Studies on the Chemistry of Thienoanellated *O,N*- and *S,N*-containing Heterocycles. 6 [1]. Synthesis of Some Thienoanellated [1,4]Benzoxazepines

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Substituted thieno[2,3-*b*][1,4]benzoxazepine derivatives as well as thieno[3,2-*b*][1,4]benzoxazepine derivatives have been synthesized. They are thienoanalogues of loxapine, a potent antipsychotic drug. Research activities concentrate on the preparation of structurally modified compounds of loxapine to minimize its undesirable extrapyramidal symptoms.

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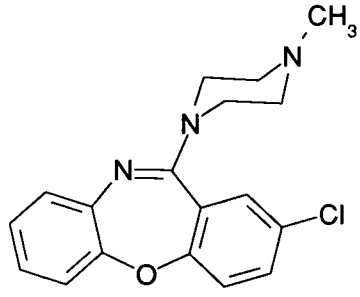
Loxapine is a highly potent neuroleptic agent [2]. It belongs to the group of tricyclic antipsychotics used in the treatment of acute and chronic schizophrenia. Beside other side effects extrapyramidal disturbances were observed.

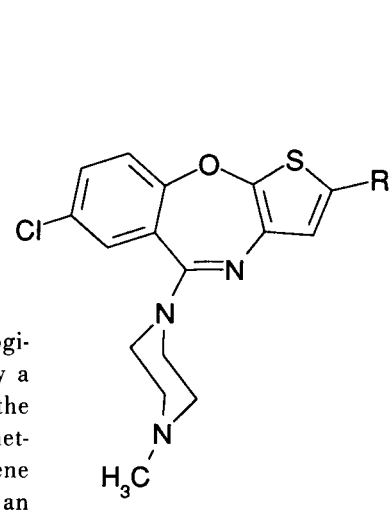


LOXAPINE

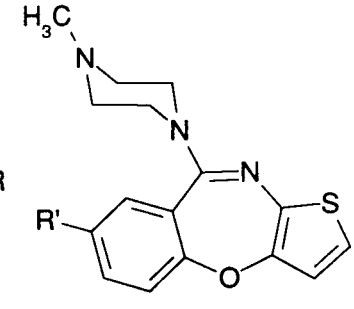
It is known from various drugs that their pharmacological activity is maintained if benzene is exchanged by a thiophene ring [3]. In the course of our studies on the chemistry of thienoanellated *O,N*- and *S,N*-containing heterocycles, it should be attempted to replace one benzene in the loxapine molecule by a thiophene ring to achieve an improved pharmacological profile. This research was to prepare the following derivatives:

As the chlorobenzene-unit has proved to be essential for the pharmacological activity [4], this structural element was part of the thienoanalog.

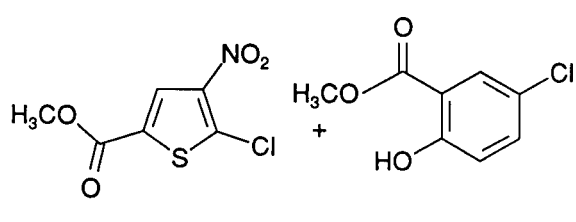
The starting material for the synthesis of structure **A** is methyl 5-chloro-4-nitrothiophene-2-carboxylate **1** prepared according to the method described by Hurd and Kreuz [5]. Reaction with methyl 5-chlorosalicylate in acetone gave compound **2** in 61% yield. The catalytic hydrogenation of



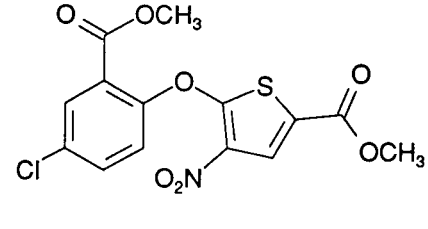
STRUCTURE A



STRUCTURE B



1



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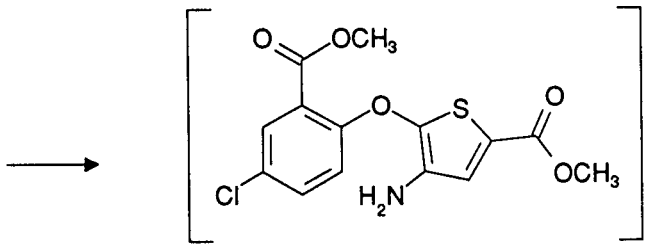

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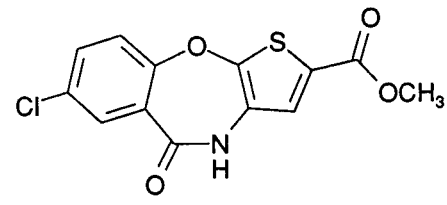

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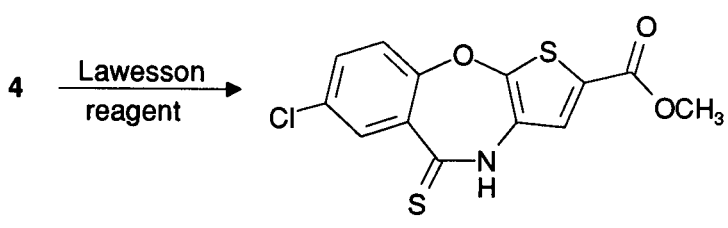

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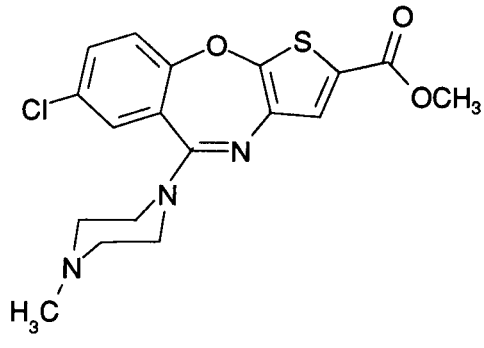
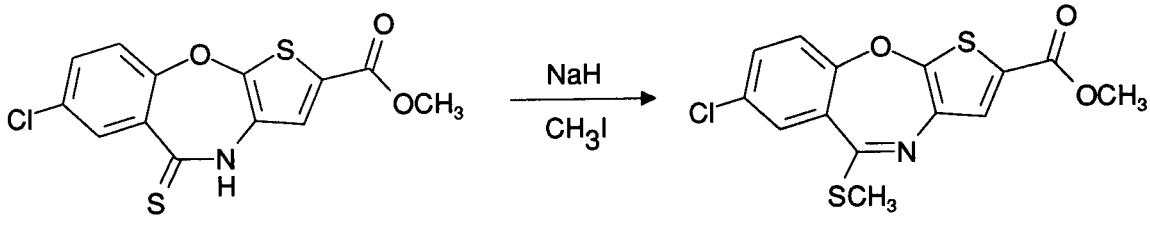


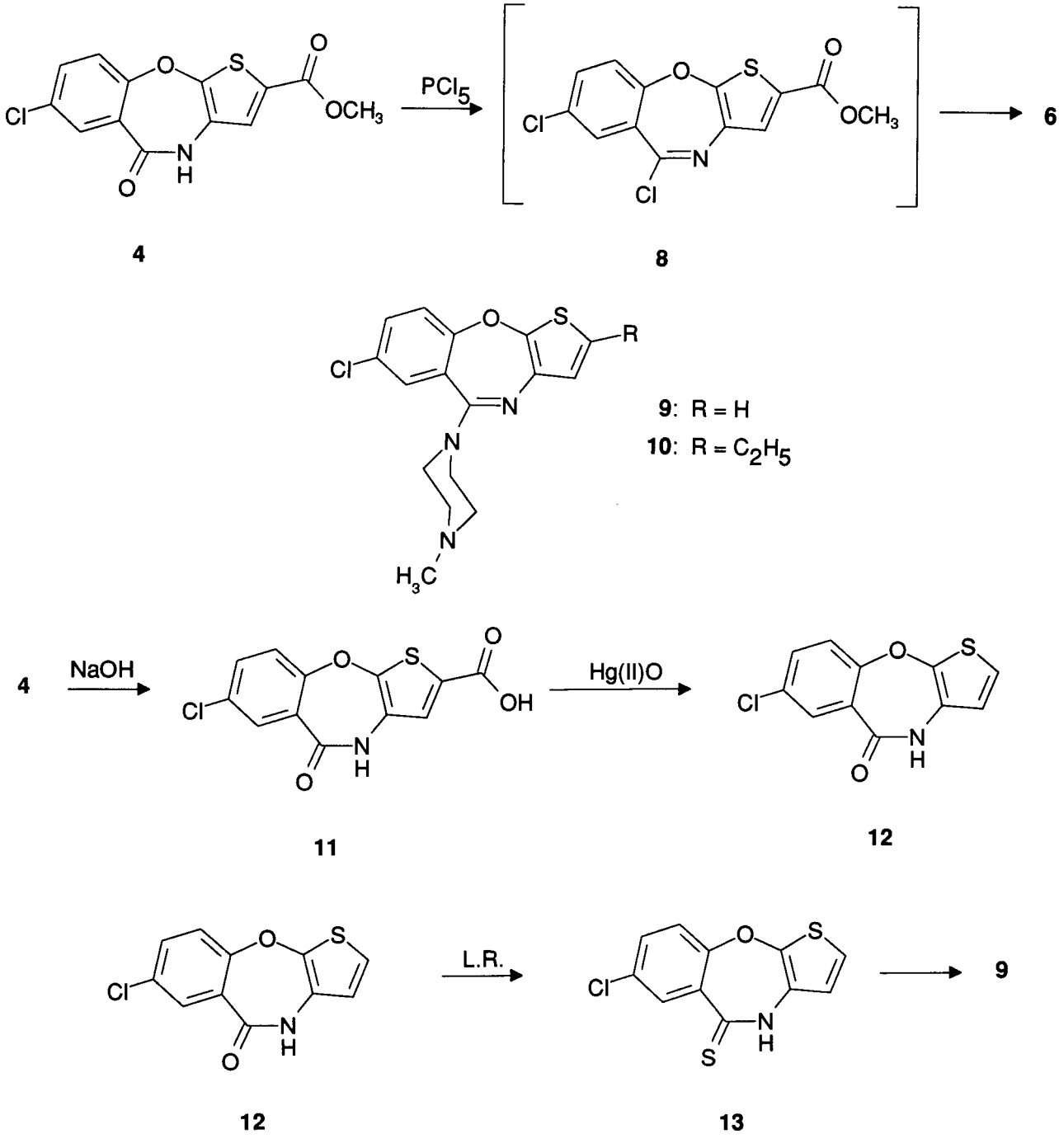
6

2 was not the method of choice for reduction due to the immense amount of catalyst needed. Alternatively compound **2** was reduced with iron powder [6] in glacial acetic acid at 70°. Analysis (tlc) revealed complete removal of **2** within 30 minutes. The isolated substance gave the following analytical data. The lack of signals of methoxycarbonyl and amino protons in the ^{1}H-nmr spectrum and the appearance of 311 units in the mass spectrum confirmed, that not only the reduction of the nitro group, but also cyclization to the expected lactam **4** occurred. This functional group was converted with Lawesson reagent into the thiolactam. No conversion of the ester group into the thioester group took place, which could be confirmed by mass spectroscopy. Compound **5** obtained was refluxed with *N*-methylpiperazine to give the desired product **6**, but only in poor yield. Since we were interested in better yields, a further activation of the thiolactam into the methylthiolactam should facilitate nucleophilic attack and provide better reaction conditions. Compound **7** was obtained by reaction of **5** with sodium hydride and methyl iodide. After reaction of **7** with *N*-methylpiperazine, compound **6** could be isolated in a 58% yield. In addition the imido chloride **8** was produced by treatment of the lactam **4** with phosphorus pentachloride. The subsequent reaction with *N*-methylpiperazine provided compound **6** but in lower yield than in both of the other synthetic routes described above. Moreover derivatives of compound **6** unsubstituted or ethylated in position 2 should be synthesized and tested for their biological activity.

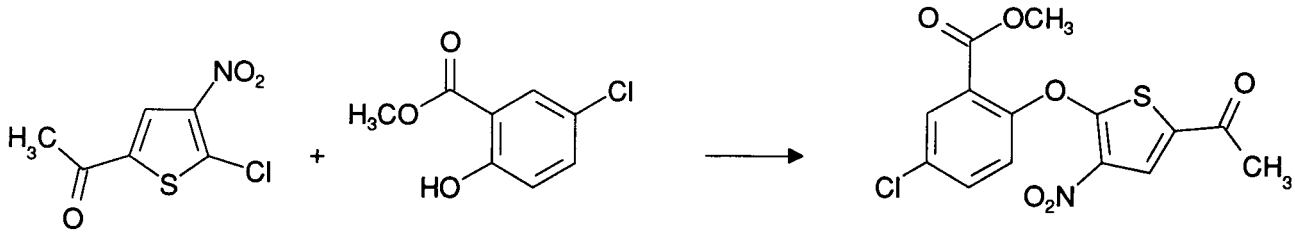
The synthetic approach to **9** is accomplished by ester hydrolysis and subsequent decarboxylation. Attempts to



5 7



saponify compound **6** with 5% sodium hydroxide/ethanol (1:1) or with alumina/potassium hydroxide provided only tarry products. Therefore saponification of the lactam was tried. Sulfuric acid (1*M* solution) was added to compound **4** but no satisfactory reaction could be accomplished because of its slight solubility. In contrast the reaction under basic conditions led to **11** in 81% yield. Decarboxylation of **11** by dry heating could not afford the desired product **12**. Heating of **11** in quinoline in the presence of copper powder [7] gave an intractable mixture. However, reaction of **11** with mercury(II) oxide [8] in glacial acetic acid converted **11** into **12** in 73% yield.



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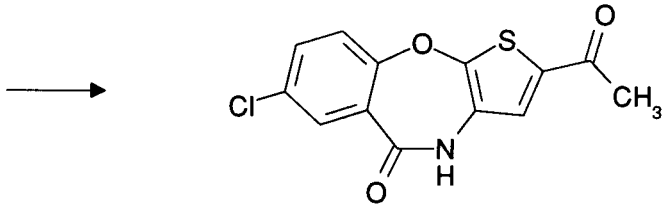

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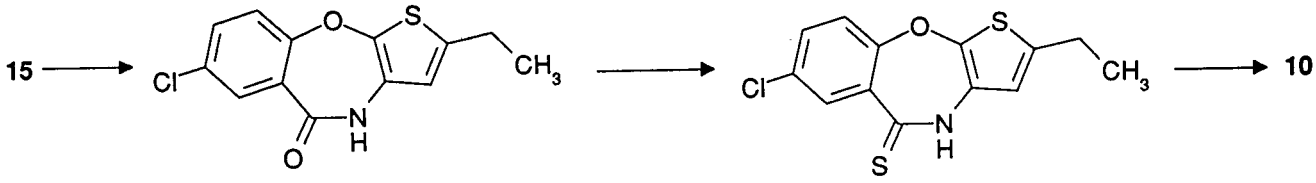
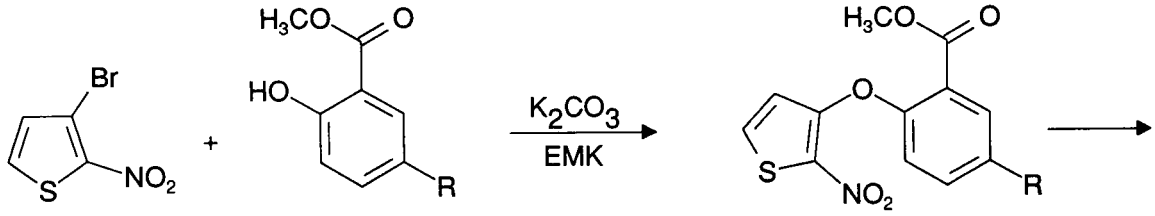
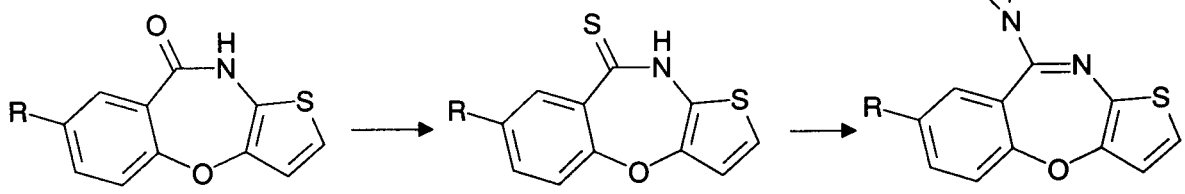


16 **17**



R = H
= Cl

21: R = H
22: R = Cl



23 : R = H
24 : R = Cl

25 : R = H
26 : R = Cl

19 : R = H
20 : R = Cl

The activation to the thiolactam **13** by Lawesson reagent and further treatment with *N*-methylpiperazine resulted in the corresponding amine **14**. In this case no further activation of the thiolactam to methylthiolactam was necessary because of the high yield.

The perparation of compound **10** was accomplished by combination of acetylchlorothiophene and ethyl chlorosalicylate. Compound **14** obtained was reduced with iron powder in glacial acetic acid at 70-75° bath temperature and in consequence cyclized to **15**. Compound **15** was treated with triethylsilane/TFA providing **16** [9], activation of the lactam group with Lawesson reagent and further treatment with an excess of *N*-methylpiperazine at 120° gave compound **10** in a good yield. Hydrogen chloride in dry ether transformed compound **10** to the corresponding hydrochloride **18**.

Finally, we prepared two isomeric compounds to **10, 19** and **20** by an analogous synthetic route as already described. For this purpose 3-bromo-2-nitrothiophene was allowed to react with methyl salicylate or methyl 5-chlorosalicylate in 2-butanone/potassium carbonate, respectively. These nucleophilic substitutions led to compounds **21** and **22** which reduced with iron powder in a mixture of glacial acetic acid/toluene/methanol and afterwards cyclized. After working up the isolated compounds, **23** [10] and **24** were treated with Lawesson reagent in THF to obtain **25** and **26**. Subsequent reaction with *N*-methylpiperazine at 120° resulted in the target molecules **19** and **20**, respectively.

Compounds **9, 18** and **19** have been tested for their neuroleptic activity [11]. None of them had the potency of loxapine. The pharmacological properties in details 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).

Methyl 5-[4-Chloro-2-(methoxycarbonyl)phenoxyl]-4-nitrothiophene-2-carboxylate (**2**).

To a suspension of 1.24 g (9 mmoles) of potassium carbonate in 20 ml dry acetone, 0.856 g (4.6 mmoles) methyl 5-chlorosalicylate were added. After 20 minutes, 1.00 g (4.5 mmoles) of **1** was added. After 3 days the reaction mixture was acidified with diluted hydrochloric acid and filtered. The filtrate was concentrated under reduced pressure and the residue partitioned between dichloromethane and water. The organic layer was dried with sodium sulfate, filtered and evaporated. The crude product was recrystallized from ethanol to give 0.95 g (57%) of **2**, mp 79-80°; ms: m/z 371 (M^+, 5%), 340 (M^+ -OCH_3, 20%), 294 (M^+ -OCH_3, -NO_2, 45%), 263 (M^+ -2 OCH_3, -NO_2, 43%), 185 (100%); ^{1}H-nmr (deuteriochloroform): δ 8.15 (s, 1H, thiophene H), 8.11-7.36 (m, 3H, phenyl H), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3).

Anal. Calcd. for $C_{14}H_{10}ClNO_7S$: C, 45.23; H, 2.71; N, 3.76. Found: C, 45.05; H, 2.79; N, 3.72.

Methyl 7-Chloro-4,5-dihydro-5-oxothieno[2,3-*b*][1,4]benzoxazepine-2-carboxylate (**4**).

A suspension of 3.71 g (10 mmoles) of **2** and 3.85 g (70 mmoles) iron powder in 100 ml glacial acetic acid was heated at 75°. After one hour the suspension was cooled and poured into 300 ml of ice water. The precipitate was collected, washed with water and recrystallized from ethyl acetate to give 2.14 g (69%) of **4**, mp 270-271°; ms: m/z 309 (M^+, 64%), 250 (M^+ -$COOCH_3$, 100%); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.42 (s-broad, exchangeable, 1H, NH), 7.88-7.56 (m, 4H, arom H), 3.83 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_8ClNO_4S$: C, 50.42; H, 2.60; N, 4.52. Found: C, 49.99; H, 2.79; N, 4.31.

Methyl 7-Chloro-4,5-dihydro-5-thioxothieno[2,3-*b*][1,4]benzoxazepine-2-carboxylate (**5**).

A solution of 0.62 g (2 mmoles) of **4** and 1.01 g (2.5 mmoles) of Lawesson reagent in 50 ml of dry tetrahydrofuran was refluxed for 4 hours. After cooling the precipitate was collected and recrystallized from toluene to give 0.48 g (74%) of **5** as yellow crystals, mp 238-240°; ms: m/z 325 (M^+, 100%), 310 (M^+ -CH_3, 29%), 266 (M^+ -$COOCH_3$, 88%); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 12.6 (s-broad, 1H, NH), 8.07-7.19 (m, 4H, arom H), 3.82 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_8ClNO_3S_2$: C, 47.93; H, 2.48; N, 4.29. Found: C, 47.82; H, 2.62; N, 4.10.

Methyl 7-Chloro-5-(4-methyl-1-piperazinyl)thieno[2,3-*b*][1,4]-benzoxazepine-2-carboxylate (**6**).

A solution of 0.98 g (3 mmoles) of **5** and 10 ml of *N*-methylpiperazine was treated for 4 hours under reflux. After cooling the excess of the base was distilled under reduced pressure and the residue purified on silica gel column eluting with toluene/ethyl acetate/triethylamine (4:4:1) to give 0.48 g (41%) of **6**, mp 158-160°; ms: m/z 391 (M^+, 100%), 308 (M^+ -$CH_3N(CH_2CH)_2$, 71%), 99 (*N*-methylpiperazinyl, 83%); ^{1}H-nmr (deuteriochloroform): δ 7.70-7.12 (m, 4H, arom H), 3.84 (s, 3H, CH_3), 3.55-3.43 (m, 4H, $(CH_2)_2N$), 2.60-2.47 (m, 4H, $(CH_2)_2N$), 2.37 (s, 3H, NCH_3).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_3S$: C, 55.17; H, 4.63; N, 10.72. Found: C, 55.44; H, 4.44; N, 10.72.

Methyl 7-Chloro-5-methylthiothieno[2,3-*b*][1,4]benzoxazepine-2-carboxylate (**7**).

To a suspension of 0.30 g (10 mmoles) of sodium hydride (80%) in 30 ml of dry tetrahydrofuran 3.25 g (10 mmoles) of **5** was added. After 10 minutes 2.84 g (20 mmoles) of methyl iodide was added and stirred for 1 hour. The solvent was evaporated and the residue recrystallized from ethanol to give 2.60 g (77%) of **7**, mp 209°; ms: m/z 339 (M^+, 56%), 324 (M^+ -CH_3, 100%); ^{1}H-nmr (deuteriochloroform): δ 7.69-7.02 (m, 4H, arom H), 3.85 (s, 3H, CH_3), 2.53 (s, 3H, SCH_3).

Anal. Calcd. for $C_{14}H_{10}ClNO_3S_2$: C, 49.48; H, 2.97; N, 4.12. Found: C, 49.24; H, 3.04; N, 3.98.

7-Chloro-5-(4-methyl-1-piperazinyl)thieno[2,3-*b*][1,4]benzoxazepine (**9**).

A solution of 0.53 g (2 mmoles) of **13** in 10 ml *N*-methylpiperazine was heated to reflux for 8 hours. After cooling the excess of

the base was distilled under reduced pressure and the residue recrystallized from *n*-hexane/ethyl acetate (1:1) to give 0.42 g (63%) of **9**; mp 121-122°; ms: m/z 333 (M^+, 27%), 250 ($M^+ - CH_3N(CH_2CH_2)_2$, 40%), 70 (100%); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 7.72-6.73 (m, 5H, arom H), 3.49-3.40 (m, 4H, 2 CH_2), 2.60-2.43 (m, 4H, 2 CH_2), 2.30 (s, 3H, NCH_3).

Anal. Calcd. for $C_{16}H_{16}ClN_3OS$: C, 57.57; H, 4.83; N, 12.59. Found: C, 57.60; H, 4.72; N, 12.49.

7-Chloro-2-ethyl-5-(4-methyl-1-piperazinyl)thieno[2,3-*b*][1,4]benzoxazepine (**10**).

A solution of 0.59 g (2 mmoles) of **17** in 10 ml of *N*-methylpiperazine was heated for 2 hours under reflux. After cooling the excess of the base was distilled under reduced pressure and the residue 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 toluene-ethyl acetate-triethylamine (4:4:1) to give 0.20 g (28%) of **10** as an oil; ms: m/z 361 (M^+, 17%), 277 (17%), 70 (100%); ^{1}H-nmr (deuteriochloroform): δ 7.49-7.00 (m, 3H, arom H), 6.40 (s, 1H, thiophene H), 3.55-3.37 (m, 4H, CH_2N), 2.77 (q, 2H, J = 7.0 Hz, CH_2), 2.58-2.47 (m, 4H, CH_2N), 2.35 (s, 3H, NCH_3), 1.22 (t, 3H, J = 7.0 Hz, CH_3).

7-Chloro-4,5-dihydro-5-oxothieno[2,3-*b*][1,4]benzoxazepine-2-carboxylic acid (**11**).

A solution of 1.55 g (5 mmoles) of **4** in 20 ml 5% sodium hydroxide and 80 ml ethanol was stirred for 6 hours. The reaction mixture was diluted with 200 ml water and acidified with 2*M* hydrochloric acid. The precipiate was collected, washed and dried to give 1.16 g (79%) of **11**; mp >350°; ms: m/z 295 (M^+, 91%), 294 (M^+ -H, 70%), 250 (M^+ -COOH, 100%); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.67 (s, 1H, COOH), 7.78-7.32 (m, 5H, arom H, NH).

Anal. Calcd. for $C_{12}H_6ClNO_4S \cdot H_2O$: C, 45.94; H, 2.57; N, 4.46. Found: C, 45.75; H, 2.09; N, 4.21.

7-Chloro-4,5-dihydrothieno[2,3-*b*][1,4]benzoxazepin-5-one (**12**).

To a suspension of 1.48 g (5 mmoles) of **11** in 100 ml of glacial acetic acid, 1.0 g of mercuric(II) oxide was added and refluxed for 16 hours. After cooling and filtration the solution was diluted with 200 ml of ice water. The precipitate was collected, washed and recrystallized from ethanol to give 0.79 g (63%) of **12**, mp 268° dec; ms: m/z 251 (M^+, 100%), 250 (M^+ -H, 38%), 223 (M^+ -CO, 39%); ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 10.55 (s, 1H, NH), 7.74-6.63 (m, 5H, arom H).

Anal. Calcd. for $C_{11}H_6ClNO_2S$: C, 52.49; H, 2.40; N, 5.57. Found: C, 52.53; H, 2.48; N, 5.48.

7-Chloro-4,5-dihydrothieno[2,3-*b*][1,4]benzoxazepine-5-thione (**13**).

To a solution of 1.00 g (4 mmoles) of **12** in 60 ml of dry toluene 2.02 g (5 mmoles) of Lawesson reagent was added. After refluxing for 1 hour and cooling the precipitate was collected and recrystallized to give 0.71 g (67%) of **13** as yellow needles, mp 260-262°; ms: m/z 267 (M^+, 100%), 232 (M^+ -Cl, 100%); ^{1}H-nmr (deuteriochloroform): δ 12.80 (s, 1H, NH), 8.15-6.80 (m, 5H, arom H).

Anal. Calcd. for $C_{11}H_6ClNOS_2 \cdot 0.5H_2O$: C, 47.74; H, 2.55; N, 5.06. Found: C, 48.02; H, 2.23; N, 4.99.

Methyl 2-(5-Acetyl-3-nitro-2-thienyloxy)-5-chlorobenzoate (**14**).

To a suspension of 2.76 g (20 mmoles) of potassium carbonate in 50 ml of dry acetone, 2.05 g (11 mmoles) of methyl 5-chlorosalicylate was added and stirred for 20 minutes. This suspension was treated with 2.05 g (10 mmoles) of 5-acetyl-2-chloro-3-nitrothiophene stirred for 48 hours and acidified with diluted hydrochloric acid. After filtration the solvent was evaporated and the residue partitioned between water and dichloromethane. The organic layer was separated, dried and concentrated *in vacuo*. After recrystallization, 2.44 g (58%) of **14** was obtained, mp 98-99°; ms: m/z 355 (M^+, 0.6%), 43 (100%); ^{1}H-nmr (deuteriochloroform): δ 8.03 (s, 1H, thiophene H), 8.07-7.30 (m, 3H, arom H), 3.83 (s, 3H, OCH_3), 2.51 (s, 3H, $COCH_3$).

Anal. Calcd. for $C_{14}H_{10}ClNO_6S$: C, 47.27; H, 2.83; N, 3.94. Found: C, 47.08; H, 2.80; N, 3.73.

2-Acetyl-7-chlorothieno[2,3-*b*][1,4]benzoxazepin-5(4*H*)-one (**15**).

A suspension of 3.56 g (10 mmoles) of **14** and 13.85 g (70 mmoles) of iron powder in 100 ml of glacial acetic acid was heated at 75° for 2 hours. After cooling the suspension was poured into 300 ml of ice water, the precipitate collected, washed and recrystallized from 1,4-dioxane to give 1.31 g (45%) of **15**, mp 310-312°; ms: m/z 293 (M^+, 89%), 251 ($M^+ - COCH_3$, 100%); ^{1}H-nmr (deuteriochloroform): δ 7.28 (s, 1H, thiophene H), 7.91-7.09 (m, 3H, arom H), 3.97 (s-broad, 1H), 2.45 (s, 3H, CH_3).

Anal. Calcd. for $C_{13}H_8ClNO_3S$: C, 53.16; H, 2.75; N, 4.77. Found: C, 53.28; H, 2.72; N, 4.94.

7-Chloro-2-ethylthieno[2,3-*b*][1,4]benzoxazepin-5(4*H*)-one (**16**).

A solution of 2.93 g (10 mmoles) of **15** in 6 ml of trifluoroacetic acid and 15 ml of triethylsilane was stirred for 4 days at 30°. After cooling to 0° the solution was neutralized with saturated sodium hydrogen carbonate solution. The precipitate was collected, washed with water and recrystallized from ethanol to give 2.07 g (74%) of **16**, mp 200-202°; ms: m/z 299 (M^+, 80%), 250 (71%), 54 (100%); ^{1}H-nmr (deuteriochloroform, 6 drops of dimethyl sulfoxide-d_6): δ 9.92 (s-broad, 1H, NH), 7.86-7.07 (m, 3H, arom H), 6.33 (s, 1H, thiophene H), 2.71 (q, 2H, J = 7.2 Hz, CH_2), 1.20 (t, 3H, J = 7.2 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{10}ClNO_2S$: C, 55.82; H, 3.60; N, 5.01. Found: C, 55.57; H, 3.47; N, 4.77.

7-Chloro-2-ethylthieno[2,3-*b*][1,4]benzoxazepine-5(4*H*)-thione (**17**).

To a mixture of 0.84 g (3 mmoles) of **16** in 50 ml of dry toluene 0.91 (2.25 mmoles) of Lawesson reagent was added and heated for 1 hour at 120°. After cooling the solvent was reduced *in vacuo* to one-half. The precipitate was washed and dried to give 0.56 g (63%) of **17**, mp 198°; ms: m/z 295 (M^+, 100%), 262 (48%); ^{1}H-nmr (deuteriochloroform): δ 10.31 (s-broad, 1H, NH), 8.18-7.00 (m, 3H, arom H), 6.34 (s, 1H, thiophene H), 2.71 (q, 2H, J = 7.2 Hz, CH_2), 1.24 (t, 3H, J = 7.2 Hz, CH_3).

Anal. Calcd. for $C_{13}H_{10}ClNOS_2$: C, 52.79; H, 3.41; N, 4.74. Found: C, 53.06; H, 3.13; N, 4.51.

7-Chloro-2-ethyl-5-(4-methyl-1-piperazinyl)thineo[2,3-*b*][1,4]benzoxazepine Hydrochloride (**18**).

To 20 ml of an ether solution of 3.61 g (10 mmoles) of **10**, a saturated ether solution of hydrogen chloride was added. The precipitate was filtered and washed with cold ether to give 3.19 g (72%) of **18**, mp 179-180°.

Anal. Calcd. for $C_{18}H_{20}ClN_3OS \cdot HCl$: C, 54.27; H, 5.31; N, 10.55. Found: C, 54.01; H, 5.42; N, 10.48.

9-(4-Methyl-1-piperazinyl)thieno[3,2-*b*][1,4]benzoxazepine (**19**).

A mixture of 0.47 g (2 mmoles) of **25** in 10 ml of *N*-methylpiperazine was heated at 120° for 3 hours. The excess of the amine was removed under reduced pressure. The residue was purified by column chromatography using toluene/ethyl acetate/triethylamine (6 + 3 + 1) as an eluent to give 0.46 g (76%) of **19**, mp 99-101°; ms: m/z 299 (M^+, 100%), 255 (79%), 229 (22%), 216 (42%); ^{1}H-nmr (deuteriochloroform): δ 7.62-7.04 (m, 4H, phenyl H), 6.74 (A-part of an AB-system, 1H, J = 5.8 Hz, thiophene H), 6.65 (B-part of an AB-system, 1H, J = 5.8 Hz, thiophene H), 3.63-3.42 (m, 4H, CH_2N), 2.60-2.41 (m, 4H, $(CH_2)_2N$), 2.35 (s, 3H, NCH_3).

Anal. Calcd. for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04. Found: C, 64.42; H, 5.52; N, 13.92.

7-Chloro-9-(4-methyl-1-piperazinyl)thieno[3,2-*b*][1,4]benzoxazepine (**20**).

Compound **20** was synthesized analogously to compound **19**. After purification by column chromatography using toluene/ethyl acetate/triethylamine (6 + 3 + 1) as an eluent 0.44 g (66%) of **20** was obtained, mp 135-137°; ms: m/z 334 (M^+, 18%), 250 (35%), 70 (100%); ^{1}H-nmr (deuteriochloroform): δ 7.53-7.01 (m, 3H, phenyl H), 6.77 (A-part of an AB-system, 1H, J = 5.8 Hz, thiophene H), 6.64 (B-part of an AB-system, 1H, J = 5.8 Hz, thiophene H), 3.62-3.40 (m, 4H, CH_2N), 2.66-2.41 (m, 4H, $(CH_2)_2N$), 2.35 (s, 3H, NCH_3).

Anal. Calcd. for $C_{16}H_{16}ClN_3OS$: C, 57.57; H, 4.83; N, 12.59. Found: C, 57.62; H, 4.68; N, 12.34.

Methyl 2-(2-Nitro-3-thienyloxy)benzoate (**21**).

To a suspension of 2.76 g (20 mmoles) of potassium carbonate in 50 ml of dry 2-butanone 1.87 g (10 mmoles) of methyl 5-chlorosalicylate was added and stirred for 20 minutes. Then 3.01 g (15 mmoles) of 3-bromo-2-nitrothiophene was added and the reaction mixture was heated for 48 hours at 100°. After cooling the solvent was distilled under reduced pressure and the residue partitioned between dichloromethane and water. The organic layer was dried with sodium sulfate, filtered and evaporated. The crude product was recyrstallized from ethanol to give 1.65 g (59%) of **21**, mp 112-113°; ms: m/z 279 (M^+, 1%), 233 ($M^+ - NO_2$, 33%), 128 (M^+ -methyl salicylate, 100%); ^{1}H-nmr (deuteriochloroform): δ 8.07-6.37 (m, 6H, arom H), 3.79 (s, 3H, OCH_3).

Anal. Calcd. for $C_{12}H_9NO_5S$: C, 51.61; H, 3.25; N, 5.02. Found: C, 51.41; H, 3.11; N, 4.84.

Methyl 5-Chloro-2-(2-nitro-3-thienyloxy)benzoate (**22**).

Compound **22** was synthesized analogously to compound **21**. Recrystallization from ethanol gave 2.38 g (76%) of **22**; mp 125-126°; ms: m/z 313 (M^+, 4%), 128 (M^+ -methyl chlorosalicylate, 100%); ^{1}H-nmr (deuteriochloroform): δ 8.00-6.43 (m, 5H, arom H), 3.81 (s, 3H, OCH_3).

Anal. Calcd. for $C_{12}H_8ClNO_5S$: C, 45.95; H, 2.57; N, 4.47. Found: C, 46.16; H, 2.65; N, 4.35.

Thieno[3,2-*b*][1,4]benzoxazepin-9(10*H*)-one (**23**) [10].

To a solution of 1.95 g (7 mmoles) of **21** in 5 ml of methanol, 20 ml of toluene and 3.5 ml of glacial acetic acid, 1.40 g of iron powder was added. This mixture was heated at 90° under argon for 2 hours. After this, 20 ml of toluene and 5 ml of acetic acid were added and the mixture was refluxed for 15 hours. After cooling the solid was collected and washed with ether. The filtrate was washed with a saturated sodium hydrogen carbonate solution, dried and evaporated. The crude product was recrystallized from toluene to give 0.79 g (52%) of **23**, mp 228°.

7-Chlorothieno[3,2-*b*][1,4]benzoxazepin-9(10*H*)-one (**24**).

Compound **24** was synthesized analogously to compound **23**. After recrystallization from toluene 0.65 g (37%) of **24** was obtained, mp 228-230°; ms: m/z 251 (M^+, 100%), 223 (M^+ -CO), 19%); ^{1}H-nmr (deuteriochloroform/dimethyl sulfoxide-d_6): δ 10.65 (s-broad, 1H, NH), 8.01-7.08 (m, 3H, phenyl H), 6.86 (A-part of an AB-system, 1H, J = 5.8 Hz, thiophene H), 6.73 (B-part of an AB-system, 1H, J = 5.8 Hz, thiophene H).

Anal. Calcd. for $C_{11}H_6ClNO_2S$: C, 52.49; H, 2.40; N, 5.57. Found: C, 52.40; H, 2.23; N, 5.41.

Thieno[3,2-*b*][1,4]benzoxazepine-9(10*H*)-thione (**25**).

To a solution of 0.65 g (3 mmoles) of **23** and 1.01 g (2.5 mmoles) of Lawesson reagent in 15 ml of dry toluene was refluxed for 2 hours. After cooling the precipitate was separated and the filtrate evaporated. The residue was recrystallized from ethanol to give 0.49 g (70%) of **25**, mp 193-197°; ms: m/z 233 (M^+, 100%), 206 ($M^+ - C_2H_3$, 50%); ^{1}H-nmr (deuteriochloroform/dimethyl sulfoxide-d_6): 8.20-6.92 (m, 4H, phenyl H), 6.89 (A-part of an AB-system, 1H, J = 5.7 Hz, thiophene H), 6.72 (B-part of an AB-system, 1H, J = 5.7 Hz, thiophene H).

Anal. Calcd. for $C_{11}H_7NOS_2$: C, 56.63; H, 3.02; N, 6.00. Found: C, 56.64; H, 3.04; N, 5.73.

7-Chlorothieno[3,2-*b*][1,4]benzoxazepine-9(10*H*)-thione (**26**).

Compound **26** was synthesized analogously to compound **25**. After recrystallization from toluene 1.04 g (65%) of **26** was obtained, mp 222-225°; ms: m/z 267 (M^+, 100%), 240 ($M^+ - C_2H_3$, 40%), 205 ($M^+ - C_2H_3$-Cl, 50%); ^{1}H-nmr (deuteriochloroform/dimethyl sulfoxide-d_6): δ 12.51 (s-broad, 1H, NH), 8.11-6.52 (m, 5H, arom H).

Anal. Calcd. for $C_{11}H_6ClNOS_2$: C, 49.35; H, 2.26; N, 5.23. Found: C, 49.56; H, 2.14; N, 5.06.

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