Oxazepines and Thiazepines, XXV: Chemical Transformations of 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-ones

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2,3-Dihydro-1,5-benzothiazepine-4(5*H*)-thiones **13-22** were prepared by the reaction of the appropriate 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones with *Lawesson's* reagent. *N*-Acyl (**23-25**) and *N*-alkyl (**26-28**) derivatives have also been synthesized. Oxidation with 3-chloroperoxybenzoic acid afforded sulfoxides **29-32**, and sulfones **33-40** were obtained by using H_2O_2 as an oxidizing agent.

Oxazepine und Thiazepine, 25. Mitt.: Zur Umsetzung von 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-onen

Die 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-thione **13-22** wurden durch Umsetzung der entspr. 2,3-Dihydro-1,5-benzothiazepin-4(5*H*)-one mit *Lawesson*-Reagenz dargestellt. Es wurden die *N*-Acylderivative **23-25** und die *N*-Alkylderivate **26-28** ebenfalls synthetisiert. Die Oxidation mit *m*-Chlorperbenzoesäure ergab die Sulphoxide **29-32**, die Sulfone **33-40** wurden durch Oxidation mit H_2O_2 gewonnen.

In the last few decades 2,3-dihydro-1,5-benzothiazepin-4-(5*H*)-ones got prominent places in the drug research. Especially the synthesis and bioactivities of their *N*-alkyl derivatives with basic groups were investigated by several research groups[2-7]. These benzothiazepines possess various important effects, e.g. anti-hypertensive, calcium antagonistic, spasmolytic, anti-ulcer, etc., activities[8-13]. Recently, their optically active derivatives with angiotensin converting enzyme inhibitory activity have been synthesized[14,15]. Syntheses of the carboxylic acid derivatives of such benzothiazepinones have been described[16,17]. Therefore, it seemed expedient to investigate further chemical transformations of the 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones and to synthesize new benzothiazepine derivatives of potential bioactivities in this way.

Few representatives of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-thiones were prepared by the reaction of the appropriate benzothiazepinones with P_4H_{10} in hot pyridine[18,19]. In the case of some thiazepinones, we observed difficulties if this reagent was used for the amide → thioamide conversion. For this reason, 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **1-10** were allowed to react with *Lawesson's* reagent*) in hot toluene to afford thiones **13-22**.

So it can be concluded that *Lawesson's* reagent seems to be convenient for the conversion of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones into thiones.

5-Acetyl-1,5-benzothiazepine derivatives were synthesized by *Kaupp* et al.[20]. In our present studies 2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **2**, **4**, and **5** have been acetylated with acetic anhydride/anhydrous pyridine to give 5-acetyl-2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **23-25** in good yield. 2,3-Dihydro-5-methyl-1,5-benzothiazepin-4(5*H*)-ones **26-28** were obtained by methylation of compounds **1**, **2**, and **9** with CH_3I in anhydrous dimethylformamide in the presence of NaH. These 5-methyl-1,5-benzothiazepinones have been utilized as intermediates for the oxidation experiments.

Previously we synthesized 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one-1-oxides by the oxidation of 1,5-benzothiazepinones with a mixture of H_2O_2 and formic acid[21]. The disadvantage of this procedure is that, in some cases, the formation of the sulfone as a by-product cannot be avoided. Now, 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **2**, **7**, **10**, and **27** have been oxidized with 3-chloroperoxybenzoic acid to afford the appropriate sulfoxides **29-32**. Sulfone formation was not detected by TLC, therefore, this is an efficient method for the preparation of 1,5-benzothiazepine-1-oxides. The synthesis of some 1,5-benzothiazepine-1,1-dioxides by means of H_2O_2 oxidation has been reported[22,23] as well. However, to our knowledge, no systematic investigation has hitherto been performed to develop a general procedure for the preparation of benzothiazepine sulfones. For this reason, variously substituted 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones **2**, **7**, **10-12**, and **26-28** were allowed to react with 30% H_2O_2 in acetic acid solution to afford sulfones **33-40** in good yield. On all these bases it appears that we managed to develop convenient procedures for the synthesis of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one sulfoxides and sulfones providing substances without contamination with the other oxidized product.

The structure of all new compounds has been elucidated by ^{1}H-NMR spectroscopy and elemental analysis and the relevant data are summarized in Tables 1 and 2.

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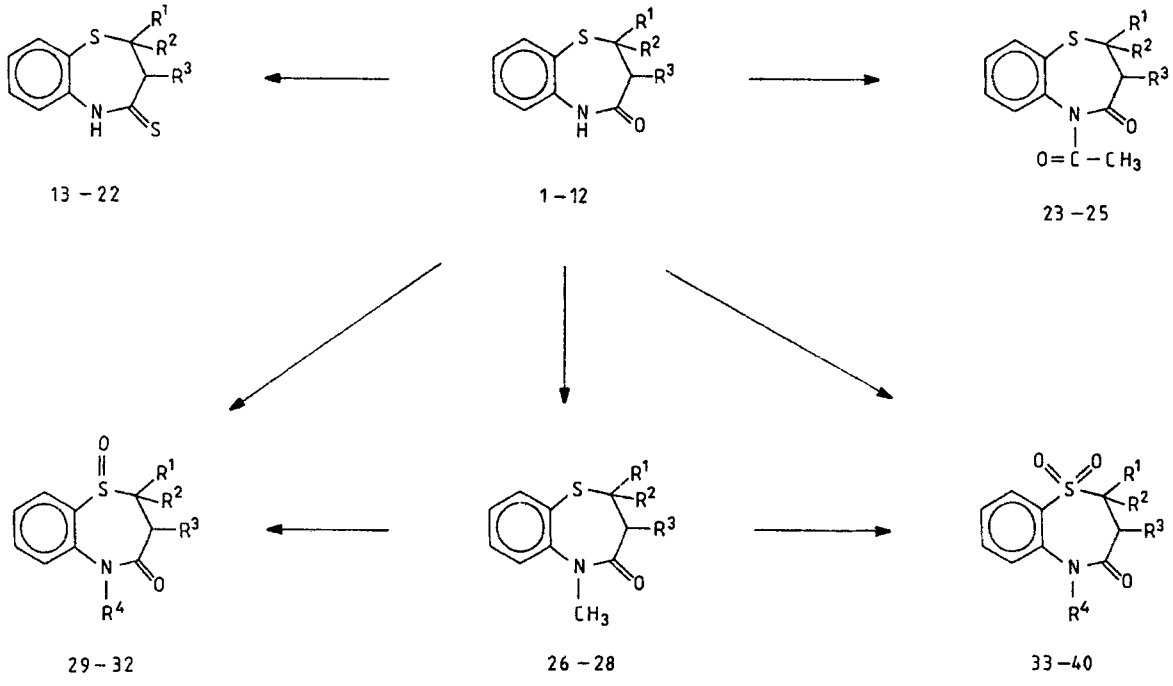

Scheme 1

1, 13, 26: $R^1 = CH_3$, $R^2 = R^3 = H$
2, 14, 23, 27: $R^1 = C_6H_5$, $R^2 = R^3 = H$
3, 15: $R^1 = 4\text{-}OCH_3\text{-}C_6H_4$, $R^2 = R^3 = H$
4, 16, 24: $R^1 = 3,4\text{-}(OCH_3)_2\text{-}C_6H_3$, $R^2 = R^3 = H$
5, 17, 25: $R^1 = 3,4,5\text{-}(OCH_3)_3\text{-}C_6H_2$, $R^2 = R^3 = H$
6, 18: R^1 = 2-naphthyl, $R^2 = R^3 = H$
7, 19: R^1 = 2-furyl, $R^2 = R^3 = H$
8, 20: R^1 = 2-thienyl, $R^2 = R^3 = H$
9, 21, 28: $R^1 = R^2 = CH_3$, $R^3 = H$
10, 22: $R^1 = R^3 = C_6H_5$, $R^2 = H$
11, 36: $R^1 = C_6H_5$, $R^2 = H$, $R^3 = CH_3$
12, 37: $R^1 = C_6H_5$, $R^2 = H$, $R^3 = NHCOCH_3$
29, 33: $R^1 = C_6H_5$, $R^2 = R^3 = R^4 = H$
30, 34: R^1 = 2-furyl, $R^2 = R^3 = R^4 = H$
31, 35: $R^1 = R^3 = C_6H_5$, $R^2 = R^4 = H$
32, 39: $R^1 = C_6H_5$, $R^2 = R^3 = H$, $R^4 = CH_3$
38: $R^1 = R^4 = CH_3$, $R^2 = R^3 = H$
40: $R^1 = R^2 = R^4 = CH_3$, $R^3 = H$

Experimental Part

^{1}H-NMR spectra: Bruker WP 200 SY spectrometer at 200 MHz in $CDCl_3$ (internal standard TMS, δ = 0.0 ppm). TLC: Kieselgel 60 F_{254} (Merck), hexane:acetone (7:3 v/v).- Starting materials **1-8** and **10-12** were prepared as described[16,17,24]. Physical constants, analysis, and ^{1}H-NMR spectral data: Tables 1 and 2.

2,3-Dihydro-2,2-dimethyl-1,5-benzothiazepin-4(5H)-one (9)

A mixture of 3,3-dimethylacrylic acid (5.0 g), 2-aminothiophenol (6.5 ml), and piperidine (0.5 ml) was heated at 150°C for 1.5 h, then cooled to room temp. and crystallized from methanol to afford compound **9**.

2,3-Dihydro-1,5-benzothiazepine-4(5H)-thiones 13-22

A mixture of the appropriate 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**1-12**; 10.0 mmol), *Lawesson's* reagent (5.0 mmol), and anhydrous toluene (30 ml) was refluxed for 3 h, the solvent evaporated *i.vac.*, and the residue crystallized from methanol to obtain pale yellow crystalline materials.

5-Acetyl-2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5H)-ones 23-25

2-Aryl-2,3-dihydro-1,5-benzothiazepin-4(5H)-one (**2**, **4**, and **5**; 5.0 mmol) was heated in acetic anhydride (10.0 ml) and anhydrous pyridine (5.0 ml) at 80°C for 5 h, then poured into water. The precipitate was filtered off, washed with water, and crystallized from methanol to yield white crystalline substances.

2,3-Dihydro-5-methyl-1,5-benzothiazepin-4(5H)-ones 26-28

CH_3I (2.6 ml) dissolved in anhydrous dimethyl-formamide (50 ml) was added to a stirred mixture of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**1**, **2**, and **9**; 20.0 mmol), anhydrous dimethylformamide (150 ml) and NaH (1.0 g) at 0°C. The mixture was stirred at room temp. for 16 h, diluted with water, and extracted with chloroform. The org. phase was washed with water, dried with $CaCl_2$, and the solvent evaporated *i.vac.* to afford compounds **26-28**.

2,3-Dihydro-1,5-benzothiazepin-4(5H)-one-1-oxides 29-32

A mixture of 2,3-dihydro-1,5-benzothiazepin-4(5H)-one (**2**, **7**, **10**, and **27**; 5.0 mmol), dichloromethane (40 ml), and 3-chloroperoxybenzoic acid (Aldrich 50-60%) (5.0 mmol) was stirred at room temp. for 3 h, the solvent evaporated i.vac., and the residue crystallized from methanol to obtain white crystalline products.

Table 1: Physical constants and analysis data of compounds prepared

Compound	M.p. °C	Yield %	Overall formula	Analysis, % Calcd S	Found S
9	223-224	52	$C_{11}H_{13}NOS$	15.44	15.57
12	188-189	65	$C_{10}H_{11}NS_2$	30.59	30.11
14	209-210	70	$C_{15}H_{13}NS_2$	23.59	23.64
15	211-212	85	$C_{16}H_{15}NOS_2$	21.24	21.25
16	135-136	66	$C_{17}H_{17}NO_2S_2$	19.31	19.24
17	160-161	75	$C_{18}H_{19}NO_3S_2$	17.71	17.14
18	244-245	76	$C_{19}H_{15}NS_2$	19.91	19.97
19	165-166	85	$C_{13}H_{11}NOS_2$	24.50	24.27
20	170-171	89	$C_{13}H_{11}NS_3$	34.61	34.15
21	196-197	84	$C_{11}H_{13}NS_2$	28.67	28.78
22	256-257	63	$C_{21}H_{17}NS_2$	18.42	18.53
23	155-156[a]	94	$C_{17}H_{15}NO_2S$	10.76	10.66
24	134-135	95	$C_{19}H_{19}NO_4S$	8.95	9.04
25	189-190	93	$C_{20}H_{21}NO_5S$	8.26	8.19
26	oil	72	$C_{11}H_{13}NOS$	15.44	15.40
27	93-94[b]	87	$C_{16}H_{15}NOS$	11.88	11.84
28	oil	68	$C_{12}H_{15}NOS$	14.46	14.48
29	177-178	66	$C_{15}H_{13}NO_2S$	11.79	11.76
30	163-164	75	$C_{13}H_{11}NO_3S$	12.25	12.43
31	241-242	64	$C_{21}H_{17}NO_2S$	9.21	9.23
32	164-165	71	$C_{16}H_{15}NO_2S$	11.21	11.30
33	239-240	72	$C_{15}H_{13}NO_3S$	11.15	11.26
34	161-162	71	$C_{13}H_{11}NO_4S$	11.55	11.66
35	308-309	83	$C_{21}H_{17}NO_3S$	8.81	8.71
36	306-308	86	$C_{16}H_{15}NO_3S$	10.63	10.44
37	264-265	82	$C_{17}H_{16}N_2O_4S$	9.30	9.18
38	149-150	88	$C_{11}H_{13}NO_3S$	14.21	13.94
39	89-90	63	$C_{16}H_{15}NO_3S$	10.62	10.56
40	148-149	67	$C_{12}H_{15}NO_3S$	12.63	12.65

Lit. (8) m.p. [a]161 °C, [b]95 °C

2,3-Dihydro-1,5-benzothiazepin-4(5H)-one-1,1-dioxides ***33-40***

A mixture of 2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**2**, **7**, **10-12**, and **26-28**; 10.0 mmol), acetic acid (50 ml), and 30% H_2O_2 (10 ml) was heated at 80 °C for 2 h, then poured into water. The precipitate was filtered off, washed with water, and crystallized from methanol to yield white crystalline materials.

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Table 2: ^{1}H-NMR spectroscopic data of compounds prepared

Compound	δ(ppm)
9	1.53 (s, 6H), 2.44 (s, 2H), 7.10 - 7.60 (m, 4 arom.), 8.36 (s, NH)
13	1.47 (d, 3H, J = 6.5 Hz), 2.73 (dd, 1H, J = 12.4; 6.1 Hz), 3.16 (dd, 1H, J = 12.4; 6.1 Hz), 3.98 (m, 1H), 7.15 - 7.67 (m, 4 arom.), 10.30 (s, NH)
14	(3.22 (dd, 1H, J = 12.4; 10.2 Hz), 3.40 (dd, 1H, J = 13.1; 5.6 Hz), 4.99 (dd, 1H, J = 13.1; 5.6 Hz), 7.19 - 7.72 (m, 9 arom.), 9.92 (s, NH)
15	3.20 (dd, 1H, J = 12.1; 10.4 Hz), 3.35 (dd, 1H, J = 12.9; 5.7 Hz), 3.80 (s, 3H), 4.97 (dd, 1H, J = 12.9; 5.7 Hz), 6.82 - 7.72 (m, 8 arom.), 10.05 (s, NH)
16	3.20 (dd, 1H, J = 12.0; 10.5 Hz), 3.39 (dd, 1H, J = 13.0; 6.0 Hz), 3.82 (s, 3H), 3.88 (s, 3H), 4.97 (dd, 1H, J = 13.0; 6.0 Hz), 6.80 - 7.73 (m, 7 arom.), 10.24 (s, NH)
17	3.20 (dd, 1H, J = 12.1; 10.4 Hz), 3.40 (dd, 1H, J = 12.9; 6.0 Hz), 3.83 (s, 9H), 4.92 (dd, 1H, J = 12.9; 6.1 Hz), 6.57 - 7.78 (m, 6 arom.), 10.34 (s, NH)
18	3.20 (dd, 1H, J = 12.0; 10.1 Hz), 3.38 (dd, 1H, J = 12.8; 6.0 Hz), 5.25 (dd, 1H, J = 12.0; 6.0 Hz), 7.33 - 7.91 (m, 11 arom.), 12.20 (s, NH)
19	3.25 (dd, 1H, J = 12.1; 10.4 Hz), 3.46 (dd, 1H, J = 12.8; 6.1 Hz), 5.01 (dd, 1H, J = 12.9; 6.0 Hz), 6.15 - 7.60 (m, 7 arom.), 10.04 (s, NH)
20	3.16 (dd, 1H, J = 12.0; 10.3 Hz), 3.53 (dd, 1H, J = 13.0; 6.0 Hz), 5.27 (dd, 1H, J = 13.0; 6.0 Hz), 6.95 - 7.71 (m, 7 arom.), 9.92 (s, NH)
21	1.57 (s, 6H), 2.90 (s, 2H), 7.19 - 7.63 (m, 4 arom.), 9.90 (s, NH)
22	4.60 (d, 1H, J = 12.5 Hz), 4.92 (d, 1H, J = 12.5 Hz), 7.05 - 7.67 (m, 14 arom.), 12.14 (s, NH)
23	2.79 (s, 3H), 2.83 (t, 2H, J = 8.2 Hz), 4.68 (t, 1H, J = 8.2 Hz), 7.04 - 7.63 (m, 9 arom.)
24	2.75 (s, 3H), 2.80 (t, 2H, J = 8.4 Hz), 3.76 (s, 3H), 3.79 (s, 3H), 4.64 (6, 1H, J = 8.4 Hz), 6.52 - 7.66 (m, 7 arom.)
25	2.77 (s, 3H), 2.82 (t, 2H, J = 8.3 Hz), 3.77 (s, 6H), 3.84 (s, 3H), 4.60 (t, 1H, J = 8.3 Hz), 6.25 - 7.74 (m, 6 arom.)
26	1.37 (d, 3H, J = 6.5 Hz), 2.28 (dd, 1H, J = 12.4; 6.2 Hz), 2.56 (dd, 1H, J = 12.4; 6.2 Hz), 3.35 (s, 3H), 3.82 (m, 1H), 7.19 - 7.63 (m, 4 arom.)
27	2.84 (dd, 2H, J = 12.0; 10.5 Hz), 3.41 (s, 3H), 4.84 (dd, 1H, J = 10.6; 5.7 Hz), 7.18 - 7.67 (m, 9 arom.)

Table 2 continued

Compound	δ(ppm)
28	1.30 (s, 3H), 1.60 (s, 3H), 2.36 (d, 2H, J = 13.1 Hz), 3.36 (s, 3H), 7.15 - 7.61 (m, 4 arom.)
29	2.60 (dd, 1H, J = 12.4; 3.2 Hz), 3.04 (dd, 1H, J = 13.1; 10.4 Hz), 4.63 (dd, 1H, J = 12.4; 3.2 Hz), 7.22 - 7.81 (m, 9 arom.), 10.34 (s, NH)
30	2.62 (dd, 1H, J = 12.5; 3.4 Hz), 2.98 (dd, 1H, J = 13.0; 10.6 Hz), 4.83 (dd, 1H, J = 12.6; 3.4 Hz), 6.56 - 7.80 (m, 7 arom.), 10.20 (s, NH)
31	5.22 (d, 1H, J = 12.4 Hz), 5.68 (d, 1H, J = 12.4 Hz), 7.14 - 7.92 (m, 14 arom.), 10.26 (s, NH)
32	3.03 (d, 2H, J = 13.1 Hz), 3.49 (s, 3H), 4.87 (m, 1H), 7.39 - 7.84 (m, 9 arom.)
33	3.03 (d, 2H, J = 12.4 Hz), 4.93 (m, 1H), 7.30 - 8.02 (m, 9 arom.), 10.45 (s, NH)
34	2.78 (d, 2H, J = 12.6 Hz), 4.56 (m, 1H), 6.42 - 7.83 (m, 7 arom.), 10.28 (s, NH)
35	4.57 (d, 1H, J = 12.4 Hz), 5.67 (d, 1H, J = 12.4 Hz), 7.16 - 7.89 (m, 14 arom.), 10.56 (s, NH)
36	0.98 (d, 3H, J = 6.4 Hz), 3.23 (m, 1H), 4.91 (d, 1H, J = 13.4 Hz), 7.19 - 7.90 (m, 9 arom.), 10.45 (s, NH)
37	1.67 (s, 3H), 2.54 (d, 1H, J = 12.8 Hz), 4.97 (d, 1H, J = 12.8 Hz), 7.07 - 8.58 (m, 9 arom.), 10.73 (s, NH)
38	1.50 (d, 3H, J = 6.5 Hz), 2.37 (dd, 1H, J = 12.3; 6.1 Hz), 2.80 (dd, 1H, J = 12.3; 6.1 Hz), 3.41 (s, 3H), 3.77 (m, 1H), 7.40 - 8.05 (m, 4 arom.)
39	3.04 (d, 2H, J = 12.4 Hz), 4.81 (m, 1H), 7.03 - 7.89 (m, 9 arom.)
40	1.49 (s, 3H), 1.63 (m, 3H), 2.48 (s, 2H), 3.40 (s, 3H), 7.42 - 8.04 (m, 4 arom.)

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