Studies on the Chemistry of Thieno-anellated *O,N*- and *S,N*-containing Heterocycles. 2 [1]. Synthesis of Thieno[2,3-*b*]diazepine Derivatives with Potential CNS Activity

Thomas Erker

Institute of Pharmaceutical Chemistry, University of Vienna,
A-1090 Vienna, Währinger Straße 10, Austria

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Thieno-anellated compounds analogous to Clobazam (**1**) [2] and the nootropic drugs **2** and **3** [3] were synthesized. Thus, nucleophilic substitution on halogenated nitrothiophene derivatives with aniline and reaction with ethyl malonyl chloride gave after cyclisation the thieno[2,3-*b*]diazepinedione derivatives **7** and **14**. These compounds were methylated to give the thieno-anellated heterocycles **8** and **9**.

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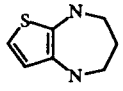
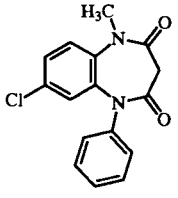
Compounds with the structure as shown below have not been described previously.

Scheme 1

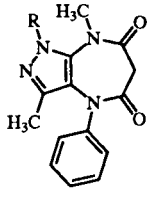


The reason to study thieno[2,3-*b*]diazepine derivatives was their structural relationship with the tranquilizer Clobazam (**1**) and the nootropic and anxiolytic active compounds **2** and **3**, respectively.

Scheme 2



1



2, R = H
3, R = CH_3

Because of the bioisosterity of the two rings, a replacement of the benzene nucleus by a thiophene ring should provide pharmacologically active compounds. Bioisosterity of pyrazole and thiophene might be confirmed by testing these compounds analogously to **2** and **3**, respectively, for nootropic activity.

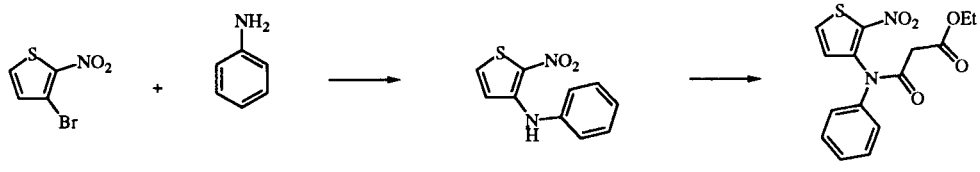
3-Bromo-2-nitrothiophene [4] was selected as the starting material and was reacted with aniline in di-*n*-butyl ether as the solvent, to give compound **4**.

The anilide **5** was obtained after reaction of **4** with ethyl malonyl chloride.

As a next step, the nitro group was to be reduced to the corresponding amine. Since the intermediate amine **6** was not supposed to remain stable, it was cyclised directly without isolation. Catalytic hydrogenation only worked with a molar amount of 10% Pd/C, thus iron powder suspended in glacial acetic acid at 70° was used as the reducing agent. The formation of compound **6** and subsequently of compound **7** was monitored *via* tlc.

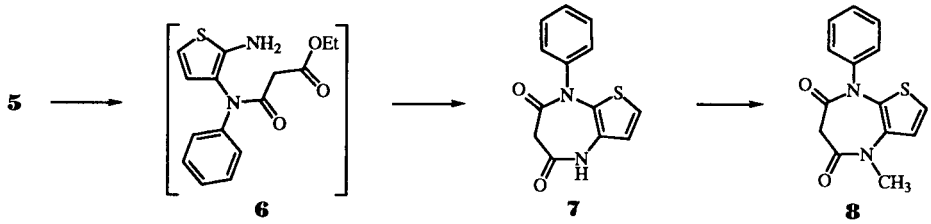
After 24 hours reprocessing led to compound **7** in 55% yield. As in all other cases, structural identification of the isolated product was carried out by ^{1}H nmr, mass spectra

Scheme 3



4 **5**

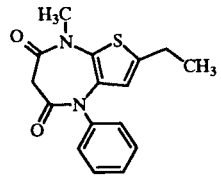
Scheme 4



5 **6** **7** **8**

data and elemental analyses, respectively. For compound **7** the ir-spectrum indicated absorption for the two lactam functions at 1666 cm^{-1} and 1695 cm^{-1}. Compound **8** was obtained by methylation of **7** with iodomethane under phase transfer conditions [5]. Compound **9** was synthesized in a similar way to **8**. The structural changes between **8** and **9** refer to the substitution pattern. The methyl and the phenyl group have been interchanged.

Scheme 5



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Furthermore, the ethyl group in position 2 was chosen as the structural element, because in a variety of drugs containing a thiophene ring biologically activity is increased when an alkyl group is introduced next to sulfur on the aromatic nucleus.

5-Acetyl-2-chloro-3-nitrothiophene [6] was used as starting material. Nucleophilic substitution of the chlorine atom with aniline and subsequent reaction of **11** with ethyl malonate chloride in benzene resulted in compound **12**. The acetyl group was then reduced with triethylsilane/trifluoroacetic acid [7] to yield the corresponding ethyl derivative **13**. Reduction of the nitro group and subsequent cyclisation reaction as previously described led to compound **14**, which was then methylated [5] to compound **9**.

As in compound **7**, the ir absorption maxima of the two lactam groups in compound **9** occur at 1666 cm^{-1} and 1695 cm^{-1}, respectively. The methylene signal in the nmr spectrum shows up at 3.60 ppm. In all cases, there is no evidence for enolisation of the lactam carbonyl double bond.

The pharmacological properties of the synthesized compounds will be described elsewhere.

EXPERIMENTAL

All melting points were measured with a Kofler hot-stage apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu gc/ms qp 1000 instrument, nmr spectra on a Bruker AC 80 spectrometer (80 MHz), ir spectra were obtained on a Jasko IRA-1 instrument.

Ethyl 3-[*N*-(2-Nitro-3-thienyl)phenylamino)]-3-oxopropionate (**5**).

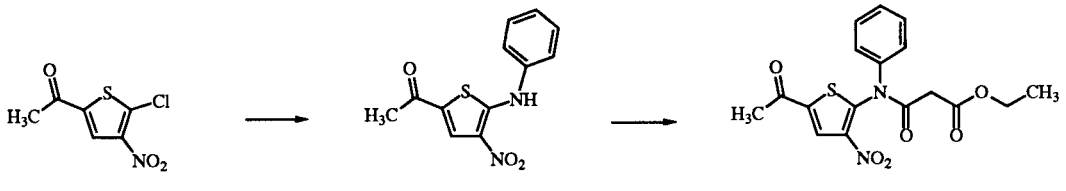
To a mixture of 2.20 g (10 mmoles) of **4** [8] in 50 ml of dry benzene 2.41 g (16 mmoles) of ethyl malonyl chloride was added and the solution was heated under reflux for 30 hours. After evaporation of the solvent the residue was recrystallized from ethanol to give 2.17 g (65%) of **5** as yellow crystals, mp 142-145°; ms: m/z 334 (M^+, 8%), 288 ($M^+ - NO_2$, 46%), 243 ($M^+ - NO_2 - OC_2H_5$, 20%), 220 ($M^+ - C_5H_7O_3$ + H, 100%); ^1H nmr (deuteriochloroform): δ 7.48-7.31 (m, 6H, ArH), 6.88 (AB-system, 1H, J_{AB} = 5.5 Hz, thiophene H), 4.17 (q, 2H, J = 7.3 Hz, OCH_2), 3.44 (s, 2H, CH_2), 1.26 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O_5S$: C, 53.89; H, 4.22; N, 8.38. Found: C, 53.80; H, 4.03; N, 8.22.

4,8-Dihydro-8-phenyl-5*H*-thieno[2,3-*b*][1,4]diazepin-5,7(6*H*)-dione (**7**).

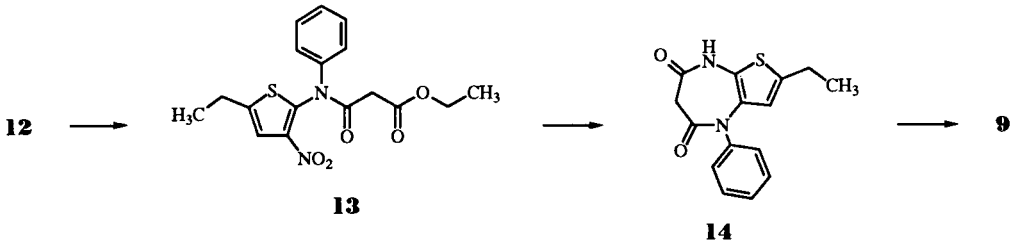
To a solution of 3.34 g (10 mmoles) of **5** in 100 ml of glacial acetic acid at 70° 3.9 g of iron powder was added in small portions. After 24 hours the suspension was filtered and the filtrate

Scheme 6



10 **11** **12**

Scheme 7



13 **14**

evaporated. The residue was partitioned between dichloromethane and 5% sodium hydrogen carbonate. The organic layer was washed with water, dried with sodium sulfate, filtered and evaporated. The crude product was recrystallized with ethanol to give 1.25 g (55%) of **7** as brown needles, mp 237-240°; ms: m/z 258 (M^+, 100%), 189 (M^+ -$(CO)_2CH$, 71%); ^1H nmr (deuteriochloroform): δ 9.21 (s-broad, 1H, NH), 7.51-7.17 (m, 5H, ArH), 6.88 (AB-system, 1H, J_{AB} = 5.8 Hz, thiophene H), 6.36 (AB-system, 1H, J_{AB} = 5.8 Hz, thiophene H), 3.63 (s, 2H, CH_2).

Anal. Calcd. for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.35; H, 3.88; N, 10.83.

4,8-Dihydro-4-methyl-8-phenyl-5*H*-thieno[2,3-*b*][1,4]diazepin-5,7(6*H*)-dione (**8**).

To a stirred solution of 2.58 g (10 mmoles) of **7** in 25 ml of toluene 0.39 g (1.7 mmoles) of benzyl triethylammonium chloride and 2.00 g (50 mmoles) sodium hydroxide in 2 ml of water was added. After 30 minutes 1.64 g (13 mmoles) dimethyl sulfate was added and the suspension was stirred for 2 hours. The solvent was evaporated to give a residue, which was partitioned between dichloromethane and water. The organic layer was washed with water, dried with sodium sulfate, filtered and evaporated. The crude product was purified on silica gel column eluting with ethyl acetate-toluene (6:4) to give 1.42 g (52%) of **8** as dark yellow crystals, mp 121-124°; ms: m/z 272 (M^+, 100%), 203 (M^+ -$C_3H_2O_2$ + H, 46%), 77 ($Phenyl^+$, 53%); ^1H nmr (deuteriochloroform): δ 7.43-7.19 (m, 5H, ArH), 6.96 (AB-system, 1H, J_{AB} = 6.4 Hz, thiophene H), 6.38 (AB-system, 1H, J_{AB} = 6.4 Hz, thiophene H), 3.61 (s, 2H, CH_2), 3.52 (s, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.62; H, 4.38; N, 10.18.

Ethyl 3-[*N*-(5-Acetyl-3-nitro-2-thienyl)phenylamino]-3-oxopropionate (**12**).

To a mixture of 2.62 g (10 mmoles) of **11** [1] in 50 ml of dry benzene 2.41 g (16 mmoles) of ethyl malonyl chloride was added and the solution was heated for 30 hours under reflux. After evaporation of the solvent the residue was recrystallized from ethanol to give 2.71 g (72%) of **12** as yellow crystals, mp 103-106°; ms: m/z 376 (M^+, 3%), 262 (M^+ -$C_5H_7O_3$ + H, 100%); ^1H nmr (deuteriochloroform): δ 7.96 (s, 1H, thiophene H), 7.48 (s, 5H, ArH), 4.17 (q, 2H, J = 7.1 Hz, OCH_2), 3.38 (s, 2H, CH_2), 2.48 (s, 3H, acetyl-H), 1.27 (t, 2H, J = 7.1 Hz, CH_3).

Anal. Calcd. for $C_{17}H_{16}N_2O_6S$: C, 54.25; H, 4.28; N, 7.44. Found: C, 54.15; H, 4.26; N, 7.32.

Ethyl 3-[*N*-(-5 Ethyl-3-nitro-2-thienyl)phenylamino]-3-oxopropionate (**13**).

To a mixture of 3.76 g (10 mmoles) of **12** in 15 ml of trifluoroacetic acid 2.90 g (25 mmoles) of triethylsilane was added dropwise. After stirring at 50° for 16 hours the solution was neutralized with saturated sodium hydrogen carbonate solution under ice cooling. After extraction with ethyl acetate the organic layer was dried with sodium sulfate and evaporated. The residue was purified on silica gel column eluting with toluene-ethyl acetate (8:2) to give 3.12 g (86%) of **13** as an oil; ms: m/z 362 (M^+, 33%), 361 (M^+ -H, 100%), 248 (M^+ -$C_5H_7O_3$ + H, 49%), 229 (82%); ^1H nmr (deuteriochloroform): δ 7.62-7.24 (m, 6H, ArH, thiophene H), 4.16 (q, 2H, J = 7.0 Hz, OCH_2), 3.44 (s, 2H, CH_2), 2.71 (q, 2H, J = 7.8 Hz, CH_2), 1.42-1.10 (m, 6H, 2 CH_3).

Anal. Calcd. for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.18; H, 4.93; N, 7.49.

2-Ethyl-4,8-dihydro-4-phenyl-5*H*-thieno[2,3-*b*][1,4]diazepin-5,7-(6*H*)-dione (**14**).

To a solution of 3.62 g (10 mmoles) of **13** in 100 ml of glacial acetic acid at 70° 3.9 g of iron powder was added in small portions. After 24 hours the suspension was filtered and the filtrate evaporated. The residue was partitioned between dichloromethane and 5% sodium hydrogen carbonate. The organic layer was washed with water, dried with sodium sulfate, filtered and evaporated. The crude product was purified on silica gel column eluting with ethyl acetate to give 1.48 g (58%) of **14** as dark yellow crystals, mp 275-276°; ms: m/z 286 (M^+, 100%), 217 (M^+ -$C_3H_2O_3$ + H, 78%); ^1H nmr (deuteriochloroform/d_6-DMSO): δ 10.45 (s-broad, exchangeable, 1H, NH), 7.41-7.13 (m, 5H, ArH), 6.46 (s, 1H, thiophene H), 3.49 (s, 2H, CH_2), 3.25 (s, 3H, CH_3), 2.56 (q, 2H, J = 8.0 Hz, CH_2), 1.19 (t, 3H, J = 8.0 Hz, CH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 62.78; H, 4.87; N, 9.69.

2-Ethyl-4,8-dihydro-8-methyl-4-phenyl-5*H*-thieno[2,3-*b*][1,4]diazepin-5,7(6*H*)-dione (**9**).

To a stirred solution of 2.86 g (10 mmoles) of **14** in 25 ml of toluene 0.39 g (1.7 mmoles) of benzyl triethylammonium chloride and 2.00 g (50 mmoles) of sodium hydroxide in 2 ml of water was added. After 30 minutes 1.64 g (13 mmoles) dimethyl sulfate was added. After 2 hours the solvent was evaporated to give a residue, which was partitioned between dichloromethane and water. The organic layer was washed with water, dried with sodium sulfate, filtered and evaporated. The crude product was purified on silica gel column eluting with ethyl acetate-toluene (6:4) to give 1.89 g (63%) of **9** as an oil; ms: m/z 300 (M^+, 100%), 257 (23%), 231 (M^+ -$(CO)_2CH_2$ + H, 71%); ^1H nmr (deuteriochloroform): δ 7.52-7.19 (m, 5H, ArH), 6.57 (s, 1H, thiophene H), 3.60 (s, 2H, CH_2), 3.41 (s, 3H, NCH_3), 2.70 (q, 2H, J = 7.4 Hz, CH_2), 1.24 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33. Found: C, 63.71; H, 5.29; N, 9.27.

Acknowledgement.

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