about 5 min and never more than 8 min. The effects on the trachea of either the isomers of 1 or isoproterenol given in increasing doses were assessed by inhibition of the rapid increase in intraluminal pressure to stimulation. Before stimulations were applied, each dose of drug was allowed to produce its maximal relaxant effect. The bathing fluid was changed immediately after each stimulation. All responses were recorded on a Devices M2 or M4 pen recorder.

Rat Passive Cutaneous Anaphylaxis Test. The PCA test was carried out by a method similar to that previously described.[25,26] Serum containing heat labile homocytotropic antibody was raised in rats to ovalbumin by a method similar to that described by Mota.[27] A 72-hr sensitization period was used and dilutions of drugs were injected sc prior to iv challenge with antigen, each dose of drug into groups of six rats; for each drug four doses giving between 0 and 100% inhibition were used and each dose was repeated at least once on separate occasions. The drugs were most active if given sc 0–10 min before iv challenge. Isoproterenol and the isomers of 1 were given just before challenge while disodium cromoglycate was given 10 min before challenge at which time it showed its highest activity.

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Naphthothiophenes. 4. Preparation of Multisubstituted 4-Naphtho[2,1-*b*]thiophenemethanols and the Effect of Side Chain Modification on Antimalarial Activity of 8-Trifluoromethyl-4-naphtho[2,1-*b*]thiophenemethanols

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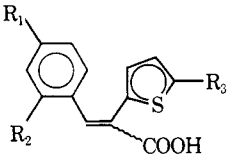
Eighteen substituted 4-naphtho[2,1-*b*]thiophenemethanols, including a series bearing substituents in the thiophene and naphthlene rings and a series in which the side chain has been modified, have been prepared and screened for antimalarial activity. Their synthesis was achieved by photocyclization of α-(2-thienyl)-β-(phenyl)acrylic acids to naphtho[2,1-*b*]thiophene-4-carboxylic acids followed by conversion of the latter into the title compounds *via* the conventional five-step route involving bromomethyl ketone intermediates. The greatest activity was observed for **21**, **23**, and **25** which gave cures against *Plasmodium berghei* at 160, 80, and 160 mg/kg dosage levels, respectively. A limited side chain modification study showed that the *N,N*-di-*n*-butylamino system is the side chain of choice among nine studied.

Previous reports from this laboratory have described the synthesis and antimalarial activity against *Plasmodium berghei* in mice and the *in vitro* DNA binding properties of several series of naphthothiophenemethanols.[1-3] Our prior work has dealt with naphthothiophenemethanols substituted only in the naphthalene ring. In view of the significant increase in activity on multisubstitution of the isosteric phenanthrenemethanol system,[4,5] particularly with substituents with positive Hammett σ constants, we have prepared a limited series of multi-substituted 4-naphtho[2,1-*b*]thiophenemethanols bearing substituents in both the naphthalene and thiophene rings.

Extensive side chain modifications in various arylcarbinolamine antimalarials have been previously reported.[6-8] It appears for *N,N*-di-*n*-alkylamino side chain types that the alkyl group which leads to optimum activity varies with the aryl system and, indeed, within a given system. The result is probably a function of transport and not due to effects on DNA binding, except in the case of drastic modification, since we have shown for the two side chain systems *N,N*-di-*n*-butylamino and *N*-piperidino in the 4-naphtho[2,1-*b*]thiophenemethanol series compounds that both bind to DNA *in vitro*[3] with comparable efficiency. Interestingly, no *in vivo* activity was found for the latter types. To obtain a general idea of the effect of side chain modifications for the naphthothiophenemethanols we report here a series of 8-trifluoromethyl-α-(alkylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanols in which limited side chain modifications have been carried out.

Chemistry. The synthetic route employed to prepare

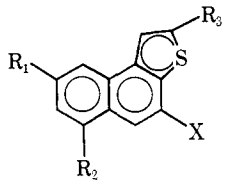
Table I. α-(2-Thienyl)-β-(phenyl)acrylic Acids



Compd no.	R_1	R_2	R_3	Mp, °C	% yield	Recrystn solvent	Formula[a]
1	Cl	Cl	Cl	113–114	51	Et_2O–pet. ether	$C_{13}H_7Cl_3O_2S$
2	CF_3	H	Cl	156–157	45	Et_2O–pet. ether	$C_{14}H_8ClF_3O_2S$
3	Br	H	Cl	218–220	55	EtOH	$C_{13}H_8O_2S$
4	Cl	Cl	CH_3	131–134	64	Et_2O–pet. ether	$C_{14}H_{10}Cl_2O_2S$
5	CF_3	H	CH_3	172–174	28	MCH[b]	$C_{15}H_{11}F_3O_2S$
6	Br	H	CH_3	102–104	34	Et_2O–pet. ether	$C_{14}H_{11}BrO_2S$

[a]All were analyzed for C and H and the results were within 0.3% of theory. [b]MCH is methylcyclohexane.

Table II. 4-Substituted Naphtho[2,1-*b*]thiophenes



Compd no.	R_1	R_2	R_3	X	Mp, °C	% yield	Recrystn solvent	Formula[a]
7	Cl	Cl	Cl	COOH	311–312	59	EtOH	$C_{13}H_5Cl_3O_2S$
8	Cl	Cl	Cl	$CHOCH_2$	195–196	62	EtOH	$C_{14}H_7Cl_3OS$
9	CF_3	H	Cl	COOH	293–294	50	CH_3CN	$C_{14}H_6ClF_3O_2S$
10	CF_3	H	Cl	$CHOCH_2$	99–100	54	Pet. ether	$C_{15}H_8ClF_3OS$
11	Br	H	Cl	COOH	326–327	65	EtOH–acetone	$C_{13}H_6BrClO_2S$
12	Br	H	Cl	$CHOCH_2$	106–108	70	Hexane	$C_{14}H_8BrClOS$
13	Cl	Cl	CH_3	COOH	343–345	60	HOAc	$C_{14}H_8Cl_2O_2S$
14	Cl	Cl	CH_3	$CHOCH_2$	174–175	46	Et_2O	$C_{15}H_{10}Cl_2OS$
15	CF_3	H	CH_3	COOH	302–303 dec	75	C_6H_6	$C_{15}H_9F_3O_2S$
16	CF_3	H	CH_3	$CHOCH_2$	78–79	75	Pet. ether	$C_{16}H_{11}F_3OS$
17	Br	H	CH_3	COOH	328–329	55	EtOH	$C_{14}H_9BrO_2S$
18[b]	H	H	H	COPy[c]	118–119	51	EtOH	$C_{18}H_{11}NOS$
19[b]	CF_3	H	H	COPy[c]	163–164	72	EtOH	$C_{19}H_{10}F_3NOS$

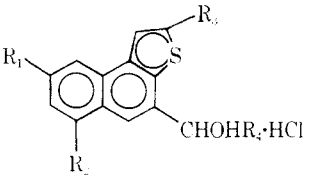
[a]All compounds except those marked with *b* were analyzed for C and H and the results were within 0.3% of theory. [b]Compound was analyzed for C, H, and N and the results were within 0.3% of theory. [c]Py = 2-pyridyl.

the naphtho[2,1-*b*]thiophene ring system has been previously described and will not be elaborated upon here.[1,2] The side chain modifications carried out on the 8-trifluoromethyl-4-naphtho[2,1-*b*]thiophene include α-(*N,N*-di-*n*-propylaminomethyl)- through α-(*N,N*-di-*n*-heptylaminomethyl)methanols. One monoalkylaminomethyl compound **31** was prepared because of the importance of this side chain in the phenanthrenemethanol system.[6] The mono and dialkyl side chains were prepared by the method we have previously employed.[1,2] One of the most commonly used side chains in the arylcarbinolamine antimalarial field is the α-piperidyl system. We have attempted to prepare α-(2-piperidyl)-4-naphtho[2,1-*b*]thiophenemethanol and 8-trifluoromethyl-α-(2-piperidyl)-4-naphtho-[2,1-*b*]thiophenemethanol by the conversion of the naphtho[2,1-*b*]thiophene-4-carboxylic acids into the corresponding 2-pyridyl ketones, by the action of 2-pyridyllithium, followed by catalytic reduction of the carbonyl group and the pyridine ring.[9] We were unsuccessful, presumably due to partial catalyst poisoning, in reducing the pyridine ring. The Experimental Section contains the details for the preparation of the compounds listed in Tables I–III.

Biological Activity. The results of screening of the 4-naphtho[2,1-*b*]thiophenemethanols against *P. berghei* in mice by the method of Rane, *et al.*,[10] are recorded in Table IV. Test data on the phenanthrene **40**,[4] which is isosteric with naphthothiophene **23**, and on two previously reported[1] naphtho[2,1-*b*]thiophenes **38** and **39** are included for comparison.

The most active compounds are **21**, **23**, and **25**. The activity of compound **23** compares reasonably well with its phenanthrenemethanol isostere **40**. Generally, the effect of additional substitution with electron-withdrawing groups in the naphthothiophene ring system containing the dibutylamino side chain is to increase activity; compare **21**, **23**, **25**, **26**, **38**, and compounds reported earlier.[1] Similar observations have been made in other carbinolamine antimalarials.[11] A generalization for the effect of the introduction of an electron donor in the analogous series cannot be made because **28** and **29** show a reduction; whereas **26** exhibits an increase in activity over the parent compounds, compare with compounds reported earlier.[1] The foregoing discussion does not deal with lipophilic differences which doubtlessly significantly influence the *in vivo* activity of these compounds. However, the generalization is in accord with the expected binding of these compounds

Table III. 4-Naphtho[2,1-*b*]thiophenemethanol Hydrochlorides[a]



Compd no.	R_1	R_2	R_3	R_4	Mp, °C[b]	% yield	Formula[c]
20	Cl	Cl	H	CH_2NHep_2	184–185	69	$C_{28}H_{40}Cl_3NOS$
21	Cl	Cl	Cl	CH_2NBu_2	266–267	43	$C_{22}H_{27}Cl_4NOS$
22	Cl	Cl	Cl	CH_2NHep_2	238–239	57	$C_{28}H_{39}Cl_4NOS$
23	CF_3	H	Cl	CH_2NBu_2	251–252	61	$C_{23}H_{28}Cl_2F_3NOS$
24	CF_3	H	Cl	CH_2NHep_2	216–217	28	$C_{29}H_{40}Cl_2F_3NOS$
25	Br	H	Cl	CH_2NBu_2	246–247	66	$C_{22}H_{28}BrCl_2NOS$
26	Cl	Cl	CH_3	CH_2NBu_2	266–267	74	$C_{23}H_{30}Cl_3NOS$
27	Cl	Cl	CH_3	CH_2NHep_2	226–227	47	$C_{29}H_{41}Cl_3NOS$
28	CF_3	H	CH_3	CH_2NBu_2	236–237	38	$C_{24}H_{31}ClF_3NOS$
29	Br	H	CH_3	CH_2NBu_2	215–216	77	$C_{23}H_{31}BrClNOS$
30	CF_3	H	H	CH_2NPr_2	232–234	49	$C_{21}H_{25}ClF_3NOS$
31	CF_3	H	H	CH_2NHBu	258–260	33	$C_{19}H_{21}ClF_3NOS$
32	CF_3	H	H	CH_2NPent_2	153–155	41	$C_{25}H_{33}ClF_3NOS$
33	CF_3	H	H	CH_2NHex_2	157–159	44	$C_{27}H_{37}ClF_3NOS$
34	CF_3	H	H	CH_2NHep_2	162–164	50	$C_{29}H_{41}ClF_3NOS$
35[d,e]	CF_3	H	H	Py[f]	105–106	82	$C_{19}H_{12}F_3NOS$
36	CF_3	H	H	Py[f]	234–235	90	$C_{19}H_{13}ClF_3NOS$
37[d,g]	H	H	H	Py[f]	110–111	85	$C_{18}H_{13}NOS$

[a] All compounds, except as noted, were recrystallized from Et_2O–EtOH. [b] All compounds except **35** and **36** melt with decomposition. [c] All compounds, except **20** and **29**, were analyzed for C, H, and N and the results were within 0.3% of theory. **20** and **29** were analyzed for C, H, and S and the results were within 0.3% of theory. [d] Free base. [e] Recrystallized from petroleum ether–Et_2O. [f] 2-Pyridyl. [g] Recrystallized from EtOH.

Table IV. Antimalarial Results[a]

Compd no.	Dosage, mg/kg					
	20	40	80	160	320	640
20	0.3	0.5	3.7	7.9	11.3	4C
21[b]	11.9	13.5	18.4	3C	5C	5C
22	0.1	0.3	0.3	0.7	2.7	10.9
23[c]	9.0	12.3	3C	5C	5C	5C
24	0.4	0.8	7.4	13.0	5C	5C
25	4.3	5.9	10.1	2C	5C	5C
26	2.5	6.9	11.7	14.1	5C	5C
27	0.6	5.0	9.5	2C	5C	5C
28	0.5	1.3	2.1	5.9	9.1	12.7
29	0.3	0.5	0.5	1.1	4.5	8.7
30	0.3	0.5	2.7	5.9	11.7	
31	0.5	2.1	3.7	5.9	9.9	12.9
32	0.7	0.7	3.3		8.7	
33	0.7	2.7	3.3	4.7	5.9	10.5
34	0.3	3.5	5.3	9.9	11.1	1C
35	0.3	0.3	0.5	0.5	0.7	0.9
36	0.1	0.1	0.1	0.3	0.3	0.5
38[d]			1.1	14.9	15.1	2C
39[e]	0.1	0.1	0.2	0.3	0.3	0.5
40[f]	3.4	1C	1C	5C	5C	5C

[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 five tested mice live 60 days postinfection. [b] At 10 mg/kg MST is 5.1 days. [c] At 10 mg/kg MST is 6.7 days. [d] 8-Trifluoromethyl-α-(di-*n*-butylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanol; see ref 1. [e] 8-Trifluoromethyl-α-(*N*-piperidino)-4-naphtho[2,1-*b*]thiophenemethanol; see ref 1. [f] 3-Chloro-6-trifluoromethyl-α-(di-*n*-butylaminomethyl)-9-phenanthrenemethanol; see ref 4.

to DNA.[3] Fewer compounds were studied in the analogous series with the diheptylamino side chain and attempts to generalize about the effect of substituents will not be made.

The results from the limited side chain modification investigation (**30**–**39**) show in the dialkylamino types that the di-*n*-butyl and di-*n*-heptyl systems (**34** and **38**) exhibit the greater activity. Compounds with the di-*n*-propyl and *n*-butyl function (**30** and **31**) do not appear to be as useful in the naphthothiophene system as they are in the phenanthrene series. We have previously reported[3] that α-pyridylcarbinols do not bind to DNA and, hence, the lack of activity of **35** and **37** is not surprising. The lack of activity of the *N*-piperidino types such as **39** which do bind to DNA has been discussed.[3] This report concludes our study of the synthesis of phenanthrenemethanol isosteres.

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 and 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.

All aldehydes and thiophene-2-acetic acid were obtained from commercial sources. 5-Methylthiophene-2-acetic acid[12] and 5-chlorothiophene-2-acetic acid[13] were prepared by literature methods.

The naphtho[2,1-*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–III.

α-(5-Chloro-2-thienyl)-β-(*p*-trifluoromethylphenyl)acrylic Acid (2). In an atmosphere of N_2, a mixture of *p*-trifluoromethylbenzaldehyde (16.6 g, 0.093 mol), 5-chlorothiophene-2-acetic acid (16.6 g, 0.093 mol), 20 ml of Ac_2O, and 10 ml of Et_3N was refluxed for 8 hr. The mixture was added to about 2 l. of H_2O and the pH was made basic with KOH. The mixture was boiled, treated with charcoal, filtered hot, and acidified with HCl. The resulting crystals were filtered and dried. The yield of crude material was 20 g, mp 150–155°. Recrystallization from Et_2O–petroleum ether (bp 30–60°) raised the melting point to 156–157°.

2-Chloro-8-trifluoromethylnaphtho[2,1-*b*]thiophene-4-car-

boxylic Acid (9). The acrylic acid **2** (2.0 g, 0.06 mol) was dissolved in 700 ml of 95% EtOH containing 0.1 g of I_2. The solution was irradiated with 2537-Å light for 24 hr in a Rayonet reactor while air was bubbled through the solution. Evaporation of the EtOH gave 1.1 g of crude **9**, mp 280–290°. Recrystallization from CH_3CN raised the melting point to 293–294°.

2-Chloro-8-trifluoromethyl[2,1-*b*]thiophene-4-ethylene Oxide (10). The carboxylic acid **9** (2.2 g, 0.066 mol) was refluxed with 20 ml of $SOCl_2$ for 4 hr. The $SOCl_2$ was removed under reduced pressure and the resulting solid was dissolved in *ca.* 100 ml of CH_2Cl_2; this solution was added to a solution of CH_2N_2 in 200 ml of Et_2O [prepared from 4.6 g (0.045 mol) of *N*-nitrosomethylurea[14]] at 0°. The solution was stirred for 4 hr while allowing the temperature to rise to room temperature and then 20 ml of HBr (48%) was added. The resultant crude bromo ketone was dissolved in 200 ml of C_6H_6 and 50 ml of 95% EtOH and allowed to react with 0.5 g of $NaBH_4$ for 15 min. To this reaction medium was added 20 ml of a 20% KOH solution and the mixture was stirred for 15 min. The organic layer was separated and evaporated under reduced pressure to yield 1.3 g of crude **10**, mp 90–95°. Recrystallization raised the melting point to 99–100°.

2-Chloro-8-trifluoromethyl-α-(*N*,*N*-di-*n*-butylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanol Hydrochloride (23). The epoxide **10** (1.8 g, 0.055 mol) was refluxed with 5 ml of $(n\text{-}Bu)_2NH$ for 1 hr. The amine was removed under vacuum and the residual oil was chromatographed on an Al_2O_3 column using C_6H_6 as the eluent. The fraction containing the carbinolamine was converted to its HCl salt by passing HCl through the solution for 10 min. Water was removed by refluxing the solution in a Dean-Stark apparatus for 4 hr. Evaporation of the C_6H_6 gave 2.0 g, mp 248–250°. Recrystallization from EtOH–Et_2O raised the melting point to 251–252°.

2-Pyridyl Naphtho[2,1-*b*]thiophen-4-yl Ketone (18). To a stirred suspension of lithium (1.6 g, 0.22 g-atom) in 50 ml of Et_2O, under N_2, 15 g (0.11 mol) of freshly distilled *n*-BuBr was added dropwise. Stirring was continued for 30 min, the solution was cooled to −70°, and 17 g (0.11 mol) of 2-bromopyridine was added dropwise. A solution of 1.25 g (0.055 mol) of naphtho[2,1-*b*]thiophene-4-carboxylic acid in 40 ml of dioxane was added and the solution was stirred at −70° for 3 hr. The cooling bath was removed and when the temperature reached −5° 200 ml of H_2O was carefully added. The mixture was extracted with Et_2O, washed (H_2O), and dried ($CaSO_4$) and the solvent was evaporated. The resultant oil was chromatographed on an Al_2O_3 column using C_6H_6 as the eluent. The yield after recrystallization from EtOH was 0.8 g, mp 118–119°.

2-Pyridylnaphtho[2,1-*b*]thiophen-4-ylcarbinol (37). Method A. A solution of 0.45 g (0.018 mol) of **18** in 150 ml of EtOH containing 2.5 ml of 0.117 *N* HCl and 0.75 g of PtO_2 was hydrogenated at 3.15 kg/cm² for 24 hr. The catalyst was removed by filtering over Celite and the EtOH solution was concentrated to *ca.* 30 ml by evaporation under reduced pressure and was poured into a stirred $NaHCO_3$ solution. The resulting aqueous suspension of the free base was extracted with Et_2O (*ca.* 300 ml). The Et_2O was evaporated and the residue was crystallized from ethanol; the yield was 0.3 g; mp 110–111°.

Method B. A solution of 0.4 g (0.016 mol) of **18** was dissolved in 150 ml of EtOH and 0.5 g of $NaBH_4$ was added and the mixture was stirred at room temperature for 30 min. The EtOH was evaporated under reduced pressure and the residue was dissolved in Et_2O, washed (H_2O), dried (Ca_2SO_4), and evaporated to yield 0.4 g, mp 110–111°.

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Antimalarials. 6. Synthesis, Antimalarial Activity, and Configurations of Racemic α-(2-Piperidyl)-4-pyridinemethanols

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Three pairs of racemic α-(2-piperidyl)-4-pyridinemethanols were prepared and tested for antimalarial activity in mice. In each of the three series, catalytic hydrogenation of the precursor pyridyl ketone afforded predominately one isomer. Inversion of this isomer to the other configurational isomer was effected *via* conversion to the oxazolium chloride followed by hydrolysis. The absolute configuration of each isomer was established by examination of the nmr spectra of the 7-aryl-8-oxa-1-azabicyclo[4.3.0]nonane derivatives obtained by treatment of the piperidylcarbinols with formaldehyde. It was thereby determined that the major isomer obtained in the hydrogenation possessed the erythro configuration, whereas the minor isomer was of the threo configuration. The six compounds were tested for antimalarial activity against *Plasmodium berghei* in mice. In each of the three series the threo isomer was significantly more active than the corresponding erythro isomer. All compounds were curative at a dosage of 160 mg/kg or less. Two of the threo isomers were curative at 20 mg/kg and one was active at 10 mg/kg.

In the preceeding papers in this series,[1-4] we reported the preparation and antimalarial activity against *Plasmodium berghei* in mice[5] of a number of α-mono- and dialkylaminomethyl-4-pyridinemethanols containing aryl,[1,2] styryl,[3] benzoyl,[3] and trifluoromethyl[4] substituents in the 2 and 6 positions of the pyridine ring. In an effort to improve further on the already significant degree of antimalarial activity demonstrated by this class of compounds, three pairs of racemic α-(2-piperidyl)-2,6-disubstituted 4-pyridinemethanols were prepared. The 2-piperidyl side