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SYNTHESIS OF NICOTINIC ACID DERIVATIVES BY THE REACTION OF SALTS OF 1-ALKYL-4,6-DIMETHYL-2-PYRIMIDINYLACETIC ACID ESTERS WITH AMINES

G. G. Danagulyan[1], L. G. Saakyan[1], and G. A. Panosyan[2]

A study was carried out on the enamine rearrangement of iodoalkylates of the ethyl ester of 4,6-dimethyl-2-pyrimidinylacetic acid to give ethyl esters of 2-alkylamino-4,6-dimethylnicotinic acid, which proceeds upon the action of various amines. The reaction with amines containing an alkyl substituent different from that at the quaternized nitrogen atom of the pyrimidinium salt leads to the formation of products of rearrangement and transamination. In the presence of water, the rearrangement is accompanied by the formation of the ethyl ester of 1,2-dihydro-2-oxo-4,6-dimethylnicotinic acid.

Keywords: amine, iodoalkylates of esters of pyrimidinylacetic acids, pyridone, 2-alkylaminonicotinic acid derivatives, enamine rearrangement.

Pyridine derivatives are the basis of many natural and synthetic biologically active products, some of which have found use in medicine and agriculture [1, 2]. These compounds play an important role in the metabolism of living organisms (vitamins B_6 and PP (niacin), and nicotinamide adenine dinucleotide (NAD)) [3]. This clearly lends importance to the search for new methods for the synthesis and functionalization of pyridine and the development of nonstandard pathways for the introduction of substituents into the pyridine ring.

In the present work, we studied the enamine rearrangement of pyrimidinium salts, which yields 2-alkylaminopyridine derivatives. These derivatives have not been readily available.

In previous work [4, 5], we reported the transformation of the iodide of ethyl 1,4,6-trimethyl-2-pyrimidinylacetate (**1a**) into the ethyl ester of 2-methylamino-4,6-dimethylnicotinic acid (**2a**), which proceeds in an ethanolic solution of methylamine. We found that when the reaction is carried out in the presence of amines containing a substituent different from that at the quaternary pyrimidinium nitrogen atom, the reaction proceeds through two alternative pathways: 1) with retention of the alkyl group of the pyrimidinium salt in the amine fragment of the nicotinic acid derivative (isomerizational recyclization) and 2) introduction of the nucleophile into the rearrangement product leading to 2-alkylaminonicotinates, containing the alkyl group not of the starting salt but rather of the amine reagent. Thus, the reaction of iodomethylate **1a** with ethanolic ethylamine gave

[1] Yerevan Institute of National Economy, Yerevan 375025, Republic of Armenia; e-mail: ysine@ysine.am. [2] Center for the Study of Molecular Structure, National Academy of Sciences of the Republic of Armenia, Yerevan 375014, Republic of Armenia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 351-357, March, 2001. Original article submitted September 21, 1999.

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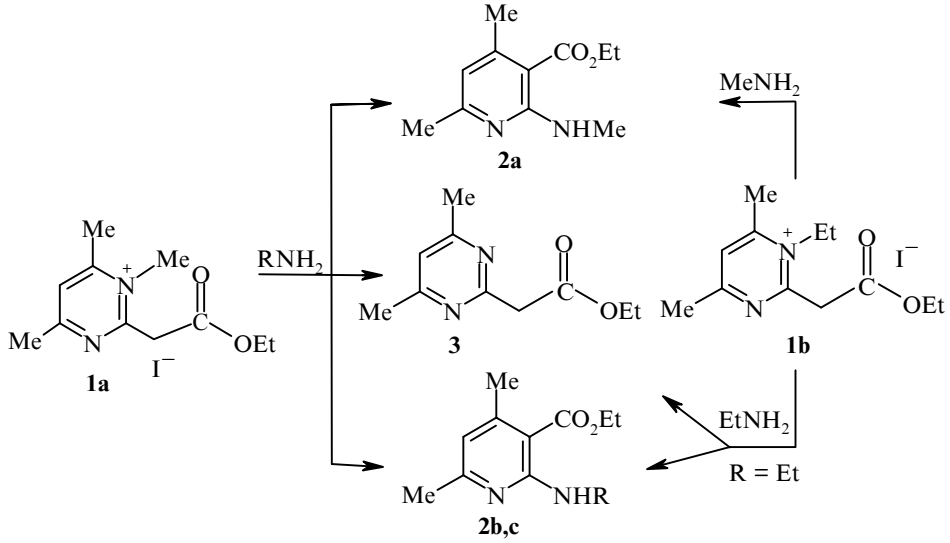
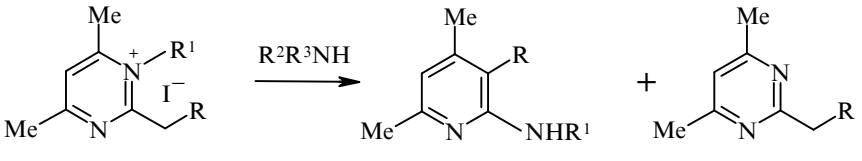
ethyl ester of 4,6-dimethyl-2-ethylaminonicotinic acid (**2b**) in 41% yield along with ester **2a** and demethylation product **3**. An analogous exchange of the amine fragment was described in our recent work on the reaction of salt **1a** with benzylamine, which gave pyrimidine **3** and enamine rearrangement products **2a** and **2c** (R = CH_2Ph) [6].

The reaction of iodoethylate **1b** with methylamine proved more selective and only pyridine **2a** was isolated in 56% yield, i.e., the rearrangement–transamination product was the sole (or possibly major) product. The reaction of iodoethylate **1b** with ethylamine gave the products of enamine rearrangement **2b** and N-dealkylation **3** as expected.



R = Et, CH_2Ph

The steric factor is likely significant in this reaction, as indicated by the high yield and formation of only the rearrangement–transamination product in the reaction of salt **1b** containing an ethyl group with methylamine. In contrast, when the substituting group is bulkier than the leaving group, both possible enamine rearrangement products are formed. Furthermore, in a number of cases, the steric factor may completely prevent formation of the rearrangement–transamination product. Thus, the results of the reaction of salt **1a** with diethylamine and of iodoethylate **1b** with *tert*-butylamine, in which rearrangement–dealkylation products are formed without rearrangement–transamination products, may be attributed to steric factors.



1 **2** **3**

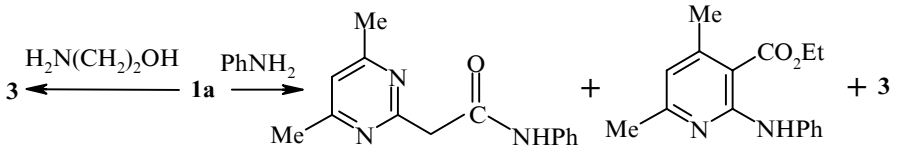
R = COOEt; **a** R^1 = Me, R^2 = R^3 = Et; **b** R^1 = Et, R^2 = CMe_3, R^3 = H

The major product in the reaction of aniline with salt **1a** is the anilide of 4,6-dimethyl-2-pyrimidinylacetic acid **4** and only slight recyclization is noted. In this case, the basicity of the base is probably insufficient for opening of the pyrimidine ring. Analogously, demethylation product **3** was isolated in the reaction of salt **1a** with ethanolamine.

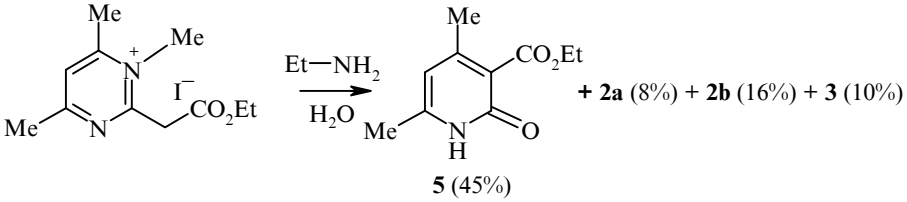
TABLE 1. Reaction of Salts **1a** and **1b** with Amines in Ethanol Solution

Salt, mmol	Amine	H_2O	Time, h	Yield, %				
				2a	**2b**	**2c**	**3**	**5**
1a								
0.9	NH_3	—	25	—	—	—	60	—
2	$MeNH_2$	—	22	60	—	—	—	—
1.5	$EtNH_2$	—	20	18	41	—	15	—
1	Et_2NH	—	20	35	—	—	20	—
2	$PhCH_2NH_2$*	—	15	30	—	35	15	—
1.5	$H_2N(CH_2)_2OH$	—	20	—	—	—	60	—
1.5	$EtNH_2$	1 ml	25	8	16	—	10	45
1.5	Et_2NH	10 drops	25	35	—	—	10	17
1.5	Et_2NH	2 ml	25	—	—	—	50	17
1.5	Me_3CNH_2	10 drops	25	15	—	—	18	20
1b								
1.4	$MeNH_2$	—	20	56	—	—	—	—
1.4	$EtNH_2$	—	25	—	44	—	20	—
0.9	Me_3CNH_2	—	20	—	37	—	15	—

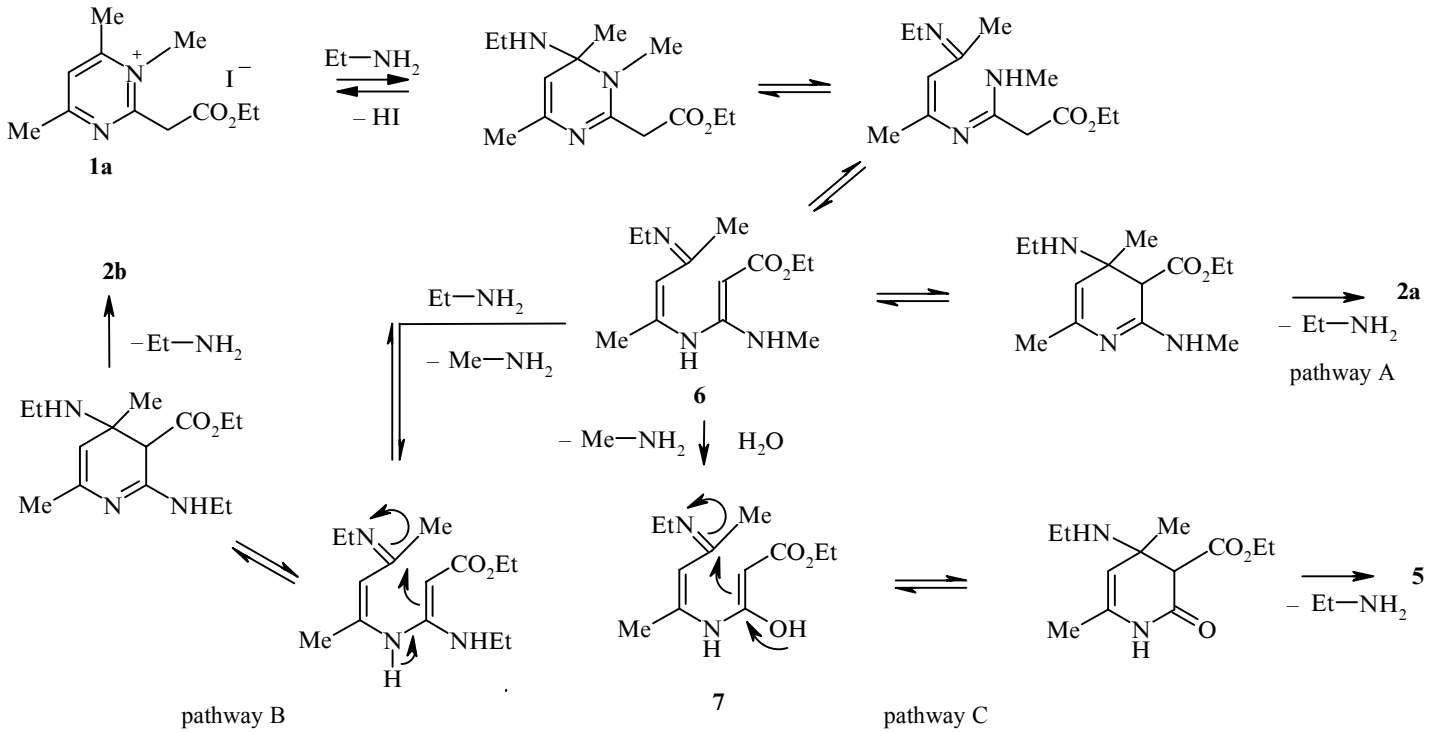
* Data given for reaction of salt with amine (without ethanol).



Water plays quite an important role in this rearrangement. Thus, the reaction of salt **1a** with an ethanol–water solution of ethylamine gives pyridone **5** as the major product along with the rearrangement products, pyridines **2a** and **2b**. We note that when the reaction is carried out in the presence of water, pyridone **5** was also isolated in the reaction of salt **1a** with diethylamine and *tert*-butylamine.



The formation of pyridone **5**, as well as the formation of enamine recyclization products **2a-d**, may be attributed to different pathways for the transformation of open form **6**. The first step in these rearrangement is probably nucleophilic attack at the pyrimidine ring with subsequent dissociation of the $N_{(1)}$–$C_{(6)}$ bond and transformation of the intermediate into open form **6**. Cyclization of **6** leads to formation of a new C–C bond and conversion to isomerizational recyclization product **2a** (pathway A). The formation of a rearrangement product with transamination due to exchange of the amine group in the enamine fragment (pathway B) or formation of pyridone **5** through mild, nonpolar hydrolysis in the enamine fragment of intermediate **6** with subsequent transformation of enol **7** into pyridone **5** (pathway C) are possible directions for the transformation of intermediate **6**.


1a
Et—NH2
– HI
2b
– Et—NH2
Et—NH2
– Me—NH2
6
– Me—NH2
H2O
2a
– Et—NH2
pathway A
pathway B
7
pathway C
5
– Et—NH2

The structures of rearrangement products **2a-d** were confirmed by their ^{1}H and ^{13}C NMR spectra, showing the alkylamino group signals are characteristic for nicotinic acid derivatives, especially the methyl group doublet in methylamino derivative **2a**, methylene group doublet in **2c**, and methylene group quartet in the ethylamino fragment of **2b**. The correctness of the signal assignment was also confirmed by double resonance experiments by suppressing the signal of the proton at the amine nitrogen atom. The rearrangement is indicated also by the absence of the signal characteristic for the protons of the methylene group of the side chain of salts **1a** and **1b** in the vicinity of 4.5 ppm.

EXPERIMENTAL

The NMR spectra were taken on a Varian Mercury 300 spectrometer used in the US CRDF RESC 17-5 program framework. Thin-layer chromatography was carried out on Silufol UV-254 plates with development by iodine vapor and the Ehrlich reagent. Preparative separation was carried out on a column packed with silica gel L40/100 with 10:1 benzene–ether as the eluent.

Ethyl Ester of 4,6-Dimethyl-2-pyrimidinylacetic Acid (3). Diethyl malonate (137 g, 0.69 mol) was added dropwise to sodium (14.5 g, 0.63 mol) suspended in toluene and transferred into absolute ether (400 ml). The mixture was stirred at room temperature for one or two days until the complete disappearance of sodium and formation of a malonate ester salt. Ether was then distilled off and dry DMF (100 ml) was added. After complete dissolution of the salt, a solution of 2-chloro-4,6-dimethylpyrimidine (43.5 g, 0.3 mol) in DMF (50 ml) was added. The reaction mixture was stirred and heated at 120°C with reflux for 15 h. The solvent was distilled off in vacuum and benzene (200 ml) was added. Acetic acid was added to neutralize the mixture. The solvent was distilled off the benzene solution and the residue was distilled in vacuum, taking the fraction at 118-121°C (3 mm). The crystals precipitated upon standing were filtered off, recrystallized from hexane, and dried in the air to give 23.5 g (40%) of compound **3**; mp 65-66°C, R_f 0.5 (3:1 benzene–acetone) (65-66°C (water) [7]). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 1.25 (3H, t, *J* = 7.1, $CH_2C\underline{H}_3$); 2.41 (6H, s, 4- and 6-CH_3); 3.78 (2H, s, CH_2); 4.15 (2H, q, *J* = 7.1, $C\underline{H}_2CH_3$); 7.0 (1H, s, 5-H). Found, %: C 61.98; H 7.35. $C_{10}H_{14}N_2O_2$. Calculated, %: C 61.84; H 7.27.

Iodoalkylates of Ethyl Ester of 4,6-Dimethyl-2-pyrimidinylacetic Acid (1a and 1b). A mixture of ester **3** (10 g, 0.05 mol) and corresponding alkyl iodide (15 ml) in a sealed glass ampule was heated on a steam bath. After 10 h, the crystalline precipitate was filtered off (after 40 h in the case of ethyl iodide), washed with a small amount of hexane, and dried in the air. Yield of salt **1a** 17 g (98%); mp 134-135°C (acetone). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.34 (3H, t, $C\underline{H}_3CH_2O$); 2.73 (3H, s, 4-CH_3); 2.93 (3H, s, 6-CH_3); 4.13 (3H, s, N–CH_3); 4.24 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 4.5 (2H, s, CH_2); 8.14 (1H, s, 5-H). Found, %: C 39.05; H 4.78. $C_{10}H_{14}N_2O_2 \cdot CH_3I$. Calculated, %: C 39.30; H 5.10.

Yield of **1b** 19 g (52%); mp 118-119°C (acetone). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 1.33 (3H, t, *J* = 7.2, $C\underline{H}_3$–CH_2O); 1.51 (3H, t, *J* = 7.1, N–$CH_2C\underline{H}_3$); 2.73 (3H, s, 4-CH_3); 2.95 (3H, s, 6-CH_3), 4.24 (2H, q, *J* = 7.2, $CH_3C\underline{H}_2O$); 4.49 (2H, s, CH_2); 4.63 (2H, q, *J* = 7.1, N–$C\underline{H}_2CH_3$); 8.17 (1H, s, 5-H). Found, %: C 40.88; H 5.21. $C_{10}H_{14}N_2O_2 \cdot C_2H_5I$. Calculated, %: C 41.16; H 5.47.

Reaction of Pyrimidinium Salts 1a and 1b with Amines (General Method). Pyrimidine salt **1** (0.002 mol) was dissolved in 15% ethanolic methylamine (or 11% ethylamine) (6 ml) and heated in a sealed ampule on a steam bath. The solvent was then distilled off and the residue was separated on a column packed with silica gel L40/100 using 10:1 benzene–acetone as the eluent. After completion of the preparatory separation, the fraction remaining at the start was eluted with acetone to give pyridone **5**.

Analogous experiments were carried out in the presence of water. The corresponding amount of water indicated in Table 1 was added to the starting mixture of the pyrimidinium salt and ethanolic amine.

Ethyl Ester of 4,6-Dimethyl-2-methylaminonicotinic Acid (2a); mp 39-40°C (39-40°C [4, 5]), R_f 0.5 (10:1 benzene–acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, J (Hz): 1.39 (3H, t, J = 7.2, $CH_2C\underline{H}_3$); 2.38 and 2.43 (6H, s, 4-CH_3 and 6-CH_3); 3.04 (3H, d, J = 5.1, NCH_3); 4.33 (2H, q, J = 7.2, $C\underline{H}_2CH_3$); 6.23 (1H, s, 5-H); 7.77 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.37 ($OCH_2C\underline{H}_3$), 23.59 (4-CH_3), 24.66 (6-CH_3), 28.22 (N–CH_3), 60.47 ($OC\underline{H}_2$), 104.04 ($C_{(4)}$), 114.69 ($C_{(5)}$), 150.97 ($C_{(6)}$), 159.61 ($C_{(2)}$), 160.77 ($C_{(3)}$), 169.13 (C=O). Found, %: C 63.69; H 7.97; N 13.31. $C_{11}H_{16}N_2O_2$. Calculated, %: C 63.44; H 7.74; N 13.45.

Ethyl Ester of 2-Ethylamino-4,6-dimethylnicotinic acid (2b) was obtained as an oil, R_f 0.65 (10:1 benzene–acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, J (Hz): 1.23 (3H, t, J = 7.2, $NHCH_2C\underline{H}_3$); 1.39 (3H, t, J = 7.1, $OCH_2C\underline{H}_3$); 2.35 and 2.44 (6H, s, 4-CH_3 and 6-CH_3); 3.51 (2H, dq, ^1J = 7.2, ^2J = 5.0, $NHC\underline{H}_2CH_3$); 4.34 (2H, q, J = 7.1, $OC\underline{H}_2CH_3$); 6.23 (1H, s, 5-H); 7.73 (1H, s, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.31 ($NHCH_2C\underline{H}_3$), 14.89 ($OCH_2C\underline{H}_3$), 23.58 (4-CH_3), 24.62 (6-CH_3), 35.99 (N–$C\underline{H}_2$), 60.42 ($OC\underline{H}_2$), 103.74 ($C_{(4)}$), 114.66 ($C_{(5)}$), 151.08 ($C_{(6)}$), 159.01 ($C_{(2)}$), 160.87 ($C_{(3)}$), 169.18 (C=O). Found, %: C 64.68; H 8.01; N 12.81. $C_{12}H_{18}N_2O_2$. Calculated, %: C 64.84; H 8.16; N 12.60.

Reaction of Salt 1a with Aniline. Aniline (5 ml) was added to salt **1a** (1 g, 0.003 mol) and heated at 95-100°C in a sealed ampule for 40 h. The reaction mixture was then treated as in the general method described above. The residue was separated on a column packed with silica gel L40/100 using 5:1 benzene–acetone as the eluent to give 0.36 g (50%) of anilide **4** and 0.065 g (8%) **2d**.

Anilide of 4,6-Dimethyl-2-pyrimidinylacetic Acid (4); mp 109-110°C, R_f 0.3 (3:1 benzene–acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, J (Hz): 2.53 (6H, s, 4-CH_3 and 6-CH_3); 4.03 (2H, s, CH_2); 6.97 (1H, s, 5-H); 7.09 (1H, dd, ^1J = 7.2, ^2J = 1.9, 4'-H); 7.31 (2H, m, 3'-H); 7.57 (2H, dd, ^1J = 7.8, ^2J = 1.9, 2'-H); 10.29 (1H, br. s, NH).

Ethyl Ester of 4,6-Dimethyl-2-phenylaminonicotinic Acid (2d), R_f 0.56 (3:1 benzene–acetone). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.39 (3H, t, $OCH_2C\underline{H}_3$); 2.25 (3H, s, 4(6)-CH_3); 2.31 (3H, s, 6(4)-CH_3); 4.38 (2H, q, $OC\underline{H}_2CH_3$); 5.95 (1H, s, 5-H); 7.31 (5H, m, Ph).

The spectra of **2c** and **5** were described in our previous work [6, 8].

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