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# Synthesis of 1-(1,3-Dialkyl-2-oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic Acids

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**Abstract**—Nitration of 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one gave its 5-nitro derivative which was subjected to alkylation with dimethyl sulfate, diethyl sulfate, and benzyl(dimethyl)phenylammonium chloride. The resulting 1,3-dimethyl-, 1,3-diethyl-, and 1,3-dibenzyl-5-nitro-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones were reduced to the corresponding 1,3-dialkyl-5-amino-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones, and the latter reacted with itaconic acid to produce 1-(1,3-dialkyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic acids. 1-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic acid was obtained by analogous reaction with 5-amino-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-2-one.

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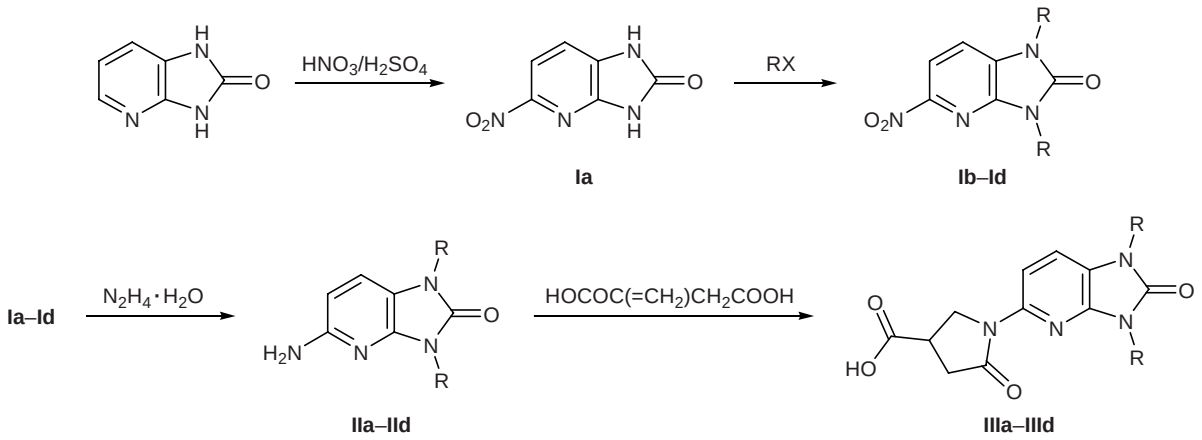
In the recent years, derivatives of imidazo[4,5-*b*]-pyridine, which can be regarded as a purine analog, attract increasing interest. Some of these compounds were found to exhibit antiviral, cytostatic, antimicrobial, fungicide, cardiovascular, and antisecretory activity, as well as properties of angiotensin II antagonists [1]. Versatile and pronounced biological activity of imidazo[4,5-*b*]pyridine derivatives has stimulated search for new methods of synthesis of these compounds with a view to study their pharmacological properties and develop medical agents and drug compositions based thereon.

1-Substituted 5-oxopyrrolidine-3-carboxylic acids were synthesized previously from various aryl(arylalkyl)amines and itaconic acid [2]. We believe it to be reasonable to examine the reaction of itaconic acid with heterocyclic amines, in particular with 1,3-dialkyl-5-amino-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-

**Scheme 1.**




R = H (**a**), Me (**b**), Et (**c**), Bzl (**d**).

[†] Deceased.

ones and their 1,3-unsubstituted analog. New compounds obtained in such a way could attract interest from the viewpoint of biological activity, for their molecules contain both imidazo[4,5-*b*]pyridin-2-one and 5-oxopyrrolidine-3-carboxylic acid fragments; the latter may be regarded as cyclic amino acids. This assumption was based on the fact that some medical agents whose molecules contain pyrrolidine, 2-oxopyrrolidine, and pyrrolidinecarboxylic acid fragments are effective antibiotics; in addition, they possess other useful properties [3].

As starting compound for the synthesis of 1,3-dialkyl-5-nitro-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones we used 5-nitro-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-2-one (**Ia**) which was prepared in 82% yield by direct nitration of 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one with a mixture of concentrated nitric and sulfuric acids. 1,3-Dialkyl derivatives **Ib**–**Id** were obtained by alkylation of nitro compound **Ia** with dimethyl sulfate, diethyl sulfate, and benzyl(dimethyl)phenylammonium chloride (Scheme 1). The yields of **Ib**–**Id** were 51–81%. Their $^1$H NMR spectra contained doublets from the vicinal 6-H (δ 8.04– 8.16 ppm) and 7-H protons (δ 7.17–7.75 ppm) and signals from the methyl, ethyl, and benzyl groups on $N^1$ and $N^3$ in the imidazole ring.

Nitro compounds **Ia**–**Id** were reduced to the corresponding 5-amino derivatives **IIa**–**IId** by heating in boiling hydrazine hydrate for 10–14 h. The yields of **IIa**–**IId** were fairly high (74–82%). Compounds **IIa**–**IId** displayed in the $^1$H NMR spectra doublets from the vicinal 6-H and 7-H protons, signals from protons in the alkyl groups on $N^1$ and $N^3$, and a signal at δ 4.26–5.67 ppm from the amino group.

Aminoimidazo[4,5-*b*]pyridin-2-ones **IIa**–**IId** reacted with itaconic acid at 120–125°C (2–3 h) to give 45–55% of 1-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic (**IIIa**) and 1-(1,3-dialkyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic acids **IIIb**–**IIId**. The $^1$H NMR spectra of **IIIa**–**IIId** lacked signals from $NH_2$ protons, but those belonging to $CH_2$ protons in the pyrrolidine fragment appeared.

## EXPERIMENTAL

The $^1$H NMR spectra were recorded on a Varian Gemini-200 spectrometer (200 MHz). The purity of the products was checked by TLC on Silufol UV-254 plates using ethanol as eluent; spots were detected by treatment with iodine vapor and by UV irradiation. 2,3-Dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one was synthesized according to the procedure described in [4].

**5-Nitro-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (Ia).** A solution of 13.5 g (10 mmol) of 2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one in 9 ml of concentrated sulfuric acid was cooled to 0°C, and 0.55 ml (12.5 mmol) of concentrated nitric acid ($d$ = 1.5 g/cm$^3$) was added dropwise under stirring at such a rate that the temperature did not exceed 5°C. The mixture was stirred for 1 h, allowed to warm up to 15°C, kept for 2 h at that temperature, and poured onto ice, and the precipitate was filtered off, washed with cold water until neutral washings, dried, and recrystallized from water. Yield 1.47 g (82%), mp 350–353°C; published data [6]: mp 338–339°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 7.51 d (1H, 7-H, $J$ = 8.3 Hz), 8.06 d (1H, 6-H, $J$ = 8.3 Hz). Found, %: C 39.78; H 2.19; N 30.86. $C_6H_4N_4O_3$. Calculated, %: C 40.01; H 2.24; N 31.04.

**1,3-Dimethyl-5-nitro-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (Ib).** Compound **Ia**, 18 g (10 mmol), was added under vigorous stirring to a solution of 8.8 g (0.22 mol) of sodium hydroxide in 180 ml of water, and 21 ml (0.22 mol) of dimethyl sulfate was then slowly added at room temperature. After 2 h, the light yellow precipitate was filtered off, washed with cold water and ethanol–diethyl ether (1:1), and recrystallized from ethanol. Yield 8.2 g (81%), light yellow solid, mp 277–279°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 3.48 d (6H, 1-$CH_3$, 2-$CH_3$), 7.75 d (1H, 7-H, $J$ = 8.3 Hz), 8.15 d (1H, 6-H, $J$ = 8.3 Hz). Found, %: C 46.00; H 3.79; N 26.75. $C_8H_8N_4O_3$. Calculated, %: C 46.16; H 3.87; N 26.91.

**1,3-Diethyl-5-nitro-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (Ic).** Potassium carbonate, 33.2 g (335 mmol), was added to a solution of 20 g (133 mmol) of 5-nitro-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-2-one (**Ia**) in 150 ml of DMF. The mixture was stirred for 0.5 h, 40 ml (305 mmol) of diethyl sulfate was added in portions over a period of 1 h under vigorous stirring at room temperature, and the mixture was heated for 14 h at 90–95°C and evaporated under reduced pressure on a water bath. The dry residue was extracted with benzene, and the solvent was distilled off from the extract. Yield 13.5 g (51%), orange solid, mp 117–119°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.44 t (3H, 1-$CH_2C\mathbf{H}_3$), 1.47 t (3H, 3-$CH_2C\mathbf{H}_3$), 4.06 q (2H, 1-$CH_2$), 4.16 q (2H, 3-$CH_2$), 7.39 d (1H, 7-H,

$J$ = 8.3 Hz), 8.16 d (1H, 6-H, $J$ = 8.3 Hz). Found, %: C 50.68; H 5.06; N 23.55. $C_{10}H_{12}N_4O_3$. Calculated, %: C 50.84; H 5.12; N 23.72.

**1,3-Dibenzyl-5-nitro-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (Id).** A solution of 14.5 g (58.5 mmol) of benzyl(dimethyl)phenylammonium chloride in 15 ml of water was added under stirring at room temperature to a solution of 4.5 g (25 mmol) of compound **Ia** in 20% aqueous sodium hydroxide. The mixture was heated for 7 h at the boiling point and subjected to steam distillation to remove *N*,*N*-dimethylaniline. After cooling, the orange precipitate was filtered off, washed with cold water, dried, and treated with hexane. Yield 7.2 g (80%), mp 178–179°C. $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 5.17 s (2H, 1-$CH_2$), 5.30 s (2H, 3-$CH_2$), 7.17 d (1H, 7-H, $J$ = 8.3 Hz), 7.37 s (5H, 1-$CH_2$**Ph**), 7.39 s (5H, 3-$CH_2$**Ph**), 8.04 d (1H, 6-H, $J$ = 8.3 Hz). Found, %: C 66.45; H 4.39; N 15.40. $C_{20}H_{16}N_4O_3$. Calculated, %: C 66.66; H 4.47; N 15.55.

**5-Amino-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-ones IIa–IId (*general procedure*).** A mixture of 25 mmol of nitro compound **Ia**–**Id** and 30 ml of hydrazine hydrate was heated for 14 h at 115–120°C in a stream of argon. Excess hydrazine hydrate was distilled off, the residue was dissolved in water, the solution was cooled, and the precipitate was filtered off and recrystallized from appropriate solvent.

**5-Amino-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-2-one (IIa).** Yield 80%, mp 312–314°C (from water). $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 4.32 br.s (2H, $NH_2$), 6.13 d (1H, 7-H, $J$ = 8.1 Hz), 6.99 d (1H, 6-H, $J$ = 8.1 Hz). Found, %: C 47.79; H 3.99; N 37.14. $C_6H_6N_4O$. Calculated, %: C 48.00; H 4.03; N 37.32.

**5-Amino-1,3-dimethyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIb).** Yield 83%, mp 233–235°C (from propan-2-ol); published data [7]: mp 233–234°C. $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 3.29 d (6H, 1-$CH_3$, 3-$CH_3$), 6.19 d (1H, 7-H, $J$ = 8.2 Hz), 7.24 d (1H, 6-H, $J$ = 8.2 Hz). Found, %: C 53.71; H 5.59; N.23. $C_8H_{10}N_4O$. Calculated, %: C 53.92; H 5.66; N 31.44.

**5-Amino-1,3-diethyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IIc).** Yield 77%, mp 135–137°C (from benzene–heptane, 1:1). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.35 t (3H, 1-$CH_2C\mathbf{H}_3$), 1.39 t (3H, 3-$CH_2C\mathbf{H}_3$), 3.91 q (2H, 1-$CH_2$), 3.99 q (2H, 3-$CH_2$), 4.31 br.s (2H, $NH_2$), 6.24 d (1H, 7-H, $J$ = 8.3 Hz), 7.06 d (1H, 6-H, $J$ = 8.3 Hz). Found, %: C 58.05; H 6.78; N 27.01. $C_{10}H_{14}N_4O$. Calculated, %: C 58.24; H 6.84; N 27.16.

**5-Amino-1,3-dibenzyl-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-2-one (IId).** Yield 74%, mp 173–175°C (from propan-2-ol). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 4.26 br.s (2H, $NH_2$), 5.04 s (2H, 1-$CH_2$), 5.14 s (2H, 3-$CH_2$), 6.11 d (1H, 7-H, $J$ = 8.2 Hz), 6.83 d (1H, 6-H, $J$ = 8.2 Hz), 7.30 s (5H, 1-$CH_2$**Ph**), 7.32 s (5H, 3-$CH_2$**Ph**). Found, %: C 72.54; H 5.45; N 16.79. $C_{20}H_{18}N_4O$. Calculated, %: C 72.71; H 5.49; N 16.96.

**1-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic acids IIIa–IIId (*general procedure*).** A mixture of 10 mmol of compound **IIa**–**IId** and 10 mmol of itaconic acid was heated for 2–3 h at 120–125°C. The resulting melt was dissolved in alcohol, the solution was cooled, and the precipitate was filtered off, dried, and recrystallized from appropriate solvent.

**5-Oxo-1-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]-pyridin-5-yl)pyrrolidine-3-carboxylic acid (IIIa).** Yield 46%, mp > 250°C (from propan-1-ol). $^1$H NMR spectrum ($CD_3COOD$), δ, ppm: 2.13 s (2H, 4-H), 3.30–3.45 m (1H, 3-H), 4.31 q (2H, 2-H), 7.47 d (1H, 7′-H, $J$ = 8.6 Hz), 7.93 d (1H, 6′-H, $J$ = 8.6 Hz). Found, %: C 50.20; H 3.76; N 21.23. $C_{11}H_{10}N_4O_4$. Calculated, %: C 50.38; H 3.84; N 21.38.

**1-(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic acid (IIIb).** Yield 55%, mp 212–214°C (from propan-2-ol). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 2.16 s (2H, 4-H), 3.20–3.31 m (1H, 3-H), 3.42 s (6H, 1′-$CH_3$, 3′-$CH_3$), 4.40 q (2H, 2-H), 7.24 d (1H, 7′-H, $J$ = 8.5 Hz), 8.11 d (1H, 6′-H, $J$ = 8.5 Hz). Found, %: C 53.51; H 4.79; N 19.12. $C_{13}H_{14}N_4O_4$. Calculated, %: C 53.79; H 4.86; N 19.30.

**1-(1,3-Diethyl-2-oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic acid (IIIc).** Yield 49%, mp 135–137°C (from propan-2-ol). $^1$H NMR spectrum ($CDCl)_3$, δ, ppm: 1.37 t (6H, 1′-$CH_2C\mathbf{H}_3$, 3′-$CH_2C\mathbf{H}_3$), 2.15 s (2H, 4-H), 3.22–3.35 m (1H, 3-H), 3.95 q (4H, 1′-$CH_2$, 3′-$CH_2$), 4.35 q (2H, 2-H), 6.26 d (1H, 7′-H, $J$ = 8.0 Hz), 7.08 d (1H, 6′-H, $J$ = 8.0 Hz). Found, %: C 56.41; H 5.66; N 17.44. $C_{15}H_{18}N_4O_4$. Calculated, %: C 56.60; H 5.70; N 17.60.

**1-(1,3-Dibenzyl-2-oxo-2,3-dihydro-1*H*-imidazo-[4,5-*b*]pyridin-5-yl)-5-oxopyrrolidine-3-carboxylic acid (IIId).** Yield 45%, mp 213–215°C (from ethanol). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 2.17 t (2H, 4-H), 3.30–3.45 m (1H, 3-H), 4.38 q (2H, 2-H), 5.10 t (2H, 1′-$CH_2$), 5.17 t (2H, 3′-$CH_2$), 7.06 d (1H, 7′-H, $J$ =

8.4 Hz), 7.32–7.52 m (10H, $H_{arom}$), 8.00 d (1H, 6′-H, $J$ = 8.4 Hz). Found, %: C 67.69; H 4.94; N 12.48. $C_{25}H_{22}N_4O_4$. Calculated, %: C 67.86; H 5.01; N 12.66.

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