FUSED IMIDAZOACRIDINES: SYNTHESIS OF NEW SUBSTITUTED IMIDAZO[4,5-*b*] AND IMIDAZO[4,5-*a*] ACRIDINEDIONE DERIVATIVES

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Abstract : The synthesis of new imidazo[4,5-*b*]acridin-2,11-dione **5** and imidazo[4,5-*a*]acridin-2,10-dione **6** derivatives is reported. Yields and structures of each isomer were determined by NMR spectroscopy.

In a previous review[1], we have collected the publications and patents dealing with the synthesis and biological properties of tetracyclic acridines. Pyrazoloacridines[2,3] and imidazoacridines[4,5] have shown interesting antitumor activities. Therefore, according to our experience in the synthesis of thiazolo and pyrazoloacridines derivatives[6-9], we decided to prepare a new class of acridinic tetracycles pharmacophores bearing an imidazole ring fused to the acridine moiety.

In the literature only one example of imidazoacridine is reported[10], obtained by the reaction of 2,3-diamino-9-acridinone with cyanogen bromide in dichloromethane. We propose here to use another synthetic pathway, (see scheme 1), based on the copper catalysed *N*-arylation of the commercially available 5-amino-1,3-dihydro-2*H*-benzimidazol-2-one **1** with potassium *o*-chlorobenzoate (Ullmann reaction); followed by cyclization with polyphosphoric acid (PPA), sulfuric acid (H_2SO_4), or phosphorus oxychloride ($POCl_3$).

These cyclizations could led to a mixture of two isomers, e.g. 1,3-dihydroimidazo[4,5-*b*]acridin-2,10-dione **3** and 1,3-dihydro-imidazo[4,5-*a*]-acridin-2,11-dione **4** which were separated by column chromatography.

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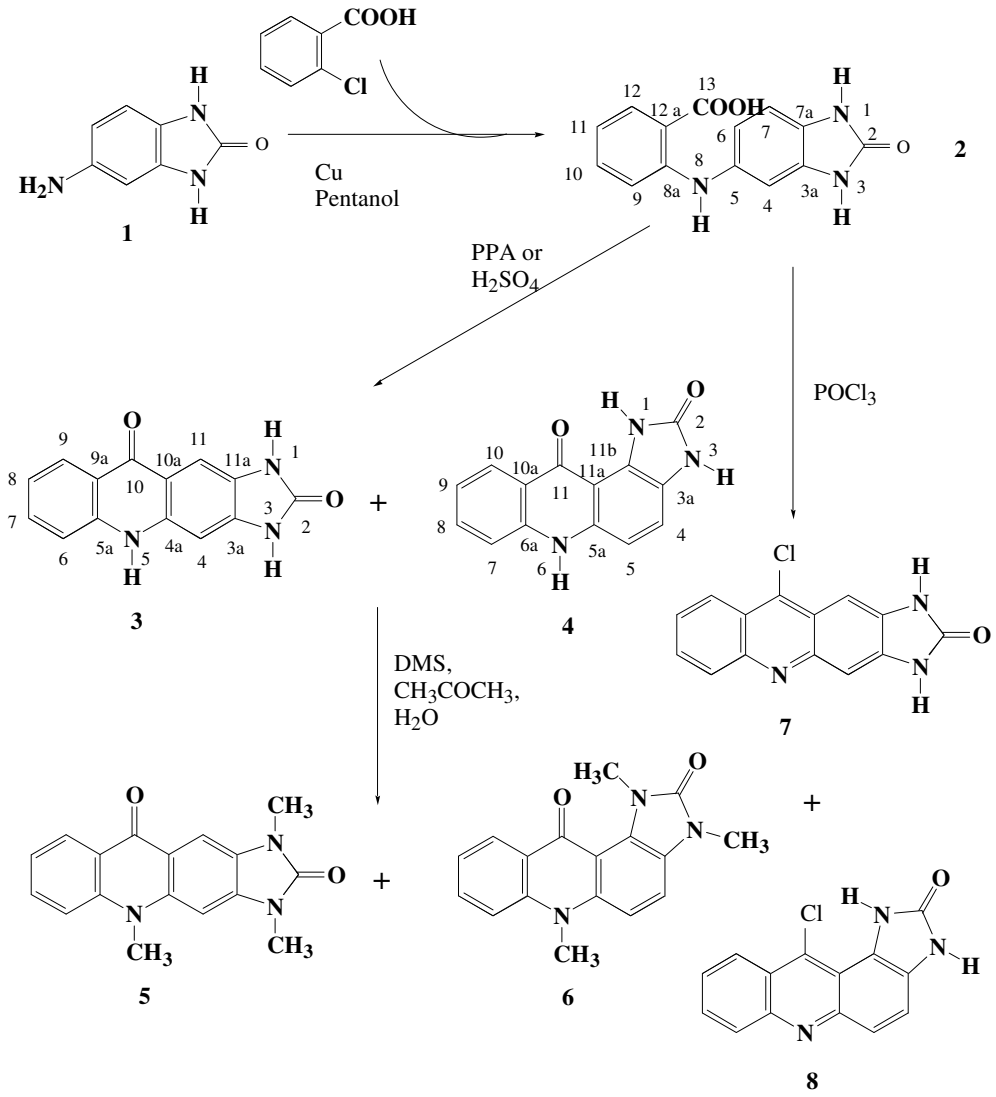
Starting from compound **1** we obtained, after treatment with potassium *o*-chlorobenzoate in the presence of copper and 1-pentanol, the 5-(2´-carboxyphenylamino)-1,3-dihydro-2*H*-benzimidazol-2-one **2**, (scheme 1), Cyclization of this compound with either PPA or H_2SO_4 led to a mixture of the two "linear" and "bent" isomers **3** and **4** with 24 % and 31 % yields respectively after purification. Moreover, use of $POCl_3$ to cyclize **2** afforded also a mixture of two chloroacridine derivatives **7** and **8** with 10 % and 20 % yields. Thus, the use of $POCl_3$ modify the orientation of the reaction in favour of the bent derivative **8**.



In table 1 are given the yields of each isomers of the crude mixtures determined by ^{1}H-NMR spectroscopy, and the ^{1}H chemical shifts of the pure products.

Then, methylation of the crude mixture of **3** and **4** with dimethylsulfate in the presence of aqueous potassium hydroxide and acetone led to the corresponding trimethyl acridinones **5** and **6** which were separated by crystallisation in ethanol.
Structure of compounds (**3**-**8**) was unambiguously established by ^{1}H-NMR spectroscopy; in particular the "linear" structure of compounds **3**, **5** and **7** was in agreement with the presence of two singlets due to H-4 and H-11 protons (for example 6.78 and 7.98 ppm for compound **5**); while the "bent" structure of compounds **4**, **6** and **8** was deduced from the appearance of two clean doublets characteristics from an AB system assigned to H-4 and H-5 (for example 7.29 and 7. 17 ppm for **6**).
In conclusion we reported the synthesis of new tetracyclic imidazo acridinediones derivatives using Ullmann reaction. Two regioisomers of cyclization were obtained.

EXPERIMENTAL

All melting points were determined with a Mettler FP 61 apparatus and are uncorrected. The ^{1}H and ^{13}C spectra were recorded in DMSO-d$_6$ on a BRUKER AC 200 spectrometer. Chemical shifts were reported in ppm relative to TMS as the internal standard. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel. Separations were performed on silica gel (Merck, 70-230 mesh). 5-Amino-1,3-dihydro-2*H*-benzimidazol-2-one **1** was purchased from Janssen.

5-(2'-Carboxyphenylamino)-1,3-dihydro-2*H*-benzimidazol-2-one (2) A mixture of 5-amino-1,3-dihydro-2*H*-benzimidazol-2-one (**1**) (1 g, 6.7 mmol), potassium *o*-chlorobenzoate (2 g, 10 mmol), powdered copper (0.1 g, 1.6 mmol) and 1-pentanol (30 ml) was heated at 130°C with stirring for 12 hours. The warmed mixture was filtered and the solvent was removed under reduced pressure. Next, ethyl acetate (30 ml) was added to the residue and the mixture was extracted three times with 100 ml of sodium hydroxide (0.1N). The alkaline layer was acidified (pH = 6) with concentrated hydrochloric acid to give 0.68 g (38%) of a greenish powder, mp 252°C (acetone).
^{1}H NMR : δ 10.58 (s, 3 H, NH-1; NH-3; NH-8); 7.84 (d, 1H, H-13); 7.29 (ddd, 1H, H-11); 6.96 (d, 1H, H-10); 6.90 (d, 1H, H-7); 6.80 (d,1H, H-4); 6.79 (dd, 1H,

H-6); 6.66 (ddd, 1H, H-12).
^{13}C NMR : δ 104.39 (C-4); 108.98 (C-7); 111.97 (C-12a); 112.96 (C-6); 116.13 (C-9); 116.21 (C-11); 126.54 (C-7a); 130.51 (C-3a); 131.69 (C-12); 133.55 (C-5); 133.76 (C-10); 148.79 (C-8a); 155.45 (C-2); 170.07 (C-13)
Anal. Calcd for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.09; N, 15.61. Found: C, 62.30; H, 4.12; N, 15.43.

1,3-Dihydro-5*H*-imidazo[4,5-*b*]acridin-2,10-dione (3) and 1,3-dihydro-6*H*-imidazo[4,5-*a*]acridin-2,11-dione (4)

Polyphosphoric acid procedure : To well stirred PPA (3 g, 21 mmol), heated to 90°C, was added 5-(2'-carboxyphenylamino)-1,3-dihydro-2*H*-benzimidazol-2-one **2** (0.3 g, 1.11 mmol); the mixture was stirred at 110°C during 2 hours and poured onto ice (5 g). The solid precipitated was filtered, washed with a saturated solution of sodium hydrogen carbonate and dried. 0.22 g of crude **3** and **4** was obtained (79% yield).

Sulfuric acid procedure : A mixture of **2** (0.3 g, 1.1 mmol), and 3 ml of sulfuric acid (95%, 56 mmol) was heated at 100°C with vigorous stirring during 2 hours. Then, ice (5 g) was added carefully into the flask. The resulting solution was neutralized with cold dilute aqueous ammonia (32 %). The precipitate was filtered, washed with water and dried. 0.17 g of crude **3** and **4** was obtained (59% yield).

The crude mixture was purified by chromatography on silica gel, eluting with a gradient of chloroform/ethanol (1/0 to 1/1). Compound **4** was obtained from the first fraction and compound **3** from the second fraction.

1,3-Dihydro-5*H*-imidazo[4,5-*b*]acridin-2,10-dione (**3**). Yield 66 mg (24 %), as a yellow powder. mp > 300°C.
Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.58; N, 16.73. Found: C, 66.65; H, 3.59; N, 16.57.
^{13}C-NMR δ : 94.58 (C-4), 102.76 (C-11), 115.35 (C-10a), 116.78 (C-6), 119.37 (C-9a), 120.03 (C-8), 125.68 (C-9), 126.58 (C-11a), 132.23 (C-7), 136.06 (C-3a), 137.07 (C-4a), 140.40 (C-5a), 155.81 (C-2), 175.71 (C-10).

1,3-Dihydro-6*H*-imidazo[4,5-*a*]acridin-2,11-dione (**4**). Yield 91 mg (31 %), as yellow crystals. mp > 300°C.
Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.58; N, 16.73. Found: C, 66.68; H,

3.62; N, 16.54.

^{13}C-NMR δ: 106.68 (C-11a), 108.14 (C-5), 115.62 (C-4), 117.22 (C-7), 119.80 (C-10a), 120.39 (C-9), 122.26 (C-3a), 125.46 (C-10), 126.86 (C-11b), 133.21 (C-8), 136.26 (C-5a), 140.88 (C-6a), 155.03 (C-2), 177.09 (C-11).

1,3,5-Trimethylimidazo[4,5-*b*]acridin-2,10-dione (5) and 1,3,6-trimethylimidazo[4,5-*a*]acridin-2,11-dione (6)

A mixture of **3** and **4** (0.7 g, 2.79 mmol), water (10 ml), KOH (0.9 g, 16 mmol), acetone (40 ml) was stirred at room temperature during 1 hour. Then, a solution of dimethylsulfate (2.4 ml, 25.2 mmol) and acetone (10 ml) was added dropwise. After 16 hours at 80°C with stirring, the reaction mixture was cooled, filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in water (400 ml) and extracted with chloroform (2x100 ml). The organic layers were dried over anhydrous sodium sulphate and evaporated in vacuo to give 0.49 g of a mixture of **5** and **6**, (60% yield).

Crystallization of this mixture from ethanol (15 ml) yielded the bent isomer **6** after 1 hour of cooling, whereas the linear **5** was obtained after two days in the same conditions.

1,3,5-Trimethylimidazo[4,5-*b*]acridin-2,10-dione (**5**). Yield 228 mg (28%), as a yellow powder. mp > 300°C.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12; N, 14.33. Found: C, 69.48; H, 5.30; N, 14.58.

^{13}C-NMR δ: 27.58 (N1-CH_3 and N3-CH_3), 34.39 (N5-CH_3), 92.26 (C-4), 104.45 (C-11), 114.59 (C-6), 117.73 (C-10a), 121.12 (C-8), 121.81 (C-9a), 126.44 (C-11a), 127.71 (C-9), 133.28 (C-7), 136.20 (C-3a), 139.82 (C-4a), 142.13 (C-5a), 155.19 (C-2), 177.25 (C-10).

1,3,5-Trimethylimidazo[4,5-*a*]acridin-2,11-dione (**6**). Yield 212 mg (26%), as a yellow crystals. mp > 300°C.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12; N, 14.33. Found: C, 69.82; H, 5.24; N, 14.08.

^{13}C-NMR δ: 27.48 (N1-CH_3), 34.75 (N6-CH_3), 35.19 (N3-CH_3), 107.13 (C-5), 110.23 (C-11a), 113.01 (C-4), 114.54 (C-7), 120.92 (C-9), 123.31 (C-10a), 125.06 (C-3a), 127.36 (C-10), 129.27 (C-11b), 133.51 (C-8), 139.74 (C-5a), 142.21 (C-6a), 156.26 (C-2), 177.50 (C-11).

10-Chloro-1,3-dihydroimidazo[4,5-*b*]acridin-2-one (7) and 11-chloro-1,3-dihydroimidazo[4,5-*a*]acridin-2-one (8)

A mixture of 5-(2'-carboxyphenyl-amino)-1,3-dihydro-2*H*-benzimidazol-2-one **2** (0.5 g, 1.85 mmol) and $POCl_3$ (5 ml, 54.6 mmol) was heated at 120°C during 30 min. After cooling the excess of $POCl_3$ was extracted with petroleum ether (20 ml). The sticky residue was neutralized with aqueous ammonia (10 %, **X** mL). The filtered green precipitate was washed with water and dried. 0.25 g of crude product was obtained (72% yield).

The crude mixture was purified by chromatography, eluting with CH_2Cl_2/ethanol (95/5), to yield two separated fractions. Compound **8** was obtained from the first fraction and compound **7** from the second fraction.

10-Chloro-1,3-dihydroimidazo[4,5-*b*]acridin- 2-one (**7**). Yield 99 mg (20%). as a yellow powder. mp > 300°C.

Anal. Calcd. for $C_{14}H_8ClN_3O$: C, 62.34; H, 2.97; N, 15.58. Found: C, 62.20; H, 3.19; N, 15.73.

^{13}C-NMR δ : 97.66 (C-11), 103.46 (C-4), 120.76 (C-10a), 122.09 (C-9a), 123.57 (C-9), 126.26 (C-8), 128.84 (C-6), 129.41 (C-7), 134.00 (C-11a), 136.78 (C-10), 136.88 (C-3a), 146.43 (C-5a), 146.46 (C-4a), 156.08 (C-2).

11-Chloro-1,3-dihydroimidazo[4,5-*a*]acridin-2-one (**8**). Yield 50 mg (10%). as a yellow powder. mp > 300°C.

Anal. Calcd. for $C_{14}H_8ClN_3O$: C, 62.34; H, 2.97; N, 15.58. Found: C, 62.48; H, 2.76; N, 15.50.

^{13}C-NMR δ : 113.11 (C-4), 117.35 (C-5), 119.03 (C-10a), 123.26 (C-10), 125.83 (C-9), 128.81 (C-7), 127.52 (C-11b), 129.74 (C-8), 134.36 (C-3a), 136.85 (C-11), 145.41 (C-5a), 145.97 (C-6a), 154.80 (C-2).

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Table 1: ^{1}H-NMR chemical shifts (ppm) and isomeric ratios (DMSO-d$_6$).

Compound	Molecular formula	Relative amounts*	^{1}H-NMR after purification
3	$C_{14}H_9N_3O_2$	30%	11.97 (s, 1H, NH-5); 11.01 (s, 1H, NH-1); 10.79 (s, 1H, NH-3); 8.18 (dd, 1H, H-9); 7.64 (ddd, 1H, H-7); 7.64 (s, 1H, H-11); 7.46 (dd, 1H, H-6); 7.16 (ddd, 1H, H-8); 7.02 (s, 1H, H-4)
4	$C_{14}H_9N_3O_2$	70%	11.67 (s, 1H, NH-5); 10.85 (s, 1H, NH-1); 10.72 (s, 1H, NH-3); 8.19 (dd, 1H, H-10); 7.69 (ddd, 1H, H-8); 7.50 (dd, 1H, H-7); 7.40 (d, 1H, H-4); 7.21 (ddd, 1H, H-9); 7.13 (d, 1H, H-5)
5	$C_{17}H_{15}N_3O_2$	50%	8.51 (dd, 1H, H-9); 7.98 (s, 1H, H-11); 7.65 (ddd, 1H, H-7); 7.42 (dd, 1H, H-6); 7.24 (ddd, 1H, H-8); 6.78 (s,1H, H-4); 3.83 (s, 3H, N_5-CH_3); 3.44 (s, 6H, N_1 and N_3-CH_3)
6	$C_{17}H_{15}N_3O_2$	50%	8.40 (dd, 1H, H-10); 7.67 (ddd, 1H, H-8); 7.43 (dd, 1H, H-7); 7.29 (d, 1H, H-4); 7.24 (ddd, 1H, H-9); 7.17 (d, 1H, H-5); 3.87 (s, 3H, N_1-CH_3); 3.83 (s, 3H, N_6-CH_3); 3.45 (s, 3H, N_3-CH_3)
7	$C_{14}H_8ClN_3O$	70%	11.40 (s, 2H, N_1 and N_3-H); 8.30 (dd, 1H, H-9); 8.09 (dd, 1H, H-6); 7.80 (ddd, 1H, H-7); 7.65 (s, 1H, H-11); 7.65 (ddd, 1H, H-8); 7.50 (s, 1H, H-4)
8	$C_{14}H_8ClN_3O$	30%	11.40 (s, 1H, N_1-H); 11.30 (s, 1H, N_3-H); 8.35 (dd, 1H, H-10); 8.13 (dd, 1H, H-7); 7.91 (d, 1H, H-4); 7.80 (ddd, 1H, H-8); 7.68 (d, 1H, H-5); 7.65 (ddd, 1H, H-9)

* Estimated by NMR on the crude product of the reaction.