Preparation of Benzothieno[2,3-*f*]-1,4-oxazepin- and -thiazepin-5(2*H*)-ones and of Benzothieno[3,2-*e*]-1,4-diazepin-5-ones

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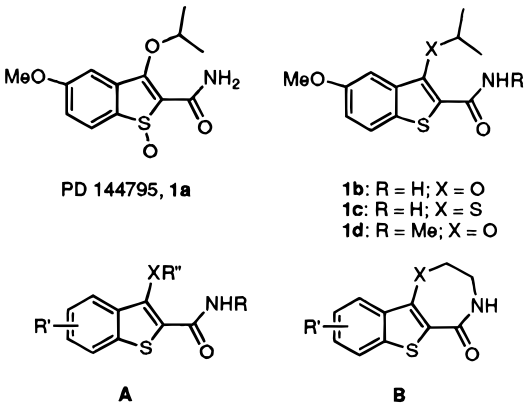
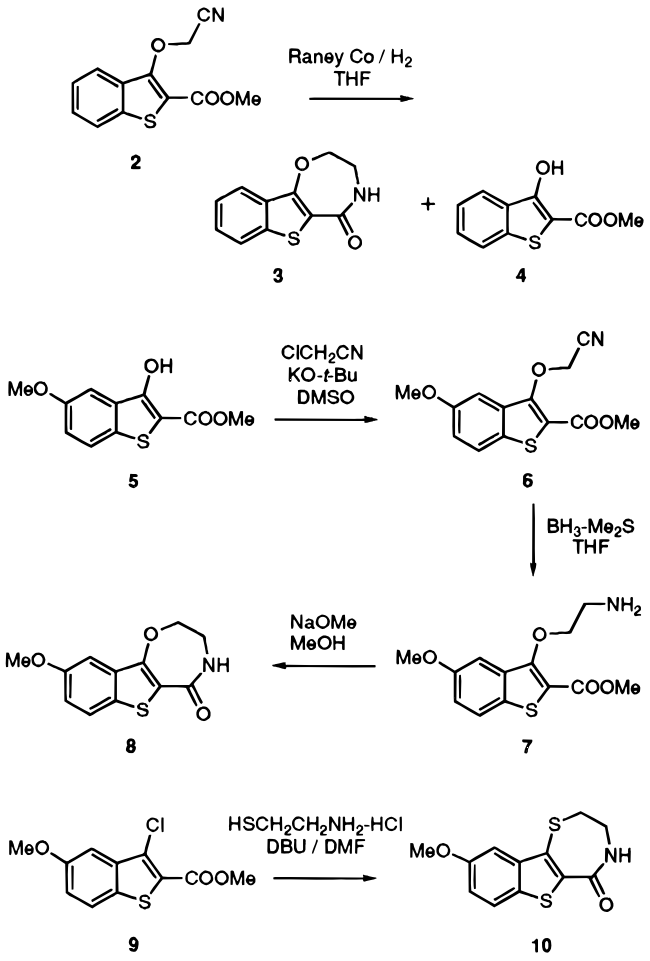
The antiinflammatory agent PD 144795, **1a**, reduces the expression of adhesion molecules on the surface of activated endothelial cells.[1,2] This property is shared by additional benzo[*b*]thiophene-2-carboxamides of structure **A**, including **1b, 1c**, and **1d**. We were interested in preparing the novel tricyclic derivatives of **A**, namely **B**, that contain a seven-membered ring.[3]



Treatment of readily available **2**[4] with Raney cobalt and hydrogen under elevated pressure yielded the oxazepine **3** directly (Scheme 1). Due to ether cleavage occurring under these conditions varying amounts of **4** were also obtained. Reduction of **2** with other hydrogenation catalysts including 10% rhodium and 2% Pd/C gave exclusively **4**. Compound **6** was prepared by reaction of **5**[5] with chloroacetonitrile in the presence of potassium *tert*-butoxide. After unsuccessful attempts to cyclize **6** to **8** by the Raney cobalt method, we employed a two-step protocol. The nitrile group of **6** was reduced with borane−methyl sulfide to the corresponding amine **7**, which upon treatment with sodium methoxide provided

Scheme 1



the oxazepine **8**. The thiazepine analog, **10**, was readily obtained by reaction of **9**[2] with cysteamine−HCl and 1,8-diazabicyclo[5.4.0]undec-7-ene. As in the preparation of **3**, the intermediate amine was not isolated. Since displacement of the 3-chloro group of **9** does not occur with amines unless the benzo[*b*]thiophene sulfur is first oxidized to the corresponding sulfone or sulfoxide,[6] a different route was required to prepare the diazepine analog of **3**.

The reaction of 2-(4,5-dihydro-1*H*-imidazol-2-yl)benzenethiol, **11**, with 2-bromo-4′-chloroacetophenone was reported to provide the hydrobromide salt of the benzothieno-1,4-diazepine **12**.[7] By analogy, reaction of **11** with methyl chloroacetate followed by treatment with base could be expected to yield the desired benzothieno-1,4-diazepine-5-one, **13**. However, a 1975 paper claimed that this reaction provided not **13** but the isomeric imidazo-1,4-benzothiazepin-5(6*H*)-one, **15**, via intermediate **14**.[8] A patent by these same workers also claimed that reaction of **11** with 2,4′-dichloroacetophenone followed by treatment with sodium methoxide provided **16**, an isomer of **12**.[9]

In our hands, reaction of **11** with methyl chloroacetate and subsequent treatment with sodium methoxide pro-

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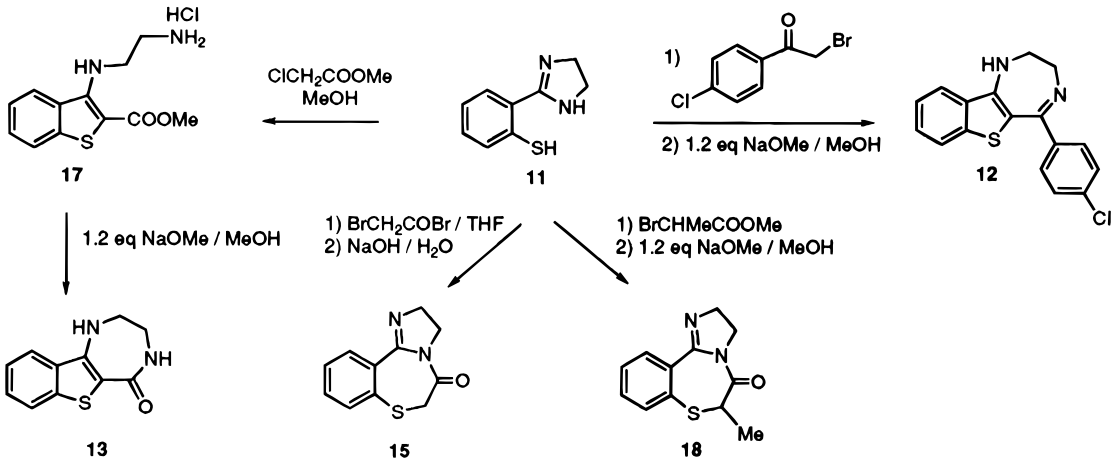
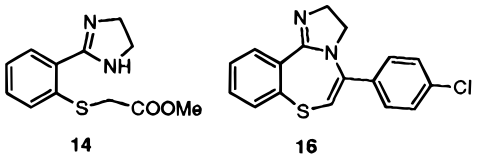
Scheme 2



vided material with a melting point, combustion analysis, and mass spectrum corresponding to that reported for **15**. However, the NMR spectrum of the product was not consistent with this structure (Scheme 2). Instead of a signal for the two methylene protons the NMR showed the presence of two exchangeable protons, suggesting that the product was the benzothiophene derivative **13**. Our attempts to isolate the product of the acylation of **11** with methyl chloroacetate gave traces of **14,** but the NMR spectrum of the major product showed three exchangeable protons. The mass spectrum and combustion analysis implied that this material was isomeric to **14**. All attempts at purification of **14** resulted in conver-



sion to the isomeric material that was assigned the benzothiophene structure **17**. Treatment of **17** with sodium methoxide provided **13**. As additional confirmation, we repeated the reaction of **11** with 2-bromo-4′-chloroacetophenone. The NMR spectrum of the isolated material confirmed the product to be the hydrobromide salt of **12**, not **16**. Treatment of this salt with sodium methoxide provided a solid with spectral and analytical data consistent with **12**.

As reported, we obtained the expected **18** in the reaction of **11** with methyl 2-bromopropionate and base, since in this case the α-methyl group prevents rearrangement.[8] An alternative route to **18** by treatment of **11** with 2-chloropropionyl chloride has also been published.[10] We modified this reaction and reacted **11** with bromoacetyl bromide, followed by base, and obtained an authentic sample of **15**, as confirmed by NMR, MS, and analytical data.

Although **11** was first prepared in 1929, via reaction of 4,5-benzo-1,2-dithiole-2-thione with 1,2-ethylenediamine,[11] there are only limited reports in the literature utilizing this versatile compound. We are therefore continuing to investigate the usefulness of **11** in the preparation of additional novel heterocyclic systems.

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Experimental Section

Melting points are uncorrected. Elemental analyses were performed by the Parke-Davis Analytical Chemistry staff. Reactions were run under an atmosphere of nitrogen or argon unless otherwise noted. Flash chromatography was performed with E. Merck silica gel 60, 230−400 mesh. The THF, DMSO, and DMF used were Sure-Seal solvents purchased from Aldrich Chemical Co.

3,4-Dihydro[1]benzothieno[2,3-*f*]-1,4-oxazepin-5(2*H*)-one (3). A mixture of methyl 3-(cyanomethoxy)benzo[*b*]-thiophene-2-carboxylate, **2**[4] (405 mg, 1.64 mmol), and 0.5 mL of Et_3N was treated with 0.5 g of Raney cobalt in 50 mL of THF at 100 °C and 1200 psi of hydrogen. After 14 h the reaction mixture was concentrated *in vacuo*. Column chromatography eluting with a gradient of 1:1 hexane/ethyl acetate to all ethyl acetate provided 199 mg (55%) of **3**: mp 244−245 °C; ^{1}H NMR (DMSO-d_6) δ 3.54 (m, 2H), 4.56 (m, 2H), 7.41 (t, J = 7 Hz, 1H), 7.51 (t, J = 7 Hz, 1H), 7.76 (d, J = 8 Hz, 1H), 7.88 (d, J = 8 Hz, 1H), 8.37 (m, 1H-NH); MS(CI) (m + 1)/z 220. Anal. Calcd for $C_{11}H_9NO_2S$: C, 60.26; H, 4.14; N, 6.39. Found: C, 60.00; H, 4.13; N, 6.43.

Methyl 3-(Cyanomethoxy)-5-methoxybenzo[*b*]thiophene-2-carboxylate (6). To a solution of **5** [5] (2.0 g, 8.4 mmol) in 35 mL of DMSO at room temperature was added potassium *tert*-butoxide (990 mg, 8.8 mmol). The mixture was stirred for 15 min, and chloroacetonitrile (1.6 mL, 25.2 mmol) was added. The reaction was stirred at 40 °C for 1.5 h and then partitioned between ethyl acetate and 0.5 N HCl. The organic phase was washed three times with water and once with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide a yellow-brown solid. The residue was crystallized from methanol/water to give 1.9 g (82%) of **6**. Recrystallization from ethyl acetate/hexane provided an analytical sample of **6**: mp 159.5−160.0 °C; ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H), 3.88 (s, 3H), 5.33 (s, 2H), 7.26 (dd, J = 9, 2.5 Hz, 1H), 7.36 (d, J = 2.5 Hz, 1H), 7.93 (d, J = 9 Hz, 1H); MS(CI) (m + 1)/z 278; Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.26; H, 3.94; N, 5.18.

3,4-Dihydro-9-methoxy[1]benzothieno[2,3-*f*]-1,4-oxazepin-5(2*H*)-one (8). A solution of **6** (2.5 g, 9.0 mmol) in 50 mL of THF was heated to reflux. Borane−methyl sulfide (9.0 mL, 90.2 mmol) was rapidly added and heating continued for 25 min with THF being added as it evaporated. An additional amount of borane−methyl sulfide (4.0 mL) was added and heating continued for 10 min. The reaction mixture was cooled to 0 °C, and 50 mL of 6 N HCl was carefully added, maintaining the temperature of the reaction mixture below 40 °C. A solution of 1 N NaOH (451 mL) was added, and the resultant precipitate was collected by filtration, washed with water, and dried *in vacuo* to give 2.3 g of **7**.

The solid (**7**) (2.3 g, 8.2 mmol) was added to a freshly prepared solution of sodium methoxide (from 1.9 g, 82.0 mmol of sodium) in 40 mL of MeOH. The reaction mixture was warmed to 50 °C for 2 h and then heated at reflux for 2 h. After the mixture was cooled to 0 °C, the precipitate was collected and washed with

cold MeOH followed by cold diethyl ether. Drying the solid *in vacuo* overnight gave 1.2 g (52%) of **8**. An analytical sample of **8** was obtained by recrystallization from ethyl acetate/hexane: mp 264−265 °C; ^{1}H NMR (DMSO-d_6) δ 3.51−3.58 (m, 2H), 3.82 (s, 3H), 4.55 (t, J = 3.5 Hz, 2H), 7.13 (dd, J = 8.5, 2.5 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 8.32 (t, J = 4.5 Hz, 1H-NH); MS(CI) (m + 1)/z 250. Anal. Calcd for $C_{12}H_{11}NO_3S$: C, 57.82; H, 4.45; N, 5.62. Found: C, 57.42; H, 4.25; N, 5.37.

3,4-Dihydro-9-methoxy[1]benzothieno[2,3-*f*]-1,4-thiazepin-5(2*H*)-one (10). To a solution of methyl 3-chloro-5-methoxybenzo[*b*]thiophene-2-carboxylate, **9**[2] (500 mg, 1.95 mmol), in 20 mL of DMF at room temperature was added cysteamine−HCl (885 mg, 7.79 mmol) followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (2.33 mL, 15.58 mmol). The reaction mixture was stirred at room temperature for 1.5 h and then warmed to 70 °C. The mixture was diluted with ethyl acetate and washed with aqueous HCl, water, and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Recrystallization from hexane/ethyl acetate provided 380 mg (74%) of **10**: mp 209−209.5 °C; ^{1}H NMR (DMSO-d_6) δ 3.39−3.43 (m, 2H), 3.61−3.67 (m, 2H), 3.84 (s, 3H), 7.16−7.20 (m, 2H), 7.88−7.92 (m, 1H), 8.49 (t, J = 5.5 Hz, 1H-NH); MS(EI) m/z 265. Anal. Calcd for $C_{12}H_{11}NO_2S_2$: C, 54.32; H, 4.18; N, 5.28. Found: C, 54.01; H, 3.96; N, 5.14.

Methyl 3-[(2-Aminoethyl)amino]benzo[*b*]thiophene-2-carboxylate Hydrochloride (17). A solution of 2-(4,5-dihydro-1*H*-imidazol-2-yl)benzenethiol, **11**[8] (1.00 g, 5.62 mmol), and methyl chloroacetate (610 mg, 5.62 mmol) in 15 mL of MeOH was heated at reflux for 90 min. The reaction was cooled to room temperature and filtered. The filtrate was concentrated to dryness and the residue dissolved in hot chloroform. After several hours the resulting precipitate was collected and dried. The mother liquor afforded a second crop of crystals, giving **17** in an overall yield of 61%: mp 219−220 °C; ^{1}H NMR (DMSO-d_6) δ 3.11 (t, J = 6.5 Hz, 2H), 3.81 (s, 3H), 3.90 (q, J = 6.5 Hz, 2H), 7.40−7.44 (m, 2H, includes 1H-NH), 7.54 (t, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 8.13 (br s, 2H), 8.22 (d, J = 8 Hz, 1H); MS(CI) (m + 1)/z 250. Anal. Calcd for $C_{12}H_{14}N_2O_2S$·HCl: C, 50.26; H, 5.27; N, 9.77. Found: C, 50.16; H, 5.15; N, 9.49.

1,2,3,4-Tetrahydro-5*H*-[1]benzothieno[3,2-*e*]-1,4-diazepin-5-one (13). A solution of **17** (339 mg, 1.18 mmol) and freshly prepared sodium methoxide (from 134 mg, 2.48 mmol, of sodium) in 5 mL of MeOH was heated at reflux for 18 h. After the mixture was cooled to room temperature, the reaction was neutralized with 25 mL of 1 N HCl and cooled to 0 °C for 1 h. The resulting yellow crystalline material was filtered and dried under vacuum at 60 °C for several hours to provide 165 mg (64%) of **13**. Chromatography, eluting with a gradient of 2% methanol in ethyl acetate to 5% methanol in ethyl acetate, gave an analytically pure sample: mp 210−212 °C; ^{1}H NMR (DMSO-d_6) δ 3.34−3.37 (m, 2H), 3.49−3.51 (m, 2H), 7.34 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.49 (t, J = 4 Hz, 1H-NH), 7.75−7.79 (m, 2H, includes 1H-NH), 7.93 (d, J = 8 Hz, 1H); MS(CI) (m + 1)/z 219. Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.51; H, 4.71; N, 12.71.

5-(4-Chlorophenyl)-2,3-dihydro-1*H*-[1]benzothieno[3,2-*e*]-1,4-diazepine Hydrobromide (12-HBr). A solution of **11** (200 mg, 1.12 mmol) and 2-bromo-4′-chloroacetophenone (262 mg, 1.12 mmol) in 5 mL of 2-ethoxyethanol was heated at reflux. After 30 min additional 2-ethoxyethanol (5 mL) was added to dissolve the orange solid that formed. The reaction solution was heated at reflux for 2.5 h and then cooled to room temperature and allowed to stand overnight. The precipitated salt was collected by filtration to provide 150 mg of the HBr salt of **12** as an orange-yellow solid. Concentration of the filtrate provided an additional 142 mg (66% total) of the HBr salt: mp 316−318 °C (lit.[7] mp 317−318 °C); ^{1}H NMR (DMSO-d_6) δ 3.78−4.08 (br s, 4H), 7.53 (t, J = 8 Hz, 1H), 7.66 (t, J = 8 Hz, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8 Hz, 1H), 8.35 (d, J = 8 Hz, 1H), 10.14 (br s, 1H), 11.16 (br s, 1H); MS(CI) (m + 1)/z 313.

5-(4-Chlorophenyl)-2,3-dihydro-1*H*-[1]benzothieno[3,2-*e*]-1,4-diazepine (12). A solution of the hydrobromide salt of **12** (50 mg, 0.13 mmol) and 130 μL of 1 M sodium methoxide in 10 mL of MeOH was heated at reflux for 1 h. The reaction mixture was cooled to room temperature, and the solvent was removed *in vacuo* to provide a yellow oil. Ethyl acetate and hexane were added, and the mixture was filtered. The filtrate was concentrated *in vacuo* to give 18 mg (45%) of **12** as a bright yellow solid: mp 180−182 °C (lit.[9] mp 191 °C); ^{1}H NMR (DMSO-d_6) δ 3.51 (br s, 2H), 4.07 (br s, 2H), 7.37−7.44 (m, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H + obscured 1H-NH), 7.73 (d, J = 8 Hz, 1H), 7.98 (d, J = 8 Hz, 1H); MS(CI) (m + 1)/z 313; Anal. Calcd for $C_{17}H_{13}N_2S$: C, 65.27; H, 4.19; N, 8.96. Found: C, 64.87; H, 4.39; N, 8.84.

2,3-Dihydroimidazo[1,2-*d*][1,4]benzothiazepin-5(6*H*)-one (15). A solution of **11** (300 mg, 1.68 mmol) and bromoacetyl bromide (373 mg, 1.85 mmol) in 5 mL of THF was heated at reflux for 90 min. After the solution was cooled to room temperature, the precipitated salt was dissolved in 4 mL of water and made basic with 1 N NaOH. The solution was extracted with several portions of ethyl acetate, and the organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The product was purified by chromatography, eluting with ethyl acetate, to afford 117 mg (32%) of **15**: mp 135−136 °C; ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 2H), 3.87 (d, J = 9 Hz, 2H), 4.00 (d, J = 9 Hz, 2H), 7.40−7.47 (m, 2H), 7.54 (d, J = 7 Hz, 1H) 8.02 (d, J = 7 Hz, 1H); MS(CI) (m + 1)/z 219. Anal. Calcd for $C_{11}H_{10}N_2OS$: C, 60.53; H, 4.62; N, 12.83. Found: C, 60.42; H, 4.61; N, 12.67.

2,3-Dihydro-6-methylimidazo[1,2-*d*][1,4]benzothiazepin-5(6*H*)-one (18). A solution of **11** (300 mg, 1.68 mmol) and methyl 2-bromopropionate (309 mg, 1.85 mmol) in 5 mL of MeOH was heated at reflux for 3 h. The reaction was cooled to room temperature, concentrated, and redissolved in 5 mL of MeOH. A solution of sodium methoxide in MeOH (prepared from 91 mg, 1.68 mmol, of sodium) was added, and the reaction was heated at reflux for 90 min and then stirred at room temperature for 18 h. The mixture was concentrated and purified by chromatography, eluting with ethyl acetate, to give 133 mg (34%) of **18** as a white solid: mp 110−112 °C (lit.[8,10] mp 115, 119 °C); ^{1}H NMR (DMSO-d_6) δ 1.34 (d, J = 7 Hz, 3H), 3.79−3.97 (m, 4H), 4.06−4.13 (m, 1H), 7.40−7.48 (m, 2H), 7.54 (d, J = 7.5 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H); MS(CI) (m + 1)/z 233. Anal. Calcd for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.21; N, 12.06. Found: C, 62.00; H, 5.26; N, 11.96.

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