Synthesis and Structure-Activity Relationship Studies of a Series of 5-Aryl-4,6-dithianonanedioic Acids and Related Compounds: A Novel Class of Leukotriene Antagonists

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A series of 5-alkynyl- and 5-aryl-4,6-dithianonanedioic acids and related compounds has been prepared for evaluation of leukotriene antagonist activity. The alkynyl compounds were prepared by thioacetal exchange from the corresponding acetylenic acetals. The aryl derivatives were synthesized from the appropriate benzaldehydes, most of which were prepared by one of three general routes: Meyers' oxazoline method, a palladium coupling procedure, and a hydroxybenzaldehyde alkylation. The analogues were examined in vitro for their ability to antagonize an LTD_4-induced contraction of isolated guinea pig tracheal smooth muscle and to compete with [^{3}H]LTD_4 for receptor sites on guinea pig lung membrane. A number of structure-activity relationships have emerged from this study. There is an optimal chain length of 10–12 atoms (or its equivalent) in the lipid tail and two methylenes in the polar region. In the aromatic series, the ortho- and meta-substituted compounds have comparable activity, whereas the para derivatives are inactive. Substitution in the aromatic ring and lipid tail is generally well tolerated, with the terminal phenyl (**6**) and acetylene (**33**) analogues having especially good activity. Conformational restriction of either the polar region or lipid tail produced compounds devoid of activity. A number of selected analogues were also evaluated in vivo as antagonists of LTD_4-induced bronchoconstriction in the guinea pig. The data establish these compounds as a novel class of leukotriene antagonists with potential utility for the treatment of asthma and other immediate hypersensitivity diseases.

Slow-reacting substance of anaphylaxis (SRS-A) has long been held to be a key mediator of immediate hypersensitivity reactions,[1] and much effort has been devoted to the identification and development of SRS-A antagonists. In particular, SRS-A's ability to cause potent bronchoconstriction, increased microvascular permeability, and altered mucous production and transport,[2] all characteristic of asthma, has given rise to the belief that an SRS-A antagonist would provide novel and effective therapy for this disease. The recent discovery of leukotrienes C_4, D_4, and E_4 as the components of SRS-A[3] has intensified research in this area, since the structures of the natural products provide for the first time a rational basis for the design of antagonists.

Our initial efforts in this area focused on the structure of LTD_4 (1). Systematic modification of this compound resulted in the discovery of 4(*R*)-hydroxy-5(*S*)-cysteinylglycyl-6(*Z*)-nonadecenoic acid (**2**, SK&F 101132), the first leukotriene analogue having antagonist activity,[4,5] albeit of limited duration. Additional studies[6] revealed that deletion of the amino group of **2** produced a compound having 10-fold greater potency, and that further deletion of the glycine moiety afforded an analogue (**3**) having still higher activity. In addition to its enhanced potency, however, **3** also possessed a small amount of contractile activity and was thus ill-suited for in vivo studies.

Struck by the near symmetry of **3** and by the possibility that the two polar chains might in fact be functionally interchangeable at the leukotriene receptor, we set out to synthesize and investigate compounds in which these chains are identical, as in **4**. From this effort emerged 5-(2-dodecylphenyl)-4,6-dithianonanedioic acid (**5**, SK&F 102081) and 5-[2-(8-phenyloctyl)phenyl]-4,6-dithianonanedioic acid (**6**, SK&F 102922),[7] prototypes of a novel class of selective leukotriene antagonists having improved potency and an increased duration of action, in addition to being completely devoid of agonist activity. We now describe the synthesis and structure-activity relationship studies of some members of this class of compounds, the alkynyl- and aryldithiaalkanedioic acids ("dithioacetals") having the structures indicated in Tables I–IV.

Chemistry. The acetylenic dithioacetals (Table I) were prepared via the corresponding acetals as shown in Scheme I. Conversion of a terminal acetylene (**7**) to its Grignard reagent, followed by treatment with trimethyl orthoformate, afforded an acetylenic dimethyl acetal (**8**). Reaction with the appropriate mercaptoalkanoic acid, using BF_3·Et_2O as catalyst, then afforded **9**.

The majority of compounds described in this paper (Tables I–IV) were derived from the corresponding aldehyde in high yield by an acid-catalyzed reaction with an appropriate mercaptan, in most cases 3-mercaptopropionic acid.

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(1) Piper, P. J. *Ann. Rep. Med. Chem.* **1980**, *15*, 69.
(2) Kreutner, W.; Siegel, M. I. *Ann. Rep. Med. Chem.* **1984**, *19*, 241.
(3) Clark, D. A.; Marfat, A. *Ann. Rep. Med. Chem.* **1982**, *17*, 291.
(4) Gleason, J. G.; Ku, T. W.; McCarthy, M. E.; Weichman, B. M.; Holden, D.; Osborn, R. R.; Zabko-Potapovich, B.; Berkowitz, B.; Wasserman, M. A. *Biochem. Biophys. Res. Commun.* **1983**, *117*, 732.
(5) Weichman, B. M.; Wasserman, M. A.; Holden, D. A.; Osborn, R. R.; Woodward, D. F.; Ku, T. W.; Gleason, J. G. *J. Pharmacol. Exp. Ther.* **1983**, *227*, 700.
(6) Perchonock, C. D.; Uzinskas, I.; Ku, T. W.; McCarthy, M. E.; Bondinell, W. E.; Volpe, B. W.; Gleason, J. G.; Weichman, B. M.; Muccitelli, R. M.; DeVan, J. F.; Tucker, S. S.; Vickery, L. M.; Wasserman, M. A. *Prostaglandins* **1985**, *29*, 75.
(7) Perchonock, C. D.; McCarthy, M. E.; Erhard, K. F.; Gleason, J. G.; Wasserman, M. A.; Muccitelli, R. M.; DeVan, J. F.; Tucker, S. S.; Vickery, L. M.; Kirchner, T.; Weichman, B. M.; Mong, S.; Crooke, S. T.; Newton, J. F. *J. Med. Chem.* **1985**, *28*, 1145.

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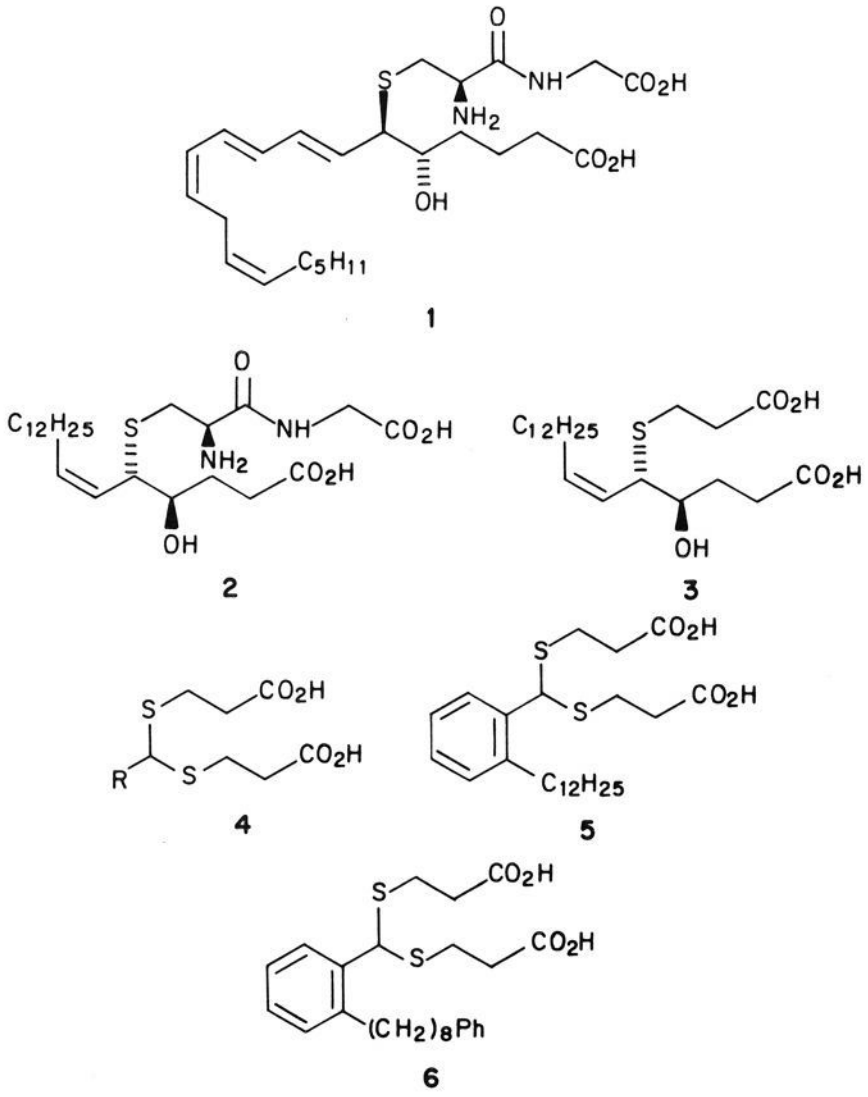
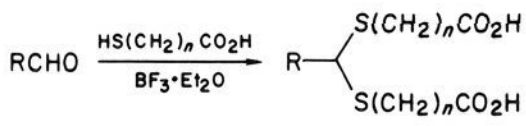




Most of the benzaldehydes, in turn, were synthesized by one of three general procedures. The first procedure (method A, Scheme II) involved the oxazoline methodology developed by Meyers et al.[8] Thus, the Grignard reagent (**10**) derived from the corresponding alkyl halide was reacted with (2-methoxyphenyl)oxazoline **11**, affording the ortho-substituted derivative **12**, generally in yields of 80–90%. Quaternization of the heterocycle with methyl iodide gave **13** (90–95%), which was sequentially reduced with $NaBH_4$ and hydrolyzed with HCl[9] to afford the ortho-substituted benzaldehyde **14** (55–65%).

Alternatively, the benzaldehydes could be prepared through a shorter and more versatile sequence involving a palladium-catalyzed coupling process[10] (method B, Scheme III). Reaction of a bromobenzaldehyde (**15**) with a terminal acetylene (**7**) afforded the coupled product **16** in yields of 80–90%. Catalytic hydrogenation then produced near-quantitative yields of **17**. In some instances, when the hydrogenation product contained small amounts of the over-reduced benzyl alcohol, it was treated with MnO_2 prior to purification.

Finally (method C, Scheme IV), the alkoxy-substituted benzaldehydes (**19**) were synthesized simply by alkylating the appropriate hydroxybenzaldehyde (**18**) with an alkyl halide (ca. 75%).

The syntheses of compounds not available through these general methods, along with the alkyl halides and acetylenes that were not commercially available, are described in the Experimental Section.

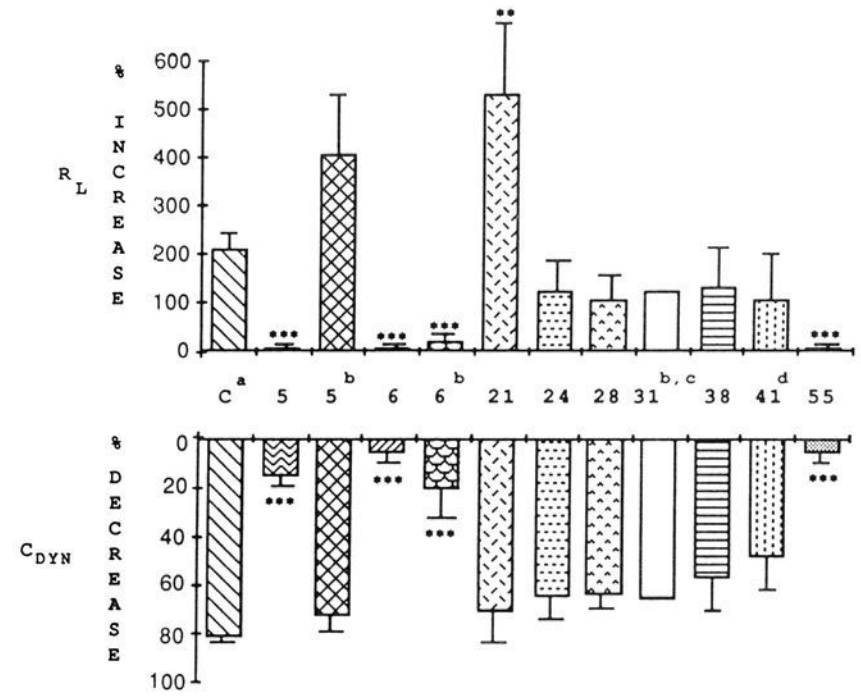
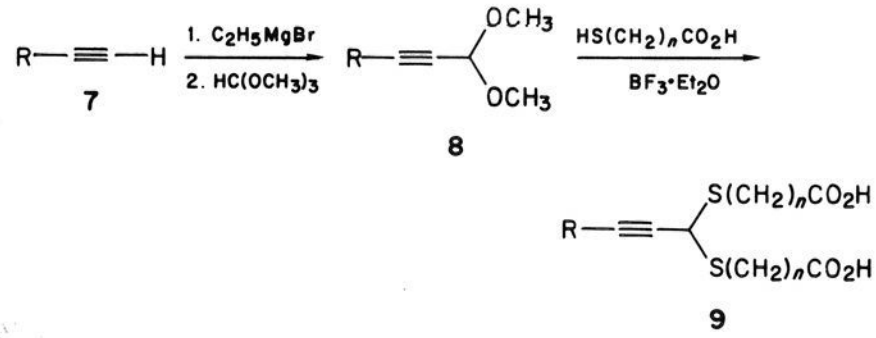
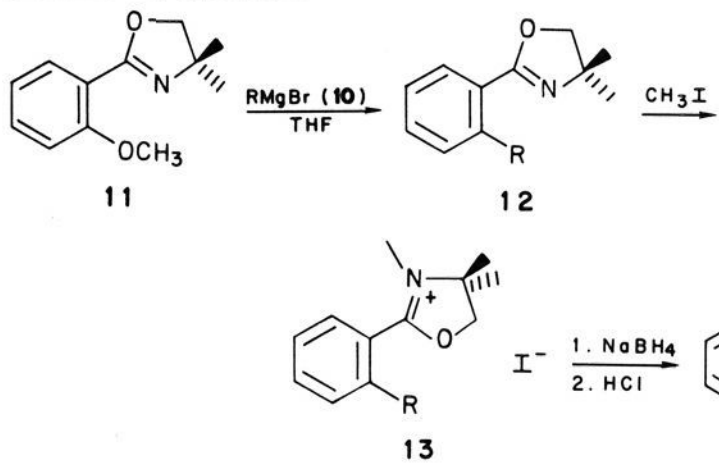


Figure 1. Comparison of the effects of selected compounds on LTD_4-induced changes in dynamic lung compliance (C_{DYN}) and airway resistance (R_L) in anesthetized guinea pigs. Except where noted, the compounds were administered at a dose of 5 mg/kg, iv, 1 min prior to challenge by LTD_4 (0.3–1.0 nmol/kg, iv). The results are expressed as the mean percentage changes ± SEM of three to four animals each, with statistical significance achieved at the indicated level (unpaired t test): (**) $p \leq 0.025$, (***) $p \leq 0.005$. [a]Control, $n = 25$; [b]5-min pretreatment time; [c]$n = 2$; [d]dose of compound = 10 mg/kg.

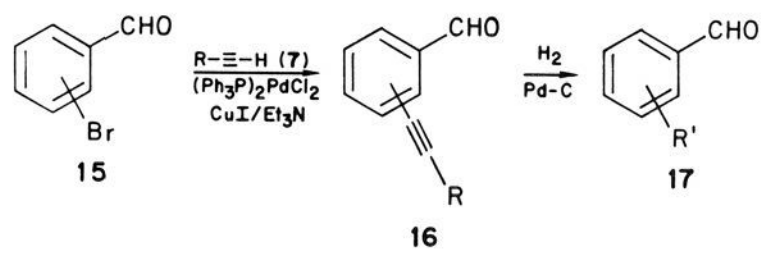
Scheme I



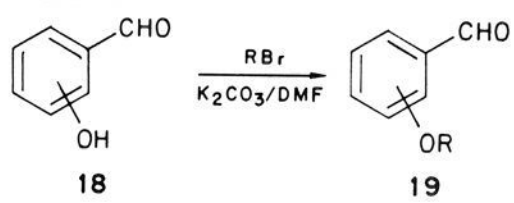
Scheme II. Method A



Scheme III. Method B



Scheme IV. Method C



(8) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372.
(9) Nordin, I. C. *J. Heterocycl. Chem.* **1966**, *3*, 531.
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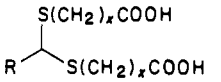
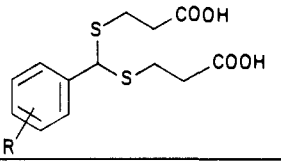
Table I. Chemical and Biological Data for Aliphatic and Acetylenic Dithiaalkanedioic Acids



compd	R	x	mp, °C	formula	anal.[a]	method[b]	-log K_B[c]
20	$C_{14}H_{29}$	2	81.5–82.5	$C_{21}H_{40}O_4S_2$	C, H, S	1	NA[d]
21	$C_{12}H_{25}$	2	76–78	$C_{19}H_{36}O_4S_2$	C, H, S	1	5.2 ± 0.1 (3)
22	$C_{12}H_{25}C{\equiv}C$	2	60–63	$C_{21}H_{36}O_4S_2$	C, H	2	5.7 ± 0.1 (5)
23	$C_{10}H_{21}C{\equiv}C$	3	56–57	$C_{21}H_{36}O_4S_2$	C, H	2	5.6 ± 0.3 (2)
24	$C_{10}H_{21}C{\equiv}C$	2	59–61	$C_{19}H_{32}O_4S_2$	C, H	2	6.1 ± 0.1 (5)
25	$C_{10}H_{21}C{\equiv}C$	1	64–65	$C_{17}H_{28}O_4S_2$	C, H	2	5.3
26	$C_8H_{17}C{\equiv}C$	2	63–65	$C_{17}H_{28}O_4S_2$	C, H	2	5.0

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] Method of preparation: 1, from saturated aldehyde; 2, from acetylenic acetal. [c] Determined at a concentration of 100 μM. Values are mean ± SEM for (n) experiments, if $n > 1$. [d] Not active at a concentration of 100 μM.

Table II. Chemical and Biological Data for Tail-Modified 5-Aryl-4,6-dithianonanedioic Acids



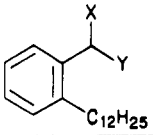
compd	R	mp, °C	formula	anal.[a]	method[b]	-log K_B[c,d]	K_i,[d] nM
27	2-($C_{14}H_{29}$)	38–40.5	$C_{27}H_{44}O_4S_2$	H, S; C[e]	A-1	NA[f]	1246 ± 89 (2)
5	2-($C_{12}H_{25}$)	35–37	$C_{25}H_{40}O_4S_2$	C, H, S	A-1, B-1	6.0 ± 0.1 (35)	445 ± 48 (11)
28	2-($C_{10}H_{21}$)	66–69.5	$C_{23}H_{36}O_4S_2$	C, H, S	A-1	6.5 ± 0.2 (5)	1180 ± 156 (2)
29	2-(C_8H_{17})	61–64	$C_{21}H_{32}O_4S_2$	C, H, S	A-1	5.2	5674 ± 2336 (2)
30	2-(C_4H_9)	71–73	$C_{17}H_{24}O_4S_2$	C, H, S	E	NA	>20000
31	2-($C_{11}H_{22}CF_3$)	42–44.5	$C_{25}H_{37}F_3O_4S_2$	C, H, S	A-2	6.2 ± 0.6 (2)	147 ± 23 (4)
32	2-(C_8H_{16}-c-C_6H_{11})	61–63.5	$C_{27}H_{42}O_4S_2$	C, H, S	B-2	5.5 ± 0.1 (2)	1958 ± 254 (4)
6	2-(C_8H_{16}Ph)	59–60	$C_{27}H_{36}O_4S_2$	C, H, S	A-2, B-2	6.7 ± 0.1 (11)	245 ± 32 (5)
33	2-($C_{10}H_{20}C{\equiv}CH$)	34–38	$C_{25}H_{36}O_4S_2$	C, H	A-2	6.8 ± 0.1 (4)	141 ± 15 (3)
34	2-($C{\equiv}CC_{10}H_{21}$)	oil	$C_{25}H_{36}O_4S_2$	H, S; C[g]	B-1	5.9 ± 0.2 (4)	2515 ± 1936 (2)
35	2-(*Z*-CH=$CHC_{10}H_{21}$)	48–52	$C_{25}H_{38}O_4S_2$	C, H	D	NA	1380 ± 283 (4)
36	2-(*E*-CH=$CHC_{10}H_{21}$)	37–40	$C_{25}H_{38}O_4S_2$	C, H	D	5.8	491 ± 76 (3)
37	2-(C_4H_8-1,4-C_6H_4-C_4H_9)	oil	$C_{27}H_{36}O_4S_2$	C, H, S	A-2	5.6	4228 ± 1113 (2)
38	2-($OC_{11}H_{23}$)	76–78.5	$C_{24}H_{38}O_5S_2$	C, H, S	C-1	6.4 ± 0.1 (13)	287 ± 27 (6)
39	2-(OC_9H_{19})	76–78.5	$C_{22}H_{34}O_5S_2$	C, H, S	C-1	5.8	4094 ± 2136 (2)
40	2-(*Z,Z*-$OCH_2CH{=}CHCH_2CH{=}CHC_5H_{11}$)	oil	$C_{24}H_{34}O_5S_2$	C, H	C[h]	6.0	1002 ± 112 (2)
41	2-(OC_6H_{12}Ph)	71–74	$C_{25}H_{32}O_5S_2$	C, H, S	C-2	5.3	11526 ± 2487 (3)
42	2-(OC_3H_6-c-C_6H_{11})	62–67	$C_{22}H_{32}O_5S_2$	C, H, S	C-1	NA	1009 ± 171 (3)
43	2-($OC_9H_{18}OH$)	80–83	$C_{22}H_{34}O_6S_2$	C, H	C-2	NA	>20000
44	2-([OC_2H_4]$_4$H)	42–44	$C_{21}H_{32}O_8S_2$	C, H	C-2	NA	>20000
45	2-($OC_5H_{10}O$-[4-acetyl-3-hydroxy-2-propylphenyl])	146–148 (dec)	$C_{29}H_{36}O_8S_2Na_2 \cdot {}^3/_4H_2O$	C, H, S	D	6.6	3149 ± 993 (4)
46	2-($SC_{11}H_{23}$)	oil	$C_{24}H_{38}O_4S_3$	C, H; S[i]	D	6.0	646 ± 112 (2)
47	3-(C_8H_{16}Ph)	56–60	$C_{27}H_{36}O_4S_2$	C, H, S	B-2	6.0	430 ± 65 (3)
48	3-($OC_{13}H_{27}$)	73–74	$C_{26}H_{42}O_5S_2$	C, H	C-1	NA	530 ± 60 (3)
49	3-($OC_{11}H_{23}$)	59–60.5	$C_{24}H_{38}O_5S_2$	C, H	C-1	6.1 ± 0.4 (2)	78 ± 16 (3)
50	3-(OC_9H_{19})	78–79	$C_{22}H_{34}O_5S_2$	C, H	C-1	6.0 ± 0.2 (3)	624 ± 45 (2)
51	3-(*Z,Z*-$OCH_2CH{=}CHCH_2CH{=}CHC_5H_{11}$)	oil	$C_{24}H_{34}O_5S_2 \cdot {}^3/_8H_2O$	C, H	C[h]	6.2 ± 0.2 (2)	187 ± 9 (2)
52	4-($C_{10}H_{21}$)	73–75.5	$C_{23}H_{36}O_4S_2$	C, H, S	B-1	NA	7565 ± 3115 (2)
53	4-($OC_{13}H_{27}$)	82.5–84	$C_{26}H_{42}O_5S_2$	C, H, S	C-1	NA	>20000
54	4-($OC_{11}H_{23}$)	76–77.5	$C_{24}H_{38}O_5S_2$	C, H, S	C-1	NA	>20000
55						6.8	2007 ± 178 (5)

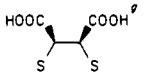
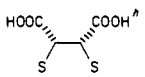
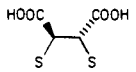
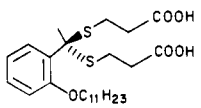
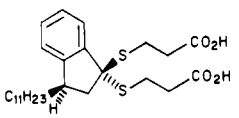
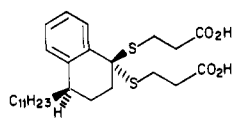
[a] Analyses of the listed elements were within 0.4% of the theoretical values unless otherwise noted. [b] Method of aldehyde synthesis: A, oxazoline method (Scheme II); B, acetylene coupling method (Scheme III); C, hydroxybenzaldehyde method (Scheme IV); D, see Experimental Section; E, commercially available; 1, halide or acetylene was commercially available; 2, halide or acetylene was prepared as described in Experimental Section. [c] Determined at concentration of 10 μM. [d] Values are mean ± SEM for (n) experiments, if $n > 1$. [e] C: calcd, 65.28; found, 65.89. [f] Not active at a concentration of 10 μM. [g] C: calcd, 64.62; found, 63.90. [h] For preparation of the halide, see ref 17. [i] S: calcd, 19.76; found, 19.06.

Pharmacology. The compounds were evaluated for their ability to antagonize a leukotriene D_4 induced contraction of guinea pig trachea in vitro, utilizing a previously described procedure.[5] Each experiment involved triplicate determinations of the leukotriene concentration response curves in the presence and absence of test compound. The results are presented in Tables I–IV as -log K_B values, where K_B is an estimate of the dissociation constant of the antagonist, assuming a competitive interaction. It was determined from the ratio (X) of the leukotriene concentrations needed to produce equieffective responses in the presence and absence of test compound according to the equation: K_B = (concentration of antagonist)/(X - 1). Binding studies were also carried out as previously described,[11] with the K_i values in the tables reflecting the ability of the compounds to compete with [^{3}H]LTD_4 for receptor sites on guinea pig lung membranes. A number

(11) Mong, S.; Wu, H.; Hogaboom, G. K.; Clark, M. A.; Crooke, S. T. *Eur. J. Pharmacol.* **1984**, *102*, 1.

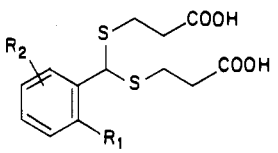
Table III. Chemical and Biological Data for Polar Region Modified Analogues



compd	X	Y	mp, °C	formula	anal.[a]	$-\log K_B$[b,c]	K_I,[c] nM
56	$SC_3H_6CO_2H$	$SC_3H_6CO_2H$	38–48	$C_{27}H_{44}O_4S_2$	H, S; C[d]	NA[e]	934
5	$SC_2H_4CO_2H$	$SC_2H_4CO_2H$	35–37	$C_{25}H_{40}O_4S_2$	C, H, S	6.0 ± 0.1 (35)	445 ± 48 (11)
57	SCH_2CO_2H	SCH_2CO_2H	80–81.5	$C_{23}H_{36}O_4S_2$	C, H, S	5.9 ± 0.1 (3)	846
58	$S(O)C_2H_4CO_2H$	$SC_2H_4CO_2H$	oil	$C_{25}H_{40}O_5S_2 \cdot {}^1/_2H_2O$	C, H, S	5.8	423 ± 67 (2)
59	$C_3H_6CO_2H$	$C_3H_6CO_2H$	oil	$C_{27}H_{44}O_4$	H; C[f]	NA	2337 ± 423 (2)
60			81–84	$C_{23}H_{34}O_4S_2$	C, H	NA	
61			86–89	$C_{23}H_{34}O_4S_2$	C, H	NA	17578 ± 3783 (2)
62			85–87	$C_{23}H_{34}O_4S_2$	C, H	NA	401 ± 89 (2)
63			oil	$C_{25}H_{40}O_5S_2$	H; C[i]	5.6	>20000
64			82–84	$C_{26}H_{40}O_4S_2$	C, H, S	NA	2092 ± 201 (3)
65			90–92	$C_{27}H_{42}O_4S_2$	C, H	NA	>20000

[a] Analyses of the listed elements were within 0.4% of the theoretical values unless otherwise noted. [b] Determined at a concentration of 10 μM. [c] Values are mean ± SEM for (*n*) experiments, if $n > 1$. [d] C: calcd, 65.28; found, 64.39. [e] Not active at a concentration of 10 μM. [f] C: calcd, 74.96; found, 74.01. [g] Acids syn to dodecylphenyl group. [h] Acids anti to dodecylphenyl group. [i] C: calcd, 61.95; found, 61.15.

Table IV. Chemical and Biological Data for Ring-Modified 5-Aryl-4,6-dithianonanedioic Acids



compd	R_1	R_2	mp, °C	formula	anal.[a]	method[b]	$-\log K_B$[c,d]	K_I,[d] nM
5	$C_{12}H_{25}$	H	35–37	$C_{25}H_{40}O_4S_2$	C, H, S	A-1, B-1	6.0 ± 0.1 (35)	445 ± 48 (11)
66	$C_{12}H_{25}$	6-CH_3	71–75	$C_{26}H_{42}O_4S_2$	C, H, S	D	NA[e]	3672 ± 779 (2)
38	$OC_{11}H_{23}$	H	76–78.5	$C_{24}H_{38}O_5S_2$	C, H, S	C-1	6.4 ± 0.1 (13)	287 ± 27 (6)
67	$OC_{11}H_{23}$	5-OH	102–105	$C_{24}H_{38}O_6S_2$	C, H	C-1	6.0	156 ± 31 (2)
68	$OC_{11}H_{23}$	5-OCH_3	55–57	$C_{25}H_{40}O_6S_2$	C, H	C-1	5.9	579 ± 45 (2)
69	$OC_{11}H_{23}$	5-Br	79–81	$C_{24}H_{37}BrO_5S_2$	C, H	C-1	6.0	624 ± 45 (2)
70	$OC_{11}H_{23}$	5-NO_2	99–101	$C_{24}H_{37}NO_7S_2$	C, H	C-1	6.1	303 ± 45 (3)
6	$C_8H_{16}Ph$	H	59–60	$C_{27}H_{36}O_4S_2$	C, H, S	A-2, B-2	6.7 ± 0.1 (11)	245 ± 32 (5)
71	$C_8H_{16}Ph$	5-CF_3	258 dec	$C_{28}H_{33}F_3O_4S_2K_2$	C, H	B-2[f]	7.0	476 ± 74 (3)

[a] Analyses of the listed elements were within 0.4% of the theoretical values. [b] See footnote *b*, Table II. [c] Determined at a concentration of 10 μM. [d] Values are mean ± SEM for (*n*) experiments, if $n > 1$. [e] Not active at a concentration of 10 μM. [f] For preparation of the bromobenzaldehyde, see Experimental Section.

of selected compounds were evaluated in vivo as antagonists of LTD_4-induced bronchoconstriction in anesthetized guinea pigs.[5] The effects of these compounds on the LTD_4-induced changes in the pulmonary parameters of airway resistance (R_L) and dynamic lung compliance (C_{DYN}) are presented in Figure 1.

Results and Discussion

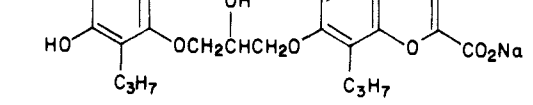
All of the compounds (Tables I–IV) were assayed for their ability to antagonize an LTD_4-induced contraction of isolated guinea pig trachea. In addition, most of them (Tables II–IV) were examined as antagonists of LTD_4 binding to guinea pig lung membrane receptors. Overall, the data from these two assays correlate rather well, despite the fact that different tissues are employed. This indicates that the compounds are acting at a receptor level in the trachea, and that this receptor resembles that found in membranes prepared from whole lung. Most of the exceptional cases may be attributed to system variability. Differences in solubility among the analogs are unlikely to be responsible for these cases, since all compounds (whether salts or free acids) were completely soluble in the assay mixtures.

A number of structure–activity relationships emerge from the data in Tables I–IV. The greater activity of the acetylenic dithioacetals (**22** and **24**, Table I) relative to their saturated analogues (**20** and **21**) reveals the preference for a π-electron system adjacent to the sulfur substituent,

a finding in agreement with the leukotriene agonist series.[12] There is an optimal chain length of 10–12 atoms (22 and 24) in the lipid tail, indicating the necessity of defined structural features, as opposed to mere lipophilicity, in this region. There is also a preferred spacing between the sulfur and carboxyl groups, with two methylenes being optimal (24 > 23, 25). These length optima in both the lipid and polar regions parallel observations made with analogues of 3.[6]

With regard to the nature of the lipid tail on the aromatic ring (Table II), there is likewise a preference for a specific chain length of 10–12 atoms or its equivalent. For example, compounds 5 and 28 both have good LTD_4 antagonist activity, whereas the analogues with just slightly longer (27) and shorter (29) tails show substantially reduced activity. There also seems to be an orientational preference of the tail with respect to the dithioacetal moiety. In general, ortho and meta substitution provide compounds of comparable activity in both biological assay systems (e.g., 38, 49), whereas the para-substituted analogues (e.g., 54) are uniformly inactive. Inexplicably, some of the meta compounds (49, 51) show unexpectedly good receptor binding activity—greater than the corresponding ortho isomers (38, 40) and higher than the tracheal contraction data would predict.

The effect of functionality at various locations on the tail was extensively investigated. With regard to the beginning of the chain, a comparison of compounds 5, 38, and 46 demonstrates that carbon, oxygen, and sulfur are all suitable lynchpins, with oxygen being slightly superior in vitro. Acetylenic analogue 34 and the *E*-olefin 36 have activity comparable to that of the saturated compound 5, but the *Z*-derivative 35 is inactive. These results may indicate the necessity of an extended conformation of the chain near the aromatic ring, which the *Z*-olefin 35 is unable to attain. Compounds with functionality in the middle of the lipid tail include 40 and 51, whose *Z,Z*-diene moieties mimic those found in the natural leukotrienes. However, these compounds offer no advantage over their saturated counterparts 38 and 49. Considerable improvements in biological activity were obtained from some of the analogues having substitution at the terminus of the aliphatic chain. In particular, the phenyl derivative 6 and the terminal acetylene 33 display potent antagonist activity, comparable to any compounds reported to date, including the standard leukotriene antagonist 55 (FPL 55712).[13] In addition, these compounds are far superior



55

to 55 in receptor binding, to an extent not expected on the basis of the guinea pig trachea results. The very low receptor affinity of 55 suggests that this compound effects its LTD_4 antagonist activity largely by mechanisms other than receptor blockade. Analogue 45, whose terminal moiety is identical with the acetophenone portion of 55, shows in vitro activity comparable to this standard but likewise displays very weak receptor affinity. Trifluoromethyl compound 31 shows activity similar to its parent compound (5), whereas the terminal cyclohexyl derivative 32 is substantially less active than the corresponding phenyl analogue (6). Compound 42 is inactive, probably due to insufficient tail length. Finally, the lack of activity of derivatives 43 and 44 indicates the necessity of a hydrophobic moiety in this region.

Results from modification of the polar groups (Table III) likewise indicate certain length and orientational preferences in this region. Relative to the standard mercaptopropionate compound (5), the mercaptobutyrate derivative 56 is inactive, whereas mercaptoacetate 57 has comparable activity. Conformational restriction of the thioacetal group of 57 (dithiolanes 60–62) produces compounds devoid of contractile antagonist activity, suggesting that close proximity of the carboxyl groups is undesirable. Significantly, replacement of sulfur with carbon produces an analogue (59) lacking activity entirely. This clearly indicates the critical role played by sulfur in these antagonists and, presumably, in the natural leukotrienes themselves. Placement of a methyl group on the thioacetal carbon atom (63) results in a significant loss of activity relative to 38, perhaps indicating either bulk intolerance at this position or undesirable restriction of rotational freedom around the aryl–thioacetal bond. The inactivity of the rigid indan (64) and tetralin (65) compounds (conformationally restricted analogues of 5) can be explained by the arguments put forth for 63 and/or an inappropriate disposition of the lipid tail relative to the aromatic ring, analogous to the situation of the *Z*-olefin 35.

The third region of modification was the aromatic ring (Table IV). Placement of a methyl group at the 6-position of 5 (66) produces a loss of activity, again indicating bulk intolerance in this region of the molecule. However, substitution of the 5-position with a variety of substituents, i.e., OH (67), OMe (68), Br (69), NO_2 (70), and CF_3 (71), gives compounds whose activity does not vary appreciably from that of the corresponding parent, thus indicating bulk and lipophilicity tolerance at this position.

A selected number of these analogues were also evaluated in vivo for their ability to antagonize an LTD_4-induced bronchoconstriction in anesthetized guinea pigs (Figure 1). A previously reported,[7] intravenous administration of 5 mg/kg of compounds 5 and 6, as well as the standard 55, provided excellent protection against the changes in airway resistance (R_L) and dynamic lung compliance (C_{DYN}) induced by a subsequent (1 min) challenge with LTD_4. The present results demonstrate that 5 is not active after a pretreatment time of 5 min, presumably as a consequence of rapid metabolic oxidation of lipid tail.[14] In contrast, compound 6, designed to have a metabolically stable ω-phenyl substituent, affords substantial protection to LTD_4-induced bronchoconstriction after the extended pretreatment time. This strategy of ω substitution was not uniformly successful, however, as evidenced by the inactivity of the CF_3 analogue 31 after the 5-min pretreatment time. In addition, analogues that are closely related to 5 (e.g., 28 and 38) do not show in vivo activity.

Discrepancies between in vitro potency and in vivo efficacy are most likely explained by differences in pharmacokinetics among the various analogues. Two major factors that are likely to affect the disposition of these compounds are metabolism and protein/tissue binding. Recent studies with 5 have documented that this antagonist is rapidly metabolized in the guinea pig, primarily by

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ω oxidation.[14] Since small structural alterations in simple fatty acids are known to markedly alter rates of in vitro ω hydroxylation,[15,16] the inactivity of **28** and **38** in vivo may be due to greater rates of metabolic degradation via ω oxidation (in comparison to **5**). Alternatively, differences among these compounds in the extent of protein/tissue binding may dramatically alter the concentration of free drug available at the receptor.

Conclusion

The data presented here establish the 5-aryl-4,6-dithianonanedioic acids as a novel class of leukotriene receptor antagonists, having substantial in vitro activity in a standard bronchoconstriction model, the guinea pig trachea. The structural prototypes, compounds **5** and **6**, have good in vivo activity as well. Studies are currently underway to extend these findings and to determine the potential utility of leukotriene antagonism in the treatment of human asthma.

Experimental Section

Melting points were determined in open capillaries on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were obtained as liquid films or Nujol mulls on a Perkin-Elmer 783 spectrophotometer and are expressed as reciprocal centimeters. NMR spectra were obtained in $CDCl_3$ solution on a Varian EM390 spectrometer and are expressed as parts per million downfield from internal Me_4Si. Although only selected spectral absorptions are reported, the complete data were consistent with the assigned structures. Elemental analyses were obtained by the Analytical, Physical, and Structural Chemistry Department of Smith Kline & French Laboratories and were within 0.4% of the theoretical values for the indicated elements unless otherwise noted. "Chromatography" refers to the "flash chromatography" method[18] and was effected with the indicated solvent systems.

In Vitro Studies. Adult male albino Hartley strain guinea pigs weighing 400–600 g were killed by a sharp blow to the head and the appropriate tissue sections immediately removed. Tracheal spiral strips of approximate dimensions 2–3-mm cross-sectional width and 3.5-cm length were prepared according to standard technique. The tissue strips were placed in jacketed 10-mL tissue baths and connected via silk suture to Grass Model FT03C force displacement transducers (Grass Instrument Co., Quincey, MA) for recording isometric tension. The tissue strips were bathed in modified Krebs' solution of the following composition (millimolar): NaCl, 118; KCl, 4.6; $MgSO_4 \cdot 7H_2O$, 1.1; $CaCl_2$, 1.8; $NaHCO_3$, 24.9; KH_2PO_4, 1.0; and glucose, 11.1. The tissue baths were maintained at 37.5 °C and continuously aerated with 95% O_2–5% CO_2. The tracheal strips were placed under a resting load of 2.0 g. After a 60-min equilibration period, the tissues were incubated for 30 additional min with test compound or vehicle (20 mM sodium carbonate). Tracheal strips were pretreated with 1 μM meclofenamic acid 15 min before addition of the test compound. A cumulative concentration–response curve was generated for each tissue by successive increases in the bath concentration of agonist. Only one concentration–response curve per tissue was generated. In order to minimize intertissue variability, the contractile responses were normalized by expressing them as a percentage of the maximum response to a reference standard (10^{-5} M carbachol). Expressing the contractions relative to the reference agonist reduced the SEM for each agonist concentration–response curve but did not affect the antagonist profile of test compound. Similar results were observed when the contraction was expressed as absolute change in grams from the resting load. When antagonism by a test compound was observed as a parallel shift of the LT concentration–response curve, the K_B was determined from the ratio (X) of the LT concentration required to elicit 50% of the maximal LT contraction in the presence of the drug to that in its absence according to the equation: K_B = concentration of antagonist/(X − 1).

In Vivo Studies. Adult male albino Hartley strain guinea pigs weighing 400–600 g were anesthetized by urethane, 1–2 g/kg ip. Cannulas were introduced into the trachea and right jugular vein by standard surgical techniques. Airflow was measured with a heated Fleisch pneumotachograph head (type no. 3.0, Instrumentation Associates, Inc., New York, NY) connected to the tracheal cannula and a Validyne differential pressure transducer (Model MP 45-1-871, range ± 2 cm water). Electrical integration of the flow signal provided a recording of tidal volume. Changes in transpulmonary pressure were measured with a second Validyne differential pressure transducer (Model MP 45-1, range ± 2 cm water) via a needle inserted into the chest cavity measuring interpleural pressure and a sidearm on the airflow pneumotachograph measuring mouth pressure. While the animals breathed spontaneously, data were collected for computing R_L and C_{DYN} from the signals of the airflow rate and the transpulmonary pressure at isovolumic points with an on-line analog computer (Buxco Electronics, Inc., Sharon, CT). The animals were stabilized for at least 20 min, during which time resting control values were continuously recorded. Test compound (5 mg/kg) or its 25 mM sodium carbonate vehicle was administered iv via a cannulated jugular vein followed 1 min later by LTD_4 (0.3–1 nmol/kg). The pulmonary responses were expressed as percentage changes in C_{DYN} and R_L from the initial control values. Statistical analysis of the data was performed by using the unpaired t test with significance achieved at the indicated level.

Binding Studies. Male albino guinea pigs (Hartley strain, 400–500 g of body weight) were sacrificed by decapitation. The lungs were removed, frozen in liquid nitrogen, and stored at −70 °C until use. The frozen tissue (5 g) was thawed, minced into small pieces, and rinsed in phosphate-buffered saline. The tissue was placed in 40 mL of homogenization buffer (0.25 M sucrose, 10 mM tris·HCl) (pH 7.5) containing the protease inhibitors soybean trypsin inhibitor (5 μg/mL), benzamidine (10^{-3} M), and phenylmethanesulfonyl fluoride (10^{-4} M) to avoid proteolysis during the processes of homogenization and centrifugation. The tissue was then homogenized with a Brinkman PT-20 polytron for a total of 1 min with 10-s pulses at a setting of 6 at 0 °C. The homogenate was then centrifuged (1000g for 10 min) to remove tissue clumps, unbroken cells, and nuclei. The supernatant was recentrifuged at 30000g for 30 min to yield pellets. This fraction was then resuspended in the incubation buffer (10 mM Pipes buffer, pH 7.5, 50 mM NaCl), homogenized in a Teflon homogenizer, and recentrifuged at 30000g for 30 min. The pellets were finally resuspended in the incubation buffer with a Teflon homogenizer at a concentration of 10–20 mg/mL of protein in the suspension. The concentration of proteins was determined with the Bradford reaction kit.

The incubation mixture contained [^{3}H]LTD_4 in the presence or absence of unlabeled LTD_4 or other competing ligands. Incubations were performed from 0 to 50 min at 37 or 22 °C. For saturation and Scatchard analyses, duplicate aliquots of 100-μL samples were taken from the incubation mixture (250 μL) and analyzed. For kinetic studies, duplicate 100-μL aliquots were taken from the incubation mixture (1 mL) and analyzed.

Free ligands were separated from membrane-bound ligands by the following filtration technique: aliquots taken from the reaction mixture were diluted in a reservoir containing 4 mL of the washing buffer (10 mM Tris·HCl, 100 mM NaCl) at 0 °C and then filtered through Whatman GF/C fiberglass filters (2.4-cm diameter) under reduced pressure. The membrane-bound ligands were retained on the filter. The filters were then washed four times with the washing buffer at 0 °C. The length of time involved in filtration and washing was ca. 10–15 s. The filters were placed in vials and dried at room temperature overnight and 10 mL of scintilation fluid (Ready-Solv HP/b) was added to each vial. The radioactivity retained on the filter was counted in a Beckman LS-7800 liquid scintillation spectrometer.

5-(1-Decynyl)-4,6-dithianonanedioic Acid (26). A solution of 6.9 g (49.9 mmol) of 1-decyne in 25 mL of Et_2O was added to the Grignard reagent prepared from 6.6 g (60.5 mmol) of EtBr and 1.45 g (59.7 mmol) of Mg in 25 mL of Et_2O, and the mixture

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was refluxed for 2 h. A solution of 7.95 g (75.0 mmol) of $CH(OMe)_3$ in 25 mL of Et_2O was added, and the Et_2O was then distilled off. The resulting paste was taken up in 50 mL of dry toluene and the mixture was refluxed for 1 h. It was then cooled, taken up in 50 mL of Et_2O, washed with 100-mL portions of saturated NH_4Cl solution and H_2O, and dried over $MgSO_4$. Removal of solvent and unreacted starting materials under high vacuum left 7.7 g (73%) of **1,1-dimethoxy-2-undecyne**. IR 1060 (C–O); NMR 2.26 (2 H, m, $C{\equiv}CCH_2$), 3.36 (6 H, s, OCH_3), 5.13 (1 H, br s, $CH(OCH_3)_2$).

To an ice-cold solution of 1.10 g (5.18 mmol) of the acetal and 1.22 g (11.50 mmol) of 3-mercaptopropionic acid in 20 mL of CH_2Cl_2 was added dropwise 0.78 g (5.50 mmol) of distilled $BF_3{\cdot}Et_2O$. After stirring for 10 min, the dark red mixture was taken up in 20 mL of Et_2O, washed with 3 × 20 mL of H_2O, and dried over $MgSO_4$. Evaporation and chromatography (30% EtOAc/hexane, 0.5% HCO_2H) afforded an oil, which solidified upon trituration with petroleum ether. A 0.80-g (44%) sample of **26** was obtained, mp 63–65 °C. IR 1700 (C=O); 2.27 (2 H, m, $C{\equiv}CCH_2$), 2.90 (8 H, m, $SCH_2CH_2CO_2H$), 4.70 (1 H, br s, SCHS). Anal. ($C_{17}H_{28}O_4S_2$) C, H.

2-Dodecylbenzaldehyde. Method A. A solution of 3.67 g (17.88 mmol) of 4,4-dimethyl-2-(2-methoxyphenyl)-2-oxazoline in 30 mL of freshly distilled THF was added to the Grignard reagent prepared from 7.51 g (30.13 mmol) of dodecyl bromide and 637 mg (26.20 mmol) of Mg in 50 mL of THF. The resulting solution was stirred under Ar at ambient temperature for 20 h. It was then cooled in ice, quenched with 100 mL of aqueous NH_4Cl, and extracted with 100 mL of Et_2O. The organic phase was washed with 50 mL of brine, dried over $MgSO_4$, and evaporated to an oil. Chromatography (5% EtOAc/hexane) afforded 5.97 g (97%) of **4,4-dimethyl-2-(2-dodecylphenyl)-2-oxazoline**. IR 1650 (C=N); NMR 1.37 (6 H, s, Me_2), 2.92 (2 H, t, J = 7, Ar CH_2), 4.06 (2 H, s, OCH_2). Anal. ($C_{23}H_{37}NO$) C, H, N.

A solution of 5.90 g (17.17 mmol) of this oxazoline in 20 mL of MeI (45.6 g, 321.3 mmol) was refluxed under Ar for 18 h. Evaporation and trituration with 25 mL of EtOAc afforded 7.44 g (89%) of **2-(2-dodecylphenyl)-3,4,4-trimethyl-2-oxazolinium iodide**, mp 78–84 °C. IR 1640 (C=N); NMR 1.87 (6 H, s, Me_2), 2.60 (2 H, t, J = 7, Ar CH_2), 3.36 (3 H, s, MeN^+), 5.23 (2 H, s, OCH_2). Anal. ($C_{24}H_{40}INO$) C, H, N.

An ice-cold solution of 3.70 g (7.62 mmol) of this methiodide in 30 mL of MeOH was treated with 298 mg (7.88 mmol) of $NaBH_4$, added in small portions over 15 min. After an additional 15 min, the reaction was quenched with 50 mL of 5% NaOH and was extracted with 2 × 50 mL of Et_2O. The extract was washed with 50 mL of brine, dried over $MgSO_4$, and evaporated to an oil. The oil was dissolved in 50 mL of acetone, treated with 10 mL of 3 N HCl, and stirred under Ar at ambient temperature for 19 h. The volatiles were evaporated, and the residue was partitioned between 50 mL of Et_2O and 50 mL of H_2O. The organic layer was washed with 50 mL of brine, dried over $MgSO_4$, and evaporated to an oil. Chromatography (2% EtOAc/hexane) afforded 1.32 g (63%) of the title compound. IR 1705 (C=O); NMR 3.02 (2 H, t, J = 8, Ar CH_2), 10.33 (1 H, s, CHO).

5-(2-Dodecylphenyl)-4,6-dithianonanedioic Acid (5). General Procedure for Dithioacetal Preparation. Distilled $BF_3{\cdot}Et_2O$ (0.60 g, 4.23 mmol) was added dropwise to an ice-cold solution of 1.16 g (4.23 mmol) of 2-dodecylbenzaldehyde and 0.99 g (9.30 mmol) of 3-mercaptopropionic acid in 25 mL of CH_2Cl_2. After 15 min, the mixture was taken up in 100 mL of Et_2O, washed with 5 × 100 mL of H_2O, and dried over $MgSO_4$. Evaporation left a colorless oil, which crystallized upon refrigeration. A 1.76-g (89%) sample of compound **5** was obtained, mp 35–37 °C. IR 1720 (C=O); NMR 5.35 (1 H, s, methine CH). Anal. ($C_{25}H_{40}O_4S_2$) C, H, S.

In the preparation of other dithioacetals, whenever analytically pure material was not obtained directly upon workup, the products were purified by recrystallization or chromatography.

8-Phenyloctyl Bromide (Precursor to 6). A solution of 8.18 g (31.19 mmol) of Ph_3P in 50 mL of CH_2Cl_2 was added dropwise to an ice-cold solution of 5.32 g (25.78 mmol) of 8-phenyloctanol and 10.39 g (31.33 mmol) of CBr_4 in 50 mL of CH_2Cl_2. After 1 h, the volatiles were evaporated, and the residue was triturated with 100 mL of ice-cold Et_2O. Filtration and evaporation left an oil, which was purified by Kugelrohr distillation. A 6.55-g (94%) sample of the title compound was obtained, bp 95–99 °C (0.03 mmHg). IR 1605 (C=C); NMR 2.60 (2 H, t, J = 7, $PhCH_2$), 3.40 (2 H, t, J = 7, CH_2Br). Anal. ($C_{14}H_{21}Br$) H; C: calcd, 62.46; found, 61.83.

1-Bromo-12,12,12-trifluorododecane (Precursor to 31). A mixture of 30.0 g (0.11 mol) of 12-bromododecanoic acid and 65 g (0.60 mol) of SF_4 was heated at 125 °C for 10 h in a high-pressure bomb. The cooled mixture was carefully vented and was then quenched with H_2O. It was extracted with 400 mL of hexane and the extract was washed with H_2O, treated with $MgSO_4$ and charcoal, and evaporated. Kugelrohr distillation afforded 25.95 g (80%) of the title compound, bp 80–88 °C (0.55 mmHg). NMR 3.41 (2 H, t, J = 7, CH_2Br). Anal. ($C_{12}H_{22}BrF_3$) H, Br; C: calcd, 47.54; found, 46.75.

12-Bromo-1-(trimethylsilyl)-1-dodecyne (Precursor to 33). To a solution of 6.55 g (66.6 mmol) of (trimethylsilyl)acetylene in 100 mL of THF at −15 °C was added 25.6 mL (66.6 mmol) of 2.6 M *n*-BuLi in hexane, and the solution was stirred for 15 min. Twenty-five milliliters of HMPA was added, and stirring was continued for another 15 min. The mixture was then cooled to −78 °C and treated with a solution of 20.0 g (66.6 mmol) of 1,10-dibromodecane in 150 mL of THF. It was allowed to come to ambient temperature over 1 h and was then taken up in 250 mL of Et_2O, washed with 3 × 250 mL of H_2O and 250 mL of brine, and dried over $MgSO_4$. Evaporation left an oil, which was purified by chromatography (hexane) to afford 8.02 g (38%) of the title compound. IR 2180 (C≡C); NMR 0.10 (9 H, s, Me_3Si), 2.17 (2 H, br t, J = 7, $C{\equiv}CCH_2$), 3.38 (2 H, t, J = 7, CH_2Br).

The bromide was converted to 2-[12-(trimethylsilyl)-11-dodecyn-1-yl]benzaldehyde by method A and the Me_3Si group was removed by the following procedure. A solution of 0.98 g (2.86 mmol) of the benzaldehyde in 10 mL of MeOH was treated with 100 mg (0.72 mmol) of K_2CO_3 and the solution was stirred at ambient temperature for 14 h. The solvent was evaporated and the residue was taken up in 25 mL of CH_2Cl_2, washed with 25-mL portions of 5% $NaHCO_3$, H_2O, and brine, and dried over $MgSO_4$. Evaporation left 0.74 g (95%) of **2-(11-dodecyn-1-yl)benzaldehyde**. IR 3320 (C≡CH), 1705 (C=O), 1610 (C=C); NMR 1.89 (1 H, t, J = 2, C≡CH), 2.15 (2 H, m, $C{\equiv}CCH_2$), 3.00 (2 H, t, J = 7, Ar CH_2), 10.30 (1 H, s, CHO).

4-(4-Butylphenyl)butyl Bromide (Precursor to 37). Anhydrous $AlCl_3$ (30.0 g, 0.23 mol) was added in portions to a mixture of 13.42 g (0.10 mol) of butylbenzene and 11.03 g (0.11 mol) of succinic anhydride in 100 mL of 1,2-dichloroethane, maintained at ca. 13 °C. After stirring for 30 min, the mixture was poured into 250 mL of ice-cold 3 N HCl and was extracted with 2 × 100 mL of EtOAc. The extract was washed with 100 mL of brine, dried over $MgSO_4$, and evaporated to a white solid. Recrystallization from EtOAc afforded 7.52 g (32%) of **4-(4-butylphenyl)-4-oxobutanoic acid**, mp 107–111.5 °C. IR 1680 (C=O). Anal. ($C_{14}H_{18}O_3$) C, H. An additional 11.88 g (51%) of crystals, mp 106–110 °C, were obtained from the mother liquors.

A mixture of 7.41 g (31.63 mmol) of the keto acid, 755 mg of 10% Pd/C, 0.5 mL of H_2SO_4, and 150 mL of EtOAc was shaken under an initial pressure of 50 psi of H_2 until uptake ceased (15 min). The catalyst was filtered and the filtrate was washed with 2 × 50 mL of brine, dried over $MgSO_4$, and evaporated to a white solid. Recrystallization from hexane afforded 6.05 g (87%) of **4-(4-butylphenyl)butanoic acid**, mp 56–58 °C. IR 1700 (br, C=O). Anal. ($C_{14}H_{20}O_2$) C, H.

A solution of 5.96 g (27.05 mmol) of the acid in 25 mL of THF was added dropwise to 30 mL (30.0 mmol) of an ice-cold solution of 1.0 M $BH_3{\cdot}THF$. The cold bath was removed and the mixture was stirred under Ar at ambient temperature for 1 h. It was then cooled in ice and quenched by the careful addition of 5 mL of MeOH. The volatiles were evaporated, and the residue was taken up in 100 mL of Et_2O, washed with 50-mL portions of 10% NaOH and brine, and dried over $MgSO_4$. Evaporation left 5.68 g of **4-(4-butylphenyl)-1-butanol** as a colorless oil. IR 3350 (br, O–H); NMR 2.5 (4 H, m, Ar CH_2), 3.64 (2 H, t, J = 7, CH_2OH).

A solution of 8.59 g (32.75 mmol) of Ph_3P in 50 mL of CH_2Cl_2 was added dropwise to an ice-cold solution of the alcohol and 10.80 g (32.56 mmol) of CBr_4 in 50 mL of CH_2Cl_2. The cold bath was removed and the mixture was stirred for an additional 45 min. The volatiles were then evaporated, and the residue was triturated with 2 × 100 mL of hexane. The combined hexane fractions were

filtered and evaporated to an oil, which was purified by chromatography (hexane) to afford 5.90 g (81% from the butanoic acid) of the title compound. NMR 2.6 (4 H, m, Ar CH_2), 3.40 (2 H, t, J = 7, CH_2Br). Anal. ($C_{14}H_{21}Br$) C, H.

2-Dodecylbenzaldehyde. Method B. A mixture of 32.7 g (177 mmol) of 2-bromobenzaldehyde, 35.3 g (213 mmol) of 1-dodecyne, 2.4 g (3.4 mmol) of $(Ph_3P)_3PdCl_2$, and 0.39 g (2.0 mmol) of CuI in 510 mL of Et_3N was refluxed under Ar for 15 min. It was then cooled and filtered, and the filtrate was evaporated. The residual oil was dissolved in 500 mL of hexane, washed with 200-mL portions of 5% HCl, 5% $NaHCO_3$, and brine, and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by chromatography (2% EtOAc/hexane) to afford 40.6 (85%) of **2-(1-dodecynyl)benzaldehyde**. IR 2240 (C≡C), 1700 (C=O), 1600 (C=C); NMR 2.47 (2 H, t, J = 6, C≡CCH_2), 10.60 (1 H, s, CHO).

A mixture of 16.4 g (60.7 mmol) of the acetylene and 0.8 g of 10% Pd/C in 160 mL of EtOAc was hydrogenated for 1.25 h at an initial pressure of 40 psi. Filtration and evaporation left 15.7 g (96%) of the title compound, identical with that prepared by method A.

1-Phenyl-1,7-octadiyne (Precursor to 6, 47, and 71). To an ice-cold solution of 10.0 g (102 mmol) of 5-hexyn-1-ol in 150 mL of pyridine was added 38.8 g (204 mmol) of p-TsCl·H_2O, and the resulting solution was maintained at 4 °C for 18 h. It was poured into 500 mL of ice-cold H_2O and extracted with 2 × 250 mL of Et_2O. The extract was washed with 2 × 200 mL of ice-cold 10% HCl, 3 × 200 mL of H_2O, and 200 mL of brine, and dried over $MgSO_4$. Evaporation left 24.5 g (95%) of **6-(tosyloxy)-1-hexyne**. IR 3300 (C≡CH), 2120 (C≡C); NMR 1.91 (1 H, t, J = 2, C≡CH), 2.13 (2 H, d of t, J = 2, 7, C≡CCH_2), 2.42 (3 H, s, Ar CH_3), 4.00 (2 H, t, J = 7, OCH_2).

To a solution of 9.91 g (97 mmol) of phenylacetylene in 200 mL of THF at −10 °C was added 37.3 mL of 2.6 M n-BuLi in hexane, and the solution was stirred for 10 min. Twenty-one milliliters of HMPA was added, and stirring was continued for another 10 min. A solution of 23.8 g (97 mmol) of the tosylate in 100 mL of THF was added, and the mixture was stirred at ambient temperature for 17 h. It was then diluted with 300 mL of Et_2O, washed with 250 mL of H_2O and 3 × 250 mL of brine, and dried over $MgSO_4$. Evaporation and purification by chromatography (hexane, then 1% EtOAc/hexane) afforded 13.0 g (73%) of the title compound. IR 3305 (C≡CH), 2240 (disubstituted C≡C), 2120 (terminal C≡C); NMR 1.94 (1 H, t, J = 2, C≡CH), 2.0–2.5 (4 H, m, C≡CCH_2). Anal. ($C_{14}H_{14}$) C, H.

1-Cyclohexyl-7-octyne (Precursor to 32). To an ice-cold solution of 4.07 g (49.6 mmol) of 1-hexyne in 50 mL of freshly distilled THF was added 22 mL (49.5 mmol) of a 2.25 M solution of n-BuLi in hexane. After 10 min, 10.0 mL (10.3 g, 57.5 mmol) of dry HMPA was added, and the deep red solution was stirred for an additional 10 min. A solution of 9.81 g (51.3 mmol) of 2-cyclohexylethyl bromide in 10 mL of THF was added, and the mixture was stirred under Ar at ambient temperature for 18 h. It was taken up in 100 mL of Et_2O, washed with 3 × 100 mL of H_2O and 1 × 100 mL of brine, and dried over $MgSO_4$. Evaporation left a yellow oil, which was purified by chromatography (hexane) to afford 8.92 g (94%) of **1-cyclohexyl-3-octyne**. NMR 2.15 (4 H, m, C≡CCH_2). Anal. ($C_{14}H_{24}$) H; C: calcd, 87.42; found, 85.92.

In flame-dried equipment under Ar, 6.0 mL of a 24.6% suspension of KH in mineral oil (1.47 g of KH, 36.8 mmol) was washed with 5 × 10 mL of dry hexane. The residual hexane was removed in vacuo, and 30 mL of freshly distilled 1,3-diaminopropane was added. The mixture was then mechanically stirred for 5 h to generate the KAPA reagent.[19] Four grams (20.8 mmol) of the internal acetylene was added and the mixture was stirred at ambient temperature overnight. It was then cooled in ice and a few drops of 2-propanol were added, followed by 50 mL of H_2O. The mixture was extracted with 2 × 50 mL of hexane, and the extract was washed with 50-mL portions of 3 N HCl and brine and dried over $MgSO_4$. Evaporation left a yellow oil, which was purified by chromatography (hexane) to afford 2.93 g (73%) of the title compound. IR 3315 (C≡CH), 2120 (terminal C≡C); NMR 1.90 (1 H, t, J = 2, C≡CH), 2.15 (2 H, m, C≡CH_2). Anal. ($C_{14}H_{24}$) H; C: calcd, 87.42; found, 86.79.

2-(Nonyloxy)benzaldehyde. Method C. A mixture of 1.23 g (10.07 mmol) of 2-hydroxybenzaldehyde, 2.11 g (10.19 mmol) of 1-bromononane, and 1.61 g (11.65 mmol) of K_2CO_3 in 10 mL of DMF was heated at 100 °C for 1 h. It was then cooled to ambient temperature, taken up in 50 mL of hexane, and washed with 50-mL portions of 5% NaOH and brine. Treatment with $MgSO_4$ and charcoal, followed by evaporation, left a colorless oil, which was purified by chromatography (5% EtOAc/hexane) to afford 1.92 g (77%) of the title compound. IR 1700 (C=O), 1600 (C=C); NMR 4.10 (2 H, t, J = 7, OCH_2), 10.60 (1 H, s, CHO). Anal. ($C_{16}H_{24}O_2$) C, H.

6-Phenylhexyl Bromide (Precursor to 41). This compound was prepared by the method used for the synthesis of 8-phenyloctyl bromide (vide supra). The yield was 77%. IR 1600 (C=C); NMR 2.60 (2 H, t, J = 8, PhCH_2), 3.37 (2 H, t, J = 7, CH_2Br).

9-Bromo-1-nonanol (Precursor to 43). A solution of 1.66 g (6.0 mmol) of 9-bromononanoic acid in 20 mL of THF was treated with 12 mL (12.0 mmol) of 1.0 M BH_3·THF, and the mixture was refluxed for 2 h. The cooled solution was treated with MeOH and then evaporated. The residue was redissolved in CH_2Cl_2, dried over $MgSO_4$, and evaporated. Chromatography (hexane, then EtOAc) afforded 1.2 g (90%) of the title compound. IR 3340 (br, O–H).

1-Bromo-3,6,9-trioxoundecane (Precursor to 44). A solution of 1.36 g (7.64 mmol) of triethylene glycol monoethyl ether and 3.32 g (10.0 mmol) of CBr_4 in 25 mL of CH_2Cl_2 was treated with 2.38 g (9.10 mmol) of Ph_3P, and the mixture was stirred at ambient temperature for 16 h. It was then concentrated in vacuo and triturated with hexane. The hexane extract was evaporated to an oil, which was purified by chromatography (20% EtOAc/hexane). A 1.0-gram sample (54%) of the title compound was obtained. IR 1110 (C–O).

2-[(*Z*)-1-Dodecenyl]benzaldehyde (Precursor to 35). A mixture of 450 mg of Pd/$BaSO_4$ and 0.9 mL of quinoline in 100 mL of hexane was hydrogenated for 30 min at 40 psi. Then 1.0 g (3.7 mmol) of 2-(1-dodecynyl)benzaldehyde (vide supra) was added and hydrogenation was continued, being monitored by capillary GC. After 6 h, a prereduced mixture of another 700 mg of catalyst and 1.4 mL of quinoline in 20 mL of hexane was added. Five hours later, the catalyst was filtered, and the filtrate was washed with 2 × 100 mL of 10% HCl, 2 × 100 mL of H_2O, and 100 mL of brine. It was then dried over $MgSO_4$ and evaporated, and the crude product was purified by chromatography (1% EtOAc/hexane) to afford 0.83 g (83%) of the title compound. Capillary GC analysis indicated a purity of 93%, with 1.5% of 2-dodecylbenzaldehyde and 5.5% of the starting acetylene being present. IR 1700 (C=O), 1600 (C=C); NMR 5.90 (1 H, d of t, J = 12, 7, Ar CH=C*H*), 6.79 (1 H, d, J = 12, Ar C*H*=CH), 10.28 (1 H, s, CHO).

2-[(*E*)-1-Dodecenyl]benzaldehyde (Precursor to 36). To a suspension of 0.84 g (22.2 mmol) of $LiAlH_4$ in 30 mL of THF under Ar was added 3.0 g (11.1 mmol) of 2-(1-dodecynyl)benzaldehyde in 10 mL of THF, and the mixture was refluxed for 15 h. It was then cooled in ice and quenched by the careful addition of H_2O. It was taken up in 100 mL of Et_2O and washed with 100 mL of 3 N HCl. The aqueous layer was back-extracted with 100 mL of Et_2O, and the combined organic fractions were washed with 3 × 100 mL of H_2O and 100 mL of brine. Drying over $MgSO_4$ and evaporation left 3 g of solid. NMR and capillary GC analysis indicated a mixture of *E* and *Z* olefins in the ratio of 70:30. To obtain the desired *E* isomer, the solid was recrystallized three times from CH_3CN, affording 0.22 g of **2-[(*E*)-1-dodecenyl]benzyl alcohol**. Capillary GC indicated an isomeric purity of 95%. IR 3260 (br, OH); NMR 4.68 (2 H, s, Ar CH_2O), 6.10 (1 H, d of t, J = 15, 7, Ar CH=C*H*), 6.64 (1 H, d, J = 15, Ar C*H*=CH).

A mixture of 0.22 g (0.8 mmol) of the benzyl alcohol and 1.1 g (12.6 mmol) of MnO_2 in 10 mL of EtOAc was stirred for 15 h at ambient temperature. Filtration and evaporation left 0.21 g (96%) of the title compound. IR 1700 (C=O), 1600 (C=C); NMR 6.11 (1 H, d of t, J = 15, 7, Ar CH=C*H*), 7.16 (1 H, d, J = 15, Ar C*H*=CH), 10.33 (1 H, s, CHO).

2-[[5-(4-Acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]benzaldehyde (Precursor to 45). A solution of 10.0 g (82.0 mmol) of 2-hydroxybenzaldehyde in 50 mL of acetone was added

(19) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891.

dropwise to a refluxing mixture of 20.74 g (90.2 mmol) of 1,5-dibromopentane, 12.48 g (90.2 mmol) of K_2CO_3, and 0.4 g of KI in 200 mL of acetone, and the mixture was refluxed for 15 h. It was then cooled and filtered, and the filtrate was evaporated. The residue was taken up in 250 mL of Et_2O, washed with 250-mL portions of ice-cold 10% NaOH, H_2O, and brine, and dried over $MgSO_4$. Evaporation left an oil, which was purified by chromatography (4% EtOAc/hexane) to afford 6.20 g (28%) of **2-[(5-bromopentyl)oxy]benzaldehyde**. IR 1690 (C=O), 1605 (C=C); NMR 3.42 (2 H, t, J = 7, CH_2Br), 4.08 (2 H, t, J = 7, OCH_2), 10.55 (1 H, s, CHO).

A mixture of 3.0 g (11.1 mmol) of the bromide, 2.26 g (11.6 mmol) of 2,4-dihydroxy-3-propylacetophenone,[20] and 0.77 g (5.5 mmol) of K_2CO_3 in 20 mL of acetone was refluxed for 6 days. It was then cooled and filtered, and the filtrate was evaporated. The residue was taken up in 50 mL of EtOAc, washed with 50-mL portions of ice-cold 5% NaOH, H_2O, and brine, and dried over $MgSO_4$. Evaporation left an oil, which was purified by chromatography (15% EtOAc/hexane) to afford 2.52 g (59%) of the title compound. NMR 2.47 (3 H, s, CH_3C=O), 4.06 (4 H, m, OCH_2), 10.52 (1 H, s, CHO).

2-(Undecylthio)benzaldehyde (Precursor to 46). A mixture of 3.06 g (19.8 mmol) of 2-mercaptobenzoic acid, 5.27 g (22.4 mmol) of undecyl bromide, and 3.56 g (25.7 mmol) of K_2CO_3 in 20 mL of dry DMF was heated to 100 °C over 1 h and was then cooled to ambient temperature. It was poured into 200 mL of H_2O, acidified with 3 N HCl, and extracted with 100 mL of EtOAc. The extract was washed with 100 mL of brine, treated with $MgSO_4$ and charcoal, and evaporated to a white solid. Recrystallization from hexane afforded 3.97 g (65%) of **2-(undecylthio)benzoic acid**, mp 89–90 °C. IR 1680 (C=O); NMR 2.94 (2 H, t, J = 7, SCH_2). Anal. ($C_{18}H_{28}O_2S$) C, H, S.

A solution of 3.89 g (12.6 mmol) of the acid in 20 mL of THF was added dropwise to 15.0 mL (15.0 mmol) of 1.0 M BH_3·THF, and the mixture was stirred under Ar at ambient temperature for 1 h. The reaction was quenched by the careful addition of 3 mL of MeOH, and the volatiles were evaporated. The residue was taken up in 100 mL of Et_2O, washed with 100-mL portions of 2.5 M NaOH and brine, and dried over $MgSO_4$. Evaporation left a white solid, which was recrystallized from hexane to afford 3.34 g (90%) of **2-(undecylthio)benzyl alcohol**, mp 47.5–49 °C. IR 3340, 3260 (O–H); NMR 2.90 (2 H, t, J = 7, SCH_2), 4.77 (2 H, br s, CH_2OH). Anal. ($C_{18}H_{30}OS$) C, H, S.

A solution of 0.95 g (7.45 mmol) of $(COCl)_2$ in 20 mL of CH_2Cl_2 was cooled in a dry ice/2-propanol bath under Ar. A solution of 1.10 g (14.09 mmol) of Me_2SO[21] in 5 mL of CH_2Cl_2 was added over 15 min with mechanical stirring, followed 5 min later by a solution of 1.89 g (6.11 mmol) of the alcohol in 10 mL of CH_2Cl_2. The resulting white slurry was stirred for 20 min and was treated with 2.90 g (28.06 mmol) of Et_3N. The mixture was then allowed to reach ambient temperature and was washed with 50 mL of H_2O. The aqueous fraction was extracted with 50 mL of CH_2Cl_2, and the combined organics were washed with 50 mL of brine, dried over $MgSO_4$, and evaporated. The resulting oil was purified by chromatography (2% EtOAc/hexane) to afford 1.22 g (68%) of the title compound. IR 1700 (C=O), 1600 (C=C); NMR 2.93 (2 H, t, J = 7, SCH_2), 10.46 (1 H, s, CHO). Anal. ($C_{18}H_{28}OS$) C, H, S.

5-(2-Dodecylphenyl)-4-sulfinyl-6-thianonanedioic Acid (58). A solution of 606 mg (2.81 mmol, assuming a purity of 80%) of MCPBA in 25 mL of CH_2Cl_2 was added dropwise to an ice-cold solution of 1.32 g (2.82 mmol) of **5** in 25 mL of CH_2Cl_2, and the mixture was stirred for 45 min. The volatiles were evaporated, and the residue was purified by chromatography (50% EtOAc/hexane, 0.5% HCO_2H) to afford 0.75 g (55%) of **58** as a pale yellow oil. IR 1720 (C=O); NMR 5.35, 5.40 (1 H, 2 s, diastereomeric methine H). Anal. ($C_{25}H_{40}O_5S_2 \cdot {}^1/_2H_2O$) C, H, S.

5-(2-Dodecylphenyl)nonanedioic Acid (59). A mixture of 10.5 g (48.8 mmol) of methyl 2-bromobenzoate, 9.72 g (58.4 mmol) of 1-dodecyne, 689 mg (0.98 mmol) of $(Ph_3P)_2PdCl_2$, and 101 mg (0.53 mmol) of CuI in 100 mL of Et_3N was refluxed under Ar for 16 h. It was then cooled to room temperature, filtered, and evaporated. The residue was taken up in 100 mL of Et_2O, washed with 100-mL portions of 3 N HCl and brine, and treated with $MgSO_4$ and charcoal. Evaporation left a dark oil, which was purified by chromatography (5% EtOAc/hexane) to afford 3.11 g (21%) of **methyl 2-(1-dodecynyl)benzoate**. IR 2240 (C≡C), 1720, 1740 (C=O); NMR 2.47 (2 H, t, J = 7, $C{\equiv}CCH_2$), 3.90 (3 H, s, CO_2CH_3); MS (CI), 301 (M + H).

A mixture of 3.06 g (10.19 mmol) of this product and 312 mg of 10% Pd/C in 100 mL of EtOAc was hydrogenated for 6 h at an initial pressure of 40 psi. Capillary GC analysis showed the presence of trace amounts of starting material. Another 49 mg of catalyst was added, and the mixture was hydrogenated for an additional 50 min. Filtration and evaporation left an oil, which was purified by Kugelrohr distillation, affording 2.08 g (67%) of **methyl 2-dodecylbenzoate**, bp 115–125 °C (0.05 mmHg). IR 1730 (C=O); NMR 2.93 (2 H, t, J = 7, Ar CH_2), 3.86 (3 H, s, CO_2CH_3); MS (CI), 305 (M + H).

A Grignard reagent was prepared from 4.50 g (23.35 mmol) of 4-(tetrahydropyranyloxy)-1-chlorobutane and 491 mg (20.20 mmol) of Mg in 30 mL of THF at reflux for 2 h. The mixture was cooled to ambient temperature, treated with a solution of 2.05 g (6.73 mmol) of the benzoate in 5 mL of THF, and allowed to stir under Ar for 18 h. It was then quenched by the addition of 10 mL of 3 N HCl, and the mixture was refluxed for 1 h to remove the THP groups. It was taken up in 50 mL of Et_2O, washed with 2 × 50 mL of brine, and dried over $MgSO_4$. Evaporation left an oil, which was purified by chromatography (25% EtOAc/hexane, then 50% EtOAc/hexane). Spectral characterization of the major chromatographic fraction (1.11 g, 33%) showed it to be **1,5-dihydroxy-5-(2-dodecylphenyl)-9-(tetrahydropyranyloxy)nonane**, formed by incomplete hydrolysis of the Grignard product. IR 3400 (br, O–H); NMR 3.60 (6 H, m, CH_2O), 4.54 (1 H, br s, OCHO); MS (CI), 505 (M + H).

Jones reagent was prepared from 7.00 g of CrO_3 and 6.0 mL of H_2SO_4 in a total volume of 50 mL of H_2O. A 9.0-mL sample of this reagent was added dropwise to a solution of 1.08 g (2.14 mmol) of the diol in 25 mL of acetone, and the mixture was stirred at ambient temperature for 2 h. 2-Propanol was added to destroy excess oxidant, and the mixture was partitioned between 100 mL of Et_2O and 50 mL of H_2O. The aqueous layer was extracted with 50 mL of Et_2O, and the combined organic fractions were washed with 50-mL portions of aqueous $Na_2S_2O_3$ and brine. Drying ($MgSO_4$) and evaporation left an oil, which was purified by chromatography (33% EtOAc/hexane, 0.5% HCO_2H) to afford 0.41 g (45%) of **5-(2-dodecylphenyl)-5-(3-carboxypropyl)-δ-valerolactone**. IR 1715, 1740 (C=O); MS (FD), 430 (M^+). Anal. ($C_{27}H_{42}O_4$) C, H.

A mixture of 0.40 g (0.93 mmol) of the lactone and 397 mg of 10% Pd/C in 50 mL of EtOAc containing 5 drops of H_2SO_4 was hydrogenated for 8 min at an initial pressure of 50 psi. It was then filtered, washed with 2 × 50 mL of brine, and dried over $MgSO_4$. Evaporation left 0.40 g (100%) of **59** as a colorless oil. IR 1715 (C=O); MS ($C_{27}H_{44}O_4$) calcd 432.324, found 432.324. Anal. ($C_{27}H_{44}O_4$) H; C: calcd, 74.96; found, 74.01.

4,5-Dicarboxy-2-(2-dodecylphenyl)-1,3-dithiolane: The Cis-Syn (60), Cis-Anti (61), and Trans (62) Isomers. To an ice-cold mixture of 1.41 g (5.13 mmol) of 2-dodecylbenzaldehyde and 0.98 g (4.66 mmol) of dimethyl *meso*-dimercaptosuccinate in 35 mL of $CH_2Cl_2$was added dropwise 0.80 g (5.64 mmol) of distilled BF_3·Et_2O. After stirring for 15 min, the mixture was diluted with 75 mL of Et_2O, washed with 50 mL of 5% $NaHCO_3$, H_2O, and brine, and dried over $MgSO_4$. The solvent was evaporated and the material was purified by chromatography (5% EtOAc/hexane) to afford two products. First off the column was ***cis*-4,5-dicarbomethoxy-*anti*-2-(2-dodecylphenyl)-1,3-dithiolane** (0.27 g, 12%). IR 1745 (C=O); NMR 2.70 (2 H, t, J = 7, Ar CH_2), 3.80 (6 H, s, CO_2CH_3), 4.86 (2 H, s, $SCHCO_2CH_3$), 6.34 (1 H, s, SCHS); MS (CI), 467 (M + H). The more polar component was ***cis*-4,5-dicarbomethoxy-*syn*-2-(2-dodecylphenyl)-1,3-dithiolane** (0.99 g, 46%). IR 1745 (C=O); NMR 2.66 (2 H, t, J = 7, Ar CH_2), 3.76 (6 H, s, CO_2CH_3), 4.58 (2 H, s, $SCHCO_2CH_3$), 5.94 (1 H, s, SCHS); MS (CI), 467 (M + H). There was also obtained 0.52 g (24%) of a mixture of the two products. The stereochemistry was assigned on the basis of a NOE enhancement between the two different methine protons of the syn, but not the anti, isomer.

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The trans isomer could be obtained by epimerization of either the cis-syn or cis-anti isomers. For example, a solution of 135 mg (0.29 mmol) of the cis-syn isomer in 20 mL of MeOH was treated with ca. 10 mg of NaOMe and stirred for 15 min. The solvent was evaporated and the residue was taken up in 25 mL of EtOAc, washed with 25 mL of 5% $NaHCO_3$, H_2O, and brine, and dried over $MgSO_4$. Evaporation left 114 mg (84%) of ***trans*-4,5-dicarbomethoxy-2-(2-dodecylphenyl)-1,3-dithiolane.** IR 1740 (C=O); NMR 2.68 (2 H, t, J = 7, Ar CH_2), 3.80 (6 H, s, CO_2CH_3), 4.84, 4.91 (2 H, d, J = 4, SC*H*CO_2CH_3), 6.14 (1 H, s, SCHS); MS (CI), 467 (M + H).

Hydrolysis of the diesters to the title compounds was effected under acidic conditions. Thus, a solution 113 mg (0.24 mmol) of the trans diester in 5 mL of 90% HCO_2H containing 0.05 mL of CH_3SO_3H was refluxed for 24 h. It was taken up in 50 mL of CH_2Cl_2, washed with 3 × 50 mL of H_2O, and dried over $MgSO_4$. Evaporation left an oil, which was purified by chromatography (17% EtOAc/hexane, 0.5% HCO_2H) and trituration with hexane to afford 31 mg (29%) of **62**, mp 85–87 °C. IR 1710 (C=O); NMR 2.70 (2 H, br t, J = 7, Ar CH_2), 4.90, 4.98 (2 H, d, J = 4, SC*H*CO_2CH_3), 6.20 (1 H, s, SCHS); MS (FD), 439 (M + H). Anal. ($C_{23}H_{34}O_4S_2$) C, H.

Similar hydrolysis of either the cis-syn or cis-anti isomers gave a mixture of **60**, **61**, and **62**. Thus, of a mixture 237 mg (0.51 mmol) of the cis-syn and cis-anti isomers was hydrolyzed and purified as above to afford 39 mg (17%) of **62**, 50 mg (22%) of **61**, and 32 mg (14%) of **60**. **61**: mp 86–89 °C; IR 1720 (C=O); NMR 2.70 (2 H, br t, J = 7, ArCH_2), 4.98 (2 H, s, SC*H*CO_2H), 6.38 (1 H, s, SCHS); MS (FD), 439 (M + H). Anal. ($C_{23}H_{34}O_4S_2$) C, H. **60**: mp 81–84 °C; IR 1720 (C=O); NMR 2.70 (2 H, br t, J = 7, Ar CH_2), 4.70 (2 H, s, SC*H*CO_2H), 6.02 (1 H, s, SCHS); MS (FD), 439 (M + H). Anal. ($C_{23}H_{34}O_4S_2$) C, H.

3-Undecyl-1-indanone Bis(2-carboxyethyl) Thioacetal (64). A mixture of 5.02 g (34.35 mmol) of 1,3-indanedione, 4.45 g (71.73 mmol) of ethylene glycol, and 100 mg of *p*-TsOH·H_2O in 40 mL of toluene was refluxed for 4 h with azeotropic removal of H_2O. It was then cooled, diluted with 50 mL of Et_2O, washed with 50-mL portions of 5% $NaHCO_3$ and brine, and treated with $MgSO_4$ and charcoal. Evaporation left an oil, which was purified by chromatography (25% EtOAc/hexane). A 1.99-g (30%) sample of **1,3-indandione mono(ethylene acetal)** was obtained. IR 1725 (C=O); NMR 2.91 (2 H, s, CH_2C=O), 4.20 (4 H, m, OCH_2CH_2O); MS, 191 (M + H).

A 5.4-mL (11.88 mmol) sample of a 2.2 M solution of *n*-BuLi in hexane was added dropwise to an ice-cold solution of 5.57 g (11.20 mmol) of undecyltriphenylphosphonium bromide in THF. The solution was stirred under Ar for 10 min and was then cooled to −78 °C. A solution of 1.92 g (10.09 mmol) of the indanone in 6 mL of THF was added, and the mixture was allowed to come to ambient temperature over 4 h. It was taken up in 50 mL of Et_2O, washed with 50-mL portions of NH_4Cl solution and brine, and treated with $MgSO_4$ and charcoal. Evaporation left an oil, which was purified by chromatography (5% EtOAc/hexane) to afford 0.89 g (27%) of **3(*E*)-undecylidene-1-indanone ethylene acetal.** NMR 2.90 (2 H, br s, CH_2C=C), 4.10 (4 H, m, OCH_2CH_2O), 6.00 (1 H, t of t, J = 2, 7, C=CH). Anal. ($C_{22}H_{32}O_2$) C, H.

A mixture of 0.81 g (2.47 mmol) of the olefin and 206 mg of PtO_2 in 50 mL of EtOAc was hydrogenated for 2.5 h at an initial pressure of 40 psi. Filtration and evaporation left an oil, which was purified by chromatography (5% EtOAc/hexane). A 0.47-g (57%) sample of **3-undecyl-1-indanone ethylene acetal** was obtained. NMR 4.15 (4 H, m, OCH_2CH_2O). Anal. ($C_{22}H_{34}O_2$) C, H.

To an ice-cold solution of 0.40 g (1.21 mmol) of the acetal and 0.28 g (2.64 mmol) of 3-mercaptopropionic acid in 10 mL of CH_2Cl_2 was added dropwise 0.17 g (1.22 mmol) of distilled BF_3·Et_2O. After 30 min, the mixture was taken up in 50 mL of Et_2O, washed with 5 × 50 mL of H_2O, and dried over $MgSO_4$. Evaporation left an oil, which was purified by chromatogrphy (20% EtOAc/hexane, 0.5% HCO_2H). Evaporation of the appropriate fractions and trituration with hexane afforded 0.24 g (41%) of **64**, mp 82–84 °C. IR 1715 (C=O). Anal. ($C_{26}H_{40}O_4S_2$) C, H, S.

4-Undecyl-1-tetralone Bis(2-carboxyethyl) Thioacetal (65). To an ice-cold solution of 5.76 g (30.0 mmol) of methyl 3-benzoylpropionate in 50 mL of Et_2O was added dropwise a solution of the Grignard reagent prepared from 9.74 g (41.4 mmol) of bromoundecane and 1.01 g (41.6 mmol) of Mg in 50 mL of Et_2O. The mixture was stirred at 0 °C for 30 min and then at ambient temperature for 16 h. It was quenched by the addition of 100 mL of NH_4Cl solution and was extracted with 100 mL of Et_2O. The organic phase was washed with 100 mL of H_2O, dried over $MgSO_4$, and evaporated to an oil. Purification by chromatography (10% EtOAc/hexane) afforded 6.1 g (64%) of **4-phenyl-4-undecyl-γ-butyrolactone.** IR 1780 (C=O).

A mixture of 6.1 g (19.3 mmol) of the lactone and 600 mg of 10% Pd/C in 100 mL of EtOH was hydrogenated at an initial pressure of 50 psi until uptake ceased. Filtration and evaporation left 5.6 g (91%) of **4-phenylpentadecanoic acid.** IR 1720 (C=O).

A 5.4-g (16.9 mmol) sample of the acid was added to a rapidly stirred mixture of 8.0 g of P_2O_5 and 80.0 g of CH_3SO_3H, and the homogeneous mixture was stirred at ambient temperature for 3 h. It was poured into 800 mL of H_2O and extracted with 3 × 200 mL of Et_2O. The extract was washed with 100 mL portions of 5% $NaHCO_3$ and H_2O, dried over $MgSO_4$, and evaporated to give 3.7 g (73%) of **4-undecyl-1-tetralone.** IR 1700 (C=O).

A mixture of 1.0 g (3.3 mmol) of the tetralone and 2.0 g (18.9 mmol) of 3-mercaptopropionic acid was treated with gaseous HCl for 10 s and was then stirred at ambient temperature for 4 h. It was taken up in 50 mL of CH_2Cl_2, washed with 5 × 50 mL of H_2O, and dried over $MgSO_4$. Evaporation left a waxy solid, which was triturated with petroleum ether to afford 0.9 g (61%) of **65**, mp 90–92 °C. IR 1700 (C=O). Anal. ($C_{27}H_{42}O_4S_2$) C, H.

2-Dodecyl-6-methylbenzaldehyde (Precursor to 66). To an ice-cold solution of 2.22 g (21.9 mmol) of diisopropylamine in 10 mL of freshly distilled THF was added 8.4 mL (21.8 mmol) of a 2.6 M solution of *n*-BuLi in hexane. The solution was stirred under Ar for 5 min and was then treated with a solution of 1.50 g (10.0 mmol) of 2,6-dimethylbenzoic acid in 10 mL of THF. After 20 min, 2.64 g (11.2 mmol) of undecyl bromide was added, and the mixture was stirred for another 20 min. It was then taken up in 50 mL of Et_2O, washed with 50 mL of 3 N HCl, and dried over $MgSO_4$. Evaporation left an oil, which was purified by chromatography (10% EtOAc/hexane, 0.5% HCO_2H) to afford 1.28 g (42%) of **2-dodecyl-6-methylbenzoic acid** as a waxy solid. IR 1700 (C=O); NMR 2.40 (3 H, s, Ar CH_3), 2.70 (2 H, t, J = 7, Ar CH_2).

A solution of 1.25 g (4.10 mmol) of the acid in 10 mL of THF was treated with 20 mL (ca. 10 mmol) of ca. 0.5 M BH_3·THF, and the mixture was refluxed for 16 h. It was then cooled in ice and quenched by the careful addition of 5 mL of MeOH. The volatiles were evaporated, and the residue was taken up in 100 mL of Et_2O, washed with 100 mL portions of 2.5 M NaOH and brine, and dried over $MgSO_4$. Evaporation left 1.15 g (97%) of **2-dodecyl-6-methylbenzyl alcohol** as a colorless oil. IR 3300 (O–H); NMR 2.42 (3 H, s, Ar CH_3), 2.74 (2 H, t, J = 7, Ar CH_2), 4.74 (2 H, s, Ar CH_2OH).

A solution of 1.12 g (3.85 mmol) of the alcohol in 50 mL of CH_2Cl_2 was treated with 1.23 g (5.70 mmol) of PCC, and the mixture was stirred for 45 min. It was diluted with 150 mL of Et_2O and filtered from a black residue. The filtrate was washed with 100 mL portions of 3 N HCl and brine, treated with $MgSO_4$ and charcoal, and evaporated. The resulting oil was purified by chromatography (1% Et_2O/hexane) to afford 0.57 g (51%) of the title compound as a pale yellow solid, mp 32–35.5 °C. IR 1700 (C=O), 1600 (C=C); NMR 2.56 (3 H, s, Ar CH_3), 2.92 (2 H, t, J = 7, Ar CH_2), 10.70 (1 H, s, CHO). Anal. ($C_{20}H_{32}O$) C, H.

2-Bromo-5-(trifluoromethyl)benzaldehyde (Precursor to 71). A 25.0-mL (25.0 mmol) sample of a 1.0 M solution of Dibal in hexane was added dropwise to a solution of 5.04 g (20.16 mmol) of 2-bromo-5-(trifluoromethyl)benzonitrile[22] in 50 mL of CH_2Cl_2. The solution was stirred under Ar at ambient temperature for 30 min and was then diluted with 50 mL of Et_2O and cooled in ice. Fifty milliliters of 3 N HCl was carefully added, and the mixture was vigorously stirred at ambient temperature for 15 min. The organic fraction was washed with 50 mL of brine, treated with $MgSO_4$ and charcoal, and evaporated. The resulting oil was purified by Kugelrohr distillation, affording 4.17 g (82%) of the

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title compound, bp 50–55 °C (0.05 mmHg). IR 1710 (C=O), 1610 (C=C); NMR 10.40 (1 H, s, CHO).

This compound was converted to 71 via method B, utilizing 1-phenyl-1,7-octadiyne (vide infra).

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Ligand–Receptor Interactions via Hydrogen-Bond Formation. Synthesis and Pharmacological Evaluation of Pyrrolo and Pyrido Analogues of the Cardiotonic Agent 7-Hydroxycyclindole

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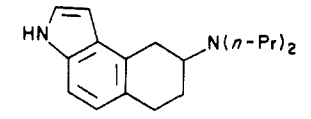
The syntheses of *N,N*-dimethyl-6,7,8,9-tetrahydro-3*H*,10*H*-pyrrolo[3,2-*a*]carbazol-7-amine (**8**), *N,N*-dimethyl-7,8,9,10-tetrahydro-11*H*-pyrido[3,2-*a*]carbazol-8-amine (**9a**), and the *N,N*,11-trimethyl analogue (**9b**) are described. The in vitro inotropic activity of these compounds, as well as the known cardiotonics amrinone and 7-hydroxycyclindole (**7**), was investigated. Compound **8**, a pyrrolo analogue of **7**, was devoid of inotropic activity, while the pyrido analogues **9** were equiactive to **7** and amrinone. These results suggest that the hydroxyl group of **7** functions as an H-bond acceptor, rather than a donor, and that on interaction of **7**, and the pyrido analogues **9**, with a common receptor, an orbital occupied by one of the oxygen lone pair electrons of **7** must assume the same orientation as the orbital occupied by the pyridine nitrogen lone pair.

Bioisosterism between a phenolic hydroxyl group and a pyrrolo ring has been demonstrated in two instances. Thus, the pyrrolo analogue **1** of the dopamine agonist **2** was shown also to be a potent dopaminergic agent,[1] and the pyrrolo analogue **3** of the antihypertensive α/β-adrenergic blocker labetalol (**4**) was shown also to have similar pharmacological properties.[2]



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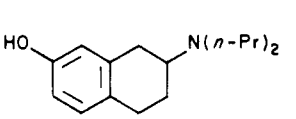

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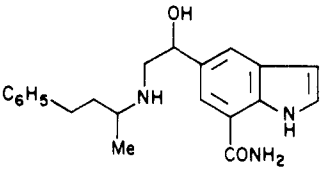

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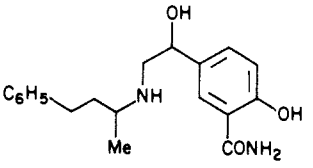

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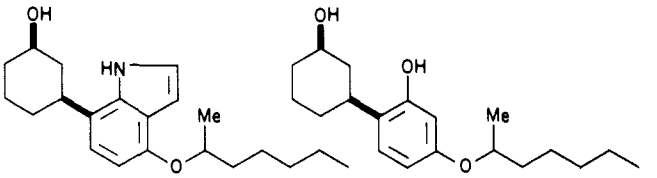
The observed bioisosterism was ascribed to "bioisofunctionality" between the phenolic hydroxyl and pyrrolo groups, in the sense that both of these groups can function as H-bond donors to a common acceptor nucleus on a receptor macromolecule with which the ligands interact.[1,2]

A third probe of bioisofunctionality between phenolic hydroxyl and pyrrolo groups was, however, negative; the pyrrolo analogue **5** of the analgesic **6** was found to be devoid of analgesic activity.[3] The absence of bioisofunctionality in this third instance may be due to one or more of several factors: (1) the phenolic hydroxyl of **6** may



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not function as an H-bond donor; (2) the receptor may not be able to accommodate the incremental volume requirements of the pyrrolo ring; (3) the unique directional vector of the H bond involving the pyrrolo ring may not coincide with the one (of the mulitple directional vectors that a freely rotating hydroxyl group can assume) that is required for interaction with a uniquely located acceptor nucleus on the receptor; and/or (4) a conformation of the flexible **6** required for interaction with its receptor may be unfavorably perturbed by the replacement of a phenolic hydroxyl by a pyrrolo group.

The following is an investigation, in a broader sense, of ligand–receptor interactions via hydrogen-bond formation. We chose the cardiotonic agent 7-hydroxycyclindole,[4,5] **7**, as our target. In this compound, the 7-hydroxyl group is necessary for activity, as the deshydroxy compound is inactive.[4]

We wished to investigate whether the hydroxyl group functions as an H-bond donor or acceptor. To this end, we have synthesized and evaluated the pyrrolo analogue **8**, the pyrido analogue **9a**, and analogue **9b** in which the indolic nitrogen is methylated. Pyrido analogues were selected for investigation, since the pyridine nitrogen atom can function as an acceptor nucleus in H-bond formation.

Chemistry. The reactions leading to the synthesis of the pyrrolo[3,2-*a*]carbazol-7-amine **8** are outlined in Scheme I. The α-arylation of cyclohexanone by very reactive aryl halides using enamines as intermediates was shown by Kuehne[6] to occur in high yields. The pyrrolidino

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