# Kurzmitteilungen:

# Pyrazine Heterocycles from 2,3-Pyrazinedicarboxylic Anhydride

## Pyrazinderivate aus 2,3-Pyrazindicarbonsäureanhydrid

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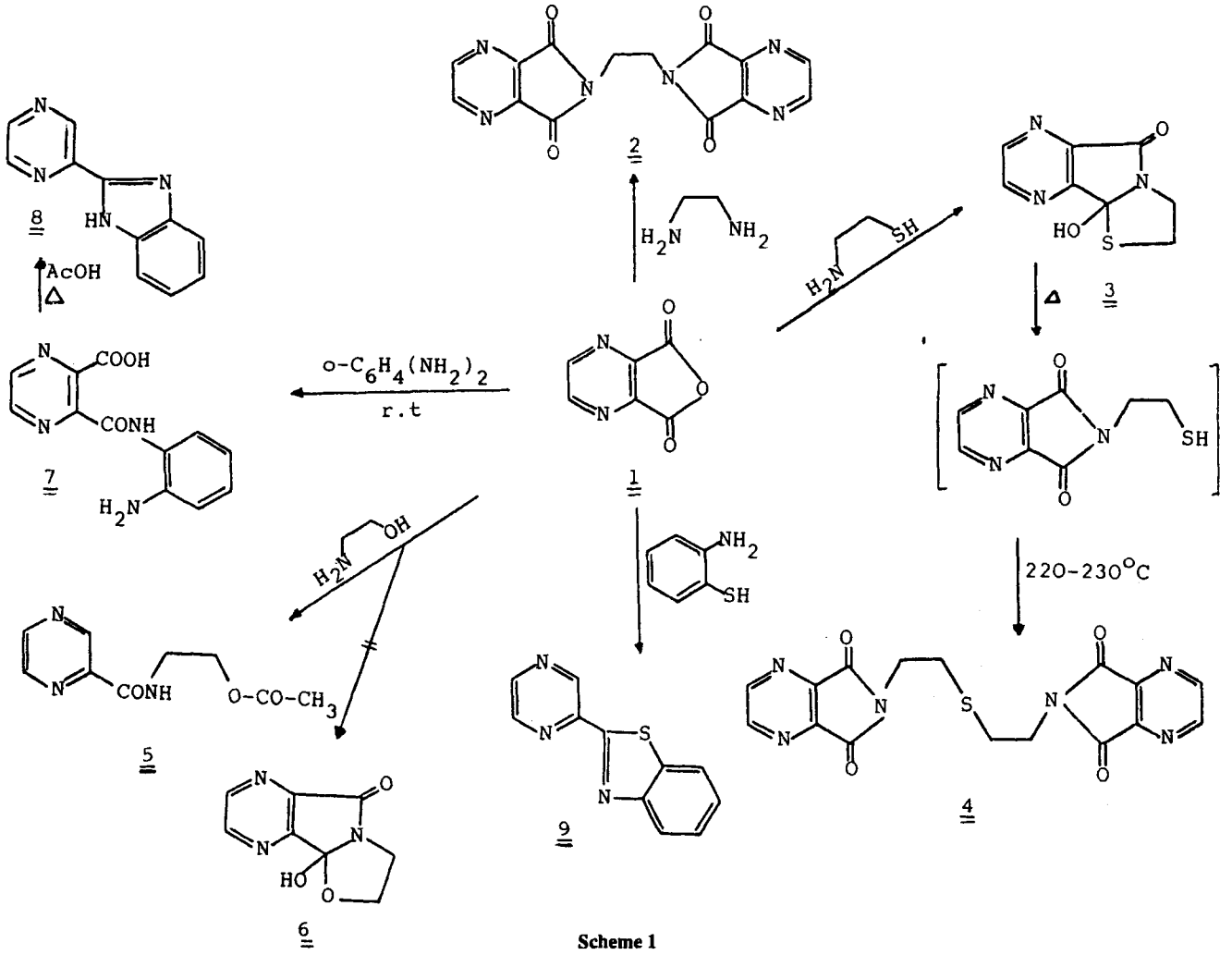
Pyrazine derivatives show a wide range of biological activities. Some derivatives are used for tuberculosis treatment[1]. Pyrazinosulfonamides are long acting sulfonamides[2] and in combination with certain pyrimidine derivatives have shown dramatic effects in clinical trials against resistant falciparum malaria[3]. A group of diuretics has been found among substituted amidinocarbamoyl-aminopyrazines[4].

We have described the synthesis of some fused pyridine heterocycles from 2,3-pyridinedicarboxylic anhydride[5]. We now carried out synthetic studies of some pyrazine derivatives using 2,3-pyrazinedicarboxylic anhydride as the starting material with the aim to find compounds useful as tranquilizers and anticonvulsants[6]. This paper deals with syntheses of novel pyrrolopyrazines (2-4) and related reactions.

2,3-Pyrazinedicarboxylic anhydride (1) reacted with ethylenediamine in acetic acid/sodium acetate to give 1,2-bis(*N*-pyrazinedicarboximide)ethane (2). Analogous treating of 1 with 2-aminoethanethiol afforded 9b-hydroxy-(9b*H*)thiazolidino[3',2':1,2]pyrrolo[3,4-*b*]pyrazine-5(5*H*)-one (3). The formation of analogous heterocycles involving a similar nucleophilic addition has been described[5,7].




Scheme 1

  0365-6233/91/0303-0185 $ 3.50+.25/0

**Table 1:** Analytical and Spectroscopic Data

| Comp. No. | mp °C | Yield % | Mol. Formula | IR ($cm^{-1}$) | $^1$H-NMR (DMSO) (ppm) | Analysis Calc. / Found C% | H% | N% |
|---|---|---|---|---|---|---|---|---|
| 2 | 283-285 | 74 | $C_{14}H_8N_6O_4$ (324.2) | 1750(C=O) | 3.92(s,4H,2$CH_2$),8.87 (s,4H,pyrazine-H) | 51.9<br>51.9 | 2.48<br>2.3 | 25.9<br>26.1 |
| 3 | 198-200 (dec.) | 88 | $C_8H_7N_3O_2S$ (209.16) | 3450(OH)<br>1720(C=O) | ---- | 45.9<br>45.7 | 3.37<br>3.12 | 20.1<br>20.1 |
| 4 | 223-225 | 87 | $C_{16}H_{12}N_6O_4S$ (384.3) | 1720(C=O) | 3.05(t,J=6.3Hz,4H,2$CH_2$),<br>3.89(t,J=6.3Hz,4H,2$CH_2$),<br>8.92(s,4H,pyrazine-H). | 50.0<br>49.7 | 3.14<br>3.30 | 21.9<br>21.8 |
| 5 | 75-77 | 59 | $C_9H_{11}N_3O_3$ (209.19) | 3100(NH)<br>2950($CH_3$)<br>1725(C=O) | 1.97(s,3H,$CH_3$),3.55 (t,J=5.1Hz,2H,N-$CH_2$),4.13 (t,J=5.1Hz,2H,O-$CH_2$),8.61 (d,J=1.8Hz,1H,H-6),8.78 (d,J=1.8Hz,1H,H-5),8.93 (broad,1H,NH),9.11(s,1H,H-3) | 51.7<br>51.5 | 5.30<br>5.16 | 20.1<br>20.2 |
| 7 | 118-120 | 88 | $C_{12}H_{10}N_4O_3$ (258.2) | 3430(OH)<br>3300(NH)<br>1690(C=O) | 6.2-7.03(m,6H,Ar-Hand $NH_2$) 7.22(s,1H,COOH),8.7(two s, 2H,H-5 and H-6),9.88(broad, 1H,NH). | 55.8<br>55.5 | 3.90<br>3.60 | 21.7<br>21.5 |
| 8 | 220-222 | 79 | $C_{11}H_8N_4$ (196.2) | 3220(NH) | 3.85(s,1H,NH),7.21-7.6(m, 4H,Ar-H),8.71(s,2H,H-5, H-6),9.48(s,1H,H-3). | 67.3<br>67.5 | 4.11<br>3.87 | 28.5<br>28.4 |
| 9 | 170-172 | 67 | $C_{11}H_7N_3S$ (213.2) | -- | 7.54-8.12(m,4H,Ar-H),8.75 (s,2H,H-5,H-6),9.64(s,1H, H-3). | 62.0<br>61.9 | 3.31<br>3.33 | 19.7<br>19.6 |

Heating **3** at 220-230°C caused elimination of $H_2S$ to give 2,2'-bis(*N*-pyrazinedicarboximide)diethyl sulfide (**4**).

Ethanolamine derivatives exhibit hypolipidic activities[8]. Hence, we tried the synthesis of an oxazolidine analogue of **3** (**6**): Treatment of **1** with ethanolamine in refluxing acetic acid/sodium acetate gave 1-acetyloxy-2-(2-pyrazinecarbamoyl)ethane (**5**) instead of the target product **6**.

The reaction of **1** with *o*-phenylenediamine in benzene at room temp. gave 2-(2-aminophenylcarbamoyl)-3-pyrazine carboxylic acid (**7**). Refluxing **7** in glacial acetic acid afforded 2-(2-benzimidazolyl)pyrazine (**8**).

The reaction of 1 with *o*-aminothiophenol yielded 2-(2-benzothiazolyl)pyrazine (**9**). Mass spectral analysis of **9** revealed $M^{+\cdot}$ at m/z = 213 with 100% rel. abundance.

All the suggested structures were confirmed from their spectral and analytical data (Table 1).

Formation of **8** and **9** probably takes place by amidation, cyclization followed by decarboxylation of the intermediate **10** (Scheme 2).

## Experimental Part

Mps. are uncorrected.- IR-spectra: Unicam SP 1000, KBr.- $^1$H-NMR: Varian EM 390 90 MHz.- Mass spectrum: Varian MAT CH-5, 70 eV.- Elemental analysis: Microanalytical unit, Regensburg University, Germany.

*1,2-Bis(N-pyrazinedicarboximide)ethane* (**2**)

2,3-Pyrazinedicarboxylic anhydride (**1**) (0.5 g, 3.33 mmol) was refluxed with a solution of ethylenediamine (0.26 ml, 3.89 mmol) in glacial acetic acid (10 ml)/sodium acetate (0.3 g, 3.65 mmol) for 4 h. After cooling the precipitate formed was purified by column chromatography on silica gel/ether: white needles of **2**.

*9b-Hydroxy-(9bH)thiazolidino[3'2':1,2]pyrrolo[3,4-b]pyrazin-5(5H)-one* (**3**)

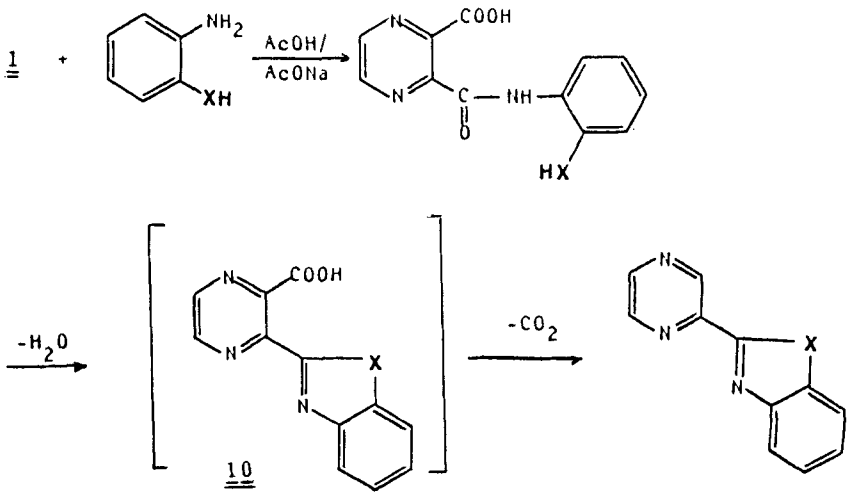
A mixture of **1** (0.5 g, 3.33 mmol) and 2-aminoethanethiol (0.38 g, 3.35 mmol) in glacial acetic acid (10 ml)/sodium acetate (0.1 g, 1.2 mmol) was refluxed for 4 h. The precipitate formed was crystallized from ethanol: white crystals of **3**.

*2,2'-Bis(N-pyrazinedicarboximide)diethyl sulfide* (**4**)

**3** (0.8 g, 3.8 mmol) was heated to 220-230°C in an oil bath for 30 min until evolution of $H_2S$ had nearly stopped. The solid formed on cooling was crystallized from ethanol: white crystals of **4**.

*1-Acetyloxy-2-(2-pyrazinecarbamoyl)ethane* (**5**)

**1** (0.5 g, 3.33 mmol) was added to a solution of ethanolamine (0.2 ml, 3.31 mmol) in glacial acetic acid (10 ml)/sodium acetate (0.1 g, 1.2 mmol). The mixture was refluxed for 4 h, cooled, poured onto ice-water and extracted with chloroform. The org. layer was separated, dried and evaporated in vacuo. The precipitate formed was crystallized from ethanol: white crystals of **5**.




**Scheme 2**

*2-(2-Aminophenylcarbamoyl)-3-pyrazine-carboxylic acid* (**7**)

To a solution of *o*-phenylenediamine (0.72 g, 6.66 mmol) in benzene, **1** (1.0 g, 6.66 mmol) was added with stirring at room temp. The yellow precipitate formed was purified by column chromatography on silica gel/ether to give **7** as yellow crystals.

*2-(Benzimidazolyl)pyrazine* (**8**)

**7** (1.0 g, 3.87 mmol) was refluxed in glacial acetic acid for 4 h. After cooling, the precipitated product was crystallized from benzene/methanol: pale yellow crystals of **8**.

*2-(2-Benzothiazolyl)pyrazine* (**9**)

To a solution of o-aminothiophenol (0.48 ml, 4.61 mmol) in glacial acetic acid (15 ml) and sodium acetate (0.1 g, 1.2 mmol), **1** (0.7 g, 4.66 mmol) was added. The mixture was refluxed for 4 h, cooled and the precipitate formed was crystallized from ethanol to give **9** as white crystals.-MS (70 eV): 213 (100% $M^{+\cdot}$), 186 (3), 160 (29), 159 (7), 158 (6), 134 (20), 108 (12), 98 (4), 82 (4), 79 (3), 69 (7), 63 (3).

## References

1 S. Kushner, H. Dalalian, J.L. Sanjurjo, F.L. Bach, S.R. Safir, V.K. Smith, and J.H. Williams, J. Am. Chem. Soc. *74*, 3617 (1952).
2 M. Ghione, C. Betazzoli, A. Buogo, T. Chieli, and V. Zavaglio, Chemotherapia 6, 344 (1963); C.A. *68*, 2227 (1963).
3 W. Modell, Science *162*, 1346 (1968).
4 J.B. Bicking, J.W. Mason, O.W. Woltersdorf, J.H. Jones, S.F. Kwong, C.M. Robb, and E.J. Cragoe, J. Med. Chem. *8*, 638 (1965).
5 M.A. Hassan, S.E. Zayed, W.N. El-Gazirie, and Saoud A.M. Metwally, Arch. Pharm. (Weinheim), in press.
6 C. Claude, Fr. Demand 2, 263, 752; C.A. *84*, 121901 (1976).
7 J.D. Coyle and L.E. Smart, J. Chem. Soc. I *1985*, 121.
8 K. Seki, T. Yamashita, and M. Ohki, Chem. Pharm. Bull. *31*, 4116 (1983). [KPh544]