The Synthesis and Transformations of 3-Ethoxycarbonyl-2-isothiocyanatopyridine. Pyrido[2,3-*d*]pyrimidines and Some Azolopyrido[2,3-*d*]pyrimidines

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3-Ethoxycarbonyl-2-isothiocyanatopyridine (**2**), prepared from 2-amino-3-ethoxycarbonylpyridine (**1**) by the thiophosgene method, was converted into thiouretanes **3** and **4**, 1,4-disubstituted thiosemicarbazide **6**, thioamide **8**, and thioureas **15** and **18**. The compounds **2** and **3** were converted into bicyclic pyrido[2,3-*d*]pyrimidines **5**, **9**, **10**, **11**, **12**, **16**, and **17**, and tricyclic azolopyrido[2,3-*d*]pyrimidines **13** and **14**.

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Derivatives of pyrido[2,3-*d*]pyrimidine system are of great interest because of its dihydrofolate reductase inhibiting, antibacterial [1,2], antitumor [3], and antiepileptic activity [4] and therefore there are numerous methods of preparation of derivatives of this system described in the literature [5-13].

Recently, we described the synthesis of 2-ethoxycarbonyl-3-isothiocyanatopyridine and some of its transformations [14]. In this communication, we report on the synthesis and some transformations of the isomeric 3-ethoxycarbonyl-2-isothiocyanatopyridine (**2**) prepared by essentially the same procedure as the isomeric 2-ethoxycarbonyl-3-isothiocyanatopyridine [14] from 2-amino-3-ethoxycarbonylpyridine (**1**). Since it represents an interesting reactive intermediate, we studied some of its transformations, such as reactions with alcohols and *N*-nucleophiles, including amino acids and their derivatives, and further cyclizations into pyrido[2,3-*d*]pyrimidine derivatives.

When **2** was heated with ethanol or ethylene glycol, the corresponding thiouretanes **3** and **4** were formed, respectively. In the reaction of **2** with phenylhydrazine at room temperature cyclization occurred to give pyrido[2,3-*d*]-pyrimidine derivative **5**, while with methylhydrazine noncyclized product was isolated, to which either structure **6** or **7** could be ascribed. Since this compound did not react with benzaldehyde and furthermore it could not be deaminated by treatment with nitrous acid, it means that it does not contain a primary amino group, and therefore it seems, that the structure **6** is the most probable. Pyrrole reacted at C_2 to give **8**, similarly as we observed in the isomeric isothiocyanate [14], while butylamine and methylamine gave in anhydrous ethanol at room temperature the cyclized compounds **9** and **10**, respectively.

Also, the compound **3** turned out to be a versatile intermediate in the synthesis of pyrido[2,3-*d*]pyrimidines. Thus, **3** reacted with methylamine in anhydrous ethanol to give two cyclized products, **10** and **11**, while with benzylamine only **12** was formed. With 1,2-diaminoethane **13**, a derivative of a new heterocyclic system, imidazo[1,2-*a*]-pyrido[2,3-*d*]pyrimidine, was produced. The structural proof is based on the comparison of the ^{1}H nmr data (Table I) with the isomeric system [14]. Since in both cases the chemical shifts for a CH_2 group at position 3 of the dihydroimidazole part are equal, it means that cyclization took place at nitrogen at position 3 in the pyrimidine ring and not at position 1. Analogously, **3** reacted with aminoethanethiol hydrochloride to give **14**, a derivative of thiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidine system (Scheme 1).

Table I

^{1}H NMR Data for Ring Protons of some Pyrido[2,3-*d*]-pyrimidine Derivatives

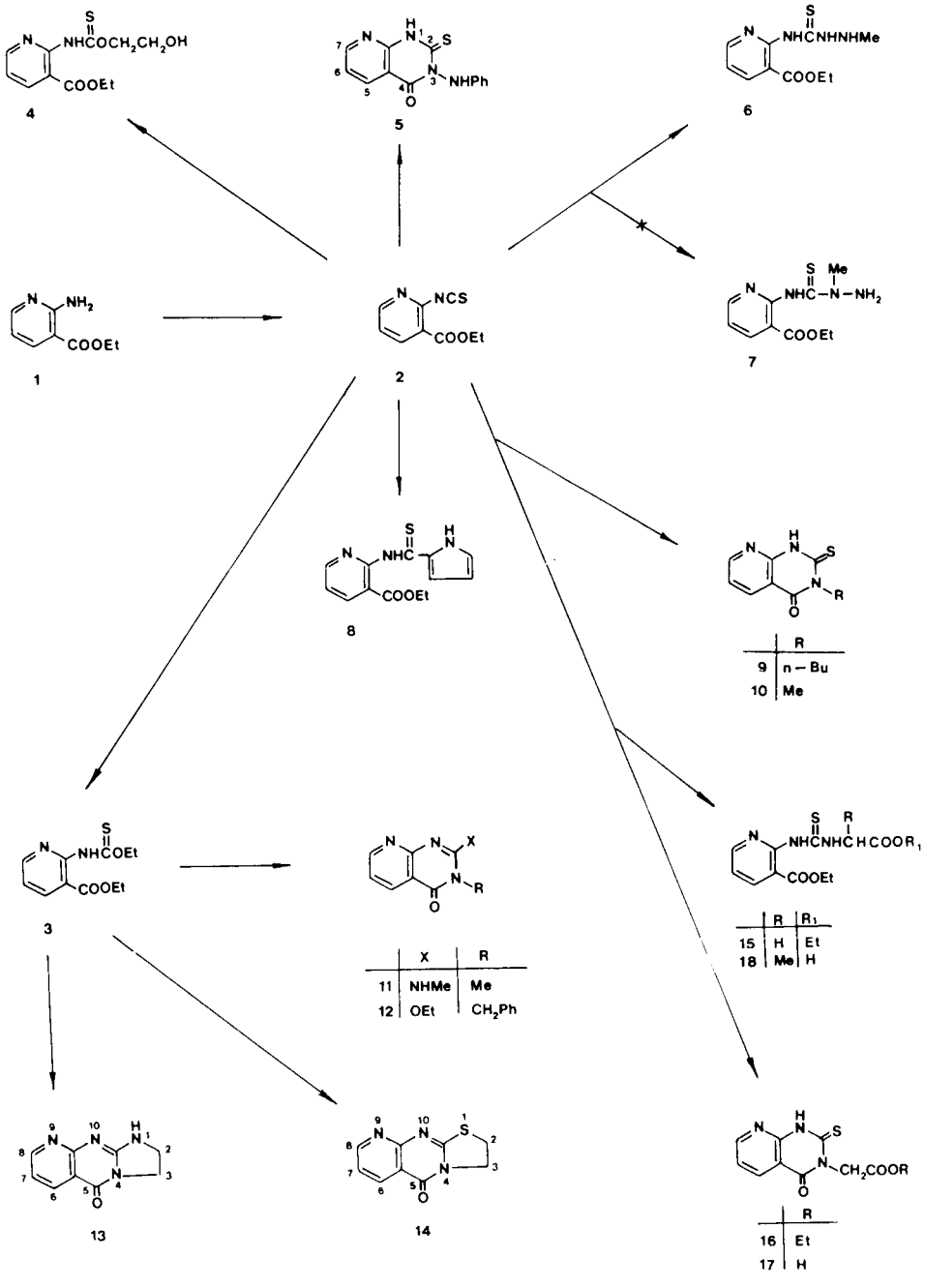
Compound	δ (ppm)				
	H_5	H_6	H_7	H_8	other
5	8.40	7.41	8.80	–	
10	8.33	7.33	8.68	–	
12	8.42	–	8.73	–	
13	–	8.15	6.97	8.51	2-CH_2, 3.66; 3-CH_2, 4.0
14	–	8.43	7.44	8.85	2-CH_2, 3.59; 3-CH_2, 4.45
16	8.12	7.17	8.50	–	

In the reaction with esters of α-amino acids two types of products were obtained. With ethyl glycinate noncyclized product **15** and cyclized product **16** were isolated, while with glycine only cyclized product **17** and with L-alanine only noncyclized compound **18** were formed. The differentiation between noncyclized and cyclized compounds could be done not only on the basis of elemental analyses, but also on the basis of nmr spectra, since the chemical shifts for protons H_4 and H_6 in noncyclized products **15** and **18** are the same, while the chemical shifts for the corresponding protons H_5 and H_7 in **16** and **17** are different.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a JEOL 90 Q FT spectrometer with

Scheme 1



TMS as internal standard, mass spectra on Hitachi-Perkin-Elmer RMU-6L mass spectrometer and elemental analyses for C, H, and N on Perkin-Elmer CHN Analyser 240 C.

2-Amino-3-ethoxycarbonylpyridine (**1**) was prepared according to the procedure described in the literature [10].

3-Ethoxycarbonyl-2-isothiocyanatopyridine (**2**).

This compound was prepared from **1** in essentially the same way as the isomeric 3-isothiocyanato-2-ethoxycarbonylpyridine [14] in a two phase system dichloromethane-water, in 50% yield. The compound was purified by column chromatography (Kieselgel 60, 0.400-0.063 mm, E. Merck, and chloroform/acetone, 50:1, as solvent), liquid at room temperature; ^{1}H nmr (deuteriochloroform): δ 1.44 (t, OCH_2Me), 4.40 (q, OCH_2Me), 7.20 (dd, H_5), 8.25 (dd, H_4), 8.50 (dd, H_6), J_{CH_2Me} = 8.3 Hz, J_{H_4,H_5} = 7.6 Hz. J_{H_4,H_6} = 1.8 Hz, J_{H_5,H_6} = 4.6 Hz.

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.91; H, 3.87; N, 13.45. Found: C, 51.71; H, 3.92; N, 13.24.

3-Ethoxycarbonyl-2-ethoxythiocarbonylaminopyridine (**3**).

A solution of **2** (100 mg) in ethanol (5 ml) was heated under reflux for 24 hours. Ethanol was evaporated *in vacuo* and the

residue purified by column chromatography (Kieselgel 60, 0.400-0.063 mm, E. Merck, chloroform/acetone, 30:1, as solvent, to give **3** (47 mg, 46%), liquid at room temperature; ^{1}H nmr (deuteriochloroform): δ 1.43 (t, *Me*CH_2CH_2OCO, *Me*CH_2OCS), 4.40 (q, MeC*H*$_2$OCO), 4.65 (q, MeC*H*$_2$OCS), 7.07 (dd, H_5), 8.32 (dd, H_4), 8.59 (dd, H_6), J_{MeCH_2} = 7.2 Hz, J_{H_4,H_5} = 8.7 Hz, J_{H_4,H_6} = 1.8 Hz, J_{H_5,H_6} = 4.5 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02. Found: C, 51.74; H, 5.46; N, 10.93.

3-Ethoxycarbonyl-2-(2-hydroxyethyloxy)thiocarbonylaminopyridine (**4**).

A solution of **2** (213 mg) and ethylene glycol (80 mg) in benzene (5 ml) was heated under reflux for 6 hours. The solvent was evaporated *in vacuo*, methanol (2 ml) was added to the oily residue and left in the refrigerator for 12 hours. The precipitate was collected by filtration to give **4** (123 mg, 45%), mp 75-78° (from ethanol): ^{1}H nmr (deuteriochloroform): δ 1.43 (t, OCH_2*Me*), 3.94 (m, HOC*H*$_2$), 4.45 (q, OC*H*$_2$Me), 4.77 (m, HOCH_2C*H*$_2$OCS), 7.12 (dd, H_5), 8.37 (dd, H_4), 8.49 (dd, H_6), J_{MeCH_2} = 7.1 Hz, J_{H_4,H_5} = 7.9 Hz, J_{H_4,H_6} = 1.9 Hz, J_{H_5,H_6} = 4.8 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 49.13; H, 5.24; N, 10.39.

3-Anilino-2-thiooxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**5**).

A solution of **2** (131 mg) and phenylhydrazine (68 mg) in dichloromethane (5 ml) was stirred at room temperature for 24 hours. The precipitate was collected by filtration to give **5** (45 mg, 27%), mp 280-283° (from methanol); nmr (DMSO-d_6): δ 6.6-7.3 (m, PhN), 7.41 (dd, H_6), 8.40 (dd, H_7), J_{H_5,H_6} = 7.8 Hz, J_{H_5,H_7} = 1.5 Hz, J_{H_6,H_7} = 4.5 Hz.

Anal. Calcd. for $C_{13}H_{10}N_4OS$: C, 57.76; H, 3.73; N, 20.73. Found: C, 57.47; H, 3.85; N, 20.63.

1-Methyl-4-(3-ethoxycarbonylpyridinyl-2)-thiosemicarbazide (**6**).

To a solution of **2** (287 mg) in dichloromethane (5 ml) methylhydrazine (1 ml) was added dropwise at 0°, and stirring was continued at room temperature for 3 hours. The volatile components were evaporated *in vacuo*, and a mixture of ethanol and water (1:1, 3 ml) was added to the residue. The precipitate was collected by filtration to give **6** (73 g, 21%), mp 170-172° (from a mixture of ethanol and water); ^{1}H nmr (DMSO-d_6): δ 1.30 (t, *Me*CH_2O), 3.42 (s, NMe), 4.27 (q, MeC*H*$_2$), 6.80 (dd, H_5), 7.47 (br s, NH_2), 8.07 (dd, H_4), 8.25 (dd, H_6), J_{CH_2Me} = 6.8 Hz, J_{H_4,H_5} = 7.5 Hz, J_{H_4,H_6} = 1.5 Hz, J_{H_5,H_6} = 4.5 Hz.

Anal. Calcd. for $C_{10}H_{14}N_4O_2S$: C, 47.23; H, 5.55; N, 22.03. Found: C, 47.66; H, 5.23; N, 22.47.

3-Ethoxycarbonyl-2-[(2-pyrrolyl)thiocarbonylamino]pyridine (**8**).

A mixture of **2** (187 mg) and pyrrole (70 mg) was heated at 100° for 18 hours. After cooling, chloroform (10 ml) was added to the mixture and the solution was separated from the solid by filtration. Filtrate was reduced to one-third by evaporation *in vacuo* and purified by column chromatography (Kieselgel 60, 0.400-0.063 mm, E. Merck, and chloroform/acetone, 30:1, as solvent). Evaporation of the solvent *in vacuo* gave **8** (35 mg, 14%), mp 133-135° (from 1-propanol) ; ^{1}H nmr (deuteriochloroform): δ 1.39 (t, OCH_2*Me*), 4.35 (q, OC*H*$_2$Me), 6.20 (m, 4'-CH), 6.89 (m, 3'-CH, 5'-CH), 6.97 (dd, H_5), 8.20 (dd, H_4), 8.50 (dd, H_6), J_{CH_2Me} = 6.8 Hz, J_{H_4,H_5} = 7.8 Hz, J_{H_4,H_6} = 1.8 Hz, J_{H_5,H_6} = 4.5 Hz.

Anal. Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.70; H, 4.87; N, 15.26.

3-*n*-Butyl-2-thiooxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**9**).

A solution of **2** (410 mg) and *n*-butylamine (0.3 ml) in dichloromethane (5 ml) was stirred at room temperature for 1 hour, and then heated under reflux for 3 hours. The solvent was evaporated *in vacuo*, methanol (3 ml) was added to the oily residue and the precipitate was collected by filtration and purified by column chromatography (Kieselgel 60, 0.400-0.063 mm, E. Merck, and chloroform/acetone, 30:1, as solvent) to give **9** (108 mg, 23%), mp 162-164°; ^{1}H nmr (deuteriochloroform): δ 0.85-2.05 (m, *Me*CH_2-C*H*$_2$CH_2), 4.46 (t, Me(CH_2)$_2$C*H*$_2$), 7.18 (dd, H_6), 8.34 (dd, H_5), 9.15 (dd, H_7), 13.0 (br s, NH).

Anal. Calcd. for $C_{11}H_{13}N_3OS$: C, 56.15; H, 5.57; N, 17.86. Found: C, 56.31; H, 5.55; N, 18.06.

3-Methyl-2-thiooxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**10**).

A mixture of **2** (300 mg) and methylamine (33% in anhydrous ethanol, 5 ml) was stirred at room temperature for 30 minutes. The precipitate was collected by filtration to give **10** (186 mg, 67%), mp (sublimed over 215°); ^{1}H nmr (DMSO-d_6): 145°, δ 3.69 (s, Me), 7.33 (dd, H_6), 8.33 (dd, H_5), 8.68 (dd, H_7), J_{H_5,H_6} = 7.9 Hz, J_{H_5,H_7} = 1.8 Hz, J_{H_6,H_7} = 4.6 Hz.

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.74; H, 3.65; N, 21.76. Found: C, 49.92; H, 3.87; N, 22.01.

3-Methyl-2-methylaminopyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**11**).

A solution of **3** (600 mg) and methylamine (33% solution in anhydrous ethanol, 5 ml) was stirred at room temperature for 20 hours. The precipitate was collected by filtration to give **11** (160 mg, 36%), mp 273-275° (from methanol); ms: M^+ = 190; ^{1}H nmr (DMSO-d_6): δ 2.9 (br s, MeNH), 3.33 (s, MeN), 6.97 (dd, H_6), 8.10 (dd, H_5), 8.51 (dd, H_7), J_{H_5,H_6} = 7.8 Hz, J_{H_5,H_7} = 1.8 Hz, J_{H_6,H_7} = 4.5 Hz.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.90; H, 5.28; N, 29.13.

3-Benzyl-2-ethoxypyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**12**).

A solution of **3** (334 mg) and benzylamine (368 mg) in anhydrous ethanol (5 ml) was heated under reflux for 3 hours. The solvent was evaporated *in vacuo*, ether was added to the oily residue and the precipitate was collected by filtration to give **12** (99 mg, 27%), mp 102-103° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.40 (t, *Me*CH_2O), 4.57 (q, MeC*H*$_2$O), 5.20 (s, PhC*H*$_2$), 7.05-7.40 (m, Ph, H_6), 8.42 (dd, H_5), 8.73 (dd, H_7), J_{MeCH_2} = 6.8 Hz, J_{H_5,H_6} = 7.8 Hz, J_{H_5,H_7} = 1.8 Hz, J_{H_6,H_7} = 4.5 Hz.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.62; H, 5.60; N, 14.96.

2,3-Dihydroimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(1*H*)-one (**13**).

A solution of **3** (300 mg) and 1,2-diaminoethane (118 mg) in benzene (3 ml) was heated under reflux for 19 hours. The precipitate was, after cooling, collected by filtration to give **13** (100 mg, 45%), mp 309-312° (from water); ^{1}H nmr (DMSO-d_6): δ 3.66 (t, NCH_2C*H*$_2$), 4.0 (t, NC*H*$_2$CH$_2$), 6.97 (dd, H_7), 8.15 (dd, H_6), 8.51 (dd, H_8), (NH-exchanged), $J_{CH_2CH_2}$ = 6.75 Hz, J_{H_6,H_7} = 8.25 Hz, J_{H_6,H_8} = 1.5 Hz, J_{H_7,H_8} = 4.5 Hz.

Anal. Calcd. for $C_9H_8N_4O$: C, 57.44; H, 4.29; N, 29.77. Found:

C, 57.44; H, 4.26; N, 29.64.

2,3-Dihydrothiazolo[3,2-*a*]pyrido[2,3-*d*]pyrimidin-5-one (**14**).

To the solution of **3** (460 mg) in anhydrous pyridine (10 ml) aminoethanol hydrochloride (300 mg) was added and the mixture was heated under reflux for 28 hours. The solvent was evaporated *in vacuo*, sodium hydroxide (aqueous solution, 10%, 10 ml) was added and the precipitate was collected by filtration to give **14** (287 mg, 91%), mp 220-223° (from water); ^{1}H nmr (DMSO-d_6): δ 3.59 (t, 2-CH_2), 4.45 (t, 3-CH_2), 7.44 (dd, H_7), 8.43 (dd, H_6), 8.85 (dd, H_8), $J_{CH_2CH_2}$ = 7.8 Hz, J_{H_6,H_7} = 7.8 Hz, J_{H_6,H_8} = 2.2 Hz, J_{H_7,H_8} = 4.4 Hz.

Anal. Calcd. for $C_9H_7N_3OS$: C, 52.68; H, 3.44; N, 20.48. Found: C, 52.83; H, 3.51; N, 20.63.

3-Ethoxycarbonyl-2-(*N*-ethoxycarbonylmethylthioureido)pyridine (**15**) and 3-Ethoxycarbonylethyl-2-thiooxo-1,2-dihydropyrido-[2,3-*d*]pyrimidin-4(3*H*)-one (**16**).

To a solution of ethyl glycinate hydrochloride (390 mg) in a mixture of water (4 ml), dioxane (4 ml) and sodium hydroxide (1 *M*, 2.7 ml) **2** (560 mg) was added and the mixture was heated during stirring at 50° for 5 hours, and then at room temperature for 12 hours. The precipitate was collected by filtration and separated by column chromatography (Kieselgel 60, 0.400-0.063 mm, E. Merck, chloroform/acetone, 50:1, as solvent). The first fraction gave, after evaporation of solvent **15** (120 mg, 21%), mp 150° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.21 (t), 1.58 (t) (*Me*CH_2O, *Me*CH_2O), 4.16 (q), 4.42 (q) (MeCH_2O, MeCH_2O), 4.44 (d, $OCOCH_2$), 6.87 (dd, H_5), 8.22 (m, H_4, H_6), J_{MeCH_2} = 5.7 Hz, J_{H_4,H_5} = 7.5 Hz, J_{H_4,H_6} = 1.5 Hz, J_{H_5,H_6} = 4.8 Hz.

Anal. Calcd. for $C_{13}H_{17}N_3O_4S$: C, 50.15; H, 5.50; N, 13.50. Found: C, 50.21; H, 5.53; N, 13.61.

The second fraction gave, after evaporation of the solvent, **16** (135 mg, 23%), mp 248-249° (from DMF), nmr (DMSO-d_6): 110°, δ 1.16 (t, *Me*CH_2O), 4.05 (q, MeCH_2O), 5.02 (s, CH_2COOEt), 7.17 (dd, H_6), 8.12 (dd, H_5), 8.50 (dd, H_7), J_{MeCH_2} = 6.75 Hz, J_{H_5,H_6} = 7.5 Hz; J_{H_5,H_7} 1.8 Hz, J_{H_6,H_7} = 4.5 Hz.

Anal. Calcd. for $C_{11}H_{11}N_3O_3S$: C, 49.80; H, 4.18; N, 15.84. Found: C, 49.48; H, 4.21; N, 15.92.

3-Carboxymethyl-2-thiooxo-1,2-dihydropyrido[2,3-*d*]pyrimidin-4(3*H*)-one (**17**).

To a stirred solution of glycine (375 mg) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1 *M*, 5 ml), **2** (1.04 g) was added and the mixture was heated at 50° for 5 hours, and at room temperature for 12 hours. The solvent was evaporated *in vacuo*, water (10 ml) was added to the residue and acidified with hydrochloric acid (18%) to *p*H 3. The precipitate was collected by filtration to give **17** (980 mg, 83%), mp 296-299° (from methanol); nmr (DMSO-d_6): δ 5.12 (s, CH_2COOH), 7.44 (dd, H_6), 8.40 (dd, H_5), 8.78 (dd, H_7), J_{H_5,H_6} = 7.8 Hz, J_{H_5,H_7} = 1.8 Hz, J_{H_6,H_7} = 4.9 Hz.

Anal. Calcd. for $C_9H_7N_3O_3S$: C, 45.57; H, 2.97; N, 17.71. Found: C, 45.25; H, 2.96; N, 17.45.

2-[(*N*-(1-Carboxyethyl)thioureido]-3-ethoxycarbonylpyridine (**18**).

To a stirred solution of L-alanine (445 mg) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1 *M*, 5 ml) a solution of **2** (1.04 g) was added and the mixture was heated under reflux for 4 hours. The solvent was evaporated *in vacuo*, water (10 ml) was added to the oily residue and acidified with hydrochloric acid (18%) to *p*H 3. The precipitate was collected by filtration to give **18** (1.10 g, 74%), mp 162-163° (from a mixture of methanol and water); ^{1}H nmr (deuteriochloroform): δ 1.40 (t, OCH_2Me), 1.65 (d, *Me*CH), 4.35 (q, OCH_2Me), 5.13 (m, MeC*H*NH), 6.90 (dd, H_5), 8.2 (m, H_4,H_6), 9.91 (br s) and 11.2 (br s) (NH, COOH), 11.85 (br d, N*H*CH), J_{MeCH} = 7.2 Hz, J_{MeCH_2} = 7.2 Hz.

Anal. Calcd. for $C_{12}H_{15}N_3O_4S$: C, 48.48; H, 5.05; N, 14.13. Found: C, 48.18; H, 5.08; N, 13.95.

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