Chemistry of Heterocyclic Compounds, Vol. 40, No. 3, 2004

THE KOST–SAGITULLIN REARRANGEMENT IN A SERIES OF 1-ALKYL-2-(CARBAMOYLMETHYL)-4,6-DIMETHYLPYRIMIDINIUM IODIDES

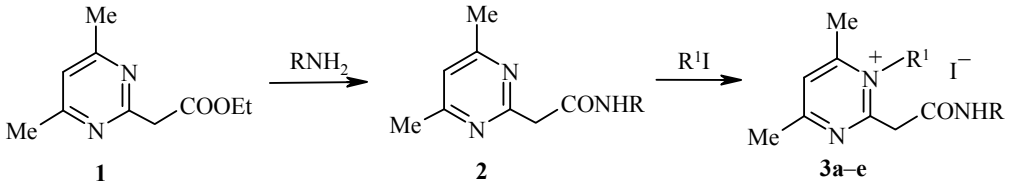
G. G. Danagulyan and L. G. Sahakyan

The rearrangement of 1-alkyl-2-(carbamoylmethyl)pyrimidinium iodides into substituted 2-alkylaminonicotinamides occurring in alcoholic solutions of amines has been studied. It was shown that in the presence of water the rearrangement of 2-(carbamoylmethyl)-1,4,6-trimethylpyrimidinium iodide is accompanied by the formation of a derivative of 2-oxo-1,2-dihydronicotinic acid, and under the action of ethylamine a "rearrangement and transamination" occurs leading to 2-ethylamino-4,6-dimethylnicotinamide.

Keywords: 2-alkylaminonicotinamide, alkylamines, nucleophiles, pyrimidinium salt, Kost–Sagitullin rearrangement.

We recently reported the rearrangement of 2-(carbamoylmethyl)-4,6-dimethylpyrimidinium iodomethylate into 4,6-dimethyl-2-methylaminonicotinamide [1]. The present communication continues this investigation and is also devoted to a study of the Kost–Sagitullin rearrangement in a series of 1-alkyl-2-(carbamoylmethyl)-4,6-dimethylpyrimidinium iodides, i.e. pyrimidinium salts containing an acetic acid amide (or alkylamide) in position 2 of the heterocycle. In a previously published series of studies on the recyclization of pyrimidinium salts into derivatives of 2-alkylaminopyridine [2-6] the influence was investigated of individual amine reactants and also certain substituents in the pyrimidine ring on the possibility and direction of conversion. In the present communication the effect has been studied of the amide group in the side chain of the heterocycle on the course of the transformation.

The models for the rearrangement, salts **3a-e**, were synthesized by the reaction of 2-(ethoxycarbonylmethyl)-4,6-dimethylpyrimidine with ammonia or alkylamines and subsequent quaternization of the obtained 2-(carbamoylmethyl)-4,6-dimethylpyrimidines **2** with alkyl iodides.



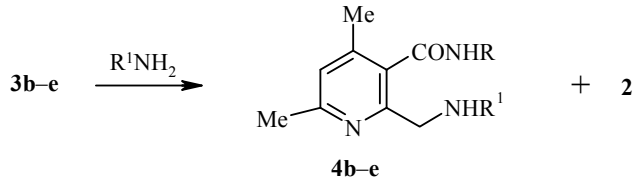
1 **2** **3a–e**

a R = H, R^1= Me; **b** R = H, R^1 = Et; **c** R = Me, R^1 = Me; **d** R = Me, R^1 = Et; **e** R = Et, R^1 = Me

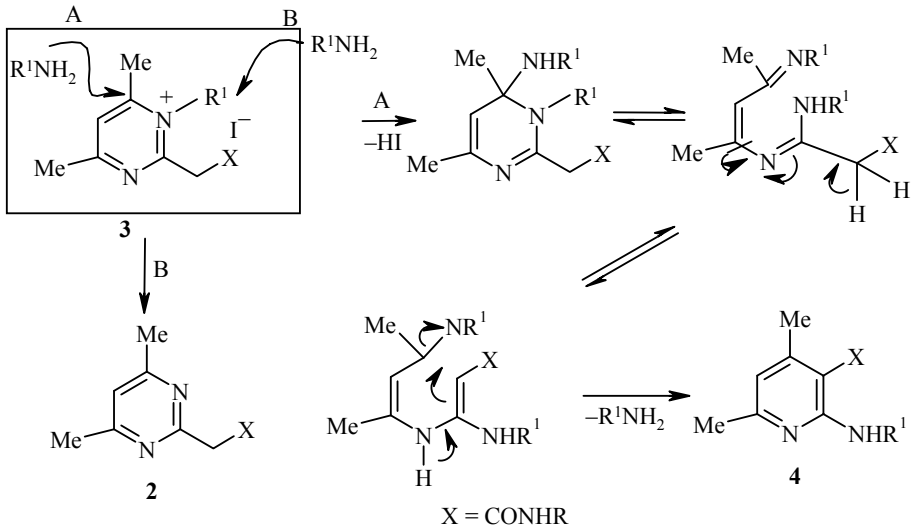
Institute of Organic Chemistry, National Academy of Sciences of the Armenian Republic, Erevan 375094; e-mail: gdanag@email.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 395-400, March, 2004. Original article submitted August 28, 2001.

 0009-3122/04/4003-0320

On heating iodides **3b-e** in a sealed glass ampule with alcoholic solutions of alkylamines the products of rearrangement, 2-alkylaminonicotinamide **4**, and of dealkylation, pyrimidines **2**, were isolated though in all conversions the main reaction product was the corresponding nicotinamide **4**.

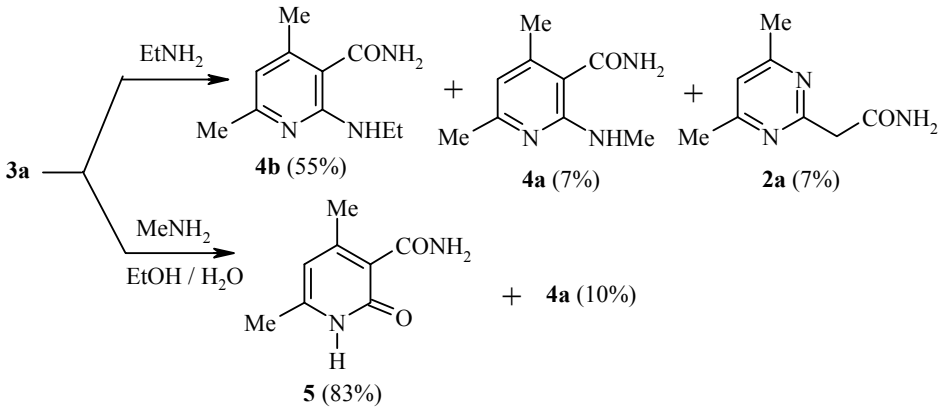


It is proposed that the rearrangement, beginning with attack of the amine at position 6 of the pyrimidine ring of iodide **3** (route A in the scheme), leads to fission of the $C_{(6)}$–$N_{(1)}$ bond of the ring and subsequent recyclization of the acyclic intermediate with the formation of a new C–C bond. It should be noted that the rearrangement may also be represented by attack at position 2 of the heterocycle, which however requires separate discussion. The alternative direction of attack of the nucleophile at the alkyl group located at the quaternized nitrogen atom (route B) leads to the dealkylation product **2**, although in this case it is impossible to exclude other schemes of carrying out the reaction.



In the reaction of iodide **3a**, containing a methyl group at the quaternized nitrogen atom, with an alcoholic solution of ethylamine a "rearrangement with transamination" might be expected, similar to the conversion described by us previously in a series of iodoalkylates of 4,6-dimethylpyrimidinylacetic acid ester [5, 6]. In reality it turned out that here also the main reaction product was the substance obtained by including a fragment of the amine reactant (ethylamine) into the final structure, namely 2-ethylamino-4,6-dimethylnicotinamide (**4b**), although the recyclization is accompanied partially by the formation of the products of the normal rearrangement **4a** and demethylation (pyrimidine **2**).

In the presence of water the rearrangement of the same iodide **3a** with methylamine led to 4,6-dimethyl-2-oxo-1,2-dihydronicotinamide (**5**) in 83% yield and partially to pyridine **4a**. We note that the formation of a pyridone derivative (analogous in structure to compound **5**) was observed previously by us on rearranging 2-(ethoxycarbonylmethyl)-1,4,6-trimethylpyrimidinium iodide in aqueous alcoholic solutions of amines [7], which indicates the regularity of such conversions and their general character. In the IR spectrum of compound

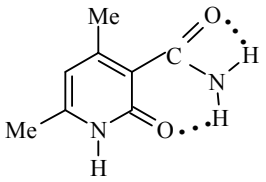


5 absorption was noted at 3580 cm^{-1} corresponding to an intramolecular hydrogen bond. This possibly explains the fact of the appearance in the ^1H NMR spectrum of the amide group protons as two separate (in different regions of the spectrum) broadened signals.

TABLE 1. Characteristics of 1-Alkyl-2-(carbamoylmethyl)-4,6-dimethyl-pyrimidinium Iodides **3b-e***

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz)	Yield, %
		C	H			
3b	$C_8H_{11}N_3O \cdot C_2H_5I$	37.11 / 37.40	4.72 / 5.02	172-173	1.55 (3H, t, *J* = 8.2, $CH_2\underline{CH_3}$); 2.73 (3H, s, 4(6)-CH_3); 2.97 (3H, s, 6(4)-CH_3); 4,31 (2H, s, $\underline{CH_2}CONH_2$); 4.63 (2H, q, *J* = 8.2, $\underline{CH_2}CH_3$); 7.3 (1H, br. s, NH); 7.8 (1H, br. s, NH); 8.15 (1H, s, 5-H)	40
3c	$C_9H_{13}N_3O \cdot CH_3I$	37.14 / 37.40	4.73 / 5.02	158-160	2.67 (3H, s, 4-CH_3); 2.85 (3H, s, 6-CH_3); 2.90 (3H, d, *J* = 4.8, NH$\underline{CH_3}$); 4.05 (3H, s, 1-CH_3); 4.3 (2H, s, CH_2); 7.35 (1H, br. s, NH); 8.01 (1H, s, 5-H)	83
3d	$C_9H_{13}N_3O \cdot C_2H_5I$	39.56 / 39.42	5.16 / 5.41		1.53 (3H, t, *J* = 7.1, 1-$CH_2\underline{CH_3}$); 2.7 (3H, s, 4-CH_3); 2.85 (3H, s, 6-CH_3); 2.95 (3H, d, *J* = 4.8, NH$\underline{CH_3}$); 4.35 (2H, q, *J* = 7.1, 1-$\underline{CH_2}CH_3$); 4.41 (2H, s, CH_2); 7.81 (1H, br. s, N$\underline{H}CH_3$); 8.09 (1H, s, 5-H)	70
3e	$C_{10}H_{15}N_3O \cdot CH_3I$	39.22 / 39.42	5.12 / 5.41	161-162	1.17 (3H, t, *J* = 7.1, $CH_2\underline{CH_3}$); 2.75 (3H, s, 4-CH_3); 2.9 (3H, s, 6-CH_3); 3.19 (3H, d, *J* = 7.1, $\underline{CH_2}CH_3$); 4.13 (3H, s, N-CH_3); 4.35 (2H, s, CH_2); 8.07 (1H, s, 5-H); 8.33 (1H, br. s, NH)	74

* The data on iodide **3a** are given in [1].



The structure was confirmed by ^{1}H NMR spectroscopy. In the ^{1}H NMR spectra of all the recyclization products signals were present for the protons of the 4- and 6-CH_3 groups, the alkylamine and amide fragments, and also the signals for the 5-H protons. It is noteworthy that the signal for the latter is displayed at significantly higher field (6.09-6.26 ppm) than the signals of the 5-H protons of the pyrimidinium salts (7.98-8.15 ppm) or even of the corresponding pyrimidines **2** (6.9-7.0 ppm), which enables the formation of the rearrangement product to be established unequivocally, based on NMR spectra. We add that the appearance of a white spot on spraying chromatograms with Ehrlich reagent is also a qualitative sign characteristic of all the recyclization products, including those described previously in [1-7]. This makes it possible to control the process of forming recyclization products chromatographically.

EXPERIMENTAL

The NMR spectra were obtained on a Varian Mercury-300 (300 MHz) spectrometer in the Center for the Investigation of Molecular Structure of the National Academy of Sciences of Armenia (program US CRDF RESC 17-5).

Silufol UV-254 plates were used for thin-layer chromatography (to determine R_f), visualizing with iodine vapor and Ehrlich's reagent. Preparative separation was carried out by column chromatography on silica gel (Silica gel L 5/40μ Merck).

2-(Alkylcarbamoylmethyl)-4,6-dimethylpyrimidine (2). A solution of 2-pyrimidinylacetic acid ester **1** (1 g, 5 mmol) in a 13% alcoholic solution of alkylamine (10 ml) was heated at 90-100°C in a sealed ampule for 20 h. The solvent was distilled off, hexane was added, the precipitated crystals were filtered off, washed with hexane, and dried. Compounds **2b,c** were obtained.

4,6-Dimethyl-2-(methylcarbamoylmethyl)pyrimidine (2b). Yield 0.8 g (88%); mp 106-107°C, R_f 0.17 (acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.46 (6H, s, 4- and 6-CH_3); 2.83 (3H, d, J = 3, NH$\underline{CH_3}$); 3.85 (2H, s, CH_2); 6.94 (1H, s, 5-H); 7.5 (1H, br. s, $\underline{NH}CH_3$). Found, %: C 59.94; H 6.97; N 23.69. $C_9H_{13}N_3O$. Calculated, %: C 60.31; H 7.31; N 23.45.

2-(Ethylcarbamoylmethyl)-4,6-dimethylpyrimidine (2c). Yield 0.85 g (89%); mp 90-91°C, R_f 0.16 (acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.29 (3H, t, J = 7.2, $CH_2\underline{CH_3}$); 2.44 (6H, s, 4- and 6-CH_3); 2.78 (2H, dq, J_1 = 3, J_2 = 7.2, NH$\underline{CH_2}CH_3$); 3.84 (2H, s, CH_2); 6.98 (1H, s, 5-H); 7.25 (1H, br. s, N$\underline{H}CH_2CH_3$). Found, %: C 61.79; H 8.07; N 21.57. $C_{10}H_{15}N_3O$. Calculated, %: C 62.15; H 7.82; N 21.74.

The synthesis of **2a** was described previously in [1].

1-Alkyl-2-(carbamoylmethyl)-4,6-dimethylpyrimidinium Iodides (3a-e). General procedure. The appropriate pyrimidine **2** (10 mmol) and alkyl iodide (10 ml) were heated in a sealed glass ampule in a boiling water bath. After 10 h the precipitated crystals were filtered off, washed with a small quantity of hexane, and dried in the air (Table 1).

2-Ethylamino-4,6-dimethylnicotinic Acid Amide (4b). A. Iodide **3a** (0.75 g, 2.4 mmol) was mixed with 13% alcoholic ethylamine solution (8 ml) and heated in a sealed glass ampule at 95-100°C for 35 h. The precipitated crystals were then filtered off, washed with cold hexane, and dried. Water (3 ml) was added to the crystals, the solution was made alkaline with dilute KOH solution, extracted with chloroform, and the extract dried over magnesium sulfate. After distilling off the solvent, the residue was chromatographed on a column

(silica gel L 5/40, eluent was acetone). Pyridine **4b** (0.25 g, 55%) was obtained; mp 161-162°C, R_f 0.7 (benzene–acetone, 1:3). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.2, $NHCH_2\underline{CH_3}$); 1.61 (1H, br. s, NH), 2.35 (3H, s, 4(6)-CH_3); 2.38 (3H, s, 6(4)-CH_3); 3.45 (2H, dq, J_1 = 7.2, J_2 = 5.0, $NH\underline{CH_2}CH_3$); 5.75 (1H, br. s, NH); 5.94 (1H, br. s, NH); 6.25 (1H, s, 5-H). Mass spectrum, *m/z* (I_{rel}, %): 194 (8), 193 (65) $[M]^+$, 178 (13), 176 (35), 175 (13), 165 (14), 161 (82), 149 (14), 148 (47), 147 (100), 134 (47), 133 (12), 122 (20), 121 (12), 119 (8), 108 (11), 107 (61), 106 (46). Found, %: C 62.34; H 7.59; N 21.98. $C_{10}H_{15}N_3O$. Calculated, %: C 62.15; H 7.82; N 21.74.

Amide **4a** (0.03 g, 7%) and the demethylation product, pyrimidine **2** (0.03 g, 7%), were isolated by preparative separation and were identical in mp and by TLC with known samples [1].

B. Analogously, according to the general procedure, the reaction of iodide **3b** (0.6 g, 1.8 mmol) with 13% ethanolic ethylamine solution (10 ml) gave nicotinamide **4b** (0.2 g, 58%) [mp 161-162°C, R_f 0.7 (benzene–acetone, 1:3)] and amide **2a** (0.06 g, 19%) [mp 126-127°C, R_f 0.16 (benzene–acetone, 1:3)].

4,6-Dimethyl-2-methylaminonicotinic Acid Methylamide (4c). A mixture of iodide **3c** (0.65 g, 2 mmol) and a 15% ethanolic methylamine solution (10 ml) was heated in a sealed ampul at 95-100°C for 15 h. The solvent was then removed and the residue washed with benzene. After evaporating the solvent from the benzene extract the residual mass was separated on a column of silica gel (eluent acetone–benzene, 2:1). Nicotinamide **4c** (0.15 g, 40%) was obtained; mp 128-130°C and R_f 0.75 (acetone) or R_f 0.66 (benzene–acetone, 1:2) and compound **2** (R = Me) (0.04 g, 10%), which was identical to a known sample in mp and by TLC. ^{1}H NMR spectrum of compound **4c** ($CDCl_3$), δ, ppm (*J*, Hz): 2.23 (3H, s, 4(6)-CH_3); 2.35 (3H, s, 6(4)-CH_3); 2.94 (3H, d, *J* = 4.8, $NH\underline{Me}$); 2.98 (3H, d, *J* = 5.1, $NH\underline{CH_3}$); 5.61 (1H, br. s, NH); 5.76 (1H, br. s, NH); 6.23 (1H, 5-H). Mass spectrum, *m/z* (I_{rel}, %): 194 (7), 193 (54), 178 (19), 163 (27), 150 (9), 136 (19), 119 (8), 108 (17), 107 (100), 106 (19), 79 (11), 77 (13). Found, %: C 61.94; H 7.56; N 21.51. $C_{10}H_{15}N_3O$. Calculated, %: C 62.15; H 7.82; N 21.74.

2-Ethylamino-4,6-dimethylnicotinic Acid Methylamide (4d). A solution of iodide **3d** (0.5 g, 1.5 mmol) in 13% alcoholic ethylamine solution (8 ml) was heated in a sealed ampule at 90-100°C for 25 h. The solvent was distilled off, and the residue was passed through a column of silica gel (L 5/40), eluting with benzene–acetone, 2:1. The rearrangement product, pyridine **4d** (0.14 g, 45%), and pyrimidine **2** (R = Me) (0.03 g, 10%) were obtained.

Compound **4d**: mp 104-105°C, R_f 0.66 (benzene–acetone, 1:2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.23 (3H, t, *J* = 7.2, $NHCH_2\underline{CH_3}$); 2.23 (3H, s, 4(6)-CH_3); 2.33 (3H, s, 6(4)-CH_3); 3.0 (3H, d, *J* = 5.1, $NH\underline{CH_3}$); 3.2 (2H, dq, *J* = 7.2, $NH\underline{CH_2}CH_3$); 5.54 (1H, br. s, NH); 5.69 (1H, br. s, NH); 6.23 (1H, s, 5-H). Found, %: C 63.88; H 8.51; N 20.08. $C_{11}H_{17}N_3O$. Calculated, %: C 63.74; H 8.27; N 20.27.

4,6-Dimethyl-2-methylaminonicotinic Acid Ethylamide (4e). The interaction of 2-(ethylcarbamoylmethyl)-1,4,6-trimethylpyrimidinium iodide **3e** (1 g, 3 mmol) with 15% alcoholic methylamine solution (15 ml), according to the general rearrangement procedure (20 h, 90-100°C) and subsequent column resolution (eluent benzene–acetone, 2:1), gave pyridine **4e** (0.2 g, 35%) and pyrimidine **2** (R = Et) (0.06 g, 10%). The latter was identical with a known sample by mp (172-173°C) and TLC.

Compound **4e**: oil, R_f 0.5 (acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.25 (3H, t, *J* = 7.2, $NHCH_2\underline{CH_3}$); 2.37 (3H, s, 4(6)-CH_3); 2.65 (3H, s, 6(4)-CH_3); 3.43 (2H, dq, J_1 = 7.2, J_2 = 5.1, $NH\underline{CH_2}CH_3$); 3.58 (3H, d, *J* = 5.0, $NH\underline{CH_3}$); 5.63 (1H, br. s, NH); 6.09 (1H, s, 5-H); 9.58 (1H, br. s, NH). Found, %: C 63.94; H 8.47; N 20.02. $C_{11}H_{17}N_3O$. Calculated, %: C 63.74; H 8.27; N 20.27.

Conversion of 2-(Carbamoylmethyl)-1,4,6-trimethylpyrimidinium Iodide (3a) in Aqueous Alcoholic Methylamine Solution. Water (2 ml) was added to a solution of iodide **3a** (0.4 g, 1.3 mmol) in 15% alcoholic methylamine solution (10 ml) and the mixture was heated in a sealed ampule at 90-100°C for 20 h. The solution was then evaporated to dryness under reduced pressure, and hexane was added to the residue. The precipitated crystals were filtered off, washed with hot hexane, and then with several drops of water, and dried. 3-Carbamoyl-4,6-dimethyl-1,2-dihydro-2-pyridone (**5**) (0.18 g, 83%) was obtained; mp 214-215°C, R_f 0.3

(acetone). The solvent was distilled from the hexane solution, and nicotinamide **4a** (20 mg, 10%) was obtained, which corresponded with a known sample in ^{1}H NMR spectrum, TLC, and melting point. ^{1}H NMR spectrum of compound **5** ($CDCl_3$), δ, ppm: 2.35 (3H, s, 4(6)-CH_3); 2.70 (3H, s, 6(4)-CH_3); 5.95 (1H, br. s, NH); 6.1 (1H, s, 5-H); 9.35 (1H, br. s, NH); 12.6 (1H, br. s, NH). Found, %: C 58.09; H 6.21; N 16.71. $C_{11}H_{17}N_3O$. Calculated, %: C 57.82; H 6.07; N 16.86.

The work was carried out within the framework of scientific theme 00-405b of the Ministry of Science and Education of the Armenian Republic, and also jointly with Prof. A. R. Katritzky (University of Florida) grant No. ACH-006 98/ACI-955 of the National Fund for Science and Advanced Technology of Armenia (NFSAT), and the US Civil Research and Development Fund (US CRDF).

REFERENCES

1. G. G. Danagulyan, L. G. Sahakyan, and G. A. Panosyan, *Khim. Zh. Armen.*, **53**, 62 (2000).
2. G. G. Danagulyan, L. G. Sahakyan, A. R. Katritzky, and S. N. Denisenko, *Heterocycles*, **53**, 419 (2000).
3. G. G. Danagulyan and L. G. Sahakyan, *Khim. Geterotsikl. Soedin.*, 698 (2000).
4. G. G. Danagulyan, L. G. Sahakyan, and G. A. Panosyan, *Khim. Geterotsikl. Soedin.*, 351 (2001).
5. G. G. Danagulyan and L. G. Sahakyan, *Khim. Geterotsikl. Soedin.*, 1434 (1999).
6. G. G. Danagulyan and L. G. Sahakyan, *Khim. Zh. Armen.*, **53**, 147 (2000).
7. G. G. Danagulyan, L. G. Sahakyan, A. R. Katritzky, and S. N. Denisenko, *Khim. Geterotsikl. Soedin.*, 1572 (1999).