Fused Imidazoacridines: Synthesis of 1,3-Dihydroimidazo[4,5-*b*]acridin-2-one and 1,3-Dihydroimidazo[4,5-*a*]acridin-2-one

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The synthesis of new 1,3-dihydroimidazo[4,5-*a*]acridin-2-one and 1,3-dihydroimidazo[4,5-*b*]acridin-2-one derivatives is reported. The yield and the structure of each isomer were determined by nmr spectroscopy.

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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] showed interesting antitumor activity. For that reason we decided to undertake the synthesis of 1,3-dihydroimidazo[4,5-*a*]acridin-2-one **3** and 1,3-dihydroimidazo[4,5-*b*]acridin-2-one **4**, which could be interesting pharmacophores for new antitumor compounds.

Based on our experience in the synthesis of thiazoloacridines [6,7] and pyrazoloacridine derivatives [8,9], we decided to prepare another class of tetracyclic acridine compounds containing an imidazole ring fused to the acridine moiety.

In the literature only one example of imidazoacridine is reported [10], which was obtained by reaction of 2,3-diamino-9-acridinone with cyanogen bromide in dichloromethane.

We propose here to use another synthetic pathway based on the copper-catalyzed *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, sulfuric acid or phosphorus oxychloride. These cycliza-

Scheme 1

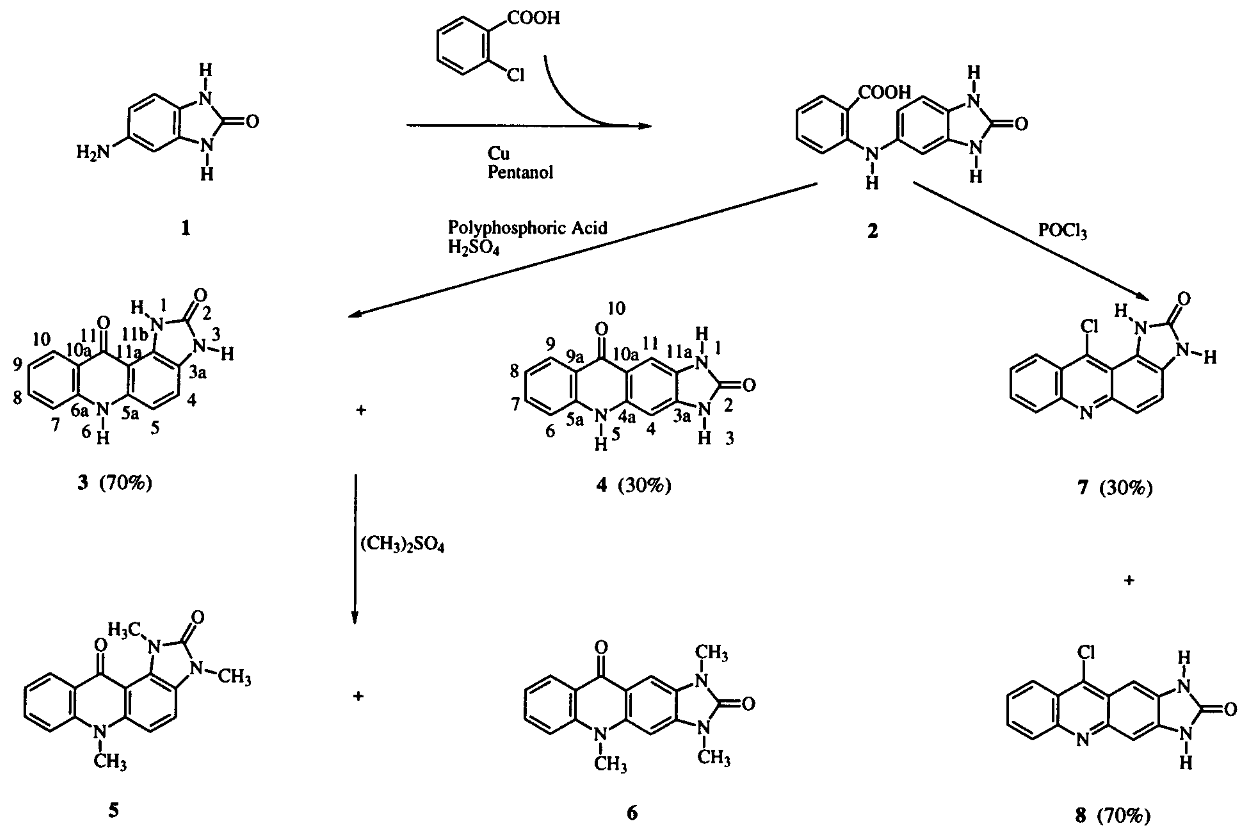

Table 1

^{1}H NMR Chemical Shifts (ppm) and Isomeric Ratios

Compound	Molecular Formula	Relative Amounts [a]	^{1}H-NMR
3	$C_{14}H_9N_3O_2$	70%	11.67 (s, 1H, N_5-H), 10.85 (s, 1H, N_1-H), 10.72 (dd, 1H, N_3-H), 8.19 (dd, 1H, C_{10}-H), 7.69 (ddd, 1H, C_8-H), 7.50 (dd, 1H, C_7-H), 7.40 (d, 1H, C_4-H), 7.21 (ddd, 1H, C_9-H), 7.13 (d, 1H, C_5-H)
4	$C_{14}H_9N_3O_2$	30%	11.62 (s, 1H, N_5-H), 11.01 (s, 1H, N_1-H), 10.79 (s, 1H, N_3-H), 8.18 (dd, 1H, C_9-H), 7.64 (ddd, 1H, C_7-H), 7.64 (s, 1H, C_{11}-H), 7.46 (dd, 1H, C_6-H), 7.16 (ddd, 1H, C_8-H), 7.02 (s, 1H, C_4-H)
5	$C_{17}H_{15}N_3O_2$	50%	8.40 (dd, 1H, C_{10}-H), 7.67 (ddd, 1H, C_8-H), 7.43 (dd, 1H, C_7-H), 7.29 (d, 1H, C_4-H), 7.24 (ddd, 1H, C_9-H), 7.17 (d, 1H, C_5-H), 3.87 (s, 1H, N_1-CH_3), 3.83 (s, 1H, N_6-CH_3), 3.45 (s, 1H, N_3-CH_3)
6	$C_{17}H_{15}N_3O_2$	50%	8.51 (dd, 1H, C_9-H), 7.98 (s, 1H, C_{11}-H), 7.65 (ddd, 1H, C_7-H), 7.42 (dd, 1H, C_6-H), 7.24 (ddd, 1H, C_8-H), 6.78 (s, 1H, C_4-H), 3.83 (s, 1H, N_5-CH_3), 3.44 (s, 1H, N_1, N_3-CH_3)
7	$C_{14}H_8ClN_3O$	30%	11.40 (s, 1H, N_1-H), 11.30 (s, 1H, N_3-H), 8.35 (dd, 1H, C_{10}-H), 8.13 (dd, 1H, C_7-H), 7.91 (d, 1H, C_4-H), 7.80 (d, 1H, C_8-H), 7.68 (d, 1H, C_5-H), 7.65 (ddd, 1H, C_9-H)
8	$C_{14}H_8ClN_3O$	70%	11.40 (s, 2H, N_1 and N_3-H), 8.30 (dd, 1H, C_9-H), 8.09 (dd, 1H, C_6-H), 7.80 (ddd, 1H, C_7-H), 7.65 (s, 1H, C_{11}-H), 7.65 (ddd, 1H, C_8-H), 7.50 (s, 1H, C_4-H)

[a] Estimated by nmr on the crude product of the reaction.

tions led to a mixture of two isomers which were separated by column chromatography. The synthetic pathway is shown in Scheme 1.

Starting from 5-amino-1,3-dihydro-2*H*-benzimidazol-2-one **1** which, after treatment with potassium *o*-chlorobenzoate in the presence of copper and 1-pentanol gave 5-(2'-carboxyphenylamino)-1,3-dihydro-2*H*-benzimidazol-2-one **2**. Cyclization of compound **2** with either polyphosphoric acid or sulfuric acid gave a mixture of the angular **3** and linear isomer **4** in 70% and 30% yield, respectively. Cyclization of **2** with phosphorus oxychloride afforded the two chloroacridine derivatives **7** and **8** in 30% and 70% yields. Thus the use phosphorus oxychloride modifies the orientation of the reaction.

Yields of the isomers were determined by ^{1}H-nmr spectroscopy of the crude material. Methylation of the mixture of **3** and **4** with dimethyl sulfate in the presence of aqueous potassium hydroxide and acetone gave a mixture of trimethylacridinones which were separated by recrystallization.

The structure of compounds **3-8** was established by ^{1}H-nmr spectroscopy. The angular structure of compounds **3**, **5** and **7** was assigned from the appearance of two doublets assigned to C_4-H and C_5-H, while the linear structure of **4**, **6** and **8** was in agreement with the presence of two singlets due to the C_4-H and C_{11}-H protons, respectively, (see Table 1).

EXPERIMENTAL

Melting points were determined with a Mettler FP 61 apparatus and are uncorrected. The ^{1}H and ^{13}C spectra were recorded in deuterio dimethylsulfoxide solution on a Bruker AC 200 spectrometer. Chemical shifts were reported in ppm relative to tetramethylsilane as the internal standard. Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel. Separations were accomplished on silica gel (Merck, 70-230 mesh). 5-Amino-1,3-dihydro-2*H*-benzimidazol-2-one (**1**) is a commercial product.

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 mmoles), potassium *o*-chlorobenzoate (2 g, 10 mmoles), powdered copper (0.1 g) and 1-pentanol (30 ml) was heated at 130° with stirring for 12 hours. The mixture was filtered and the solvent was removed under reduced pressure. Next, ethyl acetate was added to the residue and the mixture was extracted with 0.1*N* sodium hydroxide. The alkaline layer was acidified (*p*H 6) with concentrated hydrochloric acid to give 0.68 g (38%) of a greenish powder, mp 252° (acetone); ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ 10.58 (s, 3H, H-1, H-3, H-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).

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

Polyphosphoric Acid Procedure.

To well stirred polyphosphoric acid (3 g), heated to 90°, was added 5-(2'-carboxyphenylamino)-1,3-dihydro-2*H*-benzimidazol-2-one (**1**) (0.3 g, 1.11 mmoles). The mixture was stirred at 110° during 2 hours and poured onto ice. The solid that precipitated was filtered, washed with a saturated solution of sodium hydrogen carbonate and dried, yield 0.22 g (79%).

Sulfuric Acid Procedure.

A mixture of **1**, (0.3 g, 1.1 mmoles), and 3 ml of sulfuric acid (95%) was heated at 100° with vigorous stirring during 2 hours. Then ice was added carefully into the flask. The resulting solution was neutralized with dilute aqueous ammonia. The precipitate was filtered, washed with water and dried, yield 0.17 g (59%).

The crude product was purified by chromatography on silica gel, eluting with a gradient chloroform/ethanol. Compound **3** was obtained from the first fraction and compound **4** from the second fraction.

1,3-Dihydro-6*H*-imidazo[4,5-*a*]acridine-2,11-dione (**3**).

This compound was obtained in a yield of 31% as yellow crystals, mp >300°.

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.58; N, 16.73. Found: C, 66.93; H, 3.62; N, 16.54.

1,3-Dihydro-5*H*-imidazo[4,5-*b*]acridine-2,10-dione (**4**).

This compound was obtained in a yield of 24% as a yellow powder, mp >300°.

Anal. Calcd. for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.58; N, 16.73. Found: C, 66.45; H, 3.59; N, 16.57.

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

A mixture of **3** and **4** (0.7 g, 2.79 mmoles), water (10 ml), potassium hydroxide (0.9 g), acetone (40 ml) was stirred at room temperature during 1 hour. Then, a mixture of dimethyl sulfate (2.4 ml) and acetone (10 ml) was added dropwise. After 16 hours at 80°, 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. The organic layers were dried over anhydrous sodium sulphate and evaporated *in vacuo*, yield 0.49 g (60%). The residue was recrystallized from ethanol. Compound **5** precipitated after 1 hour and compound **6** after two days under the same conditions.

1,3,5-Trimethylimidazo[4,5-*a*]acridine-2,11-dione (**5**).

This compound was obtained in the amount of 212 mg (26%) as yellow crystals, mp >300°.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12; N, 14.33. Found: C, 69.58; H, 5.30; N, 14.28.

1,3,5-Trimethylimidazo[4,5-*b*]acridine-2,10-dione (**6**).

This compound was obtained in the amount of 228 mg (28%) as a yellow powder, mp >300°.

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.62; H, 5.12; N, 14.33. Found: C, 69.58; H, 5.30; N, 14.28.

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

A mixture of 5-(2'-carboxyphenylamino)-1,3-dihydro-2*H*-benzimidazol-2-one **2** (0.5 g, 1.85 mmoles) and phosphorus oxychloride (5 ml) was heated at 120° during 30 minutes. After cooling, the excess phosphorus oxychloride was extracted with petroleum ether. The sticky residue was neutralized with aqueous ammonia. The filtered green precipitate was washed with water and dried to yield 0.25 g (72%) of crude material. The crude product was purified by chromatography, eluting with chloroform/ethanol (95/5) to yield two separated fractions. Compound **7** was obtained from the first fraction and compound **8** from the second one.

11-Chloro-1,3-dihydroimidazo[4,5-*a*]acridin-2-one (**7**).

This compound was obtained in the amount of 50 mg (10%), mp >300°.

Anal. Calcd. for $C_{14}H_8ClN_3O$: C, 62.34; H, 2.97; N, 15.58. Found: C, 62.48; H, 2.84; N, 15.50.

10-Chloro-1,3-dihydroimidazo[4,5-*b*]acridin-2-one (**8**).

This compound was obtained in the amount of 99 mg (20%), mp >300°.

Anal. Calcd. for $C_{14}H_8ClN_3O$: C, 62.34; H, 2.97; N, 15.58. Found: C, 62.30; H, 2.99; N, 15.63.

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