Synthesis of Tricyclic Pyrido[2,3-*b*][1,4]-thiazines *via* Nucleophilic Substitution of Activated Precursors

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Pyrido-anellated compounds analogous to tricyclic 1,4-benzothiazine derivatives were synthesized. Thus, under mild reaction conditiones substitution of thiolactim **3** with different *N*-nucleophiles yielded the precursors for compounds, which were cyclized in a further step to the corresponding tricyclic derivatives.

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The 1,4-benzothiazine bicycle and its heterocyclic derivatives are well known compounds, which are important in medicinal chemistry as therapeutic agents. For example, some compounds influence the growth hormone releasing system [1] or have antimicrobial properties [2].

On the other hand it is known that pharmacological activities may be maintained if bezene is exchanged for instance by a pyridine ring.

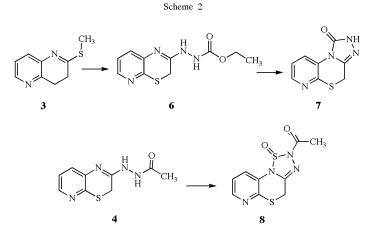
Furthermore, it is also known from 1,4-benzodiazepine derivatives, that their pharmacological profile is enhanced by attachment of a further heterocyclic ring. By combining both principles – exchange of the aromatic ring and attachment of a third ring – we hope to increase the efficiency of this class of compounds.

Compound 1 [3] was activated with Lawesson regent to give the thiolactam 2. Reaction with a carbohydrazide was supposed to lead to the N-substituted compound 4, which should be cyclized in a further step to the corresponding tricyclic derivative 5 as shown in Scheme 1.

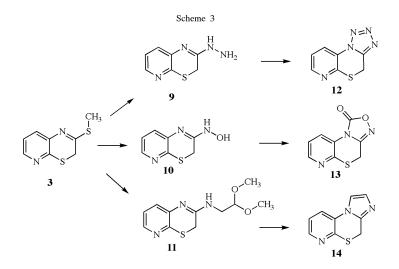
However, tentative investigations revealed that due to the required high reaction temperature an one-step formation of the triazolo[4,3-d]pyrido[2,3-b][1,4]thiazine derivate **5** took place, and in consequence, isolation of the intermediate **4** was impossible.

Since we were interested in this intermediate, further activation of the thiolactam into the methyl thiolactim 3 should facilitate the nucleophilic attack of the carbo-hydrazide and provide migitated reaction conditions. The

thiolactim 3 could be synthesized by reaction of bicycle 2 with sodium hydride and methyl iodide. Due to its high reactivity an ethanolic solution of the methyl thiolactim 3 gave with acetic hydrazide the expected derivative 4 even at room temperature. In consequence, product 4 was cyclized to the tricyclic compound 5 in boiling toluene catalysed by glacial acetic acid. Another triazolopyrido[1,4]thiazine derivate was synthesized as shown in Scheme 2 by reacting bicycle 3 with ethyl carbazate to yield the heterocycle 6. After cyclisation as described above the tricycle 7 was obtained. On the other side, reaction [4,5] of compound 4 with thionyl chloride gave the tricyclic substance 8.



Reaction of compound **3** with different *N*-nucleophiles afforded precursors for further tricyclic compounds. The conversion with hydrazine hydrate, hydroxylamine hydrochloride or aminoacetaldehyde dimethyl acetal gave the expected derivatives **9-11**. Consequently, bicycle **9** was brought to reaction with sodium nitrite in hydrochloric acid to yield the tricycle **12**. These two compounds have been cited in the literature [7]. The oxadiazolo –pyrido-thiazin derivative **13** was synthesized by reaction of **10** with *N*,*N*'-carbonyl diimidazole in dry tetrahydrofuran. Compound **14** was obtained as shown in Scheme 3 by refluxing the heterocycle **11** in glacial acetic acid.



EXPERIMENTAL

Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected. The ¹H and ¹³C nmr spectra were recorded on a Bruker Avance 200 (200 MHz), a Bruker Avance 400 DPX (400 MHz) or on a Varian Unity*Plus*-300 (300 MHz) using deuteriochloroform as solvent, if not otherwise stated, and tetramethylsilane as internal standard. Mass spectra were obtained by using a Shimadzu GC/MS QP 1000 EX or a Hewlett Packard (GC: 5890; MS 5970) spectrometer. Column chromatography was performed using silica gel 60, 70 - 230 mesh ASTM (Merck). Solutions in organic solvents were dried over anhydrous sodium sulphate. All materials were commercially available unless otherwise noted.

1H-Pyrido[2,3-b][1,4]thiazin-2(3H)-thione (2) [6].

To a mixture of 2.49 g (15 mmoles) of **1** [3] in 150 mL of dry tetrahydrofuran, 3.03 g (7.5 mmoles) of Lawesson reagent was added and the solution was stirred for 1 hour. The reaction mixture was concentrated and the residue was purified by recrystallization from diluted ethanol to give 2.30 g (84%) of **2**, mp 220-224°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 12.50 (s, 1H, NH), 8.14 (dd, J = 4.7 Hz, J = 1.5 Hz, 1H, pyridine H), 7.47 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H, pyridine H), 7.12 (dd, J = 4.7 Hz, J = 8.0 Hz, 1H, pyridine H), 3.98 (s, 2H, CH₂); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 189.9, 144.1, 143.1, 131.8, 123.2, 120.0, 35.9; ms: m/z 182 (100), 149 (37), 137 (23), 118 (31).

Anal. Calcd. for C₇H₆N₂S₂: C, 46.13; H, 3.32; N, 15.37. Found: C, 46.25; H, 3.25; N, 15.24.

2-Methylsulfanyl-3*H*-pyrido[2,3-*b*][1,4]thiazine (3).

To a suspension of 400 mg sodium hydride (60% dispersion in mineral oil) in 100 mL of dry tetrahydrofuran, 1.82 g (10 mmoles) of **2**, and after 10 minutes 1.25 mL of methyl iodide were added and stirred for 0.5 hour. The reaction mixture was concentrated and the residue was purified by recrystallization from diluted ethanol to give 1.65 g (84%) of **3**, mp 62-63°; ¹H nmr (deuteriochloroform): δ 8.20 (dd, J = 4.7 Hz, J = 1.7 Hz, 1H, pyridine H), 7.50 (dd, J = 7.9 Hz, J = 1.7 Hz, 1H, pyridine H), 7.10 (dd, J = 4.7 Hz, J = 7.9 Hz, 1H, pyridine H), 3.47 (s, 2H, CH₂), 2.55 (s, 3H, CH₃); ¹³C nmr (deuteriochloroform): δ 160.7,

146.7, 145.9, 139.0, 132.6, 121.5, 29.5, 13.5; ms: m/z 196 (100), 163 (87), 149 (38), 119 (42).

Anal. Calcd. for $C_8H_8N_2S_2$: C, 48.95; H, 4.11; N, 14.27. Found: C, 48.71; H, 3.97; N, 13.97.

N'-(3H-Pyrido[2,3-b][1,4]thiazin-2-yl)acetohydrazide (4).

A mixture of 1.96 g (10 mmoles) of **3** and 2.22 g (30 mmoles) of acetohydrazide in 30 mL dry ethanol was stirred at 40° for 72 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from water to give 1.84 g (83%) of **4**, mp 191-192°; ¹H nmr (deuteriochloroform/dimethyl-d₆ sulfoxide): δ 8.41 (dd, J = 4.7 Hz, J = 1.3 Hz, 1H, pyridine H), 8.06 (dd, J = 8.3 Hz, J = 1.3 Hz, 1H, pyridine H), 7.38 (dd, J = 4.7 Hz, J = 8.3 Hz, 1H, pyridine H), 4.30 (s, 2H, CH₂), 2.68 (s, 3H, CH₃), the two NH protons were not found; ¹³C nmr (dimethyl-d₆ sulfoxide): δ 149.7, 149.5, 148.3, 146.9, 129.1, 127.2, 121.7, 22.5, 12.7; ms: m/z 222 (100), 179 (20), 163 (34), 136 (48).

Anal. Calcd. for C₉H₁₀N₄OS: C, 48.64; H, 4.54; N, 25.21. Found: C, 48.87; H, 4.67; N, 25.11.

1-Methyl-4H-[1,2,4]triazolo[4,3-d]pyrido[2,3-b][1,4]thiazine (5).

A mixture of 2.22 g (10 mmoles) of **4** in 30 mL dry toluene and 1 mL of glacial acetic acid was refluxed for 8 hours. After this, the reaction mixture was concentrated and the residue purified by recrystallization from toluene to give 1.65 g (81%) of **5**, mp 235°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 8.41 (dd, J = 4.7 Hz, J = 1.4 Hz, 1H, pyridine H), 8.15 (dd, J = 8.2 Hz, J = 1.4 Hz, 1H, pyridine H), 7.42 (dd, J = 4.7 Hz, J = 8.2 Hz, 1H, pyridine H), 4.36 (s, 2H, CH₂), 2.64 (s, 3H, CH₃); ¹³C nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 149.6, 148.5, 148.2, 146.8, 128.0, 127.1, 121.6, 22.5, 12.7; ms: m/z 204 (83), 175 (100), 162 (37).

Anal. Calcd. for C₉H₈N₄S: C, 52.93; H, 3.95; N, 27.43. Found: C, 52.75; H, 3.91; N, 27.19.

Ethyl N'-(3*H*-pyrido[2,3-*b*][1,4]thiazin-2-yl)hydrazinecarbox-ylate (**6**).

A mixture of 1.96 g (10 mmoles) of **3** and 2.08 g (20 mmoles) of ethyl carbazate in 30 mL dry ethanol was stirred under reflux for 7 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from ethanol to give

2.37 g (94%) of **6**, mp 308-312°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 9.46 (s, 1H, NH), 9.24 (s, 1H, NH), 7.99 (dd, J = 4.7 Hz, J = 1.5 Hz, 1H, pyridine H), 7.25 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H, pyridine H), 7.13 (dd, J = 4.7 Hz, J = 8.1 Hz, 1H, pyridine H), 4.12 (q, J = 7.1 Hz, 2H, OCH₂), 3.64 (s, 2H, CH₂), 1.24 (t, J = 7.1 Hz, 3H, CH₃); ¹³C nmr (dimethyl-d₆ sulfoxide): δ 154.8, 153.3, 145.0, 144.7, 131.8, 126.5, 122.2, 61.8, 25.2, 14.4; ms: m/z 252 (100), 206 (70), 149 (57).

Anal. Calcd. for $C_{10}H_{12}N_4O_2S$: C, 47.61; H, 4.79; N, 22.21. Found: C, 47.71; H, 4.66; N, 22.08.

2,4-Dihydro-1*H*-[1,2,4]triazolo[4,3-*d*]pyrido[2,3-*b*][1,4]thiazin-1-one (**7**).

A mixture of 2.52 g (10 mmoles) of **6** in 30 mL dry toluene and 1 mL of glacial acetic acid was refluxed for 24 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from toluene to give 1.53 g (74%) of **7**, mp 303-305°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 12.22 (s, 1H, NH), 8.60 (dd, J = 8.2 Hz, J = 1.5 Hz, 1H, pyridine H), 8.40 (dd, J = 4.5 Hz, J = 1.5 Hz, 1H, pyridine H), 7.46 (dd, J = 4.5 Hz, J = 8.2 Hz, 1H, pyridine H), 4.30 (s, 2H, CH₂); ¹³C nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 152.2, 146.3, 146.0, 139.5, 129.1, 125.1, 121.6, 22.5; ms: m/z 206 (100).

Anal. Calcd. for C₈H₆N₄OS: C, 46.59; H, 2.93; N, 27.17. Found: C, 46.79; H, 3.11; N, 26.92.

2-Acetyl-2,4-dihydro-1*H*-[1,2,3,5]thiatriazolo[5,4-*d*]pyrido[2,3*b*][1,4]thiazin-1-one (**8**).

A suspension of 2.22 g (10 mmoles) of **4** in 30 mL thionyl chloride was stirred for 48 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from ethanol to give 1.05 g (39%) of **8**, mp 160-163°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 8.30 (dd, J = 4.7 Hz, J = 1.5 Hz, 1H, pyridine H), 7.94 (dd, J = 8.2 Hz, J = 1.5 Hz, 1H, pyridine H), 7.34 (dd, J = 8.2 Hz, J = 4.7 Hz, 1H, pyridine H), 4.25 (m, 2H, CH₂), 2.43 (s, 3H, CH₃); ¹³C nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 170.2, 146.4, 145.3, 142.3, 129.5, 124.8, 121.8, 22.5, 21.3; ms: m/z 268 (35), 226 (42), 150 (100).

Anal. Calcd. for C₉H₈N₄O₂S₂: C, 40.29; H, 3.01; N, 20.88. Found: C, 40.45; H, 2.80; N, 20.71.

N-(3*H*-Pyrido[2,3-*b*][1,4]thiazin-2-yl)hydrazine (9).

A mixture of 1.96 g (10 mmoles) of **3** and 2.0 mL of hydrazine hydrate in 30 mL dry tetrahydrofuran was stirred for 24 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from ethanol to give 1.46 g (81%) of **9**, mp 274-276°; ¹H nmr (deuteriochloroform/dimethyl-d₆ sulfoxide): δ 12.5 (s, 1H, NH), 7.97 (d, J = 4.5 Hz, 1H, pyridine H), 7.38 (d, J = 7.9 Hz, 1H, pyridine H), 7.14 (dd, J = 4.5 Hz, J = 7.9 Hz, 1H, pyridine H), 5.5 – 4.2 (s, 2H, NH₂), 3.59 (s, 2H, CH₂); ¹³C nmr (deuteriochloroform/dimethyl-d₆ sulfoxide): δ 146.0, 140.3, 136.0, 134.8, 121.9, 121.1, 27.8; ms: m/z 180 (100), 136 (26).

Anal. Calcd. for C₇H₈N₄S: C, 46.65; H, 4.47; N, 31.09. Found: C, 46.42; H, 4.33; N, 30.80.

N-(3*H*-Pyrido[2,3-*b*][1,4]thiazin-2-yl)hydroxylamine (**10**).

A mixture of 1.96 g (10 mmoles) of **3** and 1.39 g (20 mmoles) of hydroxylamine hydrochloride in 50 mL dry ethanol was stirred

for 16 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from ethyl acetate to give 1.10 g (61%) of **10**, mp 185-188°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 10.01 (s, 1H, NH/OH), 9.29 (s, 1H, NH/OH), 7.91 (dd, J = 4.6 Hz, J = 1.5 Hz, 1H, pyridine H), 7.49 (dd, J = 8.1 Hz, J = 1.5 Hz, 1H, pyridine H), 7.04 (dd, J = 8.1 Hz, J = 4.6 Hz, 1H, pyridine H), 3.57 (s, 2H, CH₂); ¹³C nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 141.6, 141.5, 140.6, 134.3, 122.7, 121.2, 25.5; ms: m/z 181 (100), 163 (73), 136 (100).

Anal. Calcd. for C₇H₇N₃OS: C, 46.40; H, 3.90; N, 23.19. Found: C, 46.71; H, 3.79; N, 22.97.

N-(3*H*-Pyrido[2,3-*b*][1,4]thiazin-2-yl)aminoacetaldehyde dimethyl acetale (**11**).

A mixture of 1.96 g (10 mmoles) of **3** and 2.10 g (20 mmoles) of aminoacetaldehyde dimethyl acetale in 50 mL dry methanol was stirred at 40° for 55 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from toluene to give 2.22 g (88%) of **11**, mp 30°; ¹H nmr (deuteriochloroform): δ 8.06 (dd, J = 4.7 Hz, J = 1.5 Hz, 1H, pyridine H), 7.32 (dd, J = 7.9 Hz, J = 1.5 Hz, 1H, pyridine H), 7.32 (dd, J = 4.7 Hz, 1H, pyridine H), 4.98 (s, 1H, NH), 4.57 (t, J = 5.1 Hz, 1H, CH), 3.67 (d, J = 5.1 Hz, 2H, CH₂), 3.44 (s, 6H, CH₃), 3.31 (s, 2H, CH₂); ¹³C nmr (deuteriochloroform): δ 152.8, 145.0, 142.7, 140.7, 130.9, 121.6, 102.1, 54.3, 42.8, 26.9; ms: m/z 253 (37), 222 (23), 165 (100).

Anal. Calcd. for C₁₁H₁₅N₃O₂S: C, 52.16; H, 5.97; N, 16.59. Found: C, 51.81 H, 6.03; N, 16.33.

4*H*-[1,2,3,4]Tetrazolo[1,5-*d*]pyrido[2,3-*b*][1,4]thiazine (**12**).

To a suspension of 1.80 g (10 mmoles) of **9** in 30 mL 2 *N* hydrochloric acid a solution of 1.032 g (15 mmoles) sodium nitrite in 120 mL water was added dropwise at 5°. After stirring for 24 hours the mixture was neutralized with a saturated solution of sodium hydrogen carbonate and the precipitate was collected by suction filtration and recrystallized from ethanol to give 0.89 g (47%) of **12**, mp 187°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 8.51 (dd, J = 4.7 Hz, J = 1.2 Hz, 1H, pyridine H), 8.34 (dd, J = 8.1 Hz, J = 1.2 Hz, 1H, pyridine H), 7.48 (dd, J = 8.1 Hz, J = 4.7 Hz, 1H, pyridine H), 4.79 (s, 2H, CH₂); ¹³C nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 147.4, 145.8, 145.3, 126.9, 124.1, 120.3, 18.7; ms: m/z 191 (10), 162 (56), 136 (100). *Anal.* Calcd. for C₇H₅N₅S: C, 43.97; H, 2.64; N, 36.63. Found:

C, 44.21; H, 2.64; N, 36.42.

1*H*,4*H*-[1,2,4]Oxadiazolo[4,3-*d*]pyrido[2,3-*b*][1,4]thiazin-1-one (**13**).

A mixture of 1.81 g (10 mmoles) of **10** and 1.78 g (11 mmoles) of *N*,*N*⁻carbonyldiimidazole in 50 mL of dry tetrahydrofuran was stirred under reflux for 24 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from ethyl acetate to give 1.64 g (79%) of **13**, mp 182-185°; ¹H nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 8.47 (dd, J = 4.7 Hz, J = 1.5 Hz, 1H, pyridine H), 8.44 (dd, J = 8.2 Hz, J = 1.5 Hz, 1H, pyridine H), 7.50 (dd, J = 8.2 Hz, J = 4.7 Hz, 1H, pyridine H), 4.47 (s, 2H, CH₂); ¹³C nmr (deuteriochloroform/ dimethyl-d₆ sulfoxide): δ 154.7, 152.2, 147.0, 146.3, 127.5, 125.0, 121.9, 21.0; ms: m/z 207 (100), 162 (33), 136 (51).

Anal. Calcd. for $C_8H_5N_3O_2S$: C, 46.37; H, 2.43; N, 20.28. Found: C, 46.53; H, 2.39; N, 20.26. 4*H*-Imidazo[1,2-*d*]pyrido[2,3-*b*][1,4]thiazine (14).

A solution of 2.53 g (10 mmoles) of **11** in 50 mL of glacial acetic acid was stirred under reflux for 16 hours. After this, the reaction mixture was concentrated and the residue was purified by recrystallization from 50% ethanol to give 0.89 g (47%) of **14**, mp 138-140°; ¹H nmr (deuteriochloroform): δ 8.36 (dd, J = 4.7 Hz, J = 1.3 Hz, 1H, pyridine H), 7.58 (dd, J = 8.1 Hz, J = 1.3 Hz, 1H, pyridine H), 7.58 (dd, J = 8.1 Hz, J = 1.3 Hz, 1H, pyridine H), 7.17 (d, J = 1.5 Hz, 1H, imidazole H), 4.23 (s, 2H, CH₂); ¹³C nmr (deuteriochloroform): δ 148.3, 146.4, 140.1, 130.6, 130.0, 124.2, 121.3, 115.5, 25.0; ms: m/z 189 (100), 161 (29), 149 (68).

Anal. Calcd. for C₉H₇N₃S: C, 57.12; H, 3.73; N, 22.21. Found: C, 56.93; H, 3.67; N, 21.86.

REFERENCES AND NOTES

[1] J. R. De Vita, W. R. Schoen, G. A: Doldouras, M. H. Fisher, M. J. Wyvratt, K. Cheng, W. W.-S. Chan, B. S. Bridget, and R. G. Smith, *Bioorg. Med. Chem. Lett.*, **5**, 1281 (1995).

[2] D. Armenise, G. Trapani, V. Arrivo, E. Laraspata, and F. Morlacchi, *J. Heterocyclic Chem.*, **37**,1611 (2000).

[3] A. D. Dunn and R. Norrie, J. Prakt. Chem., 332, 444 (1990).

[4] H. Bartsch and T. Erker, J. Heterocyclic Chem., 27, 991 (1990).

[5] H. Bartsch, T. Erker and G. Neubauer, J. Heterocyclic Chem., 26, 205 (1989).

[6] K. Hwang and J. D. Ratajcyk, US. Pat. 3728343; *Chem. Abstr.*, **79**, 5357 (1973).

[7] T. S. Safonova, M. P. Memeryuk, N. I. Traven, L. A. Myshkina, L. G. Levkovskaya, L. O. Aparnikova, A. F. Keremov, L. F. Linberg and E. I. Mameva, *TezisyDokl.-Vses. Konf. Khiomioter. Zlokach. Opkholei*, 32 (1979).