

# Synthesis of [1,5]Benzothiazepine Derivatives

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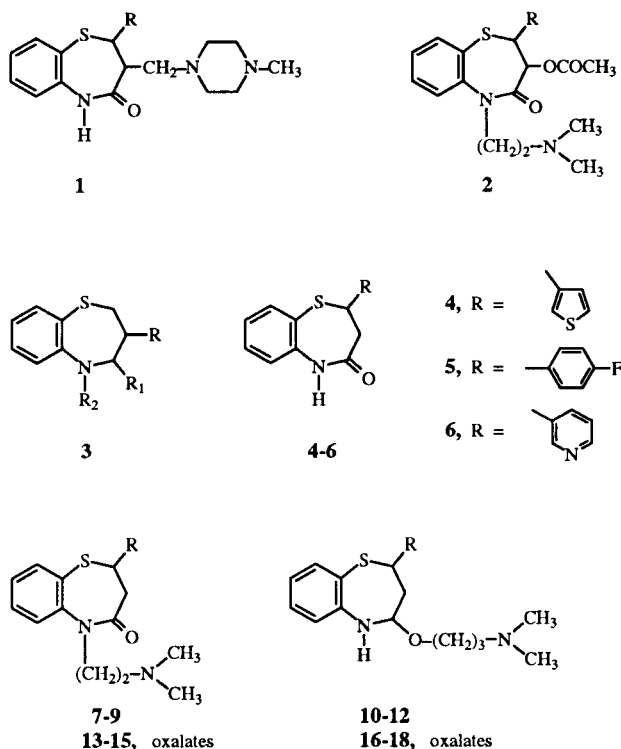
Various derivatives of 2,3-dihydro[1,5]benzothiazepin-4(5*H*)-ones were synthesized. Alternative route for the synthesis of 5-dimethylaminoethyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-ones and 4-dimethylaminopropoxy-(2*H*,5*H*)-[1,5]benzothiazepines are described.

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The interesting biological activities of the recently reported dihydrobenzothiazepines **1-3** [1-12] prompted us to continue our efforts directed to the synthesis of novel benzothiazepines of therapeutic interest. In a previous paper we have described a method leading to the 2,3-dihydro[1,5]benzothiazepinones **4-6** by cyclizing *o*-aminothiophenol with either cinnamic acid or acrylic acid [13]. In this paper we describe the study of some *N*- or *O*-alkylation reactions of these 2,3-dihydro[1,5]benzothiazepinones. Thus, when the thiazepinones **4-6** were allowed to interact with *N,N*-dimethylaminoethyl chloride in refluxing acetone in the presence of sodium carbonate, selective *N*-

alkylation reaction occurred giving the *N,N*-dimethylaminoethyl derivatives **7-9**. These compounds could be easily converted into the corresponding water soluble oxalates giving **13-15**. On the other hand, when the thiazepinones **4-6** were heated under reflux in a solution of sodium propoxide in propanol containing chloroalkylamines, these latter reacted differently with the thiazepinones where *O*-alkylation occurred giving 4-dimethylaminopropoxy-(2*H*,5*H*)-[1,5]benzothiazepines **10-12**. These basic derivatives were also converted, in turn, into the corresponding oxalates **16-18**. The structure of these 5-*N,N*-dimethylaminoethyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-ones and 4-dimethylaminopropoxy-(2*H*,5*H*)-[1,5]benzothiazepines was confirmed by ir and nmr spectra (Tables 1 and 2). These preliminary results will be completed by the synthesis of new variously substituted dihydrobenzothiazepines.

Chart 1



## EXPERIMENTAL

Melting points were determined with a Kofler Heiz bank apparatus and are uncorrected. The ir spectra were recorded as potassium bromide pellets on a Philips PU spectrometer and the <sup>1</sup>H-nmr spectra were obtained on a Varian EM 90 spectrometer using DMSO-*d*<sub>6</sub> as the solvent. Chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane as an internal reference.

The 2,3-dihydro[1,5]benzothiazepin-4(5*H*)-ones **4-6** were prepared according to the literature method [14].

Preparation of 5-*N,N*-Dimethylaminoethyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **7**. General Procedure.

A mixture of (0.019 mole) of 2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **4**, (0.019 mole) *N,N*-dimethyl-2-aminoethyl chloride hydrochloride, and (0.038 mole) potassium carbonate in 200 ml of acetone was refluxed for 20 hours. Insoluble materials were removed by filtration, and the filtrate was evaporated under reduced pressure. The oily residue was purified by distillation to afford pure **7** (4.60 g, yield 70%) as a colorless oil of bp 130-132° (5 mm Hg); ir (potassium bromide):  $\nu$  cm<sup>-1</sup> 2820, 2960, 1650 (C=O); <sup>1</sup>H nmr (DMSO-*d*<sub>6</sub>): δ 7.46, 7.23, 6.90 (7H, m, ArH), 4.86 (1H, q,

Table 1  
Physical and Analytical Data for [1,5]Benzothiazepine Derivatives

Compound	Reaction time (hours)	IR (KBr) ( $\nu$ $\text{cm}^{-1}$ )	Bp ( $^{\circ}\text{C}$ ) (mm Hg)	Mp ( $^{\circ}\text{C}$ )	Yield (%)	Formula	Analysis (%)			
							C	H	O	S
8	25	1650 (CO)	145 [5]		60	$\text{C}_{19}\text{H}_{21}\text{FN}_2\text{OS}$	66.65	6.14	8.13	9.31
							66.49	6.15	8.20	9.36
9	20	1650 (CO)	150 [5]		40	$\text{C}_{18}\text{H}_{21}\text{N}_3\text{OS}$	66.02	6.46	12.83	9.79
							66.05	6.50	12.90	9.67
11	6	3220 (NH)	140 [5]		38	$\text{C}_{20}\text{H}_{24}\text{FN}_2\text{OS}$	67.00	8.97	7.81	8.94
							67.10	8.90	7.92	8.90
12	6	3260 (NH)	150 [5]		41	$\text{C}_{19}\text{H}_{23}\text{N}_3\text{OS}$	66.82	6.78	12.30	9.39
							67.00	6.80	12.31	9.42
14	1	3400 (OH) 2900, 2600 (NH <sup>+</sup> ) 1720, 1640 (CO)		147	78	$\text{C}_{21}\text{H}_{23}\text{FN}_2\text{O}_5\text{S}$	58.05	5.33	6.44	7.38
							57.93	5.31	6.50	7.32
15	1	3420 (OH), 2900 2600 (NH <sup>+</sup> ), 1720 1640 (CO)		152	40	$\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_5\text{S}$	57.53	5.52	10.06	7.68
							57.46	5.50	10.10	7.72
17	1	3400 (OH), 3280 (NH) 2900, 2700 (NH <sup>+</sup> ) 1720 (CO)		161	60	$\text{C}_{22}\text{H}_{26}\text{FN}_2\text{O}_5\text{S}$	58.91	5.61	6.24	7.14
							59.00	5.60	6.30	7.20
18	1	3400 (OH), 3260 (NH) 2900, 2700 (NH <sup>+</sup> ) 1720 (CO)		174	60	$\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_5\text{S}$	58.45	5.80	9.73	7.42
							58.52	5.84	9.80	7.38

Table 2  
 $^1\text{H-NMR}$  Spectroscopic Data for [1,5]Benzothiazepine Derivatives

Compound	$^1\text{H-nmr}$ DMSO- $d_6$	$\delta/\text{TMS}$ ppm
8		7.50, 7.00 (8H, m, ArH), 4.80 (1H, q, $\text{C}_2\text{-H}$ ), 2.66 (2H, m, $\text{C}_3\text{-H}_2$ ), 4.26, 3.63 (4H, m, $(\text{CH}_2)_2$ ), 2.26 (6H, s, $(\text{CH}_3)_2$ )
9		8.50, 8.46, 7.63, 7.20 (8H, m, ArH), 4.85 (1H, q, $\text{C}_2\text{-H}$ ), 2.70 (2H, m, $\text{C}_3\text{-H}_2$ ), 4.30, 3.60 (4H, m, $(\text{CH}_2)_2$ ), 2.24 (6H, s, $(\text{CH}_3)_2$ )
11		7.83 (1H, s, NH, deuterium oxide exchangeable), 7.60, 7.36, 7.00 (9H, m, ArH, $\text{C}_2\text{-H}$ ), 6.80 (1H, d, $\text{C}_3\text{-H}$ , J $\text{C}_3\text{-H}$ , $\text{C}_2\text{-H}$ : 15Hz), 2.72, 2.35, 1.70 (6H, m, $(\text{CH}_2)_3$ ), 2.13 (6H, s, $(\text{CH}_3)_2$ )
12		9.60 (1H, s, NH, deuterium oxide exchangeable), 8.60, 8.40, 7.80, 7.30 (9H, m, ArH, $\text{C}_2\text{-H}$ ), 6.90 (1H, d, $\text{C}_3\text{-H}$ , J $\text{C}_3\text{-H}$ , $\text{C}_2\text{-H}$ : 15Hz), 2.70, 2.30, 1.80 (8H, m, $(\text{CH}_2)_3$ ), 2.10 (6H, s, $(\text{CH}_3)_2$ )
14		7.33, 6.83 (8H, m, ArH, $\text{C}_2\text{-H}$ ), 7.23 (2H, s, $(\text{CO}_2\text{H})_2$ , deuterium oxide exchangeable), 4.66 (1H, q, $\text{C}_2\text{-H}$ ), 2.36 (2H, m, $\text{C}_3\text{-H}_2$ ), 3.83, 2.90 (4H, m, $(\text{CH}_2)_2$ ), 2.46 (6H, s, $(\text{CH}_3)_2$ )
15		8.40, 8.36, 7.60, 7.10 (8H, m, ArH), 7.10 (2H, s, $(\text{CO}_2\text{H})_2$ , deuterium oxide exchangeable), 4.86 (1H, q, $\text{C}_2\text{-H}$ ), 2.66 (2H, m, $\text{C}_3\text{-H}_2$ ), 3.80, 2.80 (4H, m, $(\text{CH}_2)_2$ ), 2.60 (6H, s, $(\text{CH}_3)_2$ )
17		9.70 (1H, s, NH, deuterium oxide exchangeable), 9.42 (2H, s, $(\text{CO}_2\text{H})_2$ , deuterium oxide exchangeable), 7.53, 7.33, 7.16 (9H, m, ArH, $\text{C}_2\text{-H}$ ), 3.80, 2.80 (4H, m, $(\text{CH}_2)_2$ ), 2.60 (6H, s, $(\text{CH}_3)_2$ )
18		9.63 (1H, s, NH, deuterium oxide exchangeable), 9.42 (2H, s, $(\text{CO}_2\text{H})_2$ , deuterium oxide exchangeable), 8.50, 7.83, 7.50, 7.33, 6.96 (10H, m, ArH, $\text{C}_2\text{-H}$ , $\text{C}_3\text{-H}$ ), 3.00, 2.46, 1.80 (6H, m, $(\text{CH}_2)_3$ ), 2.66 (6H, s, $(\text{CH}_3)_2$ )

$\text{C}_2\text{-H}$ ), 2.66 (2H, q,  $\text{C}_3\text{-H}_2$ ), 4.23, 3.66 (4H, m,  $(\text{CH}_2)_2$ ), 2.23 (6H, s,  $(\text{CH}_3)_2$ ).

Anal. Calcd. for  $\text{C}_{17}\text{H}_{20}\text{N}_2\text{O}_5\text{S}_2$ : C, 61.41; H, 6.06; N, 8.42; S, 19.28. Found: C, 61.40; H, 6.12; N, 8.36; S, 19.32.

The 5-*N,N*-dimethylaminoethyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **7** (0.01 mole) was boiled for 1 hour in a mixture of 2-propanol and (0.01 mole) of oxalic acid. The solid precipitated from the solution was isolated by filtration and recrystallized from ethanol to obtain (3.80 g, yield 87%) of the oxalate of 5-*N,N*-dimethylaminoethyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **13**; ir (potassium bromide):  $\nu$   $\text{cm}^{-1}$  3400, 2600, 2500, 1720 ( $\text{CO}_2\text{H}$ ), 1650 ( $\text{C}=\text{O}$ )  $^1\text{H}$  nmr (DMSO- $d_6$ ):  $\delta$  7.40, 7.20, 6.76 (7H, m, ArH), 4.93 (1H, q,  $\text{C}_2\text{-H}$ ), 2.56 (2H, q,  $\text{C}_3\text{-H}_2$ ), 2.66 (6H, s,  $(\text{CH}_3)_2$ ), 4.06, 3.13 (4H, m,  $(\text{CH}_2)_2$ ), 9.00 (2H, s,  $(\text{CO}_2\text{H})_2$ , deuterium oxide exchangeable).

Anal. Calcd. for  $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5\text{S}_2$ : C, 54.00; H, 5.24; N, 6.63; S, 15.17. Found: C, 53.83; H, 5.31; N, 6.68; S, 15.02.

The yields and conditions for the isolated products **8-9**, **14-15** are summarized in Tables 1 and 2.

Preparation of 4-*N,N*-Dimethylaminopropoxy-2-(3-thienyl)-(2*H*, 5*H*)-[1,5]benzothiazepines **10**.

A solution of (0.03 mole) of 2,3-dihydro-2-(3-thienyl)-[1,5]benzothiazepin-4(5*H*)-one **4** and (0.074 mole) of sodium propoxide in propanol was heated under reflux during 1 hour. A solution of (0.035 mole) of 3-*N,N*-dimethylaminopropyl chloride hydrochloride and 15 ml of propanol was added in one portion. The resulting suspension was refluxed for 5 hours. The insoluble material was filtered off and the filtrate concentrated *in vacuo*. The oily residue was taken up with water and extracted with diethyl ether. The organic extracts were dried over anhydrous sodium sulfate then evaporated to dryness. The oily residue was purified by distillation to afford **10** (7 g, yield 67%) as a colorless oil, bp 145-147 $^{\circ}$  (5 mm Hg); ir (potassium bromide):  $\nu$   $\text{cm}^{-1}$  3320 (NH);

<sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 8.66 (1H, s, NH, deuterium oxide exchangeable), 8.50, 7.41, 7.00 (7H, m, ArH), 7.73 (1H, d, C<sub>2</sub>-H, J C<sub>2</sub>-H, C<sub>3</sub>-H, 15 Hz), 6.40 (1H, d, C<sub>3</sub>-H, J C<sub>3</sub>-H, C<sub>2</sub>-H, 15 Hz), 2.76, 2.30, 1.70 (6H, m, (CH<sub>2</sub>)<sub>3</sub>), 2.13 (6H, s, (CH<sub>3</sub>)<sub>2</sub>).

*Anal.* Calcd. for C<sub>18</sub>H<sub>22</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>: C, 62.39; H, 6.40; N, 8.08; S, 18.50. Found: C, 62.50; H, 6.44; N, 8.10; S, 18.58.

The oil (0.014 mole) is converted to oxalate which was recrystallized from acetonitrile, 4.90 g, 80% of 4-*N,N*-dimethylamino-propoxy-2-(3-thienyl)-(2*H*,5*H*)-[1,5]benzothiazepine **16** oxalate was obtained; ir (potassium bromide): ν cm<sup>-1</sup> 3330 (NH), 2900, 2280, 1720 (CO<sub>2</sub>H)<sub>2</sub>; <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 9.26 (1H, s, NH, deuterium oxide exchangeable), 5.76 (2H, s, (CO<sub>2</sub>H)<sub>2</sub>, deuterium oxide exchangeable), 7.46, 7.36, 7.10, 6.96 (8H, m, ArH, C<sub>2</sub>-H, J C<sub>2</sub>-H, C<sub>3</sub>-H, 15 Hz), 6.66 (1H, d, C<sub>3</sub>-H, J C<sub>3</sub>-H, C<sub>2</sub>-H, 15 Hz), 2.76, 1.60 (6H, m, (CH<sub>2</sub>)<sub>3</sub>), 2.43, 2.13 (6H, s, (CH<sub>3</sub>)<sub>2</sub>).

*Anal.* Calcd. for C<sub>20</sub>H<sub>24</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>: C, 55.03; H, 5.54; N, 6.42; S, 14.69. Found: C, 55.01; H, 5.55; N, 6.50; S, 14.69.

The yields and conditions for the isolated products **11-12**, **17-18** are summarized in Tables 1 and 2.

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