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A series of monomethoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolines has been prepared by photocyclization of the appropriate *N*-methoxyphenyl-1-chloronaphtho[2,1-*b*]thiophene-2-carboxamides. Some of the lactams obtained were converted into the thiolactams and their *S*-methyl derivatives. The lactams were also converted into the corresponding 6-chloro derivatives. Some of these were catalytically dechlorinated into the monomethoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolines which were then quaternized into the *N*-methyl quaternary salts.

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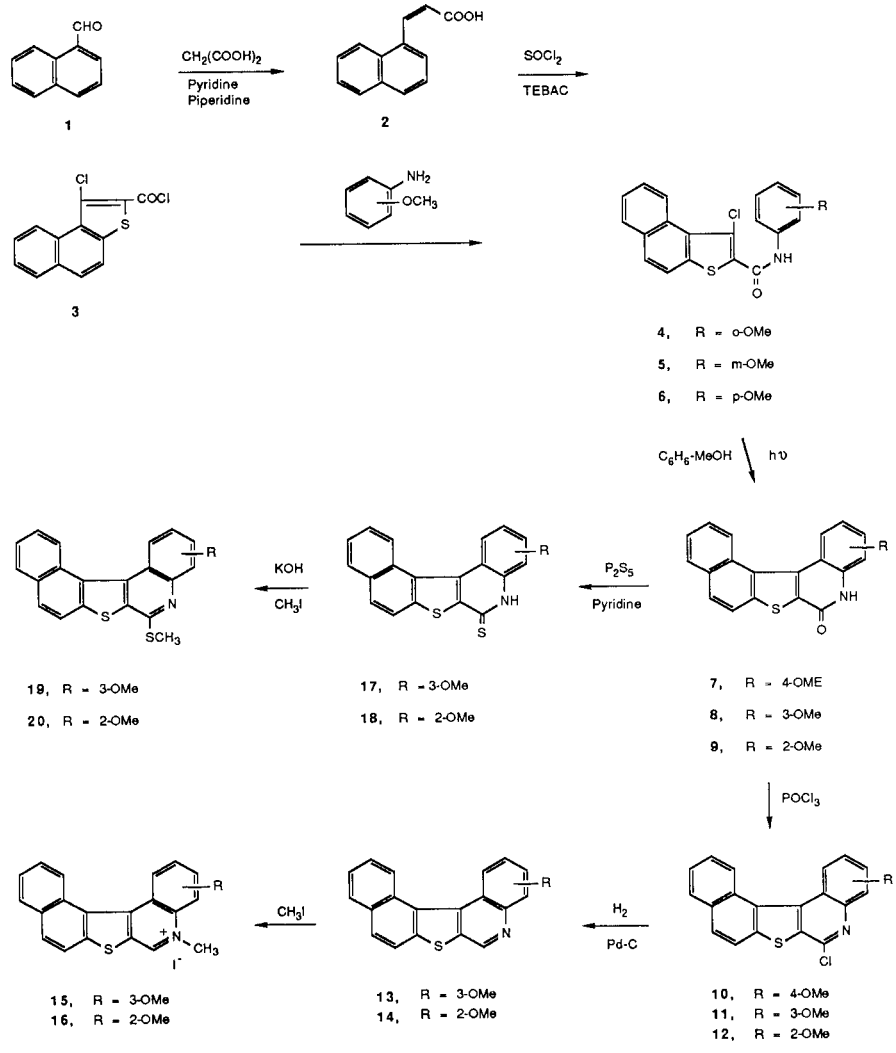
In an extension of our studies on nitrogen and sulfur polycyclic heterocycles [2], we wish to report the synthesis of some monomethoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolines, their *N*-methyl quaternary salts, thiolactams, and 6-methylthio derivatives. Some of these compounds have been prepared for antimetabolite studies.

When naphthalene-1-carboxaldehyde (**1**) was allowed to react with malonic acid, 3-(1-naphthyl)propenoic acid (**2**) [3] was obtained in 70% yield, which when allowed to react with thionyl chloride and triethylbenzylammonium chloride (TEBAC) gave 1-chloronaphtho[2,1-*b*]thiophene-2-carboxoyl chloride (**3**) [4] in 30% yield. The reaction of **3** with



o-anisidine, *m*-anisidine, or *p*-anisidine afforded the required carboxamides [5] namely: 1-chloro-*N*-(2-methoxyphenyl)naphtho[2,1-*b*]thiophene-2-carboxamide (**4**) (58% yield), 1-chloro-*N*-(3-methoxyphenyl)naphtho[2,1-*b*]thiophene-2-carboxamide (**5**) (70% yield), and 1-chloro-*N*-(4-methoxyphenyl)naphtho[2,1-*b*]thiophene-2-carboxamide (**6**) (62% yield), respectively. Upon photocyclization (triethylamine, benzene-methanol) compounds **4**, **5**, and **6** were transformed into the corresponding lactams [5]: 4-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolin-6(5*H*)-one (**7**) (45% yield), 3-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolin-6(5*H*)-one (**8**) (67% yield), and 2-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolin-6(5*H*)-one (**9**) (89% yield), respectively.

Chlorination of **7**, **8**, and **9** was accomplished by refluxing with phosphorus oxychloride. 6-Chloro-4-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**10**) (48% yield), 6-chloro-3-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**11**) (67% yield), and 6-chloro-2-methoxynaphtho[1',2':4,5]-thieno[2,3-*c*]quinoline (**12**) (84% yield), respectively, were obtained. Catalytic dechlorination of **11** and **12** over Pd/C gave 3-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**13**) in 79% yield, and 2-methoxynaphtho[1',2':4,5]thieno-[2,3-*c*]quinoline (**14**) in 83% yield, respectively. When compound **10** was subjected to catalytic dechlorination it gave a mixture of compounds from which the desired product could not be isolated either by crystallization or column chromatography on alumina.

N-Methylation of **13** and **14** with methyl iodide afforded the corresponding quaternary salts, 3-methoxy-5-methylnaphtho[1',2':4,5]thieno[2,3-*c*]quinolinium iodide (**15**) (35% yield) and 2-methoxy-5-methylnaphtho[1',2':4,5]-thieno[2,3-*c*]quinolinium iodide (**16**) (60% yield).

When compounds **8** or **9** were treated with phosphorus pentasulfide in pyridine the required thiolactams were obtained [6] namely: 3-methoxynaphtho[1',2':4,5]thieno-[2,3-*c*]quinoline-6(5*H*)-thione (**17**) (86% yield) and 2-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline-6(5*H*)-thione (**18**) (67% yield). Compounds **19** and **20** were prepared by *S*-methylation of **17** and **18** with methyl iodide in potassium hydroxide solution to furnish the methylthio derivatives [6]: 3-methoxy-6-methylthionaphtho[1',2':4,5]thieno-[2,3-*c*]quinoline (**19**) in 75% yield and 2-methoxy-6-methylthio[1',2':4,5]thieno[2,3-*c*]quinoline (**20**) in 79% yield, respectively. All attempts to convert **7** into the corresponding lactam with phosphorus pentasulfide in pyridine solution were unsuccessful.

EXPERIMENTAL

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

1-Chloronaphtho[2,1-*b*]thiophene-2-carboxoyl Chloride (**3**).

One third of the thionyl chloride (45.6 g, 0.38 mole) was added to a mixture of 3-(1-naphthyl)propenoic acid (4.50 g, 0.047 mole) and triethylbenzylammonium chloride (10.7 g, 0.047 mole). The mixture was heated to 140° and the remaining thionyl chloride was added dropwise over a period for 30 minutes. Stirring was continued for 2 hours after which the mixture was cooled, the product extracted with boiling benzene and precipitated with hexane. The resulting solid was collected and used for the next step without further purification. The overall yield was 30% (4.0 g), mp 140-143°, lit mp 147-149° [4]; nmr (deuteriochloroform): 7.25-8.16 (m, 6H, ArH); ir (potassium bromide): 1684 cm^{-1}.

1-Chloro-*N*-(2-methoxyphenyl)naphtho[2,1-*b*]thiophene-2-carboxamide (**4**).

A mixture of **3** (4.0 g, 0.014 mole), *o*-anisidine (3.50 g, 0.028 mole) and benzene (150 ml) was heated for 1 hour on a water bath. After cooling the resulting solid was collected by filtration and the filtrate was evaporated under reduced pressure. The residue was recrystallized from ethanol to give 3.0 g (58% yield) of **4**, mp 184-186°; nmr (deuteriochloroform): 3.96 (s, 3H, OCH_3), 6.99-7.57 (m, 3H, ArH), 7.61-7.99 (m, 4H, ArH), 8.50-8.53 (m, 2H, ArH), 8.60 (m, 1H, ArH), 9.45 (bs, 1H, NH).

Anal. Calcd. for $C_{20}H_{14}ClNO_2S$: C, 65.30; H, 3.38; S, 8.71; Cl, 9.63. Found: C, 65.12; H, 3.65; S, 8.57; Cl, 9.49.

4-Methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolin-6(5*H*)-one (**7**).

A solution of **4** (0.5 g, 0.00135 mole) and triethylamine (0.5 ml) in 1% methanol-benzene solution (500 ml) was irradiated with a 450 Watt Hanovia medium pressure mercury lamp for 3 hours. The resulting white solid was separated by filtration, washed with water and dried. The material obtained was used without further purification in the next step, 0.2 g (45% yield), mp >250°; nmr (DMSO-d_6): 3.81 (s, 3H, OCH_3), 7.05-8.16 (m, 9H, ArH), 8.53-8.61 (m, 1H, NH).

6-Chloro-4-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**10**).

A mixture of **7** (0.4 g, 0.0012 mole) and phosphorus oxychloride (20 ml) was refluxed for 3 hours. The residue which was obtained upon removal of the phosphorus oxychloride by distillation was poured into ice-water and the resulting solid was collected by filtration. Recrystallation from benzene gave 0.2 g (48% yield) of pale yellow crystals, mp 226-228°; nmr (deuteriochloroform): 4.14 (s, 3H, OCH_3), 7.10-7.99 (m, 7H, ArH), 8.34-8.36 (d, 1H, ArH), 8.45 (m, 1H, ArH).

Anal. Calcd. for $C_{20}H_{12}ClNOS$: C, 68.66; H, 3.45; S, 9.16; Cl, 10.13. Found: C, 68.64; H, 3.53; S, 9.27; Cl, 10.33.

1-Chloro-*N*-(3-methoxyphenyl)naphtho[2,1-*b*]thiophene-2-carboxamide (**5**).

This compound was prepared from **3** (8.9 g, 0.0316 mole), *m*-anisidine (7.60 g, 0.062 mole) in benzene (250 ml) in a similar manner to that described for the preparation of **4** and 8.1 g (70% yield) was obtained as beige crystals, mp 144-145°; nmr (deuteriochloroform): 3.84 (s, 3H, OCH_3), 6.78-7.88 (m, 9H, ArH), 7.99 (bs, 1H, NH), 9.39 (m, 1H, ArH).

Anal. Calcd. for $C_{20}H_{14}ClNO_2S$: C, 65.30; H, 3.83; S, 8.71; Cl, 9.63. Found: C, 65.14; H, 4.00; S, 8.53; Cl, 9.56.

3-Methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolin-6(5*H*)-one (**8**).

Compound **8** was prepared as described for **7** using 0.5 g (0.00136 mole) of **5**, 0.5 ml of triethylamine in 1% methanol-benzene (500 ml) to provide 0.3 g (67% yield) of a white solid, mp >250° which was used without further purification; nmr (DMSO-d_6): 3.86 (s, 3H, OCH_3), 6.71-8.12 (m, 6H, ArH), 9.96 (bs, 1H, NH).

6-Chloro-3-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**11**).

A mixture of **8** (2.0 g, 0.006 mole) and phosphorus oxychloride (35 ml) was refluxed for 3.5 hours following the same procedure described for the preparation of **10** and 1.4 g (67% yield) was obtained as yellow crystals, mp 208-210°; nmr (deuteriochloroform): 3.99 (s, 3H, OCH_3), 7.17-7.30 (m, 1H, ArH), 7.54-7.65 (m, 3H, ArH), 7.93-8.07 (m, 3H, ArH),

8.69-8.79 (m, 2H, ArH).

Anal. Calcd. for $C_{20}H_{12}ClNOS$: C, 68.66; H, 3.45; S, 9.16; Cl, 10.13. Found: C, 68.67; H, 3.61; S, 9.19; Cl, 10.26.

3-Methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**13**).

The chloro compound **11** (1.0 g, 0.0028 mole) was catalytically dechlorinated in 200 ml of benzene-methanol (1:1) containg 0.1 g of potassium hydroxide in the presence of 10% Pd-C (0.1 g) 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 0.7 g (79% yield) of white prisms, mp 204-206°; nmr (deuteriochloroform): 3.71 (s, 3H, OCH_3), 7.23-7.51 (m, 9H, ArH), 7.91-8.01 (m, 1H, H6).

Anal. Calcd. for $C_{20}H_{13}NOS$: C, 76.16; H, 4.15; S, 10.16. Found: C, 76.24; H, 4.10; S, 10.12.

3-Methoxy-5-methylnaphtho[1',2':4,5]thieno[2,3-*c*]quinolinium Iodide (**15**).

A solution of **13** (0.1 g, 0.00031 mole), methyl iodide (0.5 ml), and benzene (25 ml) was refluxed for 24 hours. The resulting yellow solid was collected by filtration. Recrystallization from ethanol afforded 0.05 g (35% yield) of **15** as yellow needles, mp 200-210°; nmr (DMSO-d_6): 3.47 (s, 3H, OCH_3), 3.99 (s, 3H, NCH_3), 7.23-7.77 (m, 7H, ArH), 7.88-8.77 (m, 2H, ArH), 9.27-9.31 (d, 1H, ArH).

Anal. Calcd. for $C_{21}H_{16}INOS$: C, 55.15; H, 3.52; S, 7.01; I, 27.74. Found: C, 55.14; H, 3.74; S, 6.86; I, 28.00.

3-Methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline-6(5*H*)-thione (**17**).

Compound **8** (0.5 g, 0.0015 mole), phosphorus pentasulfide (1.0 g), and 20 ml of pyridine was refluxed 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 0.45 g (86% yield) of the desired product, mp >250°; nmr (DMSO-d_6): 3.87 (s, 3H, OCH_3), 7.29-8.17 (m, 9H, ArH), 8.56-8.61 (m, 1H, NH).

Anal. Calcd. for $C_{20}H_{13}NOS_2$: C, 69.13; H, 3.77; S, 18.45. Found: C, 69.06; H, 3.96; S, 18.51.

3-Methoxy-6-methylthionaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**19**).

A suspension of thiolactam **17** (0.45 g, 0.00124 mole), methyl iodide (0.5 ml), and potassium hydroxide (0.05 g) in 50% aqueous methanol (60 ml) was stirred at room temperature for 1 hour after which 2 drops of glacial acetic acid was added. The solid was separated by filtration, washed with water, dried, and recrystallized from ethanol to give 0.35 g (75% yield) of off white flakes, mp 166-167°; nmr (deuteriochloroform): 2.89 (s, 3H, SCH_3), 3.99 (s, 3H, OCH_3), 7.05-7.22 (m, 1H, ArH), 7.51-7.62 (m, 3H, ArH), 7.92-8.05 (m, 3H, ArH), 8.62-8.77 (m, 2H, ArH).

Anal. Calcd. for $C_{21}H_{15}NOS_2$: C, 69.77; H, 4.18; S, 17.73. Found: C, 69.71; H, 4.29; S, 17.54.

1-Chloro-*N*-(4-methoxyphenyl)naphtho[2,1-*b*]thiophene-2-carboxaldehyde (**6**).

This compound was prepared from **3** (6.0 g, 0.021 mole), *p*-anisidine (5.1 g, 0.042 mole), and benzene (150 ml) by a method similar to that described for the preparation of **4** and there was obtained 4.80 g (62% yield) of the amide, mp 166-167°; nmr (deuteriochloroform): 3.67 (s, 3H, OCH_3), 7.12-8.23 (m, 10H, ArH), 8.77 (bs, 1H, NH).

Anal. Calcd. for $C_{20}H_{14}ClNO_2S$: C, 65.30; H, 3.83; S, 8.71; Cl, 9.63. Found: C, 65.41; H, 3.84; S, 8.91; Cl, 9.77.

2-Methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolin-6(5*H*)-one (**9**).

A solution of **6** (0.5 g, 0.00136 mole), and triethylamine (0.5 ml) in a 1% methanol-benzene solution (500 ml) was photocyclized for 3 hours as described for the preparation of **7**. The product (0.4 g, 89% yield) had mp >250° and was used in the next step without purification; nmr (DMSO-d_6): 3.93 (s, 3H, OCH_3), 7.14-8.27 (m, 9H, ArH), 8.68-8.75 (m 1H, NH).

6-Chloro-2-methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**12**).

A mixture of lactam **9** (1.7 g, 0.0051 mole) and phosphorus oxychloride (30 ml) was refluxed for 3.5 hours. The work-up procedure was similar to that for the preparation of **10**. Recrystallization from benzene afforded 1.5 g (84% yield) of yellow crystals, mp 194-195°; nmr (deuteriochloroform): 3.86 (s, 3H, OCH_3), 7.23-7.65 (m, 3H, ArH), 7.97-8.16 (m, 5H, ArH), 8.86-8.91 (m, 1H, ArH).

Anal., Calcd. for $C_{20}H_{12}ClNOS$: C, 68.66; H, 3.45; S, 9.16; Cl, 10.13. Found: C, 68.84; H, 3.39; S, 9.08; Cl, 9.96.

2-Methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**14**).

This compound was prepared from **12** (0.8 g, 0.0023 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 there was obtained 0.6 g (83% yield) of white crystals, mp 193-194°; nmr (deuteriochloroform): 3.89 (s, 3H, OCH_3), 7.26-7.69 (m, 9H, ArH), 8.01-8.09 (m, 1H, H6).

Anal. Calcd. for $C_{20}H_{13}NOS$: C, 68.36; H, 3.72; S, 9.12. Found: C, 68.90; H, 3.85; S, 9.12.

2-Methoxy-5-methylnaphtho[1',2':4,5]thieno[2,3-*c*]quinolinium Iodide (**16**).

A solution of **14** (0.4 g, 0.00126 mole) and methyl iodide (0.5 ml) in benzene (100 ml) was refluxed for 24 hours. After cooling the yellow solid was collected and recrystallized from ethanol to give 0.35 g (60% yield) of the salt, mp 200-204°; nmr (DMSO-d_6): 3.87 (s, 3H, OCH_3), 4.65 (s, 3H, NCH_3), 7.73 (m, 3H, ArH), 7.77-8.65 (m, 6H, ArH), 10.15 (s, 1H, H6).

Anal. Calcd. for $C_{21}H_{16}INOS$: C, 55.15; H, 3.52; S, 7.01; I, 27.74. Found: C, 54.91; H, 3.50; S, 6.81; I, 27.58.

2-Methoxynaphtho[1',2':4,5]thieno[2,3-*c*]quinolin-6(5*H*)-one (**18**).

To 1.0 g (0.0030 mole) of **9** in 20 ml of pyridine was added 1.5 g of phosphorus pentafulfide. The reaction was carried out in a similar manner to the procedure described for the preparation of **17** and there was obtained 0.7 g (67% yield) of a yellow solid, mp >250°; nmr (DMSO-d_6): 3.71 (s, 3H, OCH_3), 7.18-8.56 (m, 9H, ArH), 8.62-8.67 (m, 1H, NH).

Anal. Calcd. for $C_{20}H_{13}NOS_2$: C, 69.13; H, 3.77; S, 18.45. Found: C, 69.07; H, 4.00; S, 18.22.

2-Methoxy-6-methylthionaphtho[1',2':4,5]thieno[2,3-*c*]quinoline (**20**).

Methyl iodide (0.5 ml) was added to a stirred solution of thiolactam **18** (0.5 g, 0.0014 mole) and potassium hydroxide (0.05 g) in 50 ml of benzene-methanol (1:1). The reaction mixture was stirred for 3 hours at room temperature. The work-up procedure was similar to that for the preparation of **19**, yield 0.4 g (79%), mp 172-174°; nmr (deuteriochloroform): 2.89 (s, 3H, SCH_3), 3.86 (s, 3H, OCH_3), 7.24-7.64 (m, 3H, ArH), 7.96-8.14 (m, 5H, ArH), 8.82-8.93 (m, 1H, ArH).

Anal. Calcd. for $C_{21}H_{15}NOS_2$: C, 69.77; H, 4.18; S, 17.73. Found: C, 69.69; H, 4.11; S, 17.66.

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