The Synthesis of Monomethoxy[1]benzothieno[2,3-*c*]quinolines

Steven L. Castle, Phillip J. Buckhaults, Larry J. Baldwin,
J. Dew McKenney, Jr., and Raymond N. Castle*

Department of Chemistry, University of South Florida,
Tampa, Florida 33620

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A series of monomethoxy[1]benzothieno[2,3-*c*]quinolines **24-28** were prepared by photocylization of the appropriate 3-chloro-*N*-phenylbenzo[*b*]thiophene-2-carboxamides **9-13** to [1]benzothieno[2,3-*c*]quinolin-6(5*H*)-ones **14-18** followed by chlorination to 6-chloro[1]benzothieno[2,3-*c*]quinolines **19-23** then dechlorination resulting in the title compounds except for **25** which was achieved by direct reduction of **15**. Reaction of **24-28** with methyl iodide provided the corresponding *N*-methyl quaternary salts **29-33**. Also, conversion of 4-methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **16** to 4-methoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline **35** and 4,6-dimethoxy[1]benzothieno[2,3-*c*]quinoline **36** is described.

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As part of our studies on polycyclic nitrogen and sulfur heterocycles [1-3], we would like to report the synthesis of some monomethoxy[1]benzothieno[2,3-*c*]quinolines and their *N*-methyl quaternary salts. The synthesis of a 6-methylthio and a 6-methoxy derivative is also included in this report. Some of these compounds have been submitted for antitumor screening and these data will be described elsewhere.

p-Anisaldehyde **1** or *m*-anisaldehyde **2** were allowed to react with malonic acid to give 4-methoxycinnamic acid **4** (62%) or 3-methoxycinnamic acid **5** (75%) respectively. Starting with cinnamic acid **3**, 3-chlorobenzo[*b*]thiophene-2-carboxoyl chloride **6** (59%) was synthesized in a similar manner to that described by Wright and Brabander [4]. Reaction of 4-methoxycinnamic acid **4** with thionyl chloride in the presence of pyridine and *N,N*-dimethylformamide afforded 3-chloro-6-methoxybenzo[*b*]thiophene-2-carboxoyl chloride **7** in 33% yield following the reaction conditions of Ried and coworkers [5]. In the absence of *N,N*-dimethylformamide, 3-methoxycinnamic acid **5** was converted into 3-chloro-5-methoxybenzo[*b*]thiophene-2-carboxoyl chloride **8** (44%) according to the procedure of Higa and Krubsack [6].

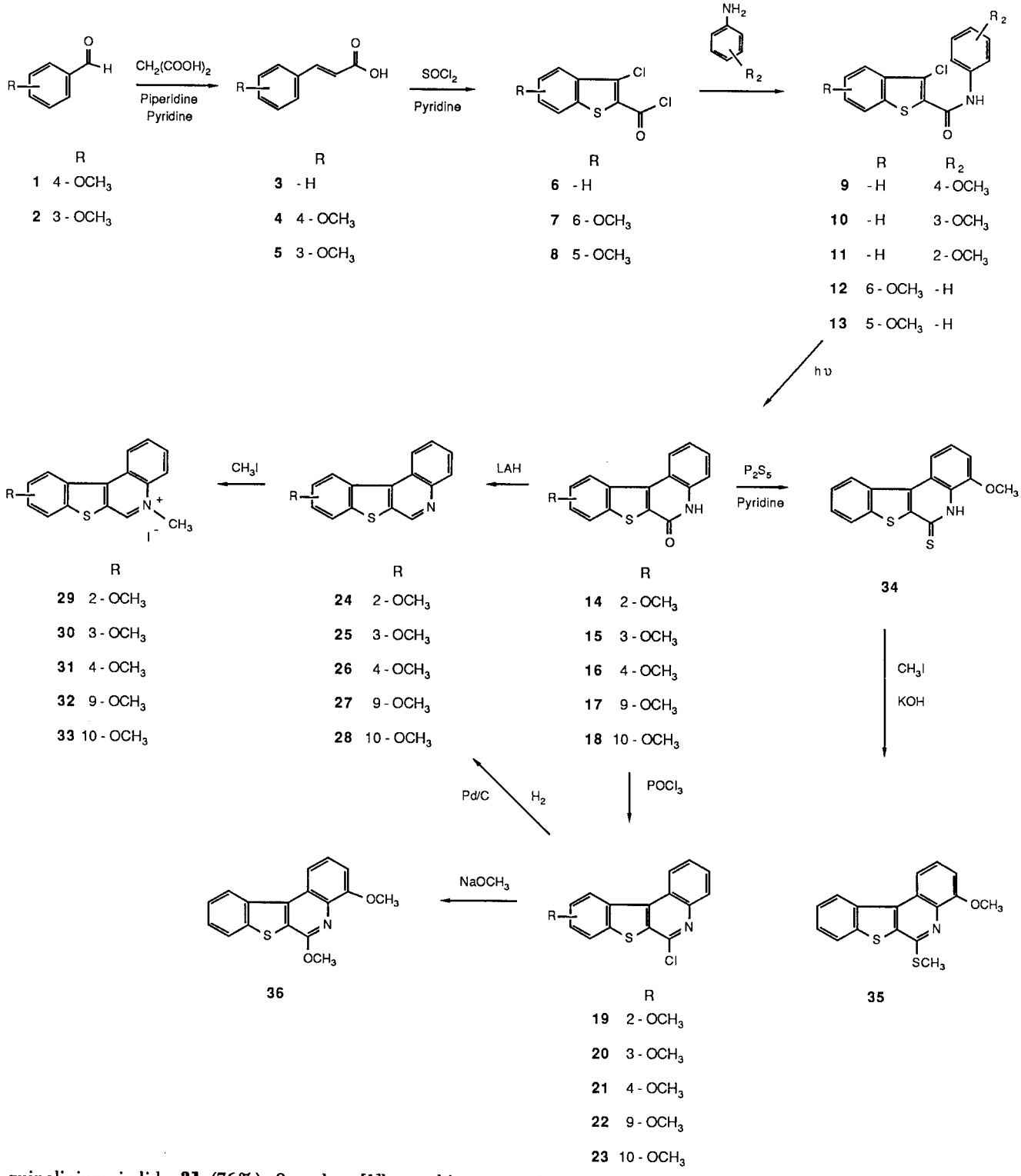
When 3-chlorobenzo[*b*]thiophene-2-carboxoyl chloride **6** was treated with *p*-anisidine, *m*, or *o*-anisidine, the corresponding carboxamides were formed in high yields, namely, 3-chloro-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide **9** (90%), 3-chloro-*N*-(3-methoxyphenyl)-benzo [*b*]thiophene-2-carboxamide **10** (90%), or 3-chloro-*N*-(2-methoxyphenyl)-benzo[*b*]thiophene-2-carboxamide **11** (95%). A two molar excess of aniline was reacted with 3-chloro-6-methoxybenzo[*b*]thiophene-2-carboxoyl chloride **7** or 3-chloro-5-methoxybenzo[*b*]thiophene-2-carboxoyl chloride **8** to give 3-chloro-6-methoxy-*N*-phenylbenzo[*b*]thiophene-2-carboxamide **12** (90%) or 3-chloro-5-methoxy-*N*-phenylbenzo[*b*]thiophene-2-carboxamide **13** (62%), respectively.

Dehydrochlorinative photocyclization of the above carboxamides was carried out to afford 2-methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **14** (92%), 3-methoxy[1]-benzothieno[2,3-*c*]quinolin-6(5*H*)-one **15** (45%), 4-methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **16** (44%), 9-methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **17** (95%), and 10-methyl[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **18** (70%). Equal molar amounts of triethylamine were present during photocyclization using acetone as the solvent except in the case of **11** when benzene proved to be the superior solvent.

The lactams were chlorinated in refluxing phosphorus oxychloride to give 6-chloro-2-methoxy[1]benzothieno-[2,3-*c*]quinoline **19** (38%), 6-chloro-3-methoxy[1]benzothieno[2,3-*c*]quinoline **20** (38%), 6-chloro-4-methoxy[1]-benzothieno[2,3-*c*]quinoline **21** (38%), 6-chloro-9-methoxy-[1]benzothieno[2,3-*c*]quinoline **22** (61%), and 6-chloro-10-methoxy[1]benzothieno[2,3-*c*]quinoline **23** (57%).

Two methods were utilized in the formation of 2-methoxy[1]benzothieno[2,3-*c*]quinoline **24**. When the lactam **14** was allowed to stir with a suspension of lithium aluminum hydride in refluxing tetrahydrofuran under a nitrogen atmosphere (Method A) a 32% yield of **24** was obtained. In comparison, dechlorination of **19** with a 5% palladium on carbon catalyst in a solution of potassium hydroxide, methanol, and benzene (Method B) resulted in 57% of **24**. Lithium aluminum hydride reduction of **15** yielded 3-methoxy[1]benzothieno[2,3-*c*]quinoline **25** (57%) whereas catalytic dechlorination of **21**, **22**, and **23** furnished 4-methoxy[1]benzothieno[2,3-*c*]quinoline **26** (69%), 9-methoxy[1]benzothieno[2,3-*c*]quinoline **27** (24%), and 10-methoxy[1]benzothieno[2,3-*c*]quinoline **28** (49%), respectively.

N-Methylation of **24-28** was accomplished with methyl iodide in refluxing benzene to give the methyl iodide salts, namely, 2-methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **29** (43%), 3-methoxy[1]benzothieno[2,3-*c*]quinolinium iodide **30** (65%), 4-methoxy[1]benzothieno[2,3-*c*]-



quinolinium iodide **31** (76%), 9-methoxy[1]benzothieno-[2,3-*c*]quinolinium iodide **32** (64%), and 10-methoxy[1]benzothieno[2,3-*c*]quinolinium iodide **33** (44%).

4-Methoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione **34** (75%) could readily be achieved by the action of phosphorus pentasulfide on **16** in refluxing pyridine. *S*-Methylation of the thiolactam with methyl iodide afforded 4-methoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline **35** (57%). Finally, 4,6-dimethoxy[1]benzothieno[2,3-*c*]quinoline **36** was prepared from **21** in 63% yield.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckman FT 1100 spectrometer as potassium bromide pellets and frequencies are expressed in cm^{-1}. The uv spectra were determined on an IBM 9420 spectrometer in the solvent indicated. Routine ^{1}H-nmr were obtained on either a Varian EM-360 or on a JEOL FX-90Q spectrometer in the solvent indicated with TMS as the internal standard and chemical shifts are reported in ppm (δ) and J values are in Hz. The mass spectra were carried out on a Hewlett-Packard model 5980A mass spectrometer. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona.

4-Methoxycinnamic Acid (**4**).

Piperidine (8.0 ml, 0.08 mole) was added in one portion to a stirred solution of *p*-anisaldehyde **1** (54.5 g, 0.40 mole) and malonic acid (45.8 g, 0.44 mole) in pyridine (300 ml) at room temperature. The yellow solution was heated at reflux for 12 hours, cooled to room temperature then poured into a mixture of hydrochloric acid (400 ml, d 1.20) and crushed ice (*ca* 400 g). After standing 2 hours the precipitate was collected by filtratoin and dried. This solid was dissolved in hot ethanol (*ca* 800 ml), treated with charcoal, allowed to cool, and the precipitate collected by filtration to give 43.9 g (62%) of **4** as long thick white needles, mp 170-173° (lit [7] mp 174°); ir: 1684; ^{1}H-nmr (deuteriochloroform): 3.85 (s, 3H), 6.32 (d, 1H, J = 10.6), 6.92 (d, 2H, J = 5.9), 7.51 (d, 2H, J = 5.9), 7.75 (d, 1H, J = 10.5), no proton was observed for the carboxylic acid downfield from 10 ppm.

3-Methoxycinnamic Acid (**5**).

The title compound was prepared from *m*-anisaldehyde **2** (54.5 g, 0.4 mole) as described for the synthesis of 4-methoxycinnamic acid **4** to afford 27.4 g of **5** as long thick needles, mp 116-118°. The filtrate was concentrated *in vacuo* to dryness to give another 26.2 g (75% yield based on 53.6 g recovered) of **5** as a white solid, mp 112-116° (lit [8] mp 117°), ir: 1682; ^{1}H-nmr (deuteriochloroform): 3.82 (s, 3H), 6.42 (d, 1H, J = 10.7), 6.87-7.31 (m, 4H), 7.76 (d, 1H, J = 10.6), no proton was observed for the carboxylic acid downfield from 10 ppm.

3-Chlorobenzo[*b*]thiophene-2-carboxoyl Chloride (**6**).

A stirred mixture of cinnamic acid **3** (74.1 g, 0.50 mole), pyridine (4.0 ml, 0.05 mole), thionyl chloride (150 ml, 0.77 mole), and chlorobenzene (300 ml) was heated at reflux for 3 days. Excess thionyl chloride was removed under reduced pressure and the remaining material was suspended in hot hexane (*ca* 800 ml) then filtered. The hot filtrate was treated with charcoal, allowed to cool, then the precipitate collected by filtration to give 68.1 g (59%) of **6** as yellow needles, mp 114-117° (lit [4] mp 114-116°); ir: 1766; ^{1}H-nmr (deuteriochloroform): 7.30-8.10 (m, 4H).

3-Chloro-6-methoxybenzo[*b*]thiophene-2-carboxoyl Chloride (**7**).

Thionyl chloride (15 ml, 205.6 mmoles) was added dropwise to a stirred suspension of *p*-methoxycinnamic acid **4** (10.0 g, 56.1 mmoles), pyridine (1.0 ml, 12.4 mmoles), and *N,N*-dimethylformamide (2.0 ml, 25.8 mmoles) at room temperature. After the addition was complete, the mixture was heated between 128-130° for 3 hours then allowed to cool. The resulting brown solid was suspended in hexane (500 ml), heated to boiling for 30 minutes, then the hexane was decanted from the dark residue. After cooling at *ca* −15° for 12 hours, the yellow precipitate was collected by filtration. This solid was recrystallized from hexane (*ca* 250 ml) to give 4.9 g (33%) of **7** as a yellow solid, mp 109-113° (lit [5] mp 119°]; ir: 1754, 1602, 882, 836; ^{1}H-nmr (deuteriochloroform): 3.93 (s, 3H), 7.07-7.26 (m, 2H), 7.86 (dd, 1H, J = 5.9, J′ = 0.5). This compound was used without further purification.

3-Chloro-5-methoxybenzo[*b*]thiophene-2-carboxoyl Chloride (**8**).

Thionyl chloride (33 ml, 452.4 mmoles) was added dropwise to a stirred mixture of 3-methoxycinnamic acid **5** (10 g, 56.1 mmoles) and pyridine (1.0 ml, 12.4 mmoles) at room temperature. After the addition was complete, the light yellow solution was heated between 100-102° for 18 hours then the excess thionyl chloride was removed under reduced pressure to give an orange solid. This solid was suspended in hot hexane (*ca* 800 ml), treated with charcoal, then allowed to cool and stand at room temperature for 12 hours. The precipitate was collected by filtration to afford 6.4 g (44%) of **8** as a light yellow solid, mp 145-147° (lit [6] mp 147.3-148.3°). The filtrate was concentrated to dryness *in vacuo* whereupon another 4.3 g of crude **8** was recovered, mp 139-143°; ir: 1769, 1607, 923, 849; ^{1}H-nmr (deuteriochloroform): 3.92 (s, 3H), 7.17-7.29 (m, 2H), 7.68 (dd, 1H, J = 5.7, J′ = 0.8). This compound was used without further purification.

3-Chloro-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**9**).

p-Anisidine (2.66 g, 21.6 mmoles) was added to a stirred solution of 3-chlorobenzo[*b*]thiophene-2-carboxoyl chloride **6** (5.00 g, 21.6 mmoles) in benzene (100 ml) at room temperature. After the addition was complete, pyridine (1.71 g, 21.6 mmoles) was added and the mixture was heated at reflux for 1 hour. Excess solvent was removed *in vacuo* and the resulting solid was washed with water and dried. This solid was recrystallized from ethanol to give 6.2 g (90%) of **9**, mp 174-175°; ir: 3335, 1643, 1597, 1530; ^{1}H-nmr (deuteriochloroform): 3.8 (s, 3H), 6.9 (d, 2H, J = 5), 7.7 (m, 6H) no NH proton was observed; ms: m/e 317 (23.2), 319 (9.0); uv (ethanol): 288.8 (2.04×10^4), 225.6 (1.8×10^4), 210.4 (160×10^4).

Anal. Calcd. for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.80; N, 4.40; S, 10.09. Found: C, 60.67; H, 3.97; N, 4.43; S, 9.88.

3-Chloro-*N*-(3-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**10**).

The title compound was prepared from 3-chlorobenzo[*b*]thiophene-2-carboxoyl chloride **6** and *m*-anisidine as described for 3-chloro-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide **9**. Recrystallization from ethanol yielded 6.2 g (90%) of **10**, mp 133°; ir: 3332, 1643, 1604, 1540; ^{1}H-nmr (deuteriochloroform): 3.84 (s, 3H), 7.00-7.30 (m, 2H), 7.40-7.60 (m, 3H), 7.80-7.96 (m, 2H), 8.90 (bs, 1H); ms: m/e 317 (9.3), 319 (3.2).

Anal. Calcd. for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.80; N, 4.40; S, 10.09. Found: C, 60.46; H, 4.00; N, 4.52; S, 9.92.

3-Chloro-*N*-(2-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**11**).

The title compound was prepared from 3-chlorobenzo[*b*]thiophene-2-carboxoyl chloride **6** and *o*-anisidine as described for 3-chloro-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide **9**. Recrystallization from ethanol yielded 6.5 g (95%) of **11**, mp 140-141°; ir: 3361, 1653, 1607, 1543; ^{1}H-nmr (deuteriochloroform): 3.9 (s, 3H), 6.8 (m, 3H), 7.3 (m, 2H), 7.7 (m, 2H), 8.5 (m, 1H), 9.7 (bs, 1H).

Anal. Calcd. for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.80; N, 4.40; S, 10.09. Found: C, 60.52; H, 3.94; N, 4.47; S, 10.21.

3-Chloro-6-methoxy-*N*-phenylbenzo[*b*]thiophene-2-carboxamide (**12**).

A solution of aniline (2.1 ml, 23.0 mmoles) in benzene (20 ml) was added dropwise to a stirred solution of 3-chloro-6-methoxybenzo[*b*]thiophene-2-carboxoyl chloride **7** (3.0 g, 11.5 mmoles) in benzene (100 ml) at room temperature. After the addition was complete, the mixture was heated at reflux for 2 hours, cooled, then the precipitate was collected by filtration, washed with water (25 ml), and dried. This solid was dissolved in hot ethyl acetate (*ca* 1600 ml), treated with charcoal, cooled, and after standing 12 hours, the precipitate was collected by filtration. This material was recrystallized from ethyl acetate (2×) to give 3.3 g (90%) of **12** as long white needles, mp 228-230°; ir: 3317, 1638, 1599, 1535; ^{1}H-nmr (DMSO-d_6): 100°, 3.91 (s, 3H), 7.04-7.46 (m, 4H), 7.62-7.85 (m, 4H), 9.98 (bs, 1H).

Anal. Calcd. for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81; N, 4.41; S, 10.09. Found: C, 60.54; H, 3.71; N, 4.39; S, 9.96.

3-Chloro-5-methoxy-*N*-phenylbenzo[*b*]thiophene-2-carboxamide (**13**).

The title compound was prepared from 3-chloro-5-methoxybenzo[*b*]-thiophene-2-carboxoyl chloride **8** (5.0 g, 19.1 mmoles) in a manner similar to that described for the synthesis of 3-chloro-6-methoxy-*N*-phenylbenzo-[*b*]thiophene-2-carboxamide **12**. The isolated crude product was recrystallized from ethanol to afford 3.75 g (62%) of **13** as long white needles, mp 156-157°. The combined recrystallization filtrates were concentrated

(*ca* 75%) and another 1.02 g of **13** was collected, mp 152-154°; ir: 3309, 1643, 1602, 1540; ^{1}H-nmr (deuteriochloroform): 3.92 (s, 3H), 7.08-7.46 (m, 5H), 7.63-7.75 (m, 3H), 8.84 (bs, 1H).

Anal. Calcd. for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81; N, 4.41; S, 10.09. Found: C, 60.53; H, 4.00; N, 4.40; S, 9.96.

2-Methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**14**).

A stirred solution of 3-chloro-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide **9** (1.0 g, 3.1 mmoles) and triethylamine (0.4 ml, 3.1 mmoles) in acetone (500 ml) was irradiated under a slow stream of air for 5 hours with a 450 watt Hanovia medium pressure mercury vapor lamp. The precipitate was collected by filtration, washed with water (10 ml), then acetone (10 ml) and dried to give 0.8 g (92%) of **14** as a white solid, mp >280° (lit [9] mp >290°); Beilstein test negative; ir: 3307, 1665, 1598, 1514; ^{1}H-nmr (DMSO-d_6): 100°, 3.95 (s, 3H), 7.22 (dd, 1H, J = 5.9, J' = 1.7), 7.48-7.71 (m, 3H), 8.04-8.25 (m, 2H), 8.71-8.81 (m, 1H), the NH proton was not observed; ms: m/e 281 (100), 282 (18.5). This material was used without further purification.

3-Methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**15**).

The title compound was prepared from 3-chloro-*N*-(3-methoxyphenyl)-benzo[*b*]thiophene-2-carboxamide **10** as described for the synthesis of 2-methoxybenzo[*b*]thieno[2,3-*c*]quinolin-6(5*H*)-one **14** to give 0.4 g (45%) of **15** as a white solid, mp >280°; Beilstein test negative; ir: 3309, 1656, 1599, 1530; ^{1}H-nmr (DMSO-d_6): 100°, 3.88 (s, 3H), 6.99 (dd, 1H, J = 6.0, J' = 1.8), 7.11 (d, 1H, J = 1.8), 7.57-7.68 (m, 2H), 8.11-8.22 (m, 1H), 8.60 (d, 1H, J = 6.0), 8.73-8.84 (m, 1H), the NH proton was not observed. This compound was used without further purification.

4-Methoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-one (**16**).

The title compound was prepared from 3-chloro-*N*-(2-methoxyphenyl)-benzo[*b*]thiophene-2-carboxamide **11** (0.5 g, 1.6 mmoles) in a manner similar to that described for 2-methoxybenzo[*b*]thieno[2,3-*c*]quinolin-6(5*H*)-one **14** except benzene was utilized as the solvent to give 0.2 g (44%) of **16** as a white solid, mp 280-282° dec, (lit [9] mp 290°); Beilstein test negative; ir: 3296, 1658, 1592, 1523; ^{1}H-nmr (DMSO-d_6): 100°, 4.00 (s, 3H), 7.26-7.46 (m, 2H), 7.60-7.70 (m, 2H), 8.15-8.35 (m, 2H), 8.77-8.87 (m, 1H), no NH proton was observed; uv (ethanol): 316 (1.5×10^4), 291 (1.28×10^4), 246.4 (1.44×10^4), 229 (1.58×10^4), 208 (1.58×10^4). This compound was utilized without further purfication.

9-Methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**17**).

The title compound was prepared from 3-chloro-6-methoxy-*N*-phenyl-benzo[*b*]thiophene-2-carboxamide **12** (0.5 g, 1.6 mmoles) in a manner similar to that described for the synthesis of 2-methoxy[1]benzothieno-[2,3-*c*]quinolin-6(5*H*)-one **14** to give 0.42 g (95%) of **17** as a white solid, mp >280°; Beilstein test negative; ir: 3320, 1664, 1602, 1520; ^{1}H-nmr (DMSO-d_6): 100°, 3.93 (s, 3H), 7.18-7.58 (m, 4H), 7.75 (d, 1H, J = 1.8), 8.58-8.78 (q, 2H), no NH proton was observed. This compound was used without further purification.

10-Methoxy[1]benzothieno[2,3-*c*]quinlin-6(5*H*)-one (**18**).

The title compound was prepared from 3-chloro-5-methoxy-*N*-phenyl-benzo[*b*]thiophene-2-carboxamide **13** (0.5 g, 1.6 mmoles) in a manner similar to that described for the synthesis of 2-methoxy[1]benzothieno-[2,3-*c*]quinolin-6(5*H*)-one **14** to give 0.31 g (70%) of **18** as a white solid, mp >280°; Beilstein test negative; ir: 3301, 1658, 1589, 1514; ^{1}H-nmr (DMSO-d_6): 100°, 3.99 (s, 3H), 7.26-7.59 (m, 4H), 8.09 (d, 1H, J = 5.9), 8.20 (d, 1H, J = 1.7), 8.58-8.69 (m, 1H), no NH proton was observed. This compound was used without further purification.

6-Chloro-2-methoxy[1]benzothieno[2,3-*c*]quinoline (**19**).

A mixture of 2-methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **14** (1.0 g, 3.6 mmoles) in phosphorus oxychloride (40 ml) was heated at reflux for 5 hours then the excess solvent was removed under reduced pressure. The residual material was quenched with ice and the resulting precipitate was collected by filtration and dried. Recrystallization from benzene afforded 0.4 g (38%) of **19** as colorless crystals, mp 180°; Beilstein test positive; ^{1}H-nmr (deuteriochloroform): 3.97 (s, 3H), 7.50 (m, 3H), 8.03 (m, 3H), 9.70 (dd, 1H, J = 8.0, J' = 4.0); ms: m/e 299 (100), 300 (18.1), 301 (39.8), 302 (6.1).

Anal. Calcd. for $C_{16}H_{10}ClNOS$: C, 64.11; H, 3.36; N, 4.67; S, 10.70. Found: C, 63.99; H, 3.33; N, 4.44; S, 10.46.

6-Chloro-3-methoxy[1]benzothieno[2,3-*c*]quinoline (**20**).

The title compound was prepared from 3-methoxy[1]benzothieno-[2,3-*c*]quinolin-6(5*H*)-one **15** as described for the synthesis of 6-chloro-2-methoxy[1]benzothieno[2,3-*c*]quinoline **19** to give 0.4 g (38%) of **20**, mp 190-194°; Beilstein test positive; ^{1}H-nmr (deuteriochloroform): 4.02 (s, 3H), 7.34 (dd, 1H, J = 9.0, J' = 2.5), 7.60 (m, 2H), 7.98 (m, 2H), 8.09 (s, 1H), 8.54 (dd, 1H, J = 6.5, J' = 3.5); ms: m/e 299 (100), 301 (38.3).

Anal. Calcd. for $C_{16}H_{10}ClNOS$: C, 64.11; H, 3.36; N, 4.67; S, 10.70. Found: C, 64.21; H, 3.40; N, 4.70; S, 10.61.

6-Chloro-4-methoxy[1]benzothieno[2,3-*c*]quinoline (**21**).

The title compound was prepared from 4-methoxy[1]benzothieno-[2,3-*c*]quinolin-6(5*H*)-one **16** as described for the synthesis of 6-chloro-2-methoxy[1]benzothieno[2,3-*c*]quinoline **19** to afford 0.4 g (38%) of **21** after recrystallization from benzene, mp 186-188°; Beilstein test positive; ^{1}H-nmr (deuteriochloroform): 4.11 (s, 3H), 7.13 (dd, 1H, J = 5.2, J' = 0.6), 7.51-7.73 (m, 3H), 7.95-8.07 (m, 1H), 8.36 (dd, 1H, J = 5.8, J' = 0.8), 8.68-8.79 (m, 1H); ms: m/e 299 (96.7), 300 (100), 301 (43.4), 302 (30).

Anal. Calcd. for $C_{16}H_{10}ClNOS$: C, 64.11; H, 3.36; N, 4.67; S, 10.70. Found: C, 64.21; H, 3.22; N, 4.70; S, 10.56.

6-Chloro-9-methoxy[1]benzothieno[2,3-*c*]quinoline (**22**).

The title compound was prepared from 9-methoxy[1]benzothieno-[2,3-*c*]quinolin-6(5*H*)-one **17** (2.0 g, 7.1 mmoles) in a manner similar to that described for 6-chloro-2-methoxy[1]benzothieno[2,3-*c*]quinoline **19** to afford 1.3 g (61%) of **22** after recrystallization from hexane, mp 156-157°; Beilstein test positive; ^{1}H-nmr (deuteriochloroform): 3.94 (s, 3H), 7.17 (dd, 1H, J = 6.1, J' = 1.6), 7.38 (d, 1H, J = 1.6), 7.64-7.76 (m, 2H), 8.11-8.22 (m, 1H), 8.58 (d, 1H, J = 6.1), 8.68-8.76 (m, 1H).

Anal. Calcd. for $C_{16}H_{10}ClNOS$: C, 64.10; H, 3.36; N, 4.67; S, 10.70. Found: C, 64.31; H, 3.41; N, 4.69; S, 10.53.

6-Chloro-10-methoxy[1]benzothieno[2,3-*c*]quinoline (**23**).

The title compound was prepared from 10-methoxy[1]benzothieno-[2,3-*c*]quinolin-6(5*H*)-one **18** (2.0 g, 7.1 mmoles) in a manner similar to that described for 6-chloro-2-methoxy[1]benzothieno[2,3-*c*]quinoline **19** to afford 1.21 g (57%) of **23** after recrystallization from benzene, mp 209-210°; Beilstein test positive; ^{1}H-nmr (deuteriochloroform): 4.0 (s, 3H), 7.25 (dd, 1H, J = 6.1, J' = 1.6), 7.67-7.78 (m, 2H), 7.87 (d, 1H, J = 6.1), 8.12-8.25 (m, 2H), 8.64-8.75 (m, 1H).

Anal. Calcd. for $C_{16}H_{10}ClNOS$: C, 64.10; H, 3.36; N, 4.67; S, 10.70. Found: C, 64.40; H, 3.51; N, 4.77; S, 10.49.

2-Methoxy[1]benzothieno[2,3-*c*]quinoline (**24**).

Method A. To a stirred suspension of lithium aluminum hydride (0.7 g, 18.4 mmoles) in dry tetrahydrofuran under a nitrogen atmosphere was added 2-methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **14** (1.0 g, 3.6 mmoles) in one portion. The mixture was heated at reflux for 24 hours then cooled to ice bath temperature whereupon the excess lithium aluminum hydride was deactivated by the stepwise addition of water (0.7 ml), 10% sodium hydroxide (0.7 ml) and water (0.7 ml). Solids were removed by filtration then stirred with ether (25 ml) and filtered. The combined organic filtrates were dried (magnesium sulfate) then the excess solvent was removed *in vacuo* to give a light yellow solid. This solid was suspended in a solution of hot hexane:benzene (1:1, 25 ml), treated with charcoal, and allowed to cool. The precipitate was collected by filtration then treated the same as above to afford 0.3 g (32%) of **24** as thick light tan branches, mp 152-153°. The above filtrates were combined and the solvent was removed under reduced pressure to give another 0.2 g of **24** as a beige solid, mp 148-150°; Beilstein test negative; ^{1}H-nmr (deuterio-

chloroform): 4.05 (s, 3H), 7.39 (dd, 1H, J = 6.2, J' = 1.8), 7.54-7.69 (m, 2H), 7.96-8.08 (m, 2H), 8.19 (d, 1H, J = 6.2), 8.61-8.72 (m, 1H), 9.14 (s, 1H).

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.42; H, 4.18; N, 5.28; S, 12.09. Found: C, 72.38; H, 4.32; N, 5.37; S, 12.01.

Method B. A 5% Pd/C catalyst (0.5 g) was added portionwise to a stirred solution of 6-chloro-2-methoxy[1]benzothieno[2,3-*c*]quinoline **19** (0.6 g, 2.0 mmoles) in a solution of sodium hydroxide (0.1 g, 2.5 mmoles), methanol (50 ml), and benzene (30 ml). This mixture was stirred at room temperature under a hydrogen atmosphere for 24 hours. The catalyst was removed by filtration and the excess solvent was removed under reduced pressure to give a yellow solid. This solid was suspended in water and extracted with benzene. The organic portion was dried (magnesium sulfate) then the benzene was evaporated *in vacuo* to afford a solid. Recrystallization from benzene-hexane yielded 0.3 g (57%) of **24**.

3-Methoxy[1]benzothieno[2,3-*c*]quinoline (**25**).

The title compound was prepared from 3-methoxy[1]benzothieno-[2,3-*c*]quinolin-6(5*H*)-one **15** (1.5 g, 5.3 mmoles) as described for the synthesis of 2-methoxy[1]benzothieno[2,3-*c*]quinoline **24** (Method A) to afford 0.8 g (57%) of **25** as short yellow needles, mp 152-153°; Beilstein test negative; ^{1}H-nmr (deuteriochloroform): 4.00 (s, 3H), 7.38 (dd, 1H, J = 6.2, J' = 1.8), 7.54-7.67 (m, 3H), 7.97-8.07 (m, 1H), 8.70-8.80 (m, 2H), 9.27 (s, 1H).

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.42; H, 4.18; N, 5.28; S, 12.09. Found: C, 72.28; H, 4.28; N, 5.24; S, 11.87.

4-Methoxy[1]benzothieno[2,3-*c*]quinoline (**26**).

The title compound was prepared from 6-chloro-4-methoxy[1]benzothieno[2,3-*c*]quinoline **21** (1.0 g, 3.3 mmoles) in a manner similar to that described for 2-methoxy[1]benzothieno[2,3-*c*]quinoline **24** (Method B) except that a 10% Pd/C catalyst (0.1 g) was utilized and the mixture containing potassium hydroxide (0.19 g, 3.3 mmoles), methanol (80 ml), and benzene (100 ml) was stirred for 3 days. The crude isolated product was dissolved in hot hexane, treated with charcoal, allowed to cool and the precipitate collected by filtration. Recrystallization from hexane (3×) afforded 0.6 g (69%) of **26** as long white needles, mp 145-146°; Beilstein test negative; ^{1}H-nmr (deuteriochloroform): 4.15 (s, 3H), 7.14 (dd, 1H, J = 5.4, J' = 0.7), 7.56-7.77 (m, 3H), 7.99-8.10 (m, 1H), 8.45 (dd, 1H, J = 5.7, J' = 0.7), 8.77-8.87 (m, 1H), 9.37 (s, 1H).

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.42; H, 4.18; N, 5.28; S, 12.09. Found: C, 72.53; H, 4.07; N, 5.17; S, 11.84.

9-Methoxy[1]benzothieno[2,3-*c*]quinoline (**27**).

The title compound was prepared from 6-chloro-9-methoxy[1]benzothieno[2,3-*c*]quinoline **22** (1.0 g, 3.3 mmoles) as described for the synthesis of 2-methoxy[1]benzothieno[2,3-*c*]quinoline **24** (Method B) except that a 10% Pd/C catalyst (0.1 g) was utilized and the mixture containing potassium hydroxide (0.19 g, 3.3 mmoles), methanol (100 ml), and benzene (100 ml) was stirred for 3 days. The crude isolated product was dissolved in a hot solution of benzene:hexane (1:1, *ca* 50 ml), treated with charcoal, allowed to cool and stand overnight at room temperature. The precipitate was collected by filtration, then recrystallized from benzene:hexane (1:1, 2×) to give 0.21 g (24%) of **27** as fine white clusters, mp 155-156°; Beilstein test negative; ^{1}H-nmr (deuteriochloroform): 3.93 (s, 3H), 7.19 (dd, 1H, J = 6.1, J' = 1.8), 7.43 (d, 1H, J = 1.6), 7.66-7.82 (m, 2H), 8.22-8.33 (m, 1H), 8.66 (d, 1H, J = 6.0), 8.75-8.82 (m, 1H), 9.25 (s, 1H).

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28; S, 12.09. Found: C, 72.19; H, 4.23; N, 5.30; S, 12.01.

10-Methoxy[1]benzothieno[2,3-*c*]quinoline (**28**).

The title compound was prepared from 6-chloro-10-methoxy[1]benzothieno[2,3-*c*]quinoline **23** (1.5 g, 5 mmoles) as described for the synthesis of 2-methoxy[1]benzothieno[2,3-*c*]quinoline **24** (Method B) except that a 10% Pd/C catalyst (0.1 g) was utilized and the mixture containing potassium hydroxide (0.28 g, 5 mmoles), methanol (100 ml), and benzene (500 ml) was stirred for 3 days. The crude isolated solid was dissolved in hot ethyl acetate (*ca* 50 ml), treated with charcoal, allowed to cool and stand at room temperature overnight. The precipitate was collected by filtration then recrystallized from ethyl acetate to give 0.65 g (49%) of **28** as long white needles, mp 128-129°; Beilstein test negative; ^{1}H-nmr (deuteriochloroform): 4.00 (s, 3H), 7.23 (dd, 1H, J = 5.9, J' = 1.6), 7.67-7.92 (m, 3H), 8.19-8.34 (m, 2H), 8.69-8.79 (m, 1H), 9.29 (s, 1H).

Anal. Calcd. for $C_{16}H_{11}NOS$: C, 72.43; H, 4.18; N, 5.28; S, 12.09. Found: C, 72.59; H, 4.03; N, 5.22; S, 11.86.

2-Methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**29**).

Methyl iodide (1.0 ml, 16.1 mmoles) was added dropwise to a stirred solution of 2-methoxy[1]benzothieno[2,3-*c*]quinoline **24** (0.3 g, 1.1 mmoles) in benzene (50 ml) at room temperature. After the addition was complete, the solution was heated at reflux for 12 hours, cooled, then the precipitate collected by filtration and dried. This solid was dissolved in hot methanol (*ca* 75 ml), treated with charcoal, allowed to cool to room temperature whereupon the precipitate was collected by filtration. This material was treated as above to afford 0.2 g (43%) of **29** as fine yellow needles, mp 274-276° dec; ^{1}H-nmr (DMSO-d_6): 100°, 4.21 (s, 3H), 4.71 (s, 3H), 7.83-8.04 (m, 3H), 8.43-8.65 (m, 3H), 9.10-9.20 (m, 1H), 10.15 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}INOS$: C, 50.13; H, 3.46; N, 3.44; S, 7.87. Found: C, 50.15; H, 3.32; N, 3.40: S, 7.73.

3-Methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**30**).

The title compound was prepared from 3-methoxy[1]benzothieno-[2,3-*c*]quinoline **25** (0.7 g, 2.6 mmoles) in a manner similar to that described for the synthesis of 2-methoxy[1]benzothieno[2,3-*c*]quinolinium iodide **29** to give 0.7 g (65%) of **30** as short bright yellow needles, mp >280°; ^{1}H-nmr (DMSO-d_6): 100°, 4.17 (s, 3H), 4.69 (s, 3H), 7.74-7.96 (m, 4H), 8.39-8.50 (m, 1H), 9.14-9.40 (m, 2H), 10.19 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}INOS$: C, 50.13; H, 3.46; N, 3.44; S, 7.87. Found: C, 50.10; H, 3.44; N, 3.50; S, 7.93.

4-Methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**31**).

The title compound was prepared from 4-methoxy[1]benzothieno-[2,3-*c*]quinoline **26** (0.3 g, 1.1 mmoles) as described for the synthesis of 2-methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **29** to afford 0.35 g (76%) of **31** as yellow needles, mp >280°; ^{1}H-nmr (DMSO-d_6): 60°, 4.15 (s, 3H), 4.88 (s, 3H), 7.74-8.04 (m, 3H), 8.15 (d, 1H, J = 5.5), 8.46-8.57 (m, 1H), 8.96 (d, 1H, J = 5.8), 9.17-9.27 (m, 1H), 10.17 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}INOS$: C, 50.13; H, 3.46; N, 3.44; S, 7.87. Found: C, 50.05; H, 3.54; N, 3.40: S, 7.71.

9-Methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**32**).

The title compound was prepared from 9-methoxy[1]benzothieno-[2,3-*c*]quinoline **27** (0.3 g, 1.1 mmoles) as described for the synthesis of 2-methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **29** to afford 0.27 g (64%) of **32** as short yellow clusters, mp >280°; ^{1}H-nmr (DMSO-d_6): 80°, 4.03 (s, 3H), 4.67 (s, 3H), 7.45 (dd, 1H, J = 6.2, J' = 1.7), 8.05-8.31 (m, 3H), 8.53-8.65 (m, 1H), 9.15 (d, 1H, J = 6.2), 9.28-9.40 (m, 1H), 10.18 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}INOS$: C, 50.13; H, 3.46: N, 3.44; S, 7.87. Found: C, 50.33; H, 3.57; N, 3.45; S, 7.77.

10-Methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**33**).

The title compound was prepared from 10-methoxy[1]benzothieno-[2,3-*c*]quinoline **28** (0.50 g, 1.9 mmoles) as described for the synthesis of 2-methoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **29** to afford 0.36 g (44%) of **33** as short fine yellow needles, mp 254-256° dec; ^{1}H-nmr (DMSO-d_6): 4.08 (s, 3H), 4.71 (s, 3H), 7.64 (dd, 1H, J = 6.1, J' = 1.6), 8.18-8.70 (m, 5H), 9.32-9.44 (m, 1H), 10.34 (s, 1H).

Anal. Calcd. for $C_{17}H_{14}INOS$: C, 50.13; H, 3.46: N, 3.44; S, 7.87. Found: C, 50.38; H, 3.63; N, 3.36; S, 8.00.

4-Methoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**34**).

A stirred suspension of 4-methoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **16** (1.0 g, 3.6 mmoles) and phosphorus pentasulfide (1.6 g, 3.6 mmoles) in pyridine (75 ml) was heated at reflux for 12 hours then poured

into boiling water (400 ml) and after stirring for 15 minutes the precipitate was collected by filtration. This solid was suspended in methanol (100 ml), heated at a slow boil for 15 minutes, then allowed to cool to room temperature. The precipitate was collected by filtration, washed with hexane (20 ml), then dried to give 0.8 g (75% crude yield) of **34** as a bright yellow solid, mp >280°; ir: 1540; ^{1}H-nmr (DMSO-d_6): 60°, 4.07 (s, 3H), 7.34 (dd, 1H, J = 5.4, J′ = 0.8), 7.49 (d, 1H, J = 5.4), 7.62-7.77 (m, 2H), 8.15-8.25 (m, 1H), 8.41 (dd, 1H, J = 5.4, J′ = 0.8), 8.83-8.95 (m, 1H), no NH proton was observed. This compound was used without further purification.

4-Methoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**35**).

Methyl iodide (1.1 ml, 17.7 mmoles) was added dropwise to a stirred suspension of 4-methoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione **34** (0.5 g, 1.7 mmoles) and potassium hydroxide (0.1 g, 1.8 mmoles) in methanol (60 ml) at room temperature. After the addition was complete, the mixture was heated at reflux for 12 hours then the excess solvent was removed *in vacuo* to give a solid. This material was suspended in water (25 ml), stirred for 15 minutes, then the precipitate was collected by filtration. The precipitate was suspended in hot hexane (*ca* 200 ml), treated with charcoal, cooled, the solids collected by filtration and recrystallized from hexane to afford 0.3 g (57%) of **35** as light yellow needles, mp 152-154°; ^{1}H-nmr (deuteriochloroform): 2.96 (s, 3H), 4.12 (s, 3H), 7.13 (dd, 1H, J = 5.2, J′ = 0.8), 7.47-7.69 (m, 3H), 7.98-8.08 (m, 1H), 8.41 (dd, 1H, J = 5.6, J′ = 0.8), 8.74-8.84 (m, 1H).

Anal. Calcd. for $C_{17}H_{13}NOS_2$: C, 65.56; H, 4.21; N, 4.50; S, 20.59. Found: C, 65.73; H, 4.35; N, 4.50; S, 20.61.

4,6-Dimethoxy[1]benzothieno[2,3-*c*]quinoline (**36**).

A solution of 6-chloro-4-methoxy[1]benzothieno[2,3-*c*]quinoline **21** (0.8 g, 2.7 mmoles) in benzene (50 ml) was added dropwise to a stirred solution of sodium methoxide in methanol [prepared by the portionwise addition of sodium metal (0.31 g, 13.3 mg atoms) to 25 ml of methanol] at ice bath temperature. After the addition was complete, the mixture was heated at reflux for 12 hours then the excess solvent was removed under reduced pressure to give a solid. This solid was suspended in water (15 ml), allowed to stir for 15 minutes, then the precipitate collected by filtration and dried. This material was dissolved in hot hexane (*ca* 200 ml), treated with charcoal, cooled, and the precipitate collected by filtration. The precipitate was treated as above then recrystallized from hexane to give 0.5 g (63%) of **36** as long white needles, mp 156-158°; ^{1}H-nmr (deuteriochloroform): 4.12 (s, 3H), 4.34 (s, 3H), 7.13 (dd, 1H, J = 5.3, J′ = 0.7), 7.43-7.65 (m, 3H), 7.99-8.10 (m, 1H), 8.42 (dd, 1H, J = 5.5, J′ = 0.8), 8.76-8.86 (m, 1H).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.44; N, 4.74; S, 10.86. Found: C, 69.21; H, 4.47; N, 4.83; S, 10.91.

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