Dithieno- and Thienobenzothiazines (1)

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The synthesis of some isomeric dithienothiazine systems has been described. These thiazines were made by an Ullman type cyclization reaction, starting with the appropriate dithienylsulphides. During the ring closure reaction hydrogen chloride was eliminated from the β-chloropropionyl side chain resulting in the formation of the acryloylthiazines **5**, **7** and **11**. This reaction was studied under various conditions and some of the byproducts were identified. The general applicability of the reaction was demonstrated by the synthesis of two isomeric thienobenzothiazines **14** and **16**. Addition of *N*-methylpiperazine afforded the (*N*-methylpiperazinyl)propionylthienothiazines, which were isolated as their hydrochloride salts. The latter compounds were tested for neuroleptic and antidepressive properties, but were shown to be devoid of activity. This lack of activity is discussed in terms of the hampered formation of the radicalcations, as was shown by the electrochemical oxidation of these compounds. Efforts to reduce the carbonyl function to give the propyl chain failed, due to an elimination of the side chain.

Despite extensive pharmacological and chemical research on the phenothiazines, the neuroleptic mode of action of these drugs is still obscure (2-5). Since in 1959 Karreman *et al.* (6) proposed a relationship between the biological activity and the electron donating properties of chlorpromazine, much emphasis has been placed on this phenomenon (7-11).

Besides the question whether charge-transfer complexes play indeed a vital role in the physiological activity of phenothiazines, the formation of radical-cations has received attention in recent years (12-16), especially after it appeared that these radical-cations could inhibit enzyme systems, such as microsomal ATP-ase (17). However, research on the role of the radical-cations of different substituted phenothiazines is hampered by the differences in the physico-chemical properties of these substances (18). For example, the introduction of different substituents and side chains not only changes the electronic character but it also affects factors like stereochemistry, protein-binding and lipophilicity as well. Thus, to what extent the radical-cation determines the biological activity of such substances is therefore difficult to say.

In our opinion it would be worthwhile to synthesize a series of thiazines that would differ in electronic properties but otherwise would exhibit similar physical properties. In this way the components would form different radical cations but would, at least theoretically, reach the same receptors in comparable concentrations. As in a series of compounds with a similar tricyclic structure the majority of the physical properties depends primarily on the substituents and the side chain, the latter being kept the same in such a series of thiazines. The electronic differences in such a series should then be made in the tricyclic system, which could be done by replacing one or two benzene moieties by an aromatic heterocycle. For isosteric reasons we chose thiophene as this aromatic heterocycle. The synthesis of a new member in the thienobenzothiazine series and the first synthesis of a dithienothiazine, both sulfur analoga of the phenothiazines (19), are described in our first paper (20). In this paper we describe the evaluation of the general synthetic route to these new heterocyclic compounds and some preliminary experiments to obtain the required physiologically active compounds.

In order for the thienothiazines to be pharmocologically active, the thiazine nitrogen atom should have a side chain consisting of two or three carbon atoms and a terminal tertiary amino group (21). Efforts to prepare the unsubstituted dithienothiazine system, in which the proper side chain could be introduced by alkylation, were unsuccessful due to decomposition of this unsubstituted dithienothiazine system. To circumvent the need for an unsubstituted dithienothiazine as an intermediate, a reaction scheme was developed in which the side chain could be introduced prior to the formation of the dithienothiazine system.

The synthesis was started with amine **1** from which the amide **2** was made by a reaction with β-chloropropionyl chloride. Bromination of the amide **2** was performed with

NBS in chloroform-acetic acid, giving the bromocompound **3** in 80% yield. After ring closure of **3** with copper bronze and potassium carbonate in nitrobenzene, a product was isolated which was not the expected thiazine **4** but the acryloylderivative **5**. The structure of this new substituted

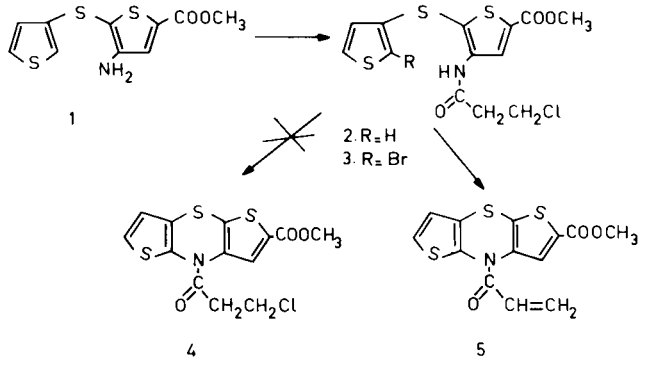


Fig. 1

thiazine was supported by elemental analysis, the infrared spectrum and the pmr spectrum, the latter showing absorptions at δ 5.93 and δ 6.69 ppm for the vinyl protons. The low yield in which the thiazine was isolated from the coloured reaction mixture might be due to the formation of several by-products.

For example, analogous to phenothiazine chemistry (22,23), elimination of the side chain can take place. The thus formed *N*-unsubstituted dithienothiazine could rapidly oxidize to a radical-cation which is then transposed into several coloured products (24).

In order to increase the yield of the ring closure we performed this reaction under various conditions.

a) Heating amide **3** for 30 hours in dimethylformamide with copper-bronze and potassium-acetate gave, besides 10% of **5**, the debrominated compound **6** in 20% yield. The structure of the latter was supported by elemental analysis and its pmr spectrum, showing a characteristic

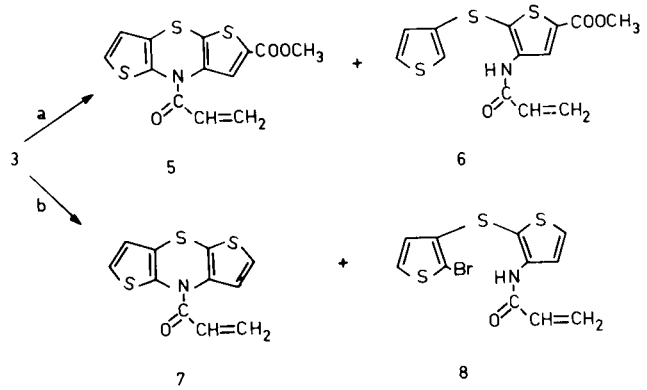


Fig. 2

pattern of a 3-substituted thiophene nucleus (25). The reductive substitution of the bromide atom may have taken place under the influence of copper with the solvent serving as a hydrogen donor (26, 27).

b) Heating **3** with potassium acetate in dimethylformamide for 20 hours, then adding copper-bronze and further heating for 8 hours resulted in the formation of equal amounts (10%) of the products **7** and **8**. The structures of these compounds were confirmed by spectroscopic data and elemental analysis. An explanation for this reaction can be given in terms of acetate-catalyzed hydrolysis (28, 29), followed by a copper-catalysed decarboxylation (30).

c) Finally some reactions with amide **3** were performed by refluxing in nitrobenzene with copper and potassium carbonate or potassium acetate and by refluxing in diphenyl ether with copper and potassium acetate. The reaction in diphenyl ether gave the highest yield (30-50%) of the acryloylthiazine **5**.

An isomer of the dithienothiazine **5** was synthesized, using **10** as starting material but otherwise following the same reaction sequence as described for the thiazine **5**. The 2-methoxycarbonyl-8-acryloyl-8*H*-dithieno[2,3-*b*:3',-2'-*e*]-1,4-thiazine **11** was obtained in 20% yield from the ring closure reaction. The structure was supported by spectroscopic evidence and an elemental analysis.

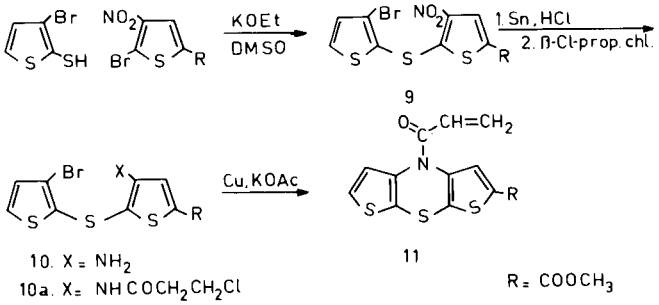


Fig. 3

Because of our aim to develop a general route for the synthesis of thiophene isosters we also investigated whether the thienobenzothiazines could be synthesized by this route. In the same way as described for the synthesis of the thiazines **5** and **11** we prepared the thienobenzothiazines **14** and **16** in 53% and 27% yield, respectively, using the ring closure procedure as described earlier under c.

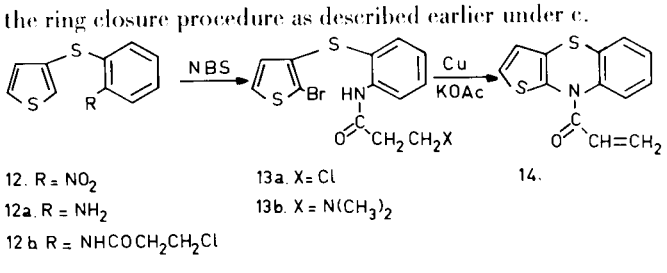
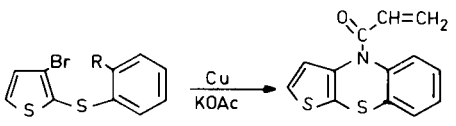


Fig. 4

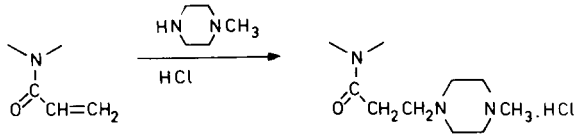


15. R = NO_2
15a. R = NH_2
15b R = NH CO CH_2CH_2Cl

16.

Fig. 5

As is evident from the structures of all thiazines, hydrogen chloride was eliminated from the side chain during the ring closure reactions. Substitution of the chlorine by a dimethylamine group as in **13b** did not prevent the formation of the acryloyl chain during the reaction. The acryloyl group, however, offered an easy route to the desired compounds because a terminal amine group can now be introduced by a Michael-type addition. By adding *N*-methylpiperazine to the activated double bond of the compounds **5**, **7**, **11**, **14** and **16** the respective thiazines **17-21** were obtained as yellow oils and characterized by their infrared spectra.

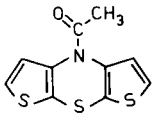


5, 7, 11, 14, 16

17, 18, 19, 20, 21

Fig. 6

In order to obtain the psychotropic phenothiazine analogs, the carbonyl group in the synthesized thienothiazines **17-21** has to be reduced. Because of the rather small amounts of the dithienothiazines available, we initially chose to study this reduction reaction with a model compound namely the *N*-acetyldithienothiazine **22** (31).



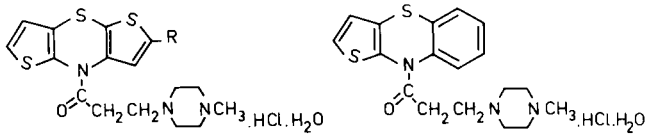
22

Fig. 7

All attempts to reduce the carbonyl function with lithium aluminium hydride and aluminium hydride resulted in the formation of dark coloured reaction mixtures from which no product could be isolated.

With the thienobenzothiazine **20** the same negative results were obtained but after reduction of **21** with aluminium hydride in tetrahydrofuran a small amount of the unsubstituted thienobenzothiazine was isolated. These results seems to indicate that elimination of the side chain occurs, with the respective dealkylated thiazines of **22** and **20** being unstable.

The failure to reduce the carbonyl function thus prevents the formation of thienothiazines with possible neuroleptic activity as this would require a propyl group to be present in the side chain. However, as the carbonyl components have a structural resemblance to chloracizine (32), a phenothiazine derivative with a carbonyl group showing antidepressive properties, it seemed appropriate to check the pharmacological activity of the newly synthesized thiazines in this area.



17. R = $COOCH_3$
18. R = H

20

Fig. 8

The thienothiazines **17**, **18** and **20** were converted to their hydrochloride salts by passing dry hydrogen chloride gas through a solution of the thiazines in dry benzene. The structure of the resulting salts was established by spectroscopic data and elemental analysis. The compounds were submitted for acute toxicity and behavioural studies in mice using the methods described by Swinyard (33). Antagonism to footshock-induced agression (p.o. 100 mg./kg.), antagonism to apomorphine in rats with unilateral laesis (p.o. 30 mg./kg.), potentiation of hexobarbital sleeping time (46 mg./kg.) and α-sympaticolytic effects in the isolated *vas deferens* of the rat were studied as was antagonism for tetrabenazine ptosis, which would be indicative for a possible anti-depressive action (34).

The compounds were found to be devoid of activity in these test systems. If radical-cations are required for activity *in vivo*, the presence of the carbonyl group may be the reason for the lack of activity of the thiazines, because the free electron pair on the ring nitrogen atom will be delocalised over the carbonyl function, thus hampering radical-cation formation. This assumption is supported by an experiment in which the radical-cations were formed by electrochemical oxidation.

The half wave potentials of the first oxidation wave of the hydrochloride salts of the thiazines **17-21** were found to be 730, 610, 805, 750 and 835 mV, respectively. These values are much higher than the corresponding value of chlorpromazine, for which we found 385 mV, thus indicating easier radical-cation formation in the latter. On the other hand the differences in half wave values within the thienothiazine group would confirm our initial assumption that these components would indeed show different electronic properties.

We intend to elaborate further on substituted thienobenzothiazinesystems in a subsequent paper.

EXPERIMENTAL

Melting points were determined with an electrically heated oil bath and are uncorrected. Analyses were performed at the Analytical Department of the Chemical Laboratories. Ir spectra were measured with a Beckmann IR-33 spectrophotometer, uv spectra were determined in 95% ethanol using a Zeiss PMQ II spectrophotometer. The nmr spectra were recorded on a Varian Model A-60 (TMS as internal standard).

3-(β-Chloro)propionylamino-5-methoxycarbonyl-2,3′-dithienyl Sulfide (2).

To a stirred solution of 3.5 g. (13 mmoles) of amine **1** (20) and 1.5 ml. of pyridine in 20 ml. of benzene was added 2.0 g. (15 mmoles) of β-chloropropionyl chloride. The mixture was stirred for 0.5 hour at ambient temperature, water was added and stirring was continued for 0.5 hour. The solid product was collected (3.4 g.), the filtrate dried (calcium chloride) and concentrated *in vacuo* to give a second crop (0.5 g.). The amide **2** was recrystallized from ethanol to give 3.5 g. (75%) of white crystals (m.p. 131-131.5°).

Anal. Calcd. for $C_{13}H_{12}ClNO_3S_3$: C, 43.14; H, 3.34; N, 3.87; S, 26.58; Cl, 9.80. Found: C, 43.0; H, 3.5; N, 3.8; S, 26.4; Cl, 9.9.

3-(β-Chloro)propionylamino-5-methoxycarbonyl-2′-bromo-2,3′-dithienyl Sulfide (**3**).

A mixture of amide **2** (3.5 g., 9.6 mmoles) in chloroform-acetic acid (1:1) was treated portionwise with 1.33 g. (9.5 mmoles) of *N*-bromosuccinimide (NBS). The mixture was stirred for 1.5 hours and was poured into 50 ml. of water. The aqueous layer was extracted with chloroform and the combined chloroform layers were washed with 10% potassium hydroxide and water. The dried solution was evaporated and recrystallized from ethanol to afford 3.4 g. (80%) of amide **3**, m.p. 139.5-140°.

Anal. Calcd. for $C_{13}H_{11}BrClNO_3S_3$: C, 35.42; H, 2.52; N, 3.18; S, 21.82; Br, 18.13; Cl, 8.04. Found: C, 35.3; H, 2.5; N, 3.2; S, 21.9; Br, 18.1; Cl, 8.1.

6-Methoxycarbonyl-8-acryloyl-8*H*-dithieno[2,3-*b*:2′,3′-*e*]-1,4-thiazine (**5**).

A stirred mixture of 1.0 g. (2.2 mmoles) amide **3**, 0.2 g. of potassium acetate and 0.2 g. of copper bronze in 25 ml. of diphenyl ether was heated under nitrogen for 20 hours at 170-175°. The mixture was cooled, filtered and the filtrate chromatographed over a silica gel column. After elution with *n*-hexane to remove the diphenyl ether the material eluted with benzene was collected. The crude product was chromatographed over a short aluminium oxide (neutral) column with chloroform and recrystallized from ethanol (0.4 g., m.p. 117-118°); pmr: (deuteriochloroform): δ 3.87 (s, 3H); 5.93 (tr, 1H, J = 5.5 Hz); 6.69 (d, 3H, J = 5.5 Hz) 7.14 (d, 1H, J = 5.5 Hz); 7.51 (s, 1H); uv: λ max 265 nm (log ε 4.15); 3.42 (3.86).

Anal. Calcd. for $C_{13}H_9NO_3S_3$: C, 48.28; H, 2.82; S, 29.74. Found: C, 48.3; H, 3.0; S, 29.4.

3-Acryloylamino-5-methoxycarbonyl-2,3-dithienyl Sulfide (**6**).

A mixture of amide **3** (3.0 g., 6.6 mmoles), 0.6 g. of potassium acetate and 0.6 g. of copper bronze in dimethylformamide (60 ml.) was stirred under nitrogen at reflux temperature for 30 hours. The suspension was cooled and filtered. The filtrate was evaporated partially and the residue was dissolved in chloroform. The organic solution was washed with water, dried (magnesium sulfate) and concentrated *in vacuo*. The black oil was chromatographed over a silica gel column with benzene. From the first fractions, the thiazine **5** was isolated (140 mg., 7%). Further elution gave starting material followed by the sulfide **6** (200 mg., 14%). The crude product **6** was recrystallized from methanol with decoulorizing carbon to give white crystals, m.p. 118-119.5°; pmr (deuteriochloroform): δ 3.70 (s, 3H); 5.51 (q, 1H, J = 7.2 Hz, 3.8 Hz) 6.01 (d, 1H, J = 7.2 Hz); 6.05 (d, 1H, J = 3.8 Hz); 6.56 (q, 1H, J = 4.5 Hz, 1.2 Hz); 6.76 (q, 1H, J = 3.0 Hz, 1.2 Hz); 6.96 (q, 1H, J = 4.5 Hz, 3.0 Hz); 7.5 (br. s, 1H); 8.20 (s, 1H); uv: λ max 238 nm (log ε 4.27); 283 (4.32) sh 315 (4.00).

Anal. Calcd. for $C_{13}H_{11}NO_3S_3$: C, 47.98; H, 3.40; N, 4.30; S, 29.56. Found: C, 47.9; H, 3.4; N, 4.2; S, 29.2.

8-Acryloyl-8*H*-dithieno[2,3-*b*:2′,3′-*e*]-1,4-thiazine (**7**) and 3-Acryloylamino-2′-bromo-2,3′-dithienyl Sulfide (**8**).

A stirred solution of 1.0 g. (2.2 mmoles) of amide **3** and 0.5 g. of potassium acetate in dry dimethylformamide (30 ml.) was refluxed under nitrogen for 8 hours. Copper bronze was added and refluxing continued for 3 hours. The mixture was cooled, filtered and concentrated *in vacuo*. The residue was extracted into chloroform, the chloroform washed with water and dried (magnesium sulfate) and concentrated *in vacuo*. The oil was chromatographed over a silica gel column with benzene. The first compound that was isolated was chromatographed over a neutral aluminium oxide column with chloroform and recrystallized from methanol to give thiazine **7**, m.p. 151.5-152.5°; pmr (carbon tetrachloride): δ 5.85 (q, 1H, J = 7.0 Hz, 4.8 Hz); 6.63 (d, 1H, J = 4.8 Hz) 6.66 (d, 2H, J = 5.5 Hz); 6.81 (d, 1H, J = 5.8 Hz); 7.01 (d, 1H, J = 5.8 Hz); 7.20 (d, 1H, J = 5.5 Hz); uv: λ max 247 nm (log ε 4.13): 332 (3.70).

Anal. Calcd. for $C_{11}H_7NOS_3$: C, 49.78; H, 2.66; N, 5.28; S, 36.25. Found: C, 49.6; H, 2.7; N, 5.3; S, 35.9.

The second compound from the silica gel column was recrystallized from diisopropyl ether and afforded in variable amounts the sulfide **8**, m.p. 103-104.5°; pmr (carbon tetrachloride): δ 5.66 (q, 1H, J = 7.0 Hz, 4.5 Hz); 6.30 (d, 1H, J = 7.0 Hz); 6.31 (d, 1H, J = 4.5 Hz); 6.53 (d, 1H, J = 5.5 Hz); 7.11 (d, 1H, J = 5.5 Hz); 7.35 (d, 1H, J = 6.0 Hz); 8.05 (d, 1H, J = 6.0 Hz); 8.1 (br. s, 1H); uv: λ max 246 nm (log ε 4.11); 2.74 (4.17).

Anal. Calcd. for $C_{11}H_8BrNOS_3$: C, 38.16; H, 2.32. Found: C, 38.4; H, 2.5.

3-Nitro-5-methoxycarbonyl-3′-bromo-2,2′-dithienyl Sulfide (**9**).

To a solution of 2.0 g. (10 mmoles) of 3-bromo-2-thiophenethiol and 2.5 g. (10 mmoles) of methyl 2-bromo-3-nitrothiophene-5-carboxylate in 30 ml. of dimethylsulfoxyde was added 2.5 ml. of 4 *N* potassium ethoxide in absolute ethanol. The solution was stirred for 1 hour at ambient temperature, water was added and the yellow precipitate was collected. The nitrosulfide **9** was recrystallized from carbon tetrachloride to yield 2.3 g. (60%) of yellow crystals, m.p. 172-173.5°.

Anal. Calcd. for $C_{10}H_6BrNO_4S_3$: C, 31.58; H, 1.59; N, 3.68; S, 25.30; Br, 21.01. Found: C, 31.8; H, 1.7; N, 3.7; S, 25.0; Br, 20.6.

3-(β-Chloro)propionylamino-5-methoxycarbonyl-3′-bromo-2,2′-dithienyl Sulfide (**10a**).

The reduction of **9** was performed as described for amine **1** and afforded in 50% yield the amine **10**; pmr (carbon tetrachloride): δ 3.81 (s, 3H); 4.0 (br. s, 2H); 6.90 (d, 1H, J = 6.0 Hz); 7.18

(s, 1H); 7.21 (d, 1H, J = 6.0 Hz).

The amine **10** was treated with β-chloropropionyl chloride as described for the amide **2**, to give 75% of the amide **10a** m.p. 153-153.5°.

Anal. Calcd. for $C_{13}H_{11}BrClNO_3S_3$: C, 35.42; H, 2.52; N, 3.18; S, 21.84; Br, 18.13; Cl, 8.04. Found: C, 35.7; H, 2.5; N, 3.2; S, 21.8; Br, 17.9; Cl, 8.1.

2Methoxycarbonyl-8-acryloyl-8*H*-dithieno[2,3-*b*:3',2'-*e*]-1,4-thiazine (**11**).

The thiazine was synthesized in 20% yield analogous to the preparation of the thiazine **6**. After recrystallization from methanol, light brown needles were obtained m.p. 177.5-179°; pmr (carbon tetrachloride): δ 3.88 (s, 3H); 5.83 (q, 1H, J = 7.0 Hz, 5.5 Hz); 6.61 (d, 1H, J = 5.5 Hz); 6.63 (d, 1H, J = 7.0 Hz); 7.16 (d, 1H, J = 5.5 Hz); 7.28 (d, 1H, J = 5.5 Hz); 7.85 (s, 1H).

Anal. Calcd. for $C_{13}H_9NO_3S_3$: C, 48.28; H, 2.82; N, 4.33; S, 29.74. Found: C, 47.9; H, 2.9; N, 4.1; S, 29.6.

2-Nitrophenyl-3'-thienyl Sulfide (**12**).

To a stirred solution of 11.6 g. (0.1 mole) of 3-thiophenethiol and 25 ml. of 4 *N* potassium ethoxide in 75 ml. of dry dimethylsulfoxide was added portionwise 15.7 g. (0.1 mole) of *o*-chloronitrobenzene. The mixture was stirred for 1 hour, poured into water and the resulting oil was extracted with chloroform. The chloroform solution was washed, dried (calcium chloride) and evaporated. The yellow oil crystallized after some time and was recrystallized from methanol to give 14.2 g. (60%) of nitrosulfide **12** m.p. 77-77.5°.

Anal. Calcd. for $C_{10}H_7NO_2S_2$: C, 50.62; H, 2.97; N, 5.90; S, 27.02. Found: C, 50.3; H, 2.8; N, 5.9; S, 27.0.

2-Nitrophenyl-2'-(3-bromo)thienyl Sulfide (**15**).

The nitrosulfide **15** was synthesized in an analogous way as described above and gave 60% of yellow crystals m.p. 94-95°.

Anal. Calcd. for $C_{10}H_6BrNO_2S_2$: C, 37.99; H, 1.92; N, 4.43; S, 20.28; Br, 25.27. Found: C, 38.0; H, 1.9; N, 4.4; S, 20.2; Br, 25.4.

2-Aminophenyl-3'-thienyl Sulfide (**12a**).

The nitrosulfide **12** (11.0 g., 4.6 mmoles) was dissolved in a mixture of acetic acid (75 ml.) and water. The solution was heated at 90° and 11.0 g. of iron powder was introduced over a period of 25 minutes. When the addition was complete the mixture was refluxed for 4 hours. The clear solution was then poured into water and extracted into dichloromethane. The extract was washed with aqueous sodium bicarbonate, dried (calcium chloride) and evaporated to yield an amber coloured oil. The oil was distilled at reduced pressure and afforded 7.5 g. (80%) of colourless product, b.p. 156-160°/ 1 mm n_D^{20} 1.6808.

Anal. Calcd. for $C_{10}H_9NS_2$: C, 57.94; H, 4.38; N, 6.76; S, 30.93. Found: C, 57.7; H, 4.1; N, 6.8; S, 31.1.

2-(β-Chloro)propionylaminophenyl-3'-thienyl Sulfide (**12b**).

A solution of 13.0 g. (0.1 mole) of β-chloropropionyl chloride was added to a stirred solution of 18.5 g. (0.08 mole) of amine **12** in 200 ml. of benzene and 10 ml. of pyridine. The reaction mixture was stirred for 1 hour at ambient temperature and 100 ml. of water was added. After additional stirring for 30 minutes the benzene layer was separated. The aqueous phase was extracted with benzene and the combined extracts were washed (hydrochloric acid, water), dried (sodium sulfate) and evaporated. The residue was recrystallized from diisopropyl ether to yield 16.7 g. (70%) of amide **12b** m.p. 59-60°.

Anal. Calcd. for $C_{13}H_{12}ClNOS_2$: C, 52.44; H, 4.06; N, 4.70; S, 21.53; Cl, 11.90. Found: C, 52.6; H, 4.1; N, 4.6; S, 21.4; Cl, 12.2.

2-(β-Chloro)propionylaminophenyl-2'-(3'-bromo)thienyl Sulfide (**15b**).

From amine **15a**, synthesized as described for amine **12a**, b.p. 56-60°/ 0.2 mm, the amide **15b** was prepared analogous as described above for **12b**. The yield was 76% of white crystals from diisopropyl ether m.p. 106-107°.

Anal. Calcd. for $C_{13}H_{11}BrClNOS_2$: C, 41.46; H, 2.95; N, 3.73; S, 17.02; Br, 21.22; Cl, 9.42. Found: C, 41.8; H, 3.1; N, 3.7; S, 17.1; Br, 21.2; Cl, 9.4.

Amine **15a**.

Anal. Calcd. for $C_{10}H_8BrNS_2$: C, 41.96; H, 2.82; N, 4.89. Found: C, 42.0; H, 2.8; N, 4.8.

2-(β-Chloro)propionylaminophenyl-3'-(2'-bromo)thienyl Sulfide (**13a**).

Bromination of amide **12b** was performed as described for **3**. From 12.0 g. (4.0 mmoles) of amide **12b**, 12.2 g. (81%) of the brominated product **13a** was obtained after recrystallization from diisopropyl ether, m.p. 69-70°.

Anal. Calcd. for $C_{13}H_{11}BrClNOS_2$: C, 41.46; H, 2.95; N, 3.79; Br, 21.21; Cl, 9.41. Found: C, 41.5; H, 3.0; N, 3.8; Br, 20.9; Cl, 9.3.

2-(β-Dimethylamino)propionylaminophenyl-3'-(2'-bromo)thienyl Sulfide (**13b**).

A solution of 5.6 g. (15 mmoles) amide **13a** in 110 ml. of benzene was saturated with dimethylamine and refluxed for 5 hours. The reaction mixture was poured into water and the benzene layer was extracted with 10% hydrochloric acid. The acidic phase was treated with 2 *N* sodium hydroxide and extracted with dichloromethane. The organic layer was washed with water, dried (magnesium sulfate) and concentrated *in vacuo*. The remaining oil was, after solidification, recrystallized from ethanol to give 3.2 g. (71%) of amide **13b** m.p. 94-95°.

Anal. Calcd. for $C_{15}H_{17}BrN_2OS_2$: C, 46.75; H, 4.45; N, 7.27; S, 16.64; Br, 20.73. Found: C, 46.5; H, 4.5; N, 7.2; S, 16.7; Br, 21.0.

9-Acryloyl-9*H*-thieno[3,2-*b*]benzo-1,4-thiazine (**14**) and 4-Acryloyl-4*H*-thieno[2,3-*b*]benzo-1,4-thiazine (**16**).

The thiazines **14** and **16** were synthesized by heating the amides **13a** and **15b** in diphenyl ether with potassium acetate and copper bronze as described for the synthesis of the thiazine **5**.

The diphenyl ether was removed by elution with *n*-hexane over a silica gel column. The thiazine **14** m.p. 119-120° was isolated in 53% after subsequent elution with benzene, chromatography over a short aluminium oxide column with chloroform and recrystallization from ethanol; mass spectrum: m/e 259 (26), 205 (20), 204 (100), 160 (14), 128 (5), 116 (5), 109 (5) 101 (5), 83 (8), 69 (10), 55 (8).

Anal. Calcd. for $C_{13}H_9NOS_2$: C, 60.20; H, 3.50; N, 5.40; S, 24.73. Found: C, 60.6; H, 3.8; N, 5.4; S, 24.6.

Thiazine **16** was obtained in 27% yield as light brown needles m.p. 144-144.5° after elution with chloroform and chromatography over aluminium oxide with chloroform-benzene (2:1) followed by recrystallization from methanol. The compound showed a mass spectrum strong resembling that of thiazine **14**; mass spectrum: m/e 259 (20), 205 (20), 204 (100), 160 (6), 128 (5), 102 (8), 69 (9), 55 (6).

Hydrochloride Salts of the Thiazines.

The hydrochloride salts were obtained following the next procedure described for the synthesis of **17**.

The acryloylthiazine (280 mg.) was dissolved in 10 ml. of dry benzene and 1.5 g. of *N*-methylpiperazine was added. The mixture was kept 10 hours at room temperature, 0.1 ml. of water was added and the solution was evaporated *in vacuo*. The mixture was dissolved in benzene 0.1 ml. of water added and the solution was again evaporated. A solution of the *N*-methylpiperazine derivative in benzene was dried over molecular sieves and treated with dry hydrogen chloride gas. The precipitate was collected, dried and recrystallized from ethanol to yield 160 mg. (43%) of hydrochloride salt.

Anal. Calcd. for $C_{18}H_{21}N_3O_3S_3 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 42.77; H, 4.79; N, 8.31; S, 19.03; Cl, 14.03. Found: C, 42.6; H, 4.9; N, 8.3; S, 19.1; Cl, 14.4.

Compound **18**.

Yield 80% recrystallized from ethanol, m.p. 218° dec.

Anal. Calcd. for $C_{16}H_{19}N_3OS_2 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 42.95; H, 4.96; N, 9.39; S, 21.50; Cl, 15.85. Found: C, 42.9; H, 5.1; N, 9.8; S, 21.6; Cl. 16.0.

Compound **19**.

Pmr (perdeuteriomethanol + deuterium oxide): δ 2.98 (s, 3H); δ 3.2-3.5 (m, 12H); δ 3.90 (s, 3H); δ 7.28 (d, 1H = 5.8 Hz); δ 7.58 (d, 1H = 5.8 Hz); δ 7.95 (s, 1H); ir: 3400, 2500, 2400, 1710, 1680 cm^{-1}; uv (water): λ max 246 nm (log ε 4.15) sh 295 (3.73) 330 (3.73); mass spectrum: m/e 423.

Compound **20**.

Yield 60%, recrystallized from ethanol, m.p. 196° dec.

Anal. Calcd. for $C_{18}H_{21}N_3OS_2 \cdot HCl \cdot H_2O$: C, 52.24; H, 5.85; N, 10.16; S, 15.49; Cl, 8.57. Found: C, 52.5; H, 5.8; N, 10.3; S, 15.5; Cl, 9.3.

Compound **21**.

Pmr (perdeuteriomethanol + deuterium oxide) δ 3.00 (s, 3*H*); δ 3.2-3.5 (m, 12*H*); δ 7.2-7.5 (m, 6*H*); ir: 3400, 2400, 1690 cm^{-1} uv (water): λ max 241 nm (log ε 4.02), 275 (3.87); mass spectrum: m/e 359.

Voltammetry.

A two-electrod polarograph with electronic scan was used. The polarograph was assembled from modules of the MPI-system. A rotating platinum electrode (length 5 mm, diameter 0.5 mm) and a saturated calomel electrode were used. The platinum electrode was pretreated by polarizing during 15 minutes at -0.5 V and 5 minutes at +1.0 V in a solution of 12 *N* sulfuric acid. Solutions of 2×10^{-4} *M* in 12 *N* sulfuric acid were made by dissolving the hydrochloride salts in water and diluting with 12 *N* sulfuric acid. Before running the voltage-current curves a nitrogen stream was passed through the solution for 5 minutes. The following values of the first oxidation waves of the hydrochloride salts were obtained: **17**, 730 mV; **18**, 610 mV; **19**, 805 mV; **20**, 750 mV; **21**, 835 mV.

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