calcd 301.2406, found 301.2402.

RBL-1 5-Lipoxygense Inhibition Assay. 5-Lipoxygenase activity was measured in the 20000*g* supernatant from homogenized rat basophilic leukemia (RBL-1) cells. Inhibitors or vehicle (2% Me_2SO) were preincubated for 20 min with the RBL-1 supernatant (7.5×10^6 cell equivalents/mL) at 37 °C in pH 6.8 buffer (10 mM BES, 10 mM PIPES, 1 mM EDTA, 0.1 M NaCl, 0.7 mM $CaCl_2$) prior to initiating the 5-lipoxygenase reaction by addition of 66 μM [^{14}C]arachidonic acid. [^{3}H]-5-HETE added to the reaction mixture served as a recovery standard. Reactions were terminated by acidification to pH 3 and the mixtures were extracted with diethyl ether. The ether extracts were evaporated under nitrogen and the reaction products were separated from nonconverted substrate by thin-layer chromatography. Radioactivity comigrating with 5-HETE was measured by liquid scintillation counting and corrected for recovery of [^{3}H]-5-HETE. Inhibition was calculated as the percent reduction from control levels of [^{14}C]-5-HETE formation. Concentrations causing 50% inhibition (IC_{50}'s) and their 95% confidence limits were calculated as the 50% intercept and their fiducial limits from linear regression analysis[22] of percent inhibition vs. log concentration plots.

Acknowledgment. We thank Dr. R. Walters for helpful discussions, D. Bornemeier for excellent technical assistance, and the spectroscopic services department at Abbott for the NMR and MS data.

(22) Ostle, B. *Statistics in Research*, 2nd ed., The Iowa State University Press: Ames, IA, 1963; pp 159–221.

Structure–Activity Relationships among Di- and Tetramine Disulfides Related to Benextramine

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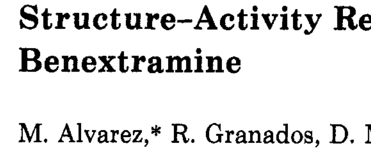
The synthesis and irreversible α-blocking activity in the rat vas deferens of a series of tetra- and diamine disulfides **2–38**, structural analogues of benextramine (BHC), are described. All compounds containing a central cystamine moiety displayed an irreversible α-adrenergic blockade at concentrations ranging from 10^{-4} to 6×10^{-6} M. Potency was increased in cystamines N,N'-disubstituted with 6-aminohexyl groups, especially when the outer nitrogen atoms bear arylalkyl substituents or are enclosed in a ring. However, N,N,N',N'-tetrasubstituted cystamines were poor blockers. Structural specificity in the outer portion of the tetramine disulfide is low, since many types of substituents gave rise to potent α-blockers. Even replacement of the outer amines with nonbasic ethers or amides was observed to maintain irreversible α-blockade.

In a series of structure–activity relationship (SAR) studies of tetramine disulfides carried out by Melchiorre and Belleau,[1] optimum α-adrenergic blocking potency was found for compounds *N,N'*-bis[6-[(*o*-methoxybenzyl)-amino]hexyl]cystamine (BHC, **1**) and *N,N'*-bis(8-aminooctyl)cystamine, (AOC, **39**). From the structural features of these compounds, the authors proposed a topographical model for the α-adrenoceptor in the rate vas deferens.

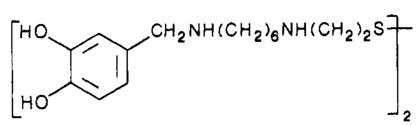


1 (BHC)

$[H_2N(CH_2)_8NH(CH_2)_2S]_2$

39 (AOC)

Accordingly, BHC would interact with a set of four anionic centers and two flat areas complementary to the aromatic rings, and AOC would bind to a different set of four anionic centers. These two binding areas would be symmetrically disposed on the surface of the receptor and share a common central thiol group. According to the hypothesis, the initial electrostatic interactions between the four cationic nitrogen atoms and the anionic centers would lead to a conformational change unmasking the thiol group. This would allow a disulfide–thiol exchange reaction, which in turn results in a covalent blockade of the α-adrenoceptor. The analogues of tetramine disulfides BHC and AOC showed different SAR. Thus, the optimum chain length between the "inner" and "outer" nitrogen atoms was found to be six carbon atoms in BHC and eight methylene groups in AOC. Substitution on the outer nitrogen atom led to a reduced potency in AOC, while in BHC a benzylic substituent (especially an *o*-methoxybenzyl group) on this position gave maximal potency. On the other hand, methylation of the inner nitrogen atoms led to a marked reduction in potency in the BHC series while the AOC methylated analogues showed almost no changes in activity. On the basis of the high α-blocking activity of the catechol-containing disulfide **40**, which was



40

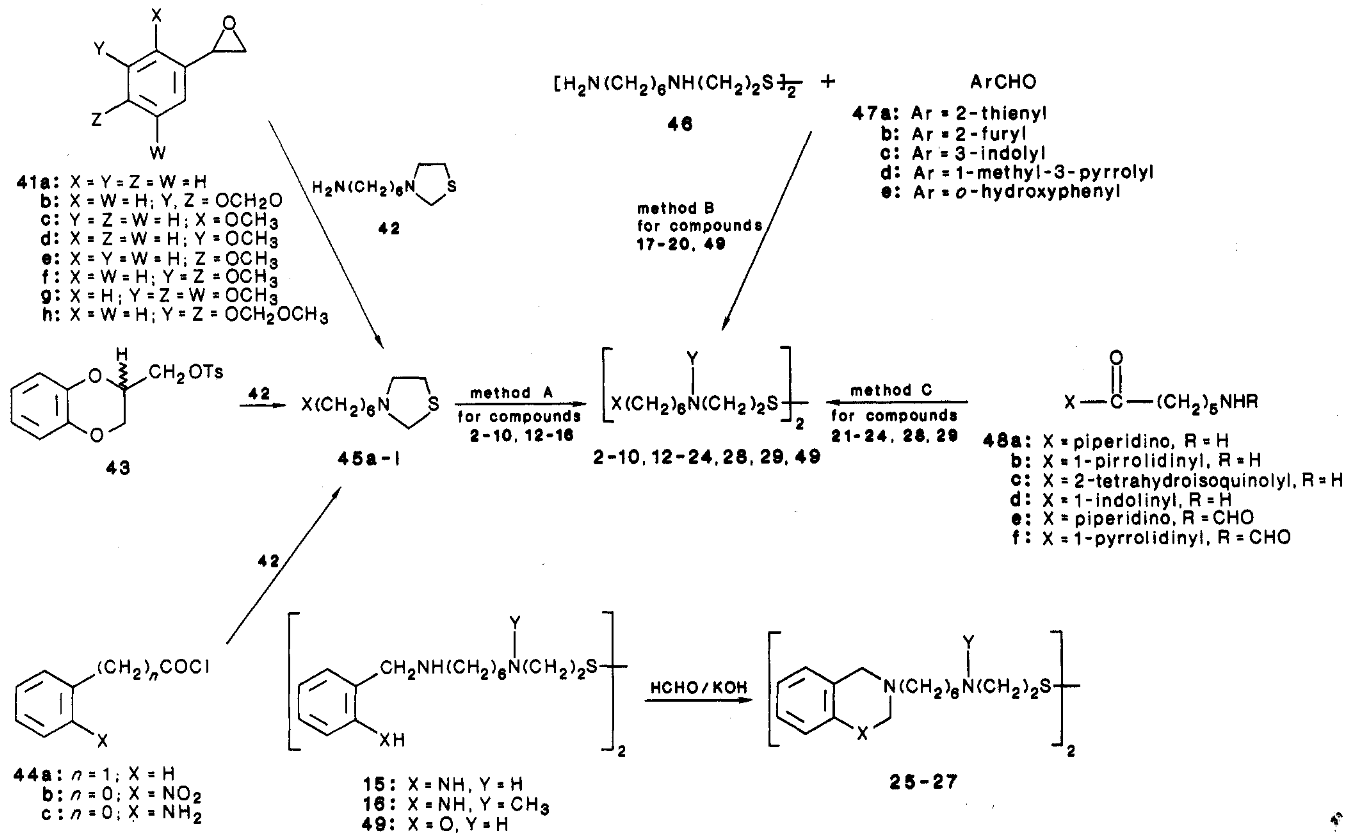
equiactive with BHC, Melchiorre also suggested a common binding site for the outer (3,4-dihydroxybenzyl)amino moiety of **40**, as well as the (*o*-methoxybenzyl)amino group of BHC and the catecholamine neurotransmitters, in spite of the benzylic nature of the N-substituent and the lack of a benzylic hydroxyl group found in catecholamines.

Aiming to extend and evaluate the above possibilities and especially the predicted relationship between the catecholamine and BHC binding sites, we undertook the synthesis of a new series of polyamine disulfides containing terminal moieties structurally related in some instances to α-adrenergic drugs.[2] Thus, compounds **2–9** (Table I)

(1) (a) Melchiorre, C.; Yong, M. S.; Benfey, B. G.; Belleau, B. *J. Med. Chem.* **1978**, *21*, 1126. (b) Melchiorre, C.; Giardina, D.; Brasili, L.; Belleau, B. *Farmaco* **1978**, *33*, 999. (c) Melchiorre, C.; Giannella, M.; Brasili, L.; Benfey, B. G.; Belleau, B. *Eur. J. Med. Chem.* **1981**, *16*, 111. (d) Melchiorre, C. *Trends Pharmacol. Sci.* **1981**, *2*, 209. (e) Angeli, P.; Brasili, L.; Brancia, E.; Giardina, D.; Quaglia, W.; Melchiorre, C. *J. Med. Chem.* **1985**, *28*, 1643. (f) Bertini, R.; Giardina, D.; Gullini, U.; Pigini, M.; Melchiorre, C.; Carpy, A. *Eur. J. Med. Chem.* **1985**, *20*, 309.

0022-2623/87/1830-1186$01.50/0

Scheme I



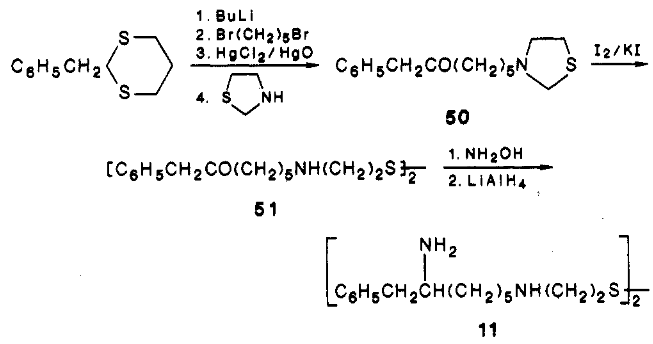
are structural combinations of BHC and phenylethanolamines; in disulfide **9** the group replacing the (*o*-methoxybenzyl)amino substituent is specifically norepinephrine. Compound **11** is related to amphetamine and disulfides **10** contain the α-blocking (1,4-benzodioxan-2-ylmethyl)amino moiety.

The results of pharmacological testing of the above disulfides prompted us to carry out our synthesis of new BHC analogues bearing modified outer portions. The changes made were related to (a) change in the substitution pattern of the aromatic ring and in the distance between this ring and the outer nitrogen atom (**14–16**), (b) replacement of heterocycles for the aryl group (**17–20**), (c) change of the amino groups into nonbasic amide or ether functions (**12**, **13**, **30–34**), (d) replacement of nonaromatic heterocycles for the benzylamino moiety (**21–24**), (e) introduction of a new ring linking the Ar/N moieties (**25–29**), and (f) suppression of the whole outer moiety, leading to N-substituted cystamines (**35–38**).

Chemistry

Preparation of symmetrical disulfides **2–10**, **12–29** (see specific structures in Table I), and **49**[1c] is outlined in Scheme I. In method A, reaction of 3-(6-aminohexyl)-1,3-thiazolidine (**42**)[2a] with an appropriate alkylating agent (epoxides **41a–h**[2c] for **2–9** and racemic[3a] or optically pure[3b] tosylate **43** for **10**) gave the required thiazolidines **45**

Scheme II. Method D



(structures in Table II). Oxidative ring opening and dimerization by treatment with 0.1 N I_2/KI[2] yielded disulfides **2–10**. Compounds **12** and **13** were obtained from (aminoalkyl)thiazolidine **42** by acylation with acyl chlorides **44a,c** and oxidative coupling. Reduction of amide group of **12** with $LiAlH_4$ gave the cystamine **14**. Simultaneous reduction of amide and nitro groups of the cystamine obtained from thiazolidine **45k** gave **15**. Ring opening and reduction of the amide group of thiazolidine **45l** with $LiAlH_4$ gave a (methylamino)ethanethiol, which upon reaction with I_2 gave the N-methylated hexamine **16**. The tetrahydroquinazoline derivatives **25** and **26** and the benzoxazine **27** were obtained by ring closure of *o*-aminobenzylamines **15** and **16** or hydroxybenzylamine **49**, respectively, with HCHO in alkaline solution.

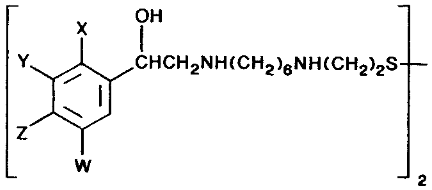
The heteroarylmethyl-substituted disulfides **17–20** were obtained from *N,N'*-bis(6-aminohexyl)cystamine (**46**)[1a] through method B consisting of a reductive alkylation of the primary amino groups with an appropriate heterocyclic aldehyde, **47**.

In method C the starting materials were the terminal heterocycle (piperidine, pyrrolidine, tetrahydroisoquinoline, or indoline) and 6-phthalimidohexanoyl chlo-

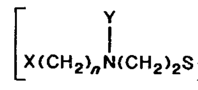
(2) The preparation of some of these compounds has been previously described; see: (a) Granados, R.; Alvarez, M.; Valls, N.; Salas, M. *J. Heterocycl. Chem.* **1983**, *20*, 1271. (b) Granados, R.; Valls, N.; Alvarez, M.; Bardaji, E. *An. Quim., Ser. C* **1983**, *79*, 303. (c) Alvarez, M.; Granados, R.; Lavilla, R.; Salas, M. *J. Heterocycl. Chem.* **1985**, *22*, 145. (d) Alvarez, M.; Granados, R.; Rosell, G.; Santaló, P.; Salas, M. *An. Quim., Ser. C* **1984**, *80*, 283.

(3) (a) Koo, J.; Avacain, S.; Martin, G. J. *J. Am. Chem. Soc.* **1955**, *77*, 5373. (b) Nelson, W. L.; Wennerstrow, J. E.; Dyer, D. C.; Engel, U. *J. Med. Chem.* **1977**, *20*, 880.

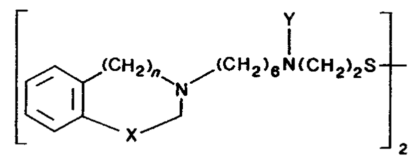
Table I. Structures of the Tetra- and Diamine Disulfides and α-Adrenergic Blocking Results



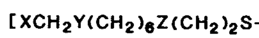
2-9



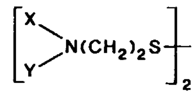
10-24



25-29



30-34



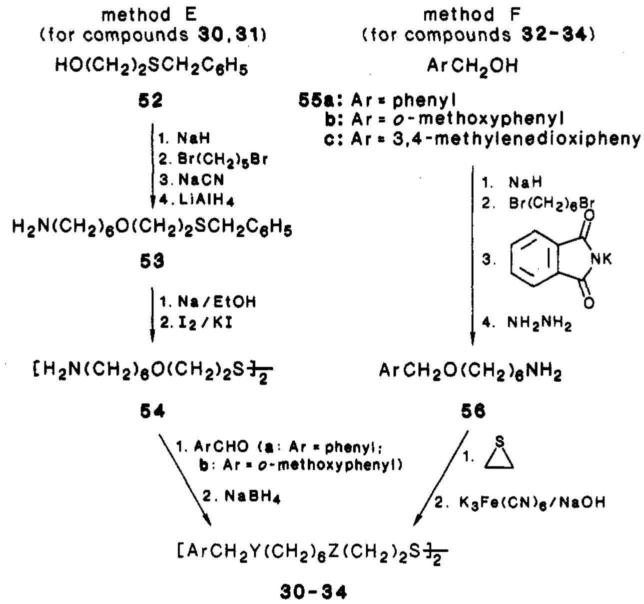
35-38

no.	X	Y	Z	W	n	yield, % (method)	mp, °C	purifn solvent	formula[a]	α-blockade[b] 10^{-4} M	α-blockade[b] 2×10^{-5} M	α-blockade[b] 6×10^{-6} M
1[f]						ref 1a					100	35
2	H	H	H	H		75 (A)	180–181	EtOH	$C_{32}H_{54}N_4O_2S_2 \cdot 4C_2H_2O_4 \cdot 3H_2O$	40	13	
3	H	–OCH₂O–		H		75 (A)	155–160	MeOH	$C_{34}H_{52}N_4O_6S_2 \cdot 3C_2H_2O_4 \cdot 2H_2O$		43	
4	OMe	H	H	H		88 (A)	133–136	MeOH	$C_{34}H_{58}N_4O_4S_2 \cdot 4C_2H_2O_4 \cdot 2H_2O$		82	
5	H	OMe	H	H		77 (A)	135–138	MeOH	$C_{34}H_{58}N_4O_4S_2 \cdot 3C_2H_2O_4 \cdot H_2O$		91	
6	H	H	OMe	H		54 (A)	135–138	MeOH	$C_{34}H_{58}N_4O_4S_2 \cdot 4C_2H_2O_4$		81	
7	H	OMe	OMe	H		88 (A)	200–203	MeOH	$C_{36}H_{62}N_4O_6S_2 \cdot 4C_2H_2O_4$		87	
8	H	OMe	OMe	OMe		89 (A)	200–203	MeOH	$C_{38}H_{66}N_4O_8S_2 \cdot 4C_2H_2O_4 \cdot H_2O$		98	
9	H	OH	OH	H		60 (A)	107–110	EtOH–Et₂O	$C_{32}H_{54}N_4O_6S_2 \cdot 4HCl \cdot C_4H_{10}O$		92	
10	(1,4-benzodioxan-2-ylmethyl)amino	H			6	61 (A)	260–262	MeOH–Et₂O	$C_{34}H_{54}N_4O_4S_2 \cdot 4HCl$	53	inact	
(*S*,*S*)-10	(1,4-benzodioxan-2-ylmethyl)amino	H			6	63 (A)	262–264	MeOH–Et₂O	$C_{34}H_{54}N_4O_4S_2 \cdot 4HCl$	79	inact	
(*R*,*R*)-10	(1,4-benzodioxan-2-ylmethyl)amino	H			6	65 (A)	262–264	MeOH–Et₂O	$C_{34}H_{54}N_4O_4S_2 \cdot 4HCl$	68	inact	
11	$C_6H_5CH_2CH(NH_2)$	H			5	56 (D)	152–155	MeOH	$C_{30}H_{50}N_4S_2 \cdot 4C_2H_2O_4$		57	
12	$C_6H_5CH_2CONH$	H			6	51 (A)	184–188	MeOH	$C_{32}H_{50}N_4O_2S_2 \cdot 2C_2H_2O_4 \cdot CH_3OH$		44	
13	o-$NH_2C_6H_4CONH$	H			6	37 (A)	indef	EtOH	$C_{30}H_{48}N_6O_2S_2 \cdot 4HCl$[c]	55	inact	
14	$C_6H_5CH_2CH_2NH$	H			6	95 (A)	194–196	MeOH	$C_{32}H_{54}N_4S_2 \cdot 3C_2H_2O_4 \cdot H_2O$	32	inact	
15	o-$NH_2C_6H_4CH_2NH$	H			6	43 (A)	134–136	EtOH	$C_{30}H_{52}N_6S_2 \cdot 6HCl \cdot C_2H_5OH$		79	
16	o-$NH_2C_6H_4CH_2NH$	Me			6	56 (A)	210–215	EtOH	$C_{32}H_{56}N_6S_2 \cdot 6HCl$	38	inact	
17	2-thenylamino	H			6	67 (B)	275–277	H_2O	$C_{26}H_{46}N_4S_2 \cdot 4HCl$		70	
18	furfurylamino	H			6	75 (B)	221–223	MeOH–H₂O	$C_{26}H_{46}N_4O_2S_2 \cdot 4C_2H_2O_4$		100	79
19	3-indolylmethylamino	H			6	80 (B)	186–190	EtOH	$C_{34}H_{52}N_6S_2 \cdot 4C_2H_2O_4$	46[d]	inact[d]	
20	[(1-methyl-3-pyrrolyl)methyl]amino	H			6	80 (B)	indef	MeOH	$C_{28}H_{52}N_6S_2 \cdot 4C_2H_2O_4$[c]		100	54
21	piperidino	H			6	50 (C)	121–123	MeOH	$C_{26}H_{54}N_4S_2 \cdot 4C_2H_2O_4 \cdot H_2O$		100	56
22	1-pyrrolidinyl	H			6	45 (C)	120–121	MeOH	$C_{24}H_{50}N_4S_2 \cdot 4C_2H_2O_4$		98	
23	1-piperidinyl	Me			6	54 (C)	229–231	EtOH	$C_{28}H_{58}N_4S_2 \cdot 4HCl \cdot 2H_2O$		34	
24	1-pyrrolidinyl	Me			6	50 (C)	185–188	EtOH	$C_{26}H_{54}N_4S_2 \cdot 4HCl \cdot 2H_2O$		41	
25	NH	H			1	90 (A)	69–70	EtOH	$C_{32}H_{52}N_6S_2 \cdot 6C_6H_3N_3O_7$		89	
26	NH	Me			1	84 (A)	80–85	MeOH	$C_{34}H_{56}N_6S_2 \cdot 6C_2H_2O_4$	6	inact	
27	O	H			1	78 (B)	164–167	MeOH	$C_{32}H_{50}N_2O_2S_2 \cdot 4C_2H_2O_4 \cdot CH_3OH$	34[d]	inact[d]	
28	CH_2	H			1	40 (C)	105–108	MeOH	$C_{34}H_{54}N_4S_2 \cdot 4C_2H_2O_4 \cdot 3H_2O$	66[d]	inact[d]	

29	CH_2	H		0	35 (C)	158–160	MeOH	$C_{32}H_{50}N_4S_2\cdot 2C_2H_2O_4$		37
30	$C_6H_5CH_2$	NH	O		15 (E)	192–194	MeOH	$C_{30}H_{48}N_2O_2S_2\cdot 2C_2H_2O_4$		32
31	o-$MeOC_6H_4CH_2$	NH	O		72 (E)	138–140	MeOH	$C_{32}H_{52}N_2O_4S_2\cdot 2C_2H_2O_4$		36
32	$C_6H_5CH_2$	O	NH		60 (F)	201–204	Me_2CO	$C_{30}H_{48}N_2O_2S_2\cdot 2HCl$		60
33	o-$MeOC_6H_4CH_2$	O	NH		80 (F)	198–200	MeOH	$C_{32}H_{52}N_2O_4S_2\cdot 2C_2H_2O_4$		58
34	3,4-(methylenedioxy)-benzyl	O	NH		61 (F)	185–188	MeOH–H_2O	$C_{32}H_{48}N_2O_6S_2\cdot 2C_2H_2O_4$	45	inact
35	C_2H_5	Et			48 (G)	88–90	EtOH	$C_{12}H_{28}N_2S_2\cdot 2HCl$	inact[e]	inact
36	t-Bu	H			10 (G)	197–199	EtOH	$C_{12}H_{28}N_2S_2\cdot 2HCl$	inact[e]	inact
37	$C_6H_5CH_2$	H			55 (G)	263–265	MeOH–H_2O	$C_{18}H_{24}N_2S_2\cdot 2HCl$	48	12
38	–$(CH_2)_5$–				83 (G)	249–251	MeOH	$C_{14}H_{28}N_2S_2\cdot 2HCl$	inact[e]	inact

[a] All compounds were analyzed for C, H, and N and analytical values were within ±0.4% of calculated values. [b] Potencies as irreversible inhibitors of NE-induced responser in rat vas deferens with BHC as standard (see Experimental Section). All compounds were tested at least five times and the percent inhibition is accurate to within ±5%. [c] These compounds have indefinite melting points. [d] Precipitation in the organ bath was observed during the incubation period. [e] These disulfides were tested also at a 10^{-3} M concentration, showing the blockade values of 34% (35), 84% (36), and 83% (38). [f] Benextramine (BHC).

Scheme III



ride. The phthalimido protecting group in the resulting amides was removed by hydrazine treatment to give the amino amides **48a–d**. Reduction of amino amides **48a–d** with $LiAlH_4$ followed by condensation with thiirane and oxidative dimerization yielded compounds **21**, **22**, **28**, and **29**. The *N*-methyl derivatives **23** and **24** were also obtained from **48a**,**b** through N-formylation with AcOCHO, reduction of resulting formamides **48e**,**f** with $LiAlH_4$, and the subsequent steps of method C.

The amphetamine-related tetramine disulfide **11** was synthesized following method D (Scheme II). Alkylation of 2-benzyl-1,3-dithiane[4] with 1,5-dibromopentane and elimination of the protective group afforded a bromo ketone. This compound was used for alkylation of 1,3-thiazolidine to give the compound **50**. Oxidative ring opening of **50** by I_2/KI treatment gave the dioxo disulfide **51**. The carbonyl groups in disulfide **51** were easily transformed into amino groups by their conversion to oximes and reduction with $LiAlH_4$.

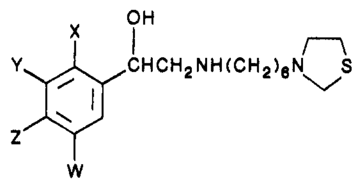
Disulfides **30** and **31**, whose inner nitrogen atoms have been replaced by oxygen atoms, were prepared as indicated in Scheme III (method E). The starting material, S-protected mercaptoethanol[5] **52**, was O-alkylated with 1,5-dibromopentane. The remaining bromine atom was displaced by a cyano group that served as the precursor of the primary amino function in **53**. Cleavage of the C–S benzylic bond with Na in EtOH followed by oxidative coupling of the resulting thiol yielded disulfide **54** having the required functionalization. The last step of method E was the introduction of the benzylic N-substituents achieved through reductive alkylation of disulfide **54** with benzaldehyde or *o*-methoxybenzaldehyde.

Amino ethers **32–34**, lacking the external nitrogen atoms, were obtained through method F (Scheme III) with alcohols **55a–c** as the starting material, respectively. Alkylation of the corresponding alkoxide with 1,6-dibromohexane, followed by reaction with potassium phthalimide and removal of the *N*-phthaloyl group, yielded the amino ethers **56**. These compounds were converted into **32–34** by mercaptoethylation with thiirane and oxidative dimerization with $K_3Fe(CN)_6$.

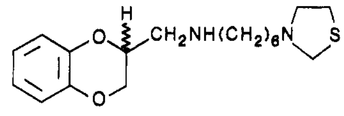
Finally, cystamines **35–38** were synthesized in two steps (method G) from the corresponding amine (diethylamine,

(4) Nagao, Y.; Seno, K.; Fujita, E. *Tetrahedron Lett.* **1979**, 4403.
(5) Szabo, J. L.; Stiller, E. T. *J. Am. Chem. Soc.* **1948**, *70*, 3667.

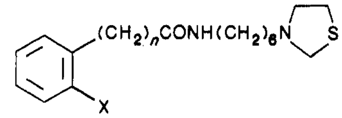
Table II. Structures and Physical Properties of Compounds 45, 48, 50, 51, 53, 54, and 56



45a–h



45i



45j–l

no.	X	Y	Z	W	*n*	yield, %	mp, °C	purifn solvent	formula[a]
45a	H	H	H	H		81	129–135	EtOH	$C_{17}H_{28}N_2OS{\cdot}2C_2H_2O_4{\cdot}3H_2O$
45b	H	-OCH$_2$O-		H		49	93–95	MeOH–Et$_2$O	$C_{18}H_{28}N_2O_3S{\cdot}2C_2H_2O_4$
45c	OMe	H	H	H		81	75–80	MeOH–Et$_2$O	$C_{18}H_{30}N_2O_2S{\cdot}2C_2H_2O_4$
45d	H	OMe	H	H		62	50–52	MeOH–Et$_2$O	$C_{18}H_{30}N_2O_2S{\cdot}2C_2H_2O_4{\cdot}C_4H_{10}O$
45e	H	H	OMe	H		64	134–136	MeOH–Et$_2$O	$C_{18}H_{30}N_2O_2S{\cdot}2C_2H_2O_4$
45f	H	OMe	OMe	H		66	162–165	MeOH–Et$_2$O	$C_{19}H_{32}N_2O_3S{\cdot}2C_2H_2O_4{\cdot}CH_3OH$
45g	H	OMe	OMe	OMe		77	100–102	MeOH–Et$_2$O	$C_{20}H_{34}N_2O_4S{\cdot}2C_2H_2O_4$
45h	H	OCH$_2$OCH$_3$	OCH$_2$OCH$_3$	H		75	68–70	MeOH–Et$_2$O	$C_{21}H_{36}N_2O_5S{\cdot}2C_2H_2O_4$
45i						86	198–200	MeOH	$C_{18}H_{28}N_2O_2S{\cdot}2C_2H_2O_4$
45j	H				1	92	144–146	MeOH	$C_{17}H_{26}N_2OS{\cdot}C_2H_2O_4{\cdot}CH_3OH$
45k	NO$_2$				0	99	173–175	MeCN	$C_{16}H_{23}N_3O_3S{\cdot}HCl$
45l	NH$_2$				0	92	indef	EtOH	$C_{16}H_{25}N_3OS{\cdot}HCl$[b]
48a						72	95–97	MeOH–Me$_2$CO	$C_{11}H_{22}N_2O{\cdot}C_2H_2O_4$
48b						70	121–122	MeOH–Et$_2$O	$C_{10}H_{20}N_2O{\cdot}C_2H_2O_4$
48c						70	110–115	MeOH	$C_{15}H_{22}N_2O{\cdot}C_2H_2O_4{\cdot}CH_3OH$
48d						60	200–215	MeOH–H$_2$O	$C_{14}H_{20}N_2O{\cdot}C_2H_2O_4$
48e						69	200[c]		$C_{12}H_{22}N_2O_2$
48f						61	190[c]		$C_{11}H_{20}N_2O_2$
50						41	145–149	MeOH	$C_{16}H_{23}NOS{\cdot}C_2H_2O_4$
51						97	192–195	MeOH	$C_{34}H_{48}N_2O_2S_2{\cdot}2C_2H_2O_4$
53						14	97–100	MeOH	$C_{15}H_{25}NOS{\cdot}C_2H_2O_4{\cdot}CH_3OH$
54						90	*d*		$C_{16}H_{36}N_2O_2S_2$
56a						85	118–120	Me$_2$CO	$C_{13}H_{21}NO{\cdot}C_2H_2O_4$
56b						85	110–112	Me$_2$CO	$C_{14}H_{23}NO_2{\cdot}C_2H_2O_4$
56c						85	176–180	Me$_2$CO	$C_{14}H_{21}NO_3{\cdot}C_2H_2O_4$

[a] All compounds were analyzed for C, H, and N and analytical values were within ±0.4% of calculated values. [b] This compound has an indefinite melting point. [c] Boiling point at 0.07 mmHg. [d] Purified by column chromatography.

tert-butylamine, benzylamine, or piperidine) by mercaptoethylation with thiirane and oxidative coupling of the resulting thiols by I_2/KI treatment.

Results and Discussion

The disulfides **1–38** were tested as irreversible blockers of the norepinephrine-induced contractions in rat was deferens. With benextramine (BHC, **1**) as a standard for comparison, the relative potencies observed are assembled in Table I.

A blockade of 91% of the NE contraction, almost equivalent to the inhibition caused by BHC, was found for the catechol-containing disulfide **9**, a molecular combination of BHC and NE. This result does not disagree with the hypothesis of Melchiorre attributing a single binding site for the catecholamines and the outer moieties of tetramine disulfides. Although it is well-known that methylation of the phenolic groups of catecholamines greatly reduces their α-adrenergic affinity, this result was not found in our series of phenylethanolamine-bearing disulfides. Even though the aromatic ring of compounds **4–8** contains one, two, or three methoxy groups and no hydroxyl functionalities, these disulfides are potent blockers, especially the trimethoxy derivative, which almost completely inhibits the NE-induced response. Compounds **4–8** could be seen as structural analogues of some methoxyl-containing α-blockers, such as WB-4101. However, their binding is not very specific since the number and/or position of methoxyl groups does not greatly influence their adrenergic blocking potency. On the other hand, Melchiorre has recently reported[1f] a study on the molecular combination of WB-4101 and BHC and concluded that these two kinds of α-blockers have different binding sites.

In good agreement with the above results, 1,4-benzodioxan-2-ylmethyl-substituted tetramine disulfide **10** showed a very poor blocking activity. The stereoselectivity of α-adrenoceptors toward competitive antagonists such as 2-(aminoethyl)-1,4-benzodioxanes is a well-established phenomenon.[3b] In these drugs, 2*S* isomers are consistently more potent than the corresponding 2*R* enantiomers. The adrenergic blocking potency of the enantiomeric benzodioxane-containing disulfides (*S,S*)-**10** and (*R,R*)-**10** was found to be very low at 2×10^{-5} M and almost equivalent for both isomers at higher concentrations. The low activity of derivatives **10** suggests that either the normal benzodioxan blocking site is not being occupied or that the molecule cannot orient itself properly to take advantage of optimum binding at the site. The small difference in activity between optical isomers (*S,S*)-**10** and (*R,R*)-**10** also suggests that the binding is not very specific.

Isosteric replacement of the *o*-methoxyl groups in BHC for amino groups, as in **15**, or formation of a new ring between the outer nitrogen atoms and the aromatic ring, as in **25**, did not bring about a significant change in blocking activity. Again, these results suggest that the flexibility of the binding site can accommodate structural changes such as substitution of nitrogen for oxygen or ring closed systems. The benzoxazinyl and isoquinolyl derivatives **27** and **28** were only slightly soluble in the Krebs solution and therefore did not give reliable results.

Further evidence for the ability of the tetramine disulfide binding site to accommodate many types of compounds is given by the high blocking activity of some heteroarylmethyl-substituted tetramines. Furan and pyrrole analogues **18** and **20** show even greater potency than BHC at 6×10^{-6} M. The low blockade exerted by

19 can be ascribed again to lack of solubility since we observed a precipitate in the organ bath during the incubation period. Although the heteroarylmethyl moieties of compounds **17–20** do not bear any structural resemblance to the adrenergic arylethanolamines, they could bind strongly with a site capable of accommodating flat aromatic substituents, similar to those found in BHC and in conventional α-antagonists. However, this terminal site has very low structural specificity since it can bind efficiently to compounds possessing a saturated heterocyclic ring, as in piperidinyl and pyrrolidinyl derivatives **21** and **22**. Lacking an aromatic rings does not reduce their blocking potencies, given that **21** is even more potent than BHC. On the other hand, 1-indolinyl-substituted disulfide **29** is only a mild blocker even though it has an aromatic ring condensed to the heterocycle and thus is structurally more similar to BHC than **22**. It could be thought that disulfides **21–24** are not related to BHC, but to (aminooctyl)cystamine (AOC), also a potent blocker in the rat vas deferens. Nevertheless, **21** and **22** retain the structure–activity relationships described for BHC[1a] as in systems containing a six-carbon chain between the amino groups and the marked decrease in activity observed after methylation of the inner nitrogen atoms (compounds **23** and **24**).

Although removal of the entire (benzylamino)alkyl moieties of BHC to give diamine disulfides **35–38** caused a marked decrease in blockade, probably through a loss of binding ability, these diamines were not completely inactive. The *tert*-butyl derivative of cystamine, **36**, was as potent as some tetramine disulfides (compounds **2**, **10**) that have all the structural requirements for efficient binding. This result seems to indicate that all four protonatable nitrogen atoms may not be essential for activity. To test this possibility, we undertook the syntheses of diamine disulfides **32–34** having oxygen atoms in place of the outer amino groups of BHC. Two of these compounds, **32** and **33**, showed a considerable degree of blockade, which seems to deny the necessity for the presence of four anionic centers on the binding area for BHC. Similar results were obtained when substitution of oxygen for nitrogen was carried out in the inner cystamine moiety (compounds **30** and **31**) and when the protonable amino groups were changed into nonbasic amide functions (compound **12**). In fact, the diamine–diamide **12** is a more potent blocker than the corresponding tetramine **14**, a result supportive of a dipolar interaction between the outer portions of tetramine disulfides and their binding areas.

In conclusion, we have found that all compounds containing the central cystamine moiety display an irreversible blockade of the NE contraction of the rat vas deferens. This effect is more apparent in cystamines N,N'-disubstituted with 6-aminohexyl groups, especially when the outer nitrogen atoms bear arylalkyl substituents or are enclosed in a ring. Disubstitution of nitrogen atoms in the cystamine moiety leads to poor blockers. Structural specificity in the outer portion of the tetramine disulfide is low since many types of substituents and even the change of amines into nonbasic groups were observed to be potent α-adrenergic blockers.

Experimental Section

Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. Prior to concentration under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ powder. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck, 63–200 μm) and the compounds were detected in TLC with UV light or iodoplatinate reagent. Molecular distillations were effected by use of a Büchi GKR-50 Kugelrohr apparatus; the temperatures cited are the highest reached by the oven during distillation. Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

General Procedure for Preparation of 3-[[(2-Hydroxy-2-arylethyl)amino]hexyl]-1,3-thiazolidines (45a–h). A solution of the aryloxirane **41a–h** (20 mmol)[2c] and 3-(6-aminohexyl)-1,3-thiazolidine (**42**)[2a] (20 mmol) in *i*-PrOH (60 mL) was stirred for 22 h at reflux temperature under a N_2 atmosphere. The solvent was removed at reduced pressure; the residue was dissolved in CH_2Cl_2 (100 mL) and extracted with 2 N HCl (4 × 25 mL). The aqueous layers were basified with 5 N NaOH and extracted with CH_2Cl_2. The organic extracts were dried and evaporated under reduced pressure to give thiazolidines **45a–h** as oils. Purifications were achieved by successive crystallization of the dioxalate derivative.

3-[6-[(1,4-Benzodioxan-2-ylmethyl)amino]hexyl]-1,3-thiazolidines (45i). A solution of (*RS*)-2-(tosylmethyl)-1,4-benzodioxane (**43**)[3a] (1.56 mmol) and Et_3N (0.47 g) in *i*-PrOH (20 mL) was stirred at 25 °C under N_2 atmosphere. After a few minutes, a solution of **42** (4.68 mmol) in *i*-PrOH (15 mL) was added and the mixture was stirred at reflux for 24 h. Upon removal of the solvent under reduced pressure, the residue was taken up in CH_2Cl_2 (200 mL) and extracted with 2 N HCl. The aqueous layer was basified with 5 N NaOH and extracted with benzene. The organic extracts were dried and evaporated, and compound **45i** was obtained in 86% yield. Enantiomers of this compound were prepared in a similar way, with the corresponding chiral tosylate as the starting material.[3b]

***N*-[6-(1,3-Thiazolidin-3-yl)hexyl]phenylacetamide (45j) or Benzamides 45k–l.** To a vigorously stirred solution of **42** (2 g, 10.6 mmol) and Et_3N (2.7 g, 26 mmol) in dry benzene (80 mL) was added dropwise a solution of the suitable acid chloride **44a–c** (10.6 mmol) in anhydrous benzene. Stirring was continued for 5 h at 25 °C. The reaction mixture was washed with H_2O and extracted with 2 N HCl. The aqueous layer was basified with 2 N NaOH and extracted with benzene. The organic extracts were dried and evaporated, yielding the corresponding compound **45j–l** as an oil.

General Procedure for Oxidative Dimerization of Thiazolidines. Preparation of 2–8, 10, 12, and 13. Method A. To a stirred solution of the appropriate thiazolidine **45a–l** (20 mmol) in EtOH (200 mL) was added slowly a solution of 0.1 N I_2/2.5% KI (200 mL) followed by the addition of 2 N HCl (5 mL). The mixture was stirred at 25 °C for 12 h. The solvent was removed at reduced pressure and the residue taken up in 2.5 N NaOH (150 mL). The alkaline solution was washed with CH_2Cl_2 (3 × 75 mL). The organic extracts were dried and concentrated, giving the corresponding disulfides **2–8, 10, 12,** and **13** in high yield. Purifications of these disulfides were achieved by crystallizations of suitable derivatives.

Preparation of *N,N'*-Bis[6-[[2-hydroxy-2-(3,4-dihydroxyphenyl)ethyl]amino]hexyl]cystamine (9). The thiazolidine **45h** was transformed by the previous general procedure into the *N,N'*-bis[6-[[2-hydroxy-2-(3,4-bis(methoxymethoxy)phenyl)ethyl]amino]hexyl]cystamine. Through a solution of this cystamine (1.77 g, 2.13 mmol) in dry methanol (40 mL) and methylene chloride (35 mL) was passed a current of dry hydrogen chloride until the solution pH was acidic. The solution was stirred for 20 h at room temperature, the solvent was removed at reduced pressure, and a yellow solid (1.1 g, 60%) was obtained and identified as the tetrahydrochloride of **9**.

Preparation of *N,N'*-Bis[6-[(phenylethyl)amino]hexyl]cystamine (14). $LiAlH_4$ (0.58 g, 15.3 mmol) was slowly added to a solution of **12** (3 g, 5 mmol) in dioxane (80 mL), and the resulting mixture was stirred at reflux temperature for 4 h. After cooling, excess $LiAlH_4$ was destroyed with H_2O, and the resulting mixture was basified with 2 N NaOH. The organic layer was separated, dried, and evaporated to give compound **14** as an oil (2.01 g, 95%).

Preparation of *N,N'*-Bis[6-[(*o*-aminobenzyl)amino]hexyl]cystamine (15). The thiazolidine **45k** was transformed by the previous general procedure into the *N,N'*-bis[6-[(*o*-nitrobenzoyl)amino]hexyl]cystamine. A solution of this cystamine (4.39 g, 6 mmol) in dry dioxane (150 mL) was slowly added to a suspension of $LiAlH_4$ (3.59 g, 90 mmol) in dry dioxane (70 mL). The mixture was stirred at reflux temperature for 5 h. A nitrogen atmosphere was maintained in a system during the entire process.

The solution was cooled and H_2O (3.6 mL), dioxane (3.6 mL), 2 N NaOH (7.6 mL), and H_2O (10 mL) were added in the order indicated. The suspension that formed was filtered, the solid was washed several times with $CHCl_3$, all the liquid fractions were combined and dried, and the solvent was removed under vacuum to give **15** as an oil (1.6 g, 43%).

Preparation of *N*,*N'*-Bis[6-[(*o*-aminobenzyl)amino]hexyl]-*N*,*N'*-dimethylcystamine (16). $LiAlH_4$ (4.46 g, 117 mmol) was slowly added to a solution of **45l** (4.42 g, 13 mmol) in dry dioxane (200 mL) and the mixture was stirred at relfux temperature under N_2 atmosphere for 5 h. The solution was cooled, and dioxane (4.5 mL), H_2O (4.5 mL), 2 N NaOH (7 mL), and H_2O (13 mL) were added in the order indicated. The suspension that formed was filtered, the solid was washed several times with $CHCl_3$, and the combined organic layers were dried and evaporated to give an oil (3 g). This oil was dissolved in EtOH (50 mL) and over this ethanolic solution 0.1 N aqueous I_2 was added until no decoloration was observed. The solution was stirred for 1 h and evaporated and the residue was dissolved in H_2O. The aqueous solution was basified with 2 N NaOH and extracted with CH_2Cl_2. The organic layer was dried and evaporated to give the disulfide **16** (2.16 g, 56%).

General Procedure for Preparation of Cystamines 17–20. Method B. A solution of *N*,*N'*-bis(6-aminohexyl)cystamine (**46**)[1a] (10 mmol) in dry benzene (140 mL) was added dropwise to a solution of the suitable heterocyclic aldehyde **47a–e** (20 mmol) in dry benzene. The mixture was stirred at reflux temperature for 5 h. The solvent was removed at reduced pressure, and the residue was dissolved in MeOH (160 mL). The solution was cooled to 0 °C, $NaBH_4$ (24 mmol) was added, and the mixture was stirred at room temperature for 1 h. Concentrated HCl was added until acid pH was reached. MeOH was removed at reduced pressure and the residue washed with CH_2Cl_2. The aqueous layer was basified with 2 N NaOH and extracted with CH_2Cl_2. Organic extracts were dried and evaporated to give **17–20**, which were purified by crystallization of a suitable derivative.

General Procedure for Preparation of Amino Amides 48a–d. A solution of 6-phthalimidohexanoyl chloride (140 mmol) in dry CH_2Cl_2 (250 mL) was slowly added to a solution of the heterocyclic amine (piperidine, pyrrolidine, tetrahydroisoquinoline, or indoline) (140 mmol) and Et_3N (420 mmol) in dry CH_2Cl_2 (200 mL), and the resulting mixture was stirred at 25 °C for 5 h. The organic solution was washed with H_2O, 10% HCl, and 1 N NaOH. Drying and evaporation gave good yields of phthalimido amides, which were used without further purification for the next reaction. To a solution of the phthalimido amide product (118 mmol) in EtOH (620 mL) was added 80% aqueous hydrazine (118 mmol) and the mixture was stirred at reflux temperature for 3 h. The solvent was evaporated, the residue dissolved in 5 N NaOH, and the product extracted with $CHCl_3$. The organic layer was dried and evaporated to give the corresponding heterocyclic amino amide **48a–d**.

Preparation of Diamides 48e,f. A mixture of Ac_2O (27.2 g, 260 mmol) and formic acid (10.6 mL, 260 mmol) was stirred for 4 h at 55 °C. After cooling, a solution of the appropriate amide **48a,b** (110 mmol) in dry THF (200 mL) was added and the resulting solution was stirred at reflux temperature for 20 h. The organic solution was washed several times with an aqueous solution of Na_2CO_3, dried, and evaporated to give **48e,f**.

General Procedure for Preparation of Cystamines 21–24, 28, and 29 (Method C). A solution of the appropriate amino amide (**48a–d**) or diamide (**48e,f**) (25 mmol) in dry THF was added to a suspension of $LiAlH_4$ (126 mmol) in dry THF (250 mL) and the resulting mixture was stirred at reflux temperature for 5 h. After the mixture cooled to 25 °C, excess $LiAlH_4$ was destroyed with H_2O and the mixture was filtered. The organic layer was dried and evaporated to give the corresponding *N*-(6-aminohexyl) heterocycle as an oil, which was purified by vacuum distillation.

A solution of thiirane (11 mmol) in dry benzene (15 mL) was slowly added to a solution of *N*-(6-aminohexyl) heterocycle (11 mmol) in benzene (25 mL), and the mixture was stirred for 14 h at reflux temperature. The solvent was evaporated, the resulting oil was dissolved in EtOH (100 mL), and aqueous 0.1 N I_2 was added over the solution until no decoloration was observed. The solvent was evaporated, the resulting solid was dissolved in 2 N NaOH and extracted with CH_2Cl_2, and the resulting organic layer was dried and evaporated. Distillation of the residue allowed recovery of a quantity of the starting diamine. Purification of the product residue by crystallization of a suitable solid derivative allowed us to obtain cystamines **21–24**, **28**, **29**.

Preparation of Cystamines 25–27. A 40% aqueous solution of HCHO (10 mmol) was added to a solution of the suitable compound **15**, **16**, or **49**[1c] (3 mmol) and KOH (0.23 g, 4 mmol) in MeOH (50 mL). The mixture was stirred at reflux temperature for 1 h, MeOH was removed, and H_2O was added to the resulting residue. The aqueous layer was extracted with $CHCl_3$, and the organic solvent was dried and evaporated to give the cystamines **25–27**, respectively.

Preparation of *N*,*N'*-Bis(6-amino-7-phenylheptyl)cystamine (11). Method D. (a) 3-(7-Phenyl-6-oxoheptyl)-1,3-thiazolidine (50). A 1.26 M solution of *n*-BuLi in hexane (18.2 mL) was slowly added to a solution of 2-benzyl-1,3-dithiane[4] (6.2 g, 20 mmol) in THF (80 mL) at –35 °C and stirring was continued for 35 min. The resulting solution was added to a –10 °C solution of 1,5-dibromopentane (14.5 g, 62 mmol) in THF (100 mL). The mixture was stirred at this temperature for 30 min, warmed to 2–3 °C, and stirred for 21 h. A N_2 atmosphere was maintained in the system throughout the entire process. Reaction workup required that H_2O (6 mL) be added and the solvent separated, and the residue was dissolved in H_2O, acidified with 2 N HCl, and extracted with $CHCl_3$. The organic layer was successively washed with an aqueous solution of 5% Na_2SO_3, 5% KOH, and H_2O. Drying and evaporation yielded an oil, which when distilled at 70 °C (0.09 mmHg) yielded 1,5-dibromopentane. The remaining residue was the desired 2-benzyl-2-(5-bromopentyl)-1,3-dithiane (82%). A suspension of this dithiane (4.4 g, 12 mmol), $HgCl_2$ (14.3 g, 52 mmol), and HgO (4.2 g, 19 mmol) in MeOH (300 mL) and H_2O (18 mL) was stirred under a N_2 atmosphere at reflux temperature for 4 h. The solution was cooled and filtered and the solid washed with CH_2Cl_2. The organic layers were evaporated, and the residue was dissolved in H_2O and extracted with CH_2Cl_2. This solution was successively washed with saturated aqueous NH_4Cl solution, 10% HCl, 10% NaOH, and H_2O. The organic layer upon drying and evaporation gave 7-bromo-1-phenyl-2-heptanone (86%). A suspension of this bromo ketone (3.8 g, 14 mmol), 1,3-thiazolidine (1.4 g, 16 mmol), and anhydrous K_2CO_3 (1.7 g, 16 mmol) in *i*-PrOH (150 mL) was stirred at reflux temperature for 23 h under N_2 atmosphere. The mixture was filtered and the solution evaporated to dryness. The residue was dissolved in $CHCl_3$ and extracted with 10% HCl. The aqueous layer was basified with 2 N NaOH and extracted with $CHCl_3$. The organic layer when dried and evaporated gave **50** as an oil.

(b) *N*,*N'*-Bis(7-phenyl-6-oxoheptyl)cystamine (51). The oil **50** was dissolved in EtOH and to this solution was added an aqueous 0.1 N I_2 solution (83 mL). After the mixture was stirred for 2 h, the solvent was eliminated, and the residue was basified with 2 N NaOH and extracted with $CHCl_3$. The organic layer was dried and evaporated to give *N*,*N'*-bis(7-phenyl-6-oxoheptyl)cystamine (**51**) (56%).

(c) Preparation of Cystamine 11. A solution of diketone **51** (2.5 g, 4.8 mmol) in pyridine/EtOH (2:1) (46 mL) and hydroxylamine hydrochloride (1 g, 14.4 mmol) was stirred at reflux temperature for 5 h. The solution was evaporated to dryness, and the residue was dissolved in 1 N NaOH and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried, and evaporated to give the intermediate oxime. The oxime was dissolved in THF (75 mL) and dioxane (25 mL) and $LiAlH_4$ (0.34 g, 8.9 mmol) was added. The mixture was stirred at reflux temperature for 1 h under N_2 atmosphere. The suspension was cooled, and 2 mL of H_2O and 2 mL of 2 N NaOH were successivly added. It was filtered and the residue dissolved in $CHCl_3$. The combined organic layers were washed with H_2O, dried, and evaporated to give the cystamine **11** (20%).

Preparation of Bis[2-[[6-[(arylmethyl)amino]hexyl]oxy]ethyl] Disulfides 30 and 31. Method E. (a) 11-Phenyl-7-oxa-10-thiaundecylamine (53). Under N_2 atmosphere, a solution of 2-(benzylthio)ethanol[5] (**52**) (8.4 g, 50 mmol) in THF (35 mL) and DMF (15 mL) was slowly added to a suspension of NaH (1.4 g, 59 mmol) in THF (35 mL) and DMF (15 mL). The resulting mixture was stirred for 5 min after which a solution of 1,5-dibromopentane (22.9 g, 100 mmol) in THF (35 mL) and DMF (15 mL) was slowly added. The reaction mixture was warmed to reflux temperature and stirred for 1 h. After this time H_2O and Et_2O were added. The organic layer was dried and evaporated to give 30.8 g of an oil. Distillation of the oil gave 12.5 g of 1,5-dibromopentane (85 °C, 0.07 mmHg) and a residue, which was purified by column chromatography; on elution with $CHCl_3$, 6.2 g of 10-bromo-1-phenyl-5-oxa-2-thiadecane was obtained. A solution of KCN (1.5 g, 23 mmol) in H_2O (63 mL) was added to a solution of the above alkyl bromide (6.2 g, 20 mmol) in EtOH (145 mL) and the mixture was stirred at reflux temperature for 4 h. After this time, the EtOH was removed, H_2O was added, and the compound was extracted with Et_2O. The organic layer was dried and evaporated to give 4.9 g of 11-phenyl-7-oxa-10-thiaundecanenitrile (38%). A solution of this nitrile (4.9 g, 18 mmol) in dioxane (50 mL) was added to a suspension of $LiAlH_4$ (2.1 g, 56 mmol) in dioxane (100 mL) and the resulting mixture was stirred at reflux temperature for 3 h. After cooling, 3 mL of H_2O, 3 mL of dioxane, 4 mL of 2 N NaOH, and 9 mL of H_2O were successively added. The mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in $CHCl_3$ and extracted with 10% HCl. The aqueous layer was basified with 2 N NaOH and washed with $CHCl_3$. The chloroform extracts were dried and evaporated to give 3.29 g of an oil. This oil was distilled and the fraction collected between 175 and 200 °C (0.05 mmHg) yielded 2.26 g of **53** (44%).

(b) Bis[2-[(6-aminohexyl)oxy]ethyl] Disulfide (54). Under N_2 atmosphere, small pieces of Na (4.5 g, 195 mmol) were added to a solution of **53** (0.5 g, 1.8 mmol) in EtOH (56 mL). The reaction was strongly exothermic. When spontaneous boiling ceased, the solution was maintained at reflux temperature until all of the Na had dissolved (40 min). The solution was cooled and solid CO_2 was added. The resulting white paste was diluted with EtOH and CH_2Cl_2 and filtered, and the solid was washed with CH_2Cl_2. The organic layers were evaporated to dryness, and the residue was dissolved in EtOH. Over this ethanolic solution was added 0.1 N aqueous I_2 until no decoloration was observed, and the mixture was stirred for 1 h. The solution was evaporated, and the residue was dissolved in H_2O, basified with 2 N NaOH, and extracted with CH_2Cl_2. The organic layer was dried and evaporated to give the disulfide **54** (0.3 g, 90%).

(c) Bis[2-[[6-[(arylmethyl)amino]hexyl]oxy]ethyl] Disulfides 30 and 31. A solution of disulfides **54** (0.3 g, 0.9 mmol) and the suitable aldehyde (benzaldehyde or *o*-methoxybenzaldehyde) (1.9 mmol) in dry benzene (50 mL) was stirred at reflux temperature for 15 h in a system equipped with a Dean–Stark trap. After this time the solvent was evaporated and the residue dissolved in MeOH. To this methanolic solution was added $NaBH_4$ (0.08 g, 2.1 mmol) and the mixture was stirred at reflux temperature for 30 min. The mixture was cooled, acidified with 2 N HCl, and washed with Et_2O. The aqueous solution was basified with 2 N NaOH and extracted with $CHCl_3$. The chloroform extracts were dried and evaporated to give the expected disulfides **30** or **31**.

General Procedure for Preparation of *N,N'*-Bis[(arylmethoxy)hexyl]cystamines 32–38. Method F. (a) [(Arylmethoxy)hexyl]amines 56a–c. A solution of the suitable alcohol **55a–c** (80 mmol) in anhydrous THF (20 mL) was slowly added to a suspension of NaH (100 mmol) and 1,6-dibromohexane (200 mmol) in THF (60 mL). The resulting mixture was stirred at reflux temperature for 30 min, then poured into H_2O, and extracted with Et_2O. The organic layer was washed with H_2O, dried, and evaporated to give an oil. Upon distillation, excess 1,6-dibromopentane and a residue identified as the corresponding bromo ether were isolated. The bromo ether and potassium phthalimide (50 mmol) in DMF (50 mL) were heated at 100 °C for 5 h. After this time the mixture was poured into H_2O and extracted with Et_2O. The organic layer was washed with H_2O, dried, and evaporated to give the corresponding phthalimide. A solution of this phthalimide (80 mmol) and 80% hydrazine hydrate (104 mmol) in EtOH (300 mL) was heated for 3 h at reflux temperature. The solvent was removed, the residue was dissolved in 5 N NaOH, and the desired product was extracted with $CHCl_3$. The $CHCl_3$ extracts were dried and evaporated to give the corresponding amines **56a–c**.

(b) Cystamines 32–38. A solution of the suitable amine (**56a–c**, ethylamine, *tert*-butylamine, benzylamine, or piperidine) (75 mmol) in benzene (20 mL) was stirred at reflux temperature for 1 h in a system equipped with a Dean–Stark trap.

The solution was cooled at 0 °C and a thiirane (63 mmol) in benzene (20 mL) solution was slowly added. The resulting mixture was refluxed for 3 h. The solvent was evaporated, the residue was dissolved in H_2O, and 2 N HCl was added until a pH of 8–9 was reached. A solution of $K_3Fe(CN)_6$ (8 mmol) in H_2O (25 mL) was added. The mixture was allowed to stand, and after a 30-min period, NaOH pellets (6 g, 150 mmol) were added. A sufficient amount of NaCl was next added to saturate the solution. The aqueous solution was washed with CH_2Cl_2, and the organic extracts were dried and evaporated to give disulfides **32–38**. These compounds were purified by crystallization of a solid derivative.

Pharmacology. The following protocol[1a] was applied for the relative potencies listed in Table I. Male rats weighing 200–250 g were killed by a sharp blow on the head and both vasa deferentia were isolated. These were mounted individually in organ baths of 30-mL vol containing Krebs bicarbonate buffer (113 mmol of NaCl, 4.7 mmol of KCl, 2.4 mmol of $CaCl_2$, 1.2 mmol of $MgSO_4$, 1.2 mmol of KH_2PO_4, 25 mmol of $NaHCO_3$, and 11.5 mmol of dextrose). The medium was maintained at 32 °C while being aerated with 95% O_2–5% CO_2. The loading tension was 0.50 g, and the contractions were recorded by means of force transducers connected to a Omni-Scribe recorder. The tissues were allowed to equilibrate for 1 h, and the medium was changed prior to addition of the antagonists. After a 30-min incubation period, the bath was drained and the tissues were washed with the bath solution for 30 min. Cumulative concentration–response curves for NE were constructed after treatment with each antagonist. The decrease in maximum response was expressed in percent of the control value. The percent blockade for each compound is expressed as the mean ± SEM of five separate experiments.

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Modifications of Primaquine as Antimalarials. 4. 5-Alkoxy Derivatives of Primaquine

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Thirty-two 5-alkoxyprimaquines have been synthesized and evaluated as blood schizonticides (*Plasmodium berghei*, mouse) and tissue schizonticides (*Plasmodium cynomolgi*, monkey). Several of these compounds were extremely active in both screens. Such a broad spectrum of antimalarial efficacy offers the possibility of a single drug that could cure the various relapsing and nonrelapsing malarias.

The major forms of human malaria are caused by the parasites *Plasmodium falciparum* and *Plasmodium vivax*. Elimination of the blood form of falciparum malaria clears the body of this disease. Vivax malaria, however, gives rise

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