Studies on the Chemistry of *O,N*- and *S,N*-Containing Heterocycles. 16 [1]. Investigations on the Synthesis of New Tricyclic β-Lactams *via* [2+2]Cycloaddition Reaction

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Dedicated with best wishes to Prof. Dr. W. Wiegrebe on the occasion of his 65th birthday.

Starting from methylthioimidates **1-8** a series of corresponding tricyclic β-lactams was synthesized *via* [2+2]cycloaddition with ketenes generated *in situ* from substituted acetyl chlorides. Dependent on the bicyclic starting material and on the substituent of the corresponding acetyl chloride *N*-acetyl derivatives were obtained as by- or sole products.

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Since the determination of the chemical structure of penicillin and the identification of the β-lactam subunit as the key structural element endowing these compounds with life-saving antibacterial activity, the significance of this small heterocyclic ring to the field of organic synthesis was established. More recently, β-lactams have also been recognized as useful chiral starting materials for the synthesis of non-proteinogenic amino acids and peptides [2-21] and as inhibitors of human leukocyte elastase [22].

Ketene-imine and enolate-imine reactions are versatile pathways for the formation of mono-, bi-, tri-, and spirocyclic azetidinones.

Employing ketene-imine reactions, from bicyclic methylthioimidates azeto-annellated tricycles should be obtained *via* [2+2]cycloaddition reaction.

From electron-acceptor substituted acetyl chlorides various ketenes were formed *in situ* under basic conditions (triethylamine) and were reacted with the benzo-annellated methylthioimidates **1-8** to yield the reactive intermediates **A/B** [23,24]. These zwitterions **A/B** are then stabilized by cyclization to yield the corresponding β-lactams and/or by shift of a proton to give the *N*-acetyl derivatives, respectively.

Except the reaction of the benzoxazepine derivative **7**, a solution of the corresponding acetyl chloride was added dropwise to an ice-cold solution of the methylthioimidates **1-6** or **8** and triethylamine in dichloromethane under an argon atmosphere. Since under basic conditions ring contraction of **7** is expected [25], the reaction was carried out under reversed addition conditions. Thus, the base was added slowly to a solution of the methylthioimidate and the corresponding acetyl chlorides.

Whereas by reaction with benzyloxyacetyl chloride solely the tricyclic azetidinones were obtained (which were the main products with methoxyacetyl chloride as well), reaction of compounds **5** and **8** with chloroacetyl chloride gave the *N*-chloroacetyl derivatives as major products. In contrast, methylthioimidates **3**, **4**, **6** and **7** with chloroacetyl chloride did not show any conversion.

In Table 1 the yields of the obtained β-lactams and the *N*-acetyl derivatives, depending on the starting compounds and the corresponding acetyl chlorides, are given.

All structures of the products obtained were elucidated by ^{1}H nmr, ^{13}C nmr, mass and ir spectra as well as elemental analyses. β-Lactams show a characteristic singlet of the azetidinone ring proton at 4.3-5.3 ppm and a characteristic C=O stretching at 1744-1772 cm^{-1}, whereas the shift of the C=O absorption to approximately 1680 cm^{-1} in the *N*-acetyl derivatives was also consistent with the assigned structures.

Scheme 1

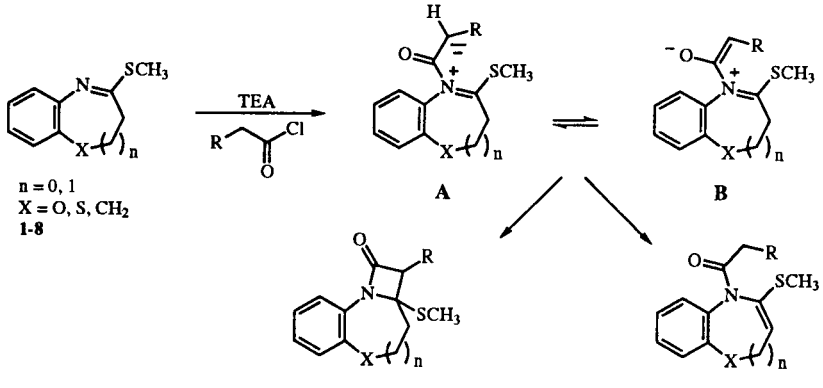
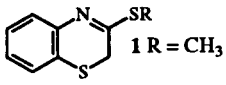
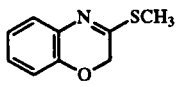
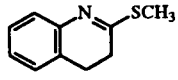
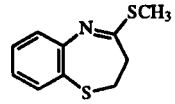
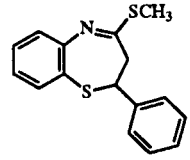
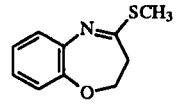
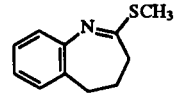


Table 1

Reaction of Methylthioimidates **1-8** with Acetyl Chlorides under Basic Conditions

R_2CH-COCl	R = H, OCH_3	R = H, Cl	R = Cl, Cl	R = H, OC_6H_5	R = H, $OCH_2C_6H_5$
1  **1** R = CH_3	9 βl 69% 10 N 0%		11 βl 0% 12 N 43%		13 βl 69% 14 N 0%
2 **2** R = $C_6H_5CH_2$	15 βl 89% 16 N 0%				
3 	17 βl 74% 18 N 0%	19 βl 0% 20 N 0%			21 βl 46% 22 N 0%
4 	23 βl 68% 24 N 0%	25 βl 0% 26 N 0%		27 βl 41% 28 N 0%	29 βl 64% 30 N 0%
5 	31 βl 60% 32 N 24%	33 βl 9% 34 N 38%		35 βl 25% 36 N 41%	37 βl 64% 38 N 0%
6 	39 βl 22% 40 N 1%	41 βl 0% 42 N 0%		43 βl 8% 44 N 2%	45 βl 33% 46 N 0%
7 	47 βl 11% 48 N 16%	49 βl 0% 50 N 0%			51 βl 31% 52 N 0%
8 	53 βl 39% 54 N 0%	55 βl 0% 56 N 14%		57 βl 59% 58 N 0%	59 βl 36% 60 N 0%

βl = β-lactam derivative

N = *N*-acetyl derivative

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ir spectra were obtained with a Perkin-Elmer 1600 FTir (potassium bromide pellets), nmr spectra were recorded on a Varian Unityplus 300 spectrometer (^{1}H nmr: 300 Mhz; ^{13}C nmr: 75 Mhz; TMS as internal reference, δ values in ppm) and mass spectra on a Hewlett-Packard 5970 and a Shimadzu GC/MS QP 1000 spectrometer, respectively. Analytical tlc was performed on silica gel F254 plates, psc on silica gel F254s plates. Column chromatography was carried out on Merck silica gel 60, 0.063-0.200 mm. Solvents were dried by sodium sulfate and were removed under reduced pressure.

3-Benzylthio-2*H*-1,4-benzothiazine (**2**).

To a suspension of 0.3 g (10 mmoles) of sodium hydride (80%) in 50 ml of dry tetrahydrofuran, 1.81 g (10 mmoles) 2*H*-1,4-benzothiazine-3(4*H*)-thione [26] was added and the mixture was stirred for 15 minutes. After addition of 1.9 g (15 mmoles) of benzyl chloride, the mixture was stirred at room temperature until consumption of the starting material was completed. The solvent was evaporated and the residue was purified by column chromatography (toluene) to yield 2.49 g (92%) of **2** as an oil; ^{1}H nmr (deuteriochloroform): δ 3.23 (s, 2H, SCH_2), 4.45 (s, 2H, SCH_2Ph), 6.92-7.52 (m, 9H, aromatic protons); ms: m/z 271 (M^+, 14), 165 (47), 136 (40), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{15}H_{13}NS_2$: C, 66.38; H, 4.83; N, 5.16. Found: C, 66.10; H, 4.75; N, 5.10.

General Procedure for the Reaction of the Methylthioimidates **1-8** with Substituted Acetyl Chlorides.

To an ice-cold solution of 4 mmoles of the methylthioimidates **1-6** or **8** and 0.81 g (8 mmoles) of triethylamine in 20 ml of dry dichloromethane, 8 mmoles of the corresponding acetyl chloride in 10 ml of dry dichloromethane was added under an argon atmosphere. In the case of **7**, triethylamine in 10 ml of dry dichloromethane was added dropwise to an ice-cold solution of both reagents in 20 ml of dry dichloromethane. After being warmed to room temperature the mixture was heated overnight at 45°. The mixture was washed with water, saturated sodium hydrogencarbonate solution and again with water. After drying the solvent was evaporated and the residue was purified by column chromatography and/or by crystallization.

2a,3-Dihydro-2-methoxy-2a-methylthioazeto[2,1-*c*][1,4]benzothiazin-1(2*H*)-one (**9**).

This compound was obtained from 0.78 g of **1** [26] and 0.868 g of methoxyacetyl chloride after separation by column chromatography (toluene:ethyl acetate 9:1, v/v) and crystallization (ethanol) as colourless needles, 0.736 g (69%), mp 143°; ir: ν 1756 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.21 (s, 3H, SCH_3), 3.25 (s, 2H, SCH_2), 3.69 (s, 3H, OCH_3), 4.38 (s, 1H, CH), 6.91-7.32 (m, 3H, 5-H, 6-H, 7-H), 7.60-7.86 (m, 1H, 8-H); ms: m/z 267 (M^+, 68), 252 (M^+ -CH_3, 27), 192 (100).

Anal. Calcd. for $C_{12}H_{13}NO_2S_2$: C, 53.91; H, 4.90; N, 5.24. Found: C, 53.87; H, 4.88; N, 5.21.

4-Dichloroacetyl-3-methylthio-4*H*-1,4-benzothiazine (**12**).

This compound was obtained from 0.78 g of **1** [26] and 1.18 g of dichloroacetyl chloride after crystallization (ethanol) as white crystals, 0.526 g (43%), mp 109°; ir: ν 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.42 (s, 3H, SCH_3), 6.61 (s, 1H, CH), 6.82 (br s, 1H, CH), 7.09-7.62 (m, 4H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 17.0 (SCH_3). 64.1 (*C*HCO), 120.4 (SCH), 126.4, 127.3, 127.4, 127.6 (4 CH_{aromat}), 133.8, 134.4, 135.9 (3 C_{qu}), 163.1 (C=O); ms: m/z 309; 307; 305 (M^+, 2, 9, 13), 194 (100).

Anal. Calcd. for $C_{11}H_9Cl_2NOS_2$: C, 43.14; H, 2.96; N, 4.57. Found: C, 42.99; H, 2.83; N, 4.31.

2-Benzyloxy-2a,3-dihydro-2a-methylthioazeto[2,1-*c*][1,4]benzothiazin-1(2*H*)-one (**13**).

This compound was obtained from 0.78 g of **1** [26] and 1.476 g of benzyloxyacetyl chloride after separation by column chromatography (toluene) and crystallization (ethanol) as crystals, 0.95 g (69%), mp 113-114°; ir: ν 1772 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.15 (s, 3H, SCH_3), 2.97 (B-part of an AB-system, J_{AB} = 13.6 Hz, 1H, SCH_2), 3.10 (A-part of an AB-system, J_{AB} = 13.6 Hz, 1H, SCH_2), 4.47 (s, 1H, CH), 4.76 (B-part of an AB-system, J_{AB} = 11.5 Hz, 1H, OCH_2), 4.85 (A-part of an AB-system, J_{AB} = 11.5 Hz, 1H, OCH_2), 6.96-7.40 (m, 8H, aromatic protons), 7.65-7.69 (m, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 12.2 (SCH_3), 33.6 (C-3), 66.8 (C-2a), 73.8 (OCH_2), 90.5 (C-2), 120.7-128.6 (9 CH_{aromat}), 120.0, 130.0, 136.1 (3 C_{qu}), 162.7 (C=O); ms: m/z 343 (M^+, 29), 252 (M^+ - $C_6H_5CH_2$, 60), 149 (21), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08. Found: C, 62.76; H, 4.98; N, 4.01.

2a-Benzylthio-2a,3-dihydro-2-methoxyazeto[2,1-*c*][1,4]benzothiazin-1(2*H*)-one (**15**).

This compound was obtained from 1.084 g of **2** and 0.868 g of methoxyacetyl chloride after separation by column chromatography (toluene:ethyl acetate 9:1, v/v) and crystallization (ethanol) as crystals, 1.224 g (89%), mp 130°; ir: ν 1754 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.14 (B-part of an AB-system, J_{AB} = 13.1 Hz, 1H, SCH_2), 3.20 (A-part of an AB-system, J_{AB} = 13.1 Hz, 1H, SCH_2), 3.71 (s, 3H, OCH_3), 3.93 (B-part of an AB-system, J_{AB} = 12.7 Hz, 1H, $SCH_2C_6H_5$), 4.09 (A-part of an AB-system, J_{AB} = 12.7 Hz, 1H, $SCH_2C_6H_5$), 4.38 (s, 1H, CH), 7.00-7.25 (m, 8H, aromatic protons), 7.42-7.45 (m, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 33.6 (C-3), 33.7 ($CH_2C_6H_5$), 59.6 (OCH_3), 67.3 (C-2a), 93.0 (C-2), 120.5-128.8 (9 CH_{aromat}), 119.5, 129.7, 136.8 (3 C_{qu}), 162.2 (C=O); ms: m/z 343 (M^+, 23), 271 (M^+ -$COCHOCH_3$, 19), 252 (M^+ -$C_6H_5CH_2$, 100), 238 (29), 192 (M^+ -CO, -$SCH_2C_6H_5$, 100), 177 (54), 148 ($C_6H_4SCH_2CN^+$, 45), 109 (12), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08. Found: C, 62.93; H, 4.82; N, 4.11.

2a,3-Dihydro-2-methoxy-2a-methylthioazeto[2,1-*c*][1,4]benzoxazin-1(2*H*)-one (**17**).

This compound was obtained from 0.716 g of **3** [27] and 0.868 g of methoxyacetyl chloride after separation by column chromatography (toluene:ethyl acetate 8:2, v/v) and crystallization (ethanol) as crystals, 0.374 g (74%), mp 116-117°; ir: ν 1745 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.20 (s, 3H, SCH_3), 3.67 (s, 3H, OCH_3) 3.94 (B-part of an AB-system, J_{AB} = 11.4 Hz, 1H, CH_2), 4.48 (s, 1H, CH), 4.52 (A-part of an AB-system, J_{AB} = 11.4 Hz, 1H, CH_2), 6.90-7.14 (m, 3H, 5-H, 6-H, 7-H), 7.43-7.63 (m, 1H, 8-H); ms: m/z 251 (M^+, 9), 120 (100).

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.48; H, 5.00; N, 5.71.

2-Benzyloxy-2a,3-dihydro-2a-methylthioazeto[2,1-*c*][1,4]benzoxazin-1(2*H*)-one (**21**).

This compound was obtained from 0.716 g of **3** [27] and 1.476 g of benzyloxyacetyl chloride after separation by column chromatography (toluene) and crystallization (ethanol) as crystals, 0.604 g (46%), mp 122°; ir: ν 1764 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.20 (s, 3H, SCH_3), 3.81 (B-part of an AB-system, J_{AB}= 11.6Hz, 1H, OCH_2), 4.41 (A-part of an AB-system, J_{AB} = 11.6 Hz, 1H, OCH_2), 4.55 (s, 1H, CH), 4.77 (B-part of an AB-system, J_{AB} = 11.3 Hz, 1H, $OCH_2C_6H_5$), 4.88 (A-part of an AB-system, J_{AB} = 11.3 Hz, 1H, $OCH_2C_6H_5$), 6.95-7.52 (m, 9H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 11.9 (SCH_3), 65.3 (C-3), 69.8 (C-2a), 73.7 (OCH_2), 89.2 (C-2), 117.5-128.5 (9 CH_{aromat}), 121.6, 135.9, 143.6 (3 C_{qu}), 163.2 (C=O); ms: m/z 327 (M^+, 82), 252 (M^+ -SCH_3, -CO, 100), 236 (M^+ -$C_6H_5CH_2$, 41), 179 (M^+ -$C_6H_5CH_2OCHCO$, 32), 133 (65), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{18}H_{17}NO_3S$: C, 66.04; H, 5.23; N, 4.28. Found: C, 66.03; H, 5.00; N, 4.19.

2,2a,3,4-Tetrahydro-2-methoxy-2a-methylthio-1*H*-azeto[1,2-*a*]-quinolin-1-one (**23**).

This compound was obtained from 0.708 g of **4** [28] and 0.868 g of methoxyacetyl chloride after separation by column chromatography (toluene:ethyl acetate 8:2, v/v) and crystallization (ethanol) as crystals, 0.674 g (68%), mp 144°; ir: ν 1748 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.07 (s, 3H, SCH_3), 1.60-3.47 (m, 4H, CH_2CH_2), 3.59 (s, 3H, OCH_3), 4.30 (s, 1H, CH), 6.88-7.30 (m, 3H, 5-H, 6-H, 7-H), 7.44-7.63 (m, 1H, 8-H); ^{13}C nmr (deuteriochloroform): δ 11.8 (SCH_3), 24.8 (C-3), 29.7 (C-4), 59.1 (OCH_3), 69.4 (C-2a), 92.8 (C-2), 119.1, 124.3, 127.0, 129.1 (4 CH_{aromat}), 124.4, 132.4 (2 C_{qu}), 162.8 (C=O); ms: m/z 249 (M^+, 36), 234 (M^+ -CH_3, 37), 188 (M^+ -CH_3, -SCH_3, 30), 177 (M^+ -CH_3OCHCO, 35), 174 (M^+ -SCH_3, -CO, 100), 130 ($C_6H_4(CH_2)_2CN^+$, 14), 117 (66).

Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.35; H, 5.88; N, 5.62.

2,2a,3,4-Tetrahydro-2a-methylthio-2-phenoxy-1*H*-azeto[1,2-*a*]-quinolin-1-one (**27**).

This compound was obtained from 0.708 g of **4** [28] and 1.364 g of phenoxyacetyl chloride after separation by column chromatography (light petroleum:ethyl acetate 5:1, v/v) and

crystallization (aqueous ethanol) as white needles, 0.51 g (41%), mp 114-115°; ir: ν 1765 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.10 (s, 3H, SCH_3), 1.85-3.55 (m, 4H, CH_2CH_2), 5.08 (s, 1H, CH), 6.48-7.40 (m, 8H, aromatic protons), 7.53-7.71 (m, 1H, 8-H); ms: m/z 311 (M^+, 41), 296 (M^+ -CH_3, 32), 264 (M^+ -SCH_3, 10), 236 (M^+ -SCH_3, -CO, 100), 130 ($C_6H_4(CH_2)_2CN^+$, 20), 77 ($C_6H_5^+$, 32).

Anal. Calcd. for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.17; H, 5.41; N, 4.38.

2-Benzyloxy-2,2a,3,4-tetrahydro-2a-methylthio-1*H*-azeto-[1,2-*a*]quinolin-1-one (**29**).

This compound was obtained from 0.708 g of **4** [28] and 1.476 g of benzyloxyacetyl chloride after separation by column chromatography (toluene) and crystallization (ethanol) as crystals, 0.834 g (64%), mp 86°; ir: ν 1758 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.17 (s, 3H, SCH_3), 1.64-3.54 (m, 4H, CH_2CH_2), 4.56 (s, 1H, CH), 4.75 (B-part of an AB-system, J_{AB} = 11.3 Hz, 1H, OCH_2), 4.96 (A-part of an AB-system, J_{AB} = 11.3 Hz, 1H, OCH_2), 6.96-7.69 (m, 9H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 11.8 (SCH_3), 24.8 (C-3), 29.6 (C-4), 69.6 (C-2a), 73.1 (OCH_2), 90.4 (C-2), 119.0-129.1 (9 CH_{aromat}), 124.3, 132.3, 136.6 (3 C_{qu}), 162.8 (C=O); ms: m/z 325 (M^+, 2), 234 (M^+ -$C_6H_5CH_2$, 11), 178 (11), 130 ($C_6H_4(CH_2)_2CN^+$, 14), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{19}H_{19}NO_2S$: C, 70.13; H, 5.88; N, 4.30. Found: C, 69.87; H, 5.80; N, 4.07.

2,2a,3,4-Tetrahydro-2-methoxy-2a-methylthio-1*H*-azeto[2,1-*d*]-[1,5]benzothiazepine-1-one (**31**) and 2,5-Dihydro-5-methoxyacetyl-4-methylthio-1,5-benzothiazepine (**32**).

The residue from the reaction of 0.836 g of **5** [29] and 0.868 g of methoxyacetyl chloride was separated by column chromatography (toluene:ethyl acetate 9:1, v/v) to yield after crystallization (ethanol) 0.674 g (60%) of **31** as white crystals, mp 127-129°, and 0.274 g (24%) of **32**, mp 73°.

Compound **31** had ir: ν 1757 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.17 (s, 3H, SCH_3), 2.33-2.42 (m, 1H, CH_2CH_2), 2.62-2.78 (m, 2H, CH_2CH_2), 3.13-3.22 (m, 1H, CH_2CH_2), 3.69 (s, 3H, OCH_3), 4.49 (s, 1H, CH), 7.13-7.77 (m, 4H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 11.4 (SCH_3), 27.3 (C-3), 42.6 (C-4), 59.4 (OCH_3), 75.9 (C-2a), 92.8 (C-2), 125.8, 126.7, 128.0, 132.5 (4 CH_{aromat}), 130.5, 136.4 (2 C_{qu}), 164.7 (C=O); ms: m/z 281 (M^+, 38), 266 (M^+ -CH_3, 18), 234 (M^+ -SCH_3, 45), 206 (M^+ -SCH_3, -CO, 100), 162 ($C_6H_4S(CH_2)_2CN^+$, 67).

Anal. Calcd. for $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37; N, 4.98. Found: C, 55.48; H, 5.31; N, 5.06.

Compound **32** had ir: ν 1678 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29 (s, 3H, SCH_3), 3.43 (s, 3H, OCH_3), 3.06 (B-part of an ABX-system, J_{AB} = 14.4 Hz, J_{BX} = 6.4 Hz, 1H, CH_2CH), 3.81-4.35 (m, A-part of an ABX-system, 1H, CH_2CH, 2H, $COCH_2$), 5.65 (X-part of an ABX-system, J_{AX} = J_{BX} = 6.4 Hz, 1H, CH_2CH), 7.12-7.37 (m, 4H, aromatic protons); ms: m/z 281 (M^+, 11), 234 (M^+ -SCH_3, 100), 206 (49), 161 ($C_6H_4SCH_2CHCN^+$, 48).

Anal. Calcd. for $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37; N, 4.98. Found: C, 55.57; H, 5.40; N, 4.93.

2-Chloro-2,2a,3,4-tetrahydro-2a-methylthio-1*H*-azeto[2,1-*d*]-[1,5]benzothiazepin-1-one (**33**) and 5-Chloroacetyl-2,5-dihydro-4-methylthio-1,5-benzothiazepine (**34**).

The residue from the reaction of 0.836 g of **5** [29] and 0.904 g of chloroacetyl chloride was separated by column chromatography (*n*-hexane:ethyl acetate 7:3, v/v) to yield after crystallization (methanol) 0.104 g (9%) of **33**, mp 75-77°, and 0.434 g (38%) of **34**, mp 85°.

Compound **33** had ir: ν 1690 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 (s, 3H, SCH_3), 2.55-3.29 (m, 4H, CH_2CH_2), 4.24 (s, 1H, CH), 6.93-7.59 (m, 4H, aromatic protons); ms: m/z 287; 285 (M^+, 0.7, 1.6), 240; 238 (M^+ -SCH_3, 10, 30), 162 (100).

Anal. Calcd. for $C_{12}H_{12}ClNOS_2$: C, 50.43; H, 4.23; N, 4.90. Found: C, 50.15; H, 4.30; N, 4.68.

Compound **34** had ir: ν 1684, 1637 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29 (s, 3H, SCH_3), 3.05 (B-part of an ABX-system, J_{AB} = 14.2 Hz, J_{BX} = 6.3 Hz, 1H, CH_2CH), 3.83-4.57 (m, A-part of an ABX-system, 1H, CH_2CH, 2H, $COCH_2$), 5.68 (X-part of an ABX-system, J_{AX} = J_{BX} = 6.2 Hz, 1H, CH_2CH), 7.03-7.30 (m, 4H, aromatic protons); ms: m/z 287; 285 (M^+, 3, 5), 240; 238 (M^+ -SCH_3, 19, 51), 162 ($C_6H_4S(CH_2)_2CN^+$, 100).

Anal. Calcd. for $C_{12}H_{12}ClNOS_2$: C, 50.43; H, 4.23; N, 4.90. Found: C, 50.46; H, 4.10; N, 4.76.

2,2a,3,4-Tetrahydro-2a-methylthio-2-phenoxy-1*H*-azeto[2,1-*d*]-[1,5]benzathiazepin-1-one (**35**) and 2,5-Dihydro-4-methylthio-5-phenoxyacetyl-1,5-benzothiazepine (**36**).

The residue from the reaction of 0.836 g of **5** [29] and 1.364 g of phenoxyacetyl chloride was separated by column chromatography (toluene:ethyl acetate 9:1, v/v) to yield after crystallization (ethanol) 0.344 g (25%) of **35** as white crystals, mp 185°, and 0.558 g (41%) of **36** as an oil.

Compound **35** had ir: ν 1758 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.21 (s, 3H, SCH_3), 2.48-2.60 (m, 1H, CH_2CH_2), 2.76-2.86 (m, 2H, CH_2CH_2), 3.16-3.29 (m, 1H, CH_2CH_2), 5.29 (s, 1H, CH), 7.05-7.82 (m, 9H, aromatic protons); ^{13}C nmr (deuteriochloroform): δ 11.7 (SCH_3), 27.3 (C-3), 42.4 (C-4), 76.4 (C-2a), 89.4 (C-2), 115.6-132.7 (9 CH_{aromat}), 130.9, 136.4, 157.2 (3 C_{qu}), 163.7 (C=O); ms: m/z 343 (M^+, 39), 296 (M^+ -SCH_3, 46), 268 (M^+ -SCH_3, -CO, 100), 162 ($C_6H_4S(CH_2)_2CN^+$, 77), 109 (32).

Anal. Calcd. for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08. Found: C, 63.10; H, 5.01; N, 4.13.

Compound **36** had ir: ν 1681 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.17 (s, 3H, SCH_3), 2.93 (B-part of an ABX-system, J_{AB} = 14.5 Hz, J_{BX} = 6.5 Hz, 1H, CH_2CH), 3.72-4.95 (m, A-part of an ABX-system, 1H, CH_2CH, 2H, $COCH_2$), 5.54 (X-part of an ABX-system, J_{AX} = J_{BX} = 6.5 Hz, 1H, CH_2CH), 6.62-7.34 (m, 9H, aromatic protons); ms: m/z 343 (M^+, 7), 296 (M^+ -SCH_3, 100), 268 (50), 161 ($C_6H_4SCH_2CHCN^+$, 30), 107 ($C_6H_5OCH_2^+$, 57).

Anal. Calcd. for $C_{18}H_{17}NO_2S_2$: C, 62.95; H, 4.99; N, 4.08. Found: C, 62.66; H, 5.01; N, 3.98.

2-Benzyloxy-2,2a,3,4-tetrahydro-2a-methylthio-1*H*-azeto-[2,1-*d*][1,5]benzothiazepin-1-one (**37**).

This compound was obtained from 0.836 g of **5** [29] and 1.476 g of benzyloxyacetyl chloride after crystallization (ethanol) as white crystals, 0.916 g (64%), mp 126-127°; ir: ν 1751 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.19 (s, 3H, SCH_3), 2.27-3.34 (m, 4H, CH_2CH_2), 4.67 (s, 1H, CH), 4.83 (B-part of an AB-system, J_{AB} = 12.0 Hz, 1H, OCH_2), 4.92 (A-part of an AB-system, J_{AB} = 12.0 Hz, 1H, OCH_2), 7.12-7.83 (m, 9H, aromatic protons); ms: m/z 357 (M^+, 15), 310 (M^+

-SCH_3, 16), 282 (M^+ -SCH_3, -CO, 36), 162 ($C_6H_4S(CH_2)_2CN^+$, 59), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{19}H_{19}NO_2S_2$: C, 63.84; H, 5.36; N, 3.92. Found: C, 63.80; H, 5.40; N, 3.97.

2,2a,3,4-Tetrahydro-2-methoxy-2a-methylthio-4-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (**39**) and 2,5-Dihydro-5-methoxyacetyl-4-methylthio-2-phenyl-1,5-benzothiazepine (**40**).

The residue from the reaction of 1.140 g of **6** [29] and 0.868 g of methoxyacetyl chloride was separated by column chromatography (toluene:ethyl acetate 9:1, v/v) to yield after crystallization (ethanol) 0.314 g (22%) of **39** as white crystals, mp 185-187°, and 0.013 g (1%) of **40** as an oil.

Compound **39** had ir: ν 1762 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.21 (s, 3H, SCH_3), 2.82-2.94 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 4.43-4.56 (m, 1H, 4-H), 4.57 (s, 1H, 2-H), 7.15-7.85 (m, 9H, aromatic protons); ms: m/z 357 (M^+, 60), 342 (M^+ -CH_3, 33), 310 (M^+ -SCH_3, 57), 282 (M^+ -SCH_3, -CO, 100), 250 (100), 238 ($C_6H_4SCH(C_6H_5)CH_2CN^+$, 66), 109 (84).

Anal. Calcd. for $C_{19}H_{19}NO_2S_2$: C, 63.84; H, 5.36; N, 3.92. Found: C, 63.71; H, 5.24; N, 3.85.

Compound **40** had ir: ν 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.31 (s, 3H, SCH_3), 3.48 (s, 3H, OCH_3), 3.78-4.43 (m, 2H, CH_2), 4.61-5.79 (m, 2H, CHCH), 7.04-7.76 (m, 9H, aromatic protons); ms: m/z 131 (46), 77 ($C_6H_5^+$, 37), 45 ($CH_3OCH_2^+$, 100).

Anal. Calcd. for $C_{19}H_{19}NO_2S_2$: C, 63.84; H, 5.36; N, 3.92. Found: C, 64.05; H, 5.44; N, 3.73.

2,2a,3,4-Tetrahydro-2a-methylthio-2-phenoxy-4-phenyl-1H-azeto[2,1-*d*][1,5]benzothiazepin-1-one (**43**) and 2,5-Dihydro-4-methylthio-5-phenoxyacetyl-2-phenyl-1,5-benzothiazepine (**44**).

The residue from the reaction of 1.140 g of **6** [29] and 1.364 g of phenoxyacetyl chloride was separated by column chromatography (*n*-hexane:ethyl acetate 7:3, v/v) to yield after crystallization (ethanol) 0.134 g (8%) of **43**, mp 142-144°, and 0.035 g (2%) of **44** as an oil.

Compound **43** had ir: ν 1760 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.27 (s, 3H, SCH_3), 2.54-3.08 (m, 2H, CH_2), 4.76-5.04 (m, 1H, 4-H), 5.28 (s, 1H, 2-H), 6.70-7.90 (m, 14H, aromatic protons); ms: m/z 419 (M^+, 11), 344 (M^+ -SCH_3, -CO, 15), 251 (43), 238 ($C_6H_4SCH(C_6H_5)CH_2CN^+$, 59), 236 (100), 181 (99), 109 (24), 77 ($C_6H_5^+$, 82).

Anal. Calcd. for $C_{24}H_{21}NO_2S_2$: C, 68.71; H, 5.05; N, 3.34. Found: C, 68.79; H, 4.97; N, 3.30.

Compound **44** had ir: ν 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.32 (s, 3H, SCH_3), 4.28-5.83 (m, 4H, CHCH, $COCH_2$), 6.51-7.68 (m, 14H, aromatic protons); ms: m/z 419 (M^+, 0.5), 372 (M^+ -SCH_3, 7), 236 (74), 77 ($C_6H_5^+$, 100).

Anal. Calcd. for $C_{24}H_{21}NO_2S_2$: C, 68.71; H, 5.05; N, 3.34. Found: C, 68.96; H, 4.98; N, 3.16.

2-Benzyloxy-2,2a,3,4-tetrahydro-2a-methylthio-4-phenyl-1*H*-azeto[2,1-*d*][1,5]benzothiazepin-1-one (**45**).

This compound was obtained from 1.140 g of **6** [29] and 1.476 g of benzyloxyacetyl chloride after separation by column chromatography (*n*-hexane:ethyl acetate 7:3, v/v) and crystallization (methanol) as white crystals, 0.581 mg (33%), mp 164-167°; ir: ν 1756 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.22 (s, 3H, SCH_3), 2.59-3.11 (m, 2H, CH_2), 4.26-5.25 (m, 4H, OCH_2, 2-H, 4-H), 6.83-7.87 (m, 14H, aromatic protons); ms: m/z 433 (M^+, 5), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{25}H_{23}NO_2S_2$: C, 69.25; H, 5.35; N, 3.23. Found: C, 69.27; H, 5.40; N, 3.22.

2,2a,3,4-Tetrahydro-2-methoxy-2a-methylthio-1*H*-azeto[2,1-*d*]-[1,5]benzoxazepin-1-one (**47**) and 2,5-Dihydro-5-methoxyacetyl-4-methylthio-1,5-benzoxazepine (**48**).

The residue from the reaction of 0.772 g of **7** [25] and 0.868 g of methoxyacetyl chloride was separated by column chromatography (toluene:ethyl acetate 8:2, v/v) to yield after crystallization (ethanol) 0.117 g (11%) of **47** as white crystals, mp 105-106°, and 0.172 g (16%) of **48** as an oil.

Compound **47** had ir: ν 1744 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.16 (s, 3H, SCH_3), 2.22-2.29 (m, 1H, CH_2), 2.42-2.51 (m, 1H, CH_2), 3.68 (s, 3H, OCH_3), 4.16-4.23 (m, 1H, OCH_2), 4.38-4.42 (m, 1H, OCH_2), 4.48 (s, 1H, CH), 7.06-7.18 (m, 3H, 6-H, 7-H, 8-H), 7.65-7.68 (m, 1H, 9-H); ^{13}C nmr (deuteriochloroform): δ 11.9 (SCH_3), 40.7 (C-3), 59.4 (OCH_3), 67.8 (C-4), 74.3 (C-2a), 92.6 (C-2), 121.9, 123.9, 125.0, 127.6 (4 CH_{aromat}), 126.3, 153.0 (2 C_{qu}), 163.6 (C=O); ms: m/z 265 (M^+, 71), 250 (M^+ -CH_3, 49), 218 (M^+ -SCH_3, 100), 190 (M^+ -SCH_3, -CO, 100), 146 ($C_6H_4O(CH_2)_2CN^+$, 100).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.82; H, 5.82; N, 5.03.

Compound **48** had ir: ν 1680 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.23 (s, 3H, SCH_3), 3.34 (s, 3H, OCH_3), 4.12 (s, 2H, OCH_2), 4.26 (B-part of an ABX-system, J_{AB} = 14 Hz, J_{BX} = 6 Hz, 1H, CH_2CH), 4.93 (A-part of an ABX-system, J_{AB} = 14 Hz, J_{AX} = 6 Hz, 1H, CH_2CH), 5.52 (X-part of an ABX-system, J_{AX} = J_{BX} = 6 Hz, 1H, CH_2CH), 6.76-7.22 (m, 4H, aromatic protons); ms: m/z 265 (M^+, 6), 218 (M^+ -SCH_3, 100), 190 (100), 145 ($C_6H_4OCH_2CHCN^+$, 100).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.64; H, 5.65; N, 5.15.

2-Benzyloxy-2,2a,3,4-tetrahydro-2a-methylthio-1*H*-azeto-[2,1-*d*][1,5]benzoxazepin-1-one (**51**).

This compound was obtained from 0.772 g of **7** [25] and 1.476 g of benzyloxyacetyl chloride after separation by column chromatography (toluene) and crystallization (ethanol) as white crystals, 0.426 g (31%), mp 144-145°; ir: ν 1766 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.09 (s, 3H, SCH_3), 2.04-2.30 (m, 2H, CH_2), 4.10-4.30 (m, 2H, OCH_2), 4.56 (s, 1H, CH), 4.73 (B-part of an AB-system, J_{AB} = 11.7 Hz, 1H, $OCH_2C_6H_5$), 4.84 (A-part of an AB-system, J_{AB} = 11.7 Hz, 1H, $OCH_2C_6H_5$), 6.95-7.38 (m, 8H, aromatic protons), 7.58-7.61 (m, 1H, 9-H); ^{13}C nmr (deuteriochloroform): δ 12.0 (SCH_3), 40.7 (C-3), 67.9 (C-4), 73.5 (OCH_2), 74.9 (C-2a), 90.5 (C-2), 121.8-128.5 (9 CH_{aromat}), 125.5, 136.6, 153.0 (3 C_{qu}), 163.7 (C=O); ms: m/z 341 (M^+, 9), 294 (M^+ -SCH_3, 11), 266 (M^+ -SCH_3, -CO, 28), 250 (M^+ -$C_6H_5CH_2$, 30), 146 ($C_6H_4O(CH_2)_2CN^+$, 44), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.73; H, 5.58; N, 3.99.

2a,3,4,5-Tetrahydro-2-methoxy-2a-methylthioazeto-[1,2-*a*][1]benzazepin-1(2*H*)-one (**53**).

This compound was obtained from 0.764 g of **8** [28] and 0.868 g of methoxyacetyl chloride after separation by column chromatography (toluene:ethyl acetate 8:2, v/v) and crystallization (ethanol) as white crystals, 0.412 g (39%), mp 124°; ir: ν 1748 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.03 (s, 3H, SCH_3), 1.72-3.02 (m, 6H, $(CH_2)_3$), 3.58 (s, 3H, OCH_3), 4.33 (s, 1H, CH), 6.96-7.27 (m, 3H, 6-H, 7-H, 8-H), 7.48-7.68 (m, 1H,

9-H); ^{13}C nmr (deuteriochloroform): δ 11.4 (SCH_3), 22.2 (C-4), 36.0 (C-5), 40.1 (C-3), 59.2 (OCH_3), 75.9 (C-2a), 93.2 (C-2), 124.2, 126.4, 126.9, 130.6 (4 CH_{aromat}), 134.1, 135.8 (2 C_{qu}), 163.9 (C=O); ms: m/z 263 (M^+, 21), 248 (M^+ -CH_3, 28), 216 (M^+ -SCH_3, 39), 188 (M^+ -SCH_3, -CO, 89), 144 ($C_6H_4(CH_2)_3CN^+$, 100).

Anal. Calcd. for $C_{14}H_{17}NO_2S$: C, 63.85; H, 6.51; N, 5.32. Found: C, 63.59; H, 6.29; N, 5.04.

1-Chloroacetyl-4,5-dihydro-2-methylthio-1*H*-1-benzazepine (**56**).

This compound was obtained from 0.764 g of **8** [28] and 0.904 g of chloroacetyl chloride after separation by column chromatography (toluene:ethyl acetate 8:2, v/v) and crystallization (ethanol) as white crystals, 0.152 g (14%), mp 103-104°; ir: ν 1682 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.24 (s, 3H, SCH_3), 1.85-3.39 (m, 4H, CH_2CH_2), 3.49-4.81 (br s, 2H, $COCH_2$), 5.40 (t, J = 4.3 Hz, 1H, CH), 7.09-7.40 (m, 4H, aromatic protons); ms: m/z 269; 267 (M^+, 12; 22), 254; 252 (M^+ -CH_3, 3; 6), 222; 220 (M^+-SCH_3, 2; 8), 217 (M^+-CH_2Cl, 12), 189 (M^+-$COCH_2Cl$, 5), 143 ($C_6H_4CH_2CH_2CHCN^+$, 100).

Anal. Calcd. for $C_{13}H_{14}ClNOS$: C, 58.31; H, 5.27; N, 5.23. Found: C, 58.04; H, 5.07; N, 5.06.

2a,3,4,5-Tetrahydro-2a-methylthio-2-phenoxyazeto[1,2-*a*]-[1]benzazepin-1(2*H*)-one (**57**).

This compound was obtained from 0.764 g of **8** [28] and 1.364 g of phenoxyacetyl chloride after separation by column chromatography (toluene) and crystallization (ethanol) as white crystals, 0.762 g (59%), mp 104-105°; ir: ν 1755 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.93-2.12 (m, 2H, $(CH_2)_3$), 2.15 (s, 3H, SCH_3), 2.14-2.24 (m, 1H, $(CH_2)_3$), 2.44-2.54 (m, 1H, $(CH_2)_3$), 2.69-2.79 (m, 1H, $(CH_2)_3$), 2.94-3.03 (m, 1H, $(CH_2)_3$), 5.22 (s, 1H, CH), 7.03-7.37 (m, 8H, aromatic protons), 7.73-7.76 (m, 1H, 9-H); ^{13}C nmr: (deuteriochloroform): δ 11.6 (SCH_3), 22.1 (C-4), 36.0 (C-5), 39.9 (C-3), 76.3 (C-2a), 89.8 (C-2), 115.8-130.7 (9 CH_{aromat}), 134.0, 136.0, 157.5 (3 C_{qu}), 162.8 (C=O); ms: m/z 325 (M^+, 27), 310 (M^+ -CH_3, 26), 278 (M^+ -SCH_3, 67), 250 (M^+ -SCH_3, -CO, 100), 220 (25), 144 ($C_6H_4(CH_2)_3CN^+$, 29), 77 ($C_6H_5^+$, 22).

Anal. Calcd. for $C_{19}H_{19}NO_2S$: C, 70.13; H, 5.88; N, 4.30. Found: C, 69.85; H, 5.61 ; N, 4.21.

2-Benzyloxy-2a,3,4,5-tetrahydro-2a-methylthioazeto[1,2-*a*]-[1]benzazepin-1(2*H*)-one (**59**).

This compound was obtained from 0.764 g of **8** [28] and 1.476 g of benzyloxyacetyl chloride after separation by column chromatography (toluene) and crystallization (ethanol) as white crystals, 0.484 mg (36%), mp 114°; ir: ν 1770 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.84-2.01 (m, 3H, $(CH_2)_3$), 2.15 (s, 3H, SCH_3), 2.20-2.28 (m, 1H, $(CH_2)_3$), 2.60-2.69 (m, 1H, $(CH_2)_3$), 2.88-2.96 (m, 1H, $(CH_2)_3$), 4.61 (s, 1H, CH), 4.79 (B-part of an AB-system, J_{AB} = 11.4 Hz, 1H, OCH_2), 4.94 (A-part of an AB-system, J_{AB} = 11.4 Hz, 1H, OCH_2), 7.13-7.47 (m, 8H, aromatic protons), 7.69-7.72 (m, 1H, 9-H); ^{13}C nmr: (deuteriochloroform): δ 11.6 (SCH_3), 22.2 (C-4), 36.1 (C-5), 40.1 (C-3), 73.3 (OCH_2), 76.1 (C-2a), 90.6 (C-2), 124.3-130.7 (9 CH_{aromat}), 134.0, 136.0, 136.6 (3 C_{qu}), 164.1 (C=O); ms: m/z 339 (M^+, 1), 264 (M^+ -SCH_3, -CO, 9), 248 (M^+ -$C_6H_5CH_2$, 7), 144 ($C_6H_4(CH_2)_3CN^+$, 33), 91 (tropylium$^+$, 100).

Anal. Calcd. for $C_{20}H_{21}NO_2S$: C, 70.77; H, 6.24; N, 4.13. Found: C, 70.66; H, 6.20; N, 4.09.

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