A Novel Synthesis of Pyrimidobenzodiazepines.

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In a previous paper[1], the synthesis of pyrimido[4,5-b][1,5]benzodiazepines was described. The obtained 2-hydroxy-4-methylpyrimido[4,5-b][1,5]benzodiazepin-5-one showed an anxiolytic effect. This result encouraged us to continue research on compounds in this chemical group with potential activity on the CNS and to develop a more convenient and higher yielding method of synthesis.

In this paper a novel synthesis of pyrimido[4,5-b][1,5]benzodiazepines is reported starting from previously described[2] 1,2,3,4-tetrahydro-6-methyl-2-oxo-4-thioxo-5-pyrimidinecarboxylic acid (**1**). The acid **1** reacts with o-phenylenediamine in the presence of dicyclohexylcarbodiimide (DCC) giving 6-(N-[2-aminophenylene]carbamoyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-thioxopyrimidine (**2**) (Scheme 1). Compound **2** after S-alkylation with 10% chloroacetic acid[3] was converted into 5-(N-[2-aminophenyl]carbamoyl)-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine (**3**). **3** was then chlorinated with $POCl_3$ with diethylaniline as catalyst[4]. Instead of the expected 2,4-dichloropyrimidine **4**, the tricyclic 2-chloro-4-methyl-5-oxo-6,11-dihydropyrimido[4,5-b][1,5]-benzodiazepine (**5**) was isolated. It seems that the process goes one step further and intermediate **4** cyclizes in the reaction mixture to the tricyclic system **5**; the presence of diethylaniline facilitates the cyclization.

The structure of **5** was confirmed by its IR-spectrum, by elemental analysis and by a chemical approach. In the IR spectrum of pyrimidine **3** the bands corresponding to -CO-NH- appear at 1684 and 1670 cm^{-1}. However, in the IR spectrum of pyrimidobenzodiazepine **5**, the C=O-band is shifted to a lower frequency (1660 cm^{-1}) and corresponds to the signal of 7-membered lactams. The strong absorption band at 3260 cm^{-1} is also characteristic for N-H of lactams.

The chlorine at position 2 of pyrimidobenzodiazepine **5** easily undergoes amination with heterocyclic amines. On refluxing **5** with N-methylpiperazine, N-(2-pyrimidinyl)piperazine, and morpholine in chloroform, containing triethylamine as catalyst, the corresponding N-substituted 2-aminopyrimidobenzodiazepines **6a-c** were obtained. IR-, ^{1}H-NMR-spectra (Exp.part) and elemental analysis confirmed the structures of **6**. In the IR-spectrum of **6**, as for the pyrimidobenzodiazepine **5**, the absorption bands of C=O and N-H of the diazepine ring appear at 1620-1660 and 3260-3300 cm^{-1}, respectingly.

Pharmacology

Compounds **6a,b** were tested for antidepressant action. **6a** weakly decreased reserpine-induced hypothermia in mice. **6a,b** administered p.o. to mice in dosis 1/10 LD_{50} (200 mg/kg) showed weak analgesic activity in the writhing test[5].

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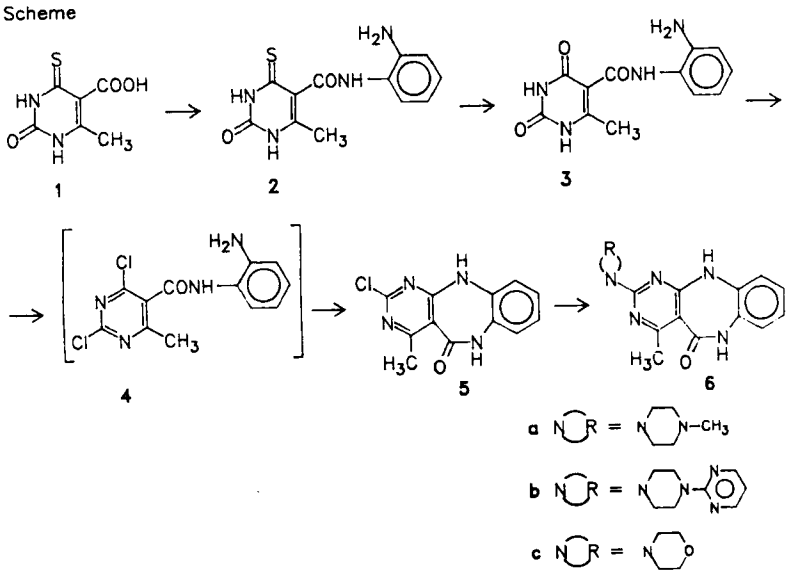
Experimental Part

M.p.: Capillary apparatus, uncorr.- IR: Unicam SP-1000.- ^{1}H-NMR: Tesla BS 587 A, 80, 60 MHz, TMS int. standard.

5-(N-[2-Aminophenyl]carbamoyl)-1,2,3,4-tetrahydro-6-methyl-2-oxo-4-thioxopyrimidine (**2**).

18.6 g (0.1 mol) **1**[2] was dissolved in 80 ml of dry dimethylformamide (DMF) at 60°C. Then 10.8 g (0.1 mol) o-phenylenediamine in 40 ml DMF

Scheme



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and 21.6 (0.1 mol) N,N-dicyclohexylcarbodiimide (DCC) in 50 ml DMF were added at 60-70°C with stirring. The mixture was left at room temp. for 24 h and dicyclohexylurea was filtered off. The filtrate was concentrated i.vac. to 1/3 volume and poured into 400 ml of water. The precipitate (20 g) was filtered and crystallized from 70% pyridine. M.p. 262°C. Yield 68%.- $C_{12}H_{12}N_4O_2S$ (276.3) Calcd. C 52.2 H 4.37 N 20.3 Found C 52.2 H 4.40 N 20.4.

5-(N-[2-Aminophenyl]carbamoyl)-1,2,3,4-tetrahydro-6-methyl-2,4-dioxopyrimidine (**3**)

2 (5.5 g, 0.02 mol) was refluxed with 50 ml of 10% chloroacetic acid. The product (2.2 g) was filtered from the hot mixture. Then 10% HCl (10 ml) was added to the filtrate and the mixture was warmed till the boiling point. The cooled mixture was neutralized with aqueous NaOH, followed by alkalization with $NaHCO_3$. An additional amount of the product (1.2 g) was collected by filtration. The product was purified by heating with 50 ml of pyridine giving 2.5 g of a white powder. M.p. 320°C (DMSO). Yield 45%.- $C_{12}H_{12}N_4O_3$ (260.2) Calcd. C 55.4 H 4.64 N 21.5 Found C 55.1 H 4.52 N 21.7.- ^{1}H-NMR (CF_3COOH): δ (ppm) = 7.2 (m, 4H, ar), 2.8 (s, 3H, CH_3).- IR (nujol): 3150; 3050 (N-H); 2940 (pyrim.); 1684 (C=O) cm^{-1}.

2-Chloro-6,11-dihydro-4-methyl-5-oxopyrimido[4,5-b]-[1,5]benzodiazepine (**5**)

3 (2.6 g, 0.01 mol) was refluxed for 6 h with 24 ml of $POCl_3$ containing 2 ml of diethylaniline. The mixture was concentrated i.vac. to 1/3 volume and the oily residue poured on ice. The mixture was extracted with benzene, the solid filtered and put into 30 ml of water. The aqueous mixture was made alkaline with aqueous K_2CO_3. The product was filtrated and washed with water. M.p. 287°C (methoxyethanol). Yield 85%.- $C_{12}H_9ClN_4O$ (260.6) Calcd. Cl 13.6 Found Cl 13.7.- IR (nujol): 3260 (NH); 2900 (pyrim.); 1660 (C=O) cm^{-1}.

4-Methyl-6,11-dihydro-2-(N-methylpiperazinyl)-5-oxopyrimido[4,5-b]-[1,5]benzodiazepine (**6a**)

The mixture of 1.3 g (5 mmol) **5**, 0.6 g (5 mmol) N-methylpiperazine and 1 ml triethylamine was refluxed for 4 h with 30 ml of chloroform. The hot mixture was filtrated and the solvent removed i.vac.. Benzene (20 ml) was added to the residue, the product was filtrated and crystallized from methanol giving 1.1 g white powder of **6a**. M.p. 244°C (methanol). Yield 68%.- $C_{17}H_{20}N_6O$ (324.4) Calcd. C 62.9 H 6.21 N 25.9 Found C 62.9 H 6.01 N 25.7.- IR (nujol): 3260 (N-H); 2940 (pyrim.); 2700 (piper.); 1660 (C=O) cm^{-1}.- ^{1}H-NMR (CF_3COOH): δ (ppm) = 7.13 (m; 4H, ar.), 4.8, 3.66, 3.16 (3m; 1H, 6H, 1H, piper.); 3.08 (s; 3H, CH_3-N), 2.75 (s; 3H, CH_3-4).

Compounds **6b,c** were prepared in a similar manner.

6b: M.p. 263°C (methoxyethanol). Yield 63%.- $C_{20}H_{20}N_8O$ (388.4) Calcd. C 61.8 H 5.19 N 28.8 Found C 61.3 H 4.95 N 29.1.- IR (nujol): 3300 (N-H); 1470; 1420 (C-N) cm^{-1}.- ^{1}H-NMR (CF_3COOH): δ (ppm) = 8.6 (d; 2H, CH-4,6, pyrim.), 8.5 (m; 1H, CH-5, pyrim.), 7.2 (m; 4H, phenyl), 4.25 (m; 8H, piper.), 2.8 (s; 3H, CH_3).

6c: M.p. 250°C (methanol). Yield 78%.- $C_{16}H_{17}N_5O_2$ (311.3) Calcd. C 61.7 H 5.50 N 22.5 Found C 61.5 H 5.30 N 22.8.- IR (nujol): 3300; 3160 (N-H); 2990 (pyrim.); 1620 (C=O); 1605 (pyrim.) cm^{-1}.- ^{1}H-NMR (CF_3COOH): δ (ppm) = 7.2 (s; 4H, ar.), 3.9 (s; 8H, CH_2), 2.7 (s; 3H, CH_3).

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