Synthesis in the Thienobenzoxazepine Series. First Synthesis of a Diethienoxazepine

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In an investigation of novel tricyclic systems, synthesis of several thieno[2,3-*b*][1,4]benzoxazepines and thieno[3,2-*b*][1,5]benzoxazepines were effected by ring closure of appropriately amino aldehyde compounds. A new oxazepine fused with two heterocyclic rings, the dithieno[3,2-*b*:2,3-*f*][1,4]oxazepine, is described.

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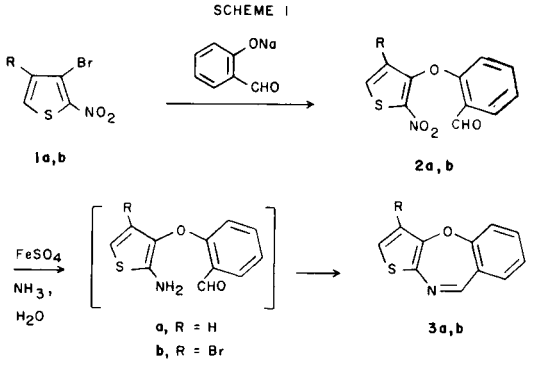
As some dibenzoxazepines have pharmacological activities [1-7], we found it interesting to prepare thiophene analogues, all the more so as only a few benzoxazepines annelated to a heterocyclic system are reported in literature [8-9]. As far as we know, the only reports in the series of thiophene are those of Press and co-workers [10-12].

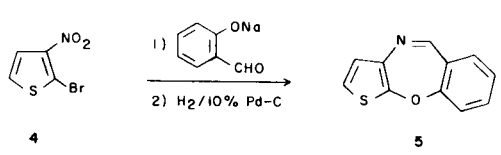
Several routes are available to obtain thienobenzoxazepines. Thus, the nucleophilic substitution [13] of *ortho*-bromonitrothiophene **1a,b** [14,15] by the sodium salt of salicylaldehyde, leads, after reduction of the nitro group with ferrous sulfate and ammonia, to an aminoaldehyde which spontaneously ring closed to thieno[3,2-*b*][1,4]benzoxazepine (**3a**) or bromo-3-thieno[3,2-*b*][1,4]benzoxazepine (**3b**). The reduction can be performed by hydrogen (10% palladium on charcoal) under pressure.

SCHEME I



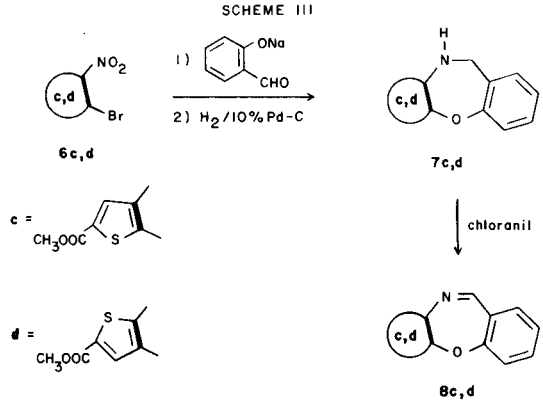
Similarly, thieno[2,3-*b*][1,4]benzoxazepine (**5**) was prepared (Scheme II) from 2-bromo-3-nitrothiophene (**4**) [16].

SCHEME II



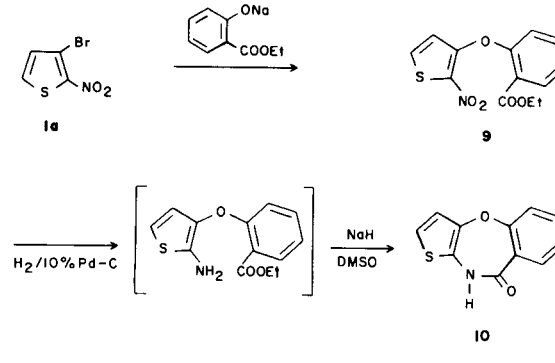
An interesting reaction (Scheme III) can be seen during the synthesis of methoxy-carbonyl derivatives of oxazepine **3a** and **5** respectively from methyl 5-bromo-4-nitrothiophene-2-carboxylate (**6c**) [16] and from methyl 4-bromo-5-nitrothiophene-2-carboxylate (**6d**) [17]. Indeed, hydrogenation leads to the two amines **7c,d**. The imines **8c,d** are reduced to amines all during their formation. As the ester function allows easier reduction, whatever the operating conditions, it was not possible to stop the reaction when it had reacted the imine stage. Thienobenzoxazepines **8c,d** were obtained by oxidizing the two amines **7c,d** with chloranil.

SCHEME III



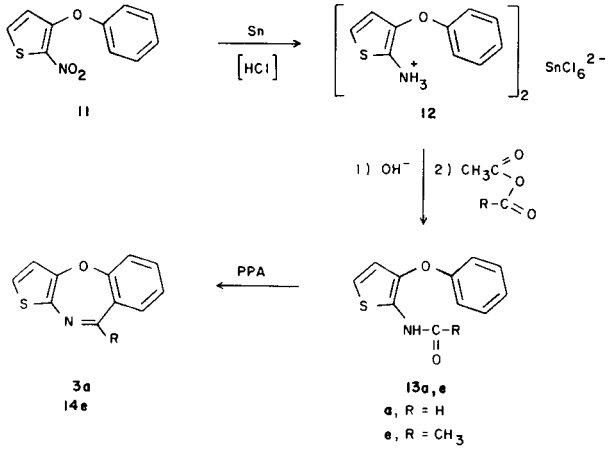
Derivatives of these oxazepines can be prepared. On the one hand, in the preceding method by replacing salicylaldehyde by ethyl salicylate, oxazepinones can be obtained. Let us mention, however, that cyclisation can be performed only in the presence of a mixture of sodium hydride and dimethylsulfoxide already used successfully to obtain diazepinones [18]. As Scheme IV shows, we have prepared one of the possible isomers, thieno[3,2-*b*][1,4]benzoxazepin-9-one (**10**).

SCHEME IV



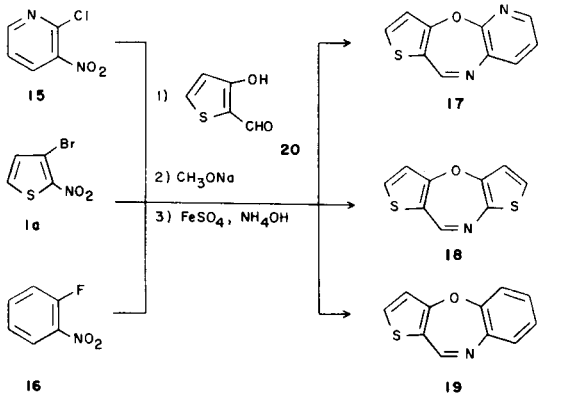
On the other hand (Scheme V), 2-nitro-3-phenoxythiophene (**11**), prepared through the action of sodium phenoxide upon 3-bromo-2-nitrothiophene (**1a**), is reduced by tin in the presence of concentrated hydrochloric acid. Tin salt **12**, treated by diluted sodium hydroxide, and then by anhydrides yields the corresponding amides **13a** and **13c**. These compounds submitted to the action of heated polyphosphoric acid, respectively cyclised into compounds **3a** and **14e**.

SCHEME V



To go deeper into our investigation field and show the generalization of the method, we replaced the benzene ring of thienobenzoxazepine by an heterocycle. As we had at our disposal some 3-hydroxy-2-formylthiophene (**20**) [19] which is the analogue of salicylaldehyde, we prepared two novel triheterocyclic ring systems: pyrido[2,3-*b*]thieno-[2,3-*f*][1,4]oxazepine (**17**) and diethieno[3,2-*b*:2,3-*f*][1,4]oxazepine (**18**). Furthermore, the reaction of **20** with *ortho*-fluoronitrobenzene (**16**) leads to an isomer of oxazepine **3a**, thieno[2,3-*f*][1,5]benzoxazepine (**19**) as shown in Scheme VI.

SCHEME VI



EXPERIMENTAL

Melting points were taken on a hot-stage apparatus and are uncorrected. The ^{1}H nmr spectra were determined using a Varian EM 360 spectrometer and chemical shifts (δ) are in ppm relative to internal hexamethyldisiloxane. Mass spectra were run on an AEI MS 30 spectrometer.

3-[2′-Formylphenoxy]-2-nitrothiophene (**2a**).

The sodium salt of salicylaldehyde (0.72 g, 0.005 mole) and 3-bromo-2-nitrothiophene (**1a**) (1.04 g, 0.005 mole) were dissolved in 10 ml of dimethylformamide. The mixture was refluxed 3 hours, cooled and diluted with ice water. The precipitate was collected and recrystallized from ethanol giving 0.65 g (50%), mp 134-135°.

Anal. Calcd. for $C_{11}H_7NO_4S$: C, 53.00; H, 2.83; N, 5.62. Found: C, 52.60; H, 2.83; N, 5.72.

Thieno[3,2-*b*][1,4]benzoxazepine (**3a**).

Compound **2a** (0.5 g, 0.002 mole) was added to a solution of ferrous sulfate (5 g) in water (15 ml). The mixture was boiled for 10 minutes, cooled to 70° and ethanol (15 ml) and concentrated ammonia (5 ml) added and then boiled for 1 hour. The black solid was filtered off and both solid and filtrate extracted with chloroform. The organic layer was dried and concentrated to give a brown solid which was triturated with petroleum ether. After removal of the solvent, the residue was recrystallized from hexane giving 80 mg (20%), mp 88-89°; ^{1}H nmr (deuteriochloroform): δ 6.40 (d, 1H, $J_{2,3}$ = 5.8 Hz, thiophene-H), 6.65-7.50 (m, 5H, aromatic-H, thiophene-H), 7.85 (S, 1H, HC=N).

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.61; H, 3.64; N, 6.82.

4-Bromo-3-(2′-formylphenoxy)-2-nitrothiophene (**2b**).

As described above, condensation of 3,4-dibromo-2-nitrothiophene (1.15 g, 0.004 mole) with sodium salt of salicylaldehyde (0.576 g, 0.004 mole) gave **2b**, 0.85 g (65%), mp 127-128° from ethanol.

Anal. Calcd. for $C_{11}H_6BrNO_4S$: C, 40.26; H, 1.84; N, 4.26. Found: C, 40.51; H, 2.05; N, 4.42.

3-Bromothieno[3,2-*b*][1,4]benzoxazepine (**3b**).

Compound **2b** (0.65 g, 0.002 mole) in a 1:1 mixture of ethanol-ethyl acetate was reduced at room temperature under pressure of hydrogen over palladium-charcoal (10%) for 5 hours. The catalyst was removed by filtration and the filtrate concentrated to give **3b**, 0.13 g (24%), mp 114-115° from hexane; ^{1}H nmr (deuteriochloroform): δ 6.90-7.70 (m, 5H, aromatic-H, thiophene-H), 8.00 (S, 1H, HC=N).

Anal. Calcd. for $C_{11}H_6BrNOS$: C, 47.16; H, 2.16; N, 5.00. Found: C, 47.32; H, 2.31; N, 5.20.

2-(2′-Formylphenoxy)-3-nitrothiophene.

Compound **4** (1.04 g, 0.005 mole) and sodium salt of salicylaldehyde (0.72 g, 0.005 mole) in the usual way gave the expected product, 0.60 g (48%), mp 130°.

Anal. Calcd. for $C_{11}H_7NO_4S$: C, 53.00; H, 2.83; N, 5.62. Found: C, 52.72; H, 3.02; N, 5.71.

Thieno[2,3-*b*][1,4]benzoxazepine (**5**).

The compound prepared above [2-(2′-formylphenoxy)-3-nitrothiophene] (0.5 g, 0.002 mole) was hydrogenated as above giving **5**, 0.08 g (20%), mp 95°; ^{1}H nmr (deuteriochloroform): δ 6.50-7.30 (m, 5H, aromatic-H, thiophene-H), 8.00 (S, 1H, H-(C-)=N-).

Anal. Calcd. for $C_{11}H_7NOS \cdot H_2O$: C, 60.25; H, 4.13; N, 6.40. Found: C, 60.51; H, 4.32; N, 6.35.

Methyl 4-(2′-Formylphenoxy)-5-nitrothiophene-2-carboxylate.

As described above, methyl 4-bromo-5-nitrothiophene-2-carboxylate (**6d**) (1.33 g, 0.005 mole) with the sodium salt of salicylaldehyde (0.72 g, 0.005 mole) gave the expected product, 0.9 g (58%), mp 108° from methanol-water.

Anal. Calcd. for $C_{13}H_9NO_6S$: C, 50.81; H, 2.95; N, 4.56. Found: C, 50.91; H, 3.10; N, 4.73.

2-Methoxycarbonyl-9,10-dihydrothieno[3,2-*b*][1,4]benzoxazepine (**7d**).

The compound prepared above [methyl 4-(2′-formylphenoxy)-5-nitro-

thiophene-2-carboxylate] (1.1 g, 0.0036 mole) was cyclised to give **7d**, 0.14 g (15%), mp 103° from hexane; ^{1}H nmr (deuteriochloroform): δ 3.75 (S, 3H, $COOCH_3$), 4.27 (S, 2H, >N-CH_2-), 6.80-7.35 (m, 5H, aromatic-H, thiophene-H).

Anal. Calcd. for $C_{13}H_{11}NO_3S$: C, 59.75; H, 4.24; N, 5.36. Found: C, 60.09; H, 4.53; N, 5.80.

Methyl 5-(2'-Formylphenoxy)-4-nitrothiophene-2-carboxylate.

In the usual way, methyl 5-bromo-4-nitrothiophene-2-carboxylate (**6c**) (2 g, 0.0075 mole) and the sodium salt of salicylaldehyde (1.1 g, 0.0075 mole) gave the expected product, 1.1 g (57%), mp 98° from methanol-water.

Anal. Calcd. for $C_{13}H_9NO_6S$: C, 50.81; H, 2.95; N, 4.56. Found: C, 50.60; H, 3.11; N, 4.72.

2-Methoxycarbonyl-4,5-dihydrothieno[2,3-*b*][1,4]benzoxazepine (**7c**).

The preceeding compound (0.8 g, 0.0026 mole) was hydrogenated in the usual way giving **7c**, 0.15 g (22%), mp 115° from hexane; ^{1}H nmr (deuteriochloroform): δ 3.73 (S, 3H, $COOCH_3$), 4.30 (S, 2H, N-CH_2-), 6.93-7.20 (m, 5H, aromatic-H, thiophene-H).

Anal. Calcd. for $C_{13}H_{11}NO_3S$: C, 59.75; H, 4.24; N, 5.36. Found: C, 59.90; H, 4.41; N, 5.72.

2-Methoxycarbonylthieno[2,3-*b*][1,4]benzoxazepine (**8c**).

Dihydrobenzoxazepine **7c** (0.15 g, 0.00058 mole) and chloranil (0.43 g, 0.0018 mole) in xylene (30 ml) was refluxed. After removal of the solvent, the solid was triturated with ether. The organic layer was then dried, and concentrated to give the product **8c**, 0.050 g, (31%), mp 152° from hexane; ^{1}H nmr (deuteriochloroform): δ 3.80 (S, 3H, $COOCH_3$), 6.80-7.30 (m, 5H, aromatic-H, thiophene-H), 7.45 (S, 1H, thiophene-H), 8.10 (S, 1H, H-(C-)=N-).

Anal. Calcd. for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40. Found: C, 60.78; H, 3.67; N, 5.15.

2-Methoxycarbonylthieno[3,2-*b*][1,4]benzoxazepine (**8d**).

Dehydrogenation of compound **7d** (0.14 g, 0.00054 mole) with chloranil in the usual way gave **8d**, 0.06 g (43%), mp 138° from hexane; ^{1}H nmr (deuteriochloroform): δ 3.80 (S, 3H, $COOCH_3$), 6.75-7.50 (m, 5H, aromatic-H, thiophene-H), 8.05 (S, 1H, H-(C-)=N).

Anal. Calcd. for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50; N, 5.40. Found: C, 60.51; H, 3.40; N, 5.69.

2-(2'-Formyl-3'-thienyloxy)-3-nitropyridine.

Condensation of the sodium salt of 2-formyl-3-hydroxythiophene (**20**) (1 g, 0.0067 mole) with 2-chloro-3-nitropyridine (**15**) as above gave the expected product, 0.95 g (57%), mp 128°.

Anal. Calcd. for $C_{10}H_6N_2O_4S$: C, 48.01; H, 2.42; N, 11.20. Found: C, 48.00; H, 2.61; N, 11.14.

3-(2'-Formyl-3'-thienyloxy)-2-nitrothiophene.

Compound **20** (0.75 g, 0.005 mole) with 3-bromo-2-nitrothiophene (**1a**) in the usual way gave the expected product, 0.75 g (60%), mp 140°.

Anal. Calcd. for $C_9H_5NO_4S_2$: C, 42.35; H, 1.97; N, 5.49. Found; C, 42.50; H, 2.08; N, 5.43.

3-(2'-Nitrophenoxy)-2-formylthiophene.

This compound was prepared from *o*-fluoronitrobenzene (**16**) (0.95 g, 0.0067 mole) and 2-formyl-3-hydroxythiophene (**20**) (0.0067 mole) as described above for **2a**, 0.95 g (57%), mp 81° from ethanol.

Anal. Calcd. for $C_{11}H_7NO_4S$: C, 53.02; H, 2.83; N, 5.62. Found: C, 52.84; H, 2.83; N, 5.68.

Pyrido[2,3-*b*]thieno[2,3-*f*][1,4]oxazepine (**17**).

Cyclisation of 2-(2'-formyl-3'-thienyloxy)-3-nitropyridine (0.75 g, 0.003 mole) with ferrous sulfate and ammonia in the usual way gave **17**, 0.13 g (21%), mp 128°; ms: m/e 202 (M^+); ^{1}H nmr (deuteriochloroform): δ 6.80-7.25 (m, 3H, pyridine-2H, thiophene-H), 7.35 (d, 1H, $J_{2,3}$ = 5,8 Hz, thiophene-H), 7.80-8.05 (m, 2H, pyridine-H, H-(C-)=N-).

Anal. Calcd. for $C_{10}H_6N_2OS$: C, 59.39; H, 2.99; N, 13.85. Found: C, 59.41; H, 3.16; N, 13.45.

Dithieno[3,2-*b*:2,3-*f*][1,4]oxazepine (**18**).

This oxazepine was obtained from 3-(2'-formyl-3'-thienyloxy)-2-nitrothiophene (0.70 g, 0.0027 mole) as described above for **17**. Recrystallization from hexane gave the product **18**, 0.07 g (12%), mp 120°; ^{1}H nmr (deuteriochloroform): δ 6.30 (d, 1H, $J_{2,3}$ = 5.7 Hz, thiophene-H_3), 6.40 (d, 1H, $J_{5,6}$ = 5.7 Hz, thiophene-H_5), 6.90 (d, 1H, $J_{2,3}$ = 5.7 Hz, thiophene-H_2), 7.25 (d, 1H, $J_{5,6}$ = 5.7 Hz, thiophene-H_6), 7.30 (S, 1H, H-(C-)=N-).

Anal. Calcd. for $C_9H_5NOS_2$: C, 52.15; H, 2.43; N, 6.76. Found: C, 51.14; H, 3.16; N, 6.45.

Thieno[2,3-*f*][1,5]benzoxazepine (**19**).

From 3-(2'-nitrophenoxy)-2-formylthiophene (0.90 g, 0.0036 mole) by a similar procedure to that described for **3a**, compound **19** was formed, 0.120 g (17%), mp 109°; ms: m/e 201 (M^+); ^{1}H nmr (deuteriochloroform): δ 6.60 (d, 1H, $J_{2,3}$ = 5.7 Hz, thiophene-H), 6.75-7.20 (m, 4H, aromatic-H), 7.30 (d, 1H, $J_{2,3}$ = 5.7 Hz, thiophene-H), 8.05 (S, 1H, H-(C-)=N-).

Anal. Calcd. for $C_{11}H_7NOS \cdot H_2O$: C, 60.25; H, 4.13; N, 6.40. Found: C, 60.18; H, 4.27; N, 6.65.

Ethyl 2-(2'-Nitro-3'-thienyloxy)benzoate (**9**).

Condensation of 3-bromo-2-nitrothiophene (**1a**) (0.75 g, 0.004 mole) with ethyl salicylate in the usual way gave **9**, 0.88 g (75%), mp 136° from ethanol.

Anal. Calcd. for $C_{13}H_{11}NO_3S$: C, 53.23; H, 3.78; N, 4.78. Found: C, 53.20; H, 3.98; N, 4.96.

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

The above compound (0.60 g, 0.002 mole) was hydrogenated in a 1:1 mixture of ethanol and ethyl acetate (50 ml) with 10% palladium on charcoal under pressure for 8 hours. The catalyst was removed by filtration and the solvent evaporated. The crude amine was dissolved in dry dimethylsulfoxide, then added under nitrogen in a mixture of sodium hydride (0.40 g of 50% dispersion in oil) and dimethylsulfoxide (25 ml) previously purged with nitrogen and heated to 70°. The mixture was stirred 10 minutes at this temperature then poured onto ice-water and extracted with ether. The extracts were washed with water, dried and evaporated. Crystallization of the residue from ethanol gave **10**, 0.11 g (25%), mp 228°; ms: m/e 217 (M^+); ^{1}H nmr (DMSO): δ 6.80 (d, 1H, $J_{2,3}$ = 5.7 Hz, thiophene-H), 7.05 (d, 1H, $J_{2,3}$ = 5.7 Hz, thiophene-H), 7.15-7.90 (m, 4H, aromatic-H).

Anal. Calcd. for $C_{12}1H_7NO_2S$: C, 60.83; H, 3.23; N, 6.45. Found: C, 60.52; H, 3.57; N, 6.68.

2-Nitro-3-phenoxythiophene (**11**).

Sodium phenate (5.8 g, 0.05 mole) and 3-bromo-2-nitrothiophene (**1a**) (10.4 g, 0.05 mole) as described earlier gave **11**, 6.7 g (60%), mp 122°.

Anal. Calcd. for $C_{10}H_7NO_3S$: C, 54.29; H, 3.19; N, 6.33. Found: C, 54.04; H, 3.26; N, 6.12.

2-Acetylamino-3-phenoxythiophene (**13e**).

To a solution of the above compound (6.6 g, 0.03 mole) in concentrated hydrochloric acid (100 ml) was added in portions at 45-50°, tin powder (7.2 g). The mixture was stirred until the tin powder had completely reacted then was allowed to cool overnight. The white solid mass was collected by filtration and washed with ether to give the tin double salt **12**, 6.4 g (60%). A suspension of a part of this salt (3.2 g, 0.0045 mole) in water was covered with ether. A solution of sodium hydroxide (5*N*) was added until the *p*H = 7. The organic layer was separated and the aqueous layer extracted twice with ether. The combined ethereal extracts were poured into an excess of acetic anhydride. The reaction mixture was then stirred for 1 hour. Water was then added, decanted and extracted three times with ether. The combined ethereal extracts were washed with sodium carbonate solution and water and dried. The solvent was evaporated and

the white solid recrystallized from a mixture of benzene-hexane giving **13e**, 1.2 g (58%), mp 121°.

Anal. Calcd. for $C_{12}H_{11}O_2NS$: C, 61.78; H, 4.75; N, 6.00. Found: C, 61.62; H, 5.00; N, 5.75.

2-Formylamino-3-phenoxythiophene (**13a**).

The preceeding double tin salt (3.2 g, 0.0045 mole) treated as above for **13e** with acetic-formic anhydride gave **13a**, 1.05 g (54%), mp 99° from benzene-petroleum ether.

Anal. Calcd. for $C_{11}H_9O_2NS$: C, 60.15; H, 4.14; N, 6.39. Found: C, 60.56; H, 4.25; N, 6.34.

9-Methylthieno[3,2-*b*][1,4]benzoxazepine (**14e**).

A stirred mixture of the amide **13e** (0.5 g, 0.0021 mole) and polyphosphoric acid (10 g) was heated in an oil-bath to a temperature of 90° for 2 hours. The mixture was cooled, diluted with water, neutralized with ammonia solution, and extracted with ether. The extracts were dried, concentrated and the residue was chromatographed on florisil eluting with benzene-hexane (1:3) to give a yellow product recrystallized from hexane, 0.15 g (33%), mp 110°; ms: m/e 215 (M^+); ^1H nmr (deuteriochloroform): δ 2.55 (S, 3H, methyl), 6.60 (d, 1H, $J_{2,3}$ = 5,7 Hz, thiophene-H), 7.10-7.50 (m, 5H, aromatic-H, thiophene-H).

Anal. Calcd. for $C_{12}H_9ONS$: C, 66.98; H, 4.19; N, 6.51. Found: C, 66.55; H, 4.28; N, 6.67.

Thieno[3,2-*b*][1,4]benzoxazepine (**3a**).

Compound **13a** (0.8 g, 0.0037 mole) was cyclised as above giving **3a**, 0.2 g (27%), mp 86°, undepressed on admixture with a sample prepared by cyclisation of compound **2a**.

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