.5 (C-10), 142.3 (C-5a), 143.9 (C-4a). Anal.Calcd.for $C_{13}H_{13}N_3$; C, 74.62 ; H, 5.30 ; N, 20.08. Found C, 74.54 ; H, 5.28 ; N, 20.18.

2*H*-9-methyl-4,5-dihydropyrrolo[4,5-*g*]pyrido[1,2-*a*]benzimidazole 17 : this compound was prepared with 67% yield according the method given for **16**. Mp 137-139°C. MS (m/z) ; 224 (18), 223 (100), 222 (64), 207 (14), 208 (12). ^{1}H-RMN ($CDCl_3$, 100 MHz) δ: 2.36 (CH_3), 3.01 (m, 4H, H_4, H_5), 6.70 (s, 1H, H-3), 6.94 (d, 1H, J_{7-8} = 9.0 Hz, H-8), 6.99 (s, 1H, H-1), 7.48 (d, 1H, H-7, J_{7-8}= 9.0 Hz), 7.79 (s, 1H, H_{10}), 9.16 (s, NH). ^{13}C-RMN ($CDCl_3$, 25 MHz) δ: 18.3 (CH_3); 21.2 (C-4), 24.8 (C-5), 108.3 (C-1), 110.0 (C-11b*), 112.6 (C-9*), 114.6 (C-3), 116,1 (C-7), 118.5 (C-11a*), 121.3 (C-8), 121.9 (C-3a*), 125.1 (C-10), 142.1 (C-5a*), 144.0 (C-6a*). Anal.Calcd.for $C_{14}H_{13}N_3$; C, 75.31 ; H, 5.87 ; N, 18.82. Found C, 75.33 ; H, 5.65 ; N, 19.02.

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