Naphthothiophenes. 3. Preparation of 4-Naphtho[1,2-b]thiophenemethanols and 5-Naphtho[1,2-b]thiophenemethanols and Attempts to Prepare 5-Naphtho[2,1-b]thiophenemethanols as Antimalarials

Bijan P. Das, Robert T. Cunningham, and David W. Boykin, Jr.*

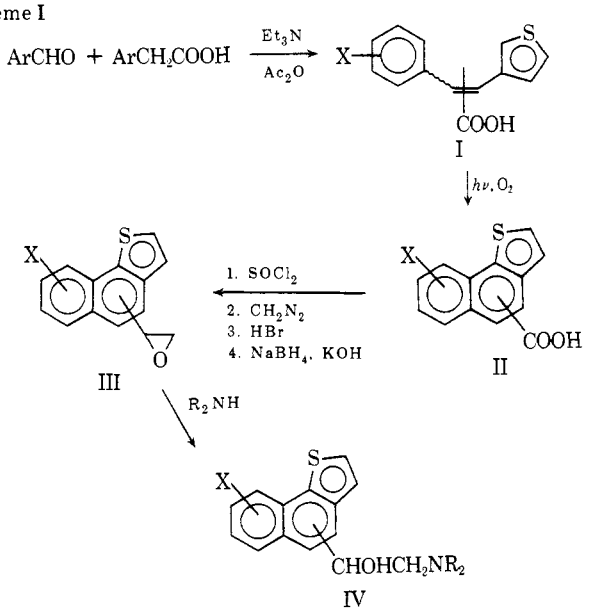
Department of Chemistry, Georgia State University, Atlanta, Georgia 30303. *Received May 11, 1973*

A series of seven substituted α-(*N,N*-dialkylaminomethyl)-4-naphtho[1,2-*b*]thiophenemethanols and a series of five substituted α-(*N,N*-dialkylaminomethyl)-5-naphtho[1,2-*b*]thiophenemethanols have been prepared and screened for antimalarial activity. Naphtho[1,2-*b*]thiophene-4-carboxylic acids and naphtho[1,2-*b*]thiophene-5-carboxylic acids, prepared by photooxidative cyclization of α-(3-thienyl)-β-arylacrylic acids and α-aryl-β-(3-thienyl)acrylic acids, respectively, were converted into the title compounds by the conventional five-step route involving bromomethyl ketone intermediates. In the 4-naphtho[1,2-*b*]thiophenemethanol series the di-*n*-heptylamino side chain exhibited greater activity than the di-*n*-butylamino side chain, whereas in the 5-naphtho[1,2-*b*]thiophenemethanol series the converse was observed. No activity was observed for the one compound in the 4-naphtho[1,2-*b*]thiophenemethanol series with a piperidino side chain. Cures were obtained against *Plasmodium berghei* in mice with six compounds. The most active compound, **32**, gave cures against *Plasmodium berghei* at 160 mg/kg dosage level and was active at 10 mg/kg. Compound **32** was active against *P. gallinaceum* at 320 mg/kg. Unsuccessful attempts to prepare substituted naphtho[2,1-*b*]thiophene-5-carboxylic acids are described.

In recent years numerous reports have appeared describing the chemistry and antimalarial activity of a variety of arylaminocarbinols.[1-3] The stimulus for this research has been the appearance of drug-resistant *Plasmodium falciparum* malaria[4] and the discovery that these structural types bind to DNA, probably by intercalation.[5,6] DNA binding is believed to be a part of their antimalarial action.[6-8] Among these arylaminocarbinols, a number of 9-phenanthrenemethanols have been prepared and reported to be potent antimalarials.[1,9] Recently, we have been engaged in the synthesis of thiophene isosteres of phenanthrenemethanols.[10,11] We have reported that the phenanthrene isosteres, α(*N,N*-dialkylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanols, exhibit significant activity against *P. berghei* in mice[10] and that they bind to DNA *in vitro*.[12] These observations led us to expand our program to the synthesis of other isosteres of the phenanthrenemethanols. Consequently, we have prepared a series of α-(*N,N*-dialkylaminomethyl)-4-naphtho[1,2-*b*]thiophenemethanols and a series of α-(*N,N*-dialkylaminomethyl)-5-naphtho[1,2-*b*]thiophenemethanols for screening in order to compare their potency as antimalarials. This report describes the synthesis and antimalarial activity of these compounds. Generally, the amino alcohol side chains selected for attachment to the naphtho[1,2-*b*]thiophene ring system were the commonly employed 2-di-*n*-butyl- and 2-di-*n*-heptylamino-1-hydroxyethyl groups (*cf.* ref 1–4). Unsuccessful attempts to prepare α-(*N,N*-dialkylaminomethyl)-5-naphtho[2,1-*b*]thiophenemethanols are described.

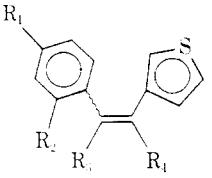
4-Naphtho[1,2-*b*]thiophenemethanols and 5-Naphtho[1,2-*b*]thiophenemethanols. The synthetic route employed for the preparation of the 4-naphtho[1,2-*b*]thiophenemethanols and the 5-naphtho[1,2-*b*]thiophenemethanols is outlined in Scheme I and is analogous to our approach to the 4-naphtho[2,1-*b*]thiophenemethanols.[10] A modified Perkin reaction[13] was used to prepare the substituted phenylthienylacrylic acids (Table I) which on 2537-Å irradiation underwent photooxidative cyclization to the polynuclear aromatic naphthothiophene ring system (Table II). Since photocyclization of the isomers of I yielded the same product II, no attempt was made to isolate and characterize both geometric isomers. The structure of naphtho[1,2-*b*]thiophene-4-carboxylic acid and naphtho[1,2-*b*]thiophene-5-carboxylic acid was verified by combustion analysis and uv absorption data and by their decarboxylation in the presence of quinoline and a copper catalyst to a compound which exhibited the properties reported in the literature for naphtho[1,2-*b*]thiophene.[14] We have previously reported the facility of cyclization, the good yields obtained from photooxidative cyclization of substituted α-(2-thienyl)-β-phenylacrylic acids, and the less satisfactory cyclization of α,β-di(2-thienyl)acrylic acids. It is interesting to note that photooxidative cyclization of α-(3-thienyl)-β-phenylacrylic acids proceeds rapidly and in good yields; however their isomers, the α-phenyl-β-(3-thienyl)acrylic acids, require relatively long irradiation times and the photooxidative cyclization yields are poor. In fact, the yield of **20** by photocyclization was exceptionally low and the preparation of candidate drugs from it was not feasible.

Scheme I



The conversion of II to its epoxide III and finally to the desired antimalarial IV was achieved *via* the conventional five-step process outlined.[15] The intermediates between II and III were only partially purified and were used as such in each subsequent step. Preparation of IV was made after careful purification of its epoxide precursor III. The syntheses of **24–35** were effected without difficulty by this route. However, crystallization and purification of α-(*N,N*-di-*n*-heptyl- and *N,N*-di-*n*-butylaminomethyl)-4-naphtho[1,2-*b*]thiophenemethanol hydrochlorides were not achieved because both were low-melting hydroscopic

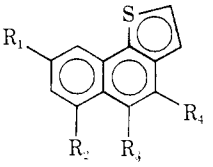
Table I. Thienylphenylacrylic Acids



Compd	R_1	R_2	R_3	R_4	Mp, °C[a]	% yield	Recrystn solvent	Formula
1	H	H	H	COOH	181–182	79	Pet. ether–Et_2O	$C_{13}H_{10}O_2S$
2	CF_3	H	H	COOH	123–126	78	Pet. ether–Et_2O	$C_{14}H_9F_3O_2S$
3	Br	H	H	COOH	219–220	64	Et_2O–EtOH	$C_{13}H_9BrO_2S$
4	Cl	Cl	H	COOH	185–186	71	Pet. ether–Et_2O	$C_{13}H_8Cl_2O_2S$
5	H	H	COOH	H	177–179	63	EtOH	$C_{13}H_{10}O_2S$
6	CF_3	H	COOH	H	237–240	75	EtOH	$C_{14}H_{11}F_3O_2S$
7	Br	H	COOH	H	217–218	31	EtOH	$C_{13}H_9BrO_2S$
8	Cl	Cl	COOH	H	195–197	32	EtOH	$C_{13}H_8Cl_2O_2S$

[a] All compounds were analyzed for C and H, and the results were within 0.3% of theory.

Table II. Naphtho[1,2-*b*]thiophene Intermediates



Compd	R_1	R_2	R_3	R_4	Mp, C°[a]	% yield	Recrystn solvent	Formula
9	H	H	H	COOH	260–261	61	C_6H_6–$(CH_3)_2CO$	$C_{13}H_8O_2S$
10	CF_3	H	H	COOH	272–273	74	C_6H_6–$(CH_3)_2CO$	$C_{14}H_7F_3O_2S$
11	Br	H	H	COOH	320.5–322	73	HOAc	$C_{13}H_7BrO_2S$
12	Cl	Cl	H	COOH	333–334	76	C_6H_6–$(CH_3)_2CO$	$C_{13}H_6Cl_2O_2S$
13	H	H	H	2-Oxacyclopropyl	Oil	60		
14	CF_3	H	H	2-Oxacyclopropyl	101–102	87	Pet. ether	$C_{15}H_9F_3OS$
15	Br	H	H	2-Oxacyclopropyl	116–117	60	Pet. ether	$C_{14}H_9BrOS$
16	Cl	Cl	H	2-Oxacyclopropyl	137.5–138.5	65	Pet. ether–Et_2O	$C_{14}H_8Cl_2OS$
17	H	H	COOH	H	250–251	20	EtOH	$C_{13}H_8O_2S$
18	CF_3	H	COOH	H	232–233	22	EtOH	$C_{14}H_7F_3O_2S$
19	Br	H	COOH	H	295–296	15	EtOH–C_6H_6	$C_{13}H_7BrO_2S$
20	Cl	Cl	COOH	H	248–250	8	HOAc	$C_{13}H_6Cl_2O_2S$
21	H	H	2-Oxacyclopropyl	H	Oil			
22	CF_3	H	2-Oxacyclopropyl	H	88–89	45	Pet. ether	$C_{15}H_9F_3OS$
23	Br	H	2-Oxacyclopropyl	H	117–118	51	Et_2O	$C_{14}H_9BrOS$

[a] All compounds, except **13** and **21**, were analyzed for C and H, and the results were within 0.3% of theory.

semisolids. In light of this result, the preparation of α-(*N,N*-di-*n*-propylaminomethyl)-4-naphtho[1,2-*b*]thiophenemethanol and α-(*N*-piperidinomethyl)-4-naphtho[1,2-*b*]thiophenemethanol hydrochlorides was attempted. Recently, the di-*n*-propylamino side chain has been used to advantage in a phenanthrenemethanol antimalarial series.[1] The piperidine side chain in a benz[*c*]acridine series led to significant activity,[16] yet in the naphtho[2,1-*b*]thiophene series it was ineffective.[10] The piperidine compound was prepared; however, the di-*n*-propyl compound was a low-melting hygroscopic material which could not be purified (Table III).

Attempts to Prepare 5-Naphtho[2,1-*b*]thiophenemethanols. In order to complete the study of the antimalarial activity of the 4- and 5-naphtho[1,2-*b*]thiophenemethanols and the 4- and 5-naphtho[2,1-*b*]thiophenemethanols we sought to prepare α-(*N,N*-dialkylaminomethyl)-5-naphtho[2,1-*b*]thiophenemethanols. As in previous approaches, the preparation of naphtho[2,1-*b*]thiophene-5-carboxylic acids was required for the preparation of these candidate drugs. During the course of our investigation of the synthesis of these types a report appeared describing the preparation of methyl naphtho[2,1-*b*]thiophene-5-carboxylate;[17] however, the carboxylic acid was unreported. Our approaches to this system were essentially the same as those reported for synthesis of the ester and analogous to that described in the previous section.

Conceivably, there are at least two relatively convenient routes to the naphtho[2,1-*b*]thiophene-5-carboxylic acids involving photocyclization of arylthienylacrylic acids (see Scheme II). One approach, involving photooxidative cyclization of α-phenyl-β-(2-thienyl)acrylic acid, is analogous to the intensively studied photoconversion of stilbene to phenanthrene[18] and is the approach we have successfully employed previously. A second approach involves photolysis of iodoarylstilbene analogs, a method reported

Scheme II

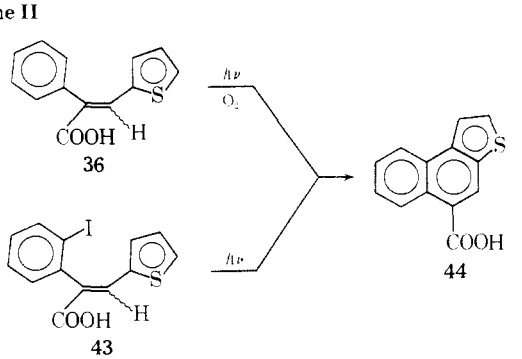
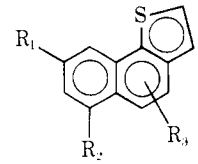


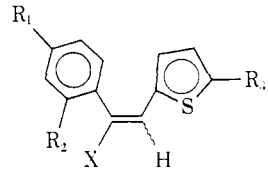
Table III. 4- and 5-α-(*N*,*N*-Dialkylaminomethyl)naphtho[1,2-*b*]thiophenemethanol Hydrochlorides[a]



Compd	R_1	R_2	R_3	Mp, °C[b]	% yield	Formula
24	H	H	4-CHOHCH$_2$N(piperidino)·HCl	251–252	31	$C_{19}H_{22}ClNOS$
25	CF_3	H	4-CHOHCH$_2$N(*n*-Bu)$_2$·HCl	146–148.5	38	$C_{23}H_{29}ClF_3NOS$
26	CF_3	H	4-CHOHCH$_2$N(*n*-Hep)$_2$·HCl	113–114	49	$C_{29}H_{41}ClF_3NOS$
27	Br	H	4-CHOHCH$_2$N(*n*-Bu)$_2$·HCl	158–159	52	$C_{22}H_{29}BrClNOS$
28	Br	H	4-CHOHCH$_2$N(*n*-Hep)$_2$·HCl	135.5–136.5	47	$C_{28}H_{41}BrClNOS$
29	Cl	Cl	4-CHOHCH$_2$N(*n*-Bu)$_2$·HCl	172–173.5	44	$C_{22}H_{28}Cl_3NOS$
30	Cl	Cl	4-CHOHCH$_2$N(*n*-Hep)$_2$·HCl	137–138	28	$C_{28}H_{40}Cl_3NOS$
31	H	H	5-CHOHCH$_2$N(Bu)$_2$·HCl	163–164	58	$C_{22}H_{30}ClNOS$
32	CF_3	H	5-CHOHCH$_2$N(Bu)$_2$·HCl	202–203	68	$C_{23}H_{29}ClF_3NOS$
33	CF_3	H	5-CHOHCH$_2$N(Hep)$_2$·HCl	134–135	22	$C_{29}H_{41}ClF_3NOS$
34	Br	H	5-CHOHCH$_2$N(Bu)$_2$·HCl	194–195	65	$C_{22}H_{29}BrClNOS$
35	Br	H	5-CHOHCH$_2$N(Hep)$_2$·HCl	135–136	42	$C_{28}H_{41}BrClNOS$

[a]All compounds were recrystallized from EtOH–Et_2O except **35**, for which petroleum ether was used. [b]All compounds were analyzed for C, H, and N, and the results were within 0.3% of theory.

Table IV. α-Phenyl-β-(2-thienyl)acrylic Acid Derivatives



Compd	R_1	R_2	R_3	X	Mp, °C	% yield	Recrystn solvent	Formula
36[a]	H	H	H	COOH	186–188	60	EtOH	
37[b]	H	H	H	CO_2CH_3	78–80	90	Pet. ether	
38[c]	CF_3	H	H	COOH	248–249	51	EtOH	$C_{14}H_9F_3O_2S$
39[c]	Br	H	H	COOH	238–240	85	EtOH	$C_{13}H_9BrO_2S$
40[c]	CF_3	H	Br	COOH	196–197	42	Et_2O–Pet. ether	$C_{14}H_8BrF_3O_2S$
41[c]	CH_3O	H	H	COOH	200–202	88	EtOH	$C_{14}H_{12}O_3S$
42[d]	H	H	H	CN	89–91	70	Hexane	
43[e]	H	I	H	COOH	198–199	40	EtOH	

[a]Lit.[7] mp 186–188°; lit. mp 194°: N. P. Buu-Hoi and M. Sy, *C. R. Acad. Sci.* **243,** 2011 (1956). [b]Lit.[7] mp 79–81°. [c]Compound was analyzed for C and H and the results were within ±0.3% of theory. [d]Lit. mp 89.5–90.5°: B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15,** 1177 (1950). [e]Lit.[7] mp 195–197°. Prepared by the method of W. S. Rapson and R. G. Shuttlewort, *J. Chem. Soc.*, 487 (1941).

by Kupchan and Wormser[19] for synthesis of phenanthrene derivatives. Both of these methods produced the desired naphtho[2,1-*b*]thiophene-5-carboxylic acid (44); however, in our hands, the yields were very low. The yields of 44 obtained by the first method were *ca.* 10%, whereas the second approach gave 44, in *ca.* 20% yields. These results are in contrast to the reported yields of 50-60% for cyclization of the ester.[17] Employing the equipment available to us photocyclization of the ester 37 gave the same range of yields as was obtained with the carboxylic acid 36.

Photocyclization of the substituted acrylates **38–41** (Table IV) was attempted with irradiation times up to eight days; however, in no case were we able to detect the formation of the expected substituted naphtho[2,1-*b*]thiophene-5-carboxylic acids. It would appear that substituents have a deleterious effect upon the rate of photocyclization.

In another approach to obtain 5-substituted naphtho[2,1-*b*]thiophenes, α-phenyl-β-(2-thienyl)acrylonitrile (42) was subjected to irradiation conditions similar to those employed to prepare 44. The cyclization of this acrylonitrile gave yields which were comparable to those of the ester 37 and carboxylic acid 36. Although no attempt to isolate 5-cyanonaphtho[2,1-*b*]thiophene was made, formation of the photocyclization product was demonstrated by hydrolysis of the crude product and subsequent esterification of the mixture of carboxylic acids with diazomethane. Nmr analysis of the mixture of methyl esters indicated that *ca.* 10% cyclization had occurred. This result is in contrast to the photocyclization of α-(thienyl)-β-phenylacrylonitrile which gave 4-cyanonaphtho[2,1-*b*]thiophene in good yield.[10]

The structure 44 was demonstrated by its chemical reactions and by combustion analysis, *m/e* 228, and characteristic uv absorptions (see Experimental Section). The copper-catalyzed decarboxylation of 44 gave a compound which was identical with the product obtained on decarboxylation of naphtho[2,1-*b*]thiophene-4-carboxylic acid[10] and whose physical properties were in accord with those reported for naphtho[2,1-*b*]thiophene.[20] Reaction of 44 with diazomethane gave a compound whose melting point agreed with that of methyl naphtho[2,1-*b*]thiophene-5-carboxylate.[17] Attention is called to these examples of stilbene analogs which fail to undergo photocyclization because of the current interest in such noncyclizable systems.[21-23] Although no calculations have been made, it is presumed that the failure of the systems described herein to undergo cyclization lies in the magnitude of the summation of the free valence numbers (ΣF^*) of the bonding atoms in the first excited state.[21-23]

Biological Activity. The results of the screening of the synthesized naphtho[1,2-*b*]thiophenemethanols (Table III)

Table V. Antimalarial Results[a]

Compd	ΔMST (days) after a single mg/kg dose						
	10	20	40	80	160	320	640
24	—	0.1	0.1	0.1	0.1	0.1	0.1
25	0.5	0.7	2.7	5.1	10.1	1C	5C
26	—	4.3	4.7	5.9	14.7	5C	5C
27	0.3	0.3	0.7	3.3	5.7	12.5	2C
28	—	0.7	3.0	3.8	5.2	—	—
29	0.5	0.9	3.7	7.9	11.5	5C	5C
30	0.3	0.3	4.3	10.1	12.1	13.9	—
31	—	0.3	0.3	0.5	0.5	5.9	10.3
32	10.6	12.6	13.3	14.4	3C	5C	5C
33	1.3	2.3	4.3	5.1	7.9	13.9	15.9
34	0.5	1.1	2.7	10.7	2C	4C	5C
35	0.3	0.7	3.1	4.1	6.5	11.3	14.1
45[b]	—	—	0.5	1.1	14.9	15.1	2C
46[c]	2.1	4.5	6.7	1C	3C	4C	4C

[a] Test data, supplied by Walter Reed Army Institute of Research, against *P. berghei* in mice. Increase in mean survival time (MST) of the controlled group is reported. A compound is active if the increase in MST exceeds 6.1 days and curative (C) if one or more of the 5 tested mice lived 60 days post-infection. [b] α-(Di-*n*-butylaminomethyl)-8-trifluoromethyl-4-naphtho[2,1-*b*]thiophenemethanol; see ref 10. [c] α-(Di-*n*-heptylaminomethyl)-6-bromo-9-phenanthrenemethanol; this compound is considered to be the "standard" for the phenanthrenemethanol series (see ref 25).

against *Plasmodium berghei* by the method of Rane[24] are listed in Table V. Also included for comparison in Table V are analogous data on a 4-naphtho[1,2-*b*]thiophenemethanol (**45**) as well as data on the standard phenanthrenemethanol **46**.[25] Representative compounds from the 4-naphtho[1,2-*b*]thiophenemethanol and the 5-naphtho[1,2-*b*]thiophenemethanol series have been shown to bind *in vitro* to calf thymus DNA.† The greatest *in vivo* activity in the 4-naphtho[1,2-*b*]thiophenemethanol series was found for **25** and **29**. The activity of these compounds is somewhat comparable with the phenanthrene standard, although at low dosage they are not as active. In the 5-naphtho[1,2-*b*]thiophenemethanol series the greatest activity is observed for **32** and **34**. Compound **32** effects cures at 160 mg/kg and is active at 10 mg/kg. This compound is also active (and toxic) at 320 mg/kg against *P. gallinaceum*. Compound **32** is the most active naphthothiophene we have reported to date, and its activity is comparable to that of the phenanthrene **46**.

It is noted that in the naphthothiophene system compounds substituted with electron-withdrawing groups are the most potent. The effect of electron-withdrawing groups as activity potentiators for arylcarbinolamines appears to be general.[26] It is interesting to note that compounds containing the di-*n*-butylamino side chain in the 4-naphtho[2,1-*b*]thiophenemethanols and 5-naphtho[1,2-*b*]thiophenemethanols series show the greatest activity, whereas in the 4-naphtho[1,2-*b*]thiophenemethanol series compounds containing the di-*n*-heptylamino side chain exhibit the greatest activity. The 4-naphtho[1,2-*b*]thiophenemethanols have activity that is slightly superior to their isomeric 4-naphtho[2,1-*b*]thiophenemethanol analogs; however, this slight enhancement in activity does not appear to be sufficient to warrant the preparation of additional analogs.

Experimental Section

Melting points reported under 300° were taken on a Thomas-Hoover melting point apparatus; the melting points of compounds melting above 300° were obtained on a Mel-Temp apparatus. All melting points are uncorrected. Ir spectra were recorded on all new compounds with a Perkin-Elmer Model 337 spectrometer and nmr spectra were recorded on selected compounds with a Varian A-60A instrument. All spectra were in accord with the structures assigned. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga.

The naphtho[1,2-*b*]thiophenes reported herein were all prepared *via* the same general reaction scheme, as typified by the following specific examples. The physical data on these compounds are included in Tables I-IV.

A New Preparation of Thiophene-3-carboxyaldehyde (*cf.* Ref 27). To 2.3 g (0.01 mol) of Na dissolved in 100 ml of EtOH was added 8.7 g (0.01 mol) of 2-nitropropane. To this solution was added dropwise 17.4 g (0.01 mol) of 3-bromomethylthiophene[28] over a 10-min period. The temperature was maintained at 25–35°. The mixture was stirred at room temperature for 5 hr, diluted with 300 ml of H_2O, and extracted with Et_2O (4 × 100 ml). The combined organic layers were washed with H_2O twice and dried ($CaSO_4$). The Et_2O was evaporated under reduced pressure to give 16 g of red-brown oil, which on distillation gave 6.2 g (56%): bp 44–54° (1 mm) (lit.[29] bp 72–78° (12 mm)).

α-(3-Thienyl)-β-(4-trifluoromethylphenyl)acrylic Acid (2). In an atmosphere of N_2 a mixture of 10.0 g (0.07 mol) of 3-thienylacetic acid[30] and 35 ml of Ac_2O was added to a mixture of 12.4 g (0.07 mol) of 4-trifluoromethylbenzaldehyde and 16.5 ml of Et_3N. After being allowed to reflux for 8 hr the mixture was added to 1.8 l. of H_2O and the pH was made basic by addition of 25 g of KOH. This mixture was allowed to boil for 2 hr (until the solution became clear). The solution was filtered to remove the residue. The filtrate was cooled and made acidic with concentrated HCl. The resulting crystals were filtered and dried; crude yield 16.9 g; mp 110–116°.

8-Trifluoromethylnaphtho[1,2-*b*]thiophene-4-carboxylic Acid (10). A solution of 16.0 g (0.05 mol) of α-(3-thienyl)-β-(4-trifluoromethylphenyl)acrylic acid and 1.0 g of I_2 in 8.5 l. of 95% EtOH was irradiated with 2537-A light for 19 hr in a Rayonet reactor while air was bubbled through the solution. Evaporation of the EtOH gave 10.1 g; mp 268–269.5°. Recrystallization from C_6H_6–$(CH_3)_2CO$ raised the melting point to 272–273°.

8-Trifluoromethylnaphtho[1,2-*b*]thiophene-5-carboxylic Acid (18). The acrylic acid **6** (4.0 g, 0.013 mol) and 0.2 g of I_2 were dissolved in 1200 ml of EtOH. The reaction mixture was subjected to irradiation with 2537-A light (Rayonet reactor) for 48 hr; air was passed through the solution during the reaction time. Evaporation of the solvent gave 1.2 g of solid. Recrystallization was from EtOH and gave 0.85 g, mp 232–233°.

8-Trifluoromethylnaphtho[1,2-*b*]thiophene-4-ethylene Oxide (14). The corresponding acid **10** (5.5 g, 0.019 mol) was refluxed with 55 ml of $SOCl_2$ for 4 hr. The excess $SOCl_2$ was removed under reduced pressure, the resulting solid was dissolved in 200 ml of CH_2Cl_2, and the solution was added to a solution of CH_2N_2 in 450 ml of Et_2O (prepared from 9.2 g (0.09 mol) of *N*-nitrosomethylurea[31]). This mixture was allowed to stir until clear (approximately 2 hr) and 30 ml of HBr (48%) was added. The resultant crude bromo ketone (6.7 g; mp 148–149°) was dissolved in 400 ml of C_6H_6 and 95 ml of 95% EtOH and allowed to react with 1.0 g of $NaBH_4$ for 15 min followed by treatment with 100 ml of 10% KOH solution. The organic solvents were removed under pressure and the residue was extracted with Et_2O. Evaporation gave 3.3 g of the crude ethylene oxide **14**, mp 99.5–101°.

8-Trifluoromethyl-α-(*N*,*N*-di-*n*-butylaminomethyl-4-naphtho[1,2-*b*]thiophenemethanol Hydrochloride (25). The ethylene oxide **14** (3.3 g, 0.011 mol) was refluxed with 5 ml of $(n\text{-}Bu)_2NH$ for 1 hr. The excess $(n\text{-}Bu)_2NH$ was removed under reduced pressure and the product was chromatographed on an Al_2O_3 column using 1 l. of C_6H_6 as the eluent. Removal of the C_6H_6 under reduced pressure left a thick, brown liquid which was dissolved in dry C_6H_6 (125 ml) and HCl was passed through the solution for 10 min. Water was removed by refluxing the solution in a Dean–Stark trap for 2 hr. Evaporation of the C_6H_6 under reduced pressure gave a brown oil. Addition of dry Et_2O produced crystals which were washed with cold Et_2O containing a small amount of absolute EtOH. The product was hygroscopic and the crude material gave a melting point of 92–108°.

Naphtho[2,1-*b*]thiophene-5-carboxylic Acid (44). Method A. A solution of 4.0 g (0.018 mol) of α-phenyl-β-(2-thienyl)acrylic acid (**36**) and 0.2 g of I_2 in 800 ml of EtOH was irradiated for 100 hr in a Rayonet reactor fitted with 2537-A lamps. Air was passed through the solution during the irradiation. The EtOH was evaporated under reduced pressure and the resulting residue was treated with hot CH_3CN. Unreacted starting material was dissolved in

† J. W. Panter, D. W. Boykin, Jr., and W. D. Wilson, unpublished results.

the CH_3CN, leaving 44 which was collected by filtration. Recrystallization from EtOH gave 0.4 g; mp 267-268°; uv λ_{max}(absolute EtOH) 41,875 (ϵ 34,700), 32,050 cm^{-1} (ϵ 13,300). *Anal.* ($C_{13}H_8O_2S$) C, H.

Method B. A solution of 3 g (0.007 mol) of **43** and 2 g of $Na_2S_2O_3$ in 400 ml of *tert*-butyl alcohol was irradiated for 41 hr in the apparatus described above. The solvent was removed under reduced pressure and the residue was dissolved in Et_2O; the Et_2O layer was washed with H_2O, dried ($CaSO_4$), and evaporated. Recrystallization from EtOH gave 0.4 g of **44**; mp 267-268°.

Photocyclization of compounds **37-42** was attempted *via* the procedure described as method A. The per cent conversion of **37** to methyl naphtho[2,1-*b*]thiophene-5-carboxylate was established by nmr analysis of the crude photoproduct in $CDCl_3$ solution. The methyl signal for the ester appeared at δ 3.97, whereas the methyl signals for the geometric isomers of **37** appeared at δ 3.86 and 3.70. Likewise, the per cent cyclization of **42**, the acrylonitrile, was established by hydrolysis of the crude photoproduct (24-hr reflux in 10% KOH in 50% EtOH solution) and subsequent esterification of the crude acid mixtures with CH_2N_2 (see below). In a set of control experiments **36**, **37**, and **42** were irradiated for 100 hr, **36** and **42** converted to the methyl ester, and all three sets analyzed by nmr. The yields by nmr were 12 ± 5%, 14 ± 5%, and 12 ± 5%.

Compounds **39** and **41** were irradiated for 100 hr, and no detectable amount of the corresponding naphtho[2,1-*b*]thiophene-5-carboxylic acid was isolated. Compound **38** was irradiated for 200 hr, and no cyclization product was detected.

Esterification of Naphtho[2,1-*b*]thiophene-5-carboxylic Acid (44). The carboxylic acid (0.15 g, 0.0007 mol) was dissolved in 100 ml of Et_2O and cooled to 0°. A CH_2N_2-Et_2O solution (made from 4.5 g (0.045 mol) of *N*-nitrosomethylurea[31] and 200 ml of Et_2O) was added and the reaction mixture was stirred for 4 hr. The excess CH_2N_2 was destroyed with acetic acid and the Et_2O was evaporated. The residue was dissolved in C_6H_6 and passed through a short alumina column and the C_6H_6 was evaporated. The solid (0.15 g) was recrystallized from hexane, mp 95-96° (lit.[17] mp 94-96°).

Decarboxylation of Naphtho[1,2-*b*]thiophene-4-carboxylic Acid (9) and Naphtho[1,2-*b*]thiophene-5-carboxylic Acid (17). A mixture of 0.4 g (0.0017 mol) of the acid **9** and 20 ml of quinoline was allowed to reflux for 5 min; then 1.0 g of copper powder was added and the mixture was refluxed for 15 min more. The mixture was cooled and filtered, and the filtrate was acidified with 10% HCl. Extraction with Et_2O, drying (K_2CO_3), and evaporation left a dark oil which was chromatographed on alumina with petroleum ether (bp 30-60°) as the eluent. The petroleum ether was removed and to the resulting clear oil was added an ethanolic solution of picric acid. The picrate which formed was recrystallized from ethanol, mp 144-145° (lit.[14] mp 145-146°). The acid **17** was decarboxylated in a similar manner and gave a picrate which melted at 144-145°. A mixture melting point determination with the two picrates showed no depression.

Decarboxylation of Naphtho[2,1-*b*]thiophene-5-carboxylic Acid (44). The carboxylic acid **44** (0.4 g, 0.0017 mol) was dissolved in 30 ml of quinoline, the solution was heated to 220-230°, 4.0 g of Cu powder was added, and the mixture was refluxed for 0.5 hr. The mixture was cooled, poured into H_2O, acidified with HCl, and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried, and evaporated under reduced pressure to yield a solid, mp 105-109°. The solid was purified by chromatography on alumina with petroleum ether (bp 30-60°) as the eluent. The yield was 0.3 g, mp 111-113° (lit.[20] mp 112-113°).

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