Synthesis of Novel 3-(2-Thienyl)-1,2-diazepino[3,4-*b*]quinoxalines with Algicidal Activity

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The reaction of the quinoxaline *N*-oxide **1** with thiophene-2-carbaldehyde gave 6-chloro-2-[1-methyl-2-(2-thienylmethylene)hydrazino]quinoxaline 4-oxide **5**, whose reaction with 2-chloroacrylonitrile afforded 8-chloro-2,3-dihydro-4-hydroxy-1-methyl-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile **6**. The reaction of compound **6** with various alcohols in the presence of a base effected alcoholysis to provide the 5-alkoxy-8-chloro-2,3,4,6-tetrahydro-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]-quinoxalines **7a-d**. The reaction of compounds **7a** and **7b** with diethyl azodicarboxylate effected dehydrogenation to give the 5-alkoxy-8-chloro-4,6-dihydro-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]-quinoxalines **8a** and **8b**, respectively. Compounds **8a** and **8b** were found to show good algicidal activities against *Selenastrum capricornutum* and *Nitzchia closterium*.

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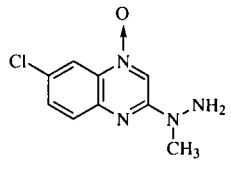
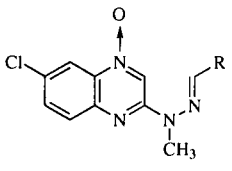
In previous papers, we reported the synthesis of the 2,3-dihydro-4-hydroxy-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitriles **3a,b** [2,3] and **3c** [4] from the quinoxaline *N*-oxide **1** *via* the hydrazones **2a,b** [2,3] and **2c** [4] (Chart 1), and the alcoholysis of compounds **3a,b** in the presence of a base gave the 5-alkoxy-2,3,4,6-tetrahydro-4-oxo-1*H*-1,2-diazepino[3,4-*b*]quinoxalines **4a,b** [2,3], respectively. From the data of the screening test, it was found that compounds **3a,b** and **4a,b** having the aryl group at the 3-position exhibited no antimicrobial activity, while compound **3c** [4] possessing the heteroaryl group at the 3-position showed weak antibacterial activity against *Xanthomonas oryzae* [5]. These screening data indicated that the replacement of the C_3-aryl group with furan brought about a favorable result for antibacterial activity in the 1*H*-1,2-diazepino[3,4-*b*]quinoxaline derivatives. In this context, we were interested in antibacterial activity of other 3-heteroaryl-1*H*-1,2-diazepino[3,4-*b*]-quinoxalines. Accordingly, we undertook the substitution of the C_3-furyl group with thiophene ring in the 1*H*-1,2-diazepino[3,4-*b*]quinoxalines following an isosteric displacement (Chart 2). This paper describes the synthesis

Chart 1

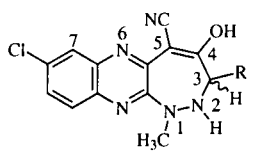


1



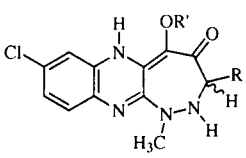
2

R: **a** - C_6H_4-4-Cl, **b** - C_6H_4-4-Br, **c** - 2-furyl



3

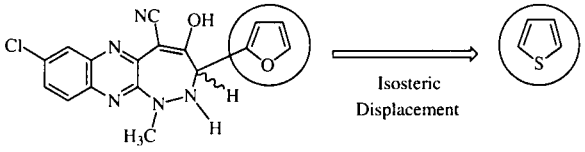
R: **a** - C_6H_4-4-Cl, **b** - C_6H_4-4-Br, **c** - 2-furyl



4

R: **a** -C_6H_4-4-Cl, **b** - C_6H_4-4-Br

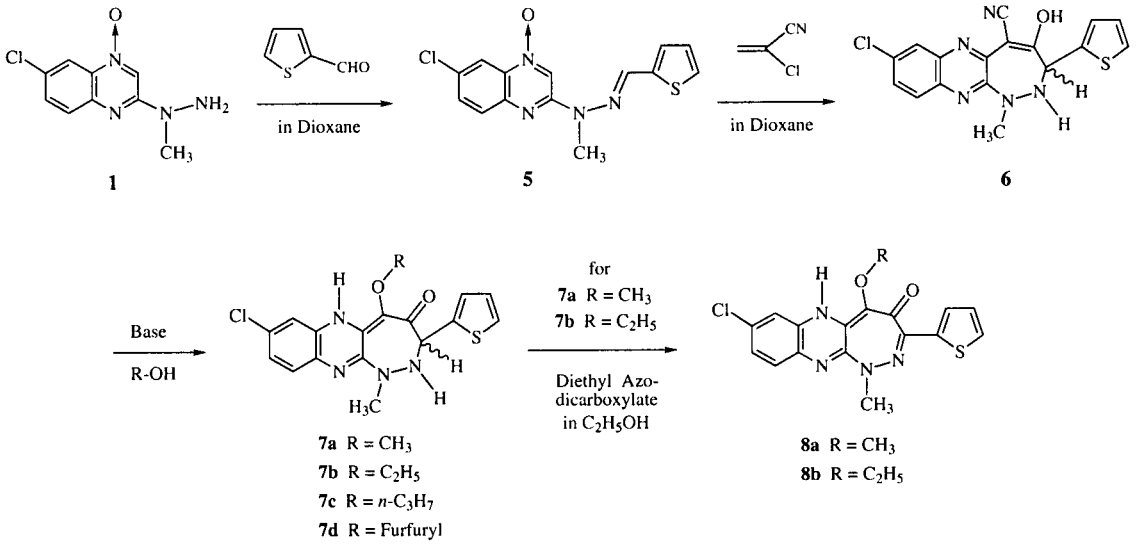
Chart 2



of various 3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxalines such as 2,3-dihydro-4-hydroxy-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile **6**, 5-alkoxy-2,3,4,6-tetrahydro-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxalines **7a-d**, and 5-alkoxy-4,6-dihydro-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]-quinoxalines **8a,b** (Scheme 1).

The reaction of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide **1** with thiophene-2-carbaldehyde gave 6-chloro-2-[1-methyl-2-(2-thienylmethylene)hydrazino]-quinoxaline 4-oxide **5**. Reaction of **5** with 2-chloro-

Scheme 1

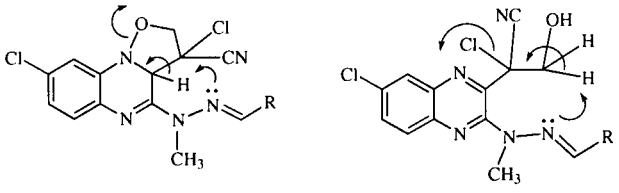


1 5 6

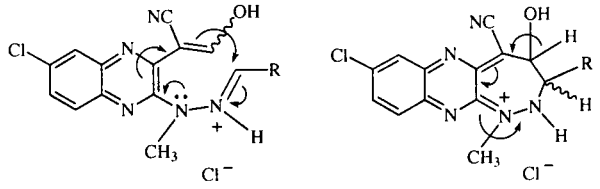
7a R = CH_3
7b R = C_2H_5
7c R = n-C_3H_7
7d R = Furfuryl

8a R = CH_3
8b R = C_2H_5

Chart 3

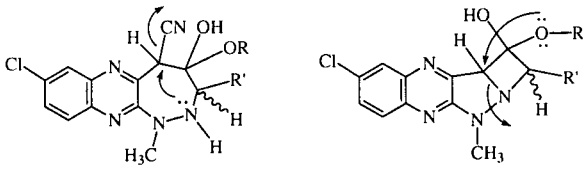


Intermediate **A** Intermediate **B**

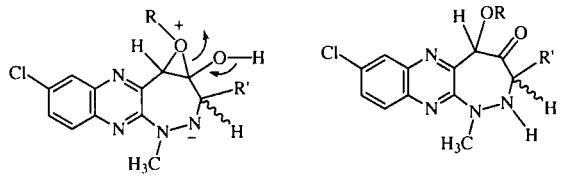


Intermediate **C** Intermediate **D**

Chart 4



Intermediate **E** Intermediate **F**



Intermediate **G** Intermediate **H**

acrylonitrile afforded 8-chloro-2,3-dihydro-4-hydroxy-1-methyl-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile **6** (Scheme 1) presumably *via* an intermediate **A** produced by 1,3-dipolar cycloaddition reaction, intermediates **B**, **C**, and **D** (Chart 3) [2,3]. The reaction of compound **6** with alcohols in the presence of a base resulted in alcoholysis to provide the 5-alkoxy-8-chloro-2,3,4,6-tetrahydro-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxalines **7a-d** presumably *via* intermediates **E** - **H** (Chart 4) [2,3,4,6,7]. The reaction of **7a,b** with diethyl azodicarboxylate in ethanol effected dehydrogenation to give 5-alkoxy-8-chloro-4,6-dihydro-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]-quinoxalines **8a,b**, respectively [7].

The structure of new compounds **6**, **7a-d**, and **8a,b** was supported by the spectral and analytical data. The 2,3-dihydro form of compounds such as **6** [2-4] and the 2,3,4,6-tetrahydro form of compounds such as **7a-d** [2,3,6,7] have already been clarified by the measurement of the NOE between the N_2-H and C_3-H protons and/or between the N_6-H and C_7-H protons in our previous papers.

Compounds **6**, **7a-d**, and **8a,b** did not show antibacterial activities, but compounds **8a,b** exhibited good algicidal activities against *Selenastrum capricornutum* and *Nitzchia closterium*.

EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO FT/IR-200 spectrometer. The nmr spectra were measured with a Varian XL-400 spectrometer at 400 MHz. The chemical shifts are given in the δ scale. The mass spectra (ms) were determined with a JEOL JMS-01S spectrometer.

Elemental analyses were performed on a Perkin-Elmer 240B instrument.

6-Chloro-2-[1-methyl-2-(2-thienylmethylene)hydrazino]quinoxaline 4-oxide (**5**).

A solution of 6-chloro-2-(1-methylhydrazino)quinoxaline 4-oxide (10 g, 44.5 mmoles) and thiophene-2-carbaldehyde (7.48 g, 66.8 mmoles) in dioxane (200 ml) was refluxed in an oil bath for 1 hour and then allowed to stand overnight to precipitate yellow prismic needles of compound **5**, which were collected by suction filtration and then washed with ethanol to give an analytically pure sample (12.91 g, 91%), mp 244-245°; ir: ν cm^{-1} 1570, 1530, 1520; ms: m/z 318 (M^+), 320 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 8.71 (s, 1H, C_3-H), 8.28 (s, 1H, hydrazone CH), 8.25 (d, J = 2.0 Hz, 1H, C_5-H), 7.81 (d, J = 9.0 Hz, 1H, C_8-H), 7.77 (dd, J = 2.0, 9.0 Hz, 1H, C_7-H), 7.61 (dd, J = 1.0, 5.0 Hz, 1H, thiophene C_5-H), 7.45 (dd, J = 1.0, 3.0 Hz, 1H, thiophene C_3-H), 7.13 (dd, J = 3.0, 5.0 Hz, 1H, thiophene C_4-H), 3.67 (s, 3H, N-CH_3).

Anal. Calcd. for $C_{14}H_{11}ClN_4OS$: C, 52.75; H, 3.48; Cl, 11.12; N, 17.58. Found: C, 52.55; H, 3.54; Cl, 11.32; N, 17.60.

8-Chloro-2,3-dihydro-4-hydroxy-1-methyl-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline-5-carbonitrile (**6**).

A solution of compound **5** (10 g, 31.4 mmoles) and 2-chloroacrylonitrile (11.0 g, 125.6 mmoles) in dioxane (400 ml) was refluxed in an oil bath for 2 hours. While the reaction mixture was hot, evaporation of the solvent *in vacuo* gave brown crystals of compound **6**, which were triturated with *n*-hexane and then collected by suction filtration (11.08 g, 96%). Recrystallization from dioxane/*n*-hexane afforded brick red granules, mp 220-221°; ir: ν cm^{-1} 1600, 1560, 1520; ms: m/z 369 (M^+), 371 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 13.22 (br, 1H, C_4-OH), 8.05 (d, J = 2.0 Hz, 1H, C_7-H), 7.48 (d, J = 9.0 Hz, 1H, C_{10}-H), 7.47 (dd, J = 1.0, 5.0 Hz, 1H, thiophene C_5-H), 7.41 (dd, J = 2.0, 9.0 Hz, 1H, C_9-H), 6.93 (dd, J = 3.5, 5.0 Hz, 1H, thiophene C_4-H), 6.87 (ddd, J = 1.0, 1.0, 3.5 Hz, 1H, thiophene C_3-H), 6.30 (d, J = 2.0 Hz, 1H, N_2-H), 5.45 (dd, J = 1.0, 2.0 Hz, 1H, C_3-H), 3.15 (s, 3H, N_1-CH_3).

Anal. Calcd. for $C_{17}H_{12}ClN_5OS$: C, 55.21; H, 3.27; Cl, 9.59; N, 18.94. Found: C, 55.17; H, 3.52; Cl, 9.57; N, 18.87.

8-Chloro-2,3,4,6-tetrahydro-5-methoxy-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline (**7a**).

A solution of compound **6** (3 g) in triethylamine (1 ml)/methanol (15 ml)/dioxane (60 ml) was heated on a boiling water bath for 2 hours. The solution was allowed to stand overnight to precipitate yellow cottony needles of compound **7a**, which were collected by suction filtration and washed with ethanol and then *n*-hexane to afford an analytically pure sample (1.85 g, 61%), mp 206-207°; ir: ν cm^{-1} 1650, 1610, 1540; ms: m/z 374 (M^+), 376 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 11.50 (s, 1H, N_6-H), 7.58 (d, J = 2.0 Hz, 1H, C_7-H), 7.34 (dd, J = 1.0, 5.0 Hz, 1H, thiophene C_5-H), 7.19 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.02 (dd, J = 2.0, 8.5 Hz, 1H, C_9-H), 6.87 (dd, J = 3.5, 5.0 Hz, 1H, thiophene C_4-H), 6.79 (ddd, J = 1.0, 1.0, 3.5 Hz, 1H, thiophene C_3-H), 6.08 (d, J = 2.5 Hz, 1H, N_2-H), 5.15 (dd, J = 1.0, 2.5 Hz, 1H, C_3-H), 3.70 (s, 3H, C_5-OCH_3), 3.08 (s, 3H, N_1-CH_3).

Anal. Calcd. for $C_{17}H_{15}ClN_4O_2S$: C, 54.47; H, 4.03; Cl, 9.46; N, 14.95. Found: C, 54.54; H, 4.21; Cl, 9.44; N, 14.78.

8-Chloro-5-ethoxy-2,3,4,6-tetrahydro-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline (**7b**).

A solution of compound **6** (3 g) in triethylamine (1 ml)/ethanol (15 ml)/dioxane (60 ml) was heated on a boiling water bath for 2 hours. Evaporation of the solvent *in vacuo* gave brown crystals of compound **7b**, which were triturated with *n*-hexane and collected by suction filtration (2.58 g, 82%). Recrystallization from dioxane/ethanol gave brown prismic needles, mp 190-191°; ir: ν cm^{-1} 1650, 1620, 1600; ms: m/z 388 (M^+), 390 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 11.54 (s, 1H, N_6-H), 7.55 (d, J = 2.0 Hz, 1H, C_7-H), 7.32 (dd, J = 1.0, 5.0 Hz, 1H, thiophene C_5-H), 7.19 (d, J = 9.0 Hz, 1H, C_{10}-H), 7.01 (dd, J = 2.0, 9.0 Hz, 1H, C_9-H), 6.88 (dd, J = 3.5, 5.0 Hz, 1H, thiophene C_4-H), 6.81 (ddd, J = 1.0, 1.0, 3.5 Hz, 1H, thiophene C_3-H), 6.08 (d, J = 2.0 Hz, 1H, N_2-H), 5.15 (dd, J = 1.0, 2.0 Hz, 1H, C_3-H), 4.24-4.10 (m, 2H, CH_2), 3.10 (s, 3H, N_1-CH_3), 1.19 (dd, J = 7.0, 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{18}H_{17}ClN_4O_2S$: C, 55.60; H, 4.41; Cl, 9.12; N, 14.41. Found: C, 55.53; H, 4.47; Cl, 9.12; N, 14.39.

8-Chloro-2,3,4,6-tetrahydro-1-methyl-4-oxo-5-propoxy-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline (**7c**).

A solution of compound **6** (3 g) in triethylamine (1 ml)/1-propanol (15 ml)/dioxane (60 ml) was heated on a boiling water bath for 2 hours. Evaporation of the solvent *in vacuo* gave an oily residue, which was crystallized from dioxane/ethanol/water to afford brown granules of compound **7c** (0.61 g, 18%), mp 123-124°; ir: ν cm^{-1} 1650, 1620, 1550; ms: m/z 402 (M^+), 404 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 11.56 (s, 1H, N_6-H), 7.56 (d, J = 2.0 Hz, 1H, C_7-H), 7.33 (dd, J = 1.0, 5.0 Hz, 1H, thiophene C_5-H), 7.19 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.01 (dd, J = 2.0, 8.5 Hz, 1H, C_9-H), 6.88 (dd, J = 3.5, 5.0 Hz, 1H, thiophene C_4-H), 6.81 (ddd, J = 1.0, 1.0, 3.5 Hz, 1H, thiophene C_3-H), 6.08 (d, J = 2.5 Hz, 1H, N_2-H), 5.17 (dd, J = 1.0, 2.5 Hz, 1H, C_3-H), 4.15-4.01 (m, 2H, CH_2), 3.09 (s, 3H, N_1-CH_3), 1.57 (qdd, J = 7.0, 7.0, 7.0 Hz, 2H, CH_2), 0.79 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{19}ClN_4O_2S$: C, 56.64; H, 4.75; Cl, 8.80; N, 13.91. Found: C, 56.43; H, 4.70; Cl, 8.80; N, 14.18.

8-Chloro-5-furfuryloxy-2,3,4,6-tetrahydro-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline (**7d**).

A solution of compound **6** (2 g) in triethylamine (1 ml)/furfuryl alcohol (10 ml)/dioxane (40 ml) was refluxed in an oil bath for 1 hour. Evaporation of the solvent *in vacuo* gave a mixture of brown oily product and furfuryl alcohol, which were dissolved in ethanol and *n*-hexane with heating on a boiling water bath. Then, the solution was allowed to stand at room temperature to precipitate yellow needles of compound **7d** (1.41 g, 59%), mp 173-174°; ir: ν cm^{-1} 1650, 1620, 1600; ms: m/z 440 (M^+), 442 ($M^+ + 2$); pmr (deuteriodimethyl sulfoxide): 11.57 (s, 1H, N_6-H), 7.64 (dd, J = 1.0, 2.0 Hz, 1H, furan C_5-H), 7.62 (d, J = 2.0 Hz, 1H, C_7-H), 7.31 (dd, J = 1.0, 5.0 Hz, 1H, thiophene C_5-H), 7.20 (d, J = 8.5 Hz, 1H, C_{10}-H), 7.03 (dd, J = 2.0, 8.5 Hz, 1H, C_9-H), 6.83 (dd, J = 3.5, 5.0 Hz, 1H, thiophene C_4-H), 6.68

(ddd, J = 1.0, 1.0, 3.5 Hz, 1H, thiophene C_3-H), 6.47 (dd, J = 1.0, 3.5 Hz, 1H, furan C_3-H), 6.43 (dd, J = 2.0, 3.5 Hz, 1H, furan C_4-H), 6.09 (d, J = 2.5 Hz, 1H, N_2-H), 5.22 (d, J = 13.0 Hz, 1H, methylene CH), 5.16 (d, J = 13.0 Hz, 1H, methylene CH), 5.12 (dd, J = 1.0, 2.5 Hz, 1H, C_3-H), 3.10 (s, 3H, N_1-CH_3).

Anal. Calcd. for $C_{21}H_{17}ClN_4O_3S$: C, 57.21; H, 3.89; Cl, 8.04; N, 12.71. Found: C, 57.32; H, 4.02; Cl, 7.96; N, 12.60.

8-Chloro-4,6-dihydro-5-methoxy-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline (**8a**).

A solution of compound **7a** (1 g, 2.67 mmoles) and diethyl azodicarboxylate (700 mg, 4.02 mmoles) in ethanol (100 ml) was refluxed on a boiling water bath for 2 hours. The reaction mixture was allowed to stand overnight to precipitate brown prismic needles of compound **8a**, which were collected by suction filtration and washed with ethanol to provide an analytically pure sample (400 mg, 47%). Evaporation of the filtrate *in vacuo* afforded brown crystals of **8a**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (390 mg), total yield (790 mg, 79%).

Compound **8a** had mp 172-173°; ir: ν cm^{-1} 1650, 1590; ms: m/z 372 (M^+), 374 (M^+ + 2); pmr (deuteriotrifluoroacetic acid): 7.37 (d, J = 5.0 Hz, 1H, thiophene C_5-H), 7.04 (d, J = 3.5 Hz, 1H, thiophene C_3-H), 6.95 (dd, J = 3.5, 5.0 Hz, 1H, thiophene C_4-H), 6.90 (d, J = 2.0 Hz, 1H, C_7-H), 6.89 (dd, J = 2.0, 9.0 Hz, 1H, C_9-H), 6.83 (d, J = 9.0 Hz, 1H, C_{10}-H), 3.74 (s, 3H, N_1-CH_3), 3.60 (s, 3H, C_5-OCH_3).

Anal. Calcd. for $C_{17}H_{13}ClN_4O_2S$: C, 54.77; H, 3.51; Cl, 9.51; N, 15.03. Found: C, 54.53; H, 3.66; Cl, 9.73; N, 14.98.

8-Chloro-5-ethoxy-4,6-dihydro-1-methyl-4-oxo-3-(2-thienyl)-1*H*-1,2-diazepino[3,4-*b*]quinoxaline (**8b**).

A solution of compound **7b** (1 g, 2.57 mmoles) and diethyl azodicarboxylate (670 mg, 3.85 mmoles) in ethanol (100 ml) was refluxed on a boiling water bath for 2 hours. Evaporation of the solvent *in vacuo* gave brown crystals of compound **8b**, which were triturated with ethanol/*n*-hexane and then collected by suction filtration (0.47 g, 47%). Recrystallization from ethanol provided brown prismic needles, mp 200-201°; ir: ν cm^{-1} 1640, 1590; ms: m/z 386 (M^+), 388 (M^+ + 2); pmr (deuteriotrifluoroacetic acid): 7.37 (d, J = 5.0 Hz, 1H, thiophene C_5-H), 7.03 (d, J = 3.5 Hz, 1H, thiophene C_3-H), 6.95 (dd, J = 3.5, 5.0 Hz, 1H, thiophene C_4-H), 6.91 (d, J = 2.0 Hz, 1H, C_7-H), 6.89 (dd, J = 2.0, 8.0 Hz, 1H, C_9-H), 6.82 (d, J = 8.0 Hz, 1H, C_{10}-H), 4.04 (q, J = 7.0 Hz, 2H, CH_2), 3.72 (s, 3H, N_1-CH_3), 0.87 (t, J = 7.0 Hz, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{16}ClN_3O_2S$: C, 55.89; H, 3.91; Cl, 9.16; N, 14.48. Found: C, 55.80; H, 4.01; Cl, 9.30; N, 14.42.

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