Synthesis of 4,10-Dihydro-4,10-dioxo-1*H*[1]benzothiopyrano[3,2-*b*]pyridine and 7-Oxo-7,13-dihydro[1]benzothiopyrano[2,3-*b*]-1,5-benzodiazepine

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3-Amino-4*H*-1-benzothiopyran-4-one (3-aminothiochromone) was easily prepared by reaction of 3-bromothiochromen-4-one with sodium azide in methanol-water. Condensation of 3-aminothiochromone with diethyl ethoxymethylenemalonate and with dimethyl acetylenedicarboxylate gave intermediates, which were thermally cyclized to give 4,10-dihydro-4,10-dioxo-1*H*[1]benzothiopyrano[3,2-*b*]pyridinecarboxylates. 3-Formylthiochromone was condensed with *o*-phenylenediamine to give 7-oxo-7,13-dihydro[1]benzothiopyrano[2,3-*b*]-1,5-benzodiazepine.

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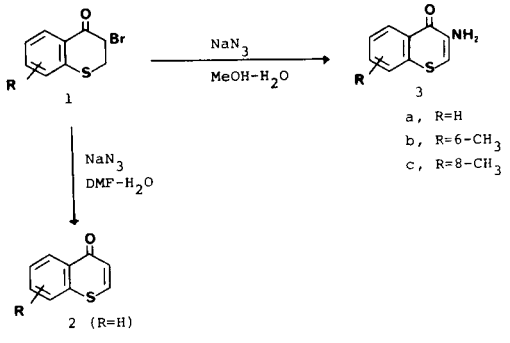
Recently, 4,10-dihydro-4,10-dioxo-benzopyranopyridines which were new heterocyclic compounds in the field of chromone chemistry have been prepared as the potential antiallergy agents [1]. Many fused pyridones are potent antibacterial agents [2]. Also, preparation of new diazepines fused to the chromone ring has been achieved by Ghosh *et al.* [3] and Fitton *et al.* [4]. However, preparation of those thio analogs is unknown. We have prepared some 2-phenyl-4*H*-1-benzothiopyran-4-ones (thioflavones) and related compounds as antimicrobial active agents [5,6,7]. Some 10-substituted benzothiopyran[3,2-*b*]pyridine derivatives showed potent activity in the passive cutaneous anaphylaxis test [8].

Scheme I

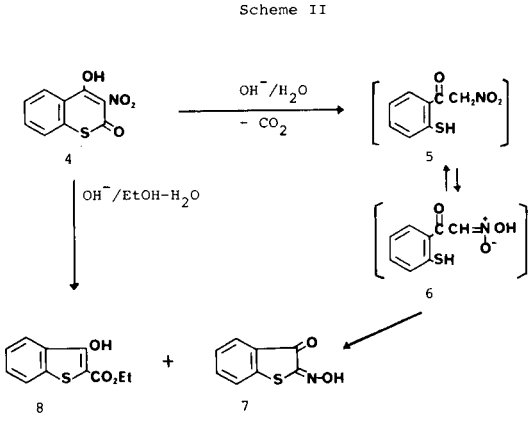


Thus various pyridine and diazepine derivatives fused to the thiochromone ring were of interest as potential antiallergy agents and antimicrobial active agents.

In this paper, we report synthesis of 4,10-dihydro-4,10-dioxo-1*H*-1-benzothiopyrano[3,2-*b*]pyridines and 7-oxo-7,13-dihydro[1]benzothiopyrano[2,3-*b*]benzodiazepine as new heterocyclic compounds.

3-Amino-4*H*-1-benzothiopyran-4-one (3-aminothiochromone) **3** appeared to be attractive starting materials from which the target compounds could be synthesized by the route shown in Scheme III. Few reports are available of the preparation of 3-aminothiochromones. Only 6-methyl-3-aminothiochromone **3b** and 2-substituted 3-aminothiochromones were known [9,10,11].

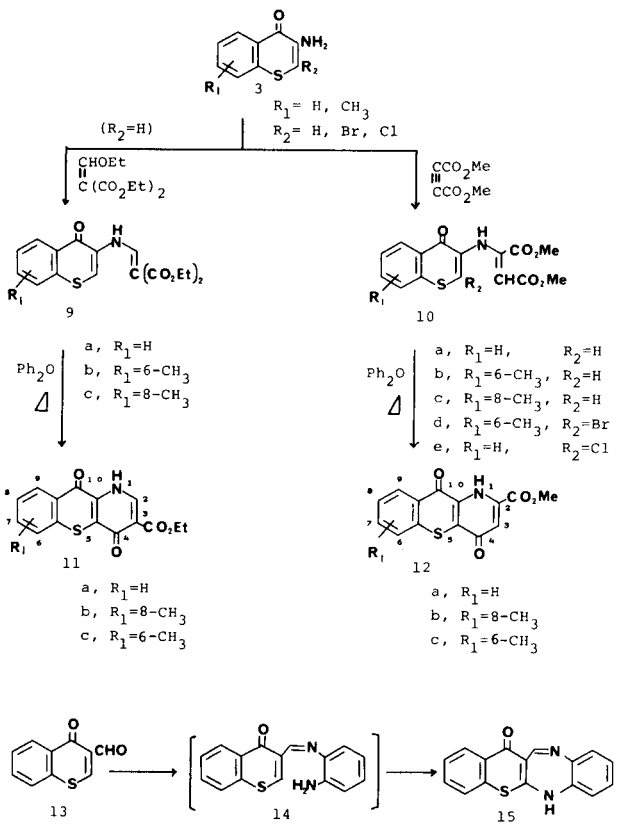
Scheme II



We now found that 3-aminothiochromone **3** was prepared by reaction of the corresponding 3-bromothiochromen-4-one **1** with sodium azido in the solution of methanol-water (Scheme I). When the solution of *N,N*-dimethylformamide-water was used, thiochromone **2** was isolated, but **3a** was not obtained. Decarboxylation of 3-nitro-4-hydroxythiocoumarin **4**, the widely applied route to 3-aminochromone [1,12], gave unexpected benzo[*b*]thiophene-2,3-dione 2-oxime **7** and ethyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate **8** (Scheme II). In this reaction, decarboxylation in a suspension of **4** in water gave only **7** which was formed *via* the nitronic acid tautomer **6** from **5**. 3-Aminothiochromones would appear useful synthons for the synthesis of potential drugs and novel heterocyclic compounds fused to the thiochromone ring.

The method of preparation of tricyclic esters **11** and **12** from 3-aminothiochromone **3** is an adaptation of the procedure of oxo analogs [1]. 3-Aminothiochromone **3a** was heated with diethyl ethoxymethylenemalonate to give **9a** in good yields. Other compounds **9b** and **9c** were similarly prepared. Reaction of compound **3a** with dimethyl acetylenedicarboxylate at room temperature for 24 hours afforded compound **10a** in a yield of 74%. Other compounds

Scheme III



10b-10e were similarly prepared from the corresponding 3-aminothiochromones in 66-89% yield. Cyclization of compounds, **9a-c** and **10a-c**, in refluxing diphenyl ether gave the desired tricyclic esters **11** and **12**, respectively. However, compounds **10d** and **10e** including a halogen atom recovered unchanged after 90 minutes in refluxing diphenyl ether. Extended reaction time gave tar.

Condensation of 3-formylthiochromone **13** with *o*-phenylenediamine in ethanol gave the fused benzodiazepine derivative **15** which was perhaps formed by air oxidation of the cyclization product of the imine **14**. This result shows that addition of the amino group to imine of thiochromone easily occurs under the mild conditions. Same condensation of 3-formylchromone gave only imine derivatives and the fused benzodiazepine derivatives were prepared by oxidation of the imine derivative [3].

EXPERIMENTAL

All the melting points are uncorrected. Proton nmr spectra were taken on a JEOL JNM-MH-100 spectrometer with tetramethylsilane as an internal standard. Elemental analyses were recorded on a Yanaco CHN recorder MT-2. Mass spectra were recorded on a Hitachi RMU-6E mass spectrometer operating at 80 eV. Infrared spectra were recorded on a Shimazu IR-420 spectrometer using potassium bromide.

General Procedure for Amination of 3-Bromothiochromen-4-one with Sodium Azide.

A solution of sodium azide (2.0 g, 0.031 mole) in methanol-water (50%, 20 ml) was added to a solution of the 3-bromothiochromen-4-one **1** [13] (0.008 mole) in methanol (30 ml). The mixture was refluxed for 6 hours, and concentrated at reduced pressure. The residue was dissolved in benzene, and then chromatographed on silica gel using benzene/acetone (20/1) to give **3**. Recrystallization from methanol gave an analytically pure material compound with typical spectral data. When *N,N*-dimethylformamide-water (1/1) was used as a solvent, compound **2** was afforded in a yield of 53%, mp 75-77° (lit [13] mp 78°).

3-Amino-4*H*-1-benzothiopyran-4-one (**3a**).

This compound was prepared in a yield of 43%, mp 127-129°; ms: m/e 177 (M^+, 10), 150 (28); ^{1}H-nmr (deuteriochloroform): 4.60 (b, 2H, NH_2), 6.90 (s, 1H, H-2), 7.34-7.80 (m, 3H, ArH), 8.55-8.75 (m, 1H, H-5); ir: 1620 (C=O), 3380, 3300 cm^{-1} (NH_2).

Anal. Calcd. for C_9H_7NOS: C, 61.00; H, 3.98; N, 7.90. Found: C, 61.11; H, 3.88; N, 8.14.

6-Methyl-3-amino-4*H*-1-benzothiopyran-4-one (**3b**).

This compound was prepared in a yield of 63%, mp 123-125° (lit [11], 125°); ^{1}H-nmr (deuteriochloroform): 2.42 (s, 3H, CH_3), 4.42 (b, 2H, NH_2), 6.72 (s, 1H, H-2), 7.21-7.51 (m, 2H, ArH), 8.27 (b, 1H, H-5); ir: 1620 (C=O), 3400, 3300 cm^{-1} (NH_2).

8-Methyl-3-amino-4*H*-1-benzothiopyran-4-one (**3c**).

This compound was prepared in a yield of 48%, mp 118-119°; ms: m/e 191 (M^+, 100), 164 (25); ^{1}H-nmr (deuteriochloroform): 2.46 (s, 3H, CH_3), 4.45 (b, 2H, NH_2), 6.80 (s, 1H, H-5), 7.25-7.50 (m, 2H, ArH), 8.43 (m, 1H, H-5); ir: 1610 (C=O), 3440, 3320 cm^{-1} (NH_2).

Anal. Calcd. for $C_{10}H_9NOS$: C, 62.80; H, 4.74; N, 7.32. Found: C, 62.92; H, 4.65; N, 7.65.

Benzo[*b*]thiophene-2,3-dione 2-Oxime (**7**) and Ethyl 3-Hydroxybenzo[*b*]-thiophene-2-carboxylate (**8**). Method A.

3-Nitro-4-hydroxythiocoumarin **4** [14] (3.0 g, 0.0135 mole) and sodium hydroxide (50 g) was dissolved in a mixture of ethanol (300 ml) and water (200 ml) at 30°. The mixture was stirred below 30° for 24 hours. An excess of concentrated hydrochloric acid was added. The mixture was extracted with benzene and then chromatographed on silica gel using benzene as an eluent to give **8** (51%), mp 72-74° (lit [15] 73-74°) and **7** (25%), mp 168-172° dec (lit [16] 173-177°); ms: m/e 179 (M^+, 93), 162 (100); ^{1}H-nmr (DMSO-d_6): 3.34 (s, 1H), 7.20-7.90 (m, 8H); ir: 1685 cm^{-1} (C=O), 3250 cm^{-1} (OH).

Method B.

Compound **4** (1.0 g, 0.00448 mole) was dissolved in aqueous sodium hydroxide (5%, 1000 ml). This solution was stirred below 20° for 24 hours. An excess of concentrated hydrochloric acid was added, and the resulting solid was filtered. Recrystallization from methanol gave **7** in a yield of 61%.

General Procedure for the Condensation of **3** with Diethyl Ethoxymethylenemalonate.

A mixture of 3-aminothiochromone **3** (0.011 mole) and diethyl ethoxymethylenemalonate (0.019 mole) was heated at 140° for 5 hours under nitrogen. The reaction mixture was cooled and filtered. Recrystallization from ethyl acetate gave an analytically pure material.

Diethyl {[(4-Oxo-4*H*[1]benzothiopyran-3-yl)amino]methylene}propanedioate (**9a**).

This compound was obtained in a yield of 78%, mp 148-149°; ms: m/e 347 (M^+, 60), 302 (33), 301 (100); ^{1}H-nmr (deuteriochloroform): 1.38 (m, 6H, CH_3), 4.34 (m, 4H, CH_2), 7.38-7.83 (m, 4H), 8.37 (d, 2.3 Hz, 1H), 8.65 (m, 1H), 11.45 (d, 2.3 Hz, 1H, NH); ir: 1680, 1640, 1610 (C=O), 3200 cm^{-1} (NH).

Anal. Calcd. for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93; N, 4.03. Found: C, 58.50; H, 5.08; N, 3.76.

Diethyl {[6-Methyl-4-oxo-4*H*[1]benzothiopyran-3-yl)amino]methylene}-propanedioate (**9b**).

This compound was obtained in a yield of 88%, mp 146-147°; ms: m/e 361 (M^+, 60), 315 (97), 215 (100); ^{1}H-nmr (deuteriochloroform): 1.38 (m, 6H, CH_3), 2.48 (s, 3H, CH_3), 4.32 (m, 4H, $-CH_2$), 7.38-7.70 (m, 3H), 8.35 (d, 2.3 Hz, 1H), 8.39 (b, 1H), 11.38 (b, 1H, NH); ir: 1675, 1644, 1620 (C=O), 3200 cm^{-1} (NH).

Anal. Calcd. for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88. Found: C, 59.69; H, 5.52; N, 3.60.

Diethyl {[8-Methyl-4-oxo-4*H*[1]benzothiopyran-3-yl)amino]methylene}-propanedioate (**9c**).

This compound was obtained in a yield of 82%, mp 192-193°; ms: m/e 361 (M^+, 80), 315 (83), 215 (100); ^{1}H-nmr (deuteriochloroform): 1.38 (m, 6H, CH_3), 2.53 (s, 3H, CH_3), 4.30 (m, 4H, CH_2), 7.28-7.54 (m, 3H), 8.26 (d, 2.3 Hz, 1H), 8.49 (b, 1H), 11.32 (d, 2.3 Hz, 1H, NH); ir: 1702, 1668, 1610 (C=O), 3400 cm^{-1} (NH).

Anal. Calcd. for $C_{18}H_{19}NO_5S$: C, 59.82; H, 5.30; N, 3.88. Found: C, 59.78; H, 5.30; N, 3.92.

General Procedure for the Condensation of **3** with Dimethyl Acetylenedicarboxylate.

A mixture of compound **3** (0.0057 mole) and dimethyl acetylenedicarboxylate (2 ml) in methanol (40 ml) was stirred at room temperature for 24 hours. The product was filtered and recrystallization from ethyl acetate gave an analytically pure material.

Dimethyl 2-[(4-Oxo-4*H*[1]benzothiopyran-3-yl)amino]-2-butenedioate **10a**.

This compound was obtained in a yield of 74%, mp 148-149°; ms: m/e 319 (M^+, 34), 287 (10), 260 (43), 228 (100); ^{1}H-nmr (deuteriochloroform): 3.74 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 5.55 (s, 1H, =CH), 7.10 (s, 1H, ArH), 7.35-7.70 (m, 3H, ArH), 8.49 (m, 1H, ArH), 9.90 (b, 1H, NH); ir: 1730, 1662, 1620 (C=O), 3250 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10; N, 4.39. Found: C, 56.65; H, 4.09; N, 4.13.

Dimethyl 2-[(6-Methyl-4-oxo-4*H*[1]benzothiopyran-3-yl)amino]-2-butenedioate (**10b**).

This compound was obtained in a yield of 81%, mp 153-155°; ms: m/e 333 (M^+, 37), 301 (7.4), 274 (46), 242 (100); ^{1}H-nmr (deuteriochloroform): 2.45 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 5.51 (s, 1H, =CH), 7.11 (s, 1H, ArH), 7.29-7.50 (m, 2H, ArH), 8.30 (b, 1H, ArH), 9.81 (b, 1H, NH); ir: 1730, 1680, 1620 (C=O), 3290 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20. Found: C, 57.93; H, 4.58; N, 4.01.

Dimethyl 2-[(8-Methyl-4-oxo-4*H*[1]benzothiopyran-3-yl)amino]-2-butanedioate (**10c**).

Ths compound was obtained in a yield of 89%, mp 153-155°; ms: m/e 333 (M^+, 42), 301 (7.5), 274 (48), 242 (100); ^{1}H nmr (deuteriochloroform): 2.51 (s, 3H, CH_3), 3.77 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 5.59 (s, 1H, =CH), 7.17 (s, 1H, ArH), 7.35-7.64 (m, 2H, ArH), 8.46 (m, 1H, ArH), 9.97 (b, 1H, NH); ir: 1720, 1682, 1600 (C=O), 3250 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20. Found: C, 57.41; H, 4.70; N, 3.93.

Dimethyl 2-[(6-Methyl-2-bromo-4-oxo-4*H*[1]benzothiopyran-3-yl)amino]-2-butenedioate (**10d**).

This compound was prepared from 6-methyl-2-bromo-3-aminothiochromone [11] in a yield of 66%, mp 174-178°; ms: m/e 413 (M^++2, 17), 411 (M^+, 17), 381 (7.7), 379 (7.7), 322 (100), 320 (97); ^{1}H-nmr (deuteriochloroform): 2.42 (s, 3H, CH_3), 3.71 (s, 3H, CH_3), 3.75 (s, 3H, CH_3), 5.64 (s, 1H, =CH), 7.38-7.60 (m, 2H, ArH), 8.23 (b, 1H, H-5), 9.78 (b, 1H, NH); ir: 1725, 1660, 1600 (C=O), 3200 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{14}BrNO_5S$: C, 46.62; H, 3.42; N, 3.40. Found: C, 46.40; H, 3.51; N, 3.27.

Dimethyl 2-[(2-Chloro-4-oxo-4*H*[1]benzothiopyran-3-yl)amino]-2-butenedioate (**10e**).

This compound was prepared from 2-chloro-3-aminothiochromone [11] in a yield of 80%, mp 197-198°; ms: m/e 355 (M^++2, 35), 353 (M^+, 90), 323 (22), 321 (53), 264 (100); ^{1}H-nmr (deuteriochloroform): 3.69 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 5.64 (s, 1H, =CH), 7.30-7.74 (m, 3H, ArH), 8.30-8.50 (m, 1H, ArH), 9.68 (b, 1H, NH); ir: 1724, 1658, 1600 (C=O), 3200 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{12}ClNO_5S$: C, 50.93; H, 3.42; N, 3.96. Found: C, 50.97; H, 3.55; N, 3.86.

General Procedure for Cyclization of the Esters **9** and **10** in Diphenyl Ether.

A solution of compound **9** or **10** (0.0045 mole) in diphenyl ether (25 g) was refluxed under nitrogen for 90 minutes. The reaction mixture was cooled and filtered. The product was washed with ethyl acetate or recrystallized from acetonitrile to give an analytically pure material.

Ethyl 4,10-Dihydro-4,10-dioxo-1*H*[1]benzothiopyrano[3,2-*b*]pyridine-2-carboxylate (**11a**).

This compound was obtained in a yield of 89%, mp 275-276°; ms: m/e 301 (M^+, 24), 229 (100); ^{1}H-nmr (trifluoroacetic acid): 1.56 (t, 3H, CH_3), 4.68 (q, 2H, CH_2), 7.60-8.16 (m, 3H, ArH), 8.68 (d, 6 Hz, 1H, ArH), 9.40 (b, 1H, ArH); ir: 1700, 1625, 1590 (C=O), 3420 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{11}NO_4S$: C, 59.79; H, 3.68; N, 4.65. Found: C, 59.58; H, 3.46; N, 4.42.

Ethyl 4,10-Dihydro-4,10-dioxo-8-methyl-1*H*[1]benzothiopyrano[3,2-*b*]pyridine-3-carboxylate (**11b**).

This compound was obtained in a yield of 90%, mp >300°; ms: m/e 315 (M^+, 25), 243 (100); ^{1}H-nmr (trifluoroacetic acid): 1.60 (t, 3H, CH_3), 2.63 (s, 3H, CH_3), 4.70 (q, 2H, CH_2), 7.89 (s, 2H, ArH), 8.16 (s, 1H, ArH), 9.46 (b, 1H, ArH); ir: 1690, 1625, 1600 (C=O), 3420 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 61.26; H, 4.07; N, 4.13.

Ethyl 4,10-Dihydro-4,10-dioxo-6-methyl-1*H*[1]benzothiopyrano[3,2-*b*]pyridine-3-carboxylate (**11c**).

This compound was obtained in a yield of 92%, mp 292° dec; ms: m/e 315 (M^+, 33), 243 (100); ^{1}H-nmr (trifluoroacetic acid): 1.59 (t, 3H, CH_3), 2.82 (s, 3H, CH_3), 4.80 (q, 2H, CH_2), 7.62-8.00 (m, 2H), 8.24 (s, 1H), 9.24 (b, 1H, NH); ir: 1720, 1630, 1610 (C=O), 3400 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 60.84; H, 4.10; N, 4.43.

Methyl 4,10-Dihydro-4,10-dioxo-1*H*[1]benzothiopyrano[3,2-*b*]pyridine-2-carboxylate (**12a**).

This compound was obtained in a yield of 40%, mp 235-237°; ms: m/e 287 (M^+, 100), 259 (32); ^{1}H-nmr (trifluoroacetic acid): 4.28 (s, 3H, CH_3), 7.66-8.08 (m, 3H, ArH), 8.16 (s, 1H), 8.74 (d, 6 Hz, 1H); ir: 1735, 1614, 1590 (C=O), 3340 cm^{-1} (NH).

Anal. Calcd. for $C_{14}H_9NO_4S$: C, 58.53; H, 3.16; N, 4.88. Found: C, 58.39; H, 2.98; N, 4.56.

Methyl 4,10-Dihydro-4,10-dioxo-8-methyl-1*H*[1]benzothiopyrano[3,2-*b*]-pyridine-2-carboxylate (**12b**).

This compound was obtained in a yield of 48%, mp 225-227°; ms: m/e 301 (M^+, 100), 273 (36); ^{1}H-nmr (trifluoroacetic acid): 2.74 (s, 3H, CH_3), 4.44 (s, 3H, CH_3), 8.12 (s, 2H, ArH), 8.38 (s, 1H), 8.80 (s, 1H, ArH); ir: 1730, 1615, 1600 (C=O), 3320 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{11}NO_4S$: C, 59.79; H, 3.68; N, 4.65. Found: C, 60.05; H, 3.46; N, 4.45.

Methyl 4,10-Dihydro-4,10-dioxo-6-methyl-1*H*[1]benzothiopyrano[3,2-*b*]-pyridine-2-carboxylate (**12c**).

This compound was obtained in a yield of 52%, mp 220-222°; ms: m/e 301 (M^+, 100), 273 (30); ^{1}H-nmr (trifluoroacetic acid): 2.70 (s, 3H, CH_3), 4.13 (s, 3H, CH_3), 7.40-7.96 (m, 2H, ArH), 8.12 (s, 1H), 8.54 (d, 6 Hz, 1H, ArH); ir: 1740, 1610, 1584 (C=O), 3350 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{11}NO_4S$: C, 59.79; H, 3.68; N, 4.65. Found: C, 60.13; H, 3.42; N, 4.28.

7-Oxo-7,13-dihydro[1]benzothiopyrano[2,3-*b*]-1,5-benzodiazepine (**15**).

A mixture of 3-formylthiochromone **13** [17] (0.57 g, 0.003 mole), *o*-phenylenediamine (0.324 g, 0.003 mole), and ethanol (30 ml) was refluxed for 1 hour. The mixture was then cooled, and the resulting solid was filtered. Recrystallization from ethanol gave a pure compound **15** in a yield of 33%, mp 247-248° dec; ms: m/e 278 (M^+, 100), 249 (18); ^{1}H-nmr (DMSO-d_6): 7.20-8.00 (m, 4H), 8.60 (m, 4H), 9.82 (s, 1H); ir: 1590 (C=O), 3380 cm^{-1} (NH).

Anal. Calcd. for $C_{16}H_{10}N_2OS$: C, 69.05; H, 3.62; N, 10.07. Found: C, 69.34; H, 3.45; N, 9.82.

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