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A Simple One-Pot Synthesis of New 4-Unsubstituted 2-Oxo(thioxo)-1,2-dihydropyridine-3-carbonitriles, -3-carboxamides, and -3-carboxylic Acid Esters and 2-Thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitriles

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Abstract—One-pot condensations of formaldehyde with CH acids and enamines afforded new 4-unsubstituted derivatives of 2-oxo(thioxo)-1,2-dihydropyridine-3-carbonitrile, 2-oxo(thioxo)-1,2-dihydropyridine-3-carboxamide, ethyl 2-oxo(thioxo)-1,2-dihydropyridine-3-carboxylate, and 2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile, which were subjected to alkylation.

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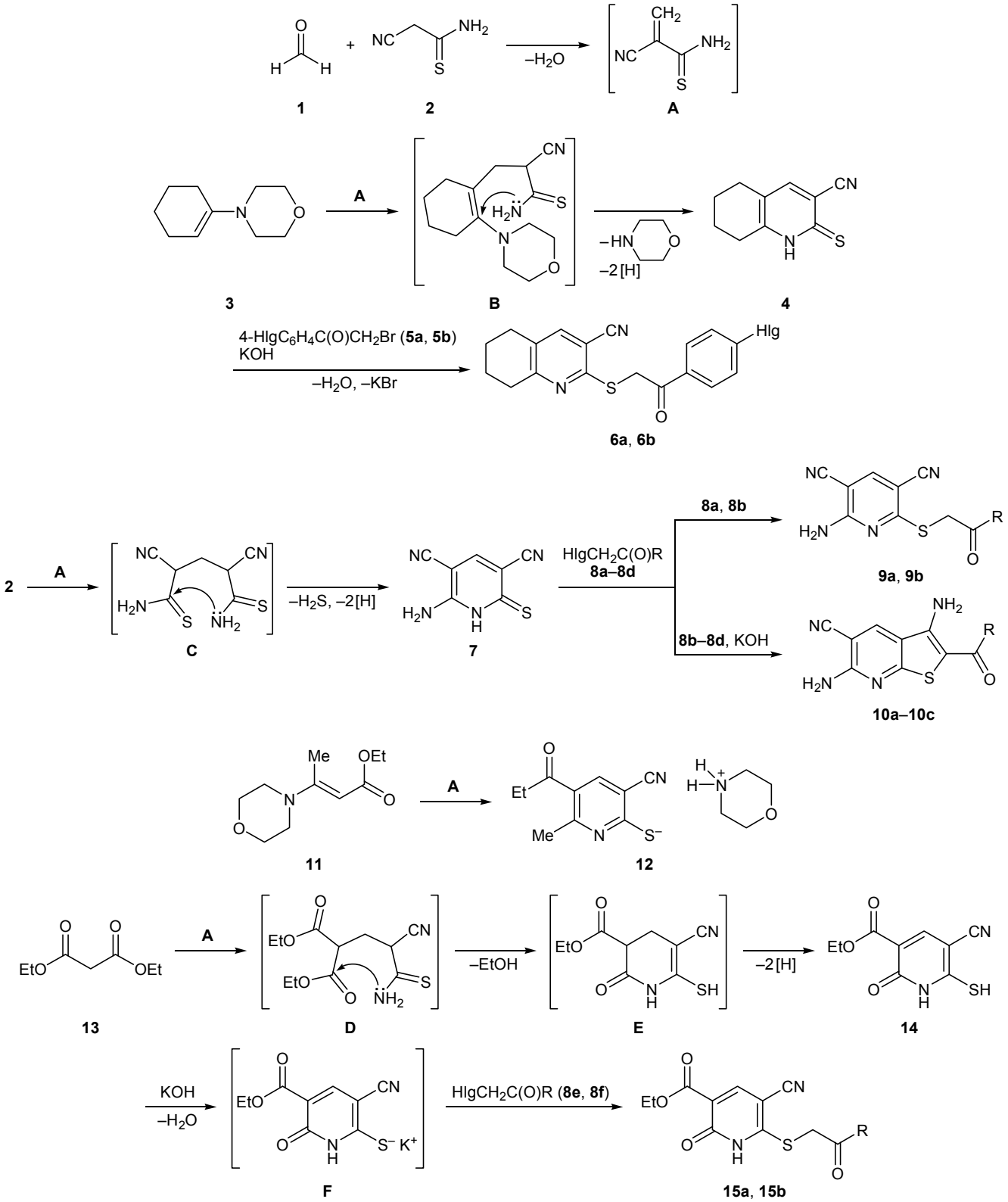
Compounds exhibiting antibacterial [1] and antitumor activity [2] were found among 2-oxo(thioxo)-nicotinic acid derivatives having no substituent on C^4. Some of them can be used for the treatment and prophylactics of human central nervous system disorders [3]. 4-Unsubstituted 2-oxo(thioxo)nicotinic acid derivatives are generally synthesized by recyclization of 2,6-diamino-4*H*-thiopyran-3,5-dicarbonitrile [4] and nucleophilic vinylic substitution in reactions of ethoxy- [5–8] or phenylaminomethylidene derivatives of CH acids [9] with CH acids.

In continuation of our studies on the chemical properties of 4-unsubstituted 2-oxo(thioxo)nicotinic acid derivatives [10–12], in the present article we describe a new method of synthesis of such compounds via three-component condensations of formaldehyde (**1**) with CH acids and enamines. The reaction of formaldehyde (**1**) with 2-cyanoethanethioamide (**2**) and 4-(cyclohex-1-en-1-yl)morpholine (**3**) in ethanol in the presence of morpholine at 20°C gave 2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (**4**). A probable mechanism is shown in Scheme 1. It is reasonable to assume intermediacy of 2-cyanoprop-2-enethioamide **A** resulting from the Knoevenagel condensation of formaldehyde with CH acid **2**. Next follows Stork alkylation of enamine **3** with alkene **A** [13], and adduct **B** thus formed undergoes intramolecular transamination [14] and dehydrogenation, yielding compound **4** as final product. The alkylation of **4** with phenacyl bromides **5a** and **5b** in DMF in the presence of alkali afforded the corresponding sulfides **6a** and **6b**, which confirmed the structure of **4** [15, 16].

6-Amino-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**7**) was obtained by condensation of formaldehyde (**1**) with 2 equiv of thioamide **2** in ethanol at 20°C in the presence of morpholine. Likewise, the reaction involves intermediate formation of Knoevenagel product **A** and Michael adduct **C**. Chemoselective intramolecular cyclization of the latter yields **7**. By alkylation of **7** with α-halo ketones **8a** and **8b** (DMF, KOH) we synthesized sulfides **9a** and **9b**. If 2 equiv of aqueous potassium hydroxide was used in the alkylation process, the products were thieno[2,3-*b*]pyridine derivatives **10a**–**10c** (Scheme 1).

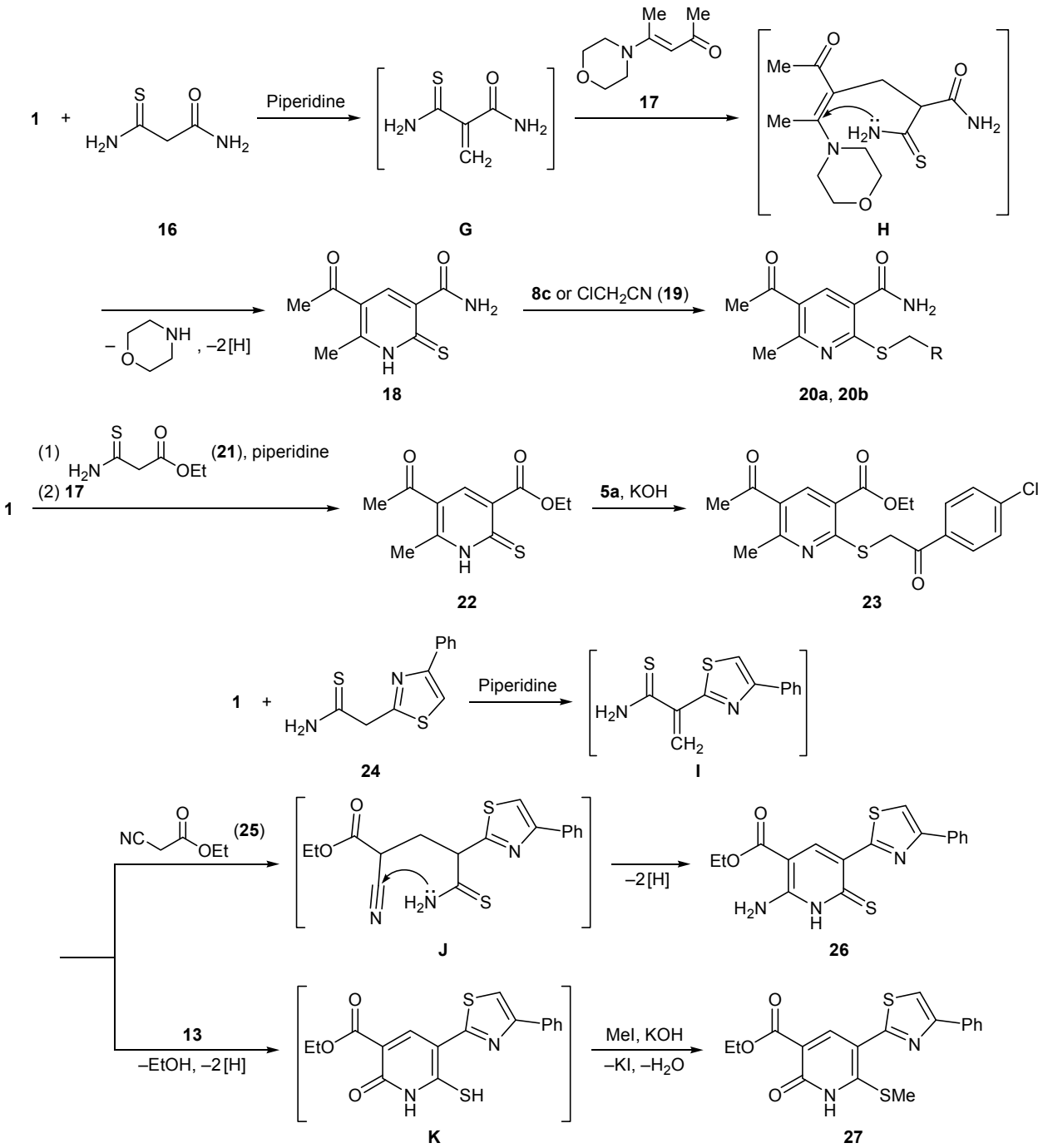
The condensation of formaldehyde (**1**) with cyanothioacetamide (**2**) and ethyl 3-(morpholin-4-yl)but-2-enoate (**11**) led to the formation of morpholinium 3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-thiolate (**12**). The reaction direction did not radically change when enamine **11** was replaced by diethyl malonate (**13**). Heterocyclization of Michael adduct **D** gave ethyl 5-cyano-2-oxo-6-sulfanyl-1,2,3,4-tetrahydropyridine-3-carboxylate **E** which was readily oxidized (presumably, with atmospheric oxygen) to the corresponding 1,2-dihydropyridine derivative **14**. Alkylation of the latter with α-halo ketones **8e** and **8f** regioselectively involved the sulfur atom through hypothetic thiolate **F** despite the presence in molecule **14** of several nucleo-

Scheme 1.



5, **6**, Hlg = Cl (**a**), Br (**b**); **8**, Hlg = Cl, R = 1,3-thiazol-2-ylamino (**a**), *i*-PrO (**b**), quinolin-8-ylamino (**e**), 6,8-dibromo-2-oxo-2*H*-chromen-3-yl (**f**); Hlg = Br, R = 4-$MeOC_6H_4$ (**c**), 2,4,5-$Me_3C_6H_2$ (**d**); **9**, R = 1,3-thiazol-2-ylamino (**a**), *i*-PrO (**b**); **10**, R = *i*-PrO (**a**), 4-$MeOC_6H_4$ (**b**), 2,4,5-$Me_3C_6H_2$ (**c**); **15**, R = quinolin-8-ylamino (**a**), 6,8-dibromo-2-oxo-2*H*-chromen-3-yl (**b**).

Scheme 2.



20, R = 4-$MeOC_6H_4C(O)$ (**a**), CN (**b**).

philic centers (SH, NH, C=O), and the products were sulfides **15a** and **15b**.

Formaldehyde (**1**) reacted with 3-amino-3-thioxopropanamide (**16**) and enamine **17** derived from acetylacetone to produce 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carboxamide (**18**) (Scheme 2). The reaction is likely to proceed through intermediates **G** and **H**. Compound **18** was alkylated with *p*-methoxyphenacyl bromide (**8c**) and chloroacetonitrile (**19**) (DMF, KOH) to obtain sulfides **20a** and **20b**. The condensation of **1** with enamine **17** and ethyl 3-amino-3-thioxopropanoate (**21**) (instead of **16**) under analogous conditions resulted in the formation of ethyl 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-car-

boxylate (**22**). Presumably, the reaction path is analogous to that leading to compound **18**. The presence of a thioxo group in molecule **22** was confirmed by alkylation with *p*-chlorophenacyl bromide (**5a**), which gave sulfide **23**. This way of synthesis of organic sulfides serves as a "qualitative test" for 2-sulfanyl-substituted pyridines [17].

By condensation of formaldehyde (**1**) with CH acid (**24**) and ethyl cyanoacetate (**25**) in DMF at 20°C in the presence of piperidine we obtained ethyl 2-amino-6-thioxo-5-(4-phenyl-1,3-thiazol-2-yl)-1,6-dihydropyridine-3-carboxylate (**26**), a potential precursor of drugs for the treatment of cardiovascular diseases [18] and tumors [19]. The reaction is likely to involve intermediate formation of Knoevenagel alkene **I** and Michael adduct **J**. The latter undergoes chemoselective intramolecular cyclization to tetrahydropyridine derivative which is oxidized to compound **26** (presumably, with atmospheric oxygen). Analogous three-component condensation with diethyl malonate (**13**) instead of CH acid **25**, followed by treatment with equimolar amounts of 10% aqueous potassium hydroxide and methyl iodide, afforded ethyl 6-(methylsulfanyl)-2-oxo-5-(4-phenyl-1,3-thiazol-2-yl)-1,2-dihydropyridine-3-carboxylate (**27**), assumingly through intermediates **I**, **J**, and **K**.

The structure of newly synthesized compounds **4**, **6**, **7**, **9**, **10**, **12**, **14**, **15**, **18**, **20**, **22**, **23**, **26**, and **27** was confirmed by spectral data. Their IR spectra contained absorption bands typical of stretching vibrations of conjugated cyano and carbonyl groups, as well as of stretching and bending vibrations of the amino group. In the ^{1}H NMR spectra of these compounds we observed signals from protons in the substituents on the pyridine ring and a singlet at δ 6.54–8.88 ppm due to 4-H, which is typical of such compounds [20–22]. The ^{1}H NMR spectrum of sulfide **15b** characteristically displayed nonequivalence of the SCH_2 protons which appeared as two doublets at δ 3.50 and 4.05 ppm with a geminal coupling constant ^2J of 16.8 Hz. Presumably, rotation of the coumarin fragment about the single bonds is restricted for steric reasons. Analogous patterns were observed by us previously for other pyridine-3-carbonitrile derivatives [23, 24]. The presence of the $[M + 2]^+$ ion peak in the mass spectrum of **26** confirmed that its molecule contains sulfur atoms [25].

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum One spectrometer. The ^{1}H NMR spectra were measured on a Varian-400 instrument at 399.97 MHz from solutions in DMSO-d_6 using tetramethylsilane as internal standard. The mass spectra (electron impact, 70 eV) were obtained on an MKh-1321 instrument with direct sample admission into the ion source (compounds **7**, **14**, **15a**, and **15b**) and on an Agilent Series LC/MS instrument with a mass-selective detector (other compounds; samples were introduced in CF_3COOH solution). The elemental compositions were determined on a Perkin Elmer CHN analyzer. The melting points were measured on a Kofler hot stage. The progress of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using acetone–hexane (3:5) as eluent; spots were detected by treatment with iodine vapor and by UV irradiation.

2-Thioxo-5,6,7,8-tetrahydroquinoline-3-carbonitrile (4). Three drops of morpholine were added under stirring at 20°C to a mixture of 0.73 mL (10 mmol) of 37% aqueous formaldehyde and 1.0 g (10 mmol) of 2-cyanoethanethioamide (**2**) in 20 mL of ethanol. The mixture was stirred for 15 min, 1.67 g (10 mmol) of enamine **3** was added, and the mixture was stirred for 1 h and left overnight. The mixture was diluted with 10% aqueous HCl to pH 5 and left to stand for 48 h. The precipitate was filtered off and washed with water, ethanol, and hexane. Yield 1.5 g (78%), yellow powder, mp 249–251°C (from AcOH); published data [26]: mp 250–252°C.

Substituted tetrahydroquinolines 6a and 6b (*general procedure*). Aqueous potassium hydroxide (10%), 5.6 mL (10 mmol), was added under stirring at 20°C to a mixture of 1.9 g (10 mmol) of compound **4** and 15 mL of DMF, 10 mmol of phenacyl bromide **5a** or **5b** was then added, and the mixture was stirred for 5 h and diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane.

2-[2-(4-Chlorophenyl)-2-oxoethylsulfanyl]-5,6,7,8-tetrahydroquinoline-3-carbonitrile (6a). Yield 2.6 g (75%), yellow powder, mp 137–139°C (from AcOH). IR spectrum, ν, cm^{-1}: 2224 (C≡N), 1702 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.52–3.76 m (4H, CH_2), 4.00 t (2H, CH_2, J = 6.5 Hz), 4.23 t (2H, CH_2, J = 5.3 Hz), 4.71 s (2H, SCH_2), 7.48 d (2H, H_{arom}, J = 8.3 Hz), 7.95 d (2H, H_{arom}, J = 8.3 Hz), 8.03 s (1H, 4-H). Mass spectrum, *m*/*z*: 343 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 62.95; H 4.33; N 8.02. $C_{18}H_{15}ClN_2OS$. Calculated, %: C 63.06; H 4.41; N 8.17. M 342.85.

2-[2-(4-Bromophenyl)-2-oxoethylsulfanyl]-5,6,7,8-tetrahydroquinoline-3-carbonitrile (6b).

Yield 2.8 g (72%), yellow crystals, mp 153–155°C (from AcOH). IR spectrum, ν, cm^{-1}: 2220 (C≡N), 1698 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.52–3.77 m (4H, CH_2), 3.99 t (2H, CH_2, J = 6.2 Hz), 4.25 t (2H, CH_2, J = 5.6 Hz), 4.72 s (2H, SCH_2), 7.62 d (2H, H_{arom}, J = 8.5 Hz), 7.89 d (2H, H_{arom}, J = 8.5 Hz), 8.09 s (1H, 4-H). Mass spectrum, m/z 388 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 55.70; H 3.78; N 7.05. $C_{18}H_{15}BrN_2OS$. Calculated, %: C 55.82; H 3.90; N 7.23. M 387.301.

6-Amino-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (7) was synthesized as described above for compound **4**, but 1.0 g (10 mmol) of 2-cyanoethanethioamide (**2**) was used instead of enamine **3**. Yield 1.23 g (70%), yellow fine crystalline powder, mp 210–212°C (from AcOH); published data [27]: mp 208–210°C. Mass spectrum, m/z (I_{rel}, %): 178 (4) $[M + 2]^+$, 177 (8) $[M + 1]^+$, 176 (100) $[M]^+$, 149 (25) $[M - HCN]^+$, 132 (41) $[M - HCN - NH_3]^+$, 118 (20), 84 (73), 55 (25), 45 (18) $[HCS]^+$, 44 (17) $[C=S]^+$, 33 (9) $[HS]^+$, 28 (26) $[H_2CN]^+$. Calculated: M 176.201.

6-Amino-2-(acylmethylsulfanyl)pyridine-3,5-dicarbonitriles **9a** and **9b** were synthesized as described above for compounds **6** from 1.8 g (10 mmol) of **7** and 10 mmol of **8a** or **8b**.

2-(6-Amino-3,5-dicyanopyridin-2-ylsulfanyl)-*N*-(1,3-thiazol-2-yl)acetamide (9a). Yield 2.6 g (81%), yellow powder, mp 177–179°C (from BuOH). IR spectrum, ν, cm^{-1}: 3341, 3270, 3232 (NH), 2222 (C≡N), 1672 (C=O), 1636 (δNH). ^{1}H NMR spectrum, δ, ppm: 4.12 s (2H, CH_2), 7.15 d (1H, 5′-H, J = 2.5 Hz), 7.44 d (1H, 4′-H, J = 2.5 Hz), 7.87 br.s and 7.94 br.s (1H each, NH_2), 8.24 s (1H, 4-H), 12.15 br.s (1H, NH). Mass spectrum: m/z 317 (I_{rel} 100) $[M + 1]^+$. Found, %: C 45.41; H 2.39; N 26.48. $C_{12}H_8N_6OS_2$. Calculated, %: C 45.56; H 2.52; N 26.56. M 316.365.

Isopropyl 2-(6-amino-3,5-dicyanopyridin-2-ylsulfanyl)acetate (9b). Yield 2.0 g (74%), yellow cotton wool-like crystals, mp 151–152°C (from AcOH). IR spectrum, ν, cm^{-1}: 3335, 3260, 3190 (N–H), 2219 (C≡N), 1714 (C=O), 1638 (δNH). ^{1}H NMR spectrum, δ, ppm: 1.25 d (6H, Me, J = 5.1 Hz), 4.03 s (2H, CH_2), 4.86–4.94 m (1H, OCH), 7.73 br.s (2H, NH_2), 8.11 s (1H, 4-H). Mass spectrum, m/z 277 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 52.03; H 4.25; N 20.11. $C_{12}H_{12}N_4O_2S$. Calculated, %: C 52.16; H 4.38; N 20.28. M 276.32.

3,6-Diamino-2-acyl-5-cyanothieno[2,3-*b*]pyridines 10a–10c (*general procedure*). To a mixture of 1.8 g (10 mmol) of compound **7** and 20 mL of DMF we added at 20°C under stirring 5.6 mL (10 mmol) of 10% aqueous potassium hydroxide and 10 mmol of α-halo ketone **8b**–**8d**, the mixture was stirred for 2 h, an additional 5.6 mL (10 mmol) of 10% aqueous potassium hydroxide was added, and the mixture was stirred for 2 h and diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane.

Isopropyl 3,6-diamino-5-cyanothieno[2,3-*b*]pyridine-2-carboxylate (10a). Yield 2.1 g (75%), yellow powder, mp 257–258°C (from AcOH); sublimes at 200°C. IR spectrum, ν, cm^{-1}: 3333, 3270, 3195 (N–H), 2220 (C≡N), 1716 (C=O), 1648 (δNH). ^{1}H NMR spectrum, δ, ppm: 1.31d (6H, Me, J = 5.0 Hz), 5.02–5.14 m (1H, OCH), 6.77 br.s (2H, 3-NH_2), 6.95 br.s (2H, 6-NH_2), 8.54 s (1H, 4-H). Mass spectrum: m/z 277 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 52.08; H 4.26; N 20.12. $C_{12}H_{12}N_4O_2S$. Calculated, %: C 52.16; H 4.38; N 20.28. M 276.32.

3,6-Diamino-2-(4-methoxybenzoyl)thieno[2,3-*b*]-pyridine-5-carbonitrile (10b). Yield 2.6 g (81%), yellow crystals, mp 285–286°C (from AcOH); sublimes at 230°C. IR spectrum, ν, cm^{-1}: 3352, 3290, 3202 (NH); 2225 (C≡N), 1702 (C=O), 1633 (δNH). ^{1}H NMR spectrum, δ, ppm: 3.84 s (3H, Me), 7.04 d (2H, H_{arom}, J = 8.6 Hz), 7.58 br.s (2H, 3-NH_2), 7.72 d (2H, H_{arom}, J = 8.6 Hz), 8.29 br.s (2H, 6-NH_2), 8.74 s (1H, 4-H). Mass spectrum: m/z 325 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 59.14; H 3.66; N 17.18. $C_{16}H_{12}N_4O_2S$. Calculated, %: C 59.25; H 3.73; N 17.27. M 324.362.

3,6-Diamino-2-(2,4,5-trimethylbenzoyl)thieno-[2,3-*b*]pyridine-5-carbonitrile (10c). Yield 2.7 g (79%), yellow–brown powder, mp 244–246°C (from BuOH). IR spectrum, ν, cm^{-1}: 3342, 3285, 3196 (N–H); 2226 (C≡N), 1698 (C=O), 1637 (δNH_2). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, Me), 2.21 s (3H, Me), 2.26 s (3H, Me), 7.02 s (1H, H_{arom}), 7.06 s (1H, H_{arom}), 7.36 br.s (2H, 3-NH_2), 8.11 br.s (2H, 6-NH_2), 8.70 s (1H, 4-H). Mass spectrum: m/z 337 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 64.12; H 4.87; N 16.56. $C_{18}H_{16}N_4OS$. Calculated, %: C 64.27; H 4.79; N 16.65. M 336.184.

Morpholinium 3-cyano-5-ethoxycarbonyl-6-methylpyridine-2-thiolate (12). Yield 2.4 g (78%), yellow fine crystalline powder, mp 208–210°C; sublimes at 140°C. IR spectrum, ν, cm^{-1}: 3300 (N–H), 2210 (C≡N), 1717 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.29 t (3H, **Me**CH_2, J = 6.2 Hz), 2.54 s (3H, Me), 3.04 t (4H, CH_2NCH_2, J = 4.4 Hz), 3.73 t (4H, CH_2OCH_2, J = 4.4 Hz), 4.16 q (2H, OCH_2, J = 6.2 Hz), 7.90 s (1H, 4-H). No $^+NH_2$ signal was observed,

presumably because of fast H–D exchange. Found, %: C 54.28; H 6.04; N 13.42. $C_{14}H_{19}N_3O_3S$. Calculated, %: C 54.35; H 6.19; N 13.58.

Ethyl 5-cyano-2-oxo-6-sulfanyl-1,2-dihydropyridine-3-carboxylate (14) was synthesized as described above for compound **4** using 0.73 mL (10 mmol) of 37% aqueous formaldehyde (**1**), 1.0 g (10 mmol) of thioamide **2**, and 1.6 mL (10 mmol) of diethyl malonate (**13**). Yield 1.64 g (73%), yellow fine crystalline powder, mp 318–320°C (from AcOH). IR spectrum, ν, cm^{-1}: 3315 (N–H), 2220 (C≡N), 1712 (C=O), 1670 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.30 t (3H, Me, *J* 7.0 Hz), 4.14 q (2H, CH_2, *J* = 7.0 Hz), 7.91 s (1H, 4-H), 11.26 br.s (1H, NH). No SH signal was observed, presumably because of fast H–D exchange. Mass spectrum, *m*/*z* (I_{rel}, %): 224 (4) $[M]^+$, 206 (75) $[M - H_2O]^+$, 178 (100) $[M - H_2O - H_2CN]^+$, 165 (43), 147 (98), 124 (42), 103 (11), 96 (18), 91 (14), 86 (5), 70 (10), 64 (63), 52 (12), 44 (95) $[C=S]^+$, 37 (10). Found, %: C 48.07; H 3.49; N 12.33. $C_9H_8N_2O_3S$. Calculated, %: C 48.21; H 3.60; N 12.49. *M* 224.239.

Substituted ethyl 6-(acylmethylsulfanyl)-5-cyano-2-oxopyridine-3-carbocylates 15a and 15b were synthesized as described above for compounds **6** from 2.24 g (10 mmol) of **14** and 10 mmol of **8e** or **8f**.

2-(5-Cyano-3-ethoxycarbonyl-2-oxo-1,2-dihydropyridin-6-ylsulfanyl)-*N*-(quinolin-8-yl)acetamide (15a). Yield 2.9 g (70%), yellow powder, mp 247–249°C (from BuOH). IR spectrum, ν, cm^{-1}: 3348 (N–H), 2223 (C≡N), 1715 (C=O), 1671 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, Me, *J* = 6.8 Hz), 4.21 s (2H, SCH_2), 4.34 q (2H, OCH_2, *J* = 6.8 Hz), 7.41–7.63 m (2H, H_{arom}), 7.94 s (1H, 4-H), 8.27 d (1H, quinoline, *J* = 8.2 Hz), 8.39 d (1H, quinoline, *J* = 7.9 Hz), 8.62 d (1H, quinoline, *J* = 7.0 Hz), 8.87 d (1H, quinoline, *J* = 8.0 Hz), 8.96 br.s (1H, CONH), 10.75 br.s (1H, 1-H). Mass spectrum, *m*/*z* (I_{rel}, %): 408 (6) $[M]^+$, 394 (8), 171 (100) [quinoline-8-ylcarbamoyl]$^+$, 144 (43) [8-aminoquinoline]$^+$, 116 (12), 89 (5), 77 (3), 45 (4) $[HCS]^+$, 44 (3) $[C=S]^+$, 34 (9) $[H_2S]^+$, 33 (5) $[HS]^+$. Found, %: C 58.72; H 3.83; N 13.66. $C_{20}H_{16}N_4O_4S$. Calculated, %: C 58.81; H 3.95; N 13.72. *M* 408.44.

Ethyl 5-cyano-6-[2-(6,8-dibromo-2-oxo-2*H*-chromen-3-yl)-2-oxoethylsulfanyl]-2-oxopyridine-3-carboxylate (15b). Yield 4.7 g (83%), yellow powder, mp 223–225°C (from DMF). IR spectrum, ν, cm^{-1}: 3378, 3188 (N–H); 2228 (C≡N), 1738 (C=O), 1684 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.18 t (3H, Me, *J* = 6.1 Hz), 3.50 d and 4.05 d (1H each, SCH_2, ^2J = 16.8 Hz), 4.15 q (2H, OCH_2, *J* = 6.1 Hz), 7.95 s (1H, 4-H), 8.20 s (1H, H_{arom}), 8.23 s (1H, H_{arom}), 8.31 s (1H, 4′-H), 8.81 br.s (1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 570 (5) $[M + 2]^+$, 569 (31) $[M + 1]^+$, 568 (100) $[M]^+$, 567 (50) $[M - 1]^+$, 269 (10), 236 (14), 176 (19), 156 (10), 138 (92), 111 (79), 99 (97), 97 (25), 94 (13). Found, %: C 42.19; H 2.02; N 4.85. $C_{20}H_{12}Br_2N_2O_6S$. Calculated, %: C 42.28; H 2.13; N 4.93. *M* 568.2.

5-Acetyl-6-methyl-2-thioxo-1,2-dihydropyridinecarboxamide (18) was synthesized as described above for compound **4** from 0.73 g (10 mmol) of 37% aqueous formaldehyde, 1.2 g (10 mmol) of 3-amino-3-thioxopropanamide (**16**), and 1.7 g (10 mmol) of enamine **17** in the presence of three drops of piperidine. Yield 1.5 g (69%), yellow powder, mp 322–324°C (from AcOH). IR spectrum, ν, cm^{-1}: 3315, 3290, 3200 (N–H); 1702 (C=O), 1668 (CONH). ^{1}H NMR spectrum, δ, ppm: 2.56 s (3H, Me), 2.71 s (3H, Me), 7.91 br.s (1H, NH_2), 8.88 s (1H, 4-H), 9.90 br.s (1H, NH_2), 13.97 br.s (NH). Mass spectrum: *m*/*z* 211 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 51.36; H 4.68; N 13.22. $C_9H_{10}N_2O_2S$. Calculated, %: C 51.41; H 4.79; N 13.32. *M* 210.256.

2-(Alkylsulfanyl)-5-acetyl-6-methylpyridine-3-carboxamides 20a and 20b were synthesized as described above for compound **6** from 2.1 g (10 mmol) of **18** and 10 mmol of **8c** or **9**.

5-Acetyl-2-[2-(4-methoxyphenyl)-2-oxoethylsulfanyl]-6-methylpyridine-3-carboxamide (20a). Yield 2.7 g (74%), yellow powder, mp 200–202°C (from DMF). IR spectrum, ν, cm^{-1}: 3342, 3280, 3205 (N–H); 1711, 1716 (C=O); 1669 (CONH). ^{1}H NMR spectrum, δ, ppm: 2.33 s (3H, Me), 2.55 s (3H, Me), 3.87 s (3H, MeO), 4.48 s (2H, CH_2), 6.99 d (2H, H_{arom}, *J* = 8.8 Hz), 7.48 br.s (1H, NH_2), 7.99 d (2H, H_{arom}, *J* = 8.8 Hz), 8.09 br.s (1H, NH_2), 8.37 s (1H, 4-H). Mass spectrum: *m*/*z* 359 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 60.24; H 4.97; N 7.70. $C_{18}H_{18}N_2O_4S$. Calculated, %: C 60.32; H 5.06; N 7.82. *M* 358.419.

5-Acetyl-2-(cyanomethylsulfanyl)-6-methylpyridine-3-carboxamide (20b). Yield 1.8 g (72%), yellow crystals, mp 243–245°C (from AcOH). IR spectrum, ν, cm^{-1}: 3338, 3291, 3199 (N–H); 2246 (C≡N), 1716 (C=O), 1665 (CONH). ^{1}H NMR spectrum, δ, ppm: 2.62 s (3H, Me), 2.70 s (3H, Me), 4.07 s (2H, CH_2), 7.73 br.s and 8.33 br.s (1H each, NH_2), 8.54 s (1H, 4-H). Mass spectrum: *m*/*z* 250 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 52.91; H 4.30; N 16.75. $C_{11}H_{11}N_3O_2S$. Calculated, %: C 53.00; H 4.45; N 16.86. *M* 249.293.

Ethyl 5-acetyl-6-methyl-2-thioxo-1,2-dihydropyridine-3-carboxylate (22) was synthesized as described above for compound **4** from 0.73 mL (10 mmol) of 37% aqueous formaldehyde, 1.5 g (10 mmol) of CH acid **21**, and 1.7 g of enamine **17** in the presence of three drops of piperidine. Yield 1.7 g (70%), yellow powder, mp 212–214°C (from AcOH). IR spectrum, ν, cm^{-1}: 3322 (N–H); 1714, 1722 (C=O). ^1H NMR spectrum, δ, ppm: 1.40 t (3H, **Me**CH_2, J = 7.2 Hz), 2.44 s (3H, Me), 2.58 s (3H, Me), 4.46 q (2H, CH_2, J = 7.2 Hz), 8.55 s (1H, 4-H); no NH signal was observed, presumably because of fast H–D exchange. Mass spectrum: m/z 240 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 55.08; H 5.33; N 5.71. $C_{11}H_{13}NO_3S$. Calculated, %: C 55.21; H 5.48; N 5.85. M 239.296.

Ethyl 5-acetyl-2-[2-(4-chlorophenyl)-2-oxoethylsulfanyl]-6-methylpyridine-3-carboxylate (23) was synthesized as described above for compound **6** from 2.4 mL (10 mmol) of **22** and 2.3 g (10 mmol) of *p*-chlorophenacyl bromide (**5a**). Yield 3.0 g (77%), yellow crystals, mp 219–221°C (from AcOH). IR spectrum, ν, cm^{-1}: 1718, 1711, 1695 (C=O). ^1H NMR spectrum, δ, ppm: 1.19 t (3H, **Me**CH_2, J = 6.8 Hz), 2.53 s (3H, Me), 3.51 s (3H, Me), 4.22 q (2H, OCH_2, J = 6.8 Hz), 5.51 s (2H, SCH_2), 7.69 d (2H, H_{arom}, J = 8.6 Hz), 7.91 d (2H_{arom}, J = 8.6 Hz), 8.57 s (1H, 4-H). Mass spectrum: m/z 392 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 58.15; H 4.52; N 3.41. $C_{19}H_{18}ClNO_4S$. Calculated, %: C 58.24; H 4.63; N 3.57. M 391.877.

Ethyl 2-amino-5-(4-phenyl-1,3-thiazol-2-yl)-6-thioxo-1,6-dihydropyridine-3-carboxylate (26) was synthesized as described above for compound **4** from 0.73 mL (10 mmol) of 37% aqueous formaldehyde, 2.34 g of CH acid **24**, and 1.1 mL (10 mmol) of ethyl cyanoacetate (**25**) in 20 mL of DMF in the presence of 1 mL (10 mmol) of piperidine. Yield 2.4 g (66%), dark red powder, mp 164–166°C (from EtOH). IR spectrum, ν, cm^{-1}: 3352, 3277, 3205 (N–H), 1716 (C=O), 1648 (δNH_2). ^1H NMR spectrum, δ, ppm: 1.13 t (3H, Me, J = 7.1 Hz), 4.20 q (2H, CH_2, J = 7.1 Hz), 6.54 s (1H, 4-H), 7.30 t (1H, Ph, J = 7.0 Hz), 7.40 t (2H, Ph, J = 7.0 Hz), 7.80 s (1H, 5′-H), 7.89 d (2H, Ph, J = 7.3 Hz), 8.22 br.s (1H, NH), 9.42 br.s and 9.51 br.s (1H each, NH_2). Mass spectrum, m/z (I_{rel}, %): 359 (11) $[M + 2]^+$, 358 (100) $[M + 1]^+$, 357 (8) $[M]^+$, 218 (6), 138 (10), 99 (8). Found, %: C 57.01; H 4.07; N 11.66. $C_{17}H_{15}N_3O_2S_2$. Calculated, %: C 57.12; H 4.23; N 11.76. M 357.457.

Ethyl 6-(methylsulfanyl)-2-oxo-5-(2-phenyl-1,3-thiazol-2-yl)-1,2-dihydropyridine-3-carboxylate (27). Piperidine, 1 mL (10 mmol), was added at 20°C to a mixture of 0.73 mL (10 mmol) of 37% aqueous formaldehyde and 2.34 g (10 mmol) of CH acid **24** in 20 mL of DMF, the mixture was stirred for 30 min, 1.6 mL (10 mmol) of diethyl malonate (**13**) was added, and the mixture was stirred for 1 h and left overnight. The mixture was treated in succession under stirring with 5.6 mL (10 mmol) of 10% aqueous potassium hydroxide and 0.62 mL (10 mmol) of methyl iodide, stirred for 5 h, and diluted with an equal volume of water. The precipitate was filtered off and washed with water, ethanol, and hexane. Yield 2.3 g (67%), mp 145–146°C (from AcOH). IR spectrum, ν, cm^{-1}: 3118 (N–H), 1711 (C=O), 1668 (CONH). ^1H NMR spectrum, δ, ppm: 1.42 t (3H, Me, J = 7.1 Hz), 2.62 s (3H, SMe), 4.40 q (2H, CH_2, J = 7.1 Hz), 7.22–7.68 m (3H, Ph), 7.93–8.17 m (3H, 4-H, Ph), 8.48 s (1H, 5′-H), 11.70 br.s (1H, NH). Mass spectrum: m/z 373 (I_{rel} 100%) $[M + 1]^+$. Found, %: C 57.93; H 4.18; N 7.42. $C_{18}H_{16}N_2O_3S_2$. Calculated, %: C 58.05; H 4.33; N 7.52. M 372.468.

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