Chemistry of Heterocyclic Compounds, Vol. 37, No. 3, 2001

SYNTHESIS OF 5-PHENYL-7-TRIFLUOROMETHYL-2,3-DIHYDRO-IMIDAZO[1,2-*a*]PYRIDINES

E. Suloeva[1], M. Yure[1], E. Gudriniece[1], S. Belyakov[2], M. Petrova[1], and I. Kalnite[1]

Syntheses are reported for a series of 2-alkylamino-6-phenyl-4-trifluoromethylpyridines. The reaction of 3-cyano-2-(hydroxyalkylamino)-6-phenyl-4-trifluoromethylpyridines with thionyl chloride gave the corresponding 2-(chloroalkylamino)pyridines, 8-cyano-5-phenyl-7-trifluoromethyl-2,3-dihydro-imidazo[1,2-a]pyridines, and 9-cyano-6-phenyl-8-trifluoromethyl-2,3,4-trihydropyrido[1,2-a]-pyrimidines. X-ray diffraction structural analysis was used to study 8-cyano-5-phenyl-7-trifluoromethyl-2,3-dihydroimidazo[1,2-a]pyridine.

Keywords: 2,3-dihydroimidazo[1,2-*a*]pyridines, 2,3,4-trihydropyrido[1,2-*a*]pyrimidines, X-ray structural analysis.

Our previous studies [1, 2] on 2- and 3-amino-6-phenyl-4-trifluoromethylpyridines have shown that these compounds have antiviral activity. In a continuation of this work, 2-chloro-3-cyano-6-phenyl-4-trifluoromethylpyridine (**1**) and 3-aminocarbonyl-2-chloro-6-phenyl-4-trifluoromethylpyridine (**2**) were used to synthesize previously unreported 2-alkylaminopyridines including a series of β- and γ-hydroxyalkylamino derivatives **3b-e,h,i, 4d,j** (Tables 1 and 2) according to our previous methods [1, 3, 4]. Products **3f,g,** and **4f** were obtained in a modification of the hydroxyl substituent in 2-(2-hydroxyethylamino)pyridine **4a**, which has antiviral activity [1], and its analog **3a** [3] by acylation with acetyl chloride and benzoyl chloride.

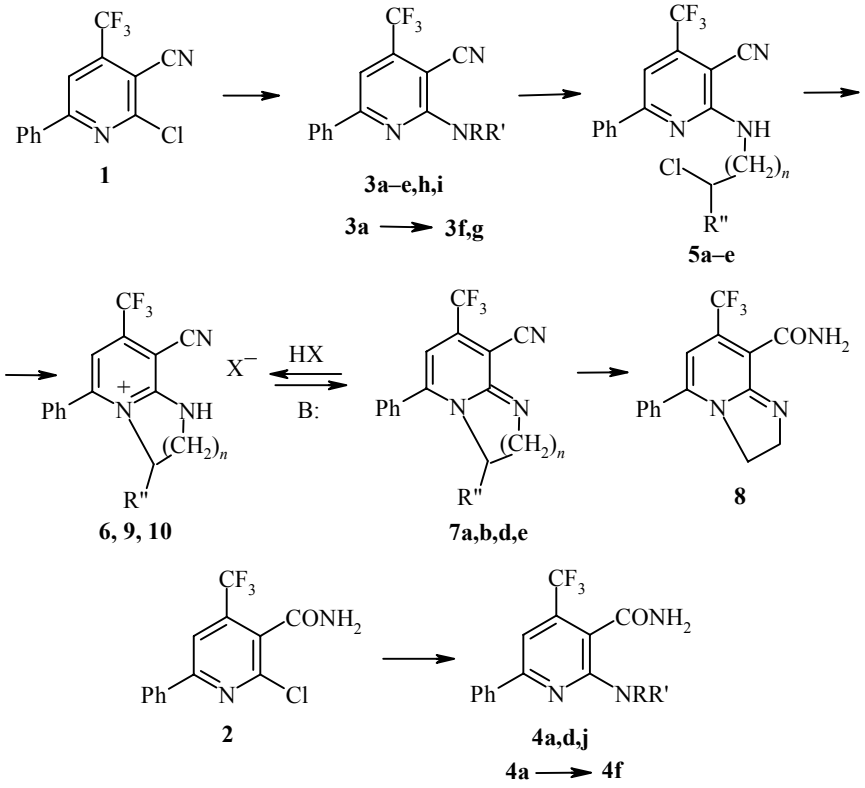
Replacement of the hydroxyl group by a chlorine atom in pyridine **3a** by treatment with thionyl chloride proved more difficult. 2-(2-Chloroethylamino)pyridine **5a** was not isolated upon heating pyridine **3a** with 46 equivalents of thionyl chloride at reflux. This reaction provided 8-cyano-5-phenyl-7-trifluoromethyl-2,3-dihydroimidazo[1,2-*a*]pyridinium chloride (**6**), which gave imidazopyridine **7a** upon treatment with aqueous ammonia. If this reaction is carried out with only one-third the amount of thionyl chloride, it leads to both bicyclic compound **7a** and chloro derivative **5a**, although the yield of **5a** does not exceed ~20%. Intramolecular cyclization proceeds even upon cooling the reagents to -5°C (the ratio of pyridine **3a** to thionyl chloride is 1:1 or 1:2). This procedure yields a mixture of pyridines **3a** and **5a** and imidazopyridinium chloride **6**. Even lower yields of chloro derivative **5** were obtained upon heating pyridines **3a,b,d,e** in $POCl_3$. The major reaction products in this case are bicyclic compounds **7**.

Intramolecular alkylation with formation of a bicyclic system occurs upon heating **3a** in concentrated sulfuric acid for 1 h, which leads to a mixture of compounds difficult to separate. The major components in this mixture are **4a** and 2,3-dihydroimidazo[1,2-*a*]pyridine **8** (the convergent synthesis of **8** was carried out by heating imidazopyridine **7a** with concentrated sulfuric acid). Similar cyclization occurs upon heating pyridine

---

[1] Riga Technical University, LV-1048 Riga, Latvia; e-mail: mara@ktf.rtu.lv. [2] Latvian Institute of Organic Synthesis, LV-1006 Riga, Latvia; e-mail: serg@osi.lv. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 358-367, March, 2001. Original article submitted March 30, 2000.

0009-3122/01/3703-0329$25.00



3, **4 a** R = CH_2CH_2OH, R' = H; **b** R = $CH_2CHMeOH$, R' = H; **c** R = $CH_2CH(Ph)OH$, R' = H; **d** R = $CH_2CH_2CH_2OH$, R' = H; **e** R = $CH_2CH_2CHMeOH$, R' = H; **f** R = CH_2CH_2OCOMe, R' = H; **g** R = CH_2CH_2OCOPh, R' = H; **h** R = Me, R' = H; **i** R = $CH_2CH{=}CH_2$, R' = H; **j** R = Et, R' = Et; **5**, **7 a** *n* = 1, R" = H; **b** *n* = 1, R" = CH_3; **c** *n* = 1, R" = Ph; **d** *n* = 2, R" = H; **e** *n* = 2, R" = Me; **6** *n* = 1, R" = H, X = Cl; **9** *n* = 1, R" = H, X = NO_3; **10** *n* = 1, R" = H, X = ClO_4

3a in acetic acid in the presence of concentrated sulfuric acid. In this case imidazopyridine **7a** was isolated in 21% yield in addition to acylated pyridine **3f**. The cyclization of N-(2-pyridyl)aminoethanols to give the imidazo[1,2-*a*]pyridine system upon the action of concentrated sulfuric acid or acetic acid has not yet been reported although it has been carried out with hydrochloric and polyphosphoric acids [5, 6].

A survey of the data on 2,3-dihydroimidazo[1,2-*a*]pyridines [7, 8] showed that these heterocyclic compounds have not been studied extensively and this led us to treat other 2-(hydroxyalkylamino)pyridines **3b-e** with thionyl chloride. Both 2-(chloroalkylamino)pyridines **5b-e** and condensed bicyclic heterocyclic derivatives, namely, imidazopyridine **7b** and pyrido[1,2-*a*]pyrimidines **7d,e** (in the case of 2-(γ-hydroxyalkylamino)-pyridines **3d,e**) were obtained (Tables 1 and 2). However, intramolecular cyclization was not observed in the case of a phenyl substituent at the carbon atom bearing the hydroxyl group in **3c**.

The imidazopyridine and pyridopyrimidine salts formed in the reactions with thionyl chloride were converted without isolation into the free bases. An exception was found for imidazopyridine **6**, which both as nitrate **9** and perchlorate **10** was obtained upon treatment of imidazopyridine **7a** with the corresponding acids. Colored bicyclic products were obtained. The melting points found for bright yellow salts **6, 9,** and **10** range from 172°C for the nitrate to 283°C for the perchlorate. Dark red imidazopyridines **7** (*n* = 1) melt in the range from 110 to 143°C. The melting points of orange pyridopyrimidines **7** (*n* = 2) are somewhat higher (136-198°C).

TABLE 1. Physico-chemical Characteristics of 6-Phenyl-4-trifluoromethyl-pyridines **3a-3i, 4a,d,f,j**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Reaction time, h (method)	Yield, % (method)
		C	H	N			
3a	$C_{15}H_{12}F_3N_3O$				134-136 (134-136 [3])		78
3b	$C_{16}H_{14}F_3N_3O$	59.62 / 59.81	4.40 / 4.39	12.96 / 13.08	124-125	2	89
3c	$C_{21}H_{16}F_3N_3O$	65.46 / 65.79	4.12 / 4.21	10.67 / 10.96	125-127	4	81
3d	$C_{16}H_{14}F_3N_3O$	59.76 / 59.81	4.15 / 4.39	13.01 / 13.08	134-135	5	87
3e	$C_{17}H_{16}F_3N_3O$	60.97 / 60.89	4.83 / 4.81	12.59 / 12.53	146-147	2	85
3f	$C_{17}H_{14}F_3N_3O_2$	58.15 / 58.45	3.98 / 4.04	11.91 / 12.03	167-170	2 (A), 4 (B)	54 (A), 82 (B)
3g	$C_{22}H_{16}F_3N_3O_2$	63.94 / 64.23	3.86 / 3.92	10.17 / 10.21	181-184	8	53
3h	$C_{14}H_{10}F_3N_3$	60.57 / 60.65	3.63 / 3.64	15.10 / 15.16	220-221	2	79
3i	$C_{16}H_{12}F_3N_3$	63.27 / 63.36	3.97 / 3.99	13.81 / 13.86	118-119	1	77
4a	$C_{15}H_{14}F_3N_3O_2$				203-204 (201 [1])	2	80
4d	$C_{16}H_{16}F_3N_3O_2$	56.50 / 56.63	4.78 / 4.75	12.29 / 12.38	152-153	6	66
4f	$C_{17}H_{16}F_3N_3O_3$	55.68 / 55.59	4.37 / 4.39	11.43 / 11.44	215-218	1	84
4j	$C_{17}H_{18}F_3N_3O$	60.52 / 60.53	5.45 / 5.38	12.42 / 12.46	158-159	3	88

TABLE 2. Spectral Characteristics of 6-Phenyl-4-trifluoromethylpyridines **3b-i, 4d,f,j**

Compound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz)
1	2	3
3b	3414, 2978, 2926, 2218, 1594, 1522	1.27 (3H, d, *J* = 5, CH_3); 2.58 (1H, br. s, OH); 3.34-4.07 (3H, m, CH_2–CH); 6.00 (1H, t, *J* = 5, NH); 7.29 (1H, s, =CH–); 7.49 (3H, m, Ph); 7.98 (2H, m, Ph)
3c	3362, 2930, 2222, 1592, 1578, 1540	2.88 (1H, br. s, OH); 3.71 (1H, ddd, *J* = 5, *J* = 8, *J* = 14, CH); 4.11 (1H, ddd, *J* = 3.5, *J* = 6.5, *J* = 14, CH); 5.04 (1H, dd, *J* = 3.5, *J* = 8, CH); 6.00 (1H, t, *J* = 5, NH); 7.24-7.53 (9H, m, Ph + =CH–); 7.98 (2H, m, Ph)
3d	3376, 3072, 2904, 2216, 1644, 1588, 1576, 1544, 1536	1.76-2.02 (2H, m, CH_2); 2.28 (1H, t, *J* = 5, OH); 3.67-3.89 (4H, m, $2CH_2$); 6.00 (1H, t, *J* = 5, NH); 7.22 (1H, s, =CH–); 7.42 (3H, m, Ph); 7.93 (2H, m, Ph)
3e	3358, 2970, 2934, 2886, 2226, 1594, 1574, 1546	1.27 (3H, d, *J* = 7, CH_3); 1.80 (2H, m, CH_2); 2.42 (1H, br. s, OH); 3.44-4.29 (3H, m, CH_2–CH); 6.20 (1H, t, *J* = 5, NH); 7.26 (1H, s, =CH–); 7.49 (3H, m, Ph); 8.02 (2H, m, Ph)
3f	3389, 2341, 2221, 1731, 1693, 1593, 1579, 1537	2.07 (3H, s, CH_3); 3.98 (2H, q, *J* = 6, CH_2); 4.36 (2H, t, *J* = 6, CH_2); 5.91 (1H, t, *J* = 6, NH); 7.38 (1H, s, =CH–); 7.53 (3H, m, Ph); 8.07 (2H, m, Ph)
3g	3381, 2365-2329, 2221, 1715, 1593, 1577, 1533	4.07 (2H, q, *J* = 6, CH_2); 4.60 (2H, t, *J* = 6, CH_2); 5.93 (1H, t, *J* = 5, NH); 7.24-7.64 (7H, m, Ph + =CH–); 8.00 (4H, m, Ph)
3h	3372, 2944, 2900, 2216, 1605, 1589, 1578	3.13 (3H, d, *J* = 5, CH_3); 6.00 (1H, br. s, NH); 7.31 (1H, s, =CH–); 7.53 (3H, m, Ph); 8.00 (2H, m, Ph)

TABLE 2 (continued)

1	2	3
3i	3209, 3101, 2972, 2216, 1644, 1588, 1576, 1544, 1536	4.29 (2H, m, CH_2); 5.04-5.48 (2H, m, $=CH_2$); 5.63 (1H, t, J = 5, NH); 5.78-6.27 (1H, m, =CH–); 7.31 (1H, s, =CH–); 7.49 (3H, m, Ph); 8.03 (2H, m, Ph)
4d	3388, 3180, 2956, 2932, 2872, 1638, 1620, 1582, 1516	1.73 (2H, t, J = 6, CH_2); 3.49 (4H, m, $2CH_2$); 4.46 (1H, t, J = 6, OH); 6.24 (1H, t, J = 6, NH); 7.21 (1H, s, =CH–); 7.43 (3H, m, Ph); 7.69 (1H, br. s, NH); 8.02 (3H, m, Ph + NH)*
4f	3469, 3333, 3101, 2985, 2969, 1673, 1597, 1583	2.00 (3H, s, CH_3); 3.38 (2H, q, J = 6, CH_2); 4.22 (2H, t, J = 6, CH_2); 6.50 (1H, t, J = 6, NH); 7.38 (1H, s, =CH–); 7.50 (3H, m, Ph); 7.80 (1H, br. s, NH); 8.10 (3H, m, Ph + NH)*
4j	3368, 3172, 2964, 2932, 2880	1.16 (6H, t, J = 7, $2CH_3$); 3.53 (4H, q, J = 7, $2CH_2$); 5.89 (1H, br. s, NH); 6.22 (1H, br. s, NH); 7.40 (4H, m, Ph + =CH–); 8.00 (2H, m, Ph)

* ^{1}H NMR spectrum taken in DMSO.

Bicyclic products **7** are highly soluble in organic solvents and partially soluble in water. Thus, these compounds are often difficult to remove from solution.

TABLE 3. Physico-chemical Characteristics of Compounds **5a-e, 6, 7a,b,d,e,** and **8-10**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, % (method)
		C	H	N		
5a	$C_{15}H_{11}ClF_3N_3$	54.69 / 55.31	3.33 / 3.40	12.63 / 12.90	170-173 (dec.)	20 (A)
5b	$C_{16}H_{13}ClF_3N_3$	55.68 / 56.56	3.72 / 3.86	11.87 / 12.37	127-130 (dec.)	60 (A)*, 10 (B)
5c	$C_{21}H_{15}ClF_3N_3$	61.87 / 62.77	3.68 / 3.76	9.87 / 10.46	182-185 (dec.)	57 (A)
5d	$C_{16}H_{13}ClF_3N_3$	56.27 / 56.56	3.92 / 3.86	12.32 / 12.37	129-131 (dec.)	52 (A)*, 12 (B)
5e	$C_{17}H_{15}ClF_3N_3$	57.41 / 57.72	4.20 / 4.27	11.72 / 11.88	142-143 (dec.)	53 (A)*, 8 (B)
6	$C_{15}H_{11}ClF_3N_3$	54.99 / 55.31	3.36 / 3.40	12.01 / 12.90	231-232 (dec.)	62 (A)*, 76 (B)
7a	$C_{15}H_{10}F_3N_3$	62.15 / 62.29	3.59 / 3.48	14.58 / 14.15	142-143	92 (A), 78 (B')*, 83 (C)
7b	$C_{16}H_{12}F_3N_3$	63.37 / 63.36	3.96 / 3.99	13.98 / 13.85	108-110	17 (B'), 39 (C)*
7d	$C_{16}H_{12}F_3N_3$	63.13 / 63.36	3.92 / 3.99	13.78 / 13.85	196-198	4 (B'), 42 (C)*
7e	$C_{17}H_{14}F_3N_3$	64.13 / 64.35	4.40 / 4.45	13.17 / 13.24	136-138	13 (B')*, 36 (C)
8	$C_{15}H_{12}F_3N_4O$	58.67 / 58.63	3.96 / 3.94	13.77 / 13.68	214-216	62
9	$C_{15}H_{11}F_3N_4O_3$	51.05 / 51.14	3.29 / 3.15	15.72 / 15.90	172-174 (dec.)	70
10	$C_{15}H_{11}ClF_3N_3O_4$	46.07 / 46.23	2.76 / 2.85	10.72 / 10.78	290-292 (dec.)	74

* Elemental analysis corresponds to sample obtained by this method.

The IR spectra of imidazopyridines **7** show characteristic bands at 1640-1644 cm^{-1} for the C=N bond and 2210-2226 cm^{-1} for the C≡N stretching vibrations. A special feature of the ^1H NMR spectrum of the N–CH_2–CH_2–N fragment in imidazopyridines **7** (Table 4) is the gradual transformation of the AA'BB' system upon gradual replacement of the solvent in $CDCl_3$–DMSO–C_6D_6.

Thus, the methylene protons in the N–CH_2–CH_2–N fragment in dioxane and deuterochloroform solutions are virtually equivalent in their chemical shifts and are seen as narrow signals at 3.91 and 4.01 ppm, respectively.

TABLE 4. Spectral Characteristics of Compounds **5a-e, 6, 7a,b,d,e,** and **8-10**

Com-pound	IR spectrum, ν, cm^{-1}	^1H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz)
5a	3349, 2973, 2225, 1589, 1577, 1533	3.67-3.82 (2H, m, CH_2); 3.89-4.09 (2H, m, CH_2); 5.91 (1H, t, *J* = 5, NH); 7.33 (1H, s, =CH–); 7.51 (3H, m, Ph); 7.98 (2H, m, Ph)
5b	3362, 3090, 2930, 2222, 1590, 1558, 1538	1.60 (3H, d, *J* = 6, CH_3); 3.58-4.47 (3H, m, CH_2–CH); 6.00 (1H, t, *J* = 7, NH); 7.36 (1H, s, =CH–); 7.52 (3H, m, Ph); 8.03 (2H, m, Ph)
5c	3354, 3070, 2226, 1590, 1578, 1542, 1498	3.87-4.47 (2H, m, CH_2); 5.16-5.31 (1H, m, CH); 5.96 (1H, br. s, NH); 7.48 (8H, m, Ph); 8.07 (3H, m, Ph)
5d	3359, 2959, 2219, 1593, 1579, 1543	2.16 (2H, q, *J* = 6, CH_2); 3.58–3.94 (4H, m, *J* = 6, $2CH_2$); 5.74 (1H, br. t, *J* = 6, NH); 7.39 (1H, s, =CH–); 7.52 (3H, m, Ph); 8.07 (2H, m, Ph)
5e	3356, 2984, 2220, 1591, 1577, 1543	1.58 (3H, d, *J* = 7, CH_3); 1.84-2.36 (2H, m, CH_2); 3.56-4.02 (2H, m, CH_2); 3.93-4.29 (1H, m, CH); 5.72 (1H, t, *J* = 5, NH); 7.32 (1H, s, =CH–); 7.94 (3H, m, Ph); 8.07 (2H, m, Ph)
6	3000-2400, 2250, 1640, 1585	4.22 (2H, m, CH_2); 4.91 (2H, m, CH_2); 6.93 (1H, s, =CH–); 7.56-7.67 (5H, m, Ph); 11.07 (1H, br. s, NH)*[2]
7a*	3100-2700, 2210, 1640, 1530, 1460	4.01 (4H, m, $2CH_2$); 5.71 (1H, s, =CH–); 7.40 (2H, m, Ph); 7.53 (3H, m, Ph); 3.53 (4H, m, $2CH_2$); 5.74 (1H, s, =CH–); 7.50 (5H, m, Ph)*[3]; 3.76-3.87 (2H, m, CH_2); 3.98-4.09 (2H, m, CH_2); 5.86 (1H, s, =CH–); 7.52-7.64 (5H, m, Ph)*[2]; 2.67 (2H, t, CH_2); 3.41 (2H, t, CH_2); 5.04 (1H, s, =CH–); 6.58-6.62 (2H, m, Ph); 6.91-6.95 (3H, m, Ph)*[4]
7b	3066, 2930, 2870, 2226, 1644, 1586, 1562, 1538	0.92 (3H, d, *J* = 6, CH_3); 3.63 (1H, dd, *J* = 15, *J* = 4, CH); 4.16 (1H, dd, *J* = 15, *J* = 10, CH); 4.65 (1H, m, CH); 5.72 (1H, s, =CH–); 7.52 (5H, m, Ph)
7d*	3066, 2940, 2860, 2232, 1622, 1576, 1542, 1516	1.82 (2H, q, *J* = 6, CH_2); 3.61 (4H, t, *J* = 6, $2CH_2$); 5.68 (1H, s, =CH–); 7.24 (2H, m, Ph); 7.45 (3H, m, Ph)
7e	2974, 2938, 2866, 2234, 1622, 1578, 1546, 1518	1.09 (3H, d, CH_3); 1.53-2.02 (2H, m, CH_2); 3.31-3.82 (2H, m, CH_2); 4.11-4.33 (1H, m, CH); 5.63 (1H, s, =CH–); 7.36 (2H, m, Ph); 7.56 (3H, m, Ph)
8	3331, 3067, 1689, 1645, 1581, 1557	3.96 (4H, m, CH_2); 5.87 (1H, s, =CH–); 5.93 (1H, br. s, NH); 7.44 (5H, m, Ph); 8.40 (1H, br. s, NH)
9	3099-2650, 2235, 1657, 1587	3.96 (2H, m, CH_2); 4.64 (2H, m, CH_2); 7.39 (1H, s, =CH–); 7.69 (5H, m, Ph); 10.67 (1H, br. s, NH)*[2]
10	3238, 3098, 2926, 2238, 1654, 1560, 1544	4.18 (2H, m, CH_2); 4.71 (2H, m, CH_2); 6.87 (1H, s, =CH–); 7.58 (5H, m, Ph); 11.10 (1H, br. s, NH)*[2]

* ^1H NMR spectrum taken on a Varian-Mercury BB spectrometer at 200 MHz.

*[2] ^1H NMR spectrum taken in DMSO-d_6.

*[3] ^1H NMR spectrum taken in dioxane-d_8.

*[4] ^1H NMR spectrum taken in C_6D_6.

TABLE 5. Atomic Coordinates* in Molecules **A** and **B** in **7a** ($\times 10^4$)

Atom	Molecule A			Molecule B		
	x	*y*	*z*	*x*	*y*	*z*
N(1)	1210(11)	4375(2)	4835(8)	-3818(10)	3122(2)	5488(8)
C(2)	1954(13)	4674(2)	5787(10)	-4051(12)	2802(2)	4741(10)
C(3)	1949(14)	4679(2)	7337(11)	-5554(13)	2780(2)	3184(11)
C(4)	1498(14)	4396(2)	7899(12)	-6417(13)	3072(2)	2513(10)
C(5)	858(15)	4096(2)	6928(11)	-6053(13)	3391(2)	3336(10)
C(6)	696(12)	4092(2)	5429(11)	-4760(13)	3409(2)	4845(11)
C(7)	-50(13)	3793(2)	4359(10)	-4389(13)	3728(2)	5747(11)
C(8)	552(14)	3459(2)	4890(11)	-4106(13)	4029(2)	5124(11)
C(9)	-274(17)	3182(2)	3981(15)	-3818(15)	4340(2)	5923(16)
C(10)	-1656(17)	3226(3)	2515(13)	-3834(17)	4346(2)	7394(14)
C(11)	-2317(17)	3548(3)	1944(12)	-4193(17)	4052(3)	7974(13)
C(12)	-1560(15)	3837(2)	2918(12)	-4444(17)	3744(3)	7225(14)
C(13)	1398(14)	4420(2)	3349(10)	-2212(14)	3084(2)	7078(11)
C(14)	2221(16)	4781(2)	3535(12)	-1634(15)	2707(3)	7000(12)
N(2)	2463(12)	4908(2)	5094(9)	-2933(12)	2560(2)	5495(10)
C(15)	2596(14)	4992(2)	8197(12)	-5928(14)	2443(3)	2482(12)
N(3)	2989(16)	5252(3)	8778(13)	-6277(16)	2178(3)	1925(12)
C(16)	1645(20)	4381(3)	9517(12)	-7869(17)	3063(3)	838(13)
F(1)	740(18)	4606(3)	9850(11)	-7321(14)	2988(4)	-111(10)
F(2)	758(15)	4113(2)	9821(10)	-8841(14)	3350(2)	443(9)
F(3)	3207(15)	4375(4)	10549(10)	-9188(13)	2846(3)	684(11)
H(5)	0470	3875	7399	-6822	3610	2771
H(8)	1651	3425	6012	-4123	4025	3957
H(9)	0200	2932	4411	-3564	4572	5453
H(10)	-2251	3005	1843	-3543	4575	8097
H(11)	-3421	3579	0823	-4287	4062	9075
H(12)	-2127	4085	2545	-4705	3519	7775
H(131)	0096	4406	2360	-1163	3259	7255
H(132)	2237	4230	3202	-2613	3113	8033
H(141)	1346	4946	2612	-0299	2705	7044
H(142)	3487	4769	3439	-1626	2562	7950

In DMSO, these signals are shifted by 0.21 ppm and appear as two multiplets centered at 4.03 and 3.82 ppm. In C_6D_6, all the signals in the ^{1}H NMR spectrum are shifted upfield due to the anisotropic effect of the solvent and the difference in the chemical shifts of these methylene protons is 0.74 ppm; these signals appear as triplets at 2.67 and 3.41 ppm and the splitting between the components is 10.4 Hz. The nature of the absorption of the methylene protons in imidazopyridinium salts **6, 9,** and **10** is the same as for **7a** in DMSO.

TABLE 6. Averaged Interatomic Distances (*d*) in Molecule **7a**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
C(2)–N(1)	1.433	C(15)–C(3)	1.430	C(12)–C(7)	1.396	N(2)–C(14)	1.470
C(6)–N(1)	1.373	C(5)–C(4)	1.434	C(9)–C(8)	1.360	N(3)–C(15)	1.128
C(13)–N(1)	1.468	C(16)–C(4)	1.465	C(10)–C(9)	1.366	F(1)–C(16)	1.260
C(3)–C(2)	1.449	C(6)–C(5)	1.349	C(11)–C(10)	1.378	F(2)–C(16)	1.361
N(2)–C(2)	1.280	C(7)–C(6)	1.485	C(12)–C(11)	1.413	F(3)–C(16)	1.225
C(4)–C(3)	1.334	C(8)–C(7)	1.402	C(14)–C(13)	1.532		

TABLE 7. Bond Angles (ω) in Molecule **7a**

Angle	ω, deg.	Angle	ω, deg.	Angle	ω, deg.
N(1)–C(2)–C(3)	116.9	C(3)–C(4)–C(5)	120.5	C(7)–C(8)–C(9)	120.4
N(1)–C(2)–N(2)	113.7	C(3)–C(4)–C(16)	121.3	C(8)–C(7)–C(12)	119.1
C(2)–N(1)–C(6)	121.2	C(4)–C(3)–C(15)	125.2	C(7)–C(12)–C(11)	119.3
C(2)–N(1)–C13	107.8	C(3)–C(15)–N(3)	174.2	C(8)–C(9)–C(10)	120.4
N(1)–C(6)–C(5)	119.7	C(4)–C(5)–C(6)	121.1	C(9)–C(10)–C(11)	121.5
N(1)–C(6)–C(7)	17.5	C(5)–C(4)–C(16)	118.0	C(10)–C(11)–C(12)	118.7
C(6)–N(1)–C(13)	130.2	C(4)–C(16)–F(1)	114.9	C(13)–C(14)–N(2)	106.9
N(1)–C(13)–C(14)	102.4	C(4)–C(16)–F(2)	115.0	F(1)–C(16)–F(2)	93.9
C(2)–C(3)–C(4)	119.8	C(4)–C(16)–F(3)	114.9	F(1)–C(16)–F(3)	109.4
C(2)–C(3)–C(15)	114.7	C(5)–C(6)–C(7)	122.7	F(2)–C(16)–F(3)	106.3
C(3)–C(2)–N(2)	129.1	C(6)–C(7)–C(8)	120.3		
C(2)–N(2)–C(14)	108.9	C(6)–C(7)–C(12)	119.7		

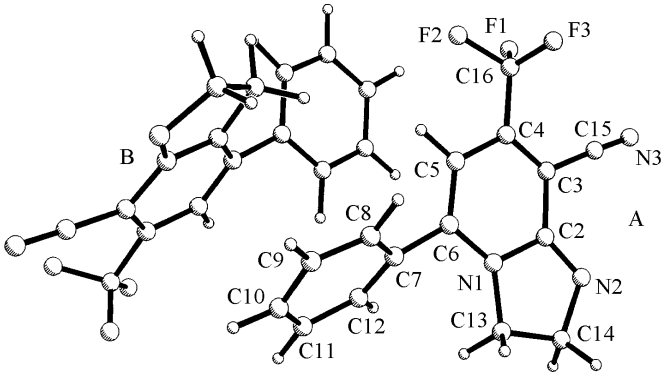


Fig. 1. Three-dimensional model of molecule **7a**.

However, the signals of the protons in the N–CH_2–CH_2–N fragment, which appear as two multiplets, are now displaced by 0.53-0.69 ppm and are found at 3.96-4.22 and 4.64-4.91 ppm. A characteristic for salts downfield signal is observed for the NH proton at 10.67-11.10 ppm.

Since no data were available in the literature for X-ray structural studies of 2,3-dihydroimidazo[1,2-*a*]-pyridines, we analyzed crystals of **7a** grown from ethanol and showed that there are two crystallographically independent molecules **A** and **B** in the unit cell (Fig. 1). The atomic coordinates are given in Table 5, the averaged interatomic distances (bond lengths) and bond angles in molecules **A** and **B** are given in Tables 6 and 7, respectively. The angle between the planes of the phenyl substituent and heterocyclic system is 132°.

In further investigations, we shall study the chemical behavior of these imidazo[1,2-*a*]pyridines.

EXPERIMENTAL

The IR spectra were taken on a Specord IR-75 spectrometer in paraffin oil using a NaCl prism for the 1500-1800 cm^{-1} region and LiF prism for the 2000-3600 cm^{-1} region. The ^1H NMR spectra were recorded on Bruker WH-90/DS and Varian-Mercury BB spectrometers at 200 MHz with TMS and HMDS as the internal standards. The reaction course and purity of the samples were checked using thin-layer chromatography on Silufol UV-254 plates and 1:9 ethanol–chloroform as the eluent.

The data for the products are summarized in Tables 1 and 2 for **3** and **4** and Tables 3 and 4 for **5-10.**

X-ray Diffraction Analysis of Imidazopyridine 7a. The unit cell parameters for monoclinic crystals of **7a** are as follows: a = 8.087(2), b = 38.880(4), c = 9.334(1) Å; β = 114.859(8)°; V = 2662.9(8) Å^3, d_{calc} = 1.443 g/cm^3; Z = 8, space group $P2_1/c$. The unit cell parameters and intensities of 3189 independent reflections were measured on a Syntex $P2_1$ automatic diffractometer with monochromatic molybdenum radiation, graphite monochromator, and ω-scanning to $2\theta_{max}$ = 50°. The structure was solved by the direct method [9] (the initial R-factor was 0.38) and refined by the full-matrix anisotropic method of least squares. The hydrogen atoms were found from the difference map. The final R-factor was 0.099. The calculations were carried out using the program package given by Gluzinskii et al. [10].

2-Alkylamino-6-phenyl-4-trifluoromethylpyridines (3a-e,h,i, 4a,d,j). A solution of chloropyridine **1** or **2** (3.5 mmol) and of the corresponding amine (4.2 mmol) in dioxane (10 ml) was heated at reflux for 1-6 h and poured into water (100 ml). The precipitate was recrystallized from ethanol.

2-(2-Acyloxyethylamino)-6-phenyl-4-trifluoromethylpyridines (3f,g, 4f). A. A solution of hydroxyethylaminopyridine **3a** (1 g, 3 mmol) in acetic acid (10 ml) with a drop of concentrated sulfuric acid was heated at reflux for 1 h, cooled, and poured into water (100 ml). The precipitate was recrystallized from ethanol to give 0.3 g (54%) of compound **3f**. A precipitate was obtained when aqueous ammonia was added to the filtrate to bring it to pH 8-9. Recrystallization from ethanol gave 0.1 g (21%) of imidazopyridine **7a**.

B. A solution of hydroxyethylaminopyridine **3a** (1 g, 3 mmol) in dioxane (10 ml) and corresponding acyl chloride (6 mmol) was heated at reflux for 2-8 h, cooled, and poured into water (100 ml). The precipitate was recrystallized, **3f** from ethanol and **3g** from 1:1 ethanol–dioxane.

The reaction of pyridine **4a** and acetyl chloride according to method B gave **4f**, which was recrystallized from ethanol.

2-(Chloroalkylamino)-3-cyano-6-phenyl-4-trifluoromethylpyridines (5a-e). A. A solution of hydroxyethylaminopyridines **5a-e** (5.2 g, 20 mmol) in thionyl chloride (20 ml) was heated at reflux for 1 h. Thionyl chloride was distilled off. At the end of the distillation, dioxane (20 ml) was added and the mixture was poured into ground ice (50 g). The precipitate was recrystallized from ethanol. The filtrates were used to obtain compounds **7a,b,d,e** (method B).

B. A solution of hydroxyethylaminopyridines **3a,b,d,e** (0.2 g, 0.69 mmol) in $POCl_3$ (5 ml) was heated at reflux for 1 h. The reaction mixture was cooled to room temperature and poured into ground ice (50 g). Products **5a,b,d,e** were filtered off and recrystallized from ethanol. The filtrates were used for the synthesis of **7a,b,d,e** (method B).

8-Cyano-5-phenyl-7-trifluoromethyl-2,3-dihydroimidazo[1,2-*a*]pyridinium chloride (6). A. A solution of pyridine **3a** (1 g, 3 mmol) in thionyl chloride (10 ml) was heated at reflux for 1 h. Thionyl chloride was distilled off. At the end of the distillation, dioxane (20 ml) was added and the mixture was filtered to give 0.69 g (62%) of yellow crystalline **6**.

B. Hydrogen chloride was bubbled through a solution of imidazopyridine **7a** (0.2 g, 0.69 mmol) in abs. dioxane (10 ml) for 10 min. The crystalline precipitate was filtered off to give 0.17 g (76%) of salt **6**.

8-Cyano-5-phenyl-7-trifluoromethyl-2,3-dihydroimidazo[1,2-*a*]pyridines (7a,b) and 9-Cyano-6-phenyl-8-trifluoromethyl-2,3,4-trihydropyrido[1,2-*a*]pyrimidines (7d,e). A. A sample of imidazopyridinium chloride **6** (1 g) was dissolved in water (50 ml) and brought to pH 8-9 by adding aqueous ammonia. The precipitate was recrystallized from ethanol.

B'. The filtrate obtained in the synthesis of **5a** (method A) was brought to pH 8-9 by adding aqueous ammonia and left at room temperature for 1 h. The precipitate was crystallized from ethanol to give 3.8 g (78%) of imidazopyridine **7a**.

C. Imidazopyridine **7a** was isolated as in method B' using the filtrate obtained in the synthesis of **5a** (method B).

Products **7b,d,e** were obtained analogously using method B' or C.

8-Aminocarbonyl-5-phenyl-7-trifluoromethyl-2,3-dihydroimidazo[1,2-*a*]pyridine (8). A sample of imidazopyridine **7a** (0.69 g, 2 mmol) in conc. sulfuric acid (5 ml) was heated for 1 h at 120°C on an oil bath and poured into ground ice (50 g). The solution was brought to pH 8-9 by adding aqueous ammonia. The precipitate was recrystallized from ethanol to give 0.13 g (62%) of orange crystals.

8-Cyano-5-phenyl-7-trifluoromethyl-2,3-dihydroimidazo[1,2-*a*]pyridinium Nitrate (9) and Perchlorate (10). A sample of nitric acid (0.2 ml) or perchloric acid (0.4 ml) was added to a solution of imidazopyridine **7a** (0.2 g, 0.69 mmol) in abs. dioxane (10 ml). The mixture was maintained at room temperature for 24 h and the precipitate was filtered off.

Samples of identical compounds synthesized by different methods had the same melting point and identical IR and ^{1}H NMR spectra.

REFERENCES

1. E. Yu. Gudriniece, M. Yu. Lidak, M. V. Yure, G. V. Vladyko, S. N. Nikolaev, E. I. Boreko, and P. G. Rytik, *USSR Inventor's Certificate No. 1769515; Byul. Izobr.*, No. 10 (1992).
2. E. Yu. Gudriniece, M. Y. Lidak, M. V. Yure, G. V. Vladyko, E. I. Boreko, and V. I. Botykov, *USSR Inventor's Certificate No. 1704417; Byul. Izobr.*, No. 1 (1992).
3. A. V. Guttsait, S. V. Belyakov, A. F. Mishnev, Ya. Ya. Breidelis, and E. Yu. Gudriniece, *Khim. Geterotsikl. Soedin.*, 1233 (1987).
4. M. V. Yure, E. Yu. Gudriniece, M. V. Petrova, E. K. Rantsane, and E. B. Mazheika, *Izv. Akad. Nauk LatvSSR, Ser. Khim.*, 439 (1990).
5. O. Bremer, *Liebigs Ann. Chem.*, **521**, 286 (1936).
6. L. Cossey, R. L. N. Harris, J. L. Hupatz, and J. N. Phillips, *Austr. J. Chem.*, **29**, 1039 (1976).
7. E. Suloeva, M. Yure, and E. Gudriniece, *Khim. Geterotsikl. Soedin.*, 1299 (1999).
8. E. Suloeva, M. Yure, and E. Gudriniece, *Khim. Geterotsikl. Soedin.*, 1011 (2000).
9. A. F. Mishnev and S. V. Belyakov, *Kristallografiya*, **33**, 835 (1988).
10. P. Gluzinskii, Ya. Kraevskii, A. Kemme, and A. Kemme, in: *Abstracts of the Second All-Union Conference on Precision Studies of Crystal Structure* [in Russian], Riga (1990), p. 30.