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Alkyl 2-amino-5,6-dialkyl-3-cyanopyridine-4-carboxylates in Reactions with Electrophilic Reagents

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Abstract—In reaction of alkyl 2-amino-5,6-dialkyl-3-cyanopyridine-4-carboxylates with isocyanates formed unstable ureas, and with nitrous acid at 60–70°C alkyl 5,6-dialkyl-2-oxo-1,2-dihydro-4-pyidinecarboxylates were obtained. It was shown for the latter that their reactions with organic acids and amides occurred at the cyano group, and the alkaline hydrolysis involved the ester group.

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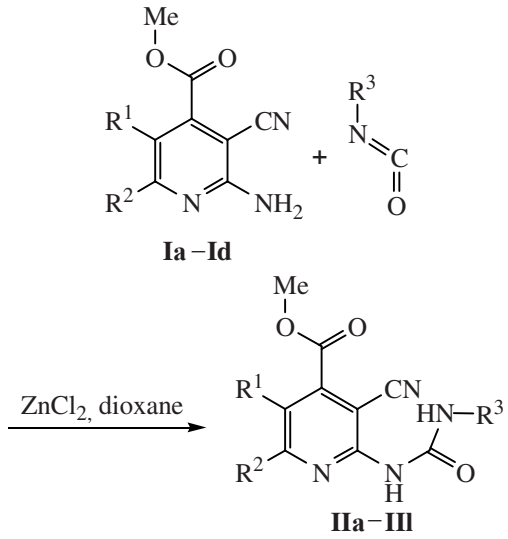
Nowadays a special attention is attracted to compounds containing the structural skeleton of the known pharmaceuticals; at the same time the presence of reactive functional groups is favorable for their further application to the synthesis of biologically active compounds. Formerly synthesized alkyl 2-amino-5,6-dialkyl-3-cyanopyridine-4-carboxylates **Ia–Ii** are promising in this respect [1, 2]. We investigated their reactions with N-, O-nucleophiles and the reduction; as a result pyrrolo[3,4-*c*]-pyridines and furo[3,4-*c*]-pyridines were obtained. In the study of the properties of the enaminonitrile fragment of pyridines **Ia–Ii** the reactivity of the functional groups combined in the structure should be taken into consideration also as separate agents. Amino group in the molecules of pyridines **Ia–Ii** possesses low basicity due to the presence of strong electron-withdrawing groups.

It is known that compounds containing in the structure an *ortho*-enaminonitrile fragment are capable to enter into electrophilic reactions at the amino group with bifunctional compounds and CH-acids (acetylacetone, ethyl acetoacetate, ethyl cyanoacetate, formamide, and formic acid), suggesting the possibility to synthesise therefrom new fused heterocycles. Amino group in pyridine **I** as show experimental data does not react by the classic scheme due to its low nucleophilicity. Therefore the reaction of pyridines **I** with active compounds like isocyanates is complicated. Notwithstanding the low nucleophilicity of the amino group we still succeeded in performing this reaction and synthesizing the corresponding ureas **IIa–III** (Scheme 1).

We used as reagents *m*-chlorophenyl isocyanate, phenyl isocyanate, and ethyl isocyanate. It was found that this reaction occurred only in the presence of Lewis acids (aluminum chloride and zinc chloride) leading to the formation of 3-cyano-2-(3-R-ureido)-5,6-dialkylpyridine-4-carboxylates **IIa–III**. The substances obtained were fine needle light-red crystals stable at room temperature.

Scheme 1.



R^3 = Et, R^1,R^2 = $(CH_2)_4$ (**a**), $(CH_2)_3$ (**b**), Me (**c**), R^1 = H, R^2 = Me, (**d**); R^3 = Ph, R^1,R^2 = $(CH_2)_4$ (**e**), $(CH_2)_3$ (**f**), Me (**g**), R^1 = H, R^2 = Me (**h**), R^3 = 3-Cl-C_6H_4, R^1,R^2 = $(CH_2)_4$ (**i**), $(CH_2)_3$ (**j**), Me (**k**), R^1 = H, R^2 = Me (**l**).

The structures of compounds **IIa–III** were suggested based on ^{1}H NMR, mass, and IR spectra. The IR spectra confirm that the ester and cyano groups remained intact as show strong bands of the stretching vibrations in the regions 1734–1703 and 2245–2233 cm^{-1} respectively. The medium absorption bands in the region 3405–3175 and 1629–1579 cm^{-1} were assigned to the stretching and bending vibrations of amino groups.

An important proof of the presence of two NH groups in the urea fragment is the appearance of singlets in the ^{1}H NMR spectrum in the region 7.79–9.92 ppm. The methoxy group gives rise to a singlet at 4.00–3.96 ppm. The presence of Lewis acids did not cause intramolecular cyclization into pyrrolo[3,4-*c*]pyridines like in reactions with formamide or other bifunctional compounds. This fact is due to the total absence of water in the system. However the prolonged heating led to the formation of insignificant amounts of the mentioned pyrrolo[3,4-*c*]-pyridines, and in some cases these substances formed in a quantitative yield. The governing factor here is the synthesis conditions and the stability of ureas obtained.

Compounds **IIa–III** are of low stability, and in acid medium or in the presence of small quantity of aluminum oxide the urea fragment suffers decomposition, and form initial pyridines **I**. A similar pattern is followed by TLC. The mass spectra of synthesized ureas **IIa–III** are characterized by molecular ions of various intensity apparently due to the nature of the used isocyanate.

A characteristic feature of aromatic amines is diazotization commonly performed by treating with nitrous acid at low temperature [3–7].

A distinctive feature of this reaction with compounds **Ia–Ii** is its uncommon conditions. Diazotization of the amino group in pyridines **Ia–Ii** occurred only at elevated temperature (60–70°C). However the stability of diazonium salts decreases with rising temperature. Apparently the observed temperature mode of this reaction is the formation not of diazopyridines **A** but alkyl 5,6-dialkyl-2-oxo-1,2-dihydropyridine-4-carboxylates **IIIa–IIIi** (Scheme 2). The obtained esters **IIIa–IIIi** are dark-yellow crystalline substances stable in air and strongly fluorescent even in highly diluted solutions.

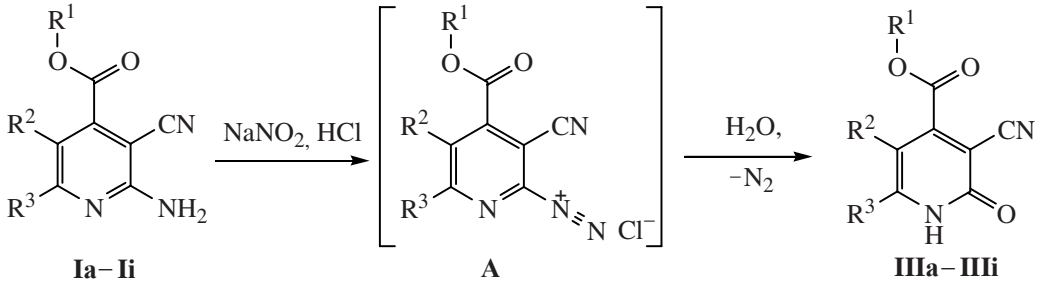
In the IR spectra of compounds **IIIa–IIIi** the presence of strong absorption bands in the region 1707–1724 and 2232–2243 cm^{-1} indicated the presence in the molecules of a carbonyl and a conjugated cyano groups. The medium bands in the region 3460–3147 and 1625–1587 cm^{-1} evidenced the presence of the stretching and bending vibrations of the NH bond, and the absorption bands in the region 1669–1630 cm^{-1} were assigned to the vibrations of the amide carbonyl.

In the ^{1}H NMR spectra of compounds **IIIa–IIIi** singlets appeared at 10.13–13.92 ppm characteristic of NH groups of a pyridone ring. Mass spectra of pyridones **IIIa–IIIi** contain molecular ions peaks of low intensity and also strong peaks of fragment ions $[M - CH_3]^+$, $[M - OCH_3]^+$ whose formation is due to the presence of ester groups in the molecules.

The spectral data suggest with a high probability that the reaction proceeds by the assumed Scheme 2. The primary formation of a diazo group by diazotization of the amino group in acid medium does not differ from the synthesis of similar known aromatic diazo structures except for the modified conditions of the process. Further the diazo product apparently suffers hydrolysis in the water medium at the formed diazo group resulting in its replacement and introduction of a hydroxy group into the pyridine ring; the product readily isomerizes into more stable pyridones **IIIa–IIIi**.

We continuously attempted to find favorable conditions and methods for introducing diazo group. Neither of the procedures used gave a positive result.

Scheme 2.



Ia–Ii **A** **IIIa–IIIi**

R^1 = Me, R^2,R^3= $(CH_2)_4$ (**a**), $(CH_2)_3$ (**b**), Me (**c**); R^1 = R^3 = Me, R^2 = H (**d**); R^1 = $HOCH_2CH_2$, R^2,R^3 = $(CH_2)_4$ (**e**), $(CH_2)_3$ (**f**), Me (**g**), R^2 = H, R^3 = Me (**h**); R^1 = Et, R^2,R^3 = $(CH_2)_4$ (**i**).

Thus the above reaction is, firstly, a preparative method of synthesis for pyridones **IIIa–IIIi**, and secondly, an illustrative example of diazotization proceeding at high temperature demonstrating the versatility of classic reactions.

The presence in the structure of pyridones **IIIa–IIIi** like in that of pyridines **Ia–Ii** of several reactive sites, such as ester and cyano groups, makes it possible to study their reactions with N- and O-nucleophiles. The hydrolysis of pyridones **IIIa–IIIi** with mineral acids occurred along the pattern analogous to the reaction of pyridines **I** involving directly the ester and cyano group and providing 6,7-dialkyl-1H-pyrrolo[3,4-*c*]pyridine-1,3,4(2*H*,5*H*)-triones **IVa–IVd** in virtually quantitative yields (Scheme 3).

Compounds **IVa–IVd** are yellow fine crystalline substances sparingly soluble in most organic solvents save hot DMSO. Their structure was assumed based on spectral data. In the IR spectra of compounds obtained two strong absorption bands are present in the region 1717–1702 cm^{-1} originating from the stretching vibrations of the carbonyl group in the imide moiety. The absorption bands in the region 3340–3110 and 1640–1630 cm^{-1} correspond to the stretching and bending vibrations of the amino group. The additional most informative signals in the region 1685–1670 and 1587–1530 cm^{-1} are the absorption bands "amide I" and "amide II". The ^1H NMR data indicate the presence of two NH groups giving rise to two informative downfield singlets at 10.80–10.87 and 12.30–12.57 ppm respectively.

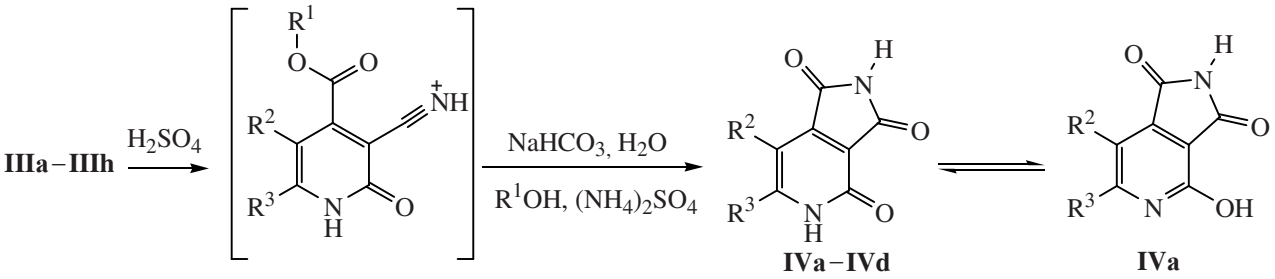
Identification of compounds **IVa–IVd** suggested a scheme assuming that the hydrolysis of 4-pyridinecarboxylates derivatives started at the cyano group located in the *ortho*-position with respect to the akoxycarbonyl moiety. We presume that this route is preferable because of more favorable stabilization by cyclization involving the ester group. Hydrolysis of cyanopyridones **III** like pyridines **I** occurred in acid medium evidently by $A_{aC}1$ mechanism. The distinctive feature of the process is that it easyly proceeded with quantitative yield even at low temperature.

^1H NMR spectroscopy revealed that pyrrolo[3,4-*c*]-pyridine-1,3,4(2*H*,5*H*)-trione **IVa** in DMSO underwent equilibrium tautomeric transformation of the amide form into imidol one **IVa'**, and the content of the latter according to ^1H NMR was 25%.

Inasmuch as compounds **III** underwent the acid hydrolysis by the same scheme as pyridines **I** [2] we additionally compared their reactions with organic acids, amides, and alkali. 6,7-Dialkyl-1*H*-pyrrolo[3,4-*c*]-pyridine-1,3,4(2*H*,5*H*)-trione (**IVa**) was also obtained by reactions of pyridone **IIIa** with organic acids and the corresponding amides. The pattern of trione **IVa** formation (Scheme 4) evidently does not differ from the analogous reaction of pyridine **I** with these reagents. Organic acids and their amides also behave as O-nucleophiles with respect to the carbon of the cyano group of pyridone **IIIa**. The used reagents were formic and butyric acids, formamide, and acetamide. This approach is distinguished by milder reaction conditions. To support the assumed scheme we identified in the reaction mixtures by GLC arising acetonitrile and methyl butyrate in reactions with acetamide and butyric acid respectively.

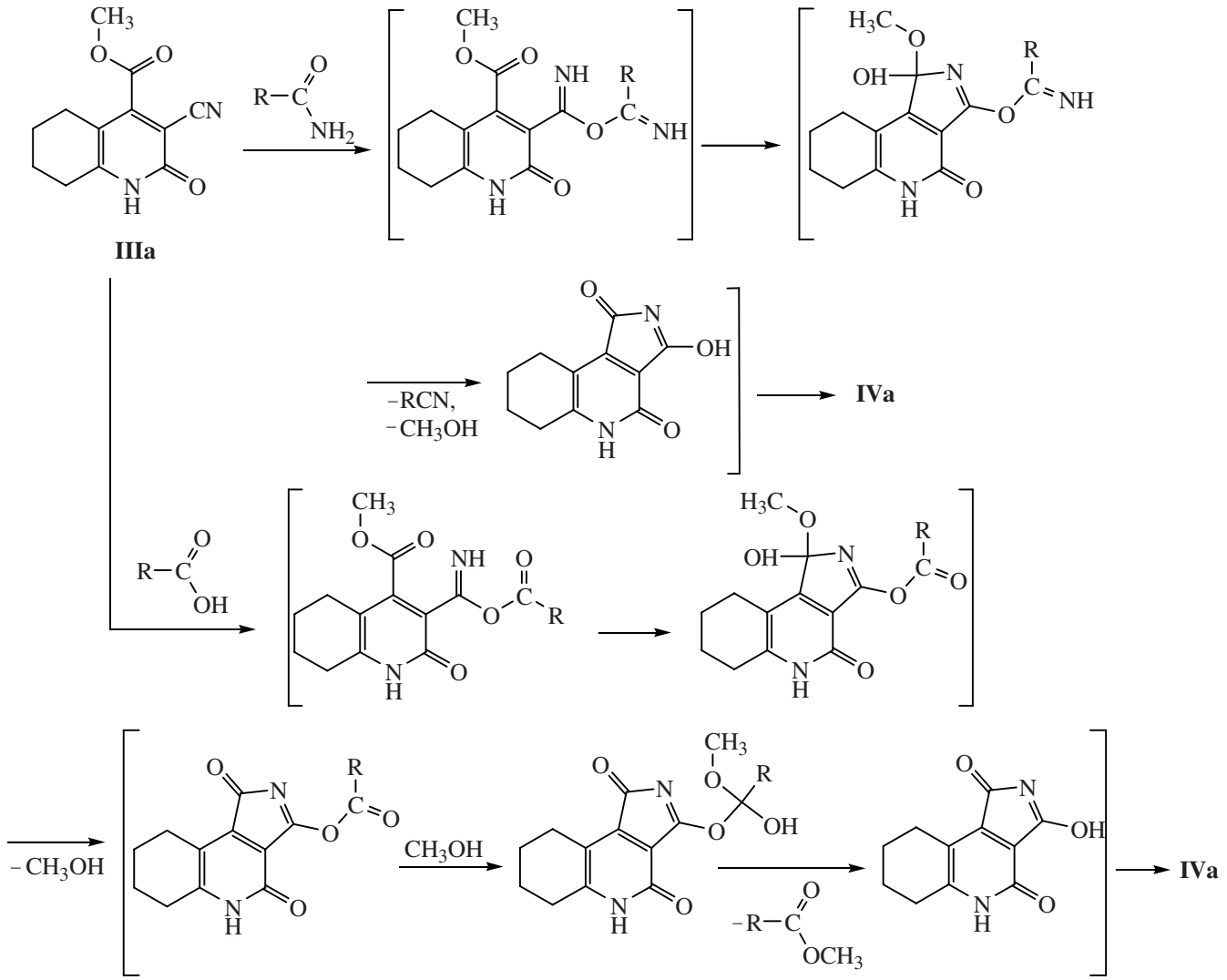
The presence of an ester fragment in pyridones **III** structure, like in pyridines **I** suggested to test their reaction with alkali. The experiments showed that pyridones **III** readily reacted with alkali solutions to give solutions of isonicotinic acids salts **B**. A specific feature of the reaction was unsuccessful attempt to isolate pyridine-4-carboxylic acid sodium salt **B**. The attempts to isolate the salt in the individual state, like in hydrolysis of pyridines **I** in alkali [2], resulted in intramolecular

Scheme 3.



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

Scheme 4.



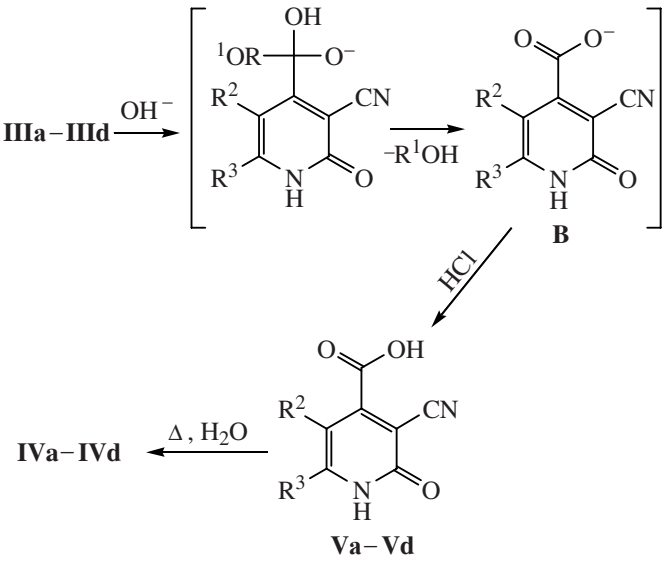
R = H, Me, Pr.

heterocyclization with a simultaneous formation of an imide ring. At the same time a cautious neutralization of the salts solutions with diluted acids till pH 4 (against Congo Red) permitted a synthesis of the corresponding acids **Va** and **Vd** that we isolated and identified.

The structure of 5,6-dialkyl-2-oxo-1,2-dihydro-4-pyridine carboxylic acids **Va–Vd** was derived from the IR and ^{1}H NMR spectra, the composition was confirmed by elemental analysis. In the IR spectra the characteristic strong bands in the region 2241–2235cm^{-1} indicate the presence of a conjugated cyano group, and the absorption in the region 1710–1707 cm^{-1} corresponds to the stretching vibrations of the carbonyl group. Absorption bands "amide I " and "amide II" appear in the region 1679–1680 and 1555–1541 cm^{-1} respectively, and in the region 3382–3227 and 1630–1617 cm^{-1} the stretching and bending vibrations of NH bonds are observed.

^{1}H NMR spectra give the best confirmation of the suggested structures by observation in the downfield region of acid hydroxy group signal at 12.20–12.75 ppm. The resonance at 9.20 ppm belongs to the NH group of the pyridone ring, but in the spectrum of compound **Vd** this peak does not appear or is of low intensity. The solutions of 2-oxoisonicotinic acids **V** and their salts are unstable and at heating or at long storage in the presence of moisture traces they undergo intramolecular cyclization into pyrrolo[3,4-*c*]pyridine-1,3,4-triones **IVa–IVd**.

Thus pyridones **III** that we synthesized are similar in reactivity to pyridines **I** in reactions with O-nucleophiles



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

and suffer hydrolysis with acids and alkali with the direct participation of cyano or ester groups.

EXPERIMENTAL

The monitoring of reactions progress and checking the purity of substances obtained was performed by TLC on Silufol UV-254 plates, development under UV irradiation (365 nm) or in iodine vapor. IR spectra were recorded on a spectrophotometer UR-20 from thin films (or mulls in mineral oil). ^{1}H NMR spectra were registered from solutions in DMSO-d_6 on spectrometers Bruker WM-250, Bruker AM-300, Bruker DRX-500 at operating frequencies 250.13, 300.13, and 500.13 M Hz respectively (internal refeence TMS). Mass spectra of high and low resolution were taken on a Finnigan MAT INCOS-50 instrument at the ionization energy 70 eV. GLC analyses were carried out on a chromatograph LKhM-6MD equipped with katharometer, column 3000×3 mm, stationary phase SP-2100 (or XE-60), 5% on the carrier Chromaton N-AW-DMCS, grains 0.250–0.315 μm, oven temperature 115–120°C, carrier gas helium, flow rate 40 ml/min, detector current 140 μA, sensitivity 10, sample volume 0.5 μl, rate of the recorder chart 240 mm/h.

Methyl 5,6-dialkyl-3-cyano-2-(3-ethylureido)-pyridine-4-carboxylates IIa–IId. To a solution of 1 mmol of pyridine **Ia–Id** in 5 ml of anhydrous dioxane at exclusion of air moisture was added 0.71 g (0.01 mol) of ethyl isocyanate and 0.0136 g (0.1 mmol) of anhydrous zinc chloride. The mixture was boiled at exclusion of air moisture till disappearance of the initial pyridine. The mixture was cooled to –5°C for 5 h, the separated colorless precipitate was quickly filtered off, washed with 5 ml of anhydrous ethyl ether, and dried in a vacuum desiccator.

Methyl 5,6-dialkyl-3-cyano-2-(3-phenylureido)-pyridine-4-carboxylates IIe–IIh were similarly prepared from 1 mmol of pyridine **Ia–Id** and 1.2 g (0.01 mol) of phenyl isocyanate.

Methyl 5,6-dialkyl-3-cyano-2-[3'-(3''-chlorophenyl)ureido]pyridine-4-carboxylates IIi–IIl were similarly prepared from 1 mmol of pyridine **Ia–Id** and 1.5 g (0.01 mol) *m* -chlorophenyl isocyanate.

Methyl 5,6-tetramethylene-3-cyano-2-(3-ethylureido)pyridine-4-carboxylate (IIa). Yield 54%, mp 112°C. IR spectrum, ν, cm^{-1}: 3305, 3292, 3185 (NH, NH_2), 1734 (C=O), 2242 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.07 t (3H, CH_3CH_2), 1.87 m (4H, $CH_2CH_2CH_2CH_2$), 2.87 t (2H, CH_2CH_2), 2.97 t (2H, CH_2CH_2), 3.18 q (2H, CH_2CH_3), 4.00 s (3H, CH_3), 7.79 s (1H, NH), 8.15 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 302 (88) $[M]^+$, 258 (71), 244 (29), 231 (86), 216 (69), 116 (55), 101 (15), 71 (17), 56 (22), 44 (100). Found, %: C 59.69; H 6.17; N 18.47. $C_{15}H_{18}N_4O_3$. Calculated, %: C 59.59; H 6.00; N 18.53. *M* 302.33.

Methyl 5,6-trimethylene-3-cyano-2-(3-ethylureido)-pyridine-4-carboxylate (IIb). Yield 57%, mp 158°C. IR spectrum, ν, cm^{-1}: 3306, 3292, 3187 (NH, NH_2), 1716 (C=O), 2237 (C≡N). Found, %: C 58.35; H 5.39; N 19.51. $C_{14}H_{16}N_4O_3$. Calculated, %: C 58.32; H 5.59; N 19.43.

Methyl 5,6-dimethyl-3-cyano-2-(3-ethylureido)-pyridine-4-carboxylate (IIc). Yield 34%, mp 147°C. IR spectrum, ν, cm^{-1}: 3405, 3356, 3276, 3190 (NH, NH_2), 1728 (C=O), 2245 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.12 t (3H, CH_3CH_2), 2.39 s (3H, CH_3), 2.60 s (3H, CH_3), 3.20 q (2H, CH_2CH_3), 4.01 s (3H, CH_3), 7.62 s (1H, NH), 8.71 s (1H, NH). Found, %: C 56.54; H 5.68; N 20.23. $C_{13}H_{16}N_4O_3$. Calculated, %: C 56.51; H 5.84; N 20.28.

Methyl 6-methyl-3-cyano-2-(3-ethylureido)-pyridine-4-carboxylate (IId). Yield 45%, mp 163°C. IR spectrum, ν, cm^{-1}: 3370, 3250, 3187 (NH, NH_2), 1717 (C=O), 2230 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.17 t (3H, CH_3CH_2), 2.59 t (3H, CH_3), 3.25 q (2H, CH_2CH_3), 3.97 s (3H, CH_3), 7.47 s (1H, CH), 7.98 C (1H, NH), 8.52 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 262 (2) $[M]^+$, 217 (3), 191 (100), 160 (24), 133 (26), 91 (19), 64

(8), 42 (20). Found, %: C 55.01; H 5.24; N 21.47. $C_{12}H_{14}N_4O_3$. Calculated, %: C 54.96; H 5.38; N 21.36. *M* 262.27.

Methyl 5,6-tetramethylene-2-(3-phenylureido)-3-cyanopyridine-4-carboxylate (IIe). Yield 36%, mp 181°C. IR spectrum, ν, cm^{-1}: 3323, 3282, 3193 (NH, NH_2), 1716 (C=O), 2237 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.80 m (2H, $CH_2CH_2CH_2CH_2$), 1.87 m (2H, $CH_2CH_2CH_2CH_2$), 2.70 t (2H, CH_2CH_2), 2.93 t (2H, CH_2CH_2), 3.96 s (3H, CH_3), 7.25 m (5H, C_6H_5), 9.18 s (1H, NH), 9.18 s (1H, NH). Found, %: C 65.01; H 5.27; N 15.86. $C_{19}H_{18}N_4O_3$. Calculated, %: C 65.13; H 5.18; N 15.99.

Methyl 5,6-trimethylene-2-(3-phenylureido)-3-cyanopyridine-4-carboxylate (IIf). Yield 41%, mp 192°C. IR spectrum, ν, cm^{-1}: 3379, 3253, 3185 (NH, NH_2), 1713 (C=O), 2241 (C≡N). Found, %: C 64.58; H 4.62; N 16.74. $C_{18}H_{16}N_4O_3$. Calculated, %: C 64.28; H 4.79; N 16.66.

Methyl 5,6-dimethylene-2-(3-phenylureido)-3-cyanopyridine-4-carboxylate (IIg). Yield 47%, mp 161°C. IR spectrum, ν, cm^{-1}: 3323, 3285, 3195 (NH, NH_2), 1717 (C=O), 2233 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.21 s (3H, CH_3), 2.59 s (3H, CH_3), 3.99 s (3H, CH_3), 6.95 m (5H, C_6H_5), 9.21 s (1H, NH), 9.51 s (1H, NH). Found, %: C 62.77; H 4.81; N 17.38. $C_{17}H_{16}N_4O_3$. Calculated, %: C 62.95; H 4.97; N 17.27.

Methyl 6-methyl-2-(3-phenylureido)-3-cyanopyridine-4-carboxylate (IIh). Yield 32%, mp 176°C. IR spectrum, ν, cm^{-1}: 3365, 3249, 3185 (NH, NH_2), 1714 (C=O), 2235 (C≡N). Found, %: C 61.85; H 4.71; N 18.17. $C_{16}H_{14}N_4O_3$. Calculated, %: C 61.93; H 4.55; N 18.06.

Methyl 5,6-tetramethylene-2-[3-(3-chlorophenyl)]-3-cyanopyridine-4-carboxylate (IIi). Yield 43%, mp 260°C. IR spectrum, ν, cm^{-1}: 3385, 3307, 3187 (NH, NH_2), 1721 (C=O), 2240 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.85 m (4H, $CH_2CH_2CH_2CH_2$), 2.73 t (2H, CH_2CH_2), 2.96 t (2H, CH_2CH_2), 3.97 s (3H, CH_3), 7.03 d (1H, C_6H_5), 7.30 d.d (1H, C_6H_5), 7.70 s (1H, CH), 9.28 s (1H, NH), 9.92 s (1H, NH). Found, %: C 59.53; H 4.56; N 9.11. $C_{19}H_{17}ClN_4O_3$. Calculated, %: C 59.30; H 4.45; N 9.21.

Methyl 5,6-trimethylene-2-[3-(3-chlorophenyl)]-3-cyanopyridine-4-carboxylate (IIj). Yield 39%, mp 215°C. IR spectrum, ν, cm^{-1}: 3382, 3264, 3178 (NH, NH_2), 1716 (C=O), 2234 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.16 m (2H, $CH_2CH_2CH_2$), 2.93 t (2H, CH_2CH_2), 3.58 t (2H, CH_2CH_2), 4.05 s (3H, CH_3), 7.03 d (1H, C_6H_5), 7.30 d.d (1H, C_6H_5), 7.70 d (1H, C_6H_5), 9.12 s (1H, NH), 9.79 s (1H, NH). Found, %: C 58.47; H 4.19; N 9.49. $C_{18}H_{15}ClN_4O_3$. Calculated, %: C 58.31; H 4.08; N 9.56.

Methyl 5,6-dimethyl-2-[3-(3-chlorophenyl)]-3-cyanopyridine-4-carboxylate (IIk). Yield 41%, mp 140°C. IR spectrum, ν, cm^{-1}: 3382, 3248, 3175 (NH, NH_2), 1720 (C=O), 2235 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 2.59 s (3H, CH_3), 4.00 s (3H, CH_3), 7.00 d (1H, C_6H_5), 7.29 d.d (1H, C_6H_5), 7.70 d (1H, C_6H_5), 9.29 s (1H, NH), 9.83 s (1H, NH). Found, %: C 56.73; H 4.17; N 9.75. $C_{17}H_{15}ClN_4O_3$. Calculated, %: C 56.91; H 4.21; N 9.88.

Methyl 6-methyl-2-[3-(3-chlorophenyl)]-3-cyanopyridine-4-carboxylate (III). Yield 52%, mp 138°C. IR spectrum, ν, cm^{-1}: 3337, 3285 (NH, NH_2), 1703 (C=O), 2234 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.63 t (3H, CH_3), 3.95 s (3H, CH_3), 7.00 s (1H, CH), 7.07 s (1H, C_6H_5), 7.29 d.d (1H, C_6H_5), 7.70 d (1H, C_6H_5), 9.11 s (1H, NH), 10.11 s (1H, NH). Mass spectrum: *m/z* (I_{rel}, %): 344(11) $[M]^+$, 217(14), 191(100), 186(23), 160(27), 153(36), 133(23), 127(46), 99(38), 63(31), 42(23). Found, %: C 55.87; H 3.77; N 10.14. $C_{16}H_{13}ClN_4O_3$. Calculated, %: C 55.74; H 3.80; N 10.28. *M* 344.76.

Alkyl 5,6-dialkyl-2-oxo-1,2-dihydropyridine-4-carboxylates IIIa–IIIi. A dispersion of 1 mmol of pyridine **Ia–Ii** in 50 ml of 10% water solution of sodium nitrite was heated to 65°C, and gradually was added dropwise 5% HCl. The diazotization process was monitored by test with iodine-starch test paper. The completion of the reaction was determined by TLC. On the completion of the reaction the mixture was cooled to 0°C. The precipitated yellow crystals of the product were filtered off, washed with 3 ml of 2-propanol, recrystallized from DMF, and dried in a vacuum desiccator.

Methyl 2-oxo-5,6-tetramethylene-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIa). Yield 43%, mp 200°C. IR spectrum, ν, cm^{-1}: 3460, 3307, 3205, 3155 (NH, NH_2), 1724 (C=O), 2232 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.71 m (4H, $CH_2CH_2CH_2CH_2$), 2.34 t (2H, CH_2CH_2), 2.64 t (2H, CH_2CH_2), 3.92 s (3H, CH_3), 12.65 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 232 (27) $[M]^+$, 217 (100), 201 (20), 200 (27), 199 (89), 71 (30), 70 (26), 69 (42), 60 (34). Found, %: C 62.13; H 5.17; N 12.11. $C_{12}H_{12}N_2O_3$. Calculated, %: C 62.06; H 5.21; N 12.06. *M* 232.24.

Methyl 2-oxo-5,6-trimethylene-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIb). Yield 68%, mp

215°C. IR spectrum, ν, cm^{-1}: 3535, 3385, 3290 (NH, NH_2), 1723 (C=O), 2235 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.11 m (4H, $CH_2CH_2CH_2$), 2.81 t (2H, CH_2CH_2), 2.86 t (2H, CH_2CH_2), 3.93 s (3H, CH_3), 13.09 s (1H, NH). Found, %: C 60.59; H 4.65; N 12.76. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.55; H 4.62; N 12.84.

Methyl 5,6-dimethyl-2-oxo-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIc). Yield 47%, mp 220°C. IR spectrum, ν, cm^{-1}: 3457, 3316, 3167 (NH, NH_2), 1720 (C=O), 2232 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.95 t (3H, CH_3), 2.31 t (3H, CH_3), 3.97 s (3H, CH_3), 12.80 s (1H, NH). Found, %: C 58.24; H 4.91; N 13.53. $C_{10}H_{10}N_2O_3$. Calculated, %: C 58.25; H 4.89; N 13.59.

Methyl 6-methyl-2-oxo-3-cyano-1,2-dihydropyridine-4-carboxylate (IIId). Yield 38%, mp 240°C. IR spectrum, ν, cm^{-1}: 3365, 3310, 3150 (NH, NH_2), 1722 (C=O), 2233 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.34 t (3H, CH_3), 6.50 s (1H, CH), 13.92 s (1H, NH). Found, %: C 56.22; H 4.21; N 14.58. $C_9H_8N_2O_3$. Calculated, %: C 56.25; H 4.20; N 14.58.

2-Hydroxyethyl 2-oxo-5,6-tetramethylene-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIe). Yield 58%, mp 262°C. IR spectrum, ν, cm^{-1}: 3437, 3352, 3185 (NH, NH_2), 1713 (C=O), 2243 (C≡N). Mass spectrum, *m/z* (I_{rel}, %): 262 (25) $[M]^+$, 217 (100), 200 (86), 172 (84), 145 (20), 118 (18), 104 (22), 91 (28), 77 (28), 41 (27). Found, %: C 59.49; H 5.39; N.65. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54; H 5.38; N 10.68. *M* 262.

2-Hydroxyethyl 2-oxo-5,6-trimethylene-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIe). Yield 63%, mp 258°C. IR spectrum, ν, cm^{-1}: 3437, 3350, 3180 (NH, NH_2), 1713 (C=O), 2244 (C≡N). Found, %: C 58.16; H 4.84; N 11.33. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.06; H 4.87; N 11.29.

2-Hydroxyethyl 5,6-dimethyl-2-oxo-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIg). Yield 70%, mp 230°C. IR spectrum, ν, cm^{-1}: 3480, 3365, 3170 (NH, NH_2), 1726 (C=O), 2237 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.62 t (3H, CH_3), 2.18 t (3H, CH_3), 2.57 t (2H, CH_2CH_2OH), 1.47 m (2H, CH_2CH_2OH), 3.71 s (1H, OH), 10.13 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %):236 (3) $[M]^+$, 235 (8), 234 (16), 216 (7), 197 (23), 159 (100), 131 (42), 118 (30), 114 (29), 104 (42), 90 (54), 77 (36), 73 (40). Found, %: C 55.56; H 5.22; N 11.78. $C_{11}H_{12}N_2O_4$. Calculated, %: C 55.93; H 5.12; N 11.86. *M* 236.23.

2-Hydroxyethyl 6-methyl-2-oxo-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIh). Yield 37%, mp 207°C. IR spectrum, ν, cm^{-1}: 3442, 3356, 3274, 3156 (NH, NH_2), 1707 (C=O), 2232 (C≡N). Mass spectrum, *m/z* (I_{rel}, %): 222 (9) $[M]^+$, 192 (19), 179 (13), 162 (69), 134 (100), 105 (12), 92 (13), 78 (10), 64 (15), 42 (39). Found, %: C 54.13; H 4.43; N 12.76. $C_{10}H_{10}N_2O_4$. Calculated, %: C 54.05; H 4.54; N 12.61. *M* 222.20.

Ethyl 2-oxo-5,6-tetramethylene-3-cyano-1,2-dihydropyridine-4-carboxylate (IIIi). Yield 65%, mp 193°C. IR spectrum, ν, cm^{-1}: 3435, 3305, 3250, 3147 (NH, NH_2), 1713 (C=O), 2232 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.35 t (3H, CH_3CH_2), 1.71 m (4H, $CH_2CH_2CH_2CH_2$), 2.35 t (2H, CH_2CH_2), 2.63 t (2H, CH_2CH_2), 4.40 q (2H, CH_2CH_3), 12.62 s (1H, NH). Found, %: C 63.43; H 5.75; N 11.31. $C_{13}H_{14}N_2O_3$. Calculated, %: C 63.40; H 5.73; N 11.38.

6,7-Dialkyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,4-(2*H*,5*H*)triones IVa–IVd. A solution of 1 mmol of pyridone **IIIa–IIIh** was heated at 150°C for 1 min in 2 ml of concn. H_2SO_4. On cooling to room temperature the reaction mixture was neutralized with concn. $NaHCO_3$ toward litmus. Yellow precipitate was filtered off, washed with 5 ml of 2 propanol, recrystallized from DMF, and dried in a vacuum desiccator.

6,7-Tetramethylene-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,4(2*H*,5*H*)trione (IVa). Yield 84%, mp 260°C. IR spectrum, ν, cm^{-1}: 3340, 3280 (NH, NH_2), 1717, 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.75 m (4H, $CH_2CH_2CH_2CH_2$), 2.51 t (2H, CH_2CH_2), 2.92 t (2H, CH_2CH_2), 6.37 s 1H, OH), 10.80 s (1H, NH), 12.30 s (1H, NH). Found, %: C 60.41; H 4.63; N 12.85. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.55; H 4.62; N 12.84.

6,7-Trimethylene-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,4(2*H*,5*H*)trione (IVb). Yield 95%, mp 271°C. IR spectrum, ν, cm^{-1}: 3221, 3157 (NH, NH_2), 1709, 1702 (C=O). Found, %: C 58.60; H 3.97; N 13.69. $C_{10}H_8N_2O_3$. Calculated, %: C58.82; H 3.95; N 13.72.

6,7-Dimethyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,4(2*H*,5*H*)trione (IVc). Yield 83%, mp 262°C. IR spectrum, ν, cm^{-1}: 3220, 3150 (NH, NH_2), 1710, 1702 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH_3), 2.37 s (3H, CH_3), 10.83 s (1H, NH), 12.50 s (1H, NH). Found, %: C 56.40; H 4.15; N 14.60. $C_9H_8N_2O_3$. Calculated,%: C 56.25; H 4.20; N 14.58.

6-Methyl-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,4-(2*H*,5*H*)trione (IVd). Yield) 87%, mp 259°C. IR spectrum, ν, cm^{-1}: 3285,3110 (NH, NH_2), 1717, 1705 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.50 s (3H, CH_3), 6.40 s (1H, CH), 10.87 s (1H, NH), 12.57 s (1H, NH).

Found, %: C 53.97; H 3.46; N 15.62. $C_8H_6N_2O_3$. Calculated,%: C 53.94; H 3.39; N 15.73.

6,7-Tetramethylene-1*H*-pyrrolo[3,4-*c*]pyridine-1,3,4(2*H*,5*H*)trione (IVa). *a.* A dispersion of 0.232 g (1 mmol) of pyridone **IIIa** in 2 ml of formamide was sealed in an ampule and heated for 12 h at 130°C. On completion of the reaction the cooled ampule was carefully opened, and the reaction mixture was diluted with 2 ml of 1,4-dioxane. The yellow precipitate was filtered off, washed with 2 ml of 1,4-dioxane, recrystallized from DMF, and dried in a vacuum desiccator. Yield 0.166 g (76%), mp 260°C. Found, %: C 60.41; H 4.63; N 12.85. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.55; H 4.62; N 12.84.

b. Under conditions similar to procedure *a* by reaction of 0.232 g (1 mmol) of pyridone **IIIa** with 0.0886 g (0.0015 mol) of acetamide we obtained 0.142 g (65%) of trione **IVa**. To prove acetonitrile formation in the reaction a fraction boiling within 76–85°C was taken from the filtrate, and the presence of acetonitrile in the fraction was confirmed by GLC.

c. Under conditions similar to procedure *a* we obtained 0.105 g (48%) of pyrrolo[3,4-*c*]pyridine (**IVa**) from 0.231 (0.001 mol) of pyridone **IIIa** and a mixture of 2 ml of butyric acid and 0.5 ml of butyric anhydride. To prove methyl butyrate formation in the reaction a fraction boiling within 95-110°C was taken from the filtrate, and the presence of methyl butyrate in the fraction was confirmed by GLC.

d. Under conditions similar to procedure *a* we obtained 0.168 g (77%) of pyrrolo[3,4-*c*]pyridine (**IVa**) from 0.231 g (0.001 mol) of pyridone **IIIa** and freshly distilled formic acid.

5,6-Dimethyl-2-oxo-3-cyano-1,2-dihydropyridine-4-carboxylic acids Va–Vd. In a mixture of 0.4 g (0.001 mol) of NaOH and 1 ml of water was dissolved at slight heating 0.001 mol of pyridone **IIIa–IIIh**. To the solution obtained was added dropwise 5% solution of hydrochloric acid till pH 4 against Congo Red. Some time later the reaction mixture get turbid. The colorless precipitate obtained was filtered off, washed with 3 ml of water, and recrystallized from water; the product was dried in a vacuum desiccator till constant weight.

2-Oxo-5,6-tetramethylene-3-cyano-1,2-dihydropyridine-4-carboxylic acid (Va). Yield 46%, mp 243°C. IR spectrum, ν, cm^{-1}: 3376, 3227 (NH, NH_2), 1710 (C=O), 2241 (C≡N). ^1H NMR spectrum, δ, ppm: 1.73 m (4H, $CH_2CH_2CH_2CH_2$), 2.34 t (2H, CH_2CH_2), 2.62 t (2H, CH_2CH_2), 9.20 s (1H, NH), 12.20 s (1H, OH). Found, %: C 60.34; H4.56; N 12.87. $C_{11}H_{10}N_2O_3$. Calculated, %: C 60.55; H 4.62; N 12.84.

2-Oxo-5,6-trimethylene-3-cyano-1,2-dihydropyridine-4-carboxylic acid (Vb). Yield 57%, mp 239°C. IR spectrum, ν, cm^{-1}: 3378, 3225 (NH, NH_2), 1708 (C=O), 2240 (C≡N). Found, %: C 58.68; H 3.93; N 13.67. $C_{10}H_8N_2O_3$. Calculated, %: C 58.82; H 3.95; N 13.72.

5,6-Dimethyl-2-oxo-3-cyano-1,2-dihydropyridine-4-carboxylic acid (Vc). Yield 43%, mp 196°C. IR spectrum, ν, cm^{-1}: 3380, 3227 (NH, NH_2), 1710 (C=O), 2237 (C≡N). Found, %: C 56.39; H 4.27; N 14.64. $C_9H_8N_2O_3$. Calculated, %: C56.25; H 4.20; N 14.58.

6-Methyl-2-oxo-3-cyano-1,2-dihydropyridine-4-carboxylic acid (Vd). Yield 34%, mp 185°C. IR spectrum, ν, cm^{-1}: 3382, 3286 (NH, NH_2), 1707 (C=O), 2235 (C≡N). ^1H NMR spectrum, δ, ppm: 2.32 s (3H, CH_3), 6.49 s (1H, CH), 12.75 s (1H, OH). Found, %: C 53.99; H 3.46; N 15.55. $C_8H_6N_2O_3$. Calculated, %: C 53.94; H 3.39; N 15.73.

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