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DERIVATIVES OF CONDENSED THIENOPYRIMIDINES. 22*. SYNTHESIS OF 2-SUBSTITUTED 4-THIOXOPYRANO-[4',3':4,5]THIENO[2,3-*d*]PYRIMIDINES

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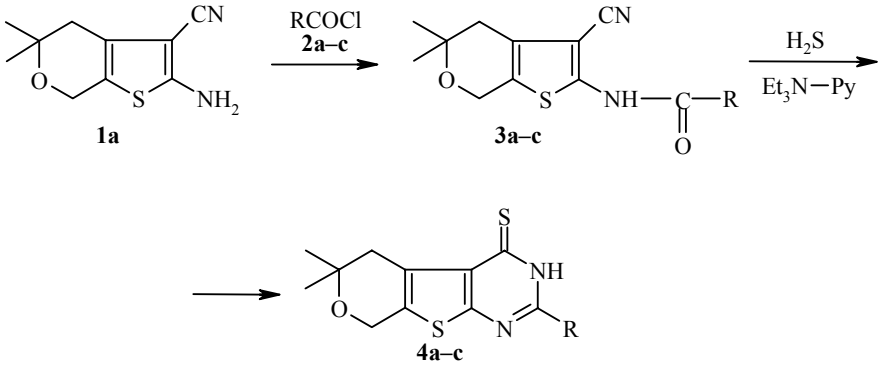
A method has been developed for the synthesis of 4-thioxopyrano[4',3':4,5]thieno[2,3-d]pyrimidines from the corresponding acyl derivatives of 2-amino-3-cyanothieno[2,3-c]pyran.

Keywords: pyranothienopyrimidine, pyranothiophene, acylation, heterocyclization.

We have previously synthesized a series of 2-thioxothieno[2,3-*d*]pyrimidines by the heterocyclization of thioureide derivatives of 2-amino-3-ethoxycarbonylthieno[2,3-*c*]pyrans [1,2].

In the present work a suitable method has been developed for the preparation of new derivatives of thieno[2,3-*d*]pyrimidines containing reactive thio group in position 4 of the pyrimidine ring.

By acylation of 2-amino-3-cyanothienopyran (**1**) [3] with propionyl (**2a**), butyryl (**2b**), and phenylacetyl (**2c**) chlorides the corresponding acyl derivatives **3a-c** were obtained. On treatment of compounds **3a-c** with hydrogen sulfide in a mixture of triethylamine and pyridine intramolecular cyclization occurred to give the required 2-substituted 4-thioxopyrano[4',3':4,5]thieno[2,3-*d*]pyrimidines **4a-c**.



2–4 **a** R = Et, **b** R = Bu, **c** R = CH_2Ph

* For part 21 see [1].

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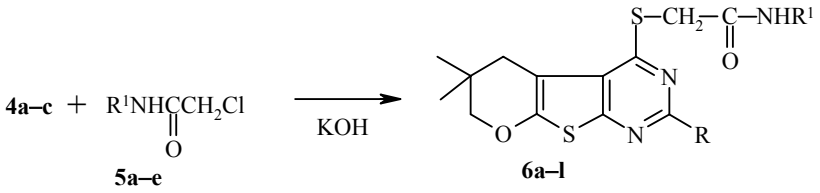
The S-substituted compounds **6a-l** were formed exclusively in all cases when compounds **4a-c** were treated with the chloroacetamides **5a-e** in the presence of KOH.



5a, **6a** R^1 = H, **5b**, **6b,e,i** R^1 = C_6H_4Me-4, **5c**, **6c,f,j** R^1 = C_6H_4Br-4, **5d**, **6d,g**,**k** R^1 = $CHPh_2$, **5e**, **6h,l** R^1 = C_6H_4Me-3, **6a-d** R = Et, **e-h** R = Bu; **i-l** R = CH_2Ph

TABLE 1. Characteristics of Compounds **3**, **4**, and **6**

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	R_f*	Yield, %
		N	S			
3a	$C_{13}H_{16}N_2O_2S$	10.28 / 10.60	12.01 / 12.12	162-163	0.61	80.2
3b	$C_{15}H_{20}N_2O_2S$	9.42 / 9.60	10.68 / 10.96	158-159	0.58	78.4
3c	$C_{18}H_{18}N_2O_2S$	8.68 / 8.59	9.70 / 9.81	167-169	0.56	82.1
4a	$C_{13}H_{16}N_2OS_2$	9.88 / 10.00	22.95 / 22.86	238-240	0.52	79.8
4b	$C_{15}H_{20}N_2OS_2$	9.01 / 9.09	20.85 / 20.78	235-237	0.53	80.2
4c	$C_{18}H_{18}N_2OS_2$	8.38 / 8.19	18.48 / 18.71	250-252	0.50	83.1
6a	$C_{15}H_{19}N_3O_2S_2$	12.30 / 12.46	18.68 / 18.99	218-220	0.49	75.5
6b	$C_{22}H_{25}N_3O_3S_2$	9.20 / 9.48	14.70 / 14.45	225-226	0.52	77.7
6c	$C_{21}H_{22}BrN_3O_2S_2$	8.18 / 8.53	13.31 / 13.01	225-227	0.61	84.5
6d	$C_{28}H_{29}N_3O_2S_2$	8.21 / 8.35	12.48 / 12.78	232-233	0.54	74.3
6e	$C_{24}H_{29}N_3O_3S_2$	8.81 / 8.92	13.62 / 13.59	212-214	0.53	78.8
6f	$C_{23}H_{26}BrN_3O_2S_2$	8.24 / 8.07	12.40 / 12.31	228-230	0.61	83.6
6g	$C_{30}H_{33}N_3O_2S_2$	7.81 / 7.91	12.18 / 12.05	220-221	0.58	75.6
6h	$C_{24}H_{29}N_3O_2S_2$	9.34 / 9.23	14.01 / 14.06	208-210	0.62	72.3
6i	$C_{27}H_{27}N_3O_3S_2$	8.12 / 8.32	12.50 / 12.67	240-242	0.59	77.5
6j	$C_{26}H_{24}BrN_3O_2S_2$	7.42 / 7.58	11.38 / 11.55	200-201	0.48	84.5
6k	$C_{33}H_{31}N_3O_2S_2$	7.40 / 7.43	11.53 / 11.33	233-235	0.57	72.2
6l	$C_{27}H_{27}N_3O_2S_2$	8.29 / 8.59	13.23 / 13.09	218-220	0.63	75.8

* Solvent systems: ethyl acetate–hexane, 1:2 (compounds **3a-c**); ethyl acetate–acetone, 1:2 (compounds **4a-c**), acetone–hexane, 1:1 (compounds **6a-l**).

EXPERIMENTAL

IR spectra of nujol mulls were recorded with UR-20 spectrometer, ^{1}H NMR spectra were recorded with Varian Mercury 300 machine (300 MHz) in $CDCl_3$ (compounds **3a,3b**) and DMSO-d_6 (compounds **4a,b** and **6a,d,j**). TLC was carried out on Silufol UV-254 plates, developed with iodine.

The characteristics of the synthesized compounds **3**, **4**, and **6** are given in Table 1.

2-Acylamino-3-cyano-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-*c*]pyrans 3a-c. Freshly distilled acid chloride **2a-c** (0.1 mol) was added with stirring to compound **1** (20.8 g, 0.1 mol) in dry benzene (150 ml). The mixture was boiled for 4h, cooled, the precipitate was filtered off, washed with ether, and dried to give products **3a-c**. IR spectra (thin layer), ν, cm^{-1}: 1675 (C=O), 2200 (C≡N), 3300 (NH). ^{1}H NMR spectra, δ, ppm (*J* , Hz): compound **3a** – 11.30 (1H, s, NH); 4.58 (2H, t, ^2J = 2.0, 2H-7); 3.00 (2H, t, ^2J = 2.0, 2H-4); 2.55 (2H, q, ^3J = 7.5, $COCH_2$); 1.30 (6H, s, $2CH_3$-5); 1.22 (2H, t, ^3J = 7.5, $CH_2\underline{CH_3}$); compound **3b** – 11.32 (1H, s , NH); 4.58 (2H, t, ^2J = 2.0, 2H-7); 2.89 (2H, t, ^2J = 2.0, 2H-4); 2.47 (2H, t, ^3J = 7.5, $COCH_2$); 1.62 (2H, tt, $^3J_1$ = 7.5, $^3J_2$ = 7.3, $COCH_2\underline{CH_2}$); 1.37 (2H, tq, $^3J_1$ = $^3J_2$ = 7.3, $\underline{CH_2}CH_3$); 1.27 (6H, s, $2CH_3$-5); 0.95 (3H, t, ^3J = 7.3, $CH_2\underline{CH_3}$).

2-R-6,6-Dimethyl-4-thioxo-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidines 4a-c. Hydrogen sulfide was passed through a solution of compounds **3a-c** (0.1 mol) in triethylamine (100 ml) and pyridine (50 ml) for 8 h at 80°C. The cooled mixture was poured into water (250 ml), the crystals of compounds **4a-c** were filtered off, washed with water, and recrystallized from butanol. IR spectra (thin layers), ν, cm^{-1}: 1430 (C=S), 1625 (C=N), 3200 (NH). ^{1}H NMR spectra, δ, ppm (*J*, Hz): compound **4a** – 13.36 (1H, s, NH); 4.71 (2H, t, ^2J = 2.0, 2H-8); 3.18 (2H, t, ^2J = 2.0, 2H-5); 2.75 (2H, t, ^3J = 7.5, $\underline{CH_2}CH_3$); 1.30 (6H, s, $2CH_3$-6); 1.29 (3H, t, ^3J = 7.5, $CH_2\underline{CH_3}$); compound **4b** – 13.23 (1H, s, NH); 4.58 (2H, t, ^2J = 2.0, 2H-8); 2.98 (2H, t, ^2J = 2.0, 2H-5); 2.48 (2H, t, ^3J = 7.5, $HetCH_2$) 1.64 (tt, $^3J_1$ = 7.5, $^3J_2$ = 7.3, $HetCH_2\underline{CH_2}$); 1.40 (2H, tq, $^3J_1$ = $^3J_2$ = 7.3, $\underline{CH_2}CH_3$); 1.30 (6H, s, $2CH_3$-6); 0.95 (3H, t, ^3J = 7.3, $CH_2\underline{CH_3}$).

2-R-6,6-Dimethyl-4-(thioxomethylamido)-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]-pyrimidines 6a-l. An N-substituted chloroacetamide **5a-e** (0.01 mol) was added with stirring to a solution of compound **4a-c** (0.01 mol) and KOH (0.01 mol) in 80% ethanol (60 ml). The precipitated crystals of products **6a-l** were filtered off, washed with ether and dried. IR spectra (thin layers), ν, cm^{-1}: 1620 (C=N), 1680 (C=O). ^{1}H NMR spectra, δ, ppm (*J*, Hz): compound **6a** – 7.08 (2H, br. s, NH_2); 4.77 (2H, t, ^2J = 2.0, 2H-8); 3.93 (2H, s, S-CH_2); 3.00 (2H, t, ^2J = 2.0, 2H-5); 2.93 (2H, q, ^3J = 7.5, $\underline{CH_2}CH_3$); 1.37 (3H, t, ^3J = 7.5, $CH_2\underline{CH_3}$); 1.34 (6H, s, $2CH_3$); compound **6d** – 8.71 (1H, d, ^3J = 8.5, NH); 7.17-7.30 (10H, m, $2C_6H_5$); 6.14 (1H, d, ^3J = 8.5, CH); 4.78 (2H, t, ^2J = 2.0, 2H-8); 4.09 (2H, s, S-CH_2); 3.01 (2H, t, ^2J = 2.0, 2H-5); 2.75 (2H, q, ^3J = 7.5, $\underline{CH_2}CH_3$); 1.34 (6H, s, $2CH_3$-6); 1.25 (3H, t, ^3J = 7.6, $CH_2\underline{CH_3}$); compound **6j** – 10.12 (1H, s, NH); 7.54 (2H, d, ^3J = 8.9, C_6H_4); 7.36 (2H, d, ^3J = 8.9, C_6H_4); 7.26 (2H, dd, ^3J = 7.5, ^4J = 2.2, C_6H_5); 7.05-7.15 (3H, m, C_6H_5); 4.77 (2H, t, ^2J = 2.0, 2H-8); 4.14 (4H, s, S-CH_2, $\underline{CH_2}C_6H_5$); 3.01 (2H, t, ^2J = 2.0, 2H-5); 1.34 (6H, s, 2-CH_3-6).

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