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Studies on Ring Opening Reactions of β-Lactams[1]

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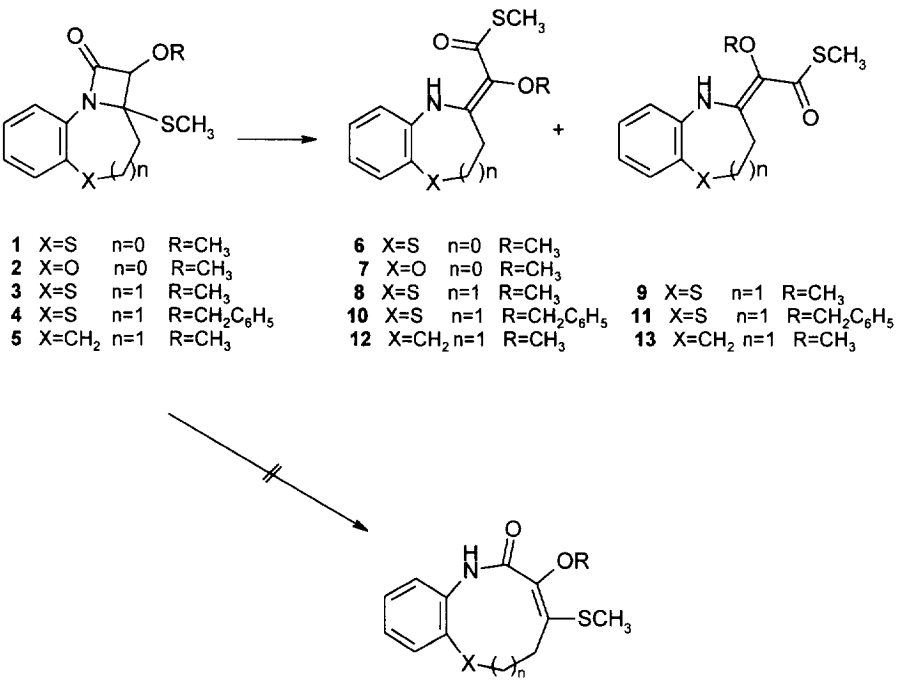
Abstract: Reaction of tricyclic azetidinones **1-5** (azetobenzoxazine, -thiazine, -thiazepine and -azepine derivatives) with trifluoroacetic acid led to bicyclic thioesters **6-13**. There is evidence for an intermolecular reaction, a possible mechanism is discussed. The structure of two representative thioesters (**8** and **9**) was elucidated by different NMR experiments, complete assignments of ^{1}H- and ^{13}C-chemical shifts are given. Reaction of the azetobenzoxazine **2** with sodium periodate and magnesium monoperoxyphthalate led to the sulfoxide **18** and the sulfone **19**, respectively.

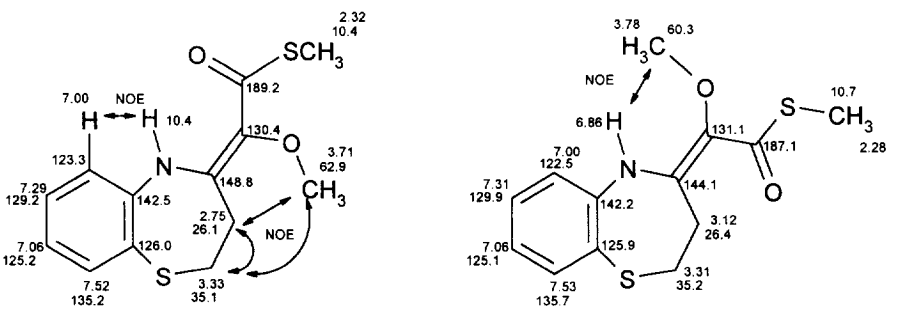
Besides their importance as antibiotics, β-lactams have also been recognized as useful chiral starting materials for the synthesis of non-proteinogenic amino acids and peptides[2-21] and inhibitors of human leukocytase elastase.[22] As β-lactams can undergo rearrangements involving various bonds of the four-membered ring system,[21] we were interested in the reaction behaviour of some azetidinones under oxidative, reductive and hydrolytic reaction conditions.

As model compounds for our studies we used tricyclic benzo-annelated azetidinones (benzo-six-four and benzo-seven-four systems) of type **1-5** described recently.[1] We found that treatment of **3** with m-chloroperbenzoic acid[23] did not lead to any conversion, nor did attempted reaction with H_2/Pd/C,[24] $NaBH_4$, $NaCNBH_3$,[25] or NaH.[26] Furthermore, ring conversion of the azetobenzothiazepine **3** under hydrolytic conditions (described by Hirai *et al.*[27]) or with LiI[28] failed. Interestingly, TLC monitoring of the reaction of **3** with TFA[29] exhibited the formation of two products (ratio 3:1), which could not be separated after work-up of the reaction mixture. Elemental analysis and GC/MS investigations suggested two structural isomers (elemental composition $C_{13}H_{15}NO_2S_2$) to be present, however, the appearence of carbonyl resonances of δ 189.2 ppm (major isomer) and δ 187.1 ppm (minor isomer) in the ^{13}C NMR spectrum of the **8/9** mixture ruled out a β-lactam structure of these compounds. Application of different NMR techniques (NOE difference spectra, long-range INEPT spectra with selective DANTE excitation,[30] HMQC[31] and HMBC experiments[32]) finally enabled us to establish structures **8** (major isomer) and **9** (minor isomer) to these products (Scheme 1), as well as to perform complete and unambiguous assignments for all proton and carbon resonances (Scheme 2): By means of NOE difference spectroscopy on the one hand we could demonstrate the spatial closeness of the OCH_3 moiety to the methylene functions of the thiazepine ring for the main isomer **8** (*E*-configuration), and on

the other hand the through-space connection between OCH_3 and NH and thus *Z*-configuration for compound **9**. Direct carbon-proton connectivities were detected via HMQC experiments, the assignment of quarternary carbon resonances was accomplished by HMBC experiments or by long-range INEPT experiments with selective excitation of unambiguously assigned proton resonances (for instance OCH_3, SCH_3, SCH_2, CH_2-C=).



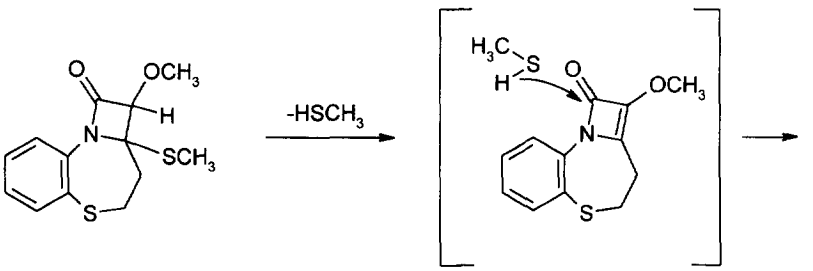
Scheme 1



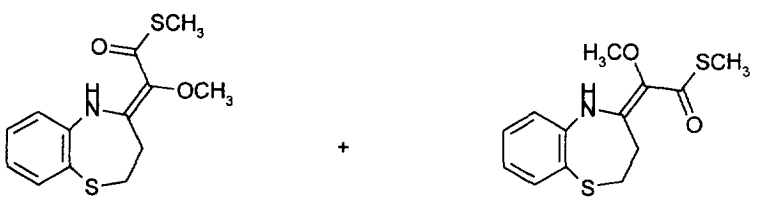
Scheme 2

Variation of reaction conditions never led to the 9-membered ring (scheme 1), but to the thioesters **8**, **9** as well. Interestingly, from the reaction of educts with a six-membered heteroring (compounds **1** and **2**) only the *E*-configurated thioesters **6** and **7**, respectively, were obtained. In contrast, reaction of **4** or **5** with TFA again resulted in the formation of *E/Z*-mixtures (tioesters **10/11** and **12/13**). As with educt **3**, also with compounds **1,2,4** and **5** ring transformation to the higher-membered systems (scheme 1) could not be detected under the reaction conditions applied.

The following mechanism for the formation of the thioesters is postulated: by acid-catalyzed elimination of methanethiol the azetinone intermediate (scheme 3) is formed, which by nucleophilic addition of the eliminated agent is converted into the isomeric thioesters **8** and **9**. Major product is the thermodynamically more favoured *E*-isomer **8**, which is stabilized by an intramolecular hydrogen bond from the amine hydrogen proton to the carbonyl oxygen atom. This situation is also reflected by the marked deshielding of the NH-proton in **8** (δ_{NH} 10.40 ppm) compared to that of isomer **9** (δ_{NH} 6.86 ppm), the latter being not involved in intramolecular hydrogen bonding.



3

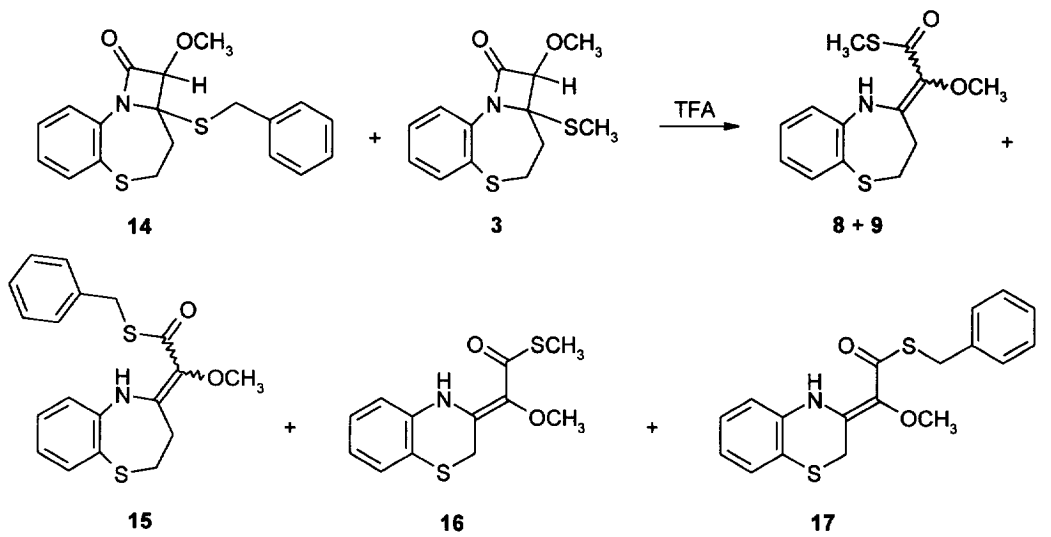


8 **9**

Scheme 3

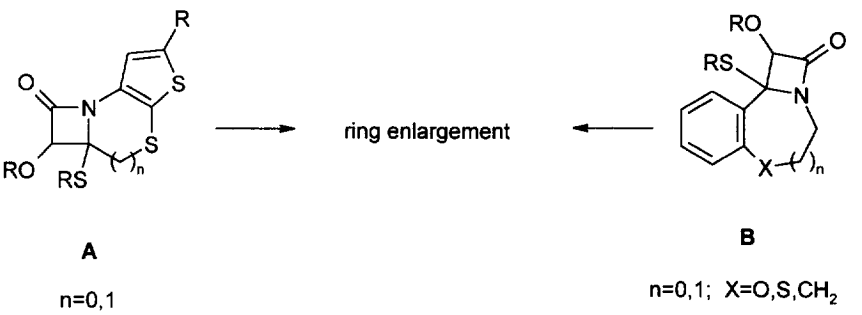
Formation of the cross products **15,16** from the reaction of the thiazine **14** and the thiazepine **3** with TFA shows an - at least partially - intermolecular reaction.

In contrast to our results, under the same reaction conditions treatment of thieno-six-four and thieno-seven-four systems (**A**) and isomeric benzo-six-four and benzo-seven-four systems (**B**) with TFA was reported



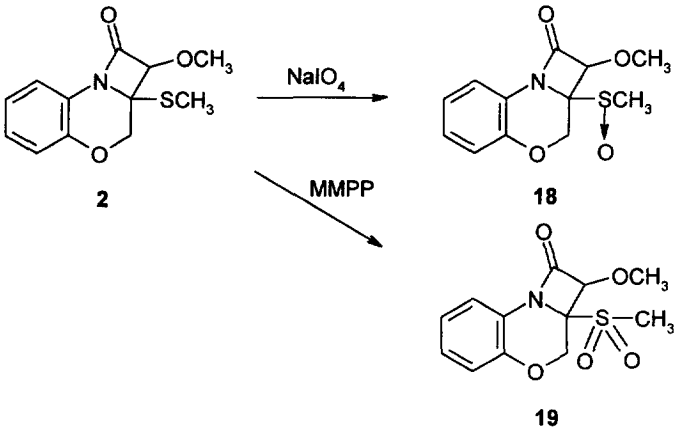
Scheme 4

to lead to 2-C enlarged heterocycles.[33,34] The first step of such a ring enlargement should be the protonation of the nitrogen atom, which is dependent on the availability of its electron pair. Considering this, the more nucleophilic N-atom in compounds **A** (thiophene as π-excessive aromatic system) and **B** (N-atom not attached to the benzene ring) compared to that in our educts of type **1-5** might be a possible explanation for the different reaction behaviour.



Scheme 5

Reaction of **2** with $NaIO_4$[23,34] led to the S-oxide **18** in low yield, which was considered as a possible intermediate for the ring enlargement reaction to 1,6-benzoxazocines. However, the next step (2-C enlargement) could not be realized due to the facts mentioned above. With magnesium monoperoxyphthalate (MMPP) from **2** the sulfone **19** was obtained.



Scheme 6

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Varian Unity*Plus* 300 (^{1}H NMR: 300 MHz; ^{13}C NMR: 75 MHz) and a Bruker AC 80 (^{1}H NMR: 80 MHz) spectrometer (TMS as internal reference, δ values in ppm). Mass spectra (MS) were obtained on a Hewlett-Packard 5890A/5970B-MSD (GC/MS) or on a Shimadzu GC/MS QP 1000 instrument, IR spectra with a Perkin-Elmer 1600 FTIR spectrometer (KBr pellets). Analytical TLC was performed on silica gel F_{254} plates, PLC on silica gel F_{254s} plates. Column chromatography (CC) was done on Merck silica gel 60 (0.063-0.200 mm). Solvents were dried by anhydrous sodium sulfate and were removed under reduced pressure.

General procedure for the preparation of compounds 6-13

A solution of the azetidinone **1-5** (2 mmol) in trifluoroacetic acid (10 ml) was stirred at room temperature for the time given below. The reaction mixture was then neutralized with saturated sodium hydrogen carbonate solution and extracted with dichloromethane. After drying the solvent was evaporated and the residue was purified by column chromatography.

(*E*)-*S*-Methyl 2-(2*H*-1,4-benzothiazin-3(4*H*)-ylidene)-2-methoxythioacetate (6)

Prepared from **1** (534 mg).[1] Reaction time 30 h, eluent: toluene/ethyl acetate 8:2; yield: 211 mg (40%) of **6** as yellow crystals (70% aqueous ethanol), mp 82-83°C; IR 1616 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 2.34 (3H, s, SCH_3), 3.67 (2H, s, SCH_2), 3.68 (3H, s, OCH_3), 6.79-7.26 (4H, m, aromat. H), 10.75 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.5 (SCH_3), 23.0 (SCH_2), 62.7 (OCH_3), 117.7 (C-5'), 120.2 (C-8a'), 122.5 (C-7'), 127.0 (C-6'), 128.1 (C-8'), 128.7 (C-2), 136.0 (C-4a'), 139.1 (C-3'), 190.4 (C=O); MS m/z 267 (M^+, 100%), 252 (M^+-CH_3, 25), 220 (M^+-SCH_3, 34), 192 (M^+-CH_3SCO, 22), 177 (18), 176 (21), 148

($C_6H_4SCH_2CN^+$, 74), 108 (10); Anal. Calcd for $C_{12}H_{13}NO_2S_2$: C, 53.91; H, 4.90; N, 5.24; found: C, 53.70; H, 4.68; N, 5.11.

(*E*)-*S*-Methyl 2-(2*H*-1,4-benzoxazin-3(4*H*)-ylidene)-2-methoxythioacetate (7)

Prepared from **2** (502 mg).[1] Reaction time 30 h, eluent: toluene/ethyl acetate 8:2; yield: 102 mg (20%) of **7** (ethanol), mp 108°C; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 2.33 (3H, s, SCH_3), 3.71 (3H, s, OCH_3), 4.86 (2H, s, CH_2), 6.58-7.25(4H, m, aromat. H), 10.52 (1H, br s, NH); MS m/z 251 (M^+, 100%). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; found: C, 57.27; H, 5.21; N, 5.54.

(*E/Z*) *S*-Methyl 2-(2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ylidene)-2-methoxythioacetate (8,9)

Prepared from **3** (562 mg).[1] Reaction time 30 h, eluent: toluene/ethyl acetate 20:1; yield: 286 mg (51%) of **8,9** as colorless crystals (acetone), mp 104°C ; ratio 3:1; IR 3301 (N-H), 1610 (C=O) cm^{-1}; MS m/z 281 (M^+, 27%), 266 (M^+-CH_3, 10), 234 (M^+-SCH_3, 51), 206 (M^+-CH_3SCO, 100), 162 ($C_6H_4SCH_2CH_2CN^+$, 63), 109 (42); Anal. Calcd for $C_{13}H_{15}NO_2S_2$: C, 55.49; H, 5.37; N, 4.98; found: C, 55.19; H, 5.27; N, 4.81.

8 (*E*-isomer, major product); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.32 (3H, s, SCH_3), 2.75 (2H, t, J=6.6 Hz, CH_2), 3.33 (2H, t, J=6.6 Hz, SCH_2), 3.71 (3H, s, OCH_3), 7.00 (1H, m, H-6'), 7.06 (1H, m, H-8'), 7.29 (1H, m, H-7'), 7.52 (1H, m, H-9'), 10.40 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.4 (SCH_3), 26.1 (CH_2), 35.1 (SCH_2), 62.9 (OCH_3), 123.3 (C-6'), 125.2 (C-8'), 126.0 (C-9'a), 129.8 (C-7'), 130.4 (C-2), 135.2 (C-9'), 142.5 (C-5'a), 148.8 (C-4'), 189.2 (C=O).

9 (*Z*-isomer, minor product); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (3H, s, SCH_3), 3.12 (2H, t, J=6.6 Hz, CH_2), 3.31 (2H, t, J=6.6 Hz, SCH_2), 3.78 (3H, s, OCH_3), 6.86 (1H, br s, NH), 6.98-7.55 (4H, m, aromat. H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.7 (SCH_3), 26.4 (CH_2), 35.2 (SCH_2), 60.3 (OCH_3), 122.5 (C-6'), 125.1 (C-8'), 125.9 (C-9'a), 129.9 (C-7'), 131.1 (C-2), 135.7 (C-9'), 142.2 (C-5'a), 144.1 (C-4'), 187.1 (C=O).

(*E/Z*) *S*-Methyl 2-benzyloxy-2-(2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ylidene)thioacetate (10,11)

Prepared from **4** (714 mg).[1] Reaction time 72 h, eluent: toluene; yield: 344 mg (48%) of **10,11** as a yellowish oil; ratio 4:1; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 2.24 and 2.27 (3H, s, SCH_3), 2.55-3.25 (4H, m, SCH_2CH_2), 4.75 and 4.86 (2H, s, OCH_2), 6.64-7.50 (9H, m, aromat. H), 6.80 and 10.43 (1H, br s, NH); MS m/z 358 (M^++1, 40%), 357 (M^+, 9), 310 (M^+-SCH_3, 12), 282 (M^+-CH_3SCO, 61), 266 (M^+-$C_6H_5CH_2$, 100), 162 ($C_6H_4SCH_2CH_2CN^+$, 90), 109 (47), 91 (tropylium$^+$, 100); Anal. Calcd for $C_{19}H_{19}NO_2S_2$: C, 63.84; H, 5.36; N, 3.92; found: C, 63.70; H, 5.39; N, 3.81.

(*E/Z*) *S*-Methyl 2-(1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-ylidene)-2-methoxythioacetate (12,13)

Prepared from **5** (562 mg).[1] Reaction time 24 h, eluent: toluene; yield: 234 mg (45%) of **12,13** as a yellow oil; ratio 5:1; IR 3291 (N-H), 1635 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.12-2.28 (2H, m, CH_2-4'), 2.28 and 2.32 (3H, s, SCH_3), 2.48 and 2.71 (2H, t, J=6.8 and 7.1 Hz, CH_2-5'), 2.73 and 2.89 (2H, t, J=6.8 and 7.1 Hz, CH_2-3'), 3.68 and 3.75 (3H, s, OCH_3), 6.91-7.98 (4H, m, aromat. H), 6.82 and 10.36 (1H, br s, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.5 and 10.8 (SCH_3), 24.3 and 24.5 (C-4'), 29.3 and 30.3 (C-5'), 29.7 and

30.5 (C-3'), 61.1 and 62.9 (OCH_3), 121.4 and 122.1, 124.69 and 124.72, 127.46 and 127.49, 129.69 and 129.71 (4 $CH_{aromat.}$), 129.9 (C-5'a), 133.9 (C-2), 138.7 (C-9'a), 151.2 (C-2'), 188.6 (C=O); MS: m/z 263 (M^+, 84%), 248 (M^+-CH_3, 29), 216 (M^+-SCH_3, 41), 188 (M^+-CH_3SCO, 13), 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, 63.70; H, 6.46; N, 5.29.

2a,3-Dihydro-2-methoxy-2a-methylsulfinylazeto[2,1-*c*][1,4]benzoxazin-1(2*H*)-one (18)

To a suspension of **2**[1] (753 mg, 3 mmol) in 2-propanol (50 ml) a 0.5 M aqueous sodium periodate solution (10 ml) was added and the reaction mixture was refluxed for 16 h. After removing the solvent the residue was partitioned between dichloromethane and water, the organic layer was dried and the solvent was evaporated. After purification by Kugelrohr distillation **18** was obtained; yield: 51 mg (6%); mp 175°C (ethanol); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 2.51 (3H, s, SCH_3), 3.66 (3H, s, OCH_3), 3.85 (1H, B-part of an AB-system, J_{AB}=12.4 Hz, CH_2), 4.57 (1H, s, CH), 5.62 (1H, A-part of an AB-system, J_{AB}=12.4 Hz, CH_2), 6.86-7.14 (3H, m, H-5, H-6, H-7), 7.41-7.61 (m, 1H, H-8); MS: m/z 251 (M^+-O, 0.5%), 204 (M^+-O, -SCH_3, 7), 176 (100). Anal. Calcd for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24; found: C, 53.63; H, 4.79; N, 5.09.

2a,3-Dihydro-2-methoxy-2a-methylsulfonylazeto[2,1-*c*][1,4]benzoxazin-1(2*H*)-one (19)

Compound **2**[1] (753 mg, 3 mmol) was dissolved in ethanol (6 ml) at 70°C and a solution of magnesium monoperoxyphthalate (1341 mg in 13 ml of water) was added. The reaction mixture was stirred for 12 h, the solvent was removed and the residue was partitioned between dichloromethane and water. After drying the organic layer the solvent was evaporated to yield **19**; yield: 50 mg (6%); mp 190-192°C (ethyl acetate); ^{1}H NMR ($CDCl_3$, 80 MHz) δ 3.03 (3H, s, SCH_3), 3.61 (3H, s, OCH_3), 4.36 (1H, B-part of an AB-system, J_{AB}=13 Hz, CH_2), 5.03 (1H, s, CH), 5.18 (1H, A-part of an AB-system, J_{AB}=13 Hz, CH_2), 6.88 7.20 (3H, m, H-5, H-6, H-7), 7.39-7.59 (m, 1H, H-8); MS: m/z 282 (M^+-H, 7%), 176 (100); Anal. Calcd for $C_{12}H_{13}NO_5S$: C, 50.88; H, 4.63; N, 4.94; found: C, 51.17; H, 4.71; N, 5.09.

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