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CONDENSED PYRIDOPYRIMIDINES. 6*. SYNTHESIS OF NOVEL PYRANO-[3',4':6,7]PYRIDO[2,3-*d*]PYRIMIDINES

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The previously unreported pyrano[3',4':6,7]pyrido[2,3-d]pyrimidines have been synthesized from 2-ethyl-2-methyltetrahydropyran-4-one.

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

Condensed pyranopyridine derivatives are of great interest as the basis for the preparation of novel condensed heterocyclic systems [2].

This work concerns the synthesis of novel condensed pyrido[2,3-*d*]pyrimidines starting from 2-ethyl-2-methyltetrahydropyran-4-one. The reaction of the pyrrolidinyl enamine of ketone **1** with ethyl ethoxymethylenecyanoacetate gave the ethyl ester of 3-(6-ethyl-6-methyl-4-pyrrolidino-5,6-dihydro-2H-pyran-3-yl)-2-cyanoacrylic acid (**2**) which was cyclized in the presence of aqueous ammonia solution to 2-amino-3-carbethoxypyrano[4,3-*b*]pyridine (**3**). Refluxing an alcohol solution of the latter with phenyl- and benzylisothiocyanates gave the corresponding 2-N'-thioureido derivatives **4a,b** which underwent heterocyclization to the 2-thio-3-substituted pyranopyrido[2,3-*d*]pyrimidines **5a,b** (Scheme 1).

Compounds **5a,b** were also prepared in a single stage from the pyranopyridine **3** and the indicated isothiocyanates at a temperature of 130-140°C. The reaction of the thiopyranopyridopyrimidines **5a,b** with ethyl chloroacetate or with phenacyl bromide gave the corresponding S-alkyl derivatives **6a-d**.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury 300 (300 MHz) instrument using chloroform-d_1 (compounds **1-3, 5a,b**) or DMSO-d_6 (compounds **4a,b, 6a,b**). TLC was carried out using Silufol UV-254 plates and revealed using iodine vapor.

The characteristics for the compounds synthesized are given in Table 1.

Pyrrolidinyl Enamine of 2-Ethyl-2-methyltetrahydropyran-4-one (1). A mixture of pyrrolidine (7.1 g), ketone (14.2 g, 0.1 mol) and *p*-toluenesulfonic acid (0.01 g) in absolute toluene (30 ml) was refluxed using a Dean–Stark apparatus until the calculated amount of water had collected. After evaporation of solvent

* For Communication 5 see [1].

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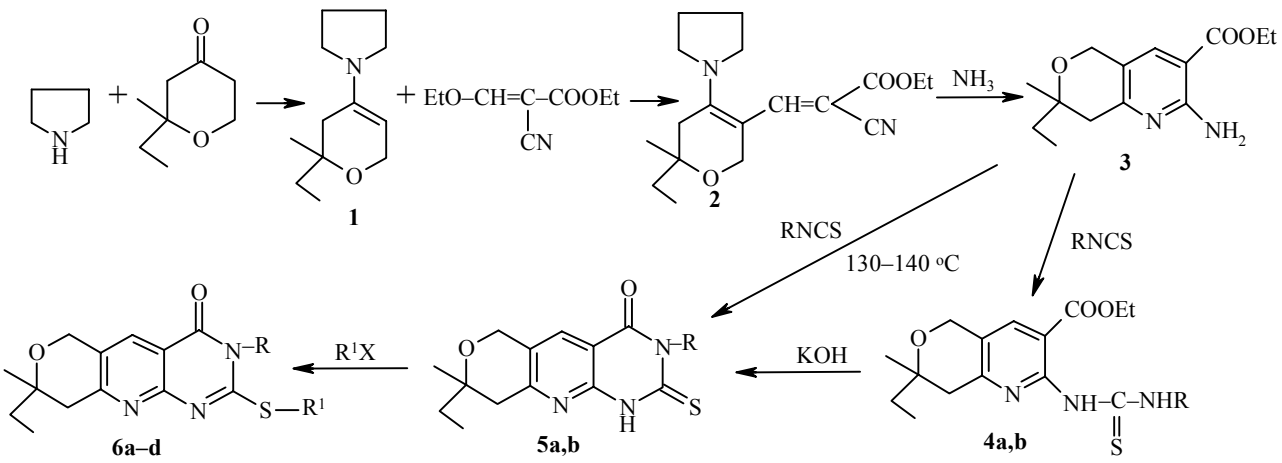
Scheme 1



4, **5 a** R = Ph, **b** R = CH_2Ph; **6 a**, **c** R = Ph, **b**, **d** R = CH_2Ph; **a**, **b** R^1 = CH_2COOEt, **c**, **d** R^1 = CH_2COPh

TABLE 1. Characteristics of Compounds **1-6**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f*[2]	Yield, % (method)
		C	H	N	S			
1	$C_{12}H_{21}NO$	74.25 / 73.85	9.87 / 10.77	7.59 / 7.18			0.61	90
2	$C_{18}H_{26}N_2O_3$	67.28 / 67.92	8.3 / 8.17	7.9 / 8.8		103-106	0.62	80
3	$C_{14}H_{20}N_3O_3$	62.87 / 63.63	8.02 / 7.58	10.3 / 10.6		125-127	0.56	76
4a	$C_{21}H_{22}N_3O_3S$	62.6 / 63.63	6.03 / 5.6	9.58 / 10.6	8.15 / 8.08	194-196	0.57	65
4b	$C_{22}H_{24}N_3O_3S$	65.08 / 64.4	5.10 / 5.85	9.11 / 10.24	8.3 / 7.8	157-159	0.59	60
5a	$C_{19}H_{19}N_3O_2S$	65.10 / 64.59	6.05 / 5.38	12.20 / 11.89	9.81 / 9.07	290	0.65	80 (A), 92 (B)
5b	$C_{20}H_{21}N_3O_2S$	64.75 / 65.40	6.25 / 5.72	12.08 / 11.44	8.12 / 8.72	300	0.63	82 (A), 91 (B)
6a	$C_{23}H_{25}N_3O_4S$	63.5 / 62.87	6.3 / 5.7	10.23 / 9.57	8.03 / 7.29	186-188	0.62	82
6b	$C_{24}H_{27}N_3O_4S$	64.3 / 63.58	5.15 / 5.96	10.20 / 9.27	7.87 / 7.06	157-160	0.58	80
6c	$C_{27}H_{25}N_3O_3S$	69.13 / 68.79	4.81 / 5.3	9.21 / 8.91	6.15 / 6.79	185-187	0.57	75
6d	$C_{28}H_{27}N_3O_3S$	68.72 / 69.28	6.22 / 5.57	8.12 / 8.66	7.23 / 6.60	168-170	0.65	77

* Compound **1**, bp 110-112°C (3 mm Hg)

*[2] Solvent systems: chloroform–ether, 2:1 (**1**); benzene–ether–methanol, 1:1:1 (**2**); benzene–ether, 1:3 (**3**); chloroform–ether, 1:2 (**4a,b**); chloroform–benzene–ether, 1:1:1 (**5a,b**); chloroform–ether–heptane, 1:1:2 (**6a,b**); benzene–ether–heptane, 1:1:1 (**6c,d**).

the residue was distilled in vacuo to give product **1** with n_D^{20} 1.543 an d_4^{20} 0.953. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 8.12 (1H, s, =CH); 4.83 (2H, s, $C_{(6)}H_2$); 3.65 (4H, m, –CH_2NCH_2–); 2.45 (2H, q, $C_{(3)}H_2$); 2.05 (4H, s, –CH_2CH_2–); 1.22 (5H, t, *J* = 7, 2-CH_3, $\underline{CH_2}CH_3$); 1.01 (3H, t, *J* = 7, $CH_2\underline{CH_3}$).

Ethyl 3-(2-Ethyl-2-methyl-4-pyrrolidino-5,6-dihydro-2H-pyran-5-yl)-2-cyanoacrylate (2). A solution of ethyl ethoxymethylenecyanoacetate (16.9 g, 0.1 mol) in THF (60 ml) was added portionwise with stirring to a solution of the enamine **1** (19.5 g, 0.1 mol) in THF (40 ml) at room temperature. The mixture was held at the same temperature for about 16 h. After evaporation of the solvent, cold absolute alcohol (20 ml) was added to the viscous mass. The precipitated crystals of the product **2** were filtered off, recrystallized from absolute ethyl alcohol, and dried. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.05 (1H, s, =CH); 4.82 (2H, s, $C_{(6)}H_2$); 4.23 (2H, q, *J* = 7, O$\underline{CH_2}CH_3$); 3.68 (4H, m, –CH_2NCH_2–); 2.48 (2H, q, $C_{(3)}H_2$); 2.0 (4H, s, –CH_2CH_2–); 1.62-1.20 (8H, t, *J* = 7, $OCH_2\underline{CH_3}$, 2-CH_3, 2-$\underline{CH_2}CH_3$); 0.8 (3H, t, *J* = 7, 2-$CH_2\underline{CH_3}$).

2-Amino-3-carbethoxy-7-ethyl-7-methyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (3). An aqueous solution of ammonia (25%, 10 ml) was added to a solution of the ester **2** (3.18 g, 0.01 mol) in THF (15 ml). The mixture was held in a closed, round bottomed flask at 50°C for 6 h. The crystals of **3** obtained after distillation of THF were filtered off, washed with water, and recrystallized from ethyl alcohol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.80 (1H, s, 4-H); 6.30 (2H, br. s, NH_2); 4.71 (2H, s, $C_{(5)}H_2$); 4.34 (2H, t, *J* = 7, O$\underline{CH_2}CH_3$); 2.70 (2H, q, 8-CH_2); 1.72 (3H, t, *J* = 7, $OCH_2\underline{CH_3}$); 1.30 (5H, s, 7-CH_3, 7-$\underline{CH_2}CH_3$); 1.0 (3H, t, *J* = 7, 7-$CH_2\underline{CH_3}$).

3-Carbethoxy-7-ethyl-7-methyl-2-(N'-phenylthioureido)-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (4a). A mixture of compound **3** (2.64 g, 0.01 mol) and phenylisothiocyanate (3.0 g, 0.02 mol) in ethanol (50 ml) was refluxed for 8 h. After cooling, the precipitated crystalline product **4a** was filtered off, washed with ether, and recrystallized from ethanol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.79 (1H, s, $\underline{NH}C_6H_5$); 8.20 (1H, s, 4-H); 7.19-7.73 (5H, m, C_6H_5); 4.71 (2H, s, $C_{(5)}H_2$); 4.42 (2H, q, *J* = 7, O$\underline{CH_2}CH_3$); 2.85 (2H, s, $C_{(8)}H_2$); 1.61 (3H, t, *J* = 7, $OCH_2\underline{CH_3}$); 1.45 (2H, q, 7-$\underline{CH_2}CH_3$); 1.22 (3H, s, 7-CH_3); 1.00 (3H, t, *J* = 7, 7-$CH_2\underline{CH_3}$).

2-(N'-Benzylthioureido)-3-carbethoxy-7-ethyl-7-methyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (4b). From a mixture of compound **3** (2.64 g, 0.01 mol) and benzylisothiocyanate (3.0 g, 0.02 mol) as described in the method given above to give the product **4b**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.05 (1H, s, NH); 11.08 (1H, s, NH); 8.10 (1H, s, 4-H); 7.32 (5H, s, –C_6H_5); 4.82 (2H, d, $\underline{CH_2}C_6H_5$); 4.62 (2H, s, $C_{(5)}H_2$); 4.40 (2H, q, *J* = 7, O$\underline{CH_2}CH_3$); 2.60 (2H, s, $C_{(8)}H_2$); 1.48 (5H, q, *J* = 7, $OCH_2\underline{CH_3}$, 7-$\underline{CH_2}CH_3$); 1.20 (3H, s, 7-CH_3); 0.90 (3H, t, *J* = 7, 7-$CH_2\underline{CH_3}$).

3-Substituted 8-Ethyl-8-methyl-4-oxo-2-thioxo-8,9-dihydro-6H-pyrano[3',4':6,7]pyrido[2,3-*d*]-pyrimidines (5a,b). A. A mixture of the thioureide **4a,b** (0.01 mol) and potassium hydroxide (0.02 mol) in aqueous ethanol (70%, 50 ml) was refluxed for 2 h. After cooling, the reaction mixture was neutralized with hydrochloric acid solution (10%). The precipitate crystals of **5a,b** were filtered off, washed with water, dried, and recrystallized from butanol. ^{1}H NMR spectrum of product **5a**, δ, ppm (*J*, Hz): 8.09 (1H, s, 5-H); 7.22-7.57 (5H, m, –C_6H_5); 4.82 (2H, s, $C_{(6)}H_2$); 3.00 (2H, m, $C_{(9)}H_2$); 1.71 (2H, m, 8-$\underline{CH_2}CH_3$); 1.31 (3H, s, 8-CH_3); 1.00 (3H, t, *J* = 7, 8-$CH_2\underline{CH_3}$).

B. A mixture of compound **3** (2.64 g) and the corresponding isothiocyanate (3 ml) was held at 130-140°C for about 7 h. The precipitated crystals obtained after cooling were filtered off, washed with ether, and recrystallized from butanol. ^{1}H NMR spectrum of product **5b**, δ, ppm (*J*, Hz): 8.42 (1H, s, 5-H); 7.46-7.28 (5H, m, –C_6H_5); 5.78 (2H, s, $\underline{CH_2}C_6H_5$); 4.92 (2H, s, $C_{(6)}H_2$); 3.00 (2H, t, $C_{(9)}H_2$); 1.71 (2H, br. q, 8-$\underline{CH_2}CH_3$); 1.35 (3H, s, 8-CH_3); 1.02 (3H, t, *J* = 7, 8-$CH_2\underline{CH_3}$).

3-Substituted 2-(Carbethoxy)thio-8-ethyl-8-methyl-4-oxo-8,9-dihydro-6H-pyrano[3',4':6,7]pyrido-[2,3-*d*]pyrimidines (6a,b). Ethyl chloroacetate (1.23 g, 0.01 mol) was added dropwise with stirring to a solution of compound **5a,b** (0.01 mol) and potassium hydroxide (0.56 g, 0.01 mol) in ethanol (90%, 20 ml) heated to 40°C. The precipitated crystals were filtered off, washed with water and ether, and recrystallized from ethanol. ^{1}H NMR spectrum, δ, ppm (*J*, Hz), **6a**: 8.18 (1H, s, 5-H); 7.38-7.60 (5H, br. d, –C_6H_5); 4.80 (2H, s, $C_{(6)}H_2$); 4.19 (2H, t, *J* = 7, O$\underline{CH_2}CH_3$); 4.02 (2H, s, SCH_2); 2.85 (2H, t, $C_{(9)}H_2$); 1.60 (2H, br. q, 8-$\underline{CH_2}CH_3$); 1.28 (6H, t,

J = 7, $OCH_2\underline{CH_3}$, 8-CH_3); 1.01 (3H, t, 8-$CH_2\underline{CH_3}$); **6b**: 8.20 (1H, s, 5-H); 7.24 (5H, s, $-C_6H_5$); 5.36 (2H, s, $\underline{CH_2}C_6H_5$); 4.81 (2H, s, $C_{(6)}H_2$); 4.18 (2H, q, SCH_2); 2.90 (2H, s, $C_{(9)}H_2$); 1.61 (2H, br. m, 8-$\underline{CH_2}CH_3$); 1.30 (6H, t, *J* = 7, $OCH_2\underline{CH_3}$, 8-CH_3); 0.98 (3H, t, 8-$CH_2\underline{CH_3}$).

3-Substituted 2-(Benzoylmethyl)thio-8-ethyl-8-methyl-4-oxo-8,9-dihydro-6H-pyrano[3',4':6,7]-pyrido[2,3-*d*]pyrimidines (6c,d). From compounds **5a,b** (0.01 mol) and phenacyl bromide (2.0 g, 0.01 mol) as described above to give compounds **6c,d**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz), **6c**: 8.11 (1H, s, 5-H); 7.40-8.07 (10H, $-C_6H_5$, COC_6H_5); 4.81 (4H, d, $C_{(6)}H_2$, SCH_2); 3.90 (2H, br. q, $C_{(9)}H_2$); 1.61 (2H, m, 8-$\underline{CH_2}CH_3$); 1.22 (3H, s, 8-CH_3); 0.98 (3H, t, 8-$CH_2\underline{CH_3}$); **6d**: 8.20 (1H, s, 5-H); 7.40-7.64 (10H, m, $CH_2C_6\underline{H_5}$, COC_6H_5); 5.78 (2H, s, $\underline{CH_2}C_6H_5$); 4.81 (4H, br. d, $C_{(6)}H_2$, SCH_2); 2.88 (2H, m, $C_{(9)}H_2$); 2.60 (2H, m, $\underline{CH_2}CH_3$); 1.22 (3H, s, 8-CH_3); 0.98 (3H, t, 8-$CH_2\underline{CH_3}$).

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