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CONDENSED PYRIDOPYRIDIMINES. 8*. SYNTHESIS OF NEW DERIVATIVES OF PYRANO[3',4':6,7]PYRIDO[2,3-*d*]PYRIMIDINE

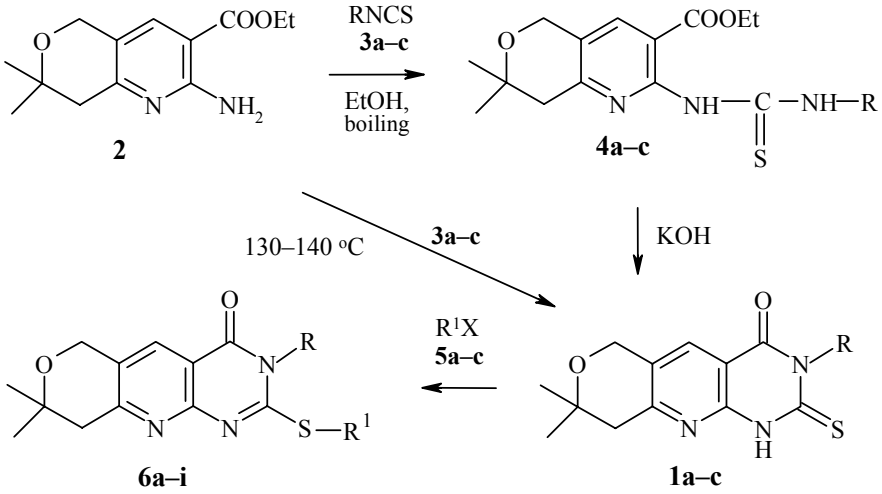
A. Sh. Oganessyan, A. S. Noravyan, and M. Zh. Grigoryan

New substituted 8,8-dimethyl-4-oxopyrano[3',4':6,7]pyrido[2,3-d]pyrimidines have been synthesized from 2-amino-3-ethoxycarbonyl-7,7-dimethylpyrano[4,3-b]pyridine.

Keywords: pyranopyridine, pyranopyridopyrimidine, pyridine, pyridopyrimidine, pyridimine, tetrahydropyran, synthesis.

We have previously prepared some derivatives of pyrano[3',4':6,7]pyrido[2,3-*d*]pyrimidine [2,3]. In a continuing search for biologically active compounds, we have synthesized new examples of this series containing various substituents in positions 2 and 3 of the pyrimidine ring.

3-Substituted 4-oxo-2-thiopyranopyridopyrimidines **1a-c** were synthesized by two methods: A) by boiling ethanolic solutions of 2-amino-3-ethoxycarbonylpyrano[4,3-*b*]pyridine **2** [2] with the isothiocyanates **3a-c** with subsequent heterocyclization of the 2-(N'-R-thioureido) derivatives **4a-c** under the influence of KOH; B) by condensation of pyranopyridine **2** with the isothiocyanates **3a-c** at 130-140°C.



1a, 3a, 4a, 6a,d,g R = CH_2Ph; **1b, 3b, 4b, 6b,e,h** R = $CH_2CH{=}CH_2$; **1c, 3c, 4c, 6c,f,i** R = C_6H_4OMe-4; **5a, 6a–c** R^1 = Et, X = I; **5b, 6d–f** R^1 = CH_2COPh, X = Br; **5c, 6g–i** R^1 = CH_2CONH_2, X = Cl

* For part 7 see [1].

A. L. Mndzhoyan Institute of Fine Organic Chemistry, National Academy of Sciences of the Armenian Republic, Erevan 375014; e-mail: west@msrc.am. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 10, 1554-1557, October, 2004. Original article submitted May 19, 2000; revision submitted March 5, 2004.

TABLE 1. Characteristics of the Compounds Synthesized, **1**, **4**, and **6**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f*	Yield, %
		C	H	N	S			
1a	$C_{19}H_{19}N_3O_2S$	64.5 / 64.6	5.4 / 5.4	11.8 / 11.9	9.1 / 9.1	310-312	0.61	88 (A) 92 (B)
1b	$C_{15}H_{17}N_3O_2S$	59.5 / 59.4	5.6 / 5.6	13.8 / 13.9	10.6 / 10.6	238-240	0.64	75.5 (A) 89 (B)
1c	$C_{19}H_{19}N_3O_3S$	62.1 / 61.8	5.7 / 5.2	11.8 / 11.4	8.1 / 8.7	300	0.67	87 (A) 90 (B)
4a	$C_{21}H_{25}N_3O_3S$	63.2 / 63.1	6.1 / 6.3	10.6 / 10.5	8.1 / 8.0	191-192	0.58	50
4b	$C_{17}H_{23}N_3O_3S$	58.6 / 58.4	6.5 / 6.6	12.1 / 12.0	9.0 / 9.2	155-156	0.61	51.2
4c	$C_{21}H_{25}N_3O_4S$	61.0 / 60.7	6.0 / 6.2	10.8 / 10.1	6.7 / 7.7	157-159	0.63	52
6a	$C_{21}H_{23}N_3O_2S$	63.65 / 63.5	5.5 / 5.8	10.7 / 10.6	8.2 / 8.1	181-183	0.57	92.3
6b	$C_{17}H_{21}N_3O_2S$	61.8 / 61.6	6.2 / 6.3	13.0 / 12.7	9.6 / 9.8	123-125	0.60	90.3
6c	$C_{21}H_{23}N_3O_3S$	63.6 / 63.5	5.6 / 5.8	11.1 / 10.6	7.9 / 8.1	175-177	0.64	75.7
6d	$C_{27}H_{25}N_3O_3S$	68.7 / 68.8	5.0 / 4.9	8.7 / 8.9	7.1 / 6.8	210-212	0.58	89.3
6e	$C_{23}H_{23}N_3O_3S$	65.7 / 65.6	5.7 / 5.9	10.3 / 10.0	6.8 / 7.6	165-167	0.53	82.5
6f	$C_{27}H_{25}N_3O_4S$	67.1 / 66.5	4.8 / 5.1	8.4 / 8.6	6.8 / 6.6	194-196	0.57	80
6g	$C_{21}H_{22}N_4O_3S$	61.6 / 61.5	5.3 / 5.4	13.5 / 13.7	7.9 / 7.8	150-152	0.62	81.5
6h	$C_{17}H_{20}N_4O_3S$	56.5 / 56.7	5.6 / 5.6	15.9 / 15.6	8.4 / 8.8	162-164	0.63	73.5
6i	$C_{21}H_{22}N_4O_4S$	60.0 / 59.2	4.9 / 5.2	13.4 / 13.2	7.3 / 7.5	208-210	0.67	75

*Solvent systems: chloroform–benzene–ether, 2:1:1 (**1a-c**); chloroform–ether, 1:2 (**4a**); chloroform–ether–isooctane, 1:2:1 (**4b,c**]; chloroform–ether–heptane, 1:1:1 (**6a-i**).

It should be noted that the single stage route B gave higher yields of the required products **1**.

The corresponding S-alkylsubstituted **6a-i** were obtained as the result of interaction of compounds **1a-c** with the halogeno derivatives **5a-c.**

EXPERIMENTAL

IR spectra of nujol mulls were recorded on a UR-20 spectrometer, ^{1}H NMR spectra of DMSO-d_6 (**1a-c**, **4a,c, 6a,c,d),** $CDCl_3$ (**4b**), and pyridine-d_5 (**6h,i**) solutions were recorded with a Varian Mercury 300 (300 MHz) machine. TLC was carried out on Silufol UV-254 plates with development with iodine vapor.

Characteristics of the compounds synthesized are given in Table 1.

2-(N'-benzylthioureido)-3-ethoxycarbonyl-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (4a). A mixture of **2** (2.5 g, 0.01 mol) and benzyl isothiocyanate **3a** (3.2 g, 0.02 mol) in ethanol (50 ml) was boiled for 10 h. The crystalline product **4a** which separated on cooling was filtered off, washed with ether and recrystallized from ethanol. IR spectrum (thin film), ν, cm^{-1}: 1470 (C=S), 1630 (C=N), 1690 (C=O), 3200 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.90 (1H, s, HNHet); 8.20 (1H, s, H-4), 7,17 (5H, s, C_6H_5); 6.86 (1H, t,

^3J = 5.0, NHR); 4.60 (2H, d, ^3J = 5.0, $\underline{CH_2}C_6H_5$); 4.53 (2H, s, 2H-5); 4.13 (2H, q, ^3J = 7.0, $O\underline{CH_2}CH_3$); 2.60 (2H, s, 2H-8); 1.25 (3H, t, ^3J = 7.0, $OCH_2\underline{CH_3}$); 1.20 (6H, br. s, $2CH_3$-7).

2-(N'-Allylthioureido)-3-ethoxycarbonyl-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (4b) was obtained from compound **2** (2.5 g, 0.01 mol) and allyl isothiocyanate **3b** (2.0 g, 0.02 mol) by the method described above. IR spectrum (thin film), ν, cm^{-1}: 1460 (C=S), 1630 (C=N), 1680 (C=O), 3250 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.90 (1H, s, NHHet); 8.20 (1H, s, H-4); 6.93 (1H, t, ^3J = 5.8, NHR); 6.22-4.95 (3H, m, $CH=CH_2$); 4.60 (2H, s, 2H-5); 4.23 (2H, q, ^3J = 6.0, $O\underline{CH_2}CH_3$); 4.02 (2H, t, ^3J = 5.8, $NH\underline{CH_2}$); 2.67 (2H, s, 2H-8); 1.28 (3H, t, ^3J = 6.0, $OCH_2\underline{CH_3}$); 1.23 (6H, s, $2CH_3$-7).

3-Ethoxycarbonyl-2-[(N'-4-methoxyphenyl)thioureido]-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]-pyridine (4c) was obtained from compound **2** (2.5 g, 0.01 mol) and 4-methoxyphenyl isothiocyanate **3c** (3.3 g, 0.01 mol) by the method described above. IR spectrum (thin film), ν, cm^{-1}: 1470 (C=S), 1620 (C=N), 1680 (C=O), 3300 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.60 (1H, s, NHR); 11.21 (1H, s, NHHet); 8.20 (1H, s, H-4); 7.60-6.85 (4H, m, C_6H_4); 4.75 (2H, s, 2H-5); 4.40 (2H, q, ^3J = 7.0, $O\underline{CH_2}CH_3$); 3.80 (3H, t, ^3J = 7.0, OCH_3); 2.80 (2H, s, 2H-8); 1.40 (3H, t, ^3J = 7.0, $OCH_2\underline{CH_3}$); 1.20 (6H, s, $2CH_3$-7).

3-Substituted 8,8-Dimethyl-4-oxo-2-thioxo-8,9-dihydro-6H-pyrano[3',4':6,7]pyrido[2,3-*d*]-pyrimidines 1a-c. A. A mixture of thioureide **4a-c** (0.01 mol), KOH (0.02 mol), and 70% ethanol (50 ml) was boiled for 1 h, cooled, and treated with 10% hydrochloric acid until slightly acidic. The crystals of the products **1a-c** which precipitated were filtered off, washed with water, dried, and recrystallized from butanol.

B. A mixture of compound **2** (2.5 g) and an isothiocyanate **3a-c** (3 ml) was maintained at 130-140°C for 7h. The crystals of compound **1a-c** which separated on cooling after treating with ethanol were filtered off, washed with ether, and recrystallized from butanol. IR spectrum (thin film), ν, cm^{-1}, **1a-c**: 1460 (C=S), 1670 (C=O). ^{1}H NMR spectra, δ, ppm (*J*, Hz): **1a**: 8.20 (1-H, s, 5-H); 7.70-7.20 (5H, m, C_6H_5); 6.00 (2H, s, NCH_2); 4.73 (2H, s, 2H-6); 2.98 (2H, s, 2H-9); 1.26 (6H, s, $2CH_3$-8); **1b**: 8.50 (1H, s, NH); 8.15 (1H, s, H-5); 6.35-5.15 (3H, m, $CH=CH_2$); 5.03 (2H, br. s, NCH_2); 4.63 (2H, s, 2H-6); 2.82 (2H, s, 2H-9); 1.23 (6H, s, $2CH_3$-8),; **1c**: 13.17 (1H, s, NH); 8.02 (1H, s, H-5); 7.09-6.83 (4H, m, C_6H_4); 4.80 (2H, s, 2H-6); 3.80 (3H, s, OCH_3); 2.80 (2H, s, 2H-9); 1.24 (6H, s, $2CH_3$-8).

3-Substituted 2-Ethylthio-8,8-dimethyl-4-oxo-8,9-dihydro-6H-pyrano[3',4':6,7]pyrido[2,3-*d*]-pyrimidines 6a-c. Ethyl iodide **5a** (1.56 g, 0.01 mol) was added dropwise with stirring to a solution of compound **1a-c** (0.01 mol) and KOH (0.56 g, 0.01 mol) in 90% ethanol (20 ml) heated to 40°C. The crystals of the product **6a-c** which separated were filtered off, washed with water and ether, and recrystallized from ethanol. ^{1}H NMR spectra, δ, ppm (*J*, Hz): **6a**: 8.20 (1H, s, H-5); 7.21 (5H, s, C_6H_5); 5.25 (2H, s, $\underline{CH_2}C_6H_5$); 4.80 (2H, s, 2H-6); 3.38 (2H, m, SCH_2); 2.81 (2H, s, 2H-9); 1.42 (3H, m, $CH_2\underline{CH_3}$); 1.26 (6H, s, $2CH_3$-8); **6c**: 8.20 (1H, s, H-5); 7.10, 7.20 (4H, two d, $^3J_1 = {}^3J_2$ = 8.8, C_6H_4); 4.81 (2H, s, H-6); 3.90 (3H, s, OCH_3); 3.19 (2H, m, SCH_2); 2.87 (2H, s, 2H-9); 1.40-1.22 (9H, m, $CH_2\underline{CH_3}$, $2CH_3$-8).

3-Substituted 2-(Benzoylmethyl)thioxo-8,8-dimethyl-4-oxo-8,9-dihydro-6H-pyrano[3',4':6,7]pyrido-[2,3-*d*]pyrimidines 6d-f were obtained from a mixture of compound **1a-c** (0.01 mol) and bromoacetophenone **5b** (2.0 g, 0.01 mol) by the method used for the synthesis of compounds **6a-c**. IR spectrum (thin film), ν, cm^{-1}, **6d-f**: 1620 (C=N), 1680 (amide C=O), 1700 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz), **6d** : 8.20-7.40 (11H, m, H-5, $CH_2C_6\underline{H_5}$, $O=CC_6\underline{H_5}$); 6.00 (2H, s, $\underline{CH_2}C_6H_5$); 4.80 (4H, s, CH_2-6, SCH_2); 2.82 (2H, s, 2H-9); 1.30 (6H, s, $2CH_3$-8).

3-Substituted 2-(Carbamoylmethyl)thioxo-8,8-dimethyl-4-oxo-8,9-dihydro-6H-pyrano[3',4':6,7]-pyrido[2,3-*d*]pyrimidines 6g-i. A mixture of compound **1a-c** (0.01 mol), chloroacetamide **5c** (1.0 g, 0.01 mol), and KOH (0.56 g, 0.01 mol) in 90% ethanol (20 ml) was boiled for 4 h. The crystals of product **6g-i** which formed on cooling the reaction mixture was filtered off, washed with water, and recrystallized from ethanol. IR spectra (thin film), ν, cm^{-1}, **6g-i**: 1630 (C=N), 1670, 1680 (amide C=O), 3400 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz), **6h**: 8.33 (2H, br. s, NH_2); 6.20-5.07 (3H, m, $CH=CH_2$); 4.93 (2H, m, NCH_2); 4.83 (2H, s, 2H-6); 4.43 (2H, s, SCH_2); 3.13 (2H, s, 2H-9); 1.28 (6H, s, $2CH_3$-8); **6i**, 8.20 (1H, s, H-5); 7.41-7.00 (6H, m, NH_2, C_6H_4); 4.81 (2H, s, 2H-6); 3.83 (5H, m, $S\underline{CH_2}$, $O\underline{CH_3}$); 2.90 (2H, s, 2H-9); 1.33 (6H, s, $2CH_3$-8).

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