Properties and Reactions of Substituted 1,2-Thiazetidine 1,1-Dioxides: Alkylation and Acylation of 3-Haloalkyl β-Sultams and Synthesis of Bicyclic β-Sultams

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Alkylation of the 3-chloroethyl substituted β-sultam **1** with bromoacetates yields the *N*- and 3-substituted β-sultams **2**; exchange of halogens affords esters **3**. Reactions of **1** or of the analogues **8** with isocyanates make the carbamoyl derivatives **5**, **6**, and **9** available. While cyclization of **6** with *n*-BuLi in the presence of HMPT yields the bicyclic β-sultams **7**, the analogous reaction of **9** failed. The bicyclic β-sultams **12** and **14** are obtained from 3-hydroxyalkyl β-sultams **11** and **13** and carbonyl compounds. None of the prepared β-sultams showed any antibacterial activity.

Eigenschaften und Reaktionen substituierter 1,2-Thiazetidin-1,1-dioxide: Alkylierung und Acylierung von 3-Haloalkyl-β-sultamen und Synthese von bicyclischen β-Sultamen

Das 3-Chlorethyl substituierte β-Sultam **1** gibt bei der Alkylierung mit Bromessigestern die disubstituierten β-Sultame **2** bzw. nach Halogenaustausch **3**. Reaktionen von **1** bzw. **8** mit Isocyanaten führen zu den Carbamoylverbindungen **5**, **6** und **9**. Während **6** mit *n*-BuLi und HMPT zu den Bicyclen **7** cyclisiert werden kann, mißlingt die analoge Reaktion bei **9**. Die bicyclischen β-Sultame **12** und **14** werden aus Hydroxyalkyl-β-sultamen wie **11** bzw. **13** und Carbonylverbindungen erhalten. Keine der dargestellten Verbindungen ist antibakteriell aktiv.

In preceding papers[1] we have described the functionalization of highly reactive 1,2-thiazetidine 1,1-dioxides (β-sultams) at C-3 and the introduction of substituents at the N-atom.

Here we report about our efforts to afford a ring closure to bicyclic β-sultams. Although some of the monocyclic β-sultams have weak β-lactamase inhibition activity[2], bicyclic systems show a closer relationship to natural products like β-lactam antibiotics and therefore, perhaps, should be the better bioisosters.

Alkylation of the naked 1,2-thiazetidine 1,1-dioxide is described[3] by reaction with alkyl halides and *n*-BuLi in tetrahydrofuran, and under phase transfer conditions[3]. When we tried to alkylate **1** with 4-nitrobenzyl bromoacetate[4], both methods failed. When the alkylation with bromoacetates was carried out, however, in the presence of small amounts of HMPT, we isolated the substituted β-sultams **2** in yields from 72 to 90%. Probably, the addition of HMPT results in complexation of Li^+ making the naked anion of the β-sultam more reactive[5]. Alkylation was possible even with addition of DMPU[6], but the yields were lower (< 40%). Exchange of chlorine *versus* iodine was accomplished as reported[2] by refluxing with NaI in acetone giving **3**, but all efforts to close the ring with NaH in DMF or by other methods[7] failed.

The higher reactivity of 1,2-thiazetidine 1,1-dioxides as compared with analogous β-lactams is demonstrated by their reaction with isocyanates. This addition works with β-lactams at elevated temp.[8], but with β-sultams it is successful only at low temp.[9]. When **1** reacts with equimolar amounts of *n*-BuLi and aryl isocyanates at -78°C, the sulfonyl ureas **5a,b** are obtained after acidic work-up with > 90% yield. Using the same conditions, the reaction with methyl isocyanate only gave small yields, but when we used catalytic amounts of *n*-BuLi (10%), **5c** was isolated with 97% yield. A similar behaviour was found in the reaction of **8** with isocyanates. Here, the addition of aryl isocyanates only occured with catalytic amounts of *n*-BuLi yielding **9**, while the addition of methyl isocyanate completely failed. Assuming that equimolar amounts of *n*-BuLi deprotonate the β-sultam, resulting in ring opening[10], the low yields of **5c** and **9**, respectively, under these conditions are explained. Using sterically more hindered isocyanates, *e.g.* *tert*-butyl isocyanate, ring opening was the only reaction observed, no traces of addition product were found.

As described[2] for **1** and **8**, the exchange of chlorine *versus* iodine was successful only, when **5** was heated with NaI in acetone, but was unsuccessful with **9**. Interestingly, **6c** could be prepared either by the normal way from isolated **5c** or by a one pot reaction by addition of methyl isocyanate to **1** in the presence of triethylamine, and then, without isolation of the intermediate, exchange of chlorine *versus* iodine. Futhermore, we were unable to cyclize **5** or **9** to the parent bicyclic system, but when **6** reacted with equimolar amounts of *n*-BuLi in the presence of HMPT at -10°C, cyclisation was successful. The bicyclic β-sultams **7** were isolated as stable, crystalline compounds. The preparation of **7a** and **7b** could be afforded even in a one-pot reaction from **4**, beginning at -78°C with the isocyanate addition followed by the cyclisation by warming to room temp. Yields are in the same range as in the two step reaction.

IR-spectra of **5**, **6**, and **7** show asymmetric sulfonyl valence bond bands shifted about 20 to 30 cm^{-1} to higher wave numbers as compared to alkyla-

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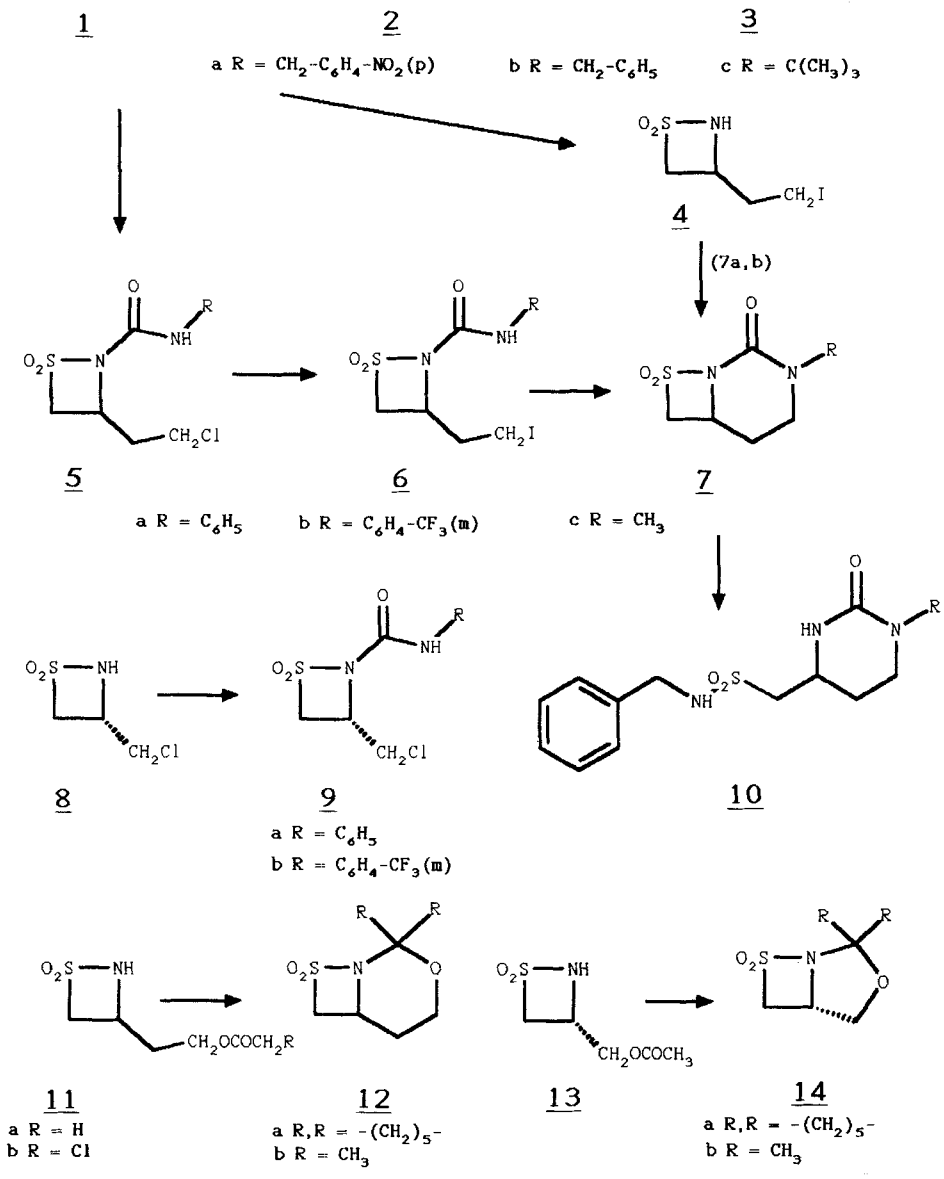

ted β-sultams due to the effect of the carbamoyl group[11]. This effect has been noted in the spectra of C-3 unsubstituted 1,2-thiazetidine 1,1-dioxides[9]. The carbamoyl group causes a strong downfield shift of the H-signals in the ^{1}H-NMR spectra of **5** and **6**. So, the signal of 3-H is found between those of 4-H and *4-H'*, but in the bicyclic β-sultams **7** the parent signal of *6-H* is found at higher field than that of 7-H as in simple monocyclic β-sultams. We deduce from the coupling constants found in the spectra of **7**, that compounds **7** show a minor folding of the bicyclic system (ca. 10°) than those β-sultams without a carbonyl group in position 2 and with a carbon in position 3, whose folding was calculated[9] to be around 15-20°.

Like other bicyclic β-sultams[12], the sultams **7b** and **7c** are relatively stable against the attack of benzylamine. But the β-sultam ring of the 3-phenyl compound **7a** was easily opened when heated with benzylamine to 50-60°C yielding the sulfonamide **10**.

Similar to β-lactams[13] the analogues 3-hydroxyalkyl substituted β-sultams should be reactive intermediates on the way to new bicyclic systems. As the unprotected hydroxy compounds are not very stable[1] we started with the acetoxy compounds **11** from which the hydroxy derivatives were liberated by sodium methanolate in MeOH and immediately reacted with a ketone and BF_3 etherate yielding the bicyclic systems **12**. The 5-ring analogues **14** were prepared from the hydroxymethyl β-sultam corresponding to **13** and cyclohexanone resp. acetone dimethylacetale with very low yields (1-6%). Reactions of **11** or **13** with other carbonyl compounds as acetophenone, 4-nitrobenzaldehyde or mesoxalic acid esters completely failed. In all experiments the hydrolytic decomposition of the starting material was much faster than the desired reaction with the carbonyl group.

None of the described compounds shows any antibacterial activity.

The antibacterial tests were performed by Chemie Linz AG, Linz, which is gratefully acknowledged.

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Experimental Part

General Remarks:[1].

*(RS)-4-Nitrobenzyl 3-(2-Chloroethyl)-1,2-thiazetidin-2-yl-acetate 1,1-Dioxide (**2a**)*

At -78°C, 20 mmol of n-BuLi are added to a solution of 3.4 g (20 mmol) of **1** and 7.2 g (40 mmol) of HMPT in 200 ml of THF. After 2 min, 11.0 g (40 mmol) of 4-nitrobenzyl bromoacetate[4] in 20 ml of THF are added, the mixture is stirred for 30 min at -78°C, warmed to 0°C, extracted with a satd. aqueous solution of NaCl, the org. layer is dried with Na_2SO_4, evaporated *in vacuo*, and the residue is purified by crystallisation; yield 6.4 g (88%), colorless crystals, m.p. 106-107°C ($CHCl_3$/CCl_4).- IR: 1755 cm^{-1} (CO); 1605 (ar); 1515; 1350 (NO_2); 1320; 1310; 1170; 1150 (SO_2); 1200 (C-O).- ^{1}H-NMR: δ (ppm) = 2.25 (m_c, 2H, C$\underline{H}_2$-CH_2Cl), 3.64 (t, J = 6 Hz, 2H, CH_2Cl), 3.75 (mc, 1H, 3-H), 3.96 (dd, J = 12 Hz, 5 Hz, 1H, 4-H), 3.98 (AB, J = 18 Hz, 2H, N-CH_2), 4.40 (dd, J = 12 Hz, 8 Hz, 1H, 4-H'), 5.30 (s, 2H, ar-CH_2), 7.47-8.30 (AA'BB', 4H, aromat.).- $C_{13}H_{15}ClN_2O_6S$ (362.8) Calcd. C 43.0 H 4.17 Cl 9.8 N 7.7 S 8.8 Found C 42.8 H 4.15 Cl 9.9 N 7.6 S 8.9.

*(RS)-Benzyl 3-(2-Chloroethyl)-1,2-thiazetidin-2-yl-acetate 1,1-Dioxide (**2b**)*

From 3.4 g (20 mmol) of **1** and 9.2 g (40 mmol) of benzyl bromoacetate as **2a**; yield 4.6 g (72%), colorless crystals, m.p. 94°C ($CHCl_3$/CCl_4).- IR: 1750 cm^{-1} (CO); 1590; 1500 (ar); 1315; 1185; 1170; 1150 (SO_2); 1220; 1210 (C-O).- ^{1}H-NMR: δ (ppm) = 2.20 (mc, 2H, C$\underline{H}_2$-CH_2Cl), 3.57 (t, J = 6.5 Hz, 2H, CH_2Cl), 3.65 (mc, 1H, 3-H), 3.90 (AB, J = 17 Hz, 2H, N-CH_2), 3.91 (dd, J = 12 Hz, 5 Hz, 1H, 4-H), 4.35 (dd, J = 12 Hz, 8 Hz, 1H, 4-H'), 5.20 (s, 2H, ar-CH_2), 7.35 (s, 5H, aromat.).- $C_{13}H_{16}ClNO_4S$ (317.8) Calcd. C 49.1 H 5.08 Cl 11.2 N 4.4 S 10.1 Found C 48.9 H 5.00 Cl 11.0 N 4.4 S 10.0.

*(RS)-tert-Butyl 3-(2-Chloroethyl)-1,2-thiazetidin-2-yl-acetate 1,1-Dioxide (**2c**)*

From 3.4 g (20 mmol) of **1** and 7.8 g (40 mmol) of *tert*-butyl bromoacetate as **2a**; yield 4.2 g (74%), colorless crystals, m.p. 63.5°C (CCl_4).- IR: 3030 cm^{-1}; 2980; 2930 (CH); 1740 (CO); 1315; 1145 (SO_2); 1235; 1205; 1200 (C-O).- ^{1}H-NMR: δ (ppm) = 1.50 (s, 9H, *tert*-Bu), 2.28 (m_c, 2H, C$\underline{H}_2$-CH_2Cl), 3.67 (t, J = 6 Hz, 2H, CH_2Cl), 3.72 (m_c, 1H, 3-H), 3.78 (AB, J = 18 Hz, 2H, N-CH_2), 3.96 (dd, J = 12 Hz, 5 Hz, 1H, 4-H), 4.40 (dd, J = 12 Hz, 8 Hz, 1H, 4-H').- $C_{10}H_{18}ClNO_4S$ (283.8) Calcd. C 42.3 H 6.40 Cl 12.5 N 4.9 S 11.3 Found C 42.1 H 6.30 Cl 12.3 N 5.1 S 11.2.

*(RS)-4-Nitrobenzyl 3-(2-Iodoethyl)-1,2-thiazetidin-1-yl-acetate 1,1-Dioxide (**3a**)*

3.6 g (10 mmol) of **2a** and 3.0 g (20 mmol) of NaI are refluxed in 30 ml of acetone for 8 h. NaCl is separated, the solvent is evaporated *in vacuo*, the residue is twice extracted with 50 ml of $CHCl_3$ each, and the solvent is evaporated; yield 3.8 g (84%), yellowish crystals, m.p. 91-92°C ($CHCl_3$/CCl_4).- IR: 1755 cm^{-1} (CO); 1605; 740 (ar); 1515; 1355 (NO_2); 1320; 1315; 1170; 1155 (SO_2); 1215 (C-O).- ^{1}H-NMR: δ (ppm) = 2.30 (m_c, 2H, C$\underline{H}_2$-CH_2I), 3.18 (t, J = 7 Hz, 2H, CH_2I), 3.65 (m_c, 1H, 3-H), 3.92 (dd, J = 12 Hz, 5 Hz, 1H, 4-H), 3.97 (AB, J = 18 Hz, 2H, N-CH_2), 4.40 (dd, J = 12 Hz, 8 Hz, 1H, 4-H'), 5.30 (s, 2H, ar-CH_2), 7.45-8.30 (AA'BB', 4H, aromat.).- $C_{13}H_{15}IN_2O_6S$ (454.2) Calcd. C 34.4 H 3.33 N 6.2 S 7.1 Found C 34.5 H 3.35 N 6.1 S 7.0.

*(RS)-Benzyl 3-(2-Iodoethyl)-1,2-thiazetidin-2-yl-acetate 1,1-Dioxide (**3b**)*

From 3.2 g (10 mmol) of **2b** and 3.0 g (20 mmol) of NaI as **3a**; yield 3.7 g (90%), light yellow crystals, m.p. 59-60°C (CCl_4).- IR: 1750 cm^{-1} (CO); 1500; 750; 700 (ar); 1325; 1320; 1165; 1150 (SO_2); 1210; 1200; 1185 (C-O).- ^{1}H-NMR: δ (ppm) = 2.28 (m_c, 2H, C$\underline{H}_2$$CH_2I$), 3.15 (t, J = 7 Hz, 2H, CH_2I), 3.65 (m_c, 1H, 3-H), 3.90 (dd, J = 12 Hz, 5 Hz, 1H, 4-H), 3.94 (AB, J = 18 Hz, 2H, N-CH_2), 4.36 (dd, J = 12 Hz, 8 Hz, 1H, 4-H'), 5.20 (s, 2H, ar-CH_2), 7.37 (s, 5H, aromat.).- $C_{13}H_{16}INO_4S$ (409.2) Calcd. C 38.1 H 3.94 N 3.4 S 7.8 Found C 38.1 H 3.87 N 3.3 S 8.0.

*(RS)-tert-Butyl 3-(2-Iodoethyl)-1,2-thiazetidin-2-yl-acetate 1,1-Dioxide (**3c**)*

From 2.8 g (10 mmol) of **3c** and 3.0 g (20 mmol) of NaI as **3a**; yield 3.7 g (99%), colorless crystals, m.p. 76-77°C (CCl_4/n-hexane).- IR: 3040 cm^{-1}; 3010; 2980; 2930 (CH); 1750 (CO); 1325; 1165; 1150 (SO_2); 1230; 1200; 1190 (C-O).- ^{1}H-NMR: δ (ppm) = 1.50 (s, 9H, *tert*-Bu), 2.32 (m_c, 2H, C$\underline{H}_2$-CH_2I), 3.22 (t, J = 7 Hz, 2H, CH_2I), 3.65 (m_c, 1H, 3-H), 3.77 (AB, J = 17.5 Hz, 2H, N-CH_2), 3.88 (dd, J = 12 Hz, 5 Hz, 1H, 4-H), 4.38 (dd, J = 12 Hz, 8 Hz, 1H, 4'-H).- $C_{10}H_{18}INO_4S$ (375.2) Calcd. C 32.0 H 4.83 N 3.7 S 8.5 Found C 32.2 H 4.64 N 3.6 S 8.3.

*(RS)-3-(2-Chloroethyl)-2-phenylcarbamoyl-1,2-thiazetidine 1,1-Dioxide (**5a**)*

At -78°C, 10 mmol of n-BuLi are added to a solution of 1.7 g (10 mmol) of **1** in 100 ml of THF. After 1 min, 1.2 g (10 mmol) of phenyl isocyanate in 10 ml of THF are added, the solution is stirred for 30 min at -78°C, neutralized with 1.2 ml (10 mmol) of concd. aqueous HCl, extracted with satd. NaCl solution, the org. layer is dried with Na_2SO_4, the solvent is evaporated *in vacuo*, and the residue is purified by crystallisation; yield 2.75 g (95%), colorless crystals, m.p. 120-121°C ($CHCl_3$).- IR: 3240 cm^{-1}; 1540 (NH); 1690; 1660 (CO); 1595; 1495; 755 (ar); 1340; 1330; 1320; 1300; 1150 (SO_2).- ^{1}H-NMR ([D_6]acetone): δ (ppm) = 2.40 (m_c, 2H, C$\underline{H}_2$-CH_2Cl), 3.77 (t, J = 7 Hz, 2H, CH_2Cl), 4.20 (dd, J = 10 Hz, 3.5 Hz, 1H, 4-H), 4.45 (m_c, 1H, 3-H), 4.67 (m_c, ^{2}J = 10 Hz, ^{3}J = 7 Hz, 1H, 4-H'), 7.0-7.65 (m, 5H, aromat.), 8.35 (br.s, 1H, NH).- $C_{11}H_{13}ClN_2O_3S$ (288.8) Calcd. C 45.8 H 4.54 Cl 12.3 N 9.7 S 11.1 Found C 45.9 H 4.50 Cl 12.1 N 9.8 S 11.0.

*(RS)-3-(2-Chloroethyl)-2-[3-(trifluoromethyl)phenylcarbamoyl]-1,2-thiazetidine 1,1-Dioxide (**5b**)*

From 1.7 g (10 mmol) of **1** and 1.9 g (10 mmol) of 3-(trifluoromethyl)phenyl isocyanate as **5a**, yield 3.3 g (92%), colorless crystals, m.p. 113°C ($CHCl_3$).- IR: 3260 cm^{-1}; 1550 (NH); 1695; 1670 (CO); 1610; 1490; 790 (ar); 1340; 1330; 1315; 1150 (SO_2).- ^{1}H-NMR ([D_6]acetone): δ (ppm) = 2.45 (m_c, 2H, C$\underline{H}_2$-CH_2Cl), 3.28 (t, J = 7 Hz, 2H, CH_2Cl), 4.26 (dd, J = 10 Hz, 7.5 Hz, 1H, 4-H), 4.50 (m_c, 1H, 3-H), 4.72 (dd, J = 10 Hz, 7.5 Hz, 1H, 4-H'), 7.35-8.05 (m, 4H, aromat.), 8.73 (br.s, 1H, NH).- $C_{12}H_{12}ClF_3N_2O_3S$ (356.8) Calcd. C 40.4 H 3.39 Cl 9.9 N 7.8 S 9.0 Found C 40.5 H 3.51 Cl 9.8 N 7.7 S 8.9.

*(RS) 3-(2-Chloroethyl)-2-methylcarbamoyl-1,2-thiazetidine 1,1-Dioxide (**5c**)*

From 1.7 g (10 mmol) of **1** and 0.57 g (10 mmol) of methyl isocyanate as **5a** but with 1 mmol of n-BuLi and 0.12 ml of concd. HCl; yield 2.2 g (97%), colorless crystals, m.p. 148°C (dec.) ($CHCl_3$/CCl_4).- IR: 3310 cm^{-1}; 1550 (NH); 3040; 2980; 2960 (CH), 1650 (CO); 1340; 1310; 1290; 1185;

1155 (SO_2).- ^{1}H-NMR ([D_6]acetone): δ (ppm) = 2.30 (m_c, 2H, C$\underline{H}_2$-CH_2Cl), 2.78 (d, J = 5 Hz, 3H, CH_3), 3.72 (t, J = 7 Hz, 2H, CH_2Cl), 4.10 (dd, J = 14 Hz, 4.5 Hz, 1H, 4-H), 4.25 (m_c, 1H, 3-H), 4.52 (dd, J = 14 Hz, 11 Hz, 1H, 4-H'), 6.25 (br.s, 1H, NH).- $C_6H_{11}ClN_2O_3S$ (226.7) Calcd. C 31.8 H 4.89 Cl 15.6 N 12.4 S 14.1 Found C 31.5 H 4.79 Cl 15.8 N 12.4 S 14.1.

(RS)-3-(2-Iodoethyl)-2-phenylcarbamoyl-1,2-thiazetidine 1,1-Dioxide (**6a**)

From 2.9 g (10 mmol) of **5a** and 3.0 g (20 mmol) of NaI as **3a**; yield 3.5 g (92%), light yellow crystals, m.p. 80°C ($CHCl_3$/CCl_4).- IR: 3350 cm^{-1}; 1530 (NH); 1690 (CO); 1600; 1500; 750 (ar); 1330; 1160 (SO_2).- ^{1}H-NMR: δ (ppm) = 2.0-2.9 (m, 2H, C$\underline{H}_2$-CH_2I), 3.23 (t, J = 7 Hz, 2H, CH_2I), 3.92 (dd, J = 11 Hz, 4 Hz, 1H, 4-H), 4.22 (m_c, 1H, 3-H), 4.47 (dd, J = 11 Hz, 8 Hz, 1H, 4-H'), 6.97 (s, 1H, NH), 7.10-7.50 (m, 5H, aromat.).- $C_{11}H_{13}IN_2O_3S$ (380.2) Calcd. C 34.7 H 3.45 N 7.4 S 8.4 Found C 34.8 H 3.55 N 7.3 S 8.3.

(RS)-3-(2-Iodoethyl)-2-[3-(trifluoromethyl)phenylcarbamoyl]-1,2-thiazetidine 1,1-Dioxide (**6b**)

From 3.55 g (10 mmol) of **5b** and 3.0 g (20 mmol) of NaI as **3a**, the product is purified by CC (silica gel, $CHCl_3$/EtOAc 4:1); yield 4.0 g (90%), white powder, m.p. 92.5-93°C ($CHCl_3$/n-hexane).- IR: 3360-3290 cm^{-1}; 1525 (NH); 1680 (CO); 1620; 1610; 1495; 800 (ar); 1350; 1335; 1315; 1190; 1170; 1160 (SO_2).- ^{1}H-NMR: δ (ppm) = 2.0-2.90 (m, 2H, C$\underline{H}_2$-CH_2I), 3.20 (t, J = 7 Hz, 2H, CH_2I), 3.95 (dd, J = 11 Hz, 4 Hz, 1H, 4-H), 4.25 (m_c, 1H, 3-H), 4.50 (dd, J = 11 Hz, 8 Hz, 1H, 4-H'), 7.20 (s, 1H, NH), 7.30-7.75 (m, 4H, aromat.).- $C_{12}H_{12}F_3IN_2O_3S$ (448.2) Calcd. C 32.2 H 2.70 N 6.2 S 7.1 Found C 32.2 H 2.73 N 6.1 S 7.2.

(RS)-3-(2-Iodoethyl)-2-methylcarbamoyl-1,2-thiazetidine 1,1-Dioxide (**6c**)

a) From 1.8 g (8 mmol) of **5c** and 2.4 g (16 mmol) of NaI as **3a**.

b) 1.7 g (10 mmol) of **1** in 50 ml of CH_2Cl_2, 0.57 g (10 mmol) of methyl isocyanate, and 1.0 g (10 mmol) of Et_3N are refluxed for 30 min. Volatile products are separated by evaporation, and the crude product is reacted with NaI as noted above; yield **a**) 2.3 g (90%), **b**) 2.0 g (63%), light yellow crystals, m.p. 157-158°C (dec., acetone/n-hexane).- IR: 3310 cm^{-1}; 1535 (NH); 3040; 2980; 2940 (CH), 1650 (CO); 1345; 1330; 1310; 1160; 1150 (SO_2).- ^{1}H-NMR ([D_6]acetone): δ (ppm) = 2.40 (m_c, 2H, C$\underline{H}_2$-CH_2I), 2.78 (d, J = 5 Hz, 3H, CH_3), 3.30 (t, J = 7 Hz, 2H, CH_2I), 4.10 (dd, J = 13.7 Hz, 4.5 Hz, 1H, 4-H), 4.17 (m_c, 1H, 3-H), 4.50 (dd, J = 13.7 Hz, 10.3 Hz, 1H, 4-H'), 6.15 (br.s, 1H, NH).- $C_6H_{11}IN_2O_3S$ (318.1) Calcd. C 22.7 H 3.49 N 8.8 S 10.1 Found C 22.9 H 3.40 N 8.9 S 10.2.

(RS)-2-Oxo-3-phenyl-1,3-diaza-8-thiabicyclo[4.2.0]octane 8,8-Dioxide (**7a**)

a) At -10°C 2.5 mmol of n-BuLi are added to a solution of 0.95 g (2.5 mmol) of **6a** and 1.8 g (10 mmol) of HMPT in 100 ml of THF. After stirring for 2 h, 20 ml of n-hexane are added and the mixture is kept at -10°C for 24 h. The product is separated by filtration.

b) At -78°C 5 mmol of n-BuLi are added to a solution of 1.3 g (5 mmol) of **4** in 100 ml of THF. After 1 min, 0.6 g (5 mmol) of phenyl isocyanate in 5 ml of THF are added, the mixture is stirred for 30 min at -78°C, 3.6 g (20 mmol) of HMPT are added, the mixture is warmed to room temp., after 2 h 20 ml of n-hexane are added, the mixture is kept at -10°C for 24 h, the product is filtered off and washed with $CHCl_3$; yield **a**) 0.4 g (63%), **b**) 0.6 g (48%), white powder, m.p. 183°C (dec.).- IR: 1665 cm^{-1} (CO); 1595; 1490; 770; 760; 700 (ar); 1340; 1305; 1160; 1150 (SO_2).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 1.95 (m_c, 1H, 5-H), 2.35 (m_c, 1H, 5-H'), 3.72 (m_c, 2H, 4-H, 4-H'), 4.25 (m_c, 1H, 6-H), 4.42 (dd, J = 13 Hz, 3.5 Hz, 1H, 7-H), 4.70 (dd, J = 13 Hz, 8.5 Hz, 1H, 7-H'), 7.35 (m_c, 5H, aromat.).- MS (70 eV): m/z = 253 (43%, M + 1)$^+$, 252 (100, M$^{+\cdot}$).- $C_{11}H_{12}N_2O_3S$ (252.3) Calcd. C 52.4 H 4.80 N 11.1 S 12.7 Found C 52.5 H 4.82 N 11.0 S 12.8.

(RS)-2-Oxo-3-[3-(trifluormethyl)phenyl]-1,3-diaza-8-thiabicyclo[4.2.0]-octane 8,8-Dioxide (**7b**)

a) From 1.1 g (2.5 mmol) of **6b**, 1.8 g (10 mmol) of HMPT, and 2.5 mmol n-BuLi in 100 ml of THF at -10°C as **7a** (**a**). After 2 h stirring at room temp., the mixture is extracted with 100 ml of satd. aqueous NaCl solution, the org. layer is dried with Na_2SO_4, the solvent is evaporated *in vacuo*, the residue dissolved in $CHCl_3$, n-hexane is added, and the product is separated.

b) At -78°C 5 mmol n-BuLi are added to a solution of 1.3 g (5 mmol) of **4** in 100 ml of THF. After 1 min, 0.95 g (5 mmol) of 3-(trifluoromethyl)phenyl isocyanate are added, stirring is continued for 30 min at -78°C, 3.6 g (20 mmol) of HMPT are added, the mixture is warmed to room temp., stirred for another 60 min and worked up as (**a**); yield **a**) 0.45 g (60%), **b**) 0.6 g (38%), colorless crystals, m.p. 182°C (chloroform).- IR: 1670 cm^{-1} (CO); 1615; 1600; 1500 (ar); 1360; 1345; 1330; 1160 (SO_2).- ^{1}H-NMR ([D_6]DMSO): δ (ppm) = 2.00 (m_c, 1H, 5-H), 2.37 (m_c, 1H, 5-H'), 3.80 (m_c, 2H, 4-H, 4-H'), 4.30 (m_c, 1H, 6-H), 4.48 (dd, J = 14 Hz, 3.3 Hz, 1H, 7-H), 4.75 (dd, J = 14 Hz, 8.7 Hz, 1H, 7-H'), 7.70 (m_c, 4-H, aromat.).- $C_{12}H_{11}F_3N_2O_3S$ (320.3) Calcd. C 45.0 H 3.46 N 8.7 S 10.1 Found C 44.7 H 3.55 N 8.6 S 10.2.

(RS)-3-Methyl-2-oxo-1,3-diaza-8-thiabicyclo[4.2.0]octane 8,8-Dioxide (**7c**)

From 0.95 g (3 mmol) of **6c**, 2.2 g (12 mmol) of HMPT, and 3 mmol of n-BuLi as **7a**; yield 0.3 g (53%), white powder, m.p. 199°C (THF).- IR: 3040 cm^{-1}, 2970-2930; 2870 (CH); 1660 (CO); 1325; 1310; 1155 (SO_2).- ^{1}H-NMR ([D_6]DMSO): δ = 1.70 (m_c, 1H, 5-H), 2.20 (m_c, 1H, 5-H'), 2.82 (s, 3H, CH_3), 3.30 (m_c, 2H, 4-H, 4-H'), 4.12 (m_c, 1H, 6-H), 4.30 (dd, J = 13.5 Hz, 3.1 Hz, 1H, 7-H), 4.62 (dd, J = 13.5 Hz, 7.9 Hz, 1H, 7-H').- MS (70 eV): m/z = 191 (12%, M + 1)$^+$, 190 (8, M$^{+\cdot}$), 42 (100).- $C_6H_{10}N_2O_3S$ (190.2) Calcd. C 37.8 H 5.30 N 14.7 S 16.9 Found C 38.0 H 5.20 N 14.6 S 16.7.

(S)-(-)-3-Chloromethyl-2-phenylcarbamoyl-1,2-thiazetidine 1,1-Dioxide (**9a**)

From 1.55 g (10 mmol) of **8** and 1.2 g (10 mmol) of phenyl isocyanate as **5c**; yield 1.8 g (66%), colorless needles, m.p. 96°C (MeOH).- $[\alpha]_D^{24}$ = -98.5° (c = 2.5, EtOH).- IR: 3350 cm^{-1}; 1520 (NH); 1695 (CO); 1595; 750 (ar); 1325; 1185; 1150 (SO_2).- ^{1}H-NMR: δ (ppm) = 3.92 (m_c, 2H, CH_2Cl), 4.05-4.55 (m, 3H, 3-H, 4-H, 4-H'), 6.35 (br.s, 1H, NH), 7.30 (m_c), 5H, aromat.).- $C_{10}H_{11}ClN_2O_3S$ (274.7) Calcd. C 43.7 H 4.04 Cl 12.9 N 10.2 S 11.7 Found C 43.8 H 4.01 Cl 12.8 N 10.3 S 11.8.

(S)-(-)-3-Chloromethyl-2-[3-(trifluoromethyl)phenylcarbamoyl]-1,2-thiazetidine 1,1-Dioxide (**9b**)

a) From 1.55 g (10 mmol) of **8** and 1.9 g (10 mmol) of 3-(trifluoromethyl)phenyl isocyanate as **5a**. The crude product is purified by CC (silica gel, $CHCl_3$/EtOAc 2:1); **b**) as **5c**, CC is not necessary; yield **a**) 1.0 g (29%), **b**) 2.5 g (73%), colorless crystals, m.p. 61-62°C ($CHCl_3$).- $[\alpha]_D^{25}$ = -82.5° (c = 2.1, EtOH).- IR: 3370 cm^{-1}, 1550 (NH), 1715 (CO), 1610, 1495 (ar), 1335, 1165 (SO_2).- ^{1}H-NMR: δ (ppm) = 3.92 (m_c, 2H, CH_2Cl), 4.15-4.60 (m, 3H, 3-H, 4-H, 4-H'), 7.12 (s, 1H, NH), 7.30-7.75 (m, 4H, aromat.).- $C_{11}H_{10}ClF_3N_2O_3S$ (342.7) Calcd. C 38.6 H 2.94 Cl 10.3 N 8.2 S 9.4 Found C 38.8 H 3.06 Cl 10.2 N 8.3 S 9.2.

(RS)-4-(Benzylaminosulfonylmethyl)-1-phenyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (**10**)

0.25 g (1 mmol) of **7a** are suspended in 2 ml of benzylamine and warmed to 60°C for 30 min, CCl_4 is added after cooling, and the precipitate is collected; yield 0.26 g (70%), colorless crystals, m.p. 183°C ($CHCl_3/CCl_4$).- IR: 3360 cm^{-1} (NH), 1630 (CO), 1305, 1140 (SO_2), 750, 690 (ar).- ^{1}H-NMR (250 MHz): δ = 1.80 (m_c, 2H, 5-H, 5-H'), 2.80 (dd, J = 14.5 Hz, 2.7 Hz, 1H, CH_2SO_2), 3.03 (dd, J = 14.5 Hz, 9.8 Hz, 1H, CH_2SO_2), 3.50 (dt, J = 12.2 Hz, 5 Hz, 1H, 6-H), 3.67 (ddd, J = 12.2 Hz, 9.3 Hz, 3.8 Hz, 1H, 6-H'), 3.95 (m_c, 1H, 4-H), 4.14 (d, J = 6 Hz, 2H, $arCH_2$), 6.21 (s, 1H, 3-H), 6.48 (t, J = 6 Hz, 1H, SO_2-NH), 7.30 (m_c, 1H, aromat.).- MS (70 eV): m/z = 360 (5%, M + 1)$^+$, 359 (6, M$^{+\cdot}$), 106 (100).- $C_{18}H_{21}N_3O_3S$ (359.4) Calcd. C 60.1 H 5.89 N 11.7 S 8.9 Found C 60.0 H 5.80 N 11.8 S 8.8.

(RS)-1-Aza-3-oxa-8-thiabicyclo[4.2.0]octane-2-spirocyclohexane 8,8-Dioxide (**12a**)

a) 2.9 g (15 mmol) of **11a** or **b**) 3.4 g (15 mmol) of **11b** in 30 ml of MeOH are stirred at 0°C under N_2 with 0.1 g of $NaOCH_3$ for 1-3 h. The mixture is neutralized with glacial AcOH, evaporated *in vacuo*, the residue is extracted three times with 20 ml of CH_2Cl_2 each, the extracts are filtered through celite, and the solvent is evaporated *in vacuo*. The residue is dissolved in 100 ml of CH_2Cl_2, cooled to 0°C, and 1.5 g (15 mmol) of cyclohexanone and 0.1 ml of BF_3 etherate are added. The mixture is stirred for 90 min at room temp., extracted with 50 ml of phosphate buffer pH 7.4, the org. layer is dried with Na_2SO_4, the solvent evaporated *in vacuo*, the residue is three times extracted with 30 ml of CCl_4 each, and CCl_4 evaporated *in vacuo*; yield **a**) 0.83 g (24%), **b**) 0.9 g (26%), colorless crystals, m.p. 112-114°C (CCl_4).- IR: 3020 cm^{-1}; 2930; 2890; 2850 (CH); 1315; 1300; 1290; 1160; 1150; 1135 (SO_2); 1190 (C-O).- ^{1}H-NMR: δ (ppm) = 1.40-2.45 (m, 12 H, $(CH_2)_5$, 5-H, 5-H'), 3.57 (dd, J = 11.5 Hz, 1.5 Hz, 1H, 7-H), 3.80 (m_c, 1H, 6-H), 3.93 (m_c, 2H, 4-H, 4-H'), 4.25 (dd, J = 11.5 Hz, 7 Hz, 1H, 7-H').- MS (70 eV): m/z = 232 (13%, M + 1)$^+$, 231 (20, M$^{+\cdot}$), 188 (100).- $C_{10}H_{17}NO_3S$ (231.3) Calcd. C 51.9 H 7.41 N 6.1 S 13.9 Found C 51.6 H 7.21 N 5.9 S 13.8.

2,2-Dimethyl-1-aza-3-oxa-8-thiabicyclo[4.2.0]octane 8,8-Dioxide (**12b**)

From 2.9 g (15 mmol) of **11a** and 0.9 g (15 mmol) of acetone as **12a**; yield 0.57 g (20%), colorless crystals, m.p. 114-115°C (CCl_4).- IR: 3040 cm^{-1}; 2980; 2950; 2900; 2880; 2870 (CH); 1315; 1170; 1160; 1150 (SO_2); 1200 (C-O).- ^{1}H-NMR (250 MHz): δ (ppm) = 1.43 (s, 3H, CH_3), 1.77 (s, 3H, CH_3), 1.78 (m_c, 1H, 5-H), 2.15 (m_c, 1H, 5-H'), 3.62 (dd, J = 12 Hz, 1.5 Hz, 1H, 7-H), 3.85 (m_c, 1H, 6-H), 3.92 (m_c, 2H, 4-H, 4-H'), 4.25 (dd, J = 12 Hz, 7 Hz, 1H, 7-H').- $C_7H_{13}NO_3S$ (191.2) Calcd. C 44.0 H 6.85 N 7.3 S 16.8 Found C 43.9 H 6.70 N 7.1 S 16.7.

(R)-(+)-1-Aza-3-oxa-7-thiabicyclo[3.2.0]heptane-2-spirocyclohexane 7,7-Dioxide (**14a**)

From 2.7 g (15 mmol) of **13** and 1.5 g (15 mmol) of cyclohexanone as **12a**; yield 0.18 g (5.5%), colorless crystals, m.p. 122.5°C (CCl_4/n-hexane).- $[\alpha]_D^{25}$ = +25.7° (c = 2.1, EtOH).- IR: 3040 cm^{-1}; 2970; 2940; 2900; 2850 (CH); 1325; 1290; 1165; 1150 (SO_2); 1190 (C-O).- ^{1}H-NMR: δ (ppm) = 1.35-2.60 [m, 10 H, $(CH_2)_5$], 3.90-4.55 (m, 5H, 4-H, 4-H', 5-H, 6-H, 6-H').- $C_9H_{15}NO_3S$ (217.3) Calcd. C 49.8 H 6.96 N 6.4 S 14.8 Found C 49.8 H 7.05 N 6.5 S 14.6.

(R)-(+)-2,2-Dimethyl-1-aza-3-oxa-7-thiabicyclo[3.2.0]heptane 7,7-Dioxide (**14b**)

From 2.7 g (15 mmol) of **13** and 1.6 g (15 mmol) of 2,2-dimethoxypropane as **12a**. The crude product is purified by flash CC with $CHCl_3$; yield 35 mg (1.3%), colorless crystals, m.p. 89-90°C (CCl_4/n-hexane).- $[\alpha]_D^{24}$ = +22.4° (c = 2.2, $CHCl_3$).- IR: 3050 cm^{-1}; 3020; 2990; 2950 (CH); 1325; 1150 (SO_2); 1270; 1200; 1190 (C-O).- ^{1}H-NMR (250 MHz): δ (ppm) = 1.28 (s, 3H, CH_3), 1.90 (s, 3H, CH_3), 4.02 (dd, J = 12.5 Hz, 3 Hz, 1H, 6-H), 4.08 (m_c, ^{2}J = 8.3 Hz, 1H, 4-H), 4.13 (m_c, 1H, 5-H), 4.25 (m_c, ^{2}J = 8.3 Hz, ^{3}J = 6.7 Hz, 1H, 4-H'), 4.45 (m_c, ^{2}J = 12.5 Hz, ^{3}J = 6.7 Hz, 1H, 6-H').- MS (70 eV): m/z = 178 (53%, M + 1)$^+$, 162 (100%).- $C_6H_{11}NO_3S$ (177.2) Calcd. C 40.7 H 6.26 N 7.9 S 18.1 Found C 40.9 H 6.06 N 7.8 S 18.2.

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