KETENE ADDITION ON THIENOANELLATED THIAZINES AND THIAZEPINES WITH SUBSEQUENT RING ENLARGEMENT REACTION TO THIENO[2,3-*b*][1,4]THIAZOCINES AND THIENO[2,3-*b*]-[1,4]THIAZONINES[1]

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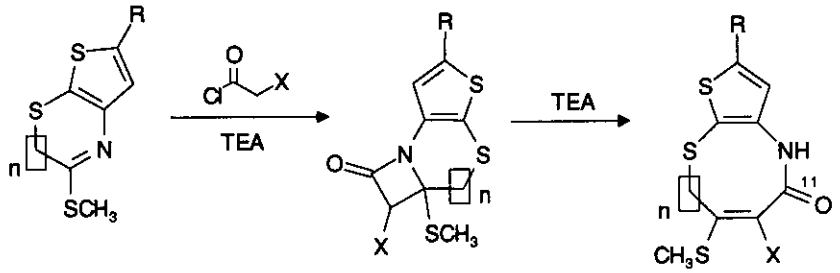
Abstract - Reaction of alkylthiothieno[2,3-*b*][1,4]thiazine derivatives or alkylthiothieno[2,3-*b*][1,4]thiazepine derivatives (**4**, **5**, **12**, **16**, and **24**) with substituted acetyl chlorides in the presence of triethylamine led to azeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazine derivatives and azeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazepine derivatives. Some of them were ring opened by treatment with trifluoroacetic acid to give the thieno[2,3-*b*][1,4]thiazocine derivatives (**27** - **30**) and the thieno[2,3-*b*][1,4]thiazonine derivative (**32**), respectively. 6-Ethyl-1*H*-thieno[2,3-*b*][1,4]thiazine-2(3*H*)-thione (**13**), after reaction with α-chlorophenylacetyl chloride and triethylamine, afforded the thiazolo[2,3-*b*][1,4]thiazine derivative (**34**).

Diazepine and thiazepine derivatives with an anellated benzene and thiophene ring among the 7-membered heterocycles are reported to have exceptional pharmacological properties.[2] Some are available as drugs, while methods for the synthesis of thienoanellated 1,4-thiazocines and 1,4-thiazonines have not been suggested in literature so far.

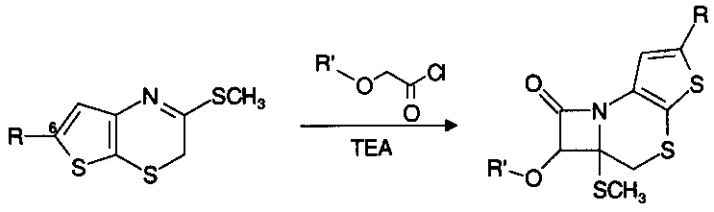
Thus it has been interesting to find a route to the synthesis of these types of compounds. We hoped to obtain these cycles as follows: Reaction of heterocycles (**1**) with ketenes formed from acetyl chlorides in the presence of triethylamine (TEA) was to give the β-lactams (**2**). Subsequently, the compounds (**2**) were to be ring opened to obtain the target molecules (**3**).

The starting materials for the synthesis of thienoanellated 1,4-thiazocines were the bicycles (**4**) and (**5**) as described in the third part of these studies.[3] Substitution at the 6-position, as observed in various cases, was to intensify any biological activity.



1 **2** **3**

Reaction of **4** and **5** with methoxyacetyl chloride/triethylamine in refluxing dichloromethane[4] afforded after processing the tricyclic lactams (**6**) and (**7**) in 55 % and 86 % yield, respectively.



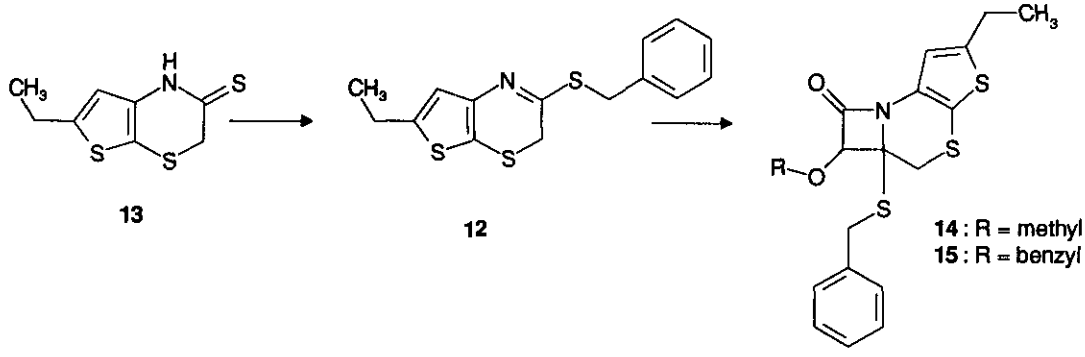
4: R = acetyl
5: R = ethyl

6:	R = acetyl	R' = methyl
7:	R = ethyl	R' = methyl
8:	R = acetyl	R' = phenyl
9:	R = acetyl	R' = benzyl
10:	R = ethyl	R' = phenyl
11:	R = ethyl	R' = benzyl

^{1}H-Nmr, ir, and mass spectra as well as the elemental analysis clearly identified the β-lactams. The ^{1}H-nmr spectra show besides the signals due to the thiophene protons and the ethyl and acetyl substituents the singlets attributable to the methylthio, methoxy, and methine groups. The signals assigned to the methylene protons in the thiazine ring display as AB system. The ir sprectra exhibit the C=O stretching band due to the lactam group at 1760 cm^{-1}.

As the first experiments employing [2+2] cycloaddition had been successful, other acetyl chlorides with electron withdrawing substituents were treated with the starting materials. Reaction with phenoxyacetyl chloride and benzyloxyacetyl chloride afforded the tricycles (**8**) - (**11**). Treatment with chloroacetyl chloride resulted in unprocessable mixtures.

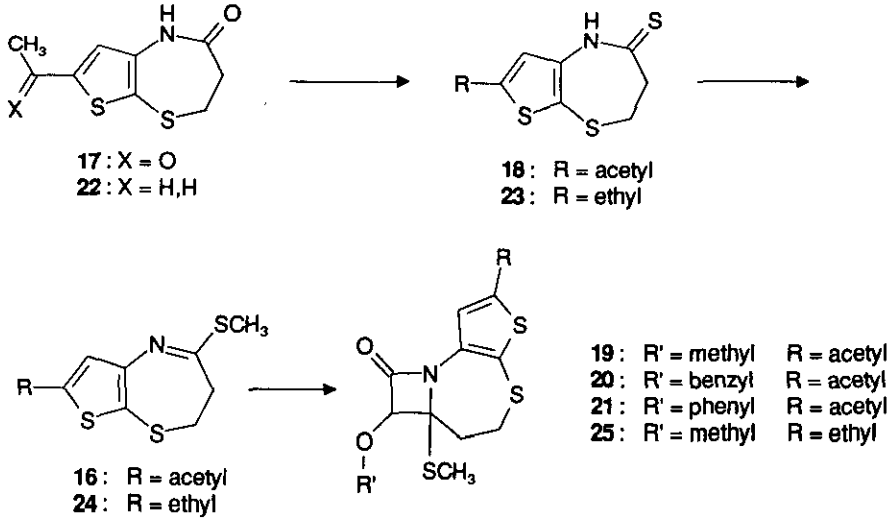
Next we had the *in situ* generated ketenes react with the benzylthiolactim (**12**). This was to produce compounds containing a benzylthio structure that should be cleavable by appropriate methods. **12** was prepared *via* reaction of compound (**13**)[3] with sodium hydride/ benzyl chloride in dry tetrahydrofuran.



13 **12** **14** : R = methyl
15 : R = benzyl

12 was treated with methoxyacetyl chloride and benzyloxyacetyl chloride/ triethylamine. After processing the lactams (**14**) and (**15**) were obtained in 48 and 53 % yield, respectively.

The cycloaddition reactions was applied in the same way to thienoanellated 1,4-thiazepines. Compound (**16**) was prepared from substance (**17**).[5] The lactam function was converted into the thiolactam group by use of Lawesson reagent . Subsequent reaction with sodium hydride/ methyl iodide afforded compound (**16**). [2+2] Addition as described above produced the tricycles (**19**) and (**20**). The substance (**22**) was obtained after reduction of compound (**17**) with triethylsilane / trifluoroacetic acid.[6] The conversion of thiolactam (**23**) into methylthiolactim (**24**) and reaction with methoxyacetyl chloride/ triethylamine gave the tricycle (**25**).



17 : X = O
22 : X = H,H

18 : R = acetyl
23 : R = ethyl

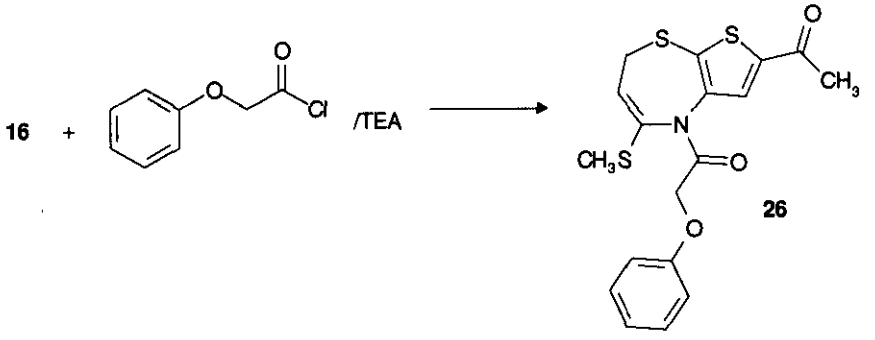
16 : R = acetyl
24 : R = ethyl

19 : R' = methyl R = acetyl
20 : R' = benzyl R = acetyl
21 : R' = phenyl R = acetyl
25 : R' = methyl R = ethyl

The reaction of **16** with phenoxyacetyl chloride/TEA is to be noted. After complete reaction of thiolactim (tlc control) a product was isolated whose spectral data were incompatible with the structure (**21**). The ^{1}H-nmr exhibited an unusual signal as broadened triplet at 5.86 ppm with an intensity of 1 relative to the intensity of the SCH_3 signal. The absence of the singlet due to the methine proton at the β-lactam ring and the shift of the ir band from the expected 1760 cm^{-1} to 1649 cm^{-1} further indicated a structure different from **21**. The molecular ion peak in the mass spectrum and the values received by the elemental analysis suggested a compound structurally isomeric to **21**.

However, the spectral data are consistent with the assigned structure (**26**): The shift of the ir band for the C=O stretch can be explained if an amide is assumed instead of the β-lactam structure. The peaks the ^{1}H-nmr spectrum exhibited besides the signals due to the aromates (7.52 to 6.57 ppm) and the singlets due to the methylthio group (2.32 ppm) and the acetyl group (2.41 ppm) could be interpreted as ABX coupling pattern (X part=5.70 ppm; A part=4.23 ppm; B part=3.10 ppm). In addition, there is a broadened signal at about 4.8 ppm due to the methylene protons of the phenoxyacetyl part corresponding in form to an AB system.

Maybe this type of reaction bases on the bigger size of the heterocyclic ring (7-membered ring) and/or the sterical demand of the aromatic ring of the used ketene.

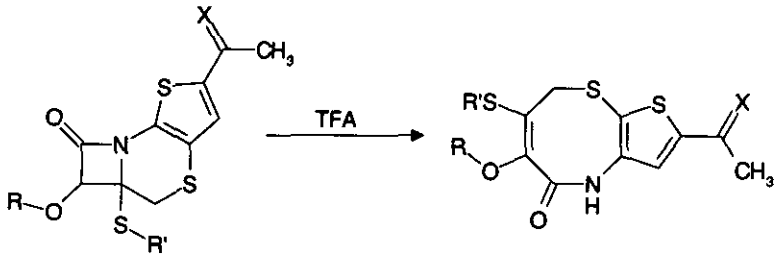


As pointed out at the beginning, the aim was to prepare thienoanellated 1,4-thiazocines and 1,4-thiayzonines from the β-lactams synthesized. We chose compound (**14**) as starting material for first experiments. Following Manhas *et al.*[4] it should be transformed into an 8-membered ring by treatment with $NaIO_4$. Tlc control showed that under the conditions specified no reaction had been accomplished. A rise in reaction temperature merely caused the decomposition of the starting material. Likewise, changing the oxidizing agent - magnesium monoperoxyphthalate instead of $NaIO_4$ - did not afford the desired ring opened product.

Finally, we succeed in transforming the tricycle (**14**) into the thienoanellated 1,4-thiazocine derivative (**27**) by use of proton catalysis.

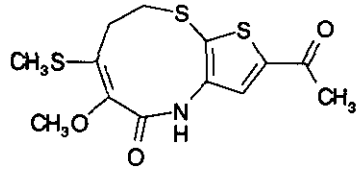
Proton donor and solvent was trifluoroacetic acid (TFA). The reaction mixture was processed after 20 hours (tlc control), and **27** was obtained in 51% yield. The structure of the bicycle was also verified by the ^{1}H-nmr spectrum. Compounds (**7**, **10**, and **11**) were opened analogously to the thienoanellated 8-membered rings (**28**, **29**, and **30**).

Under the conditions employed - stirring at room temperature - compound (**9**) did not transform into the expected ring enlarged product but into compound (**31**) by cleaving the benzyl group.



14	R = methyl	R' = benzyl	X = H, H	**27**
7	R = methyl	R' = methyl	X = H, H	**28**
10	R = phenyl	R' = methyl	X = H, H	**29**
11	R = benzyl	R' = methyl	X = H, H	**30**
31	R = H	R' = methyl	X = O	

To get 9-membered rings, compound (**19**) was chosen as starting material. 1,4-Thiazonine derivative (**32**) was formed under the conditions set above. In spite of this compound (**20**) gave with TFA an intractable mixture.



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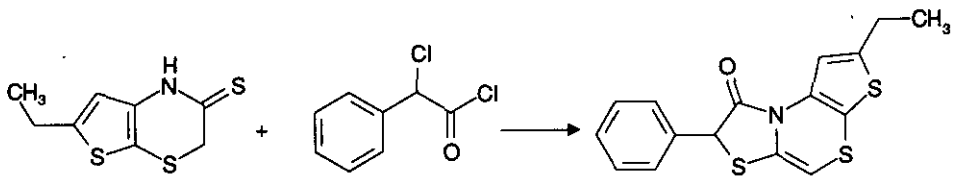
Further, we tried to apply the [2+2] cycloaddition reaction to compound (**13**).[3] In the lactim form this compound should react with ketenes in the observed way.

The thiolactam (**13**) was converted by α-chlorophenylacetyl chloride. After processing, we in fact isolated the tricycle (**34**). On basis of the spectral data and the elemental analysis this structure could be definitely assigned to the isolated compound.



13 34

We also had the biological activity of the tricyclic compounds obtained investigated. However, their slight solubility prevented tests for a β-lactamase inhibiting activity. Other tests are not yet completed.

The described methods offer a convinient and versatile pathway for the synthesis of azeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazine and -thiazepine derivatives. In addition thieno[2,3-*b*][1,4]thiazocines and thieno[2,3-*b*][1,4]thiazonines could be obtained from these tricyclic ß-lactames by a one pot procedure. By this way novel ring systems could be synthesized in good yields.

EXPERIMENTAL

Melting points were determined with a Kofler-apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded on a Bruker AC-80 spectrometer. Chemical shifts are reported in ppm downfield from internal standard. IR: JASCO IRA-1. Ms analyses were obtained with Shimadzu GC/MS QP 1000. All organic solvents were removed by evaporation under vacuum. The reaction progress were contolled by tlc analyses using merck F_{254} silica gel sheets.

General procedures for compounds (6-11, 14, 15, 19, 20, 25)

To a solution of 10 mmol of the corresponding thiolactim (**4**, **5**, **12** *or* **16**) in dry dichloromethane (30 ml) 4.04 g (40 mmol) of triethylamine were added. To this solution 40 mmol of the corresponding acetyl chloride derivative in 50 ml of dichloromethane was added dropwise.The reaction mixture was refluxed for 3 days. After cooling the mixture was washed with water, with a saturated sodium hydrgen carbonate solution and once more with water. The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was recrystallized as given.

2-Acetyl-5*a*,6-dihydro-5*a*-methylthio-6-methoxyazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (6)

After recrystallisation from ethanol 1.73 g (55%) of **6** were obtained, mp 184-189^{0}C ; Anal. Calcd for $C_{12}H_{13}NO_3S_3$: C, 45.69; H, 4.15; N, 4.44; Found: C, 45.70; H, 4.09; N, 4.32; ms: m/z = 315 (M^+, 100), 240 (99), 225 (40); nmr ($CDCl_3$): δ: 2.22 (3H, s, SCH_3), 2.52 (3H, s, CH_3), 3.15 (1H,

B-part of an AB-system, J_{AB} = 13.3 Hz, CH_2), 3.33 (1H, A-part of an AB-system, J_{AB} = 13.3 Hz, CH_2), 3.69 (3H, s, OCH_3), 4.43 (1H, s, CH), 7.77 (1H, s, thiophene H)

2-Ethyl-5*a*,6-dihydro-5*a*-methylthio-6-methoxyazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**7**)

After recrystallisation from ethanol 2.59 g (86%) of **7** were obtained, mp 110-113^{0}C ; Anal. Calcd for $C_{12}H_{15}NO_2S_3$: C, 47.81; H, 5.02; N, 4.65; Found: C, 47.88; H, 4.81; N, 4.45; ms: m/z = 301 (M^+, 64), 226 (100), 182 (42), 117 (24); nmr ($CDCl_3$): δ: 1.27 (3H, t, J = 8.2 Hz, CH_3), 2.21 (3H, s, SCH_3), 2.57 (2H, q, J = 8.2 Hz, CH_2), 3.05 (1H, B-part of an AB-system, J_{AB} = 13.2 Hz, CH_2), 3.23 (1H, A-part of an AB-system, J_{AB} = 13.2 Hz, CH_2), 3.66 (3H, s, OCH_3), 4.33 (1H, s, CH), 7.00 (1H, s, thiophene H)

2-Acetyl-5*a*,6-dihydro-5*a*-methylthio-6-phenoxyazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**8**)

After recrystallisation from ethanol 2.49 g (66%) of **8** were obtained, mp 228-230^{0}C ; Anal. Calcd for $C_{17}H_{15}NO_3S_3$: C, 54.10; H, 4.00; N, 3.70; Found: C, 53.98; H, 4.02; N, 3.53; ms: m/z = 377 (M^+, 89), 302 (100), 284 (86); nmr ($CDCl_3$): δ: 2.26 (3H, s, SCH_3), 2.55 (3H, s, CH_3), 3.28 (1H, B-part of an AB-system, J_{AB} = 13.4 Hz, CH_2), 3.47 (1H, A-part of an AB-system, J_{AB} = 13.4 Hz, CH_2), 5.18 (1H, s, CH), 7.26 (5H, s, CH), 7.82 (1H, s, thiophene H)

2-Acetyl-6-benzyloxy-5*a*,6-dihydro-5*a*-methylthioazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**9**)

After recrystallisation from ethyl acetate 2.42 g (62%) of **9** were obtained, mp 173-175^{0}C ; Anal. Calcd for $C_{18}H_{17}NO_3S_3$: C, 55.22; H, 4.38; N, 3.58; Found: C, 55.11; H, 4.34; N, 3.44; ms: m/z = 391 (M^+, 34), 91 (benzyl$^+$,100); nmr ($CDCl_3$): δ: 2.18 (3H, s, SCH_3), 2.45 (3H, s, CH_3), 2.93 (1H, B-part of an AB-system, J_{AB} = 13.3 Hz, CH_2), 3.12 (1H, A-part of an AB-system, J_{AB} = 13.3 Hz, CH_2), 4.37 (1H, s, CH), 4.83 (2H, s, OCH_2), 7.40 (5H, s, aromat.H), 7.73 (1H, s, thiophene H)

2-Ethyl-5*a*,6-dihydro-5*a*-methylthio-6-phenoxyazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**10**)

After recrystallisation from ethyl acetate 1.52 g (42%) of **10** were obtained, mp 142-145^{0}C ; Anal. Calcd for $C_{17}H_{17}NO_2S_3$: C, 56.17; H, 4.71; N, 3.85; Found: C, 56.08; H, 4.75; N, 3.74; ms: m/z = 363 (M^+, 100), 288 (65), 270 (67), 222 (83); nmr ($CDCl_3$): δ: 1.30 (3H, t, J = 8.1 Hz, CH_3), 2.20 (3H, s, SCH_3), 2.79 (2H, q, J = 8.1 Hz, CH_2), 3.21 (1H, B-part of an AB-system, J_{AB} = 13.2 Hz, CH_2), 3.38 (1H, A-part of an AB-system, J_{AB} = 13.2 Hz, CH_2), 5.09 (s, 1H, CH), 6.28-7.46 (6H, m, aromat. H)

6-Benzyloxy-2-ethyl-5*a*,6-dihydro-5*a*-methylthioazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**11**)

After recrystallisation from ethanol 3.24 g (86%) of **11** were obtained, mp 146-149^{0}C ; Anal. Calcd for $C_{18}H_{19}NO_2S_3$: C, 57.26; H, 5.07; N, 3.71; Found: C, 57.57; H, 4.90; N, 3.55; ms: m/z = 377 (M^+, 54), 91 (benzyl$^+$,100); nmr ($CDCl_3$): δ: 1.27 (3H, t, J = 8.1 Hz, CH_3), 2.23 (3H, s, SCH_3), 2.77 (2H, q, J = 8.1 Hz, CH_2), 2.93 (1H, B-part of an AB-system, J_{AB} = 13.3 Hz, SCH_2), 3.07 (1H, A-part of an AB-system, J_{AB} = 13.3 Hz, SCH_2), 4.50 (1H, s, CH), 4.80 (1H, B-part of an AB-system, J_{AB} = 11.0 Hz, CH_2), 4.90 (1H, A-part of an AB-system, J_{AB} = 11.0Hz, CH_2), 7.00 (1H, s, thiophene H), 7.25-7.49 (m, 5H, aromat. H)

2-Benzylthio-6-ethyl-3*H*-thieno[2,3-*b*][1,4]thiazine (**12**)

To a suspension of 80 % NaH (330 mg, 11 mmol) in 20 ml of dry tetrahydrofuran **13** (2.15 g, 10 mmol) was added and stirred for 10 min. Then benzyl chloride (1.52 g, 12 mmol) in 10 ml dry tetrahydrofuran was dropwise added and the reaction mixture was stirred for one day. The solvent was evaporated and the residue partitioned between dichloromethane and water. The organic layer was seperated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified on a silica gel column eluting with toluene/ ethyl acetate (10 + 1) to give 2.73 g (89%) of **12** as an oil. Anal. Calcd for $C_{15}H_{15}NS_3$: C, 58.98; H, 4.95; N, 4.59; Found: C, 58.68; H, 4.91; N, 4.32; ms: m/z = 205 (M^+, 18), 91 (benzyl$^+$, 100); nmr ($CDCl_3$): δ: 1.28 (3H, t, J = 8.1 Hz, CH_3), 2.76 (2H, q, J = 8.1 Hz, CH_2), 3.29 (2H, s, SCH_2), 4.34 (2H, s, benzyl H), 6.79 (1H, s, thiophene H), 7.18-7.45 (5H, m, aromat.H)

5*a*-Benzylthio-2-ethyl-5*a*,6-dihydro-6-methoxyazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**14**)

After recrystallisation from ethanol 1.82 g (48%) of **14** were obtained, mp 108-110^{0}C ; Anal. Calcd for $C_{18}H_{19}NO_2S_3$: C, 57.26; H, 5.07; N, 3.71; Found: C, 57.15; H, 4.87; N, 3.56; ms: m/z = 377 (M^+, 79), 286 (M^+-benzyl, 23), 226 (100); nmr ($CDCl_3$): δ: 1.25 (3H, t, J = 8.1 Hz, CH_3), 2.72 (2H, q, J = 8.1 Hz, CH_2), 3.01 (1H, B-part of an AB-system, J_{AB} = 13.3 Hz, CH_2), 3.20 (1H, A-part of an AB-system, J_{AB} = 13.3 Hz, CH_2), 3.71 (3H, s, OCH_3), 3.96 (1H, B-part of an AB-system, J_{AB} = 13.2 Hz, benzyl-CH_2), 4.08 (1H, A-part of an AB-system, J_{AB} = 13.2 Hz, benzyl-CH_2), 4.35 (1H, s, CH), 6.70 (1H, s, thiophene H), 7.10-7.31 (5H, m, aromat. H)

6-Benzyloxy-5*a*-benzylthio-2-ethyl-5*a*,6-dihydroazeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**15**)

After recrystallisation from ethanol 2.38 g (53%) of **15** were obtained, mp 110-112^{0}C ; Anal. Calcd for $C_{24}H_{23}NO_2S_3$: C, 63.55; H, 5.11; N, 3.09; Found: C, 63.40; H, 4.90; N, 3.06; ms: m/z

= 453 (M^+, 42), 362 (M^+-benzyl, 14), 91 (benzyl$^+$,100); nmr ($CDCl_3$): δ: 1.24 (3H, t, J = 8.1 Hz, CH_3), 2.71 (2H, q, J = 8.1 Hz, CH_2), 2.91 (1H, B-part of an AB-system, J_{AB} = 13.5 Hz, cyclic CH_2), 3.04 (1H, A-part of an AB-system, J_{AB} = 13.5 Hz, cyclic CH_2), 3.96 (1H, B-part of an AB-system, J_{AB} = 13.1 Hz, SCH_2), 4.09 (1H, A-part of an AB-system, J_{AB} = 13.1 Hz, SCH_2), 4.53 (1H, s, CH), 5.05 (2H, s, OCH_2), 6.70 (1H, s, thiophene H), 6.91-7.52 (10H, m, aromat. H)

2-Acetyl-6,7-dihydro-5-methylthiothieno[2,3-*b*][1,4]thiazepine (**16**)

To a suspension of 80% NaH (384 mg, 20 mmol) in 5 ml dry tetrahydrofuran **18** (2.43 g, 10 mmoles) was added and stirred for 10 min. Then methyl iodide (5 ml, 80 mmol) was added and the reaction mixture stirred for 3 h. The solvent was evaporated and the residue was partitioned between dichloromethane and water. The organic layer was seperated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was recrystallized from ethyl acetate to give 2.39 g (93%) of **16**, mp 138^{0}C ; Anal. Calcd for $C_{10}H_{11}NOS_3$: C, 46.66; H, 4.31; N, 5.44; Found: C, 46.61; H, 4.20; N, 5.22; ms: m/z = 297 (M^+, 91), 210 (M^+-SCH_3, 99), 43 (acetyl$^+$,100); nmr ($CDCl_3$): δ: 2.49 (3H, s, SCH_3), 2.51 (3H, s, CH_3), 2.82 (2H, t, J = 7.2 Hz, CH_2), 3.69 (2H, t, J = 7.2 Hz, SCH_2), 7.46 (1H, s, thiophene H)

2-Acetyl-6,7-dihydrothieno[2,3-*b*][1,4]thiazepin-5(4*H*)-thione (**18**)

To a solution of **17** (2.27 g, 10 mmol) in 20 ml dry tetrahydrofuran Lawesson reagent (2.02 g, 5 mmol) was added and stirred for 3 h. The solvent was evaporated and the crude product recrystallized from ethanol to give 1.98 g (81%) of **18**, mp 196-198^{0}C ; Anal. Calcd for $C_9H_9NOS_3$: C, 44.42; H, 3.73; N, 5.76; Found: C, 44.27; H, 3.63; N, 5.53; ms: m/z = 243 (M^+, 16), 71 (100); nmr ($CDCl_3$): δ: 2.52 (3H, s, $COCH_3$), 3.22 (2H, t, J = 6.5 Hz, CH_2), 3.73 (2H, t, J = 6.5 Hz, SCH_2), 7.40 (1H, s, thiophene H), 9.60 (1H, br s, NH)

2-Acetyl-5,6,6*a*,7-tetrahydro-7-methoxy-6*a*-methylthio-8*H*-azeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazepin-8-one (**19**)

The crude product was purified on a silica gel column eluting with toluene/ethyl acetate (4+6) to give 1.43 g (43%) of **19** as an oil ; Anal. Calcd for $C_{13}H_{15}NO_3S_3$: C, 47.39; H, 4.58; N, 4.25; Found: C, 47.67; H, 4.18; N, 3.98; ms: m/z = 329 (M^+, 48), 314 (M^+-CH_3, 11), 282 (M^+- SCH_3, 24,), 254 (100); nmr ($CDCl_3$): δ: 2.08 (3H, s, SCH_3), 2.48 (3H, s, $COCH_3$), 3.65 (3H, s, OCH_3), 2.29-3.72 (4H, m, CH_2CH_2), 4.44 (1H, s, CH), 7.80 (1H, s, thiophene H)

2-Acetyl-7-benzyloxy-5,6,6*a*,7-tetrahydro-6*a*-methylthio-8*H*-azeto[1,2-d]thieno[2,3-*b*][1,4]-thiazepin-8-one (**20**)

After recrystallisation from ethanol 2.87 g (64%) of **20** were obtained, mp 146-149^{0}C , Anal. Calcd for $C_{19}H_{19}NO_3S_3$: C, 56.27; H, 4.72; N, 3.45; Found: C, 56.37; H, 4.62; N, 3.47; ms: m/z = 405 (M^+, 13), 314 (M^+-benzyl, 12), 91 (tropylium$^+$,100); nmr ($CDCl_3$): δ: 2.13 (3H, s, SCH_3), 2.50 (3H, s, $COCH_3$), 2.08-3.54 (4H, m, CH_2CH_2), 4.63 (1H, s, CH), 4.86 (2H, s, OCH_2), 7.26-7.49 (5H, m, aromat. H), 7.83 (1H, s, thiophene H)

2-Ethyl-6,7-dihydrothieno[2,3-*b*][1,4]thiazepin-5(4*H*)-one (**22**)

To a solution of **17**[6] (2.27 g, 10 mmol) in 15 ml trifluoroacetic acid triethylsilane (2.90 g, 25 mmol) was added dropwise. After 20 h the solution was neutralized with saturated sodium hydrogen carbonate solution under ice cooling. The precipitate was collected, washed with water and recrystallized from ethanol to give 1.02 g (68%) of **22**, mp 168-170^{0}C ; Anal. Calcd for $C_9H_{11}NOS_2$: C, 50.68; H, 5.20; N, 6.57; Found: C, 50.93; H, 4.98; N, 6.48; ms: m/z = 210 (M^+, 63), 158 (M^+-$(CH_2)_2CO$, 100); nmr ($CDCl_3$): δ: 1.29 (3H, t, J=7.5 Hz, CH_3), 2.52-2.92 (4H, m, $2CH_2$), 3.52 (2H, t, J = 7.0 Hz, SCH_2), 6.59 (1H, s, thiophene H), 8.11 (1H, br s, NH)

2-Ethyl-6,7-dihydrothieno[2,3-*b*][1,4]thiazepin-5(4*H*)-thione (**23**)

To a solution of **22** (2.13 g, 10 mmol) in 100 ml dry tetrahydrofuran Lawesson regent (2.02 g, 5 mmoles) was added and the mixture was stirred for 1 h. The solvent was evaporated and the crude product recrystallized from ethanol to give 1.99 g (87%) of **23**, mp 173-176^{0}C ; Anal. Calcd for $C_9H_{11}NS_3$: C, 47.13; H, 4.83; N, 6.11; Found: C, 47.09; H, 4.69; N, 5.87; ms: m/z = 229 (M^+, 100), 196 (M^+-SH, 100), 196 (46); nmr ($CDCl_3$): δ: 1.29 (3H, t, J=7.2 Hz, CH_3), 2.79 (2H, q, J = 7.2 Hz, CH_2), 3.06 (2H, t, J = 9.1Hz, CH_2), 3.66 (2H, t, J = 9.1 Hz, SCH_2), 6.51 (1H, s, thiophene H), 9.73 (1H, br s, NH)

2-Ethyl-6,7-dihydro-5-methylthiothieno[2,3-*b*][1,4]thiazepine (**24**)

This synthesis was analogously done as described for compound (**16**). The crude product was purified on a silica gel column eluting with toluene/ ethyl acetate (8+2) to give 2.18 g (90%) of **24** as an oil; Anal. Calcd for $C_{10}H_{11}NS_3$: C, 49.35; H, 5.38; N, 5.75; Found: C, 49.61; H, 5.29; N,5.46; ms: m/z = 243 (M^+, 98), 196 (M^+-SCH_3, 100); nmr ($CDCl_3$): δ: 1.28 (3H, t, J=7.4 Hz, CH_3), 2.51 (3H, s, SCH_3), 2.76 (2H, q, J = 7.4 Hz, CH_2), 2.82 (2H, t, J = 7.3 Hz, CH_2), 3.69 (2H, t, J = 7.3 Hz, SCH_2), 7.41 (1H, s, thiophene H)

2-Ethyl-5,6,6*a*,7-tetrahydro-7-methoxy-6*a*-methylthio-8*H*-azeto[1,2-*d*]thieno[2,3-*b*][1,4]thiazepin-8-one (**25**)

After recrystallisation from ethanol 2.03 g (64%) of **25** were obtained, mp 129-131^{0}C; Anal. Calcd for $C_{13}H_{17}NO_2S_3$: C, 49.50; H, 5.43; N, 4.44; Found: C, 49.47; H, 5.21; N, 4.24; ms: m/z = 315 (M^+, 70), 268 (M^+-SCH_3, 21), 240 (100); nmr ($CDCl_3$): δ: 1.26 (3H, t, J = 7.7 Hz, CH_3), 2.09 (3H, s, SCH_3), 2.16-3.49 (4H, m, CH_2CH_2), 2.75 (2H, q, J = 7.7 Hz, CH_2), 3.66 (3H, s, OCH_3), 4.40 (1H, s, CH), 6.98 (1H, s, thiophene H)

2-Acetyl-4,7-dihydro-5-methylthio-4-phenoxyacetylthieno[2,3-*b*][1,4]thiazepine (**26**)

To a solution of phenoxyacetyl chloride (6.82 g, 40 mmol) in 15 ml of dry dichloromethane **16** (2.57 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) in 30 ml of dichloromethane were added dropwise. The suspension was refluxed for 5 days. After cooling the reaction mixture was washed with water, with saturated sodium hydrogen carbonate solution and with water. The organic layer was seperated, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified on a silica gel column eluting with toluene/ ethyl acetate (4+6). The isolated compound was recrystallized from ethanol to give 3.08g (79%) of **26**, mp 148-150^{0}C; Anal. Calcd for $C_{18}H_{17}NO_3S_3$: C, 55.22; H, 4.38; N, 3.58; Found: C, 55.22; H, 4.43; N,3.45; ms: m/z = 391 (M^+, 10), 344 (M^+-SCH_3, 100), 316(38), 107 (86), 77(68); nmr ($CDCl_3$): δ: 2.32 (3H, s, SCH_3), 2.49 (3H, s, CH_3CO), 3.10 (1H, B-part of an ABX-system, J_{AB} = 13.3 Hz, J_{BX} = 8.0 Hz, 7-CH_2), 4.23 (1H, A-part of an ABX-system, J_{AB} = 13.3 Hz, J_{AX} = 8.0 Hz, 7-CH_2), 4.71-5.23 (2H, m, OCH_2), 5.70 (1H, X-part of an ABX-system, J_{Ax} = J_{BX} = 8.0 Hz, CH), 6.57-7.38 (5H, m, aromat. H), 7.52 (1H, s, thiophene H)

General procedure for compounds **27**-**32**

A solution of 10 mmol of the corresponding ß-lactame (**7**, **10**, **11**, **14**, **19**, **20**) in 30 ml of trifluoroacrtic acid was stirred for 20 h at room temperature. The reaction mixture was neutralized with saturated sodium hydrogen carbonate solution with ice cooling. The precipitate was collected, washed with water and purified.

7-Benzylthio-2-ethyl-6-methoxy-4*H*-thieno[2,3-*b*][1,4]thiazocin-5(8*H*)-one (**27**)

After purification on a silca gel column eluting with toluene/ ethyl acetate (4+6) 1.93 g (51%) of **27** were obtained, mp 131-133^{0}C; Anal. Calcd for $C_{18}H_{19}NO_2S_3$: C, 57.26; H, 5.07; N, 3.71; Found: C, 57.02; H, 5.06; N, 3.58; ms: m/z = 377 (M^+, 49), 313 (15), 222 (100), 91 (tropylium$^+$, 7); nmr ($CDCl_3$): δ: 1.36 (3H, t, J = 7.4 Hz, CH_3), 2.96 (2H, q, J = 7.4 Hz, CH_2), 3.84 (2H, s, CH_2), 3.86 (2H, s, SCH_2), 4.01 (3H, s, OCH_3), 6.89 (1H, s, thiophene H), 7.26 (5H, s, aromat. H), 13.4 (1H, br s, NH)

2-Ethyl-6-methoxy-7-methylthio-4*H*-thieno[2,3-*b*][1,4]thiazocin-5(8*H*)-one (**28**)

After recrystallisation from acetone 1.39 g (46%) of **28** were obtained, mp 158-161^{0}C; Anal. Calcd for $C_{12}H_{15}NO_2S_3$: C, 47.81; H, 5.02; N, 4.65; Found: C, 47.52; H, 4.76; N, 4.38; ms: m/z = 301 (M^+, 24), 222 (100), 194 (12), 179 (14), 164 (25), 136 (13); nmr ($CDCl_3$): δ: 1.35 (3H, t, J = 7.5 Hz, CH_3), 2.37 (3H, s, SCH_3), 2.90 (2H, q, J = 7.5 Hz, CH_2), 4.07 (5H, s, OCH_3/SCH_2), 6.89 (1H, s, thiophene H), 13.5 (1H, br s, NH)

2-Ethyl-7-methylthio-6-phenoxy-4*H*-thieno[2,3-*b*][1,4]thiazocin-5(8*H*)-one (**29**)

After recrystallisation from ethanol 1.93 g (53%) of **29** were obtained, mp 244-246^{0}C; Anal. Calcd for $C_{17}H_{17}NO_2S_3$: C, 56.17; H, 4.71; N, 3.85; Found: C, 56.10; H, 4.52; N, 3.47; ms: m/z = 363 (M^+, 38), 284 (100), 256 (33), 223 (20), 164 (13); nmr ($CDCl_3$): δ: 1.33 (3H, t, J = 7.6 Hz, CH_3), 2.33 (3H, s, SCH_3), 2.98 (2H, q, J = 7.6 Hz, CH_2), 4.09 (2H, s, SCH_2), 6.84-7.48 (6H, m, aromat. H), 13.2 (1H, br s, NH)

6-Benzyloxy-2-ethyl-7-methylthio-4*H*-thieno[2,3-*b*][1,4]thiazocin-5(8*H*)-one (**30**)

After purification on a silica gel column eluting with toluene/ ethyl acetate (10 + 1) and recrystallisation from ethyl acetate 1.71 g (47%) of **30** were obtained, mp 142-145^{0}C; Anal. Calcd for $C_{18}H_{19}NO_2S_3$: C, 57.26; H, 5.07; N, 3.71; Found: C, 57.02; H, 4.84; N, 3.54; ms: m/z = 377 (M^+, 17), 286 (M^+-benzyl, 167), 209 (45), 182 (100), 91 (tropylium$^+$,58); nmr ($CDCl_3$): δ: 1.25 (3H, t, J = 7.5 Hz, CH_3), 2.35 (3H, s, SCH_3), 2.73 (2H, q, J = 7.5 Hz, CH_2), 3.55 (2H, s, CH_2), 4.78 (2H, s, OCH_2), 6.42 (1H, s, thiophene H), 7.21-7.50 (5H, m, aromat. H), 10.7 (1H, br s, NH)

2-Acetyl-5*a*,6-dihydro-6-hydroxy-5*a*-methylthioazeto[1,2-d]thieno[2,3-*b*][1,4]thiazin-7(5*H*)-one (**31**)

After recrystallisation from ethanol 1.02 g (34%) of **31** were obtained, mp 203-207^{0}C ; Anal. Calcd for $C_{11}H_{11}NO_3S_3$: C, 43.84; H, 3.68; N, 4.65; Found: C, 44.02; H, 3.97; N, 4.52; ms: m/z = 301 (M^+, 64), 226 (59), 197 (60), 91 (95), 69 (100); nmr ($CDCl_3$): δ: 2.17 (3H, s, SCH_3), 2.52 (3H, s, CH_3), 3.08 (1H, B-part of an AB-system, J_{AB} = 13.4 Hz, CH_2), 3.33 (1H, A-part of an AB-system, J_{AB} = 13.4 Hz, CH_2), 3.63 (1H, exchangeable, d, J = 10.9Hz, OH), 4.75 (1H, d, J = 10.9Hz, CH), 7.75 (1H, s, thiophene H)

2-Acetyl-8,9-dihydro-6-methoxy-7-methylthiothieno[2,3-*b*][1,4]thiazonin-5(4*H*)-one (**32**)

After recrystallisation from ethanol 2.13 g (53%) of **32** were obtained, mp 158-160^{0}C ; Anal. Calcd for $C_{19}H_{19}NO_3S_3$: C, 56.27; H, 4.72; N, 3.45; Found: C, 56.12; H, 4.50; N, 3.26; ms: m/z = 405 (M^+, 19), 314 (M^+-benzyl, 27), 210 (87), 84 (100); nmr ($CDCl_3$): δ: 2.36 (3H, s, SCH_3),

2.49 (3H, s, CH_3), 2.75-3.45 (4H, m, CH_2CH_2), 4.82 (2H, s, OCH_2), 7.43 (1H, s, thiophene H), 10.4 (1H, br s, NH)

2-Ethyl-7-phenylthiazolo[3,2-*d*]thieno[2,3-*b*][1,4]thiazin-8(7*H*)-one (**34**)

To a solution of **13**[3] (2.15 g, 10 mmol) in 50 ml of dry tetrahydrofuran and 5 ml of triethylamine α-chlorophenylacetyl chloride (2.83 g, 15 mmol) in 5 ml of dry tetrahydrofuran were added dropwise. After 30 min the solvent was evaporated and the residue partitioned between dichloromethane and water. The organic layer was washed with saturated hydrogen carbonate solution and water, dried and concentrated *in vacuo*. The residue was recrystallized from ethanol to give 3.01 g (91%) of **34**, mp 118-119^{0}C ; Anal. Calcd for $C_{16}H_{13}NOS_3$: C, 57.98; H, 3.95; N, 4.23; Found: C, 57.95; H, 3.74; N, 3.90; ms: m/z = 331 (M^+, 100), 303 (10), 270 (15), 213 (29), 154 (16), 121 (12); nmr ($CDCl_3$): δ: 1.23 (3H, t, J = 7.5 Hz, CH_3), 2.72 (2H, q, J = 7.5 Hz, CH_2), 5.04 and 5.13 (1H, s, 7-CH and 1H, s, 5-CH), 7.12-7.48 (5H, m, aromat. H), 7.63 (1H, s, thiophene H)

For experiments I am indepted to Manuela Kopriva and Christian Gorbach.

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