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SYNTHESIS AND PROPERTIES OF 4,5-*trans*-2-ALKYLTHIO-3-CYANO-6-HYDROXY-6-METHYL-4-PHENYL-5-PYRIDINIO-1,4,5,6-TETRAHYDRO-PYRIDINE IODIDES*

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*Alkylation of 4,5-trans-4-aryl-3-cyano-6-hydroxy-6-methyl-5-pyridinio-1,4,5,6- tetrahydropyridine-2-thiolates **1**, **2** was carried out. The presence of 5-pyridinio cation in thiolates **1**, **2** as a strong electron-withdrawing group leads to a pronoun- ced enhancement of their stability to dehydration but decreases their reactivity with electrophilic reagents. Steric structures of 2-alkylthio-6-hydroxytetrahydro-pyridines **3-5** are discussed in the light of ^{1}H NMR spectra and crystal X-ray diffraction data.*

Keywords: iodoacetamide, 5-pyridiniopyridine iodides, tetrahydropyridine-2-thiolates, X-ray difraction analysis.

Recently 2-alkylthio-6-hydroxy-1,4,5,6-tetrahydropyridine derivatives have been isolated as intermediates in the synthesis of 2-alkylthio-1,4-dihydropyridines [1-5], which are of interest as biologically active compounds [3-5]. 5-Acetyl-2-alkylthio-6-hydroxy-4-pyridyl-4,5-*trans*-1,4,5,6-tetrahydropyridines revealed a pronounced cardiovascular activity [4], but unfortunately they are unstable compounds due to splitting off water. Electron-withdrawing substituents in position 6 were found to be suitable for obtaining such compounds [6, 7].

In continuation of our efforts aimed at the synthesis of stable 2-alkylthio-6-hydroxy-1,4,5,6-tetrahydropyridines we have prepared 4,5-*trans*-4-aryl-3-cyano-6-hydroxy-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolates which appeared to be stable, even in acid media [8], and investigated their alkylation. It is worth mentioning that 1,4-dihydropyridines bearing in position 4 the pharmacophore 2-difluoromethoxyphenyl group are good calcium antagonists and vasodilators [9, 10]. So, derivatives combining 5-pyridinio-1,4,5,6-tetrahydropyridine skeleton with this pharmacophore in one molecule seem to be promising targets for the synthesis.

4,5-*trans*-3-Cyano-6-hydroxy-4-phenyl-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolate (**1**) was prepared in 96% yield by the condensation of 1-acetonylpyridinium chloride, benzaldehyde, and cyanothioacetamide [8] while its 4-(2-difluoromethoxyphenyl)-substituted analog **2** was obtained by condensation of 1-acetonylpyridinium chloride with 2-cyano-3-[2-(difluoromethoxy)phenyl]thioacrylamide using piperidine as a condensing agent (Scheme 1).

* Dedicated to Professor Edmunds Lukevics on his 65th birthday.

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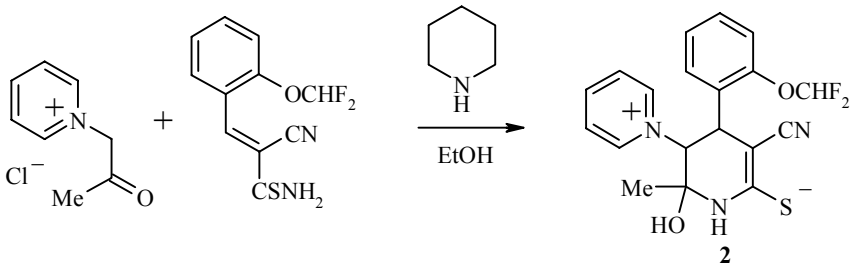
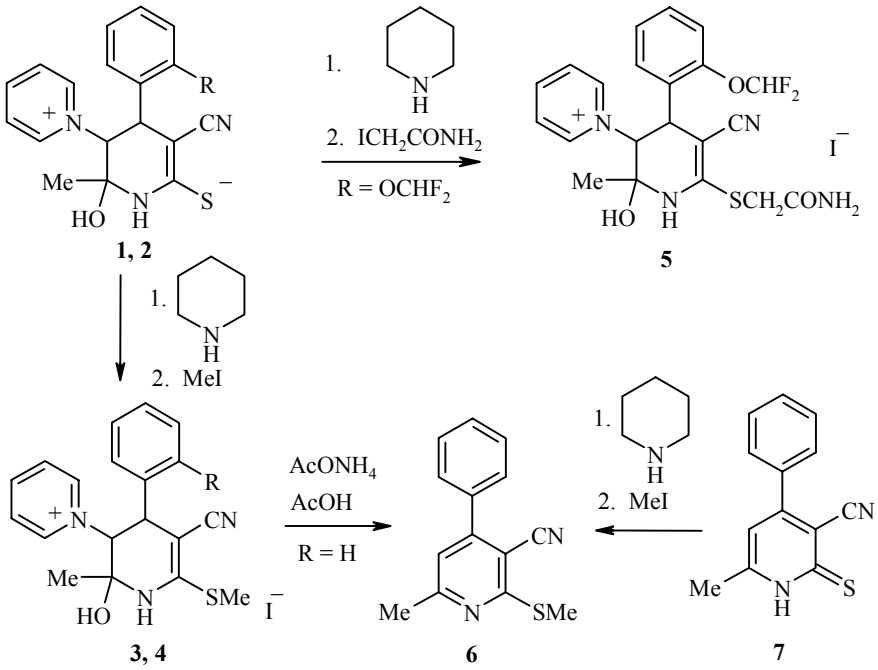
Scheme 1



The alkylation of betaines **1**, **2** with methyl iodide or iodoacetamide in the presence of piperidine takes place at the most nucleophilic center, i.e., the sulfur atom, yielding 2-alkylthio-4-aryl-3-cyano-6-hydroxy-6-methyl-5-pyridinio-1,4,5,6- tetrahydropyridine iodides **3**-**5** (Scheme 2).

Scheme 2



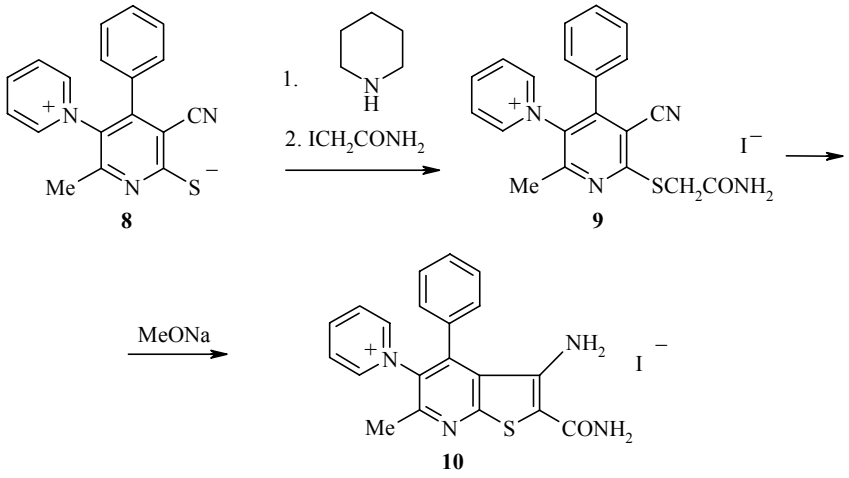
1, **3** R = H; **2**, **4** R = $OCHF_2$

In comparison with 5-(4-pyridyl)-1,4,5,6-tetrahydropyridine-2-thiolates [11] lacking a strong electron-withdrawing pyridinio group in position 5, the reactivity of betaines **1**, **2** with electrophilic alkyl halides decreases, resulting in considerably lower yields.

By treating compound **3** with ammonium acetate in acetic acid, 3-cyano-6-methyl-2-methylthio-4-phenylpyridine (**6**) was obtained. Pyridine **6** was obtai- ned also by alkylation of thione **7** [12] with methyl iodide.

By alkylation of betaine **8** [8] with iodoacetamide, 2-carbamoylmethylthio-3-cyano-6-methyl-4-phenyl-5-pyridiniopyridine iodide (**9**) was obtained (Scheme 3).

Scheme 3



By treatment of pyridine **9** with sodium methoxide under typical Thorpe's cyclization conditions, only a trace amount of thieno[2,3-*b*]pyridine **10** was formed (3-NH_2 at 5.62 ppm in ^{1}H NMR spectrum) in the mixture of the decomposition products of **9**.

The structures of compounds **3-5** and **9** were proved by spectroscopy. The IR spectra for **3-5** show the stretching vibrations of the cyano group at 2186-2195 cm^{-1}, which differ from that for **9** (ν_{CN} 2224 cm^{-1}). Stretching vibrations of NH and OH groups give characteristic absorption bands at 3180-3476 cm^{-1}. In the ^{1}H NMR spectra of 1,4,5,6-tetrahydropyridines **3-5** characteristic doublets of 4-H and 5-H protons at 4.52-4.88 and 5.24-5.40 ppm, respectively with $^3J_{4,5} \sim 12.0$ Hz are observed, which, according to [1, 13], indicates the *trans* pseudodiaxial arrangement of 4-H and 5-H protons and, correspondingly, the *trans* pseudodiequatorial arrangement of bulky aryl and pyridinio substituents in positions 4 and 5. The delocalization of the positive charge of the pyridinium ring in position 5 leads to a downfield shift of the signals for the pyridinio protons compared with the signals of the uncharged pyridyl substituent [11, 14]. Rapid deuterium exchange in the OH and NH groups provides further evidence for the structures of compounds **3-5**.

Using a high-resolution spectrometer (360 MHz), the formation of two stereoisomers of compound **4** is detected. The ratio between stereoisomers **4A** ($J_{4,5}$ = 12.1 Hz) and **4B** ($J_{4,5}$ = 11.6 Hz) equals 6 : 1. X-ray structural determinations are consistent with the above data.

The crystals of compound **4** were grown in a 50% ethanol-water solution and consist of two 4,5-*trans*-3-cyano-4-(2-difluoromethoxyphenyl)-6-hydroxy-6-methyl-2-methylthio-5-pyridinio-1,4,5,6-tetrahydropyridine cations, two iodide anions, and one molecule of crystal water in an asymmetric unit. The bond lengths and angles in **4** do not show any considerable deviations from standard values. The shortest distances from iodide anions to non-hydrogen atoms in the asymmetric unit are with oxygen atoms of the 6-hydroxy group of the cation (3.50 Å) and with the water molecule (3.57 Å). The molecule of crystal water is located between iodide anions and the >N+ moiety in both cations **4A** and **4B**. Bond lengths and angles in the cations are similar. The values of torsion angles C–O–C–F in 4-(2-difluoromethoxyphenyl) substituents differ significantly. For cation **4A** they are 164(1)° and -93(1)°, but for cation **4B** 103(3)° and -118(2)°.

The crystal X-ray diffraction analysis of stereoisomers **4** indicates that the relative configuration both of 4-H and 5-H of the tetrahydropyridine ring and of 5-H and 6-OH are *trans* (see Fig. 1).

In the tetrahydropyridine rings the chain N(1)–C(2)=C(3)–C(4) and C(6) atoms are close to being coplanar. Displacement from the plane formed by N(1)–C(2)=C(3)–C(4) is -0.655(7) Å for C(5) and 0.075(7) Å for C(6) in cation **4A** and 0.629(7) Å and -0.088(7) Å for C(5) and C(6), respectively, in cation **4B**. Therefore, the tetrahydropyridine ring apparently exists in the half-chair conformation nearly distorted to envelope.

TABLE 1. Crystal Data and Structure Refinement for Compound **4**

Empirical formula	$2\{C_{20}H_{20}F_2N_3O_2S^+\cdot I^-\}\cdot H_2O$	
Formula weight	1062.70	
Temperature	293(2) K	
Wavelength	0.71069 Å	
Crystal system, space group	triclinic, *P*-1	
Unit cell dimensions	a = 8.157(1) Å	α = 107.44(1)°
	b = 15.193(3) Å	β = 93.55(1)°
	c = 18.574(3) Å	γ = 91.14(1)°
Volume	2190.0(6) $Å^3$	
Density (calculated)	1.612 Mg/m^3	
Crystal size	0.15 × 0.25 × 0.4 mm	
θ-Range for data collection	1.53° to 22.55°	
Index ranges	$0 <= h <= 8$, $-16 <= k <= 16$, $-20 <= l <= 19$	
Reflections collected	5215	
Independent reflections	4836 [R(int) = 0.0406]	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4807 / 64 / 532	
Goodness-of-fit on F	1.016	
Final R indices [I >2σ(I)]	R_1 = 0.0462, wR_2 = 0.1067	
R indices (all data)	R_1 = 0.0551, wR_2 = 0.1205	
Largest diff. peak and hole	1.034 and -0.518 e. $Å^{-3}$	

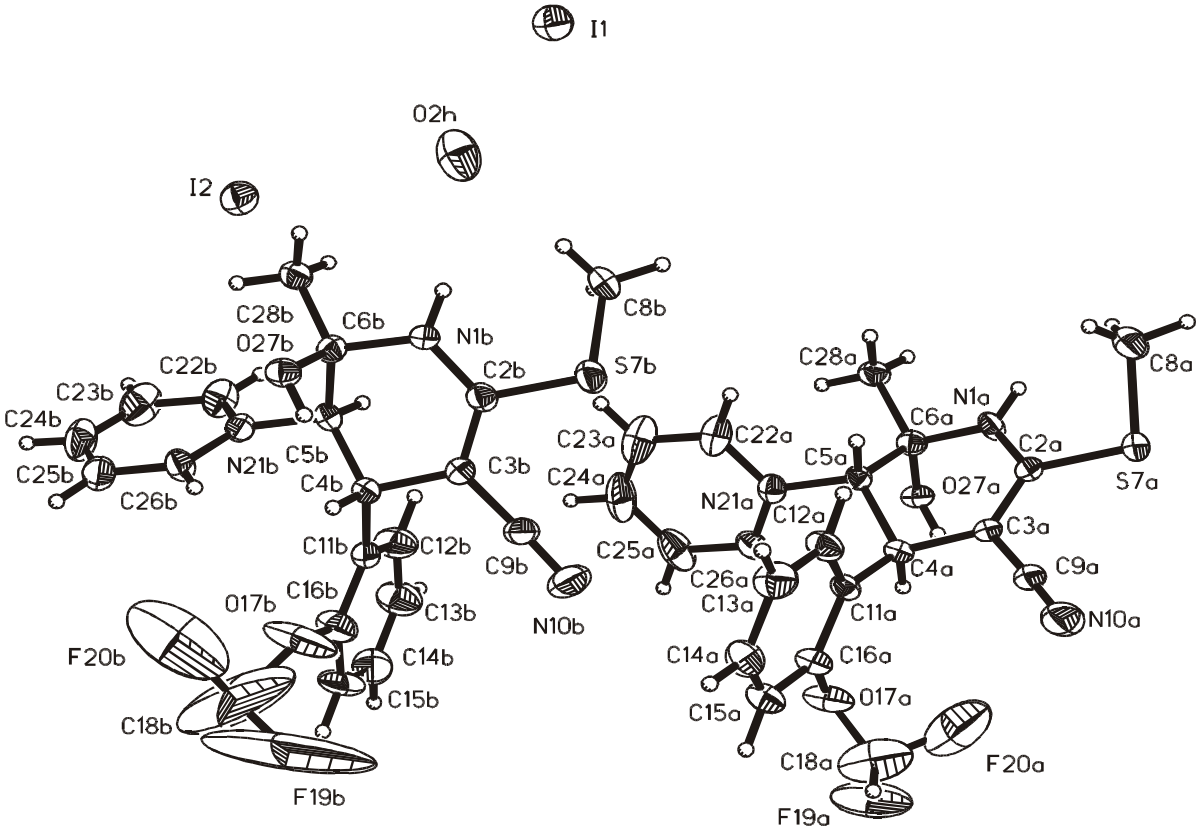


Fig. 1. Molecular structure of compound **4**

TABLE 2. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for **4**. U_{eq} are Defined as One Third of the Trace of the Orthogonalized U_{ij} Tensor

Atom	*x*	*y*	*z*	U_{eq}
1	2	3	4	5
J(1)	3628(1)	5778(1)	4222(1)	51(1)
N(1A)	-8387(7)	3682(4)	6422(3)	41(2)
C(2A)	-7560(9)	3321(5)	6924(4)	38(2)
C(3A)	-6889(9)	3866(5)	7608(4)	37(2)
C(4A)	-7017(9)	4901(4)	7850(4)	36(2)
C(5A)	-7205(8)	5173(4)	7115(4)	31(2)
C(6A)	-8684(8)	4653(5)	6596(4)	38(2)
S(7A)	-7431(3)	2114(1)	6670(1)	49(1)
C(8A)	-6990(13)	1854(6)	5693(5)	68(3)
C(9A)	-6046(10)	3463(5)	8113(4)	47(2)
N(10A)	-5372(12)	3171(5)	8542(4)	80(3)
C(11A)	-5506(8)	5390(5)	8350(4)	36(2)
C(12A)	-3950(9)	5310(5)	8085(4)	51(2)
C(13A)	-2594(11)	5724(7)	8537(5)	66(3)
C(14A)	-2748(11)	6257(6)	9272(5)	64(2)
C(15A)	-4282(12)	6361(6)	9543(5)	61(2)
C(16A)	-5634(9)	5941(5)	9085(4)	46(2)
O(17A)	-7208(8)	6089(5)	9347(3)	74(2)
C(18A)	-7547(15)	5774(13)	9906(8)	137(6)
F(19A)	-8791(11)	6084(8)	10245(4)	164(4)
F(20A)	-8283(16)	4871(9)	9487(7)	198(5)
N(21A)	-7298(7)	6192(4)	7260(3)	40(2)
C(22A)	-6454(11)	6576(6)	6820(6)	63(2)
C(23A)	-6548(13)	7482(7)	6887(8)	86(3)
C(24A)	-7497(14)	8003(7)	7404(8)	84(3)
C(25A)	-8353(13)	7620(6)	7854(6)	78(3)
C(26A)	-8241(10)	6702(5)	7773(4)	52(2)
O(27A)	-10089(6)	4892(3)	7019(3)	42(1)
C(28A)	-8908(10)	4915(5)	5863(4)	45(2)
O(2H)	830(8)	7538(4)	5001(4)	90(2)
J(2)	3856(1)	9342(1)	5853(1)	52(1)
N(1B)	-1226(8)	8727(4)	6492(3)	44(2)
C(2B)	-1867(9)	8347(5)	6990(4)	41(2)
C(3B)	-2331(9)	8853(5)	7672(4)	40(2)
C(4B)	-2096(9)	9920(5)	7928(4)	38(2)
C(5B)	-2137(9)	10202(4)	7212(4)	36(2)
C(6B)	-842(9)	9723(5)	6677(4)	38(2)
S(7B)	-2086(3)	7132(1)	6728(1)	52(1)
C(8B)	-2676(14)	6861(6)	743(5)	78(3)
C(9B)	-3047(12)	8442(5)	8168(5)	55(2)
N(10B)	-3652(13)	8137(6)	8585(5)	94(3)
C(11B)	-3413(10)	10362(5)	8458(4)	44(2)
C(12B)	-5016(11)	10330(7)	8200(5)	68(3)
C(13B)	-6235(13)	10690(7)	8682(6)	80(3)
C(14B)	-5831(15)	11094(7)	9430(7)	81(3)
C(15B)	-4247(16)	11137(7)	9697(5)	86(3)
C(16B)	-3066(11)	10788(7)	9208(5)	66(3)
O(17B)	-1411(11)	10849(8)	9457(4)	136(4)
C(18B)	-756(41)	11554(22)	10115(13)	443(34)
F(19B)	-658(27)	11031(24)	10565(7)	615(31)
F(20B)	225(22)	11844(13)	9637(10)	333(11)

TABLE 2 (continued)

1	2	3	4	5
N(21B)	-1933(7)	11218(4)	7374(3)	40(1)
C(22B)	-2910(11)	11636(6)	6986(5)	62(2)
C(23B)	-2707(14)	12578(7)	7101(7)	83(3)
C(24B)	-1526(14)	13067(7)	7604(7)	80(3)
C(25B)	-552(12)	12643(6)	8016(6)	65(3)
C(26B)	-772(10)	11716(5)	7880(5)	52(2)
O(27B)	714(6)	9964(3)	7089(3)	43(1)
C(28B)	-872(10)	9976(5)	5954(4)	47(2)

EXPERIMENTAL

Melting points were determined on a Boetius apparatus. IR spectra of suspensions of compounds in mineral oil (ν, cm^{-1}) were recorded with a Perkin Elmer 580B spectrometer. ^1H NMR spectra of solutions in $CDCl_3$ or DMSO-d_6 (δ, ppm) were obtained with a Bruker WH 90/DC (90 MHz) and an AM-360 (360 MHz) spectrometers using TMS as internal standard. X-Ray structure analysis of compound **4** was performed using a Syntex-$P2_1$ four-circle diffractometer with graphite-monochromated MoKα radiation. The structure was solved by a direct method using the program SHELXS 86 [15]. Refinement of atomic positional and thermal anisotropic parameters of all non-hydrogen atoms and isotropic geometrically fixed H-atoms was performed by the full-matrix least-squares procedure using SHELXL 93 program [16]. To achieve an equal geometry for $OCHF_2$ fragments of cations **4A** and **4B**, geometric and anisotropic displacement parameters were employed in the final stages of refinement. Crystal data and structure refinement parameters are given in Table 1.

4,5-*trans*-3-Cyano-4-[2-(difluoromethoxy)phenyl]-6-hydroxy-6-methyl-5-pyridinio-1,4,5,6-tetrahydropyridine-2-thiolate (2). A mixture of 1-acetonylpyridinium chloride (1.71 g, 10 mmol), 2-cyano-3-[2-(difluoromethoxy)phenyl]thioacrylamide (2.54 g, 10 mmol), and piperidine (1 ml, 10 mmol) in 20 ml of ethanol was heated for 5 min to 40-50°C and stirred for 1 h at the ambient temperature. Then the reaction mixture was cooled to 0°C, the precipitate was removed by filtration and washed with 10 ml of water to give 3.5 g (90 %) of **2** as a yellow powder; mp 208-210°C. IR: 2168 (C≡N), 3196, 3540 (NH, OH). ^1H NMR (DMSO-d_6), δ, ppm, *J* (Hz): 9.2-6.8 (9H, m, 4-C_6H_4 and 5-$C_5H_5N^+$); 6.92 (1H, t, *J* = 74.0, $OCHF_2$); 6.52 (1H, s, NH); 6.48 (1H, s, OH); 5.12 (1H, d, *J* = 12.0, 5-H); 4.82 (1H, d, *J* = 12.0, 4-H); 1.10 (3H, s, 6-Me). Found, %: C 58.42; H 4.37; N 10.56; S 8.31. $C_{19}H_{17}F_2N_3O_2S$. Calculated, %: C 58.60; H 4.40; N 10.79; S 8.23.

4,5-*trans*-3-Cyano-6-hydroxy-6-methyl-2-methylthio-4-phenyl-5-pyridinio-1,4,5,6-tetrahydropyridine Iodide (3). A mixture of betaine **1** (3.23 g, 10 mmol), piperidine (1 ml, 10 mmol) and methyl iodide (2.5 ml, 20 mmol) in 10 ml of ethanol was refluxed for 15 min and filtered. The reaction mixture was concentrated to half of its initial volume under reduced pressure and 10 ml dry acetone was added. After seasoning at -10°C for 10 h, the precipitated crystals were filtered off, and washed with 50 ml of water and 40 ml of acetone to yield 2.70 g (58 %) of **3**; mp 164-166°C (ethanol–acetone, 1:1). IR: 2192 (C≡N); 3392 (NH, OH). ^1H NMR (DMSO-d_6), δ, ppm, *J* (Hz): 9.6-7.2 (10H, m, 4-C_6H_5 and 5-$C_5H_5N^+$); 8.12 (1H, s, NH); 7.08 (1H, s, OH); 5.24 (1H, d, *J* = 12.0, 5-H); 4.52 (1H, d, *J* = 12.0, 4-H); 2.57 (3H, s, SMe); 1.24 (3H, s, 6-Me). Found, %: C 49.39; H 4.07; N 9.15; S 6.83. $C_{19}H_{20}IN_3OS$. Calculated, %: C 49.04; H 4.33; N 9.03; S 6.89.

4,5-*trans*-3-Cyano-4-(2-(difluoromethoxyphenyl)-6-hydroxy-6-methyl-2-methylthio-5-pyridinio-1,4,5,6-tetrahydropyridine Iodide (4). Compound **4** was prepared in the same manner as **3** from betaine **2** and methyl iodide (1:2). Instead of acetone, ether was used to precipitate **4** from the reaction mixture. The yield of **4** was 41%; mp 180-182°C. IR: 2195 (C≡N); 3200, 3284 sh. (NH,OH). ^1H NMR (DMSO-d_6), δ, ppm, *J* (Hz): 9.6-6.8 (12H, m, 4-C_6H_4, 5-$C_5H_5N^+$, OH, NH, $OCHF_2$ of **4A** and **4B** stereoisomer); **4A** stereoisomer: 5.33 (1H,

d, J = 12.1, 5-H); 4.83 (1H, d, J = 12.1, 4-H); 2.56 (3H, s, SMe); 1.26 (3H, s, 6-Me); **4B** stereoisomer: 5.02 (1H, d, J = 11.6, 5-H); 4.65 (1H, d, J = 11.6, 4-H); 2.53 (3H, s, SMe); 1.27 (3H, s, 6-Me). Found, %: C 44.48; H 3.89; N 7.76; S 6.05. $C_{20}H_{20}F_2IN_3O_2S \cdot 0.25H_2O$. Calculated, %: C 44.83; H 3.86; N 7.84; S 5.98.

4,5-*trans*-2-Carbamoylmethylthio-3-cyano-4-(2-difluoromethoxyphenyl)-6-hydroxy-6-methyl-5-pyridinio-1,4,5,6-tetrahydropyridine Iodide (5). A mixture of betaine **2** (1.95 g, 5 mmol), piperidine (0.6 ml, 6 mmol), and iodoacetamide (1.1 g, 6 mmol) in 30 ml of dry ethanol was refluxed for 10 min and filtered. The reaction mixture was kept at -10°C for 40 h and the precipitated crystals were filtered off and washed with 10 ml of water and 10 ml of ethanol to give 1.25 g (44%) of **5**; mp >200°C (decomp.). IR: 1670 (CO); 2186 (C≡N); 3180, 3220, 3374 (NH, NH_2, OH). ^{1}H NMR (DMSO-d_6), δ, ppm, J (Hz): 9.5-6.9 (13H, m, C_6H_4, $C_5H_5N^+$, $CONH_2$, NH, OH); 7.06 (1H, t, J = 74.0, $OCHF_2$); 5.40 (1H, d, J = 12.0, 5-H); 4.88 (1H, d, J = 12.0, 4-H); 3.74 (2H, s, SCH_2); 1.30 (3H, s, 6-Me). Found, %: C 44.23; H 3.68; N 9.74; S 5.80. $C_{21}H_{21}F_2IN_4O_3S$. Calculated, %: C 43.91; H 3.69; N 9.75; S 5.58.

3-Cyano-6-methyl-2-methylthio-4-phenylpyridine (6). *A.* A mixture of compound **3** (2.33 g, 5 mmol) and ammonium acetate (0.77 g, 10 mmol) in 15 ml of acetic acid was refluxed for 3 h. Then the reaction mixture was neutralized with saturated sodium hydroxide solution and 50 ml of water was added. The precipitate was filtered off and washed with 50 ml of water to yield 0.41 g (34%) of **6**; mp 110-112°C (ethanol). IR: 2208 (C≡N). ^{1}H NMR ($CDCl_3$), δ, ppm: 7.48 (5H, m, 4-C_6H_5); 6.88 (1H, s, 5-H); 2.60 (3H, s, SMe); 2.54 (3H, s, 6-Me). Found, %: C 69.64; H 5.05; N 11.46; S 13.37. $C_{14}H_{12}N_2S$. Calculated, %: C 69.97; H 5.03; N 11.66; S 13.34.

B. A mixture of thione **7** (0.23 g, 1 mmol), piperidine (0.12 ml, 1.2 mmol) and methyl iodide (0.31 ml, 5 mmol) in 5 ml of methanol was refluxed for 30 min and cooled to 0°C. Then 2 ml of water was added. The precipitate was filtered off and washed with 20 ml of water to yield 0.18 g (75 %) of **6**.

2-Carbamoylmethylthio-3-cyano-6-methyl-4-phenyl-5-pyridiniopyridine Iodide (9). A mixture of betaine **8** (3.03 g, 10 mmol), iodoacetamide (2.21 g, 12 mmol), and piperidine (1 ml, 10 mmol) in 30 ml of ethanol was refluxed for 15 min and filtered. Then 50 ml dry acetone was added and the precipitate was ground and cooled to 0°C. The precipitated crystals were filtered off and washed with 10 ml of cold water to give 3.16 g (65%) of **9**; mp 182-184°C (ethanol–acetic acid, 1:1). IR: 1670 sh, 1690 (CO); 2224 (C≡N); 3190, 3318, 3370 sh, 3476 (NH_2). ^{1}H NMR (DMSO-d_6), δ, ppm: 9.3-7.2 (12H, m, 4-C_6H_5, 5-$C_5H_5N^+$, NH_2); 4.12 (2H, s, SCH_2); 2.40 (3H, s, 6-Me). Found, %: C 48.52; H 3.68; N 11.27; S 6.58. $C_{20}H_{17}IN_4OS \cdot 0.25H_2O$. Calculated, %: C 48.74; H 3.58; N 11.37; S 6.51.

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