Kurzmitteilungen

6-Chloro-1,2,4-triazolo[4,3-b]pyrido[2,3-d]- and [3,2-d]pyridazines – Synthesis and Structure determination

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5,8-Dichloropyrido[2,3-d]pyridazine **(2)** gave with hydrazine hydrate in dioxane 5-chloro-8-hydrazino- and 8-chloro-5-hydrazinopyrido[2,3-d]pyridazines **3** and **4**. When **3** and **4** were allowed to react with formic acid they gave a mixture of the 6-chloro-1,2,4-triazolo[4,3-b]pyrido[2,3-d] – and [3,2-d]pyridazines (**5** and **6**).

6-Chlor-1,2,4-triazolo[4,3-b]pyrido[2,3-d]- und [3,2-d]pyridazine – Synthese und Strukturbestimmung

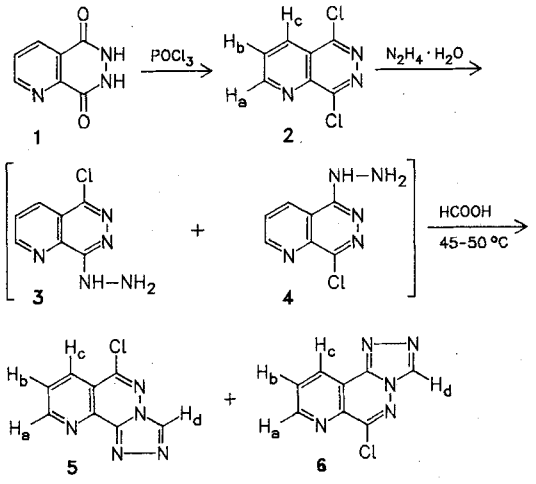
5,8-Dichlorpyrido[2,3-d]pyridazin **(2)** liefert mit Hydrazinhydrat in Dioxan die 5-Chlor-8-hydrazino- und 8-Chlor-5-hydrazino[2,3-d]pyridazine **3** und **4**. Mit Ameisensäure erhält man aus **3** und **4** das Isomerengemisch der 6-Chlor-1,2,4-triazolo[4,3-b]pyrido[2,3-d]- und [3,2-d]pyridazine **5** und **6**.

Condensed triazoles possess a variety of pharmacological activities like mitotic[1], hypotensive[2], CNS stimulant[3], antiinflammatory[4, 5], and analgesic[6, 7] effects. In continuation of our previous work on pyridopyridazine[8], we were interested in the synthesis of triazolopyridopyridazines. The synthesis of 1,2,4-triazolo systems has been reported[9–13]. In many instances formic acid has been used for the cyclization of the hydrazino compounds to the corresponding triazoles.

6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione **(1)** when treated with $POCl_3$ under N_2 gave 5,8-dichloropyrido[2,3-d]pyridazine **(2)**.

The structure of **2** was confirmed by its elemental analysis, by its ir spectrum which shows the disappearance of the absorptions due to NH and C=O, and by the ^{1}H-NMR spectrum in $CDCl_3$ showing the AMX system of the pyridine protones at δ = 8.06 (dd, 1H, H_b), 8.70 (dd, 1H, H_c), 9.45 (dd, 1H, H_a).

By treatment of **2** with hydrazine hydrate in refluxing dioxane, the two isomeric structures 5-chloro-8-hydrazinopyrido[2,3-d]pyridazine **(3)** and 8-chloro-5-hydrazinopyrido[2,3-d]pyridazine **(4)** were formed rather than the dihydrazino derivatives. The formation of **3** and **4** which could not be separated by crystallisation or column chromatography (CC) was proved when the mixture was allowed to react with formic acid: The reaction was followed by TLC, which indicated the formation of two different products in about 1 h, and was complete after 12 h. By means of CC, 6-chloro-1,2,4-triazolo[4,3-b]pyrido[2,3-d]pyridazine **(5)**, (eluted first) and 6-chloro-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine **(6)** (major product) were separated.



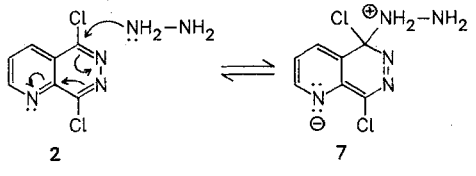
1 2 3 4 5 6

An unambigous proof for the structures of **5** and **6** is provided by their ^{1}H-NMR spectra in DMSO-d_6 in comparison with that of 1,2,4-triazolo[4,3-b]pyrido[2,3-d]pyridazines of related structure described by *Fahmy* et al.[8].

^{1}H-NMR spectrum of **5** showed δ = 7.97 (dd, 1H, H_b; Jab = 4.4, Jbc = 8.2 Hz), 9.03 (dd, 1H, H_c; Jac = 1.8, Jbc = 8.2 Hz), 9.06 (s, 1H, H_d), 9.23 (dd, 1H, H_a; Jab = 4.4, Jac = 1.8 Hz) while that of **6** showed δ = 8.07 (dd, 1H, H_b; Jab = 4.4, Jbc = 8.3 Hz), 8.73 (dd, 1H, H_c; Jac = 1.6, Jbc = 8.3 Hz), 9.33 (dd, 1H, H_a; Jab = 4.4, Jac = 1.6 Hz), 9.70 (s, 1H, H_d).

The chemical shift for H_c in **5** appeared more down field than H_c in **6** (9.03 and 8.73). This may be attributed to the -I effect of the chlorine atom in **5** and the anisotropic shielding effect of the C=N in **6**.

The formation of **6** as a major product could be explained by the ease of nucleophilic displacement of the chlorine atom in position 5 in comparison with that in position 8 in **2**, due to the formation of the intermediate **7**, which is mesomerically stabilized.



2 7

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Experimental Part

Mps. are uncorrected (Büchi apparatus). – IR-spectra: Acculab 1, Beckman spectrometer, KBr. – Mass spectra: Varian CH-5 mass spectrometer, 70 eV. – ^{1}H-NMR: 60 MHz, Varian T60, and 250 MHz: PTF-WM spectrometers. – Elemental analysis and all the spectral data were carried out at the Institute of Organic Chemistry, Regensburg, West Germany.

5,8-Dichloropyrido[2,3-d]pyridazine **(2)**

6,7-Dihydropyrido[2,3-d]pyridazine-5,8-dione **(1)** (350 mg, 2.1 mmole) was heated with pyridine (166 mg, 2.1 mmole) and $POCl_3$ (8 ml) under reflux for 1 h at 110 °C under N_2. After cooling, the mixture was poured into 100 ml ice-cold water and extracted as soon as possible with 100 ml of $CHCl_3$. The org. layer was separated, washed with water, N NaOH and finally with water. The extracted chloroform phase was dried over Na_2SO_4 and evaporated in vacuo. The oily residue obtained was purified on a silica gel column (15 cm, 2.5 cm; ether) to give **2** (320 mg, 74.5 %, m.p. 162–163 °C. – $C_7H_3Cl_2N_3$ (200.1) Calc. N 21.0 Found 21.0. – IR (cm^{-1}) 3080 (CH); 1590; 1555; 1530; 1380; 1305; 1240; 1010.

5-Chloro-8-hydrazino- and 8-chloro-5-hydrazinopyrido[2,3-d]pyridazines **(3)** *and* **(4)**

A mixture of **2** (280 mg, 1.4 mmole) and hydrazine hydrate (5 ml, 100 mmole) in dioxane (20 ml) was refluxed for 1 h. The mixture was cooled and the solid formed was filtered off and recrystallized from ethanol to give **3** and **4** (220 mg, 80 %). All attempts to separate **3** from **4** by fractional crystallization or by CC with different eluent ratios were unsuccessful. – $C_7H_6ClN_5$ (195.6) Calc. C 42.9 H 3.09 N 35.8 Found C 42.7 H 3.25 N 36.0. – IR (cm^{-1}) 3280–3420 (NH and NH_2); 1620; 1590; 1560; 1505; 1390.

6-Chloro-1,2,4-triazolo[4,3-b]pyrido[2,3-d]pyridazine **(5)** *and 6-chloro-1,2,4-triazolo[4,3-b]pyrido[3,2-d]pyridazine* **(6)**

A solution of **3** plus **4** (200 mg, 1.02 mmole) in excess formic acid (30 ml) was heated in an oil bath at 45–50 °C for 12 h. The solution was cooled and poured into ice water. The precipitate obtained was filtered, washed with Na_2CO_3 solution, then with water and dried. Using CC (silica, 30 cm, 2.5 cm; ether: petrol ether 5:1) **5** was eluted first (72 mg, 34 %) m.p. 201–203 °C. – $C_8H_4ClN_5$ (205.6) Calc. C 46.7 H 1.96 N 34.1 Found C 46.8 H 2.0 N 34.1 – MS: m/z = 205 ($M^{+\cdot}$). – Compound **6** was separated (110 mg, 52 %) m.p. 254–256 °C. – $C_8H_4ClN_5$ (205.6) Calc. C 46.7 H 1.96 N 34.1 Found C 46.8 H 1.8 N 34.1. – MS: m/z = 205 ($M^{+\cdot}$).

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