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3-Amino-3-thioxopropanamide in the Synthesis of Functionally Substituted Nicotinamides

V. D. Dyachenko and R. P. Tkachev

Lugansk State Pedagogical University, Lugansk, 91011 Ukraine, e-mail: dvd_lug@online.lg.ua

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Abstract—Derivatives of ethoxymethylenemalonic acids by condensation with 3-amino-3-thioxopropanamide in the presence of sodium ethylate furnished chalcogenopyridines and polyfunctionally substituted dienes which were converted into nicotinamide derivatives.

The nicotinamide is among the most important biologically active substances, and the synthesis of its substituted analogs is one of the most promising synthetic lines in preparation of compounds with predetermined pharmacological properties. In this connection we developed a procedure for preparation of new substituted nicotinamide derivatives and investigated their properties.

A convenient reagent for preparation of nicotinamide derivatives is 3-amino-3-thioxopropanamide (**I**) that by reaction with activated olefins provides various pyridinechalcogenones: 4,6-diaryl-3-thiocarbamoyl-3,4-dihydropyridin-2(1*H*)-ones [1, 2], 3-carbamoyl-5-(pyrid-4-yl)pyridine-2(1*H*)-thione [3], 6-amino-4-aryl-3-carbamoyl-5-cyano-1,4-dihydropyridine-2-thiolates [4], piperidinium 5-carbamoyl-2-oxo-4-phenyl-3-cyano-3,4-dihydro-6(1*H*)-thiolate [5]. We prepared formerly 2-alkylsulfanyl-6-amino-5-phenylcarbamoyl-3-cyanopyridines by alkylation of *N*-methylmorpholinium 1-amino-4-phenylcarbamoyl-2,4-dicyano-1,3-butadiene-1-thiolate [6].

In the present study we involved 3-amino-3-thioxopropanamide (**I**) into a reaction of nucleophilic vinyl substitution (S_NVin). In reaction with ethoxyolefins **II** in the presence of a base compound **I** plays the part of a CH-acid and affords nicotinamides **III**, polyfunctionally substituted dienes **IV**, or nicotinethioamides **V**. ^{1}H NMR spectra both of pyridines **III** and compounds **IV** contain proton signals from two amino groups in the region 6.6–8.2 ppm, a proton signal from the =CH group at 8.5–9.1 ppm. and also signals from the electron-acceptor group **X** in the appropriate regions. IR spectra of compounds **III, IV** contain a set of bands characteristic of amino group (3100–3470 cm^{-1}), and also characteristic signals of the stretching vibrations of the NHCO group at 1660–1690 cm^{-1}. Since we have been able in the course of reaction S_NVin to isolate free compounds **IV** it is presumable that the formation of pyridines **III** and **V** is preceded by the corresponding acyclic structures **IV**. The information on acyclic or heterocyclic structure of the product obtained in the S_NVin reaction is provided by IR spectra. In the IR spectra of compounds **IV** appears a signal of a conjugated cyano group in the region 2218–2224 cm^{-1}, whereas in the IR spectra of pyridines **III** such absorption bands are lacking. These characteristics also confirm the regioselectivity of the intramolecular heterocyclization of compounds **IV** involving the cyano group.

The formation of nicotinethioamide **V** and not of substituted nicotinamide **III** in reaction of propanamide **I** with diethyl ethoxymethylenemalonate (**IIi**) was proved by ^{1}H NMR spectrum of the product. In the spectrum of compound **V** were observed signals of two protons belonging to thioamide group as two broadened singlets at 10.0 and 10.5 ppm, whereas the signals of two protons from an amide group appeared commonly more upfield (6.6–7.7 ppm for compounds **III, IV**) in agreement with the published data [2, 5, 7].

Thus in the ring closure involving a cyano group a thiocarbamoyl group is more nucleophilic than a carbamoyl one. At the same time in intramolecular cyclization with an ester group the amide group is more reactive than the thioamide one. These differences can be rationalized basing on steric reasoning. The cyano group with the *sp*-hybridized carbon atom is digonal, and the approach thereto of a bulky thiocarbamoyl group (which in this case is apparently more nucleophilic than carbamoyl group) is not hampered. The ethoxycarbonyl group containing *sp*^{2}-hybridized carbon is trigonal, and the nucleophile attack is subject to special steric requirements. The

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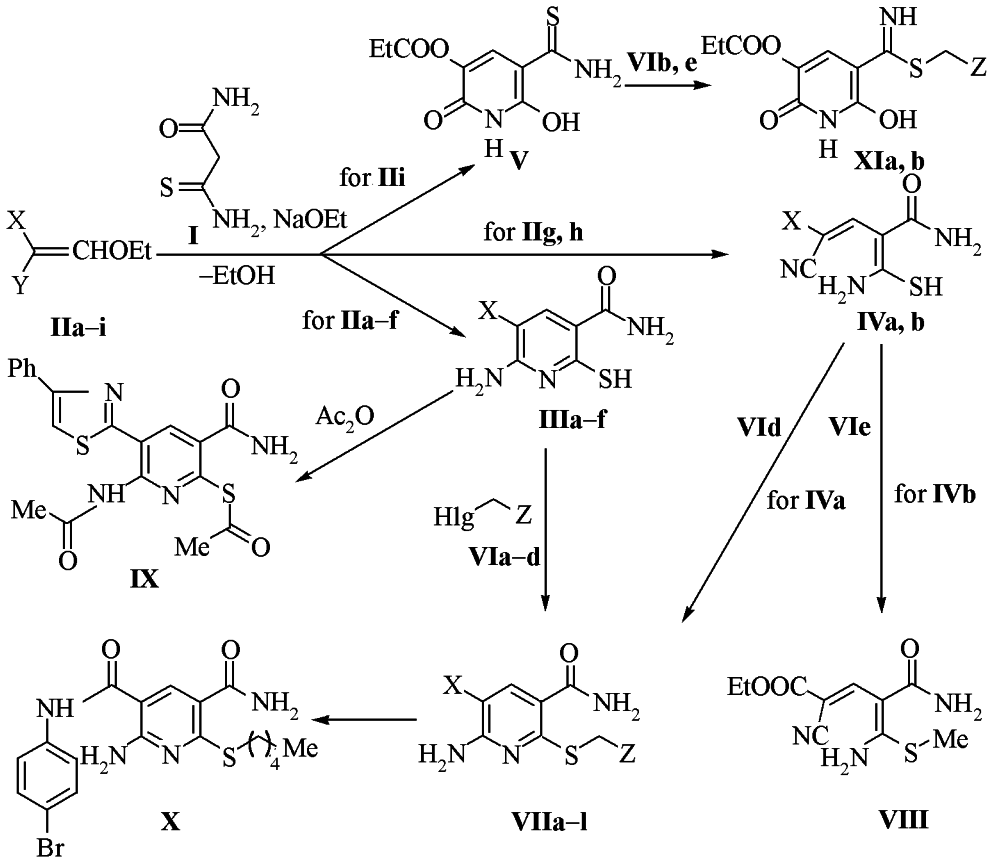

II, III, Y = CN, X = *o*-MeC_6H_4NHCO (**a**), *m*-MeC_6H_4NHCO (**b**), *o*-$MeOC_6H_4NHCO$ (**c**), *m*-$MeOC_6H_4NHCO$ (**d**), α-naphthylcarbamoyl (**e**), 4-phenyl-1,3-thiazol-2-yl (**f**), PhNHCO (**g**), EtOOC (**h**); **Y = X = EtOOC (i**). **IV, X** = PhNHCO (**a**); EtOOC (**b**). **VI**, Hlg = Cl, Z = Ph (**a**); Hlg = Br, Z = $CH=CH_2$ (**b**), C(O)Ph (**c**); Hlg = I, Z = $(CH_2)_3CH_3$ (**d**), H (**e**). **VII**, X = *o*-MeC_6H_4NHCO, Z = $(CH_2)_3CH_3$ (**a**), $CH=CH_2$ (**b**); X = *o*-$MeOC_6H_4NHCO$, Z = $(CH_2)_3CH_3$ (**c**), C(O)Ph (**d**); X = *m*-$MeOC_6H_4NHCO$, Z = $(CH_2)_3CH_3$ (**e**); X = α-naphthylcarbamoyl, Z = $(CH_2)_3CH_3$ (**f**); X = 4-phenyl-1,3-thiazol-2-yl, Z = $(CH_2)_3CH_3$ (**g**), $CH=CH_2$ (**h**), Ph (**i**); X = PhNHCO, Z = $(CH_2)_3CH_3$ (**j**). **XI**, Z = $CH=CH_2$ (**a**), H (**b**).

attack of carbamoyl group having smaller volume than the thiocarbamoyl group occurs easier at the electrophilic site of the ester group. The results obtained are well consistent with the data of [8] where has been demonstrated that under similar conditions the 6-*exo*-*dig*-process has an advantage over 6-*exo*-*trig*-process.

Pyridines **III** undergo alkylation at SH group by halides **VIa–d** affording organic sulfides **VII**. The alkylation of compound **IVa** also gives N^3-phenyl-2-amino-6-pentylmercaptopyridine-3,5-dicarboxamide **VIIj**, whereas in reaction of compound **IVb** with methyl iodide we succeeded to isolate acyclic sulfide **VIII**. This alkylation product unlike pyridines **VII** contained in the IR spectrum the band belonging to the conjugated cyano group (2216 cm^{-1}) that confirmed its acyclic structure.

The acylation of mercaptopyridine **IIIf** in excess acylating agent occurs both at NH_2 and SH groups yielding 3-carbamoyl-6-methylcarboxamido-5-(4-phenyl-1,3-thiazol-2-yl)-2-pyridylethanethioate (**IX**), and bromination of compound **VIIj** proceeds regioselectively at the benzene ring and affords derivative **X**.

The alkylation of pyridone **V** also occurs regioselectively under mild conditions at the sulfur atom, similarly to alkylation of the substituted 3-amino-(thioxo)methyl-3,4-dihydropyridin-2(1*H*)-one [2]. But in our case the carbimine group does not undergo hydrolysis, and the reaction stops at the stage of 5-alkylmercapto(imino)methylpyridines (**XI**) formation. The obtained previously unknown ethyl 5-alkylmercapto(imino)methyl-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylates are of great synthetic and

pharmacological interest and require further investigation.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer IKS-40 from mulls in mineral oil. ^{1}H NMR spectra were registered from solutions in DMSO-d_6 on spectrometers Bruker DRX500 (500.13 MHz) (compounds **IIIa, N, VIIb, XI**), and Gemini-200 (199.975 MHz) (compounds **IIIb–f, IVa, b, VIIa, c–j, VIII, IX, X**), internal reference TMS. Mass spectra were measured on Kratos MS-890 instrument (70 eV). The melting points were determined on Koeffler heating block. The reaction progress was monitored and the homogeneity of the compounds obtained was checked by TLC on Silufol UV-254 plates, eluent acetone–hexane, 3 : 5, development in iodine vapor.

Compounds IIIa–f. To a solution of 0.68 g (10 mmol) of sodium ethylate in 15 ml of ethanol was added at 20°C 1.18 g (10 mmol) of 3-amino-3-thioxopropanamide (**I**), and the mixture was stirred for 5 min till dissolution of all components. Then to the reaction mixture was added 10 ml of an appropriate olefin **II**, and the stirring was continued for 10 min. At the same time a precipitate separated. The mixture was left standing for 2 h, and then compounds **IIIa–f** were filtered off.

N^3-(*o*-Tolyl)-2-amino-6-mercaptopyridine-3,5-dicarboxamide (IIIa). Yield 2.63 g (87%), mp 333–335°C. Mass spectrum, *m/z* (I_{rel}, %): 259 (2.5), 250 (2.5), 233 (3), 153 (20), 126 (26), 106 (100), 89 (15), 77 (28), 53 (20), 34 (27). IR spectrum, cm^{-1}: 3108, 3332, 3448 [ν(NH$_2$)], 1676 [ν(C=O)], 1648 [δ(NH$_2$)]. ^{1}H NMR spectrum, δ, ppm: 2.22 s (3H, CH$_3$), 6.65 and 7.28 both br.s (2H, CONH$_2$), 7.06 d.d (1H, H$_{arom}$, *J* 7.5 Hz), 7.12 d.d (1H, H$_{arom}$, *J* 8.0 Hz), 7.16 d (1H, H$_{arom}$, *J* 8.5 Hz), 7.20 d (1H, H$_{arom}$), 7.34 br.s (2H, NH$_2$), 8.69 s (1H, C^{4}H), 9.67 s (1H, SH), 10.85 s (1H, CONH). Found, %: C 55.80; H 4.43; N 18.38. $C_{14}H_{14}N_4O_2S$. Calculated, %: C 55.61; H 4.67; N 18.53.

N^3-(*m*-Tolyl)-2-amino-6-mercaptopyridine-3,5-dicarboxamide (IIIb). Yield 2.33 g (77%), mp 325–327°C. IR spectrum, cm^{-1}: 3168, 3316, 3420 [ν(NH$_2$)], 1666 [ν(C=O)], 1626 [δ(NH2)]. ^{1}H NMR spectrum, δ, ppm: 2.30 s (3H, CH$_3$), 6.77 and 7.11 both br.s (2H, CONH$_2$), 7.09–7.51 m (4H, H$_{arom}$), 7.50 br.s (2H, NH$_2$), 8.63 s (1H, C^{4}H), 9.83 s (1H, SH), 11.01 s (1H, CONH). Found, %: C 55.71; H 4.52; N 18.39. $C_{14}H_{14}N_4O_2S$. Calculated, %: C 55.61; H 4.67; N 18.53.

N^3-(*o*-Anisyl)-2-amino-6-mercaptopyridine-3,5-dicarboxamide (IIIc). Yield 2.52 g (79%), mp 284–286°C. IR spectrum, cm^{-1}: 3166, 3330, 3466 [ν(NH$_2$)], 1666 [ν(C=O)], 1622 [δ(NH$_2$)]. ^{1}H NMR spectrum, δ, ppm: 3.98 s (3H, OCH$_3$), 6.89–7.19 m (4H, H$_{arom}$), 6.91 and 7.17 both br.s (2H, CONH$_2$), 8.00 br.s (2H, NH$_2$), 8.50 s (1H, C^{4}H), 8.92 s (1H, SH), 11.06 s (1H, CONH). Found, %: C 52.91; H 4.29; N 17.72. $C_{14}H_{14}N_4O_3S$. Calculated, %: C 52.82; H 4.43; N 17.60.

N^3-(*m*-Anisyl)-2-amino-6-mercaptopyridine-3,5-dicarboxamide (IIId). Yield 2.90 g (91%), mp 310–312°C. IR spectrum, cm^{-1}: 3174, 3330, 3430 [ν(NH$_2$)], 1670 [ν(C=O)], 1630 [δ(NH$_2$)]. ^{1}H NMR spectrum, δ, ppm: 3.79 s (3H, OCH$_3$), 6.53 and 6.95 both br.s (2H, CONH$_2$), 7.10–7.38 m (4H, H$_{arom}$), 7.41 br.s (2H, NH$_2$), 8.65 s (1H, C^{4}H), 9.91 s (1H, SH), 10.98 s (1H, CONH). Found, %: C 52.69; H 4.25; N 17.71. $C_{14}H_{14}N_4O_3S$. Calculated, %: C 52.82; H 4.43; N 17.60.

N^3-(α-Naphthyl)-2-amino-6-mercaptopyridine-3,5-dicarboxamide (IIIe). Yield 2.33 g (69%), mp 328–330°C. IR spectrum, cm^{-1}: 3316, 3394 [ν(NH$_2$)], 1672 [ν(C=O)], 1648 [δ(NH$_2$)]. ^{1}H NMR spectrum, δ, ppm: 6.98 and 7.31 both br.s (2H, CONH$_2$), 7.38–7.62 m (7H, H$_{arom}$), 8.18 br.s (2H, NH$_2$), 8.95 s (^{1}H, C^{4}H), 10.20 s (1H, SH), 10.85 s (1H, CONH). Found, %: C 60.39; H 4.09; N 16.47. $C_{17}H_{14}N_4O_2S$. Calculated, %: C 60.34; H 4.17; N 16.56.

2-Amino-6-mercapto-3-(4-phenyl-1,3-thiazol-2-yl)pyridine-5-carboxamide (IIIf). Yield 3.02 g (92%), mp 308–310°C. IR spectrum, cm^{-1}: 3118, 3292, 3434 [ν(NH$_2$)], 1661 [ν(C=O)], 1632 [δ(NH$_2$)]. ^{1}H NMR spectrum, δ, ppm: 7.11 and 7.42 both br.s (2H, CONH$_2$), 7.35 d.d (^{1}H, H$_{arom}$, *J* 6.7 Hz), 7.43 d.d (2H, H$_{arom}$), 7.81 br.s (2H, NH$_2$), 7.82 s (1H, C^{5}H), 7.92 d (2H, H$_{arom}$, *J* 7.2 Hz), 8.52 s (1H, C^{4}H), 10.92 s (1H, SH). Found, %: C 54.63; H 3.34; N 16.89. $C_{15}H_{12}N_4OS_2$. Calculated, %: C 54.86; H 3.68; N 17.06.

Compounds **IVa, b** were prepared similarly to mercaptopyridines **IIIa–f** from compounds **IIg, h**.

***N*^{1}-Phenyl-4-(1-amino-1-mercaptomethylidene)-2-cyanopent-2-enediamide (IVa).** Yield 2.45 g (85%), mp 330–335°C. IR spectrum, cm^{-1}: 3144, 3310, 3378 [ν(NH$_2$)], 2224 [ν(C≡N)], 1674, 1720 [ν(C=O)], 1644 [δ(NH$_2$)]. ^{1}H NMR spectrum, δ, ppm: 7.04 d.d

(1H, H_{arom}, *J* 7.5 Hz), 7.23 and 7.56 both br.s (2H, $CONH_2$), 7.27 d.d (2H, H_{arom}), 7.62 d (2H, H_{arom}, *J* 8.0 Hz), 7.64 br.s (2H, NH_2), 8.70 s (1H, –CH=), 9.81 s (1H, CONH), proton signal of SH group was not detected apparently due to fast exchange with protons of water present in the solvent. Found, %: C 54.47; H 4.09; N 19.77. $C_{13}H_{12}N_4O_2S$. Calculated, %: C 54.15; H 4.20; N 19.43.

Ethyl-5-amino-4-(1-amino-1-mercaptomethylidene)-5-oxo-2-cyanopent-2-enoate (IVb). Yield 1.78 g (74%), mp 220–222°C. IR spectrum, cm^{-1}: 3186, 3350 [ν(NH_2)], 2218 [ν(C≡N)], 1694 [ν(C=O)], 1646 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 1.31 t (3H, $\underline{CH}_3CH_2$), 4.28 q (2H, CH_2), 7.52 and 7.71 both br.s (2H, $CONH_2$), 8.04 br.s (2H, NH_2), 9.07 s (1H, –CH=), 9.79 s (1H, SH). Found, %: C 44.49; H 4.85; N 17.23. $C_9H_{11}N_3O_3S$. Calculated, %: C 44.80; H 4.60; N 17.42.

Ethyl-5-amino(thioxo)methyl-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate (V) was obtained similarly to compounds **IIIa–f** from compound **IIi**. Yield 2.06 g (85%), mp 226–228°C. IR spectrum, cm^{-1}: 3084, 3428 [ν(NH_2)], 1706 [ν(C=O)], 1624 [δ(NH_2)]. ^1H NMR spectrum, ppm: 1.33 t (3H, CH_3), 4.21 q (2H, CH_2, *J* 7.1 Hz), 6.71 br.s (1H, NH), 8.79 s (1H, C^4H), 10.00 br.s and 10.50 br.s (on 1H, NH_2), proton signal of OH group was not detected apparently due to fast exchange with protons of water present in the solvent. Found, %: C 44.73; H 4.08; N 11.42. $C_9H_{10}N_2O_4S$. Calculated, %: C 44.62; H 4.16; N 11.57.

Compounds VIIa–j. To a suspension of 5 mmol of mercaptopyridine **III** or pentene **IVa** in 10 ml of ethanol was added at stirring 2.8 ml (5 mmol) of 10% solution of KOH. To the solution formed was added 5 mmol of an appropriate alkyl halide **VI**, and the mixture was stirred for 1 h. The separated precipitate was filtered off and recrystallized from ethanol or glacial acetic acid.

N^3-(*o*-Tolyl)-2-amino-6-pentylmercaptopyridine-3,5-dicarboxamide (VIIa). Yield 1.69 g (91%), mp 180–182°C (AcOH). IR spectrum, cm^{-1}: 3210, 3304, 3434 [ν(NH_2)], 1700 [ν(C=O)], 1644 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.93 t (3H, CH_3), 1.41 m (4H, $SCH_2CH_2\underline{CH}_2\underline{CH}_2$), 1.63 m (2H, $SCH_2\underline{CH}_2$), 2.27 s (3H, CH_3), 3.05 t (2H, SCH_2, *J* 7.6 Hz), 6.99–7.25 m (4H, H_{arom}), 7.00 and 7.14 both br.s (2H, $CONH_2$), 7.21 br.s (2H, NH_2), 8.39 s (1H, C^4H), 9.45 s (1H, CONH). Found, %: 61.49; H 6.71; N 14.87. $C_{19}H_{24}N_4O_2S$. Calculated, %: C 61.26; H 6.49; N 15.04.

N^3-(*o*-Tolyl)-6-allylmercapto-2-aminopyridine-3,5-dicarboxamide (VIIb). Yield 1.42 g (83 %), mp 184–185°C (AcOH). Mass spectrum, *m/z* (I_{rel}, %): 342 (75) $[M]^+$, 327 (32), 309 (68), 301 (80), 236 (100), 167 (71), 107 (58), 41 (61). IR spectrum, cm^{-1}: 3208, 3306, 3424 [ν(NH_2)], 1696 [ν(C=O)], 1646 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 2.27 s (3H, CH_3), 3.72 d (2H, SCH_2, *J* 6.3 Hz), 5.04 d (1H, $=CH_2$, J_{cis} 9.6 Hz), 5.28 d (1H, $=CH_2$, J_{trans} 16.3 Hz), 5.92 m (1H, CH=), 7.02 and 7.08 both br.s (2H, $CONH_2$), 7.14 d.d (1H, H_{arom}, *J* 8.0 Hz), 7.19 d.d (1H, H_{arom}, *J* 8.0 Hz), 7.23 d (1H, H_{arom}), 7.29 d (1H, H_{arom}, *J* 8.5 Hz), 7.30 br.s (2H, NH_2), 8.39 s (1H, C*4*H), 9.46 s (1H, CONH). Found, %: C 59.39; H 5.48; N 16.12. $C_{17}H_{18}N_4O_2S$. Calculated, %: C 59.63; H 5.30; N 16.36.

N^3-(*o*-Anisyl)-2-amino-6-pentylmercapto-pyridine-3,5-dicarboxamide (VIIc). Yield 1.39 g (72%), mp 201–203°C (EtOH). IR spectrum, cm^{-1}: 3172, 3334, 3438 [ν(NH_2)], 1714 [ν(C=O)], 1642 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.90 t (3H, CH_3, *J* 6.9 Hz), 1.37 m (4H, $SCH_2CH_2\underline{CH}_2\underline{CH}_2$), 1.60 m (2H, $SCH_2\underline{CH}_2$), 3.00 t (2H, SCH_2, *J* 7.0 Hz), 3.84 s (3H, OCH_3), 6.91 d.d (1H, H_{arom}, *J* 7.6 Hz), 6.98 d (1H, H_{arom}), 7.01 and 7.47 both br.s (2H, $CONH_2$), 7.11 d.d (1H, H_{arom}, *J* 7.8 Hz), 7.33 br.s (2H, NH_2), 7.64 d (1H, H_{arom}), 8.30 s (1H, C^4H), 9.12 s (1H, CONH). Found, %: C 58.15; H 6.40; N 14.16. $C_{19}H_{24}N_4O_3S$. Calculated, %: C 58.74; H 6.23; N 14.42.

N^3-(*o*-Anisyl)-2-amino-6-benzoylmethyl-mercaptopyridine-3,5-dicarboxamide (VIId). Yield 1.92 g (88%), mp 250–252°C (AcOH). IR spectrum, cm^{-1}: 3195, 3330, 3396 [ν(NH_2)], 1688 [ν(C=O)], 1652 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 3.84 s (3H, OCH_3), 4.53 s (2H, SCH_2), 6.89 d. d (1H, H_{arom}, *J* 7.2 Hz), 6.97 d (1H, H_{arom}, *J* 7.1 Hz), 7.05 and 7.12 both br.s (2H, $CONH_2$), 7.06 d.d (1H, H_{arom}), 7.09 d.d (1H, H_{arom}), 7.44 br.s (2H, NH_2), 7.48 d.d (2H, H_{arom}, *J* 7.6 Hz), 7.63 d (1H, H_{arom}, *J* 8.1 Hz), 8.04 d (2H, H_{arom}, *J* 7.1 Hz), 8.39 s (1H, C^4H), 9.08 s (1H, CONH). Found, %: C 60.88; H 4.71; N 12.56. $C_{22}H_{20}N_4O_4S$. Calculated, %: C 60.54; H 4.62; N 12.84.

N^3-(*m*-Anisyl)-2-amino-6-pentylmercapto-pyridine-3,5-dicarboxamide (VIIe). Yield 1.26 g (65%), mp 194–196°C (EtOH). IR spectrum, cm^{-1}: 3334, 3444 [ν(NH_2)], 1666 [ν(C=O)], 1628 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3, *J* 7.0 Hz), 1.36 m (4H, $SCH_2CH_2\underline{CH}_2\underline{CH}_2$), 1.61 m (2H, $SCH_2\underline{CH}_2$), 2.99 t (2H, SCH_2, *J* 7.6 Hz), 3.75 s

(3H, OCH_3), 6.54 d (1H, H_{arom}, *J* 7.5 Hz), 7.01 and 7.18 both br.s (2H, $CONH_2$), 7.08–7.20 m (2H, H_{arom}), 7.21 br.s (2H, NH_2), 7.33 s (1H, H_{arom}), 8.26 s (1H, C^4H), 9.66 s (1H, CONH). Found, %: C 58.97; H 6.49; N 14.58. $C_{19}H_{24}N_4O_3S$. Calculated, %: C 58.74; H 6.23; N 14.42.

***N*^{3}-(α-Naphthyl)-2-amino-6-pentylmercaptopyridine-3,5-dicarboxamide (VIIf).** Yield 1.49 g (73%), mp 204–206°C (AcOH). IR spectrum, cm^{-1}: 3180, 3390 [ν(NH_2)], 1696 [ν(C=O)], 1650 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, *J* 6.9 Hz), 1.39 s (4H, $SCH_2CH_2\underline{CH}_2\underline{CH}_2$), 1.62 m (2H, $SCH_2\underline{CH}_2$), 3.06 t (2H, SCH_2, *J* 7.0 Hz), 7.06 and 7.50 both br.s (2H, $CONH_2$), 7.41 br.s (2H, NH_2), 7.49–8.05 m (7H, H_{arom}), 8.57 s (1H, C^4H), 10.03 s (1H, CONH). Found, %: C 64.30; H 5.74; N 13.45. $C_{22}H_{24}N_4O_2S$. Calculated, %: C 64.68; H 5.92; N 13.72.

2-Amino-6-pentylmercapto-3-(4-phenyl-1,3-thiazol-2-yl)pyridine-5-carboxamide (VIIg). Yield 1.65 g (83%), mp 210–212°C (AcOH). IR spectrum, cm^{-1}: 3172, 3298, 3368 [ν(NH_2)], 1661 [ν(C=O)], 1646 [δ(NH_2)]]. ^1H NMR spectrum, δ, ppm: 0.94 t (3H, CH_3, *J* 7.1 Hz), 1.43 m (4H, $SCH_2CH_2\underline{CH}_2\underline{CH}_2$), 1.67 m (2H, $SCH_2\underline{CH}_2$), 3.13 t (2H, SCH_2, *J* 7.1 Hz), 7.01 and 7.57 both br.s (2H, $CONH_2$), 7.34 d.d (1H, H_{arom}, *J* 7.2 Hz), 7.46 d.d (2H, H_{arom}), 7.82 br.s (2H, NH_2), 7.94 d (2H, H_{arom}, *J* 6.9 Hz), 7.96 s (1H, C^5H), 8.14 s (1H, C^4H). Found, %: C 60.42; H 5.39; N 14.27. $C_{20}H_{22}N_4OS_2$. Calculated, %: C 60.27; H 5.57; N 14.06.

6-Allylmercapto-2-amino-3-(4-phenyl-1,3-thiazol-2-yl)pyridine-5-carboxamide (VIIh). Yield 1.66 g (90%), mp 215–217°C (AcOH). IR spectrum, cm^{-1}: 3214, 3302, 3394 [ν(NH_2)], 1662 [ν(C=O)], 1632 [δ(NH_2)]. ^1H NMR spectrum, δ ppm: 3.78 d (2H, SCH_2, *J* 7.0 Hz), 5.05 d (1H, $=CH_2$, J_{cis} 9.9 Hz), 5.30 d (1H, $=CH_2$, J_{trans} 17.1 Hz), 5.94 m (1H, CH=), 7.02 and 7.62 both br.s (2H, $CONH_2$), 7.33 d.d (1H, H_{arom}, *J* 7.1 Hz), 7.45 d.d (2H, H_{arom}, *J* 7.6 Hz), 7.92 br.s (2H, NH_2), 7.93 d (2H, H_{arom}), 7.95 s (1H, C^5H), 8.17 s (1H, C^4H). Found, %: C 58.29; H 4.59; N 15.03. $C_{18}H_{16}N_4OS_2$. Calculated, %: C 58.67; H 4.38; N 15.21.

2-Amino-6-benzylmercapto-3-(4-phenyl-1,3-thiazol-2-yl)pyridine-5-carboxamide (VIIi). Yield 1.56 g (75%), mp 230–233°C (EtOH). IR spectrum, cm^{-1}: 3180, 3350 [ν(NH_2)], 1671 [ν(C=O)], 1642 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 4.36 s (2H, SCH_2), 7.02 and 7.36 both br.s (2H, $CONH_2$), 7.19 d.d (1H, H_{arom}, *J* 7.0 Hz), 7.22 d.d (1H, H_{arom}, *J* 7.0 Hz), 7.28 d.d (2H, H_{arom}, *J* 7.6 Hz), 7.35 d.d (2H, H_{arom}, *J* 7.1 Hz), 7.48 d (2H, H_{arom}), 7.92 d (2H, H_{arom}), 7.98 s (1H, C^5H), 8.09 br.s (2H, NH_2), 8.19 s (1H, C^4H). Found, %: C 63.04; H 4.19; N 13.53. $C_{22}H_{18}N_4OS_2$. Calculated, %: C 63.13; H 4.33; N 13.39.

N^3-Phenyl-2-amino-6-pentylmercaptopyridine-3,5-dicarboxamide (VIIj). Yield 1.39 g (78%), mp 198–200°C (AcOH). IR spectrum, cm^{-1}: 3334, 3452 [ν(NH_2)], 1664 [ν(C=O)], 1626 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 0.93 t (3H, CH_3, *J* 6.9 Hz), 1.39 m (4H, $SCH_2CH_2\underline{CH}_2\underline{CH}_2$), 1.63 m (2H, $SCH_2\underline{CH}_2$), 3.03 t (2H, SCH_2, *J* 7.0 Hz), 7.02 and 7.27 both br.s (2H, $CONH_2$), 7.06 d.d (1H, H_{arom}, *J* 7.0 Hz), 7.31 d.d (2H, H_{arom}, *J* 7.6 Hz), 7.63 d (2H, H_{arom}), 7.64 br.s (2H, NH_2), 8.31 s (1H, C^4H), 9.83 s (1H, CONH). Found, %: C 60.21; H 6.34; N 15.93. $C_{18}H_{22}N_4O_2S$. Calculated, %: C 60.31; H 6.19; N 15.63.

Ethyl-5-amino-4-carbamoyl-5-methylsylfanyl-2-cyanopenta-2,4-dienoate (VIII). To a solution of 2.41 g (10 mmol) of pentene **IVb** in 20 ml of ethanol a 20°C was added 0.62 ml (10 mmol) of methyl iodide. The mixture was left standing at room temperature for 2 days. The separated precipitate was filtered off, washed with ethanol and hexane. Yield 1.61 g (63%), mp 212–214°C. IR spectrum, cm^{-1}: 3172, 3346, 3420 [ν(NH_2)], 2216 [ν(C≡N)], 1696 [ν(C=O)], 1652 [δ(NH_2)]. ^1H NMR spectrum, δ, ppm: 1.33 t (3H, $CH_2\underline{CH}_3$, *J* 7.1 Hz), 2.35 s (3H, SCH_3), 4.26 q (2H, CH_2), 6.95 br.s (2H, NH_2), 7.25 br.s and 7.58 br.s (1H each, NH_2), 8.23 s (1H, CH=). Found, %: C 46.92; H 5.21; N 16.28. $C_{10}H_{13}N_3O_3S$. Calculated, %: C 47.05; H 5.13; N 16.46.

3-Carbamoyl-6-methylcarboxamido-5-(4-phenyl-1,3-thiazol-2-yl)-2-pyridylethanethioate (IX). To a solution of 1.64 g (5 mmol) of thiol (**IIIf**) in 10 ml of acetic anhydride was added 0.10 ml of pyridine, and the mixture was boiled for 3 h and then left standing at room temperature for 24 h. The precipitate formed was filtered off, washed with ethanol. Yield 1.71 (83%), mp 210– 212°C. IR spectrum, cm^{-1}: 3103, 3172, 3399 [ν(NH_2)], 1682, 1748 [ν(C=O)], 1610 [δ(NH_2)]]. ^1H NMR spectrum, δ, ppm: 2.29 s and 2.41 s (3H, both CH_3), 7.37–7.93 m (7H, Ph and NH_2), 8.18 s (1H, C^5H), 8.72 s (1H, C^4H), 12.76 s (1H, NH). Found, %: C 55.48; H 3.77; N 13.49. $C_{19}H_{16}N_4O_3S_2$. Calculated, %: C 55.32; H 3.91; N 13.58.

N^3-(4-Bromophenyl)-2-amino-6-pentylmercaptopyridine-3,5-dicarboxamide (X). To a solution of 1.79 g (5 mmol) of pyridine **VIIj** in 10 ml of glacial acetic acid was added while stirring dropwise 0.26 ml (5 mmol) of Br_2. The separated precipitate was filtered off, washed with ethanol and hexane. Yield 1.99 g (91%), mp 210–212°C. IR spectrum, cm^{-1}: 3184, 3286, 3380 [$\nu(NH_2)$], 1690 [$\nu(C=O)$], 1656 [$\delta(NH_2)$]. ^1H NMR spectrum, δ, ppm: 0.92 t (3H, CH_3, *J* 6.9 Hz), 1.38 m (4H, $SCH_2CH_2\underline{CH}_2\underline{CH}_2$), 1.64 m (2H, $SCH_2\underline{CH}_2$), 3.07 t (2H, SCH_2, *J* 7.0 Hz), 7.29 br.s (4H, 2 NH_2), 7.40 d and 7.74 d (on 2H, H_{arom}, *J* 8.8 Hz), 8.18 s (1H, C^4H), 10.13 s (1H, NH). Found, %: C 49.31; H 4.92; N 12.65. $C_{18}H_{21}BrN_4O_2S$. Calculated, %: C 49.43; H 4.84; N 12.81.

Compounds XIa, b were obtained analogously to alkylmercaptopyridines **VIIa–j** from pyridone **V**

Ethyl-5-allylmercapto(imino)methyl-6-hydroxy-2-oxo-1,2-dihydropyridine-3-carboxylate (XIa). Yield 1.27 g (90%), mp 323– 325°C. IR spectrum, cm^{-1}: 3210, 3262, 3400 [$\nu(NH_2)$], 1680 [$\nu(C=O)$], 1644 [$\delta(NH_2)$]. ^1H NMR spectrum, δ, ppm: 1.23 t (3H, CH_3, *J* 7.1 Hz), 3.60 d (2H, SCH_2, *J* 6.9 Hz), 4.10 q (2H, $\underline{CH}_2CH_3$), 4.97 d (1H, $=CH_2$, J_{cis} 9.9 Hz), 5.16 d (1H, $=CH_2$, J_{trans} 16.1 Hz), 5.87 m (1H, CH=), 6.79 br.s (1H, N^1H), 6.86 br.s (1H, =NH), 8.05 s (1H, C^4H), proton signal of OH group was not detected apparently due to fast exchange with protons of water present in the solvent. Found, %: C 50.82; H 4.88; N 10.21. $C_{12}H_{14}N_2O_4S$. Calculated, %: C 51.05; H 5.00; N 9.93.

Ethyl-6-hydroxy-5-imino(methylmercapto)-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (XIb). Yield 1.10 g (86%), mp 214– 216°C. IR spectrum, cm^{-1}: 3174, 3372 [$\nu(NH_2)$], 1740 [$\nu(C=O)$], 1644 [$\delta(NH_2)$]. ^1H NMR spectrum, δ, ppm: 1.41 t (3H, $CH_2\underline{CH}_3$), 2.45 s (3H, SCH_3), 4.38 q (2H, $\underline{CH}_2CH_3$), 7.20 br.s (1H, N^1H), 7.60 br.s (1H, =NH), 8.32 s (1H, C^4H), 11.49 br.s (1H, OH). Found, %: C 47.12; H 4.85; N 11.05. $C_{10}H_{12}N_2O_4S$. Calculated, %: C 46.86; H 4.72; N 10.93.

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