Imidazolyl Derivatives of the Thiochroman Ring

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The synthesis of 2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-ones **3** from 3-bromo-4*H*-1-benzothiopyran-4-ones **1** and imidazole is described. The reaction of **1** with secondary amines gives the corresponding 3-aminothiochromones **11**. Compounds **3** can be oxidized to the sulfones **4** from which the thiochromanols **5** and thiochromene **7** can be easily obtained. 3-Bromo-2,3-dihydro-6-methyl-4*H*-1-benzothiopyran-4-one **12** and imidazole led by dehydrohalogenation to thiochromone, while the ketal **13** rearranged to benzo[*b*]thiophene **16**.

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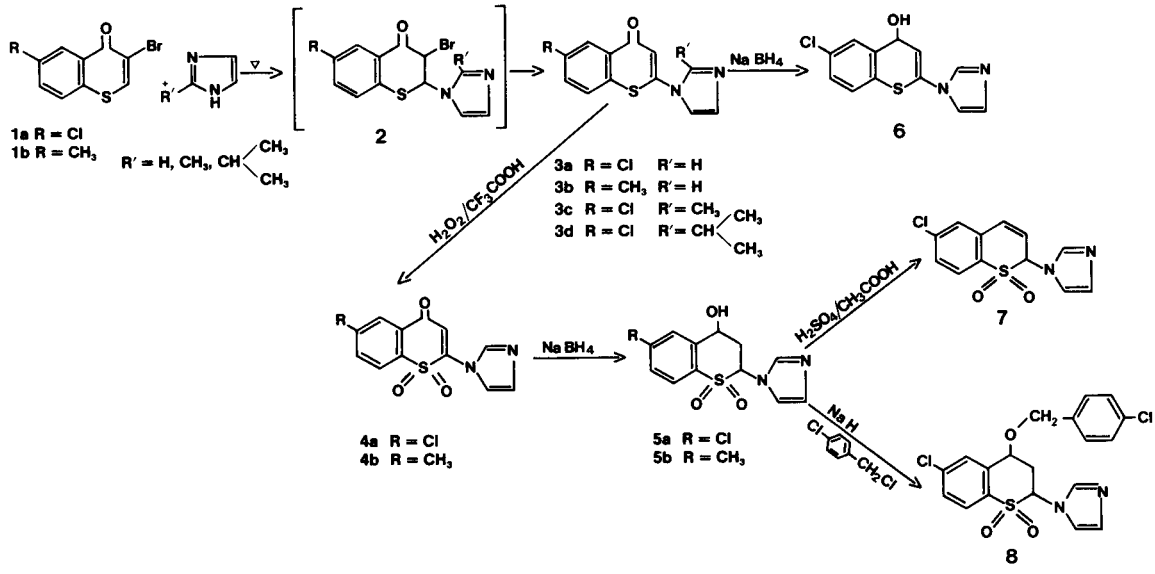
We described in a previous paper the synthesis of 2-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-ones [1]. We report now the synthesis of 2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-ones **3** analogous of the former. These compounds were synthesized by reacting 3-bromo-4*H*-1-benzothiopyran-4-ones with an excess of imidazole or 2-alkylimidazoles at 120° in a 80-90% yield range (Scheme 1).

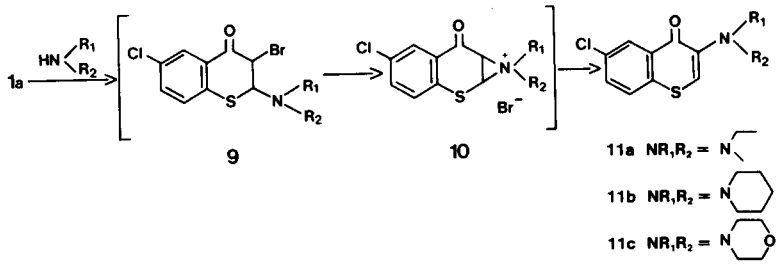
For the synthesis of the thiochromones **3**, whose structures were assigned by their ^{1}H nmr spectra and confirmed by those of their derivatives, an initial Michael addition followed by dehydrobromination of intermediate compounds **2** can be postulated as for the corresponding 2-(1*H*-imidazolyl)chromones [1]. The reaction of 3-bromothiochromones **1** with secondary amines, such as ethylmethylamine, morpholine and piperidine, led on the contrary to the 3-aminothiochromones **11**, as reported for the 3-bromochromones where an initial Michael addition, followed by rearrangement through an intermediate aziridium cation **10**, was postulated [2,3]. Only one 3-aminothiochromone, bearing a nitro group in position 2, was described by Eiden and Felbermeir [4] by a different synthesis. From the above results it appears that both 3-bromochromones and 3-bromothiochromones show the same reactivity towards imidazole and secondary amines. The reaction of thiochromones **3a** with sodium borohydride gave 6-chloro-2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-ol (**6**) while in the case of 2-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-ones both the carbonyl group and the double bond were reduced to 2,3-dihydro-2-(1*H*-imidazol-1-yl)-4*H*-1-benzopyran-4-ols [1].

Compounds **3** were oxidized with hydrogen peroxide and trifluoroacetic acid to the corresponding sulfones **4** which, by treatment with sodium borohydride, gave in good yield the 2,3-dihydro-2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-ol 1,1-dioxides **5**. Compounds **5a** were used as starting material to obtain in good yield the thio-

SCHEME 1

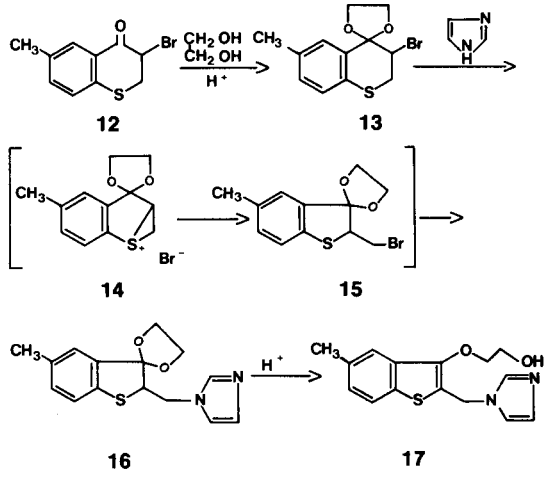


SCHEME 2



chroman **7** by dehydration with a mixture of concentrated sulfuric acid and glacial acetic acid, or the corresponding ethers by a Williamson reaction. As an example we report the benzyl ether **8**. Under the conditions experienced by us the reaction of 3-bromothiochromanones with imidazole led exclusively to the corresponding thiochromone by dehydrohalogenation, while in the case of 3-bromochromanones varying amount of the corresponding 2-(1*H*-imidazolyl)chromanones were obtained [5]. When the carbonyl group of compound **12** was protected as a ketal (compound **13**), a ring contraction took place giving 2,3-dihydro-3,3-ethylendioxy-2-(1*H*-imidazol-1-yl-methyl)-5-methylbenzo[*b*]thiophene (**16**) in good yield. This is not surprising since it is known that 3-bromo-2,3-dihydro-4*H*-1-benzothiopyran-4-ol, on heating in dioxane under reflux, rearranges to 2-bromomethylbenzo[*b*]thiophene [6,7] through an initial formation of a thiiranium cation. In our case substitution of bromo of the possible intermediate **15** with imidazole can take place as shown in Scheme 3.

SCHEME 3



Compound **16** by treatment with acids opened the ketal ring giving 3-(2-hydroxyethoxy)-2-(1*H*-imidazol-1-yl-methyl)-5-methylbenzo[*b*]thiophene (**17**) in high yield. Further studies on alternate synthesis of compounds possessing the 2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran structure are in progress and will be the subject of a further paper.

EXPERIMENTAL

Melting points were determined on a Buchi melting point apparatus and are uncorrected. The ir spectra were obtained on a Perkin-Elmer 125 spectrophotometer. The ^1H nmr and ^{13}C nmr spectra were obtained on a Bruker HFX 90 MHz spectrometer in the solvents indicated. Chemical shifts are reported in ppm from TMS as internal standard and are given in δ units. Mass spectra were obtained on a Finnigan MAT CH7 mass spectrometer. Column chromatographic separations were performed on 0.05-0.20 nm silica gel (Carlo Erba).

6-Chloro-2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-one (**3a**).

A mixture of 4.31 g (15.5 mmoles) of 3-bromo-6-chloro-4*H*-1-benzothiopyran-4-one (**1a**) and 5.44 g (80.0 mmoles) of imidazole was heated at 140 for 1 hour. After cooling, the reaction mixture was poured into water and extracted with chloroform. The resulting solution was washed with 1*N* sodium hydroxide and water, dried over sodium sulfate and evaporated to dryness. The residue, crystallized from ethanol-water, gave 3.6 g (88%) of **3a**, mp 208-210°; ^1H nmr (deuteriochloroform and trifluoroacetic acid): 7.36 (1H, s, H-3), 7.66 (4H, m, NCHCHN and H-7, H-8), 8.39 (1H, broad s, H-5), 9.26 (1H, broad s, NCHN).

Anal. Calcd. for $C_{12}H_7ClN_2OS$: C, 54.86; H, 2.68; N, 10.66; Cl, 13.49; S, 12.20. Found: C, 54.93; H, 2.67; N, 10.69; Cl, 13.53; S, 12.17.

By the above procedure the following compounds were prepared:

2-(1*H*-Imidazol-1-yl)-6-methyl-4*H*-1-benzothiopyran-4-one (**3b**).

This compound was obtained from 3-bromo-6-methyl-4*H*-1-benzothiopyran-4-one (**1b**) in 87% yield, mp 175-177° (ethanol-water); ^1H nmr (deuteriochloroform): 2.50 (3H, s, CH_3), 7.02 (1H, s, H-3), 7.25 (1H, broad s, NC*H*CHN), 7.36 (1H, broad s, NCHC*H*N), 7.50 (2H, m, H-7 and H-8), 7.99 (1H, broad s, NCHN), 8.31 (1H, broad s, H-5).

Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56; S, 13.26. Found: C, 64.56; H, 4.18; N, 11.53; S, 13.20.

6-Chloro-2-(2-methyl-1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-one (**3c**).

This compound was obtained from **1a** and 2-methylimidazole in 82% yield, mp 147-149° (methanol-water); ir (potassium bromide): 3140, 3100, 3030, 1630, 1580, 1540, 1490 cm^{-1}.

Anal. Calcd. for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.27; N, 10.12; Cl, 12.81; S, 11.58. Found: C, 56.32; H, 3.26; N, 10.09; Cl, 12.78; S, 11.61.

6-Chloro-2-(2-isopropyl-1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-one (**3d**).

This compound was obtained from **1a** and 2-isopropylimidazole in 78% yield, mp 146-148°; ^1H nmr (deuteriochloroform): 1.32 (6H, d, $2CH_3$), 3.20 (1H, m, CH), 6.96 (1H, s, H-3), 7.06 (1H, d, NC*H*CHN), 7.11 (1H, d, NCHC*H*N), 7.46-7.75 (2H, m, H-7 and H-8), 8.50 (1H, dd, H-5).

Anal. Calcd. for $C_{15}H_{13}ClN_2OS$: C, 59.10; H, 4.29; N, 9.19; Cl, 11.63; S, 10.52. Found: C, 58.99; H, 4.30; N, 9.21; Cl, 11.66; S, 10.49.

6-Chloro-2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-one 1,1-Dioxide (**4a**).

To a solution of 2.7 g (10.27 mmoles) of **3a** in 37 ml of trifluoro acetic acid, 8 ml of 36% w/v hydrogen peroxide were added. The reaction mixture was stirred at room temperature for 48 hours then was poured into water. The resulting solid was filtered, washed with water and crystallized with toluene to give 2.2 g (72%) of **4a**, mp 160-163° dec; ^{1}H nmr (deuteriochloroform and trifluoroacetic acid): 7.20 (1H, s, H-3), 7.75-8.30 (5H, m, NCHCHN, H-5, H-7 and H-8), 9.40 (1H, broad s, NCHN).

Anal. Calcd. for $C_{12}H_7ClN_2O_3S$: C, 48.90; H, 2.39; N, 9.50; Cl, 12.02; S, 10.88. Found: C, 48.83; H, 2.39; N, 9.48; Cl, 12.06; S, 10.91.

By the above procedure was prepared:

2-(1*H*-Imidazol-1-yl)-6-methyl-4*H*-1-benzothiopyran-4-one 1,1-Dioxide (**4b**).

This compound was obtained from **3b**, in 70% yield, mp 171-173° (benzene); ^{1}H nmr (DMSO-d_6): 7.25 (1H, broad s, NC*H*CHN), 7.35 (1H, s, H-3), 7.75-8.15 (4H, m, NCHN, NCHC*H*N, H-7 and H-8), 8.30 (1H, broad s, H-5).

Anal. Calcd. for $C_{13}H_{10}N_2O_3S$: C, 56.92; H, 3.67; N, 10.21; S, 11.69. Found: C, 57.00; H, 3.69; N, 10.19; S, 11.72.

6-Chloro-3,4-dihydro-2-(1*H*-imidazol-1-yl)-2*H*-1-benzothiopyran-4-ol 1,1-Dioxide (**5a**).

To a solution of 6.1 g (20.6 mmoles) of **4a** in 250 ml of dioxane 0.5 g (13.2 mmoles) of sodium borohydride was added portionwise at 10-15. After stirring at room temperature for 3 hours the mixture was poured into 200 ml of water and the dioxane was evaporated under reduced pressure. The solid residue was filtered, washed with water and dried to yield 4.4 g (71%) of **5a**, mp 164-166°; ^{1}H nmr (DMSO-d_6): 2.85 (2H, m, CH_2), 5.10 (1H, m, C*H*OH), 6.30 (1H, dd, SCH), 6.50 (1H, broad s, OH), 7.00 (1H, broad s, NC*H*CHN), 7.27 (1H, broad s, NCHC*H*N), 7.70 (1H, broad s, NCHN).

Anal. Calcd. for $C_{12}H_{11}ClN_2O_3S$: C, 48.24; H, 3.71; N, 9.37; Cl, 11.86; S, 10.73. Found: C, 48.33; H, 3.70; N, 9.40; Cl, 11.90; S, 10.70.

By the above procedure was prepared:

3,4-Dihydro-2-(1*H*-imidazol-1-yl)-6-methyl-2*H*-1-benzothiopyran-4-ol 1,1-Dioxide (**5b**).

This compound was obtained from **4b** in 73% yield, mp 205-207° (ethanol-water); ^{1}H nmr (DMSO-d_6 and deuteriochloroform): 2.42 (3H, s, CH_3), 2.8 (2H, m, CH_2), 5.10 (1H, m, C*H*OH), 6.20 (1H, dd, SCH), 7.00 (1H, broad s, NC*H*CHN), 7.20-7.70 (4H, m, NCHC*H*N, H-5, H-7 and H-8), 7.80 (1H, broad s, NCHN).

Anal. Calcd. for $C_{13}H_{14}N_2O_3S$: C, 56.09; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.17; H, 5.08; N, 10.09; S, 11.48.

6-Chloro-2-(1*H*-imidazol-1-yl)-4*H*-1-benzothiopyran-4-ol (**6**).

To a refluxing solution of 1.3 g (4.9 mmoles) of **3a** in 200 ml of methanol, 0.4 g (10.5 mmoles) of sodium borohydride was added portionwise. The reaction mixture was heated for 10 minutes at refluxing temperature, stirred at room temperature for 3 hours and poured into 300 ml of water. The methanol was evaporated under reduced pressure and the resulting solid was filtered, washed with water and crystallized from benzene to yield 1.0 g (76%) of **6**, mp 124-126°; ^{1}H nmr (DMSO-d_6): 5.20 (1H, dd, C*H*OH), 6.20 (1H, d, OH), 6.45 (1H, d, H-3), 7.10 (1H, broad s, NC*H*CHN), 7.38-7.75 (4H, m, NCHC*H*N, H-5, H-7 and H-8), 8.12 (1H, broad s, NCHN).

Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.42; N, 10.58; Cl, 13.39; S, 12.11. Found: C, 54.50; H, 3.40; N, 10.61; Cl, 13.43; S, 12.09.

6-Chloro-2-(1*H*-imidazol-1-yl)-2*H*-1-benzothiopyran 1,1-Dioxide (**7**).

A solution of 1.3 g (4.3 mmoles) of **5a** in 35 ml of glacial acetic acid and 10 ml of concentrated sulfuric acid was heated at 110 for 16 hours. After cooling, the reaction mixture was poured into crushed ice, neutralized with ammonium hydroxide and extracted with methylene chloride. The organic layer was dried over sodium sulfate and evaporated to dryness. The resulting solid was taken up with ethyl ether, filtered and evaporated to dryness yielding 0.9 g (73%) of **7**; ^{1}H nmr (deuteriochloroform and trifluoroacetic acid): 6.24 (1H, d, SCH), 6.46 (1H, dd, H-3), 7.14 (1H, d, H-4), 7.41 (1H, d, H-5), 7.53 (2H, m, NCHCHN), 7.61 (1H, dd, H-7), 7.90 (1H, d, H-8), 8.88 (1H, broad s, NCHN).

Anal. Calcd. for $C_{12}H_9ClN_2O_2S$: C, 51.34; H, 3.23; N, 9.97; Cl, 12.62; S, 11.42. Found: C, 51.26; H, 3.22; N, 10.00; Cl, 12.57; S, 11.45.

6-Chloro-4-(4-chlorobenzyloxy)-3,4-dihydro-2-(1*H*-imidazol-1-yl)-2*H*-1-benzothiopyran (**8**).

A solution of 1.48 g (4.9 mmoles) of **5a** in 20 ml of anhydrous *N,N*-dimethylformamide was added under stirring to a suspension of 0.12 g (5.0 mmoles) of sodium hydride in 5 ml of anhydrous *N,N*-dimethylformamide. The reaction mixture was stirred at room temperature for 10 minutes, then a solution of 0.8 g (4.9 mmoles) of 4-chlorobenzyl chloride in 5 ml of anhydrous *N,N*-dimethylformamide was added portionwise. After stirring at room temperature for 2 hours, the reaction mixture was evaporated to dryness under reduced pressure. The solid residue was purified by silica gel column chromatography, eluting with methylene chloride-methanol (90:10) to yield 1.4 g (66%) of **8**, mp 113-115°; ^{1}H nmr (DMSO-d_6): 3.10-3.30 (2H, m, SCHCH_2), 4.65 (1H, d, OC*H*H), 4.85 (1H, d, OCH*H*), 5.10 (1H, dd, OCH), 6.30 (1H, dd, SCH), 7.05 (1H, broad s, NC*H*CHN), 7.37-8.00 (9H, m, NCHC*H*N, NCHN and benzene H).

Anal. Calcd. for $C_{19}H_{16}Cl_2N_2O_2S$: C, 53.90; H, 3.81; N, 6.61; Cl, 16.75; S, 7.57. Found: C, 53.82; H, 3.82; N, 6.59; Cl, 16.71; S, 7.59.

6-Chloro-3-(*N*-ethyl-*N*-methylamino)-4*H*-1-benzothiopyran-4-one (**11a**).

A mixture of 2.0 g (7.2 mmoles) of **1a** and 2.3 g (38.9 mmoles) of *N*-ethylmethylamine was stirred at room temperature for 10 minutes. The reaction mixture was poured into water and the resulting solid was washed with water and crystallized from methanol-water to yield 1.6 g (88%) of **11a**, mp 120-122°; ^{1}H nmr (deuteriochloroform): 1.35 (3H, t, CH_2CH_3), 3.30 (3H, s, NCH_3), 3.55 (2H, q, CH_2), 7.40 (2H, m, H-7 and H-8), 7.90 (1H, broad s, H-5), 8.10 (1H, s, SCH).

Anal. Calcd. for $C_{12}H_{12}ClNOS$: C, 56.80; H, 4.76; N, 5.51; Cl, 13.97; S, 12.63. Found: C, 56.86; H, 4.75; N, 5.49; Cl, 14.00; S, 12.60.

By the above procedure the following compounds were prepared:

6-Chloro-3-(1-piperidyl)-4*H*-1-benzothiopyran-4-one (**11b**).

This compound was obtained from **1a** and piperidine, in 83% yield, mp 165-167° (methanol-water); ir (potassium bromide): 2925, 2910, 2840, 1650, 1590, 1550, 1440, 1330 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}ClNOS$: C, 60.10; H, 5.04; N, 5.00; Cl, 12.67; S, 11.46. Found: C, 59.99; H, 5.06; N, 4.99; Cl, 12.70; S, 11.50.

6-Chloro-3-(4-morpholinyl)-4*H*-1-benzothiopyran-4-one (**11c**).

This compound was obtained from **1a** and morpholine, in 80% yield, mp 181-183° (methanol); ir (potassium bromide): 2960, 2920, 2860, 1665, 1585, 1560, 1550, 1440, 1330, 1020 cm^{-1}; ms: m/e (relative intensity) 281 (M^+, 100), 238 (7), 224 (26), 210 (17), 196 (95), 85 (7).

Anal. Calcd. for $C_{13}H_{12}ClNO_2S$: C, 55.41; H, 4.29; N, 4.97; Cl, 12.58; S, 11.38. Found: C, 55.35; H, 4.29; N, 4.98; Cl, 12.61; S, 11.40.

3-Bromo-3,4-dihydro-4,4-ethylendioxy-6-methyl-2*H*-1-benzothiopyran (**13**).

To a solution of 2.5 g (9.7 mmoles) of **12** in 32 ml of benzene, 2.5 g (40.2 mmoles) of ethanediol and 0.15 g (0.78 mmole) of *p*-toluenesulfonic acid monohydrate were added and the mixture was refluxed, with water separation, for 24 hours. The solution was washed with 2% sodium hydroxide solution and water, dried on anhydrous sodium sulfate and evaporated to dryness. The residue was purified by silica gel column chromatography, eluting with ethyl ether-petroleum ether (1:4) to yield 2.1 g (72%) of **13**; ^{1}H nmr (deuteriochloroform): 2.27 (3H, s, CH_3), 3.47 (1H, dd, SC*H*H), 3.65 (1H, dd, SCH*H*), 4.19 (4H, broad s, OCH_2CH_2O),

4.57 (1H, dd, SCH_2CH), 6.96 (2H, m, H-7 and H-8), 7.27 (1H, broad s, H-5).

Anal. Calcd. for $C_{12}H_{13}BrO_2S$: C, 47.85; H, 4.35; Br, 26.52; S, 10.64. Found: C, 47.91; H, 4.35; Br, 26.48; S, 10.62.

2,3-Dihydro-3,3-ethylendioxy-2-(1*H*-imidazol-1-yl-methyl)-5-methylbenzo[*b*]thiophene (**16**).

A mixture of 3.0 g (9.9 mmoles) of **13**, 3.0 g (44.0 mmoles) of imidazole and 40 ml of *N,N*-dimethylformamide was heated at 120 for 6 hours. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography, eluting with methylene chloride-methanol (90:10) to yield 2.1 g (73%) of **16**, mp 98-100°; ^{1}H nmr (deuteriochloroform): 2.32 (3H, s, CH_3), 3.8-4.5 (7H, m, OCH_2CH_2O and $SCHCH_2$), 6.8-7.53 (6H, m, benzene H and imidazole H); ^{13}C nmr (deuteriochloroform): 21.0, 47.6, 56.2, 65.0, 66.1, 116.7, 119.1, 123.1, 124.9, 129.4, 131.9, 134.2, 135.1, 136.8, 137.8.

Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.47; H, 5.59; N, 9.71; S, 11.11. Found: C, 62.56; H, 5.60; N, 9.89; S, 11.09.

3-(2-Hydroxyethoxy)-2-(1*H*-imidazol-1-yl-methyl)-5-methylbenzo[*b*]thiophene (**17**).

A solution of 1 g (3.4 mmoles) of **16** and 0.5 g (2.6 mmoles) of *p*-toluenesulfonic acid monohydrate in 50 ml of 2-butanone was heated at reflux for 3 hours. The solvent was evaporated under reduced pressure and the residue, taken up with 50 ml of methylene chloride, was washed with 5% aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate and evaporated under reduced pressure to yield 0.9 g (90%) of **17**, mp 110-112°; ^{1}H nmr (deuteriochloroform and trichloroacetic acid): 2.47 (3H, s, CH_3), 4.54-4.80 (4H, m, OCH_2CH_2O), 5.52 (2H, s, NCH_2), 7.20-7.63 (5H, m, benzene H and NCHCHN), 8.76 (1H, broad s, NCHN).

Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.47; H, 5.59; N, 9.71; S, 11.11. Found: C, 62.34; H, 5.61; N, 9.68; S, 11.15.

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