Studies on the Chemistry of Thienoanellated *O,N*- and *S,N*-containing Heterocycles. **3** [1]. Synthesis of Tricyclic Thieno[2,3-*b*][1,4]-thiazines *via* Nucleophilic Substitution of Activated Precursors

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Starting from thieno[2,3][1,4-*b*]thiazine **1** new synthetic pathways to the tricyclic compounds **5, 12, 13, 14, 20** and the tetracyclic ring system **19** are described. Under mild reaction conditions some intermediates can be isolated. Reaction of **8** with several amines leads to the amidines **15-18**.

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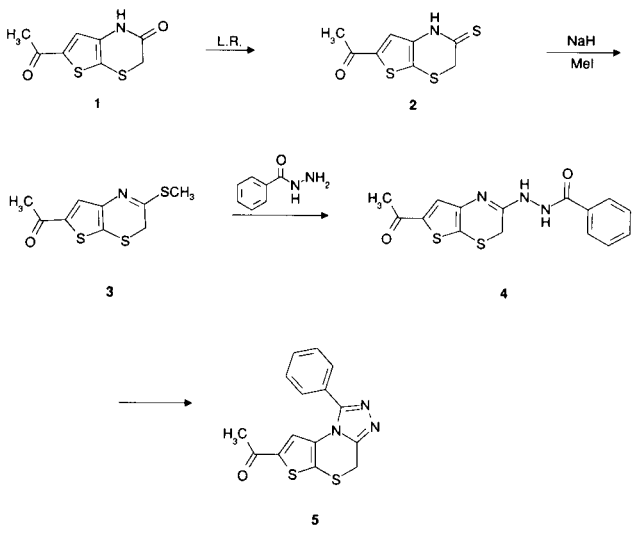
The 1,4-benzothiazine ring system is found in a great number of substances with pharmaceutical activity. For example they possess diuretic, natriuretic [2], skeletal muscle relaxing [3], anticholinergic, antiulcer [4], antihistaminic [5], antifungal and anti-inflammatory properties [6].

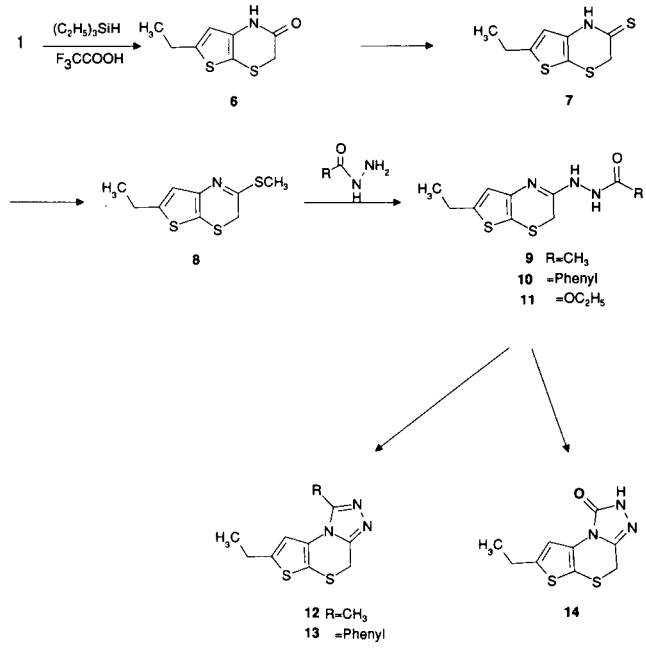
It is known from various drugs, that pharmacological activity may be maintained if benzene is exchanged by a thiophene ring [7].

Furthermore, it is known from 1,4-benzodiazepine derivatives, that their pharmacological profile is enhanced by attachment of a further heterocyclic ring.

In course of the studies concerning the synthesis of thienoanellated thiazines, it should be attempted to link both principles *via* attachment of a triazolo or an oxadiazolo ring to thieno[2,3-*b*][1,4]thiazines, respectively.

Compound **1**, obtained as published in the first part of this series [8], was activated with Lawesson reagent to give the thiolactam **2**. Reaction with a carbohydrazide was supposed to lead to the *N*-substituted hydrazide **4**, which should consequently be cyclized to the corresponding triazolo derivative **5**. However, tentative investigations revealed that due to the required high reaction temperature





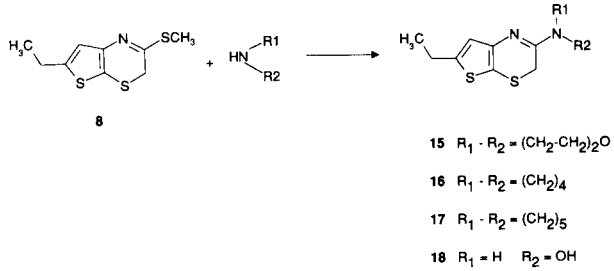
an one-step formation of the triazolo-thieno-thiazine derivate took place, and in consequence, isolation of the intermediate **4** was impossible.

Since we were interested in the hydrazide, further activation of the thiolactam into the methyl thiolactim **3** should facilitate nucleophilic attack and provide migitated reaction conditions. Compound **3** was obtained by reaction of **2** with sodium hydride and methyl iodide. Because of its high reactivity an ethanolic solution of **3** gave with benzhydrazide the expected derivate **4** at room temperture. In consequence, the hydrazide was cyclized to the tricyclic compound **5** in boiling toluene catalysed by glacial acetic acid.

It is known from a variety of drugs containing a thiophene ring, that the biological activity is increased if an alkyl group is introduced next to the sulfur at the aromatic nucleus [9]. Therefore, as a next step, the acetyl group in compound **1** should be reduced to the ethyl derivate **6**.

The desired ethyl derivate was obtained by reduction of

1 with triethylsilane/trifluoroacetic acid [10]. After conversion of the lactam **6** into the thiolactam **7** by Lawesson reagent further activation was done by reaction with sodium hydride and methyl iodide to yield **8**. With different hydrazides this compound gave the expected derivatives **9-11** at room temperature. After cyclisation as described above the triazolo-thieno-thiazines **12, 13** and **14** were obtained.



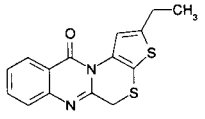
8

15 $R_1 \cdot R_2 = (CH_2{\cdot}CH_2)_2O$

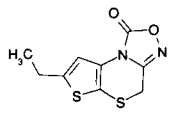
16 $R_1 \cdot R_2 = (CH_2)_4$

17 $R_1 \cdot R_2 = (CH_2)_5$

18 $R_1 = H \quad R_2 = OH$



19



20

Reaction of **8** with different amines at 50° afforded compounds **15-18**. Like in all other cases, structural identification of the isolated products were carried out by ^1H nmr, mass data and analytical data, respectively. Reaction of the amines with the thiolactame **7** also afforded the amidines. However, due to formation of decomposition products and the consequent tedious purification required, the yields were very low. Hence, it was preferred to synthesize compounds **15-18** by reaction of **8** with the corresponding bases (hydroxylamine as its hydrochloride).

Compound **19** was obtained by reaction of methyl anthranilate in an one-step procedure. The tricyclic oxadiazolo-thieno-thiazine derivate **20** featuring as well a new heterocycle was synthesized by reaction of **18** with *N,N'*-carbonyl diimidazole in dry tetrahydrofuran.

Some of the synthesized compounds will be tested. The pharmacological results will be published 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).

6-Acetyl-1*H*-thieno[2,3-*b*][1,4]thiazine-2(3*H*)-thione (**2**).

To a mixture of 2.13 g (10 mmoles) of **1** in 150 ml of dry tetrahydrofuran 2.02 g (5 mmoles) of Lawesson reagent was added and the solution was stirred for 1 hour. The solvent was removed under reduced pressure and the residue recrystallized from ethanol to give 1.48 g (65%) of **2**, mp 215-216°; ms: m/z 229 (M^+, 100%), 196 (M^+-SH, 88%), 43 (acetyl, 38%); ^1H nmr (deuteriochloroform, dimethyl sulfoxide-d_6): δ 10.23 (s-broad, exchangeable, 1H, NH), 7.40 (s, 1H, thiophene H), 3.95 (s, 2H, CH_2), 2.49 (s, 3H, CH_3).

Anal. Calcd. for $C_8H_7NOS_3$: C, 41.90; H, 3.08; N, 6.11. Found: C, 41.88; H, 2.97; N, 5.92.

6-Acetyl-2-methylthio-3*H*-thieno[2,3-*b*][1,4]thiazine (**3**).

To a mixture of 2.29 g (10 mmoles) of **2** in 30 ml of dry tetrahydrofuran 0.30 g of sodium hydride and after 10 minutes 1.25 ml of methyl iodide were added and stirred for 0.5 hour. The solvent was evaporated and the residue recrystallized from diluted ethanol to give 1.73 g (71%) of **3**, mp 92-93° ms: m/z 243 (M^+, 100%), 196 (M^+-SCH_3, 76%), 43 (acetyl, 63%); ^1H nmr (deuteriochloroform): δ 7.59 (s, 1H, thiophene H), 3.38 (s, 2H, CH_2), 2.54 (s, 3H, CO-CH_3), 2.52 (s, 3H, SCH_3).

Anal. Calcd. for $C_9H_9NOS_3$: C, 44.42; H, 3.73; N, 5.76. Found: C, 44.65; H, 3.73; N, 5.59.

N'-(6-Acetyl-3*H*-thieno[2,3-*b*][1,4]thiazin-2-yl)benzohydrazide (**4**).

To a mixture of 2.43 g (10 mmoles) of **3** in 30 ml of dry ethanol 2.72 g (20 mmoles) of benzohydrazide was added and stirred at room temperature for 48 hours. After cooling the precipitate was collected and recrystallized from ethanol to give 2.93 g (89%) of **4**, mp 217°; ms: m/z 331 (M^+, 100%), 211 (M^+-$HNCOC_6H_5$, 53%); ^1H nmr (deuteriochloroform, 4 drops trifluoroacetic acid): δ 8.23-7.18 (m, 7H, phenyl H, NH), 6.84 (s, 1H, thiophene H), 4.18 (s, 2H, SCH_2), 2.43 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{13}N_3O_2S_2$: C, 54.36; H, 3.95; N, 12.68. Found: C, 54.13; H, 3.99; N, 12.39.

7-Acetyl-1-phenyl-4*H*-thieno[2,3-*b*][1,2,4]triazolo[4,3-*d*][1,4]thiazine (**5**).

A mixture of 3.31 g (10 mmoles) of **4**, 200 ml of toluene and 1 ml of glacial acetic acid was refluxed for 8 hours. After cooling the solvent was evaporated and the residue partitioned between dichloromethane and water. The organic layer was separated, dried and concentrated *in vacuo*. The crude product was purified on a silica gel column eluting with toluene-ethyl acetate (8 + 2) to give 2.62 g (84%) of **5**, mp 264-267°; ms: m/z 313 (M^+, 88%), 284 (100%), 43 (acetyl, 51%); ^1H nmr (deuteriochloroform): δ 7.58 (s, 5H, phenyl H), 6.98 (s, 1H, thiophene H), 4.31 (s, 2H, SCH_2), 2.26 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{11}N_3OS_2$: C, 57.49; H, 3.54; N, 13.41. Found: C, 57.59; H, 3.62; N, 13.03.

6-Ethyl-1*H*-thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one (**6**).

To a mixture of 2.13 g (10 mmoles) of **1** in 15 ml of trifluoroacetic acid 2.90 g (25 mmoles) of triethylsilane was added dropwise. After stirring at room temperature for 20 hours the solution was neutralized with saturated sodium hydrogen carbonate solution with ice cooling. The precipitate was collected, washed with water and recrystallized from ethanol to give 1.85 g (93%) of **6**, mp 154-155°; ms: m/z 199 (M^+, 100%), 184 (M^+-CH_3, 73%); ^1H nmr (deuteriochloroform): δ 8.85 (s-broad, exchangable, 1H, NH), 6.44 (s, 1H, thiophene H), 3.49 (s, 2H, SCH_2), 2.75 (q, 2H, J = 7.4 Hz, CH_2), 1.27 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_8H_9NOS_2$: C, 48.22; H, 4.55; N, 7.03. Found: C, 47.94; H, 4.39; N, 6.86.

6-Ethyl-1*H*-thieno[2,3-*b*][1,4]thiazine-2(3*H*)-thione (**7**).

To a mixture of 1.99 g (10 mmoles) of **6** in 150 ml of dry tetrahydrofurane 2.02 g (5 mmoles) of Lawesson reagent was added and the solution was stirred for 1 hour. The solvent was evaporated and the residue recrystallized from ethanol to give 1.94 g (90%) of **7**, mp 155-157°; ms: m/z 215 (M^+, 100%), 182 (M^+-SH, 90%); ^{1}H nmr (deuteriochloroform): δ 10.05 (s-broad, exchangeable, 1H, NH), 6.49 (s, 1H, thiophene H), 3.92 (s, 2H, SCH_2), 2.76 (q, 2H, J = 7.3 Hz, CH_2), 1.27 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_8H_9NS_3$: C, 44.62; H, 4.21; N, 6.50. Found: C, 44.36; H, 3.94; N, 6.27.

6-Ethyl-2-methylthio-3*H*-thieno[2,3-*b*][1,4]thiazine (**8**).

To a mixture of 2.15 g (10 mmoles) of **7** in 30 ml of dry tetrahydrofurane 0.30 g of sodium hydride and after 10 minutes 1.25 ml of methyl iodide were added and stirred for 0.5 hour. The solvent was evaporated and the residue purified on silica gel column eluting with toluene-ethyl acetate (8 + 2) to give 1.81 g (79%) of **8** as an oil; ms: m/z 229 (M^+, 100%), 182 (M^+-SCH_3, 95%); ^{1}H nmr (deuteriochloroform): δ 6.77 (s, 1H, thiophene H), 3.31 (s, 2H, SCH_2), 2.77 (q, 2H, J = 7.4 Hz, CH_2), 2.52 (s, 3H, SCH_3), 1.28 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_9H_{11}NS_3$: C, 47.13; H, 4.83; N, 6.11. Found: C, 46.91; H, 4.72; N, 5.86.

N-(6-Ethyl-3*H*-thieno[2,3-*b*][1,4]thiazin-2-yl)acetohydrazide (**9**).

To a mixture of 2.29 g (10 mmoles) of **8** in 30 ml of dry ethanol, 0.92 g (20 mmoles) of acetohydrazide was added and stirred at room temperature for 72 hours. After cooling the precipitate was collected and recrystallized from ethanol to give 2.03 g (80%) of **9**, mp 180°; ms: m/z 255 (M^+, 100%), 197 (M^+-$NHCOCH_3$, 68%); ^{1}H nmr (deuteriochloroform, 4 drops trifluoroacetic acid): δ 9.79 (s-broad, exchangeable, 2H, NH), 6.75 (s, 1H, thiophene H), 4.25 (s, 2H, SCH_2), 2.88 (q, 2H, J = 7.4 Hz, CH_2), 2.68 (s, 3H, CH_3CO), 1.26 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_{10}H_{13}N_3OS_2$: C, 47.04; H, 5.13; N, 16.46. Found: C, 47.18; H, 4.90; N, 16.18.

N'-(6-Ethyl-3*H*-thieno[2,3-*b*][1,4]thiazin-2-yl)benzohydrazide (**10**).

Compound **10** was synthesized analogously to compound **9**. The crude product was recrystallized from diluted ethanol to give 2.09 g (66%) of **10**, mp 198°; ms: m/z 317 (M^+, 63%), 197 (M^+-C_6H_5CONH, 35%), 105 ($C_6H_5CON_2$, 100%), 77 (C_6H_5CO, 71%); ^{1}H nmr (deuteriochloroform, 5 drops trifluoroacetic acid): δ 8.06-7.57 (m, 7H, phenyl H, NH), 6.81 (s, 1H, thiophene H), 4.02 (s, 2H, SCH_2), 2.78 (q, 2H, J = 7.4 Hz, CH_2), 1.23 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_{15}H_{15}N_3OS_2$: C, 56.76; H, 4.76; N, 13.24. Found: C, 56.51; H, 4.63; N, 13.02.

Ethyl-2-(6-Ethyl-3*H*-thieno[2,3-*b*][1,4]thiazin-2-yl)hydrazinecarboxylate (**11**).

Compound **11** was synthesized analogously to compound **9**. The crude product was recrystallized from ethanol to give 1.92 g (67%) of **11**, mp 172-173°; ms: m/z 285 (M^+, 77%), 240 (M^+-C_2H_5O, 12%), 224 (100%), 197 (M^+-C_2H_5CONH, 75%); ^{1}H nmr (deuteriochloroform): δ 9.12 (s-broad, exchangeable, 1H, NH), 8.68 (s-broad, exchangeable, 1H, NH), 6.39 (s, 1H, thiophene H), 4.26 (q, 2H, J = 7.5 Hz, OCH_2), 3.56 (s, 2H, SCH_2), 2.72 (q, 2H, J = 7.3 Hz, CH_2), 1.32 (t, 3H, J = 7.5 Hz, CH_3), 1.24 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_{11}H_{15}N_3O_2S_2$: C, 46.30; H, 5.30; N, 14.72. Found: C, 46.50; H, 5.05; N, 14.67.

7-Ethyl-1-methyl-4*H*-thieno[2,3-*b*][1,2,4]triazolo[4,3-*d*][1,4]thiazine (**12**).

A mixture of 2.85 g (10 mmoles) of **9**, 200 ml of toluene and 1 ml of glacial acetic acid was refluxed for 3 hours. After cooling the solvent was evaporated and the residue partitioned between dichloromethane and water. The organic layer was separated, dried and concentrated *in vacuo*. The crude product was purified by recrystallization from ethanol to give 1.89 g (80%) of **12**, mp 146°; ms: m/z 237 (M^+, 100%), 208 (M^+-C_2H_5, 92%); ^{1}H nmr (deuteriochloroform): δ 6.96 (s, 1H, thiophene H), 4.14 (s, 2H, SCH_2), 2.86 (q, 2H, J = 7.3 Hz, CH_2), 2.67 (s, 3H, CH_3), 1.34 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_{10}H_{11}N_3S_2$: C, 50.61; H, 4.67; N, 17.70. Found: C, 50.87; H, 4.50; N, 17.41.

7-Ethyl-1-phenyl-4*H*-thieno[2,3-*b*][1,2,4]triazolo[4,3-*d*][1,4]thiazine (**13**).

Compound **13** was synthesized analogously to compound **12**. After recrystallization from ethanol 1.93 g (65%) of **13** was obtained, mp 148°; ms: m/z 299 (M^+, 65%), 279 (100%), 181 (44%); ^{1}H nmr (deuteriochloroform): δ 7.65-7.34 (m, 5H, phenyl H), 6.23 (s, 1H, thiophene H), 4.21 (s, 2H, SCH_2), 2.60 (q, 2H, J = 7.4 Hz, CH_2), 1.57 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_{15}H_{13}N_3S_2$: C, 60.17; H, 4.38; N, 14.03. Found: C, 60.42; H, 4.38; N, 13.73.

7-Ethyl-2,4-dihydro-1*H*-thieno[2,3-*b*][1,2,4]triazolo[4,3-*d*][1,4]thiazin-1-one (**14**).

Compound **14** was synthesized analogously to compound **12**. After recrystallization from ethanol 1.87 g (78%) of **14** was obtained, mp 189°; ms: m/z 239 (M^+, 75%), 244 (M^+-CH_3, 100%); ^{1}H nmr (dimethyl sulfoxide-d_6): δ 12.03 (s-broad, exchangeable, 1H, NH), 7.47 (s, 1H, thiophene H), 4.15 (s, 2H, SCH_2), 2.88 (q, 2H, J = 7.5 Hz, CH_2), 1.27 (t, 3H, J = 7.5 Hz, CH_3).

Anal. Calcd. for $C_9H_9N_3OS_2$: C, 45.17; H, 3.79; N, 17.56. Found: C, 45.23; H, 3.69; N, 17.28.

General Procedure for the Formation of the Amidines **15-18**.

To **8** (2.29 g, 10 mmoles) the corresponding amine was added. After heating the mixture for 38 hours at 60° the excess of the amine was removed under reduced pressure. The residue was taken up in dichloromethane, washed with water, dried over sodium sulfate, filtered and evaporated. The crude product was purified by column chromatography or recrystallization, respectively.

6-Ethyl-2-(4-morpholinyl)-3*H*-thieno[2,3-*b*][1,4]thiazine (**15**).

The crude, pale yellow oil was purified by column chromatography (toluene/ethyl acetate/triethylamine 6 + 3 + 1) to give 1.31 (49%) of **15**; ms: m/z 268 (M^+, 82%), 182 (M^+-$N(CH_2CH_2)_2O$, 40%), 86 (morpholinyl, 55%); ^{1}H nmr (deuteriochloroform): δ 6.64 (s, 1H, thiophene H), 3.83-3.60 (m, 4H, H_2COCH_2), 3.60-3.47 (m, 4H, H_2CNCH_2), 3.29 (s, 2H, SCH_2), 2.77 (q, 2H, J = 7.4 Hz, CH_2), 1.25 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{16}N_2OS_2$: C, 53.70; H, 6.01; N, 10.44. Found: C, 53.58; H, 5.88; N, 10.23.

6-Ethyl-2-(1-pyrrolidinyl)-3*H*-thieno[2,3-*b*][1,4]thiazine (**16**).

The crude, yellow oil was purified by column chromatography (toluene/ethyl acetate/triethylamine 6 + 3 + 1) to give 1.68 g (67%) of **16**; ms: m/z 252 (M^+, 100%), 168 (M^+-$NHN(CH_2)_4$, 74%); ^1H nmr (deuteriochloroform): δ 6.67 (s, 1H, thiophene H), 3.74-3.44 (m, 4H, CH_2NCH_2), 3.33 (s, 2H, SCH_2), 2.74 (q, 2H, J = 7.4 Hz, CH_2), 2.05-1.88 (m, 2H, CH_2CH_2), 1.26 (t, 3H, J = 7.4 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{16}N_2S_2$: C, 57.11; H, 6.39; N, 11.10. Found: C, 56.93; H, 6.32; N, 10.98.

6-Ethyl-2-(1-piperidinyl)-3*H*-thieno[2,3-*b*][1,4]thiazine (**17**).

The crude oil was purified by column chromatography (toluene/ethyl acetate/triethylamine 6 + 3 + 1) to give 1.90 g (71%) of **17**; ms: m/z 266 (M^+, 35%), 182 (M^+-$N(CH_2)_5$, 98%), 84 (piperidinyl$^+$, 100%); ^1H nmr (deuteriochloroform): δ 6.65 (s, 1H, thiophene H), 3.59-3.53 (m, 4H, $N(CH_2)_2$), 3.30 (s, 2H, SCH_2), 2.68 (q, 2H, J = 7.3 Hz, CH_2), 1.58-1.36 (m, 6H, $(CH_2)_3$), 1.26 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{18}N_2S_2$: C, 58.61; H, 6.81; N, 10.51. Found: C, 58.43; H, 6.78; N, 10.40.

N-(6-Ethyl-3*H*-thieno[2,3-*b*][1,4]thiazin-2-yl)hydroxylamine (**18**).

The crude product was recrystallized from ethanol to give 1.63 g (76%) of **18**, mp 168°; ms: m/z 214 (M^+, 67%), 181 (M^+-NH_2OH, 100%); ^1H nmr (deuteriochloroform): δ 11.55 (s-broad, exchangeable, 1H, NH), 9.05 (s-broad, exchangeable, 1H, OH), 6.68 (s, 1H, thiophene H), 3.80 (s, 2H, SCH_2), 2.77 (q, 2H, J = 7.3 Hz, CH_2), 1.28 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_8H_{10}N_2OS_2$: C, 44.84; H, 4.70; N, 13.07. Found: C, 44.79; H, 4.52; N, 12.89.

2-Ethylthieno[3',2':5,6][1,4]thiazino[3,4-*b*]quinazolin-11(5*H*)-one (**19**).

A mixture of 2.29 g (10 mmoles) of **8** and 3.02 g (20 mmoles) of methyl anthranilate in 20 ml of dry ethanol was refluxed for 24 hours. After cooling the precipitate was filtered off and recrystallized from ethanol to give 1.86 g (62%) of **19**, mp 186-188°; ms: m/z 300 (M^+, 93%), 285 (M^+-CH_3, 100%); ^1H nmr (deuteriochloroform): δ 7.78-7.48 (m, 5H, aromat H), 4.00 (s, 2H, SCH_2), 2.77 (q, 2H, J = 7.3 Hz, CH_2), 1.28 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_{15}H_{12}N_2OS_2$: C, 59.88; H, 4.03; N, 9.33. Found: C, 59.77; H, 4.14; N, 9.04.

7-Ethyl-1*H*,4*H*-[1,2,4]oxadiazolo[4,3-*d*]thieno[2,3-*b*][1,4]thiazin-1-one (**20**).

To a mixture of 2.14 g (10 mmoles) of **18** in 30 ml of dry tetrahydrofurane 1.78 g (11 mmoles) of *N,N'*-carbonyldiimidazole was added. After refluxing for 7 hours the solvent was removed under reduced pressure. The residue was taken up in dichloromethane, washed with water, dried over sodium sulfate, filtered and evaporated. The crude product was recrystallized from ethanol to give 1.73 g (72%) of **20**, mp 151-152°; ms: m/z 240 (M^+, 40%), 181 (M^+-CO_2N, 100%), ^1H nmr (deuteriochloroform): δ 7.34 (s, 1H, thiophene H), 4.01 (s, 2H, SCH_2), 2.77 (q, 2H, J = 7.3 Hz, CH_2), 1.29 (t, 3H, J = 7.3 Hz, CH_3).

Anal. Calcd. for $C_9H_8N_2O_2S_2$: C, 44.99; H, 3.36; N, 11.66. Found: C, 45.27; H, 3.02; N, 11.59.

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