Properties and Reactions of Substituted 1,2-Thiazetidine 1,1-Dioxides: C-3 Substituted β-Sultams

Peter Schwenkkraus and Hans-Hartwig Otto*

Pharmazeutisches Institut, LS Pharmazeutische Chemie, Universität Freiburg, Hermann-Herder-Str. 9, D-79104 Freiburg i.Br., Germany

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(*RS*)-3-(2-Chloroethyl)-β-sultam (**6**) is obtained from methyl 4-bromocrotonate (**1**) by a five step synthesis. The analogous (*R*)-3-chloromethyl-β-sultam (**12**) is available from (*R*)-benzylcysteinol (**9**). While the chlorine in **6** is replaced easily by iodine yielding **7**, the analogous reaction with **12** fails. The 3-(hydroxyethyl/methyl) substituted β-sultams **17** and **21** are prepared by similar routes. All structures are established by spectroscopic

Eigenschaften und Reaktionen substituierter 1,2-Thiazetidin-1,1-dioxide: C-3 substituierte β-Sultame

(*RS*)-3-(2-Chlorethyl)-β-Sultam (**6**) wird aus 4-Bromcrotonsäuremethylester (**1**) in einer fünfstufigen Synthese erhalten. Das analoge (*R*)-3-Chlormethyl-β-sultam (**12**) läßt sich aus (*R*)-Benzylcysteinol auf ähnlichem Wege gewinnen. Während Chlor in **6** relativ leicht gegen Iod zu **7** ausgetauscht werden kann, mißlingt diese Reaktion bei **12**. Die 3-(Hydroxyethyl/methyl)-substituierten β-Sultame **17** und **21** sind auf analogen Wegen zugänglich. Alle Strukturen werden durch spektroskopische Methoden charakterisiert.

1,2-Thiazetidine 1,1-dioxides (β-sultams) are highly reactive sulfonyl analogues of the biologically active β-lactams. Furthermore, they are helpful for the construction of other heterocyclic systems, and eventually for the synthesis of potent drugs[1]. However, the β-sultams exhibit specific differences in some reactions, which on one hand may become valuable especially for synthetic goals, on the other hand can cause severe problems, i.e. concerning the synthetic approach or the stability[2]. We have given examples for the substitution at the nitrogen and at C-4 of the β-sultam ring[2].

Here, we present for the first time some experiments allowing substitution at C-3, and demonstrate some possible variations and synthetic uses of these substituents.

As the H-atoms at C-3 are not activated by any neighbouring group, experiments to introduce a substituent into the intact ring system have to fail. Therefore, we sought a route, allowing the introduction of substituents before ring closure. The best way we found was the following sequence: methyl bromocrotonate (**1**) reacts with benzylmercaptan to yield methyl 4-benzylthiocrotonate (**2**), yielding after addition of ammonia in a sealed vessel (±)-*S*-benzyl β-homocysteine (**3**) as described by *Birkofer*[3]. According to lit. procedures[4] **3** is reduced by $LiAlH_4$ to (±)-*S*-benzyl-β-homocysteinol (**4**). By a similar route we prepared *S*-benzyl-L-cysteinol[5] (**9**) from *S*-benzyl-L-cystein (**8**).

When **4**-HCl is treated with Cl_2 in EtOH/$CHCl_3$ at low temp., the sulfochloride **5** is formed nearly quantitatively. During this reaction the benzyl group is deleted, and the hydroxyl group is replaced by chlorine. As **5** is very sensitive against humidity, it is immediately transferred into dry $CHCl_3$ and reacted with ammonia at 0°C forming (*RS*)-3-(2-chloroethyl)-β-sultam (**6**). The overall yield from **4** to **6** is about 80%. The chlorine may be replaced by iodine by 12 h refluxing with NaI in acetone[6] giving **7** with 70% yield.

When the hydrochloride of cysteinol **9** was treated with chlorine as described for **4**-HCl, we isolated the benzylsulfonyl chloro derivative **10** in more than 80% yield instead of the analogous β-sultam. The hydroxyl group had been replaced as during the reaction of **4**, but instead of deletion of the benzyl group the S-atom was oxidized. The reason for the failure of debenzylation may be seen in the adjacent β-amino alcohol structure, although a similar case does not seem to be known[7]. Anyway, for a successful sequence we first had to cleave the S-benzyl bond by reaction with sodium in ammonia[8] to **11**, which was not isolated but immediately oxidized and cyclized yielding (*S*)-3-chloromethyl-1,2-thiazetidine 1,1-dioxide (**12**) in about 50% yield from **9**. Interestingly, it was not possible to replace the chlorine of **12** by iodine, although we tried many different methods[1]. Probably, this is caused by steric interaction. It is known, that a big substituent in the β-position inhibits substitution of halogens[9].

In order to synthesize 3-(β-hydroxyethyl)-β-sultam (**17**) we used the amino alcohol **4** as starting material. After protection of the alcohol function by acylation to **14** with acyl chlorides under anhydrous conditions, oxidative cleavage with Cl_2 resulted in **15** which was cyclized with ammonia yielding the β-sultams **16** with > 80% yield. Cleavage of the ester group had to be performed under N_2 avoiding even traces of water. It was best done with catalytic amounts of $NaOCH_3$ in absol. MeOH giving the β-sultam **17** in yields between 60 and 70%. **17** is a viscous colorless liquid which has to be stored under N_2 and at low temp.

When *S*-benzyl-L-cysteinol (**9**) was dissolved in dry $CHCl_3$, followed by saturation of the solution with HCl gas, and addition of acetyl chloride, the acetylated hydrochloride **18** was isolated nearly quantitatively. The oxidative

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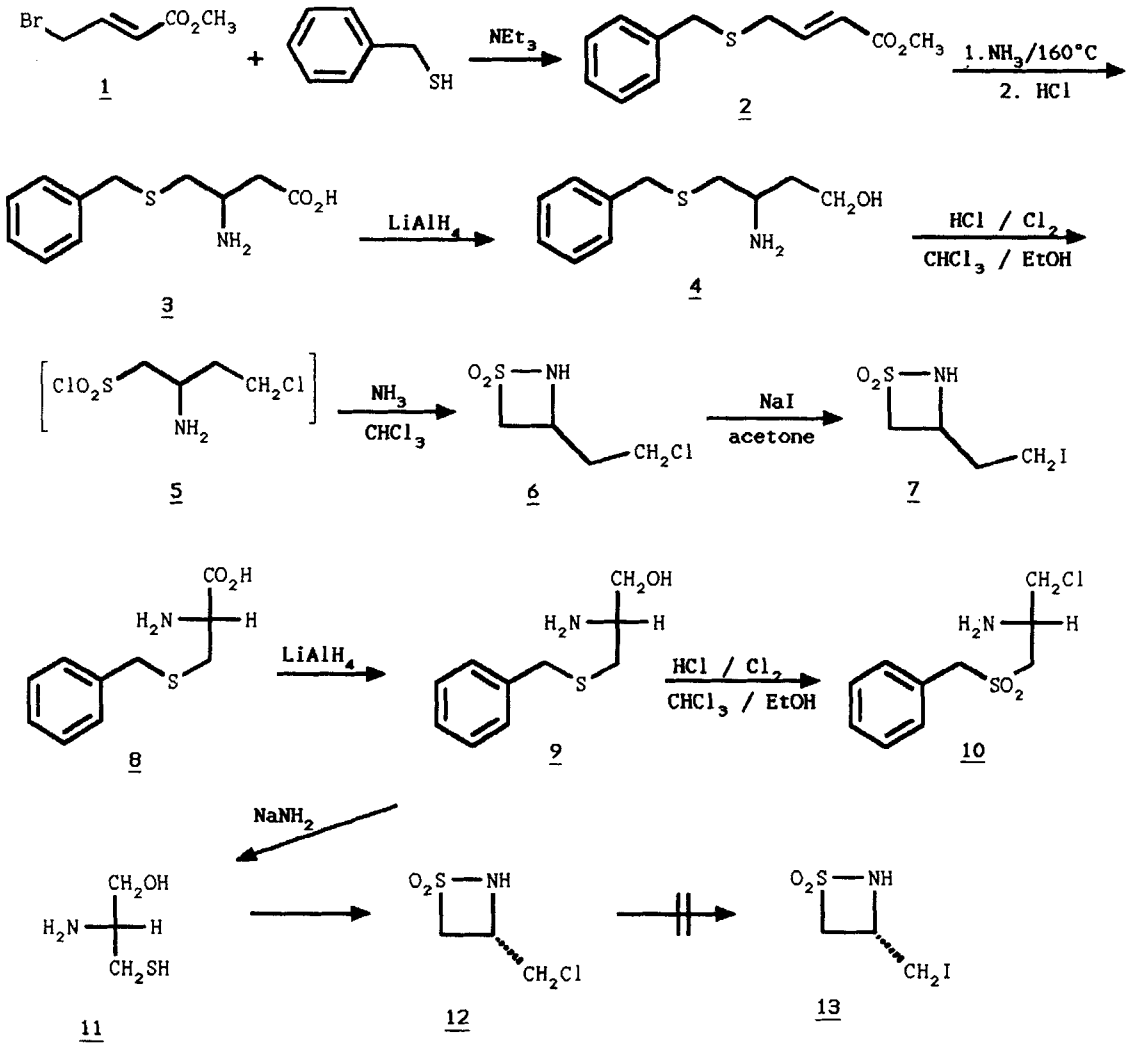

Scheme 1

cleavage to **19** is successful with Cl_2 in EtOH/$CHCl_3$ under anhydrous conditions. **19** was not isolated, but immediately transferred into chloroform and cyclized to **20** with gaseous ammonia. Finally, **20** is cleaved with $NaOCH_3$ in MeOH yielding 40% of (*R*)-3-hydroxymethyl-β-sultam (**21**) as a crystalline compound being more stable than **17**.

IR- and ^{1}H-NMR-data of the β-sultams **6**, **7**, **12**, **17**, **21**, and of all intermediates agree with their structures. In KBr IR-spectra all β-sultams exhibit a strong and sharp N-H valence bond around 3300 cm^{-1}. Only **12** shows two bands at 3310 and 3290 cm^{-1} in the solid state spectrum, probably caused by a steric interaction between the chloromethyl sidechain and the N-H inversion. In solution we only see one band near 3340 cm^{-1}. It has to be highlighted, that all β-sultams exhibit a strong C-H valence band around 3050 cm^{-1} (!) which, together with the strong SO_2-asym. bands between 1340 and 1285 cm^{-1}, establish the strained 4-membered ring. Furthermore, this is supported by the coupling constants from the ^{1}H-NMR spectra. The geminal coupling constant $^2J_{4,4'}$ is found between 12.5 and 13.5 Hz, and the vicinal coupling constants are $^3J_{cis}$ = 7.5-9 Hz and $^3J_{trans}$ = 5-5.5 Hz.

Substitution of the chlorine in **6** or **12** by other nucleophiles was either incomplete or completely unsuccessful. However, replacement of iodine in **7** by S-nucleophils was possible, as demonstrated by the reaction with alkyl thioglycolates. By refluxing of **7** for 12 h with a slight excess of thioglycolate in ether the sulfides **22** were obtained nearly quantitatively. They can be oxidized to the stable, crystalline sulfones **23**.

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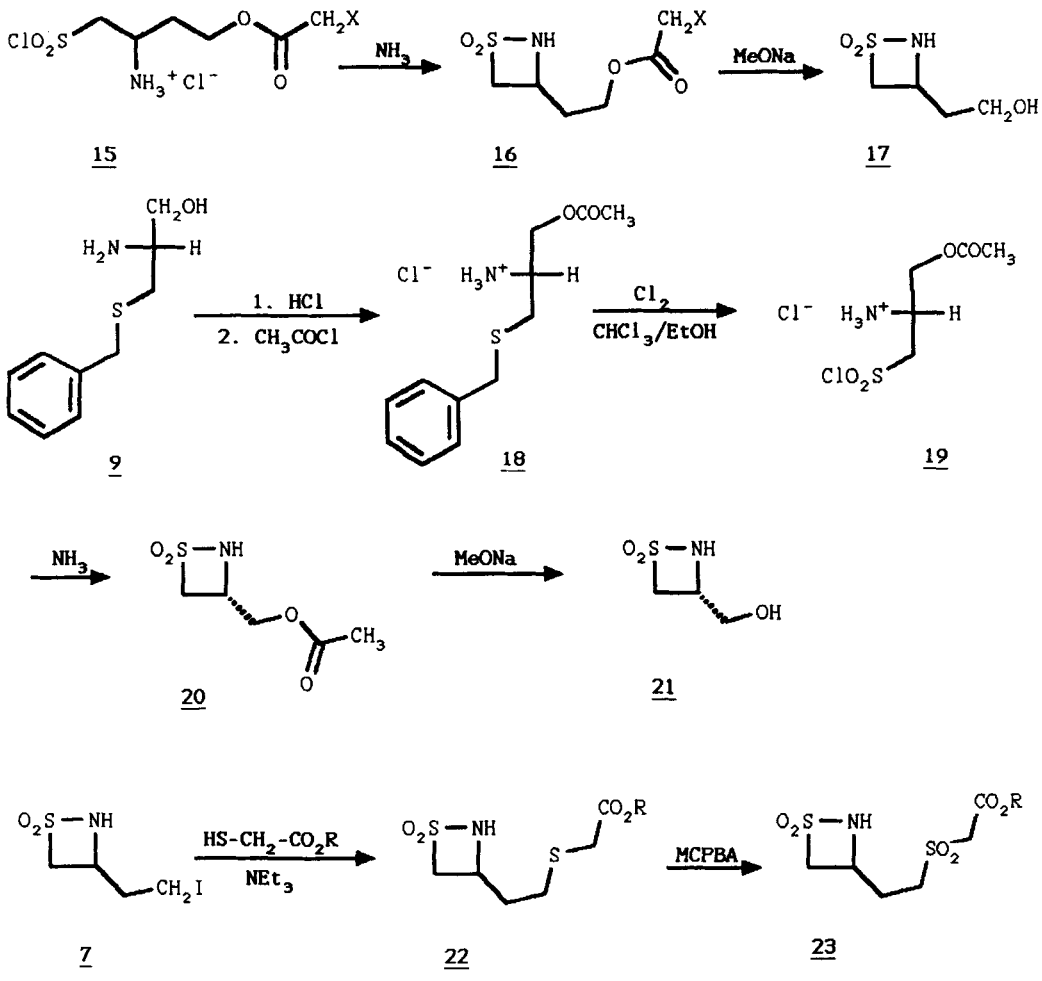
Experimental Part

Melting points (not corrected): Linström apparatus.- IR spectra: Perkin-Elmer IR 1310, Beckman IR 4240; in KBr, if not noted otherwise.- ^{1}H-NMR spectra: Varian T60, Bruker WP80, Bruker WP250; TMS as internal standard; values from 80-MHz spectra in $CDCl_3$, if not noted otherwise, δ



Scheme 2

in ppm.- Elementary analyses: Pharmazeutisches Institut or Chemisches Laboratorium der Universität Freiburg.- Solvents were dried according to lit. procedures.

Methyl 4-Benzylthiocrotonate (**2**)

From 179 g (1 mol) of methyl 4-bromocrotonate (**1**), 124 g (1 mol) of benzylmercaptan, and 101.2 g (1 mol) of triethylamin; yield 156 g (70%), colorless crystals, m.p. 41-42°C (MeOH) (ref.[3]: 45-46°C).- IR: 1710 cm^{-1} (CO); 1640 (C=C); 1600; 1490; 700 (ar); 1230; 1210 (C-O).- ^{1}H-NMR (CCl_4): δ = 2.97 (dd; J = 7.5 Hz; 1 Hz; 2H, 4-H_2), 3.55 (s; 2H, ar-CH_2), 3.60 (s; 3H, CH_3), 5.70 (dd; J = 8 Hz; 1 Hz; 1H, 2-H), 6.75 (dt; J = 8 Hz; 7.5 Hz; 1H, 3-H), 7.20 (s; 5H, arH).

(RS)-3-Amino-4-benzylthiobutyric acid (**3**)

From 44.6 g (0.2 mol) of **2** and 270 ml of conc. ammonia (d = 0.91); yield 9.0-31.5 g (20-70%), light brown powder, m.p. 194-197°C (ref.[3]: 203-204°C).- IR: 3100-2600 cm^{-1} (NH_3^+); 1570 (COO^-); 1490; 700 (ar).

(RS)-3-Amino-4-benzylthiobutanol (**4**)

22.5 g (0.1 mol) of **3** are added to an icecold suspension of 10 g (0.26 mol) of $LiAlH_4$ in 300 ml of THF in small portions. The mixture is refluxed for 5 h, cooled to 0-5°C, diluted with 200 ml of ether, and carefully hydrolyzed with 30 ml of water. The precipitate is separated and extracted with 3 x 200 ml of EtOH. The combined org. layers are concentrated *in vacuo*, dissolved in 200 ml of ether, separated from the residue, and concentrated *in vacuo* again. The residue is distilled *in vacuo*; yield 15.8 g (75%), colorless liquid, b.p. 142-143°C/0.02 Torr, n^{20} = 1.5740.- IR (film): 3340 cm^{-1}; 2910; 1600-1580 (OH, NH_2); 1490, 700 (ar).- ^{1}H-NMR: δ = 1.55 (mc; 2H, 2-H_2), 2.50 (mc; 2H, 4-H_2), 2.60 (s; 3H, OH, NH_2), 2.93 (mc; 1H, 3-H), 3.67 (s; 2H, ar-CH_2), 3.72 (t; J = 6 Hz, 2H, 1-H_2), 7.32 (s; 5H, ar-H).- $C_{11}H_{17}NOS$ (211.3) Calcd. C 62.5 H 8.11 N 6.6 S 15.2 Found C 62.8 H 8.06 N 6.5 S 15.1.

(RS)-3-(2-Chloroethyl)-1,2-thiazetidine 1,1-Dioxide (**6**)

HCl is bubbled for 2 min into an icecold solution of 10.5 g (50 mmol) of **4** in 200 ml of $CHCl_3$. After addition of 60 ml of EtOH (96%), the mixture is saturated with Cl_2 below 10°C, the excess of chlorine is blown out with N_2, and 200 ml of ether are added. After cooling at 0°C for 24 h, the precipitate (sulfochloride **5**) is separated and dried *in vacuo*. The acid chloride is suspended in 150 ml of dried $CHCl_3$, and with cooling slowly cyclized with a saturated solution of NH_3 in $CHCl_3$. The solution is filtered through celite and evaporated *in vacuo*; yield 6.5 g (77%), colorless crystals, m.p. 45°C ($CHCl_3$/CCl_4).- IR: 3300 cm^{-1} (NH); 3055; 2980; 2970; 2960; 2940; 2910 (CH); 1340; 1325; 1285; 1170; 1150 (SO_2).- ^{1}H-NMR: δ = 2.22 (q; J = 6 Hz; 2H, CH_2-CH_2Cl), 3.65 (t; J = 6 Hz, 2H, CH_2Cl), 3.80 (mc; 1H, 3-

H), 3.95 (mc; ^2J = 13.5 Hz, ^3J = 5 Hz, 1H, 4-H), 4.40 (mc; ^2J = 13.5 Hz, ^3J = 9.0 Hz, 1H, 4-H), 6.05 (br.s, 1H, NH).- $C_4H_8ClNO_2S$ (169.6) Calcd. C 28.3 H 4.75 Cl 20.9 N 8.3 S 18.9 Found C 28.6 H 4.68 Cl 20.7 N 8.2 S 18.8.

(RS)-3-(2-Iodoethyl)-1,2-thiazetidine 1,1-dioxide (**7**)

1.7 g (10 mmol) of **6** and 3.0 g (20 mmol) of NaI are refluxed in 30 ml of acetone for 12 h. The precipitate (NaCl) is separated, the solvent is concentrated *in vacuo*, and the residue is twice extracted with 50 ml of $CHCl_3$. The $CHCl_3$ solution is purified by CC (silica gel, $CHCl_3$/ethyl acetate 9:1), the filtrate is concentrated *in vacuo*; yield 1.85 g (71%), colorless crystals, m.p. 43-44°C ($CHCl_3/CCl_4$).- IR: 3300 cm^{-1} (NH); 3040; 2950 (CH); 1310; 1295; 1155 (SO_2).- ^{1}H-NMR: δ = 2.25 (q; J = 6 Hz, 2H, C<u>H</u>$_2$-CH_2I), 3.17 (mc; 2H, CH_2I), 3.75 (mc; 1H, 3-H), 3.95 (dd; J = 12 Hz; 5 Hz; 1H, 4-H), 4.45 (mc; ^2J = 12 Hz; ^3J = 8 Hz; 1H, 4-H'), 5.90 (br.s; 1H, NH).- $C_4H_8INO_2S$ (261.1) Calcd. C 18.4 H 3.09 N 5.4 S 12.3 Found C 18.5 H 3.00 N 5.3 S 12.4.

(S)-(-)-1-Benzylsulfonyl-3-chloro-2-propylamine (**10**)

From 2.0 g *S*-benzyl-L-cysteinol (**9**) as described for **6** via **5**; yield 2.0 g (81%), colorless crystals, m.p. 43°C (CCl_4/n-hexane).- $[\alpha]^{23}$ = -8.3 (c = 3.4, $CHCl_3$).- IR: 3370 cm^{-1}; 3310, 1580 (NH_2), 3060, 3030, 1600, 1490, 765, 700 (ar), 1295, 1280, 1140, 1125 (SO_2).- ^{1}H-NMR: δ = 1.97 (s; 2H, NH_2), 3.0 (mc; 2H, 1-H_2), 3.50 (mc; 2H, 3-H_2), 3.65 (mc; 1H, 2-H), 4.35 (s; 2H, Ar-CH_2), 7.37 (s; 5H, ArH).- $C_{10}H_{14}ClNO_2S$ (247.7) Calcd. C 48.5 H 5.70 Cl 14.3 N 5.7 S 12.9 Found C 48.2 H 5.61 Cl 14.2 N 5.6 S 12.8.

(S)-(-)-3-Chloromethyl-1,2-thiazetidine 1,1-dioxide (**12**)

To a solution of 9.9 g (50 mmol) of *S*-benzyl-L-cysteinol (**9**) in 200 ml of liquid NH_3 1.3 g of Na^0 are slowly added (until the blue colour becomes permanent). 4.3 g (80 mmol) of NH_4Cl are added very carefully, NH_3 is blown out by N_2, the residue (**11**) is dried *in vacuo* and extracted with 4 x 50 ml of $CHCl_3$. The solution is treated with HCl, Cl_2 and NH_3 as described for **6**. The liquid residue is resolved in $CHCl_3$/ethyl acetate 4:1, filtered through celite, and evaporated *in vacuo*; yield 3.7 g (47%), colorless crystals, m.p. 73°C ($CHCl_3$).- $[\alpha]^{25}$ = -17.9 (c = 2.7, EtOH).- IR: 3310 cm^{-1}; 3290 (NH); 3040; 2970; 2950 (CH); 1340; 1310; 1290; 1150 (SO_2).- ^{1}H-NMR ([D_6]-acetone): δ = 3.80-4.00 (m; 2H, CH_2Cl), 3.92 (mc; 1H, 3-H), 4.05 (mc; ^2J = 13.2 Hz, ^3J = 4.5 Hz, 1H, 4-H), 4.40 (mc; ^2J = 13.2 Hz, ^3J = 8.8 Hz, 1H, 4-H'), 7.20 (br.s, 1H, NH).- $C_3H_6ClNO_2S$ (155.6) Calcd. C 23.2 H 3.89 Cl 22.8 N 9.0 S 20.6 Found C 23.3 H 3.80 Cl 22.6 N 8.9 S 20.5.

(RS)-3-Amino-4-benzylthio-1-butyl acetate hydrochloride (**14a**)

A solution of 10.5 g (50 mmol) of **4** in 50 ml of $CHCl_3$ is saturated with HCl, 6.3 g (80 mmol) of acetyl chloride in 50 ml of Et_2O are added, and the mixture is stirred for 1 h at room temp. Et_2O is added until the precipitate is complete; yield 12.5 g (87%), colorless crystals, m.p. 122°C (EtOH/acetone).- IR: 3050-2660 cm^{-1}; 2600; 1590 (NH_3^+); 1730 (CO); 1590; 1510; 700 (ar); 1260; 1240 (C-O).- ^{1}H-NMR ([D_6]DMSO): δ = 1.97 (mc; 2H, 2-H_2), 2.00 (s; 3H, CH_3), 2.77 (mc; 2H, 4-H_2), 3.32 (mc; 1H, 3-H), 3.82 (s; 2H, $ArCH_2$), 4.10 (t; J = 6.5 Hz; 2H, 1-H_2), 7.35 (mc; 5H, arH), 8.48 (br.s, 3H, NH_3^+).- $C_{13}H_{20}ClNO_2S$ (289.8) Calcd. C 53.9 H 6.96 Cl 12.2 N 4.8 S 11.1 Found C 53.6 H 6.86 Cl 12.1 N 4.7 S 10.9.

(RS)-3-Amino-4-benzylthio-1-butyl chloroacetate hydrochloride (**14b**)

From 10.5 g (50 mmol) of **4** and 9.0 g (80 mmol) of chloroacetyl chloride as described for **14a**; the crude product was transformed into **15b**.- **14b**: yield 13.g (80%), white powder, m.p. 101-103°C ($CHCl_3/Et_2O$).- IR: 3050-2750 cm^{-1}; 1580 (NH_3^+); 1750 (CO); 1590; 1500; 1490; 695 (ar); 1190 (C-O).- ^{1}H-NMR: δ = 2.15 (mc; 2H, 2-H_2), 2.80 (mc; 2H, 4-H_2), 3.50 (mc; 1H, 3-H), 3.75 (s; 2H, $arCH_2$), 4.07 (s; 2H, CH_2Cl), 4.30 (mc; 2H, 1-H_2), 7.30 (mc; 5H, arH), 8.50 (br.s, 3H, NH_3^+).

(RS)-3-Amino-4-chlorosulfonyl-1-butyl chloroacetate hydrochloride (**15b**)

13 g (40 mmol) of crude **14b** are dissolved in 150 ml of $CHCl_3$ and 50 ml of EtOH (96%), 200 ml of CCl_4 are added, the mixture is cooled to 0°C, and saturated with Cl_2. Excess of Cl_2 is blown out with N_2, 100 ml of Et_2O are added, the mixture is stored at -5°C for 24 h, and the precipitate is collected; yield 10.8 g (90%), white powder, m.p. 138°C (dec.).- IR: 3260 cm^{-1}; 3000-2500; 1590; 1490 (NH_3^+); 1745 (CO); 1360; 1175; 1160 (SO_2).- ^{1}H-NMR ([D_6]DMSO): δ = 2.05 (mc; 2H, 2-H_2), 2.85 (mc; 2H, 4-H_2), 3.05 (mc; 1H, 3-H), 4.20 (t; J = 6 Hz; 2H, 1-H_2), 4.40 (s; 2H, CH_2Cl), 8.25 and 14.1 (br.s, 3H, NH_3^+).- $C_6H_{12}Cl_3NO_4S$ (300.6) Calcd. C 24.0 H 4.03 Cl 35.4 N 4.7 S 10.7 Found C 24.3 H 4.08 Cl 35.2 N 4.6 S 10.8.

(RS)-2-(1,2-Thiazetidin-3-yl)ethyl acetate 1,1-dioxide (**16a**)

3-Amino-4-chlorosulfonyl-1-butyl acetate hydrochloride (**15a**):

From 11.6 g (40 mmol) of **14a** as described for **15b**; yield nearly quantitative. **16a**: 200 ml of $CHCl_3$ are added to crude **15a**, and with stirring the mixture is neutralized with a saturated solution of NH_3 in $CHCl_3$ below 10°C. After 10-12 h the solution is filtered through celite, the solvent is evaporated *in vacuo*, and the residue is purified by CC (silica gel; $CHCl_3$/ethyl acetate 4:1); yield 6.6 g (85%), colorless, viscous liquid.- IR (film): 3300 cm^{-1} (NH); 3040; 2970; 2930 (CH); 1735 (CO); 1310; 1160 (SO_2); 1250 (C-O).- ^{1}H-NMR: δ = 2.02 (mc; 2H, C<u>H</u>$_2$-CH_2O), 2.07 (s; 3H, CH_3), 3.75 (mc; 1H, 3-H), 3.93 (mc; ^2J = 12.7 Hz; ^3J = 5.5 Hz; 1H, 4-H), 4.17 (t; J = 6 Hz, 2H, CH_2O), 4.40 (mc; ^2J = 12.7 Hz; ^3J = 7.3 Hz; 1H, 4-H'), 5.90 (br.s; 1H, NH).- $C_6H_{11}NO_4S$ (193.2) Calcd. C 37.3 H 5.74 N 7.3 S 16.6 Found C 37.5 H 5.92 N 7.1 S 16.4.

(RS)-2-(1,2-Thiazetidin-3-yl)ethyl chloroacetate 1,1-dioxide (**16b**)

From 9.0 g (30 mmol) of **15b** as described for **16a**; yield 5.7 g (83%), colorless crystals, m.p. 55.5-56.5°C ($CHCl_3/CCl_4$).- IR: 3260 cm^{-1} (NH); 3050; 2980; 2950; 2930 (CH); 1760 (CO); 1310; 1155 (SO_2); 1195; 1180 (C-O).- ^{1}H-NMR: δ = 2.10 (q; J = 6 Hz; 2H, C<u>H</u>$_2$-CH_2O), 3.78 (mc; 1H, 3-H), 3.97 (dd; ^2J = 12.5 Hz, ^3J = 5 Hz; 1H, 4-H), 4.10 (s; 2H, CH_2Cl), 4.27 (t; J = 6 Hz; 2H, CH_2O), 4.48 (mc; ^2J = 12.5 Hz; ^3J = 7.5 Hz; 1H, 4-H'), 6.0 (br.s; 1H, NH).- $C_6H_{12}ClNO_4S$ (227.7) Calcd. C 31.7 H 4.43 Cl 15.6 N 6.2 S 14.1 Found C 31.7 H 4.52 Cl 15.4 N 6.3 S 13.8.

(RS)-3-(2-Hydroxyethyl)-1,2-thiazetidine 1,1-dioxide (**17**)

0.06 g (1.1 mol) of $NaOCH_3$ are slowly added to a solution of a) 1.95 g (10 mmol) of **16a** or b) 2.3 g (10 mmol) of **16b** in 30 ml of absol. MeOH with stirring under N_2 at 0°C. After a) 3 h or b) 2 h the mixture is carefully neutralized with glacial acetic acid, volatile components are evaporated *in vacuo*, the residue is extracted three times with 20 ml of CH_2Cl_2 each, the solution is filtered through celite, and purified by CC (silica gel, $CHCl_3$/MeOH 4:1); yield a) 1.0 g (66%), b) 1.05 g (69%), colorless, viscous liquid.- IR (film): 3500 cm^{-1}; 3300; 1650; 1550 (OH, NH); 3040; 2960; 2890 (CH); 1300 (b); 1160 (SO_2).- ^{1}H-NMR ([D_6]acetone/D_2O): δ = 1.90 (q; J = 6 Hz, 2H, C<u>H</u>$_2$-CH_2OH), 3.60 (t; J = 6 Hz; 2H, CH_2OH), 3.78 (mc; 1H, 3-H), 3.93 (mc; ^2J = 12.5 Hz; ^3J = 5 Hz; 1H, 4-H), 4.32 (dd; J = 12.5 Hz and 7.5 Hz; 1H, 4-H').- $C_4H_9NO_3S$ (151.2) Calcd. C 31.8 H 6.00 N 9.3 Found C 32.0 H 5.96 N 9.1.

(R)-(-)-2-Amino-3-benzylthio-1-propyl acetate hydrochloride (**18**)

From 9.8 g (50 mmol) of **9** and 6.3 g (80 mmol) of acetyl chloride as described for **14**; yield 13.75 g (100%), colorless crystals, m.p. 114-115°C (EtOH/acetone).- $[\alpha]^{25}$ = -8.5 (c = 3.2, EtOH).- IR: 3050-2500 (cm^{-1}; 2020; 1980; 1590 (NH_3^+); 1740 (CO); 1590; 1515; 1500; 710 (ar); 1250 cm^{-1} (C-O).- ^{1}H-NMR: δ = 2.10 (s; 3H, CH_3), 2.87 (mc; 2H, 3-H_2), 3.55 (mc; 1H, 2-H), 3.78 (s; 2H, $ArCH_2$), 4.40 (mc; 2H, 1-H_2), 7.30 (mc; 5H, arH), 8.65 (br.s; 3H, NH_3^+).- $C_{12}H_{18}ClNO_2S$ (275.8) Calcd. C 52.3 H 6.58 Cl 12.9 N 5.1 S 11.6 Found C 52.0 H 6.50 Cl 12.7 N 5.15 S 11.7.

(R)-(+)-1,2-Thiazetidin-3-ylmethyl acetate 1,1-dioxide (**20**)

From 11.0 g (40 mmol) of **18** as described for **16a**. The crude product is dissolved in $CHCl_3$/ethyl acetate (3:1), filtered through silica gel, and the solvents are evaporated *in vacuo*; yield 5.2 g (73%), colorless crystals, m.p. 50.5°C ($CHCl_3/CCl_4$).- $[\alpha]^{25}$ = +7.9 (c = 3.3, EtOH).- IR: 3340 cm^{-1} (NH); 3050; 2980; 2960 (CH); 1735 (CO); 1320; 1310; 1300; 1155 (SO_2); 1230; 1220 (C-O).- ^{1}H-NMR: δ = 2.10 (s; 3H, CH_3), 3.70-4.55 (m; 5H), 5.85 (br.s; 1H, NH).- $C_5H_9NO_4S$ (179.2) Calcd. C 33.5 H 5.06 N 7.8 S 17.9 Found C 33.8 H 5.18 N 7.7 S 17.7.

(R)-(-)-3-Hydroxymethyl-1,2-thiazetidine 1,1-dioxide (**21**)

From 1.8 g (10 mmol) of **20** as described for **17**. The residue is extracted with CH_2Cl_2/ethyl acetate (1:1), the solution is filtered through celite, dried (Na_2SO_4), and concentrated *in vacuo*; yield 0.55 g (40%), colorless crystals, m.p. 70-71°C (CH_2Cl_2).- $[\alpha]^{23}$ = -9.1 (c = 2.5, MeOH).- IR: 3420 cm^{-1}; 1650 (OH); 3160; 1550 (NH); 3040; 2970; 2920; 2880 (CH); 1320; 1295; 1150 (SO_2).- ^{1}H-NMR ([D_6]DMSO/D_2O): δ = 3.47 (mc; 3H, $C\underline{H}_2OH$, 3-H), 3.90 (mc; ^{2}J = 12.5 Hz; ^{3}J = 5 Hz; 1H, 4-H), 4.30 (mc; ^{2}J = 12.5 Hz; ^{3}J = 8 Hz; 1H, 4-H').- $C_3H_7NO_3S$ (137.2) Calcd. C 26.3 H 5.14 N 10.2 S 23.4 Found C 26.5 H 5.04 N 10.0 S 23.2.

(RS)-Methyl 2-(1,2-thiazetidin-3-yl)ethyl thioglycolate 1,1-dioxide (**22a**)

A solution of 2.6 g (10 mmol) of **7**, 1.3 g (12 mmol) of methyl thioglycolate, and 2.0 g (20 mmol) of triethylamine in 100 ml of Et_2O is refluxed for 12 h, evaporated *in vacuo*, the residue is resolved in 100 ml of $CHCl_3$, washed with 100 ml of water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue is purified by CC (silica gel, ethyl acetate/n-hexane 6:4); yield 2.3 g (97%), colorless liquid.- IR (film): 3300 cm^{-1} (NH); 3040; 2960; 2860 (CH); 1730 (CO); 1320-1290; 1155 (SO_2).- ^{1}H-NMR: δ = 2.05 (mc; 2H, $C\underline{H}_2$-CH_2-S), 2.73 (t; J = 7 Hz, 2H, CH_2-$C\underline{H}_2$-S), 3.25 (s; 2H, CH_2-CO), 3.75 (s; 3H, CH_3), 3.77 (mc; 1H, 3-H), 3.92 (mc; ^{2}J = 14 Hz; ^{3}J = 5 Hz; 1H, 4-H), 4.38 (mc; ^{2}J = 14 Hz; ^{3}J = 8 Hz; 1H, 4-H'), 6.15 (br.s, 1H, NH).- $C_7H_{13}NO_4S_2$ (239.3) Calcd. C 35.1 H 5.47 N 5.9 S 26.8 Found C 35.3 H 5.59 N 5.7 S 26.6.

(RS)-Benzyl 2-(1,2-thiazetidin-3-yl)ethyl thioglycolate 1,1-dioxide (**22b**)

From 2.6 g (10 mmol) of **7** and 2.2 g (12 mmol) of benzyl thioglycolate as described for **22a**; yield 3.1 g (98%), colorless liquid.- IR (film): 3280 cm^{-1} (NH); 1720 (CO); 1600; 1580; 1495; 750; 700 (ar); 1320-1270; 1150 (SO_2).- ^{1}H-NMR: δ = 1.98 (mc; 2H, $C\underline{H}_2$-CH_2S), 2.65 (t; J = 7 Hz; 2H, CH_2-$C\underline{H}_2$-S), 3.25 (s; 2H, CH_2-CO), 3.68 (mc; 1H, 3-H), 3.82 (mc; ^{2}J = 14 Hz; ^{3}J = 5 Hz; 1H, 4-H), 4.28 (mc; ^{2}J = 14 Hz; ^{3}J = 9 Hz; 1H, 4-H'), 5.17 (s; 2H, ar-CH_2), 5.80 (br.s; 1H, NH), 7.38 (s; 5H, arH).- $C_{13}H_{17}NO_4S_2$ (315.4) Calcd. C 49.5 H 5.43 N 4.4 Found C 49.5 H 5.44 N 4.3.

(RS)-Methyl 2-(1,2-thiazetidin-3-yl)ethylsulfonyl acetate 1,1-dioxide (**23a**)

1.2 g (5 mmol) of **22a** in 20 ml of $CHCl_3$ are added at -5°C to a solution of 2.2 g (10 mmol calcd. as 80%) *m*-chloroperbenzoic acid in 30 ml of $CHCl_3$. The mixture is stirred for 24 h at room temp., the precipitate is separated, washed with a small portion of $CHCl_3$ and dried; yield 1.0 g (74%), colorless crystals, m.p. 135-136°C (MeOH).- IR: 3320 cm^{-1} (NH); 3010; 2960 (CH); 1745 (CO); 1330; 1320; 1295; 1160; 1145 (SO_2).- ^{1}H-NMR ([D_6]DMSO): δ = 2.05 (mc; 2H, $C\underline{H}_2$-CH_2-SO_2), 3.28 (mc; 2H, CH_2-$C\underline{H}_2$-SO_2), 3.65 (mc; 1H, 3-H), 3.70 (s; 3H, CH_3), 4.01 (dd; ^{2}J = 13 Hz; ^{3}J = 5 Hz; 1H, 4-H), 4.42 (mc; ^{2}J = 13 Hz; ^{3}J = 8 Hz; 1H, 4-H'), 4.45 (s; 2H, CH_2-CO), 8.05 (br.s; 1H, NH).- $C_7H_{13}NO_6S_2$ (271.3) Calcd. C 31.0 H 4.83 N 5.2 S 23.6 Found C 31.3 H 4.79 N 5.2 S 23.5.

(RS)-Benzyl 2-(1,2-thiazetidin-3-yl)ethylsulfonyl acetate 1,1-dioxide (**23b**)

From 1.6 g (5 mmol) of **22b** as described for **23a**; yield 1.4 g (80%), colorless crystals, m.p. 148-149°C (MeOH/water).- IR: 3340 cm^{-1} (NH); 1720 (CO); 1500; 760; 700 (ar); 1325; 1310; 1300; 1270; 1160; 1150 (SO_2).- ^{1}H-NMR ([D_6]DMSO): δ = 2.02 (mc; 2H, $C\underline{H}_2$-CH_2-SO_2), 3.30 (mc; 2H, CH_2-$C\underline{H}_2$-SO_2), 3.60 (mc; 1H, 3-H), 3.98 (dd; J = 13 Hz; 5 Hz; 1H, 4-H), 4.40 (mc; 1H, 4-H'), 4.50 (s; 2H, CH_2-CO), 5.20 (s; 2H, ar-CH_2), 7.35 (s; 5H, arH), 8.05 (br.s; 1H, NH).- $C_{13}H_{17}NO_6S_2$ (347.4) Calcd. C 44.9 H 4.93 N 4.0 S 18.5 Found C 44.9 H 4.89 N 4.1 S 18.6.

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