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Antimalarials. Synthesis and Antimalarial Activity of 1-(4-Methoxycinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine and Derivatives

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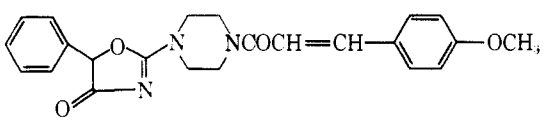
The preparation and activity against *Plasmodium berghei* of derivatives of 1-(4-methoxycinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine are described. Replacement of the cinnamoyl group was accomplished by acylation or alkylation of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine. Modifications of the 5-phenyl group were prepared either by a sequence of reactions involving mandelic ester–pemoline–piperazine pemoline or by the reaction of 5-aryl-2-thio-2,4-oxazolidinedione with piperazine or N-substituted piperazines. In a similar manner, pemoline was allowed to react with *N*-arylpiperazine, hexahydro-1*H*-1,4-diazepine, and 2,6-dimethylpiperazine to provide *N*-arylpiperazine pemoline derivatives and variations in the piperazine moiety. Several compounds in which the 2-oxazolin-4-one ring was replaced with other heterocyclic rings were prepared as were several open-chain analogs. Five compounds (three of them substituted in the para position of the 5-phenyl group and two *N*-arylpiperazine pemoline derivatives) were found to be active against *Plasmodium berghei*. The remaining active compound possessed changes in the cinnamoyl group and substitution on the 5-phenyl group.

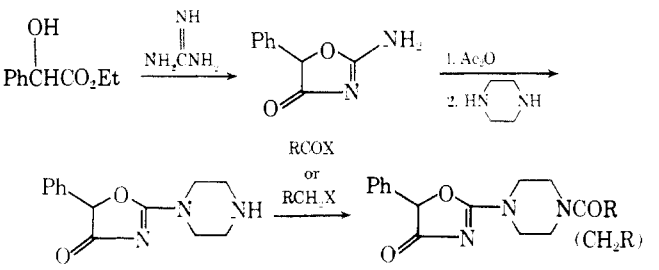
In an agreement with Walter Reed, compounds from Abbott were screened for blood schizonticidal activity against *Plasmodium berghei* in mice. Compound 1 was found to possess sufficient activity to warrant further interest. While 2-amino-5-phenyl-4-oxo-2-oxazoline (pemoline) is a constituent of the clinically useful drug Cylert in the treatment of minimal brain dysfunction in children,[1] compounds containing the (4-oxo-2-oxazolin-2-yl)piperazine moiety and possessing antimalarial activity have not to our knowledge been reported.[2] Structural variations of 1 and



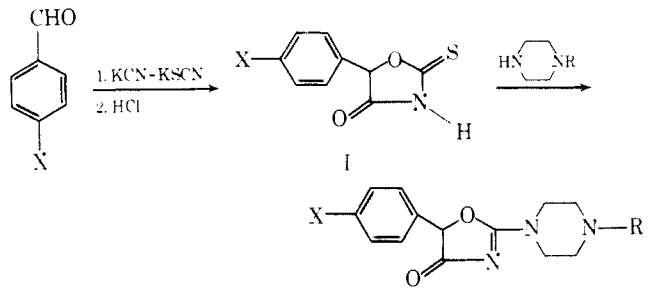
1

their activity against *P. berghei* are the subject of this paper.

Chemistry. The starting material for the compounds listed in Tables I–III containing the (5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine moiety was 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (piperazine pemoline). Condensation of mandelic ester with guanidine gave 2-amino-5-phenyl-2-oxazolin-4-one (pemoline).[3] Using the unpublished procedure of C. Lee (this laboratory), pemoline was activated by acylation with acetic anhydride to yield a monoacetyl derivative which reacted smoothly with piperazine to give piperazine pemoline. Acylation or alkylation with epoxides of α-bromo ketones of piperazine pemoline gave the corresponding compounds listed in Tables I–III. In the preparation of compounds **50–52**, the reaction of piperazine pemoline with the α-bromo ketones did not give an isolable compound. As the desired compounds were β-hydroxyethylpiperazine pemoline compounds, piperazine pemoline was alkylated with the epoxide to give the desired compounds directly.



The 5-aryl-4-oxo-2-oxazolinyl derivatives, compounds **15, 16, 19–21, 23,** and **25**, were prepared by allowing 5-aryl-2-thio-2,4-oxazolidinedione (I) to react with piperazine to



I

II

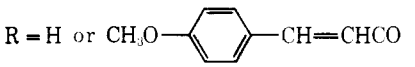
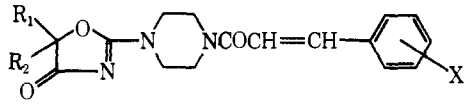


Table I. 1-(Substituted cinnamoyl)-4-(5-substituted-4-oxo-2-oxazolin-2-yl)piperazines

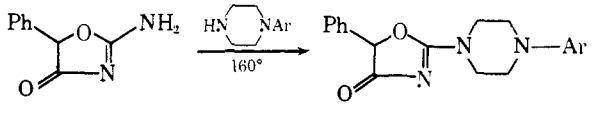


No.	R_1	R_2	X	Mp, °C	Method of prepn
2	C_6H_5	H	3,4-(OCH_2O)	215–218	A
3	C_6H_5	H	4-NO_2	238–240	A
4	C_6H_5	H	4-CH_3	213.5–215.5	A
5	C_6H_5	H	4-$(CH_3)_2N$	235–239.5	A′
6	C_6H_5	H	3,4-$(CH_3O)_2$	211–213	A
7	C_6H_5	H	4-CH_3S	210–212	A′
8	C_6H_5	H	4-CH_3CONH	224–228	A′
9	C_6H_5	H	4-CH_3CH_2O	220–222	A
10	C_6H_5	H	2-CH_3O	166–169	A
11	C_6H_5	H	3-CH_3O	178–179	A
12	C_6H_5	H	4-Cl	236.5–239.5	A
13	C_6H_5	H	4-CF_3	261–263	A
14	C_6H_5	H	H	215–217	A
15	4-ClC_6H_4	H	4-CH_3O	209–212	B
16	4-$CF_3C_6H_4$	H	4-CH_3O	198–204	B
17	3,4-$Cl_2C_6H_3$	H	4-CH_3O	215–225	A
18	C_6H_5	C_6H_5	4-CH_3O	220–222	A
19	4-FC_6H_4	H	4-CH_3O	211.5–224	B
20	4-ClC_6H_4	H	4-CH_3S	197–198	B
21	4-ClC_6H_4	H	4-CH_3CH_2O	175–176	B
22	C_6H_5	CH_3	4-CH_3O	171–174	C
23	4-BrC_6H_4	H	4-CH_3O	174–176	B
24	$-(CH_2)_5-$		4-CH_3O	195–197	C
25	4-$CH_3OC_6H_4$	H	4-CH_3O	179–184	B
26	$C_6H_5CH_2$	H	4-CH_3O	155–157	B′
27[a]	4-$CF_3OC_6H_4$	H	4-CH_3O	181.5–183.0	B′
28	1-Naphthyl	H	4-CH_3O	180–187	B′

[a] Anal. ($C_{23}H_{22}F_3N_3O_5$) H, N; C: calcd, 57.86; found, 58.52.

give (5-aryl-4-oxo-2-oxazolin-2-yl)piperazine (II). While 5-aryl-2-thio-2,4-oxazolidinedione was prepared in poor yield, the number of steps was less by this route. In the case of costly aldehydes, e.g., 4-trifluoromethoxybenzaldehyde, (4-methoxycinnamoyl)piperazine was allowed to react with 5-aryl-2-thio-2,4-oxazolidinedione to give the desired product in two steps. Since 5-(3,4-dichlorophenyl)-2-thio-2,4-oxazolidinedione could not be prepared, the mandelic ester–pemoline–piperazine pemoline sequence was used for the preparation of **17**.

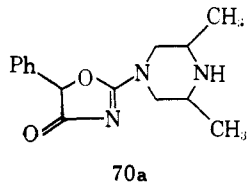
N-Alkyl- or *N*-arylpiperazine pemolines (III) were prepared by heating the monosubstituted piperazines with pemoline (no solvent) at 160° for several hours. After numerous attempts to prepare the thiazoline analog of 1 via the reaction of piperazine with 5-phenylrhodanine, compound **69** was successfully prepared in high purity by the reaction of 1-(4-methoxycinnamoyl)piperazine with 2-amino-5-phenyl-2-thiazolin-4-one in refluxing ethanol.



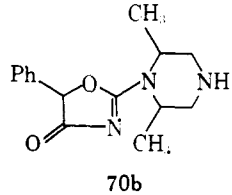
III

To provide variations in the piperazine moiety, pemoline was allowed to react with hexahydro-1*H*-1,4-diazepine in refluxing ethanol to yield 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)hexahydro-1*H*-1,4-diazepine.

The reaction of 2,6-dimethylpiperazine and pemoline at 165° (no solvent) led to **70**. The NMR of **70** showed, in addition to the pemoline protons, a broad triplet at 4.03 ppm (2 H), a broad multiplet at 2.43–3.26 ppm, and a doublet at 1.00 ppm (6 H). In piperazine pemolines the protons adjacent to the nitrogen attached to the 4-oxo-2-oxazoline ring will resonate at lower field due to the "amide" nature of that nitrogen. In the unsubstituted case in $CDCl_3$, the methylene proton resonances appear at approximately 3.8 and 3.0 ppm. In the NMR of **70**, spin-decoupling experiments reveal that the 4.0-ppm protons are not coupled to the methyl protons and therefore the nitrogen adjacent to the site of methyl substitution is not "amide-like" supporting structure **70a**.



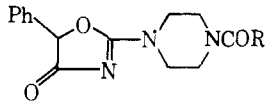
70a



70b

Attempts to prepare **71–73** by the reaction of excess *N*-methyl- or *N*,*N*′-dimethylethylenediamine with pemoline led to extensive decomposition. However, the reaction of 1 mol of *N*-methylethylenediamine gave a crystalline solid **74** which from the NMR spectrum clearly no longer possessed

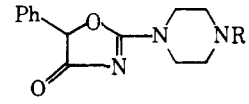
Table II. 1-Acyl-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)-piperazines



No.	R	Mp, °C	Method
29	4-$CH_3OC_6H_4CH_2$	116–136	A
30	4-$CH_3OC_6H_4C(CH_3)$=CH	215–218	A
31	4-$CH_3OC_6H_4CH$=$C(CH_3)$	192–193	A
32	C_6H_5	193–195	A
33	4-ClC_6H_4	211–213	A
34	$C_6H_5C(CH_3)_2CH_2$	161–164	A
35	4-C_5H_4NCH=CH[a]	229–232	A′
36	6-$CH_3OC_{10}H_8$[b]	192.5–194.0	A
37	5-$NO_2C_4H_2OCH$=CH[c]	189–192.5	A′
38	C_6H_5C≡C	175–176	A
39	4-$CH_3OC_6H_4$	221.5–223	A
40	4-$CH_3OC_6H_4CH_2CH_2$	158–160	A

[a] 2-(4-Pyridyl)ethenyl. [b] 6-Methoxy-3,4-dihydro-2-naphthyl. [c] 2-(5-Nitro-2-furyl)ethenyl.

Table III. 1-(Alkyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)-piperazines

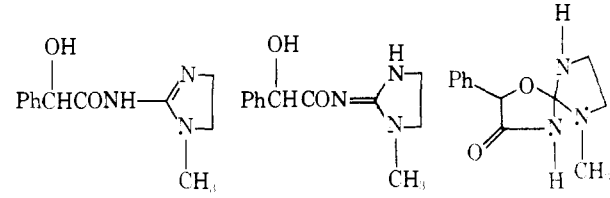


No.	R	Mp, °C	Method
41	$CH_3OC_6H_4COCH_2$	164–170	E
42	$CH_3OC_6H_4CH(OH)CH_2$	133–160	F
43	1-$C_{10}H_{15}COCH_2$[a]	155–159	E
44	1-$C_{10}H_{15}CH(OH)CH_2$[b]	190–192	F
45	$CH_3OC_6H_4COCH_2CH_2$	133.5–134.0	H
46	4-$CH_3OC_6H_4CH(OH)CH_2CH_2$	119–136	F
47	2-$C_4H_3SCOCH_2$[c]	147–150	E
48	$C_4H_3SCH(OH)CH_2$[d]	203–205	F
49	4-$BrC_6H_4COCH_2$	157.5–159.0	E
50	4-$BrC_6H_4CH(OH)CH_2$	151.5–155.5	G
51	3-$CF_3C_6H_4CH(OH)CH_2$	81[e]	G
52	4-$ClC_6H_4CH(OH)CH_2$	152–156	G

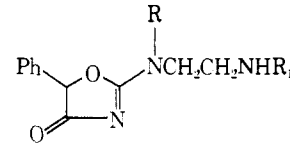
[a] 2-(1-Adamantyl)-2-oxoethyl. [b] 2-(1-Adamantyl)-2-hydroxyethyl. [c] 2-Thenoylmethyl. [d] 2-Hydroxy-2-(2-thienyl)ethyl. [e] Not a clear melt.

a 2-amino-5-phenyl-2-oxazolin-4-one ring. The chemical shift of the H_{C-5} in the (5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine derivatives listed in Tables I–III is 5.76 ppm, while in **74** the chemical shift is 4.86 ppm. The relatively sharp phenyl singlet in the 5-phenyl-4-oxo-2-oxazolin-2-yl derivatives was replaced by a broad complex multiplet. The NMR showed two exchangeable protons. The ir at high dilution showed bands at 3440 and 3350 cm^{-1} suggestive of N–H amide and intramolecular bonded OH groups.[4] From the spectral data (NMR, ir, and uv) it was not possible to eliminate any of the three possible structures **74a–c**.

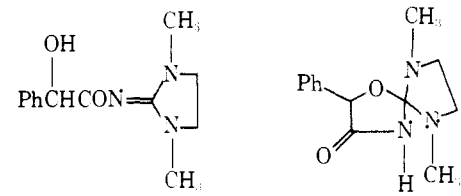
In a similar manner, 1 mol of *N,N′*-dimethylethylenediamine was allowed to react with pemoline to give a crystalline solid **75**. In analogous manner to the monomethylethylenediamine reaction, two possible compounds exist, the imidazolidine structure **75a** and the spiro structure **75b**. The NMR of **75** was very similar to **74**, having a broad phenyl multiplet and a similar chemical shift of the C-5 proton. The NMR showed one exchangeable proton and the ir spectrum at high dilution showed a band at 3420 cm^{-1}, suggestive of an N–H lactam, but not providing definitive evidence for an OH (structure **75a**) or NH (structure **75b**).



74a **74b** **74c**



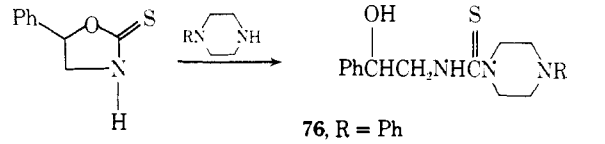
71. R_1 = H; R = CH_3
72. R_1 = CH_3; R = H
73. R_1 = R = CH_3



75a **75b**

The ethylenediamine analog of **1** was eventually prepared in a conventional but long synthesis with *N,N*-dibenzylethylenediamine chosen as the properly blocked ethylenediamine. Acylation of *N,N*-dibenzylethylenediamine with *tert*-butyloxycarbonyl azide followed by hydrogenolysis yielded *N*-(*tert*-butyloxycarbonyl)ethylenediamine. Acylation with 4-methoxycinnamoyl chloride followed by HCl–dioxane treatment gave 4-methoxycinnamoylethyl enediamine. Reaction of the latter with 5-phenyl-2-thio-2,4-oxazolidinedione gave the desired product.

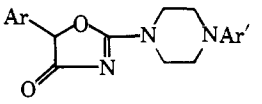
1-Phenylpiperazine was allowed to react with 5-phenyl-2-thio-2-oxazolidinone in hopes of obtaining 1-phenyl-4-(5-phenyl-2-oxazolin-2-yl)piperazine. However, the isolated product was the open-chain compound **76**. The NMR of **76** showed an exchangeable doublet (1 H) at 5.43 ppm assigned to the OH proton.



76, R = Ph
77, R = 4-$CH_3OC_6H_4CH$=$CHCO$

Two open-chain analogs of **1** were prepared. Hydrogenolysis of piperazine pemoline followed by acylation with 4-methoxycinnamoyl chloride gave *N*-(phenylacetyl)-4-(4-methoxycinnamoyl)-1-piperazinecarboxamide (**81**). 2-Amino-1-phenylethanol and triethyl orthoformate gave 5-phenyl-2-oxazoline as a distillable liquid. 5-Phenyl-2-oxazoline reacted readily with phenylpiperazine to give a crystalline compound **78**. The ir of **78** showed a strong band at 1670 cm^{-1} (C=N) and at high dilution (0.03%) a broad band at about 3520 cm^{-1} suggestive of an intramolecularly

Table IV. 1-Aryl-4-(5-aryl-4-oxo-2-oxazolin-2-yl)-piperazines

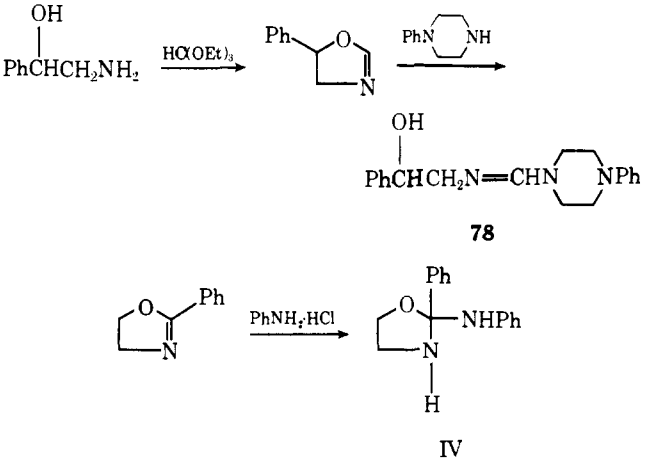


No.	Ar	Ar'	Mp, °C	Method
53[a]	C_6H_5	C_6H_5	193.5–194.5	D
54[b]	C_6H_5	4-$CH_3OC_6H_4$	178–179	D
55[c]	C_6H_5	$C_6H_5CH_2$	160–161	D
56	C_6H_5	3,4-$Cl_2C_6H_3$	161.0–164.5	D
57	C_6H_5	3-ClC_6H_4	199–201	D
58	C_6H_5	3-$CF_3C_6H_4$	164–171	D
59	4-ClC_6H_4	C_6H_5	182–184	D
60	C_6H_5	4-C_5H_4N[d]	198–201	D
61	C_6H_5	2-C_5H_4N[e]	229–233.5	D

[a] Lit.[22] mp 190–192°. [b] Lit.[22] mp 182–184°. [c] Lit.[22] mp 162–164°. [d] 4-Pyridyl. [e] 2-Pyridyl.

bonded OH. The ir data suggest structure **78**. It has been reported that the addition of aniline hydrochloride to 2-phenyl-2-oxazoline yields a cyclic product[5] (IV).

Biological Results. All compounds listed in Tables I–V and the titled compounds in the Experimental Section were evaluated for blood schizonticidal activity against *Plasmodium berghei* in mice by the Rane Laboratory, University of Miami, as described elsewhere.[6,7] All compounds considered active (mean survival time 100% greater than controls) are listed in Table VI. The two most active compounds prepared were **15** and **23**. Compound **25** was active but less active than **23**. The only major variants from 1 with activity were **53** and **59**. Relatively minor variations of 1, e.g., replacement of O with S (compounds 1 and **69**) and replacement of OCH_3 with OCH_2CH_3 (compounds 1 and **9**),



78

IV

resulted in inactive compounds making any structure–activity correlations difficult.

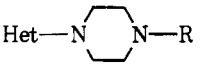
As has been previously pointed out, the substitution of halogens Br and Cl for H often leads to enhanced antimalarial activity.[8] Replacement of H with Br or Cl on the 4 position of the 5-phenyl group of 1 led to greater activity. In the cluster analysis of Hansch, Unger, and Forsythe,[9] the differences among the functional groups Cl, Br, OCF_3, and CF_3 for the parameters used do not appear until the 20 and 60 level. However, compounds **16** (4-CF_3) and **27** (4-CF_3O) in our study were inactive. Stogryn[8] found the substitution of 4-CF_3O for 4-Cl on the 5-phenyl group of pyrimethamine led to decreased activity.

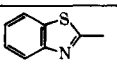
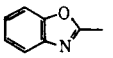
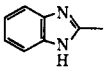
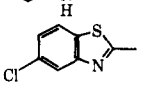
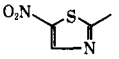
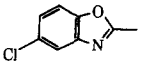
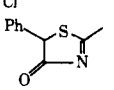
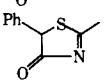
In summary, the biological activity of 1 and its derivatives indicates that the (5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine moiety is a sensitive antimalarial pharmacophoric group and no significant enhancement of activity was discovered.

Experimental Section

General. Melting points were determined in open capillary tubes on a Thomas-Hoover melting point apparatus and are not

Table V. 1-Acyl- or Aryl-4-(heterocyclic)piperazines



No.	Het	R	Mp, °C	Method
62		4-$CH_3OC_6H_4CH$=$CHCO$	188.5–190	I
63		4-$CH_3OC_6H_4CH$=$CHCO$	171–179	I
64		4-$CH_3OC_6H_4CH$=$CHCO$	277–280.5	J
65		4-$CH_3OC_6H_4CH$=$CHCO$	222–223.5	I
66		C_6H_5	183.5–185.0	K
67		4-$CH_3OC_6H_4CH$=$CHCO$	226.5–228	I
68		4-$CH_3C_6H_4$	167–169	D[a]
69[b]		4-$CH_3OC_6H_4CH$=$CHCO$	231–233	C[c]

[a] 2-Amino-5-phenyl-2-thiazolin-4-one was used in place of 2-amino-5-phenyl-2-oxazolin-4-one. [b] Anal. ($C_{23}H_{23}N_3O_3S$) H, N; C: calcd, 65.54; found, 65.12. [c] 2-Amino-5-phenyl-2-thiazolin-4-one was used in place of 2-amino-5-methyl-5-phenyl-2-oxazolin-4-one.

Table VI. Antimalarial Activity against *Plasmodium berghei*[a]

No.	Dosage, mg/kg	Mean survival time (MST)	Activity
1	80	9.4	
	160	13.2	Active
	320	15.0	Active
	640	19.6	Active
15	80	9.0	
	160	14.8	Active
	320	16.0	Active
	640	21.3	Active (1 cure)
21	80	11.6	
	160	14.2	Active
	320	14.8	Active
	640	16.2	Active
23	40	7.2	
	80	12.6	Active
	160	14.2	Active
	320	17.0	Active (1 cure)
25	160	7.4	
	320	12.6	Active
	640	18.8	Active
53	320	9.2	
	640	14.5	Active
59	320	9.6	
	640	17.4	Active

[a]Activity was determined by the Rane Laboratory, University of Miami, by administering the compounds suspended in peanut oil subcutaneously to blood-induced *P. berghei* infected mice.[6,7] A compound is considered active only if it effects at least a 100% extension of survival time over untreated infected controls. Untreated animals die within 6–8 days with a mean survival time of 6.2 days.

corrected. The yields on target compounds (Tables I–V and titled compounds in the Experimental Section) are reported for material which gave acceptable C, H, and N analytical values (within 0.4% of theoretical values) unless otherwise indicated. Ir and NMR spectra were run on all target compounds and NMR spectra were run on all intermediates. In all cases the spectra were consistent with the assigned structures.

Each method of preparation from Tables I–V is illustrated with one example typical of that method. The other compounds prepared by the same method were done without significant changes in the procedure.

4-Methoxyphenylacetic, 4-, 3-, and 2-methoxycinnamic, 3-(4-methoxyphenyl)propionic, 3,4-dimethoxycinnamic, 4-acetamidocinnamic, 4-chlorocinnamic, 4-nitrocinnamic, and 4-methylcinnamic acids were obtained from the Aldrich Chemical Co. 3,4-Methylenedioxycinnamic and 4-dimethylaminocinnamic acids were obtained from Research Org/Inorg (ROC/RIC). α-Methyl-4-methoxycinnamic [mp 154–156° (lit.[10] 154.5–155.5°)], β-methyl-4-methoxycinnamic [mp 155–157° (lit.[11] 156.5–157°)], 3-phenyl-3-methylbutanoic [mp 51–54° (lit.[12] 57–58°)], and 3-(5-nitro-2-furyl)acrylic[13] [mp 238–240° dec (lit.[14] 235–236°)] acids were prepared by literature methods. 4-Methylthiocinnamic [mp 169–175° (lit.[15] 170–171°)], 3-(4-pyridyl)acrylic [mp 304° dec (lit.[16] 290–291° dec)], 4-trifluoromethylcinnamic [mp 231–232° (lit.[17] mp 229.5–230.5°)], and 4-ethoxycinnamic [mp 194–198° (lit.[18] 190°)] acids were prepared by the general procedure[19] of condensing the corresponding aryl aldehyde with malonic acid. Saponification of methyl 6-methoxy-3,4-dihydro-2-naphthoate [mp 46–47° (hexane) [lit.[20] mp 51–52° (aqueous EtOH)]] gave the acid.

Method A. 1-(4-Chlorocinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (12). Method A was the procedure used by C. Lee (Abbott Laboratories) for the preparation of 1. 2-Amino-5-phenyl-2-oxazolin-4-one (pemoline) was available from Abbott Laboratories (Abbott Code-55655) and can be made by condensing ethyl mandelate with guanidine.[3] 2-Amino-5-(3,4-dichlorophenyl)-2-oxazolin-4-one, prepared in a similar manner, was isolated in 81% yield: mp 190° dec. Anal. ($C_9H_6Cl_2N_2O_2$) C, H, N. 2-Amino-5-methyl-5-phenyl-2-oxazolin-2-one,[21] 2-amino-5,5-diphenyl-2-oxazolin-2-one,[22] and 2-amino-1-oxa-3-azaspiro[4.5]dec-2-en-4-one[23] are known compounds and were prepared by a similar method.

Pemoline was treated with 350 ml of Ac_2O at 110–120° for 4 hr and the precipitate was filtered, washed with Et_2O, and dried to give 104 g (84%) of product. The above product, 66.15 g (0.303 mol), was added to a solution of 52.18 g (0.067 mol) of anhydrous piperazine in 2300 ml of dioxane. The reaction mixture was stirred for 5 hr at room temperature and filtered, the solvent was evaporated at reduced pressure, and the residue was crystallized twice from benzene to give 53.7 g (72%) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine, mp 148–149° (lit.[24] 146–148°). To a solution of 9.8 g (0.04 mol) of the above product in 150 ml of dimethylacetamide (DMAC), chilled in an ice bath, was added 7.0 ml of Et_3N followed by a solution of 0.05 mol of freshly prepared 4-chlorocinnamoyl chloride in 20 ml of DMAC. The reaction was allowed to warm gradually to room temperature and stirred overnight. The mixture was poured onto 500 g of ice and filtered, and the precipitate crystallized from EtOH to yield 8.0 g (49%) of product, mp 236.5–239.5°. Anal. ($C_{22}H_{20}ClN_3O_3$) C, H, N.

Method A'. 1-(4-Dimethylaminocinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (5). For compounds **5**, 7, 8, 35, and 37, the corresponding acids were coupled with the monosubstituted piperazine by forming the mixed anhydride of the acid with ethyl chloroformate as in the following example. 4-Dimethylaminocinnamic acid, 7.65 g, was dissolved in 50 ml of DMAC and 6.1 ml (0.044 mol) of Et_3N added. The solution was chilled in an ice bath and 3.48 ml (0.044 mol) of ethyl chloroformate was added dropwise while maintaining the temperature below 10°. After the addition was complete, the reaction was stirred for 1.5 hr, and a solution of 8.58 g (0.035 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine in 75 ml of DMAC was added. The mixture was allowed to warm gradually to room temperature and then was stirred for 2 hr. The mixture was worked up as described above to yield, after one crystallization from EtOH, 6.77 g (46%) of product, mp 233–237°. Anal. ($C_{24}H_{26}N_4O_3$) C, H, N.

Method B. 1-(4-Methoxycinnamoyl)-4-[5-(4-chlorophenyl)-4-oxo-2-oxazolin-2-yl]piperazine (15). Arylaldehydes were converted to the corresponding 5-aryl-2-thio-2,4-oxazolidinediones by a literature method.[25] The 2-thio-2,4-oxazolidinediones were allowed to react with piperazine to form 1-(2-oxazolin-2-yl)piperazines which were acylated to yield the target compounds. The following 5-aryl-2-thio-2,4-oxazolidinediones were prepared by the method of Lindberg and Pedersen.[25]

5-(4-Fluorophenyl)-2-thio-2,4-oxazolidinedione was prepared in 34% yield, mp 141–145°. Anal. ($C_9H_6FNO_2S$) C, H, N.

5-(4-Bromophenyl)-2-thio-2,4-oxazolidinedione was prepared in 6% yield, mp 157–161°. Anal. ($C_9H_6BrNO_2S$) C, H, N.

5-(4-Trifluoromethylphenyl)-2-thio-2,4-oxazolidinedione was isolated in 13% yield, mp 156–158°. Anal. ($C_{10}H_6F_3NO_2S$) C, H, N.

5-(4-Methoxyphenyl)-2-thio-2,4-oxazolidinedione was isolated in 15% yield, mp 159–161° (lit.[25] mp 159–160°).

5-(1-Naphthyl)-2-thio-2,4-oxazolidinedione was isolated in 15% yield, mp 166–168°. Anal. ($C_{13}H_9NO_2S$) C, H, N.

5-Benzyl-2-thio-2,4-oxazolidinedione was isolated in 16% yield (crude), mp 91–93°. Anal. ($C_{10}H_9NO_2S$) C, H, N.

5-(4-Trifluoromethoxyphenyl)-2-thio-2,4-oxazolidinedione was isolated in 18% yield (crude), mp 140.5–143.5°. Anal. ($C_{10}H_6F_3NO_3S$) C, H, N.

4-Trifluoromethoxybenzaldehyde, the precursor for the last compound, was prepared by reduction of 4-trifluoromethoxybenzoic acid (Pierce Chemical Co.) to the benzyl alcohol followed by oxidation with $(NH_4)_2Ce(NO_3)_6$. To a solution of 19.10 g (0.0927 mol) of 4-trifluoromethoxybenzoic acid in 90 ml of dry THF, cooled in a salt–ice bath, was added gradually over 1 hr 97.33 ml (0.0973 mol) of a 1 *M* solution of diborane in THF stabilized with 5 mol % $NaBH_4$ (Aldrich). The reaction mixture was allowed to warm gradually to room temperature and stirred overnight. The solvent was evaporated at reduced pressure. The residue was treated with ice and subsequently acidified with 40 ml of 5% HCl. The mixture was extracted with Et_2O and the Et_2O washings were dried with saturated brine and $MgSO_4$. The solvent was evaporated and the product distilled, bp 53–54° (0.5 mm), to give 15.50 g (87%) of 4-trifluoromethoxybenzyl alcohol.

A solution of 110 g (0.200 mol) of $(NH_4)_2Ce(NO_3)_6$ in 400 ml of 50% aqueous HOAc was added to 11.52 g (0.06 mol) of 4-trifluoromethoxybenzyl alcohol. The resulting red solution was heated on a

steam bath for 0.5 hr and allowed to cool gradually to room temperature for the next 0.5 hr. The yellow solution was diluted with ice and extracted thoroughly with Et_2O. The Et_2O extract was washed successively with 1 *M* KOH and saturated brine and dried over $MgSO_4$. The solvent was evaporated and the product distilled, bp 59–64° (20 mm) [lit.[26] bp 93° (27 mm)], to give 8.34 g (73.5%) of aldehyde.

To a solution of 11.35 g (0.05 mol) of 5-(4-chlorophenyl)-2-thio-2,4-oxazolidinedione in 75 ml of EtOH was added a solution of 10.3 g (0.12 mol) of anhydrous piperazine in 40 ml of EtOH. A stream of N_2 was passed through the solution while H_2S was being evolved. The solution was stirred at room temperature for 4.5 hr, heated at 80° for 2 hr, and stirred overnight at room temperature. The precipitate was filtered and crystallized from benzene to give 8.55 g (60%), mp 181–182°, of 1-[5-(4-chlorophenyl)-4-oxo-2-oxazolin-2-yl]piperazine.

The product was acylated with 4-methoxycinnamoyl chloride as described in method A to give 1-(4-methoxycinnamoyl)-4-[5-(4-chlorophenyl)-4-oxo-2-oxazolin-2-yl]piperazine, mp 209–212°, in 52% yield. Anal. ($C_{23}H_{22}ClN_3O_4$) C, H, N.

Method B′. 1-(4-Methoxycinnamoyl)-4-[5-(4-trifluoromethoxyphenyl)-4-oxo-2-oxazolin-2-yl]piperazine (27). In method B′, the 2-thio-2,4-oxazolidinediones were allowed to react with 4-methoxycinnamoylpiperazine to give the target compounds directly. 5-(4-Trifluoromethoxyphenyl)-2-thio-2,4-oxazolidinedione, 2.1 g (7.58 mmol), and 2.87 g (11.6 mmol) of 4-methoxycinnamoylpiperazine were added to 75 ml of EtOH and refluxed for 19 hr. The mixture was cooled to 45° and filtered, and the precipitate was crystallized twice from EtOH to give 1.69 g (46%) of product, mp 181.5–183.0°. Anal. ($C_{24}H_{22}F_3N_3O_5$) H, N; C: calcd, 57.71; found, 58.52.

Method C. 1-(4-Methoxycinnamoyl)-4-(5-methyl-5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (22). 2-Amino-5-methyl-5-phenyl-2-oxazolin-4-one,[21] 2.28 g (0.012 mol), and 3.0 g (0.012 mol) of 4-methoxycinnamoylpiperazine were refluxed in 25 ml of EtOH overnight. The solvent was evaporated at reduced pressure and the residue crystallized from CH_3OH–H_2O to give 1.3 g (26%) of product, mp 171–174°. Anal. ($C_{24}H_{25}N_3O_4$) C, H, N.

Method D. 1-(3,4-Dichlorophenyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (56). 1-(3,4-Dichlorophenyl)piperazine, 9.20 g (0.04 mol), and 5.30 g (0.03 mol) of 2-amino-5-phenyl-2-oxazolin-4-one were mixed and then heated at 130–135° (oil bath) for 3.5 hr. The crude reaction mixture was crystallized three times from EtOH to give 4.60 g (39%) of product, mp 161.0–164.5°. Anal. ($C_{19}H_{17}Cl_2N_3O_2$) C, H, N.

Method E. 1-(4-Anisoylmethyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (41). 1-(5-Phenyl-4-oxo-2-oxazolin-2-yl)piperazine, 7.35 g (0.03 mol), 7.60 g (0.023 mol) of 4-methoxyphenacyl bromide, and 4.60 g (0.033 mol) of powdered anhydrous $KHCO_3$ were heated at reflux in 750 ml of CH_3COCH_3 for 41 hr. The mixture was filtered hot and concentrated to about 80 ml and, upon standing, 7.85 g of product, mp 147–150°, was deposited. This material was crystallized from CH_3COCH_3 to give 6.0 g (50%) of product, mp 164–170°. Anal. ($C_{22}H_{23}N_3O_4$) C, H, N.

Method F. 1-[2-Hydroxy-2-(2-thienyl)ethyl]-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (48). 1-(2-Thenoylmethyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (47), prepared by method E, 6.0 g (0.016 mol), was dissolved in 200 ml of CH_3OH and 0.59 g of $NaBH_4$ was added slowly to the solution. The mixture was stirred at room temperature for 22 hr and filtered, and the precipitate was crystallized three times from CH_3OH to give 2.37 g (40%) of product, mp 203–205°. Anal. ($C_{19}H_{21}N_3O_3S$) C, H, N.

Method G. 1-[2-(4-Bromophenyl)-2-hydroxyethyl]-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (50). A solution of 11.76 g (0.048 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine and 9.60 g (0.048 mol) of 4-bromostyrene oxide in 100 ml of EtOH was refluxed for 5.5 hr. The mixture was filtered hot and the filtrate allowed to stand at room temperature. The precipitate was crystallized twice from EtOH to give 5.8 g (27%) of product, mp 151.5–155.5°. Anal. ($C_{21}H_{22}BrN_3O_3$) C, H, N.

Method H. 1-[2-(4-Methoxybenzoyl)ethyl]-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (45). 3-Dimethylamino-1-(4-methoxyphenyl)-1-propanone hydrochloride,[27] 4.90 g (0.02 mol), and 4.90 g (0.02 mol) of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine were dissolved in 25 ml of H_2O and allowed to stand 2 days at room temperature. The mixture was filtered and the precipitate crystallized twice from EtOH to give 5.01 g (62%) of product, mp 134–135°. Anal. ($C_{23}H_{25}N_3O_4$) C, H, N.

Method I. 1-(2-Benzothiazolyl)-4-(4-methoxycinnamoyl)piperazine (62). The unpublished procedure of Dr. M. Winn (Abbott Laboratories) was used for the preparation of 1-(2-benzothiazolyl)piperazine. A solution of 16.9 g (0.10 mol) of 2-chlorobenzothiazole in 10 ml of 2-PrOH was added dropwise to a solution of 25 g of anhydrous piperazine in 100 ml of 2-PrOH warmed to 45°. The reaction was exothermic and the rate of addition was adjusted to maintain a reaction temperature of 45°. The reaction mixture was stirred overnight and filtered, and the filtrate was evaporated to dryness at reduced pressure. The residue was added to H_2O and the mixture made basic with 10% NaOH. The mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution washed with Na_2CO_3 and dried over $MgSO_4$. The solvent was evaporated and the residue dissolved in 25 ml of Et_2O and chilled. The crystals were collected and dried to give 16.6 g (75%) of product, mp 75–78.5°. This product (8.2 g) was acylated with 4-methoxycinnamoyl chloride as described in method A to yield, after two crystallizations from EtOH, 5.60 g (39%) of product, mp 188.5–190°. Anal. ($C_{21}H_{21}N_3O_2S$) C, H, N.

Method J. 1-(2-Benzimidazolyl)-4-(4-methoxycinnamoyl)piperazine (64). The unpublished procedure of Dr. M. Winn (Abbott Laboratories) was used for the preparation of 1-(2-benzimidazolyl)piperazine. 2-Chlorobenzimidazole, 17 g, and 28 g of benzylpiperazine were refluxed in 60 ml of 2-PrOH for 7 hr. The mixture was cooled to 45° and diluted with Et_2O, and the precipitate was collected and crystallized from 2-PrOH–Et_2O to give 15.75 g of 1-(2-benzimidazolyl)-4-benzylpiperazine. The above product, 15 g, was debenzylated with H_2 and Pd/C in EtOH to give, after crystallization from EtOH, 13.8 g of 1-(2-benzimidazolyl)piperazine. The above product, 8.76 g, was converted to the free base with NaOH and acylated with 4-methoxycinnamoyl chloride as described in method A to yield, after two crystallizations from EtOH, 6.6 g of the title compound (60% for the last step), mp 277–280.5°. Anal. ($C_{21}H_{22}N_4O_2$) C, H, N.

Method K. 1-(5-Nitro-2-thiazolyl)-4-phenylpiperazine (66). A literature procedure was followed.[28] To a mixture of 5 g of $NaHCO_3$ in 200 ml of EtOH was added 1.78 g (0.011 mol) of phenylpiperazine and 2.09 g (0.01 mol) of 2-bromo-5-nitrothiazole (Aldrich). The mixture was refluxed for 1 hr, cooled to room temperature, and filtered, and the precipitate was combined with a second experiment run on twice the scale to yield, after crystallization from EtOH, 5.57 g (48%) of product, mp 183.5–185.0°. Anal. ($C_{13}H_{14}N_4O_2S$) C, H, N.

***N*-(2-Hydroxy-2-phenylethyl)-4-phenylpiperazinethiocarboxamide (76).** Phenylpiperazine, 3.24 g (0.02 mol), and 3.60 g (0.02 mol) of 5-phenyl-2-thio-2-oxazolidinone were refluxed in 50 ml of EtOH for 29 hr. After cooling the solution to room temperature, the precipitate was filtered and crystallized from EtOH to give 2.81 g (46%) of product, mp 148.5–150.5°. Anal. ($C_{19}H_{23}N_3OS$) C, H, N.

4-(4-Methoxycinnamoyl)-*N*-(2-hydroxy-2-phenylethyl)piperazinethiocarboxamide (77). 1-(*tert*-Butyloxycarbonyl)-4-(4-methoxycinnamoyl)piperazine, 7.0 g (0.02 mol), was treated with 4 *N* HCl–dioxane. The resulting HCl salt was neutralized with 5% NaOH and extracted from the aqueous solution with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated at reduced pressure. After dissolving the residue in 50 ml of EtOH, 3.60 g (0.02 mol) of 5-phenyl-2-thio-2-oxazolidinone was added and the mixture refluxed for 40 hr. The reaction was worked up as described above and the product crystallized from EtOH to give 2.67 g (31%) of product, mp 180–181°. Anal. ($C_{23}H_{27}N_3O_3S$) C, H, N.

1-[[(2-Hydroxy-2-phenylethyl)imino]methyl]-4-phenylpiperazine (78). The method of Taylor and Ehrhart[30] was used for the preparation of 5-phenyl-2-oxazoline. 2-Amino-1-phenylethanol (Aldrich, 6.85 g, 0.05 mol) was added to a heated (150° oil bath) solution of 3.0 ml of HOAc in 50 ml of $(EtO)_3CH$. The solution was held at 150° for 2 hr. The solvent was evaporated and the residue was dissolved in Et_2O, washed with saturated $NaHCO_3$ and saturated brine, and dried over $MgSO_4$. The solvent was evaporated and the residue distilled to give 4.32 g (59%) of 5-phenyl-2-oxazoline, bp 89–93° (0.5 mm).

Upon addition of 4.76 g (0.0294 mol) of phenylpiperazine to 4.32 g (0.0294 mol) of 5-phenyl-2-oxazoline, a white solid immediately began to form. The solid was crystallized twice from Et_2O to give 3.6 g (23% from 2-amino-1-phenylethanol) of the title compound, mp 118–121°. Anal. ($C_{19}H_{23}N_3O$) C, H, N.

1-(4-Methoxycinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)hexahydro-1*H*-1,4-diazepine (79). Pemoline, 8.80 g (0.05 mol), and 5.00 g (0.05 mol) of hexahydro-1*H*-1,4-diazepine were dissolved in 750 ml of EtOH and heated at reflux for 15 hr. The solvent was evaporated, the residue was dissolved in benzene,

washed with H_2O, and dried over $MgSO_4$, and the solvent was evaporated to give 2.50 g of a viscous residue. The residue was acylated with 4-methoxycinnamoyl chloride as described in method A. Two crystallizations from EtOH gave 1.0 g of product, mp 141–143° dec. Anal. ($C_{24}H_{25}N_3O_4$) C, N; H: calcd, 6.01; found, 6.44.

1-(4-Methoxycinnamoyl)-2,6-dimethyl-4-(5-phenyl-2-oxo-2-oxazolin-2-yl)piperazine (80). Pemoline, 8.80 g (0.05 mol), and 8.55 g (0.075 mol) of 2,6-dimethylpiperazine (Carbide and Carbon Chemicals Co.) were heated in a 165° oil bath for 2.5 hr. The residue was dissolved in benzene, washed with H_2O and saturated brine, and dried over $MgSO_4$, and the solvent was evaporated to give 7.5 g of crude product. The crude product was acylated with 4-methoxycinnamoyl chloride as described in method A and the product crystallized twice from EtOH to give 3.00 g (14% from pemoline) of product, mp 187–204°. Anal. ($C_{25}H_{27}N_3O_4$) C, N; H: calcd, 6.28; found, 6.78.

Reaction of Pemoline and *N,N'*-Dimethylethylenediamine. Pemoline, 8.80 g (0.05 mol), and 4.84 g (0.055 mol) of *N,N'*-dimethylethylenediamine were added to 750 ml of EtOH and heated at reflux for 20.5 hr. The solution was concentrated to 100 ml and the unreacted pemoline removed by filtration. Evaporation of the remaining solvent gave a residue which slowly solidified, yielding 9.65 g of crude product. Part of this material, 7.9 g, was crystallized three times from benzene–hexane to give 3.35 g of product, mp 100–109°. Analytical purity was obtained by chromatography of this material on 280 g of Florisil. Elution with 20% MeOH–benzene, followed by crystallization from benzene–hexane, gave 1.45 g, mp 110–113°, of analytically pure material: NMR (Me_2SO-d_6) δ 2.58 (s, 6), 3.50 (s, 4), 4.90 [q, 2 (1 exchange)], 7.35 (m, 5); uv (95% EtOH) 230 nm (ϵ 13500). Anal. ($C_{13}H_{17}N_3O_2$) C, H, N.

Reaction of Pemoline and *N*-Methylethylenediamine. Pemoline, 8.80 g (0.05 mol), and 3.70 g (0.05 mol) of *N*-methylethylenediamine were refluxed in 750 ml of EtOH for 16 hr. The solution was evaporated at reduced pressure until a precipitate formed. The mixture was chilled and filtered and the precipitate crystallized from EtOH to give 3.13 g, mp 139–141.5°, of product. A second crystallization gave analytically pure material: mp 140–141.5°; NMR (Me_2SO-d_6) δ 2.82 (s, 3), 3.42 (s, 4), 4.90 [s, 2 (1 exchange)], 7.38 (m, 5), and 8.37 (s, 1 exchange); uv (95% EtOH) 238 nm (ϵ 10200). Anal. ($C_{12}H_{15}N_3O_2$) C, H, N.

***N*-(Phenylacetyl)-4-(4-methoxycinnamoyl)-1-piperazinecarboxamide (81).** Piperazine pemoline, 6.9 g (0.0282 mol), was treated with H_2 in the presence of Pd/C catalyst in 90% EtOH–H_2O until 1 equiv of H_2 was absorbed. The mixture was filtered and the solvent evaporated to give a solid which was acylated with 4-methoxycinnamoyl chloride as described in method A. The yield of the title compound was 4.72 g (41% from piperazine pemoline), mp 176.5–177.5°. Anal. ($C_{23}H_{25}N_3O_4$) C, H, N.

1-(4-Methoxycinnamoyl)piperazine Hydrochloride (82). To a solution of 35.2 g (0.2 mol) of benzylpiperazine and 31.40 g (0.022 mol) of *tert*-butyloxycarbonyl azide (Pierce Chemical Co.) in 120 ml of 50% aqueous dioxane at room temperature was added dropwise 4 *N* NaOH until the mixture reached pH 10. The reaction was stirred for 1 hr at room temperature and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with saturated $NaHCO_3$ and dried over $MgSO_4$. The solvent was evaporated and the residue crystallized from hexane to give 36.4 g (66%) of 1-(*tert*-butyloxycarbonyl)-4-benzylpiperazine, mp 72–75°. A second crop of 4.8 g (8%), mp 71.5–74.5°, was obtained.

tert-Butyloxycarbonylbenzylpiperazine, 22.55 g, was debenzylated with H_2 and a Pd/C catalyst in EtOH to give 17.91 g (97%) of crude *tert*-butyloxycarbonylpiperazine. An oxalate salt was prepared, mp >340°. Anal. ($C_{11}H_{20}N_2O_6$) C, H, N.

1-(*tert*-Butyloxycarbonyl)piperazine (9.90 g) was acylated with 4-methoxycinnamoyl chloride as described in method A to give, after crystallization from EtOH–H_2O, 15.1 g (30% from *tert*-butyloxycarbonylbenzylpiperazine) of 1-(*tert*-butyloxycarbonyl)-4-(4-methoxycinnamoyl)piperazine, mp 144–146°. Anal. ($C_{19}H_{26}N_2O_4$) C, H, N. The HCl salt of 4-methoxycinnamoylpiperazine was prepared by treatment of *tert*-butyloxycarbonyl-4-methoxycinnamoylpiperazine with 4 *N* HCl in dioxane. The precipitate was crystallized from EtOH–Et_2O to give the title compound, mp 250–251.5°. Anal. ($C_{14}H_{19}ClN_2O_2$) C, H, N.

***N*-(4-Methoxycinnamoyl)-*N'*-(5-phenyl-4-oxo-2-oxazolin-2-yl)ethylenediamine (83).** *N,N*-Dibenzylethylenediamine was prepared by a slightly modified literature method[31] and was used in the next step without purification. Crude dibenzylethylenediamine, 34.0 g (0.141 mol), was acylated with *tert*-butyloxycarbonyl azide as described in the preparation of *tert*-butyloxycarbonylbenzylpiperazine to yield, after crystallization from hexane, 26.2 g (57% from dibenzylaminoethylphthalimide) of product, mp 50–54°. This material, 26 g, was debenzylated with H_2 in EtOH using Pd/C catalyst to give 12.97 g (crude) of *tert*-butyloxycarbonylethylenediamine. *tert*-Butyloxycarbonylethylenediamine, 12.97 g, was acylated with 4-methoxycinnamoyl chloride (method A) to give 17.0 g [69% from *N*-(*tert*-butyloxycarbonyl)-*N',N'*-dibenzylethylenediamine] of *N*-butyloxycarbonyl-*N'*-(4-methoxycinnamoyl)ethylenediamine, mp 136.5–139.0°. The latter compound, 4.0 g, was treated twice with 25 ml of 4 *N* HCl–dioxane to give, after crystallization from EtOH, 2.2 g (69%) of *N*-(4-methoxycinnamoyl)ethylenediamine hydrochloride, mp 256–257°. Anal. ($C_{12}H_{16}N_2O_2$·HCl) H, N; C: calcd, 56.14; found, 55.72.

N-(*tert*-Butyloxycarbonyl)-*N'*-(4-methoxycinnamoyl)ethylenediamine, 800 g (0.025 mol), was treated with 4 *N* HCl–dioxane to give 7.60 g of 4-methoxycinnamoylethylenediamine hydrochloride. Attempts to convert the HCl salt, 7.60 g, to the free base with 5% NaOH led to an emulsion, resulting in the loss of some material. The $CHCl_3$ suspension was evaporated to dryness and the residue added to 4.82 g (0.025 mol) of 5-phenyl-2-thio-2,4-oxazolidinedione in 50 ml of EtOH and refluxed for 15 hr. The mixture was filtered and the precipitate extracted with hot CH_3OH. The CH_3OH solution was evaporated to dryness and the residue crystallized from EtOH to give 1.2 g of *N*-(4-methoxycinnamoyl)-*N'*-(5-phenyl-4-oxo-2-oxazolin-2-yl)ethylenediamine, mp 226–227.5°. Anal. ($C_{21}H_{21}N_3O_4$) C, H, N.

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Antimalarials. 3. 3-Substituted 1-Naphthalenemethanols[1]

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The synthesis and antimalarial activity of 22 3-substituted 1-naphthalenemethanols whose substitution was patterned after the antimalarial 2-substituted 4-quinolinemethanols are described. The compounds were active against *Plasmodium berghei* in mice, the most active being 6-chloro-α-(dibutylaminomethyl)-3-(3,4-dichlorophenyl)-1-naphthalenemethanol hydrochloride (**3b**). The naphthalenemethanols tested, **1b** and **2b**, were not photosensitizing to albino mice. Structure–activity relationships between the naphthalene and quinoline isosteres are discussed.

2-Substituted 4-quinolinemethanols, as a class, are active against avian, murine, and human malarias,[2] but most of the members of the class are photosensitizers.[3] Molecular modifications designed to reduce phototoxicity reduced antimalarial activity in most instances.[2] Rothe and Jacobus[3] have suggested that phototoxicity varies with different functional groups at the 2 position of the quinoline in a manner that indicates an association with their relative electronegativities. All quinolinemethanol antimalarials show absorption maxima in the 320–360-nm region;[4] even the relatively nonphototoxic 2-trifluoromethyl-4-quinolinemethanols have this ultraviolet absorption,[5] which is not present in naphthalene ring compounds of similar structure. Comparison of the activity and phototoxicity of phenanthrene and azaphenanthrene isosteres showed that the phenanthrene compounds were more active vs. *Plasmodium berghei* and less photosensitizing than the nitrogen-containing analogs.[6] These observations suggested a study of the biological activity of 3-substituted 1-naphthalenemethanols patterned after the active, but phototoxic, 2-substituted 4-quinolinemethanols.

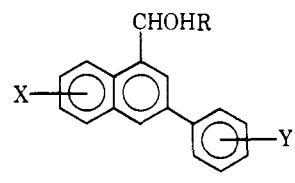
1- and 2-naphthalenemethanols were prepared some years ago by Jacobs, Winstein, and coworkers.[7] They were found to be less active than the phenanthrenemethanols and approximately as active against avian malarias[8] as the quinolinemethanols without a blocking 2-phenyl group.

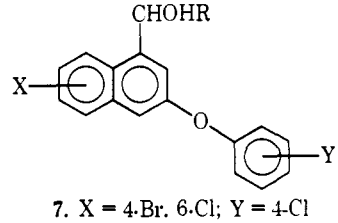
Chemistry. The 1-naphthalenemethanols prepared for this study are illustrated in Chart I. Synthesis of the 3-aryl-1-naphthalenemethanols (**1–6**) followed well-known procedures[1a,9] from the corresponding 3-aryl-1-naphthaldehydes, syntheses of which have been described.[10] The preparation of the 3-aryloxy (**7–11**) and 3-aroyl (**12**) derivatives required a different synthetic sequence, described elsewhere,[11] for the preparation of the aldehyde precursers, the 3-bromo-1-methylnaphthalenes. Conversion of the appropriately substituted 1-methylnaphthalenes to the naphthaldehydes was accomplished by the steps outlined in Scheme I.

The availability of 3-methylindanones[11] made it possible to obtain a 4-aryl-1-naphthalenemethanol (**13b**) by the pathway illustrated in Scheme II.

Structure–Activity Relationships. The activity (as determined by the Rane Laboratories[12]) of the 1-naphthalenemethanols vs. *Plasmodium berghei* is presented in Table I. Most of the compounds have antimalarial activity, the best of them, **3b**, being highly active. In Table II the minimum effective dose (MED) in the same test system of exactly comparable quinoline- and naphthalenemethanols is given together with comparisons in which there is a difference in the amino alcohol side chain between the two otherwise comparable compounds. Within both classes of

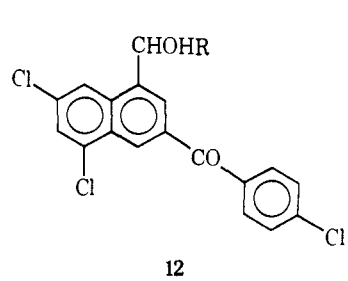
Chart I



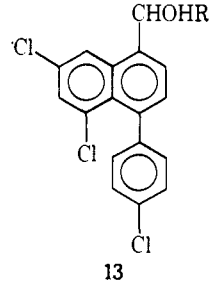


1. X = H; Y = 4-Cl
2. X = 6-Cl; Y = 4-Cl
3. X = 6-Cl; Y = 3,4-Cl_2
4. X = 7-CH_3O; Y = 4-Cl
5. X = 6-Cl, 7-CH_3O; Y = 4-Cl
6. X = 6-Cl, 7-CH_3O; Y = 3,4-Cl_2

7. X = 4-Br, 6-Cl; Y = 4-Cl
8. X = 5,7-Cl_2; Y = 4-Cl
9. X = 5,7-Cl_2; Y = 3-CF_3
10. X = 5,7-Cl_2; Y = 3,5-Cl_2
11. X = 5,7-Cl_2; Y = 3,4-Cl_2



12



13

a. R = $-CH_2N(C_2H_5)_2$
b. R = $-CH_2N(C_4H_9)_2$
c. R = $-CH_2N(C_7H_{15})_2$
d. R = $-CH_2NHC_4H_9$