Synthesis of *trans*-Thienyl-3-ethoxycarbonyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-ones

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A series of *trans*-thienyl-3-ethoxycarbonyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-ones **6-8** was synthesized from thienylmethylidenemalonates **3a-3c** and 2-aminobenzenethiol **3d** in the presence of triethylamine hydrochloride at 160°. The [1,5]benzothiazepines **6-8** were alkylated using 2-dimethylaminochloroethane, 3-dimethylaminochloropropane and 3-(*N*-piperidino)chloropropane in order to obtain the corresponding 5-aminoalkylbenzothiazepinones **9-14**.

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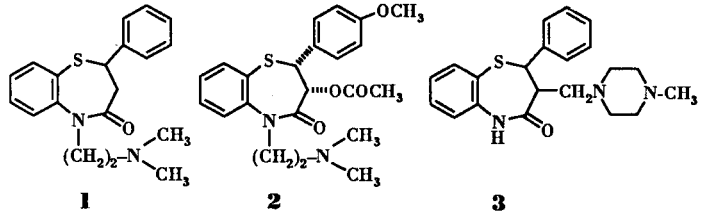
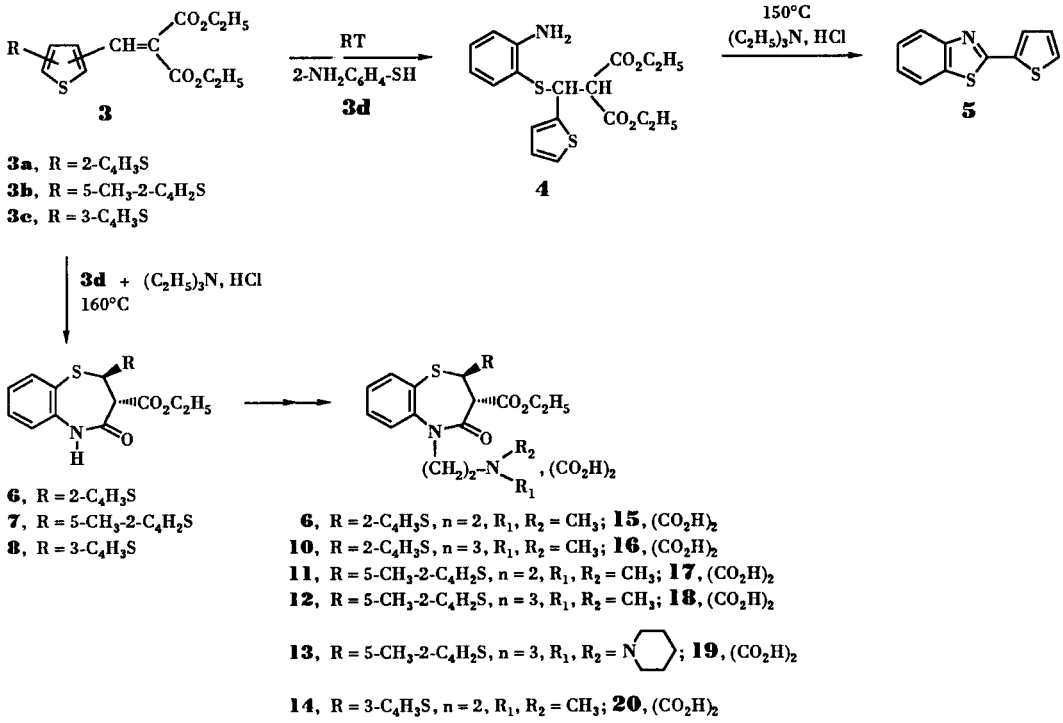
Several [1,5]benzothiazepines, namely Thiazesim **1** [1], Diltiazem **2** [2] or 2-phenyl-2,3-dihydro-3-(*N'*-methyl-*N*-piperazino)methyl[1,5]benzothiazepin-4(5*H*)-one (BTM-1086) **3** [3-5] are known for there pharmacological activities and we wish to describe herein the synthesis of *trans*-2-thienyl-3-ethoxycarbonyl-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-ones **15-20** which at present are being tested for there coronary vasodilator properties.



1 **2** **3**

The cyclization of 2-thienylmethylidenemalonate **3a** [6-8] at ambient temperature with 2-aminobenzenethiol **3d** afforded diethyl ester **4**, 2-thienylbenzothiazole **5** [9] was obtained in 35% yield by heating **4** at 150° with triethylamine hydrochloride. 3-ethoxycarbonylbenzothiazepi-

Chart 1



3a, R = 2-C_4H_3S
3b, R = 5-CH_3-2-C_4H_2S
3c, R = 3-C_4H_3S

6, R = 2-C_4H_3S
7, R = 5-CH_3-2-C_4H_2S
8, R = 3-C_4H_3S

6, R = 2-C_4H_3S, n = 2, R_1, R_2 = CH_3; **15**, $(CO_2H)_2$
10, R = 2-C_4H_3S, n = 3, R_1, R_2 = CH_3; **16**, $(CO_2H)_2$
11, R = 5-CH_3-2-C_4H_2S, n = 2, R_1, R_2 = CH_3; **17**, $(CO_2H)_2$
12, R = 5-CH_3-2-C_4H_2S, n = 3, R_1, R_2 = CH_3; **18**, $(CO_2H)_2$

13, R = 5-CH_3-2-C_4H_2S, n = 3, R_1, R_2 = N⟨⟩; **19**, $(CO_2H)_2$

14, R = 3-C_4H_3S, n = 2, R_1, R_2 = CH_3; **20**, $(CO_2H)_2$

Table 1

Physical and Analytical Data for [1,5]Benzothiazepin-4(5*H*)-one Derivatives

Compound	IR ν KBr (cm^{-1}) (CO)	Formula	Analysis % Calcd. C	H	N	Analysis % Found C	H	N
9 [a]	1685-1650	$C_{20}H_{24}N_2S_2O_3$	59.40	5.98	6.93	59.32	5.92	6.92
10 [a]	1690-1655	$C_{21}H_{26}N_2S_2O_3$	60.28	6.26	6.70	60.31	6.27	6.80
11 [a]	1690-1650	$C_{21}H_{26}N_2S_2O_3$	60.28	6.26	6.70	60.29	6.31	6.74
12 [b]	1680-1650	$C_{22}H_{28}N_2S_2O_3$	61.10	6.53	6.48	61.35	6.49	6.51
13 [a]	1680-1650	$C_{25}H_{32}N_2S_2O_3$	63.54	6.83	5.93	63.60	6.87	5.94
14 [a]	1695-1665	$C_{21}H_{26}N_2S_2O_3$	60.28	6.26	6.70	60.36	6.30	6.75

[a] Elution with chloroform-ethanol (4/1). [b] Elution with chloroform-hexane (1/1).

Table 2

^{1}H-NMR Spectroscopic Data for [1,5]Benzothiazepin-4(5*H*)-one Derivatives

Compound	^{1}H-NMR DMSO-d_6 δ/TMS ppm
9	7.46 (7H, m, ArH), 4.18 (3H, m, C*H*$_2$-CH$_3$, C$_2$-H), 2.83 (3H, m, CH$_2$, C$_3$-H), 2.18 (2H, m, CH$_2$), 1.98 (6H, s, (CH$_3$)$_2$), 1.26 (3H, t, CH$_2$-C*H*$_3$)
10	7.45 (7H, m, ArH), 4.23 (3H, m, C*H*$_2$-CH$_3$, C$_2$-H), 2.83 (3H, m, CH$_2$, C$_3$-H), 2.23 (2H, m, CH$_2$), 1.60 (2H, m, CH$_2$), 2.06 (6H, s, (CH$_3$)$_2$), 1.30 (3H, t, CH$_2$-C*H*$_3$)
11	7.38 (6H, m, ArH), 4.12 (3H, m, C*H*$_2$-CH$_3$, C$_2$-H), 3.20 (2H, m, CH$_2$), 2.75 (3H, m, CH$_2$, C$_3$-H), 2.26 (3H, s, CH$_3$-thienyl), 1.90 (6H, s, (CH$_3$)$_2$), 1.16 (3H, t, CH$_2$-C*H*$_3$)
12	7.46 (6H, m, ArH), 4.18 (3H, m, C*H*$_2$-CH$_3$, C$_2$-H), 2.80 (3H, m, CH$_2$, C$_3$-H), 2.35 (3H, s, CH$_3$-thienyl), 2.20 (2H, m, CH$_2$), 2.05 (6H, s, (CH$_3$)$_2$), 1.63 (2H, m, CH$_2$), 1.26 (3H, s, CH$_2$-C*H*$_3$)
13	7.35 (6H, m, ArH), 4.20 (3H, m, C*H*$_2$-CH$_3$, C$_2$-H), 3.58 (2H, m, CH$_2$), 3.30 (3H, s, CH$_3$-thienyl), 2.72 (3H, m, CH$_2$, C$_3$-H), 2.35, 2.22, 1.35 (12H, m, piperidino, CH$_2$), 1.08 (3H, s, CH$_2$-C*H*$_3$)
14	7.50 (7H, m, ArH), 4.18 (3H, m, C*H*$_2$-CH$_3$, C$_2$-H), 2.83 (3H, m, CH$_2$, C$_3$-H), 2.18 (2H, m, CH$_2$), 1.95 (6H, s, (CH$_3$)$_2$), 1.23 (3H, t, CH$_2$-C*H*$_3$)

nones **6-8** were directly cyclized by heating thienylidene malonates **3a-3c** [6-8] with triethylamine hydrochloride and 2-aminobenzenethiol **3d** at 160°. Benzothiazepinones **6-8** could be *N*-alkylated [10] with 2-*N*,*N*-dimethylaminoethyl chloride, 3-*N*,*N*-dimethylaminopropyl chloride and 3-*N*-piperidinopropyl chloride by heating in acetone in the presence of sodium carbonate. The 5-aminoalkylbenzothiazepinones **9-14** were isolated as an oil by column chromatography on silica gel (Table 1). Amines **9-14** were converted to the oxalates **15-20** which were purified by recrystallization. The structures of these compounds were confirmed on the basis of infrared and ^{1}H nmr spectra and elemental analysis.

EXPERIMENTAL

Melting points were determined with a Kofler Heiz bank apparatus and are uncorrected. The ir spectra were recorded as potassium bromide pellets on a Perkin-Elmer 257G spectrometer and the ^{1}H nmr spectra were obtained on a Varian EM 90 spectrometer using DMSO-d_6 as the solvent. Chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane as an internal reference.

trans-3-Ethoxycarbonyl-2-(2-thienyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **6**.

A mixture of **3a** (25.4 g, 0.10 mole), **3d** (12.5 g, 0.10 mole) and triethylamine hydrochloride (6 g, 0.043 mole) was heated at about 160° for 4 hours. After being cooled, the reaction mixture was crystallized with diethyl ether and petroleum ether. The resulting crystals were collected, washed with ethanol, and dried to give **6**, mp 175°, 2.2 g (6.6%); ir (potassium bromide): ν cm^{-1} 3180 (NH), 1750, 1660 (CO); ^{1}H nmr (DMSO-d_6): δ 10.20 (1H, s, NH, deuterium oxide exchangeable), 7.23, 6.98 (7H, m, ArH), 5.36 (1H, d, C$_2$-H, $J_{H_2H_3}$ = 11.4 Hz), 3.90 (2H, q, CH$_2$), 3.63 (1H, d, C$_3$-H), 1.00 (3H, t, CH$_3$).

Anal. Calcd. for $C_{16}H_{15}NO_3S_2$: C, 57.63; H, 4.53; N, 4.21; S, 19.23. Found: C, 57.45; H, 4.60; N, 4.30; S, 19.16.

trans-3-Ethoxycarbonyl-2-(5-methyl-2-thienyl)-2,3-dihydro[1,5]-benzothiazepin-4(5*H*)-one **7**.

Reaction of **3b**, 32.0 g (0.119 mole), **3d**, 14.87 g (0.119 mole) and triethylamine hydrochloride, 6 g (0.043 mole) gave **7**, mp 248°, 14.0 g (34%); ir (potassium bromide): ν cm^{-1} 3170 (NH), 1745, 1660 (CO); ^{1}H nmr (DMSO-d_6): δ 10.25 (1H, s, NH, deuterium oxide exchangeable), 7.25 (4H, m, ArH), 6.66 (1H, d, $H_{3'}$, $J_{H_{3'}H_{4'}}$ = 4.8 Hz), 5.30 (1H, d, C$_2$-H, $J_{H_2H_3}$ = 11.4 Hz), 3.86 (2H, q, CH$_2$), 3.57 (1H, d, C$_3$-H), 2.16 (3H, s, CH$_3$), 0.96 (3H, t, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{17}H_{17}NO_3S_2$: C, 58.76; H, 4.93; N, 4.03; S, 18.45. Found: C, 58.66; H, 5.00; N, 4.07; S, 18.38.

trans-3-Ethoxycarbonyl-2-(3-thienyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **8**.

Reaction of **3c**, 35.0 g (0.137 mole), **3d**, 17.22 (g (0.137 mole)

and triethylamine hydrochloride, 6 g (0.043 mole) gave **8**, mp 171° 10.0 g (22%); ir (potassium bromide): ν cm^{-1} 3260 (NH), 1800, 1735 (CO); ^1H nmr (DMSO-d_6): δ 10.22 (1H, s, NH, deuterium oxide exchangeable), 7.30, 6.88 (7H, m, ArH), 5.18 (1H, d, C_2-H, $J_{H_2H_3}$ = 11.4 Hz), 3.92 (2H, q, CH_2), 3.82 (1H, d, C_3-H), 1.03 (3H, t, CH_2-CH_3).

Anal. Calcd. for $C_{16}H_{15}NO_3S_2$: C, 57.63; H, 4.53; N, 4.21; S, 19.23. Found: C, 57.66; H, 4.47; N, 4.22; S, 19.16.

trans-5-(2-Dimethylaminoethyl)-3-ethoxycarbonyl-2-(2-thienyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **15** (Oxalate).

A mixture of the *trans*-lactam **6** 4.50 g (0.0135 mole), 2-dimethylaminoethyl chloride hydrochloride 2.88 g (0.02 mole), powdered sodium carbonate 6.36 g (0.06 mole), acetone (150 ml) and water (1.5 ml) was heated under reflux for 20 hours. After cooling, inorganic compounds were filtered off and the solvent was evaporated. The residue was dissolved in diethyl ether and the solution was washed with water, dried and concentrated. The oil was chromatographed on a silica gel column (Tables 1 and 2) yielding 4.05 g (71%) of **9**. The oil **9** (0.01 mole) was dissolved in acetone and converted to the oxalate salt **15** which was recrystallized from ethanol, mp 124°, 3.4 g (69%); ir (potassium bromide): ν cm^{-1} 3440 (OH), 2670 (NH^+), 1695, 1650, 1610 (CO); ^1H nmr (DMSO-d_6): δ 10.05 (2H, s, $(CO_2H)_2$), 7.73, 7.43 (7H, m, ArH), 4.20 (3H, q, CH_2-CH_3, d, C_2-H), 3.10 (5H, m, $(CH_2)_2$, C_3-H), 2.63 (6H, s, $(CH_3)_2$), 1.23 (3H, t, CH_2-CH_3).

Anal. Calcd. for $C_{22}H_{26}N_2O_7S_2$: C, 53.42; H, 5.30; N, 5.66; S, 12.96. Found: C, 53.42; H, 5.35; N, 5.70; S, 12.84.

trans-5-(3-Dimethylaminopropyl)-3-ethoxycarbonyl-2-(2-thienyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **16** (Oxalate).

Compound **6** 4.50 g (0.0135 mole), 3-dimethylaminopropyl chloride hydrochloride 3.16 g (0.02 mole) and powdered sodium carbonate 6.36 g (0.06 mole) was refluxed in acetone (150 ml) and water (1.5 ml) for 20 hours to give **10**, oil (3.10 g, 55%) (Tables 1 and 2). The oil **10** (0.0074 mole) was dissolved in acetone and converted to the oxalate salt **16** (ethanol), mp 112°, 3.0 g (51%); ir (potassium bromide): ν cm^{-1} 3420 (OH), 2680 (NH^+), 1695, 1645, 1610 (CO); ^1H nmr (DMSO-d_6): δ 7.55, 7.10 (7H, m, ArH), 6.40 (2H, s, $(CO_2H)_2$), 4.23 (3H, q, CH_2-CH_3, d, C_2-H, J = 10 Hz), 2.90 (5H, m, $(CH_2)_2$, C_3-H), 2.60 (6H, s, $(CH_3)_2$), 1.80 (2H, m, CH_2), 1.23 (3H, t, CH_2-CH_3).

Anal. Calcd. for $C_{23}H_{28}N_2O_7S_2$: C, 54.31; H, 5.55; N, 5.51; S, 12.61. Found: C, 54.36; H, 5.47; N, 5.60. S, 12.70.

trans-5-(2-Dimethylaminoethyl)-3-ethoxycarbonyl-2-(5-methyl-2-thienyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **17** (Oxalate).

Compound **7** 4.50 g (0.0129 mole), 2-dimethylaminoethyl chloride hydrochloride 2.88 g (0.020 mole) and powdered sodium carbonate 6.36 g (0.06 mole) was refluxed in acetone (150 ml) and water (1.5 ml) for 20 hours to give **11**, oil (3.5 g, 65%) (Tables 1 and 2). The oil **11** (0.0083 mole) was dissolved in acetone and converted to the oxalate salt **17** (ethanol), mp 149°, 3.7 g (87%); ir (potassium bromide): ν cm^{-1} 3450 (OH), 2980 (NH^+), 1695, 1650, 1610 (CO); ^1H nmr (DMSO-d_6): δ 9.73 (2H, s, $(CO_2H)_2$), 7.96, 7.06 (6H, m, ArH), 4.16 (3H, q, CH_2-CH_3, d, C_2-H), 3.10 (5H, m, $(CH_2)_2$, C_3-H), 2.66 (6H, s, $(CH_3)_2$), 2.30 (3H, s, CH_3-thienyl), 1.23 (3H, s, CH_2-CH_3).

Anal. Calcd. for $C_{23}H_{28}N_2O_7S_2$: C, 54.31; H, 5.55; N, 5.51; S, 12.61. Found: C, 54.32; H, 5.60; N, 5.45; S, 12.70.

trans-5-(3-Dimethylaminopropyl)-3-ethoxycarbonyl-2-(5-methyl-2-thienyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **18** (Oxalate).

Compound **7** 4.50 g (0.0129 mole), 3-dimethylaminopropyl chloride hydrochloride 3.16 g (0.020 mole) and powdered sodium carbonate 6.36 g (0.06 mole) was refluxed in acetone (150 ml) and water (1.5 ml) for 20 hours to give **12**, an oil (3.70 g, 66%) (Tables 1 and 2). The oil **12** (0.0085 mole) was dissolved in acetone and converted to the oxalate salt **18** (ethanol), mp 112°, 2.9 g (66%); ir (potassium bromide): ν cm^{-1} 3420 (OH), 2670 (NH^+), 1695, 1660, 1605 (CO); ^1H nmr (DMSO-d_6): δ 8.56 (2H, s, $(CO_2H)_2$), 7.63, 7.13 (6H, m, ArH), 4.13 (3H, q, CH_2-CH_3, d, C_2-H), 2.86 (3H, m, CH_2, C_3-H), 2.56 (6H, s, $(CH_3)_2$), 2.30 (3H, s, CH_3-thienyl), 1.76 (4H, m, $(CH_2)_2$), 1.20 (3H, s, CH_2-CH_3).

Anal. Calcd. for $C_{24}H_{30}N_2O_7S_2$: C, 55.15; H, 5.79; N, 5.36; S, 12.27. Found: C, 55.13; H, 5.69; N, 5.26; S, 12.20.

trans-3-Ethoxycarbonyl-2-(5-methyl-2-thienyl)-5-(3-piperidinopropyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **19** (Oxalate).

Compound **7** 4.50 g (0.0129 mole), 3-chloropropyl-1-piperidine hydrochloride 3.96 g (0.020 mole) and powdered sodium carbonate 6.36 g (0.06 mole) was refluxed in acetone (150 ml) and water (1.5 ml) for 20 hours to give **13**, and oil (3.40 g, 56%) (Tables 1 and 2). The oil **13** (0.0072 mole) was dissolved in acetone and converted to the oxalate salt **19** (ethanol), mp 102°, 2.3 g (57%); ir (potassium bromide): ν cm^{-1} 3410 (OH), 2650 (NH^+), 1705, 1645, 1605 (CO); ^1H nmr (DMSO-d_6): δ 5.20 (2H, s, $(CO_2H)_2$), 7.63, 7.23, 6.90 (6H, m, ArH), 4.16 (3H, q, CH_2-CH_3, d, C_2-H), 2.86 (5H, m, $(CH_2)_2$, C_3-H), 2.26 (3H, s, CH_3-thienyl), 1.56, 1.20 (12H, m, CH_2, piperidino), 0.96 (3H, t, CH_2-CH_3).

Anal. Calcd. for $C_{27}H_{34}N_2O_7S_2$: C, 57.63; H, 6.09; N, 4.98; S, 11.39. Found: C, 57.70; H, 6.10; N, 4.92; S, 11.40.

trans-5-(2-Dimethylaminoethyl)-3-ethoxycarbonyl-2-(3-thienyl)-2,3-dihydro[1,5]benzothiazepin-4(5*H*)-one **20** (Oxalate).

Compound **8** 4.50 g (0.0135 mole), 3-dimethylaminoethyl chloride hydrochloride 2.88 g (0.020 mole) and powdered sodium carbonate 6.36 g (0.06 mole) was refluxed in acetone (150 ml) and water (1.5 ml) for 20 hours to give **14**, an oil (3.20 g, 59%) (Tables 1 and 2). The oil **14** (0.0079 mole) was dissolved in acetone and converted to the oxalate salt **20** (ethanol), mp 116°, 2.7 g (69%); ir (potassium bromide): ν cm^{-1} 3440 (OH), 2670 (NH^+), 1700, 1660, 1620 (CO); ^1H nmr (DMSO-d_6): δ 4.90 (2H, s, $(CO_2H)_2$), 8.06, 7.46 (7H, m, ArH), 4.26 (3H, q, CH_2-CH_3, d, C_2-H), 3.10 (5H, m, $(CH_2)_2$, C_3-H), 2.63 (6H, s, $(CH_3)_2$), 1.26 (3H, s, CH_2-CH_3).

Anal. Calcd. for $C_{22}H_{26}N_2O_7S_2$: C, 53.42; H, 5.30; H, 5.30; N, 5.66; S, 12.96. Found: C, 53.40; H, 5.35; N, 5.72; S, 12.98.

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