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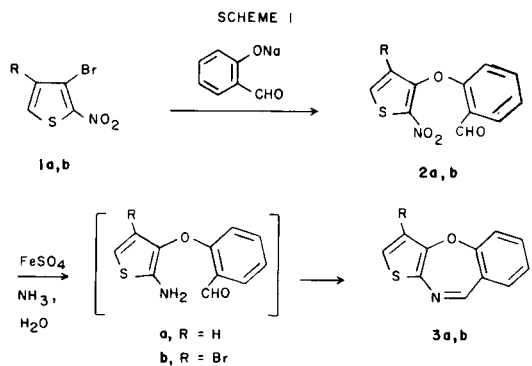
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In an investigation of novel tricyclic systems, synthesis of several thieno[2,3-*b*][1,4]benzoxazepines and thieno[3,2-*b*][1,5]benzoxazepines were effected by ring closure of appropriately amino aldehyde compounds. A new oxazepine fused with two heterocyclic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

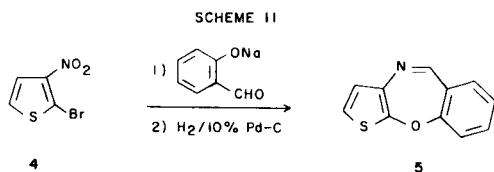
J. Heterocyclic Chem., **21**, 877 (1984).

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 annealed 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.

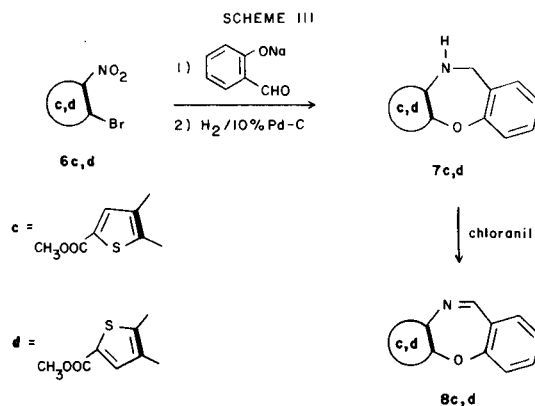


Similarly, thieno[2,3-*b*][1,4]benzoxazepine (**5**) was prepared (Scheme II) from 2-bromo-3-nitrothiophene (**4**) [16].

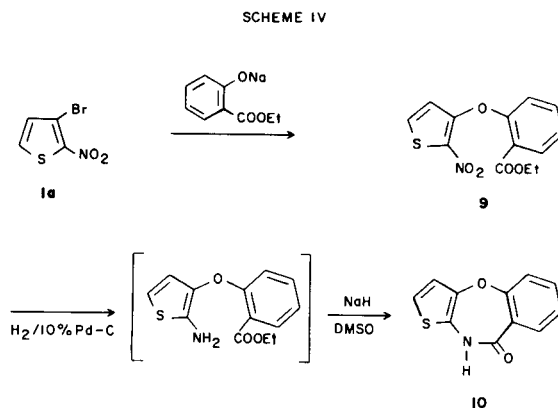


An interesting reaction (Scheme III) can be seen during the synthesis of methoxy-carbonyl derivatives of oxazepine **3a** and **5** respectively from methyl 5-bromo-4-nitrothiophene-2-carboxylate (**6c**) [16] and from methyl 4-bromo-5-nitrothiophene-2-carboxylate (**6d**) [17]. Indeed, hydrogenation leads to the two amines **7c,d**. The imines **8c,d** are re-

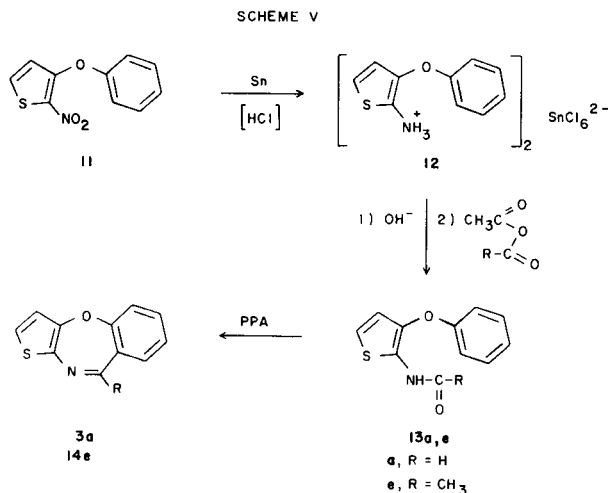
duced to amines all during their formation. As the ester function allows easier reduction, whatever the operating conditions, it was not possible to stop the reaction when it had reacted the imine stage. Thienobenzoxazepines **8c,d** were obtained by oxidizing the two amines **7c,d** with chloranil.



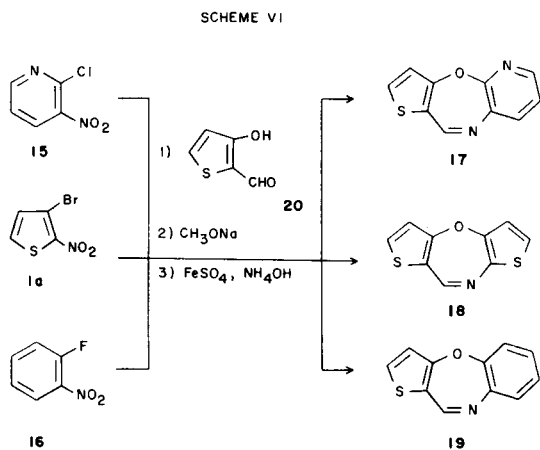
Derivatives of these oxazepines can be prepared. On the one hand, in the preceding method by replacing salicylaldehyde by ethyl salicylate, oxazepinones can be obtained. Let us mention, however, that cyclisation can be performed only in the presence of a mixture of sodium hydride and dimethylsulfoxide 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**).



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**.



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.



EXPERIMENTAL

Melting points were taken on a hot-stage apparatus and are uncorrected.

The ¹H 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 C₁₁H₇NO₄S: 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°; ¹H 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 C₁₁H₇NOS: 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 C₁₁H₆BrNO₄S: 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; ¹H nmr (deuteriochloroform): δ 6.90-7.70 (m, 5H, aromatic-H, thiophene-H), 8.00 (s, 1H, HC=N).

Anal. Calcd. for C₁₁H₆BrNOS: 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 C₁₁H₇NO₄S: 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°; ¹H nmr (deuteriochloroform): δ 6.50-7.30 (m, 5H, aromatic-H, thiophene-H), 8.00 (s, 1H, H-C(=N)-).

Anal. Calcd. for C₁₁H₇NOS·H₂O: 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 C₁₃H₉NO₆S: 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; ¹H nmr (deuteriochloroform): δ 3.75 (s, 3H, COOCH₃), 4.27 (s, 2H, >N-CH₂), 6.80-7.35 (m, 5H, aromatic-H, thiophene-H).

Anal. Calcd. for C₁₃H₁₁NO₃S: 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 C₁₃H₉NO₆S: 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 preceding compound (0.8 g, 0.0026 mole) was hydrogenated in the usual way giving **7c**, 0.15 g (22%), mp 115° from hexane; ¹H nmr (deuteriochloroform): δ 3.73 (s, 3H, COOCH₃), 4.30 (s, 2H, N-CH₂), 6.93-7.20 (m, 5H, aromatic-H, thiophene-H).

Anal. Calcd. for C₁₃H₁₁NO₃S: 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; ¹H nmr (deuteriochloroform): δ 3.80 (s, 3H, COOCH₃), 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 C₁₃H₉NO₃S: 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; ¹H nmr (deuteriochloroform): δ 3.80 (s, 3H, COOCH₃), 6.75-7.50 (m, 5H, aromatic-H, thiophene-H), 8.05 (s, 1H, H-(C)=N).

Anal. Calcd. for C₁₃H₉NO₃S: 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 C₁₀H₆N₂O₄S: 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 C₉H₅NO₄S₂: 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 C₁₁H₇NO₄S: 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⁺); ¹H 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 C₁₀H₆N₂OS: 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°; ¹H nmr (deuteriochloroform): δ 6.30 (d, 1H, J_{2,3} = 5.7 Hz, thiophene-H₃), 6.40 (d, 1H, J_{5,6} = 5.7 Hz, thiophene-H₃), 6.90 (d, 1H, J_{2,3} = 5.7 Hz, thiophene-H₂), 7.25 (d, 1H, J_{5,6} = 5.7 Hz, thiophene-H₆), 7.30 (s, 1H, H-(C)=N).

Anal. Calcd. for C₉H₆NOS₂: 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⁺); ¹H 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 C₁₁H₇NOS₂: 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 C₁₃H₁₁NO₃S: 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⁺); ¹H 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 C₁₂H₇NO₂S: 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 C₁₀H₇NO₃S: 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 pH = 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 C₁₂H₁₁O₂NS: 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 preceding 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 C₁₁H₉O₂NS: 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 C₁₂H₉ONS: 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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