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INTERACTION OF ALKYL 5,6-DIALKYL-2-AMINO-3-CYANO-4-PYRIDINECARBOXYLATES WITH O-NUCLEOPHILES. SYNTHESIS OF 6,7-DIALKYL-4-AMINO-2,3-DIHYDRO-1H-PYRROLO[3,4-*c*]PYRIDINE-1,3-DIONES

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The reaction of alkyl 5,6-dialkyl-2-amino-3-cyano-4-pyridinecarboxylates with certain O-nucleophiles was investigated, as a result of which 6,7-dialkyl-4-amino-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-diones were synthesized.

Keywords: amide, aminopyridines, enamines, isonicotinic acid, imide, nitriles, nucleophiles, pyridines, hydrolysis.

Previously we reported the preparation of alkyl 5,6-dialkyl-2-amino-3-cyano-4-pyridinecarboxylates **1a-d** [1]. The presence in these compounds of various functional groups opens broad possibilities for modifying them. The hydrolysis of pyridines **1a-d** has been investigated by us under various conditions. It was found that the hydrolysis does not occur in dilute mineral acid even on extended boiling, which is evidently linked with steric hindrance caused by substituents *ortho* to the ester and nitrile groups. However by the action of concentrated sulfuric acid with subsequent neutralization with saturated sodium carbonate solution (conditions for carrying out hydrolysis by a $A_{ac}1$ mechanism [2]) the hydrolysis takes place even on light heating and leads to the formation of 6,7-dialkyl-4-amino-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-diones **2a-d** in practically quantitative yield (Table 1). The structure of compounds **2a-d** was demonstrated by data of IR, mass, and NMR spectroscopy. In the IR spectra of pyrrolo[3,4-*c*]pyridines **2a-d** (Table 2) absorption bands were present at 3450-3460 cm^{-1} belonging to the stretching vibrations of the NH bond in the amide fragment. Absorption bands at 1705-1738 and 1686-1696 cm^{-1} correspond to vibrations of the carbonyl group and the deformation vibrations of the amino group respectively, but the stretching vibrations of the amino group are displayed as a medium intensity bands at 3180-3315 cm^{-1}. It appears hydroxyl ion is less susceptible to the influence of steric hindrance, as a result of which the hydrolysis of compounds **1a-d** proceeds even at normal temperatures in the presence of sodium hydroxide.

Initially only the ester group is subject to hydrolysis and leads to the formation of sodium 5,6-dialkyl-2-amino-3-cyano-4-pyridinecarboxylates **3a-d** which may be isolated by the careful evaporation of a solution of equimolar amounts of reactants.

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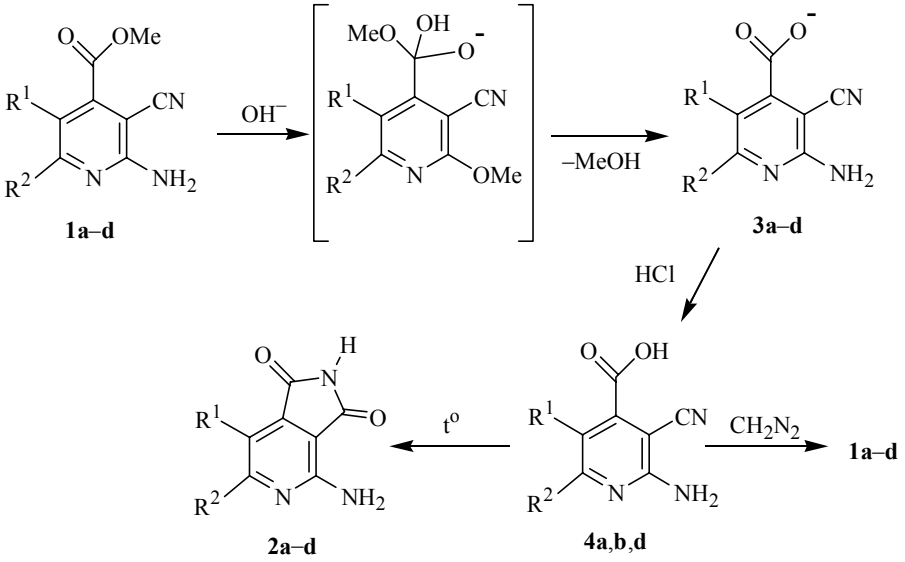


2-4 a $R^1+R^2 = (CH_2)_4$, **b** $R^1+R^2 = (CH_2)_3$, **d** $R^1 = H$, $R^2 = Me$; **2**, **3 c** $R^1 = R^2 = Me$

The structure of salts **3a-d** was presumed from the data of IR spectroscopy and elemental analysis. The IR spectra of compounds **3a-d** (Table 2) are characterized by the presence of high intensity absorption band for the conjugated cyano group at 2210-2230 cm^{-1}. The intense absorption bands at 3315-3500 cm^{-1} belong to the asymmetric and symmetric stretching vibrations of the amino group, but the absorption bands at 1580-1605 and 1620-1640 cm^{-1} belong to the vibrations of the carboxylate ion and the deformation vibrations of the amino group respectively. In addition it was found that on careful neutralization of solutions of salts **3a,b,d** 5,6-dialkyl-2-amino-3-cyanoisonicotinic acids **4a,b,d** were formed. The structure of acids **4a,b,d** was assumed from the data of IR and NMR spectroscopy and elemental analysis. In the IR spectra (Table 2) of compounds **4a,b,d**

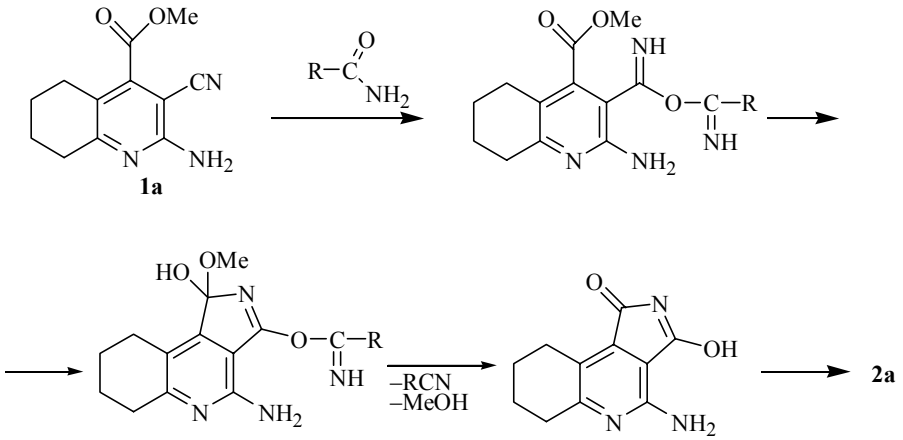
TABLE 1. Characteristics of Compounds **2a-d**, **3a-d**, and **4a,b,d**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{11}H_{11}N_3O_2$	60.85 / 60.83	5.05 / 5.07	19.36 / 19.35	223	99
2b	$C_{10}H_9N_3O_2$	59.14 / 59.11	4.44 / 4.43	20.70 / 20.69	235	98
2c	$C_9H_9N_3O_2$	56.53 / 56.54	4.72 / 4.71	22.01 / 21.99	269	96
2d	$C_8H_7N_3O_2$	54.25 / 54.23	3.93 / 3.92	23.72 / 23.71	235	98
3a	$C_{11}H_{10}N_3NaO_2$	55.21 / 55.23	4.22 / 4.21	17.58 / 17.57	295	84
3b	$C_{10}H_8N_3NaO_2$	53.35 / 53.34	3.57 / 3.58	18.65 / 18.66	296	92
3c	$C_9H_8N_3NaO_2$	50.69 / 50.71	3.77 / 3.78	19.69 / 19.71	240	79
3d	$C_8H_6N_3NaO_2$	48.24 / 48.25	3.05 / 3.04	21.11 / 21.10	260	96
4a	$C_{11}H_{11}N_3O_2$	60.82 / 60.83	5.05 / 5.07	19.37 / 19.35	250	87
4b	$C_{10}H_9N_3O_2$	59.13 / 59.11	4.41 / 4.43	20.71 / 20.69	290	84
4d	$C_8H_7N_3O_2$	54.20 / 54.23	3.95 / 3.92	23.74 / 23.71	160	78

highly intense absorption band was present at 2223-2242 cm^{-1}, indicating the presence in the obtained compounds of a conjugated cyano group. The absorption bands at 1683-1692 and 1650-1670 cm^{-1} correspond to the vibrations of the carbonyl group and the deformation vibrations of the amino group respectively. Stretching vibrations characteristic of the amino group are displayed at 3320-3390 cm^{-1}. The structures of acids **4a,b,d** were also confirmed by conversion of them to the initial esters **1a-d** by the action of diazomethane.

Compounds **3** and **4** were unstable in solution and on heating or on extended storage cyclize intramolecularly to pyrrolo[3,4-*c*]pyridine-1,3-diones **2a-d**.

Reaction with bifunctional compounds such as formamide is widely known for compounds having an *o*-enaminonitrile fragment, leading to the formation of the corresponding pyrido[2,3-*b*]pyrimidine derivatives [3]. Unexpectedly we found that the products of the reaction of pyridines **1** with formamide were pyrrolo[3,4-*c*]-pyridines **2**. Pyrrolo[3,4-*c*]pyridines **2** are also formed on reaction of pyridines **1** with homologs of formamide. We assumed the following scheme for this reaction process:



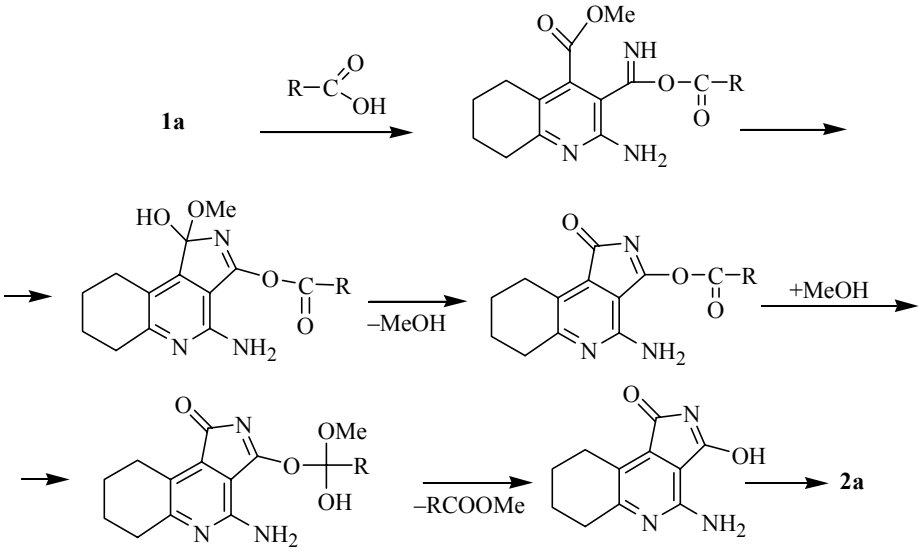
R = H, Me

According to this scheme the amides act as O-nucleophiles which initially probably add to the cyano group. An intramolecular cyclization then occurs with subsequent elimination of a molecule of methanol and a molecule of the corresponding nitrile. In support of the scheme described above for the interaction of pyridines **1** with amides is the fact that the acetonitrile eliminated was identified by GLC from the reaction mixture in the case of acetamide.

TABLE 2. IR Spectra of Compounds **2a-d**, **3a-d**, and **4a,b,d**

Compound	IR spectrum, cm^{-1}				
	ν_{NH}	δ_{NH}	$\nu_{C=O}$	$[RCO_2]^-$	$\nu_{C\equiv N}$
2a	3455, 3307, 3185	1686	1705, 1726	—	—
2b	3455, 3311, 3182	1696	1720, 1738	—	—
2c	3460, 3310, 3180	1685	1705, 1727	—	—
2d	3450, 3315, 3190	1686	1702, 1720	—	—
3a	3300, 3450	1620	—	1595	2230
3b	3315, 3445	1630	—	1590	2225
3c	3315, 3420	1640	—	1580	2225
3d	3500, 3460	1620	—	1605	2210
4a	3372, 3320	1660	1683	—	2235
4b	3390, 3320	1670	1692	—	2223
4d	3335, 3360	1650	1690	—	2242

Probably pyridines **1** interact with organic acids by an analogous scheme. Since it is possible to carry out these reactions in the complete absence of water (such as with butyric acid in a medium of butyric anhydride), it was assumed that carboxylic acids also react as O-nucleophiles. We therefore propose the following scheme:



R = C_3H_7

After adding the carboxylic acid at the cyano group and subsequent intramolecular cyclization with formation of the pyrrole ring, fission of the ester group occurs with ejection of a molecule of acid as the methyl ester.

Confirmation of this mechanism may be the fact that on using butyric acid methyl butyrate was isolated and identified by GLC among the reaction products.

EXPERIMENTAL

A check on the progress of reactions and the purity of the synthesized substances was effected by TLC on Silufol UV-254 plates, visualizing with UV light and iodine vapor. The IR spectra were obtained in thin films (of nujol suspensions) with a UR-20 instrument. The NMR spectra were recorded on Bruker WM-250 (250 MHz) and AM-300 (300 MHz) instruments, solvent was DMSO-d_6, internal standard was HMDS. The high and low resolution mass spectra were obtained on a Varian MAT-212 instrument with an ionization energy of 70 eV. Chromatographic investigations were carried out on a LXhM 8MD chromatograph, thermal conductivity detector, the column (3000 × 3 mm) was packed with chromaton N-AW-DMCS, granule size 0.250-0.315, liquid phase 5% XE-60, column temperature was 120°C, carrier gas helium at 40 ml/min, detector current 140 μA, sensitivity 30, sample volume 1 μl, tape speed 240 mm/h.

Sodium 5,6-Dialkyl-2-amino-3-cyano-4-pyridinecarboxylates (3a-d). Pyridine **1a-d** (0.01 mol) was dissolved in a mixture of NaOH (0.4 g, 0.01 mol) and water (1 ml) at 60°C. A portion of the solvent was then carefully evaporated from the obtained solution on a water bath. The mixture was cooled to room temperature, and the obtained suspension was filtered off. The solid was washed with 2-propanol (2 ml), then with diethyl ether (5 ml). The product was dried in a vacuum desiccator over P_2O_5 to constant weight. Mass spectrum of compound **3d**, *m/z* (I_{rel}, %): 177 (9), 45 (100), 44 (32) (3 available fragment ions are given).

5,6-Dialkyl-2-amino-3-cyano-4-pyridinecarboxylic Acids (4a,b,d). Pyridine **1a,b,d** (0.01 mol) was dissolved in a mixture of NaOH (0.4 g, 0.01 mol) in water (1 ml) with gentle warming. A 5% solution of hydrochloric acid was added dropwise to the solution obtained to pH 4 to litmus. After some time a cloudiness was observed in the reaction mixture. A white solid crystallized out. The obtained solid was filtered off, and washed with water (5 ml). The product was recrystallized from water, and dried in a desiccator over P_2O_5 to constant weight. ^{1}H NMR spectrum, δ, ppm: **4a** 1.72 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_2$); 2.60 (2H, t, CH_2); 2.70 (2H, t, CH_2); 6.45 (2H, s, NH_2); **4b** 2.02 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.85 (2H, t, CH_2); 2.97 (2H, t, CH_2); 6.50 (2H, s, NH_2); **4d** 2.40 (3H, s, CH_3); 6.59 (2H, s, NH_2); 6.83 (1H, s, CH).

6,7-Dialkyl-4-amino-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-diones (2a-d). Pyridine **1a-d** (0.01 mol) was dissolved in concentrated sulfuric acid (2 ml) at room temperature. The solution obtained was cooled to room temperature, then neutralized to litmus with concentrated sodium bicarbonate solution. In the course of neutralization a yellow solid crystallized out, and was then filtered off. The solid was washed with 2-propanol (5 ml), and recrystallized from DMF, then dried in a vacuum desiccator over P_2O_5 to constant weight. ^{1}H NMR spectrum, δ, ppm: **2a** 1.77 (4H, m, $CH_2\underline{CH_2}\underline{CH_2}CH_2$); 2.77 (2H, t, CH_2); 2.90 (2H, t, CH_2); 6.53 (2H, s, NH_2); 10.95 (1H, s, NH); **2b** 2.16 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.86 (2H, t, CH_2); 3.00 (2H, t, CH_2); 6.53 (2H, s, NH_2); 10.85 (1H, s, NH); **2c** 2.43 (3H, s, CH_3); 2.45 (3H, s, CH_3); 6.38 (2H, s, NH_2); 10.85 (1H, s, NH); **2d** 2.50 (3H, s, CH_3); 5.17 (2H, s, NH_2); 6.86 (1H, s, CH); 11.15 (1H, s, NH). Mass spectrum of compound **2a**, *m/z* (I_{rel}, %): 217 (100), 202 (23), 189 (15), 161 (11), 171 (16), 118 (11), 91 (39), 63 (22), 77 (37), 44 (47) (the molecular ion peak and nine intense peaks for fragment ions are given).

4-Amino-6,7-tetramethylene-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-dione (2a). A. Pyridine **1a** (0.231 g, 1 mmol) was suspended in formamide (2 ml) and the suspension sealed into an ampule. The ampule was then heated at 130°C for 12 h, then opened carefully. The contents were diluted with 1,4-dioxane (2 ml), the yellow crystalline solid was filtered off, washed with 1,4-dioxane (2 ml), and recrystallized from DMF. The product was dried in a vacuum desiccator over P_2O_5 to constant weight. Compound **2a** (0.117 g, 54%) was obtained; mp 223°C. Found, %: C 60.84; H 5.07; N 19.36. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.83; H 5.07; N 19.35.

B. Under conditions analogous to method A, on interacting pyridine **1a** (0.231 g, 1 mmol) with acetamide (0.0886 g, 1.5 mmol) compound **2a** (0.097 g, 45%) was obtained; mp 223°C. Found, %: C 60.82; H 5.05; N 19.34. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.83; H 5.07; N 19.35.

To demonstrate the formation of acetonitrile in the reaction the filtrate was distilled and the fraction with bp 76-85°C collected. The presence of acetonitrile in this mixture was demonstrated by GLC.

C. Pyridine **1a** (0.231 g, 1 mmol) was suspended in freshly distilled butyric acid (2 ml). The suspension was sealed in an ampule. The ampule was heated at 130°C for 12 h, then opened carefully. The contents of the ampule were diluted with 2-propanol (2 ml), and the crystalline yellow solid was filtered off, then recrystallized from DMF. The solid was washed with 2-propanol, and dried in a vacuum desiccator over P_2O_5 to constant weight. Compound **2a** (0.137 g, 63%) was obtained; mp 223°C. Found, %: C 60.81; H 5.05; N 19.37. $C_{11}H_{11}N_3O_2$. Calculated, %: C 60.83; H 5.07; N 19.35.

To demonstrate the formation of methyl butyrate in the reaction the fraction of boiling point 95-110°C was distilled from the filtrate. The presence of methyl butyrate in this mixture was demonstrated by GLC.

Interaction of 2-Amino-3-cyano-5,6-tetramethyleneisonicotinic Acid 3a with Diazomethane. Acid **3a** (0.217 g, 1 mmol) was dissolved in dioxane (20 ml). A current of diazomethane was passed through this solution until the disappearance of the initial compound from the reaction mixture. The solvent was distilled off, and the residue of methyl 2-amino-3-cyano-5,6-tetramethylene-4-pyridinecarboxylate **1a** was filtered off. The product was recrystallized from ethyl acetate, and dried in a vacuum desiccator over P_2O_5 to constant weight. Compound **1a** (0.215 g, 93%) was obtained; mp 195°C. Found, %: C 62.31; H 5.72; N 18.14. $C_{11}H_{11}N_3O_2$. Calculated, %: C 62.33; H 5.66; N 18.17 [1].

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