Studies on the Chemistry of O,N- and S,N-containing Heterocycles. 4 [1]. Investigations on the Nucleophilic Substitution of Activated 1,5-Benzothiazepines

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The reaction of the activated 1,5-benzothiazepine **1a** with various amines is studied. In contrast to the phenylsubstituted derivative **1b** no ring contraction but nucleophilic substitution is observed. Two novel ring systems **8** and **9** are obtained by nitrosation of **3g** and by reaction of **1a** with anthranilic acid, respectively.

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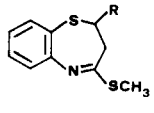
Recently we were able to prove [1], that activated 1,5-benzothiazepines **1a** and **1b** can be substituted at C-4 by weak basic nitrogen nucleophiles. In course of our proceeding investigations concerning the chemistry of S,N-containing heterocycles, we became interested in the synthesis of C-4 amino-substituted 1,5-benzothiazepines.



1a R = H
1b R = C_6H_5

As reported by Wilhelm and Schmidt [2] reaction of **1b** with morpholine leads to 2-styrylbenzothiazole by ring contraction on elimination of methanethiole.

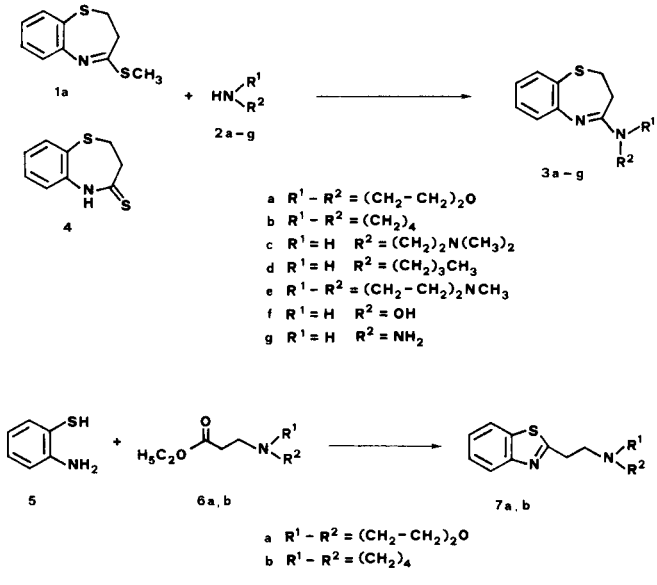
Since this rearrangement is obviously influenced by the CH-acidity of the substrate, we now investigated the reactivity of the dephenylated derivative **1a** - expected to possess lower CH-acidity towards amines.

Reaction of **1a** with morpholine (**2a**) at 80° afforded a compound with spectroscopic data (nmr: two tripletts at 2.67 and 3.33 ppm (CH_2CH_2), a multiplett at 3.50-3.92 ppm (morpholine protons); ms: 248 (M^+), 162 (M^+ - morpholine, 100%)) providing no unambiguous evidence to distinguish between the benzothiazepine **3a** and the ring contracted product **7a**. Hence, the structure of the reaction product was elucidated by unequivocal synthesis of **7a** obtained from **5** and **6a**. Significant differences in the nmr and mass spectra of **7a** (two multipletts of the morpholine protons at 2.52 and 3.73 ppm; base peak at 100 m/z ([morpholine-CH_2]$^+$)), and the compound deriving from **1a** confirmed structure **3a**. The structure of compound **3b** obtained by reaction with pyrrolidine (**2b**) was ascertained by comparison with the analogue **7b** -prepared in a similar manner.

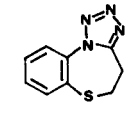
Reaction of **2a** with the thiolactame **4** also afforded benzothiazepine **3a**. However, due to formation of decomposition products and the consequently required tedious purification, the yield was very low.

Hence, we preferred to synthesize the amidines **3c-f** by reaction of **1a** with the bases **2c-f** (**2f** as the hydrochloride).

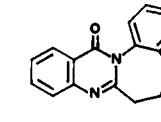
Scheme



For the synthesis of **3g**, however, the less reactive thiolactame **4** was used instead of **1a** in order to avoid disubstitution of **2g**. By reaction of **3g** with sodium nitrite in acidic medium the synthesis of the hitherto unknown tricyclic ring system **8** was accomplished. Compound **9** featuring as well a new heterocycle was obtained by reaction of **1a** with anthranilic acid in a one-step procedure.



8



9

Our investigations showed, that the reaction of activated 1,5-benzothiazepines with N-nucleophiles is directed by the CH-acidity of the substrate as well as the basicity of the attacking nucleophile.

EXPERIMENTAL

All melting points are measured with a Kofler hot-stage apparatus and are uncorrected. Mass spectra were recorded on a Varian MAT-311 instrument (70 eV) and nmr spectra on a Bruker AC 80 spectrometer (80 MHz) using TMS as internal standard in deuteriochloroform unless otherwise stated.

General Procedure for the Formation of Amidines **3a-3e**.

To **1a** (2.09 g, 10 mmoles) the amines **2a-e** (10 ml) were added. After heating the mixture for 8 hours at 80° the excess of the amine was removed under reduced pressure. The residue was taken up in dichloromethane, washed with water, dried over sodium sulfate, filtered and evaporated. The crude product was purified by column chromatography or recrystallization, respectively.

2,3-Dihydro-4-(4-morpholinyl)-1,5-benzothiazepine (**3a**).

The crude, pale yellow oil was purified by column chromatography (toluene/ethyl acetate/triethylamine 6 + 3 + 1) to give 2.40 g (97%) of **3a**; the substance could not be distilled; ms: m/z 248 (M^+, 66%), 162 (M^+ - morpholinyl, 100%); nmr: δ 2.67 (t, J = 7 Hz, 2H, CH_2), 3.33 (t, J = 7 Hz, 2H, CH_2), 3.50-3.92 (m, 8H, morpholine), 6.70-7.63 (m, 4H, aromatic).

Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.48; H, 6.47; N, 10.91.

When **4** (1.95 g, 10 mmoles) was reacted with **2a** under the same reaction conditions, 1.26 g (51%) of **3a** was obtained.

2,3-Dihydro-4-(1-pyrrolidinyl)-1,5-benzothiazepine (**3b**).

After column chromatography (eluent see **3a**) and recrystallization from petroleum benzine (60-80°) 1.16 g (50%) of **3b** as yellow crystals was obtained, mp 65-67°; ms: m/z 232 (M^+, 99%), 162 (M^+ - pyrrolidinyl, 84%); nmr: δ 1.83-2.06 (m, 4H, pyrrolidine), 2.57 (t, J = 6 Hz, 2H, CH_2), 3.42 (t, J = 6 Hz, 2H, CH_2), 3.51-3.69 (m, 4H, pyrrolidine), 6.67-7.60 (m, 4H, aromatic).

Anal. Calcd. for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 67.20; H, 7.11; N, 11.75.

4-[2-(Dimethylamino)ethylamino]-2,3-dihydro-1,5-benzothiazepine (**3c**).

After column chromatography (eluent see **3a**) 1.12 g (45%) of **3c** as an yellow oil was obtained, picrate mp (from ethanol) 176-178°; ms: m/z 249 (M^+, 1%), 58 (100%); nmr: δ 2.22 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 2.40-2.86 (m, 2H, CH_2), 2.53 (t, J = 6 Hz, 2H, CH_2), 3.10-3.58 (m, 2H, CH_2), 3.43 (t, J = 6 Hz, 2H, CH_2), 3.66 (s-broad, 1H, NH), 6.66-8.03 (m, 4H, aromatic).

Anal. Calcd. for $C_{19}H_{22}N_6O_7S$ (**3c**-picrate): C, 47.69; H, 4.63; N, 17.56. Found: C, 47.45; H, 4.65; N, 17.74.

4-Butylamino-2,3-dihydro-1,5-benzothiazepine (**3d**).

After column chromatography (eluent see **3a**) and recrystallization from petroleum benzine (60-80°) 2.01 g (86%) of **3d** as white crystals was obtained, mp 84-85°; ms: m/z 234 (M^+, 66%), 162 (M^+ - butylamino, 100%); nmr: δ 0.98 (t, J = 7 Hz, 3H, CH_3), 1.20-1.82 (m, 4H, CH_2), 2.40 (t, J = 7 Hz, 2H, CH_2), 3.40 (t, J = 7 Hz, 2H, CH_2), 3.42 (t, J = 7 Hz, 2H, CH_2), 4.63 (s-broad, 1H, NH), 6.76-7.53 (m, 4H, aromatic).

Anal. Calcd. for $C_{13}H_{18}N_2S$: C, 66.63; H, 7.74; N, 11.95. Found: C, 66.69; H, 7.60; N, 12.06.

2,3-Dihydro-4-(4-methyl-1-piperazinyl)-1,5-benzothiazepine (**3e**).

The crude product was purified by column chromatography (toluene/ethyl acetate/triethylamine 4 + 4 + 1) to give 1.57 g (60%) of **3e** as a pale yellow oil; the substance decomposed by distillation; ms: m/z 261 (M^+, 14%), 162 (M^+ - methylpiperazinyl, 39%); nmr: δ 2.33 (s, 3H, CH_3), 2.40-2.73 (m, 4H, CH_2), 2.53 (t, J = 7 Hz, 2H, CH_2), 3.37 (t, J = 7 Hz, 2H, CH_2), 3.53-3.80 (m, 4H, CH_2), 6.67-8.00 (m, 4H, aromatic).

Anal. Calcd. for $C_{14}H_{19}N_3S$: C, 64.33; H, 7.33; N, 16.08. Found: C, 63.95; H, 7.46; N, 16.43.

N-(2,3-Dihydro-1,5-benzothiazepin-4-yl)hydroxylamine (**3f**).

To a solution of **1a** (2.09 g, 10 mmoles) and hydroxylamine hydrochloride (0.76 g, 11 mmoles) in dry ethanol (30 ml) a solution of triethylamine (1.11 g, 11 mmoles) in dry ethanol (5 ml) was added. After stirring for 16 hours at 20° the solvent was evaporated and the residue was recrystallized from 70% ethanol to give 1.09 g (56%) of **3f** as white crystals; mp 194-195°; ms: m/z 194 (M^+, 99%), 162 (M^+ - NHOH, 38%); nmr (deuteriochloroform-hexadeuteriodimethyl sulfoxide): δ 2.43 (t, J = 6 Hz, 2H, CH_2), 3.06 (t, J = 6 Hz, 2H, CH_2), 6.83-7.57 (m, 4H, aromatic), 7.97 (s-broad, 1H, NH), 9.50 (s-broad, 1H, OH).

Anal. Calcd. for $C_9H_{10}N_2OS$: C, 55.65; H, 5.19; N, 14.42. Found: C, 55.76; H, 5.42; N, 14.09.

2,3-Dihydro-1,5-benzothiazepin-4-ylhydrazine (**3g**).

The solution of hydrazine hydrate (1.5 ml) in THF (5 ml) was treated dropwise with a solution of **4** (1.95 g, 10 mmoles) in THF (100 ml) at 20°. After stirring for 2 hours the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, washed with water, dried over sodium sulfate, filtered and evaporated. The crude product was recrystallized from dichloromethane/*n*-hexane to give 0.93 g (48%) of **3g** as white crystals, mp 162-164°; ms: m/z 193 (M^+, 100%), 162 (M^+ - $NH-NH_2$, 84%); nmr (deuteriochloroform-trifluoroacetic acid): δ 2.83 (t, J = 7 Hz, 2H, CH_2), 2.93-3.40 (m, 3H, NH), 3.47 (t, J = 7 Hz, 2H, CH_2), 7.15-8.00 (m, 4H, aromatic).

Anal. Calcd. for $C_9H_{11}N_3S$: C, 55.93; H, 5.74; N, 21.74. Found: C, 56.27; H, 5.41; N, 21.38.

4,5-Dihydrotetrazolo[5,1-*d*][1,5]benzothiazepine (**8**).

To a suspension of **3g** (1.93 g, 10 mmoles) in 0.5 n hydrochloric acid (40 ml) a solution of sodium nitrite (1.03 g, 15 mmoles) in water (10 ml) was added dropwise at 5°. After stirring for 2 hours the mixture was neutralized with a saturated solution of sodium hydrogen carbonate and the precipitate was filtered with suction. The crude product was recrystallized from ethanol to give 1.26 g (62%) of **8** as pale yellow crystals, mp 140°; ms: m/z 204 (M^+, 29%); nmr: δ 3.30-3.53 (m, 4H, CH_2). 7.30-7.97 (m, 4H, aromatic).

Anal. Calcd. for $C_9H_8N_4S \times \frac{1}{4} H_2O$: C, 51.78; H, 4.10; N, 26.84. Found: C, 51.70; H, 3.99; N, 26.63.

6,7-Dihydro-13*H*-quinazolino[2,3-*d*][1,5]benzothiazepin-13-one (**9**).

The solution of **1a** (2.09 g, 10 mmoles) and anthranilic acid (1.37 g, 10 mmoles) in dry ethanol (70 ml) was refluxed for 24 hours. After cooling the precipitate was filtered with suction and recrystallized from 70% ethanol to give 1.76 g (63%) of **9** as white crystals, mp 208°; ms: m/z 280 (M^+, 100%); nmr: δ 2.33-3.52 (m, 4H, CH_2), 7.30-8.46 (m, 8H, aromatic).

Anal. Calcd. for $C_{16}H_{12}N_2OS$: C, 68.55; H, 4.31; N, 9.99. Found: C, 68.42; H, 4.33; N, 9.93.

General Procedure for the Formation of Benzothiazoles **7a,b**.

The mixture of **5** (1.25 g, 10 mmoles) and **6** (10 mmoles) in polyphosphoric acid (15 ml) was stirred at 175° for 1 hour. After cooling the reaction mixture was poured into an excess of a saturated solution of sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was washed with water, dried over sodium sulfate, filtered and evaporated.

2-[2-(4-Morpholinyl)ethyl]benzothiazole (**7a**).

From **6a** (1.87 g) after distillation 1.04 g (42%) of **7a** as an oil was obtained; bp 145°, 0.001 mm Hg; ms: m/z 248 (M^+, 1%), 100 ([morpholinyl-CH_2]$^+$, 100%); nmr: 2.47-2.65 (m, 4H, NCH_2), 2.73-3.03 (m, 2H, CH_2), 3.16-3.47 (m, 2H, CH_2), 3.66-3.85 (m, 4H, OCH_2), 7.26-8.13 (m, 4H, aromatic).

Anal. Calcd. for $C_{13}H_{16}N_2OS$: C, 62.87; H, 6.49; N, 11.28. Found: C, 62.99; H, 6.64; N, 11.23.

2-[2-(1-Pyrrolidinyl)ethyl]benzothiazole (**7b**).

Compound **6b** (1.71 g) afforded 1.44 g (62%) of **7b** after column chromatography (eluent see **3a**) as a yellow oil (not distillable); ms: m/z 232 (M^+, 1%), 84 ([pyrrolidinyl-CH_2]$^+$, 100%); nmr: δ 1.56-2.00 (m, 4H, CH_2), 2.31-2.74 (m, 4H, NCH_2), 2.81-3.06 (m, 2H, CH_2), 3.15-3.43 (m, 2H, CH_2), 7.13-7.98 (m, 4H, aromatic).

Anal. Calcd. for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06. Found: C, 66.82; H, 6.68; N, 11.74.

Acknowledgement.

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REFERENCES AND NOTES

[1] Part **3**: H. Bartsch and Th. Erker, *J. Heterocyclic Chem.*, **25**, 1151 (1988).

[2] M. Wilhelm and P. Schmidt, *Helv. Chim. Acta*, **53**, 1697 (1970).