Table III. ED_{50} (mg/kg) of Penicillin Derivatives[a]

No.	Gram positive[b]		Gram negative[b]	
	S.a.	S.p.	S.s.	E.c.
21	3.5	47	>100	>100
22	2.5	5.2	>100	>100
23	1.2	6.0	>100	>100
24	<1.0	3.2	100	>100
25	<1.0	5.3	11	30
26	19	19	52	>100
27	6.7	6.8	100	>100
28	<1.0	10	6.5	>100
29		4.4	37	>100
30	32	3.6	29	>100
31	14	2.8	19	31
32	1.0	5.6	16	>100
33	1.0	5.3	36	>100
34	<1.0	2.4	28	36
35	<1.0	5.2	44	68
36	<1.0	4.3	19	>100
37	1.1	6.7	16	100
38	<1.0	10	48	>100
39	<10	19.3	>100	>100
Penicillin G	1.0	10		
Ampicillin				25
Chloromycetin			50	

[a] Each compound was given to mice infected with a fatal infection. Doses of 1, 10, or 100 mg/kg were given in four doses at −1, +1, +19, and +25 h. The challenge was given at 0 h. ED_{50} calculated according to L. J. Reed and H. Muench, *Am. J. Hyg.*, 27, 493, 497 (1938). [b] *S.a.* = *Staphylococcus aureus; S.p.* = *Streptococcus pneumoniae; S.s.* = *Salmonella schottmuelleri; E.c.* = *Escherichia coli.*

dissolved in methanol (150 mL, some insoluble material, filtered off) and reprecipitated with ether: yield of reprecipitated product 6.8 g; mp 219–221 °C dec; IR (KBr) 1760, 1670, 1620, and 770 cm^{-1}; NMR (D_2O–DSS) δ 1.58 (d, J = 4 Hz, 6 H), 4.27 (s, 1 H), 4.88 (s, 2 H), 5.62 (s, 2 H), 7.5–8.3 (m, 5 H); iodine titration 92.2%.

3,3-Dimethyl-6-[2-[2-oxo-1(2*H*)-pyridyl]acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid Sodium Salt (25) (Method B). A solution of 1,2-dihydro-2-oxopyridine-1-acetic acid (3.1 g, 0.02 mol) and triethylamine (2 g, 0.02 mol) in DMF (50 mL) was chilled to −25 °C. Ethyl chloroformate (2.17 g, 0.02 mol) was added and the mixture was stirred at −25 °C for 30 min. A chilled solution of bis(Me_3-6-APA) [from 4.3 g (0.02 mol) of 6-APA and hexamethyldisilazine] in $CHCl_3$ (50 mL) was added and the mixture was stirred at −20 °C for 1 h and allowed to come to room temperature. Dioxane (100 mL) was added, and the mixture was filtered. Water (0.2 mL) was added to the filtrate; the mixture was stirred for 30 min and filtered free of unreacted 6-APA. Ten milliliters of a 2 N butanol solution of sodium 2-ethylhexanoate and 1 L of ether were added to the filtrate. The precipitated product was filtered off, dissolved in methanol (100 mL), and reprecipitated by the addition of ether. The yield was 3.6 g of white powder, which decomposed over a 20 °C range beginning at 120 °C: IR (KBr) 1780, 1660, 1610, 1580, 1540, 1400, 1320, and 765 cm^{-1}; NMR (D_2O–DSS) δ 1.60 (d, J = 6 Hz, 6 H), 4.25 (s, 1 H), 4.8 (s, 2 H), 5.57 (s, 2 H), 6.4–6.8 (m, 2 H), 7.5–7.9 (m, 2 H); iodine titration 80.3%.

6-[2-[2-Oxo-1(2*H*)-quinoxalinyl]acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic Acid Sodium Salt (24) (Method C). A solution of 1,2-dihydro-2-oxoquinoxaline-1-acetic acid (3.3 g, 0.016 mol) in DMF (20 mL) was chilled to −10 °C and carbonyldiimidazole (2.6 g, 0.016 mol) was added. The mixture was stirred at 0 °C under an N_2 atmosphere for 20 min, warmed to room temperature, and placed under a vacuum for 5 min (to remove the CO_2 liberated during the imidazolide formation). A solution of 6-APA (3.5 g, 0.016 mol) and triethylamine (3.2 g, 0.032 mol) in $CHCl_3$ (100 mL) was added and the reaction mixture was stirred for 18 h under an N_2 atmosphere. Eight milliliters of a 2 N butanol solution of sodium 2-ethylhexanoate and 1 L of ether were added. The mixture was filtered and the product was reprecipitated from methanol with ether to give 3.5 g of white powder: mp 227–229 °C dec; IR (KBr) 1770, 1660, 1620, and 760 cm^{-1} NMR (D_2O–DSS) δ 1.58 (d, J = 5 Hz, 6 H), 4.3 (s, 1 H), 5.05 (s, 2 H), 5.55 (s, 2 H), 7.15–8.9 (m, 4 H), 8.2 (s, 1 H); iodine titration 98%.

References and Notes

(1) J. H. Dewar and G. Shaw, *J. Chem. Soc.*, 3254 (1961).
(2) M. R. Atkinson, G. Shaw, and R. N. Warrener, *J. Chem. Soc.*, 4118 (1956).
(3) K. E. Price, A. Gourevitch, and L. C. Cheney, *Antimicrob. Agents Chemother.*, 670 (1966).
(4) Agar dilution assay, described in M. L. Edwards, R. E. Bambury, and H. W. Ritter, *J. Med. Chem.*, 19, 330 (1976).
(5) Prepared from chlorotrimethylsilane, triethylamine, and 4-hydroxypyridine in toluene (reflux, 18 h).

Tetramisole Analogues as Inhibitors of Alkaline Phosphatase, an Enzyme Involved in the Resistance of Neoplastic Cells to 6-Thiopurines

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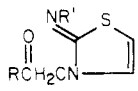
A series of tetramisole derivatives was synthesized and tested for inhibitory activity against alkaline phosphatase which was partially purified from a murine ascitic neoplasm resistant to 6-thiopurines (Sarcoma 180/TG). These agents included derivatives substituted with halogens, CH_3, or NO_2 groups at either the meta or para position of the phenyl ring of tetramisole and 2,3-dehydrotetramisole. The phenyl ring of tetramisole and 2,3-dehydrotetramisole was also replaced by a naphthyl ring, and the phenyl ring of 2,3-dehydrotetramisole was substituted by a thienyl ring system. The presence of both the thiazolidine and dihydroimidazole rings of tetramisole was found to be essential for enzyme inhibitory activity. Substitution of a naphthyl for the phenyl group and dehydrogenation at the 2,3 position of the thiazolidine ring were found to significantly enhance inhibitory activity for alkaline phosphatase. Tests employing (*S*)-(−)-6-(4-bromophenyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole oxalate in combination with 6-thioguanine demonstrated that the inhibitor of alkaline phosphatase was capable of increasing the toxicity of 6-thioguanine to Sarcoma 180/TG cells in tissue culture.

We have provided evidence[2-4] which demonstrates that the acquisition of insensitivity to the antileukemic 6-thiopurines (i.e., 6-mercaptopurine and 6-thioguanine) by the murine neoplasm Sarcoma 180/TG and by acute lymphocytic leukemia cells of man is at least in part due to an increase in the activity of a particulate-bound alkaline phosphatase(s) which causes an elevation in the rate of degradation of the active tumor-inhibitory nucleotide

Table I. Intermediates in the Preparation of Analogues of 2,3-Dehydrotetramisole and Tetramisole



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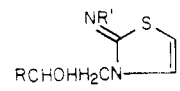

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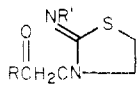

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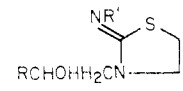


19, 20

Compd	R	R'	Method	Mp, °C	Recrystn solvent	Yield, %	Formula	Analyses
1	*p*-BrC_6H_4	H	A	144-145	EtOH	95	$C_{11}H_9BrN_2OS$	C, H, N
2	*p*-$NO_2C_6H_4$	H	A	290-dec	EtOH	96	$C_{11}H_9N_3O_3S$	C, H, N
3	*p*-$CH_3C_6H_4$	H	A	126-128	EtOH-H_2O	98	$C_{12}H_{12}N_2OS$	C, H, N
4	$C_{10}H_7$[a]	H	A	165-166	EtOH	92	$C_{15}H_{12}N_2OS$	C, H, N, S
5	*p*-BrC_6H_4	$COCH_3$	B	173-174	$CH_3C_6H_5$	80	$C_{13}H_{11}BrN_2O_2S$	C, H, N
6	*p*-$NO_2C_6H_4$	$COCH_3$	B	234-236	$CH_3C_6H_5$	76	$C_{13}H_{11}N_3O_4S$	C, H, N
7	*p*-$CH_3C_6H_4$	$COCH_3$	B	143-145	$CH_3C_6H_5$	79	$C_{14}H_{14}N_2O_2S$	C, H, N
8	3,4-$(CH_3)_2C_6H_3$	$COCH_3$	B	164-165	EtOH	72	$C_{15}H_{16}N_2O_2S$	C, H, N
9	$C_{10}H_7$[a]	$COCH_3$	B	178-180	EtOH	78	$C_{17}H_{14}N_2O_2S$	C, H, N, S
10	*p*-BrC_6H_4	$COCH_3$	C	168-169	$CH_3C_6H_5$	84	$C_{13}H_{13}BrN_2O_2S$	C, H, N
11	*p*-$NO_2C_6H_4$	$COCH_3$	C	234-235	$CH_3C_6H_5$	78	$C_{13}H_{13}N_3O_4S$	C, H, N
12	*p*-$CH_3C_6H_4$	$COCH_3$	C	130-132	$CH_3C_6H_5$	80	$C_{14}H_{16}N_2O_2S$	C, H, N
13	3,4-$(CH_3)_2C_6H_3$	$COCH_3$	C	139-141	$CH_3C_6H_5$	81	$C_{15}H_{18}N_2O_2S$	C, H, N
14	$C_{10}H_7$[a]	$COCH_3$	C	197-198	$CH_3C_6H_5$	78	$C_{17}H_{16}N_2O_2S$	C, H, N, S
15	*m*-$CH_3C_6H_4$	H	D	55-56	EtOH-H_2O	92	$C_{12}H_{14}N_2OS$	C, H, N
16	$C_{10}H_7$[a]	H	D	288-290	EtOH	91	$C_{15}H_{14}N_2OS$	C, H, N, S
17	*m*-$CH_3C_6H_4$	$COCH_3$	B	115-117	$CH_3C_6H_5$	80	$C_{14}H_{16}N_2O_2S$	C, H, N
18	$C_{10}H_7$[a]	$COCH_3$	B	130-132	$CH_3C_6H_5$	74	$C_{17}H_{16}N_2O_2S$	C, H, N, S
19	*m*-$CH_3C_6H_4$	$COCH_3$	C	127-129	$CH_3C_6H_5$	84	$C_{14}H_{18}N_2O_2S$	C, H, N
20	$C_{10}H_7$[a]	$COCH_3$	C	112-114	$CH_3C_6H_5$	83	$C_{17}H_{18}N_2O_2S$	C, H, N, S

[a] 2-Naphthyl.

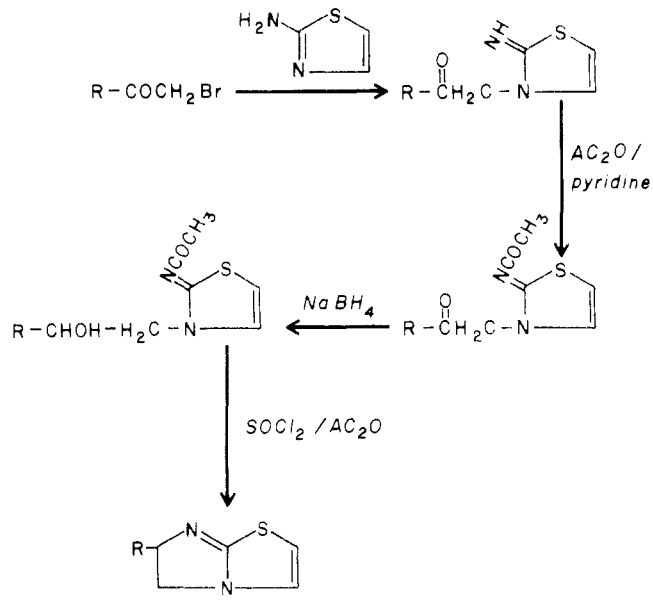
form(s) of the 6-thiopurines. The availability of a potent inhibitor of alkaline phosphatase would appear to have clinical utility in these situations, since in theory such an agent might restore sensitivity to the 6-thiopurines.

The anthelmintic tetramisole [(±)-2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole hydrochloride] and certain of its analogues have recently been reported to be relatively potent stereospecific inhibitors of nonspecific alkaline phosphatase activity (orthophosphoric monoester phosphohydrolase, E.C. 3.1.3.1.).[5-9] This class of compounds is inhibitory toward the alkaline phosphatases of most mammalian tissues; the intestinal enzyme, however, is an exception, being resistant to the action of these agents.[6-8] Since this class of agents appeared to have potential as inhibitors of the enzyme(s) of neoplastic cells, we examined the inhibitory potential of several available tetramisole derivatives using a partially purified particulate-bound alkaline phosphatase of Sarcoma 180/TG, the 6-thioguanine insensitive variant of Sarcoma 180 which appears to have achieved resistance through elevation of alkaline phosphatase(s) activity.[9] The most potent agent tested in this initial study was (±)-6-(*m*-bromophenyl)-5,6-dihydroimidazo[2,1-*b*]thiazole oxalate (R8231). The mechanism of inhibition of alkaline phosphatase from Sarcoma 180/TG caused by this class of compounds was of the uncompetitive type, a finding which corroborated an earlier report[6] documenting this type of inhibition with other enzyme systems.

In the present study the relationship between structure and inhibitory potency against alkaline phosphatase for derivatives of this class was expanded by the synthesis and testing of a series of analogues for inhibitory activity toward partially purified alkaline phosphatase from Sarcoma 180/TG ascites cells.

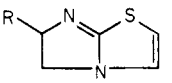
Chemistry. A series of meta- and para-substituted phenyl derivatives of (±)-2,3-dehydrotetramisole and (±)-tetramisole was synthesized following the procedures described by Raeymaekers et al.[10] In the case of 2,3-dehydrotetramisole the para substituents were Br, CH_3, or NO_2 and in one instance both the meta and para substituents were CH_3 groups. In the tetramisole series

Scheme I

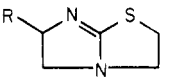


the meta substituents were CH_3 or NO_2 and the para substituents were CH_3, Br, Cl, or F. In addition, the phenyl group was replaced by a naphthyl ring system in an attempt to examine the effect of increased bulk at this position on enzyme inhibitory potency. The phenyl ring of 2,3-dehydrotetramisole was also substituted by a thienyl ring according to the synthetic procedure of Raeymaekers et al.[10] The procedure employed for the synthesis of 2,3-dehydrotetramisole analogues involved condensation of a bromomethyl aryl ketone and 2-aminothiazole, followed by acetylation, sodium borohydride reduction, and ring closure with thionyl chloride and acetic anhydride (Scheme I). A similar sequence of reactions was utilized to obtain the tetramisole analogues except that method D was employed for the condensation of the bromomethyl aryl ketone with 2-aminothiazoline. The newly synthesized intermediates in this sequence of reactions are listed in

Table II. Substituted 2,3-Dehydrotetramisoles and Tetramisoles



21-23



24, 25

Compd	R	Mp, °C	Yield, %	Formula	Analyses
21	p-BrC_6H_4	206-208	60	$C_{11}H_9BrN_2SC_2H_2O_4$	C, H, N
22	3,4-$(CH_3)_2C_6H_3$	204-206	63	$C_{13}H_{14}N_2SC_2H_2O_4$	C, H, N
23	$C_{10}H_7$[a]	215-217	52	$C_{15}H_{12}N_2SC_2H_2O_4$	C, H, N, S
24	m-$CH_3C_6H_4$	160-162	42	$C_{12}H_{14}N_2SC_2H_2O_4$	C, H, N
25	$C_{10}H_7$[a]	198-199	52	$C_{15}H_{14}N_2SC_2H_2O_4$	C, H, N, S

[a] 2-Naphthyl.

Scheme II

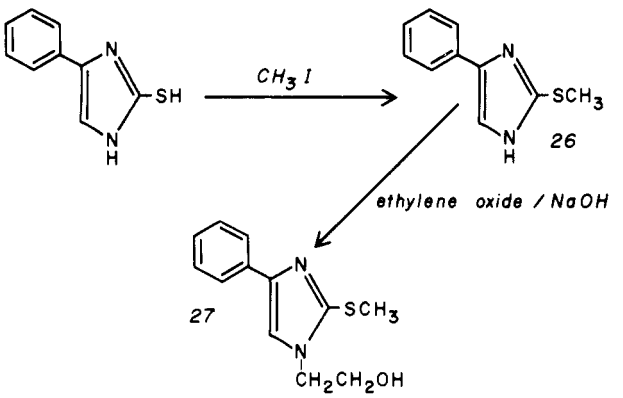
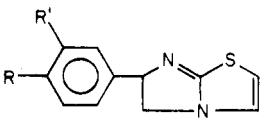
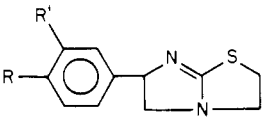


Table I and the new analogues of tetramisole or 2,3-dehydrotetramisole are listed in Table II.

To determine the necessity for an intact thiazolidine ring system in the tetramisole analogues for inhibition of the activity of alkaline phosphatase, we have synthesized 1-β-hydroxyethyl-2-mercaptomethyl-4-phenylimidazole (**27**). Compound **27** was obtained by the procedure shown in Scheme II; this involved initially reacting 2-mercapto-4(5)-phenylimidazole with methyl iodide to yield the corresponding $-SCH_3$ derivative **26**,[11] which was then converted to the desired product (**27**) using ethylene oxide in the presence of a catalytic amount of NaOH.[12]

Biological Results and Discussion. The concentrations of analogues of 2,3-dehydrotetramisole and tetramisole required to produce 50% inhibition of the activity of a particulate bound alkaline phosphatase from Sarcoma 180/TG ascites cells are shown in Table III. Intermediates providing a series of structural modifications on either the thiazoline, thiazolidine, or the imidazole rings were also tested for their capacities to inhibit alkaline phosphatase but are not included in Table III, since none of these derivatives, listed in Table I, nor compounds **26** and **27** were found to possess significant inhibitory activity up to a concentration of at least 5×10^{-4} M. These findings support the concept that both the thiazolidine and dihydroimidazole rings are required for inhibitory potency toward alkaline phosphatase. The data of Table III demonstrate that substitution of either an electronegative group at the para position of the phenyl ring or the bulky naphthyl ring system in place of the phenyl group increases the inhibitory activity of these compounds relative to the unsubstituted derivative. Dehydrogenation of the thiazolidine ring of compound **25** at positions 2,3 to give **23** increased inhibitory activity; however, dehydrogenation of other analogues (i.e., p-BrPh and p-CH_3Ph derivatives) did not markedly alter potency. Compound **23** was the most active agent tested as an inhibitor of alkaline phosphatase, requiring only one-half the concentration of R8231, which was previously reported to be the most active agent of the tetramisole series,[6] to produce 50% inhibition of enzyme activity. To determine whether inhibitors of alkaline phosphatase of this class have the potential to restore the sensitivity of Sarcoma 180/TG to 6-thioguanine, the effects of (*S*)-(−)-6-(4-bromophenyl)-2,3,5,6-tetrahydroimidazo[2,1-*b*]thiazole oxalate (L-*p*-bromotetramisole) on the growth-inhibitory properties of 6-thioguanine were measured in tissue culture. L-*p*-

Table III. Concentrations of Analogues of 2,3-Dehydrotetramisole and Tetramisole Required for 50% Inhibition of the Activity of Particulate Bound Alkaline Phosphatase from Sarcoma 180/TG Ascites Cells

Compd[a]	Structure	R	R'	I_{50}, μM[b]
				
		H	H	45.0
21		Br	H	1.3
		NO_2	H	8.3
22		CH_3	CH_3	11.0
		CH_3	H	6.6
R8231		H	Br	2.0
23	5,6-Dihydro-6-(2-naphthyl)imidazo-[2,1-*b*]thiazole			1.0
	5,6-Dihydro-6-(2-thienyl)imidazo-[2,1-*b*]thiazole			50.0
				
		H	H	38.0
		Br	H	2.6
		Cl	H	4.5
		F	H	16.0
		CH_3	H	8.1
24		H	CH_3	40.0
		H	NO_2	38.0
25	2,3,5,6-Tetrahydro-6-(2-naphthyl)imidazo-[2,1-*b*]thiazole			9.0

[a] Compounds which are not numbered were synthesized for studies of structure-activity relationships according to published procedures.[10] All compounds were tested as oxalate salts. [b] The I_{50} is the concentration of drug required to reduce by 50% the observed activity of the enzyme. The activity of alkaline phosphatase used in these experiments was 4360 units/mL; the activity units for the enzyme were defined previously.[13] For each experiment 50 μL of enzyme was used.

Table IV. Effect of L-*p*-Bromotetramisole on the Growth of Sarcoma 180/TG Cells in Culture[a]

L-*p*-Bromotetramisole concn, μM	Growth (cell no./mL × 10^{-5}) (−)-6-Thioguanine	(+)-6-Thioguanine	Ratio of (+)-6-thioguanine/(−)-6-thioguanine × 100
0	2.5	2.0	80
10	3.6	2.5	69
50	3.5	2.3	66
100	1.3	0.64	49

[a] Log phase Sarcoma 180/TG cells were treated with the indicated concentrations of L-*p*-bromotetramisole oxalate in the presence or absence of 6-thioguanine (10^{-6} M) for 96 h. Cells were inoculated at a concentration of 10^4 cells/mL in Fischer's medium supplemented with 10% horse serum and incubated at 37 °C. At 96 h, cell numbers were determined using a Model ZBI Coulter counter.

Bromotetramisole was selected for such tests since (a) it is a relatively stable, water-soluble derivative of this class and (b) it is among the most potent known inhibitors of the alkaline phosphatase activity of this neoplasm (I_{50} = 1.8×10^{-6} M). Tests in culture showed that L-*p*-bromotetramisole required a concentration of 10^{-4} M to cause inhibition of the growth of Sarcoma 180/TG (Table IV). At this level, L-*p*-bromotetramisole produced significant enhancement of the toxicity of 6-thioguanine to Sarcoma 180/TG; however, the high concentration of the alkaline phosphatase inhibitor required to accomplish this effect in vitro indicates the need for an even more efficacious derivative to achieve restoration of sensitivity of neoplastic cells to 6-thioguanine in vivo.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were performed by the Baron Consulting Company, Orange, Conn. Spectral data were obtained using a Perkin-Elmer grating IR spectrophotometer, Model 257, and a Varian T-60A NMR spectrophotometer. Tetramethylsilane was used as an internal standard for NMR determinations. NMR and IR spectra were as expected.

Inhibition of Alkaline Phosphatase. Alkaline phosphatase from the murine ascitic neoplasm Sarcoma 180/TG was isolated and partially purified according to a procedure previously described;[13] the solubilized enzyme (enzyme A) after the ethanol fractionation step was employed in this investigation. The assay procedure was the same as previously reported.[9]

Synthesis of Intermediates of 2,3-Dehydrotetramisole and Tetramisole. Method A. Bromomethyl aryl ketone (0.02 mol) was refluxed for 1 h with 0.02 mol of 2-aminothiazole in 25 mL of 2-propanol. The resulting solid, 2-imino-3-aroylmethylthiazoline, was filtered, dried, and macerated with a 10% Na_2CO_3 solution. The mixture was filtered and crystallized from an appropriate solvent as listed in Table I.

Method B. To a mixture of 2-imino-3-aroylmethylthiazoline (0.01 mol) and 5 mL of pyridine in 50 mL of chloroform was added acetic anhydride (0.02 mol). The mixture was refluxed for 1.5 h and the chloroform was removed by distillation to leave an oil which was crystallized by maceration with petroleum ether. The acetate was then recrystallized from an appropriate solvent.

Method C. To a solution of 2-acetylimino-3-aroylmethylthiazoline (0.005 mol) in 25 mL of methanol maintained at 10 °C was added in small portions 0.0025 mol of $NaBH_4$. The solution was stirred at room temperature for 2 h, solvent was removed under vacuum, and the residue was suspended in water and extracted with chloroform. The chloroform layer was dried (anhydrous Na_2SO_4) and the solvent was removed to leave a solid which was crystallized from an appropriate solvent.

Method D. 2-Aminothiazoline (0.01 mol) was dissolved in 20 mL of acetonitrile and was added in small portions to 0.01 mol of bromomethyl aryl ketone. The mixture was stirred at room temperature for 30 min and filtered. The precipitate was dried and macerated with a 10% Na_2CO_3 solution. The free base was then crystallized from ethanol.

Cyclization Reaction for Tetramisole and 2,3-Dehydrotetramisole Derivatives. The 2-acetylimino-3-(2-hydroxyarylethyl) derivatives (0.005 mol) obtained from method C were added in small portions to 3.0 mL of thionyl chloride at 5 °C over a period of 30 min. The mixture was stirred at room temperature for 1 h, Ac_2O (15 mL) was added, and the acetyl chloride which formed was removed under vacuum. The mixture was refluxed for another 0.5 h and the excess Ac_2O was removed under vacuum. The residue was dissolved in dilute HCl and filtered. The filtrate was made alkaline (pH 8.5) and extracted with chloroform. The chloroform layer was dried (anhydrous Na_2SO_4) and flash evaporated. The residue was dissolved in a minimum amount of 2-propanol and oxalate salts were prepared by adding a solution of oxalic acid in 2-propanol. The final products as oxalates were recrystallized from ethanol.

2-Mercaptomethyl-4(5)-phenylimidazole. A solution of 0.352 g (0.002 mol) of 2-mercapto-4(5)-phenylimidazole[11] and methyl iodide (0.3 g, 0.003 mol) in 20 mL of methanol was stirred for 4 h at room temperature. Solvent was removed by flash evaporation and the residue was macerated with 10% $NaHCO_3$ solution and crystallized from ethyl alcohol–ethyl ether as white prisms to yield 0.27 g (75%), mp 131–133 °C.

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References and Notes

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