CONDENSED PYRIDOPYRIMIDINES.
7*. SYNTHESIS OF CONDENSED TRIAZOLO-
[4,3-*c*]- AND TETRAZOLO[1,5-*c*]PYRIMIDINES

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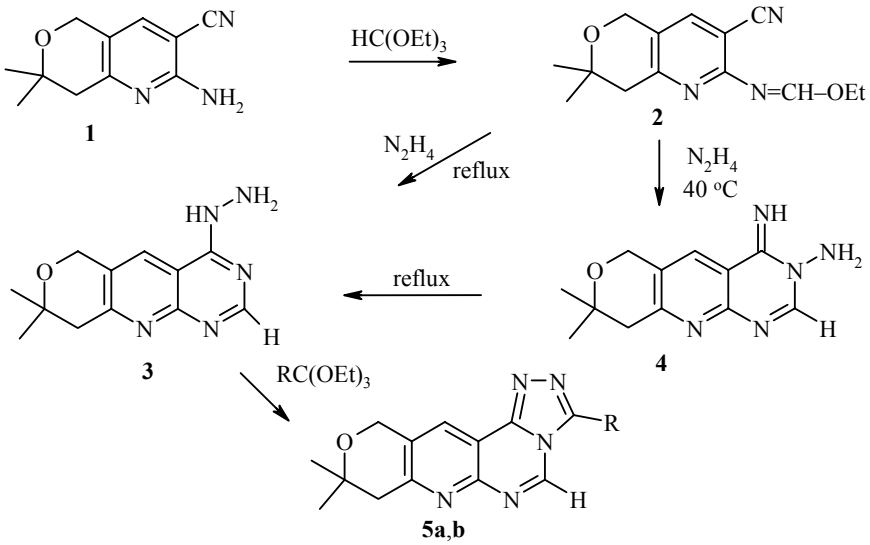
Novel dihydro-5H-pyrano[3',4':5',6']pyrido[2,3-d]-1,2,4-triazolo[4,3-c]pyrimidines and 1,2,3,4-tetrazolo-[1,5-c]pyrimidines have been synthesized from 2-amino-3-cyano-7,7-dimethyl-7,8-dihydro-5H-pyrano-[4,3-b]pyridine.

Keywords: dihydro-5H-pyrano[3',4':5',6']pyrido[2,3-*d*]-1,2,4-triazolo[4,3-*c*]pyrimidines, dihydro-5H-pyrano[3',4':5',6'][2,3-*d*]-1,2,3,4-tetrazolo[1,5-*c*]pyrimidines, condensed pyridopyrimidines, annelation.

In continuing our systematic study of condensed pyrano[4,3-*b*]pyridines [2] there are current and promising developments of suitable methods for the synthesis and the study of the biological activity of novel condensed pyrano[3',4':5,6]pyrido[2,3-*d*]pyrimidines annelated with different heterocycles along the *c* bond of the pyrimidine ring.



5 a R = H, **b** R = Me

* For Communication 6 see [1].

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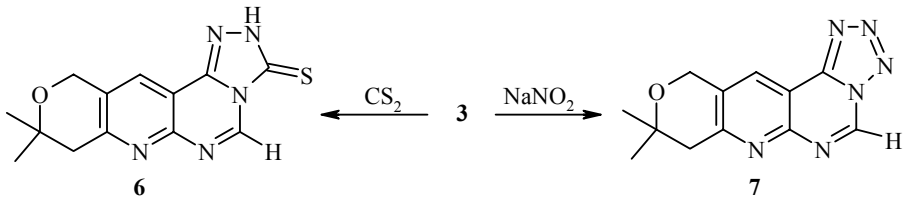
Condensation of 2-amino-3-cyano-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine **1** [3] with ethyl orthoformate gave the corresponding 2-ethoxymethyleneamino derivative **2** which was refluxed with an alcoholic solution of hydrazine hydrate to give the 4-hydrazinodihydro-5H-pyranopyridopyrimidine **3**. The intermediate 3-amino-4-iminodihydro-5H-pyranopyridopyrimidine **4** was also separated and this could be heated in the presence of hydrazine hydrate to give the product **3** *via* a Dimroth rearrangement.

Condensation of compound **3** with the orthoformate and orthoacetate esters gave high yields of the products of annelation of a triazole ring along the *c* bond of the pyrimidine ring (**5a,b**).



6 **7**

Treatment of compound **3** with carbon disulfide or sodium nitrite (in the presence of acetic acid) led to similar products with annelated 3-thioxotriazole and tetrazole rings **6** and **7** respectively.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument using vaseline oil and ^{1}H NMR spectra on a Varian Mercury 300 (300 MHz) instrument. TLC was carried out on Silufol UV-254 plates and revealed using iodine vapor. The parameters for the compounds **2-7** synthesized are given in Table 1.

TABLE 1. Characteristics of compounds **2-7**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	R_f*	Yield, %
		C	H	N			
2	$C_{14}H_{17}N_3O_2$	64.61 / 64.85	7.01 / 6.61	16.85 / 16.21	120-122	0.63	85
3	$C_{12}H_{15}N_5O$	59.03 / 58.76	5.81 / 6.16	29.07 / 28.55	300-303	0.56	90
4	$C_{12}H_{15}N_5O$	58.71 / 58.76	5.81 / 6.16	28.87 / 28.55	348-350	0.62	87
5a	$C_{13}H_{13}N_5O$	61.82 / 61.16	5.31 / 5.13	26.85 / 27.44	292-295	0.57	88
5b	$C_{14}H_{15}N_5O$	61.85 / 62.44	5.02 / 5.61	26.82 / 26.01	212-214	0.61	78
6*[2]	$C_{13}H_{13}N_5OS$	57.41 / 57.12	4.61 / 4.79	20.40 / 20.50	275-277	0.70	75
7	$C_{12}H_{12}N_6O$	55.73 / 56.24	5.12 / 4.72	32.15 / 32.80	225-228	0.64	86

* Solvent systems: ether–isooctane, 1:2 (**2**); pyridine–ether, 1:1 (**3**); ether–chloroform–pyridine, 2:1:1 (**4**); butanol–pyridine, 4:2 (**5a,b, 6**), ether–chloroform, 2:1 (**7**).

*[2] Found, %: S 11.17. Calculated, %: S 11.73.

3-Cyano-2-(ethoxymethylene)amino-7,7-dimethyl-7,8-dihydro-5H-pyrano[4,3-*b*]pyridine (2). A mixture of compound **1** (2 g, 0.01 mol) and ethyl orthoformate (20 ml) was refluxed for 10 h. After distillation of the ortho ester the viscous mass was treated with ether or petroleum ether (5 ml). The precipitated crystals of product **2** were filtered off and dried. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 8.43 (1H, s, 4-CH); 7.80 (1H, s, N=CH); 4.68 (2H, t, *J* = 1.8, 5,5-H_2); 4.43 (2H, t, *J* = 7, O$\underline{CH_2}$); 2.78 (2H, t, *J* = 1.8, 8,8-CH_2); 1.43 (3H, t, *J* = 7, $CH_2\underline{CH_3}$); 1.28 (6H, s, 7,7-$(CH_3)_2$).

4-Hydrazino-8,8-dimethyl-8,9-dihydro-6H-pyrano[3',4':5,6]pyrido[2,3-*d*]pyrimidine (3). A. A mixture of compound **2** (2.59 g, 0.01 mol), hydrazine hydrate (98%, 5 ml), and ethanol (20 ml) was refluxed for 3 h. After cooling, the precipitated crystalline product **3** was filtered off, washed with cold alcohol, and recrystallized from ethanol.

B. The product **3** was obtained as described above using compound **4** (2.45 g, 0.01 mol) (see below), hydrazine hydrate (98%, 2 ml), and ethanol (20 ml). IR spectrum (thin film), ν, cm^{-1}: 1630 (C=N), 3200-3370 (NH, NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 14.00 (1H, br. s, NH); 8.20 (1H, s, 5-H); 7.90 (1H, s, 2-H); 6.80 (2H, br. s, NH_2); 4.63 (2H, s, 6,6-H_2); 2.90 (2H, t, *J* = 1.9, 9,9-H_2); 1.30 (6H, s, 8,8-$(CH_3)_2$).

3-Amino-4-imino-8,8-dimethyl-8,9-dihydro-6H-pyrano[5',4':5,6]pyrido[2,3-*d*]pyrimidine (4). A mixture of compound **2** (2.59 g, 0.01 mol), hydrazine hydrate (5 ml), and ethanol (10 ml) was heated with stirring at 40°C for 1 h. After cooling, the precipitated crystals of product **4** were filtered off, washed with cold alcohol, and dried. IR spectrum (thin film), ν, cm^{-1}: 1630 (C=N), 3100-3350 (NH, NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 12.79 (1H, s, 4-NH); 8.20 (1H, s, 2-H); 7.85 (1H, s, 5-H); 7.73 (2H, s, 3-NH_2); 4.62 (2H, s, 6,6-H_2); 2.70 (2H, s, 9,9-H_2); 1.28 (6H, s, 8,8-$(CH_3)_2$).

9,9-Dimethyl-8,9-dihydro-11H-pyrano[5',4':5,6]pyrido[3,2-*e*]triazolo[4,3-*c*]pyrimidine (5a). A mixture of compound **3** (2.45 g, 0.01 mol) and ethyl orthoformate (20 ml) was refluxed for 3 h. The precipitated crystals of product **5a** were filtered off, washed with cold alcohol, and dried. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.50 (1H, s, 5-H); 9.23 (1H, s, 3-H); 7.86 (1H, s, 12-H); 4.98 (2H, s, 11,11-H_2); 3.32 (2H, t, *J* = 1.8, 8,8-H_2); 1.42 (6H, s, 9,9-$(CH_3)_2$).

3,9,9-Trimethyl-8,9-dihydro-11H-pyrano[5',4':5,6]pyrido[3,2-*e*]triazolo[4,3-*c*]pyrimidine (5b). Prepared from a mixture of compound **3** (2.45 g, 0.01 mol) and ethyl orthoacetate (20 ml) as described above to give the product **5b**. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.50 (1H, s, 5-H); 7.86 (1H, s, 12-H); 4.98 (2H, s, 11,11-H_2); 3.32 (2H, t, *J* = 1.8, 8,8-H_2); 2.05 (3H, s, 3-CH_3); 1.42 (6H, s, 9,9-$(CH_3)_2$).

9,9-Dimethyl-3-thioxo-2,3,8,9-tetrahydro-11H-pyrano[5',4':5,6]pyrido[3,2-*e*]triazolo[4,3-*c*]pyrimidine (6). A mixture of compound **3** (2.45 g, 0.01 mol) and carbon disulfide (7.6 g, 0.1 mol) in absolute pyridine (10 ml) was refluxed for 6 h. The precipitated crystals of the product **6** were filtered off and recrystallized from pyridine. IR spectrum (thin layer), ν, cm^{-1}: 1430 (C=S), 1620 (C=N), 3100-3300 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.22 (1H, s, 2-NH); 8.44 (1H, s, 5-H); 8.20 (1H, s, 12-H); 4.80 (2H, s, 11,11-H_2); 2.82 (2H, t, *J* = 1.8, 8,8-H_2); 1.43 (6H, s, 9,9-$(CH_3)_2$).

9,9-Dimethyl-8,9-dihydro-11H-pyrano[5,4':5,6]pyrido[3,2-*e*]tetrazolo[5,1-*c*]pyrimidine (7). A solution of sodium nitrite (1 g, 0.015 mol) in water (3 ml) was added dropwise with stirring to a solution of compound **3** (2.45 g, 0.01 mol) in acetic acid (20 ml) at room temperature. Stirring was continued for 20 min. The precipitated crystals of the product **7** were filtered, washed with water, and recrystallized from ethanol. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 9.90 (1H, s, 5-H); 8.20 (1H, s, 12-H); 4.82 (2H, s, 11,11-H); 3.05 (2H, t, *J* = 1.8, 8,8-H_2); 1.45 (6H, s, 9,9-$(CH_3)_2$).

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