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

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A series of dimethoxy[1]benzothieno[2,3-*c*]quinolines have been prepared by photocyclization of the appropriate *N*-phenyl-3-chlorobenzo[*b*]thiophene-2-carboxamides. The lactams obtained were converted into the thiolactams and their *S*-methyl derivatives. The lactams were also converted into the corresponding chloro derivatives which were catalytically dechlorinated into the dimethoxy[1]benzothieno[2,3-*c*]quinolines. The latter compounds were converted into the *N*-methyl quaternary salts.

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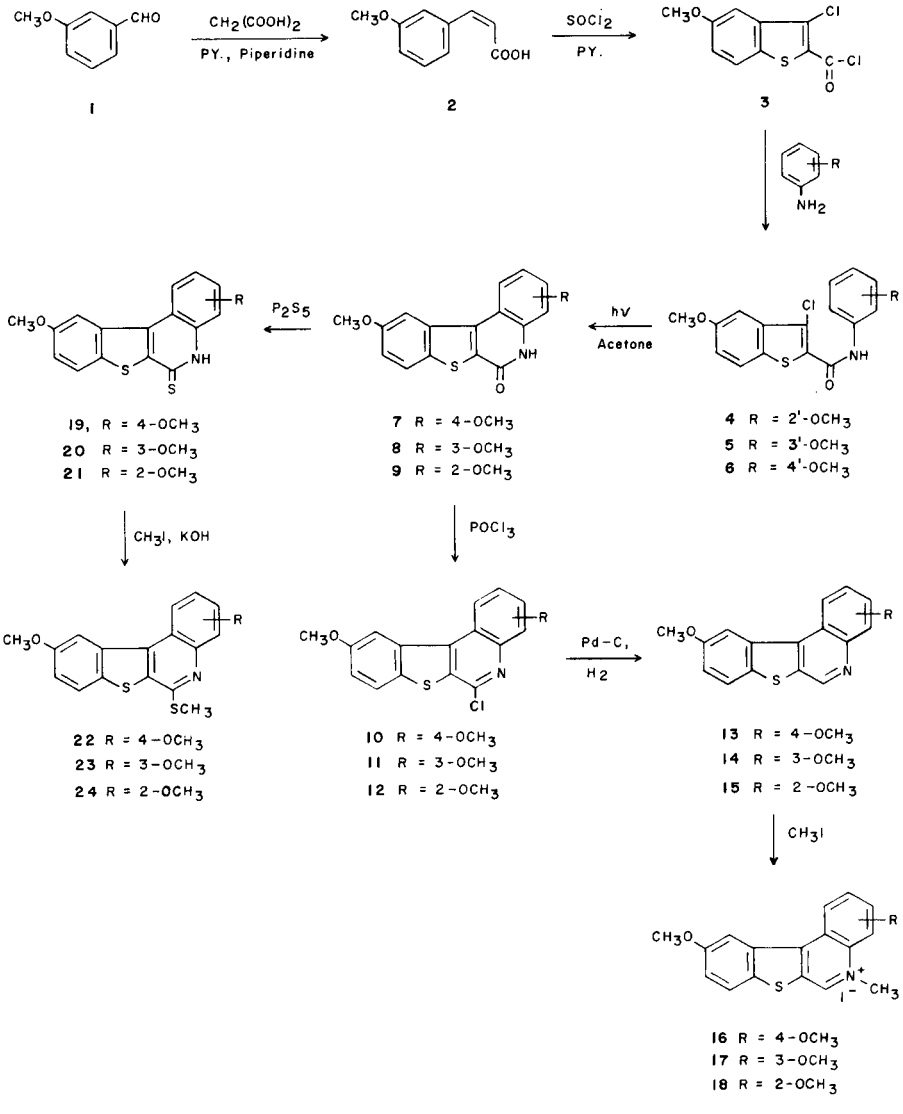
Certain methoxy derivatives of quino[1,2-*c*]quinazoline and indazolo[2,3-*a*]quinoline [2,3] were synthesized as synthetic relatives of the antitumor alkaloids nitidine, fagaronine and coralyne [4] and some of the synthetic quino[1,2-*c*]quinazolines and indazolo[2,3-*a*]quinolines were shown to be approximately equal in antileukemic activity against L-1210 when compared with the activity of the above alkaloids [5].

The reported synthesis of [1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one [6,7,8] prompted us to consider the [1]benzo-

Scheme I



thieno[2,3-*c*]quinolines as analogs of the antileukemic alkaloids when appropriately substituted. We have therefore undertaken the synthesis of a series of methoxy analogs.

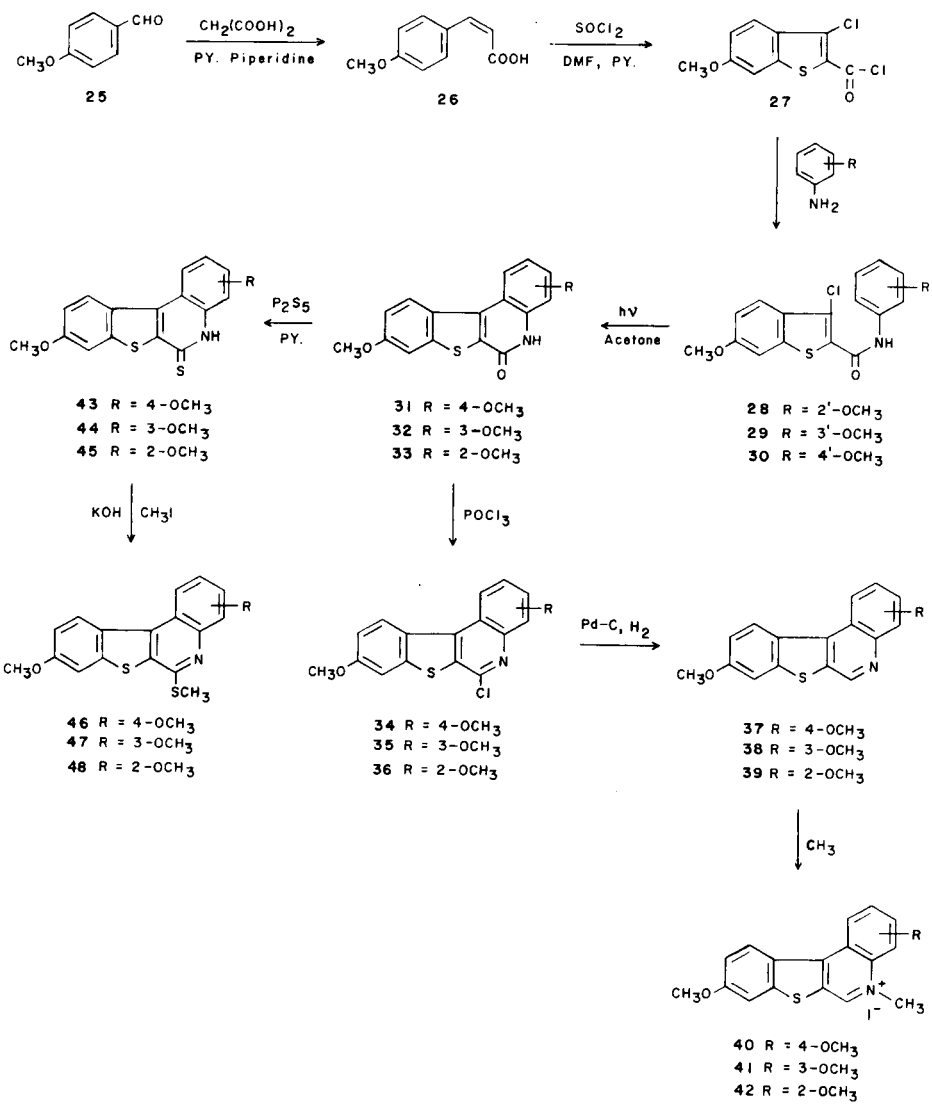
The first synthetic route chosen for the preparation of 4,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**13**), 3,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**14**), 2,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**15**), their *N*-methyl salts **16**, **17**, **18** and the 6-methylthio derivatives **22**, **23**, and **24** is illustrated in Scheme I.

Reaction of *m*-anisaldehyde (**1**) with malonic acid gave *m*-methoxycinnamic acid (**2**) [9] in 79% yield. Treatment of **2** with thionyl chloride gave 3-chloro-5-methoxybenzo-[*b*]thiophene-2-carbonyl chloride (**3**) [10] in 46% yield. The reaction of **3** with *o*-anisidine, *m*-anisidine, and *p*-anisidine gave the corresponding carboxamides [11] namely, 3-chloro-5-methoxy-*N*-(2-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**4**) (64% yield), 3-chloro-5-methoxy-*N*-(3-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**5**) (57% yield), and 3-chloro-5-methoxy-*N*-(4-methoxyphenyl)-benzo[*b*]thiophene-2-carboxamide (**6**) (63% yield) respectively.

Dehydrochlorinative photocyclization of **4**, **5**, and **6** in acetone in the presence of triethylamine [8] afforded 4,10-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**7**) (46% yield), 3,10-dimethoxy[1]benzothieno[2,3,*c*]quinolin-6(5*H*)-one (**8**) (92% yield), and 2,10-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**9**) (34% yield). This dehydrochlorinative photocyclization of the *m*-methoxyanilide **8** as well as all other *m*-methoxyanilides always gave higher yields than the corresponding *o*- and *p*-methoxyanilides. We do not have a satisfactory explanation for this fact.

Chlorination of **7**, **8**, and **9** was accomplished by refluxing these compounds with phosphorus oxychloride [11] to

Scheme 2



afford 6-chloro-4,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**10**) (54% yield), 6-chloro-3,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**11**), and 6-chloro-2,10-dimethoxy-[1]benzothieno[2,3-*c*]quinoline (**12**) (66% yield).

Two different methods of chemical and catalytic dechlorination of **10**, **11**, and **12** revealed that the catalytic method [11] was superior to the lithium aluminum hydride dechlorination [12]. Therefore the dechlorination of **10**, **11**, and **12** (hydrogen, Pd-C) gave 4,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**13**) (68% yield), 3,10-dimethoxy[1]-benzothieno[2,3-*c*]quinoline (**14**) (94% yield), and 2,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**15**) (56% yield).

Compounds **13**, **14**, and **15** were allowed to react with methyl iodide in refluxing benzene. 4,10-Dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide (**16**) (52% yield), 3,10-dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide (**17**) (48% yield), and 2,10-dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide (**18**) (55% yield) were obtained.

Treatment of the lactams **7**, **8**, and **9** with phosphorus pentasulfide in pyridine afforded the desired compounds [13] namely, 4,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**19**) (48% yield), 3,10-dimethoxy[1]-benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**20**) (68% yield) and 2,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**21**) (48% yield).

Compounds **22**, **23**, and **24** were easily prepared by *S*-methylation of **19**, **20**, and **21** with methyl iodide in potassium hydroxide solution to furnish the methylthio derivatives namely, 4,10-dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**22**) (48%), 3,10-dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**23**) (73%) yield), and 2,10-dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**24**) (54% yield).

The syntheses of 4,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**37**), 3,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**38**), 2,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**39**), the *N*-methyl salts **40**, **41**, **42**, and their *S*-methyl derivatives **46**, **47**, and **48** are depicted in Scheme II. As the starting material for these syntheses we selected *p*-methoxycinnamic acid (**26**) obtained in a yield of 77% from *p*-anisaldehyde (**25**) by reaction with malonic acid [9]. Refluxing **26** with thionyl chloride and DMF in pyridine produced the desired acid chloride (**27**) (55% yield) [14], which when allowed to react with *o*-anisidine, *m*-anisidine, and *p*-anisidine afforded the corresponding carboxamides, namely 3-chloro-6-methoxy-*N*-(2-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**28**) (64% yield), 3-chloro-6-methoxy-*N*-(3-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**29**) (66% yield), and 3-chloro-6-methoxy-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**30**) (34% yield). Photocyclization (acetone, triethylamine) of **28**, **29**, and **30** gave the desired lactams, 4,9-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**31**) (42% yield), 3,9-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**32**) (89% yield), and 2,9-dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**33**) (57% yield). Treatment of **31**, **32**, and **33** with phosphorus oxychloride provided the chloro compounds, 6-chloro-4,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**34**) (47% yield), 6-chloro-3,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**35**) (39% yield), and 6-chloro-2,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**36**) (47% yield).

In order to prepare **37**, **38**, and **39**, the corresponding chloro compounds were catalytically dechlorinated (hydrogen, Pd-C) to the desired products, 4,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**37**) (75% yield), 3,9-dimethoxy[1]-benzothieno[2,3-*c*]quinoline (**38**) (83% yield), and 2,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**39**) (56% yield). *N*-Methylation of **37**, **38**, and **39** with methyl iodide afforded the corresponding salts, 4,9-dimethoxy-5-methyl[1]-benzothieno[2,3-*c*]quinolinium iodide (**40**) (57% yield), 3,9-dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide (**41**) (52% yield), and 2,9-dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium iodide (**42**) (55% yield). When **31**, **32**, and **33** were treated with phosphorus pentasulfide in pyridine, the corresponding thiolactams were obtained, namely, 4,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**43**) (48% yield), 3,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**44**) (87% yield), and 2,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**45**) (52% yield). Compounds **46**, **47**, and **48** were prepared by the *S*-methylation of **43**, **44** and **45** with methyl iodide in potassium hydroxide solution to furnish the methylthio compounds, namely, 4,9-dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**46**) (49% yield), 3,9-dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**47**) (65% yield), and 2,9-dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**48**) (55% yield).

These compounds have been submitted for antitumor screening and these data will be reported elsewhere.

EXPERIMENTAL

All melting points (uncorrected) were taken on a Thomas-Hoover capillary melting point apparatus. The ^{1}H-nmr spectra were recorded on a Varian EM-360 and a JEOL FX-90Q Fourier Transform spectrometer in deuteriochloroform or DMSO-d_6, and are reported in δ ppm relative to TMS. All elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

m-Methoxycinnamic Acid (**2**).

A mixture of *m*-anisaldehyde (32.67 g, 0.24 mole), malonic acid (50.98 g, 0.49 mole), pyridine (300 ml) and piperidine (16 ml) was refluxed for 90 minutes. The resulting solution was poured into ice-water followed by addition of concentrated hydrochloric acid (200 ml). The product precipitated and it was separated by filtration, washed with water and dried. Recrystallization from ethanol afforded 34.3 g (79% yield) as long white needles, mp 120-121° (lit mp 118-119° [9]); nmr (DMSO-d_6): δ 3.81 (s, 3H, OCH_3), 6.21 (dd, 1H, J = 8.5 Hz), 6.85-7.43 (m, 3H, ArH), 7.55 (dd, 1H, J = 8.5 Hz), 8.87 (s, 1H, OH).

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

A solution of **2** (14.0 g, 0.078 mole) in 1 ml of pyridine and 40 ml of thionyl chloride was heated at 95-98° for 21 hours. The excess thionyl chloride was removed by distillation and the black gummy residue was taken up in hot hexane (500 ml) and decanted. On cooling 9.5 g (46% yield) of a yellow solid was obtained and was used without further purification, mp 139-141°, (lit mp 147-148° [2]); nmr (deuteriochloroform): 3.85 (s, 3H, OCH_3), 7.25 (dd, 1H, J = 8.2 Hz), 7.6 (s, 1H, H4), 7.82 (dd, 1H, J = 8.2 Hz).

3-Chloro-5-methoxy-*N*-(2-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**4**).

A mixture of **3** (14.0 g, 0.053 mole), *o*-anisidine (13.0 g, 0.106 mole), and benzene (350 ml) was refluxed on a water bath for 1 hour. The resulting solid was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was crystallized from ethanol to give pale yellow prisms, 11.8 g (64% yield), mp 141-142°; nmr (deuteriochloroform): 3.71 and 3.85 (2 s, 6H, 2 OCH_3), 6.81-8.33 (m, 7H, ArH), 9.51 (b s, 1H, NH).

Anal. Calcd. for $C_{17}H_{14}ClNO_3S$: C, 58.70; H, 4.05; S, 9.21; Cl, 10.19. Found: C, 58.54; H, 4.30; S, 9.12; Cl, 9.97.

4,10-Dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-one (**7**).

A stirred solution of **4** (0.5 g, 0.0014 mole) and triethylamine (0.5 ml) in 500 ml of acetone was irradiated with a 450 watt Hanovia medium pressure mercury lamp for 3 hours. The acetone solution was evaporated under reduced pressure and the residue was washed with water, dried and recrystallized from ethanol to yield 0.2 g (46%) of the lactam, mp >250°; nmr (DMSO-d_6): 3.98 and 3.99 (2 s, 6H, 2 OCH_3), 7.11-8.24 (m, 6H, ArH), 10.27 (bs, 1H, NH). This lactam was used in the next step without further purification.

6-Chloro-4,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**10**).

A mixture of lactam **7** (2.1 g, 0.0067 mole) and phosphorus oxychloride (30 ml) was refluxed for 4 hours. The residue which was obtained upon distillation of the phosphorus oxychloride was poured into ice-water and the resulting solid was collected by filtration. Recrystallization from benzene furnished 1.2 g (54%) of yellow crystals, mp 222-224°; nmr (DMSO-d_6): 4.00 and 4.04 (2s, 6H, 2 OCH_3), 7.36-8.40 (m, 6H, ArH).

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.66; S, 9.72; Cl, 10.74. Found: C, 62.12; H, 3.85; S, 9.76; Cl, 10.56.

4,10-Dimethoxy[1]benzothieno[2,3-*c*]quinoline (**13**).

The chloro compound **10** (0.5 g, 0.0015 mole) was catalytically dechlorinated in 160 ml of benzene-methanol (1:1) containing 0.1 g of potassium hydroxide in the presence of 10% Pd-C at atmospheric pressure and room temperature for 24 hours. The catalyst was removed by filtration and the solvent was evaporated. The residue was washed with water, dried and recrystallized from benzene affording 0.3 g (68%) of white prisms, mp 154-155°; nmr (deuteriochloroform): 3.82-3.91 (2s, 6H, 2 OCH_3), 6.95-8.42 (m, 6H, ArH), 9.27 (s, 1H, H6).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.43; S, 10.85. Found: C, 69.27; H, 4.54; S, 10.96.

4,10-Dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**16**).

A stirred solution of **13** (0.2 g, 0.00067 mole), methyl iodide (0.5 ml) and benzene (30 ml) was refluxed for 24 hours. The resulting yellow solid was collected by filtration. Recrystallization from ethanol gave 0.15 g (52%) of **16** as pale yellow needles, mp 194-196°; nmr (DMSO-d_6): 3.97-4.10 (2s, 6H, 2 OCH_3), 4.58 (s, 3H, NCH_3), 7.38-7.95 (m, 4H, ArH), 8.92-9.20 (m, 2H, ArH), 9.98 (s, 1H, H6).

Anal. Calcd. for $C_{18}H_{16}INO_2S$: C, 49.44; H, 3.68; S, 7.33; I, 29.03. Found: C, 49.59; H, 3.72; S, 7.47; I, 29.04.

4,10-Dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**19**).

Compound **7** (0.5 g, 0.0016 mole), phosphorus pentasulfide (1.8 g, 0.008 mole), and 20 ml of pyridine was heated under reflux for 24 hours. The resulting suspension was poured into 100 ml of boiling water. The yellow solid which was obtained upon filtration was recrystallized from ethanol to afford 0.25 g (48%) of the desired product, mp >250°; nmr (DMSO-d_6): 3.93-3.98 (2s, 6H, 2 OCH_3), 7.18-7.59 (m, 3H, ArH), 8.02-8.41 (m, 3H, ArH). This compound was used for the preparation of **22** without further purification.

4,10-Dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**22**).

A suspension of thiolactam **19** (0.2 g, 0.00061 mole), methyl iodide (0.5 ml) and potassium hydroxide (0.05 g) in 50% aqueous methanol (30 ml) was stirred at room temperature for 30 minutes after which 2 drops of glacial acetic acid was added to this solution. The solid was separated by filtration, washed with water, dried, and recrystallized from ethanol to give 0.1 g (48%) of beige crystals, mp 154-156°; nmr (deuteriochloroform): 2.94 (s, 3H, SCH_3), 3.99 and 4.11 (2s, 6H, 2 OCH_3), 7.17-7.24 (m, 2H, ArH), 7.27-7.56 (t, 1H, ArH), 7.84-7.94 (d, 1H, ArH), 8.22-8.39 (m, 2H, ArH).

Anal. Calcd. for $C_{18}H_{15}NO_2S_2$: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.25; H, 4.48; S, 18.93.

3-Chloro-5-methoxy-*N*-(3-methoxyphenyl)benzo[*b*]thiophene-3-carboxamide (**5**).

This compound was prepared from **3** (9.5 g, 0.036 mole), *m*-anisidine (10.9 g, 0.088 mole), and benzene (300 ml) in a manner similar to the preparation of **4**. Beige crystals were obtained upon crystallization from ethanol, 7.1 g (57%), mp 120-122°; nmr (deuteriochloroform): 3.71 and 3.85 (2s, 6H, 2 OCH_3), 6.55-7.79 (m, 7H, ArH), 8.25 (b s, 1H, NH).

Anal. Calcd. for $C_{17}H_{14}ClNO_3S$: C, 58.70; H, 4.05; S, 9.21; Cl, 10.19. Found: C, 58.91; H, 4.06; S, 9.13; Cl, 9.92.

3,10-Dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**8**).

A solution of the amide **5** (0.5 g, 0.0014 mole), triethylamine (0.5 ml), and acetone (500 ml) was irradiated for 2.5 hours as described for **7**. The product (0.4 g, 92% yield), mp >250° was used in the next step without purification; nmr (DMSO-d_6): 3.86 and 3.90 (2s, 6H, 2 OCH_3), 6.97-8.36 (m, 6H, ArH), 10.78 (b s, 1H, NH).

6-Chloro-3,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**11**).

A mixture of lactam **8** (0.8 g, 0.0025 mole) and phosphorus oxychloride (30 ml) was refluxed for 3.5 hours. The work-up procedure was similar to the preparation of **10**. Recrystallization from benzene afforded 0.6 g (73%) of pale yellow prisms, mp 207-208°; nmr (DMSO-d_6): 3.97 and 4.01 (2s, 6H, 2 OCH_3), 7.34-7.59 (m, 3H, ArH), 8.11-8.27 (m, 2H, ArH), 8.81-8.92 (d, 1H, ArH).

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.66; S, 9.72; Cl, 10.74. Found: C, 62.08; H, 3.77; S, 9.67; Cl, 10.63.

3,10-Dimethoxy[1]benzothieno[2,3-*c*]quinoline (**14**).

This compound was prepared from **11** (0.3 g, 0.0009 mole), potassium hydroxide (0.05 g) and 10% Pd-C (0.1 g) in 160 ml of benzene-methanol (1:1) in a manner similar to the preparation of **13** and 0.25 g (94%) of white prisms was obtained, mp 170-172°; nmr (deuteriochloroform): 3.93 and 3.94 (2s, 6H, 2 OCH_3), 7.30-8.49 (m, 6H, ArH), 8.60 (s, 1H, H6).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.43; S, 10.85. Found: C, 69.30; H, 4.46; S, 10.91.

3,10-Dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**17**).

A solution of **14** (0.1 g, 0.00033 mole) and methyl iodide (0.5 ml) in benzene (25 ml) was refluxed for 24 hours. After cooling the yellow solid was collected and recrystallized from ethanol to give 0.07 g (48%) of the corresponding salt, mp 230-240°; nmr (DMSO-d_6): 4.15 and 4.23 (2s, 6H, 2 OCH_3), 4.66 (s, 3H, NCH_3), 7.53-7.84 (m, 5H, ArH), 8.10-9.20 (d, 1H, ArH), 10.14 (s, 1H, H6).

Anal. Calcd. for $C_{18}H_{16}INO_2S$: C, 49.44; H, 3.68; S, 7.33; I, 29.02. Found: C, 49.17; H, 3.88; S, 7.17; I, 28.89.

3,10-Dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**20**).

To 1.4 g (0.005 mole) of **8** in 30 ml of pyridine was added 1.5 g of phosphorus pentasulfide. The reaction was carried out in a manner similar to the preparation of **19** and afforded 1 g (68%) of a yellow solid upon crystallization from ethanol, mp >250°; nmr (DMSO-d_6): 3.92 and 3.96 (2s, 6H, 2 OCH_3), 6.07-8.60 (m, 6H, ArH). This compound was used without additional purification.

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

Methyl iodide (0.5 ml) was added to a stirred solution of thiolactam **20** (0.4 g, 0.0012 mole), and potassium hydroxide (0.05 g) in 40 ml of benzene-methanol (1:1). The reaction mixture was stirred for 1 hour. The work-up was similar to the preparation of **22**, yield 0.3 g (73%), upon crystallization from ethaol, mp 119-120°; nmr (deuteriochloroform): 2.85 (s, 3H, SCH_3), 3.95 and 4.04 (2s, 6H, 2 OCH_3), 7.05-8.61 (m, 6H, ArH).

Anal. Calcd. for $C_{18}H_{15}NO_2S_2$: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.39; H, 4.57; S, 18.66.

3-Chloro-5-methoxy-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**6**).

This compound was prepared from **3** (4.0 g, 0.015 mole), *p*-anisidine (3.7 g, 0.03 mole) and benzene (150 ml) in a manner similar to the preparation of **4** and was obtained as grey crystals (3.3 g, 63%), mp 170-172°; nmr (deuteriochloroform): 3.71 and 3.81 (2s, 6H, 2 OCH_3), 6.75-7.81 (m, 7H, ArH), 7.85 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{14}ClNO_3S$: C, 58.70; H, 4.05; S, 9.21; Cl, 10.19. Found: C, 58.81; H, 4.08; S, 9.07; Cl, 9.99.

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

A stirred solution of **6** (1.0 g, 0.0028 mole) and triethylamine (0.5 ml) in acetone (500 ml) was irradiated. The resulting solid was washed with water, dried, and used for the next step without further purification, yield 0.3 g (34%); mp >250°; nmr (DMSO-d_6): 3.89 and 3.92 (2s, 6H, 2 OCH_3), 7.09-7.99 (m, 4H, ArH), 8.04-8.09 (2s, 2H, ArH).

6-Chloro-2,10-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**12**).

A solution of **9** (0.1 g, 0.00032 mole) and phosphorus oxychloride (10 ml) was refluxed for 3.5 hours. The work-up was similar to the preparation of **10** and there was obtained 0.07 g (66%) of off-white prisms upon crystallization from benzene, mp 204-205°; nmr (DMSO-d_6): 3.96 and 3.99 (2s, 6H, 2 OCH_3), 7.39-7.59 (m, 3H, ArH), 8.05-8.26 (m, 3H, ArH).

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.66; S, 9.72; Cl, 10.74. Found: C, 62.07; H, 3.84; S, 9.81; Cl, 10.53.

2,10-Dimethoxy[1]benzothieno[2,3-*c*]quinoline (**15**).

This compound was prepared from **12** (0.4 g, 0.0012 mole), potassium hydroxide (0.1 g), 10% Pd-C (0.1 g) in 160 ml of methanol-benzene (1:1) in a manner similar to the preparation of **13**. White prisms (0.2 g, 56%), mp 190-192° were obtained upon crystallization from benzene; nmr (deuteriochloroform): 3.81 and 3.89 (2s, 6H, 2 OCH_3), 6.99-8.35 (m, 6H, ArH), 9.11 (s, 1H, H6).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.43; S, 10.85. Found: C, 69.01; H, 4.50; S, 10.87.

2,10-Dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**18**).

A mixture of **15** (0.1 g, 0.00033 mole), methyl iodide (0.5 ml), and benzene (50 ml) was refluxed for 24 hours. The resulting solid was collected and recrystallized from ethanol to afford 0.08 g (65%) of yellow needles, mp 220-222°; nmr (DMSO-d_6): 4.20 and 4.37 (2s, 6H, 2 OCH_3), 4.67 (s, 3H, NCH_3), 7.63-8.62 (m, 6H, ArH), 10.14 (s, 1H, H6).

Anal. Calcd. for $C_{18}H_{16}INO_2S\cdot H_2O$: C, 47.48; H, 3.54; S, 7.04; I, 27.87. Found: C, 47.68; H, 3.96; S, 7.26; I, 28.00.

2,10-Dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**21**).

A solution of **9** (0.1 g, 0.00032 mole), phosphorus pentasulfide (0.5 g) and pyridine (25 ml) was refluxed for 18 hours as described for the preparation of **19**. Thiolactam **21** was obtained in 48% yield (0.05 g), mp >250°; nmr (DMSO-d_6): 3.83 and 3.98 (2s, 6H, 2 OCH_3), 7.41-8.38 (m, 6H, ArH). This compound was used without further purification.

2,10-Dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**24**).

A solution of **21** (0.5 g, 0.0015 mole), methyl iodide (0.5 ml), potassium hydroxide (0.05 g) in 40 ml of 50% aqueous methanol was stirred at room temperature for 1 hour. Glacial acetic acid (2 drops) was added and the solid was collected, washed with water, dried, and recrystallized from ethanol to yield 0.3 g (59%), mp 170-171°; nmr (deuteriochloroform): 2.92 (s, 3H, SCH_3), 3.99 and 4.04 (2s, 6H, 2 OCH_3), 7.21-7.31 (m, 3H, ArH), 7.84-8.19 (m, 3H, ArH).

Anal. Calcd. for $C_{18}H_{15}NO_2S_2$: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.29; H, 4.37; S, 18.68.

p-Methoxycinnamic Acid (**26**).

This compound was prepared as described for **2**, yield 77% upon crystallization from ethanol, mp 163-164° (lit mp 174° [9]); nmr (DMSO-d_6): 3.65 (s, 3H, OCH_3), 6.01 (dd, 1H, J = 8 Hz), 6.75 (dd, 1H, J = 4 Hz, ArH), 7.43 (dd, 1H, J = 4 Hz, ArH), 7.52 (dd, 1H, J = 8 Hz), 7.95 (s, 1H, OH).

3-Chloro-6-methoxybenzo[*b*]thiophene-2-carbonyl Chloride (**27**).

To a mixture of *p*-methoxycinnamic acid (4.2 g, 0.023 mole), pyridine (0.5 ml), and DMF (1 ml) was added 6 ml of thionyl chloride dropwise. After stirring for 30 minutes at 140°, the reaction mixture was taken up in 100 ml of dry hexane, heated and decanted from the gummy residue. The yellow decanted solution solidified to give 3.3 g (55%) of the product, mp 116-119° (lit 118-119° [14]); nmr (deuteriochloroform): 3.75 (s, 3H, OCH_3), 6.85 (dd, 1H, H5, J = 8.5 Hz), 7.15 (s, 1H, H6), 7.55 (dd, 1H, H4, J = 8.5 Hz).

3-Chloro-6-methoxy-*N*-(2-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**28**).

This compound was prepared from **27** (4.5 g, 0.017 mole), *o*-anisidine (5 g, 0.04 mole), and benzene (150 ml) in a manner similar to the preparation of **4** and was obtained as beige crystals, 3.8 g (64%), mp 194-196°; nmr (deuteriochloroform): 3.79 and 3.85 (2s, 6H, 2 OCH_3), 6.75-8.35 (m, 7H, ArH), 9.45 (b s, 1H, NH).

Anal. Calcd. for $C_{17}H_{14}ClNO_3S$: C, 58.70; H, 4.05; S, 9.21; Cl, 10.19. Found: C, 58.64; H, 4.13; S, 9.14; Cl, 10.36.

4,9-Dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**31**).

This compound was prepared from **28** (0.8 g, 0.0023 mole), triethylamine (0.5 ml), and acetone (500 ml) in a manner similar to the preparation of **7** and was obtained as white flakes after crystallization from ethanol, 0.3 g (42%), mp >250°; nmr (DMSO-d_6): 3.93 and 3.99 (2s, 6H, 2 OCH_3), 7.38-7.45 (m, 3H, ArH), 7.9-8.2 (m, 1H, ArH), 8.29-8.78 (dd, 2H, J = 5 Hz), 10.93 (b s, 1H, NH). This compound was used for the preparation of **34** without additional purification.

6-Chloro-4,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**34**).

A mixture of lactam **31** (0.4 g, 0.00128 mole) and phosphorus oxychloride (20 ml) was refluxed for 3.5 hours following the procedure for the preparation of **10** and yellow needles were obtained 0.2 g (47%) upon crystallization from benzene, mp 194-195°; nmr (DMSO-d_6): 3.80 and 3.89 (2s, 6H, 2 OCH_3), 7.08-7.63 (m, 4H, ArH), 8.23-8.67 (2d, 2H, ArH).

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.66; S, 9.72; Cl, 10.74. Found: C, 61.83; H, 3.88; S, 9.68; Cl, 10.59.

4,9-Dimethoxy[1]benzothieno[2,3-*c*]quinoline (**37**).

This compound was prepared from **34** (0.15 g, 0.00045 mole), potassium hydroxide (0.1 g, 0.0017 mole) and 10% Pd-C (0.1 g) in 160 ml of benzene-methanol (1:1) in a manner similar to the preparation of **13** and there was obtained 0.1 g (75%) upon crystallization from benzene, mp 188-189°; nmr (deuteriochloroform): 3.91 and 4.11 (2s, 6H, 2 OCH_3), 7.03-7.68 (m, 4H, ArH), 8.26-8.65 (dd, 2H, ArH, J = 4 Hz), 9.26 (s, 1H, H6).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.43; S, 10.85. Found: C, 69.11; H, 4.54; S, 10.60.

4,9-Dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**40**).

A solution of **37** (0.5 g, 0.0016 mole) and methyl iodide (0.5 ml) in benzene (25 ml) was refluxed for 24 hours. The yellow solid was collected and recrystallized from ethanol to yield 0.4 g (67%) of the salt, mp 205-206°; nmr (DMSO-d_6): 3.61 and 3.74 (2s, 6H, 2 OCH_3), 3.97 (s, 3H, NCH_3), 7.40-8.69 (m, 6H, ArH), 9.56 (s, 1H, H6).

Anal. Calcd. for $C_{18}H_{16}INO_2S$: C, 49.44; H, 3.68; S, 7.33; I, 29.02. Found: C, 49.21; H, 3.89; S, 7.51; I, 29.43.

4,9-Dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**43**).

This compound was prepared from **31** (1.0 g, 0.0032 mole), phosphorus pentasulfide (2.7 g, 0.006 mole) in pyridine (30 ml) in a manner similar to the preparation of **19** and there was obtained 0.5 g (48%) of the thiolactam upon crystallization from ethanol, mp >250°; nmr (DMSO-d_6): 3.00 and 3.08 (2s, 6H, 2 OCH_3), 6.22-7.30 (m, 6H, ArH). This compound was used without further purification in the preparation of **46**.

4,9-Dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**46**).

Methyl iodide (0.5 ml) was added to a stirred solution of the thiolactam **43** (0.4 g, 0.0012 mole) and potassium hydroxide (0.1 g) in 40 ml of benzene-methanol (1:1) as described for the preparation of **22** and was obtained in 49% yield (0.2 g) upon crystallization from ethanol, mp 150-152°; nmr (deuteriochloroform): 2.87 (s, 3H, SCH_3), 3.97 and 4.09 (2s, 6H, 2 OCH_3), 7.17-7.88 (m, 5H, ArH), 8.67-8.70 (d, 1H, ArH).

Anal. Calcd. for $C_{18}H_{15}NO_2S_2$: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.05; H, 4.63; S, 18.59.

3-Chloro-6-methoxy-*N*-(3-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**29**).

A solution of **27** (7 g, 0.026 mole), *m*-anisidine (6.4 g, 0.052 mole), and benzene (200 ml) was refluxed for 1 hour. The solution was filtered and the filtrate was evaporated. Recrystallization of the solid from ethanol afforded pale yellow crystals (6 g, 66% yield), mp 165-166°; nmr (deuteriochloroform): 3.79 and 3.83 (2s, 6H, 2 OCH_3), 6.27-7.79 (m, 7H, ArH), 8.69 (b s, 1H, NH).

Anal. Calcd. for $C_{17}H_{14}ClNO_3S$: C, 58.70; H, 4.05; S, 9.21; Cl, 10.19. Found: C, 58.76; H, 4.02; S, 9.16; Cl, 10.35.

3,9-Dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**32**).

A stirred solution of **29** (0.5 g, 0.0014 mole) and triethylamine (0.5 ml) in 500 ml of acetone was irradiated for 3 hours. The solvent was evaporated and the solid was washed with water, dried and recrystallized from ethanol to afford 0.4 g (89% yield) of white flakes, mp >250°; nmr (DMSO-d_6): 3.90 and 3.91 (2s, 6H, 2 OCH_3), 7.13-7.70 (m, 4H, ArH), 8.45-8.81 (m, 2H, ArH). This compound was used without additional purification in the preparation of **35**.

6-Chloro-3,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**35**).

This compound was prepared from **32** (1.9 g, 0.0061 mole) and phosphorus oxychloride (40 ml) in a manner similar to the preparation of **10** and there was obtained 0.8 g (39%) of pale yellow crystals upon crystallization from benzene, mp 186-188°; nmr (DMSO-d_6): 3.85 and 3.94 (2s, 6H, 2 OCH_3), 6.97-7.99 (m, 5H, ArH), 8.85 (d, 1H, ArH).

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.66; S, 9.72; Cl, 10.74. Found: C, 61.96: H, 3.74; S, 9.61; Cl, 10.57.

3,9-Dimethoxy[1]benzothieno[2,3-*c*]quinoline (**38**).

Compound **35** (0.2 g, 0.0006 mole) was catalytically dechlorinated using 0.1 g (0.0017 mole) of potassium hydroxide, 0.1 g of 10% Pd-C in benzene (100 ml) and methanol (100 ml) in a manner similar to the preparation of **13**. There was obtained 0.15 g (83%) of off-white crystals upon crystallization from benzene, mp 214-215°; nmr (deuteriochloroform): 3.93 and 3.98 (2s, 6H, 2 OCH_3), 7.11-8.62 (m, 6H, ArH), 8.68 (s, 1H, H6).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.43; S, 10.85. Found: C, 69.07; H, 4.49; S, 10.65.

3,9-Dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**41**).

A stirred solution of **38** (0.2 g, 0.00066 mole), methyl iodide (0.5 ml), and benzene (35 ml) was refluxed for 24 hours. The solid was removed by filtration and recrystallized from ethanol to afford 0.15 g (52%) of the product, mp >240°; nmr (DMSO-d_6): 3.99 and 4.09 (2s, 6H, 2 OCH_3), 4.79 (s, 3H, NCH_3), 7.61-8.37 (m, 6H, ArH), 10.05 (s, 1H, H6).

Anal. Calcd. for $C_{18}H_{16}INO_2S$: C, 49.44; H, 3.68; S, 7.33; I, 29.02. Found: C, 49.19; H, 3.80; S, 7.51; I, 28.83.

3,9-Dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**44**).

A mixture of **32** (1.1 g, 0.0035 mole), phosphorus pentasulfide (2 g), and pyridine (25 ml) was refluxed for 24 hours. The work-up was as described for the preparation of **19**. There was obtained 1 g of yellow solid (87% yield) upon crystallization from ethanol, mp >250°; nmr (DMSO-d_6): 4.00 and 4.05 (2s, 6H, 2 OCH_3), 7.07-7.75 (m, 4H, ArH), 8.74-8.84 (m, 2H, ArH). This compound was used without further purification in the preparation of **47**.

3,9-Dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**47**).

This compound was prepared from **44** (0.9 g, 0.0027 mole), methyl iodide (0.5 ml), and potasium hydroxide (0.05 g) in 40 ml of aqueous methanol (1:1) in a manner similar to the preparation of **22**. There was obtained 0.6 g (65%) of tan crystals upon crystallization from ethanol, mp 170-172°; nmr (deuteriochloroform): 2.85 (s, 3H, SCH_3), 3.90 and 4.01 (2s, 6H, 2 OCH_3), 6.98-7.72 (m, 5H, ArH), 8.86-8.97 (d, 1H, ArH).

Anal. Calcd. for $C_{18}H_{15}NO_2S_2$: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.33; H, 4.37; S, 18.66.

3-Chloro-6-methoxy-*N*-(4-methoxyphenyl)benzo[*b*]thiophene-2-carboxamide (**30**).

This compound was prepared from **27** (5.5 g, 0.0021 mole), *p*-anisidine (5.1 g, 0.042 mole), and benzene (200 ml) in a manner similar to the procedure for the preparation of **4**. There was obtained 2.5 g (34%) of yellow crystals upon crystallization from ethanol, mp 202-204°; nmr (deuteriochloroform): 3.79 and 3.87 (2s, 6H, 2 OCH_3), 6.83-7.69 (m, 7H, ArH), 7.79 (b s, 1 H, NH).

Anal. Calcd. for $C_{17}H_{14}ClNO_3S$: C, 58.70; H, 4.05; S, 9.21; Cl, 10.19. Found: C, 58.95; H, 4.09; S, 9.26; Cl, 10.12.

2,9-Dimethoxy[1]benzothieno[2,3-*c*]quinolin-6(5*H*)-one (**33**).

A stirred solution of **30** (0.5 g, 0.0014 mole) and triethylamine (0.5 ml) in acetone (500 ml) was irradiated in a manner similar to the preparation of **7** and there was obtained 0.25 g (57%) of white solid upon crystallization from ethanol, mp >250°; nmr (DMSO-d_6): 3.92 and 3.94 (2s, 6H, 2 OCH_3), 7.28-7.32 (m, 2H, ArH), 7.45 (s, 1H, ArH), 7.75-8.00 (dd, 2H, J = 5 Hz, ArH), 8.60 (d, 1H, ArH). This compound was used for preparation of **36** without further purification.

6-Chloro-2,9-dimethoxy[1]benzothieno[2,3-*c*]quinoline (**36**).

A mixture of **33** (0.3 g, 0.00096 mole) and phosphorus oxychloride (15 ml) was refluxed for 3.5 hours as described for the preparation of **10** and there was obtained 0.15 g (47%) of pale yellow crystals upon crystallization from benzene, mp 178-180°; nmr (DMSO-d_6): 3.99 and 4.01 (2s, 6H, 2 OCH_3), 7.14-8.49 (m, 5H, ArH), 8.60-9.19 (d, 1H, ArH).

Anal. Calcd. for $C_{17}H_{12}ClNO_2S$: C, 61.91; H, 3.66; S, 9.72; Cl, 10.74. Found: C, 62.14; H, 3.84; S, 9.60; Cl, 10.81.

2,9-Dimethoxy[1]benzothieno[2,3-*c*]quinoline (**39**).

This compound was prepared from **36** (0.2 g, 0.0006 mole), potassium hydroxide (0.1 g, 0.0017 mole) and 0.1 g of 10% Pd-C in methanol-benzene (1:1) in a manner similar to the procedure described for the preparation of **13** to afford off-white crystals upon crystallization from benzene, 0.1 g (56%), mp 185-186°; nmr (deuteriochloroform): 3.89 and 3.91 (2s, 6H 2 OCH_3), 7.24-8.31 (m, 6H, ArH), 9.23 (s, 1H, H6).

Anal. Calcd. for $C_{17}H_{13}NO_2S$: C, 69.13; H, 4.43; S, 10.85. Found: C, 68.93: H, 4.50; S, 10.61.

2,9-Dimethoxy-5-methyl[1]benzothieno[2,3-*c*]quinolinium Iodide (**42**).

A stirred solution of **39** (0.1 g, 0.00033 mole), methyl iodide (0.5 ml), and benzene (30 ml) was refluxed for 24 hours. The resulting yellow solid

was collected by filtration and recrystallized from ethanol to afford 0.08 g (55%) mp 240-245°; nmr (DMSO-d_6): 4.06 and 4.11 (2s, 6H, 2 OCH_3), 4.53 (s, 3H, NCH_3), 7.63-8.41 (m, 6H, ArH), 9.94 (s, 1H, H6).

Anal. Calcd. for $C_{18}H_{16}INO_2S \cdot 0.5H_2O$: C, 48.44; H, 3.61; S, 7.18; I, 28.43. Found: C, 48.66; H, 3.84; S, 7.11; I, 28.29.

2,9-Dimethoxy[1]benzothieno[2,3-*c*]quinoline-6(5*H*)-thione (**45**).

A mixture of **33** (0.8 g, 0.0025 mole), phosphorus pentasulfide (2.5 g) in pyridine (25 ml) was refluxed for 24 hours. The treatment was similar to the preparation of **19** and there was obtained 0.5 g (55%) of yellow solid upon crystallization from ethanol, mp >250°; nmr (DMSO-d_6): 3.89 and 3.92 (2s, 6H, 2 OCH_3), 6.17-8.65 (m, 6H, ArH). This compound was used for the preparation of **48** without further purification.

2,9-Dimethoxy-6-methylthio[1]benzothieno[2,3-*c*]quinoline (**48**).

This compound was prepared from **45** (0.4 g, 0.0012 mole), methyl iodide (0.5 ml), potassium hydroxide (0.1 g) in 50 ml of aqueous methanol (1:1) in a manner similar to the preparation of **23** and there was obtained 0.3 g (61%) of the product upon crystallization from ethanol, mp 166-168°; nmr (deuteriochloroform): 2.93 (s, 3H, SCH_3), 3.91 and 3.95 (2s, 6H, 2 OCH_3), 7.02-8.51 (m, 6H, ArH).

Anal. Calcd. for $C_{18}H_{15}NO_2S_2$: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.11; H, 4.29; S, 18.55.

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