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Reactions of 1,3-Dialkyl-5-amino-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-2-ones with Acetylacetone and Ethyl Acetoacetate

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Abstract—1,3-Dialkyl-5-amino-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones reacted with acetylacetone to give the corresponding 4-(1,3-dialkyl-2-oxo-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-5-ylamino)pent-3-en-2-ones which underwent intramolecular cyclization to 1,3-dialkyl-5,7-dimethyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]-[1,8]naphthyridin-2-ones on heating in polyphosphoric acid or diphenyl ether. Analogous reaction of 1,3-dialkyl-5-amino-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-ones with ethyl acetoacetate led to the formation of ethyl 3-(1,3-dialkyl-2-oxo-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-5-ylamino)but-2-enoates whose cyclization afforded 1,3-dialkyl-8-hydroxy-7-methyl-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridin-2-ones.

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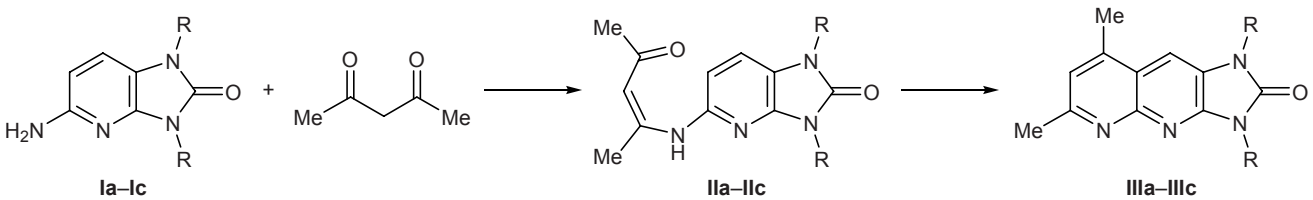
Imidazo[4,5-*b*]pyridines are the closest structural analogs of purine which displays diverse biological activity [1]. Structural analogy between purine and imidazo[4,5-*b*]pyridine is also reflected in chemical and biological properties of the latter. Some imidazo-[4,5-*b*]pyridine derivatives were found to possess a broad spectrum of biological properties, including herbicidal, bacteriostatic, antiviral, antitumor, and other kinds of activity [2]. The recent discovery of antihypertensive agents among compounds of the imidazo[4,5-*b*]pyridine series [3] has stimulated again interest in this heterocyclic system, and efforts have been made to search for new more effective and selective medical agents for the treatment of severe hypertension in humans.

We previously described tricyclic systems containing an imidazo[4,5-*c*]pyridine fragment, namely diimidazo[1,2-*a*:4,5-*c*]pyridin-2-one and imidazo[4,5-*c*]-[1,2,4]triazolo[4,3-*a*]pyridine derivatives, which were found to exhibit analgesic, antiinflammatory, spasmolytic, and morphine-like activity [4]. With a view to build up new tricyclic heterocyclic systems on the basis of amino-substituted 1,3-dialkyl-2*H*-imidazo-[4,5-*b*]pyridin-2-ones it seemed worthwhile to study reactions of the latter with acetylacetone and ethyl acetoacetate under the Combes and Conrad–Limpach conditions [5]. These reactions were successfully applied to the synthesis of derivatives of quinoline, thienopyridine, thienonaphthyridine, benzothienopyridine, thienopyridopyrimidine, and other heterocyclic compounds that can be used for the preparation of potential biologically active substances [6].

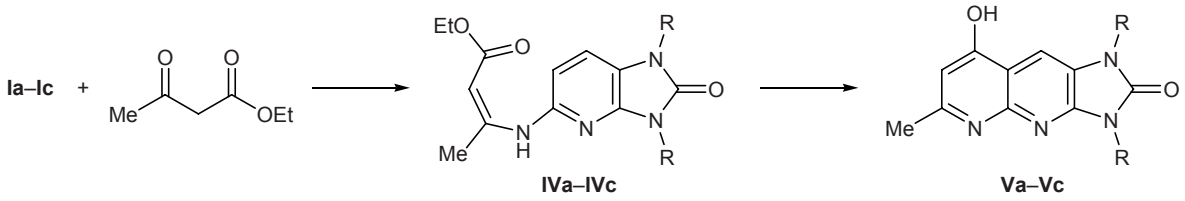
The reactions of 1,3-dialkyl-5-amino-2*H*-imidazo-[4,5-*b*]pyridin-2-ones **Ia**–**Ic** with acetylacetone at 150–155°C resulted in the formation of 81–92% of the corresponding 4-(1,3-dialkyl-2-oxo-2*H*-imidazo[4,5-*b*]pyr-

Scheme 1.



R = Me (**a**), Et (**b**), $PhCH_2$ (**c**).

Scheme 2.



R = Me (**a**), Et (**b**), $PhCH_2$ (**c**).

idin-5-ylamino)pent-3-en-2-ones **IIa**–**IIc** (Scheme 1). In the ^{1}H NMR spectra of enamino ketones **IIa**–**IIc**, olefinic proton in the side-chain resonated as a singlet at δ 5.18–5.27 ppm, and the NH signal was located in the region δ 12.27–13.02 ppm. Heating of enamino ketones **IIa**–**IIc** in polyphosphoric acid at 130–140°C or in diphenyl ether at 250°C promoted their intramolecular cyclization to 1,3-dialkyl-5,7-dimethyl-2-oxo-2*H*-imidazo[5,4-*b*][1,8]naphthyridines **IIIa**–**IIIc** in 47–70% yield. Compounds **IIIa**–**IIIc** displayed in the ^{1}H NMR spectra signals from the methyl group on C^6, alkyl groups on the nitrogen atoms, and protons in positions *7* and *9* of the imidazonaphthyridine fragment (δ 7.62–7.69 and 8.16–8.19 ppm, respectively).

Likewise, 1,3-dialkyl-5-amino-2*H*-imidazo[4,5-*b*]-pyridin-2-ones **Ia**–**Ic** reacted with ethyl acetoacetate at 130–140°C to afford ethyl 3-(1,3-dialkyl-2-oxo-2*H*-imidazo[4,5-*b*]pyridin-5-ylamino)but-2-enoates **IVa**–**IVc** in 61–73% yield (Scheme 2). The ^{1}H NMR spectra of **IVa**–**IVc** contained signals from the side-chain olefinic proton at δ 4.74–4.75 ppm, and the NH proton resonated at δ 10.97 ppm. Like ketones **IIa**–**IIc**, esters **IVa**–**IVc** underwent intramolecular cyclization on heating in polyphosphoric acid at 130–140°C or in diphenyl ether at 250°C. The cyclization was accompanied by elimination of ethanol molecule, and the products were 8-hydroxy-1,3-dialkyl-7-methyl-2*H*-imidazo[5,4-*b*][1,8]naphthyridin-2-ones **Va**–**Vc** (yield 35–70%). In the ^{1}H NMR spectra of **Va**–**Vc** we observed signals from the C-methyl and N-alkyl groups and singlets from protons in positions *7* and *9* of the imidazonaphthyridine fragment at δ 7.97–8.33 and 5.93–6.63 ppm, respectively.

Compounds **IIIa**–**IIIc** and **Va**–**Vc** contain a naphthyridine fragment fused to imidazole ring, and they attract interest as pharmacologically active substances, taking into account that some naphthyridine derivatives were found to exhibit diverse biological activity, including bactericidal, antioxidant, hypotensive, antituberculous, and other properties [7].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer at 200 MHz. The purity of the products was checked by TLC on Silufol UV-254 plates using ethanol as eluent; spots were visualized under UV light or by treatment with iodine vapor. Initial 1,3-dialkyl-5-amino-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-2-ones **Ia**–**Ic** were synthesized according to the procedure described in [8].

4-(1,3-Dialkyl-2-oxo-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-5-ylamino)pent-3-en-2-ones IIa–IIc (*general procedure*). A mixture of 5.76 mmol of compound **Ia**–**Ic** and 17 ml (166 mmol) of acetylacetone was heated for 6–7 h at 150–155°C. Excess acetylacetone was distilled off, and the residue was purified by recrystallization from appropriate solvent.

4-(1,3-Dimethyl-2-oxo-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-5-ylamino)pent-3-en-2-one (IIa). Yield 92%, mp 130–132°C (from decane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.16 s (3H, CH_3), 2.46 s (3H, CH_3), 3.45 s (3H, 1-CH_3), 3.47 s (3H, 3-CH_3), 5.27 s (1H, CH), 6.64 d (1H, 7-H, J = 8.3 Hz), 7.17 d (1H, 6-H, J = 8.3 Hz), 13.02 s (1H, NH). Found, %: C 59.72; H 6.20; N 21.43. $C_{13}H_{16}N_4O_2$. Calculated, %: C 59.98; H 6.19; N 21.52.

4-(1,3-Diethyl-2-oxo-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-5-ylamino)pent-3-en-2-one (IIb). Yield 88%, mp 114–116°C (from petroleum ether). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 t (6H, $CH_2C\mathbf{H}_3$), 2.10 s (3H, CH_3), 2.41 s (3H, CH_3), 3.94 q (4H, $C\mathbf{H}_2CH_3$), 5.21 s (1H, CH), 6.60 d (1H, 7-H, J = 8.1 Hz), 7.13 d (1H, 6-H, J = 8.1 Hz), 12.92 s (1H, NH). Found, %: C 62.31; H 7.03; N 19.32. $C_{15}H_{20}N_4O_2$. Calculated, %: C 62.47; H 6.99; N 19.42.

4-(1,3-Dibenzyl-2-oxo-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-5-ylamino)pent-3-en-2-one (IIc). Yield 81%, mp 137–138°C (from petroleum ether). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.09 s (3H, CH_3), 2.31 s (3H, CH_3), 5.04 s (2H, 1-CH_2), 5.11 s (2H, 2-CH_2), 5.18 s (1H, CH), 6.48 d (1H, 7-H, J = 8.2 Hz),

6.93 d (1H, 6-H, J = 8.2 Hz), 7.30 br.s (10H, C_6H_5), 12.99 s (1H, CH). Found, %: C 72.60; H 5.03; N 13.42. $C_{25}H_{24}N_4O_2$. Calculated, %: C 72.79; H 5.86; N 13.58.

1,3-Dialkyl-5,7-dimethyl-2-oxo-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridines IIIa and IIIb (*general procedure*). A mixture of 6.29 mmol of enamino ketone **IIa** or **IIb** in 9–10 ml of polyphosphoric acid was heated for 3 h 130–140°C. The resulting dark solution was poured into 40–50 ml of water and neutralized with ammonium carbonate. The precipitate was filtered off, washed with a small amount of cold water, dried, and recrystallized from appropriate solvent.

1,3,6,8-Tetramethyl-2-oxo-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridine (IIIa). Yield 70%, mp >230°C (from water). ^{1}H NMR spectrum (CD_3COOD), δ, ppm: 2.95 s (6H, 6-CH_3, 8-CH_3), 3.57 s (6H, 1-CH_3, 3-CH_3), 7.63 s (1H, 7-H), 8.16 s (1H, 9-H). Found, %: C 64.30; H 5.80; N 23.00. $C_{13}H_{14}N_4O$. Calculated, %: C 64,44; H 5.82; N 23.13.

1,3-Diethyl-6,8-dimethyl-2-oxo-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridine (IIIb). Yield 45%, mp 112–115°C (from water). ^{1}H NMR spectrum (CD_3COOD), δ, ppm: 1.47 s (6H, C**H**$_3$), 3.00 s (6H, 6-CH_3, 8-CH_3), 4.20 q (4H, NCH_2), 7.69 s (1H, 7-H), 8.19 s (1H, 9-H). Found, %: C 66.52; H 6.65; N 20.58. $C_{15}H_{18}N_4O$. Calculated, %: C 64.64; H 6.71; N 20.72.

1,3-Dibenzyl-6,8-dimethyl-2-oxo-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridine (IIIc). A mixture of 7 ml of diphenyl ether and 2.4 mmol of enamino ketone **IIc** was heated for 30 min at 250–255°C. The mixture was cooled, 50–60 ml of petroleum ether (bp 60–80°C) was added, and the precipitate was filtered off, dried, and recrystallized from toluene. Yield 65%, mp 130–132°C. ^{1}H NMR spectrum (CD_3COOD), δ, ppm: 2.92 s (6H, 6-CH_3, 8-CH_3), 5.27 s (4H, NCH_2), 7.34 s (10H, C_6H_5), 7.62 s (1H, 7-H), 8.17 s (1H, 9-H). Found, %: C 76.01; H 5.58; N 14.04. $C_{25}H_{22}N_4O$. Calculated, %: C 76.11; H 5.62; N 14.20.

Ethyl 3-(1,3-dialkyl-2-oxo-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-5-ylamino)but-2-enoates IVa–IVc (*general procedure*). A mixture of 5.62 mmol of compound **Ia**–**Ic** and 7–8 ml of ethyl acetoacetate was heated for 6–7 h at 140–150°C. Excess ethyl acetoacetate was distilled off under reduced pressure, and the residue was purified by recrystallization.

Ethyl 3-(1,3-dimethyl-2-oxo-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-5-ylamino)but-2-enoate (IVa). Yield 61%, mp 149–151°C (from heptane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.30 t (3H, OCH_2C**H**$_3$), 2.42 s (3H, CH_3), 3.42 s (6H, NCH_3), 4.17 q (1H, CH), 6.57 d (1H, 7-H, J = 8.2 Hz), 7.11 d (1H, 6-H, J = 8.2 Hz), 10.97 s (1H, NH). Found, %: C 57.79; H 6.21; N 19.15. $C_{14}H_{18}N_4O_3$. Calculated, %: C 57.92; H 6.25; N 19.30.

Ethyl 3-(1,3-diethyl-2-oxo-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-5-ylamino)but-2-enoate (IVb). Yield 67%, mp 90–92°C (from heptane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32 t (6H, NCH_2C**H**$_3$), 1.36 t (3H, OCH_2C**H**$_3$), 2.42 s (3H, CH_3), 3.93 q (4H, NCH_2), 4.21 q (2H, OCH_2), 4.75 s (1H, CH), 6.55 d (1H, 7-H, J = 8.2 Hz), 7.13 d (1H, 6-H, J = 8.2 Hz), 10.67 s (1H, NH). Found, %: C 60.22; H 6.89; N 17.50. $C_{16}H_{22}N_4O_3$. Calculated, %: C 60.35; H 6.97; N 17.60.

Ethyl 3-(1,3-dibenzyl-2-oxo-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-5-ylamino)but-2-enoate (IVc). Yield 73%, mp 80–82°C (from heptane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, OCH_2C**H**$_3$), 2.36 s (3H, CH_3), 4.17 q (2H, OCH_2), 4.74 s (1H, CH), 5.08 s (2H, 1-CH_2), 5.15 s (2H, 3-CH_2), 6.45 d (1H, 7-H, J = 8.2 Hz), 6.95 d (1H, 6-H, J = 8.2 Hz), 7.35 s (10H, C_6H_5), 10.97 s (1H, NH).

8-Hydroxy-1,3,6-trimethyl-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridin-2-one (Va) was synthesized as described above for compound **IIIa** from 6.29 mmol of enamino ester **IVa** in 9–10 ml of polyphosphoric acid. Yield 70%, mp 256–257°C (from water). ^{1}H NMR spectrum (CD_3COOD), δ, ppm: 2.58 s (3H, CH_3), 3.40 s (3H, 1-CH_3), 3.52 s (3H, 3-CH_3), 6.63 s (1H, 9-H), 8.25 s (1H, 7-H). Found, %: C 59.82; H 4.90; N 22.80. $C_{12}H_{12}N_4O_2$. Calculated, %: C 59.01; H 4.95; N 22.94.

1,3-Diethyl-8-hydroxy-6-methyl-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridin-2-one (Vb) was synthesized in a similar way from 6.29 mmol of enamino ester **IVb** in 9–10 ml of polyphosphoric acid. Yield 35%, mp 294–296°C (from water). ^{1}H NMR spectrum (CD_3COOD), δ, ppm: 1.40 t (6H, NCH_2C**H**$_3$), 2.58 s (3H, CH_3), 4.09 q (4H, NCH_2), 6.61 s (1H, 9-H), 8.33 s (1H, 7-H). Found, %: C 61.60; H 5.86; N 20.42. $C_{14}H_{16}N_4O_2$. Calculated, %: C 61.75; H 5.92; N 20.58.

1,3-Dibenzyl-8-hydroxy-7-methyl-1,3-dihydro-2*H*-imidazo[5,4-*b*][1,8]naphthyridin-2-one (Vc) was synthesized as described above for compound **IIIb** from 2.4 mmol of enamino ester **IVc** in 7 ml of diphenyl ether. Yield 66%, mp >300°C (from decane). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.60 s (3H,

CH_3), 5.10 s (4H, NCH_2), 5.93 s (1H, 9-H), 7.35 s (10H, C_6H_5), 7.97 s (1H, 7-H), 11.86 s (1H, NH). Found, %: C 72.60; H 5.03; N 14.00. $C_{24}H_{20}N_4O_2$. Calculated, %: C 72.71; H 5.09; N 14.13.

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