and brine, dried, and evaporated. Chromatography with CH_2Cl_2 as eluant gave **35** as a yellow solid (504 mg, 54%): mp 124–5 °C; ^1H NMR ($CDCl_3$) δ 8.2–6.92 (13 H, m), 7.1 (1 H, d, J = 2 Hz), 5.32 (2 H, s), 3.5 (2 H, d, J = 2 Hz). Anal. ($C_{23}H_{17}NOS$) C, H, N.

6-(Naphth-2-ylmethoxy)-1-(thiazol-2-yl)indan (20). A solution of **35** (606 mg, 1.7 mmol) in EtOAc (55 mL), AcOH (55 mL), and MeOH (55 mL) was hydrogenated over PtO_2 (90 mg) at 70 psi for 72 h. The catalyst was filtered and the solvent was evaporated. The residue was partitioned between ether and water, and the ether layer was separated, dried, and evaporated. Chromatography with ether–CH_2Cl_2 (5:95) as eluant gave **20** (500 mg): ^1H NMR ($CDCl_3$) δ 8.0–6.9 (12 H, m), 5.2 (2 H, s), 4.8 (1 H, t, J = 8 Hz), 3.2–2.2 (4 H, m).

Resolution of (±)-2j. Racemic **2j** was resolved by using preparative HPLC on a Pirkle chiral column (ionic form) with (*S*)-(+)-(3,5-dinitrobenzoyl)phenylglycine [(*S*)-(+)-DNBPG] as chiral support.[21] Elution with dioxane–hexane (3:97) provided (+)-**2j**, mp 83–4 °C. The opposite enantiomer (−)-**2j**, $[\alpha]_D$ −5 ● 0.5°, was obtained under identical conditions with a preparative (*R*)-(−)-DNBPG column. Optical purity was assessed as ≥95% by analytical HPLC with an (*R*)-(−)-DNBPG column.

Acknowledgment. We warmly acknowledge the invaluable contributions made to this work by the following: R. I. Dowell, M. T. Briggs, D. Glarvey, E. Hadley, P. M. Hamilton, G. Lloyd-Jones, J. I. Mayall, D. P. Whalley, M. G. Baudart, C. Delvare, M. Lamorlette, G. Pasquet, D. J. Masters, M. E. McCormick, K. E. Proudman, V. Jacobs, V. Vickers. We thank Dr. B. M. Weichmann, Wyeth-Ayerst Research, for a sample of WY-50295.

(21) Pirkle, W. H.; Finn, J. M. *J. Org. Chem.* **1981**, *46*, 2935; **1982**, *47*, 4037.

Novel Thiophene-, Pyrrole-, Furan-, and Benzenecarboxamidotetrazoles as Potential Antiallergy Agents

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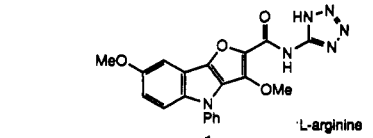
The synthesis and antiallergic activity of a series of novel thiophene-, pyrrole-, furan-, and benzenecarboxamidotetrazoles are described. A number of compounds inhibit the release of histamine from anti-IgE-stimulated human basophils. Optimal inhibition is exhibited in compounds with a 3-alkoxy, a 4-halo, and a 5-methyl, 5-methoxy, or 5-bromo on a thiophene-2-carboxamidotetrazole.

Introduction

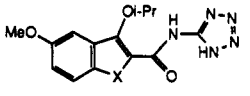
Inflammatory mediators such as histamine, leukotrienes, prostaglandins, proteases, and chemotactic factors released by various cells are responsible for the symptoms of allergic diseases.[1] Thus, inhibition of mediator release has been an attractive approach for the development of antiallergic drugs. Historically, the passive cutaneous anaphylaxis (PCA) model in the rat has been the primary allergic model for characterizing mast cell stabilizers. To date, the use of this model has failed to provide therapeutically useful agents.[2] Although drugs currently used as antiallergic agents have been found to inhibit mediator release from various cells, it is not clear that this is their primary mode of action since high concentrations are required for this effect.

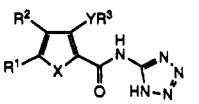
Our strategy for the discovery of well-defined inhibitors of mediator release for the prophylactic treatment of allergic diseases employed the inhibition of IgE-dependent histamine release from human basophils as an initial in vitro screen.[3]

Recently, the antiallergic activities of series of furo[3,2-*b*]indoles,[3c,4,5] indoles,[5a] and benzo[*b*]thiophenes[5b] have been described. These series contained potent inhibitors of mediator release in the basophil assay, i.e., CI-922 (**1**),[3c,5] CI-949 (**2a**),[5a] and CI-959 (**2b**).[5b] Conceptually, **2** was derived from **1** by removing the furan ring in **1**. As a result of this modification **2a** and **2b** are more water soluble (Table III) and can be prepared by shorter synthetic routes than **1**. In an attempt to further increase water solubility and synthetic accessibility and to further decrease the lipophilicity of the carboxamidotetrazoles, another ring was removed from **2** to give the monocyclic compounds **3**.



1





3

2a X = NPh; L-arginine salt

2b X = S; sodium salt

X = S, NR^5, O, CR^6=CH

Y = O, S

R^3 = Me, Et, i-Pr, CH_2Ph

(1) (a) Kay, A. B. *Eur. J. Respir. Dis.* **1986**, (Suppl. 147), *69*, 38. (b) Raphael, G. D.; Metcalfe, D. D. *Ibid.* **1986** (Suppl. 147), *69*, 44. (c) Holgate, S. T.; Howarth, P. H.; Beasly, R.; Agius, R.; Church, M. K. *Ibid.* **1986**, (Suppl. 144), *68*, 34. (d) Holgate, S. T.; Kay, A. B. *Clin. Allergy* **1985**, *15*, 221. (e) MacGlashan, D. W.; Schleimer, R. P.; Peters, S. P.; Schulman, E. S.; Adams, G. K.; Sobotka, A. K.; Newball, H. H.; Lichtenstein, L. M. *Fed. Proc.* **1983**, *42*, 2504. (f) Findlay, S. R.; Lichtenstein, L. M. *Am. Rev. Resp. Dis.* **1980**, *122*, 53.

(2) Auty, R. M. *Eur. J. Respir. Dis.* **1986** (Suppl. 147), *69*, 120.

(3) (a) Lichtenstein, L. M.; Osler, A. G. *J. Exp. Med.* **1964**, *120*, 507. (b) Siraganian, R. P.; Brodsky, M. J. *J. Allergy Clin. Immunol.* **1976**, *57*, 525. (c) Conroy, M. C.; Kennedy, J. A.; Thueson, D. O. *Int. Archs. Allergy Appl. Immun.* **1985**, *77*, 222. (d) Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A., Jr.; Tarrant, M. E.; Torley, L. W.; Wrenn, S. *J. Med. Chem.* **1990**, *33*, 1230.

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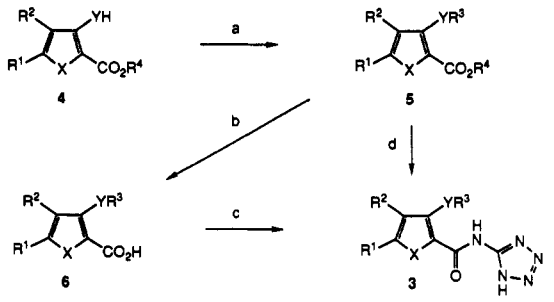
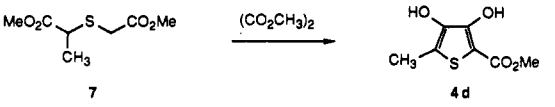
Scheme I[a,b]



[a] Y = O, S; X = S, NR^5, O, CR^6=CH. [b] (a) method A, triisopropylisourea, MeCN; method B, *t*-BuOK, 2-PrBr, DMSO; method C, K_2CO_3, R^3Br or $(R^3O)_2SO_2$, acetone; (b) NaOH or KOH, H_2O; (c) CDI, NEt_3, 5-aminotetrazole, MeCN; (d) 2 equiv of NaH, 5-aminotetrazole, DMSO.

Scheme II



This modification led to thiophenes (X = S), pyrroles (X = NR^5), furans (X = O), and benzenes (X = CR^6=CH) as target compounds. The synthesis, antiallergic activity, physical properties, and structure–activity relationships (SAR) of **3** will be described in this paper.[6]

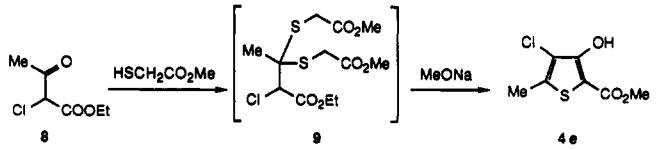
Biology

For the basophil assay,[3] whole human blood was obtained from allergic volunteer donors. The leukocytes were isolated following erythrocyte sedimentation, washed, and resuspended in an isotonic buffer solution. This suspension of cells was pretreated with the test compound for 10 min and then challenged with anti-IgE. Percent histamine release from drug and anti-IgE or buffer-treated cells was compared following quantitation of histamine in the supernatant fluids using an automated fluorometric assay. Each test compound was screened in triplicate at drug concentrations of 33 and 10 μm. The most potent compounds were evaluated at 0.3, 1.0, 3.3, 10.0, 33.0, and 100 μM to determine IC_{50} values.

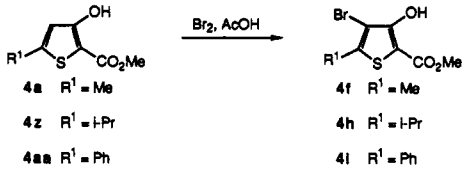
Chemistry

The general synthetic pathway for the preparation of carboxamidotetrazoles **3** is shown in Scheme I. O-Alkylation of enol esters **4** using (1) triisopropylisourea, acetonitrile (method A),[7] (2) *t*-BuOK, 2-bromopropane, DMSO (method B), or (3) K_2CO_3, R^3Br or $(R^3O)_2SO_2$, acetone (method C) gave *o*-alkoxy esters **5**. Many of the esters **5** were oils and were utilized crude for conversion to the acids **6** (Table I). Coupling of **6** with 5-aminotetrazole was effected with 1,1′-carbonyldiimidazole (CDI) and triethylamine to give **3** (Table II). The preparation of **4** and the synthetic routes that enter the general synthetic pathway in Scheme I via **5** and **6** are described below.

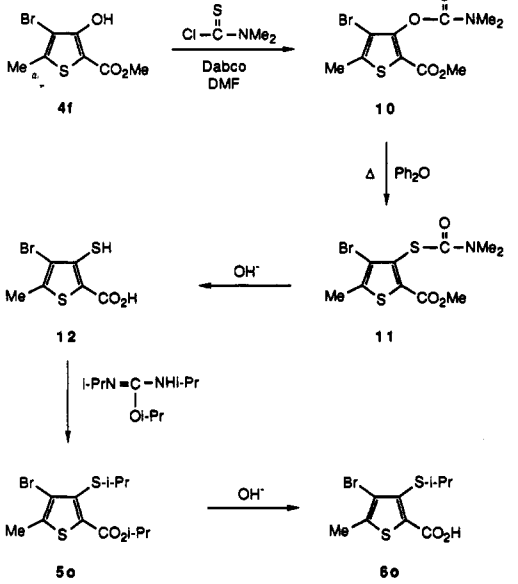
Scheme III



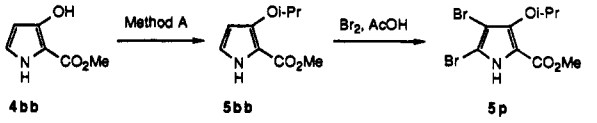
Scheme IV



Scheme V



Scheme VI



Scheme VII

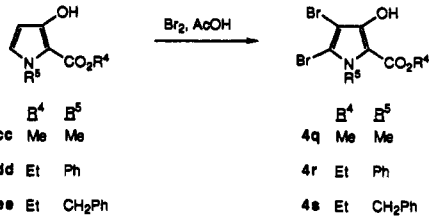


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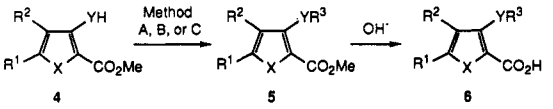
Table I. Intermediate Carboxylic Acids 6[a]



4 5 6

no.	starting enol ester	alkyl.[b] method	alkyl. yield, %	sapon.[c] yield, %	mp, °C, of 6	recryst. solvent	microanal.[d]
6a	4a[e]	A	76	61	110–111	*i*-PrOH	$C_9H_{12}O_3S$
6b	4b[f]	B	96	33[g]	133–134	acetone	$C_{10}H_{14}O_3S$
6c	4c	A	99	63	163–164	EtOH	$C_{12}H_{18}O_3S$
6d	4d	A	71	86	82–84	*h*	$C_{12}H_{18}O_4S$
6e	4e	A	99	84	132–134	*h*	$C_9H_{11}ClO_3S$
6f	4f	A	98	74	129–130	*h*	$C_9H_{11}BrO_3S$
6g	4g[i]	A	98	82	127–128	*h*	$C_8H_9BrO_3S$
6h	4h	A	96	96	131–132	*h*	$C_{11}H_{15}BrO_3S$
6i	4i	A	90	98	159–160	*h*	$C_{14}H_{13}BrO_3S$
6j	4j[i]	A	76	87	138–142	*h*	$C_8H_8Br_2O_3S$
6k	4k[j]	A	96	91	115–116	*h*	$C_9H_{11}BrO_4S$
6l	4f	C[k]	51	73	172–173	EtOH	$C_{13}H_{11}BrO_3S$
6m	4f	C[l]	99	48	157–158	EtOAc	$C_8H_9BrO_3S$
6n	4f	C	51	92	172–173	*h*	$C_7H_7BrO_3S$
6o		*m*		87	132–134	*h*	$C_9H_{11}BrO_2S_2$
6p		*m*		99	oil	*h*	*o*
6q	4q	B	33	96	89 dec	*h*	*o*
6r	4r[p]	B	92	93[n]	76 dec	*h*	*o*
6s	4s[p]	B	85	94[n]	122 dec	*h*	*o*
6v		*m*		89	162–163	EtOAc/hexane	$C_{14}H_{22}O_4Si$
6w		*m*		74	109–110	EtOAc/hexane	$C_{11}H_{13}BrO_4$
6y	4y	B	55	66[g]	103–104	EtOAc/hexane	$C_{11}H_{12}Br_2O_4$

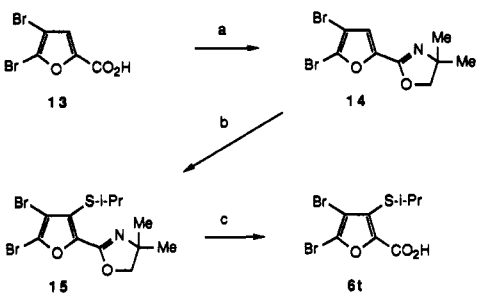
[a] X, R^1, R^2, and YR^3 are defined in Table IV. [b] Examples of general alkylation methods are given in the Experimental Section. Method A: triisopropylisourea, MeCN. Method B: *t*-BuOK, 2-bromopropane, DMSO. Method C: dimethyl sulfate, K_2CO_3, acetone, Δ. [c] A general saponification method is given in the Experimental Section. [d] All the carboxylic acids analyzed were within 0.4% of calculated formula values for C, H, and N and for S, Cl, Br, and I where applicable. [e] See ref 8 (Fiesselmann, H.; et al). [f] See ref 8 (Brelivet, J.; et al). [g] See Experimental Section for method of saponification for this compound. [h] Recrystallization was not necessary. [i] See ref 8 (Corral, C.; et al. *Synthesis*). [j] See ref 8 (Corral, et al. *J. Chem. Soc.*). [k] Benzyl bromide was used instead of dimethyl sulfate. [l] Diethyl sulfate was used instead of dimethyl sulfate. [m] See Experimental Section for the preparation of alkylated ester 5. [n] Reaction mixture was acidified with aqueous H_3PO_4 instead of aqueous HCl. [o] No microanalytical data due to instability of compound. [p] Ethyl ester.

Thiophenes. The methyl 3-hydroxythiophene-2-carboxylates **4a,b,g,j,k**, starting materials for **3a,b,g,j,k**, respectively, were prepared as previously described,[8] and **4c** was prepared analogously to **4a**. Methyl 3,4-dihydroxy-5-methyl-2-thiophenecarboxylate (**4d**) was prepared by the condensation of dimethyl oxalate with **7**[9] (Scheme II). Treatment of ethyl 2-chloroacetoacetate (**8**) with methyl thioglycolate gave **9**, which under basic reaction conditions (MeONa, MeOH) condensed to give 3-chlorothiophene (**4e**) (Scheme III). Bromination of **4a**, **4z**, and **4aa**[8] using bromine in acetic acid gave 4-bromothiophenes **4f**, **4h**, and **4i**, respectively (Scheme IV). The preparation of the 3-isopropylthio compound **6o** involved a Newman[10] rearrangement converting **4f** to **12** (Scheme V). S-Alkylation and esterification of **12** with triisopropylisourea[7] gave **5o**, which was saponified to give **6o**.

Pyrroles. The 1*H*-pyrrole **5p** was prepared by O-alkylation of enol ester **4bb** to give **5bb**, which was in turn brominated to give **5p** (Scheme VI). 4,5-Dibromopyrroles **4q**, **4r**, and **4s** were prepared by bromination of **4cc**, **4dd**,[11] and **4ee**,[11] respectively (Scheme VII).

Furan. The preparation of the appropriately tetrasubstituted furan **6t** is shown in Scheme VIII. The oxazoline **14** of 4,5-dibromo-2-furancarboxylic acid (**13**)[12] was

Scheme VIII[a]



13 14 15 6t

[a] (a) $(COCl)_2$, cat. DMF, CH_2Cl_2; $H_2NC(CH_3)_2CH_2OH$, 0–25 °C, 2.5 h; $SOCl_2$, toluene, 0–25 °C, 18 h; (b) LDA, diisopropyl disulfide, −78 to −10 °C, 3.75 h; (c) 4 N HCl, Δ, 0.5 h; LiOH, H_2O, MeOH, THF, 0–25 °C, 16 h.

treated with LDA and diisopropyl disulfide, and the resulting 3-isopropylthio compound **15** was deprotected to give **6t**.[13] Attempts to introduce the 3-isopropylthio group using carboxylic acid **13** or its methyl ester were unsuccessful.

Benzenes. Methyl 3,5-dibromo-2-hydroxy-4-methoxybenzoate (**4y**) was prepared by bromination of methyl 2-hydroxy-4-methoxybenzoate (**4u**) using bromine and acetic acid in chloroform (Scheme IX). The regiospecific introduction of a bromo and iodo group in the 3-position

(8) For preparation of **4a** and **4aa**, see: Fiesselmann, H.; Thoma, F. *Chem. Ber.* **1956**, *89*, 1907. **4b**, see: Brelivet, J.; Appriou, P.; Teste, J. *Bull. Soc. Chim. Fr.* **1971**, *11*, 1344. **4g** and **4j**, see: Corral, C.; Lissavetzky, J. *Synthesis* **1984**, 847. **4k**, see: Corral, C.; Lissavetzky, J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2711.
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(10) Newman, M. S.; Karnes, H. A. *J. Org. Chem.* **1966**, *31*, 3980.
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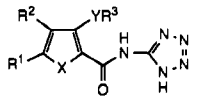
(13) For related furan chemistry, see: Carpenter, A. J.; Chadwick, D. J. *Tetrahedron Lett.* **1985**, *43*, 5335. Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1343.

Table II. Carboxamidotetrazoles[a]



no.	method[b]	yield, %	mp, °C	recryst. solvent	microanal.[c]
3a	A	79	235 dec	*d*	$C_{10}H_{13}N_5O_2S$
3b	A	81	246 dec	*d*	$C_{11}H_{15}N_5O_2S$
3c	B	39	136–137	Et_2O	$C_{13}H_{19}N_5O_2S$
3d	B	59	193–195	EtOAc	$C_{13}H_{19}N_5O_3S$
3e	B	67	214–215	EtOH	$C_{10}H_{12}ClN_5O_2S$
3f	A	85	117 dec	*d*	$C_{10}H_{12}BrN_5O_2S$
3g	B	92	193–194	*d*	$C_9H_{10}BrN_5O_2S$
3h	B	62	218–219	MeOH	$C_{12}H_{12}BrN_5O_2S$
3i	B	55	226–227	MeOH	$C_{15}H_{14}BrN_5O_2S$
3j	B	74	230 dec	MeOH	$C_9H_9Br_2N_5O_2S$
3k	B	53	211–212	EtOAc	$C_{10}H_{12}BrN_5O_3S$
3l	A	54	199–200	MeOH	$C_{14}H_{12}BrN_5O_2S$
3m	B	73	211–213	MeOH	$C_9H_{10}BrN_5O_2S$
3n	B	59	208–209	*d*	$C_8H_8BrN_5O_2S$
3o	B	95	235 dec	*d*	$C_{10}H_{12}BrN_5OS_2$
3p	B	16	194–196	MeCN	$C_9H_{10}BrN_6O_2$
3q	B	50	218–220	EtOAc	$C_{10}H_{12}Br_2N_6O_2$
3r	B	56	184 dec	*t*-BuOMe	$C_{14}H_{14}Br_2N_6O_2$
3s	B	49	199–205	MeCN	$C_{16}H_{16}Br_2N_6O_2$
3t	C	72	242–243	EtOAc/hexane	$C_9H_9Br_2N_5O_2S$
3u	*e*	24	212–213	EtOH (95%)	$C_{12}H_{15}N_5O_3$
3v	C	79	212–213	EtOAc/hexane	$C_{15}H_{23}N_5O_3Si$
3w	C	84	255–256	*d*	$C_{12}H_{14}BrN_5O_3$
3x	*e*	71	250 dec	DMF/H_2O	$C_{12}H_{14}IN_5O_3$
3y	C	88	232–233	DMF/EtOH	$C_{12}H_{13}Br_2N_5O_3$

[a] X, R^1, R^2, and YR^3 are defined in Table IV. [b] See general methods A, B, and C in the Experimental Section. [c] All the carboxamidotetrazoles analyzed for C, H, N and S, Cl, Br, I, where applicable. The observed values were within 0.4% of calculated values. [d] Product was not recrystallized. [e] See the Experimental Section for specific procedure.

Table III. log *P* and Solubility Values for Carboxamidotetrazoles **3**

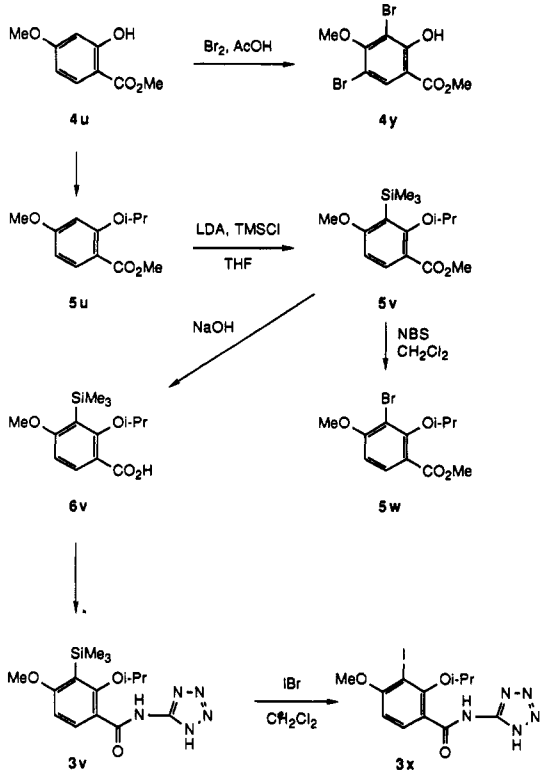
no.	log *P*[a]	solubility[b]
3f	1.72	3.3
3j	1.85	0.8
3k	1.35	1.9
3q	2.52	1.9
3x	1.17	c
1[d]	2.8[e]	<0.001[f]
2a[d]	2.66	0.07
2b[d]	1.78	1.84

[a] log *P* determination at pH 7.4 using correlation (HPLC) method. [b] Solubility in mg/mL determined at pH 7.4. [c] Not determined. [d] Values on parent compound. [e] log *P* determination at pH 7.4 using shake flask method. [f] Solubility in mg/mL determined at pH = 7.0.

of the benzene compounds is also outlined in Scheme IX. The regiospecific silylation of **5u** was effected by heteroatom-directed lithiation[14] using LDA in the presence of chlorotrimethylsilane[15] at −78 °C to give **5v**. Ipso substitution of the silyl group in **5v**, using NBS, gave only the 3-bromo compound **5w**. Carboxamidotetrazole **3v**, prepared by our usual method from **5v**, was treated with IBr in CH_2Cl_2 to give 3-iodo compound **3x**.[16]

Table III, containing log *P* and solubility values for a select group of compounds from each monocyclic series,

Scheme IX



shows that the lipophilicity was reduced and solubility was increased for **3** compared to **1** and **2**.

Biological Results and Discussion

The SAR of the indoles for the basophil assay revealed that a carboxamidotetrazole ortho to an alkoxy group with a chloro or methoxy group in the indole 5 or 6 positions were necessary for potency.[5a] The indole SAR, optimized in **2a**, was used to design targets for the monocyclic compounds **3**. As in the indole series, the *o*-alkoxy carboxamidotetrazole substitution pattern in compounds **3** resulted in potent inhibitors of histamine release. The corresponding *o*-alkoxy carboxylic acids **6** were inactive. The antiallergic activity of carboxamidotetrazoles **3**, assessed by the inhibition of anti-IgE-stimulated histamine release from human basophils, is shown in Table IV.

In the thiophene series we found, when holding YR^3 as isopropoxy and R^1 as methyl, that high potency was achieved when R^2 was bromo (**3f**) or chloro (**3e**). When R^2 was hydrogen (**3a**), methyl (**3b**), isopropyl (**3c**) or isopropoxy (**3d**), the resulting compounds were inactive. When R^2 was chosen as bromo, YR^3 was kept as isopropoxy, and R^1 was varied, we found that the R^1 = methyl (**3f**), bromo (**3j**), and methoxy (**3k**) compounds were highly potent, whereas the R^1 = hydrogen (**3g**) analogue was moderately active and the isopropyl (**3h**) and phenyl (**3i**) compounds were inactive. Thus, R^1 substituents that project out of the plane of the thiophene are not desirable. To examine the effects of various YR^3 groups, we kept R^1 as methyl and R^2 as bromo. The ethoxy (**3m**), isopropoxy (**3f**), benzyloxy (**3l**), and isopropylthio (**3o**) analogues exhibited high potency in the basophil assay; however the methoxy (**3n**) analogue was moderately active, indicating that a bulky, lipophilic group is optimal for R^3.

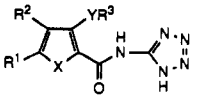
For extension of the thiophene SAR to the pyrrole (X = NR^5), furan (X = O), and benzene (X = CR^6=CH) series, key compounds were prepared for each ring system. On the basis of synthetic accessibility and SAR, the 4,5-dibromo-3-isopropoxy substitution pattern of thiophene

(14) For reviews on heteroatom-directed lithiations of aromatic compounds, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. Beak, P.; Sniekus, V. *Acc. Chem. Res.* **1982**, *15*, 306.

(15) The compatibility of trimethylsilyl chloride with lithium tetramethylpiperidide at −78 °C is described in Kirzan, T. D.; Martin, J. C. *J. Org. Chem.* **1982**, *47*, 2681.

(16) This methodology is described in Felix, G.; Dunogues, J.; Pisciotti, F.; Calas, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 488.

Table IV. Inhibition of Histamine Release from Human Basophils by Carboxamidotetrazoles



no.	X	R^1	R^2	YR^3	basophil: % inhibition[a,b] 33 μM	10 μM	IC_{50} (μM)[c]
3a	S	Me	H	O-*i*-Pr	N	N	
3b	S	Me	Me	O-*i*-Pr	N	N	
3c	S	Me	*i*-Pr	O-*i*-Pr	N	N	
3d	S	Me	O-*i*-Pr	O-*i*-Pr	N	N	
3e	S	Me	Cl	O-*i*-Pr	88 ± 2 (3)	55 ± 5 (3)	8
3f	S	Me	Br	O-*i*-Pr	97 ± 1 (7)	85 ± 3 (7)	2
3g	S	H	Br	O-*i*-Pr	47 ± 1	30 ± 2	
3h	S	*i*-Pr	Br	O-*i*-Pr	N	N	
3i	S	Ph	Br	O-*i*-Pr	N	N	
3j	S	Br	Br	O-*i*-Pr	88 ± 7 (4)	59 ± 14 (4)	7
3k	S	OMe	Br	O-*i*-Pr	95 ± 6 (4)	92 ± 6 (2)	2
3l	S	Me	Br	OCH_2Ph	91 ± 3 (3)	68 ± 7 (3)	5
3m	S	Me	Br	OEt	100 ± 1 (2)	77 ± 2 (2)	5
3n	S	Me	Br	OMe	53 ± 2	N	
3o	S	Me	Br	S-*i*-Pr	90 ± 1	74 ± 1	5
3p	NH	Br	Br	O-*i*-Pr	N	N	
3q	NMe	Br	Br	O-*i*-Pr	69 ± 2	37 ± 4	25
3r	NPh	Br	Br	O-*i*-Pr	N	N	
3s	NCH_2Ph	Br	Br	O-*i*-Pr	N	N	
3t	O	Br	Br	S-*i*-Pr	N	N	
3u	CH=CH	OMe	H	O-*i*-Pr	41 ± 1	N	
3v	CH=CH	OMe	$SiMe_3$	O-*i*-Pr	N	N	
3w	CH=CH	OMe	Br	O-*i*-Pr	60 ± 3	N	
3x	CH=CH	OMe	I	O-*i*-Pr	73 ± 1	51 ± 3	10
3y[d]	CBr=CH	OMe	Br	O-*i*-Pr	28	N	
1	CI-922				91 ± 1 (6)	66 ± 5 (6)	8.5
2a	CI-949				82 ± 2 (45)	46 ± 3 (43)	15.0
2b	CI-959				97 ± 1 (6)	95 ± 2 (6)	1.1
nedocromil					N	N	

[a] Percent inhibition ± standard error from mean of basophil histamine release stimulated by anti-IgE. The number of experiments run is equal to one unless otherwise indicated in parentheses (*n*). [b] Inactive (N) is defined as <25% inhibition at the screening concentration. [c] Concentration of compound (μM) inhibiting anti-IgE-stimulated histamine release by 50%. [d] Bromine atoms in 3 and 5 positions of the benzene ring.

3j was chosen to examine the effect of variation of the pyrrole nitrogen substituents (R^5) on activity in the basophil assay. The *N*-methylpyrrole **3q** was the only pyrrole that showed activity, although it was significantly less potent than the corresponding thiophene **3j**. The *N*-H (**3p**), *N*-phenyl (**3r**), and the *N*-benzyl (**3s**) compounds were all inactive.

Furan **3t** was an inactive compound. Although this is not surprising when compared to the inactive pyrroles **3p**, **3r**, and **3s**, the thiophene SAR (see **3j** and **3o**) strongly suggested that it would be active.

When the substitution pattern of the potent thiophene **3k** was applied to the benzene series (X = CR^6=CH), good efficacy was achieved in compounds **3w** (R^1 = OMe, R^2 = Br) and **3x** (R^1 = OMe, R^2 = I). Replacement of the halogen in **3w** and **3x** with hydrogen (**3u**) or trimethylsilyl (**3v**) gave inactive compounds. Introduction of a 5-bromo substituent on the active **3w** also gave inactive compound **3y**.

In general, the compounds containing the thiophene core are more potent in the basophil assay than the pyrrole, furan, or benzene compounds with the same or similar substitution patterns. The thiophenes **3e**, **3f**, **3j**, **3k**, **3l**, **3m**, and **3o** exhibited potency equivalent to **1** and **2**. Nedocromil was inactive in the basophil assay.

Conclusions

Series of thiophene-, pyrrole-, furan-, and benzenecarboxamidotetrazoles have been prepared in which the preliminary antiallergic activity was assessed by measuring the inhibition of histamine release from human basophils stimulated by anti-IgE. This work extends and further defines the structure–activity relationships for the basophil assay initiated in the indole and benzothiophene series. In addition, the most potent monocyclic compounds were more water soluble, less lipophilic, and synthetically more accessible than **1** and **2**, see Table I. The compounds that were the most potent inhibitors in the basophil assay contained (1) a 3-alkoxy group larger than methoxy, (2) a 4-bromo group, and (3) a 5-methyl, 5-methoxy, or 5-bromo group on a *N*-1*H*-tetrazol-5-yl-2-thiophenecarboxamide. Thiophene **3f**, with potency comparable to CI-922 (**1**), CI-949 (**2a**), and CI-959 (**2b**), was selected for further evaluation, including additional in vitro testing and evaluation in in vivo allergic models.

Experimental Section

Melting points were determined on a Mel-Temp or Electrothermal capillary apparatus and are uncorrected. The ^{1}H NMR spectra were determined at 90 MHz on a Varian EM-390, at 100 MHz on an IBM WP100SY, or at 200 MHz on a Varian XL-200 spectrometer with tetramethylsilane as an internal standard. The infrared spectra were recorded on a Digilab FTS-14 or a Nicolet FT-IRMS-1 spectrophotometer. Elemental analyses were provided by the Analytical Chemistry staff of this department. All new compounds yielded spectral data consistent with the proposed structure and microanalysis within ±0.4% of the theoretical values unless indicated otherwise.

Methods for the Preparation of Carboxamidotetrazoles 3. Method A. 5-Methyl-3-(1-methylethoxy)-*N*-1*H*-tetrazol-5-yl-2-thiophenecarboxamide (3a). A solution of 2.0 g (10 mmol) of acid **6a** in 25 mL of tetrahydrofuran was stirred under an inert atmosphere at room temperature while 1.7 g (10 mmol) of 1,1′-carbonyldiimidazole was added and then heated to reflux.

After 1.5 h, heating was interrupted, 0.85 g (10 mmol) of anhydrous 5-aminotetrazole was added, and then heating resumed. After an additional 2.5 h, the mixture was cooled to 0–5 °C and filtered. The solid was rinsed with cold THF and dried. This material was then stirred for 10 min in 50 mL of aqueous 2 N HCl, filtered, rinsed with water, and dried to afford 2.1 g (79%) of the pure adduct **3a**: mp 235 °C dec; IR (KBr) 1669, 1606, 1520, 1108 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.43 (d, J = 6 Hz, 6 H, $CH(CH_3)_3$), 2.50 (s, 3 H, CH_3), 4.85 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 7.05 (s, 1 H, Ar H), 10.15 (s, 1 H, CONH). Anal. ($C_{10}H_{13}N_5O_2S$) C, H, N, S.

Method B. 4-Bromo-3-(1-methylethoxy)-*N*-1*H*-tetrazol-5-yl-2-thiophenecarboxamide (3g). A solution of 3.5 g (13 mmol) of the acid **6g** in 50 mL of tetrahydrofuran was stirred under an inert atmosphere, treated with 2.2 g (14 mmol) of 1,1′-carbonyldiimidazole, and then heated under reflux. After 1.5 h, 1.1 g (13 mmol) of anhydrous 5-aminotetrazole was added and heating continued. After an additional 2.5 h, the mixture was stirred into 200 mL of ice water and acidified with concentrated HCl. After 1 h, the reaction was filtered and the solid was rinsed with water and dried to afford 4.1 g (92%) of the pure product **3g**: mp 193–194 °C; IR (KBr) 1676, 1598, 1015 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.33 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 4.65 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 8.15 (s, 1 H, Ar H), 11.28 (br s, 1 H, CONH), 15.5–16.7 (br s, 1 H, NH). Anal. ($C_9H_{10}BrN_5O_2S$) C, H, N, Br, S.

Method C. 4,5-Dibromo-3-[(1-methylethyl)thio]-*N*-1*H*-tetrazol-5-yl-2-furancarboxamide (3t). A mixture of 1.90 g (5.69 mmol) of carboxylic acid **6t** and 1.11 g (6.85 mmol) of 1,1′-carbonyldiimidazole in 25 mL of acetonitrile was warmed at reflux for 30 min under an N_2 atmosphere. The cooled reaction mixture was treated with 0.58 g (6.82 mmol) of anhydrous 5-aminotetrazole and 1.38 g (13.63 mmol) of triethylamine. The reaction was warmed at reflux for 18 h and poured onto 250 mL of ice water. The mixture was acidified with aqueous 10% HCl and filtered to give the product as a tan solid. Recrystallization from ethyl acetate–hexane afforded 1.43 g as a tan solid: mp 242–243 °C. A second crop (0.26 g), mp 242–243 °C, was isolated, bringing the total yield to 1.69 g (72%): IR (KBr) 1687, 1607, 1589, 1475, 1267, 982 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.30 (d, J = 7 Hz, 6 H, $CH(CH_3)$), 3.92 (heptet, J = 7 Hz, 1 H, $CH(CH_3)$), 12.79 (br s, 1 H, CONH), 15.89 (br s, 1 H, tetrazole NH). Anal. ($C_9H_9Br_2N_5O_2S$), C, H, N, Br, S.

4-Methoxy-2-(1-methylethoxy)-*N*-1*H*-tetrazol-5-ylbenzamide (3u). A solution of 3.0 g (35.3 mmol) of anhydrous 5-aminotetrazole in 20 mL of dimethyl sulfoxide was added dropwise to a 15 to 20 °C slurry of 2.8 g (70.0 mmol) of 60% NaH (oil dispersion) in 75 mL of dimethyl sulfoxide under nitrogen atmosphere. The resulting mixture was stirred at 25 °C for 2.5 h. A solution of 6.50 g (28.98 mmol) of methyl 4-methoxy-2-(1-methylethoxy)benzoate (**5u**) in 25 mL of dimethyl sulfoxide was added dropwise to the reaction, and the mixture was stirred at 25 °C for 18 h. The reaction was poured onto 600 g of ice water and the resulting aqueous solution was acidified with aqueous 10% HCl. The product was isolated by vacuum filtration and recrystallization from 95% ethanol gave 1.90 g (24%) of 4-methoxy-2-(1-methylethoxy)-*N*-1*H*-tetrazol-5-ylbenzamide as fine, white needles: mp 212–213 °C; IR (KBr) 3273, 1664, 1589, 1270, 1125 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 3.89 (s, 3 H, OCH_3), 4.94 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 6.74 (d, J = 10 Hz, Ar H), 6.79 (s, 1 H, Ar H), 7.90 (d, J = 10 Hz, 1 H, Ar H), 12.01 (br s, 1 H, CONH). Anal. ($C_{12}H_{15}N_5O_3$) C, H, N.

3-Iodo-4-methoxy-2-(1-methylethoxy)-*N*-1*H*-tetrazol-5-ylbenzamide (3x). A solution of 2.45 g (11.85 mmol) of iodine monobromide in 12 mL of CH_2Cl_2 was added dropwise to a 0 °C solution of 4.00 g (11.45 mmol) of 4-methoxy-2-(1-methylethoxy)-*N*-1*H*-tetrazol-5-yl-3-(trimethylsilyl)benzamide (**3v**) in 28 mL of CH_2Cl_2 under a nitrogen atmosphere. The reaction was stirred for 15 min at 0 °C and 1 h at room temperature. The reaction was concentrated in vacuo and the resulting solid was suspended in hexane and filtered, washing with diethyl ether. Recrystallization from dimethylformamide–water gave 3.29 g (71%) of the carboxamidotetrazole as a white fluffy solid: mp 250–260 °C dec; IR (KBr) 1637, 1614, 1587, 1272, 1073, 807 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.22 (d, J = 6 Hz, $CH(CH_3)_2$), 3.92 (s, 3 H, OCH_3), 4.34 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 6.92 (d, J = 9 Hz, 1 H, Ar H), 7.68 (d, J = 9 Hz, 1 H, Ar H), 12.11 (s, 1 H, CONH), 16.11 (br s, 1 H, tetrazole NH). Anal. ($C_{12}H_{14}IN_5O_3$) C, H, N, I.

Methyl 3-Hydroxy-5-methyl-4-(1-methylethyl)-2-thiophenecarboxylate (4c). A mixture of 14.9 g (140 mmol) of methyl thioglycolate and 12.0 g (70 mmol) of 2-(1-methylethyl)acetoacetate was stirred under an inert atmosphere and cooled to −30 °C. HCl gas was bubbled in for 1 h, and the mixture was allowed to warm to room temperature. After 16 h, the mixture was partitioned between 200 mL of ice water and 200 mL of ether, and the layers were separated. The aqueous phase was extracted with 200 mL of ether, and the combined organic extracts were washed twice with aqueous 0.5 M K_2CO_3, then twice with water, and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the resulting clear, colorless oil was dissolved in 20 mL of methanol and added slowly to a solution of 3.2 g (139 mmol) of sodium in 60 mL of methanol under an inert atmosphere, and the solution was stirred at room temperature. The mixture was stirred for 24 h, poured into 500 mL of ice water, and extracted with 100 mL of ether. The ether was discarded, and the aqueous layer was acidified with concentrated HCl and extracted with dichloromethane (2 × 300 mL). The combined extracts were washed twice with saturated aqueous NaCl, dried over $MgSO_4$, and stripped of solvent under reduced pressure. The oily residue was distilled under vacuum to afford 5.4 g (33%) of the pure product **4c**: bp 68–71 °C (0.3 mmHg); IR (film) 1656, 1580, 1356 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 2.36 (s, 3 H, CH_3), 2.99 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 3.85 (s, 3 H, OCH_3), 9.87 (s, 1 H, OH). Anal. ($C_{10}H_{14}O_3S$) C, H, S.

Methyl 3,4-Dihydroxy-5-methyl-2-thiophenecarboxylate (4d). A mixture of 8.9 g (53 mmol) of methyl 2-bromopropionate and 5.4 g (53 mmol) of triethylamine was stirred under an inert atmosphere and cooled in an ice bath while 5.6 g (53 mmol) of methyl thioglycolate was added. After 16 h at room temperature, the mixture was stirred into 150 mL of ice water and extracted with ether (2 × 125 mL). The combined extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, and stripped of solvent under reduced pressure to give methyl 2-[[(methoxycarbonyl)methyl]thio]propanoate (**7**)[9] as a clear, colorless oil. Compound **7** was dissolved in 25 mL of methanol, mixed with 9.4 g (79 mmol) of dimethyl oxalate, and added dropwise to a 0 °C solution of 3.8 g (165 mmol) of sodium in 35 mL of methanol. Following the addition, the mixture was gradually warmed to reflux and after 1 h was cooled and concentrated on a rotary evaporator. The resulting mixture was filtered and the solid was rinsed with cold methanol and ether, dried, dissolved in a small amount of water, and acidified with aqueous 4 N HCl. The precipitate was isolated by filtration, rinsed with water, and dried to afford 4.3 g (43%) of the pure product **4d**. Concentration and similar treatment of the organic filtrates gave an additional 2.5 g (68% total) of the product: mp 116–117 °C; IR (KBr) 3240, 1700, 1520, 1345 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.23 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 5.18 (s, 1 H, OH), 9.48 (s, 1 H, OH). Anal. ($C_7H_8O_4S$) C, H, S.

Methyl 4-Chloro-3-hydroxy-5-methyl-2-thiophenecarboxylate (4e). A mixture of 74.3 g (0.70 mol) of methyl thioglycolate and 57.6 g (0.35 mol) of ethyl α-chloroacetoacetate was stirred under an inert atmosphere and cooled to −25 °C. HCl gas was bubbled in for 1 h and the mixture allowed to warm to room temperature. After 16 h, the mixture was stirred into 500 mL of water and extracted with ether (2 × 400 mL). The combined extracts were washed successively with water, aqueous 0.5 M $NaHCO_3$ (3×), and water (3×) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residual oil was dissolved in 100 mL of methanol and added dropwise to a stirred solution of 19.7 g (0.86 mol) of sodium in 450 mL of methanol under an inert atmosphere at room temperature. After 72 h, the methanol was removed on a rotary evaporator, the residue stirred in 1.2 L of water, and acidified with concentrated HCl. The mixture was filtered and the solid was rinsed with water and dried to afford 54 g of a yellow-brown powder. This crude material was recrystallized from 110 mL of ethyl acetate and the first crop removed by filtration. The mother liquor was stripped of solvent under reduced pressure, the residue was triturated in 20 mL of chloroform and filtered, and the filtrate was passed

through a short column of silica gel, eluting with additional chloroform. The effluent was stripped of solvent to leave 11 g of yellow-orange crystalline solid, which was recrystallized to constant melting point from 2-propanol, ultimately yielding 2.8 g (5%) of the pure product **4e**: mp 105–107 °C; IR (KBr) 1685, 1565, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3 H, CH_3), 3.88 (s, 3 H, OCH_3), 9.70 (s, 1 H, OH). Anal. ($C_7H_7ClO_3S$) C, H, S.

Methyl 4-Bromo-3-hydroxy-5-methyl-2-thiophenecarboxylate (4f). A solution of 5.0 g (29 mmol) of methyl 3-hydroxy-5-methyl-2-thiophenecarboxylate (**4a**) in 25 mL of acetic acid was treated with 4.6 g (29 mmol) of bromine and stirred at room temperature. After 16 h, the mixture was stirred into 200 mL of ice water. The precipitate was isolated by filtration, rinsed with water, aqueous 5% sodium thiosulfate, and water, and dried. Recrystallization from methyl *tert*-butyl ether gave 4.8 g (66%) of pure product **4f**: mp 96–97 °C; IR (KBr) 1682, 1559, 1347 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H, CH_3), 3.87 (s, 3 H, OCH_3), 9.78 (s, 1 H, Ar H). Anal. ($C_7H_7BrO_3S$) C, H, S.

Methyl 4-Bromo-3-hydroxy-5-(1-methylethyl)-2-thiophenecarboxylate (4h). A solution of 3.0 g (15 mmol) of the ester **4z** in 15 mL of acetic acid was stirred under an inert atmosphere at room temperature and treated with 2.6 g (6 mmol) of bromine. After 16 h, the mixture was stirred into 150 mL of ice water, and the precipitate was washed by decantation with water (3×), aqueous 0.5 M $NaHCO_3$, aqueous 5% $NaHSO_3$, and water, filtered, and dried. Recrystallization from 2-propanol gave 1.9 g (45%) of the pure product **4h**: mp 57–59 °C; IR (KBr) 1675, 1550, 1343 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 3.37 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 3.89 (s, 3 H, OCH_3), 9.76 (s, 1 H, OH). Anal. ($C_9H_{11}BrO_3S$) C, H, Br, S.

Methyl 4-Bromo-3-hydroxy-5-phenyl-2-thiophenecarboxylate (4i). The procedure described for the preparation of compound **4f** was repeated, using 5.0 g (21 mmol) of ester **4aa**[8] and 3.4 g (21 mmol) of bromine. Recrystallization of the crude product from methanol gave 4.0 g (60%) of the pure product **4i**: mp 85–87 °C; IR (KBr) 1683, 1551, 1187 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.92 (s, 3 H, OCH_3), 7.41–7.51 (m, 3 H, Ar H), 7.63–7.71 (m, 2 H, Ar H), 9.87 (s, 1 H, OH). Anal. ($C_{12}H_9BrO_3S$) C, H, Br, S.

Methyl 4,5-Dibromo-3-hydroxy-1-methyl-1*H*-pyrrole-2-carboxylate (4q). The procedure described for compound **5p** was repeated, using 5.0 g (32 mmol) of methyl 3-hydroxy-1-methyl-1*H*-pyrrole-2-carboxylate (**4cc**)[17] and 10.4 g (65 mmol) of bromine, to afford 6.9 g (68%) of the pure product **4q**: mp 128–130 °C; IR (KBr) 1664, 1543, 1459 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.76 (s, 3 H, CH_3), 3.78 (s, 3 H, CH_3), 9.03 (s, 1 H, OH). Anal. ($C_7H_7Br_2NO_3$) C, H, N, Br.

Ethyl 4,5-Dibromo-3-hydroxy-1-phenyl-1*H*-pyrrole-2-carboxylate (4r). The procedure described for compound **5p** was repeated, using 3.0 g (13 mmol) of ethyl 3-hydroxy-1-phenyl-1*H*-pyrrole-2-carboxylate (**4dd**)[11] and 2.9 g (18 mmol) of bromine. Recrystallization of the crude product from ethanol gave 1.4 g (28%) of the pure product **4r**: mp 144–145 °C; IR (KBr) 1700, 1543, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7 Hz, 3 H, CH_3), 4.03 (q, J = 7 Hz, 2 H, CH_2), 7.17–7.25 (m, 2 H, Ar H), 7.41–7.48 (m, 3 H, Ar H), 8.63 (s, 1 H, OH). Anal. ($C_{13}H_{11}Br_2NO_3$) C, H, N, Br.

Ethyl 4,5-Dibromo-3-hydroxy-1-(phenylmethyl)-1*H*-pyrrole-2-carboxylate (4s). The procedure described for compound **5p** was repeated, using 3.1 g (13 mmol) of ethyl 3-hydroxy-1-(phenylmethyl)-1*H*-pyrrole-2-carboxylate (**4ee**)[11] and 4.2 g (26 mmol) of bromine. Recrystallization of the crude material from ethanol gave 3.9 g (77%) of the pure product **4s**: mp 107–108 °C; IR (KBr) 1657, 1545, 1173 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.23 (t, J = 7 Hz, 3 H, CH_3), 4.28 (q, J = 7 Hz, 2 H, CH_2), 5.52 (s, 2 H, CH_2), 6.87–7.17 (m, 2 H, Ar H), 7.21–7.50 (m, 3 H, Ar H), 8.60 (s, 1 H, OH). Anal. ($C_{14}H_{13}Br_2NO_3$) C, H, N, Br.

Methyl 3,5-Dibromo-2-hydroxy-4-methoxybenzoate (4y). A solution of 14.0 g (87.8 mmol) of bromine in HOAc/$CHCl_3$ (20 mL of 2.2:1) was added dropwise to a stirred solution of 7.4 g (40.6 mmol) of methyl 2-hydroxy-4-methoxybenzoate (**4u**) in HOAc/$CHCl_3$ (60 mL of 2.2:1) immersed in a 20 °C water bath. The reaction was stirred at room temperature for 20 h. An additional portion of 7.5 g (46.8 mmol) of bromine was added, and the reaction was stirred for 2 h. The reaction was poured onto 400 mL of Et_2O, washed with H_2O (2×), aqueous 5% $NaHCO_3$, aqueous 5% $Na_2S_2O_3$, H_2O, and saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a white solid. The reaction was incomplete, being a mixture of the 5-bromo and the 3,5-dibromo products. The solid in HOAc/$CHCl_3$ (150 mL of 2:1) was treated with 69.0 g (43.2 mmol) of bromine and allowed to stir at room temperature for 4 days. The reaction was concentrated in vacuo to give a white solid. Recrystallization from hexane gave 8.8 g (64%) of the desired product as a white, fluffy solid: mp 99 °C; IR (KBr) 2961, 1682, 1603, 1443, 1322, 1234, 976, 791, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 8.07 (s, 1 H, Ar H), 8.52 (s, 1 H, OH). Anal. ($C_9H_8Br_2O_4$) C, H, Br.

Methyl 3-Hydroxy-5-(1-methylethyl)-2-thiophenecarboxylate (4z). A mixture of 47.0 g (0.28 mol) of ethyl isobutyrylacetate and 59.4 g (0.56 mol) of methyl thioglycolate was stirred under an inert atmosphere, cooled to −30 °C, and saturated with HCl gas. After 1 h, gas addition was stopped and the solution allowed to warm to room temperature. After 20 h more, the mixture was partitioned between 1 L of ice water and 1 L of ether, and the layers were separated. The aqueous layer was extracted with 1 L of ether, and the combined ethereal extracts were washed with aqueous 0.5 M K_2CO_3 (2 × 750 mL) and water (2 × 750 mL) and dried over $MgSO_4$. The solvent was removed on a rotary evaporator and the oily residue dissolved in 70 mL of methanol and added dropwise to a stirred solution of 13.7 g (0.60 mol) of sodium in 250 mL of methanol under an inert atmosphere at room temperature. After 25 h, the mixture was stirred into 1 L of ice water, and the precipitate was isolated by filtration, rinsed with cold ethanol, resuspended in water, acidified with concentrated HCl, and extracted with dichloromethane (2 × 400 mL). The combined extracts were washed with saturated brine (2 × 500 mL), dried over $MgSO_4$, and stripped of solvent under reduced pressure to leave 15.1 g (27%) of the pure product **4z** as a clear yellow syrup: IR (film) 1660, 1563, 1444, 1107 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 3.07 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 3.87 (s, 3 H, OCH_3), 6.50 (s, 1 H, Ar H), 9.57 (s, 1 H, OH). Anal. ($C_9H_{12}O_3S$) C, H, S.

Methods for the Preparation of O- and S-Alkylated Enol Esters 5. Method A. Methyl 3-(1-Methylethoxy)-5-methyl-2-thiophenecarboxylate (5a). A solution of 20.0 g (116 mmol) of the enol ester **4a** in 450 mL of acetonitrile was stirred under an inert atmosphere, treated with 86.6 g (465 mmol) of triisopropylisourea,[7] and heated under reflux. After 24 h, the mixture was cooled, filtered, and washed with acetonitrile. The filtrate was stripped of solvent on a rotary evaporator, and the excess triisopropylisourea was removed by distillation under reduced pressure. The residue was dissolved in a few milliliters of ethyl acetate, cooled, filtered, and passed through a short column of silica gel, eluting with ethyl acetate. Evaporation of the effluent under reduced pressure left 18.8 g (76%) of the pure product **5a** as a clear oil: IR (film) 1715, 1689, 1558, 1471 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 2.42 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 4.49 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 6.52 (s, 1 H, Ar H). Anal. ($C_{10}H_{14}O_3S$) C, H, S.

Method B. Ethyl 4,5-Dibromo-3-(1-methylethoxy)-1-phenyl-1*H*-pyrrole-2-carboxylate (5r). A solution of 4.0 g (10 mmol) of enol ester **4r** in 20 mL of dimethyl sulfoxide was stirred under an inert atmosphere at room temperature and treated with 1.2 g (11 mmol) of potassium *tert*-butoxide. After 15 min, 2.6 g (21 mmol) of 2-bromopropane was added. The mixture was stirred for 20 h, poured onto 300 mL of ice water, and extracted with dichloromethane (3 × 100 mL). The combined extracts were washed twice with saturated aqueous NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure to leave 4.1 g (92%) of the product **5r** as a clear amber oil: IR (film) 1705, 1628, 1598, 1532 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (t, J = 7 Hz, 3 H, CH_3), 1.40 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 4.09 (q, J = 7 Hz, 2 H, CH_2), 4.59 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 7.19–7.24 (m, 2 H, Ar H), 7.43–7.50 (m, 3 H, Ar H). Anal. ($C_{16}H_{17}Br_2NO_3$) C, H, N, Br.

Method C. Methyl 4-Bromo-3-methoxy-5-methyl-2-thiophenecarboxylate (5n). A solution of 7.0 g (28 mmol) of the enol ester **4f** in 50 mL of acetone was stirred under an inert

(17) A manuscript describing a novel pyrrole synthesis including the synthesis of **4bb** and **4cc** is in preparation.

atmosphere and treated with 5.5 g (40 mmol) of anhydrous potassium carbonate followed by 4.4 g (35 mmol) of dimethyl sulfate, and the mixture was heated to reflux. After 12 h, the solvent was removed on a rotary evaporator, and the residue stirred in 60 mL of water. After 1 h, the reaction was filtered, and the solid was rinsed with water and dried under vacuum. Recrystallization from acetonitrile afforded 3.8 g (51%) of the pure product **5n**: mp 77–78 °C; IR (KBr) 1717, 1546, 1486 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 4.00 (s, 3 H, CH_3). Anal. ($C_8H_9BrO_3S$) C, H, Br, S.

1-Methylethyl 4-Bromo-5-methyl-3-[(1-methylethyl)thio]-2-thiophenecarboxylate (5o). A mixture of 1.8 g (9.7 mmol) of triisopropylisourea,[7] 25 mL of acetonitrile, and 0.6 g (2.4 mmol) of the acid **12** was stirred under an inert atmosphere and heated to reflux. After 19 h, the mixture was allowed to cool and was concentrated in vacuo. The residue was stirred in 10 mL of ether, cooled, and filtered. The residue was rinsed with cold ether and the combined filtrates were dried over $MgSO_4$. The solvent was removed under reduced pressure and the residual oil was dissolved in ethyl acetate and passed through a short column of silica gel. The effluent was evaporated to leave 0.7 g (88%) the ester **5o** as a clear syrup, which was hydrolyzed to **6o** without additional purification.

Methyl 4,5-Dibromo-3-(1-methylethoxy)-1*H*-pyrrole-2-carboxylate (5p). A solution of 1.5 g (8 mmol) of the ester **5bb** in 10 mL of acetic acid was stirred at room temperature, and 2.6 g (16 mmol) of bromine was added dropwise. After 2 h, the mixture was stirred into 200 mL of water and filtered. The solid was rinsed with water and dried to give 2.2 g (79%) of the pure product **5p**: mp 124–125 °C; IR (KBr) 1687, 1439, 1265 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 3.87 (s, 3 H, OCH_3), 4.50 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 9.30 (br s, 1 H, NH). Anal. ($C_9H_{11}Br_2NO_3$) C, H, N, Br.

Methyl 4-Methoxy-2-(1-methylethoxy)benzoate (5u). Following method B, 10.0 g (54.9 mmol) of methyl 2-hydroxy-4-methoxybenzoate (**4u**) was O-alkylated to give 7.45 g (61%) of **5u** as a colorless oil after chromatography (flash, SiO_2, 230–400 mesh, 6.5 × 18 cm, 15% ethyl acetate–hexane eluant): IR (film) 2980, 1729, 1610, 1516, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (d, J = 9 Hz, 6 H, $CH(CH_3)_2$), 3.80 (s, 6 H, OCH_3/CO_2CH_3), 4.57 (heptet, J = 9 Hz, 1 H, $CH(CH_3)_2$), 6.43–6.57 (m, 2 H, Ar H), 7.28 (d, J = 8 Hz, 1 H, Ar H). Anal. ($C_{12}H_{16}O_4$) C, H.

Methyl 3-Bromo-4-methoxy-2-(1-methylethoxy)benzoate (5w). A solution of 15.80 mL (24.49 mmol) of 1.55 M *n*-BuLi/hexane was added to a −70 °C solution of 2.48 g (24.54 mmol) of diisopropylamine in 60 mL of dry THF under a nitrogen balloon. The reaction was warmed to 0 °C, stirred for 15 min, then recooled to −70 °C, and treated with a solution of 5.00 g (22.30 mmol) of methyl 4-methoxy-2-(1-methylethoxy)benzoate (**5u**) and 4.79 g (44.12 mmol) of chlorotrimethylsilane in 15 mL of THF.[15] The reaction was stirred for 20 h while slowly being allowed to warm to room temperature. The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo. Chromatography (flash, SiO_2, 230–400 mesh, 27 × 6.5 cm, 10% EtOAc–hexane eluant) gave 3.98 g (60%; 78% based on recovered **5u**) of **5v** as a colorless oil: ^1H NMR ($CDCl_3$) δ 0.33 (s, 9 H, $Si(CH_3)_3$), 1.34 (d, J = 5 Hz, 6 H, $CH(CH_3)_2$), 3.88 and 3.93 (two s, 3 H each, OCH_3/CO_2CH_3), 4.22 (heptet, J = 5 Hz, 1 H, $CH(CH_3)_2$), 6.30 (d, J = 9 Hz, 1 H, Ar H), 7.55 (d, J = 9 Hz, 1 H, Ar H). The material was sufficiently pure for use in the subsequent reaction.

A solution of 2.85 g (9.61 mmol) of **5v** in 10 mL of CH_2Cl_2 was added dropwise to a slurry of 2.03 g (11.41 mmol) of *N*-bromosuccinimide (NBS) in 30 mL of CH_2Cl_2 at −70 °C. The reaction was slowly allowed to warm to room temperature over 18.5 h. Two additional portions of NBS (0.51 g, 2.87 mmol each) were added to the reaction mixture at 18.5 and 23.5 h. At 31.5-h reaction time, the mixture was concentrated in vacuo, suspended in Et_2O and filtered (2×), and concentrated in vacuo. Chromatography (flash, SiO_2, 230 × 400 mesh, 26 × 6.5 cm, 20% EtOAc–hexane eluant) gave 2.52 g (87%) of **5w** as a colorless oil; IR (film) 1726, 1592, 1283, 1257, 1228, 1079 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 5 Hz, 6 H, $CH(CH_3)_2$), 3.88 and 3.93 (two s, 3 H each, OCH_3/CO_2CH_3), 4.44 (heptet, J = 5 Hz, 1 H, $CH(CH_3)_2$), 6.70 (d, J = 8 Hz, 1 H, Ar H), 7.88 (d, J = 8 Hz, 1 H, Ar H). Anal. ($C_{12}H_{15}BrO_4$) C, H, Br.

Methyl 3-(1-Methylethoxy)-1*H*-pyrrole-2-carboxylate (5bb). The procedure described for compound **5a** (method A) was followed, using 3.3 g (23 mmol) of methyl 3-hydroxy-1*H*-pyrrole-2-carboxylate (**4bb**)[17] and 17.0 g (91 mmol) of triisopropylisourea.[7] Recrystallization from 1:1 ether/hexane gave 2.2 g (51%) of the pure product **5bb**: mp 71–72 °C; IR (KBr) 1662, 1559, 1501, 1293 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 3.83 (s, 3 H, OCH_3), 4.40 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 5.90 (t, 1 H, Ar H), 6.75 (t, 1 H, Ar H), 8.60 (br s, 1 H, NH). Anal. ($C_9H_{13}NO_3$) C, H, N.

General Saponification Method. 4-Bromo-3-(1-methylethoxy)-5-phenyl-2-thiophenecarboxylic Acid (6i). A mixture of 4.8 g (14 mmol) of the ester **5i**, 5 mL of methanol, and 27 mL of aqueous 1 N NaOH was stirred under an inert atmosphere and heated to reflux. After 3 h, the mixture was stirred into 300 mL of water and acidified with concentrated HCl and filtered. The precipitate was rinsed with water and dried to afford 4.7 g (98%) of the pure product **6i**: mp 159–160 °C; IR (KBr) 1685, 1658, 1530, 1499 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 4.94 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 7.37–7.82 (m, 5 H, Ar H). Anal. ($C_{14}H_{13}BrO_3S$) C, H, Br, S.

4,5-Dimethyl-3-(1-methylethoxy)-2-thiophenecarboxylic Acid (6b). A solution of 18.0 g (79 mmol) of the ester **5b** in 150 mL of tetrahydrofuran was added to a solution of 25.0 g (392 mmol) of potassium hydroxide in 150 mL of water, and the resulting solution was heated to reflux under an inert atmosphere. After 20 h, the THF was removed on a rotary evaporator, and the aqueous suspension cooled in an ice bath, acidified with aqueous 4 N HCl, stirred for 1 h, and filtered. The precipitate was rinsed with water, dried, and recrystallized from acetone to afford 5.5 g (33%) of the pure product **6b**: mp 133–134 °C; IR (KBr) 1646, 1554, 1461 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 2.00 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 4.60 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$). Anal. ($C_{10}H_{14}O_3S$) C, H, S.

4-Bromo-5-methyl-3-[(1-methylethyl)thio]-2-thiophenecarboxylic Acid (6o). A mixture of 25 mL of methanol, 70 mL of aqueous 1 N NaOH and 11.1 g (33 mmol) of the ester **5o** was stirred and heated to reflux. After 4.5 h, the mixture was allowed to cool, stirred into 400 mL of water, and extracted with ether (2 × 50 mL). The aqueous phase was acidified with concentrated HCl, stirred for 20 min, and filtered. The solid was rinsed three times with water and dried to afford 8.4 g (67%) of the pure acid **6o**: mp 132–134 °C; IR (KBr) 1679, 1648, 1444, 1258 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.15 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 1.18 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 3.66 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$). Anal. ($C_9H_{11}BrO_2S_2$) C, H, Br, S.

4,5-Dibromo-3-[(1-methylethyl)thio]-2-furancarboxylic Acid (6t). A mixture of 3.01 g (7.58 mmol) of oxazoline **15** and 30 mL of aqueous 4 N HCl was warmed at reflux for 30 min. The reaction was cooled to 0 °C, diluted with 60 mL of MeOH and 30 mL of THF, and treated carefully with 4.25 equiv of LiOH. The reaction was stirred for 2 h at 0 °C and 16 h at room temperature and concentrated in vacuo. The residue was dissolved in water and extracted with Et_2O (3×). The aqueous layer was acidified with aqueous 10% HCl and extracted with EtOAc (4×). The combined organic layers were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to give 1.90 g (62%) of **6t** as a yellow solid. Material was sufficiently pure for use in subsequent reactions. A sample was recrystallized from Et_2O–hexane: mp 130–131 °C; IR (KBr) 1689, 1559, 1479, 1465, 1292, 984 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 3.64 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 10.58 (br s, 1 H, CO_2H). Anal. ($C_8H_8Br_2O_2S$) C, H, N, Br, S.

4-Methoxy-2-(1-methylethoxy)-3-(trimethylsilyl)benzoic Acid (6v). Following the method described for the preparation of **6y**, 15.0 g (ca. 38 mmol, ca. 75% pure) of ester **5v** was saponified (reflux, 6 h, room temperature, 18 h) to give 9.57 g (89%) of **6v** as a white solid, sufficiently pure for the next reaction. A sample of **6v** was recrystallized from EtOAc–hexane: mp 162–163 °C; IR (KBr) 3000 (br), 1668, 1581, 1257, 1079, 844 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.35 (s, 9 H, $Si(CH_3)_3$), 1.29 (d, J = 6 Hz, 6 H, $CH(CH_3)_2$), 3.86 (s, 3 H, OCH_3), 4.33 (heptet, J = 6 Hz, 1 H, $CH(CH_3)_2$), 6.72 (d, J = 8 Hz, 1 H, Ar H), 8.16 (d, J = 8 Hz, 1 H, Ar H), 11.37 (br s, 1 H, CO_2H). Anal. ($C_{14}H_{22}O_4Si$) C, H.

3-Bromo-4-methoxy-2-(1-methylethoxy)benzoic Acid (6w). Following the method for the preparation of **6y**, 2.34 g (7.72 mmol)

of **5w** was saponified (room temperature, 65 h) to give 2.23 g (74%) of **6w**: mp 109–110 °C (EtOAc–hexane); IR (KBr) 1670, 1588, 1430, 1287, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 3.98 (s, 3 H, OCH_3), 4.93 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 6.80 (d, J = 9 Hz, 1 H, Ar H), 8.09 (d, J = 9 Hz, 1 H, Ar H). Anal. ($C_{11}H_{13}BrO_4$) C, H, Br.

3,5-Dibromo-4-methoxy-2-(1-methylethoxy)benzoic Acid (6y). A solution of 4.9 g (12.8 mmol) of **5y** and 25 mL (25 mmol) of aqueous 1.0 N NaOH in CH_3OH (35 mL) and THF (20 mL) was stirred at room temperature for 4 days. The reaction was poured onto 175 mL of ice/H_2O and acidified with aqueous 10% HCl. The acidic mixture was extracted with EtOAc (3×). The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to give a white solid. Recrystallization from EtOAc–hexane gave 3.10 g (66%) of **6y** as white needles: mp 103–104 °C; IR (KBr) 3000 (br), 1698, 1292, 1102, 976 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 3.93 (s, 3 H, OCH_3), 4.89 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$), 8.31 (s, 1 H, Ar H). Anal. ($C_{11}H_{12}Br_2O_4$) C, H, Br.

Methyl 4-Bromo-3-[(dimethylamino)thioxomethoxy]-5-methyl-2-thiophenecarboxylate (10). A solution of 2.5 g (10 mmol) of enol ester **4f** in 20 mL of dimethylformamide was stirred under an inert atmosphere at room temperature while 0.6 g (12.5 mmol) of sodium hydride (50% dispersion in mineral oil) was added portionwise. After gas evolution had ceased, the mixture was cooled to 5–10 °C and 1.5 g (12 mmol) of dimethylthiocarbamoyl chloride was added. The mixture was gradually heated at reflux for 1 h, cooled to room temperature, poured into 35 mL of aqueous 0.5% potassium hydroxide, and stirred for 20 min. The mixture was filtered, and the solid was rinsed twice with aqueous 1 N HCl and three times with water and dried. Recrystallization from 2-propanol afforded 1.6 g (48%) of pure product **10**: mp 152–153 °C; IR (KBr) 1713, 1540, 1279, 969 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H, CH_3), 3.39 (s, 3 H, CH_3), 3.46 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3). Anal. ($C_{10}H_{12}BrNO_3S_2$) C, H, N, Br, S.

Methyl 4-Bromo-3-[[(dimethylamino)carbonyl]thio]-5-methyl-2-thiophenecarboxylate (11). One gram (3 mmol) of the ester **10** was heated under argon in an oil bath at 220 °C for 30 min and allowed to cool. The residue was recrystallized from ethyl acetate to afford 0.4 g (40%) of the pure product **11**: mp 175–176 °C; IR (KBr) 1720, 1663, 1447, 1238 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.49 (s, 3 H, CH_3), 3.04–3.17 (m, 6 H, CH_3), 3.86 (s, 3 H, CH_3). Anal. ($C_{10}H_{12}BrNO_3S_2$), C, H, N, Br, S.

4-Bromo-3-mercapto-5-methyl-2-thiophenecarboxylic Acid (12). A mixture of 3 mL of methanol, 10 mL of aqueous 5 N NaOH, and 1.5 g (4 mmol) of the ester **11** was stirred and heated to reflux. After 2.5 h, the mixture was stirred into 200 mL of ice water and acidified with concentrated HCl. The precipitate was isolated by filtration, rinsed three times with water, and dried to give 1.0 g (89%) of acid **12**. Recrystallization of a sample from ethyl acetate gave a crystalline solid: mp 202–204 °C; IR (KBr) 1654, 1453, 1287 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3 H, CH_3), 6.58 (s, 1 H, SH), 10.75 (br s, 1 H, CO_2H). Anal. ($C_6H_5BrO_2S_2$) C, H, Br.

2-(4,5-Dibromo-2-furanyl)-4,5-dihydro-4,4-dimethyloxazole (14). A mixture of 11.18 g (41.42 mmol) of 4,5-dibromo-2-furancarboxylic acid (**13**)[12] and 6.3 g (49.3 mmol) of oxalyl chloride in CH_2Cl_2 (150 mL) was treated with 3 drops of DMF. Gas immediately evolved from the reaction and was controlled with occasional cooling in an ice/H_2O bath. The reaction was concentrated in vacuo after being stirred for 2 h. The residue was distilled under vacuum on a Kugelrohr apparatus to afford 11.69 g of the acid chloride as a pale, yellow oil.

A solution of the acid chloride (40.54 mmol) in CH_2Cl_2 (35 mL) was cooled to 0 °C, and 7.22 g (81.08 mmol) of 2-amino-2-methyl-1-propanol in CH_2Cl_2 (20 mL) was added dropwise. The reaction was stirred at 25 °C for 2.5 h, and the reaction was filtered. The filtrate was concentrated in vacuo. The precipitate from the filtration was washed with aqueous 10% HCl, H_2O, and diethyl ether. The washed precipitate was combined with the filtrate residue. The resulting mixture was suspended in toluene (100 mL) and cooled to 0 °C. Thionyl chloride 14.4 g (120.6 mmol) in toluene (10 mL) was added dropwise to the 0 °C suspension. The reaction was stirred at 25 °C for 18 h, concentrated in vacuo, taken up in H_2O, and made basic with aqueous 4 N NaOH. The basic aqueous solution was extracted with diethyl ether (4×). The combined extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo to afford 9.91 g (74%) of the desired oxazoline. The material was sufficiently pure (>95% by NMR) for use in subsequent reactions. A sample was purified by sublimation: mp 65–66 °C; IR (KBr) 2973, 1678, 1654, 1486, 1365, 1305, 1068, 979 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, 6 H, CH_3), 4.09 (s, 2 H, CH_2), 6.94 (s, 1 H, Ar H). Anal. ($C_9H_9Br_2NO_2$) C, H, N, Br.

2-[4,5-Dibromo-3-[(1-methylethyl)thio]-2-furanyl]-4,5-dihydro-4,4-dimethyloxazole (15). A solution of 9.63 g (29.81 mmol) of **14** in dry THF (30 mL) was added to a −78 °C solution of freshly generated lithium diisopropylamide (33.89 mmol) in THF (80 mL) under an argon atmosphere. The resulting solution was stirred at −78 °C for 10 min, and then a solution of 5.49 g (46.49 mmol) of diisopropyl disulfide in THF (20 mL) was added dropwise to the reaction. The reaction was stirred for 3.75 h, while being warmed to −10 °C, poured onto aqueous 5% HCl, (350 mL), and extracted with Et_2O (4×). The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated in vacuo. Chromatography (flash, SiO_2, 230–400 mesh, 25 × 7 cm, 10% CH_2Cl_2/10% EtOAc/hexane eluant) afforded 7.67 g (65%) of **15** as a yellow solid, sufficiently pure for use in subsequent reactions. A sample was recrystallized from hexane: mp 71–72 °C; IR (KBr) 1654, 1485, 1372, 1130, 985, 932 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (d, J = 7 Hz, 6 H, $CH(CH_3)_2$), 1.43 (s, 6 H, oxazoline $(CH_3)_2$), 4.88 (heptet, J = 7 Hz, 1 H, $CH(CH_3)_2$). Anal. ($C_{12}H_{15}Br_2NOS$) C, H, N, S.

Acknowledgment. We are grateful to the Chromatography Support Services of Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, especially A. Michael Young and Boguslawa Leja, for log P and solubility determinations.

Registry No. **3a**, 113588-89-9; **3b**, 113588-92-4; **3c**, 113589-10-9; **3d**, 113589-00-7; **3e**, 113589-01-8; **3f**, 113588-95-7; **3g**, 113588-83-3; **3h**, 113589-03-0; **3i**, 113588-88-8; **3j**, 113588-97-9; **3k**, 113589-05-2; **3l**, 113588-96-8; **3m**, 113588-94-6; **3n**, 113588-93-5; **3o**, 113589-11-0; **3p**, 113589-15-4; **3q**, 113589-14-3; **3r**, 113589-12-1; **3s**, 113589-13-2; **3t**, 113589-24-5; **3u**, 117401-83-9; **3v**, 117401-92-0; **3w**, 117401-84-0; **3x**, 117401-85-1; **3y**, 133753-51-2; **4a**, 5556-22-9; **4aa**, 5556-23-0; **4bb**, 79068-31-8; **4c**, 113589-28-9; **4cc**, 113602-62-3; **4d**, 113589-33-6; **4dd**, 65171-92-8; **4e**, 113589-29-0; **4ee**, 65171-91-7; **4f**, 113589-26-7; **4h**, 113589-31-4; **4i**, 113589-27-8; **4q**, 113602-65-6; **4r**, 113602-63-4; **4s**, 113602-64-5; **4u**, 5446-02-6; **4y**, 133753-52-3; **4z**, 113589-30-3; **5a**, 113589-38-1; **5b**, 133753-53-4; **5bb**, 123342-06-3; **5i**, 123342-05-2; **5h**, 123342-03-0; **5o**, 113602-90-7; **5p**, 113602-70-3; **5r**, 113602-67-8; **5u**, 117401-87-3; **5v**, 117401-88-4; **5w**, 117401-89-5; **5y**, 133753-54-5; **6a**, 113589-52-9; **6b**, 113589-55-2; **6c**, 113589-65-4; **6d**, 113589-64-3; **6e**, 113589-66-5; **6f**, 113589-58-5; **6g**, 113589-60-9; **6h**, 113602-56-5; **6i**, 113589-48-3; **6j**, 113589-61-0; **6k**, 113628-91-4; **6l**, 113589-59-6; **6m**, 113589-57-4; **6n**, 113589-56-3; **6o**, 113602-91-8; **6p**, 113602-74-7; **6q**, 113602-73-6; **6r**, 113602-71-4; **6s**, 113602-72-5; **6t**, 113602-86-1; **6v**, 133753-55-6; **6w**, 117401-90-8; **6y**, 133753-56-7; **7**, 19757-47-2; **10**, 113602-87-2; **11**, 113602-88-3; **12**, 113602-89-4; **13**, 2434-03-9; **13** acid chloride derivative, 35900-96-0; **14**, 113602-83-8; **15**, 113602-85-0; 5-aminotetrazole, 4418-61-5; methyl thioglycolate, 2365-48-2; 2-(1-methylethyl)-acetoacetate, 59144-21-7; methyl 2-bromopropionate, 5445-17-0; dimethyl oxalate, 553-90-2; ethyl α-chloroacetoacetate, 105-39-5; ethyl isobutyrylacetate, 7152-15-0; triisopropylisourea, 63460-32-2; 2-bromopropane, 75-26-3; 2-amino-2-methyl-1-propanol, 124-68-5.