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SYNTHESIS OF NEW CONDENSED DERIVATIVES OF PYRANO[4,3-*b*]THIENO[3,2-*e*]PYRIDINE AND PYRIDO[3',2':4,5]THIENO[3,2-*d*]PYRIMIDINE

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The reactions of 2-methyl (propyl) substituted 8,8-dimethyl-7,10-dihydro-4H,8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-d][1,3]oxazines with primary amines give 2-methyl (propyl) substituted 8,8-dimethyl-7,10-dihydro-8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-d][1,3]pyrimidin-4(3H)-ones or 3-acetyl-N-alkyl- and N-alkyl-3-butyrylamino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-b]thieno[3,2-e]-pyridine-2-carboxamides depending on steric hindrance in the amines.

Keywords: 3-acylamino-N-alkyl-7,8-dihydro-5H-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamides, 7,10-dihydro-8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-ones, 7,10-dihydro-4H,8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-ones, 7,8-dihydro-5H-pyrano-[4,3-*b*]-thieno[3,2-*e*]pyridines, cyclization.

Derivatives of condensed compounds containing the thieno[2,3-*b*]pyridine system as a fragment display valuable biological properties [1, 2]. In order to obtain and study the biological activity of new compounds in this series, we developed a method for their synthesis starting from 3-amino-7,7-dimethyl7,8-dihydro-5H-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxylic acid (**1**).

Acid **1** was obtained by the hydrolysis of its ethyl ester [3] using aqueous sodium hydroxide. This acid was previously synthesized from 3-cyano-7,7-dimethyl-2-sulfanyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine and bromoacetic acid [4]. Heating amino acid **1** with acetic anhydride (**2a**) or butyric anhydride (**2b**) at reflux leads to 2-methyl- (**3a**) or 2-propyl-8,8-dimethyl-7,10-dihydro-4H,8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno-[3,2-*d*][1,3]oxazin-4-one (**3b**). A study of the reaction of compounds **3a** and **3b** with primary amines **4a–h** showed that various products are formed depending on the structure of these amines. Thus, amines **4a–e** gave derivatives of 7,10-dihydro-8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidine **5a–j** in 63–76% yield. Under the same conditions, sterically hindered amines **4f–h** gave 7,8-dihydro-5H-pyrano[4,3-*b*]-thieno[3,2-*e*]pyridine derivatives **6a–f** in 63–67% yield. Thienopyridine derivatives **6a–f** do not cyclize even upon prolonged heating.

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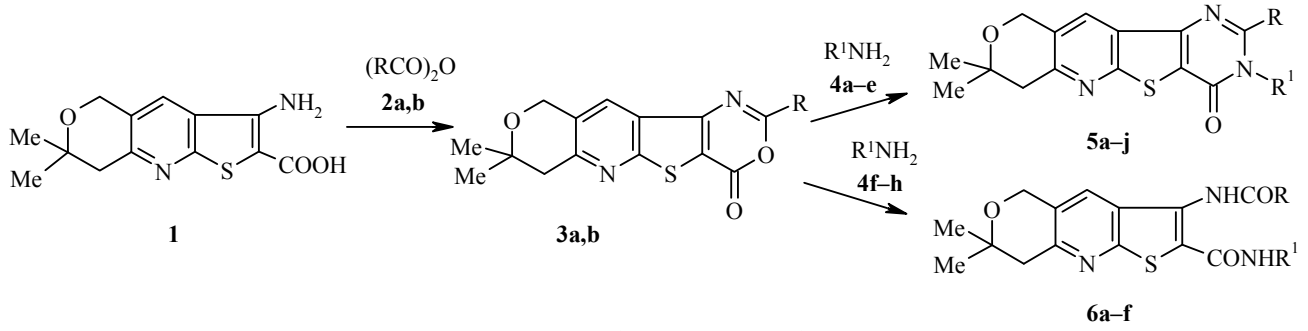
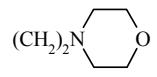
TABLE 1. Physicochemical Characteristics of Compounds **1, 3b, 5a–j,** and **6a–f**

Compound	Empirical formula	Found, % / Calculated, %				mp, ºC	R_f	Yield, %
		C	H	N	S			
1	$C_{13}H_{14}N_2O_3S$	56.25 / 56.10	5.01 / 5.07	10.12 / 10.06	11.45 / 11.52	204–205 204–206 [4]	0.56	89
3b	$C_{17}H_{18}N_2O_3S$	61.68 / 61.79	5.56 / 5.49	8.59 / 8.48	9.93 / 9.70	202–204	0.57	58
5a	$C_{16}H_{17}N_3O_2S$	60.88 / 60.93	5.60 / 5.43	13.45 / 13.32	10.11 / 10.17	222–223	0.61	73
5b	$C_{20}H_{25}N_3O_2S$	64.56 / 64.66	6.61 / 6.78	11.45 / 11.31	8.75 / 8.63	162–163	0.62	69
5c	$C_{22}H_{21}N_3O_2S$	67.54 / 67.50	5.58 / 5.41	10.61 / 10.73	8.28 / 8.19	209–210	0.63	76
5d	$C_{23}H_{23}N_3O_2S$	68.436 / 8.12	5.88 / 5.72	10.47 / 10.36	8.13 / 7.91	229–230	0.59	76
5e	$C_{21}H_{26}N_4O_3S$	60.76 / 60.85	6.41 / 6.32	13.39 / 13.52	7.82 / 7.74	180–185	0.58	76
5f	$C_{18}H_{21}N_3O_2S$	63.12 / 62.95	6.25 / 6.16	12.32 / 12.23	9.28 / 9.34	167–168	0.57	66
5g	$C_{22}H_{29}N_3O_2S$	65.99 / 66.13	7.28 / 7.32	10.61 / 10.52	8.22 / 8.03	150–151	0.61	63
5h	$C_{24}H_{25}N_3O_2S$	68.77 / 68.71	6.13 / 6.02	9.98 / 10.02	7.59 / 7.64	210–211	0.63	69
5i	$C_{25}H_{27}N_3O_2S$	69.33 / 69.26	6.13 / 6.28	9.58 / 9.69	7.43 / 7.40	185–186	0.62	69
5j	$C_{23}H_{30}N_4O_3S$	62.33 / 62.42	6.78 / 6.83	12.77 / 12.66	7.38 / 7.25	175–176	0.59	71
6a	$C_{21}H_{27}N_3O_3S$	62.70 / 62.82	6.83 / 6.78	10.29 / 10.47	8.11 / 7.99	209–210	0.61	67
6b	$C_{19}H_{25}N_3O_3S$	60.82 / 60.78	6.59 / 6.71	11.22 / 11.19	8.49 / 8.54	241–242	0.62	65
6c	$C_{24}H_{27}N_3O_3S$	65.79 / 65.88	6.13 / 6.22	9.71 / 9.60	7.44 / 7.33	198–199	0.63	65
6d	$C_{23}H_{31}N_3O_3S$	64.28 / 64.31	7.33 / 7.27	9.83 / 9.78	7.39 / 7.46	192–193	0.59	66
6e	$C_{21}H_{29}N_3O_3S$	62.44 / 62.50	7.28 / 7.24	10.33 / 10.41	8.12 / 7.95	169–170	0.60	63
6f	$C_{26}H_{31}N_3O_3S$	67.13 / 67.07	6.59 / 6.71	9.13 / 9.02	6.94 / 6.89	182–183	0.58	64

The composition and structure of synthesized compounds were supported by elemental analysis (Table 1), ^{1}H NMR spectroscopy (Tables 2 and 3), and IR spectroscopy.



2a, 3a, 5a–e, 6a–c R = Me; **2b, 3b, 5f–j, 6d–f** R = Pr; **4a, 5a,f** R^1 = Me; **4b, 5b,g** R^1 = C_5H_{11},

4c, 5c,h R^1 = CH_2Ph; **4d, 5d,i** R^1 = $(CH_2)_2Ph$; **4e, 5e,j** R^1 = 

4f, 6a,d R^1 = *c*-Hex; **4g, 6b,e** R^1 = *s*-Bu; **4h, 6c,f** R^1 = $CHMeCH_2Ph$

TABLE 2. ^{1}H NMR Spectra of Compounds **5a–j**

Compound	Chemical shifts, δ, ppm (*J*, Hz)							
	8H-Pyran fragment			R			R[1]	11-CH (1H, s)
	8-$(CH_3)_2$ (6H, s)	7-CH_2 (2H, s)	10-CH_2 (2H, s)	CH_3 (3H)	$C\underline{H}_2CH_3$ (2H, m)	$CH_2C\underline{H}_2CH_3$ (2H, t)		
5a	1.33	2.95	4.90	2.52 (s)	–	–	3.62 (3H, s, CH_3)	8.18
5b	1.33	2.96	4.90	2.70 (s)	–	–	0.97 (3H, m, CH_3); 1.39–1.47 (4H, m, $(C\underline{H}_2)_2CH_3$); 1.73 (2H, m, $NCH_2C\underline{H}_2$); 4.10 (2H, m, NCH_2)	8.18
5c	1.33	2.97	4.90	2.59 (s)	–	–	5.46 (2H, s, NCH_2); 7.21–7.36 (5H, m, C_6H_5)	8.20
5d	1.33	2.97	4.90	2.50 (s)	–	–	3.05 (2H, m, $C\underline{H}_2C_6H_5$); 4.33 (2H, m, NCH_2); 7.19–7.32 (5H, m, C_6H_5)	8.18
5e	1.33	2.97	4.90	2.74 (s)	–	–	2.52 (4H, m, CH_2NCH_2); 2.66 (2H, t, *J* = 6.7, 3-$NCH_2C\underline{H}_2$); 3.59 (4H, m, CH_2OCH_2); 4.24 (2H, t, *J* = 6.7, 3-NCH_2)	8.18
5f	1.33	2.96	4.90	1.12 (t, *J* = 7.3)	1.91	2.88 (*J* = 7.5)	3.65 (3H, s, CH_3)	8.16
5g	1.33	2.96	4.91	1.12 (t, *J* = 7.4)	1.93	2.87 (*J* = 7.5)	0.97 (3H, m, CH_3); 1.44 (4H, m, $(C\underline{H}_2)_2CH_3$); 1.72 (2H, m, $NCH_2C\underline{H}_2$); 4.10 (2H, m, NCH_2)	8.16
5h	1.33	2.98	4.92	0.99 (t, *J* = 7.4)	1.82	2.78 (*J* = 7.4)	5.46 (2H, s, NCH_2); 7.17–7.36 (5H, m, C_6H_5)	8.19
5i	1.33	2.98	4.92	1.03 (t, *J* =7.4)	1.83	2.67 (*J* = 7.4)	3.04 (2H, m, $C\underline{H}_2C_6H_5$); 4.33 (2H, m, NCH_2); 7.18–7.32 (5H, m, C_6H_5)	8.17
5j	1.32	2.97	4.91	1.12 (t, *J* = 7.4)	1.94	2.94 (*J* = 7.5)	2.53 (4H, m, CH_2NCH_2); 2.66 (2H, t, *J* = 6.7, 3-$NCH_2C\underline{H}_2$); 3.60 (4H, m, CH_2OCH_2); 4.25 (2H, t, *J* = 6.7, 3-NCH_2)	8.17

TABLE 3. ^{1}H NMR Spectra of Compounds **6a–f**

Compound	Chemical shifts, δ, ppm (*J*, Hz)									
	5H-Pyran fragment			R			R^1	3-NH (1H, br. s)	2-CONH (1H, d)	4-CH (1H, s)
	7-$(CH_3)_2$ (6H, s)	5-CH_2 (2H, s)	8-CH_2 (2H, s)	CH_3 (3H)	$C\underline{H}_2CH_3$ (2H, m)	$C\underline{H}_2CH_2CH_3$ (2H, t)				
6a	1.31	4.85	2.91	2.17 (s)	–	–	1.16–1.47 (5H, m) and 1.62–1.95 (5H, m, $(CH_2)_5$); 3.78 (1H, m, NCH)	10.44	7.79 (*J* = 8.0)	7.89
6b	1.32	4.85	2.91	2.17 (s)	–	–	0.96 (3H, m, $CH_2C\underline{H}_3$); 1.20 (3H, d, *J* = 6.6, $CHC\underline{H}_3$); 1.56 (2H, m, CH_2); 3.94 (1H, m, CH)	10.35	7.75 (*J* = 8.1)	7.88
6c	1.32	4.86	2.90	2.15 (s)	–	–	1.18 (3H, d, *J* = 6.6, CH_3); 2.72 (1H, d. d, J_1 = 13.1, J_2 = 7.5) and 2.98 (1H, d. d, J_1 = 13.1, J_2 = 6.5, CH_2); 4.24 (1H, m, CH); 7.11–7.29 (5H, m, C_6H_5)	10.49	7.95 (*J* = 8.0)	7.94
6d	1.31	4.85	2.91	1.05 (t, *J* = 7.4)	1.75	2.41 (*J* = 7.3)	1.16–1.47 (5H, m) and 1.62–1.95 (5H, m, $(CH_2)_5$); 3.78 (1H, m, CH)	10.44	7.79 (*J* = 8.0)	7.89
6e*	1.32	4.86	2.91	0.95 (t, *J* = 7.4)	1.75	2.41 (*J* = 7.4)	0.95 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$); 1.20 (3H, d, *J* = 6.5, $CHC\underline{H}_3$); 1.45–1.65 (2H, m, CH_2); 3.94 (1H, m, $C\underline{H}CH_3$)	10.47	7.78 (*J* = 8.1)	7.90
6f	1.32	4.86	2.91	1.04 (t, *J* = 7.3)	1.74	2.39 (*J* = 7.3)	1.20 (3H, d, *J* = 6.6, CH_3); 2.70 (1H, d. d, J_1 = 13.1, J_2 = 7.5) and 2.99 (1H, d. d, J_1 = 13.1, J_2 = 6.5, CH_2); 4.25 (1H, m, CH); 7.10–7.28 (5H, m, C_6H_5)	10.48	7.95 (*J* = 8.0)	7.93

* Mass spectrum, *m/z* (I_{rel}, %): 403 $[M]^+$ (39), 333 (20), 332 (100), 276 (8), 274 (10), 260 (34).

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for suspensions in vaseline oil. The ^{1}H NMR spectra were taken on a Varian Mercury 300VX spectrometer at 300 MHz in DMSO-d_6 with TMS as internal standard. The mass spectra were obtained on an MKh-1321A mass spectrometer with direct sample inlet into the ion source and 70 eV ionizing electron energy. The purity of the compounds was monitored by thin-layer chromatography on Silufol UV-254 plates using eluents: pyridine–butanol, 1:3 (for compounds **1, 3b,** and **5**), or pyridine–butanol, 1:1 (for compound **6**). The R_f values obtained under these conditions are given in Table 1.

3-Amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxylic acid (1). A mixture of ethyl ester of acid **1** (3.1 g, 0.01 mol) and 5% aqueous sodium hydroxide (50 ml) was heated at reflux for 4 h. After cooling, the reaction mixture was brought to pH 6 by adding acetic acid. The crystalline precipitate of acid **1** was filtered off, washed with water and ethanol, dried, and recrystallized from ethanol. The IR spectral data corresponded to our previous results [4]. ^{1}H NMR spectrum, δ, ppm: 1.30 (6H, s, 7-$(CH_3)_2$); 2.87 (2H, s, 8-CH_2); 4.82 (2H, s, 5-CH_2); 6.95 (2H, br. s, NH_2); 8.11 (1H, s, 4-CH); 12.00 (1H, br. s, CO_2H).

2,8,8-Trimethyl-7,10-dihydro-4H,8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]oxazin-4-one (3a) was prepared as described in our previous work [4] by heating acid **1** with acetic anhydride at reflux for 1 h. After cooling the reaction mixture, the crystalline precipitate of oxazinone **3a** was filtered off, washed with water and ether, dried, and recrystallized from ethanol to give compound **3a** in 74% yield; mp 243–244°C (mp 242–243°C [4]).

8,8-Dimethyl-2-propyl-7,10-dihydro-4H,8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-*d*][1,3]-oxazin-4-one (3b) was obtained analogously to compound **3a** by heating a mixture of acid **1** (2.8 g, 0.01 mol) and butyric anhydride (20 ml) at reflux and subsequent work-up. IR spectrum, ν, cm^{-1}: 1560, 1590, 1620 (C=C, C=N), 1750 (C=O lactone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, t, *J* = 7.5, $CH_2CH_2C\underline{H}_3$); 1.33 (6H, s, 8-$(CH_3)_2$); 1.94 (2H, m, $C\underline{H}_2CH_3$); 2.79 (2H, t, *J* = 7.4, $C\underline{H}_2CH_2CH_3$); 2.99 (2H, s, 7-CH_2); 4.91 (2H, s, 10-CH_2); 8.20 (1H, s, 11-CH).

3-Alkyl-2,8,8-trimethyl-7,10-dihydro-8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-ones (5a–e) and 3-Alkyl-8,8-dimethyl-2-propyl-7,10-dihydro-8H-pyrano[3",4":5',6']pyrido[3',2':4,5]thieno[3,2-*d*]pyrimidin-4(3H)-ones (5f–j), 3-Acetylamino-N-alkyl-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamides (6a–c), and N-Alkyl-3-butanoylamino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]thieno[3,2-*e*]pyridine-2-carboxamides (6d–f) (General Method). A mixture of compound **3** (0.01 mol) and amine **4** (0.01 mol) in dioxane (30 ml) and water (5 ml) was heated at reflux for 3 h. The reaction mixture was cooled and the solvents evaporated off. Water was added to the residue. The crystalline precipitate of compounds **5** or **6** was filtered off, washed with water and ether, dried, and recrystallized from ethanol. The IR spectra of products **5a–j** contain characteristic stretching and deformation bands at 1550, 1600, 1620 (C=C, C=N), 1680 cm^{-1} (C=O). The IR spectra of products **6a–f** have characteristic bands at 1560, 1590, 1600 (C=C), 1650, 1660 (C=O), 3340, 3350 cm^{-1} (NH).

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