Kurzmitteilungen:

Synthesis of Some Pyrido[2,3-d]pyrimidine and Pyrido[3,2-d]pyrimidine Derivatives

Synthese einiger Pyrido[2,3-d]pyrimidin- und Pyrido[3,2-d]pyrimidin-Derivate

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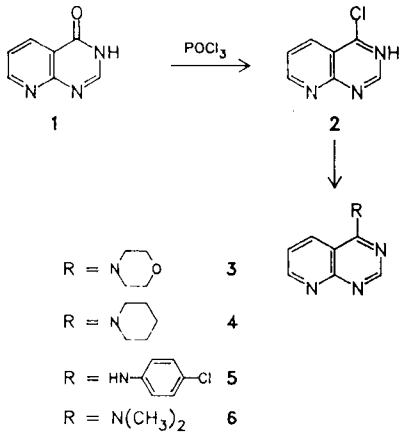
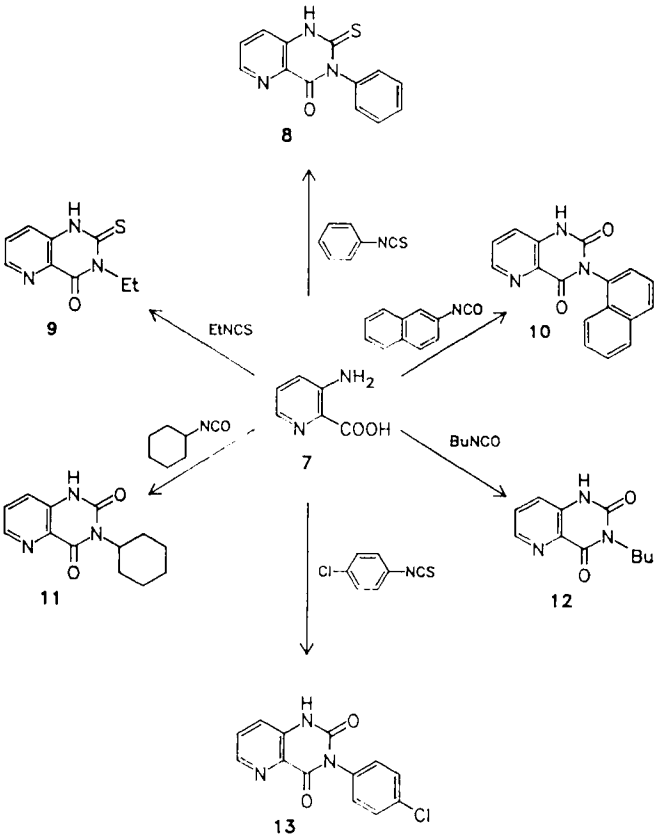
As a continuation of our screening programme seeking new heterocyclic compounds of potential hypotensiv activity derivatives of pyrido[2,3-d]pyrimidine were synthesized[1a-c]

Mannich reaction of the appropriate aromatic amines with formaline was unsatisfactory and did not result in the desired derivatives. Moreover these derivatives are susceptible to hydrolysis and are unsuitable as orally given drugs. In order to obtain the title compounds the known reactivity of the 3,4-dihydropyrido[2,3-d]pyrimidine-4-one carbonyl moiety[1b] was used. So compound **1** was reacted with $POCl_3$[2b] yielding 4-chloro-pyrido[2,3-d]pyrimidine (**2**), which was treated with various amines yielding the corresponding aminoderivatives **4-6**, analogously to the similar reaction of thiazolopyrimidine found by *Tominaga* et al[2b]. Compounds **8-13** were obtained by cyclization of 3-aminopicolinic acid (**7**) with isothiocyanates or isocyanates, according to *Lakhan* et al.[2a], who investigated a similar reaction of the quinazoline system.

The structures of compounds **2-6** and **8-13** (Schemes 1,2) were veryfied by their elemental analyses (Tab. 1) and by ^{1}H-NMR spectra (Tab. 2).





Experimental Part

^{1}H-NMR spectra: TESLA 80 MHz BS 487C.

4-Chloropyrido[2,3-d]pyrimidine (**2**)

10 g (0.67 mole) of 3,4-dihydropyrido[2,3-d]pyrimidine-4-one[2b] and 100 ml of $POCl_3$ were heated at 100°C for 3 h after solubilization of the substrate. Excess of $POCl_3$ was removed and the residue was poured into ice and neutralized with K_2CO_3 solution. The product was extracted into chloroform. Removal of the solvent led to crystals: 6g (53%) of **2**, m.p. 240°C.

4-Morpholinopyrido[2,3-d]pyrimidine (**3**)

1 g (6 mmole) of **2** and 2.4 g (0.027 mole) of morpholine were heated at 130°C for 2 h. After cooling the resulting precipitate was collected, washed with acetone and recrystallized from methanol/benzene yielding 1.09 g (84%) of compound **3**, m.p. 207-209°C.

4-Piperidinopyrido[2,3-d]pyrimidine (**4**)

1 g (6 mmole) of **2** and 2.4 g (0.028 mole) of piperidine were reacted and worked up as described for **3**, m.p. 212-213°C (benzene/methanol), yielding 0.93 g (72%) of **4**.

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Table 1: Derivatives of pyrido[2,3-d]pyrimidines **2-6** and pyrido[3,2-d]pyrimidines **8-13**.

Comp.	M.p. °C Solvent*	Yield %	Formula m.wt.	Analyses, % C	H	N	S	Calcd. found Cl
2	240	53	$C_7H_4N_3Cl$	50.8	2.43	25.4		21.4
			165.6	50.7	2.3	25.1		20.9
3	207-209	83	$C_{11}H_{12}N_4O$	61.1	5.59	25.9		
	MeOH/C_6H_6		216.2	60.8	5.53	25.8		
4	212-213	72	$C_{12}H_{14}N_4$	67.3	6.58	26.2		
	MeOH/C_6H_6		214.3	67.2	6.5	26.0		
5	359-360	72	$C_{13}H_9N_4Cl$	60.8	3.53	21.8		
	MeOH		256.7	60.7	3.45	21.6		
6	187-188	76	$C_9H_{10}N_4$	62.0	5.78	32.2		
	MeOH		174.2	61.0	5.65	32.1		
8	283-285	48	$C_{11}H_9N_3OS$	57.1	3.92	18.2	13.9	
	EtOH		231.3	57.0	3.90	18.1	13.8	
9	305	83	$C_9H_9N_3OS$	52.1	4.37	20.3	15.5	
	MeOH/AcMe		207.3	52.0	4.2	20.1	15.3	
10	330	75	$C_{17}H_{11}N_3O_2$	70.6	3.83	14.5		
	MeOH		289.3	70.4	3.65	14.4		
11	228-230	82	$C_{13}H_{14}N_3O_2$	63.9	5.77	17.2		
	MeOH/H_2O		244.3	63.8	5.65	17.1		
12	255-256	85	$C_{11}H_{13}N_3O_2$	60.3	5.97	19.2		
	MeOH		219.2	60.2	5.83	19.1		
13	213	81	$C_{13}H_8N_3O_2Cl$	57.0	2.94	15.3		13.0
	EtOH		233.7	56.9	2.77	15.2		12.8

* - solvents for recrystallization

Table 2: 80 MHz ^{1}H-NMR spectra of derivatives of pyrido[2,3-d]pyrimidines **2-6** and pyrido[3,2-d]pyrimidines **8-13**

Comp.	Chemical shifts (DMSO)
2	5.96-7.05 (m, 4H- aromat. H)
3	1.93-2.06 (m, 2 NCH_2, 4H - morpholine H); 2.72-2.85 (m, 2 OCH_2, 4H - morpholine H); 5.97-6.37 (m, 4H - aromat. H)
4	2.15-2.50 (m, 10H - piperidine H); 5.82-6.50 (m, 4H - aromat. H)
5	5.7-5.98 (m, 4H - aromat. H); 6.2-6.51 (m, 4H - aromat. H)
6	2.9 (s, 6H - $N(CH_3)_2$); 5.48-7.4 (m, 4H - aromat. H)
8	3.73 (s, 1H - NH); 7.2-7.35 (m, 5H - aromat. H); 7.5-7.75 (m, 3H- aromat. H)
9	1.40 (t, 3H - CH_3, J = 7 Hz); 4.64 (q, 2H - CH_2, J = 7.2 Hz); 8.40-9.16 (m, 3H - aromat. H)[a]
10	7.8-7.96 (m, 7H - naphthyl H); 8.18-8.23 (m, 3H - aromat. H)
11	1.92-2.40 (m, 11H - cyclohexyl H); 7.1-7.3 (m, 3H- aromat. H)
12	1.02-1.97 (m, 7H, CH_2-CH_2-CH_3); 3.86-4.11 (m, 2H - NCH_2); 7.68-7.73 (m, 1H - aromat. H); 8.55-8.66 (m, 2H - aromat. H)
13	3.22 (s, 1H - NH), 7.0-7.22 (m, 4H - aromat. H); 7.5-7.8 (m, 3H - aromat. H)

a) in CF_3COOD

4-p-Chlorophenylaminopyrido[2,3-d]pyrimidine (**5**)

See above; 72%, m.p. 359-360°C (methanol).

4-Dimethylaminopyrido[2,3-d]pyrimidine. (**6**)

See above; 76%, m.p. 187-188°C (methanol).

3-Phenyl-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-4-one-2-thione (**8**)

To the solution of 1.0 g (7.2 mmole) **7** in 50 ml of N,N-dimethylformamide, 1.1 g (8.1 mmole) of phenyl isothiocyanate were added dropwise. The mixture was refluxed for 24 h. After cooling, the solvent was removed in vacuo and the product was filtered off and sublimed: 0.8 g (48%) of **8**, m.p. 283-285°C.

3-Ethyl-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-4-one-2-thione (**9**)

From 1.0 g **7** and 0.7 g ethyl isothiocyanate as described above. Yield 1.25 g (83%), m.p. 305°C (methanol/acetone 2:1).

3-Naphthyl(1)-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-2,4-dione (**10**)

From 1.0 g **7** and 1.35 g 2-naphthyl isocyanate as described above. Yield 0.5 g (75%); after sublimation at 305°C m.p. 330°C.

3-Cyclohexyl-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-2,4-dione (**11**)

From 1.0 g **7** and 1.1 g cyclohexyl isocyanate as described above. Yield 1.4 g (82%), m.p. 228-230°C (30% aqueous methanol).

3-Butyl-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-2,4-dione (**12**)

From 1.0 g **7** and 0.8 g n-butyl isocyanate as described above. Yield 1.35 g (85%), m.p. 255-256°C (methanol).

3-p-Chlorophenyl-1,2,3,4-tetrahydropyrido[3,2-d]pyrimidin-2,4-dione (**13**)

From 1.0 g **7** and 1.23 g 4-chlorophenyl isocyanate as described above. 1.6 g colorless crystals (81%), m.p. 213°C (methanol).

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