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Reduction of Alkyl-2-amino-5,6-dialkyl-3-cyanopyridine-4-carboxylates

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Abstract—Reduction of alkyl-2-amino-5,6-dialkyl-3-cyanopyridine-4-carboxylates with sodium borohydride in protic solvents gave rise to 4-amino-3-imino-6,7-dialkyl-1,3-dihydrofuro[3,4-*c*]pyridines that at hydrolysis in acid medium afforded the corresponding lactones.

We formerly reported on the synthesis of esters of 2-amino-5,6-dialkyl-3-cyanopyridine-4-carboxylic acids **Ia–Id** [1]. The presence of chemically active groups in the structure of pyridines **I** obtained provides a possibility of extensive investigation of their chemical properties. Their reactions with O- and N-nucleophiles were studied [2]. We carried out reactions of compounds **I** with various oxidants in order to introduce carboxy groups in the structure. It was found however that both oxidation with strong oxidants (potassium permanganate or potassium dichromate in acid medium) or with moderate oxidation agents (chromyl chloride) did not give the desired results and led to decomposition of the molecules. The oxidation apparently did not occur at the alkyl substituents but resulted in the opening of the pyridine ring and in the polymerization of the reactive linear intermediates leading to tarring. We failed to prepare pyridines **I** N-oxides by oxidation with hydrogen peroxide, and under Radziszewsky reaction conditions the cyano group proved to be stable against conversion into amide moiety.

A logical extension of the study was testing the behavior of compounds **I** in reduction processes. The molecules of these compounds contain moieties potentially capable to be reduced: the pyridine ring and functional groups (cyano and ester groups) that can be hydrogenated. The latter process is especially interesting for it may provide a structural analog of the widely known vitamin pyridoxal by transforming the ester group into a hydroxymethyl one. Besides many naturally occurring biologically active compounds contain in their structure di-, tetra-, and hexahydrogenated pyridine rings (anabasine, atropine, cocaines, aceclidine, felodipine, cerebrokrast). The compounds of pyridine series are known to be more sensitive to hydrogenation than benzene derivatives [3]. Therefore we studied the reduction effected by nucleophilic agents like complex metal hydrides, in particular, the reaction of pyridine **I** with sodium borohydride in protic solvents (alcohols and amines). The application of this reductant is justified by its availability and selectivity with respect to the mentioned groups [4]. Therewith the sensitivity of its reducing power to the reaction conditions makes this reagent the most suitable for our study since in the molecule in question several reactive centers are present [3, 4].

We found that reaction with sodium borohydride in alcohols, especially in lower alcohols, was vigorous and afforded suspension. Further treating the reaction mixture with water resulted in precipitation of fine cream-colored crystals. The compounds obtained were identified with the use of a set of physicochemical methods. The IR spectra lacked the absorption bands characteristic of cyano groups, and in the region 3420–3378 and 1669–1662 cm^{-1} appeared bands of moderate intensity which might be assigned to the stretching and bending vibrations of an imino group. The presence of the imino group in the structure of compounds **IIa–IId** was also confirmed by a singlet in the ^1H NMR spectra in the region δ 7.49–7.70 ppm. The lack of the characteristic carbonyl bands in the IR spectra and appearance of a singlet in the ^1H NMR spectra in the region 5.13–5.80 ppm revealed a presence of a methylene group apparently arising from the chemical modification of the ester moiety. The mass spectra of compounds **IIa** and **IIc** contain no molecular ion peaks, and the fragmentation is governed by the presence of an imine structure and of hydrocarbon substituents attached to the pyridine ring.

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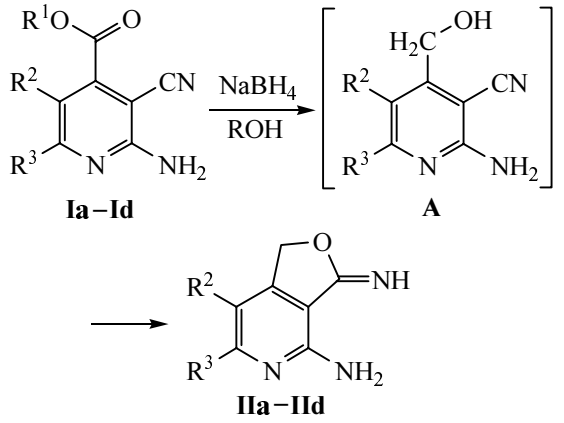
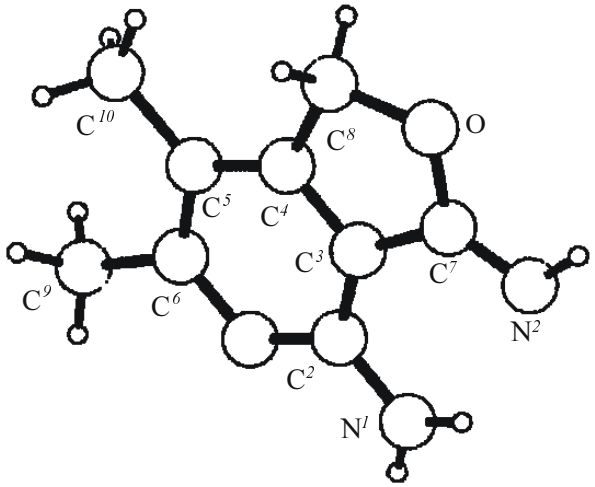


$R^1 = CH_3$, R^2,$R^3 = (CH_2)_4$ (**a**), $(CH_2)_3$ (**b**), CH_3 (**c**), $R^2 = H$, $R^3 = CH_3$ (**d**).

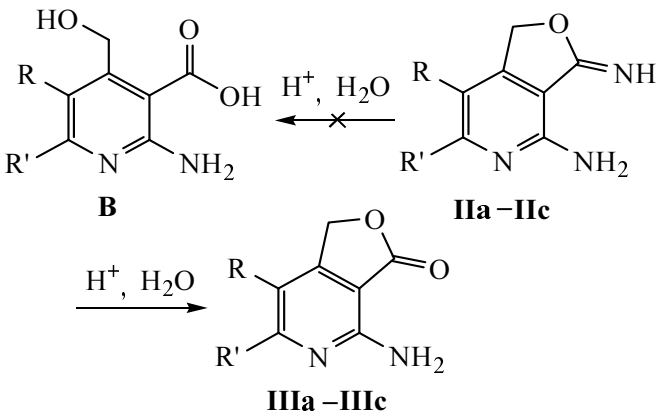
The hydride anion attack apparently occurs at the most sterically available carbon of the ester group than at the carbon atom of the pyridine ring. Therefore it is presumable that the reduction under these conditions occurs at the ester group affording a hydroxymethyl group. The resulting intermediates **A** easily undergo an intramolecular heterocyclization into 4-amino-3-imino-6,7-dialkyl-1,3-dihydrofuro[3,4-*c*]-pyridines **IIa–IId.** It should be pointed out that the pyridine ring is not reduced even at a large excess of sodium borohydride [4]. This is a novel result since in the literature is described a selective reduction of the ring in electron-deficient pyridines (pyridinecarboxylates and pyridinecarbonitriles) effected by borohydrides not affecting ester and cyano groups [3]. We believe that the formation of 1,3-dihydrofuro[3,4-*c*]-pyridine **II** along with the steric effects is due to the presence in the structure of the substrate of strong donor groups like amino group and alkyl substituents which increase the electron density in the position *4* of the pyridine ring. Besides the X-ray diffraction analysis of the structure of compound **Ic** [1] showed that the methoxycarbonyl group was not conjugated with the pyridine ring, and thus its electron-withdrawing effect did not show in a full strength. The alternative attack direction is the most available electron-deficient carbon of the ester group, and just this path is realized.



Molecular structure of 4-amino-6,7-dimethyl-3-imino-1,3-dihydrofuro[3,4-*c*]pyridine (**IIc**).

Inasmuch as the data of IR spectra on the stretching vibrations of C=NH bond were unlike published values, and in the mass spectra molecular ion peaks were lacking we carried out X-ray diffraction study on a single crystal of compound **IIc** (see figure).

The synthesized 1,3-dihydrofuro[3,4-*C*]pyridines **IIa–IId** contain in the molecule an imine fragment thus providing a possibility to study their hydrolysis. This process can afford the corresponding lactone or products of deeper transformations accompanied by ring opening, for instance, giving rise to 4-hydroxymethylpyridine-3-carboxylic acid **B** related by its structure to a number of biologically active compounds. We found that the hydrolysis of synthesized 3-iminofuro[3,4-*c*]pyridines **IIa–IIc** in 27% sulfuric acid occurred at the imino group and furnished 4-amino-6,7-dialkylfuro[3,4-*c*]pyridin-3(1*H*)-ones **IIIa–IIIc.**



R,R' = $(CH_2)_4$ (**a**), $(CH_2)_3$ (**b**), CH_3 (**c**).

The IR spectra lack the vibration bands of imino groups, but at the same time appear the stretching vibrations of the carbonyl group at 1726 cm^{-1} characteristic of conjugated γ-lactones. In the ^1H NMR spectra the resonances of the imino groups also disappear. The spectral data suggest that under the

reaction conditions the imino group is hydrolyzed, and lactones **III** form stable under given conditions against recyclization into hydroxyacids **B**. The concentration of sulfuric acid used is limiting, for at higher concentrations the initial compound suffers degradation and consequently tarring is observed.

Thus the reduction of compounds **II** under investigation effected by sodium borohydride and occurring solely at the ester group provided a possibility to synthesize 4-amino-6,7-dialkyl-3-imino-1,3-dihydrofuro[3,4-*c*]-pyridines **II** whose hydrolysis furnished the corresponding lactones **III**.

EXPERIMENTAL

The reaction progress was monitored and the purity of compounds synthesized was checked by TLC on Silufol UV-254 plates, visualizing of spots by UV radiation (365 nm) and iodine vapor. IR spectra were recorded on a spectrophotometer UR-20 from mulls in mineral oil. ^{1}H NMR spectra were registered on spectrometers Bruker WM-250, AM-300, and DRX-500 at operating frequencies 250.13, 300.13, and 500.13 MHz respectively from solutions in DMSO-d_6 (internal reference TMS). Mass spectra of high and low resolution were measured on Finnigan MAT. INCOS. 50 instrument at the ionizing electrons energy 70 eV. Parameters of unit cell and intensity of reflections in the X-ray diffraction analysis were measured on an automatic four-circle diffractometer Siemens P3/PC (λMoK_a, graphite monochromator, θ/2θ scanning).

6,7-Dialkyl-4-amino-3-imino-1,3-dihydrofuro-[3,4-*c*]pyridines IIa–IId. To a dispersion of 0.001 mol of pyridine **Ia–Id** in 10 ml of methanol at room temperature was added 0.19 g (0.005 mol) of sodium borohydride. The reaction mixture was heated at reflux for 3 h. On cooling to room temperature the mixture was diluted with 20 ml of water. The precipitated gray crystals were filtered off and washed with 1 ml of 2-propanol. The product was purified by sublimation in a vacuum and dried in a desiccator over P_2O_5.

Yield of compound **IIa** 45%, mp 180°C. IR spectrum, ν, cm^{-1}: 3378, 3304, 3287, 3164 (NH, NH_2), 1667 (C=NH). ^{1}H NMR spectrum, δ, ppm: 1.70 m (4H, CH_2CH_2 CH_2CH_2), 2.48 t (2H, CH_2CH_2), 2.68 t (2H, CH_2CH_2), 5.13 s (2H, CH_2O), 6.40 s (2H, NH_2), 7.49 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 186 (21), 175(30), 159 (34), 157 (51), 147 (73), 146 (41), 131 (18), 130 (20), 66 (20), 65 (100). Found, %: C 65.01; H 6.41; N 20.65. $C_{11}H_{13}N_3O$. Calculated, %: C 65.01; H 6.45; N 20.67.

Yield of compound **IIb** 38%, mp 176°C. IR spectrum, ν, cm^{-1}: 3386, 3297, 3279, 3140 (NH, NH_2), 1669 (C=NH). Found, %: C 63.47; H 5.84; N 22.18. $C_{10}H_{11}N_3O$. Calculated, %: C 63.48; H 5.86; N 22.21.

Yield of compound **IIc** 55%, mp 190°C. IR spectrum, ν, cm^{-1}: 3397, 3287, 3170 (NH, NH_2), 1662 (C=NH). Mass spectrum, *m/z* (I_{rel}, %): 162 (14), 148(14), 132 (42), 122 (12), 107 (10), 92 (7), 79 (9), 65(11), 52 (8), 42 (18). Found, %: C 61.02; H 6.22; N 23.68. $C_9H_{11}N_3O$. Calculated, %: C 61.00; H 6.26; N 23.71. X-ray diffraction analysis of compound **IIc**. Principal crystallographic data: *a* 7.1920 (10), *b* 7.6200 (10), *c* 9.0640 (10) Å, α 111.900 (10), β 95.580 (10), γ 108.210 (10)°, *V* 424.73(9) Å^3, *d* 1.292 mg/m^3; space group TRICLINIC, P1. All calculations were performed on PC using software SHELXTL PLUS. Atomic coordinates are available from the authors.

Yield of compound **IId** 50%, mp 185°C. IR spectrum, ν, cm^{-1}: 3420, 3288, 3230, 3130 (NH, NH_2), 1660 (C=NH). ^{1}H NMR spectrum, δ, ppm: 2.37 s (3H, CH_3), 5.80 s (2H, CH_2O), 6.50 s (1H, CH), 6.72 s (2H, NH_2), 7.70 s (1H, NH). Found, %: C 58.93; H 5.60; N 25.75. $C_8H_9N_3O$. Calculated, %: C 58.89; H 5.56; N 25.75.

4-Amino-6,7-dialkylfuro[3,4-*c*]pyridin-3-(1*H*)-ones IIIa–IIIc. A dispersion of 0.001 mol of dihydrofuro[3,4-*c*]pyridine **IIa–IIc** in 10 ml of 27% solution of sulfuric acid was heated at reflux till complete dissolution of the initial furo[3,4-*c*]pyridine. On completion of the reaction the mixture was cooled to room temperature and neutralized with a saturated solution of sodium hydrogen carbonate. Then the mixture was cooled for 1–2 h to –20°C. The separated white precipitate was filtered off, washed with 2 ml of cold 2-propanol, and purified by sublimation in a vacuum.

Yield of compound **IIIa** 78%, mp 178°C. IR spectrum, ν, cm^{-1}: 3413, 3300, 3176 (NH, NH_2), 1726 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.75 m (2H, $CH_2CH_2CH_2$), 1.79 m (2H, $CH_2CH_2CH_2$), 2.50 t (2H, CH_2CH_2), 2.69 t (2H, CH_2CH_2), 5.19 s (2H, CH_2O), 6.46 s (2H, NH_2). Found, %: C 64.59; H 5.97; N 13.92. $C_{11}H_{12}N_2O_2$. Calculated, %: C 64.69; H 5.92; N 13.72.

Yield of compound **IIIb** 67%, mp 194°C. IR spectrum, ν, cm^{-1}: 3413, 3300, 3172 (NH, NH_2), 1724 (C=O). Found, %: C 63.18; H 5.25; N 14.67. $C_{10}H_{10}N_2O_2$. Calculated, %: C 63.15; H 5.30; N 14.73.

Yield of compound **IIIc** 58%, mp 158°C. IR spectrum, ν, cm^{-1}: 3413, 3300, 3178 (NH, NH_2), 1726 (C=O). Found,

%: C 60.11; H 5.69; N 15.69. $C_9H_{10}N_2O_2$. Calculated, %: C 60.16; H 5.66; N 15.72.

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