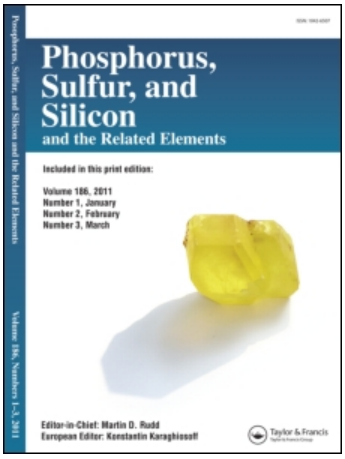

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Synthesis of 3-Substituted Pyrido[4',3':4,5]thieno[2,3-d]pyrimidines and Related Fused Thiazolo Derivatives

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SYNTHESIS OF 3-SUBSTITUTED PYRIDO[4′,3′:4,5]THIENO[2,3-D]PYRIMIDINES AND RELATED FUSED THIAZOLO DERIVATIVES

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*New ethyl 3-(substituted)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine-7-carboxylates (**3a**,**b**), (**6**), (**11–13**), ethyl 3-methyl-5-oxo-2,3,6,9-tetrahydro 5*H*-pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7H)-carboxylate (**4**), and ethyl 2-methyl-5-oxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno-[2,3-d][1,3]thiazolo[3,2-a]-pyrimidine-8(7H)-carboxylate (**8**) have been synthesized from diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno-[2,3-c]pyridine-3,6-dicarboxylate 1. The structure of these compounds as well as their intermediates have been established by their spectral data.*

Keywords: Pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidines; pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidines; synthesis; thieno[2,3-c]-pyridines

Compounds containing a fused pyrimidine ring represent a broad class of compounds which have received considerable attention over the past years due to their wide range of biological activity. As an example, pyridothienopyrimidines long have been used as antiinflammatory,[1–3] antipyretic,[4,5] analgesic,[6] and antianaphylactic[7,8] activity. On the other hand, thiazoles represent a very interesting class of compounds due to their wide applications in pharmaceutical, phytosanitary, analytical, and industrial aspects, such as fungicides, anthelmintics, and herbicides.[9] Because of these findings, our interest was focused on investigating efficient and convenient routes to construct the titled novel ring systems. In continuation of our interest in the synthesis of pharmacologically interesting new heterocyclic systems containing the thienopyrimidine moiety.[10–16] We have succeeded in the synthesis of new derivatives of pyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine

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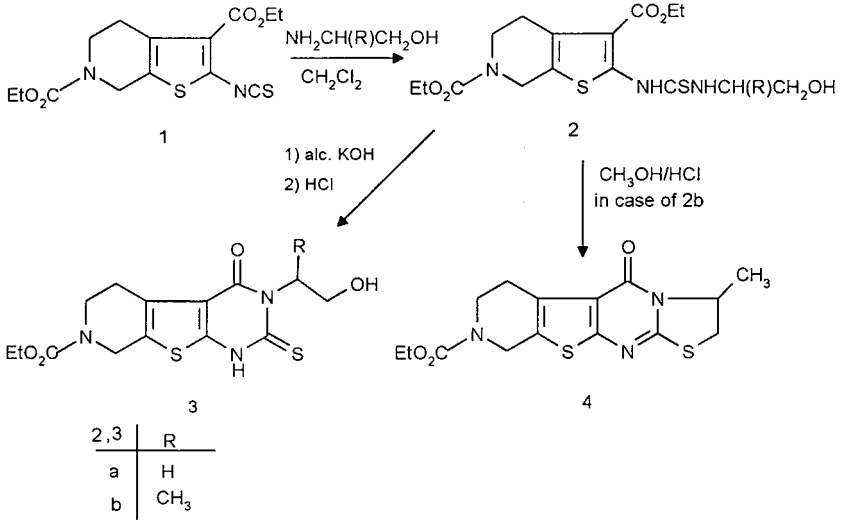
and pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine with expected potential biological activity.

In the syntheses presented in this paper, the conveniently available diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1**[11] was employed as the starting material. Reaction of compound **1** with aminoalcohols under mild reaction conditions provided the corresponding thioureido derivatives **2a**,**b**. Compound **2b** could be cyclized into the corresponding ethyl 3-methyl-5-oxo-2,3, 6,9-tetrahydro-5*H*-pyrido[4′,3′: 4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8 (7H)-carboxylate (**4**) by heating in methanolic hydrogen chloride at reflux temperature in good yield. During this reaction course no intermediate pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine derivative was isolated, although in a separate reaction, pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine derivatives **3a**,**b** were synthesized by heating corresponding thiourea derivatives **2a**,**b** in ethanolic potassium hydroxide solution. Structures **4** and **3a,b** were confirmed by the results of elemental analysis and spectral data (Scheme 1 and see Experimental).



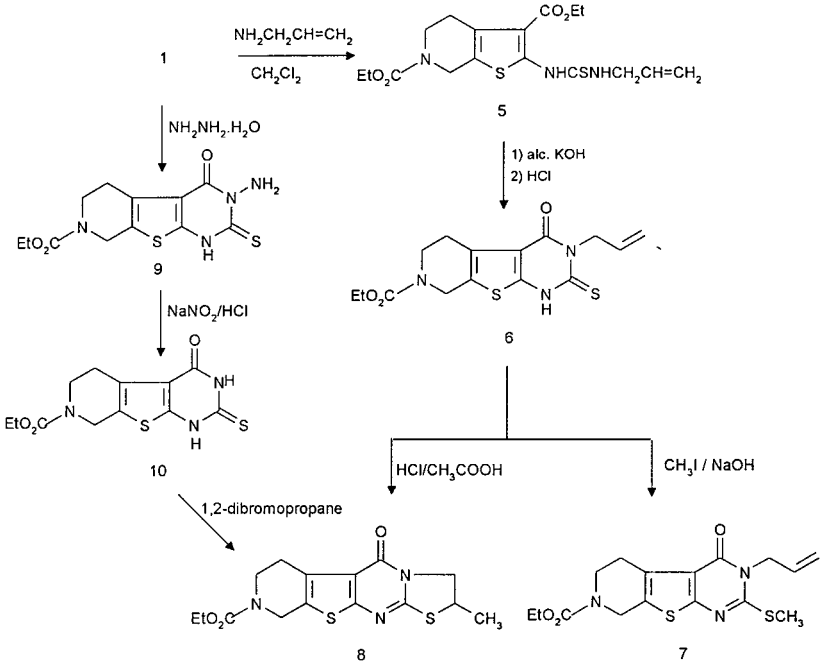
SCHEME 1

For the synthesis of ethyl 2-methyl-5-oxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7H)carboxylate (**8**), compound **1** was reacted with allylamine to give ethyl 2-{[(2-propenyl)aminothioxomethyl]amino}-4,5,6,7-tetrahydrothieno-[2,3-c]pyridine-3,6-dicarboxylate (**5**), which could be cyclized into ethyl 3-(2-propenyl)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido-[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (**6**) through heating

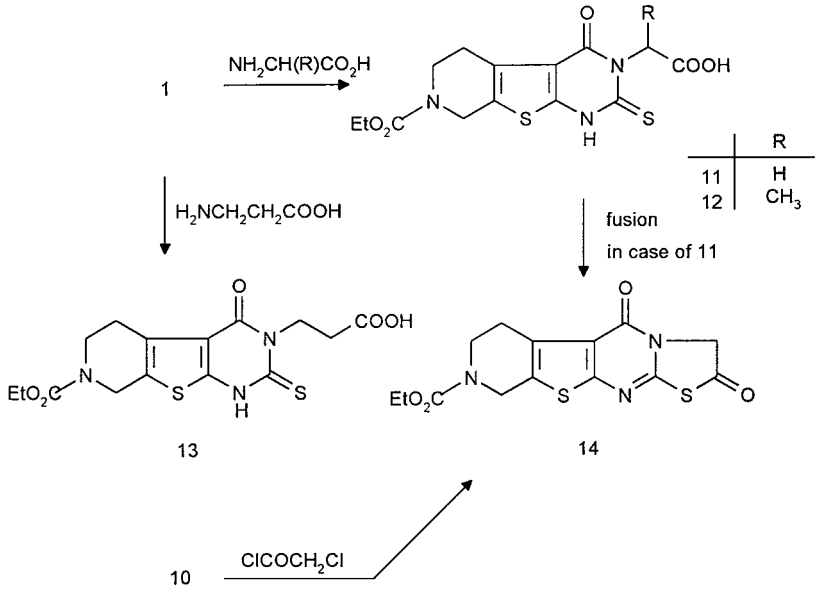
under reflux in potassium hydroxide solution. The structure of **6** was substantiated by elemental analysis and spectroscopic data. Thus, IR spectrum revealed absorption band at $\nu = 3180$, 1710, and 1680 cm^{-1} due to the NH, CO ester, and CO of the pyrimidine ring respectively. Moreover, the ^1H NMR spectrum gave strong evidence for the formation of **6**, which revealed the presence of signals at $\delta = 4.90$–5.12 assignable to two allylic proton—CH_2—CH=CH_2. It also gave two multiplets at δ 5.80–6.10 (1H) and at δ 5.18–5.30 (2H), the former assigned to one vinylic protons CH=CH_2 and —CH=C**H**$_2$. A singlet at δ 13.7 attributable to pyrimidine NH. Other analytical and spectroscopic data are given in the experimental section. Treatment of **6** with methyl iodide under basic conditions afforded the *S*-methylated compound (**7**) in excellent yield. The target product (**8**) was prepared in 68% yield by ring closure of **6** in a mixture of hydrochloric acid and acetic acid. Compound **8** was alternatively obtained from isothiocyanate **1** by initial conversion to ethyl 3-amino-4-oxo-2-thioxo-1,3,4,5,6,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(2*H*)-carboxylate (**9**),[16] followed by deamination with nitrous acid to yield ethyl 4-Oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (**10**). Compound **10** proved to be a key intermediate for subsequent conversion leading to (**8**) when was allowed to react with 1,2-dibromopropane (Scheme 2).

Our interest in developing synthetic approches with a view to synthesize new derivatives of intersting heterocyclic pyridothienopyrimidine ring system led us to investigate the reaction of isothiocyanate **1** with amino acid derivatives in which pyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine derivatives with the nitrogen of the amino acid component being incorporated into the fused pyrimidine ring at position **3**. When isothiocyanate **1** was reacted with glycine, L-alanine, and β-alanine in a mixture of dioxane and water in slightly alkaline media (pH = 8–9) under mild conditions, it gave ethyl 3-carboxymethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]-thieno[2,3-d]pyrimidine7-carboxylate (**11**), ethyl 3-[(*S*)-1-carboxyethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7carboxylate (**12**), and ethyl 3-(2-carboxyethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido-[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (**13**), respectively, with the amino acid residue attached to nitrogen at position **3** in pyrimidine part of the tricyclic system. The structures of **11–13** were established on the basis of their elemental and spectral data (Scheme 3 and see Experimental).

Ethyl 2,5-dioxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-d]-[1,3]thiazolo-[3,2-a]pyrimidine-8 (7*H*)-carboxylate (**14**) could be obtained either by fusion of compound **11** over its melting point



SCHEME 2



SCHEME 3

or by the reaction of compound **10** with chloroacetyl chloride in DMF.

EXPERIMENTAL

All m.p.s were recorded on a GallenKamp apparatus and are uncorrected. Microanalyses were performed at the Microanalytical Data Unit, Cairo University. ^{13}C and ^{1}H NMR spectra were measured in deuterated dimethyl sulfoxide on a Bruker AC 300 (^{1}H:300.13 MHz, ^{13}C:75.5 Mhz) spectrometer using TMS as an internal standered; chemical shifts are expressed as δ-values (ppm). IR-spectra were recorded on a Shimadzu 470 spectrophotometer in KBr pellets.

Diethyl 2-({[(2-Hydroxyethyl)amino]carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (2a)

To a stirred solution of diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate 1 (0.34 g, 0.001 mmol) in 8 ml dichloromethane, 2-amino-ethanol (0.07 g, 0.0011 mmol) was added, and stirred at room temperature for 20 min. After evaporation of the solvent at reduced pressure the solid product was collected and crystallized from ethanol. Yield 0.28 g (70%) of compound **2a** as colorless crystals, m.p. 158–160°C; (found: C, 47.65; H, 5.83; N, 10.59; S, 15.87. $C_{16}H_{23}N_3O_5S_2$ (401.51) requires C, 47.86; **H**, 5.77; N, 10.46; S, 15.97%); ν_{max}/cm^{-1}:3500 (OH), 3200 (NH), 2990 (aliph. CH), 1720, 1690 (2 CO ester); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 1.30 (t, 3H, $COOCH_2CH_3$), 2.80 (t, 2H, H-4), 3.60 (t, 2H, H-5), 3.70 (q, 2H, $-NCH_2$), 3.90 (t, 2H, $-CH_2OH$), 4.10 (q, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-7), 4.80–4.90(t, 1H, CH_2OH), 9.60 (s, 1H, NH), 11.40 (broad s, 1H, NH); δ_c (DMSO-d_6): 14.11 (q, $COOCH_2CH_3$), 14.41 (q, $COOCH_2CH_3$), 25.87 (t, C-4), 41.04 (t, C-5), 42.57 (t, C-7), 46.94 (t, $NHCH_2$), 58.56 (t, CH_2OH), 60.26 (t, $COOCH_2CH_3$), 60.86 (t, $COOCH_2CH_3$), 110.02 (s, C-3), 121.30 (s, C-7a), 129.98 (s, C-3a), 154.78 (s, CO ester), 165.65 (s, CO ester), 175.12 (s, C-2), 177.42 (s, CS).

Diethyl 2-({[(2-Hydroxy-1-methylethyl)amino]-carbothioyl}amino)-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine-3,6-dicarboxylate (2b)

This compound was obtained from diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1** (0.34 g,

0.001 mmol), 2-aminopropanol (0.08 g, 0011 mmol) at room temperature for 30 min. After evaporation of the solvent at reduced pressure the solid product was collected and crystallized from ethanol. Yield 0.37 g (89.1%) of compound **2b** as pale yellow crystals, m.p. 166–168 °C; (found: C, 49.32; H, 6.18; N, 10.30; S, 15.29. $C_{17}H_{25}N_3O_5S_2$ (415.54) requires C, 49.13; H, 6.06; N, 10.11; S, 15.43%); ν_{max}/cm^{-1}: 3500 (OH), 3220 (NH), 2980 (CH aliph.), 1710, 1690 (2 CO ester); δ_H (DMSO-d_6): 1.10 (d, 3H, C*H*$_3$CH-), 1.20 (t, 3H, COOCH$_2$*CH*$_3$), 1.35 (t, 3H, COOCH$_2$*CH*$_3$), 2.80 (t, 2H, H-4), 3.40–3.55 (m, 2H, –*CH*$_2$OH), 3.65 (t, 2H, H-5), 4.10 (q, 2H, COO*CH*$_2$CH$_3$), 4.20–4.35 (m, 3H, COO*CH*$_2$CH$_3$, NH*CH*(CH$_3$)CH$_2$OH), 4.40 (s, 2H, H-7), 4.70–4.85 (t, 1H, –CH$_2$*OH*), 9.40–9.50 (broad s, 1H, NH), 11.40 (s, 1H, NH); δ_c (DMSO-d_6): 14.11 (q, COOCH$_2$CH$_3$), 14.43 (q, COOCH$_2$CH$_3$), 16.19 (q, CH$_3$), 25.79 (t, C-4), 40.69 (t, C-5), 42.10 (t, C-7), 51.89 (d, CH), 60.24 (t, COOCH$_2$CH$_3$), 60.85 (t, COOCH$_2$CH$_3$), 63.32 (t, CH$_2$OH), 109.91 (s, C-3), 121.29 (s, C-7a), 128.33 (s, C-3a), 154.54 (s, CO ester), 165.25 (s, CO ester), 176.49 (s, C-2), 179.33 (s, CS).

Ethyl 3-(2-Hydroxyethyl)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (3a)

Compound **2a** (0.4 g, 0.001 mmol) was added to a solution of potassium hydroxide (0.06 g, 0.0011 mmol) in absolute ethanol (10 ml), and the mixture was refluxed with stirring for 15 min. The potassium salt of compound **3a** was collected by filtration then dissolved in water and acidified (to pH = 6.6) with hydrochloric acid, the product was collected by filtration, washed with water, dried, and recrystallized from ethanol. Yield 0.27 g (77.1%) of compound **3a** as colorless crystals, m.p. 177–179°C; (found: C, 47.18; H, 4.89; N, 11.60; S, 18.26. $C_{14}H_{17}N_3O_4S_2$ (355.44) requires C, 47.31; H, 4.81; N, 11.82; S, 18.04%); ν_{max}/cm^{-1}: 3550 (OH), 3180 (NH), 2800 (aliph. CH), 1720 (CO ester), 1680 (CO pyrimidine ring); δ_H (DMSO-d_6): 1.20 (t, 3H, COOCH$_2$*CH*$_3$), 2.90 (t, 2H, H-5), 3.60–3.80 (m, 4H, H-6, NCH$_2$*CH*$_2$OH), 4.10 (q, 2H, COOCH$_2$*CH*$_3$), 4.40 (s, 2H, H-8), 4.65 (t, 2H, –N*CH*$_2$CH$_2$OH), 4.70 (t, 1H, –CH$_2$*OH*), 11.85 (br, 1H, NH); δ_c (DMSO-d_6): 14.45 (q, COOCH$_2$CH$_3$), 25.31 (t, C-5), 40.20 (t, C-6), 42.64 (t, C-8), 46.68 (t, NCH$_2$), 58.36 (t, CH$_2$OH), 60.84 (t, COOCH$_2$CH$_3$), 113.55 (s, C-4a), 120.30 (s, C-4b), 128.68 (s, C-8a), 152.67 (s, C-9a), 154.67 (s, C-4), 164.68 (s, CO ester), 175.81 (s, C-2).

Ethyl 3-(2-Hydroxy-1-methylethyl)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno-[2,3-d]pyrimidine-7-carboxylate (3b)

Compound **2b** (0.41 g, 0.001 mmol) was added to a solution of potassium hydroxide (0.06 g, 0.0011 mmol) in absolute ethanol (10 ml), and the mixture was refluxed with stirring for 1 h. The potassium salt of compound **3b** was collected by filtration then dissolved in water and acidified (to pH = 6.6) with hydrochloric acid, the product was collected by filtration, washed with water, dried, and recrystallized from ethanol. Yield 0.25 g (69.4%) of compound **3b** as colorless crystals, m.p. 188–190°C; (found: C, 48.89; H, 5.10; N, 11.50; S, 17.22. $C_{15}H_{19}N_3O_4S_2$ (369.47) requires C, 48.76; H, 5.18; N, 11.37; S, 17.35%); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2\mathit{CH}_3$), 1.40 (d, 3H, CH_3CH—), 2.90 (t, 2H, H-5), 3.55 (t, 2H, H-6), 3.80–3.95 (m, 2H, —CH_2OH), 4.20 (q, 2H, $COO\mathit{CH}_2CH_3$), 4.55 (s, 2H, H-8), 4.80–4.90 (br, 1H, $CH_2\mathit{OH}$); 5.80–6.04 (m, 1H, —$\mathit{CH}(CH_3)CH_2OH$)), 11.80 (s, 1H, NH); δ_c (DMSO-d_6): 14.56 (q, $COOCH_2CH_3$), 18.72 (q, CH_3), 25.51 (t, C-5), 40.68 (t, C-6), 42.72 (t, C-8), 61.84 (t, $COOCH_2CH_3$), 64.41 (d, CH), 68.94 (t, CH_2OH), 116.60 (s, C-4a), 121.40 (s, C-4b), 128.70 (s, C-8a), 151.6 (s, C-9a), 155.71 (s, C-4), 165.60 (s, CO ester), 174.82 (s, C-2).

Ethyl 3-Methyl-5-oxo-2,3,6,9-tetrahydro-5*H*-pyrido-[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7H)-carboxylate (4)

Compound **2b** (0.4 g, 0.001 mmol) was dissolved in 10 ml of methanolic hydrogen chloride and stirred at reflux temperature for 10 h, and after evaporation of the solvent under reduced pressure the yellow residue was dissolved in 10 ml of water and neutralized to pH = 7.5 with ammonium hydroxide and extracted with chloroform. The organic layer was dried (magnesium sulfate) and evaporated to yield the solid which was recrystallized from ethanol. Yield 0.21 g (62.1%) of compound **4** as yellow crystals, m.p. 136–138°C; (found: C, 51.10; H, 4.79; N, 11.80; S, 18.36. $C_{15}H_{17}N_3O_3S_2$ (351.45) requires C, 51.26; H, 4.87; N, 11.95; S, 18.24%); ν_{max}/cm^{-1}: 2990 (aliph. CH), 1720 (CO ester), 1700 (CO pyrimidine ring); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2\mathit{CH}_3$), 1.45 (d, 3H, CH_3CH—), 2.90 (t, 2H, H-6), 3.20–3.30 (d, 2H, H-2), 3.65 (t, 2H, H-7), 4.15 (q, 2H, $COO\mathit{CH}_2CH_3$), 4.60 (s, 2H, H-9), 5.10–5.20 (m, 1H, H-3); δ_c (DMSO-d_6): 14.15 (q, $COOCH_2CH_3$), 21.83 (q, CH_3), 25.12 (t, C-6), 31.81 (t, C-2), 40.71 (t, C-7), 42.70 (s, C-9), 58.86 (d, C-3), 61.08 (t, $COOCH_2CH_3$), 117.48 (s, C-5a), 127.03 (s, C-5b), 128.92

(s, C-9a), 154.72 (s, C-10a), 156.19 (s, C-11a), 160.77 (s, C-5), 163.43 (s, CO ester).

Ethyl 2-{[(2-Propenyl)-aminothioxomethyl]-amino}-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (5)

A solution of isothiocyanate **1** (0.34 g, 0.001 mmol) in dichloromethane (10 ml) was added with stirring to a solution of an equimolar amount of allylamine (0.06 g, 0.001 mmol) in dichloromethane (10 ml), and the mixture was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the solid product was collected by filtration, washed with dichloromethane, dried, and recrystallized from ethanol. Yield 0.36 g (90.6%) of compound **5** as pale yellow crystals, m.p. 148–150°C; (found: C, 51.18; H, 5.92; N, 10.41; S, 15.95. $C_{17}H_{23}N3O_4S_2$ (397.52) requires C, 51.36; H, 5.83; N, 10.57; S, 16.13%); ν_{max}/cm^{-1}: 3290 (NH), 2982 (aliph. CH), 1720, 1690 (2 CO ester) ; δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2\mathit{CH}_3$), 1.35 (t, 3H, $COOCH_2\mathit{CH}_3$), 2.80 (t, 2H, H-4), 3.65 (t, 2H, H-5), 3.85 (d, 2H, CH_2—CH=CH_2), 4.20 (q, 2H, —$COO\mathit{CH}_2CH_3$), 4.55 (s, 2H, H-7), 4.95–5.40 (m, 2H, CH_2—CH=CH_2), 5.70–5.90 (m, 1H, —CH=CH_2), 6.55–6.65 (br, 1H, NH), 11.90 (s, 1H, NH); δ_c (DMSO-d_6): 14.20 (q, $COOCH_2CH_3$), 14.63 (q, $COOCH_2CH_3$), 26.28 (t, C-4), 41.10 (t, C-5), 42.53 (t, C-7), 46.69 (t, $NHCH_2$), 60.84 (t, $COOCH_2CH_3$), 61.60 (t, $COOCH_2CH_3$), 111.22 (s, C-3), 115.91 (t, —CH=CH_2),122.20 (s, C-7a), 131.78 (s, C-3a), 133.96 (d, —CH=CH_2), 153.56 (s, CO ester), 166.52 (s, CO ester), 169.98 (s, C-2), 177.73 (s, CS).

Ethyl 3-(2-Propenyl)-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (6)

Compound **5** (0.4 g, 0.001 mmol) was added to a solution of potassium hydroxide (0.07 g, 0.0012 mmol) in absolute ethanol (10 ml), and the mixture was refluxed with stirring for 10 min. The potassium salt of compound **6** was collected by filtration then dissolved in water and acidified (to pH = 6.6) with hydrochloric acid, the product was collected by filtration, washed with water dried, and recrystallized from ethanol. Yield 0.3 g (85.7%) of compound **6** as pale yellow crystals, m.p. 178–180°C; (found: C, 51.39; H, 4.95; N, 12.11; S, 18.38. $C_{15}H_{17}N_3O_3S_2$ (351.45) requires C, 51.26; H, 4.87; N, 11.95; S, 18.24%); ν_{max}/cm^{-1} 3180 (NH), 2990 (aliph. CH), 1710 (CO ester), 1680 (CO pyrimidine ring), 1620 (C=N); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2\mathit{CH}_3$), 2.85 (t, 2H, H-5), 3.65 (t, 2H, H-6), 4.10 (q, 2H, $COO\mathit{CH}_2CH_3$), 4.55 (s, 2H, H-8), 4.90–5.12

(d, 2H, —*CH*$_2$—CH=CH$_2$), 5.18–5.30 (m, 2H, CH$_2$—CH=C*H*$_2$), 5.80–6.10 (m, 1H, —*CH*=CH2), 13.70 (s, 1H, NH); δ_c (DMSO-d$_6$): 14.43 (q, COOCH$_2$CH$_3$), 24.87 (t, C-5), 40.21 (t, C-6), 42.39 (t, C-8), 47.12 (t, NCH$_2$), 60.99 (t, COOCH$_2$CH$_3$),114.88 (t, CH=*CH*$_2$), 116.94 (s, C-4a), 124.51 (s, C-4b), 129.57 (s, C-8a), 134.51 (d, —*CH*=CH$_2$), 149.52 (s, C-9a), 154.59 (s, C-4), 159.96 (s, CO ester), 173.45 (s, C-2).

Ethyl 3-(2-Propenyl)-2-(methylsulfanyl)-4-oxo-, 3,4,5,6,7,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine-7-carboxylate (7)

A solution of **6** (0.35 g, 0.001 mmol) in 1 M aqueous sodium hydroxide (1.5 ml) was treated with methyl iodide (0.16 g, 0.0011 mmol) and the mixture was stirred at room temperature. The methylthio compound **7** started to crystallize almost immediately. After 30 min, it was filtered, washed with water, dried, and recrystallized from ethanol. Yield 0.32 g (88.8%) of compound **7** as colorless crystals, m.p. 130–132°C; (found: C, 52.47; H, 5.18; N, 11.40; S, 17.41. $C_{16}H_{19}N_3O_3S_2$ (365.48) requires C, 52.58; H, 5.23; N, 11.49; S, 17.54%); ν_{max}/cm^{-1} 2990 (aliph. CH), 1710 (CO ester), 1670 (CO pyrimidine ring), 1620 (C=N); δ_H (DMSO-d$_6$): 1.20 (t, 3H, COOCH$_2$*CH*$_3$), 2.65 (s, 3H, S*CH*$_3$), 2.80 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.20 (q, 2H, COO*CH*$_2$CH$_3$), 4.60 (s, 2H, H-8), 4.80–5.10 (d, 2H, —*CH*$_2$—CH=CH$_2$), 5.25–5.55 (m, 2H, CH$_2$—CH=*CH*$_2$), 5.80–6.10 (m, 1H, —CH=CH$_2$); δ_c (DMSO-d$_6$): 14.41 (q, COOCH$_2$CH$_3$), 15.66 (q, SCH$_3$), 25.09 (t, C-5), 40.20 (t, C-6), 42.64 (t, C-8), 45.16 (t, NCH$_2$), 60.96 (t, COOCH$_2$CH$_3$), 114.30 (t, —CH=*CH*$_2$), 116.80 (s, C-4a), 126.99 (s, C-4b), 129.11 (s, C-8a), 134.30 (d, —CH—*CH*$_2$), 151.20 (s, C-9a), 154.61 (s, C-4), 158.10 (s, C-2), 161.90 (s, CO ester).

Ethyl 2-Methyl-5-oxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]-pyrimidine-8(7H)-carboxylate (8)

Method A

A mixture of **6** (0.35 g, 0.001 mmol) in acetic acid (1 ml) and concentrated hydrochloric acid (2 ml) was refluxed for 1 h. After cooling to room temperature, the solid formed by neutralizing the mixture with 10% sodium hydroxide was collected by filtration and washed with water (20 ml), affording 0.32 g of crude product which was recrystallized from 15% aqueous ethanol. Yield 0.24 g (68.5%) of compound **8** as yellow crystals, m.p. 138–140°C; (found: C, 51.17; H, 4.95; N, 11.82; S, 18.13. $C_{15}H_{17}N_3O_3S_2$ (351.45) requires C, 51.26; H, 4.87; N, 11.95; S, 18.24%); ν_{max}/cm^{-1} 2980 (aliph. CH), 1720 (CO ester), 1680 (CO pyrimidine

ring); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 1.60 (d, 3H, CH_3), 2.90 (t, 2H, H-6), 3.60 (t, 2H, H-7), 3.95–4.10 (d, 2H, H-3), 4.20 (q, 2H, $COOCH_2CH_3$), 4.40–4.55 (m, 1H, H-2), 4.65 (s, 2H, H-9).

Method B

1,2-Dibromopropane (0.22 g, 0.0011 mmol) in DMF (5 ml) was added to a stirred solution containing **10** (0.31 g, 0.001 mmol), water (5 ml), and sodium hydroxide (0.05 g). The mixture was heated at 90°C for 1 h and then stirred at room temperature for an additional 1 h. The reaction mixture was poured into cold water, the precipitated product was collected by filtration, dried, and recrystallized from 15% aqueous ethanol. Yield 0.24 g (68.7%) of compound **8** as yellow crystals. m.p. 139–140°C. The compound is identical to that obtained according to method A.

Ethyl 3-Amino-4-oxo-2-thioxo-1,3,4,5,6,8-hexahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7(2*H*)-carboxylate (9)

A solution of diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate **1** (0.6 g, 0.0017 mmol) in benzene (10 ml) was added dropwise at room temperature to a stirred solution of hydrazine hydrate (0.6 g, 0.018 mmol) in benzene (5 ml). The suspension was refluxed with stirring for 8 h. After cooling, the solid product was collected, by filtration washed with ethanol, dried, and recrystallized from dioxane. Yield 0.57 g (91.2%) of compound **9** as yellow crystals, m.p. 232–234°C (dec.); (found: C, 44.07; H, 4.30; N, 17.01; S, 19.50. $C_{12}H_{14}N_4O_3S_2$ (326.40) requires C, 44.15; H, 4.32; N, 17.16; S, 19.64%); ν_{max}/cm^{-1} 3400, 3320, 3180 (NH_2, NH), 1710 (CO ester), 1680 (CO pyrimidine ring), 1200 (C=S); δ_H (DMSO-d_6): 1.20 (t, J 7 Hz, 3H, $COOCH_2CH_3$), 2.90 (t, J 5.6 Hz, 2H, H-5), 3.60 (t, J 5.6 Hz, 2H, H-6), 4.20 (q, J 7 Hz, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 6.30–6.50 (br, 2H, NH_2); 13.40 (s, 1H, NH); δ_c (DMSO-d_6): 14.56 (q, $COOCH_2CH_3$), 25.26 (t, C-5), 40.74 (t, C-6), 46.75 (t, C-8), 60.95 (t, $COOCH_2CH_3$), 113.31 (s, C-4a), 128.28 (s, C-4b), 141.03 (s, C-8a), 154.76 (s, C-4), 157.64 (s, C-9a) 161.63 (s, CO), 168.83 (s, C-2). MS: m/z = 326 (M^+).

Ethyl 4-Oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (10)

To a suspention of **9** (0.32 g, 0.001 mmol) in 2 ml of acetic acid and 10 ml of water, a solution of sodium nitrite (0.27 g, 0.0039 mmol) in 1 ml of

water was added, After 15 min stirring at room temperature, 5 ml of a 40% sodium hydroxide solution was added and warmed to obtain a clear solution. After cooling it was acidified with a 50% solution of sulfuric acid to give colorless crystals. The crystals were washed with cold water, dried, and recrystallized from ethanol. Yield 0.2 g (65.5%) of compound **10** as colorless crystals, m.p. 287–289°C; (found: C, 46.18; H, 3.15; N, 13.32; S, 20.52. $C_{12}H_{13}N_3O_3S_2$ (311.38) requires C, 46.28; H, 4.20; N, 13.49; S, 20.59%); ν_{max}/cm^{-1} 3300 (NH), 2980 (aliph. CH), 1700 (CO ester), 1670 (CO pyrimidine ring); δ_H (DMSO-d_6) 1.20 (t, J 7 Hz, 3H, $COOCH_2\mathit{CH}_3$), 2.90 (t, J 5.6 Hz, 2H, H-5), 3.70 (t, J 5.6 Hz, 2H, H-6), 4.10 (q, J 7 Hz, 2H, $COO\mathit{CH}_2CH_3$), 4.60 (s, 2H, H-8), 12.40 (s, 1H, NH), 13.40 (s, 1H, NH); δ_c (DMSO-d_6): 14.3 (q, $COOCH_2CH_3$), 24.7 (t, C-5), 40.2 (t, C-6), 42.3 (s, C-8), 60.9 (t, $COOCH_2CH_3$), 115.7 (s, C-4a), 124.5 (s, C-4b), 129.4 (s, C-8a), 150.7 (s, C-9a), 154.8 (s, C-4), 156.6 (s, CO), 172.9 (s, C-2).

Ethyl 3-Carboxymethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine-7-carboxylate (11)

To a solution of glycine (0.08 g, 0.001 mmol) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1M, 5 ml) 1 (0.34 g, 0.001 mmol) was added and the mixture was stirred at 50°C for 5 h. The volatile components were evaporated in vacuo, water was added to the solid residue and acidified with hydrochloric acid (18%) to pH = 3. The precipitate was collected by filtration, dried, and recrystallized from DMF/water. Yield 0.26 g (70.6%) of compound **11** as yellow crystals, m.p. 280–282°C; (found: C, 45.39; H, 4.19; N, 11.24; S, 17.48. $C_{14}H_{15}N_3O_5S_2$ (369.43) requires C, 45.51; H, 4.09; N, 11.37; S, 17.35%); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2\mathit{CH}_3$), 2.80 (t, 2H, H-5), 3.70 (t, 2H, H-6), 4.10 (q, 2H, $COO\mathit{CH}_2CH_3$), 4.60 (s, 2H, H-8), 5.10 (s, 2H, $-N\mathit{CH}_2$), 13.40 (s, 1H, NH). δ_c (DMSO-d_6): 14.45 (q, $COOCH_2CH_3$), 24.73 (t, C-5), 40. 43 (t, C-6), 42.43 (t, C-8), 45.99 (t, $-NCH_2$), 60.83 (t, $COOCH_2CH_3$), 115.76 (s, C-4a), 125.06 (s, C-4b), 129.53 (s, C-8a), 150.06 (s, C- 9a), 154.61 (s, C-4), 166.44 (s, CO ester), 169.29 (s, C-2), 173.75 (s, COOH).

Ethyl 3-[(*S*)-1-Carboxyethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]-pyrimidine-7-carboxylate (12)

To a stirred solution of L-alanine (0.09 g, 0.001 mmol) in a mixture of water (5 ml), dioxane (5 ml) and sodium hydroxide (1 M, 5 ml) 1 (0.34 g, 0.001 mmol) was added and the mixture was stirred at 50°C for 10 h.

The volatile components were evaporated in vacuo, water was added to the solid residue, and acidified with hydrochloric acid (18%) to pH = 3. The precipitate was collected by filtration dried and recrystallized from DMF/water. Yield 0.24 g (63.1%) of compound **12** as yellow crystals, m.p. 290–292°C; (found: C, 46.91; H, 4.39; N, 10.82; S, 16.61. $C_{15}H_{17}N_3O_5S_2$ (383.45) requires C, 46.98; H, 4.46; N, 10.95; S, 16.72%); δ_H (DMSO-d_6): 1.10 (t, 3H, $COOCH_2CH_3$), 1.52 (d, 3H, —CH(CH_3)COOH), 2.80 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-8), 6.20 (q, 1H, —CH(CH_3)COOH), 13.20 (s, 1H, NH). δ_c (DMSO-d_6): 14.54 (q, $COOCH_2CH_3$), 17.44 (q, CH_3), 24.89 (t, C-5), 40.75 (t, C-6), 42.55 (t, C-8), 49.95 (d, CH), 61.12 (t, $COOCH_2CH_3$), 115.43 (s, C-4a), 125.48 (s, C-4b), 129.60 (s, C-8a), 150.48 (s, C-9a), 155.66 (s, C-4), 161.67, 170.51 (s, C-2), 174.47 (s, COOH).

Ethyl 3-(2-Carboxyethyl-4-oxo-2-thioxo-1,2,3,4,5,6,7,8-octahydropyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine-7-carboxylate (13)

To a solution of β-alanine (0.09 g, 0.001 mmol) in water (5 ml), dioxane (5 ml) and sodium hydroxide (1M, 5 ml) 1 (0.34 g, 0.001 mmol) was added and the mixture was stirred at 50°C for 3 h, and then at room temperature for 4 h. The volatile components were evaporated in vacuo, water (10 ml) was added to the residue and the mixture was acidified with hydrochloric acid (18%) to pH = 3. The precipitate was collected by filtration, dried, and recystallized from DMF/water. Yield 0.26 g (68.4%) of compound **13** as yellow crystals, m.p. > 300°C; (found: C, 46.84; H, 4.39; N, 10.82; S, 16.59. $C_{15}H_{17}N_3O_5S_2$ (383.45) requires C, 46.98; H, 4.46; N, 10.95; S, 16.72%); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2CH_3$), 2.65 (t, 2H, —CH_2COOH), 2.85 (t, 2H, H-5), 3.60 (t, 2H, H-6), 4.10 (q, 2H, $COOCH_2CH_3$), 4.60–4.80 (m, 4H, H-8, —CH_2CH_2COOH), 13.60 (br, 1H, NH); δ_c (DMSO-d_6): 14.40 (q, $COOCH_2CH_3$), 24.77 (t, C-5), 30.55 (t, —NCH_2), 36.65 (t, CH_2COOH), 40.23 (t, C-6), 42.41 (t, C-8), 60.99 (t, $COOCH_2CH_3$), 115.80 (s, C-4a), 124.81 (s, C-4b), 129.54 (s, C-8a), 149.45 (s, C-9a), 154.61 (s, C-4), 163.55 (s, CO ester), 170.12 (C-2), 173.22 (s, COOH).

Ethyl 2,5-Dioxo-2,3,6,9-tetrahydro-5*H*-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]-pyrimidine-8 (7*H*)-carboxylate (14)

Method A

Compound **11** (0.5 g, 0.0013 mmol) was heated over its melting point for 15 min, then the residue was cooled and crystallized from DMF.

Yield 0.28 g (58.9%) of compound **14** as brown crystals, m.p 260–262°C; (found: C, 47.76; H, 3.64; N, 11.81; S, 18.33. $C_{14}H_{13}N_3O_4S_2$ (351.41) requires C, 47.85; H, 3.72; N, 11.95; S, 18.24%); %); ν_{max}/cm^{-1}: 1740, 1720, 1680, (3 CO), 1640 (C=N); δ_H (DMSO-d_6): 1.20 (t, 3H, $COOCH_2\mathit{CH}_3$), 2.85 (t, 2H, H-6), 3.60 (t, 2H, H-7), 3.90 (s, 2H, H-3), 4.20 (q, 2H, $COO\mathit{CH}_2CH_3$), 4.60 (s, 2H, H-9).

Method B (from Compound 10)

To a solution of 10 (0.31 g, 0.001 mmol) in 10 ml dimethylformamide was added chloroacetyl chloride (0.14 g, 0.0012 mmol) dropwise under stirring. The reaction mixture was then heated on a water-bath for 2 h and, after cooling, poured into 100 ml of cold water with vigorous stirring. The precipitate was collected by filtration, washed with water, dried, and recrystallized from DMF. Yield 0.21 g (62.1%) of compound **14** as yellow crystals, m.p. 260–261°C, The compound is identical to that obtained according to method A.

REFERENCES

[1] S. Leistner, G. Wagner, M. Guetscharo, and E. Glusa, *Pharmazie*, **41,** 54 (1986).
[2] M. Chaykovsky, M. Lin, A. Rosowsky, and E. J. Modest, *J. Med. Chem.*, **10,** 188 (1973).
[3] E. F. Elslager, P. W. Jacob, and M. Leslic, *J. Heterocyclic Chem.*, **9,** 775 (1972).
[4] E. Bousquet, G. Romero, F. Guerrera, A. Caruso, and M. A. Roxas, *Farmaco Ed. Sci.*, **40,** 869 (1985).
[5] E. Bousquet, F. Guerrera, N. A. Siracusa, A. Caruso, and M. A. Roxas, *Farmaco Ed. Sci.*, **39,** 110 (1984).
[6] C. G. Dave, P. R. Shah, K. C. Dave, and V. J. Patel, *J. Indian Chem. Soc.*, **66,** 48 (1989).
[7] H. Vieweg, S. Leistner, G. Wagner, N. Boehm, U. Krasset, R. Grupe, D. Lohmann, and G. Loban, *East Ger. Pat*. DD 257, 830 (1988); *C.A.*, **110,** 95262p (1989).
[8] H. Vieweg, S. Leistner, G. Wagner, N. Boehm, U. Krasset, R. Grupe, D. Lohmann, and G. Loban, *East Ger. Pat.* DD 258, 234 (1988); *C.A.*, **110,** 95263q (1989).
[9] J. V. Metzger, *Comprehensive Heterocyclic Chemistry*, edited by A. R. Katritzky, W. Rees, and K. T. Potts (Pergamon Press, Oxford, 1984), vol. 6 (4b), p. 328.
[10] E. Kh. Ahmed, A. M. N. Gohar, and M. A. Ameen, *Pharmazie*, **55**(1), 31 (2000).
[11] E. Kh. Ahmed, U. Sensfuss, and W. D. Habicher, *J. Heterocyclic Chem.*, **36,** 1119 (1999).
[12] F. Sauter, J. Frohlich, and E. Kh. Ahmed, *Monatsh. Chem.*, **127,** 319 (1996).
[13] E. Kh. Ahmed, J. Frohlich, and F. Sauter, *Collect. Czech. Chem. Commun.*, **61,** 147 (1996).
[14] E. Kh. Ahmed, *Monatsh. Chem.*, **126,** 953 (1995).
[15] F. Sauter, U. Jordis, J. Frohlich, K. Gewald, F. Grohmann, and E. Kh. Ahmed, *ACH Models in Chemistry*, **131**(3–4), 489 (1994).
[16] E. Kh. Ahmed, *Phosphorous, Sulfur, and Silicon* (in press).