Naphthothiophenes. 1. α-(Alkylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanols as Antimalarials†

B. P. Das, J. A. Campbell, F. B. Samples, R. A. Wallace, L. K. Whisenant, R. W. Woodard, and D. W. Boykin, Jr.*

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303. *Received October 1, 1971*

A series of substituted alkylaminomethylnaphtho[2,1-*b*]thiophene-4-methanols has been synthesized and screened for antimalarial activity. The key step in the synthesis of the naphtho[2,1-*b*]thiophene ring system was accomplished by photooxidative cyclization of arylthienylethylenes. The side chains were attached by the classical 5-step synthesis involving diazo ketone intermediates. Two types of amino alcohol side chains were attached to the naphthothiophene ring system: α-(di-*n*-butylaminomethyl)- and α-(*N*-piperidinomethyl)methanols. Cures were obtained against *Plasmodium berghei* in mice with **24** and **28** bearing the former side chain. No activity was observed for compounds bearing the *N*-piperidinomethyl side chain.

The appearance of drug-resistant *Plasmodium falciparum* malaria has stimulated numerous investigations of many structural types which have previously been shown to exhibit antimalarial activity.[1] A large number of phenanthrene amino alcohols were prepared during World War II and were reported to have considerable antimalarial activity.[2,3] Recently, these early reports have been elaborated on and a number of new phenanthrene amino alcohols have been found to be very active against *P. berghei* in mice.[1,4]

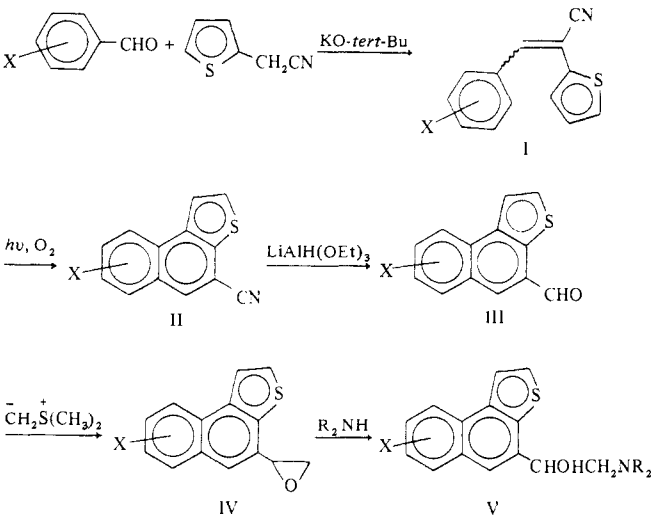
Isosteric relationships have been frequently employed to develop new series of biologically active compounds.[5] The isosteric relationship between benzene and thiophene has been widely used to develop a large number of thiophene analogs of benzene-containing drugs.[6]

This report contains the synthesis and antimalarial activity of naphtho[2,1-*b*]thiophene-4-amino alcohols which are isosteres of the phenanthrene amino alcohol antimalarials. The amino alcohol side chains selected for attachment to the naphtho[2,1-*b*]thiophene ring system were the 2-di-*n*-butylamino-1-hydroxyethyl and the 2-*N*-piperidino-1-hydroxyethyl groups. The former have been shown to be efficacious in quinoline[1] and in phenanthrene[1-4] amino alcohol series. The *N*-piperidinohydroxyethyl function appeared as a useful side chain in a benzacridine series.[7]

Chemistry. The synthesis of the naphthothiophene ring system by classical approaches[8] is laborious and time consuming; consequently, a more advantageous route was sought. The photooxidative cyclization of stilbene analogs to polynuclear aromatic systems[9] provides an attractive synthetic approach to the naphthothiophene ring system[10] (see Scheme I).

The synthesis of candidate antimalarials required a usable functional group in the 4 position of the naphtho[2,1-*b*]thiophene ring. We initially attempted to use the elegant route recently reported by Henry, *et al.*,[11] for which side-chain attachment requires the carboxaldehyde function at position 4. The synthesis outlined in Scheme I delineates the route employed to prepare the carboxaldehyde. The thienylphenylacrylonitriles I were obtained in good yields by KO-*tert*-Bu-catalyzed condensation of 2-thienylacetonitrile and arylaldehydes.[12] Irradiation of I with 2537-Å light afforded the 4-cyanonaphtho[2,1-*b*]thiophene II in good yields. In addition to the usual physical data, the structure of II (in one case, **12**) was verified by

Scheme I



hydrolysis of the nitrile to the carboxylic acid VII (*vide infra*). The reduction of the nitrile II to the carboxaldehyde was accomplished only in low yields. The conversion of III to IV also was achieved only in poor yields. Because of the poor yields attained in both these steps an alternate route to the alkylaminomethylnaphtho[2,1-*b*]thiophenemethanols V was sought.

The route outlined in Scheme II, which employs the classical method[13] for attaching the dialkylaminoethanol side chain to an aromatic nucleus, was used for the preparation of the candidate drugs. The preparation of the sub-

Scheme II

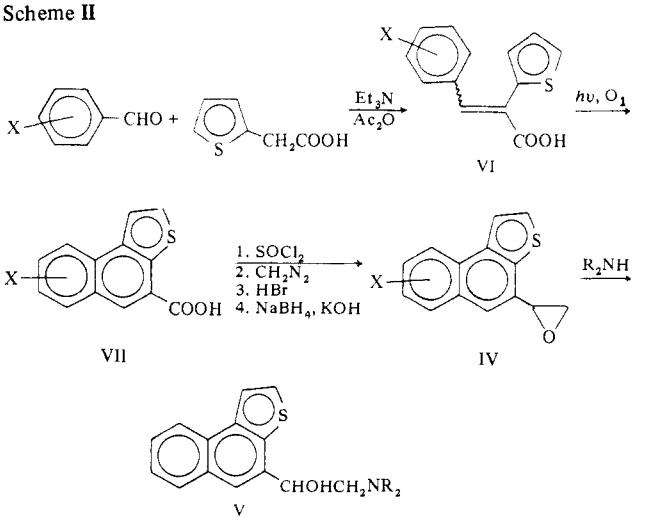


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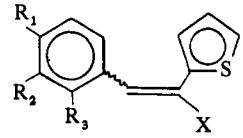
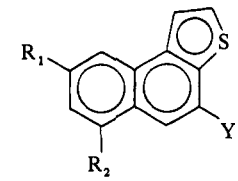
Table I. Arylthienylacrylonitriles and Arylthienylacrylic Acids

Compound	R_1	R_2	R_3	X	Mp, °C	% yield	Recrystn solvent	Formula[a]
								
1	H	H	H	CN	74–75	60	MC[b]	$C_{13}H_9NS$
2	Br	H	H	CN	90–91	75	Hexane	$C_{13}H_8BrNS$
3	CF_3	H	H	CN	110–111	42	EtOH	$C_{14}H_8F_3NS$
4	Cl	Cl	H	CN	110–111	89	EtOH	$C_{13}H_7Cl_2NS$
5	Cl	H	Cl	CN	145–146	96	EtOH	$C_{13}H_7Cl_2NS$
6	H	H	H	COOH (isomer A)	168–170	40	MeCN	$C_{13}H_{10}O_2S$
7	H	H	H	COOH (isomer B)	114–116	20	MC[b]	$C_{13}H_{10}O_2S$
8	Br	H	H	COOH	200–202	55	MC[b]	$C_{13}H_9BrO_2S$
9	CF_3	H	H	COOH	142–143	86	Et_2O–petr ether	$C_{14}H_9F_3O_2S$
10	Cl	H	Cl	COOH	128–130	50	Hexane	$C_{13}H_8Cl_2O_2S$

[a] Analyzed within ±0.4% for C, H. [b] Methylcyclohexane.

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

Compound	R_1	R_2	Y	Mp, °C	% yield	Recrystn solvent	Formula
							
11	H	H	CN	124–125	60	C_6H_6	$C_{13}H_7NS$[a]
12	CF_3	H	CN	183–184	51	Et_2O–EtOH	$C_{14}H_6F_3NS$[b]
13	Cl	Cl	CN	268–269	20	EtOH–acetone	$C_{13}H_5Cl_2NS$[b]
14	H	H	CHO	86–87	10	Hexane	$C_{13}H_8OS$[c]
15	H	H	COOH	282–283	80	C_6H_6	$C_{13}H_8O_2S$[a]
16	CF_3	H	COOH	306–307	85	EtOH	$C_{14}H_7F_3O_2S$[c]
17	Br	H	COOH	332–333	15	HOAc	$C_{13}H_7BrO_2S$[a]
18	Cl	Cl	COOH	337–339	15	HOAc	$C_{13}H_6Cl_2O_2S$[a]
19	CF_3	H		81–82	70	Petr ether	$C_{15}H_9F_3OS$[a]
20	Br	H		100–102	45	Petr ether	$C_{14}H_9BrOS$[c]
21	Cl	Cl		117–118	60	Petr ether	$C_{14}H_8Cl_2OS$[c]

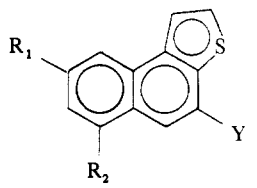
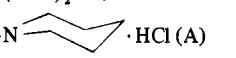
[a] Analyzed within ±0.4% for C, H. [b] Analyzed within ±0.4% for C, H, N. [c] Analyzed within ±0.4% for C, H, S.

stituted phenylthienylacrylic acids, required for photocyclization to the naphthothiophene ring system, was carried out by using a modified Perkin reaction.[14] In general, no attempt was made to isolate and characterize both the geometric isomers of VI, since the case in which two geometric isomers were isolated, irradiation of either isomer with 2537-Å light, leads to the same naphtho[2,1-*b*]thiophene-4-carboxylic acid (VII) in good yields. The structure of the cyclized material was demonstrated for **15** by characteristic uv absorptions, by combustion analysis, and by its Cu-catalyzed decarboxylation in quinoline to yield a compound which has the properties reported in the literature for naphtho[2,1-*b*]thiophene.[15] The conversion of VII to the candidate drug V went smoothly by employing the 5-step process as described by Lutz[13] (see Scheme II). Routinely, the intermediates between VII and IV were neither extensively purified nor characterized but were simply partially purified and used in the appropriate subsequent step. The epoxides IV were characterized by their combustion analysis and their nmr spectra which show typical ABC patterns for the protons of the ethylene oxide systems, with the protons usually appearing as 4-line signals at *ca.* τ 5.7, 6.8, and 7.0. That the ring opening of IV with the secondary amine gave the ethanolamine V, and not the product from attack at the hindered C, a 4-[1-*n*-dialkylamino-2-hydroxylethyl]naphtho[2,1-*b*]thiophene, was demonstrated in one case (**22**) by reaction of *n*-Bu_2NH directly with bromo ketone **31** to yield the corresponding dibutylamino ketone. Reduction of the amino ketone **32** with Pt–H_2 or $NaBH_4$ gave the same amino alcohol (**22**) obtained from the epoxide. Each amino alcohol listed in Table III was carefully examined by tlc and nmr spectroscopy and no evidence for the formation of the 2-hydroxy isomer was noted.[4b,c]

Biological Activity. Most of the intermediates in Tables I and II and all the target compounds shown in Table III were tested for antimalarial activity against *P. berghei* in mice by the method of Rane.[16] The results of these tests were provided by the Walter Reed Army Institute of Research.‡ None of the intermediates showed significant antimalarial activity. The naphthothiophene-

‡ The test results were made available by Drs. T. R. Sweeney and E. A. Steck.

Table III. α-(Alkylaminomethyl)-4-naphtho[2,1-*b*]thiophenemethanols[a]

Compound	R_1	R_2	Y	Mp, °C	% yield	Formula[b]
						
22	H	H	$CHOHCH_2N(n\text{-}Bu)_2 \cdot HCl$	152–153 dec	70	$C_{22}H_{30}ClNOS$
23	H	H	 (A)	227–229 dec	80	$C_{19}H_{22}ClNOS$
24	CF_3	H	$CHOHCH_2N(n\text{-}Bu)_2 \cdot HCl$	167–170 dec	70	$C_{23}H_{29}ClF_3NOS$
25	CF_3	H	A	285–286 dec	50	$C_{20}H_{21}ClF_3NOS$
26	Br	H	$CHOHCH_2\text{-}N(n\text{-}Bu)_2 \cdot HCl$	178–180 dec	64	$C_{22}H_{29}BrClNOS$
27	Br	H	A	260–261 dec	67	$C_{19}H_{21}BrClNOS$
28	Cl	Cl	$CHOHCH_2N(n\text{-}Bu)_2 \cdot HCl$	194–195 dec	50	$C_{22}H_{28}Cl_3NOS$
29	Cl	Cl	A	271–272 dec	71	$C_{19}H_{20}Cl_3NOS$

[a] All compounds were recrystd from Et_2O–EtOH. [b] All compds analyzed within ±0.4% for C, H, N, S.

Table IV. Antimalarial Activity

Compound	D[a]	IMST[b]	Cures[c,d]	Comment[d]
22	80	0.3	0	
	160	0.5	0	
	320	2.7	0	
	640	5.9	0	
24	80	1.1	0	
	160	14.9	0	Active
	320	15.1	0	Active
	640	17.9	2	Curative
26	80	0.5	0	
	160	4.3	0	
	320	10.5	0	Active
	640	12.7	0	Active
28	80	5.9	0	
	160	10.9	0	Active
	320	16.9	3	Curative
	640		5	Curative

[a] *D*, dose in mg/kg. [b] IMST, increase in mean survival time of treated mice over the control animals. [c] The number of mice in groups of 5 that were cured. [d] A compd is active if IMST exceeds 6.1 days and curative if one or more mice live for 60 days post-infection.

methanols with the piperidinomethyl side chain **23**, **25**, **27**, and **29** exhibited no activity against *P. berghei* in contrast to similarly substituted benzacridines.[7] None of the compounds shown in Table III showed activity against *P. gallinaceum* in chicks.

All of the naphthothiophenemethanols with dibutylaminoethanol side chains, **22**, **24**, **26**, and **28**, showed significant activity against *P. berghei* (see Table IV). The 8-trifluoromethyl-substituted compound **24** gave cures at 640 mg/kg and the 6,8-dichloro-substituted **28** at 320 mg/kg. Apparently, the only phenanthrene isostere of the compounds reported in Table III for which test data are available for comparison is 3-trifluoro-α-(di-*n*-butylaminomethyl)-9-phenanthrenemethanol (**30**),[4a] an isostere of **24**. The spectra of activity of **24** and **30** are virtually identical, both showing cures for 2 out of 5 mice at 640 mg/kg. The activity of these naphtho[2,1-*b*]thiophenemethanols demonstrates once again the value of isosteric considerations for drug design.[5,6]

For comparison of the activity of these compounds with the classic antimalarial drug it is noted that quinine sulfate shows only a 7.1-day extension of survival time at 640 mg/kg.‡ Speculation about structure–reactivity relationship of this new class of antimalarials is deferred until additional structural variations are complete.

Experimental Section

Melting points were obtianed on a Thomas-Hoover melting point apparatus for compds melting below 300°; those melting over 300° were obtained on a Mel-Temp apparatus and all are uncorrected. Elemental analyses were performed by Atlantic Microlab, Atlanta, Ga. Satisfactory uv and ir spectra were recorded for each compd listed in the Tables. Nmr spectra were obtained in $CDCl_3$ or DMSO-d_6 for each compd listed in Table III; random nmr determinations were made on all the other intermediates.

α-(2-Thienyl)-β-(substituted phenyl)acrylonitriles[12] (I). See Table I. In a typical procedure,§ to a stirred soln of 2,4-dichlorobenzaldehyde (17.5 g) and 2-thienylacetonitrile[17] (12.3 g) in 80 ml of EtOH at room temp was added KO-*tert*-Bu (1.0 g). A solid rapidly formed, the resulting slurry was stirred for 10 min, and the solid was filtered and washed with cold hexane; yield 27 g. Recrystn from EtOH gave mp 145–146°.

α-(2-Thienyl)-β-(substituted phenyl)acrylic Acids[14] (VI). See Table I. In a representative example§ a mixt of 2-thienyl acetic acid (15.0 g), 2,4-dichlorobenzaldehyde (17.5 g), 16 ml of distd $(Et)_3N$, and 32 ml of Ac_2O were refluxed for 8 hr. The mixt was poured into *ca.* 2 l. of H_2O and made alk with KOH. The alk soln was gently boiled with charcoal for *ca.* 1 hr, filtered, allowed to cool, and acidified with HCl, and the resulting solid was filtered, washed (H_2O), and recrystallized from hexane; yield 14.0 g, mp 128–130°.

4-Cyanonaphtho[2,1-*b*]thiophenes (II). See Table II. In a representative procedure a soln of 2.0 g of α-(2-thienyl)-β-phenylacrylonitrile, 2.0 g of $CuBr_2$,[18] and 0.1 g of I_2 in 500 ml of EtOH was irradiated for 24 hr in a Rayonett reactor fitted with 2537-Å sources. Throughout the reaction, air was passed through the soln. All photolyses were monitored by periodic scanning of the uv spectrum of the soln. The reaction mixt was concd under reduced pressure to *ca.* 50 ml and poured into *ca.* 800 ml of H_2O; the resulting solid was filtered and dissolved in hot C_6H_6. The hot soln was filtered to remove remaining inorganic salts. The filtrate yielded 1.1 g of 11; mp 123–124° after recrystn from C_6H_6.

Naphtho[2,1-*b*]thiophene-4-carboxylic Acids (VI). See Table II. In a typical example a soln of 2.0 g of α-(2-thienyl)-β-(*p*-trifluoromethylphenyl)acrylic acid and 0.2 g of I_2 in 700 ml of EtOH was irradiated for 24 hr as above at 2537 Å. Air was passed through the soln during the irradiation period. The EtOH was removed under reduced pressure and the residue was washed with small amounts of cold Et_2O and finally with hexane to yield 1.75 g of solid **16** which after recrystn from EtOH gave a mp of 206–207°. Similar results were obtained by irradiation for 1 hr

§ For the condensation of the extremely easily oxidizable *p*-trifluoromethylbenzaldehyde it was necessary to carry out this reaction under N_2.

with a 450-W Hanovia high pressure Hg arc lamp placed in a quartz immersion well.

Naphtho[2,1-*b*]thiophene-4-carboxaldehyde (14).[19] To a stirred slurry of 0.28 g of LAH in 50 ml of Et_2O, under N_2, was added 1.0 g of abs EtOH dropwise to the hydride reagent at 0° and stirring was contd at 0° for 0.5 hr. To this soln was added dropwise 1.5 g of 11 in Et_2O, and the mixt was stirred under N_2 for 0.5 hr. Excess hydride was decomposed with H_2O, followed by addn of 25 ml of 10% H_2SO_4. The Et_2O layer was separated, washed (H_2O), dried ($CaSO_4$), and evapd under reduced pressure. The residual oil was chromatographed on an Al_2O_3 column, the aldehyde 14 appeared in the hexane–Et_2O eluent; yield 0.2 g which on recrystn from hexane gave a mp 86–87°. The yields from several runs ranged from 0 to 20%; in one case a 50% yield was obtained, out this could not be duplicated.

Naphtho[2,1-*b*]thiophen-4-ylethylene Oxide (IV). Method A.[11,20] NaH (0.48 g) was added to 10 ml of DMSO and heated at 70° for 0.5 hr under N_2. The soln was cooled to 0° and 2.0 g of $(CH_3)_3S^+I^-$ in 10 ml of DMSO was added and stirred at 0° for 0.75 hr. A soln of 1.0 g of 14 in 20 ml of THF was added dropwise and the mixt was stirred at 0° for 1 hr. The soln was raised to 50° and maintd there for 0.5 hr and then the mixt was treated with H_2O, extd (Et_2O), washed (H_2O), and dried ($CaSO_4$), and the Et_2O was removed under reduced pressure to yield an oil. Chromatography of the crude material over Al_2O_3 gave in low-boiling petr ether eluent 0.25 g of an oil which did not crystallize. Similarly, an identical oil was obtained by method B for naphtho[2,1-*b*]thiophen-4-ylethylene oxide. The 2 materials gave identical nmr and ir spectra and gave only 1 spot on tlc upon admixture. This oxide was used without further characterization to prepare 22 and 23.

Naphtho[2,1-*b*]thiophen-4-ylethylene Oxides (IV). Method B.[13] A soln of 2.2 g of naphtho[2,1-*b*]thiophene-4-carboxylic acid in 50 ml of $SOCl_2$ was refluxed for 3 hr and the excess $SOCl_2$ was removed under reduced pressure. The crude acid chloride was triturated with anhyd low-boiling petr ether and the solid acid chloride was dried *in vaccuo* at room temp for 1 hr. The acid chloride in a 100 ml soln of CH_2Cl_2 (0°) was added slowly to an Et_2O soln of CH_2N_2 (dried over KOH) prepd in the usual manner from 4.2 g of nitrosomethylurea.[21] The acid chloride–CH_2N_2 soln was stirred at 0° for 2 hr and allowed to stand at room temp overnight. It was cooled to *ca.* 0° and 50 ml of 48% HBr was added dropwise. Addn of the acid started immediate liberation of N_2; the mixt was stirred at 0° for 0.5 hr and then at 40° for 0.5 hr. Addl Et_2O was added and the organic layer was separated, washed (H_2O), and dried ($CaSO_4$), and the Et_2O was removed. The purity of the bromo ketone, as determined by nmr and tlc, was usually sufficient to use in the next step. In a few cases, recrystn from $CHCl_3$ was required.

To a stirred soln of 2.1 g of bromo ketone in 150 ml of C_6H_6 and 50 ml of EtOH, 0.3 g of $NaBH_4$ was added. After stirring for 10 min at room temp, a soln of 7 g of KOH in 15 ml of H_2O was added and stirring was contd for 5 min. The solvent was removed under reduced pressure and the residual solid was poured into H_2O and extd with Et_2O. The Et_2O was washed (H_2O), dried ($CaSO_4$), and removed under reduced pressure to yield 1.5 g of crude material which on Al_2O_3 chromatography gave an oil which was identical with that obtained by method A.

4-[2-*n*-Dialkylamino-1-hydroxyethyl]naphtho[2,1-*b*]thiophenes (IV). See Table III. In a typical example, a soln of 1.9 g of **21** and 5 ml of dist *n*-Bu_2NH was refluxed for 1.5 hr. The excess amine was removed by vacuum distn. The residual product was chromatographed over Al_2O_3; the amino alcohol appeared in the Et_2O eluent. The amino alcohol was dissolved in dry C_6H_6 and dry HCl was passed through the soln until satd. The soln was refluxed employing a Dean–Stark trap until all the H_2O had sepd. Concn of the soln gave solid material which on recrystn from EtOH–Et_2O gave 0.75 g; mp 271–272° dec.

Preparation of 22 by Reduction of 4-(*N,N*-Dibutylaminoacetyl)naphtho[2,1-*b*]thiophene (32). The 4-bromoacetylnaphtho[2,1-*b*]thiophene (31) required for this reaction was prepared as described above and purified by recrystn from $CHCl_3$, mp 169–170°. *Anal.* ($C_{14}H_9BrOS$), C, H.

The bromo ketone 31 (1.0 g) was mixed with 3 g of *n*-Bu_2NH and warmed on a steam bath where an exothermic reaction occurred. Heating and stirring was contd for 0.5 hr. The excess amine was removed by vacuum distn, the residual oil was extd (Et_2O), washed (H_2O), and dried ($CaSO_4$), the Et_2O was concd to a small vol, and 0.15 g of yellow solid was precipitated, 4-(*N,N*-dibutylaminoacetyl)naphtho[2,1-*b*]thiophene (**32**). Crystn from Et_2O–hexane gave mp of 140–141°. *Anal.* ($C_{22}H_{27}NSO$) C, H. Reduction of **32** as described above for reduction of the bromo ketones with $NaBH_4$ or by reduction with PtO_2–H_2 at 3.15 kg/cm² gave a compd which on treatment with HCl (*vide supra*) gave ir and nmr spectra and tlc chromatograms identical with that of **22**.

Decarboxylation of Naphtho[2,1-*b*]thiophene-4-carboxylic Acid. The acid (0.5 g) was dissolved in 30 ml of quinoline heated to 220–230°, 5 g of Cu powder was added, and the soln was refluxed for 0.5 hr. The mixt was cooled, poured into H_2O, acidified with HCl, and extd (Et_2O). The Et_2O layer was washed (H_2O), dried ($CaSO_4$), and evapd to yield a solid, mp 107–110°. Purification by chromatography over Al_2O_3 (low boiling petr ether eluent) gave 0.4 g; mp 112–112.5° (lit. mp 112–113°).[15]

Hydrolysis of 8-Trifluoromethyl-4-cyanonaphtho[2,1-*b*]-thiophene. The nitrile (0.2 g) was mixed with 50 ml of 20% KOH and 50 ml of EtOH and refluxed for 6 hr. The EtOH was removed under reduced pressure and the residual material was cooled and acidified with HCl to yield a solid which was extd with Et_2O. The Et_2O soln was washed (H_2O) and dried ($CaSO_4$), and the Et_2O was removed to yield the acid (**16**); mp 305–307°; mmp with a sample of **16** obtained from photocyclization of **9** was 305–307°.

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Influence of Stereochemistry and Lipophilicity on Biological Activity of Some Ganglionic Blocking Agents

Robert A. Wiley,* Bahjat A. Faraj, Allen Jantz,†

Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044

and Milos M. Hava

Department of Pharmacology, The University of Kansas Medical Center, Kansas City, Kansas 66103. *Received September 10, 1971*

Numerous diverse compounds exhibit ganglionic blocking activity. It is possible that this might involve a nonspecific drug–receptor interaction based on drug lipophilicity. To test this proposal, the rigid analogs of hexamethonium 2(e),6(e)-bis(dimethylamino)-*cis*-decalin dimethiodide (**10**), 2(a),6(e)-bis(dimethylamino)-*cis*-decalin dimethiodide (**11**), and 2(a),6(e)-bis(dimethylamino)-*trans*-decalin dimethiodide (**12**) were synthesized. These were found to be more lipophilic than hexamethonium. Preliminary biological results on the cat nictitating membrane–superior cervical ganglion preparation indicated that they were less efficient ganglionic blocking agents than hexamethonium. However, the synthesis of 2-methyl-6-dimethylaminomethyl-2-azabicyclo[2.2.2]octane dimethiodide (**16**) provided a very active ganglionic blocker with lipophilicity comparable to that of hexamethonium.

Among ganglionic blocking agents,[1] bisquaternary ammonium salts represent a chemical group where the changes in activity which result from relatively minor alterations in molecular structure have been thoroughly investigated. Studies by Barlow and Ing[2] and Paton and Zaimis[3] indicated that among polymethylene α,ω-bis(trimethylammonium) compounds with chain lengths of C_2 to C_{12} a sharp peak of ganglionic blocking potency appeared with chain length of C_5 and C_6. The dependence of activity on chain length in the polymethylene bisoniums was interpreted by assuming that the blocking agent made simultaneous contact with 2 anionic receptor groups and that the C chain length of the most active compounds was a measure of the interreceptor distance.[4-6] The validity of the 2-point contact hypothesis has been questioned by a number of investigators.[7-9]

It is the purpose of this study to examine the possibility that the biological potency of these bisquaternary ammonium compounds, maximum in hexamethonium, is actually a nonspecific drug–receptor interaction based on drug lipophilicity rather than the previously postulated specific spatial arrangement of the drug at the ganglionic receptor. To test this proposal it was thought that if one could freeze hexamethonium into relatively rigid conformations maintaining a 6-C separation between the 2 onium heads, one could examine the contribution of the stereochemistry of the C skeleton and the orientation of the onium heads to the lipophilicity and ganglionic blocking potency of these compounds. For this purpose the decalin system was chosen in its cis (**10**, **11**) and trans (**12**) forms.

Furthermore, if the ganglionic blocking activity of bisquaternary ammonium compounds were truly a function of their lipophilicity, it should be possible to design a biologically active compound structurally different from hexamethonium but having comparable lipophilicity to it. The design of such a compound was achieved in the synthesis of 2-methyl-6-dimethylaminomethyl-2-azabicyclo[2.2.2]-octane dimethiodide (**16**).

†NSF Undergraduate Research Participant, 1970–1971.

Lipophilicity. Partition coefficients, which provide a convenient measure of lipophilicity, have been used by many investigators to correlate biological activity within drug families with lipid solubility. In the case of saturated bisquaternary ammonium compounds it was necessary first to develop a method for measuring their partition coefficients. A modified procedure of Higuchi and coworkers[10] was applied which involved the conversion of bisquaternary ammonium halides to their picrate salts. The picrate salts, apparently because they form tight ion pairs in organic solvents, were sufficiently lipophilic that their relative partitioning behavior between H_2O and $CHCl_3$ could be measured.

The measured partition coefficients and calcd π values for **1** to **16** are shown in Table I. In the case of the decalin system, it was observed that rigidity of the C chain contributed to an increase in drug lipophilicity. This effect was more pronounced in 2(e)-dimethylamino-*trans*-decalin methiodide (**14**), where the ring juncture is trans and the onium head in an equatorial position. Thus **10**, **11**, **12**, **13**, and **14** were more lipophilic than both hexamethonium and decamethonium. However, the introduction of a bicyclic system resulted in an increase in the polarity of the molecule. For example, **15**[11] was found to be less lipophilic than hexamethonium but had a π value comparable to that of the trimethylene bis(trimethylammonium) salt **2**. Similarly, **16** was less lipophilic than octamethylene bis(trimethylammonium) salt (**7**) but had a π value comparable to that of hexamethonium. The significance of this will be discussed in the biological section.

Chemistry. Catalytic reduction of 2,6-dihydroxynaphthalene (**17**) under two different conditions afforded stereospecifically the cis or trans decalin system. Hydrogenation of **17** in 1% AcOH–MeOH over 5% Rh/Al_2O_3 by a modified procedure of Meyers and coworkers[12] gave 2(e),6(a)-dihydroxy-*cis*-decalin (**18**) and 2(e),6(e)-dihydroxy-*cis*-decalin (**19**). On the other hand, hydrogenation of **17** in MeOH over Raney Ni gave 2(a),6(e)-dihydroxy-*trans*-decalin (**24**) and 2(e),6(e)-dihydroxy-*trans*-decalin (**25**,Scheme I).