Studies on the Chemistry of Thienoannelated *O,N*- and *S,N*-Containing Heterocycles. **16** [1]. Synthesis of Some Thieno[1,4]thiazine Derivatives with Potential Calcium Antagonistic Activity

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Substituted thieno[1,4]thiazine derivatives have been synthesized. They are thienoanalogues of compound **3** [2], a potent cerebral protectant and calcium antagonist. Research activities concentrate on the preparation of structurally modified compounds of **3** to minimize its undesirable symptoms.

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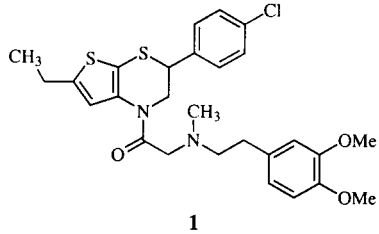

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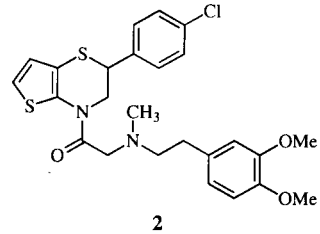

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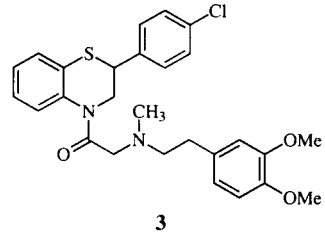

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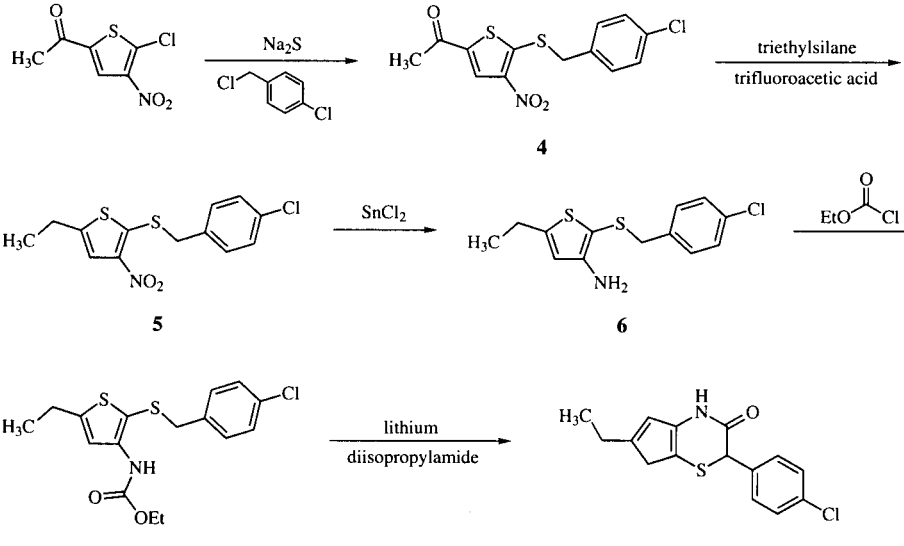
In continuation of the studies concerning thienoannelated thiazines with calcium antagonistic activity here the synthesis of compounds **1** and **2** is described. These substances are thienoanalogues of the benzothiazine derivative **3** [2], which is a cerebral protectant and a calcium antagonist. The minor modification of the ring structure obtained through replacing the benzene by a thiophene residue permits us to anticipate that while basic properties of compound **3** will be



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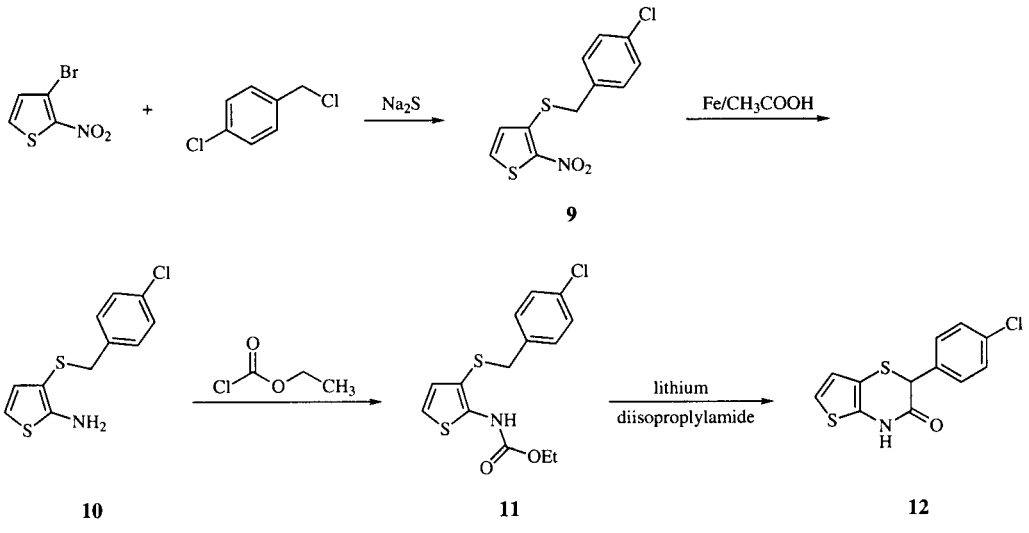
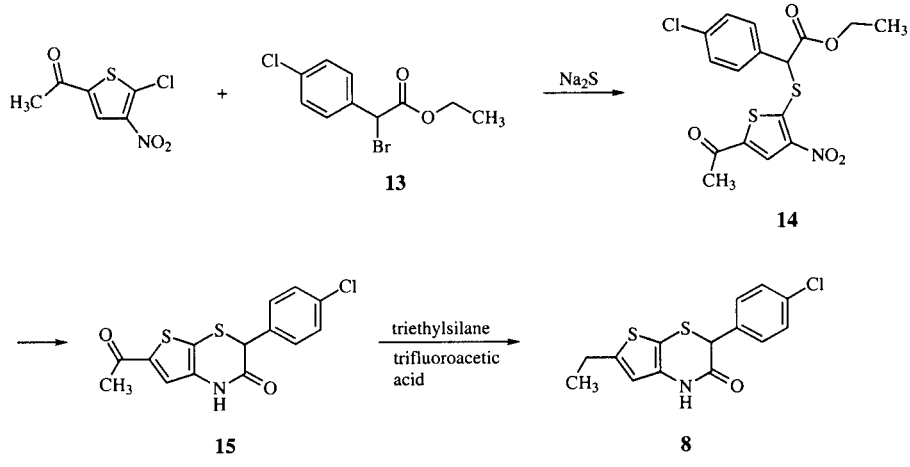


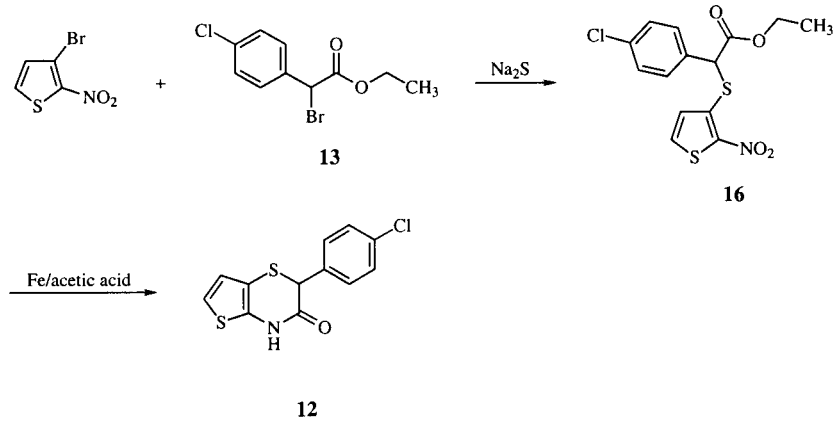
preserved, subtle changes might result, particularly with respect to an improved pharmacological profile.

the compounds **1** and **2**, respectively. Reaction of 5-acetyl-2-chloro-3-nitrothiophene [3] with 4-chlorobenzyl chlo-



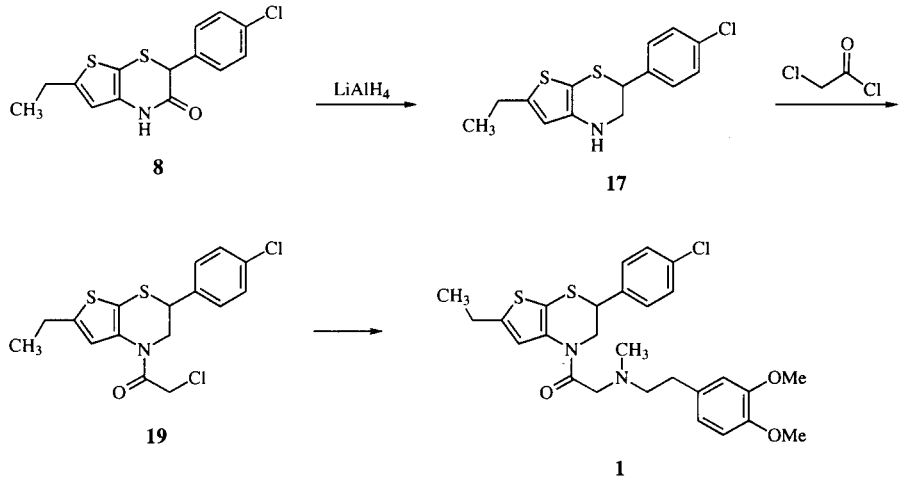
Thus it has been interesting to find a route to sythesize compounds **8** and **12**, which are the starting marterials for

ride in presence of sodium sulphide afforded the thioether **4**. It is known from a varity of drugs containing a thio-

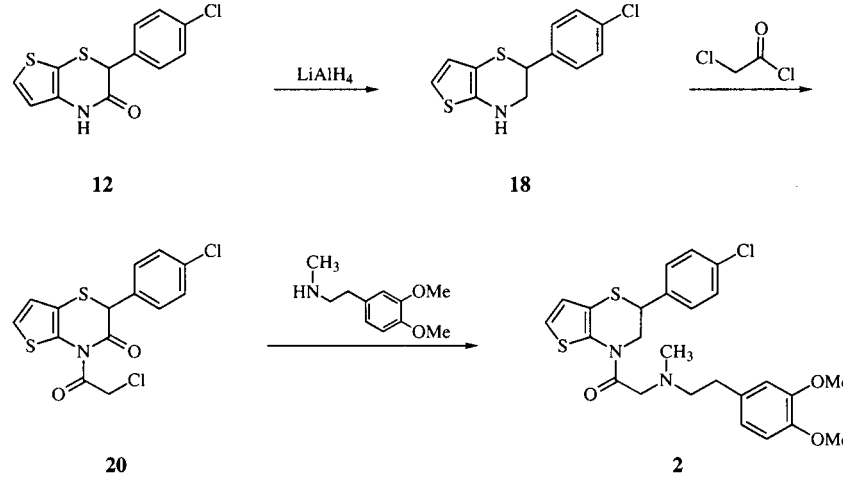


phene ring, that the biological activity is increased if an alkyl group is introduced next to the sulfur at the aromatic nucleus. Therefore, as a next step, the acetyl group should be reduced in compound **4** to an ethyl substituent. The derivative **5** was obtained by reduction of **4** with triethylsilane/trifluoroacetic acid [4]. The catalytic hydrogenation of the nitro group was only completed after applying a molar amount of 10% palladium on carbon. Therefore, tin(II) chloride in boiling ethanol was used as a reducing agent to give compound **6**. Reaction of the amine with ethyl chloroformate yielded substance **7**. When the amide **7** was treated with lithium diisopropylamide in tetrahydrofurane at -78° the desired thieno[2,3-*b*][1,4]thiazinone **8** was obtained in a poor yield of 2%. Variation of the reaction conditions (temperature and solvent) did not improve this result.

Compound **12** was synthesized in a similar manner. The starting material 3-bromo-2-nitrothiophen [5] was reacted with 4-chlorobenzyl chloride to give substance **9**. Reduction with iron powder in glacial acetic acid led to the amine **10**. Subsequent reaction with ethyl chloroformate converted **10** into compound **11**, which then could be reacted with lithium diisopropylamide to provide the desired compound **12**. As observed for the lactam **8** the thieno[3,2-*b*][1,4]thiazine derivative **12** was isolated also in a poor yield.



An alternative route to the target compounds was developed subsequently. The ester **14** was prepared by reaction of 5-acetyl-2-chloro-3-nitrothiophene with ethyl α-bromo-4-chlorophenylacetate (**13**) in the presence of sodium sulphide. Substance **15** was derived from reduction with an excess of iron powder in glacial acetic acid. In the next step **15** was reacted with triethylsilane in trifluoroacetic acid to provide **8**. As well the absence of signals of the ester group and of the amino protons in the ^{1}H-nmr spectrum as the molecular weight of the isolated compound proved the formation of the desired lactam *via* a reductive cyclisation. In a similar manner, substance **12** could be



synthesized in good yield. Therefore, the reaction of 3-bromo-2-nitrothiophene with ethyl α-bromo-4-chlorophenylacetate (**13**) in presence of sodium sulphide yielded the expected ester **16**, which after reduction and cyclisation led to the lactam **12**.

The amines **17** and **18** were formed by reaction of compound **8** and **12** with lithium aluminium hydride. In the final step of the synthesis, the basic side chains could be introduced. The acylation of the cyclic nitrogen was accomplished with chloroacetyl chloride in the presence of triethylamine. The resulting products **19** and **20** were finally reacted with *N*-(3,4-dimethoxyphenylethyl)-*N*-methylamine to provide the target molecules **1** and **2**.

Compounds **1** and **2** will be tested. The pharmacological results will be published elsewhere.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler hot-stage apparatus. The ^{1}H-nmr spectra were recorded with deuteriochloroform as solvent, except otherwise stated, on a Bruker AC 80 (80 MHz) spectrometer with tetramethylsilane as the internal standard. The ^{13}C-nmr spectra were obtained at 100 MHz on a Bruker AM 400 spectrometer for deuteriochloroform solutions, except otherwise stated, with tetramethylsilane as internal reference. Mass spectra were determined with a Shimadzu GC/MS QP 1000 spectrometer with ionisation energy maintained at 70 eV.

3-(4-Chlorophenyl)-1-[*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylaminoacetyl]-6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*]-[1,4]thiazine (**1**).

A solution of 372 mg (1 mmole) of **19**, 215 mg (1.1 mmoles) of 2-(3,4-dimethoxyphenyl)-*N*-methyl-1-ethaneamine and 202 mg (2 mmoles) of triethylamine in 20 ml of absolute ethanol was heated for 4 hours at reflux. After this, the solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with toluene-ethyl acetate-triethylamine (6 + 3 + 1) to yield 446 mg (84%) of an oil; ^{1}H nmr (deuteriochloroform): 7.28-7.19 (m, 5H, phenyl H), 6.71-6.62 (m, 3H, phenyl H and thiophene H), 4.7-2.0 (broad m, 12H), 3.82 (s, 6H, OCH_3), 2.72 (q, J = 7.5 Hz, 2H, CH_2), 1.28 (t, J = 7.5 Hz, 3H, CH_3); ^{13}C nmr (deuteriochloroform): 169.1, 168.2, 147.9, 146.5, 143.0, 141.4, 137.9, 136.4, 134.2, 132.7, 130.7, 128.6, 120.9, 110.9, 61.9, 59.9, 55.8, 50.0, 46.8, 44.0, 42.5, 34.8, 32.9, 24.2, 16.1; ms: 530 (6), 379 (100), 208 (44).

Anal. Calcd. for $C_{27}H_{31}ClN_2O_3S_2$: C, 61.06; H, 5.88; N, 6.67. Found: C, 61.31; H, 5.89; N, 6.49.

2-(4-Chlorophenyl)-4-[*N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methylaminoacetyl]-3,4-dihydro-2*H*-thieno[3,2-*b*]-1,4-thiazine (**2**).

A solution of 344 mg (1 mmole) of **20**, 215 mg (1.1 mmoles) of 2-(3,4-dimethoxyphenyl)-*N*-methyl-1-ethaneamine and 202 mg (2 mmoles) of triethylamine in 20 ml of absolute ethanol was heated for 4 hours at reflux. After this, the solvent was evaporated and the residue was partitioned between ethyl acetate and water. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with toluene-ethyl acetate-triethylamine (7 + 3 + 1) to yield 156 mg (31%), mp 137-139°; ^{1}H nmr (deuteriochloroform): 7.35-6.56 (m, 9H, phenyl H and thiophene H), 4.44-4.36 (m, 1H), 4.14-4.08 (m, 1H), 3.86-3.66 (m, 1H), 3.80 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.38-3.09 (m, 2H), 2.75-2.55 (m, 4H), 2.25 (s, 3H, NCH_3); ^{13}C nmr (deuteriochloroform): 167.3, 148.9, 147.4, 136.7, 134.1, 132.1, 129.3, 129.1, 128.2, 125.3, 122.5, 120.3, 119.5, 114.8, 111.7, 111.2, 61.6, 58.6, 55.9, 55.7, 52.1, 42.9, 42.1, 33.0; ms: 503 (7), 351 (100), 208 (49).

Anal. Calcd. for $C_{25}H_{27}ClN_2O_3S_2$: C, 59.69; H, 5.41; N, 5.57. Found: C, 59.62; H, 5.11; N, 5.42.

5-Acetyl-2-(4-Chlorobenzylthio)-3-nitrothiophene (**4**).

A mixture of 410 mg (2 mmoles) of 5-acteyl-2-chloro-3-nitrothiophene and 480 mg (2 mmoles) of sodium sulphide nonahydrate in 10 ml of ethanol was stirred under argon at room temperature for 1 hour. After addition of 644 mg (4 mmoles) of 4-chlorobenzyl chloride the suspension was heated at reflux for 12 hours. Then the mixture was poured into ice-water. The precipitate was filtered and recrystallized from ethanol to yield 438 mg (67%), mp 125-128°; ^{1}H nmr (deuteriochloroform): 8.12 (s, 1H, thiophene H), 7.37 (s, 4H, phenyl H), 4.27 (s, 2H, CH_2), 2.55 (s, 3H, CH_3); ms: m/z 329 (3.1), 187 (31), 127 (100).

Anal. Calcd. for $C_{13}H_{10}ClNO_3S_2$: C, 47.63; H, 3.07; N, 4.27. Found: C, 47.33; H, 2.98; N, 4.28.

2-(4-Chlorobenzylthio)-5-ethyl-3-nitrothiophene (**5**).

To a solution of 327 mg (1 mmole) of **4** in 1.5 ml of trifluoroacetic acid 290 mg (2.5 mmoles) of triethylsilane were added dropwise and stirred at room temperature. After 12 hours the reaction mixture was poured into ice-water and neutralized with 5% aqueous sodium bicarbonate solution. The precipitate was filtered and recrystallized from ethanol to yield 291 mg (93%), mp 114-116°; ^{1}H nmr (deuteriochloroform): 7.34 (s, 4H, phenyl H), 7.26 (s, 1H, thiophene H), 4.19 (s, 2H, CH_2), 2.76 (q, J = 8 Hz, 2H, CH_2), 2.55 (t, J = 8 Hz, 3H, CH_3); ms: m/z 315 (2.1), 173 (7), 127 (100).

Anal. Calcd. for $C_{13}H_{12}ClNO_2S_2$: C, 49.75; H, 3.82; N, 4.46. Found: C, 49.83; H, 3.58; N, 4.44.

3-Amino-2-(4-Chlorobenzylthio)-5-ethylthiophene (**6**).

A mixture of 314 mg (1 mmole) of compound **5** and 1.13 g (5 mmoles) of tin(II)chloride in 15 ml of ethanol was heated 12 hours at reflux. After cooling the solvent was evaporated and the residue partitioned between ethyl acetate and 5% aqueous sodium bicarbonate solution. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with toluene-ethyl acetate (7 + 3) to yield 241 mg (85%) of an oil; ^{1}H nmr (deuteriochloroform): 8.15 (broad s, exchangeable, 2H, NH_2), 7.27 (s, 4H, phenyl H), 6.89 (s, 1H, thiophene H), 4.08 (s, 2H, CH_2), 2.73 (q, J = 7.2 Hz, 2H, CH_2), 1.20 (t, J = 7.2 Hz, 3H, CH_3); ms: m/z 285 (5), 158 (100), 127 (6).

Anal. Calcd. for $C_{13}H_{14}ClNS_2$: C, 55.05; H, 4.97; N, 4.93. Found: C, 54.82; H, 4.87; N, 4.73.

Ethyl *N*-[2-(4-Chlorobenzylthio)-5-ethyl-3-thienyl]oxamate (**7**).

A solution of 284 mg (1 mmole) of **6**, 216 mg (2 mmoles) of ethyl chloroformate and 101 mg (1 mmole) of triethylamine in 30 ml of toluene was heated for 12 hours at reflux. After this the solvent was evaporated and the residue was partitioned between ether and a 5% aqueous sodium bicarbonate solution. The organic layer

was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane-ethyl acetate (97 + 3) to yield 178 mg (50%) of an oil; ^{1}H nmr (deuteriochloroform): 8.87-7.37 (m, 4H, phenyl H), 7.36 (s, 1H, thiophene H), 6.67 (broad s, exchangeable, 1H, NH), 4.10 (q, J = 7.3 Hz, 2H, OCH_2), 3.67 (s, 2H, CH_2), 2.75 (q, J = 7.4 Hz, 2H, CH_2), 1.27 (t, J = 7.4 Hz, 6H, 2 CH_3); ms: m/z 357 (12), 230 (100), 127 (34).

Anal. Calcd. for $C_{16}H_{18}ClNO_2S_2$: C, 54.00; H, 5.10; N, 3.94. Found: C, 54.24; H, 5.02; N, 4.16.

3-(4-Chlorophenyl)-6-ethyl-1*H*-thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one (**8**).

Method a.

A solution of 357 mg (1 mmole) of **7** and 269 mg (1.5 mmoles) of hexamethylphosphoric triamide in 50 ml of tetrahydrofuran was cooled to -70° under an argon atmosphere. A solution of lithium diisopropylamide, prepared from 253 mg (2.5 mmoles) of diisopropylamine and 1.56 ml (2.5 mmoles, 1.6 *M* in hexane) of *n*-butyllithium in 10 ml of tetrahydrofuran, was added dropwise to the cooled solution and then the mixture was stirred for thirty minutes. Saturated ammonium chloride solution was added. The mixture was extracted with ethyl acetate and the organic layer was dried and evaporated. The residue was recrystallized from ethanol to yield 6 mg (2%).

Method b.

To a solution of 324 mg (1 mmole) of **15** in 1.5 ml of trifluoroacetic acid 290 mg (2.5 mmoles) of triethylsilane was added dropwise and stirred at room temperature. After 12 hours the reaction mixture was poured into ice-water and neutralized with 5% aqueous sodium bicarbonate solution. The precipitate was filtered off and recrystallized from ethanol to yield 281 mg (91%), mp 213°; ^{1}H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): 10.30 (broad s, exchangeable, 1H, NH), 7.29 (s, 4H, phenyl H), 6.46 (s, 1H, thiophene H), 4.59 (s, 1H, CH), 2.72 (q, J = 8.0 Hz, 2H, CH_2), 1.24 (t, J = 8.0 Hz, 3H, CH_3); ms: 309 (64), 154 (100).

Anal. Calcd. for $C_{14}H_{12}ClNOS_2$: C, 54.27; H, 3.90; N, 4.52. Found: C, 54.24; H, 4.16; N, 4.36.

3-(4-Chlorobenzylthio)-2-nitrothiophene (**9**).

A mixture of 416 mg (2 mmoles) of 3-bromo-2-nitrothiophene and 480 mg (2 mmoles) of sodium sulphide nonahydrate in 10 ml of ethanol was stirred under argon at room temperature for 1 hour. After addition of 644 mg (4 mmoles) of 4-chlorobenzyl chloride the suspension was heated at reflux for 12 hours. Then the mixture was poured into ice-water. The precipitate was filtered and recrystallized from ethanol to yield 359 mg (63%), mp 136-137°; ^{1}H nmr (deuteriochloroform): 7.47 (A-part of an AB-system, 1H, J = 5.7 Hz, thiophene H), 7.35 (s, 4H, phenyl H), 6.93 (B-part of an AB-system, 1H, J = 5.7 Hz, thiophene H), 4.24 (s, 2H, CH_2); ms: m/z 287 (0.1), 145 (29), 89 (14).

Anal. Calcd. for $C_{11}H_8ClNO_2S_2$: C, 46.23; H, 2.82; N, 4.90. Found: C, 46.17; H, 2.67; N, 4.86.

2-Amino-3-(4-chlorobenzylthio)thiophene (**10**).

A mixture of 286 mg (1 mmole) of compound **9** and 200 mg of iron powder in 100 ml glacial acetic acid was heated at 75° for 1 hour. After cooling the solvent was evaporated and the residue partitioned between ethyl acetate and 5% aqueous sodium bicarbonate solution. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with toluene-ethyl acetate (8 + 2) to yield 201 mg (78%) of an oil; ^{1}H nmr (deuteriochloroform): 8.48 (broad s, exchangeable, 2H, NH_2), 7.32 (s, 4H, phenyl H), 7.02 (A-part of an AB-system, 1H, J = 5.7 Hz, thiophene H), 6.93 (B-part of an AB-system, 1H, J = 5.7 Hz, thiophene H), 4.09 (s, 2H, CH_2); ms: m/z 257 (3).

Anal. Calcd. for $C_{11}H_{10}ClNS_2$: C, 51.65; H, 3.94; N, 5.48. Found: C, 51.82; H, 4.07; N, 5.29.

Ethyl *N*-[3-(4-Chlorobenzylthio)-2-thienyl]oxamate (**11**).

A solution of 258 mg (1 mmole) of **10**, 216 mg (2 mmoles) of ethyl chloroformate and 101 mg (1 mmole) of triethylamine in 30 ml of toluene was heated for 10 hours at reflux. After this the solvent was evaporated and the residue partitioned between ether and a 5% aqueous sodium bicarbonate solution. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane-ethyl acetate (97 + 3) to yield 214 mg (65%) of an oil; ^{1}H nmr (deuteriochloroform): 7.28 (s, 4H, phenyl H), 7.08 (A-part of an AB-system, 1H, J = 5.7 Hz, thiophene H), 6.91 (B-part of an AB-system, 1H, J = 5.7 Hz, thiophene H), 6.34 (broad s, exchangeable, 1H, NH), 4.12 (q, J = 7.4 Hz, 2H, OCH_2), 3.61 (s, 2H, CH_2), 1.26 (t, J = 7.4 Hz, 3H, CH_3); ms: m/z 327 (11).

Anal. Calcd. for $C_{14}H_{14}ClNO_2S_2$: C, 51.29; H, 4.30; N, 4.27. Found: C, 51.24; H, 4.92; N, 4.16.

2-(4-Chlorophenyl)-2*H*-thieno[3,2-*b*][1,4]thiazin-3(4*H*)-one (**12**).

Method a.

A solution of 328 mg (1 mmole) of **11** and 269 mg (1.5 mmoles) of hexamethylphosphoric triamide in 50 ml of tetrahydrofuran was cooled to -70° under an argon atmosphere. A solution of lithium diisopropylamide, prepared from 253 mg (2.5 mmoles) of diisopropylamine and 1.56 ml (2.5 mmoles, 1.6 *M* in hexane) of *n*-butyllithium in 10 ml of tetrahydrofuran, was added dropwise to the cooled solution and then the mixture was stirred for thirty minutes. Saturated ammonium chloride solution was added and the mixture was extracted with ethyl acetate. The organic layer was dried and evaporated. The residue was recrystallized from toluene to yield 9 mg (3%).

Method b.

To a solution of 357 mg (1 mmole) of **16** in 5 ml of methanol, 1 ml of acetic acid and 10 ml of toluene 200 mg of iron powder was added. After heating at reflux for 48 hours the reaction mixture was concentrated *in vacuo*. The residue was partitioned between 5% aqueous sodium bicarbonate solution and ethyl acetate. Then the organic layer was dried and evaporated. The residue was recrystallized from toluene to yield 169 mg (60%); ^{1}H nmr (deuteriochloroform): 10.89 (broad s, exchangeable, 1H, NH), 7.28 (s, 4H, phenyl H), 6.91 (A-part of an AB-system, 1H, J = 5.6 Hz, thiophene, H), 6.83 (B-part of an AB-system, 1H, J = 5.6 Hz, thiophene H), 4.61 (s, 1H, CH); ms: 281 (75), 152 (100).

Anal. Calcd. for $C_{12}H_8ClNO_2S_2$: C, 51.15; H, 2.86; N, 4.97. Found: C, 51.16; H, 2.60; N, 4.69.

Ethyl α-(5-Acetyl-3-nitro-2-thienylthio)-4-chlorophenylacetate (**14**).

A mixture of 410 mg (2 mmoles) of 5-acteyl-2-chloro-3-nitrothiophene and 480 mg (2 mmoles) of sodium sulphide nonahydrate in 10 ml of ethanol was stirred under argon at room temperature for 1 hour. After addition of 1104 mg (4 mmoles) of ethyl α-bromo-4-chlorophenylacetate the suspension was stirred at room temperature for a further 15 hours. Then the mixture was

poured into ice-water. The precipitate was filtered and recrystallized from ethanol to yield 393 mg (49%), mp 111-113°; ^{1}H nmr (deuteriochloroform): 8.08 (s, 1H, thiophene H), 7.47 (A-part of an AB-system, 1H, J = 8 Hz, phenyl H), 7.34 (B-part of an AB-system, 1H, J = 8 Hz, phenyl H), 5.12 (s, 1H, SCH), 4.25 (q, 2H, J = 7.7 Hz, CH_2), 2.52 (s, 3H, CH_3CO), 1.27 (t, 3H, J = 7.7 Hz, CH_3); ms: m/z 399 (3.1), 197 (100).

Anal. Calcd. for $C_{16}H_{14}ClNO_5S_2$: C, 48.06; H, 3.53; N, 3.50. Found: C, 47.91; H, 3.43; N, 3.46.

6-Acetyl-3-(4-chlorophenyl)-1*H*-thieno[2,3-*b*][1,4]thiazin-2(3*H*)-one (**15**).

To a solution of 400 mg (1 mmole) of **14** in 5 ml of methanol, 1 ml of acetic acid and 10 ml of toluene 200 mg of iron powder was added. After heating at reflux for 48 hours the reaction mixture was concentrated *in vacuo*. The residue was partitioned between 5% aqueous sodium bicarbonate solution and ethyl acetate. Then the organic layer was dried and evaporated. The residue was recrystallized from toluene to yield 296 mg (91%), mp 213°; ^{1}H nmr (deuteriochloroform/dimethyl-d_6 sulfoxide): 10.95 (s-broad, exchangeable, 1H, NH), 7.61 (s, 1H, thiophene H), 7.31 (s, 4H, phenyl H), 4.75 (s, 1H, CH), 2.47 (s, 3H, CH_3); ms: 323 (100), 154 (28).

Anal. Calcd. for $C_{14}H_{10}ClNO_2S_2$: C, 51.93; H, 3.11; N, 4.33. Found: C, 51.68; H, 2.96; N, 4.19.

Ethyl α-(2-Nitro-3-thienylthio)-4-chlorophenylacetate (**16**).

A mixture of 416 mg (2 mmoles) of 3-bromo-2-nitrothiophene and 480 mg (2 mmoles) of sodium sulphide nonahydrate in 10 ml of ethanol was stirred under argon at room temperature for 1 hour. After addition of 1104 mg (4 mmoles) of ethyl α-bromo-4-chlorophenylacetate the suspension was stirred at room temperature for a further 20 hours. Then the mixture was poured into ice-water. The precipitate was filtered and recrystallized from ethanol to yield 407 mg (57%), mp 146°; ^{1}H nmr (deuteriochloroform): 7.51-7.35 (m, 5H, phenyl H and thiophene H), 6.93 (B-part of an AB-system, 1H, J = 5.6 Hz, thiophene H), 5.12 (s, 1H, SCH), 4.23 (q, 2H, J = 7.2 Hz, CH_2), 1.25 (t, 3H, J = 7.7 Hz, CH_3); ms: m/z 357 (0.6), 197 (72), 145 (100).

Anal. Calcd. for $C_{14}H_{12}ClNO_4S_2$: C, 46.99; H, 3.38; N, 3.91. Found: C, 47.23; H, 3.20; N, 3.75.

3-(4-Chlorophenyl)-6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*]-[1,4]thiazine (**17**).

To a mixture of 326 mg (1 mmole) of compound **8** in 10 ml of dry 1,4-dioxane 1.2 ml of a 0.1 *M* solution of lithium aluminium hydride in tetrahydrofuran was added dropwise. After the addition was complete, the solution was stirred at room temperature for 3 hours. After this, ethyl acetate and afterwards water were added. By-products were removed by filtration of the reaction mixture through silica gel. The silica gel was washed with ethyl acetate. The organic solution was washed twice with water, dried and evaporated. The residue was recrystallized from diluted ethanol to give 186 mg (63%), mp 123-125°; ^{1}H nmr (deuteriochloroform): 7.28 (s, 4H, phenyl H), 6.26 (s, 1H, thiophene H), 4.10 (s, 1H, CH), 3.95 (broad s, exchangeable, 1H, NH), 3.77-3.56 (m, 2H, CH_2), 2.71 (q, J = 8.0 Hz, 2H, CH_2), 1.25 (t, J = 8.0 Hz, 3H, CH_3); ms: 295 (47), 170 (100).

Anal. Calcd. for $C_{14}H_{14}ClNS_2$: C, 56.84; H, 4.77; N, 4.73. Found: C, 56.66; H, 4.56; N, 4.38.

2-(4-Chlorophenyl)-3,4-dihydro-2*H*-thieno[3,2-*b*][1,4]thiazine (**18**).

To a mixture of 281 mg (1 mmole) of compound **8** in 10 ml of dry 1,4-dioxane 1.2 ml of a 0.1 *M* solution of lithium aluminum hydride in tetrahydrofuran was added dropwise. After the addition was complete the solution was stirred at room temperature for 12 hours. After this ethyl acetate and afterwards water were added. By-products were removed by filtration of the reaction mixture through silica gel. The silica gel was washed with ethyl acetate. The organic solution was washed twice with water, dried and evaporated. The residue was purified by column chromatography eluting with toluene-ethyl acetate (8 + 2) to yield 114 mg (43%) of an oil; ^{1}H nmr (deuteriochloroform): 7.24 (s, 4H, phenyl H), 6.83 (A-part of an AB-system, 1H, J = 5.6 Hz, thiophene H), 6.76 (B-part of an AB-system, 1H, J = 5.6 Hz, thiophene H), 4.16-3.02 (m, 3H, CH and CH_2), 3.70 (broad s, exchangeable, 1H, NH); ms: 267 (31), 142 (66), 91 (100).

Anal. Calcd. for $C_{12}H_{10}ClNS_2$: C, 53.82; H, 3.76; N, 5.23. Found: C, 53.94; H, 3.86; N, 4.98.

1-Chloroacetyl-3-(4-chlorophenyl)-6-ethyl-2,3-dihydro-1*H*-thieno[2,3-*b*][1,4]thiazine (**19**).

A solution of 296 mg (1 mmole) of **17**, 126 mg (2 mmoles) of chloroacetyl chloride and 202 mg (2 mmoles) of triethylamine in 5 ml of tetrahydrofuran was stirred for 12 hours at room temperature. After this the solvent was evaporated and the residue partitioned between ether and a 5% aqueous sodium bicarbonate solution. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with hexane-ethyl acetate (9 + 1) to yield 189 mg (50%) of an oil; ^{1}H nmr (deuteriochloroform): 7.34-7.30 (m, 4H, phenyl H), 7.26 (s, 1H, thiophene H), 4.56 (s, 1H, CH), 4.86-4.01 (m, 2H, NCH_2), 4.7-3.1 (m, 2H, $ClCH_2$), 2.80 (q, J = 7.0 Hz, 2H, CH_2), 1.30 (t, J = 7.0 Hz, 3H, CH_3); ms: 371 (85), 170 (100).

Anal. Calcd. for $C_{16}H_{15}Cl_2NOS_2$: C, 51.61; H, 4.06; N, 3.76. Found: C, 51.70; H, 3.83; N, 3.48.

4-Chloroacetyl-2-(4-chlorophenyl)-3,4-dihydro-2*H*-thieno-[3,2-*b*][1,4]thiazine (**20**).

A solution of 267 mg (1 mmole) of **18**, 126 mg (2 mmoles) of chloroacetyl chloride and 202 mg (2 mmoles) of triethylamine in 5 ml of tetrahydrofuran was stirred for 3 hours at room temperature. After this the solvent was evaporated and the residue partitioned between ether and a 5% aqueous sodium bicarbonate solution. The organic layer was separated, dried and concentrated *in vacuo*. The residue was purified by column chromatography eluting with toluene-ethyl acetate (9 + 1) to yield 156 mg (45%) of an oil; ^{1}H nmr (deuteriochloroform): 7.28 (s, 4H, phenyl H), 7.00 (A-part of an AB-system, 1H, J = 6.4 Hz, thiophene H), 6.79 (B-part of an AB-system, 1H, J = 6.4 Hz, thiophene H), 4.50-3.81 (m, 5H, CH and 2 CH_2); ms: 343 (100), 266 (89), 142 (74).

Anal. Calcd. for $C_{14}H_{11}Cl_2NOS_2$: C, 48.84; H, 3.22; N, 4.07. Found: C, 48.98; H, 3.58; N, 3.88.

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