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Synthesis and Transformations of 4,5-Dihydro-1,4-benzothiazepin-3(2*H*)-one Derivatives[1,2]

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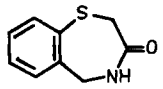
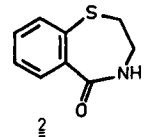
The attempted cyclization of *S*-(3,4-dimethoxyphenyl)-*N*-(hydroxymethyl)thioglycolamide (**6**) with phosphoryl chloride gave, instead of the expected benzothiazepinone **7e**, (3,4-dimethoxyphenylthio)acetonitrile (**8**). The product of ring closure of *N*-[[2-(benzoylthio)-4,5-dimethoxyphenyl]methyl]-2-chloroacetamide (**11**) with sodium ethoxide was 4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepin-3(2*H*)-one (**7e**). The latter compound can also be prepared in good yield from ethyl *S*-[2-(aminomethyl)-4,5-dimethoxyphenyl]thioglycolate (**15**) in alkaline solution. The thiophenols **16a, b** reacted with α-halogenocarboxylic esters **17** in the presence of sodium methoxide to furnish the corresponding 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-ones **7a–i** in high yields in one step. Several conversions of these benzothiazepinones were effected; 3-thiones **18a, b**, sulfones **19a, b**, sulfoxide **20**, *N*-benzoyl **22a** and *N*-phenylcarbamoyl **22b** derivatives were synthesized. $LiAlH_4$ reduction of **7e** gave 2,3,4,5-tetrahydro-7,8-dimethoxy-1,4-benzothiazepine (**21a**).

1,4-Benzothiazepine derivatives are of considerable interest from both chemical and pharmacological aspects; their thorough investigation started only recently. We earlier developed a new method for the preparation of 4,5-dihydro-1,4-benzothiazepine derivatives[3,4]. In continuation of these studies we dealt with the syntheses of the closely related 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one (**1**) and its derivatives. The syntheses and chemical reactions of 5-one and 3,5-dione derivatives **2** and **3** have been the subject of several publications[5–18], but compounds of type **1** have not been studied so far (Scheme 1).

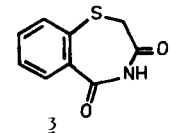
Scheme 1



1



2



3

Synthesis

The starting material in the first attempt to prepare the 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-one derivative **7e** was sodium 3,4-dimethoxythiophenolate (**4**). The reaction with 2-chloroacetamide gave amide **5**, which was converted with formaldehyde into the *N*-

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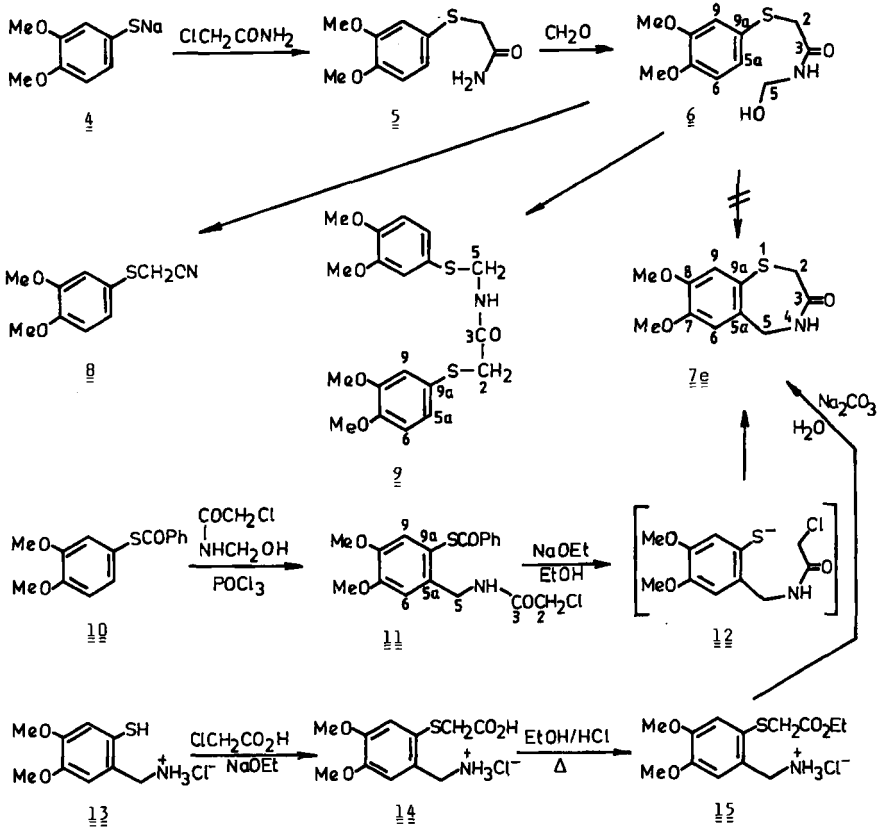
hydroxymethyl derivative **6**. However, attempted cyclization of **6** with phosphoryl chloride did not furnish the expected 1,4-benzothiazepine derivative **7e**, but gave rise by fragmentation to (3,4-dimethoxyphenylthio)acetonitrile (**8**). To obtain evidence of the structure of **6**, it was condensed with 3,4-dimethoxythiophenol in ethanol containing hydrogen chloride to yield product **9**.

Scheme 2



Compound **7e** was then synthesized by sodium ethoxide cyclization of chloroacetamide derivative **11**, prepared by condensation of 2-chloro-*N*-(hydroxymethyl)acetamide with thioester **10**. During the cyclization, compound **11** is instantly debenzoylated by sodium ethoxide and, *via* the intermediate **12**, the 1,4-benzothiazepine ring is formed. However, **7e** was obtained only in very low yields, and therefore a better synthesis was sought.

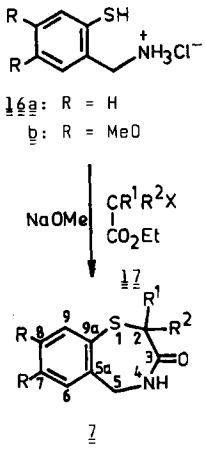
The reaction of 2-mercapto-4,5-dimethoxybenzylammonium chloride (**13**) with chloroacetic acid in the presence of sodium ethoxide gave the thioglycolic acid derivative **14**. Esterification of **14** and alkaline treatment of the ester hydrochloride **15** with sodium carbonate in aqueous solution resulted in the separation of **7e** in crystalline form and in 85% yield.

A generally applicable one-step procedure affording high yields has been developed in our laboratory for the synthesis of the 4,5-dihydro-1,4-benzothiazepin-3(2*H*)-ones **7a–i** by

the reaction of 2-mercaptobenzylammonium chlorides **16a, b** and α-halogenocarboxylic esters **17.**

Subsequently several chemical reactions of the new 1,4-benzothiazepinones were investigated. Compounds **7e, i** were converted with phosphorus pentasulfide into the corresponding 1,4-benzothiazepine-3(2*H*)-thiones **18a, b**. Oxidation of **7e, i** with peracetic acid gave sulfones **19a, b**, and oxidation with sodium periodate the sulfoxide **20**. $LiAlH_4$ reduction of **7e** afforded the tetrahydro derivative **21a**, which was treated with acetyl chloride to yield the *N*-acetylated compound **21b**. Benzoyl chloride in the presence of TEA reacted with **7e** to give the expected *N*-benzoyl derivative **22a**, and treatment with phenyl isocyanate furnished the product **22b** with 4-phenylcarbamoyl substitution.

Scheme 3



7

	R	R^1	R^2
7a	H	H	H
b	H	H	Me
c	H	Me	Me
d	H	H	Ph
e	MeO	H	H
f	MeO	H	Me
g	MeO	Me	Me
h	MeO	H	CO_2Et
i	MeO	H	Ph

Scheme 4

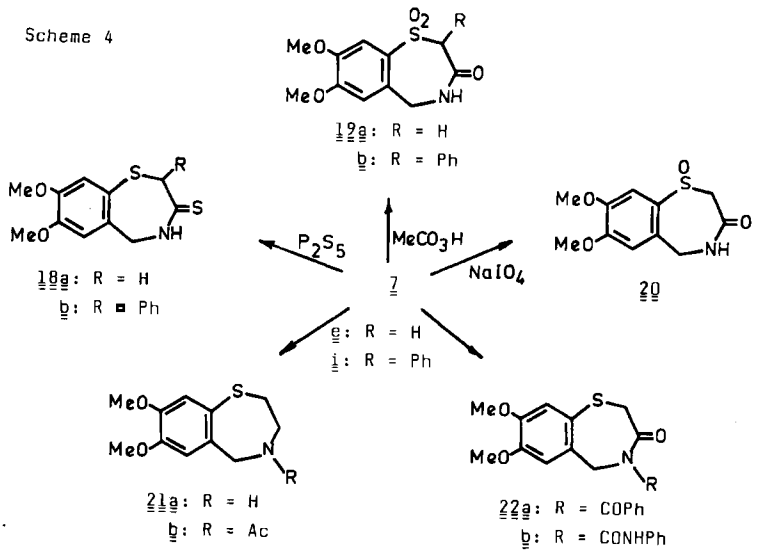


Table 1. IR (KBr, cm^{-1})*[a] and ^1H NMR data ($\delta_{TMS} = 0$ ppm) in $CDCl_3$[a] solution at 250 MHz[b] (coupling constants are given in Hz, in brackets)

Compound	νNH Band	Amide-I Band	δNH Band	2-H s(1H)[c]	5-H s, d or 2xdd (2H)[d]	MeO (7,8) 2xs (2x3H)	6-H[e] 9-H[e] s (1H) s (1H)	NH t (1H)[f]
7a	≈3320	1635	740	3.88	4.40	-	7.0-7.2	8.20
7b	≈3190	1670	800	4.54	4.01, 4.87	-	7.05-7.2	6.65
7c	≈3270, ≈3180	1640	840, 824	-	4.32	-	7.25-7.35 7.55-7.65	7.10
7d	3290	1680		5.27	4.23, 4.62	-	7.1-7.35[g]	7.48
7e	3180, 3050	1678	800	3.66	4.44	3.859, 3.863	6.89[g], 6.71	≈6.9[g]
7f[b]	3220	1670	800	4.40	4.02, 4.75	3.85[h]	6.60, 6.65	?
7g[h]	3280, 3200	1650	815	-	4.48	3.90[h]	6.85, 7.05	7.3
7h	3300, 3235	1664		4.47	4.12[g], 4.80	3.85, 3.86	6.85, 6.98	7.9
7i[b]	3270, 3180	1640	815	5.20	4.23, 4.51	3.65, 3.75	6.65, 6.70	7.95
10a	3290, 3160	-		4.20	4.55	3.83[h]	6.65, 6.75	9.63
10b	3155	-		5.57	4.37, 4.63	3.65, 3.76	6.57, 6.65	10.1
12a	3220, 3100	1600	805	4.42	4.59	3.94[h]	6.81 7.42	8.33
12b	3200, 3150	1655	805	6.41	4.34, 5.28	3.80, 3.90	7.19 7.25	8.86
20	3330	1695		3.93, 4.47	4.27, 4.48	3.85[h]	7.09 7.29	8.39
22a	-	1675, 1695[i]		3.95	5.10	3.84[h]	6.72, 6.76	-
22b	3215, 3170	1720, 1650		4.02	5.06	3.78, 3.84	6.55, 6.78	-

*) Further characteristic IR bands: $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ (monosubstituted ring): 750 and 700 (**7d**), 750 and 705 (**7i**), 725 and 670 (**18b**), 712 and 698 (**19b**), 750, 725 and 700 (**22a**), 750 (**22b**), νC=S (thioamide): 1255 (**18a**), $\nu_{as}SO_2-\nu_sSO_2$: 1300 and 1130 (**19a**), 1315 and 1135 (**19b**), νSO: 1040 (**20**), ester bands (**7h**): 1730 (νC=O), 1215, 1053 and 1038 (νC−O). – Signals of R^2 (**7**) or R (**18**–**22**): CH_3 1.45 d (6.9) (**7b**), CH_3 (R^1 and R^2) 1.48 s (6H) (**7c**), ArH 7.1–7.35 m (5H)[g] (**7d**), CH_3 1.40 d (7) (**7f**), CH_3 (R^1 and R^2) 1.48 s (6H) (**7g**), CH_3 1.17 t (3H), OCH_2 4.12 q (2H)[g], $J = 7.1$ (**7h**), Ar 7.20 ≈s (5H) (**7i**), ArH 7.15 ≈s (5H) (**18b**), ArH-3′,4′,5′ ≈7.42 m, ArH-2′,6′ ≈7.58 d (**19b**), 3′,5′-H 7.36 t, 4′-H 7.46 t, 2′,6′-H 7.66 d (**22a**), 4′-H 7.07 t, 3′,5′-H 7.29 t, 2′,6′-H 7.47 d (**22b**).

[a] For **7a**, **19** and **20** the solvent was [D_6]DMSO. – [b] Measuring frequency 60 MHz. – [c] For **7a**, **e**, **18a**, **19a**, and **22a**, **b** the intensity was 2H, for **7b**, **f**, **g**, for **20** AB m, J(A, B) = 14.2 Hz. – [d] Doublet, $J = 6.5$ (**7a**), 5.0 (**7c**, **g**), 6.0 (**7e**, **18a**, **19a**), AB part of an ABX m (2 × dd), J(A,B), J(A,X) and J(B,X) are 16.2, 6.8, and 6.3 (**7b**), 15.5, 6.2, and 5.8 (**7d**), 15, ?, and ? (**7f**)$^+$, 15.6, 6.8, 4.7 (**7h**)*, 16, 6, and 6 (**7i**), 14.8, 6.5, and 4.5 (**18b**), 16.7, 6.9, and 4.7 (**19b**), respectively, singlet (2H) for **22a**, **b**. – [e] For **7a**–**d** overlapping m's of 6,7,8,9-H (intensity: 4H), for **7c** two m's of (3H-1H) intensity. – [f] Broad signal. – [g] Overlapping signals. – [h] Two coalesced singulets of 6H intensity. – [i] Coalesced amide-I bands of the two amide carbonyl groups. – + Due to the fast exchange of the NH protons, the ABX system of the NH and the 5-H atoms reduces to a singlet and an AB m. Consequently, determination of the values of J(A,X) and J(B,X) is not possible. – *Values measured in [D_6]DMSO.

The structures of the new compounds are supported by IR, ^1H, and ^{13}C NMR spectroscopic evidence[19–21].

The IR and ^1H NMR spectral data of the 1,4-benzothiazepine derivatives prepared are listed in Table 1; those of the other compounds are given in the Experimental Section; the ^{13}C NMR data are to be found in Table 2.

Experimental

Melting points are uncorrected. – ^1H NMR spectra: in 5 mm tubes; room temperature; Bruker WM-250 FT spectrometer at 250.13 MHz or a Varian A 60 D or Jeol 60 HL instrument; in $CDCl_3$ solution; deuterium signal of the solvent as lock and TMS as internal standard. FT spectra: sweep width 5 kHz, pulse width 1 μs (≈20° flip angle), acquisition

Table 2. ^{13}C NMR chemical shifts ($\delta_{TMS} = 0$ ppm) for compounds **6**, **7a**, **c**, **d**, **e**, **h**, **9**, **11**, **18b**, **19b**, **20**, **21a** and **22a**, **b** in $CDCl_3$ or $[D_6]DMSO$ solution (**7a**, **e**, **19b** and **20**) at 20 or 63 MHz (**7a**, **c**, **d**, **18b** and **22a**, **b**)[a]

Compound	C-2	C-3	C-5	C-5a[b]	C-6	C-7	C-8	C-9	C-9a	OCH_3
6	39.8	170.5	64.8	123.8	115.0	149.5[c]	149.8[c]	112.6	125.5	56.2, 56.3
7a	33.6	170.8	41.4	?	129.5[c]	126.7	151.3	129.0[c]	136.2	-
7c	51.6	175.9	48.3	143.0	129.2[c]	128.3	134.7	128.7[c]	135.4	-
7d	51.2	167.8	47.1	?	129.1[c]	127.1	130.6	128.1[c]	136.7	-
7e[e]	34.0	170.9	46.3	129.6	116.3	149.4[c]	150.2[c]	113.7	127.1	57.6, 57.7
7h[e]	51.4	166.9[f]	46.1	133.2	115.6	148.9[c]	149.4[c]	112.7	123.7	55.9[d]
9[g]	39.0	167.7	44.8	122.8 124.9	114.0 115.8	148.8[c] 149.2[c]	149.1[c] 149.3[c]	111.9 112.1	124.3 125.2	55.7[d]
11	42.6[c]	165.7	42.7[c]	136.5	119.5	149.2[f]	151.4[f]	113.7	117.5	56.2, 56.3
18b	58.5	202.0	50.4	130.0	115.9	149.3[c]	150.0[c]	113.6	125.9	56.4, 56.6
19b	74.2	166.9	45.6	131.5[c]	114.4	153.8	150.2	111.0	130.3[c]	57.9[d]
20	57.4	167.0	44.2	130.7	114.8[c]	152.4	150.4	114.2[c]	135.2	57.7[d]
21b	33.5 34.9[h]	49.6 51.2[h]	53.2[h] 54.2	134.2 135.5[h]	116.1[h] 116.9	147.5[c] 148.3[c]	148.1[c] 148.4[c]	113.8 115.0[h]	126.3[h] 127.6	56.9[h], 56.1
22a	36.3	172.5	47.3	124.4[d]	115.2	148.1[c]	149.8[c]	112.4	125.8[d]	56.4, 56.5
22b	36.0	172.1	46.3	124.0[c]	116.0	147.6	150.1	111.2	124.3[c]	56.4, 56.6

Signals of R^2 (**7**), *S*-benzoyl (**11**), or R (**18**–**22**) substituents: CH_3 29.1 (**7c**), C-1′ 137.2, C-2′,3′,5′,6′ 128.6, 128.8[d], C-4′ 128.8[d] (**7d**), CH_3 13.6, OCH_2 61.6, C=O (ester) 166.7[f] (**7h**), see C-5a,6-9,9a[g] (**9**), SCO 191.2, C-1′ 135.1, C-2′,6′ 127.7, C-3′,5′ 128.9, C-4′ 134.0 (**11**), C-1′ 139.4, C-2′,6′ 127.8, C-3′,5′ 128.5, C-4′ 127.6 (**18b**), C-1′ 134.6, C-2′,6′ 133.5, C-3′,5′ 129.4, C-4′ 130.4[e] (**19b**), CH_3 21.3, 21.5[h], C=O 168.6, 169.6[h] (**21b**), C=O 171.1, C-1′ 136.0, C-2′,3′,5′,6′ 128.0, 128.2, C-4′ 131.7 (**22a**), C=O 151.3, C-1′ 137.8, C-2′,6′ 120.8, C-3′,5′ 129.0, C-4′ 124.4 (**22b**).

[a] For numbering of the carbon atoms, see formulae. For **6**, **9**, and **11** the numbering of the benzothiazepines is retained to facilitate the comparison of analogous spectroscopic signals. – [b] Due to saturation, the C-5a signal was not identifiable for compounds **7a**, **d**. – [c,f] Reversed assignment may also be possible. – [d] Overlapping lines. – [e] The order of the carbons corresponding to the individual spectral lines was proved in DEPT experiments[22,23]. – [g] All line pairs corresponding to the two veratryl groups are interchangeable. – [h] All lines are doubled due to amide rotamers in the case of **21b**. The more intense line of the pairs is denoted by the index[h].

time 1.64 s, number of scans 16 or 32. Lorentzian exponential multiplication was used to obtain signal to noise enhancement (line width 0.7 Hz). – ^{13}C NMR spectra: in 5 or 10 mm tubes; room temperature; in $CDCl_3$ solution; Bruker WM-250 or WP 80-SY FT spectrometer, at 63 and 20 MHz, respectively; deuterium signal of the solvent as lock and TMS as internal standard; sweep width 5 and 16 KHz, pulse width 3, 5 and 18 or 7 μs (flip angles ≈30°, 90° and 35°), acquisition time 0.8–1.64 s, number of scans 2^{10}–2^{14}, relaxation delay 0–0.5 s. For signal to noise enhancement Lorentzian exponential multiplication of time domain spectra ("FID's"), line width 0.1 Hz, and complete proton noise decoupling (≈1.5 or ≈3.0 W) were used. – IR spectra: Perkin-Elmer 577, KBr pellets.

S-(3,4-Dimethoxyphenyl)thioglycolamide (**5**): 1.7 g (10 mmol) of 3,4-dimethoxythiophenol and 0.23 g sodium were dissolved in 10 ml of anhydrous ethanol; 0.94 g (10 mmol) of chloroacetamide was added and the mixture was refluxed for 1 h. The precipitated product was filtered off and crystallized from ethanol to give colourless prisms (2.05 g, 90%), m.p.

146–147°C. – IR: $\nu_{as}NH_2$ 3350, ν_sNH_2 3170, amide-I 1615 cm^{-1}. – ^1H NMR: CH_2 δ = 3.52 s (2H), OCH_3 4.84 s (6H), ArH ≈6.88 ≈s (3H).

$C_{10}H_{13}NO_3S$ (227.3) Calcd. C 52.84 H 5.76 N 6.16 Found C 52.86 H 5.96 N 6.30

S-(3,4-Dimethoxyphenyl)-N-(hydroxymethyl)thioglycolamide (6): 11.3 g (50 mmol) of **5** was mixed with 1 g of potassium carbonate dissolved in 5 ml of water; 6 ml of formaldehyde solution was added, and dissolution of **5** was achieved by warming. The mixture was allowed to stand for one day in a refrigerator. The precipitated product was filtered off, washed with water, and dried. Crystallization from benzene gave colourless crystals (8.7 g, 70%), m.p. 81–84°C. – IR: νOH 3300, νNH 3500–2700 (overlapping with the νOH and νCH bands), amide-I 1661 cm^{-1}. – ^1H NMR: SCH_2 δ = 3.53 s (2H), OCH_3 3.84 s (3H) and 3.85 s (3H), NCH_2 4.74 d (*J* = 6.6 Hz, 2H) Ar-6-H 6.80 d (8), Ar-2,5-H ≈6.95 m (2H), OH ≈7.0 broad (1H), NH 7.72 t (1H).

$C_{11}H_{15}NO_4S$ (257.3) Calcd. C 51.34 H 5.88 N 5.44 Found C 51.64 H 5.48 N 5.46

(3,4-Dimethoxyphenylthio)acetonitrile (**8**): 1.28 g (5.0 mmol) of the amide **6** was dissolved, with gentle heating, in 4 ml of phosphoryl chloride, and the reaction mixture was left to stand for 30 min. After decomposition with ice-water, the precipitated crystals were collected by filtration and recrystallized from 50% ethanol to give colourless needles (0.75 g, 72%), m.p. 101–102°C. – IR: δC≡N 2235 cm^{-1}. – ^1H NMR: CH_2 δ = 3.47 s (2H), OCH_3 3.87 s (6H), Ar-5-H 6.80 ≈d (*J* = 8 Hz), Ar-2-H 7.10 ≈s (1H), Ar-6-H 7.15 dd (1H).

$C_{10}H_{11}NO_2S$ (209.3) Calcd. C 57.39 H 5.30 N 6.69 Found C 57.50 H 5.35 N 6.80

S-(3,4-Dimethoxyphenyl)-N-[(3,4-dimethoxyphenylthio)methyl]thioglycolamide (**9**): 1.29 g (5.0 mmol) of **6** and 0.72 ml (5.0 mmol) of 3,4-dimethoxythiophenol were dissolved in 5 ml of ethanol saturated with hydrogen chloride, and the mixture was allowed to stand overnight. It was then diluted with water, extracted with benzene, dried over sodium sulfate, and evaporated. Crystallization of the product from ethanol furnished colourless crystals (1.0 g, 49%), m.p. 90–91°C. IR: νNH 3323, amide-I 1645 cm^{-1}. – ^1H NMR: SCH_2 δ = 3.52 s (2H), OCH_3 3.81 s (3H), 3.85 s (6H) and 3.86 s (3H), NCH_2 4.62 d (*J* = 6.3 Hz, 2H), ArH 6.7–7.0 m (6H), NH 7.18 t (1H).

$C_{19}H_{23}NO_5S_2$ (409.5) Calcd. C 55.72 H 5.66 N 3.42 S 15.66
Found C 56.07 H 5.91 N 3.80 S 15.21

N-[[2-(Benzoylthio)-4,5-dimethoxyphenyl]methyl]-2-chloroacetamide (**11**): 2.74 g (10 mmol) of *S*-(3,4-dimethoxyphenyl)thiobenzoate (**10**) and 1.24 g (10 mmol) of 2-chloro-*N*-(hydroxymethyl)-acetamide were dissolved, with gentle warming, in 3 ml of phosphoryl chloride, and the mixture was allowed to stand for 1 h. It was then decomposed by pouring it into ice-water. The crystals which separated were collected by filtration and heated in 20 ml of ethanol to the boiling point; cooling to ambient temperature gave 1.0 g (26%) of a crystalline product as colourless needles, m.p. 184–185°C (from ethanol). –IR: νNH 3288, νSC=O 1680, amide-I 1641 cm^{-1}. – ^1H NMR: OCH_3 δ 3.88 s (3H) and 3.93 s (3H), $COCH_2$ 4.00 s (2H), NCH_2 4.52 d (*J*= 5.6 Hz, 2H), Ar-3,6-H 6.98 s (1H) and 7.05 s (1H)*, NH ≈7.0 (1H)* (*overlapping signals), Ar-3,5-H 7.50 ≈t (3H), Ar-4-H 7.64 ≈t (1H), Ar-2,6-H 8.05 ≈d (2H).

$C_{18}H_{18}ClNO_4S$ (379.85) Calcd. C 56.91 H 4.78 Cl 9.34 S 8.44
Found C 57.12 H 5.03 Cl 9.26 S 8.34

4,5-Dihydro-7,8-dimethoxy-1,4-benzothiazepin-3(2H)-one (**7e**) *from* **11**: 3.79 g (10 mmol) of **11** was refluxed for 30 min in 30 ml of ethanol containing 1.36 g (20 mmol) of sodium

ethoxide. The reaction product was isolated by preparative TLC on a silica gel plate, using benzene/methanol (10:1) as the developing solvent. Crystallization from ethanol gave colourless needles (50 mg, 2%), m.p. 217–218°C.

$C_{11}H_{13}NO_3S$ (239.3) Calcd. C 55.21 H 5.48 N 5.84 Found C 55.56 H 5.61 N 5.75

S-[2-(Aminomethyl)-4,5-dimethoxyphenyl]thioglycolic Acid Hydrochloride (**14**): 2.35 g (10 mmol) of 2-mercapto-4,5-dimethoxybenzylammonium chloride (**13**) and 0.94 g (10 mmol) of chloroacetic acid were dissolved in 50 ml of ethanol; 2.04 g (30 mmol) of sodium ethoxide was added, and the mixture was refluxed for 30 min. It was then acidified with ethanolic hydrogen chloride, the precipitated sodium chloride was removed by filtration, and the solution was concentrated to 10 ml. After cooling, the crystals which deposited (1.70 g, 58%) were filtered off and recrystallized from glacial acetic acid as colourless needles, m.p. 207–208°C (decomp.). – IR: νN^+H_3 3250–2300, $\nu C{=}O$ (carboxyl group) 1710 cm^{-1}. – ^1H NMR ([D_6]DMSO): SCH_2 δ = 3.70 s (2H), OCH_3 3.85 s (6H), NCH_2 4.20 q (≈2 Hz, 2H), ArH 7.20 s (1H), 7.40 s (1H), NH_3 + OH (carboxyl group) ≈8.5 (broad, 4H).

$C_{11}H_{16}ClNO_4S$ (293.8) Calcd. C 44.97 H 5.49 Cl 12.07 N 4.77
Found C 45.07 H 5.59 Cl 12.00 N 4.97

Ethyl S-[2-(Aminomethyl)-4,5-dimethoxyphenyl]thioglycolate Hydrochloride (**15**): 1.47 g (5.0 mmol) of **14** was mixed with 30 ml of ethanol and 10 ml of ethanol saturated with hydrogen chloride. The mixture was refluxed for 3 h and evaporated to dryness. The oily residue crystallized on standing overnight (1.3 g, 81%). Recrystallization from a mixture of ethanol and acetone gave colourless needles, m.p. 162–163°C. – IR: νN^+H_3 3300–2500, ≈2050 weak, $\nu C{=}O$ (ester) 1740, $\nu_{as}C{-}O$ 1195, $\nu_sC{-}O$ 1025 cm^{-1}. – ^1H NMR: CH_3 δ = 21 t (J = 7.2 Hz, 3H), SCH_2 3.62 s (2H), OCH_3 3.87 s (3H) and 3.95 s (3H), OCH_2 4.11 q (2H), NCH_2 4.35 q (coalesced, 2H), ArH 7.07 s (1H) and 7.50 s (1H), NH 8.76 broad s (3H).

$C_{13}H_{20}ClNO_4S$ (321.8) Calcd. C 48.52 H 6.26 Cl 11.02 N 4.35
Found C 48.22 H 6.44 Cl 11.22 N 4.10

Formation of **7e** *from* **15**: To the solution of 1.61 g (5.0 mmol) of **15** in 10 ml of water 0.5 g of sodium carbonate was added. The product first separating as an oil became crystalline on standing for 1 h (1.02 g, 85%). Recrystallization from ethanol yielded colourless needles, m.p. 217–218°C, identical in all respects with the compound prepared from **11**.

General Procedure for Preparing **7a–i**: 10 mmol of **16a** or **16b** was suspended in 20 ml of methanol and, with stirring, 20 mmol of sodium was added, followed by the dropwise addition of 10 mmol of the appropriate α-halogenocarboxylic ester **17** dissolved in 5 ml of methanol. The mixture was stirred at room temp. for 30 min, and then at reflux temp. for another 30 min. The solution was concentrated to 5 ml, and the crystals which deposited on cooling were collected by filtration, washed with water and recrystallized from ethanol to give **7a–i** (cf. Table 3).

4,5-Dihydro-7,8-dimethoxy-1,4-benzothiazepin-3(2H)-thione (**18a**) *and 4,5-Dihydro-7,8-dimethoxy-2-phenyl-1,4-benzothiazepin-3(2H)-thione* (**18b**): 10 mmol **7e** or **7i**, respectively, and 10 mmol of phosphorus pentasulfide were refluxed in 15 ml of pyridine for 2 h. The reaction mixtures were poured into 150 ml of ice-water. The precipitated solids were filtered off and dried.

18a was a brown crystalline product from chloroform/petroleum ether (1.4 g, 55%), m.p. 165–168°C.

$C_{11}H_{13}NO_2S_2$ (255.4) Calcd. C 51.73 H 5.13 S 25.12 Found C 51.17 H 5.20 S 25.14

Table 3. Physical and analytical data of compounds **7a–i** (* from benzene)

Compound	Yield, %	M.p. °C	Formula (Mol. weight)	Analysis (Calcd./Found) C	H	N
7a	61.4	183–184	C_9H_9NOS (179.2)	60.31 60.62	5.06 5.22	7.82 7.86
7b	51.8	211–212	$C_{10}H_{11}NOS$ (193.3)	62.14 61.86	5.73 5.69	7.25 7.32
7c	67.6	189–190	$C_{11}H_{13}NOS$ (207.3)	63.74 63.90	6.32 6.70	6.76 6.92
7d	39.2	172–173*	$C_{15}H_{13}NOS$ (255.3)	70.58 70.80	5.13 5.34	5.49 5.76
7e	73.2	217–218	$C_{11}H_{13}NO_3S$ (239.3)	55.21 55.45	5.48 5.50	5.85 5.90
7f	62	196–197	$C_{12}H_{15}NO_3S$ (253.3)	56.90 56.66	5.97 6.22	5.53 5.70
7g	73.8	159–160	$C_{13}H_{17}NO_3S$ (267.3)	58.40 58.60	6.41 6.72	5.24 5.16
7h	27.7	140–141	$C_{14}H_{17}NO_5S$ (311.3)	54.00 54.06	5.51 5.71	4.50 4.72
7i	55.5	149–150	$C_{17}H_{17}NO_3S$ (315.4)	64.74 65.01	5.43 5.21	4.44 4.58

18b: light-yellow crystals from benzene (2.52 g, 76%), m.p. 105–107°C.

$C_{17}H_{17}NO_2S_2$ (331.5) Calcd. C 61.60 H 5.17 N 4.23 S 19.35
Found C 62.00 H 5.56 N 4.18 S 19.70

4,5-Dihydro-7,8-dimethoxy-1,4-benzothiazepin-3(2H)-one 1,1-Dioxide (**19a**): 1.20 g (5.0 mmol) of **7e** was dissolved in a mixture of 8 ml of dioxan and 8 ml of glacial acetic acid. To this solution, with stirring and cooling, was added, in small portions, a solution of 4.0 g of potassium permanganate in 8 ml of water. The mixture was then stirred for 1 h. Manganese(IV) oxide was dissolved by adding 30% hydrogen peroxide. The mixture was diluted with 25 ml of water and stored overnight at 0°C. The precipitated crystals (0.52 g, 38%) were filtered off and recrystallized from ethanol to give plates with a nacreous lustre, m.p. 228–230°C.

$C_{11}H_{13}NO_5S$ (271.3) Calcd. C 48.70 H 4.83 N 5.16 S 11.82
Found C 48.36 H 5.13 N 5.53 S 12.10

4,5-Dihydro-7,8-dimethoxy-2-phenyl-1,4-benzothiazepin-3(2H)-one 1,1-Dioxide (**19b**): 1.58 g (5.0 mmol) of **7i** was dissolved in 16 ml of 9% peracetic acid. The mixture was allowed to stand for 30 min, then refluxed for 1 h, and poured onto ice. The crystalline precipitate (1.4 g, 80%) was filtered off and recrystallized from glacial acetic acid to give colourless crystals, m.p. 241–242°C.

$C_{17}H_{17}NO_5S$ (347.4) Calcd. C 58.77 H 4.93 N 4.03 S 9.23
Found C 58.50 H 4.99 N 4.25 S 9.40

4,5-Dihydro-7,8-dimethoxy-1,4-benzothiazepin-3(2H)-one 1-Oxide (**20**): 1.2 g (5.0 mmol) of **7e**, 10 ml of methanol, and 1.18 g of sodium periodate dissolved in 11 ml of water were mixed and stirred at room temp. for 3 days. The crystals which separated were collected by filtration, washed with water and recrystallized from ethanol to yield colourless prisms (1.0 g, 79%), m. p. 230–231 °C (decomp.).

$C_{11}H_{13}NO_4S$ (255.3) Calcd. C 51.75 H 5.13 N 5.48 Found C 51.41 H 5.13 N 5.18

2,3,4,5-Tetrahydro-7,8-dimethoxy-1,4-benzothiazepine (**21a**): 2.39 g (10 mmol) of **7e** and 0.29 g of $LiAlH_4$ were refluxed in 60 ml of ether, with constant stirring, for 2 days. The reaction mixture was decomposed by adding 1 ml of water under cooling and stirring, and the product was extracted with 100 ml of ether. After drying over sodium hydroxide, the solvent was evaporated to leave a viscous oil, from which the hydrochloride of the product (0.70 f, 27%) separated on addition of ethanolic hydrogen chloride; m. p. 198–200 °C (decomp.).

$C_{11}H_{16}ClNO_2S$ (261.8) Calcd. C 50.47 H 6.16 Cl 13.55 N 5.35
Found C 50.77 H 6.48 Cl 13.11 N 5.68

Picrate: light-yellow crystals from ethanol, m. p. 195–196 °C (decomp).

$C_{17}H_{18}N_4O_9S$ (454.4) Calcd. C 44.93 H 3.99 N 12.33 Found C 44.69 H 4.22 N 12.69

4-Acetyl-7,8-dimethoxy-2,3,4,5-tetrahydro-1,4-benzothiazepine (**21b**): 0.70 ml (5.0 mmol) of triethylamine and 0.36 ml (5.0 mmol) of acetyl chloride were added to a solution in benzene of the base liberated from 1.31 g (5.0 mmol) of 2,3,4,5-tetrahydro-7,8-dimethoxy-1,4-benzothiazepinium chloride. The mixture was allowed to stand for 1 h, the precipitated crystals were filtered off, and the benzene solution was evaporated to dryness. The residue was purified by preparative TLC on silica gel plates, using benzene/methanol (10:1) as the developing solvent. The product was a colourless oil which crystallized on standing overnight (0.53 g, 40%), m. p. 122–124 °C. – IR: amide-I 1632 cm^{-1}. – ^1H NMR: $COCH_3$ δ = 2.03 and 2.18 2 × s (3H), SCH_2 2.80, ≈t (2H), OCH_3 3.85, 3.87, 3.89, and 3.90 4 × s (8H, overlapping with the 3-H multiplet), NCH_2 4.61 and 4.64 2 × s (2H), Ar-3,6-H 6.80, 7.09 and 7.03, 7.10 2 × 2 × s (2 × 1H).

$C_{13}H_{17}NO_3S$ (267.3) Calcd. C 58.40 H 6.41 S 11.99 Found C 60.00 H 6.70 S 11.77

4-Benzoyl-4,5-dihydro-7,8-dimethoxy-1,4-benzothiazepin-3(2H)-one (**22a**): A mixture of 1.2 g (5.0 mmol) of **7e**, 40 ml of benzene, 2.8 ml of triethylamine, and 1.16 ml (10 mmol) of benzoyl chloride was stirred and refluxed for 2 h. After cooling, the crystals were filtered off and washed with benzene and then with 150 ml of warm (60 °C) water, to give 1.70 g (99%) of the product; colourless needles from benzene, m. p. 202–203 °C.

$C_{18}H_{17}NO_4S$ (343.4) Calcd. C 62.96 H 4.99 N 4.08 S 9.37
Found C 63.30 H 5.09 N 4.32 S 9.70

4,5-Dihydro-7,8-dimethoxy-4-(phenylcarbamoyl)-1,4-benzothiazepin-3(2H)-one (**22b**): 1.2 g (5.0 mmol) of **7e** and 1.2 ml of phenyl isocyanate were refluxed in 45 ml of chloroform for 24 h. The mixture was evaporated and the residue was boiled with 50 ml of ethanol. On cooling, a crystalline product deposited (1.5 g, 84%), which gave colourless crystals from ethanol, m. p. 173–174 °C.

$C_{18}H_{18}N_2O_4S$ (358.4) Calcd. C 60.32 H 5.06 N 7.82 Found C 60.50 H 5.46 N 8.01

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