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CONDENSED THIENOPYRIMIDINES. 14*. SYNTHESIS OF 10H-THIOPYRANO-[4'',3'': 4',5']THIENO[2',3': 4,5]-PYRIMIDO[2,3-*c*]-1,2,4-TRIAZINES

A. Sh. Oganisyan, G. O. Grigoryan, and A. S. Noravyan

Reaction of a substituted 2-aminothienothiopyran with methyl(phenyl) isothiocyanate, intramolecular cyclization of the obtained N'-methyl(phenyl) thioureido derivatives, and work up of the cyclization products with hydrazine hydrate gave 2-hydrazinodihydrothiopyranothienopyrimidines. Treatment of the latter with pyruvic acid gave the novel 10H-thiopyrano[4'',3'':4',5']thieno[2',3':4,5]pyrimido-[2,3-c]-1,2,4-triazines.

Keywords: 10H-thiopyrano[4'',3'': 4',5']thieno[2',3': 4,5]pyrimido[2,3-*c*]-1,2,4-triazines.

Despite a systematic investigation carried out on a series of derivatives of condensed thieno[2,3-*d*]-pyrimidines [2], compounds of the group indicated condensed with other heterocycles have been little studied. In this regard, it is of current and of long term interest to develop convenient methods for the synthesis and investigation of the biological activity of the novel, condensed thiopyranothienopyrimidotriazine derivatives **1a,b**.

Treatment of 2-amino-3-carbethoxy-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-*c*]thiopyran (**2**) [3] with methyl or phenyl isothiocyanates gave the corresponding N'-methyl(phenyl)thioureido derivatives **3a,b**. The latter can then undergo an intramolecular cyclization in the presence of potassium hydroxide to form the dihydrothiopyranothienopyrimidines **4a,b** and also their 2-methylthio derivatives **5a,b**. The heteryl hydrazines **6** were prepared by the reaction of compounds **4a,b** with hydrazine hydrate in butanol. The target compounds **1a,b** were synthesized by two methods, the first being the reaction of the hydrazines **6a,b** with pyruvic acid in methanol and subsequent cyclization of the hydrazones formed **7a,b** in acetic acid and the second method a one stage reaction *via* refluxing the hydrazines **6a,b** and pyruvic acid in ethanol in the presence of acetic acid without separation of the intermediate hydrazones **7a,b**.

* For Communication 13 see [1].

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Armenian Republic National Academy of Sciences, Yerevan 375014; e-mail: west@msrc.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1116-1119, August, 2001. Original article submitted June 16, 1999.

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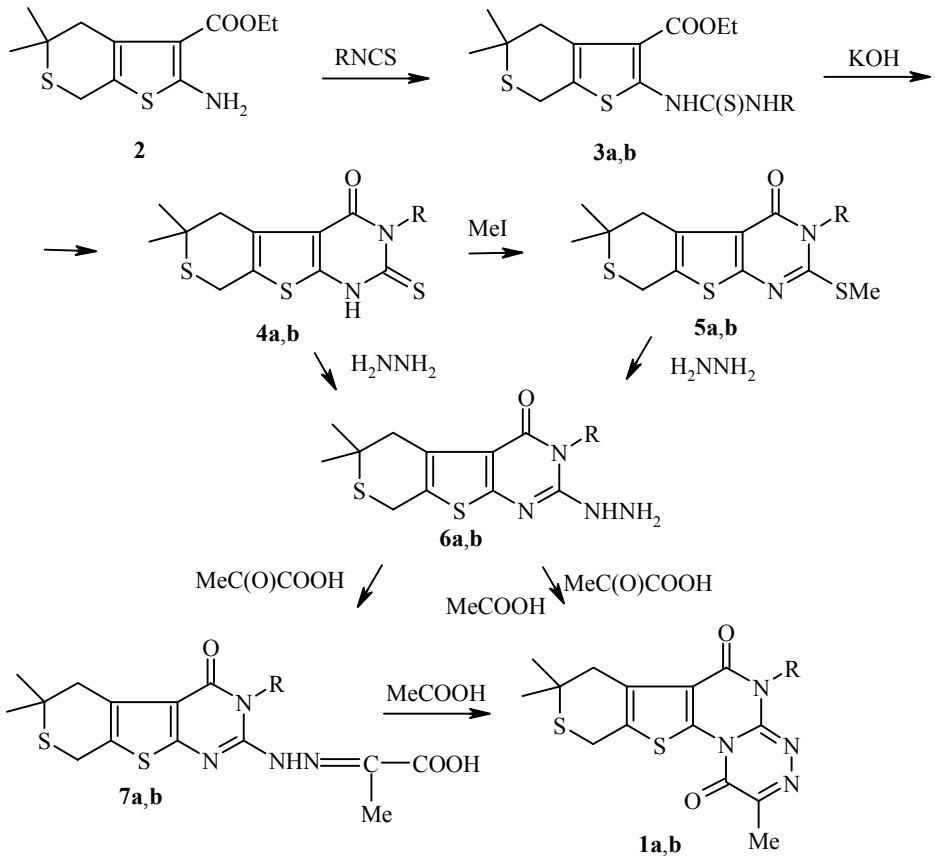

1, **3**–**7** **a** R = Me; **b** R = Ph

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument using vaseline oil, ^{1}H NMR spectra on a Varian T-60 spectrometer (60 MHz), and mass spectra on an MX-1303 instrument with an ionization energy of 70 eV. TLC was carried out on Silufol UV-254 plates and revealed using iodine vapor.

3-Carbethoxy-5,5-dimethyl-2-(N'-methylthioureido)-4,5-dihydro-7H-thieno[2,3-*c*]thiopyran (3a). A mixture of compound **2** (2.71 g, 0.01 mol), methyl isothiocyanate (0.73 g, 0.01 mol), and butanol (50 ml) was refluxed for 10 h and held for about 16 h at room temperature. The precipitated crystals were filtered off and washed with ether to give the product **3a** (3.28 g, 76%); mp 173-175°C (ethanol), R_f 0.62 (CCl_4–acetone, 2:1). IR spectrum (thin film), ν, cm^{-1}: 1450 (C=S), 1670 (C=O), 3300 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 12.06 (1H, s, NH); 6.90 (1H, d, *J* = 5, NH–CH_3); 4.25 (2H, q, *J* = 7, OCH_2); 3.62 (2H, s, 7,7-H_2); 3.06 (3H, d, *J* = 5, NH–CH_3); 2.89 (2H, s, 4,4-H_2); 1.35 (3H, t, *J* = 7, CH_2CH_3); 0.98 (6H, s, 5,5-$(CH_3)_2$). Found, %: C 47.42; H 5.53; N 8.38; S 27.61. $C_{14}H_{20}N_2O_2S_3$. Calculated, %: C 47.80; H 5.85; N 8.13; S 27.92.

3-Carbethoxy-5,5-dimethyl-2-(N'-phenylthioureido)-4,5-dihydro-7H-thieno[2,3-*c*]thiopyran (3b). From a mixture of compound **2** (2.71 g, 0.01 mol) and phenyl isothiocyanate (1.35 g, 0.01 mol) as described above to give the product **3b** (3.1 g, 77%); mp 181-182°C (ethanol), R_f 0.64 (hexane–acetone–ethyl acetate, 1:1:1). IR spectrum (thin film), ν, cm^{-1}: 1470 (C=S), 1670 (C=O), 3200 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, *J* (Hz): 12.06 (1H, s, NH); 8.46 (1H, NH–C_6H_5); 7.40 (5H, s, Ph); 4.23 (2H, q, *J* = 7, CH_2CH_3); 3.50 (2H, s, 7,7-H_2); 2.86 (2H, s, 4,4-H_2); 1.40 (3H, t, *J* = 7 , CH_2CH_3); 0.97 (6H, s, 5,5-$(CH_3)_2$). Found, %: C 56.30; H 5.53; N 6.68; S 23.91. $C_{19}H_{22}N_2O_2S_3$. Calculated, %: C 56.12; H 5.45; N 6.89; S 23.65.

3,3,6-Trimethyl-4-oxo-2-thioxo-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (4a). A mixture of compound **3a** (3.44 g, 0.01 mol) and potassium hydroxide (1.12 g, 0.02 mol) in 50% ethanol (50 ml) was refluxed for 3 h, cooled, and acidified with 10% hydrochloric acid to weakly acid reaction. The precipitated crystals were filtered off, washed with water, and dried to give the product **4a** (2.85 g, 96%); mp 274-276°C (butanol), R_f 0.58 (acetone–CCl_4, 1:1). IR spectrum (thin film), ν, cm^{-1}: 1725 (C=O), 3400-3425 (NH). Found, %: C 48.02; H 4.51; N 9.70; S 32.0. $C_{12}H_{14}N_2OS_3$. Calculated, %: C 48.29; H 4.72; N 9.38; S 32.23.

6,6-Dimethyl-4-oxo-3-phenyl-2-thioxo-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (4b). From a mixture of compound **3b** (4.06 g, 0.01 mol) and potassium hydroxide (1.12 g, 0.02 mol) as described above to give the product **4b** (3.44 g, 95%); mp 286-288°C (butanol), R_f 0.65 ($CHCl_3$–CCl_4, 2:1). Found, %: C 56.30; H 4.28; N 8.0; S 26.42. $C_{17}H_{16}N_2OS_3$. Calculated, %: C 56.63; H 4.47; N 7.77; S 26.68.

3,6,6-Trimethyl-2-methylthio-4-oxo-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (5a). Methyl iodide (1.42 g, 0.01 mol) in 90% ethanol (5 ml) was added dropwise with stirring to a solution of compound **4a** (2.98 g, 0.01 mol) and potassium hydroxide (0.56 g, 0.01 mol) in ethanol (20 ml). Stirring was continued for 2 h and the reaction mixture was then diluted with water (10 ml). The crystals formed were filtered off, washed with ether, and dried to give the product **5a** (2.85 g, 91%); mp 228-229°C (ethanol), R_f 0.56 (acetone–hexane, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.72 (2H, s, 8,8-H_2); 3.50 (3H, s, NCH_3); 2.98 (2H, s, 5,5-H_2); 2.58 (3H, s, S–CH_3); 1.20 (6H, s, 6,6-$(CH_3)_2$). Found, %: C 50.21; H 5.30; N 8.67; S 30.91. $C_{13}H_{16}N_2OS_3$. Calculated, %: C 50.0; H 5.12; N 8.97; S 30.76.

6,6-Dimethyl-2-methylthio-4-oxo-3-phenyl-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]-pyrimidine (5b). From a mixture of compound **4b** (3.60 g, 0.01 mol), potassium hydroxide (0.56 g, 0.01 mol), and methyl iodide (1.42 g, 0.01 mol) as described above to give the product **5b** (3.38 g, 90%); mp 240-242°C (ethanol), R_f 0.58 ($CHCl_3$–ethyl acetate, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.24-7.80 (5H, m, Ph); 3.70 (2H, s, 8,8-H_2); 3.0 (2H, s, 5,5-H_2); 2.63 (3H, s, S–CH_3); 1.27 (6H, s, 6,6-$(CH_3)_2$). Found, %: C 57.61; H 4.66; N 7.40; S 25.60. $C_{18}H_{18}N_2OS_3$. Calculated, %: C 57.72; H 4.84; N 7.48; S 25.68.

2-Hydrazino-3,6,6-trimethyl-4-oxo-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (6a). A. Concentrated hydrazine hydrate (10 ml) was added to a solution of compound **4a** (2.98 g, 0.01 mol) in butanol (25 ml). The mixture was refluxed for 8 h and held for about 16 h at room temperature. The precipitated crystals were filtered off, washed with water and then ether, and dried to give the product **6a** (2.66 g, 89%); mp 244-246°C (ethanol), R_f 0.61 (hexane–ethyl acetate, 1:3). IR spectrum (thin film), ν, cm^{-1}: 1450 (arom.), 1700 (C=O), 3200-3500 ($NHNH_2$). Found, %: C 49.0; H 5.15; N 18.45; S 21.40. $C_{12}H_{16}N_4OS_2$. Calculated, %: C 48.62; H 5.40; N 18.90; S 21.63.

B. Similarly from compound **5a** (3.12 g, 0.01 mol) and concentrated hydrazine hydrate (5 ml) in butanol (25 ml) to give the product **6a** (2.37 g, 80%); mp 244-246°C (pyridine). A mixed sample of compound **6a** prepared using methods A and B did not show a depression of melting point.

2-Hydrazino-6,6-dimethyl-4-oxo-3-phenyl-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (6b). A. From a mixture of compound **4b** (3.60 g, 0.01 mol) and concentrated hydrazine hydrate (10 ml) in butanol (25 ml) as described before in method A to give the product **6b** (3.2 g, 89%); mp 256-258°C (pyridine), R_f 0.60 ($CHCl_3$–CCl_4, 1:2). Mass spectrum, *m/z* (I_{rel}, %): 358 (M^+) (100), 325 (50), 315 (47), 295 (34), 285 (40), 284 (31), 269 (28), 254 (20), 192 (14), 152 (20). Found, %: C 56.77; H 4.78; N 15.91; S 17.80. $C_{17}H_{18}N_4OS_2$. Calculated, %: C 56.95; H 5.0; N 15.63; N 17.88.

B. From compound **5b** (3.74 g, 0.01 mol) and concentrated hydrazine hydrate (5 ml) in butanol (25 ml) as described in method A to give the product **6b** (3.02 g, 85%); mp 256-258°C (pyridine). A mixed sample of compound **6b** prepared using methods A and B did not show a depression of melting point.

2-(3,6,6-Trimethyl-4-oxo-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidyl) Hydrazone of 2-Ketopropanoic Acid (7a). A mixture of compound **6a** (2.90 g, 0.01 mol) and pyruvic acid (0.88 g, 0.01 mol) in methanol (80 ml) was refluxed for 3 h. The crystals produced on cooling were filtered off, washed with water, and dried in air to give the product **7a** (3.1 g, 83%); mp 211-213°C (pyridine), R_f 0.48

(chloroform–pyridine–butanol–acetic acid, 3:3:3:1). IR spectrum (thin film), ν, cm^{-1}: 1560 (arom), 1600, 1620 (C=N), 1700 (C=O), 3220 (NH), 3380 (OH). Found, %: C 53.48; H 5.83; N 16.25; S 10.05. $C_{15}H_{18}N_4O_3S_2$. Calculated, %: C 53.87; H 5.42; N 16.75; S 9.59.

2-(6,6-Dimethyl-4-oxo-3-phenyl-5,6-dihydro-8H-thiopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidyl) Hydrazone of 2-Ketopropanoic Acid (7b). From compound **6b** (3.58 g, 0.01 mol) and pyruvic acid (0.88 g, 0.01 mol) as described before to give the product **7b** (3.77 g, 88%); mp 209-211°C (pyridine), R_f 0.60 (chloroform–pyridine–butanol–acetic acid, 3:3:3:1). IR spectrum (thin film), ν, cm^{-1}: 1550 (arom.), 1600, 1640 (C=N), 1685, 1740 (C=O), 3220 (NH), 3370 (OH). Found, %: C 56.71; H 4.97; N 12.70; S 14.50. $C_{20}H_{20}N_4O_3S_2$. Calculated, %: C 56.50; H 4.70; N 13.07; S 14.96.

2,5,8,8-Tetramethyl-1,6-dioxo-7,8-dihydro-10H-thiopyrano[4'',3'':4',5']thieno[2',3':4,5]pyrimido-[2,3-*c*]-1,2,4-triazine (1a). A. A mixture of the hydrazone **7a** (3.34 g, 0.01 mol) and acetic acid (40 ml) was refluxed for 14 h. The crystals formed on cooling were filtered off, washed with water, and dried to give the product **1a** (2.5 g, 73%); mp 281-282°C (pyridine), R_f 0.62 (chloroform–pyridine–hexane, 1:1:2). IR spectrum (thin film), ν, cm^{-1}: 1550 (C=C), 1580 (C=N), 1680, 1700 (C=O). ^{1}H NMR spectrum (pyridine), δ, ppm: 4.03 (2H, s, 10,10-H_2); 3.76 (3H, s, NCH_3); 3.38 (2H, s, 7,7-H_2); 2.58 (3H, s, CH_3); 1.40 (6H, s, 8,8-$(CH_3)_2$). Found, %: C 51.46; H 4.50; N 15.89; S 17.92. $C_{15}H_{16}N_4O_2S_2$. Calculated, %: C 51.70; H 4.63; N 16.08; S 18.40.

B. A mixture of compound **6a** (2.96 g, 0.01 mol) and pyruvic acid (0.88 g, 0.01 mol) in acetic acid (15 ml) and ethanol (50 ml) was refluxed for 10 h. The crystals formed on cooling were filtered off, washed with water and then ether, and dried in air to give the product **1a** (2.4 g, 69%); mp 281-282°C. A mixed sample of compound **1a** prepared using methods A and B did not show a depression of melting point.

2,8,8-Trimethyl-1,6-dioxo-5-phenyl-7,8-dihydro-10H-thiopyrano[4'',3'':4',5']thieno[2',3':4,5]-pyrimido[2,3-*c*]-1,2,4-triazine (1b). A. From the hydrazone **7** (4.28 g, 0.01 mol) according to method A for the synthesis of compound **1a** to give the product **1b** (3.7 g, 90%); mp 302-304°C (ethanol), R_f 0.60 (chloroform–acetone–hexane, 3:3:1). IR spectrum (thin film), ν, cm^{-1}: 1550 (C=C), 1580, 1600 (C=N), 1680, 1700 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.76-7.20 (5H, m, Ph); 3.92 2H, s, 10,10-H_2); 3.22 (2H, s, 7,7-H_2); 2.57 (3H, s, CH_3); 1.22 (6H, s, 8,8-$(CH_3)_2$). Found, %: C 58.06; H 4.80; N 13.25; S 15.15. $C_{20}H_{18}N_4O_2S_2$. Calculated, %: C 58.51; H 4.42; N 13.65; S 15.62.

B. From compound **6b** (3.58 g, 0.01 mol) according to method B for the synthesis of compound **1a** to give the product **1b** (2.8 g, 68%); mp 301-304°C, identical in R_f and melting point to the sample synthesized by method A.

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