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INTERACTION OF METHYL 5,6-DIALKYL-2-AMINO-3-CYANOPYRIDINE-4-CARBOXYLATES WITH PRIMARY AMINES

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An unusual direction has been found for the interaction of alkyl 5,6-dialkyl-2-amino-3-cyanopyridine-4-carboxylates with primary amines leading to the formation of 2,6,7-trialkyl-4-amino-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine-1,3-diones.

Keywords: amide, amines, aminopyrimidines, 1,3-diones, enamines, carboxamides, nucleophiles, pyridines.

The previously synthesized alkyl 5,6-dialkyl-2-amino-3-cyanopyridine-4-carboxylates **1a-c**, being structural analogs of isonicotinic acid, are of particular interest for their further modification [1]. The presence of different functional groups, ester and cyano, affords the possibility of studying the interaction of pyridines **1a-c** with various nucleophiles. It was noted previously that the interaction of compounds **1** with amines and organic acids, outstanding as O-nucleophiles, leads to the formation of the corresponding 6,7-dialkyl-4-amino-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-diones **4j-l** [1]. The unusual course of the reaction with O-nuclepohiles presumes the need to study the interaction of such pyridines with N-nucleophiles. It was thus discovered that the interaction of pyridines **1a-c** with alcoholic ammonia solution leads to the formation of pyrrolo[3,4-*c*]pyridine-1,3-diones **4j-l**, as in the case of interaction with O-nucleophiles, but under milder conditions. The absolute identity of the IR (Table 1), mass, and ^{1}H NMR spectra is proof of this. The interaction of pyridines **1a-c** with primary aliphatic amines in a sealed ampul on heating in an absolute medium leads to the formation of the corresponding 2-alkyl-substituted analogs **4a-i**, which are yellow crystalline substances with a clearly marked yellow-green fluorescence in solution. Intense absorption bands were observed in the IR spectra of the obtained pyrrolo[3,4-*c*]pyridine-1,3-diones **4a-i** (Table 1) at 3280-3450 for the asymmetric and symmetric stretching vibrations of the amino group, and medium intensity bands at 1675-1740 and 1630-1645 cm^{-1} corresponding to the stretching vibrations of the carbonyl group and the deformation vibrations of the amino group respectively. The molecular masses of the pyrrolo[3,4-c]pyridine-1,3-diones **4**, found with the aid of high resolution mass spectra, corresponded to calculated values. In addition it was discovered that carrying out the reaction of pyridine **1a** with benzylamine in a shorter time interval enabled N-benzyl-2-amino-3-cyano-5,6,7,8-tetrahydroquinoline-4-carboxamide (**2**) and $N_{(3)}$,$N_{(4)}$-dibenzyl-2-amino-5,6,7,8-tetrahydroquinoline-3,4-dicarboxamide (**3**) to be obtained in a pure state. In the IR spectrum of 3-cyanotetrahydroquinolinamide **2**, as in the spectra of the initial compounds **1**, an intense absorption was present for the conjugated cyano group at 2215, and intense bands at 3285-3425 and 1615 cm^{-1} indicating the presence of stretching and deformation vibrations of an amino group. Absorption bands at 1640 and 1570 cm^{-1}, representing amide I and amide II bands,

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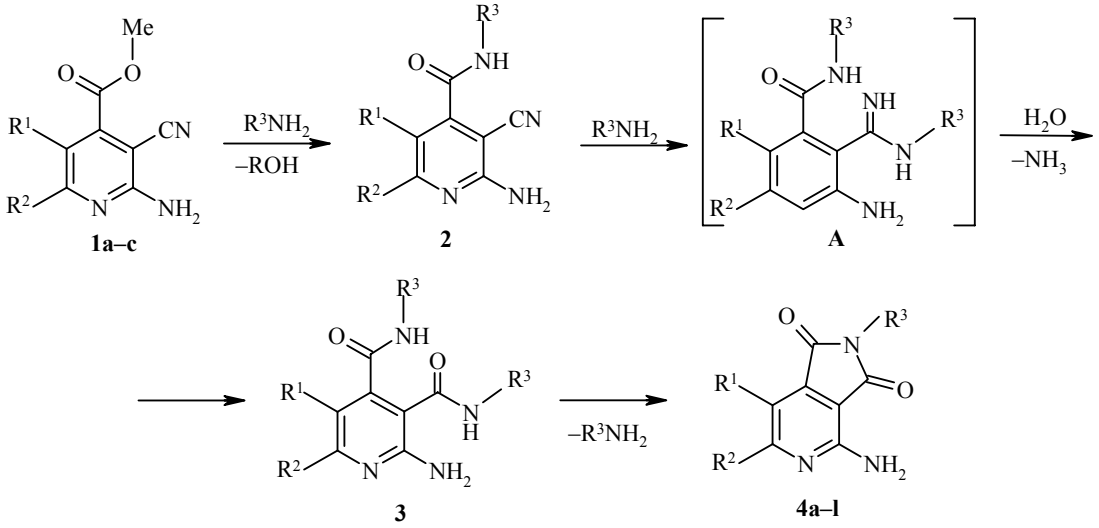
indicate the associated form of compound **2**. The main characteristic absorption bands in the IR spectrum of dicarboxamide **3** are analogous to those of the monoamide **2**, except for the absence of the absorption band of the cyano group. Attempts to isolate analogous compounds on interaction with other amines gave no positive result. We established that further heating of carboxamide **2** and dicarboxamide **3** in benzylamine leads to their conversion into the final compound **4g**. Extended storage or heating of a solution of dicarboxamide **3** leads to the same result. These additional data enabled us to assume the following scheme for the course of the reaction of the investigated pyridines **1** with primary aliphatic amines and ammonia.



1 a $R^1 + R^2 = (CH_2)_4$, **b** $R^1 = R^2 = Me$, **c** $R^2 = Me$, $R^1 = H$; **2, 3** $R^1 + R^2 = (CH_2)_4$, $R^3 = CH_2Ph$;
4 a $R^1 + R^2 = (CH_2)_4$, $R^3 = Me$, **b** $R^1 = R^2 = R^3 = Me$, **c** $R^1 = H$, $R^2 = R^3 = Me$, **d** $R^1 + R^2 = (CH_2)_4$, $R^3 = C_5H_{11}$,
e $R^1 = R^2 = Me$, $R^3 = C_5H_{11}$, **f** $R^1 = H$, $R^2 = Me$, $R^3 = C_5H_{11}$, **g** $R^1 + R^2 = (CH_2)_4$,
$R^3 = CH_2Ph$, **h** $R^1 = R^2 = Me$, $R^3 = CH_2Ph$, **i** $R^1 = H$, $R^2 = Me$, $R^3 = CH_2Ph$, **j** $R^1 + R^2 = (CH_2)_4$,
$R^3 = H$, **k** $R^1 = R^2 = Me$, $R^3 = H$, **l** $R^1 = R^3 = H$, $R^2 = Me$

TABLE 1. IR Spectra of Compounds **2**, **3**, and **4a-l**

Compound	IR spectrum, cm^{-1}				
	ν_{NH}	δ_{NH}	$\nu_{C=O}$	ν_{CN}	Amide I and II (associated form)
2	3400, 3425, 3285	1615	—	2215	1640, 1570
3	3430, 3300, 3255	1620, 1640	—	—	1645, 1575
4a	3450, 3300	1630	1737, 1680	—	—
4b	3445, 3300	1645	1700, 1738	—	—
4c	3400, 3280	1650	1715, 1675	—	—
4d	3450, 3285	1625	1730, 1675	—	—
4e	3450, 3300	1635	1740,1680	—	—
4f	3400, 3280	1635	1710, 1675	—	—
4g	3455, 3285	1635	1740, 1700	—	—
4h	3445, 3285	1645	1745, 1695	—	—
4i	3410, 3285	1630	1740, 1710	—	—
4j	3307, 3185	1686	1705, 1726	—	—
4k	3310, 3180	1685	1705, 1727	—	—
4l	3315, 3190	1686	1702, 1720	—	—

TABLE 2. Characteristics of Compounds **2**, **3**, and **4a-l**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2	$C_{18}H_{18}N_4O$	70.22 / 70.57	7.73 / 5.92	17.90 / 18.29	254	98
3	$C_{25}H_{26}N_4O_2$	72.42 / 72.44	6.30 / 6.32	13.54 / 13.52	236	76
4a	$C_{12}H_{13}N_3O_2$	62.31 / 62.33	5.65 / 5.67	18.16 / 18.17	224	94
4b	$C_{10}H_{11}N_3O_2$	58.55 / 58.53	5.39 / 5.40	20.47 / 20.48	186	87
4c	$C_9H_9N_3O_2$	56.52 / 56.54	4.78 / 4.74	21.97 / 21.98	192	91
4d	$C_{16}H_{21}N_3O_2$	66.85 / 66.88	7.35 / 7.37	14.60 / 14.62	125	78
4e	$C_{14}H_{19}N_3O_2$	64.33 / 64.35	7.31 / 7.33	16.10 / 16.08	112	84
4f	$C_{13}H_{17}N_3O_2$	63.12 / 63.14	6.95 / 6.93	16.97 / 16.99	185	76
4g	$C_{18}H_{17}N_3O_2$	70.37 / 70.34	5.55 / 5.57	13.65 / 13.67	172	85
4h	$C_{16}H_{15}N_3O_2$	68.29 / 68.31	5.38 / 5.37	14.96 / 14.94	187	92
4i	$C_{15}H_{13}N_3O_2$	67.42 / 67.41	4.92 / 4.90	15.70 / 15.72	201	87
4j	$C_{11}H_{11}N_3O_2$	60.85 / 60.83	5.05 / 5.07	19.36 / 19.35	223	99
4k	$C_9H_9N_3O_2$	56.53 / 56.54	4.72 / 4.71	22.01 / 21.99	269	96
4l	$C_8H_7N_3O_2$	54.25 / 54.23	3.93 / 3.92	23.72 / 23.71	235	98

Probably the corresponding N-alkyl-5,6-dialkyl-2-amino-3-cyanoisonicotinamides **2** are formed initially, which then add a second molecule of amine at the nitrile group with the formation of the corresponding intermediate **A**. Under the reaction conditions the latter is readily hydrolyzed into 5,6-disubstituted $N_{(3)}$,$N_{(4)}$-dialkyl-2-aminopyridine-3,4-dicarboxamides **3**. Subsequent heating of them leads to intramolecular cyclization of the vicinal carboxamide groups into the imide fragment of compounds **4**. It is necessary to mention that water is required to participate in the formation of compounds **3**. Since these reactions are carried out in an absolute medium it is probable that under the process conditions alkylation of the amine occurs by the methyl alcohol formed with elimination of water, which participates in the hydrolysis. In this case methylalkylamine and dimethylalkylamine must be formed in the reaction mixture as side products and were identified by us by GLC in the case of reaction with benzylamine. Aromatic (aniline) and secondary amines (diethylamine) do not participate in this reaction, which is probably linked with their low nucleophilicity and with steric hindrance.

EXPERIMENTAL

A check on the progress of reactions and the purity of the compounds synthesized was effected by TLC on Silufol UV 254 plates, visualizing with UV light (365 nm) and with iodine vapor. The IR spectra were obtained in thin films (nujol suspensions) on 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 HMDS (δ 0.05 ppm). The high and low resolution mass spectra were obtained on a Varian MAT-212 instrument at an ionizing energy of 70 eV. Chromatographic investigations were carried out on a LKhM 8MD chromatograph,

thermal conductivity detector, with a column (3000 × 3 mm) packed with chromaton N-AW-DMCS, particle size 0.250-0.315, liquid phase SP 2100, 5%; column temperature 115°C, carrier gas helium, 40 ml/min, detector current 140 μA, sensitivity 10, volume of test sample 0.5 μl, tape flow rate 240 mm/h. Reactants and solvents used in the work were purified by standard methods [2].

N-Benzyl-2-amino-3-cyano-5,6,7,8-tetrahydroquinoline-4-carboxamide (2). Pyridine **1a** (0.231 g, 1 mmol) was suspended in benzylamine (3 ml, 27 mmol) at room temperature. The suspension was placed in an ampul and sealed. The ampule was heated at 130° C for 12 h. The end of the reaction was determined by TLC (R_f 0.35, eluent ethyl acetate, violet fluorescence on UV irradiation). After cooling, the ampul was opened carefully. The contents were diluted with 1,4-dioxane (5 ml), The white solid was filtered off, washed with 1,4-dioxane (10 ml), recrystallized from 2-propanol, and dried in a vacuum desiccator over P_2O_5. Compound **2** (0.306 g, 98%) was obtained. ^{1}H NMR spectrum, δ, ppm: 1.65 (2H, m, $CH_2\underline{CH_2}CH_2$); 1.72 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.43 (2H, t, $\underline{CH_2}CH_2$); 2.62 (2H, t, $\underline{CH_2}CH_2$); 4.00 (2H, s, $\underline{CH_2}$–NHC(O)); 5.97 (2H, s, NH_2); 7.45 (5H, m, C_6H_5); 8.39 (1H, s, $\underline{NH}$–CH_2).

$N_{(3)}$,$N_{(4)}$-Dibenzyl-2-amino-5,6,7,8-tetrahydroquinoline-3,4-dicarboxamide (3) (Table 2) was synthesized analogously by heating pyridine **1a** (0.231 g, 1 mmol) in benzylamine (3 ml, 27 mmol) for 18 h. ^{1}H NMR spectrum, δ, ppm: 1.67 (2H, m, $CH_2\underline{CH_2}CH_2$); 1.76 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.43 (2H, t, $\underline{CH_2}CH_2$); 2.62 (2H, t, $\underline{CH}\ _2CH_2$); 4.20 (2H, d, $\underline{CH_2}$–N(CO)); 4.28 (2H, d, $\underline{CH_2}$–NHC(O)); 5.85 (2H, s, NH_2); 7.25 (5H, m, Ph); 7.30 (5H, m, Ph); 7.81 (1H, s, $\underline{NH}$–CH_2); 8.74 (1H, s, $\underline{NH}$–CH_2).

6,7-Dialkyl-4-amino-2-methyl-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-diones (4a-c) (Table 2). A suspension of pyridine **1a-c** (1 mmol) in a saturated solution of methylamine in dioxane (5 ml) was heated at 130°C in a sealed ampul for 48 h. The end of the reaction was determined by TLC (eluent ethyl acetate, the compound fluoresces yellow-green on UV irradiation). After cooling to -10°C the ampul was opened carefully. The contents were diluted with 1,4-dioxane (5 ml), the yellow solid was filtered off, washed with 1,4-dioxane (10 ml), and purified by vacuum sublimation or recrystallization from DMF. The product was dried in a vacuum desiccator over P_2O_5. ^{1}H NMR spectrum, δ, ppm: **4a**, 1.78 (2H, m, $CH_2\underline{CH_2}CH_2$); 1.85 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.75 (2H, t, $\underline{CH_2}CH_2$); 2.93 (2H, t, $\underline{CH_2}CH_2$); 2.97 (3H, s, CH_3); 6.50 (2H, s, NH_2); **4b**, 2.48 (3H, s, CH_3); 2.49 (3H, s, CH_3); 2.95 (3H, s, CH_3); 6.50 (2H, s, NH_2); **4c**, 2.4 (3H, s, CH_3); 2.95 (3H, s, CH_3); 6.83 (1H, s, CH); 6.59 (2H, s, NH_2).

6,7-Dialkyl-4-amino-2-pentyl-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-diones (4d-f) were synthesized analogously by heating pyridines **1a-c** (1 mmol) in pentylamine (0.5 ml) at 130°C for 36 h. ^{1}H NMR spectrum, δ, ppm: **4e**, 0.79 (3H, t, $\underline{CH_3}CH_2$); 1.25 (2H, m, $CH_2\underline{CH_2}CH_3$); 1.34 (2H, m, $CH_2\underline{CH_2}CH_2$); 1.58 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.42 (3H, s, CH_3); 2.43 (3H, s, CH_3); 3.50 (2H, t, $\underline{CH_2}CH_2$); 6.50 (2H, s, NH_2). Mass spectrum, *m/z* (I_{rel}, %): **4d**, 287 (100), 269 (10), 258 (7), 230 (67), 216 (28), 202 (14), 174 (6), 145 (20), 84 (5), 41 (14) (the molecular ion and 9 intense fragment ion peaks are given); **4f**, 247 (77), 230 (14), 218 (100), 190 (46), 177 (46), 160 (58), 92 (21), 66 (17), 42 (25) (the molecular ion and 8 intense fragment ion peaks are given).

6,7-Dialkyl-4-amino-2-benzyl-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-diones (4g-i) were synthesized analogously by heating pyridines **1a-c** (1 mmol) in benzylamine (0.6 ml, 5.7 mmol) at 160°C for 36 h. ^{1}H NMR spectrum, δ, ppm: **4g**, 1.78 (2H, m, $CH_2\underline{CH_2}CH_2$); 1.85 (2H, m, $CH_2\underline{CH_2}CH_2$); 2.78 (2H, t, $\underline{CH_2}CH_2$); 2.95 (2H, t, $\underline{CH_2}CH_2$); 4.69 (2H, s, CH_2); 6.55 (2H, s, NH_2); 7.28 (5H, m, Ph); **4h**, 2.43 (3H, s, CH_3); 2.44 (3H, s, CH_3); 4.69 (2H, s, CH_2); 6,57 (2H, s, NH_2); 7.30 (5H, m, Ph); **4i**, 2.48 (3H, s, CH_3); 6.87 (1H, s, CH); 4.70 (2H, s, CH_2); 4.88 (2H, s, NH_2); 7.31 (5H, m, Ph).

Compound 4g was obtained under analogous conditions by heating amide **2** (0.306 g, 1 mmol) or amide **3** (0.400 g, 1 mmol) with benzylamine (0.6 ml, 5.7 mmol) at 160°C for 36 h. To demonstrate the formation of methylbenzylamine and dimethylbenzylamine in the reaction a fraction with bp 75-85°C (12 mm Hg) was distilled from the filtrate. The presence of the amines in this mixture was demonstrated by GLC.

6,7-Dialkyl-4-amino-2,3-dihydro-1H-pyrrolo[3,4-*c*]pyridine-1,3-diones (4j-l) were obtained analogously by heating pyridines **1a-c** (1 mmol) with a solution (10 ml) of ammonia in 2-propanol, saturated at room temperature, at 50°C for 12 h.

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