Heteroatom Chemistry
Volume 13, Number 3, 2002

Syntheses of Some New Azolopyrido-[4′,3′:4,5]thieno[2,3-*d*]pyrimidines

Essam Kh. Ahmed

Chemistry Department, Faculty of Science, El-Minia University, El-Minia 61519, Egypt

Received 1 May 2001; revised 2 October 2001

ABSTRACT: *Diethyl 2-[(ethoxythioxomethyl)amino]-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine-3,6-dicarboxylate* **2**, *prepared from diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate* **1** *by boiling in anhydrous ethanol, was converted into pyrido[4′,3′:4,5]thieno[2,3-d]pyrimidine derivatives* **3, 4** *by treatment with hydrazine hydrate. The tetracyclic systems imidazo[1,2-a]pyrido-[4′,3′:4,5]-thieno[2,3-d]pyrimidine* **9** *and pyrido[4′,3′:4,5]-thieno[2,3-d][1,3]thiazolo-[3,2-a]pyrimidine* **10** *were synthesized by the reaction of* **2** *with 1,2-diaminoethane and aminoethanethiol, respectively. The hydrazino derivative* **4** *underwent cyclization reactions with orthoesters and nitrous acid to give the corresponding pyrido[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]pyrimidines* **5, 6** *and pyrido[4′,3′:4,5]thieno[3,2-e]-[1,2,3,4]tetrazolo[1,5-a]pyrimidine* **8**, *respectively. Moreover, reactions of* **3** *with cyanogen bromide, N-carbethoxyhydrazine, carbon disulfide, and ethyl chloroformate resulted in the formation of the new pyrido[4′,3′:4,5]thieno[2,3-d][1,3,4]thiadiazolo-[3,2-a]pyrimidine derivatives* **12–15**. © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:280–286, 2002; Published online in Wiley Interscience (www.interscience.wiley.com). DOI 10.1002/hc.10030

INTRODUCTION

The antiparasitic properties exhibited by a variety of isothiocyanates have been very well documented [1]. Furthermore, various substituted thioureas also have been reported to possess broad-spectrum anthelmintic activity [2]. Although there are many methods reported in the literature for the preparation of isothiocyanates [3], heterocyclic isothiocyanates with an ester group at the ortho position have been only recently reported [4–11]. This prompted us to investigate the utility of heterocyclic isothiocyanates with an ester group at the ortho position. We have shown that these compounds are versatile starting materials for the syntheses of heterocyclic thiourea derivatives, and different fused heterocyclic systems [12,13]. In our ongoing search for new heterocycles containing the thienopyrimidine ring systems [14–17], the present paper follows this line of research by reporting on a new, rapid, and convenient synthesis of diethyl 2-[(ethoxythioxomethyl)amino]-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate **2** and its utility in the synthesis of not yet reported pyrido[4′,3′:4,5]-thieno[2,3-*d*]pyrimidines **3, 4**, pyrido[4′,3′:4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidines **5, 6** and pyrido[4′,3′:4,5]thieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidines **12–15**.

RESULTS AND DISCUSSION

It has been found that refluxing diethyl 2-isothiocyanato-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine-3,6-dicarboxylate **1** [12] with anhydrous ethanol for 20 h resulted in the formation of diethyl 2-[(ethoxythioxomethyl)amino]-4,5,6,7-tetrahydrothieno-[2,3-*c*]pyridine-3,6-dicarboxylate **2**. Compound **2**, with two reactive groups at ortho positions, was converted into 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 **3** by the action of

Correspondence to: Essam Kh. Ahmed; e-mail: essamkhalaf24@hotmail.com.

hydrazine hydrate at room temperature, while, by heating, the replacement of the mercapto group by the hydrazino group took place to give the hydrazino derivative **4**.

Compound **4** was also obtained by treatment of **3** with hydrazine hydrate in ethanol at reflux temperature. Compound **4** could be further cyclized into tetracyclic azolopyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidine derivatives. For example, when **4** was refluxed with triethyl orthoformate, only one product was obtained, and this was identified as the new heterocycle ethyl 3-amino-10-oxo-3,8,9,10-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5*a*]pyrimidine-7-(6*H*)-carboxylate **5**. The structure assignment of compound **5** was obtained by elemental analyses, IR and ^{1}H NMR spectroscopy. The ^{1}H NMR spectrum showed a two hydrogen proton singlet at $\delta = 6.20$, which was assigned to the NH_2 group. This band disappeared after D_2O exchange. Other analytical and spectroscopic data are given in the experimental section. In the same manner, when compound **4** was refluxed with triethyl orthoacetate, it gave ethyl 3-amino-2-methyl-10-oxo-3,8,9,10-tetrahydro[4′,3′:4,5]thieno[2,3-*d*][1,2,4]triazolo[1,5-*a*]pyrimidine-7-(6*H*)-carboxylate **6**. Treatment of compound **4** with nitrous acid in a molar ratio of 1:1 gave ethyl 4-amino-5-oxo-4,5,6,9-tetrahydropyrido[4′,3′:4,5]thieno-[3,2-*e*][1,2,3,4]tetrazolo[1,5-*a*]pyrimidine-8(7*H*)-carboxylate **8** through the intermediate formation of the 2-azido derivative **7**. The proof for this latter reaction is the signal in the ^{1}H NMR spectrum at $\delta = 5.87$ for the amino group, and its IR spectrum showed no azide band. This compound exists only in the tetrazolo form.

When the thiourethane **2** reacted with 1,2-diaminoethane, it gave ethyl 5-oxo-1,2,3, 6,7,9-hexahydroimidazo[1,2-*a*]pyrido[4′,3′:4,5]thieno[2,3-*d*]pyrimidin-8(5*H*)-carboxylate **9**. In this case, the cyclization took place only to the nitrogen at position 3 in the pyrimidine system. Similarly, ethyl 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(7*H*)-carboxylate **10** was obtained from the reaction of **2** with aminoethanethiol hydrochloride in pyridine (Scheme 1).

As illustrated in Scheme 2, compound **3** was proved to be a versatile starting material for the synthesis of the new pyrido[4′,3′:4,5]thieno[2,3-*d*][1,3,4]thiadiazolo-[3,2-*a*]pyrimidine derivatives **12–15**. Upon treatment of **3** with cyanogen bromide, the thiadiazolo compound, namely ethyl 2-amino-10-oxo-8,9-dihydro-10*H*-pyrido[4′,3′:4,5]thieno[2,3-*d*]-[1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7(6*H*)-carboxylate **12**, was obtained. This reaction proceeded via the thiocyanate **11** as an intermediate. The analytical and spectral data are in accordance with the structure assigned. The IR spectrum showed two broad bands in the region 3200–3400 cm^{-1} characteristic of the NH_2 group. The 2-amino group protons resonate further downfield, at $\delta = 7.99$ than the 3-amino group protons of the precursor **3**. Condensation of **3** with *N*-carbethoxyhydrazine in the presence of hydrochloric acid afforded ethyl 2-hydrazino-10-oxo-8, 9-dihydro-10*H*-pyrido[4′,3′:4,5]thieno-[2,3-*d*][1,3,4]-thiadiazolo[3,2-*a*]pyrimidine-7(6*H*)-carboxylate **13**, which in its IR spectrum showed absorption bands at 3240, 3205, and 3160 cm^{-1} due to NH and NH_2 groups. It also showed another band at 1670 due to the cyclic amide mooiety (—CO—N).

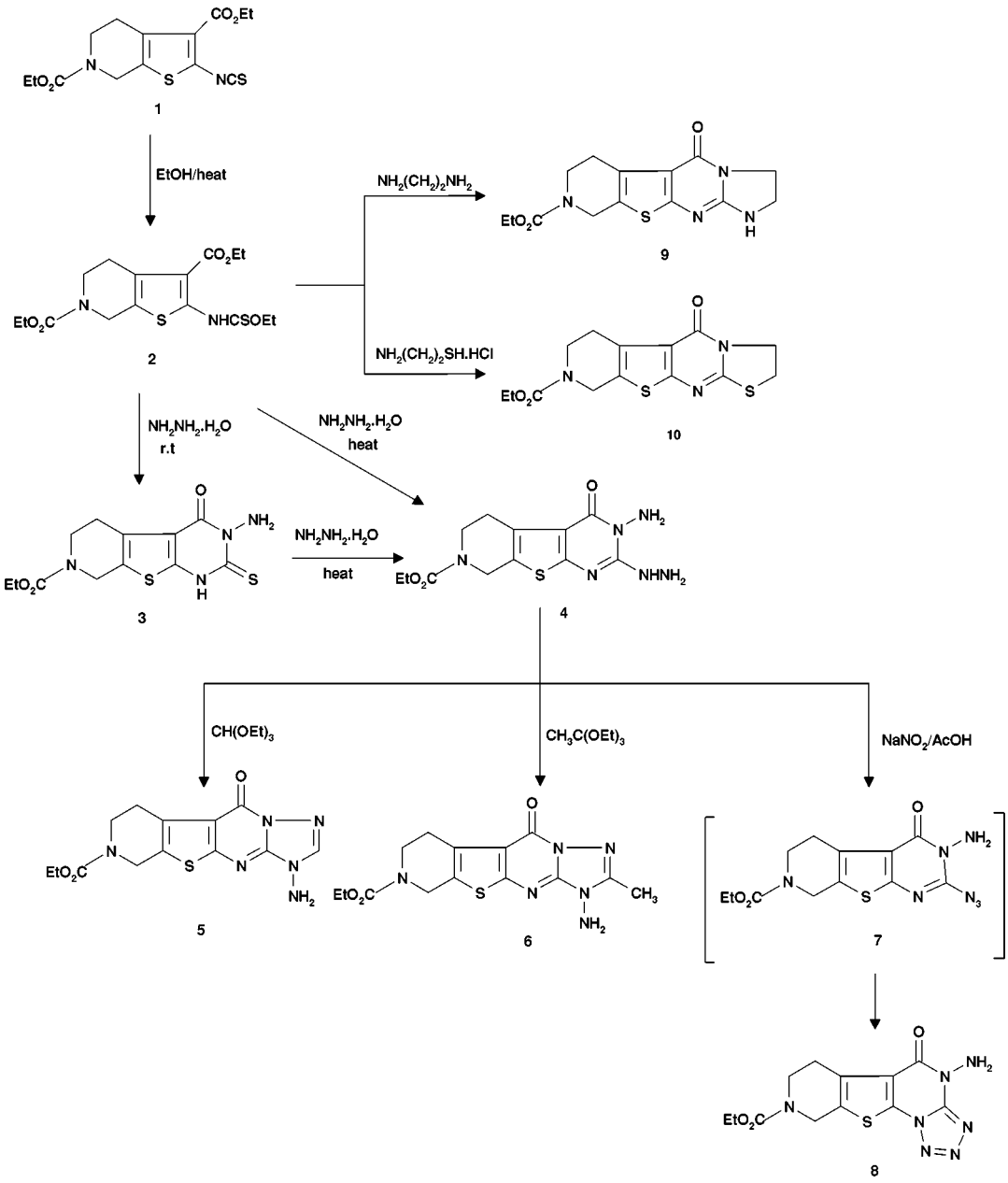
Refluxing of compound **3** with carbon disulfide in pyridine afforded ethyl 2-thioxo-10-oxo-6,7,8,9-tetrahydropyrido[4′,3′:4,5]thieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-7-carboxylate **14**. The structure of **14** has been confirmed on the basis of IR and ^{1}H NMR studies. The IR spectrum showed a band at 3200–3180 cm^{-1} for the NH group, and NMR spectra showed a singlet at $\delta = 5.30$ (1H, NH) and this showed that compound **14** exists preferably in the thione rather than in the thiol form. Another new thiadiazolo derivative **15** was synthesized from **3** by reaction with ethyl chloroformate.

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Elemental analyses were performed at the microanalytical Laboratory, Cairo University. ^{13}C and ^{1}H NMR spectra: Bruker AC 200 (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz), 5 mm dual ^{1}H/^{13}C-VT probe at 300 K; solvent: DMSO-d_6 and $CDCl_3$, respectively, δ values are given relative to the internal standard TMS ($\delta = 0$ ppm). IR spectra were recorded on a Shimadzu 470 Spectrophotometer in KBr pellets. Mass spectra were recorded on a Finnigan MAT 95-A spectrometer.

*Diethyl 2-[(ethoxythioxomethyl)amino]-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3,6-dicarboxylate (**2**)*

A solution of **1** (0.41 g, 0.0012 mol) in anhydrous ethanol (30 ml) was heated under reflux for 20 h. The solvent was evaporated in vacuo to give 0.35 g (75.2% yield) of **2**. An analytical sample was obtained by recrystallization from ethanol; as yellow crystals, mp 116–117°C. IR: $\nu = 3100$, 2990, 1700, 1680, 1580, and 1540 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ =1.10–145 (m, 9H, 3 $COOCH_2CH_3$), 2.90 (t, $J = 5.6$ Hz, 2H, H-4), 3.70 (t, $J = 5.6$ Hz, 2H, H-5), 4.20 (q, $J =$ 7.0 Hz, 2H, $COOCH_2CH_3$), 4.40 (q, $J = 7.0$ Hz, 2H,

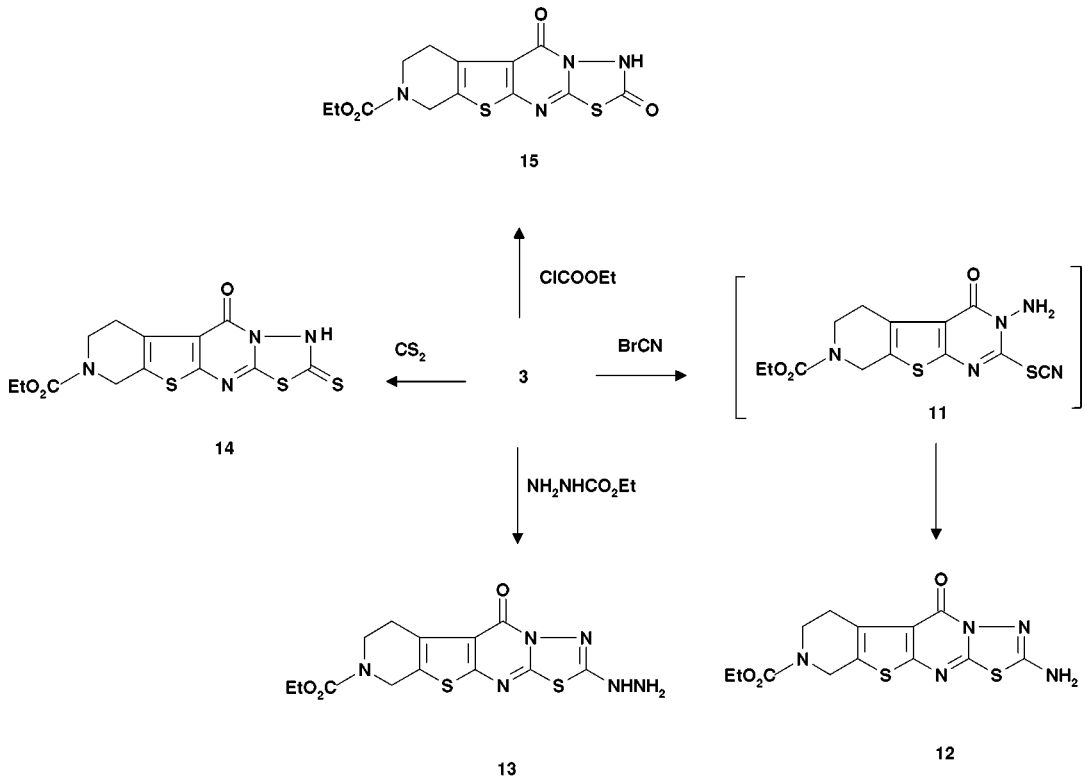


SCHEME 1

$COOCH_2CH_3$), 4.45–4.60 (m, 4H, H-7, $-OCH_2CH_3$). ^{13}C NMR ($CDCl_3$): $\delta = 13.88$ (q, OCH_2CH_3), 14.08 (q, $COOCH_2CH_3$), 14.52 (q, $NCOOCH_2CH_3$), 26.34 (t, C-4), 40.97 (t, C-5), 42.41 (t, C-7), 60.76 (t, $COOCH_2CH_3$), 61.46 (t, $N-COOCH_2CH_3$), 66.82 (t, OCH_2CH_3), 112.02 (s, C-3), 122.32 (s, C-7a), 129.94 (s, C-3a), 150.95 (s, CO ester), 155.29 (s, N—CO), 166.06 (s, C-2), 184.71 (s, CS). MS: $m/z = 386$ [M^+]. $C_{16}H_{22}N_2O_5S_2$ (386.49) calcd.: C, 49.72; H, 5.73; N, 7.24; S, 16.59. Found: C, 49.59; H, 5.65; N, 7.11, S, 16.44.

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

To a solution of **2** (0.77 g, 0.002 mol) in ethanol (10 ml), hydrazine hydrate 99% (0.8 g, 0.024 mol)) was added and the mixture was stirred at room temperature for 30 h. The solid product that had formed was collected by filtration, dried, and recrystallized from dioxane. Yield: 0.5 g (76.9%) of **3** as yellow crystals, mp 232–234°C. IR: $\nu = 3400$, 3000, 2990, 1710, 1680,



SCHEME 2

1640, and 1600 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ 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, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.50 (s, 2H, H-8), 6.30–6.50 (br, 2H, NH_2). ^{13}C NMR (DMSO-d_6): $\delta = 14.56$ (q, $-COOCH_2CH_3$), 25.26 (t, C-5), 40.74 (t, C-6), 46.75 (t, C-8), 60.95 (t, $-COOCH_2CH_3$), 113.30 (s, C-4a), 121.03 (s, C-8a), 128.28 (s, C-4b), 153.60 (s, C-2), 154.64 (CO ester), 161.63 (s, CO), 161.63 (s, C-9a), 168.83 (s, C=S). MS: $m/z = 326$ [M^+]. $C_{12}H_{14}N_4O_3S_2$ (326.40) calcd.: C, 44.15; H, 4.32; N, 17.16. Found: C, 44.10; H, 4.22; N, 17.10.

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

*Method A (from Compound **2**).* A solution of **2** (1 g, 0.0026 mol) and hydrazine hydrate 99% (10 ml) in ethanol (30 ml) was heated under reflux for 3 h. The solid product that had formed was , after cooling, collected by filtration, dried, and recrystallized from ethanol. Yield: 0.61 g (73.5%) of **4** as colorless crystals, mp 242–244°C. IR: $\nu = 3400$, 3200, 2850, 1700, 1680, and 1620 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.30$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.80 (t, $J = 5.6$ Hz, 2H, H-5), 3.60 (t, $J = 5.6$ Hz, 2H, H-6), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.30 (s, 2H, H-8), 4.70 (s, 2H, NH_2), 5.30 (s, 2H, NH_2), 8.30 (s, 1H, NH). ^{13}C NMR (DMSO-d_6): $\delta = 14.60$ (q, $COOCH_2CH_3$), 26.10 (t-C-5), 40.20 (t, C-6), 42.10 (t, C-8), 60.80 (t, $COOCH_2CH_3$), 112.20 (s, C-4a), 120.90 (s, C-8a), 129.10 (s, C-9a), 154.20 (s, C-2), 159.30 (s, C-4), 165.40 (s, CO). MS: $m/z = 324$ [M^+]. $C_{12}H_{16}N_6O_3S$ (324.36) calcd.: C, 44.43; H, 4.97; N, 25.90. Found: C, 44.55; H, 4.80; N, 25.80.

*Method B (from Compound **3**).* To a suspension of **3** (0.32 g , 0.001 mol) in ethanol (10 ml), hydrazine hydrate (99%, 5ml) was added and the mixture was heated under reflux for 6 h. After cooling, the precipitate that had formed was collected by filtration, dried, and recrystallized from ethanol. Yield: 0.24 g (75.7%) of **4** as colorless crystals, mp 243–244°C. The compound is identical in every respect with the compound obtained by Method A.

*Ethyl 3-Amino-10-oxo-3,8,9,10-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-d][1,2,4]triazolo[1,5-a]-pyrimidine-7(6H)-carboxylate (**5**)*

A mixture of compound **4** (0.32 g, 0.001 mol) and triethyl orthoformate 98%, $d = 0.89$ (0.2 ml, 0.0016 mol) in acetic acid (5 ml) was refluxed for

40 min. The solution was then cooled to room temperature and the resulting solid was collected by filtration, washed with diethyl ether, dried, and recrystallized from ethanol/dioxane. Yield: 0.2 g (60.6%) of **5** as colorless crystals, mp 260–262°C (decom.). IR: ν = 3420, 3320, 3200, 2990, 2950, 1710, 1680, 1640, 1600, and 1580 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.90 (t, $J = 5.6$ Hz, 2H, H-9), 3.70 (t, $J = 5.6$ Hz, 2H, H-8), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 6.20 (s, 2H, NH_2), 8.90 (s, 1H, H-2). ^{13}C-NMR (DMSO-d_6): $\delta = 14.20$ (q, $COOCH_2CH_3$), 25.60 (t, C-9), 40.90 (t, C-8), 42.70 (s, C-6), 61.60 (t, $COOCH_2CH_3$), 114.60 (s, C-9b), 125.90 (s, C-9a), 130.40 (s, C-5a), 153.40 (s, C-2), 154.70 (s, C-10), 155.60 (s, C-4a), 159.80 (s, C-3a), 164.30 (s, CO ester). MS: $m/z = 334$ [M^+]. $C_{13}H_{14}N_6O_3S$ (334.35) calcd.: C, 46.69; H, 4.22; N, 25.13; S, 9.58. Found: C, 46.57; H, 4.31; N, 24.96; S, 9.43.

*Ethyl 3-Amino-2-methyl-10-oxo-3,8,9,10-tetrahydropyrido[4′,3′:4,5]thieno-[2,3-d][1,2,4]triazolo-[1,5-a]pyrimidine-7(6H)-carboxylate (**6**)*

A mixture of compound **4** (0.32 g, 0.001 mol) and triethyl orthoacetate (0.18 g, 0.0014 mol) in acetic acid (5 ml) was refluxed for 30 min. The solution was then cooled to room temprature and the resulting solid was collected by filtration, washed with diethyl ether, dried, and recrystallized from ethanol/dioxane. Yield: 0.22 g (64.7%) of **6** as colorless crystals, mp 289–291°C. IR: $\nu = 3400$, 3300, 3200, 3000, 2850, 1700, 1680, and 1600 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 2.40 (s, 3H, CH_3), 3.00 (t, $J = 5.6$ Hz, 2H, H-9), 3.70 (t, $J = 5.6$ Hz, 2H, H-8), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 5.90 (s, 2H, NH_2). MS: $m/z = 348$ [M^+]. $C_{14}H_{16}N_6O_3S$ (348.39) calcd.: C, 48.26; H, 4.62; N, 24.12; S, 9.20. Found: C, 48.39; H, 4.80; N, 24.27; S 9.28.

*Ethyl 4-Amino-5-oxo-4,5,6,9-tetrahydropyrido[4′,3′:4,5]thieno[3,2-e][1,2,3,4]-tetrazolo[1,5-a]-pyrimidine-8(7H)-carboxylate (**8**)*

To a stirred suspension of compound **4** (0.64 g, 0.002 mol) in a mixture of acetic acid (8 ml) and water (6 ml) a solution of sodium nitrite (0.17 g, 0.002 mol) in water (6 ml) was added dropwise at 0°C. The mixture was left in the refrigerator for 12 h. and the precipitate that had formed was collected by filtration, dried, and recrystallized from DMF. Yield: 0.36 g (54.54%) of **8** as yellow crystals, mp 192–194°C. IR: $\nu = 3300$, 3000, 1700, 1670, and 1580 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.90 (t, $J = 5.6$ Hz, 2H, H-6), 3.60 (t, $J = 5.6$ Hz, 2H, H-7), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-9), 5.80 (s, 2H, NH_2). MS: $m/z = 335$ [M^+]. $C_{12}H_{13}N_7O_3S$ (335.34) calcd.: C, 42.98; H, 3.90; N, 29.23. Found: C, 42.90; H, 3.78; N, 29.11.

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

To a solution of compound **2** (0.38 g, 0.001 mol) in benzene (10 ml), 1,2-diaminoethane (0.09 g, 0.0015 mol) was added, and the mixture was heated under reflux for 6 h. The precipitate that had formed was, after cooling, collected by filtration, dried, and recrystallized from ethanol. Yield: 0.25 g (80.6%) of **9** as colorless crystals, mp 294–296°C. IR: $\nu =$ 3100, 2990, 2940, 1750, 1710, 1680, and 1640 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.30$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.80 (t, $J = 5.6$ Hz, 2H, H-6), 3.50–3.70 (m, 4H, H-7, H-3), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.40 (t, $J = 7.6$ Hz, 2H, H-2), 4.50 (s, 2H, H-9), 9.05 (brs, 1H, NH). MS: $m/z = 320$ [M^+]. $C_{14}H_{16}N_4O_3S$ (320.38) calcd.: C, 52.48; H, 5.03; N, 17.48. Found: C, 52.31; H, 4.99; N, 17.37.

*Ethyl 5-Oxo-2,3,6,9-tetrahydro-5H-pyrido[4′,3′:4,5]thieno[2,3-d][1,3]thiazolo[3,2-a]pyrimidine-8(7H)-carboxylate (**10**)*

To a solution of compound **2** (0.38 g, 0.001 mol) in anhydrous pyridine (10 ml), aminoethanethiol hydrochloride (0.16 g, 0.0014 mol) was added and the mixture was heated under reflux for 24 h. The solvent was evaporated in vacuo, sodium hydroxide (aqueous solution, 10%, 10 ml) was added, and the resulting precipitate was collected by filtration, dried, and recrystallized from ethanol. Yield: 0.21 g (63.6%) of **10** as colorless crystals, mp 174–176°C. IR: $\nu = 3000$, 2980, 1700, 1680, and 1540 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.80 (t, $J = 5.6$ Hz, 2H, H-6), 3.55–3.70 (m, 4H, H-7, H-3), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.40 (t, $J =$ 7.6 Hz, 2H, H-2), 4.60 (s, 2H, H-9). ^{13}C-NMR (DMSO-d_6): $\delta = 14.15$ (q, $COOCH_2CH_3$), 25.12 (t, C-6), 26.80 (t, C-2), 40.7 (t, C-7), 42.70 (s, C-9), 48.16 (t, C-3), 61.06 (t, $COOCH_2CH_3$), 117.48 (s, C-5a), 127.03 (s, C-5b), 128.92 (s, C-9a), 154.70 (s, C-10a), 156.18 (s, C-11a), 160.76 (s, C-5), 163.43 (s, CO ester). MS: $m/z = 337$ [M^+]. $C_{14}H_{15}N_3O_3S_2$ (337.43) calcd.: C, 49.83; H, 4.48; N, 12.45; S, 19.00. Found: C, 49.75; H, 4.31; N, 12.28; S, 19.12.

*Ethyl 2-Amino-10-oxo-8,9-dihydro-10H-pyrido-[4′,3′:4,5]thieno[2,3-d][1,3,4]-thiadiazolo[3,2-a]-pyrimidine-7(6H)-carboxylate (***12***)*

A mixture of compound **3** (0.32 g, 0.001 mol) and cyanogen bromide (0.13 g, 0.0012 mol) in aqueous ethanol 75% (8 ml) was refluxed for 3 h. The reaction mixture was evaporated to one-fourth of its volume and neutralized by the addition of a saturated aqueous solution of sodium acetate. The solid product that had formed was collected by filtration, dried, and recrystallized from ethanol. Yield: 0.26 g (75.5%) of **12** as colorless crystals, mp 233–235°C. IR : $\nu = 3200$–3300, 3000, 2900, 1700, 1680, and 1620 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.90 (t, $J = 5.6$ Hz, 2H, H-9), 3.70 (t, $J = 5.6$ Hz, 2H, H-8), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 7.99 (br s, 2H, NH_2). ^{13}C NMR (DMSO-d_6): $\delta = 14.40$ (q, $COOCH_2CH_3$), 25.10 (t, C-9), 40.80 (t, C-8), 42.80 (t, C-6), 61.40 (t, $CO_2CH_2CH_3$), 118.10 (s, C-9b), 128.80 (s, C-9a), 131.90 (s, C-5a), 150.50 (s, C-4a), 154.40 (s, C-2),161.40 (s, C-10), 166.90 (s, CO ester). MS: $m/z = 351$ [M^+]. $C_{13}H_{13}N_5O_3S_2$ (351.40) calcd.: C, 44.43; H, 3.73; N, 19.92; S, 18.24. Found: C, 44.55; H, 3.80; N, 19.78; S, 18.30.

*Ethyl 2-Hydrazino-10-oxo-8,9-dihydro-10H-pyrido[4′,3′:4,5]thieno[2,3-d]-[1,3,4]thiadiazolo-[3,2-a]pyrimidine-7(6H)-carboxylate (***13***)*

To a solution of compound **3** (0.64 g, 0.002 mol) in ethanol (15 ml) was added *N*-carbethoxyhydrazine (0.22 g, 0.002 mol) and hydrochloric acid (0.26 ml). The contents were refluxed for 10 h. Ethanol was distilled off compeletly. On basification with 10% sodium carbonate solution, the solid that separated was collected by filtration, washed with water, dried, and recrystallized from ethanol. Yield: 0.45 g, (62.67%) of **13** as yellow crystals, mp 270–273°C (melt with decom.). IR: $\nu = 3250$, 3200, 3100, 3000, 1700, 1685, and 1620 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.70 (t, $J = 5.6$ Hz, 2H, H-9), 3.70 (t, $J = 5.6$ Hz, 2H, H-8), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 5.80 (s, 2H, NH_2), 8.50 (s, 1H, NH). MS: $m/z = 366$ [M^+]. $C_{13}H_{14}N_6O_3S_2$ (366.42) calcd.: C, 42.61; H, 3.85; N, 22.93; S, 17.50. Found: C, 42.70; H, 3.92; N, 22.81; S, 17.67.

*Ethyl 2-Thioxo-10-oxo-6,7,8,9-tetrahydro pyrido-[4′,3′:4,5]thieno[2,3-d][1,3,4]-thiadiazolo[3,2-a]-pyrimidine-7-carboxylate (***14***)*

A solution of **3** (0.32 g, 0.001 mol) in pyridine (5 ml) was treated with carbon disulfide (1 ml) dropwise with stirring at room temperature. The mixture was then gently heated in an oil-bath at 100°C for 6 h with continous stirring. Pyridine was removed in vacuo and the residue dissolved in benzene (5 ml) and diluted with petroleum ether bp 60–80° (20 ml). The soild product that separated was collected by filtration, dried, and recrystallized from ethyl acetate (charcoal). Yield: 0.23 g (63.8%) of **14** as faint yellow crystals, mp 183–184°C. IR: $\nu = 3350$–3250, 2900, 1710, 1670, 1620, 1140 (C=S) cm^{-1}. ^1H-NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 2.90 (t, $J = 5.6$ Hz, 2H, H-9), 3.70 (t, $J = 5.6$ Hz, 2H, H-8), 4.90 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 5.30 (s, 1H, NH). MS: $m/z = 368$ [M^+]. $C_{13}H_{12}N_4O_3S_2$ (368.46) calcd.: C, 42.37; H, 3.28; N, 15.20; S, 26.10. Found: C, 42.49; H, 3.32; N, 15.33; S, 26.20.

*Ethyl 2,10-Dioxo-6,7,8,9-tetrahydropyrido-[4′,3′:4,5]thieno[2,3-d][1,3,4]-thiadiazolo[3,2-a]-pyrimidine-7-carboxylate (***15***)*

A solution of compound **3** (0.32 g, 0.001 mol) in ethanol (10 ml) was treated with ethyl chloroformate (0.12 g, 0.0011 mol) dropwise with stirring. The mixture was then heated at 70°C for 24 h. The solution was evaporated to dryness and the residue diluted with water. The solid product was collected by filtration, washed with water, dried, and recrystallized from ethanol/water. Yield: 0.28 g (81.1%) of **15** as colorless crystals, mp 111–113°C. IR : $\nu =$ 3300, 3100, 3000, 2980, 1745, 1710, and 1685 cm^{-1}. ^1H NMR (DMSO-d_6): $\delta = 1.20$ (t, $J = 7.0$ Hz, 3H, $COOCH_2CH_3$), 3.00 (t, $J = 5.6$ Hz, 2H, H-9), 3.60 (t, $J = 5.6$ Hz, 2H, H-8), 4.10 (q, $J = 7.0$ Hz, 2H, $COOCH_2CH_3$), 4.60 (s, 2H, H-6), 8.90 (s, 1H, NH). MS: $m/z = 352$ [M^+]. $C_{13}H_{12}N_4O_4S_2$ (352.40) calcd.: C, 44.30; H, 3.43; N, 15.89. Found: C, 44.20; H, 3.51; N, 15.80.

REFERENCES

[1] Sharma, S.; Charles, E. S. Prog Drug Res 1982, 26, 9.

[2] (a) Parish, R. C. U S Pat 4 002 761, 1977, Chem Abstr 1977, 86, 13897; (b) Fischer, M. H.; Wang, C. C. Annu Rep Med Chem 1978, 13, 130; (c) Loenberg, J. Parasitology 1979, 65, 823; (d) Agarwal, V. K.; Sharma, S.; Iyer, R. N. Indian J Chem, Sect B 1981, 20, 398.

[3] For reviews see: (a) Drobnica, L.; Kristian, P.; Augustin, J. The Chemistry of Cyanates and their Thio Derivatives, Patai, S. (Ed.); Wiley: New York, 1977; p. 1003; (b) L'abbe, G. Synthesis 1987, 525.

[4] Modica, M.; Santagati, M.; Russo, F.; Parotti, L.; De Gioia, L.; Selvaggini, C.; Salmona, M.; Mennini, T. J Med Chem 1997, 40, 574.

[5] Urleb, U. J Heterocycl Chem 1998, 35, 693.
[6] Urleb, U. J Heterocycl Chem 1995, 32, 69.
[7] Urleb, U.; Neidlein, R.; Kramer, W. Helv Chim Acta 1993, 76, 431.
[8] Urleb, U.; Stanovnik, B.; Tisler, M. J Heterocycl Chem 1990, 27, 643.
[9] Urleb, U.; Neidlein, R.; Kramer, W. J Heterocycl Chem 1990, 27, 433.
[10] Urleb, U.; Stanovnik, B.; Tisler, M. J Heterocycl Chem 1990, 27, 413.
[11] Urleb, U.; Stanovnik, B.; Tisler, M. J Heterocycl Chem 1990, 27, 407.
[12] Ahmed, E. Kh.; Sensfuss, U.; Habicher, W. D. J Heterocycl Chem 1999, 36, 1119.
[13] Ahmed, E. Kh. Monatsh Chem 1995, 126, 953.
[14] Ahmed, E. Kh.; Gohar, A. M. N.; Ameen, M. A. Pharmazie 2000, 55(1), 31.
[15] Sauter, F.; Frohlich, J.; Ahmed, E. Kh. Monatsh Chem 1996, 127, 319.
[16] Ahmed, E. Kh.; Frohlich, J.; Sauter, F. Collect Czech Chem Commun 1996, 61, 147.
[17] Sauter, F.; Jordis, U.; Frohlich, J.; Gewald, K.; Grohmann, F.; Ahmed, E. Kh. ACH Models in Chemistry 1994, 131 (3/4), 489.