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.

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(5H)-one [6,7,8] prompted us to consider the [1]benzo-
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.


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-methoxybenzothiophene-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)benzothiophene-2-carboxamide (4) (64% yield), 3-chloro-5-methoxy-N-(3-methoxyphenyl)benzothiophene-2-carboxamide (5) (57% yield), and 3-chloro-5-methoxy-N(4-methoxyphenyl)benzothiophene-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(5H)-one (7) (46% yield), 3,10-dimethoxy[1]benzothieno[2,3-c]quinolin-6(5H)-one (8) (92% yield), and 2,10-dimethoxy[1]benzothieno[2,3-c]quinolin-6(5H)-one (9) (34% yield). This dehydrochlorinative photocyclization of the m-methoxyaniline 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...


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


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).


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-3-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]quinolinium-6(5H)-thione (43) (48% yield), 3,9-Dimethoxy[1]benzothieno[2,3-c]quinolinium-6(5H)-thione (44) (87% yield), and 2,9-Dimethoxy[1]benzothieno[2,3-c]quinolinium-6(5H)-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 'H-nmr spectra were recorded on a Varian EM-360 and a JEOL FX-90Q Fourier Transform spectrometer in deuteriochloroform or DMSO-d6, and are reported in ppm relative to TMS. All elemental analyses were performed by MHW Laboratories, Phoenix, AZ.

**m-Methoxycinnamic Acid (2)**

A mixture of m-aminosalicylic acid (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 129-131°C (lit mp 118-119°C [9]; nmr (DMSO-d6, δ 3.81 (s, 3H, OCH3), 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-methoxy-[1]benzothieno-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 147-149°[12]). nmr (deuteriochloroform): 3.85 (s, 3H, OCH3), 7.25 (dd, 1H, J = 8.2 Hz), 7.65 (1H, 14J), 7.62 (dd, 1H, J = 8.2 Hz).

3-Chloro-5-methoxy-N-(2-methoxyphenyl)benzo[b]thiophene-3-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 (46% yield), mp 154.1-155°. nmr (deuteriocloroform): 8.2 (d, 1H, J = 8.8 Hz). This lactam was used in the next step without further purification.


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 222.2-224°; nmr (DMSO-d6): 4.00 and 4.04 (2s, 6H, 2 OCH3), 7.36-8.40 (m, 7H, ArH), 9.51 (s, 1H, NH). This compound was used for the preparation of 12 without further purification.


A mixture of lactam 8 (0.8 g, 0.0025 mole) and phosphorus oxychloride (30 ml) was refluxed for 4 hours. The work-up procedure was similar to the preparation of 10. Recrystallization from benzene afforded 0.67 g (73%) of pale yellow prisms, mp 207-208°; nmr (DMSO-d6): 3.97 and 3.99 (s, 2H, 2 OCH3), 7.26-8.40 (6H, ArH). Found: C, 62.08; H, 3.77; S, 18.93. Anal. Calcd. for C21H16ClNO3S: C, 58.70; H, 4.05; S, 10.91. Calcd. for C21H18ClNO3S: C, 59.30; H, 4.46; S, 10.91.
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$_3$) and 4.67 (s, 3H, SCH$_3$), 7.95-8.40 (m, 6H, ArH). This compound was used without further purification.

3,10-Dimethoxy-6-methylthiophen[2,3-c]quinoline (23).

Methyl iodide (0.5 ml) was added to a stirred solution of thiolecatam 20 (0.4 g, 0.0012 mole), and potassium hydroxide (0.35 g) in 40 ml of benzene-methanol (1:1). The reaction mixture was stirred for 3 hours. The work-up was similar to the preparation of 22, yield 0.3 g (73%), upon crystallization from ethanol, mp 119-120°; nmr (deuteriochloroform): 2.85 (s, 3H, SCH$_3$), 3.87 and 4.04 (2s, 6H, 2 OCH$_3$), 7.05-8.61 (m, 6H, ArH).

Anal. Calcd. for C$_{17}$H$_{16}$O$_2$S: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.29; H, 4.37; S, 18.86.


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 (2.9 g, 60%), mp 220-222°; nmr (deuteriochloroform): 3.79 and 3.89 (2s, 6H, 2 OCH$_3$), 4.47 (s, 3H, SCH$_3$), 7.65-8.30 (m, 6H, ArH).

Anal. Calcd. for C$_{18}$H$_{18}$O$_2$N: C, 73.90; H, 6.64; N, 7.97. Found: C, 73.79; H, 6.72; N, 7.64.

2,10-Dimethoxy-6-methylthiophen[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), 7.94-8.19 (m, 3H, ArH).

Anal. Calcd. for C$_{17}$H$_{14}$NO$_2$S: C, 63.31; H, 4.42; S, 18.77. Found: C, 63.29; H, 4.37; S, 18.68.

p-Methoxyacetic Acid (26).

This compound was prepared as described for 2, yield 77%, upon crystallization from ethanol, mp 153-164° (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).

Chloro-3-methoxybenzo[b]thiophene-2-carboxyl Chloride (27).

To a mixture of p-methoxyacetic acid (4.2 g, 0.023 mole), pyridine (0.5 ml), and DMSO (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, J = 8.5 Hz), 7.15 (s, 1H, H$_5$), 7.55 (dd, 1H, J = 8.5 Hz).

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

This compound was prepared from 27 (4.5 g, 0.017 mole), p-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, 3.5 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 (s, 1H, NH).

Anal. Calcd. for C$_{18}$H$_{14}$NO$_2$S: C, 64.74; H, 4.05; S, 9.21; N, 10.19. Found: C, 64.64; H, 4.13; S, 9.14; Cl, 10.36.

4,9-Dimethoxy-5,6-dimethoxy-3,5-benzotiazoline (29).

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$_6$): 3.95 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$_{16}$NOS: C, 69.11; H, 6.64; S, 9.72. Found: C, 68.72; H, 6.64; S, 9.72.

2,10-Dimethoxy-5-methylthiophen[2,3-c]quinolinium Iodide (10).

A mixture of 15 (0.1 g, 0.0003 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, SCH$_3$), 7.63-8.62 (m, 6H, ArH), 10.14 (s, 1H, H$_6$).

Anal. Calcd. for C$_{17}$H$_{17}$NO$_2$S: C, 69.48; H, 3.54; S, 7.04, 27.87.

Found: C, 74.68; H, 3.96; S, 7.26, 28.00.


A solution of 9 (0.1 g, 0.00032 mole), phosphorus pentasulfide (10 g) and pyridine (25 ml) was refluxed for 18 hours as described for the preparation of 19. Thiocleactam 21 was obtained in 48% yield (0.05 g), mp >250°; nmr (DMSO-d$_6$): 3.83 and 3.96 (2s, 6H, 2 OCH$_3$), 7.41-8.38 (m, 6H, ArH). This compound was used without further purification.
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°.

| 8.45-8.81
| 2.87 (s, 3H, SCH$_2$), 3.97 and 4.09 (2s, 6H, 2 OCH$_3$), 7.13-7.70 (m, 5H, ArH, ArH).

Anal. Calcd. for C$_{35}$H$_{33}$CINO$_2$S: C, 58.70; H, 4.05; S, 9.21; CI, 10.19. Found: C, 58.76; H, 4.02; S, 9.16; CI, 10.57.

3-Chloro-6-methoxy-N-(4-methoxyphenyl)benzohthiophene-2-carboxamide (30)

A solution of 27 (7 g, 0.026 mole), m-anisidine (6.4 g, 0.056 mole), and benzene (200 ml) was refluxed for 1 hour. A stirred solution of the thiolactam from benzene, mp 186-188°; nmr (deuteriochloroform) 3.79 and 3.83 (2s, 6H, 2 OCH$_3$), 7.13-7.70 (m, 4H, ArH, ArH), 8.45-8.61 (m, 2H, ArH).

Anal. Calcd. for C$_{30}$H$_{29}$NO$_2$S: C, 63.31; H, 4.42; S, 7.51; I, 28.83. Found: C, 63.33; H, 4.37; S, 18.66.


This compound was prepared from 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$_6$), 6.40 and 6.05 (2s, 6H, 2 OCH$_3$), 7.70-7.75 (m, 5H, ArH), 8.74-8.84 (m, 2H, ArH).

Anal. Calcd. for C$_{36}$H$_{34}$NO$_2$S: C, 63.31; H, 4.42; S, 7.51. Found: C, 63.65; H, 4.42; S, 18.66.

3-Chloro-6-methylthio[1]benzothieno[2,3-c]quinoline (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$_6$), 6.40 and 6.05 (2s, 6H, 2 OCH$_3$), 7.70-7.75 (m, 5H, ArH), 8.74-8.84 (m, 2H, ArH). This compound was used without further purification in the preparation of 47.

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

A solution of 27 (7 g, 0.026 mole), m-anisidine (6.4 g, 0.056 mole), and benzene (200 ml) in a manner similar to the preparation of 19 was refluxed for 1 hour. The resulting yellow solid was collected and recrystallized from ethanol to afford 0.6 g (65%) of tan crystals upon crystallization from ethanol, mp 170-172°; nmr (deuteriochloroform) 2.85 (s, 3H, SCH$_2$), 3.90 and 4.01 (2s, 6H, 2 OCH$_3$), 6.83-7.69 (m, 7H, ArH), 7.79 (s, 1H, NH).

Anal. Calcd. for C$_{36}$H$_{34}$NO$_2$S: C, 63.13; H, 4.42; S, 7.51. Found: C, 63.33; H, 4.37; S, 18.66.
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$_{15}$H$_{12}$INO,S$\cdot$0.5H$_2$O: 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(5H)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.


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$_{15}$H$_{12}$NO,S: C, 63.31; H, 4.42; S, 18.77. **Found:** C, 63.11; H, 4.29; S, 18.55.

**REFERENCES AND NOTES**

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