Synthesis of 8-Substituted Naphtho[2,1-*b*]thiophenes with Cationic Side Chains at Position 4

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A series of five 8-substituted α-[bis(2-hydroxyethyl)aminoethyl]naphtho[2,1-*b*]thiophenes **7** and a series of seven *N*-(3-dimethylaminopropyl)-8-substituted naphtho[2,1-*b*]thiophene-4-carboxamides **8** have been synthesized. The naphtho[2,1-*b*]thiophene-4-carboxylic acids **4** were prepared by photooxidative cyclization of α-(2-thienyl)-β-arylacrylic acids **3**. The carboxylic acids **4** were converted by a conventional five step route involving α-bromoketone intermediates to the α-[bis(2-hydroxyethyl)aminomethyl]-8-substituted naphtho-[2,1-*b*]thiophene-4-methanols **7** and by a standard two-step amide preparation to the *N*-(3-dimethylaminopropyl)-8-substituted naphtho[2,1-*b*]thiophene-4-carboxamides **8**.

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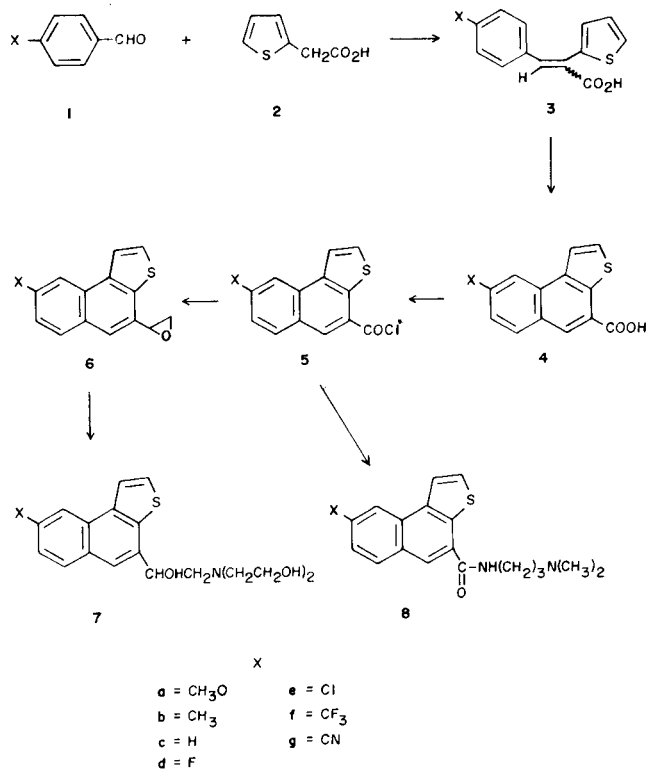
Sometime ago we reported the synthesis [1], antimalarial activity [1], and the DNA-binding properties [2,3] of a number of naphtho[2,1-*b*]thiophenes with 2-di-*n*-butylamino-1-hydroxyethyl side chains. These compounds were shown to intercalate with DNA. Preliminary studies suggested that they exhibited A-T binding specificity and that their binding constants were influenced by the electronic properties of substituents in the 8-position [2,3]. Of the hundreds of known intercalators only the tilorone class [4] and the naphthothiophenes [2,3] have been reported to show any pronounced A-T binding specificity. As part of an effort [5] designed to understand the effect of molecular topology of intercalators on binding constants and base-pair specificity, we have synthesized a series of α-[bis-(2-hydroxyethyl)aminomethyl]-8-substituted-naphtho[-2,1-*b*]-thiophene-4-methanols **7** and *N*-(3-dimethylaminopropyl)-8-substituted-naphtho[2,1-*b*]thiophene-4-carboxamides **8**.

A complication encountered in our earlier binding studies [2,3] was the limited water solubility of the naphtho-[2,1-*b*]thiophenes with 2-di-*n*-butylamino-1-hydroxyethyl side chains. The diethanolamino side chain at position-4 was chosen in anticipation of an enhancement of the water solubility of the intercalator; the *N*-(3-dimethylaminopropyl)carboxamide side chain was chosen on similar grounds since this side chain amide unit was present in highly soluble phenazines which were effective intercalators [6]. The 8-substituents, ranging from 8-CN to 8-OCH_3, were selected to provide a full range of electronic effects--from strong electron withdrawing to strong electron donating. Recent studies in our laboratory with the parent molecule in the aryl methanol series, α-[bis(2-hydroxyethyl)aminoethyl]naphtho[2,1-*b*]thiophene (**7c**) have shown that it is water soluble and that it exhibits a high order of A-T specificity on interaction with DNA [7].

The synthesis of the naphtho[2,1-*b*]thiophenes was achieved using an approach we have employed previously [1,8]. The first step in the sequence (Scheme I) employs a modified Perkin condensation [9] between the appropriate *para*-substituted benzaldehydes, **1**, and 2-thienylacetic acid, **2**, which forms α-(2-thienyl)-β-arylacrylic acids, **3**. It

Scheme I



was not necessary to determine which geometric isomer was isolated since we have earlier shown that on irradiation with 2537 Å light either isomer yielded the naphtho[2,1-*b*]thiophene-4-carboxylic acids, **4**, presumably as a consequence of photocyclization, followed by oxidation, of the *cis*-acrylic acid available from the photo-equilibration of the *cis/trans* isomers [1]. This oxidative-photocyclization method has been used extensively to prepare numerous polycyclic thiophenes [10].

Table 1

Physical Data for New Compounds in Series **4** and **6** [a,b]

Compound No.	Yield %	Mp °C	Molecular Formula	Analyses Calcd. (Found) C	H	NMR [c] (Chemical Shifts)
4a	34	283-285	$C_{14}H_{10}O_3S$	65.10 (64.82)	3.90 (3.98)	55.4, 103.8, 117.2, 120.4, 121.6, 124.6, 128.3, 128.6, 131.3, 132.2, 135.2, 135.9, 159.8, 166.8
4b	29	296-298	$C_{14}H_{10}O_2S$	69.40 (69.26)	4.16 (4.23)	21.4, 121.3, 122.0, 122.8, 127.7, 127.9, 128.4, 129.1, 129.5, 130.6, 134.8, 136.3, 138.8, 167.0
4d	39	308-311	$C_{13}H_7FO_2S$	63.40 (63.45)	2.86 (2.91)	[d] 108.0, 115.3, 121.6, 122.5, 126.8, 128.1, 129.5, 131.7, 132.6, 135.5, 136.3, 162.0, 166.6
4e	24	326-329	$C_{13}H_7ClO_2S$	59.43 (59.44)	2.69 (2.93)	121.6, 122.7, 123.3, 126.2, 127.9, 128.2, 129.9, 131.1, 131.6, 133.7, 135.7, 135.9, 166.6
4g	43	>350	$C_{14}H_7NO_2S$	[e]		
6d	50	oil	$C_{14}H_9FOS$			[f] 49.4, 51.7, 107.3, 114.7, 120.1, 121.3, 125.7, 128.7, 130.0, 130.1, 135.0, 135.5, 160.5
6e	38	88-89	$C_{14}H_9ClOS$	64.49 (64.24)	3.48 (3.75)	49.4, 51.7, 119.9, 121.2, 122.2, 125.7, 126.0, 128.7, 128.9, 129.2, 129.8, 131.6, 135.0, 135.1
6g	56	164-166	$C_{15}H_9NOS$	71.69 (71.46)	3.61 (3.68)	49.9, 51.7, 109.5, 119.2, 120.1, 121.6, 126.5, 127.9, 129.2, 132.8, 133.8, 136.4

[a] Compounds **4c**, **4f**, **6c** (58-59°) and **6f** have been previously reported [1]. [b] The compounds **4** were recrystallized from ethanol and the compounds **6** were recrystallized from hexane/dichloromethane. [c] **4a**, **4b**, **4d**, **4e**, **4g** are recorded in dimethylsulfoxide-d_6 and **6d**, **6e**, **6g** are recorded in chloroform-d. [d] 109.0 ($^2J_{C9F}$ = 21.5), 115.3 ($^2J_{C7F}$ = 25.4), 122.5 ($^4J_{C1aF}$ = 2.9), 131.7 ($^3J_{C9aF}$ = 9.8), 132.6 ($^3J_{C6F}$ = 9.8), 136.4 ($^4J_{C5aF}$ = 4.9), 162.0 ($^1J_{C8F}$ = 247.1). (Coupling constants are given in Hertz; superscripts correspond to number of bonds of coupling and subscripts correspond to carbon numbers and fluorine). [e] The acid was high melting and insoluble in all solvents used; it was converted directly without further characterization to make the epoxide **6g**. [f] 107.3 ($^2J_{C9F}$ = 21.5), 114.7 ($^2J_{C7F}$ = 24.4), 128.7 ($^4J_{C1aF}$ = 2.9), 130.0 ($^3J_{C9aF}$ = 8.8), 130.1 ($^3J_{C6F}$ = 8.9), 135.5 ($^4J_{C5aF}$ = 4.9), 160.5 ($^1J_{C8F}$ = 246.5). (Coupling constants are assigned on the basis of **4d**).

Table 2

Physical and Spectral Data for Compounds **7** and **8**

Compound No.	Yield %	Mp °C	Molecular Formula	Analyses Calcd. (Found) C	H	N	NMR [a] (Chemical Shifts)
7c	34	240-245 [d]	$C_{18}H_{22}ClNO_3S$	58.77 (58.49)	6.03 (6.00)	3.81 (3.76)	57.7, 58.6, 60.4, 69.6, 124.3, 124.6, 125.5, 128.2, 129.3, 130.8, 132.9, 133.8, 136.0, 139.1
7d	37	194-196 [d]	$C_{18}H_{21}ClFNO_3S$	56.03 (56.16)	5.49 (5.50)	3.63 (3.59)	[b] 57.5, 58.5, 60.4, 69.1, 109.1, 117.0, 123.7, 128.6, 129.4, 131.2, 132.6, 132.8, 136.4, 138.0, 162.8
7e	28	185-188 [d]	$C_{18}H_{21}Cl_2NO_3S$	53.73 (53.35)	5.26 (5.21)	3.48 (3.24)	57.3, 58.3, 60.2, 68.8, 123.1, 123.8, 127.7, 128.4, 130.4, 131.6, 133.5, 133.9, 136.1, 137.1
7f	22	228-235 [d]	$C_{19}H_{21}ClF_3NO_3S$	52.35 (52.47)	4.85 (4.89)	3.21 (3.18)	58.2, 59.3, 61.3, 70.2, 123.4, 124.5, 130.5, 130.9, 131.7, 132.4, 135.1, 136.8, 137.7, 140.2
7g	29	199-202	$C_{19}H_{21}ClN_2O_3S$	58.08 (58.14)	5.38 (5.64)	7.13 (7.00)	57.9, 58.7, 60.6, 69.3, 110.2, 122.0, 123.8, 129.0, 130.8, 134.4, 137.1, 138.6
8a	18	121-123	$C_{19}H_{22}N_2O_2S$	66.63 (66.57)	6.47 (6.50)	8.18 (8.17)	25.5, 40.6, 45.5, 55.4, 59.2, 103.3, 117.4, 120.5, 123.0, 124.7, 125.3, 129.2, 130.8, 131.9, 136.4, 159.5, 166.8
8b	47	113-114	$C_{19}H_{22}N_2OS$	69.90 (69.81)	6.79 (6.84)	8.58 (8.53)	22.6, 26.6, 41.2, 46.1, 59.8, 121.2, 123.6, 126.7, 128.3, 129.1, 129.6, 129.9, 131.1, 137.4, 138.6, 167.4
8c	70	118-120	$C_{18}H_{20}N_2OS$	69.19 (69.26)	6.45 (6.49)	8.96 (8.93)	25.2, 40.8, 45.4, 59.3, 120.4, 123.1, 123.6, 125.6, 127.0, 127.9, 129.2, 129.8, 130.3, 137.2, 166.7
8d	50	132-134	$C_{18}H_{19}FN_2OS$	65.43 (65.48)	5.79 (5.83)	8.47 (8.46)	[c] 25.5, 40.6, 45.4, 59.2, 107.8, 115.3, 120.6, 122.7, 126.8, 129.7, 131.0, 131.5, 135.9, 136.5, 161.9, 166.5
8e	71	131-133	$C_{18}H_{19}ClN_2OS$	62.32 (62.35)	5.52 (5.56)	8.07 (8.06)	25.4, 40.6, 45.4, 59.2, 120.4, 122.5, 122.7, 126.2, 127.2, 128.5, 130.1, 130.5, 133.6, 136.7, 166.4
8f	62	155-157	$C_{19}H_{19}F_3N_2OS$	59.98 (59.92)	5.03 (5.04)	7.36 (7.36)	25.3, 40.9, 45.5, 59.4, 120.5, 121.3, 122.2, 129.2, 130.0, 130.9, 131.9, 136.7, 137.5, 166.2
8g	47	157-158	$C_{19}H_{19}N_3OS$	67.62 (67.39)	5.67 (5.73)	12.45 (12.38)	25.0, 41.0, 45.6, 59.5, 110.7, 119.0, 120.3, 121.9, 126.4, 129.0, 129.2, 129.8, 130.1, 131.6, 132.0, 136.4, 136.9, 165.8

[a] **7c-7g** are recorded in water-d_2 and **8a-8g** are recorded in chloroform-d. [b] 109.1 ($^2J_{C9F}$ = 21.5), 117.0 ($^2J_{C7F}$ = 24.5), 131.2 ($^3J_{C9aF}$ = 8.8), 132.8 ($^3J_{C6F}$ = 8.8), 162.7 ($^1J_{C8F}$ = 245.5) (Coupling constants are given in Hertz; superscripts correspond to number of bonds of coupling and subscripts correspond to carbon numbers and fluorine. Coupling constants are assigned on the basis of **4d**). [c] 107.8 ($^2J_{C9F}$ = 21.5), 115.3 ($^2J_{C7F}$ = 24.4), 126.8 ($^3J_{C9aF}$ = 9.8), 131.5 ($^3J_{C6F}$ = 8.8), 136.5 ($^4J_{C5aF}$ = 4.9), 161.9 ($^1J_{C8F}$ = 249.0). (Coupling constants are assigned on the basis of **4d**).

The naphtho[2,1-*b*]thiophene-4-carboxylic acids were converted by a five-step sequence [11] to the desired aryl methanol intercalators. The sequence begins with the conversion, by use of thionyl chloride, to the acid chlorides, **5**, which on treatment with diazomethane formed diazoketones. The latter were reacted with hydrobromic acid to form the α-bromoketones. The α-bromoketones were reduced with sodium borohydride to form halohydrins which, in the same reaction vessel, were treated with potassium hydroxide to form the corresponding epoxides, **6**. Because of their lability the intermediates between the carboxylic acids and epoxides were not extensively purified but were used directly in subsequent steps. The epoxides which were crystalline were characterized by combustion analysis and the use of ^1H and ^{13}C nmr spectroscopy. Treatment of the epoxides with diethanolamine at 120° formed the naphtho[2,1-*b*]thiophene-4-methanols, **7**, which were isolated as hydrochloride salts from ether solution. No evidence of formation of the product, a 4-[1-diethanolamino-2-hydroxyethyl]naphtho[2,1-*b*]thiophene, which could arise from nucleophilic attack at the hindered benzylic carbon of the epoxide [12] was found on examination of the reaction product by ^1H and ^{13}C nmr spectroscopy. This procedure worked smoothly for all the compounds in the series except for **7a** and **7b**, which have methoxy and methyl substituents. In both these cases we were not successful in isolating the pure epoxide precursors. Although spectral evidence indicated the generation of the two epoxides, purification attempts including preparative thin-layer chromatography failed; consequently, **7a** and **7b** were not prepared.

The *N*-(3-dimethylaminopropyl)-8-substituted naphtho-[2,1-*b*]thiophene-4-carboxamides, **8**, were prepared by allowing 3-dimethylaminopropylamine to react directly with the appropriate 8-substituted naphtho[2,1-*b*]thiophene-4-carboxylic acid chlorides, **5**, in a standard amide synthesis. The amides **8** were isolated as their free bases. This procedure worked well for all the amides attempted (**8a-f**); however, inexplicably the methoxy compound **8a** was obtained only in poor yields.

EXPERIMENTAL

All melting points were recorded on a Mel-Temp and/or a Thomas-Hoover Unimelt apparatus and all are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, Georgia. The nmr spectra were recorded in deuteriochloroform or DMSO-d_6 or deuterium oxide with JEOL GX-270, JEOL FX-60Q, or Varian EM 360L spectrophotometers.

Thin layer chromatography (tlc) was carried out using silica gel plates (Whatman) and solvents used were (A) toluene: chloroform: methanol (4:2:1); (B) toluene: chloroform: methanol (2:1:1); (C) hexanes: ethylacetate (8:2); (D) ethylacetate: ethanol (3:1); (E) ethanol: acetic acid (1:1).

General Procedure for Preparation of Naphtho[2,1-*b*]thiophene-4-carboxylic Acids (**4**).

The 8-chloro compound **4e** is used as a representative example. A mixture of *p*-chlorobenzaldehyde (14.1 g, 0.1 mole), 2-thienyl acetic acid (15 g, 0.1 mole), 16 ml of distilled triethylamine and 32 ml of acetic anhydride was refluxed for 8 hours. The mixture was poured into *ca.* 2 ℓ of water and made alkaline with potassium hydroxide. The alkaline solution was gently boiled with charcoal for *ca.* 1 hour, filtered, allowed to cool and acidified with concentrated hydrochloric acid, and the resulting pale brown solid was filtered and dried. It was recrystallized from ethanol to give 12.2 g (46%) of a pale brown crystalline compound **3**, mp, 133-136°, tlc, solvent A (R_f = 0.31). The compound was used directly in the next step.

A solution of 4.0 g (15 mmoles) of α-(2-thienyl)-β-(p-chlorophenyl)-acrylic acid and 0.2 g of iodine in 600 ml of ethanol was irradiated for 39 hours in a Rayonett reactor fitted with lamps that provided 2537 Å light. Air was bubbled through the solution during the irradiation period. The ethanol was removed under reduced pressure and the residue was washed with ether (2 × 100 ml) and hexanes (2 × 100 ml). Recrystallization from ethanol gave 2.1 g (53%) of a pale greenish-yellow crystalline compound **4e**, mp, 326-329°, tlc, solvent B (R_f = 0.41). The overall yield from the aldehyde is 24%. See Table 1.

General Procedure for Preparation of naphtho[2,1-*b*]thiophen-4-ylethylene Oxides (**6**).

The 8-chloro compound is used as a typical example. Compound **4e** (2.625 g, 10 mmoles) in 48 g (400 mmoles) of thionyl chloride and 50 ml of benzene was refluxed for 3 hours and the excess thionyl chloride and benzene was distilled and the last traces of thionyl chloride were removed by codistillation with toluene. The solid when dried *in vacuo* at room temperature gave a pale yellow crystalline acid chloride (2 g, 71%), tlc, solvent B (R_f = 0.95).

The acid chloride was dissolved in methylene chloride (175 ml) and cooled to 0°. An ether solution of diazomethane (50 mmoles, freshly prepared) was added. The reaction mixture was stirred for 1 hour at 0° and allowed to stand overnight in a freezer at 0°; 50 ml of 48% hydrobromic acid were added dropwise to the reaction mixture at 0°. The mixture was stirred at 0° for 0.5 hour and at room temperature for 0.5 hour. The organic layer was separated and the aqueous layer was extracted with ether (3 × 50 ml). All of the combined organic extracts were washed with water (3 × 100 ml) and brine solution (1 × 100 ml) and dried over magnesium sulfate. The solvent was removed under reduced pressure and dried *in vacuo* at room temperature to give 2.9 g of α-bromoketone. The product was recrystallized from hexanes/methylene chloride to give 2.6 g (77%; based on carboxylic acid), tlc, solvent C (R_f = 0.49).

To a stirred solution of 0.68 g (2 mmoles) of the α-bromoketone in 30 ml of ethanol and 70 ml of benzene, 0.15 g (4 mmoles) of sodium borohydride was added at room temperature. After stirring for 15 minutes at room temperature, a solution of 2 g of potassium hydroxide in 10 ml of water was added and stirring was continued for 10 minutes. The solvent was removed under reduced pressure and treated with ice/water. A pale brown crystalline compound was separated, filtered, dried *in vacuo* at room temperature to give 0.49 g of a pale brown crystalline compound. Recrystallization from hexane/methylene chloride gave 0.36 g, mp 88-89° of a pale brown crystalline compound **6e**. The overall yield from the acid is 38%. See Table 1

General Procedure for Preparation of Naphtho[2,1-*b*]thiophene-4-diethanolaminomethylmethanol Hydrochlorides **7**.

The 8-chloro compound is used as a representative example. The epoxide **6e** (0.522 mmoles) was mixed with diethanolamine (4 g) and heated in an oil bath (122-126°) for 1 hour. The reaction mixture was cooled and diluted with ice/water. The product was extracted with ether (3 × 30 ml) and all the ether extracts were combined and washed with water (3 × 30 ml) and brine solution (1 × 30 ml). The ether solution was dried over magnesium sulfate. The solvent was removed under reduced pressure and the product dried *in vacuo* at room temperature. A pale yellow oil (0.64 g) was obtained, tlc solvent D (R_f = 0.35).

The oil was dissolved in ether (150 ml) and hydrogen chloride gas was bubbled through at 0° until the solution appeared saturated. A pale yel-

low crystalline compound was separated. The solvent was removed under reduced pressure and the remaining solid was dried *in vacuo* at room temperature to give a pale yellow crystalline compound 0.59 g (73%, based on epoxide). The product was recrystallized from ethanol to furnish 0.23 g of **7e**, mp 185-188°, tlc, solvent D (R_f = 0.35). The overall yield from the epoxide is 28%. See Table 2.

General Procedure for the Synthesis of *N*-(3-Dimethylaminopropyl)-8-substituted Naphtho[2,1-*b*]thiophene-4-carboxamides **8**.

The parent naphthothiophene **8c** is used as a typical example. A solution of naphtho[2,1-*b*]thiophene-4-carboxylic acid **4c** (0.68 g, 3 mmoles) and thionyl chloride (26 mℓ, 360 mmoles) was refluxed for 3 hours. The excess thionyl chloride was distilled and the last traces of it were removed by codistillation with toluene. The resulting acid chloride was mixed with 10 mℓ of 3-dimethylaminopropylamine and refluxed for 2 hours. The reaction mixture was diluted with ice/water and extracted with ether (3 × 100 mℓ). The combined ether extracts were washed with water (3 × 100 mℓ) and brine solution (1 × 50 mℓ). The ether solution was dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Finally, the residue was dried *in vacuo* at room temperature. The product was crystallized from ethyl acetate/hexanes and pale yellow crystals (0.52 g, 70%) were obtained, **8c**, mp 118-120°, tlc solvent E (R_f = 0.26). See Table 2.

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