

John G. Stuart [1], Shinya Khora [1a], J. Dew McKenney, Jr., and Raymond N. Castle*

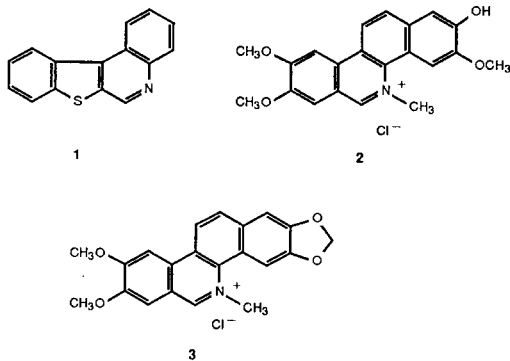
Department of Chemistry, University of South Florida,
Tampa, FL 33620

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Three dimethoxy[1]benzothieno[2,3-*c*]quinolines **24-26** were prepared by photocyclization of the appropriate 3-chloro-*N*-phenylbenzo[*b*]thiophene-2-carboxamides **15-17** to [1]benzothieno[2,3-*c*]quinolin-6(5*H*)-ones **18-20** followed by chlorination to 6-chloro[1]benzothieno[2,3-*c*]quinolines **21-23** and then dechlorination resulting in the title compounds. Reaction of **24-26** with methyl iodide furnished the corresponding *N*-methyl quaternary salts **27-29**. Sodium methoxide readily converted **21-23** to trimethoxy[1]benzothieno[2,3-*c*]quinolines **30-32**.

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We have become interested in the [1]benzothieno[2,3-*c*]quinoline **1** ring system [2] and some of its methoxy substituted derivatives as sulfur-containing analogs of the benzophenanthridine alkaloids such as fagaronine **2** [3] and nitidine **3** [4]. Therefore, as part of our continuing studies on polycyclic nitrogen and sulfur heterocycles [5-7], we wish to report the synthesis of some dimethoxy[1]benzothieno[2,3-*c*]quinolines and their *N*-methyl quaternary salts. Also, the conversion of the disubstituted derivatives into trimethoxy analogs are included in this report. Some of these compounds have been submitted for antitumor screening and the data will be described elsewhere.



3,4-Dimethoxybenzaldehyde **4** was allowed to react with malonic acid in pyridine and a catalytic amount of piperidine to give 3,4-dimethoxycinnamic acid **6** in 90% yield. Following the procedure of Wright and Brabander [8], cinnamic acid **5** was converted to 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride **7** (57%). Reaction of 3,4-dimethoxycinnamic acid **6** with thionyl chloride in the presence of pyridine afforded 3-chloro-5,6-dimethoxybenzo[*b*]thiophene-2-carbonyl chloride **8** (31%). Synthesis and characterization of **8** and the methyl and ethyl esters derived from it have previously been reported by Bonnin *et al.* [9] starting with 3,4-dimethoxyphenylpropionic acid in a 72% yield to give a material which decomposed above 170°. Although infrared and proton nmr data of **8** matched that re-

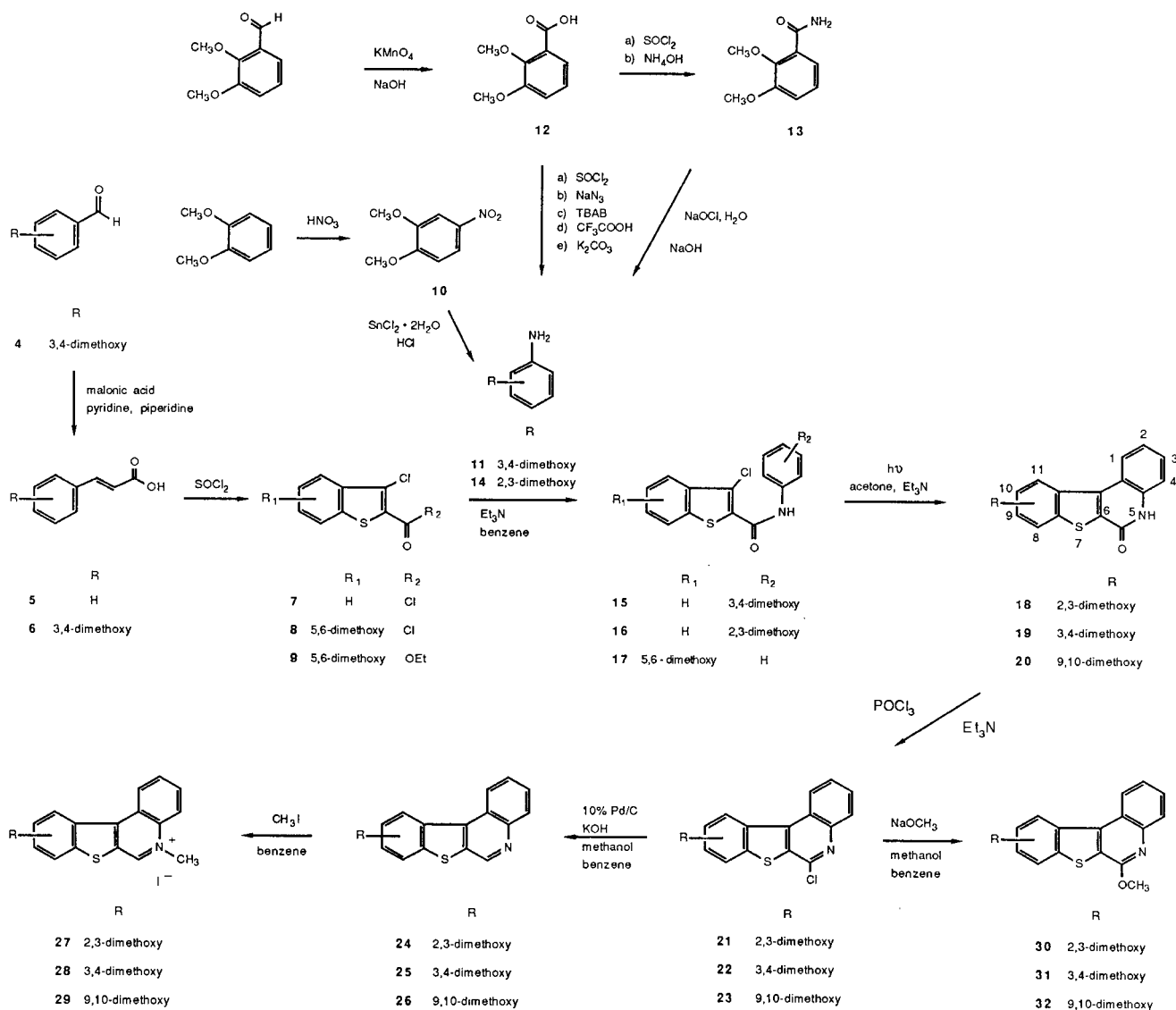
ported by Bonnin *et al.*, the discrepancy in melting points prompted us to prepare ethyl 3-chloro-5,6-dimethoxybenzo[*b*]thiophene-2-carboxylate **9** (53%) as further evidence to support our characterization of **8** compared with that of Bonnin and coworkers.

When 3-chlorobenzo[*b*]thiophene-2-carbonyl chloride **7** was treated with 3,4-dimethoxyaniline **11**, prepared by the reduction of 1-nitro-3,4-dimethoxybenzene **10** with stannous chloride, a 77% yield of 3-chloro-*N*-(3,4-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide **15** resulted. The reaction of 2,3-dimethoxyaniline **14**, prepared either from conversion of 2,3-dimethoxybenzoic acid **12** to 2,3-dimethoxybenzamide **13** followed by a Hofmann rearrangement [10] (Method A) or a modified Curtius rearrangement of **12** following the general procedure of Pfister and Wymann [11] (Method B), with **7** afforded 3-chloro-*N*-(2,3-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide **16** (83%). Synthesis of 3-chloro-5,6-dimethoxy-*N*-phenylbenzo[*b*]thiophene-2-carboxamide **17** (69%) was accomplished by reacting aniline with 3-chloro-5,6-dimethoxybenzo[*b*]thiophene-2-carbonyl chloride **8**.

Dehydrochlorinative photocyclization of the carboxamides **15-17** was carried out under oxidative conditions to furnish 2,3-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **18** (69%), 3,4-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **19** (90%), and 9,10-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **20** (69%), respectively. The photocyclizations were carried out in acetone in the presence of equal molar amounts of triethylamine.

The lactams **18-20** were chlorinated in refluxing phosphorus oxychloride to give 6-chloro-2,3-dimethoxy[1]benzothieno[2,3-*c*]quinoline **21** (31%), 6-chloro-3,4-dimethoxy[1]benzothieno[2,3-*c*]quinoline **22** (57%), and 6-chloro-9,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline **23** (85%), respectively.

The 6-chloro-dimethoxy-substituted[1]benzothieno[2,3-*c*]quinolines **21-23** were dechlorinated with a 10% Pd/C catalyst in a solution of potassium hydroxide, methanol, and benzene under a hydrogen atmosphere to yield



2,3-dimethoxy[1]benzothieno[2,3-*c*]quinoline **24** (60%), 3,4-dimethoxy[1]benzothieno[2,3-*c*]quinoline **25** (34%), and 9,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline **26** (63%), respectively.

Treatment of **24-26** with methyl iodide in refluxing benzene resulted in the *N*-methyl quaternary salts, namely, 2,3-dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **27** (43%), 3,4-dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **28** (67%), and 9,10-dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide **29** (29%).

Refluxing the 6-chloro-substituted compounds **21-23** with sodium methoxide in methanol and benzene provided 2,3,6-trimethoxy[1]benzothieno[2,3-*c*]quinoline **30** (40%), 3,4,6-trimethoxy[1]benzothieno[2,3-*c*]quinoline **31** (70%), and 6,9,10-trimethoxy[1]benzothieno[2,3-*c*]quinoline **32** (67%), respectively.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckmann FT 1100 spectrometer as potassium bromide pellets or neat (as noted) and frequencies are expressed in cm^{-1} . Routine $^1\text{H-nmr}$ were obtained on a JEOL FX-90Q in the solvent indicated with TMS as the internal standard and chemical shifts reported in ppm (δ) and J values in Hz. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

3,4-Dimethoxycinnamic Acid (**6**).

Piperidine (25.7 ml, 0.26 mole) was added in one portion to a stirred solution of 3,4-dimethoxybenzaldehyde **4** (215 g, 1.29 moles) and malonic acid (175 g, 1.68 moles) in pyridine (1000 ml) at room temperature. The solution was heated at reflux for 18 hours, cooled to room temperature, then poured into a mixture of hydrochloric acid (1000 ml, d 1.20) and crushed ice (ca 1000 g). The precipitate was collected by filtration then recrystallized from ethanol to give 242.7 g (90%) of **6** as white clusters, mp 180-182° (lit [12] mp 181-181.5°); ir: 2703, 2649, 2630, 2599, 2589, 2550, 1682, 1630, 1597, 1586; $^1\text{H-nmr}$ (DMSO- d_6): 3.80 (s, 3H), 3.82 (s,

3H), 6.45 (d, 1H, J = 10.6), 6.97 (d, 1H, J = 5.6), 7.22 (dd, 1H, J = 5.6, J' = 1.1), 7.32 (d, 1H, J = 1.1), 7.56 (d, 1H, J = 10.6).

3-Chlorobenzo[b]thiophene-2-carbonyl Chloride (7).

Thionyl chloride (182 ml, 2.5 moles) was added to a stirred suspension of cinnamic acid **5** (74.1 g, 0.5 mole) in chlorobenzene (500 ml) at room temperature. This suspension was allowed to stir for 30 minutes then pyridine (4 ml, 0.05 mole) was added dropwise. After the addition was complete, the solution was heated at reflux for 72 hours. Excess solvent was removed under reduced pressure and the residual material suspended in hot hexane (1000 ml). While hot the solids were removed by filtration and the filtrate treated with charcoal. After standing at room temperature overnight, the precipitate was collected by filtration to give 65.9 g (57%) of **7** as thick light yellow needles, mp 112-114° (lit [13] mp 114.5-115.1°); ir: 1770; ¹H-nmr (deuteriochloroform): 7.40-8.02 (m, 4H).

3-Chloro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl Chloride (8).

Thionyl chloride (35 ml, 480 mmoles) was added dropwise to a stirred mixture of 3,4-dimethoxycinnamic acid **6** (10 g, 48 mmoles) and pyridine (1 ml, 12 mmoles) at room temperature. After the addition was complete, the mixture was heated at ca 130° for 12 hours then excess thionyl chloride was removed under reduced pressure to give a yellow-brown solid. This solid was suspended in hot benzene (ca 250 ml), treated with charcoal, the precipitate collected by filtration, washed with hexane (25 ml), and dried to afford 4.4 g (31%) of **8** as long faintly yellow needles, mp 203-205° (lit [9] dec > 170°); ir: 1754, 1607; ¹H-nmr (deuteriochloroform): 4.00 (s, 6H), 7.18 (s, 1H), 7.27 (s, 1H).

Ethyl 3-Chloro-5,6-dimethoxybenzo[b]thiophene-2-carboxylate (9).

A 1.0 g (3.4 mmoles) sample of 3-chloro-5,6-dimethoxybenzo[b]thiophene-2-carbonyl chloride **8** was gently boiled for 1 hour in absolute ethanol (50 ml), treated with charcoal, then allowed to cool to room temperature where upon the precipitate was collected by filtration. This solid was recrystallized from absolute ethanol (ca 25 ml) to give 0.54 g (53%) of **9** as fine white needles, mp 153-154° (lit [9] mp 156-158°); ir: 1684; ¹H-nmr (deuteriochloroform): 1.41 (t, 3H, J = 4.7), 3.96 (s, 3H), 3.97 (s, 3H), 4.40 (q, 2H, J = 4.7), 7.14 (s, 1H), 7.23 (s, 1H).

1-Nitro-3,4-dimethoxybenzene (10).

The title compound was prepared according to the procedure described by Cardwell and Robinson [14]. Veratrole (50 g, 362 mmoles) was added dropwise to a stirred solution of nitric acid (40 ml, d 1.40) and water (40 ml) at ice bath temperatures. After the addition was complete, the ice bath was removed and the mixture manually stirred periodically over 30 minutes then transferred to crushed ice (ca 500 g). After standing at room temperature overnight, the yellow precipitate was collected by filtration. This solid was dissolved in hot ethanol (ca 600 ml), diluted with water (200 ml), treated with charcoal then allowed to cool and stand at room temperature for 12 hours. The precipitate was collected by filtration, washed with anhydrous ether (50 ml) then dried to give 55.3 g (83%) of **10** as thick yellow irregular plates, mp 95-97° (lit [15] mp 97.5°); ¹H-nmr (deuteriochloroform): 3.96 (s, 3H), 3.99 (s, 3H), 6.92 (d, 1H, J = 6.1), 7.72 (d, 1H, J = 1.8), 7.90 (dd, 1H, J = 6.1, J' = 1.8).

3,4-Dimethoxyaniline (11).

1-Nitro-3,4-dimethoxybenzene **10** (20 g, 109 mmoles) was added to a stirred solution of stannous chloride dihydrate (100 g, 443 mmoles) in hydrochloric acid (250 ml, d 1.20) at room temperature. The mixture was heated between 82-85° for 2 hours then allowed to cool to room temperature. The precipitate was collected by filtration, washed with ether (ca 100 ml), then anhydrous ether (ca 25 ml) and dried to give an off-white solid, mp 268-272° (dec, darkened ca 170°). This solid was suspended in a 20% sodium hydroxide solution (250 ml), stirred at room temperature with ethyl acetate (4 x 300 ml) then decanted. The combined organic fractions were dried (magnesium sulfate) then excess solvent removed under reduced pressure and the collected light brown solid dried to afford 11.1 g (67%) of **11**, mp 85-87° (lit [16] mp 86°); ir: 3386, 3322, 3230, 1597,

1301, 1273, 1236; ¹H-nmr (deuteriochloroform): 3.44 (bd, 2H, J = 1.3), 3.79 (s, 3H), 3.82 (s, 3H), 6.15-6.32 (m, 2H), 6.70 (d, 1H, J = 5.6).

2,3-Dimethoxybenzoic Acid (12).

A solution of potassium permanganate (11.9 g, 75 mmoles) in water (200 ml) was added dropwise to a stirred suspension of 2,3-dimethoxybenzaldehyde (25 g, 150 mmoles) in a 10% sodium hydroxide solution (200 ml) at ca 50°. After the addition was complete, the mixture was stirred for 1 hour then allowed to cool to room temperature where the stirring was continued for 12 hours. The brown precipitate was removed by filtration and the filtrate treated with charcoal, filtered, then acidified (ca pH 1) with a 10% hydrochloric acid solution at ice bath temperatures. The precipitate was collected by filtration and dried to give 17 g (62%) of **12** as a white solid, mp 119-121°. A sample of **12** (2.0 g) was recrystallized from benzene:hexane (1:1, ca 150 ml) to afford 1.4 g of the title compound as long thick white needles, mp 121-122° (lit [17] mp 120-122°); ir: 2695, 2669, 2579, 1702, 1684; ¹H-nmr (deuteriochloroform): 3.93 (s, 3H), 4.08 (s, 3H), 7.15 (s, 1H), 7.21 (d, 1H, J = 1.3), 7.71 (dd, 1H, J = 3.9, J' = 2.6), 10.48 (vbs, 1H).

2,3-Dimethoxybenzamide (13).

Thionyl chloride (120 ml, 1.65 moles) was added in one portion to 2,3-dimethoxybenzoic acid **12** (30 g, 0.165 mole) and the stirred solution heated at reflux for 6 hours. Excess thionyl chloride was removed under reduced pressure resulting in a dark liquid. After allowing this liquid to cool to room temperature, it was poured into concentrated ammonium hydroxide (150 ml) at ice bath temperatures (the quick addition resulted in a violent reaction in which a portion of the reaction solution was lost). After standing 30 minutes, the precipitate was collected by filtration and dried to give 13.7 g of a brown solid, mp 90-94°. This material was dissolved in hot benzene:hexane (1:1 ca 250 ml), treated with charcoal, then allowed to stand overnight. The precipitate was collected by filtration and dried to afford 9.3 g (31%) of **13** as long thick slightly off-white crystals, mp 93-94° (lit [18] mp 90°); ir: 3438, 3422, 1689, 1640, 1576; ¹H-nmr (deuteriochloroform): 3.90 (s, 3H), 3.93 (s, 3H), 6.24 (bs, 1H), 7.02-7.27 (m, 2H), 7.71 (dd, 1H, J = 4.7, J' = 1.9), 7.90 (bs, 1H).

2,3-Dimethoxyaniline (14).

Method A. 2,3-Dimethoxybenzamide **13** (8 g, 44 mmoles) was added in one portion to a stirred solution of sodium hypochlorite (100 ml, 5% minimum available chlorine) and sodium hydroxide (10 g, 250 mmoles) at room temperature. This mixture was heated between 75-78° for 1 hour then a solution of sodium hydroxide (20 g, 500 mmoles) in water (20 ml) was added in one portion and heating continued for 1 hour. The oily mixture was allowed to cool to room temperature then extracted with ether (2 x 200 ml). The combined ether extracts were dried (magnesium sulfate) then excess solvent removed to give a brown liquid. This liquid was subjected to a fractional distillation where 3.3 g (49%) of **14** was collected as a clear liquid between 91-93° at 1.4 mm (lit [19] bp 100-101°/1.5 mm); ir (neat): 3461, 3368, 1617, 1324; ¹H-nmr (deuteriochloroform): 3.81 (bd, 8H, exchangeable with deuterium oxide to give a doublet at 3.81 separated by 0.5 Hz), 6.29 (dd, 1H, J = 2.6, J' = 1.0), 6.38 (dd, 1H, J = 2.6, J' = 1.0), 6.84 (t, 1H, J = 5.4).

Method B. A solution of thionyl chloride (18 ml, 247 mmoles) in benzene (50 ml) was added in one portion to 2,3-dimethoxybenzoic acid **12** (15 g, 82 mmoles) and the mixture heated at reflux overnight. Excess solvent was removed under reduced pressure to give 15.6 g (95%) of crude 2,3-dimethoxybenzoyl chloride. A solution of sodium azide (6.9 g, 260 mmoles) in water (27 ml) was added in a dropwise fashion to a stirred solution of the acid chloride (15.6 g, 78 mmoles) in dichloromethane (140 ml) containing tetrabutylammonium bromide (55 mg, 0.2 mmole) at ice bath temperatures. The reaction was vigorously stirred for 2 hours at this temperature then the organic phase, separated, washed with water, and dried (magnesium sulfate). Trifluoroacetic acid (7 ml, 91 mmoles) was added to the dried filtrate and the mixture heated at reflux for 60 hours. After cooling to room temperature, the reaction mixture was washed with a saturated potassium bicarbonate solution then dried (magnesium sulfate). Excess solvent was removed *in vacuo* to afford 12.6 g (62%) of

crude 2,3-dimethoxytrifluoroacetanilide. A mixture of the anilide (12.6 g, 51 mmoles), potassium carbonate (8.7 g, 63 mmoles), methanol (45 ml), and water (100 ml) was stirred at room temperature under a nitrogen atmosphere for 20 hours. The reaction was concentrated to dryness under reduced pressure and the residual material was extracted with ether and the ether portion dried (potassium carbonate). Excess solvent was removed *in vacuo* to give 4.9 g (39%) of **14** as a light brown oil. Spectral data were consistent with that obtained in Method A. This material was utilized without further purification.

3-Chloro-*N*-(3,4-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**15**).

A solution of 3,4-dimethoxyaniline **11** (9.9 g, 65 mmoles) and triethylamine (9.1 ml, 65 mmoles) in benzene (200 ml) was added dropwise to a stirred solution of 3-chlorobenzoylthiophene-2-carbonyl chloride **7** (15 g, 65 mmoles) in benzene at room temperature. After the addition was complete, the mixture was stirred for 12 hours at *ca* 50°. Excess solvent was removed under reduced pressure to give an off-white solid. This solid was suspended in water (200 ml), to remove ammonium salts, stirred for 15 minutes and then filtered. The resulting solid was dissolved in hot ethyl acetate (*ca* 1.5 l), the solution was treated with charcoal, then allowed to cool and stand at room temperature overnight. The precipitate was collected by filtration, dried, to afford 17.4 g (77%) of **15** as long faint yellow-green needles, mp 180-181°; ir: 3309, 1635, 1607, 1538; ¹H-nmr (deuteriochloroform): 3.88 (s, 3H), 3.93 (s, 3H), 6.79-7.09 (m, 2H), 7.45-7.59 (m, 3H), 7.81-7.95 (m, 2H), 8.82 (bs, 1H).

Anal. Calcd. for C₁₇H₁₄ClNO₃S: C, 58.70; H, 4.06; N, 4.03; S, 9.22. Found: C, 58.68; H, 4.03; N, 4.03; S, 9.26.

3-Chloro-*N*-(2,3-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**16**).

The title compound was prepared from 2,3-dimethoxyaniline **14** (5 g, 33 mmoles) and 3-chlorobenzoylthiophene-2-carbonyl chloride **7** (7.5 g, 33 mmoles) in a manner similar to that described for the synthesis of 3-chloro-*N*-(3,4-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide **15**. The crude isolated product was dissolved in hot ethyl acetate, treated with charcoal, and allowed to cool to room temperature where the precipitate was collected by filtration. The collected solid was treated (3 ×) as above to give 4.3 g (37%) of **16** as white needles, mp 154-156° (softens between 138-140°). The combined recrystallization filtrates were concentrated to dryness under reduced pressure to afford 5.2 g of **16** as a white solid, mp 153-155° (softens between 138-140°), 83% yield based on 9.5 g recovered; ir: 3402, 1653, 1607, 1538; ¹H-nmr (deuteriochloroform): 3.90 (s, 3H), 3.98 (s, 3H), 6.73 (dd, 1H, J = 5.7, J' = 1.0), 7.09 (t, 1H, J = 5.6), 7.44-7.58 (m, 2H), 7.79-7.96 (m, 2H), 8.16 (dd, 1H, J = 5.5, J' = 1.0), 9.8 (bs, 1H).

Anal. Calcd. for C₁₇H₁₄ClNO₃S: C, 58.70; H, 4.06; N, 4.03; S, 9.22. Found: C, 58.72; H, 4.19; N, 4.06; S, 9.13.

3-Chloro-5,6-dimethoxy-*N*-phenylbenzo[*b*]thiophene-2-carboxamide (**17**).

The title compound was prepared from aniline (1.6 g, 17.2 mmoles) and 3-chloro-5,6-dimethoxybenzoylthiophene-2-carbonyl chloride **8** (5 g, 17.2 mmoles) in a manner similar to that described for the synthesis of 3-chloro-*N*-(3,4-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide **15**. The collected solid was dissolved in hot ethyl acetate, treated with charcoal, then allowed to cool and the precipitate collected by filtration. This solid was recrystallized (2 ×) from ethyl acetate to give 4.1 g (69%) of **17** as long white needles, mp 229-230°; ir: 3322, 1640, 1597, 1534; ¹H-nmr (deuteriochloroform): 3.97 (s, 3H), 4.00 (s, 3H), 7.15-7.48 (m, 5H), 7.63-7.74 (m, 2H), 8.82 (bs, 1H).

Anal. Calcd. for C₁₇H₁₄ClNO₃S: C, 58.70; H, 4.06; N, 4.03; S, 9.22. Found: C, 58.44; H, 4.05; N, 4.00; S, 9.56.

2,3-Dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**18**).

A stirred solution of 3-chloro-*N*-(3,4-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide **15** (0.5 g, 1.4 mmoles) and triethylamine (0.2 ml, 1.4 mmoles) in acetone (500 ml) was irradiated for 5 hours by a 450 Watt Hanovia medium pressure mercury arc lamp under a slow stream of air. The precipitate was collected by filtration, washed with water (5 ml), acetone (10 ml) then dried to give 0.3 g (69%) of **18** as a light yellow solid,

mp > 280°; Beilstein test negative; ir: 3286, 1635, 1597, 1520; ¹H-nmr (DMSO-*d*₆): 100°, 3.89 (s, 3H), 3.99 (s, 3H), 7.18 (s, 1H), 7.60-7.71 (m, 2H), 8.04 (s, 1H), 8.06-8.23 (m, 1H), 8.71-8.81 (m, 1H), no NH proton was observed. This material was used without further purification.

3,4-Dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**19**).

The title compound was prepared from 3-chloro-*N*-(2,3-dimethoxyphenyl)benzo[*b*]thiophene-2-carboxamide **16** (1 g, 2.9 mmoles) in a manner similar to that described for the synthesis of 2,3-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **18** to give 0.8 g (90%) of **19** as a white solid, mp > 280°; Beilstein test negative; ir: 1646, 1622, 1527; ¹H-nmr (DMSO-*d*₆): 3.92 (s, 3H), 3.98 (s, 3H), 7.16 (d, 1H, J = 6.0), 7.59-7.70 (m, 2H), 8.14-8.24 (m, 1H), 8.41 (d, 1H, J = 6.2), 8.74-8.85 (m, 1H), no NH proton was observed. This material was used without further purification.

9,10-Dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**20**).

The title compound was prepared from 3-chloro-5,6-dimethoxy-*N*-phenylbenzo[*b*]thiophene-2-carboxamide **17** (0.5 g, 1.4 mmoles) in exactly the same manner as described for the synthesis of 2,3-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **18** to afford 0.3 g (69%) of **20** as a white solid, mp > 280°; Beilstein test negative; ir: 3252, 1664, 1604, 1556; ¹H-nmr (DMSO-*d*₆): 100°, 3.94 (s, 3H), 4.01 (s, 3H), 7.29-7.58 (m, 3H), 7.76 (s, 1H), 8.14 (s, 1H), 8.57-8.66 (m, 1H), no NH proton was observed. This material was used without further purification.

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

A stirred mixture of 2,3-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **18** (1.8 g, 5.8 mmoles) in phosphorus oxychloride (50 ml) and triethylamine (0.8 ml, 5.7 mmoles) was heated at reflux for 12 hours then excess solvent removed under reduced pressure. The resulting dark viscous material was cooled to ice bath temperatures where residual phosphorus oxychloride was decomposed by the portionwise addition of crushed ice (*ca* 75 g). The precipitate was collected by filtration and dried. This solid was suspended in hot benzene (500 ml), stirred for 15 minutes, then solids removed by filtration. The filtrate was concentrated to dryness under reduced pressure to give a beige solid. This solid was dissolved in hot benzene (*ca* 300 ml), treated with charcoal, allowed to cool and stand at room temperature overnight. The precipitate was collected by filtration and recrystallized from benzene (2 ×) to give 0.6 g (31%) of **21** as short white needles, mp 240-241°; Beilstein test positive; ¹H-nmr (deuteriochloroform): 4.00 (s, 3H), 4.10 (s, 3H), 7.42 (s, 1H), 7.52-7.66 (m, 2H), 7.80 (s, 1H), 7.90-8.01 (m, 2H), 8.39-8.49 (m, 1H).

Anal. Calcd. for C₁₇H₁₂ClNO₂S: C, 61.91; H, 3.67; N, 4.25; S, 9.72. Found: C, 62.00; H, 3.72; N, 4.21; S, 9.61.

6-Chloro-3,4-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**22**).

The title compound was prepared from 3,4-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **19** (4 g, 12.8 mmoles) and phosphorus oxychloride (50 ml) in a manner similar to that described for 6-chloro-2,3-dimethoxy[1]benzothieno[2,3-*c*]quinoline **21**. The crude isolated solid was suspended in hot benzene (200 ml), filtered to remove undissolved solids, then allowed to cool to room temperature where the precipitate was collected by filtration and dried. This material was dissolved in hot benzene, treated with charcoal, allowed to cool, and the precipitate collected by filtration. The resulting solid was treated as above (2 ×) to give 1.1 g (26%) of **22** as faint yellow needles, mp 189-190°. The combined recrystallization filtrates were concentrated to dryness under reduced pressure to afford 1.3 g of **22** as a light yellow solid, mp 188-190°; 57% yield based on 2.4 g recovered; Beilstein test positive; ¹H-nmr (deuteriochloroform): 4.06 (s, 3H), 4.17 (s, 3H), 7.35-7.63 (m, 3H), 7.92-8.04 (m, 1H), 8.46 (d, 1H, J = 6.2), 8.58-8.69 (m, 1H).

Anal. Calcd. for C₁₇H₁₂ClNO₂S: C, 61.91; H, 3.67; N, 4.25; S, 9.72. Found: C, 61.88; H, 3.75; N, 4.13; S, 9.66.

6-Chloro-9,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**23**).

The title compound was prepared from 9,10-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one **20** (1 g, 3.2 mmoles) and phosphorus oxychloride

ide (30 ml) in a manner similar to that described for the synthesis of 6-chloro-2,3-dimethoxy[1]benzothieno[2,3-c]quinoline **21**. The crude isolated solid was suspended in hot benzene (200 ml), treated with charcoal, then allowed to cool to room temperature. Excess solvent was removed under reduced pressure to give 0.9 g (85%) of **23** as an off-white solid, mp 208-212°; Beilstein test positive. This material was used without further purification. An analytical sample was prepared by recrystallization from hexane-benzene to afford **23** as fine white needles, mp 227-228.5°; ¹H-nmr (deuteriochloroform): 4.01 (s, 3H), 4.07 (s, 3H), 7.27 (s, 1H), 7.62-7.78 (m, 2H), 7.90 (s, 1H), 8.07-8.17 (m, 1H), 8.43-8.55 (m, 1H).

Anal. Calcd. for C₁₇H₁₂ClNO₂S: C, 61.91; H, 3.67; Cl, 10.75; N, 4.25; S, 9.72. Found: C, 61.72; H, 3.89; Cl, 10.56; N, 4.25; S, 9.66.

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

A 10% Pd/C catalyst (0.1 g) was added portionwise to a stirred solution of 6-chloro-2,3-dimethoxy[1]benzothieno[2,3-c]quinoline **21** (0.3 g, 0.9 mmole) in a solution of potassium hydroxide (0.05 g, 0.9 mmole), methanol (100 ml), and benzene (100 ml). The mixture was stirred under a hydrogen atmosphere for 3 days at room temperature. The catalyst was removed by filtration through a Celite pad and the filtrate concentrated to dryness under reduced pressure to give a solid. This material was dissolved in hot hexane:benzene (1:1, ca 150 ml), treated with charcoal, then allowed to cool and stand at room temperature overnight. The precipitate was collected by filtration and recrystallized from hexane:benzene (1:1, 2 ×) to afford 0.16 g (60%) of **24** as faint yellow clusters after drying under high vacuum (0.12 mm at ca 50° for 3 hours), mp 198-199°; Beilstein test negative; ¹H-nmr (deuteriochloroform): 4.01 (s, 3H), 4.09 (s, 3H), 7.36 (s, 1H), 7.65-7.76 (m, 2H), 8.08 (s, 1H), 8.21-8.33 (m, 1H), 8.59-8.70 (m, 1H), 9.22 (s, 1H).

Anal. Calcd. for C₁₇H₁₃NO₂S: C, 69.13; H, 4.44; N, 4.74; S, 10.86. Found: C, 69.03; H, 4.54; N, 4.76; S, 11.01.

3,4-Dimethoxy[1]benzothieno[2,3-c]quinoline (**25**).

The title compound was prepared from 6-chloro-3,4-dimethoxy[1]benzothieno[2,3-c]quinoline **22** (1 g, 3 mmoles) in a solution of potassium hydroxide (0.17 g, 3 mmoles), benzene (120 ml), and methanol (120 ml) as described for the synthesis of 2,3-dimethoxy[1]benzothieno[2,3-c]quinoline **24**. The isolated crude solid was suspended in water (20 ml), stirred for 15 minutes, then the precipitate removed by filtration and dried. This material was dissolved in hot benzene, treated with charcoal, allowed to cool, and the precipitate collected by filtration. This solid was recrystallized from benzene to give 0.3 g (34%) of **25** as light yellow prisms, mp 148-150°; Beilstein test negative; ¹H-nmr (deuteriochloroform): 4.08 (s, 3H), 4.19 (s, 3H), 7.47-7.67 (m, 3H), 8.00-8.13 (m, 1H), 8.62 (d, 1H, J = 6.2), 8.73-8.84 (m, 1H), 9.36 (s, 1H).

Anal. Calcd. for C₁₇H₁₃NO₂S: C, 69.13; H, 4.44; N, 4.74; S, 10.86. Found: C, 68.94; H, 4.36; N, 4.76; S, 11.00.

9,10-Dimethoxy[1]benzothieno[2,3-c]quinoline (**26**).

The title compound was prepared from 6-chloro-9,10-dimethoxy[1]benzothieno[2,3-c]quinoline **23** (0.9 g, 2.7 mmoles) in a solution of potassium hydroxide (0.15 g, 2.7 mmoles), benzene (200 ml), and methanol (100 ml) as described for the synthesis of 2,3-dimethoxy[1]benzothieno[2,3-c]quinoline **24**. The isolated crude solid was suspended in water (50 ml), stirred for 15 minutes, filtered, and the collected solid dried. This material was dissolved in hot hexane:benzene (1:1, ca 150 ml), treated with charcoal, then allowed to cool and stand overnight at room temperature. The precipitate was collected by filtration and dried to give 0.51 g (63%) of **26** as white clusters, mp 199-200°; Beilstein test negative; ¹H-nmr (deuteriochloroform): 4.01 (s, 3H), 4.10 (s, 3H), 7.36 (s, 1H), 7.66-7.82 (m, 2H), 8.08 (s, 1H), 8.21-8.33 (m, 1H), 8.59-8.71 (m, 1H), 9.23 (s, 1H).

Anal. Calcd. for C₁₇H₁₃NO₂S: C, 69.13; H, 4.44; N, 4.74; S, 10.86. Found: C, 69.23; H, 4.59; N, 4.69; S, 10.91.

2,3-Dimethoxy-5-methyl[1]benzothieno[2,3-c]quinolinium Iodide (**27**).

Methyl iodide (1.2 g, 8.47 mmoles) was added dropwise to a stirred solution of 2,3-dimethoxy[1]benzothieno[2,3-c]quinoline **24** (0.25 g, 0.85 mmole) in benzene (50 ml) at room temperature. After the addition was

complete, the yellow solution was heated at reflux for 12 hours and after cooling to room temperature the precipitate was collected by filtration. This solid was dissolved in hot methanol (ca 250 ml), treated with charcoal, then allowed to cool to room temperature where the precipitate was collected by filtration. This material was recrystallized from methanol (2 ×) to give 0.16 g (43%) of **27** as fine yellow clusters, mp >280° (gradually darkens after 240°); ¹H-nmr (DMSO-d₆): 100°, 4.04 (s, 3H), 4.12 (s, 3H), 4.65 (s, 3H), 8.07 (s, 1H), 8.14-8.30 (m, 2H), 8.42 (s, 1H), 8.51-8.62 (m, 1H), 9.25-9.36 (m, 1H), 10.12 (s, 1H).

Anal. Calcd. for C₁₈H₁₆INO₂S: C, 49.44; H, 3.69; N, 3.20; S, 7.33. Found: C, 49.60; H, 3.87; N, 3.25; S, 7.39.

3,4-Dimethoxy-5-methyl[1]benzothieno[2,3-c]quinolinium Iodide (**28**).

The title compound was prepared from 3,4-dimethoxy[1]benzothieno[2,3-c]quinoline **25** (0.2 g, 0.68 mmole) and methyl iodide (2.28 g, 16.1 mmoles) in benzene (100 ml) in a manner similar to that described for 2,3-dimethoxy-5-methyl[1]benzothieno[2,3-c]quinolinium iodide **27**. Recrystallization from methanol afforded 0.2 g (67%) of **28** as short orange needles, mp 196-198° dec; ¹H-nmr (DMSO-d₆): 4.03 (s, 3H), 4.17 (s, 3H), 4.79 (s, 3H), 7.80-8.03 (m, 3H), 8.43-8.53 (m, 1H), 9.07-9.18 (m, 2H), 10.17 (s, 1H).

Anal. Calcd. for C₁₈H₁₆INO₂S: C, 49.44; H, 3.69; N, 3.20; S, 7.33. Found: C, 49.23; H, 3.72; N, 3.11; S, 7.07.

9,10-Dimethoxy-5-methyl[1]benzothieno[2,3-c]quinolinium Iodide (**29**).

The title compound was prepared from 9,10-dimethoxy[1]benzothieno[2,3-c]quinoline **26** (0.5 g, 1.7 mmoles) and methyl iodide (2.41 g, 17 mmoles) in benzene (75 ml) in a manner similar to that described for 2,3-dimethoxy-5-methyl[1]benzothieno[2,3-c]quinolinium iodide **27**. The crude isolated solid was dissolved in hot methanol (ca 200 ml), treated with charcoal, then allowed to cool and stand overnight at room temperature. The precipitate was collected by filtration and recrystallized from methanol to give 0.21 g (29%) of **29** as small yellow clusters, mp 279-281° (dec, started darkening at ca 240°); ¹H-nmr (DMSO-d₆): 100°, 4.04 (s, 3H), 4.11 (s, 3H), 4.66 (s, 3H), 8.05 (s, 1H), 8.13-8.30 (m, 2H), 8.39 (s, 1H), 8.51-8.62 (m, 1H), 9.23-9.34 (m, 1H), 10.13 (s, 1H).

Anal. Calcd. for C₁₈H₁₆INO₂S: C, 49.44; H, 3.69; N, 3.20; S, 7.33. Found: C, 49.54; H, 3.56; N, 3.24; S, 7.16.

2,3,6-Trimethoxy[1]benzothieno[2,3-c]quinoline (**30**).

A solution of 6-chloro-2,3-dimethoxy[1]benzothieno[2,3-c]quinoline **21** (0.5 g, 1.5 mmoles) in benzene (150 ml) was added dropwise to a stirred solution of sodium methoxide in methanol [prepared by the portionwise addition of sodium metal (0.34 g, 15 mg-atoms) in methanol (25 ml) at ice bath temperatures. After the addition was complete, the solution was heated at reflux for 72 hours. The reaction was concentrated to dryness under reduced pressure and the resulting solid suspended in water (10 ml) then filtered and dried. This solid was suspended in hot hexane (ca 400 ml), filtered, then allowed to stand overnight at room temperature. The precipitate was collected by filtration then recrystallized from hexane to give 0.21 g (40%) of **30** as small white crystals, mp 211-212°; ¹H-nmr (deuteriochloroform): 4.05 (s, 3H), 4.10 (s, 3H), 4.22 (s, 3H), 7.39 (s, 1H), 7.50-7.65 (m, 2H), 7.94 (s, 1H), 7.98-8.05 (m, 1H), 8.50-8.60 (m, 1H).

Anal. Calcd. for C₁₈H₁₅NO₃S: C, 66.44; H, 4.65; N, 4.31; S, 9.86. Found: C, 66.64; H, 4.74; N, 4.35; S, 9.71.

3,4,6-Trimethoxy[1]benzothieno[2,3-c]quinoline (**31**).

The title compound was prepared from 6-chloro-3,4-dimethoxy[1]benzothieno[2,3-c]quinoline **22** (0.5 g, 1.5 mmoles) and sodium methoxide (7.5 mmoles) in a manner similar to that described for 2,3,6-trimethoxy[1]benzothieno[2,3-c]quinoline **30** except the reaction was heated at reflux for 12 hours. The isolated solid was dissolved in hot hexane (ca 200 ml), treated with charcoal, then allowed to cool and the precipitate collected by filtration. The collected material was treated as above then the resulting solid recrystallized from hexane to give 0.1 g (20%) of **31** as fine long white clusters, mp 174-175°. The combined recrystallization fil-

trates were concentrated to dryness *in vacuo*, then dissolved in hot hexane, treated with charcoal, and the precipitate collected by filtration to afford 0.24 g of **31** as fine long white clusters, mp 173-175°; 70% yield based on 0.34 g recovered; ¹H-nmr (deuteriochloroform): 4.04 (s, 3H), 4.20 (s, 3H), 4.32 (s, 3H), 7.29 (d, 1H, J = 5.7), 7.53-7.63 (m, 2H), 7.97-8.08 (m, 1H), 8.48 (d, 1H, J = 6.2), 8.68-8.78 (m, 1H).

Anal. Calcd. for C₁₈H₁₃NO₃S: C, 66.44; H, 4.65; N, 4.31; S, 9.86. Found: C, 66.59; H, 4.65; N, 4.21; S, 9.69.

6,9,10-Trimethoxy[1]benzothieno[2,3-c]quinoline (**32**).

The title compound was prepared from 6-chloro-9,10-dimethoxy[1]benzothieno[2,3-c]quinoline **23** (0.3 g, 0.9 mmole) and sodium methoxide (4.5 mmoles) in a manner similar to that described for 2,3,6-trimethoxy[1]benzothieno[2,3-c]quinoline **30** except the reaction was heated at reflux for 12 hours. The isolated solid was suspended in hot hexane (*ca* 400 ml), filtered hot then allowed to cool. The precipitate was collected by filtration and recrystallized (2 ×) from hexane (*ca* 200 ml) to afford 0.2 g (67%) of **32** as long fine white needles, mp 194-195°; ¹H-nmr (deuteriochloroform): 4.03 (s, 3H), 4.11 (s, 3H), 4.26 (s, 3H), 7.40 (s, 1H), 7.53-7.73 (m, 2H), 8.00-8.13 (m, 2H), 8.58-8.69 (m, 1H).

Anal. Calcd. for C₁₈H₁₃NO₃S: C, 66.44; H, 4.65; N, 4.31; S, 9.86. Found: C, 66.42; H, 4.58; N, 4.30; S, 9.85.

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[1] Present Address: Department of Chemistry, University of Oklahoma, Norman, Oklahoma; [1a] Present Address: Nagasaki Univer-

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