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Treatment of 5-methylthio-2,3-dihydrothieno[3,2-*f*]-1,4-thiazepine (**9**) with acylhydrazines gave 5,6-dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*][1,4]thiazepines **10**, **11**, and that of **9** with ethyl anthranilate gave 5,6-dihydrothieno[3',2':6,7][1,4]thiazepino[5,4-*b*]quinazolin-8-one (**14**). Reaction of **9** with hydrazine hydrate or 4-chlorophenylhydrazine afforded 5-hydrazino compounds **12**, **15**, which were subsequently cyclized to ethyl 5,6-dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*][1,4]thiazepine-3-carboxylate (**13**), 2-(4-chlorophenyl)-5,6-dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*][1,4]thiazepin-3(2*H*)-one (**16**) and 2-(4-chlorophenyl)-6,7-dihydro-2*H*-thieno[3,2-*f*][1,2,4]triazino[4,3-*d*][1,4]thiazepine-3,4-dione (**17**). New thieno-anellated heterocycles were prepared with the aim of studying their affinity for the benzodiazepine receptors.

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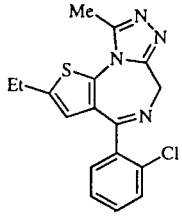
1,4-Benzodiazepine compounds are widely used as therapeutic agents with anxiolytic, anticonvulsant, muscle relaxant, and sedative/hypnotic activities. As well as classical 1,4-benzodiazepines, several non-benzodiazepines derivatives show high affinity for the benzodiazopine receptors and exhibit wide spectrum of *in vivo* activities [1]. Especially, thienoanellated tricyclic compounds, *e.g.* etizolam **1** [2] and anothers such as **2** [3], **3** [4], and **4** [5], possess high affinity for the benzodiazepine receptors. One of common features of these compounds is that they have five or six membered ring (triazole, imidazole, pyrazole, and pyridazine) containing nitrogen atoms in addition to the fused thiophene ring.

Scheme 1



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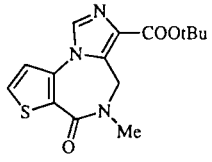

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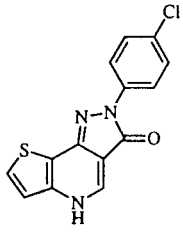

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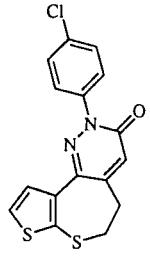

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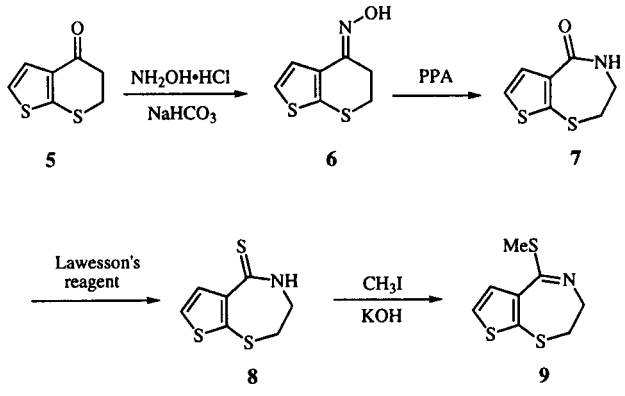
In the course of our approach in synthesizing new type of benzodiazepine receptor ligands, we designed new tricyclic or tetracyclic compounds in which a ring fuses at 4- and 5-positions of thieno[3,2-*f*]-1,4-thiazepine moiety. In this paper we report the preparation of 5,6-dihydrothieno-[3,2-*f*]-1,2,4-triazolo[4,3-*d*][1,4]thiazepines **10**, **11** and **13**, 5,6-dihydrothieno[3',2':6,7][1,4]thiazepino[5,4-*b*]quinazolin-8-one (**14**), 5,6-dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*]-[1,4]thiazepin-3(2*H*)-one (**16**), and 6,7-dihydro-2*H*-thieno[3,2-*f*][1,2,4]triazino[4,3-*d*][1,4]thiazepine-3,4-dione (**17**).

We prepared thieno[3,2-*f*]-1,4-thiazepine nucleus *via* the Beckmann rearrangement of oxime **6**. The reaction of the known ketone **5** [6] with hydroxylamine gave the oxime **6**, in which the hydroxy group in the oxime moiety was *anti* to the thiophene ring. Here, the *anti* form of the oxime **6** was determined by an NOE experiment [7]. The Beckmann rearrangement of **6** with polyphosphoric acid gave the desired lactam **7** without detectable formation of the isomeric lactam. The structure of the lactam **7** was assigned by use of ^{1}H nmr in which signal multiplicity at the 3-position was changed from multiplet to triplet by addition of deuterium oxide. Such selectivity in the Beckmann rearrangement suggests that isomerization of the oxime from *anti* to *syn* occurred in the reaction medium. After conversion of the lactam **7** into thiolactam **8** by the Lawesson's reagent, alkylation of **8** with methyl iodide and potassium hydroxide gave methyl thiolactim **9** (Scheme 2).

The thiolactim **9** was cyclocondensed with acetohydrazide to the triazole compound **10**, and with benzohydrazide to give **11**, respectively. Here, none of intermediates were isolatable. The compound **13**, which has ethoxycarbonyl substituted at the 3-position, was prepared from ethyl oxalyl chloride and the hydrazino compound **12**. Here, nucleophilic displacement of the methylthio group of **9** with hydrazine gave the compound **12**. Reaction of **9**

Scheme 2



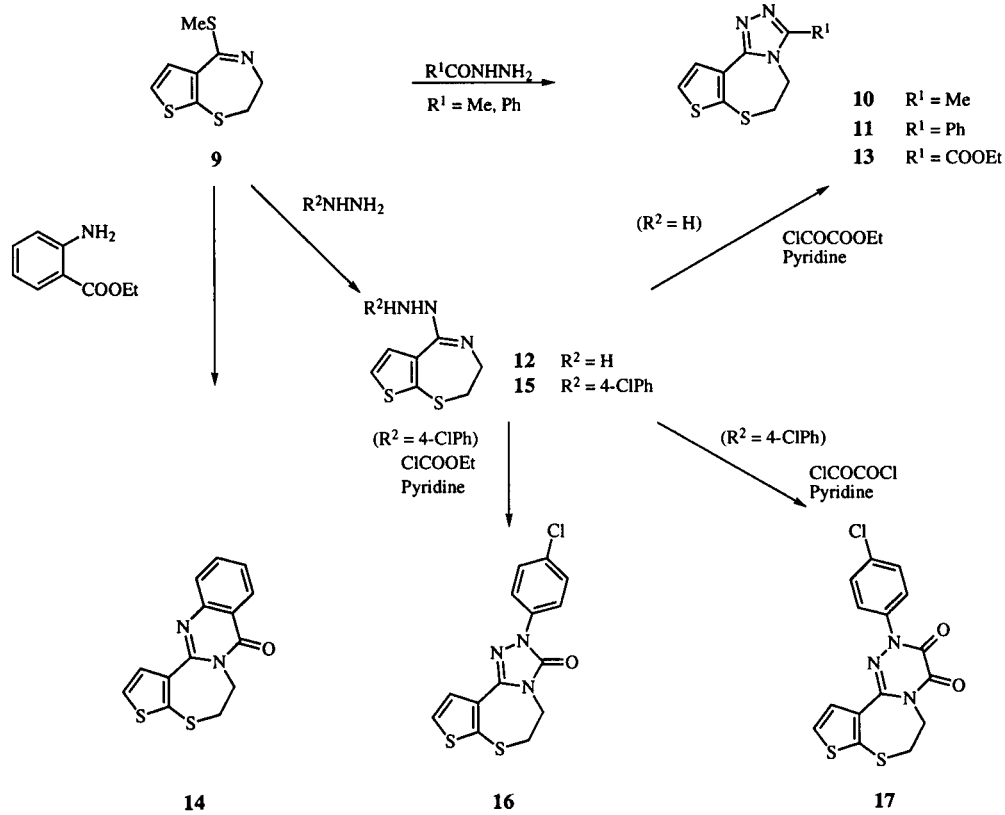
with methyl anthranilate afforded tetracyclic compound **14** in an one-step procedure. The (4-chlorophenyl)hydrazino compound **15**, which was prepared from **9** in a similar manner as **12**, was cyclized to give the tricyclic compounds **16** and **17** by use of ethyl chloroformate and oxalyl chloride, respectively (Scheme 3).

Compounds **10**, **11**, **13**, **14**, **16**, and **17** were evaluated for their affinity for the benzodiazepine receptors by an assay on their ability to displace [^{3}H]diazepam that bound to the cerebral cortex of rat [8]. Among them, compound **16** showed moderate affinity for the receptors. Further comprehensive studies on this series are currently under investigation and will be reported in due course.

EXPERIMENTAL

All melting points were determined on a Büchi 530 melting point apparatus, and are uncorrected. The ir spectra were recorded on a JEOL JIR-6500W spectrophotometer. The ^{1}H nmr spectra were recorded on a JEOL JNM-EX 270 spectrometer (270 MHz) with tetramethylsilane as an internal standard. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Chemical shifts are expressed in terms of ppm. The mass spectra were taken on a JEOL JMS-DX 300 system. The elemental analyses were performed for C, H, N, and results were within 0.4% of the theoretical val-

Scheme 3



ues. Silica gel plates (Merck F254) and silica gel 60 (Merck, 70-230 mesh) were used for analytical and column chromatography, respectively.

5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-one (**5**).

This compound was prepared according to the published method [6].

5,6-Dihydro-4*H*-thieno[2,3-*b*]thiopyran-4-one Oxime (**6**).

A mixture of **5** (80.0 g, 0.470 mole), hydroxylamine hydrochloride (36.0 g, 0.518 mole), and sodium hydrogen carbonate (43.5 g, 0.518 mole) in ethanol (800 ml) was heated under reflux for 3 hours. Inorganic by-products were removed by filtration of the reaction mixture through Celite. The Celite was washed with ethanol and the filtrate was evaporated *in vacuo* to give a white residue, which was recrystallized from isopropylalcohol to give **6** (59.0 g, 68%), mp 122-124°; ir (potassium bromide): 3215, 978, 872 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.92 (t, 2H, J = 5.94 Hz, 5-CH_2), δ 3.14 (t, 2H, J = 5.94 Hz, 6-CH_2), 7.30 (d, 1H, J = 5.28 Hz, thiophene H), 7.34 (d, 1H, J = 5.28 Hz, thiophene H), 11.10 (s, 1H, deuterium oxide-exchangeable, OH); ms: m/z 185 (M^+).

Anal. Calcd. for $C_7H_7NOS_2$: C, 45.38; H, 3.81, N, 7.56. Found: C, 45.40; H, 3.76, N, 7.43.

3,4-Dihydrothieno[3,2-*f*]-1,4-thiazepin-5(2*H*)-one (**7**).

To a stirred polyphosphoric acid (600 g) was added **6** (59.0 g, 0.318 mole) at 70-80° in small portions and the mixture was stirred at 80° for 3 hours. The reaction mixture was poured into ice-water. The precipitate was collected by filtration, washed with water, and recrystallized from ethanol to give **7** (42.0 g, 71%), mp 197-198°; ir (potassium bromide): 3327, 1670 (CO), 1626 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.26 (t, 2H, J = 5.93 Hz, 2-CH_2), 3.53-3.60 (m, 2H, 3-CH_2), 7.21 (d, 1H, J = 5.28 Hz, thiophene H), 7.35 (d, 1H, J = 5.28 Hz, thiophene H), 7.65 (s-broad, 1H, deuterium oxide-exchangeable, NH); ms: m/z 185 (M^+).

Anal. Calcd. for $C_7H_7NOS_2$: C, 45.38; H, 3.81, N, 7.56. Found: C, 45.34; H, 3.78, N, 7.58.

3,4-Dihydrothieno[3,2-*f*]-1,4-thiazepine-5(2*H*)-thione (**8**).

A mixture of **7** (30.0 g, 0.162 mole) and Lawesson's reagent (32.7 g, 0.080 mole) in toluene (400 ml) was heated under reflux for 2 hours. The reaction mixture was cooled and a precipitate was formed, which was collected by filtration and recrystallized from ethyl acetate to give **8** (25.5 g, 78%), mp 167-170°; ir (potassium bromide): 3172, 1531, 1213 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.39 (t, 2H, J = 5.94 Hz, 2-CH_2), 3.65-3.71 (m, 2H, 3-CH_2), 7.19 (d, 1H, J = 5.27 Hz, thiophene H), 7.53 (d, 1H, J = 5.27 Hz, thiophene H), 9.25 (s-broad, 1H, deuterium oxide-exchangeable, NH); ms: m/z 201 (M^+).

Anal. Calcd. for $C_7H_7NS_3$: C, 41.76; H, 3.50, N, 6.96. Found: C, 41.91; H, 3.54, N, 7.02.

5-Methylthio-2,3-dihydrothieno[3,2-*f*]-1,4-thiazepine (**9**).

To a stirred mixture of **8** (25.7 g, 0.128 mole) in tetrahydrofurane (200 ml) and 10% aqueous potassium hydroxide solution (200 ml), methyl iodide (21.7 g, 0.153 mole) was added at room temperature and stirred for 2 hours. The organic layer was separated, the aqueous layer was extracted with ethyl acetate and the organic layer was combined, washed with brine and dried over magnesium sulfate. Removal of the solvent furnished a residue which was recrystallized from isopropyl ether-*n*-hexane (3:1) to give **9** (23.5 g, 85%), mp 64-66°; ir (potassium bromide): 1587, 1211, 1105, 1054, 850 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.46 (s, 3H, SCH_3), 3.54-3.59 (m, 2H, 2-CH_2), 3.81-3.86 (m, 2H, 3-CH_2), 7.17 (d, 1H, J = 5.28 Hz, thiophene H), 7.21 (d, 1H, J = 5.28 Hz, thiophene H); ms: m/z 215 (M^+), 168 (M^+-SCH_3).

Anal. Calcd. for $C_8H_9NS_3$: C, 44.62; H, 4.21, N, 6.50. Found: C, 44.54; H, 4.16, N, 6.52.

3-Methyl-5,6-dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*][1,4]thiazepine (**10**).

A mixture of **9** (1.50 g, 6.96 mmoles) and acetohydrazide (0.62 g, 8.37 mmoles) in *n*-butyl alcohol (20 ml) was heated under reflux for 7 hours. The reaction mixture was cooled, a precipitate was collected by filtration and recrystallized from ethanol to give **10** (0.80 g, 51%), mp 206-209°; ir (potassium bromide): 1531, 1425, 858, 712 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.51 (s, 3H, CH_3), 3.38-3.41 (m, 2H, 6-CH_2), 4.37-4.41 (m, 2H, 5-CH_2), 7.23 (d, 1H, J = 5.27 Hz, thiophene H), 7.74 (d, 1H, J = 5.27 Hz, thiophene H); ms: m z 223 (M^+).

Anal. Calcd. for $C_9H_9N_3S_2$: C, 48.40; H, 4.06, N, 18.82. Found: C, 48.16; H, 4.11, N, 18.63.

3-Phenyl-5,6-dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*][1,4]thiazepine (**11**).

A mixture of **9** (0.50 g, 2.32 mmoles) and benzohydrazide (0.38 g, 2.79 mmoles) in *n*-butyl alcohol (20 ml) was heated under reflux for 15 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved with a mixture of ethyl acetate and ethanol. To the solution 15% hydrochloric acid in isopropyl alcohol (1.0 ml) was added, the resulting precipitate was collected by filtration and recrystallized from ethanol to give hydrochloric salt of **11** (0.40 g, 54%), mp 257-259° dec; ir (potassium bromide): 1531, 1425, 858, 712 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6): δ 3.68-3.72 (m, 2H, 6-CH_2), 4.60-4.63 (m, 2H, 5-CH_2), 7.62-7.87 (m, 7H, aromatic protons); ms: m/z 285 (M^+).

Anal. Calcd. for $C_{14}H_{11}N_3S_2$ HCl: C, 52.25; H, 3.76, N, 13.06. Found: C, 52.32; H, 3.83, N, 12.98.

5-Hydrazino-2,3-dihydrothieno[3,2-*f*]-1,4-thiazepine (**12**).

A mixture of **9** (2.0 g, 9.29 mmoles) and hydrazine monohydrate (1.0 g, 19.98 mmoles) in *n*-butyl alcohol (20 ml) was heated under reflux for 4 hours. The reaction mixture was concentrated *in vacuo*. The residual solid was recrystallized from isopropyl alcohol to give **12** (1.1 g, 59%), mp 161-163°; ir (potassium bromide): 3388, 3356, 3101 ($NHNH_2$), 1628, 1419 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.07 (t, 2H, J = 5.94 Hz, 2-CH_2), 3.42 (t, 2H, J = 5.94 Hz, 3-CH_2), 4.23 (s-broad, 2H, deuterium oxide-exchangeable, NH_2), 5.75 (s-broad, 1H, deuterium oxide-exchangeable, NH), 7.19 (d, 1H, J = 5.27 Hz, thiophene H), 7.24 (d, 1H, J = 5.27 Hz, thiophene H); ms: m/z 199 (M^+), 168 (M^+-$NHNH_2$).

Anal. Calcd. for $C_7H_9N_3S_2$: C, 42.19; H, 4.55, N, 21.08. Found: C, 42.19; H, 4.50, N, 20.94.

Ethyl 5,6-Dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*][1,4]thiazepine-3-carboxylate (**13**).

To a stirred mixture of **12** (0.84 g, 4.21 mmoles) in pyridine (15 ml) ethyl oxalyl chloride (0.60 g, 4.39 mmoles) was added at 5° and stirred for 1 hour at room temperature. The reaction mix-

ture was heated under reflux for 3 hours. The reaction mixture was concentrated *in vacuo,* diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, and dried over magnesium sulfate, filtered, and concentrated *in vacuo.* The residue was purified on silica gel column eluting with chloroform-ethanol (99:1) to give **13** (0.35 g, 30%), mp 133-136° after recrystallization from ethanol; ir (potassium bromide): 1732 (CO), 1190 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (t, 3H, J = 7.26 Hz, CH_2CH_3), 3.52-3.56 (m, 2H, 6-CH_2), 4.51 (q, 2H, J = 7.26 Hz, CH_2CH_3), 4.85-4.89 (m, 2H, 5-CH_2), 7.32 (d, 1H, J = 5.28 Hz, thiophene H), 7.71 (d, 1H, J = 5.28 Hz, thiophene H); ms: m/z 281 (M^+), 209.

Anal. Calcd. for $C_{11}H_{11}N_3O_2S_2$: C, 46.96; H, 3.94, N, 14.93. Found: C, 46.94; H, 3.96, N, 14.89.

5,6-Dihydrothieno[3',2':6,7][1,4]thiazepino[5,4-*b*]quinazolin-8-one (**14**).

A mixture of **9** (1.0 g, 4.64 mmoles) and methyl anthranilate (2.0 g, 13.23 mmoles) was heated at 200° without solvent for 7 hours. After cooling the precipitate was filtered off and recrystallized from chloroform-ethanol (1:19) to give **14** (0.6 g, 45%), mp 238-240°; ir (potassium bromide): 1674 (CO), 1585 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.49 (t, 2H, J = 5.94 Hz, 5-CH_2), 4.44 (t, 2H, J = 5.94 Hz, 6-CH_2), 7.38 (d, 1H, J = 5.27 Hz, thiophene H), 7.48-7.54 (m, 1H, phenyl), 7.57 (d, 1H, J = 5.27 Hz, thiophene H), 7.73-7.79 (m, 2H, phenyl), 8.32 (d, 1H, J = 8.58 Hz, phenyl), ms: m/z 286 (M^+), 253.

Anal. Calcd. for $C_{14}H_{10}N_2OS_2$: C, 58.72; H, 3.52, N, 9.78. Found: C, 58.66; H, 3.66, N, 9.70.

5-(2-(4-Chlorophenyl)hydrazino)-2,3-dihydrothieno[3,2-*f*]-1,4-thiazepine (**15**).

A mixture of **9** (3.0 g, 13.93 mmoles) and 4-chlorophenylhydrazine (2.4 g, 16.83 mmoles) in *n*-butyl alcohol (50 ml) was heated under reflux for 4 hours. The reaction mixture was concentrated *in vacuo.* The residue was purified on silica gel column eluting with chloroform-methanol (95:5) to give **15** (2.4 g, 56%), mp 120-122° after recrystallization from isopropyl alcohol; ir (potassium bromide): 3394 (NH), 3259 (NH), 1614, 1597, 1491 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.08 (t, 2H, J = 5.94 Hz, 2-CH_2), 3.43 (t, 2H, J = 5.94 Hz, 3-CH_2), 5.65 (s-broad, 1H, deuterium oxide-exchangeable, NH), 6.02 (s-broad, 1H, deuterium oxide-exchangeable, NH), 6.90 (d, 2H, J = 7.92 Hz, phenyl), 7.12 (d, 2H, J = 7.92 Hz, phenyl), 7.22 (d, 1H, J = 5.28 Hz, thiophene H), 7.37 (d, 1H, J = 5.28 Hz, thiophene H); ms: m/z 309 (M^+), 168 (M^+-NHNH(4-ClPh)).

Anal. Calcd. for $C_{13}H_{12}ClN_3S_2$: C, 50.39; H, 3.90, N, 13.56. Found: C, 50.36; H, 3.90, N, 13.29.

2-(4-Chlorophenyl)-5,6-dihydrothieno[3,2-*f*]-1,2,4-triazolo[4,3-*d*]-[1,4]thiazepin-3(2*H*)-one (**16**).

To a mixture of **15** (3.0 g, 9.68 mmoles) in pyridine (50 ml) ethyl chloroformate (1.3 g, 11.8 mmoles) was added at 5° and stirred for 1 hour. The reaction mixture was refluxed for 4 hours, concentrated *in vacuo,* diluted with water, and extracted with chloroform. The organic layer was washed with water, and dried over magnesium sulfate, filtered, and concentrated *in vacuo.* The residue was purified on silica gel column eluting with chloroform to give **16** (1.1 g, 34%), mp 184-186° after recrystallization from chloroform-ethyl acetate (1:19); ir (potassium bromide): 1699 (CO), 1495 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.34-3.38 (m, 2H, 6-CH_2), 4.34-4.38 (m, 2H, 5-CH_2), 7.22 (d, 1H, J = 5.28 Hz, thiophene H), 7.40 (d, 2H, J = 9.24 Hz, phenyl), 7.60 (d, 1H, J = 5.28 Hz, thiophene H), 8.01 (d, 2H, J = 9.24 Hz, phenyl); ms: m z 335 (M^+).

Anal. Calcd. for $C_{14}H_{10}ClN_3OS_2$: C, 50.07; H, 3.00, N, 12.51. Found: C, 50.42; H, 3.14, N, 12.52.

2-(4-Chlorophenyl)-6,7-dihydro-2*H*-thieno[3,2-*f*][1,2,4]triazino-[4,3-*d*][1,4]thiazepine-3,4-dione (**17**).

To a mixture of **15** (3.0 g, 9.68 mmoles) in pyridine (50 ml) oxalyl chloride (1.5 g, 11.8 mmoles) was added at 5° and stirred for 30 minutes. The reaction mixture was stirred for 2 hours at 50°, concentrated *in vacuo,* diluted with water, and extracted with chloroform. The organic layer was washed with water, and dried over magnesium sulfate, filtered, and concentrated *in vacuo.* The residue was purified on silica gel column eluting with chloroform to give **17** (0.8 g, 23%), mp 194-198° after recrystallization from chloroform-ethanol (1:19); ir (potassium bromide): 1710 (CO), 1677 (CO) 1491 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.40 (t, 2H, J = 5.94 Hz, 7-CH_2), 4.27 (t, 2H, J = 5.94 Hz, 6-CH_2), 7.34 (d, 1H, J = 5.28 Hz, thiophene H), 7.37 (d, 1H, J = 5.28 Hz, thiophene H), 7.43 (d, 2H, J = 9.24 Hz, phenyl), 7.70 (d, 2H, J = 9.24 Hz, phenyl); ms: m/z 363 (M^+).

Anal. Calcd. for $C_{15}H_{10}ClN_3O_2S_2$: C, 49.52; H, 2.77, N, 11.55. Found: C, 49.13; H, 2.91, N, 11.28.

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