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## SYNTHESIS OF NEW HETEROCYCLIC SYSTEM:

### 1(5)*H*-1,5-DIAZACYCL[3.3.2]AZINE-2,4-DIONE

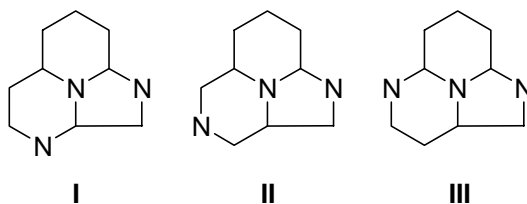
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**Abstract** – A synthesis of hitherto unknown heterocyclic system 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**5**) is presented. The cyclocondensation of 2,6-diaminopyridine (**1**) with maleic anhydride yielded (5-amino-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acid (**2**), which was converted to methyl (5-amino-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetate hydrochloride (**3**). The ester (**3**) upon treatment with sodium carbonate solution underwent intramolecular cyclization to 2a,3-dihydro-1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**4**), which was oxidized in alkaline condition to provide **5**.

## INTRODUCTION

Cyclazines are common subjects in theoretical and experimental studies.<sup>1</sup> The diazacycl[3.3.2]azines, which contain the imidazo[1,5-*a*]pyridine pharmacore, can be categorized into three types of systems (**I-III**) (Figure). To date only one report<sup>2</sup> on the synthesis of 1,3-diazacycl[3.3.2]azines (**I**) has appeared. The chemistry of 1,4-diazacycl[3.3.2]azines (**II**) has been further developed,<sup>3</sup> but there is no information on the 1,5-diazacycl[3.3.2]azine heterocyclic system (**III**) available.



Figure

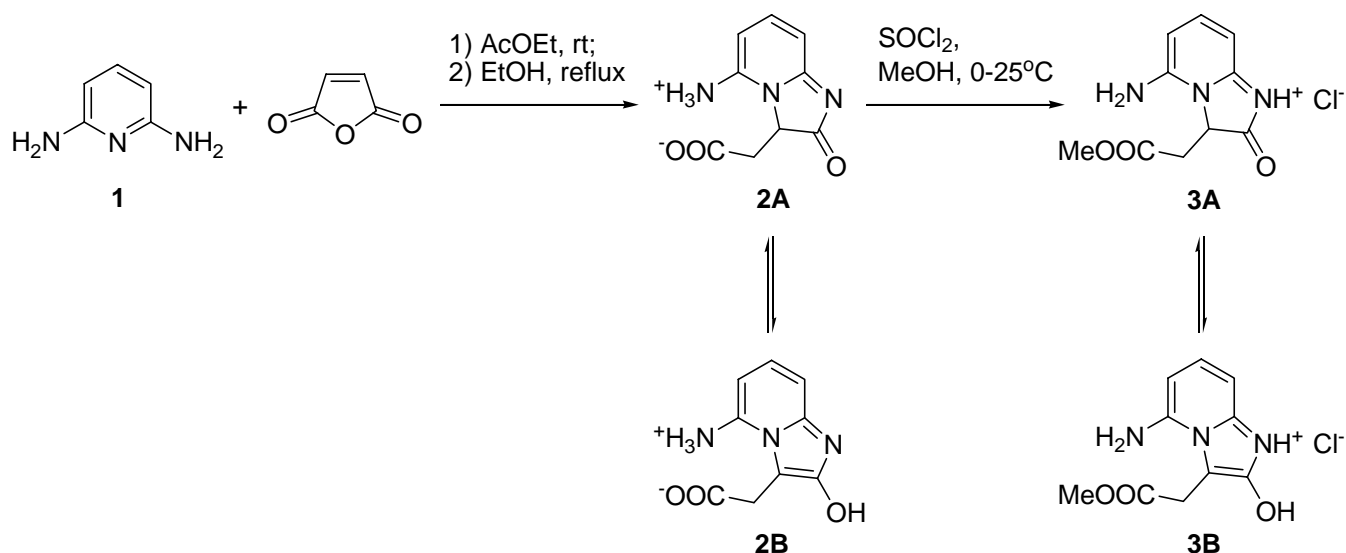
As a continuation to our program on the reactions of maleic anhydride with binucleophiles,<sup>4</sup> particularly in the synthesis of new heterocyclic systems,<sup>5</sup> we describe herein a method for the preparation of

1,5-diazacycl[3.3.2]azine system (**III**) derivative, namely 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (1,5,8b-triazaacenaphthylene-2,4-dione).

## RESULTS AND DISCUSSION

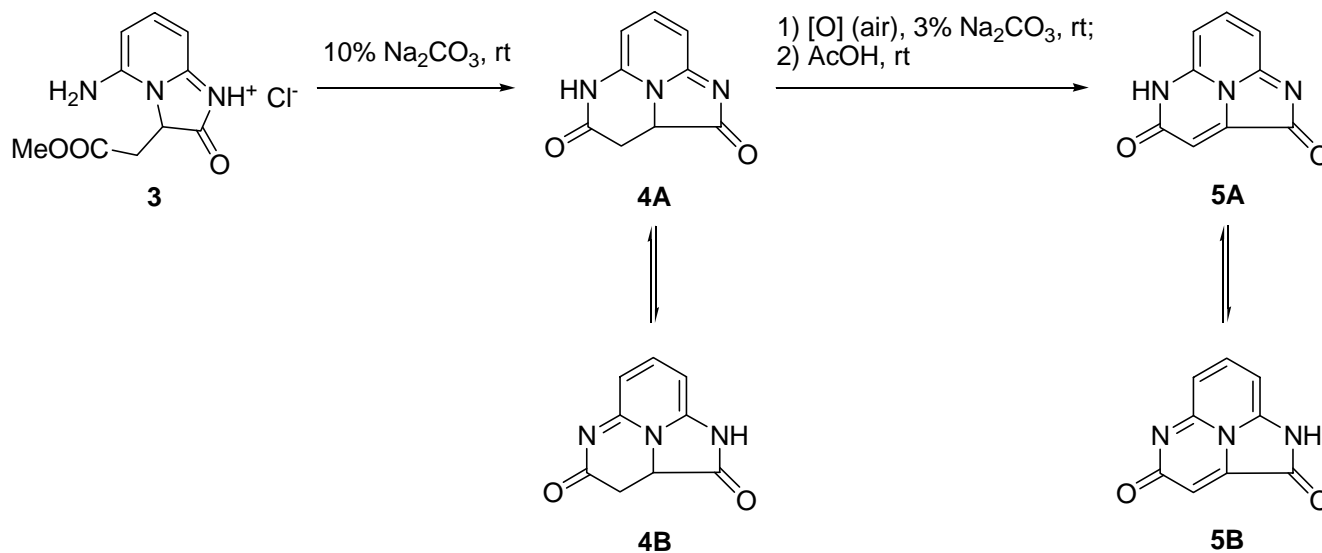
The reaction of 2-aminopyridines with maleic anhydride has been shown to afford (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acid.<sup>6</sup> Using a modification of this method we prepared amino acid (**2**) from 2,6-diaminopyridine (**1**) and maleic anhydride (Scheme 1). The tautomeric form **2A** solely was observed in the NMR spectra (DMSO-*d*<sub>6</sub> solution). However, H-3 signal in <sup>1</sup>H NMR spectrum disappeared upon addition of D<sub>2</sub>O to DMSO-*d*<sub>6</sub> solution of **2** that indicated keto-enol tautomerism in the compound (**2**). The <sup>1</sup>H NMR spectrum of **2** in D<sub>2</sub>O contained no H-3 signal, but the signals of the methylenic group appeared as AB system (instead of AMX system in DMSO-*d*<sub>6</sub>). This type of splitting confirmed diastereotopicity of the methylenic group protons that corresponded to the form **2A**. The signal of C-3 in <sup>13</sup>C NMR spectrum appeared as an equally populated triplet at 62.6 ppm (<sup>2</sup>*J*<sub>CD</sub> = 22.9 Hz), which was observed in D<sub>2</sub>O solution, also supported the existence of the form **2A**.

Attempts of the direct thermal intramolecular cyclization of **2** were not successful. Therefore, the acid (**2**) was treated with thionyl chloride in methanol to afford **3**. The tautomerism, similar to the compound (**2**), was observed for the ester (**3**). Interestingly, N-1 atom was found to be protonated in the compound (**3**) as indicated by cross-peaks between NH (12.89 ppm) and H-8 (6.40 ppm) signals in 2D NOESY experiment.



The ester (**3**) upon treatment with sodium carbonate solution in mild condition underwent intramolecular ring closure and provided the tricyclic system 2a,3-dihydro-1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**4**) (Scheme 2). The compound (**4**) was readily enolized in alkaline condition and oxidized in aqueous solution by standing exposed to air overnight. After treatment of the resulting product with acetic acid, 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione (**5**) was isolated and characterized. Annular tautomerism (forms

**5A** and **5B**) was found to be possible along with keto-enol tautomerism. However, we were not able to distinguish between these forms using the spectral data and X-ray crystallographic study might be required.



Scheme 2

In conclusion, an efficient and simple synthesis of new cyclazine type heterocyclic system *viz.* 1(5)*H*-1,5-diazacycl[3.3.2]azine-2,4-dione was successfully developed. Further investigation of the 1(5)*H*-1,5-diazacycl[3.3.2]azine chemistry is in the progress.

## EXPERIMENTAL

**General Methods.** Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. IR spectra were performed on a Shimadzu IRPrestige-21 spectrophotometer in KBr discs.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DPX-300 spectrometer, using DMSO- $d_6$  or  $\text{D}_2\text{O}$  as solvents and TMS or TSP as internal references. The assignments were made using the reported data for (2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acids,<sup>6</sup> DEPT135, 2D COSY, NOESY and HMQC spectral data.

### (5-Amino-2-oxo-2,3-dihydroimidazo[1,2-*a*]pyridin-3-yl)acetic acid (**2**).

The freshly recrystallized from toluene 2,6-diaminopyridine (**1**, 2.18 g, 20 mmol) was dissolved in EtOAc (40 mL) and a solution of maleic anhydride (1.96 g, 20 mmol) in EtOAc (20 mL) was slowly added with stirring at 0°C (ice bath). After stirring at 0°C for 30 min, ice bath was removed and stirring was continued for 12 h at rt. The precipitate was filtered, washed with EtOAc and refluxed in EtOH for 30 min. After cooling, the product (**2**) was filtered, washed with EtOH and recrystallized from water to give sandy crystals. Yield 2.82 g (68%); mp > 360°C (water).

IR (KBr,  $\nu$ ,  $\text{cm}^{-1}$ ): 3550, 3466, 3369, 3102, 1727, 1682, 1634, 1591, 1551, 1407.

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$  / TMS):  $\delta$  2.73 (1H, dd,  $^3J_{\text{AX}} = 4.5$  Hz,  $^2J_{\text{MX}} = 17.7$  Hz, H<sub>X</sub>), 3.14 (1H, dd,  $^3J_{\text{AM}} = 3.8$  Hz,  $^2J_{\text{MX}} = 17.7$  Hz, H<sub>M</sub>), 4.68 (1H, dd,  $^2J_{\text{AM}} = 3.8$  Hz,  $^2J_{\text{AX}} = 4.5$  Hz, H-3), 6.16 (1H, d,  $^3J = 8.3$  Hz, H-8), 6.19 (1H, d,  $^3J = 8.3$  Hz, H-6), 7.54 (1H, t,  $^3J = 8.3$  Hz, H-7), 8.30 (3H, br. s,  $\text{NH}_3^+$ ).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$  / TMS):  $\delta$  34.4 (CH<sub>2</sub>), 58.7 (C-3), 94.7 (C-8), 99.4 (C-6), 143.0 (C-7), 151.5 (C-5), 158.1 (C-8a), 171.5 (C-2), 178.4 (COO<sup>-</sup>).

$^1\text{H}$  NMR (300 MHz, D<sub>2</sub>O / TSP):  $\delta$  3.06 (1H, d,  $^2J_{\text{AB}} = 17.7$  Hz, H<sub>A</sub>), 3.33 (1H, d,  $^2J_{\text{AB}} = 17.7$  Hz, H<sub>B</sub>), 6.48 (1H, d,  $^3J = 7.9$  Hz, H-8), 6.63 (1H, d,  $^3J = 8.7$  Hz, H-6), 7.79 (1H, t,  $^3J = 8.3$  Hz, H-7).

$^{13}\text{C}$  NMR (75 MHz, D<sub>2</sub>O / TSP):  $\delta$  37.4 (CH<sub>2</sub>), 62.6 (t,  $^1J_{\text{CD}} = 22.9$  Hz, C-3), 97.7 (C-8), 108.1 (C-6), 147.5 (C-7), 152.0 (C-5), 154.7 (C-8a), 177.6 (C-2), 178.3 (COO<sup>-</sup>).

Anal. Calcd for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.85; H, 4.72; N, 20.28.

### ***Methyl (5-amino-2-oxo-2,3-dihydroimidazo[1,2-a]pyridin-3-yl)acetate hydrochloride (3).***

To a suspension of acid **2** (2.07 g, 10 mmol) in MeOH (30 mL), thionyl chloride (1.46 mL, 20 mmol) was added slowly with stirring at 0°C (ice bath). After stirring at 0°C for 30 min, ice bath was removed and stirring was continued for 4 h at rt. The solvent and excess of thionyl chloride were evaporated under reduced pressure and residue was recrystallized from EtOH to give sandy crystalline product (**3**). Yield 2.45 g (95%); mp > 360°C (EtOH).

IR (KBr, v, cm<sup>-1</sup>): 3372, 3075, 1757, 1730, 1675, 1646, 1586, 1410.

$^1\text{H}$  NMR (300 MHz, DMSO- $d_6$  / TMS):  $\delta$  3.17 (1H, dd,  $^3J_{\text{AX}} = 2.7$  Hz,  $^2J_{\text{MX}} = 18.1$  Hz, H<sub>X</sub>), 3.52 (3H, s, COOMe), 3.79 (1H, dd,  $^3J_{\text{AM}} = 4.9$  Hz,  $^2J_{\text{MX}} = 18.1$  Hz, H<sub>M</sub>), 5.27 (1H, dd,  $^3J_{\text{AM}} = 4.9$  Hz,  $^3J_{\text{AX}} = 2.7$  Hz, H-3), 6.40 (1H, d,  $^3J = 7.9$  Hz, H-8), 6.66 (1H, d,  $^3J = 8.7$  Hz, H-6), 7.81 (1H, t,  $^3J = 8.1$  Hz, H-7), 8.82 (2H, s, NH<sub>2</sub>), 12.89 (1H, br. s, NH).

$^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$  / TMS):  $\delta$  30.1 (CH<sub>2</sub>), 52.0 (COOMe), 57.7 (C-3), 92.7 (C-8), 104.7 (C-6), 144.3 (C-7), 148.5 (C-5), 151.7 (C-8a), 168.6 (COOMe), 170.1 (C-2).

$^1\text{H}$  NMR (300 MHz, D<sub>2</sub>O / TSP):  $\delta$  3.37 (1H, d,  $^2J_{\text{AB}} = 17.7$  Hz, H<sub>A</sub>), 3.63 (3H, s, COOMe), 3.68 (1H, d,  $^2J_{\text{AB}} = 17.7$  Hz, H<sub>B</sub>), 6.51 (1H, d,  $^3J = 7.9$  Hz, H-8), 6.62 (1H, d,  $^3J = 8.7$  Hz, H-6), 7.81 (1H, t,  $^3J = 8.3$  Hz, H-7).

$^{13}\text{C}$  NMR (75 MHz, D<sub>2</sub>O / TSP):  $\delta$  33.2 (CH<sub>2</sub>), 55.7 (COOMe), 60.9 (t,  $^1J_{\text{CD}} = 22.6$  Hz, C-3), 98.7 (C-8), 107.8 (C-6), 148.0 (C-7), 154.2, 154.8 (C-5 and C-8a), 173.6 (COOMe), 178.2 (C-2).

Anal. Calcd for C<sub>10</sub>H<sub>12</sub>N<sub>3</sub>O<sub>3</sub>Cl: C, 46.61; H, 4.69; N, 16.31. Found: C, 46.38; H, 4.87; N, 16.09.

### ***1(5)H-1,5-Diazacycl[3.3.2]azine-2,4-dione (5).***

Salt **3** (1.29 g, 5 mmol) was dissolved in 10% aqueous Na<sub>2</sub>CO<sub>3</sub> (5.5 mL) was stirred at rt. After 30 min, the precipitated bright yellow compound **4** was filtered and washed with cold water. Without further

purification, compound **4** was dissolved in 3% aqueous Na<sub>2</sub>CO<sub>3</sub> (20 mL) and stirred overnight in an open flask. To the formed suspension of sodium salt of **5**, AcOH (5 mL) was added and the orange precipitate was filtered and washed with cold water. The purification of the product (**5**) can be performed using recrystallization from DMSO or, more conveniently, by reprecipitation from the solution in aqueous 10% aqueous Na<sub>2</sub>CO<sub>3</sub> using AcOH. Yield 0.77 g (82%); mp > 360°C (DMSO).

IR (KBr, v, cm<sup>-1</sup>): 3448, 3059, 1735, 1699, 1667, 1617, 1605, 1485, 1456, 1393.

<sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub> / TMS): δ 6.69 (1H, d, <sup>3</sup>J = 7.9 Hz), 6.86 (1H, d, <sup>3</sup>J = 8.7 Hz), 6.99 (1H, s), 7.91 (1H, t, <sup>3</sup>J = 8.3 Hz), 13.01 (1H, br. s. NH).

Anal. Calcd for C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>O<sub>3</sub>: C, 57.76; H, 2.69; N, 22.45. Found: C, 57.99; H, 2.82; N, 22.78.

## ACKNOWLEDGEMENTS

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