Studies on the Chemistry of *O,N*- and *S,N*-Containing Heterocycles. 3 [1]. Synthesis of 1,5-Benzothiazepines with Potential CNS Activity

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The synthesis of a series of novel triazolo[3,4-*d*][1,5]benzothiazepines **6** and **7**, obtained from the activated 1,5-benzothiazepine derivatives **3** and carbohydrazides **4**, is described. Under mild reaction conditions some intermediates **5** can be isolated.

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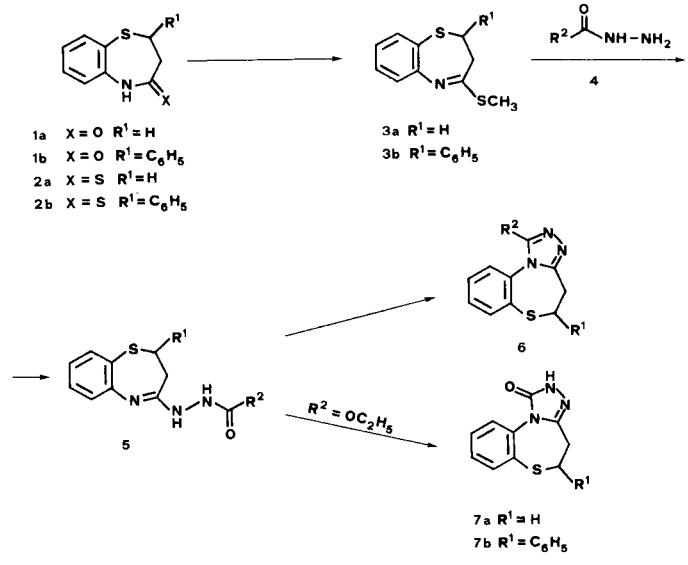
It is known from various 1,4-benzodiazepine derivatives, that their pharmacological activity is enhanced by attachment of a further heterocyclic ring system. Thus, the triazolo derivatives estazolame, triazolame, and alprazolame are successfully used as tranquilizers, hypnotics and antidepressants, respectively, in clinical practice.

Furthermore, 1,5-benzothiazepines, as diltiazeme, nictiazeme, and tiazesime possess coronary vessel dilatating and antidepressive activity, respectively.

In the course of our investigations concerning the synthesis of pharmacologically active, *S,N*-containing heterocycles we now attempted to link both principles *via* an attachment of a triazolo ring to the 1,5-benzothiazepine system in position [d].



Benzothiazepine derivatives **1a** [2] and **1b** [3], obtained by reaction of 2-aminophenol with acrylic and cinnamic acid, respectively, were activated by conversion with Lawesson reagent into the thiolactames **2a** [4] and **2b** [5]. Reaction with carbohydrazides **4** was supposed to lead to the *N*-substituted hydrazides **5**, which should consequently be cyclised to the corresponding triazolo derivatives **6**. However, tentative investigations with **2a** and acetohydrazide (**4b**) revealed that due to the required high reaction temperatures a one-step formation of the triazolobenzothiazepine **6b** took place and, in consequence, isolation of the intermediate **5b** was impossible.

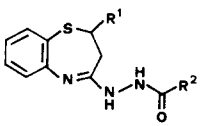
Since we were also interested in the synthesis of hydrazides **5**, a further activation of C-4 in the thiazepine ring system by conversion into the methyl thiolactime ether should facilitate nucleophilic attack and provide mitigated reaction conditions. Compounds **3a** and **3b** [5] were obtained by reaction of thiolactames **2a** and **2b** with sodium hydride and methyl iodide. Whereas ethanolic solutions of **3a** gave with **4** the expected hydrazides **5a-e** at room temperature, the phenyl-substituted derivative **3b** required reaction under reflux conditions, due to its low solubility. It could be shown that in most reactions cyclisation to the triazolo derivatives occurred, **6e-g**, **6i**. However, reaction with 4-pyridinecarbohydrazide (**4f**) and hydrazinocarboxylic acid ethyl ester (**4g**) yielded the hydrazides **5f** and **5g**, even under elevated reaction temperatures. In consequence, the hydrazides **5a-g**, obtained from **3a** and **3b**, were cyclised to the tricyclic compounds **6a-d**, **6h**, **7a** and **7b** in boiling toluene/glacial acetic acid.

The structures of the reaction products were confirmed by nmr spectroscopy, mass spectra and analytical data. The presence of a carbonyl group in **7a** and **7b** was substantiated by ir absorption at 1690 cm^{-1}.

The nmr spectra show - besides the signals of the aromatic protons - the proton absorption of the R^2 substituent at the characteristic ppm values. The signals of the CH_2-CH_2 group appear in **5a-e** as a triplett at 3.5 and 2.9 ppm, and in **6a-d** and **7a** as an A_2B_2 system at 3.5-3.3 and 3.2-3.0 ppm. The CH_2-CH group in the phenyl substituted compounds **5f** and **5g** is exhibited as an ABX system at 4.9, 3.3 and 2.9 ppm, and in **6e-i** and **7b** at 4.9-4.7, 3.7-3.4 and 3.1-2.8 ppm.

Table 1

N'-(2,3-Dihydro-1,5-benzothiazepin-4-yl)carbohydrazides **5**

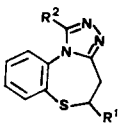


Compound	R^1	R^2	Reaction temp (°C)	Yield %	Mp (°C)	Molecular Formula	MS (70 eV) (%)	Microanalytical data (%) (Calcd./Found) C	H	N
5a	H	H	20	89	164	$C_{10}H_{11}N_3OS$ (221.3)	221 (M^+, 51) 162 (100)	54.28 54.64	5.01 5.05	18.99 18.85
5b	H	CH_3	20	80	192	$C_{11}H_{13}N_3OS$ (235.3)	235 (M^+, 30), 111 (100)	54.75 [a] 54.61	5.71 5.55	17.41 17.42
5c	H	C_6H_5	20	88	206-208	$C_{16}H_{15}N_3OS$ (297.4)	297 (M^+, 20), 173 (100)	64.62 64.56	5.08 5.25	14.13 14.17
5d	H	4-Pyridyl	20	63	193	$C_{15}H_{14}N_4OS$ (298.4)	298 (M^+, 3), 106 (100)	60.38 60.11	4.73 4.93	18.78 19.03
5e	H	OC_2H_5	20	54	209	$C_{12}H_{15}N_3O_2S$ (265.3)	265 (M^+, 34), 162 (100)	54.32 54.57	5.70 5.71	15.84 15.99
5f	C_6H_5	4-Pyridyl	80	63	212-214	$C_{21}H_{18}N_4OS$ (374.5)	374 (M^+, 37), 355 (100)	67.36 67.03	4.85 4.98	14.96 15.03
5g	C_6H_5	OC_2H_5	80	87	194	$C_{18}H_{19}N_3O_2S$ (341.4)	341 (M^+, 9), 105 (100)	63.32 63.30	5.61 5.61	12.31 12.40

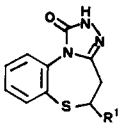
[a] Calculated with ⅓ water.

Table 2

4,5-Dihydro[1,2,4]triazolo[3,4-*d*][1,5]benzothiazepines **6a-i**



4,5-Dihydro[1,2,4]triazolo[3,4-*d*][1,5]benzothiazepin-1(2*H*)-ones **7a,b**



Compound	R^1	R^2	Method	Yield (%)	Mp (°C) (solvent)	Molecular Formula	MS (70 eV) (%)	Microanalytical data (%) (Calcd./Found) C	H	N
6a	H	H	A	83	135 [a] AcOEt	$C_{10}H_9N_3S$ (203.3)	203 (M^+, 100)	59.09 59.04	4.46 4.58	20.67 20.87
6b	H	CH_3	A	82	128 [b] AcOEt	$C_{11}H_{11}N_3S$ (217.3)	217 (M^+, 100)	60.80 60.42	5.10 5.23	19.34 19.12
6c	H	C_6H_5	A	93	224 [c] AcOEt/*n*-Hexane	$C_{16}H_{13}N_3S$ (279.4)	279 (M^+, 100)	68.79 68.68	4.69 4.79	15.04 14.76
6d	H	4-Pyridyl	A	94	156-158 toluene	$C_{15}H_{12}N_4S$ (280.4)	280 (M^+, 0.3) 78 (100)	64.27 64.00	4.31 4.63	19.98 20.32
6e	C_6H_5	H	B	83	136-138 toluene	$C_{16}H_{13}N_3S$ (279.4)	279 (M^+, 24) 278 (100)	68.79 68.52	4.69 4.79	15.04 15.11
6f	C_6H_5	CH_3	B	62	173-174 AcOEt	$C_{17}H_{15}N_3S$ (293.4)	293 (M^+, 27) 292 (100)	69.60 69.21	5.15 5.18	14.32 14.64
6g	C_6H_5	C_6H_5	B	86	237 EtOH	$C_{22}H_{17}N_3S$ (355.5)	355 (M^+, 33) 354 (100)	74.34 74.25	4.82 4.95	11.82 11.70
6h	C_6H_5	4-Pyridyl	A	68	156-158 EtOH	$C_{21}H_{16}N_4S$ (356.5)	356 (M^+, 13)	67.35 [d] 67.44	4.84 4.97	14.96 14.85
6i	C_6H_5	3-Pyridyl	B	87	249 EtOH	$C_{21}H_{16}N_4S$ (356.5)	356 (M^+, 32) 355 (100)	70.76 70.31	4.52 4.79	15.72 15.60
7a	H	– –	A (from **5e**)	62	227 70% EtOH	$C_{10}H_9N_3OS$ (219.3)	219 (M^+, 100)	54.78 54.52	4.14 4.14	19.16 19.09
7b	C_6H_5	– –	A (from **5g**)	79	112 80% EtOH	$C_{16}H_{13}N_3OS$ (295.4)	295 (M^+, 0.5) 236 (100)	65.06 65.43	4.44 4.46	14.23 13.89

[a] 132-133° [6]. [b] 109-111° [6]. [c] 224-225° [6]. [d] Calculated with 1 water.

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, nmr spectra on a Bruker AC 80 spectrometer (80 MHz), ir spectra were obtained on a Jasko IRA-1 instrument.

General Procedure for the Formation of 4-Methylthio-1,5-benzothiazepines **3**.

To sodium hydride (300 mg 80%, 10 mmoles) in dry THF (100 ml) **2** (10 mmoles) was added and the suspension was stirred for 10 minutes. Then methyl iodide (2.84 g, 20 mmoles) was added dropwise and the reaction mixture was stirred at 20° for an additional 90 minutes. The solvent was removed under reduced pressure, the residue was taken up in dichloromethane, washed with water, dried with sodium sulfate, filtered and evaporated. The crude product was recrystallized.

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

Compound **2a** (1.95 g) afforded 2.07 g (99%) of **3a**, white crystals, mp (from petroleum ether 50-70°) 51°; ms: m/z 209 (M^+, 35%), 162 (M^+ - SCH_3, 100%); nmr (deuteriochloroform/tetramethylsilane): δ 2.47 (s, 3H, CH_3-S), 2.60 (t, J = 6 Hz, 2H, CH_2), 3.53 (t, J = 6 Hz, 2H, CH_2), 6.87-7.63 (m, 4H, aromat).

Anal. Calcd. for $C_{10}H_{11}NS_2$: C, 57.38; H, 5.30; N, 6.69. Found: C, 57.45; H, 5.33; N, 6.49.

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

Compound **2b** (2.71 g) afforded 2.86 g (97%) of **3b**, pale yellow crystals, mp (from ethanol) 104° (103-105 ° [5]).

General Procedure for the Formation of *N'*-(1,5-Benzothiazepin-4-yl)carbohydrazides **5** (Table 1).

The solution of **3** (10 mmoles) and **4** (11 mmoles) in ethanol (30 ml) was stirred for 20 hours (reaction temperature see Table 1). After addition of water (20 ml) the mixture was cooled at 5°. The precipitate was filtered off, washed with diluted ethanol and recrystallized from ethanol.

General Procedure for the Formation of [1,2,4]Triazolo[3,4-*d*][1,5]benzothiazepines **6** (Table 2).

Methode A.

The mixture of **5** (10 mmoles) and glacial acetic acid (1 ml) in toluene (250 ml) was refluxed for 1 hour. After cooling the solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic layer was separated, dried and concentrated *in vacuo*. The crude product was purified by recrystallization.

Methode B.

The mixture of **3b** (2.95 g, 10 mmoles) and **4** (11 mmoles) in ethanol (30 ml) was refluxed for 8 hours. After addition of water (20 ml) and cooling at 5° the precipitate was filtered by suction, washed with diluted ethanol and recrystallized.

Acknowledgement.

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