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

Uroš Urleb, Branko Stanovnik* and Miha Tišler

Department of Chemistry, Edvard Kardelj University,
61000 Ljubljana, Yugoslavia

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2-Ethoxycarbonyl-3-isothiocyanatopyridine (**2**), prepared from 3-amino-2-ethoxycarbonylpyridine (**1**) by the thiophosgene method, was converted with nucleophiles into pyrido[3,2-*d*]pyrimidine derivatives **6-11** and **25-30** either directly, or through thiourethane **3**. Tricyclic systems **18** and **19** were obtained from **3**, and tricyclic systems **12-17** from pyrido[3,2-*d*]pyrimidine derivative **11**. Pyrrole reacted with **2** at C_2 to give **20**, and by further cyclization **21** and **22**.

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There are many methods known in the literature for the preparation of isothiocyanates [1]. However, heterocyclic isothiocyanates with an ester group at *ortho* position have not been described so far.

In this communication we report on the synthesis of 2-ethoxycarbonyl-3-isothiocyanatopyridine (**2**) from 3-amino-2-ethoxycarbonylpyridine (**1**) and thiophosgene in a mixture of water and dichloromethane as a two phase system, which allows an easy separation and isolation of isothiocyanate **2** from the reaction mixture. This compound, since it contains two reactive groups at *ortho* positions, is a versatile intermediate for the preparation of some bicyclic and polycyclic heterocyclic systems and their derivatives, especially pyrido[3,2-*d*]pyrimidines, which have been prepared previously by other methods [2-4].

The compound **2** did not react with alcohols at room temperature. However, at elevated temperatures and prolonged reaction time it gave in anhydrous ethanol the corresponding thiourethane **3**, and analogous compounds **4** and **5** were obtained with ethylene glycol and 1,3-propanediol, respectively. It is characteristic for all these urethane derivatives, that in the ^{1}H nmr spectra H_4 appears at the lowest field, at δ = 8.95-9.06 ppm (Table I), while in other pyridine derivatives, including **2**, H_6 appears at the lowest field [5]. Compound **3** with two reactive groups at *ortho* positions was converted into some pyrido[3,2-*d*]pyrimidine derivatives. It reacted with methylamine in anhydrous ethanol at room temperature to give 2-methylamino-3-methyl-derivative **6**, with benzylamine two products, 3-benzyl-2-ethoxy-derivative **7** and 3-benzyl-2-benzylamino-derivative **8**, and with hydroxylamine the corresponding 2-ethoxy-3-hydroxy-derivative **9** were formed by elimination of the SH and/or the ethoxy group. Similarly, compound **2** was transformed with hydrazine hydrate into pyrido[3,2-*d*]pyrimidine derivative **10**, while by heating the substitution of the mercapto group with the hydrazino group took place to give 2-hydrazino derivative **11** of the bicyclic system.

The same compound was obtained also by heating **10** with hydrazine hydrate. Compound **11** could be further cyclized into the tricyclic azolopyrido[3,2-*d*]pyrimidine derivatives. For example, by treatment of **11** with nitrous acid in molar ratio of 1:1 the amino derivative of a tricyclic system **12** was formed, while by treatment of **11** with nitrous acid in a molar ratio of 1:2, deamination of the amino group at position 4 was taking place to give **13**. The proof for this latter reaction is the signal in the ^{1}H nmr spectrum at δ = 5.87 ppm for the amino group in compound **12**, which is not present in the ^{1}H nmr spectrum of **13**. Both compouds, **12** and **13**, exist only in the tetrazolo form in DMSO-d_6 solution. When **11** was heated with triethyl orthoformate two isomeric triazolopyridopyrimidines **14** and **15** were formed, dependent on the cyclization which took place either to nitrogen at position 1 or at position 3. The structure determination of both systems is based on the ^{1}H nmr spectra. Namely, H_9 in **15** is shifted approximately for $\Delta\delta$ = 0.6 ppm to lower field in comparison to the H_9 in the isomeric **14**. This is further supported by the chemical shifts of H_3, since H_3 in *s*-triazolo[3,4-*b*] fused system (compound **15**) appears at lower field then H_2 in *s*-triazolo[1,5-*a*] fused system (compound **14**). On the other hand, in the reaction of **11** with triethyl orthoacetate only one product was formed, the structure of which is most probably **16**, using the same arguments as above, and not **17**.

Imidazopyridopyrimidines are little known systems, described only recently [6]. We present now another method for the preparation of these ring systems. Thiourethane **3**

Table I

^{1}H NMR Data for Ring Protons of Substituted Pyridines

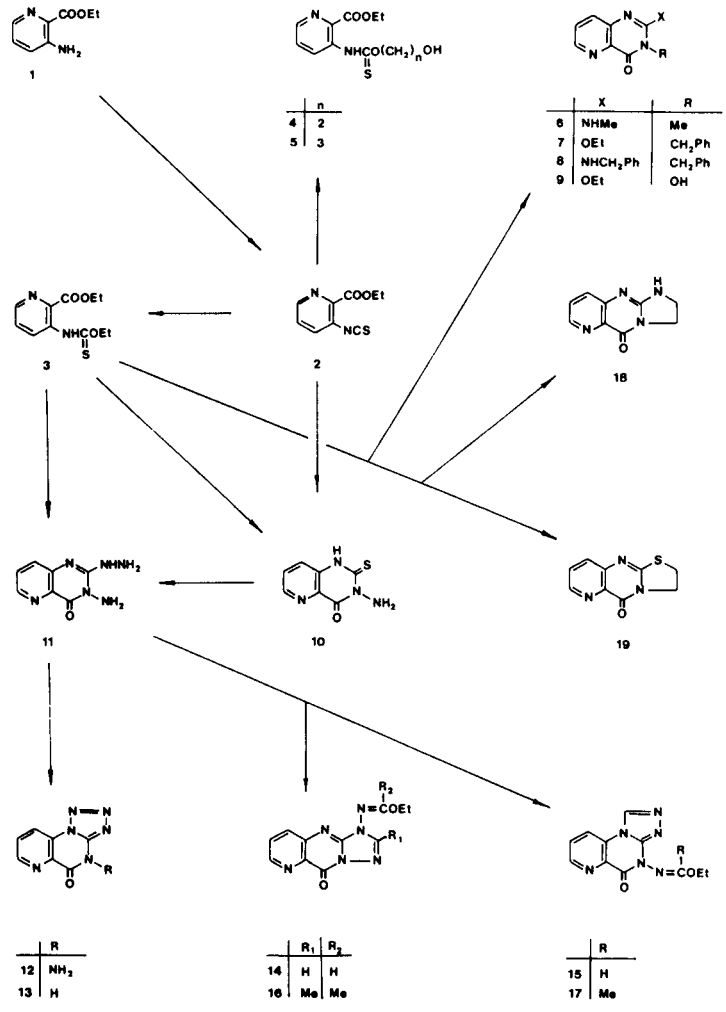
Proton	Compound, δ [ppm]				
	2	**3**	**4**	**5**	**6**
H_4	7.65	9.06	8.95	8.99	8.96
H_5	7.45	7.44	7.30	7.37	7.34
H_6	8.60	8.43	8.26	8.35	8.29

Table II

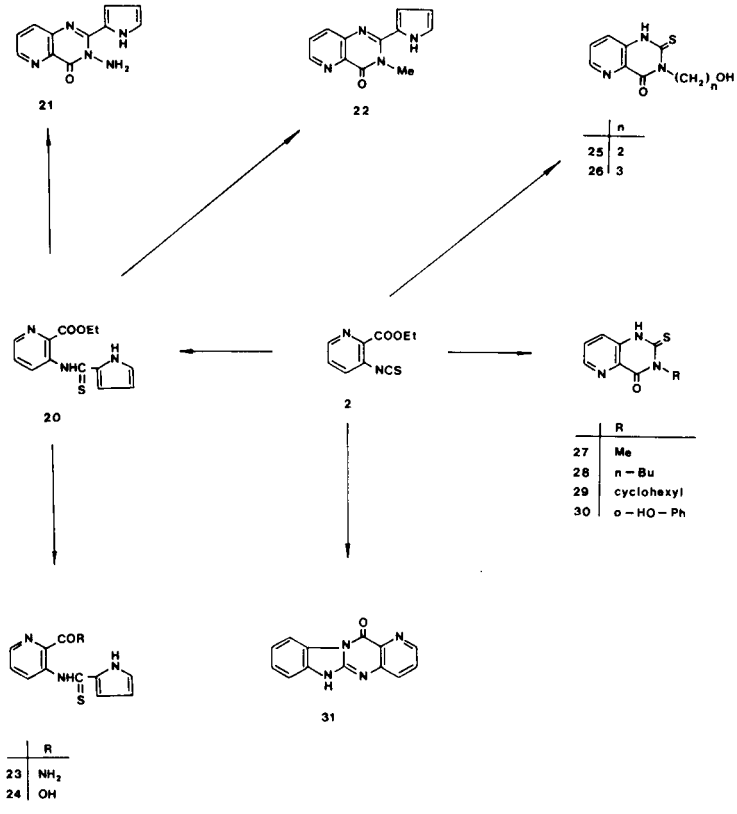
^{1}H NMR Data for Ring Protons of Pyridopyrimidine and Azolopyridopyrimidine Derivatives

Compound			δ [ppm]			
			H_6	H_7	H_8	H_9
7			8.59	7.62	7.80	-
8			8.32	7.4-7.7		-
9			8.54	7.57	7.80	-
10			8.31	7.39	7.60	-
11			8.30	7.45	7.62	-
12			-	8.88	7.90	8.65
13			-	8.89	7.93	8.64
14		H_2 9.19	-	8.75	7.78	8.08
15		H_1 9.54	-	8.88	7.99	8.68
17		-	-	8.59	7.63	7.95
18	2-CH_2, 3.66	3-CH_2, 4.05	-	8.25	7.4	
19	2-CH_2, 3.54	3-CH_2, 4.43	-	8.54	7.55	7.74

Scheme 1



Scheme 2



reacted with 1,3-diaminoethane to give 2,3-dihydro-derivative of a novel system imidazo[1,2-*a*]pyrido[3,2-*d*]pyrimidin-5(1*H*)-one **18**. In this case, the cyclization took place only to nitrogen at position 3 in the pyrimidine system. The structural evidence follows from the ^{1}H nmr spectrum, since H_9 appears close to H_8 and is not shifted downfield as in other systems fused to nitrogen at position 1. On the same argument is based the structure determination of thiazolo[3,2-*a*]pyrido[3,2-*d*]pyrimidine derivative **19** prepared from **3** and aminoethanethiol (Table II) (Scheme 1).

There are some reactions of isothiocyanates, such as phenylisothiocyanate and methyl *o*-isothiocyanatobenzoate, with pyrrole described in the literature [7,8], while the reactions of heterocyclic isothiocyanates with pyrrole are not known. Compound **2** reacted with pyrrole at C_2 to give **20**, the structure of which is supported by the ^{1}H nmr spectrum. When **20** was treated with hydrazine hydrate, cyclization occurred to give pyrido[3,2-*d*]pyrimidine derivative **21**, and similarly, with methylamine in anhydrous ethanol **22** was formed. On the other hand, when **20** was treated with ammonia in ethanol only ammonolysis of the ester group was observed to give **23**, and by heating of **20** in a mixture of concentrated hydrochloric acid and glacial acetic acid only hydrolysis of the ester group took place to give **24**.

In the reactions of **2** with other amino compounds such as aminoethanol, aminopropanol, methylamine, butylamine,cyclohexylamine and *o*-aminophenol, the corresponding compounds **25-30** were formed, respectively, while with *o*-phenylenediamine further cyclization produced new tetracyclic system **31** (Scheme 2).

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. The ^{1}H nmr spectra were obtained on a JEOL C 60 HL or 90 Q FT spectrometers with TMS the internal standard and elemental analyses for C, H, and N on a PERKIN-ELMER CHN Analyser 240 C.

3-Amino-2-ethoxycarbonylpyridine (**1**) was prepared according to the procedure described in the literature [9].

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

A suspension of **1** (1.302 g) in a mixture of water (10 ml) and hydrochloric acid (37%, 1.4 ml) was added to a suspension of calcium carbonate (1.6 g) in a mixture of water (20 ml) and dichloromethane (30 ml) during stirring. The mixture was colled to 0-5° and thiophosgene (980 mg) was added dropwise. The mixture was then stirred at room temperature (24 hours). The solid material was separated by filtration, and the organic layer, separated from aqueous layer, was washed successively with hydrochloric acid (5%, 30 ml), sodium hydrogen carbonate (5%, 30 ml) and water (50 ml). The organic layer was dried with anhydrous magnesium sulphate, solvent was evaporated *in vacuo* and the oily residue

was purified by column chromatography (silicagel, chloroform as solvent) to give **2** (1.14 g, 70%), mp 29-31°; ^{1}H nmr (deuteriochloroform): δ 1.48 (t, OCH_2Me), 4.49 (q, OCH_2Me), 7.45 (dd, 5-H), 7.65 (dd, 4-H), 8.60 (dd, 6-H), J_{CH_2Me} = 6.8 Hz, $J_{4-H,5-H}$ = 8.3 Hz, $J_{4-H,6-H}$ = 1.8 Hz, $J_{5-H,6-H}$ = 4.5 Hz.

Anal. Calcd. for $C_9H_8N_2O_2S$: C, 51.91: H, 3.87; N, 13.45. Found: C, 51.78; H, 3.96; N, 13.30.

3-Ethoxycarbonylamino-2-ethoxycarbonylpyridine (**3**).

A solution of **2** (100 mg) in anhydrous ethanol (5 ml) was heated under reflux (24 hours). The solvent was evaporated *in vacuo* to give **3** (84 mg, 82%), mp 70-71° (from ethanol); ^{1}H nmr (deuteriochloroform): δ: 1.44 (t) and 1.48 (t) ($OCOCH_2Me$ and $SCOCH_2Me$), 4.55 (q) and 4.65 (q) ($OCOCH_2Me$ and $SCOCH_2Me$), 7.44 (dd, 5-H), 8.43 (dd, 6-H), 9.06 (dd, 4-H), J_{CH_2Me} = 6.8 Hz, $J_{4-H,5-H}$ = 9.0 Hz, $J_{4-H,6-H}$ = 1.5 Hz, $J_{5-H,6-H}$ = 4.5 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02. Found: C, 51.70; H, 5.61; N, 10.98.

3-(2-Hydroxyethyloxythiocarbonylamino)-2-ethoxycarbonylpyridine (**4**).

To a solution of **2** (250 mg) in benzene (5 ml) ethylene glycol (80 mg) was added and the mixture was heated under reflux (8 hours). The precipitate, formed during the night at room temperature, was collected by filtration to give **4** (180 mg, 56%), mp 132-135° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.45 (t, OCH_2Me), 2.16 (br t, $HOCH_2CH_2$), 3.90 (m, $HOCH_2CH_2$), 4.40 (q, OCH_2Me), 4.61 (t, $HOCH_2CH_2$), 7.30 (dd, 5-H), 8.26 (dd, 6-H), 8.95 (dd, 4-H), 11.45 (br s, NH), J_{CH_2Me} 6,7 Hz, $J_{4-H,5-H}$ = 8.3 Hz, $J_{4-H,6-H}$ = 1.5 Hz, $J_{5-H,6-H}$ = 4.5 Hz.

Anal. Calcd. for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 48.85; H, 5.32; N, 10.19.

3-(3-Hydroxypropyloxythiocarbonylamino)-2-ethoxycarbonylpyridine (**5**).

To a solution of **2** (310 mg) in benzene (5 ml) 1,3-propandiol (120 mg) was added and the mixture was heated under reflux (4 hours). The solvent was evaporated *in vacuo* to give **5** (235 mg, 56%), mp 104-105° (from ethanol); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, OCH_2Me), 2.05 (m, $HOCH_2CH_2CH_2O$), 3.73 (t, $HOCH_2CH_2CH_2O$), 4.45 (q, OCH_2Me), 4.65 (t, $HOCH_2CH_2CH_2O$), 7.37 (dd, 5-H), 8.35 (dd, 6-H), 8.99 (dd, 4-H), 11.5 (br s, NH), J_{CH_2Me} = 6.7 Hz, $J_{CH_2CH_2}$ = 6.0 Hz, $J_{4-H,5-H}$ = 8.9 Hz, $J_{4-H,6-H}$ = 1.5 Hz, $J_{5-H,6-H}$ = 4.5 Hz.

Anal. Calcd. for $C_{12}H_{16}N_2O_4S$: C, 50.69; H, 5.67; N, 9.85. Found: C, 50.51; H, 5.74; N, 9.76.

3-Methyl-2-methylaminopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**6**).

A mixture of **3** (100 mg) and aqueous solution of methylamine (33%, 5 ml) in ethanol (5 ml) was stirred at room temperature for 8 days. The precipitate was collected by filtration to give **6** (25 mg, 33%), mp 257-259° (from DMF); ^{1}H nmr (DMSO-d_6): δ 2.88 (br s, $MeNH$), 3.36 (s, MeN), 7.10 (br s, NH), 7.40 (dd, H_7), 7.57 (dd, H_8), 8.30 (dd, H_6), J_{H_6,H_7} = 3.5 Hz, J_{H_6,H_8} = 1.8 Hz, J_{H_7,H_8} = 6.0 Hz.

Anal. Calcd. for $C_9H_{10}N_4O$: C, 56.83; N, 5.30; N, 29.46. Found: C, 57.12; H, 5.48; N, 29.56.

3-Benzyl-2-ethoxypyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**7**) and 3-Benzylaminopyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**8**).

To a solution of **3** (300 mg) in anhydrous ethanol (3 ml) benzylamine (330 mg) was added and the mixture was heated for 24 hours. The solvent was evaporated *in vacuo*, diethyl ether (5 ml) was added to the oily residue and the precipitate was collected by filtration to give a mixture of **7** and **8**. Separation by column chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck and chloroform/aceton, 9:1, as solvent) and evaporation of the solvent *in vacuo* gave **7** (70 mg, 21%), mp 139-141°, as the first fraction; nmr (DMSO-d_6): δ 1.30 (t, OCH_2Me), 4.43 (q, OCH_2Me), 5.16 (s, CH_2Ph), 7.62 (dd, H_7), 7.80 (dd, H_8), 8.59 (dd, H_6), J_{CH_2Me} = 6.7 Hz, J_{H_6,H_7} = 4.5 Hz, J_{H_6,H_8} = 1.8 Hz, J_{H_7,H_8} = 8.4 Hz.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.17; H, 5.51; N, 14.69.

The second fraction gave after evaporation of the solvent **8** (35 mg, 9%), mp 204-207°; ^{1}H nmr (DMSO-d_6): δ 4.55 (br d, $PhCH_2NH$), 5.34 (s, CH_2Ph), 7.10 (s, Ph) and 7.20 (s) (Ph), 7.40-7.70 (m, H_7,H_8), 8.32 (dd, H_6), J_{H_6,H_7} = 3.75 Hz, J_{H_6,H_8} = 1.5 Hz, J_{H_7,H_8} = 6.75 Hz.

Anal. Calcd. for $C_{21}H_{18}N_4O{\cdot}H_2O$: C, 71.78; H, 5.45; N, 15.94. Found: C, 71.97; H, 5.60; N, 15.07.

2-Ethoxy-3-hydroxypyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**9**).

A mixture of **3** (100 mg) and hydroxylamine (100 mg) in anhydrous ethanol (4 ml) was heated under reflux for 2 hours. The precipitate was, after cooling, collected by filtration to give **9** (75 mg, 92%), mp 221-223° (sublimed, 150°, 5 torr): ^{1}H nmr (DMSO-d_6): δ 1.38 (t, OCH_2Me), 4.46 (q, OCH_2Me), 7.57 (dd, H_7), 7.80 (dd, H_8), 8.54 (dd, H_6), J_{CH_2Me} = 6.8 Hz, J_{H_6,H_7} = 3.8 Hz, J_{H_6,H_8} = 1.5 Hz, J_{H_7,H_8} = 8.3 Hz.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: 52.25; H, 4.36; N, 19.99.

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

Method A.

To a solution of **2** (100 mg) in dichloromethane (3 ml) hydrazine hydrate (99%, 25 mg) was added and the mixture was stirred at room temperature for 2 hours. The precipitate was collected by filtration to give **10** (54 mg, 64%), mp 294-296° (from water); ^{1}H nmr (DMSO-d_6): δ 7.39 (dd, H_7), 7.60 (dd, H_8), 8.31 (dd, H_6), J_{H_6,H_7} = 4.5 Hz, J_{H_6,H_8} = 1.7 Hz, J_{H_7,H_8} = 6.8 Hz.

Anal. Calcd. for $C_7H_6N_4OS$: C, 43.29; H, 3.11; N, 28.85. Found: C, 43.15; H, 3.18; N, 28.82.

Method B.

The same compound was prepared from **3** (90 mg) in ethanol (4 ml) and hydrazine hydrate (99%, 20 mg) by stirring at room temperature for 48 hours in 79% yield. The compound is identical in every respect with the compound obtained above.

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

Method A.

A solution of **3** (100 mg) and hydrazine hydrate (99%, 1 ml) in ethanol (3 ml) was heated under reflux for 2 hours. The precipitate was, after cooling, collected by filtration to give **11** (72 mg, 95%), mp 281-283° (from water); ^{1}H nmr (DMSO-d_6): δ 7.45 (dd, H_7), 7.62 (dd, H_8), 8.30 (dd, H_6), J_{H_6,H_7} = 4.2 Hz, J_{H_6,H_8} = 1.5 Hz, J_{H_7,H_8} = 9.0 Hz.

Anal. Calcd. for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.83; H, 4.33; N, 43.52.

Method B.

To the suspension of **10** (100 mg) in ethanol (4 ml) hydrazine hydrate (99%, 1 ml) was added and the mixture was heated under reflux for 5 hours. The precipitate was, after cooling, collected by filtration to give **11** (73 mg, 74%), mp 281-283° (from water). The compound is identical in every respect with the compound obtained by method A.

4-Aminopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyrimidin-5(4*H*)-one (**12**).

To a stirred suspension of **11** (100 mg) in a mixture of acetic acid (2 ml) and water (1 ml) a solution of sodium nitrite (35 mg) in water (2 ml) was added dropwise at 0°. The mixture was left in the refrigerator for 12 hours and the precipitate was collected by filtration to give **12** (27 mg, 26%), mp 233-236° (from DMF); ^{1}H nmr (DMSO-d_6): δ 5.87 (s, NH_2), 7.90 (dd, H_8), 8.65 (dd, H_9), 8.88 (dd, H_7), J_{H_7,H_8} = 4.5 Hz, J_{H_7,H_9} = 1.5 Hz, J_{H_8,H_9} = 8.9 Hz.

Anal. Calcd. for $C_7H_5N_7O$: C, 41.38; H, 2.48; N, 48.26. Found: C, 41.62; H, 2.63; N, 47.98.

Pyrido[3,2-*d*]tetrazolo[5,1-*b*]pyrimidin-5(4H)-one (**13**).

To a stirred suspension of **11** (100 mg) in a mixture of acetic acid (2 ml) and water (1 ml) a solution of sodium nitrite (70 mg) in water (3 ml) was added dropwise at 0°, and the mixture was stirred for another 15 minutes. The precipitate was collected by filtration to give **13** (62 mg, 98%), mp >310° (from DMF); ^{1}H nmr (DMSO-d_6): δ 7.93 (dd, H_8), 8.64 (dd, H_9), 8.89 (dd, H_7), J_{H_7,H_8} = 4.4 Hz, J_{H_7,H_9} = 1.5 Hz, J_{H_8,H_9} = 8.9 Hz.

Anal. Calcd. for $C_7H_4N_6O$: C, 44.69; H, 2.14; N, 44.67. Found: C, 44.68; H, 2.29; N, 44.72.

1-Ethoxymethyleneaminopyrido[3,2-*d*]-*s*-triazolo[1,5-*a*]pyrimidin-5(1*H*)-one (**14**) and 4-Ethoxymethyleneaminopyrido[3,2-*d*]-*s*-triazolo[3,4-*b*]pyrimidin-5(4*H*)-one (**15**).

A mixture of **11** (100 mg) and triethyl orthoformate (6 ml) was heated under reflux for 8 hours. The precipitate was, after cooling, collected by filtration, dissolved in ethanol (3 ml) and separated by column chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck, and chloroform/methanol, 9:1, as solvent) into two fractions. The first fraction gave, after evaporation of solvent *in vacuo*, **14** (31 mg, 23%), mp 170-173°; ms: M^+ = 258; ^{1}H nmr (DMSO-d_6): δ 1.44 (t, OCH_2Me), 4.22 (q, OCH_2Me), 7.78 (dd, H_8), 8.08 (dd, H_9), 8.75 (dd, H_7), 9.19 (s, H_2), J_{CH_2Me} = 8.0 Hz, J_{H_7,H_8} = 4.3 Hz, J_{H_7,H_9} = 1.7 Hz, J_{H_8,H_9} = 8.6 Hz.

Anal. Calcd. for $C_{11}H_{10}N_6O_2$: C, 51.16; H, 3.90; N, 32.54. Found: C, 50.95; H, 3.91; N, 32.91.

The second fraction gave, after evaporation of solvent *in vacuo*, **15** (19 mg, 14%), mp 215-217°; ms: M^+ = 258: ^{1}H nmr (DMSO-d_6): δ 1.43 (t, OCH_2Me), 4.49 (q, OCH_2Me), 7.99 (dd, H_8), 8.68 (dd, H_9), 8.88 (dd, H_7), 9.54 (s, H_1), J_{CH_2Me} = 7.1 Hz, J_{H_7,H_8} = 4.3 Hz, J_{H_7,H_9} = 1.7 Hz, J_{H_8,H_9} = 8.6 Hz.

Anal. Calcd. for $C_{11}H_{10}N_6O_2$: C, 51.16; H, 3.90; N, 32.54. Found: C, 50.93; H, 3.73; N, 32.19.

1-Ethoxyethylideneamino-2-methylpyrido[3,2-*d*]-*s*-triazolo[1,5-*a*]-pyridin-5(1*H*)-one (**16**).

A mixture of **11** (100 mg) and triethyl orthoacetate (5 ml) was heated under reflux for 24 hours. The precipitate was, after cooling, collected by filtration and purified by chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck, and chloroform/methanol 9:1, as solvent) to give, after evaporation of the solvent *in vacuo*, **16** (75 mg, 50%), mp 216-217° (from toluene); ^{1}H nmr (DMSO-d_6): δ 1.36 (t, OCH_2Me), 2.06 (s, MeC), 2.40 (s, 1-Me), 4.28 (q, OCH_2Me), 7.60 (dd, H_8), 7.95 (dd, H_9), 8.45 (dd, H_7), J_{CH_2Me} = 6.7 Hz, J_{H_7,H_8} = 4.4 Hz, J_{H_7,H_9} = 1.5 Hz, J_{H_8,H_9} = 7.7 Hz.

Anal. Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.93; N, 29.35. Found: C, 54.69; H, 5.01; N, 29.05.

2,3-Dihydropyrido[3,2-*d*]imidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**18**).

To a solution of **3** (100 mg) in benzene (4 ml) 1,2-diaminoethane (38 mg) was added and the mixture was heated under reflux for 6 hours. The precipitate was, after cooling, collected by filtration to give **18** (65 mg, 88%), mp >310° (from water); ^{1}H nmr (DMSO-d_6): 150° δ 3.66 (t, NCH_2CH_2), 4.05 (t, NCH_2CH_2), 7.40 (m, H_8, H_9), 8.25 (dd, H_7), 9.05 (br s, NH), J_{H_7,H_8} = 7.5 Hz, J_{H_7,H_9} = 1.5 Hz, J_{H_8,H_9} = 6.0 Hz.

Anal. Calcd. for $C_9H_8N_4O$: C, 57.44; H, 2.29; N, 29.77. Found: C, 57.40; H, 4.37; N, 29.41.

2,3-Dihydrothiazolo[3,2-*a*]pyrido[3,2-*b*]pyrimidin-5-one (**19**).

To a suspension of **3** (150 mg) in anhydrous pyridine (5 ml) aminoethanethiol hydrochloride (97 mg) was added and the mixture was heated under reflux for 24 hours. The solvent was evaporated *in vacuo*. To the oily residue aqueous solution of sodium hydroxide (10%, 3 ml) and ethyl ether (2 ml) were added and the precipitate was collected by filtration to give **19** (25 mg, 21%), mp 210-212° (from water); ms: M^+ = 205; ^{1}H nmr (DMSO-d_6): δ 3.54 (t, NCH_2CH_2S), 4.43 (t, NCH_2CH_2S), 7.55 (dd, H_8), 7.74 (dd, H_9), 8.54 (dd, H_7), J_{H_7,H_8} = 4.2 Hz, J_{H_7,H_9} = 1.65 Hz, J_{H_8,H_9} = 7.7 Hz, $J_{CH_2CH_2}$ = 7.5 Hz.

Anal. Calcd. for $C_9H_7N_3OS$: C, 52.67; H, 3.44; N, 20.47. Found: C, 52.44; H, 3.64; N, 20.56.

3-[(2-Pyrrolyl)thiocarbonylamino]-2-ethoxypyridine (**20**).

A mixture of **2** (100 mg) and pyrrole (55 mg) was heated at 100° for 10 hours. The crude product was extracted with boiling petroleum ether (4 times, 5 ml each time), and finally with hot chloroform (10 ml). The combined extracts were evaporated *in vacuo* and purified by column chromatography (Kieselgel 60, 0.40-0.063 mm, E. Merck, and chloroform/acetone, 30:1, as solvent). The first fraction gave, after evaporation of solvents, **20** (79 mg, 60%), mp 114-116°; ^{1}H nmr (deuteriochloroform): δ 1.5 (t, OCH_2Me), 4.53 (q, OCH_2Me), 6.35 (m, H_4), 6.97 (m, H_3, and H_5), 7.45 (dd, H_5), 8.45 (dd, H_6), 9.92 (dd, H_4), 12.65 (br s, NH), J_{CH_2Me} = 6.75 Hz, J_{H_4,H_5} = 8.7 Hz, J_{H_4,H_6} = 1.5 Hz, J_{H_5,H_6} = 4.8 Hz.

Anal. Calcd. for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26. Found: C, 56.32; H, 4.74; N, 15.15.

3-Amino-2-(2-pyrrolyl)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**21**).

A mixture of **20** (30 mg) and hydrazine hydrate (99%, 2 ml) was heated at 120° for three hours. The precipitate was, after cooling, collected by filtration to give **21** (21 mg, 85%), mp 255-252° (from methanol); ^{1}H nmr (DMSO-d_6): δ 5.95 (br s, NH_2), 6.20 (m, H_4), 7.0 (m, H_5), 7.40 (m, H_3), 7.67 (dd, H_7), 7.95 (dd, H_8), 8.64 (dd, H_6), J_{H_6,H_7} = 4.4 Hz, J_{H_6,H_8} = 2.3 Hz, J_{H_7,H_8} = 9.0 Hz.

Anal. Calcd. for $C_{11}H_9N_5O$: C, 58.15; H, 3.99; N, 30.82. Found: C, 57.92; H, 3.99; N, 30.96.

3-Methyl-2-(2-pyrrolyl)pyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**22**).

A mixture of **20** (200 mg) and methylamine (33% aqueous solution, 5 ml) in ethanol (5 ml) was stirred at room temperature for 3 days. The precipitate was collected by filtration to give **22** (43 mg, 26%), mp 182-184° (from methanol); ms: M^+ = 226; ^{1}H nmr

(DMSO-d_6): δ 3.73 (s, 3-Me), 6.20 (m, $H_{4'}$), 6.86 (m, $H_{5'}$), 7.0 (m, $H_{3'}$), 7.63 (dd, H_7), 7.90 (dd, H_8), 8.60 (dd, H_6), J_{H_6,H_7} = 4.2 Hz, J_{H_6,H_8} = 1.5 Hz, J_{H_7,H_8} = 7.8 Hz.

Anal. Calcd. for $C_{12}H_{10}N_4O \cdot 0.5\ H_2O$: C, 61.27; H, 4.71; N, 23.82. Found: C, 61.11; H, 4.70; N, 23.93.

3-[(2-Pyrrolyl)thiocarbonylamino]-2-carboxamidopyridine (**23**).

Through stirred suspension of **20** (100 mg) in ethanol (15 ml) ammonia was bubbled at room temperature for 2 hours. The volatile components were evaporated *in vacuo* to dryness to give **23** (56 mg, 63%), mp 178-189° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 6.31 (m, $H_{4'}$), 6.97 (m, $H_{5'}$), 7.13 (m, $H_{3'}$), 7.66 (dd, H_5), 8.43 (dd, H_6), 8.26 (br s, $CONH_2$), 8.78 (br s, $CONH_2$), 9.93 (dd, H_4), J_{H_4,H_5} = 8.5 Hz, J_{H_4,H_6} = 1.8 Hz, J_{H_5,H_6} = 4.4 Hz.

Anal. Calcd. for $C_{11}H_{10}N_4OS$: C, 53.66; H, 4.09; N, 22.76. Found: C, 53.52; H, 4.23; N, 22.81.

3-[(2-Pyrrolyl)thiocarbonylamino]-2-carboxypyridine (**24**).

A solution of **20** (100 mg) in a mixture of glacial acetic acid (2 ml) and hydrochloric acid (37% aqueous solution, 0.5 ml) was heated at 100° for 20 minutes. The precipitate was, after cooling, collected by filtration to give **24** (52 mg, 63%), mp 215-217° (from ethanol); ^{1}H nmr (DMSO-d_6): δ 6.2 (m, $H_{4'}$), 7.0 (m, $H_{3'}$, $H_{5'}$), 8.43 (dd, H_6), 9.25 (dd, H_4), 12.5 (br s, NH), J_{H_4,H_5} = 8.3 Hz, J_{H_4,H_6} = 1.5 Hz, J_{H_5,H_6} = 4.5 Hz.

Anal. Calcd. for $C_{11}H_9N_3O_2S$: C, 53.43; H, 3.67; N, 16.99. Found: C, 53.16; H, 3.72; N, 16.76.

3-(2-Hydroxyethyl)-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**25**).

A mixture of **2** (300 mg) and aminoethanol (95 mg) in tetrahydrofuran (5 ml) was stirred at room temperature for 24 hours. The precipitate was collected by filtration to give **25** (275 mg, 86%), mp 286-288° (from DMF); ^{1}H nmr (DMSO-d_6): δ 3.76 (t, $HOCH_2CH_2N$), 4.65 (t, $HOCH_2CH_2N$), 7.87 (m, H_7, H_8), 8.75 (m, H_6), $J_{CH_2CH_2}$ = 7.0 Hz.

Anal. Calcd. for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.80; H, 4.20; N, 18.72.

3-(3-Hydroxypropyl)-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**26**).

A mixture of **2** (400 mg) and 3-aminopropanol (145 mg) in tetrahydrofuran (6 ml) was stirred at room temperature for 24 hours. The precipitate was collected by filtration to give **26** (384 mg, 84%), mp 253-257° (from DMF); ^{1}H nmr (DMSO-d_6): δ 1.84 (m, $HOCH_2CH_2CH_2N$), 3.45 (t, $HOCH_2CH_2CH_2N$), 4.40 (t, $HOCH_2CH_2CH_2N$), 7.60 (m, H_7, H_8), 8.43 (m, H_6), $J_{CH_2CH_2}$ = 6.8 Hz.

Anal. Calcd. for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.81; H, 4.70; N, 17.77.

3-Methyl-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**27**).

A mixture of **2** (300 mg) and methylamine (33% solution in anhydrous ethanol, (5 ml) was stirred at room temperature for 1 hour. The precipitate was collected by filtration to give **27** (227 mg, 82%), mp >300° (from DMF); ^{1}H nmr (DMSO-d_6): δ 3.72 (s, MeN), 7.53 (dd, H_7), 7.68 (dd, H_8), 8.44 (dd, H_6), J_{H_6,H_7} = 3.9 Hz, J_{H_6,H_8} = 1.7 Hz, J_{H_7,H_8} = 8.6 Hz.

Anal. Calcd. for $C_8H_7N_3OS$: C, 49.74; H, 3.65; N, 21.76. Found: C, 49.99; H, 3.41; N, 21.74.

3-Butyl-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**28**).

A mixture of **2** (300 mg) and *n*-butylamine (0.2 ml) in dichloromethane (5 ml) was stirred at room temperature for 15 minutes. The precipitate was collected by filtration and washed with methanol (5 ml) to give **28** (211 mg, 62%), mp >300° (from a mixture on methanol and DMF); ^{1}H nmr (DMSO-d_6): δ 1.0 (t, $MeCH_2CH_2CH_2N$), 1.56 (m, $MeCH_2CH_2CH_2N$), 4.48 (t, $MeCH_2CH_2CH_2N$), 7.85 (m, H_7, H_8), 8.65 (m, H_6), 13.07 (br s, NH), $J_{CH_2CH_2}$ = 6.0 Hz.

Anal. Calcd. for $C_{11}H_{13}N_3OS$: C, 56.15; H, 5.57; N, 17.86. Found: C, 56.27; H, 5.50; N, 18.12.

3-Cyclohexyl-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**29**).

A mixture of **2** (200 mg) and cyclohexylamine (100 mg) in dichloromethane (5 ml) was stirred at room temperature for 2 hours. The precipitate was collected by filtration to give **29** (161 mg, 64%), mp 299-302° (from acetone); ^{1}H nmr (DMSO-d_6): δ 0.95-2.0 (m, cyclohexyl), 7.34 (m, H_7, H_8), 8.15 (m, H_6).

Anal. Calcd. for $C_{13}H_{15}N_3OS$: C, 59.75; H, 5.79; N, 16.08. Found: C, 60.03; H, 6.14; N, 15.95.

3-(2-Hydroxyphenyl)-2-thiooxo-1,2-dihydropyrido[3,2-*d*]pyrimidin-4(3*H*)-one (**30**).

A mixture of **2** (300 mg) and *o*-aminophenol (158 mg) in tetrahydrofuran (5 ml) was heated under reflux for 4 hours. The precipitate was, after cooling, collected by filtration, and washed with methanol to give **30** (264 mg, 67%), mp 250-252°; ^{1}H nmr (DMSO-d_6): δ 6.55-7.25 (m, *o*-HO-Ph), 7.60 (m, H_7, H_8), 8.40 (dd, H_6), 9.30 (br s, HO).

Anal. Calcd. for $C_{13}H_9N_3O_2S$: C, 57.55; H, 3.34; N, 15.49. Found: C, 57.57; H, 3.35; N, 15.33.

Pyrido[5,6:2',3']pyrimido[1,2-*a*]benzimidazol-12(6*H*)-one (**31**).

A mixture of **2** (208 mg) and *o*-phenylenediamine (125 mg) in chloroform (5 ml) was heated under reflux for 5 hours. The precipitate was, after cooling, collected by filtration to give **31** (145 mg, 61%), mp >310° (from DMF); ^{1}H nmr (DMSO-d_6): δ 6.4-7.3 (m, H_7, H_8, H_9, H_{10}, NH), 7.6-8.1 (m, H_3, H_4), 8.68 (dd, H_2).

Anal. Calcd. for $C_{13}H_8N_4O \cdot H_2O$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.40; H, 3.85; N, 21.72.

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