Synthesis and Antifilarial Activity of *N*-[4-[[4-Alkoxy-3-[(dialkylamino)methyl]phenyl]amino]-2-pyrimidinyl]-*N'*-phenylguanidines[1,2]

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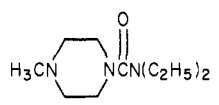
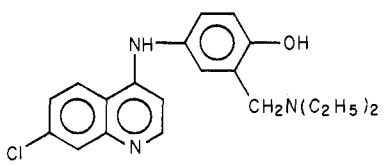
A series of *N*-[4-[[4-alkoxy-3-[(dialkylamino)methyl]phenyl]amino]-2-pyrimidinyl]-*N'*-phenylguanidines have been synthesized for antifilarial evaluation. Reaction of the appropriate benzenamines with *N*-cyanoguanidine, followed by condensation of the resultant *N*-phenylimidodicarbonimidic diamides (V) with ethyl 4,4,4-trifluoro-3-oxobutanoate provided the intermediate *N*-(4-hydroxy-2-pyrimidinyl)-*N'*-phenylguanidines VIa. Alternatively, compounds VIa were synthesized by reaction of the requisite β-keto esters (VII) with *N*-cyanoguanidine to give the (4-hydroxy-2-pyrimidinyl)cyanamides (VIII), followed by treatment with the desired benzenamines. Chlorination with $POCl_3$ and condensation with the appropriate benzenamines (IX) generated the desired guanidines (X). Antifilarial activity was confined to adult *Litomosoides carinii* infections, and a structure–activity relationship for this activity is discussed. Lack of activity against *L. carinii* microfilaria and adult *Brugia pahangi* infections preclude further work in this area pending evaluation in additional experimental models.

Filariasis is a discomforting, disfiguring disease caused by a worm—a nematode.[3] Lymphatic filariases caused by *Wuchereria bancrofti* and, to a lesser extent, by *Brugia malayi* affect some 375 million people.[4] *Onchocerca volvulus* also invades the eyes and is a notable cause of blindness, particularly in tropical Africa. Diethylcarbamazine (I) is the only available microfilaricidal drug



I



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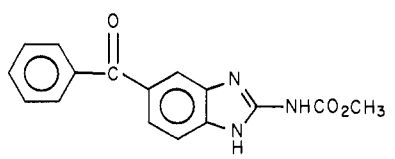
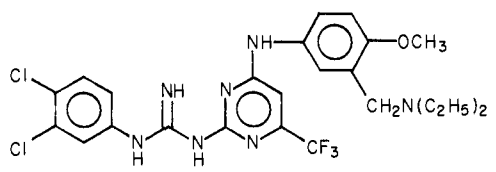


III

and is effective against all three species of the worm.[3c] It is not, however, effective against the adult *O. volvulus* worms, nor is it devoid of toxicity.[3c,e] Suramin is the only clinically available compound that kills the *O. volvulus* adults,[5] but side effects and the necessity of intravenous administration have limited its use.[5] An antimalarial 4-aminoquinoline, amodiaquine (II), has shown macrofilaricidal activity vs. *Litomosoides carinii* in the jird[6,3b] and *W. bancrofti* in man,[7] but it shows some toxicity at the doses employed.[8] A benzimidazole anthelmintic, mebendazole (III), is quite active against *L. carinii* and *Brugia pahangi*[10] infections in jirds but is devoid of activity vs. *W. bancrofti* in man[11] and *O. volvulus* in a chimpanzee[12] or in man.[13] Clearly better agents are needed for this disease.[14]

Some years ago in these laboratories, a number of *N*-(4-amino-6-methyl-2-pyrimidinyl)-*N'*-(halophenyl)-guanidines were synthesized as potential antimalarial agents.[15] A number of analogues with amodiaquine-like side chains were shown to have antifilarial activity when examined against *L. carinii* infections in the gerbil.[3b] Chemical pursuit of this lead included the preparation of a limited number of *N*-[4-[[4-alkoxy-3-[(dialkylamino)-methyl]phenyl]amino]-6-(trifluoromethyl)-2-pyrimidinyl]-*N'*-(4-chloro- and 3,4-dichlorophenyl)guanidines,[16] of which IV was the most promising.



IV

In view of the urgent need for an agent particularly against the ocular form of the disease, we have reexamined this series in depth. Particular attention has been paid to incorporating the structural features of diethylcarbamazine (I), amodiaquine (II), and mebendazole (III) in an attempt to obtain a compound active against the microfilariae, as well as the adult parasites. In accord with recent considerations that the *L. carinii* model may have

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(1) This is paper 3 of a series on antifilarial drugs. For paper 2, see Elslager, E. F.; Perricone, S. C.; Worth, D. F. *J. Med. Chem.* **1970**, *7*, 543.
(2) This investigation received financial support from the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.
(3) (a) For reviews, see Hawking, F. In "Experimental Chemotherapy"; Schnitzer, R. J.; Hawking, F., Eds.; Academic Press: New York, 1963, Vol. I, p 893. (b) Elslager, E. F. *Prog. Drug Res.* **1974**, *18*, 142. (c) Hawking, F. *Adv. Pharmacol. Chemother.* **1979**, *16*, 129. (d) Wagner, W. H. *Immun. Infekt.* **1980**, *8*(2), 64. (e) Hawking, F. *Antibiot. Chemother.* **1981**, *30*, 135.
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(9) See Table III.
(10) Denham, D. A.; Suswillo, R. R. *Trans. R. Soc. Trop. Med. Hyg.* **1978**, *72*, 546. Also, McCall, J. W., Unpublished data.
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(14) *W.H.O. Tech. Rep. Ser.* **1967**, *no. 359*, 1.
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(16) See ref 3b, p 151 (Table 42).
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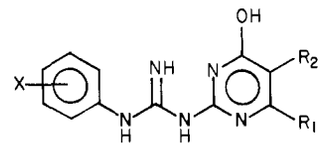
Table I. *N*-(4-Hydroxy-2-pyrimidinyl)-*N'*-phenylguanidines



no.	X	R_1, R_2	mp, °C	yield purified, %	purifcn solvent	procedure	formula	anal.
1	H	6-CF_3	253–254	51	MeOH	A	$C_{12}H_{10}F_3N_5O$	C, H, N, F
2	4-Cl	6-CF_3	270–272	47	MeOH	A	$C_{12}H_9ClF_3N_5O$	C, H, N
3	4-OCH_3	6-CF_3	251–252	45	DMF	A	$C_{13}H_{12}F_3N_5O_2$	C, H, N
4	4-CF_3	6-CF_3	274–275	36	DMF–H_2O	A	$C_{13}H_9F_6N_5O$	C, H, N
5	4-OC_6H_5	6-CF_3	238–240	19	MeOH	A	$C_{18}H_{14}F_3N_5O_2$	C, H, N
6	4-COC_6H_5	6-CF_3	279	70	MeOH	B	$C_{19}H_{14}F_3N_5O_2$	C, H, N
7	3,4-Cl_2	6-CF_3	289	40	DMF	A	$C_{12}H_8Cl_2F_3N_5O$	C, H, N
8	3,4-Cl_2	6-C_6H_5	282–285	65	EtOH	B	$C_{16}H_{13}Cl_2N_5O$	*a*
9	3,4-Cl_2	5,6-$(CH_2)_4$	268	52	EtOH	B	$C_{14}H_{15}Cl_2N_5O$	*a*

[a] These compounds were purified, spectrally characterized, and used directly in the next step without microanalyses.

limited relevance for the human *O. volvulus* infection and that *B. pahangi* might be more predictive, the compounds prepared have been examined against both infections.

Chemistry. The synthetic approaches[3b,18,19] utilized for the preparation of the *N*-[4-[[4-alkoxy-3-[(dialkylamino)methyl]phenyl]amino]-2-pyrimidinyl]-*N'*-phenylguanidines (X) are depicted in Scheme I. The appropriate benzenamine was allowed to react with *N*-cyanoguanidine,[3b,18] and condensation of the resulting *N*-phenylimidodicarbonimidic diamide V with ethyl 4,4,4-trifluoro-3-oxobutanoate[3b] provided the corresponding *N*-(4-hydroxy-2-pyrimidinyl)-*N'*-phenylguanidines VIa (compounds **1–5** and **7**, Table I) in 19–51% yield (procedure A). Alternatively, VIa (compounds **6**, **8**, and **9**, Table I) were synthesized in 52–70% yield by treatment of the requisite β-keto ester VII with *N*-cyanoguanidine[3b,19] to give the (4-hydroxy-2-pyrimidinyl)cyanamides VIII, which were allowed to react with the desired benzenamine in 2-ethoxyethanol and 4 N HCl (procedure B). Chlorination of VIa with $POCl_3$, followed by condensation of the crude *N*-(4-chloro-2-pyrimidinyl)-*N'*-phenylguanidines VIb with the appropriate benzenamine IX in EtOH, DMF, or pyridine, afforded the *N*-[4-[[4-alkoxy-3-[(dialkylamino)-methyl]phenyl]amino]-2-pyrimidinyl]-*N'*-phenylguanidines X (compounds **20–69**, Table III) in 11–68% yield (procedures C and D).

The majority of the benzenamines IV employed are known in the literature (see Experimental Section). Novel variants have been tabulated in Table II. Compounds **11–13**, **17**, and **18** were prepared by condensing 2-(chloromethyl)-4-nitrophenol[20] or 2-(chloromethyl)-1-methoxy-4-nitrobenzene[21] with the appropriate alkyl or dialkylamines,[21] followed by hydrogenation over Raney Nickel (procedure E). Compound **10** was synthesized by application of the Mannich reaction[21,22] on *N*-(4-hydroxyphenyl)acetamide,[21] followed by hydrolysis with HCl[23] (procedure F). Compounds **14–16** were prepared by alkylation of 2-[(diethylamino)methyl]-4-(acetylamino)-phenol[21] in the presence of NaH, followed by hydrolysis with HCl (for compounds **14** and **15**) or KOH (for compound **16**) (procedure G).

Scheme I

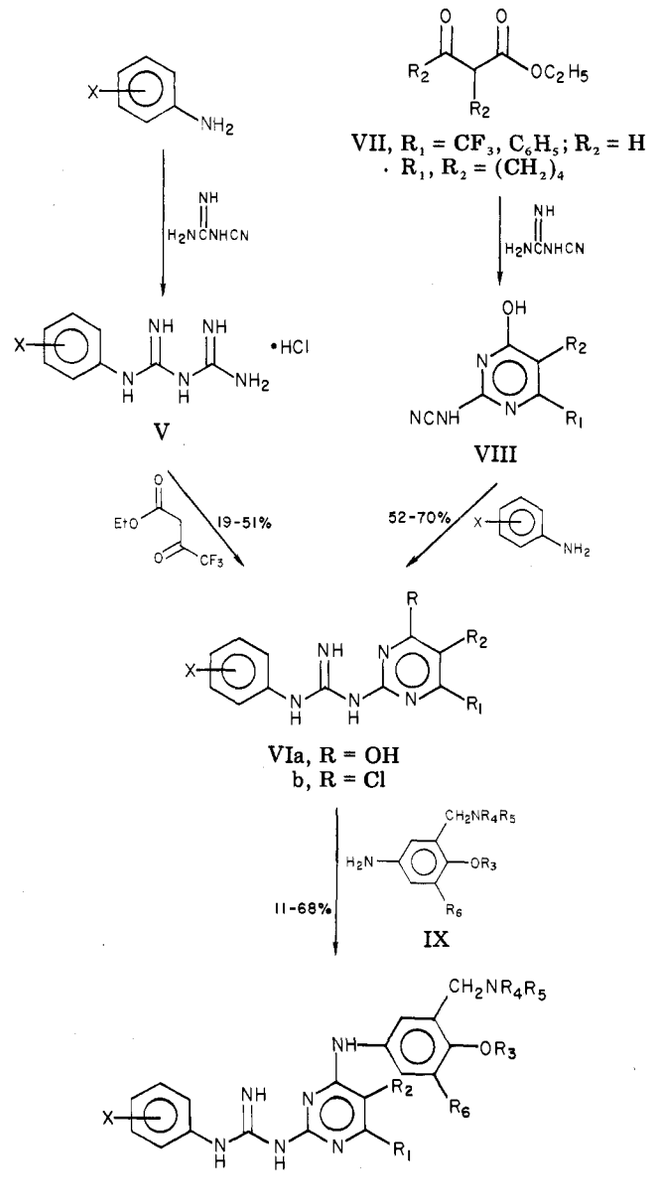


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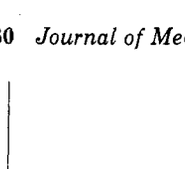
Table II. 2-Alkoxy-5-amino-*N*,*N*-dialkylbenzenemethanamines

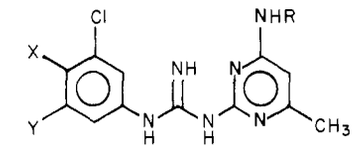


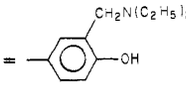
no.	R_3	NR_4R_5	R_6	mp, °C	yield purified %	purifcn solvent	procedure	formula	anal.
10[a]	H	$N(CH_3)_2$	H	232–236 dec	78	MeOH	F	$C_9H_{14}N_2O\cdot 2HCl\cdot 0.5H_2O\cdot 0.7CH_3OH$[b]	C, H, N, Cl, H_2O
11	CH_3	$N(CH_3)_2$	H	265 dec	91	*i*-PrOH	E	$C_{10}H_{16}N_2O\cdot 2HCl$	C, H, N, Cl^-
12[c]	H	NHC_2H_5	H	231–234 dec	94	*i*-PrOH	E	$C_9H_{14}N_2O\cdot 2HCl\cdot 0.25C_3H_8O$[d]	C, H, N, Cl^-
13	H	$N(CH_3)C_2H_5$	H	95–115	95	*i*-PrOH–Et_2O	E	$C_{10}H_{16}N_2O\cdot 2HCl\cdot 0.2H_2O\cdot 0.2C_3H_8O$[d]	C, H, N, Cl^-, H_2O
14	C_2H_5	$N(C_2H_5)_2$	H	175–181	96	*i*-PrOH–Et_2O	G	$C_{13}H_{22}N_2O\cdot 2HCl$	*e*
15	$CH(CH_3)_2$	$N(C_2H_5)_2$	H	124–126	92	EtOAc	G	$C_{14}H_{24}N_2O\cdot 2HCl$	*e*
16[c]	$CH_2C_6H_5$	$N(C_2H_5)_2$	H	153–156[f]	67	*i*-PrOH–Et_2O	G	$C_{18}H_{24}N_2O\cdot 2HCl$	*e*
17	H	$NHCH_2CH(CH_2)_5$	H	230–235 dec	98	EtOAc	E	$C_{14}H_{22}N_2O\cdot 2HCl$	C, H, N; Cl^-[g]
18	H	$N[(CH_2)_2]_2NCO_2C_2H_5$	H	>150 dec	90	*i*-PrOH–Et_2O	E	$C_{14}H_{21}N_3O_3\cdot 2HCl\cdot 0.7H_2O$	C, H, N, H_2O; Cl^-[h]
19	H	$N(C_2H_5)_2$	C_6H_5	oil	*i*		H		

[a] Mentioned in ref 39, but no physical data were given. [b] The ^1H NMR spectrum confirmed the presence of MeOH. [c] Mentioned in ref 23, but no physical data were given. [d] The ^1H NMR spectrum confirmed the presence of *i*-PrOH. [e] The compound was purified, spectrally characterized, and used directly in the next step without microanalyses. [f] Literature[40] mp 152–155 °C for the dihydrochloride. [g] Cl^-: calcd, 23.08; found, 23.59. [h] Cl^-: calcd, 19.43; found, 18.97. [i] The compound was isolated, spectrally characterized, and used directly in the next step.

Compound **19** was prepared as follows. Condensation of sodium nitromalonaldehyde hydrate[24] with 1-phenyl-2-propanone provided 5-nitro[1,1′-biphenyl]-2-ol[25] in 56% yield. Hydrogenation over Raney nickel, followed by acetylation with Ac_2O, gave *N*-(6-hydroxy[1,1′-biphenyl]-3-yl)acetamide in 96% yield. Treatment with diethylamine and formaldehyde, followed by hydrolysis with HCl, furnished 5-amino-3-[(diethylamino)methyl]-[1,1′-biphenyl]-2-ol (compound **19**, Table II) (procedure H).

Antifilarial Screening in Jirds. The *N*-[4-[[4-alkoxy-3-[(dialkylamino)methyl]phenyl]amino]-2-pyrimidinyl]-*N*′-phenylguanidines X (compounds **20–69**, Table III) and two of the intermediate *N*-(4-hydroxy-2-pyrimidinyl)-*N*′-phenylguanidines VIa (compounds **3** and **7**, Table I) have been evaluated in jirds (*Meriones unguiculatus*, males) with dual infections of *L. carinii* and *B. pahangi* by the oral and/or the parenteral route.[26] Two *N*-(4-amino-6-methyl-2-pyrimidinyl)-*N*′-(dichlorophenyl)-guanidines related to IV previously synthesized as antimalarials[15] (XIa,b), have been included for comparison purposes.



XIa, X = H; Y = Cl; R = 

b, X = Cl; Y = H; R = $(CH_2)_2N[(CH_2)_3CH_3]C_2H_5$

Groups of three to five jirds per dose were inoculated subcutaneously with 24–25 *L. carinii* larvae[27] 76–133 days prior to drug treatment. Subsequently, a *B. pahangi* infection was introduced by inoculation of the animals with 49–50 immature larvae 60–100 days prior to drug treatment or by implanting surgically 15 or 20 adult worms into the peritoneal cavity[28] 4–60 days pretreatment. The drugs were administered once daily for 5 days as solutions or suspensions in aqueous 1% (hydroxyethyl)cellulose and 0.1% Tween 80 (HEC Tween 80). Microfilariae counts were made from blood drawn from the retro-ocular sinus[29] on the 1st day of dosing (day 0), day 4, 5, or 6, and at necropsy. Surviving animals were sacrificed and examined for adult worms 55–70 days after the first drug dose by searching the pleural and peritoneal cavities. The number of live worms at autopsy was scored as a percentage relative to sham-dosed controls. Compounds are considered to be active when the reduction of adult worms exceeds 60% or when the reduction of circulating *L. carinii* microfilaria exceeds 90%. The data vs. *L. carinii* is summarized in Table III. Both oral and parenteral data for diethylcarbamazine, mebendazole, and amodiaquine and parenteral data for suramin are included for comparison purposes (Table III).

Compounds **3**, **7**, and **20–69** also have been evaluated by

(24) Supplied by Ash Stevens Co. For preparation, see Fanta, P. E. In "Organic Syntheses"; Rabjohn, N., Ed.; Wiley: New York, 1643; Collect. Vol. IV, p 844.
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(26) The antifilarial screening was carried out by Dr. John McCall and co-workers at the University of Georgia, Athens, GA.
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(29) Thompson, P. E.; Boche, L; Blair, L. S. *J. Parasitol.* **1968**, *54*, 834.

the parenteral route[30,31] in jirds containing a single infection of *B. pahangi*. All compounds were administered subcutaneously at 100 mg/(kg day) for 5 days, 3–4 days after the adult worms had been implanted surgically into the peritoneal cavity. The jirds were sacrificed and necropsied 2 to 4 weeks after treatment. Activity is expressed as a percentage recovery of live worms at necropsy relative to overall recovery of live worms in the test group.

Overall Results and Structure–Activity Relationships. Among the 50 *N*-[4-[[4-alkoxy-3-[(dialkylamino)-methyl]phenyl]amino]-2-pyrimidinyl]-*N'*-phenylguanidines X prepared and evaluated, those analogues that contained either 4-chloro or 3,4-dichloro in the *N'*-phenyl ring and 6-trifluoromethyl in the pyrimidine ring exhibited the highest activity vs. adult *L. carinii*. These compounds also possessed the classical amodiaquine side chain, that is, a hydroxy or alkoxy group para to the aromatic amine nitrogen flanked by a (dialkylamino)methyl group containing small alkyl groups (H, CH_3, and C_2H_5). Six analogues were extraordinarily active, providing a ≥97% reduction of live worm burden at the lowest doses tested, 3 (compound IV) and 0.5 mg/kg (compounds **25**, **30**, **52**, **55**, and **56**). This potency is greater than that of the 6-methyl-substituted (2-pyrimidinyl)guanidines XIa,b, the reference drug mebendazole (III) given orally, suramin, diethylcarbamazine, and amodiaquine (see Table III).

Activity decreases slightly when the *N'*-phenyl ring contains 4-CF_3 or 4-OCH_3 substituents, it decreases moderately when the ring is unsubstituted, and it decreases markedly in the presence of 4-phenoxy and 4-benzoyl substituents. Replacement of the 6-trifluoromethyl group of the pyrimidine ring with phenyl (compounds **64–66**) or conversion of the ring to a tetrahydroquinazoline (compounds **67–69**) results in a reduction of activity and an increase in toxicity (early deaths of the jirds). On the amodiaquine side chain, 4-alkoxy groups larger than methoxy (for example, compounds **61–63**) and 3-(dialkylamino)methyl groups larger than (diethylamino)-methyl (for example, compounds **27**, **53**, **54**, **58**, and **59**) decreased activity. Trisubstitution of the ring (compound **28**) and removal of the 4-alkoxy group (compound **51**) also lowered the activity. Overall, these compounds showed parallel activities in oral and subcutaneous tests.

No significant activity was seen for any of the compounds vs. *L. carinii* microfilariae. Moreover, all of the compounds were inactive against *B. pahangi* infections in both test systems. Two intermediate *N*-(4-hydroxy-2-pyrimidinyl)-*N'*-phenylguanidines (compounds **3** and **7**, Table I) were devoid of activity in all tests.

Conclusion

The *N*-[4-[[4-alkoxy-3-[(dialkylamino)methyl]phenyl]-amino]-6-(trifluoromethyl)-2-pyrimidinyl]-*N'*-phenylguanidines exhibit exceptional antifilarial activity against adult *L. carinii* worms over a variety of structural variations. However, similar to amodiaquine,[6] these types lack activity against the circulating microfilariae. This is interesting, in as much as diethylcarbamazine is essentially a microfilaricidal agent (and is active vs. the microfilariae and adult *L. carinii* in the jird), and several of the compounds prepared (compounds **21**, **24**, **27**, **35**, **41**, **47**, **58**, and **59**, Table III) contain diethylcarbamazine-like functional groups. This does not preclude further evaluation of these types, since amodiaquine has shown clinical activity in man[7] (vide infra), and most of the compounds possess side chains similar to that found on amodiaquine.

The lack of activity vs. *B. pahangi* is disappointing, since this test is considered to be more relevant to the human *O. volvulus* infection. Attempts at introducing functional groups found on mebendazole, a drug active against both *B. pahangi*[10] and *L. carinii*[9] infections in the jird, resulted in a loss of both *L. carinii* and *B. pahangi* activities in most cases (see compounds **45–50**, Table III).

Further synthetic effort in this area has been terminated pending the assessment of the clinical relevance of this activity through evaluation of the most potent members of this series (compounds IV, **25**, **30**, **52**, **55**, and **56**) in additional experimental models. These compounds are to be examined against *Dipetalonema viteae* infections in jirds and will be considered for evaluation against L_3 (larval) induced lymphatic infections of *B. pahangi* in jirds. Compounds active in these systems should then be evaluated against a *Brugia* species in a nonrodent host and/or the *Onchocerca* model in the cow.

Experimental Section[32,33]

The following intermediates were prepared according to the cited literature references: *N*-phenylimidodicarbonimidic diamide hydrochloride, *N*-(4-chlorophenyl)imidodicarbonimidic diamide hydrochloride, and *N*-(4-methoxyphenyl)imidodicarbonimidic diamide hydrochloride, ref 18; *N*-(3,4-dichlorophenyl)imidodicarbonimidic diamide hydrochloride, ref 34; (5,6,7,8-tetrahydro-4-hydroxy-2-quinazolinyl)cyanamide, ref 19; and (4-hydroxy-6-phenyl-2-pyrimidinyl)cyanamide and [4-hydroxy-6-(trifluoromethyl)-2-pyrimidinyl]cyanamide, ref 35.

***N*-[4-(Trifluoromethyl)phenyl]imidodicarbonimidic Diamide Hydrochloride.** A mixture of 65.5 g (0.41 mol) of 4-(trifluoromethyl)benzenamine and 36.5 g (0.43 mol) of *N*-cyanoguanidine in 205 mL of *i*-PrOH containing 41 mL of concentrated HCl was heated under reflux for 24 h, treated with an additional 10.0 g (0.12 mol) of *N*-cyanoguanidine and 10 mL of concentrated HCl, and heated under reflux for an additional 2 h. The hot mixture was filtered, and the filtrate was concentrated to dryness in vacuo. Trituration of the residue in hot CH_3CN furnished 76.1 g (66%) of product, mp 197–202 °C.

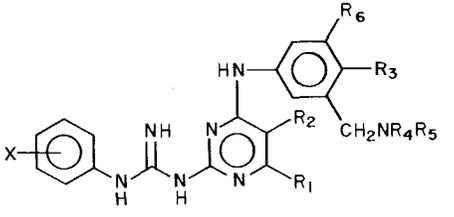
***N*-(4-Phenoxyphenyl)imidodicarbonimidic Diamide Hydrochloride.** A mixture of 191.0 g of 97% pure 4-phenoxybenzenamine (1.0 mol) and 90.0 g (1.1 mol) of *N*-cyanoguanidine in 550 mL of *n*-PrOH containing 100 mL of concentrated HCl was heated under reflux for 24 h. The solution was chilled, and the solid was collected, washed with *i*-PrOH, and dried in vacuo to provide 246.0 g of product, mp 259.5 °C.

Preparation of *N*-(4-Hydroxy-2-pyrimidinyl)-*N'*-phenylguanidines VIa (Compounds 1–5 and 7, Table I). Procedure A. To a suspension of 152.9 g (0.50 mol) of the above imidodicarbonimidic diamide in 62 g of 50% aqueous NaOH and 560 mL of 75% aqueous EtOH at 70 °C was added 139.0 g (0.75 mol) of ethyl 4,4,4-trifluoro-3-oxobutanoate. The resulting solution was allowed to cool to room temperature and stirred for 25 h. The solid that formed was collected, washed with EtOH, and triturated in hot MeOH to give 37.4 g (19%) of *N*-[4-hydroxy-6-(trifluoromethyl)-2-pyrimidinyl]-*N'*-(4-phenoxyphenyl)guanidine (**5**), mp 238–240 °C.

The reaction utilized similarly to form compound **4** was shown to be incomplete by TLC after stirring for 24 h. Therefore, the

(30) The antifilarial screening vs. *B. pahangi* was carried out by Dr. D. A. Denham of the London School of Tropical Medicine and Hygiene, London.
(31) For a description of the test method, see ref 29.
(32) Melting points (uncorrected) were taken on a Thomas-Hoover capillary melting point apparatus. ^1H NMR 90-MHz spectra were obtained with a Varian Associates EM-390 or Bruker B-NC-12 instrument. Chemical shifts are recorded in parts per million (δ) relative to Me_4Si as internal standard. IR spectra were determined on a Digilab DP-1-5 spectrophotometer.
(33) Elemental analyses were within ±0.4% of the calculated value unless otherwise indicated.
(34) Modest, E. J.; Levine, P. *J. Org. Chem.* **1956**, *21*, 14.
(35) Angelo, M. M.; Ortwine, D. F.; Worth, D. F.; Werbel, L. M. *J. Med. Chem.*, under Notes in this issue.

Table III. Chemistry and Biological Activity against Infections of *L. carinii* in the Jird of *N*-[4-[[4-Alkoxy-3-[(dialkylamino)methyl]phenyl]amino]-2-pyrimidinyl]-*N'*-phenylguanidines



										antifilarial activity		
no.	X	R_1, R_2	R_3	$NR_4R_5(R_6)$[a]	mp, °C	yield purified, %	purifcn solvent	proce-dure	formula[b]	route	dose[c]	% reduction[d] of live worms
20	H	6-CF_3	OH	$N(C_2H_5)_2$	187–192	27	MeCN	C	$C_{23}H_{26}F_3N_7O\cdot 0.4H_2O$	or	50[e]	100
										or	12[e]	47
21	H	6-CF_3	OH	$N[(CH_2)_2]_2NCH_3$	229–231	46	$CHCl_3$/heptane	C	$C_{24}H_{27}F_3N_8O\cdot 0.7C_7H_{16}$[f]	or	100[e]	91
										or	50[e]	78
										or	12[e]	0
22	H	6-CF_3	OCH_3	NHC_2H_5	190–193	38	MeCN	C	$C_{22}H_{24}F_3N_7O$	or	25	33
										sc	100	96
23	H	6-CF_3	OCH_3	$N(C_2H_5)_2$	174–176	47	heptane	C	$C_{24}H_{28}F_3N_7O$	or	50[e]	100
										or	12[e]	38
24	H	6-CF_3	OCH_3	$N[(CH_2)_2]_2NCH_3$	175–178	25	Et_2O	C	$C_{25}H_{29}F_3N_8O\cdot 0.7H_2O$	or	100[e]	100
										or	25	95
										or	3	5
25	4-Cl	6-CF_3	OH	$N(C_2H_5)_2$	205–207	51	MeCN	C	$C_{23}H_{25}ClF_3N_7O$	or	50[e]	100
										or	12[g]	100
										or	3	100
										or	0.5	100
26	4-Cl	6-CF_3	OH	$N(CH_2)_4$	214	40	EtOAc	C	$C_{23}H_{23}ClF_3N_7O$	or	50[e]	100
										or	12	87
27	4-Cl	6-CF_3	OH	$N[(CH_2)_2]_2NCH_3$	232–234	25	benzene	C	$C_{24}H_{26}ClF_3N_8O$	or	50[e]	98
										or	12[g]	38
28	4-Cl	6-CF_3	OH	$N(C_2H_5)_2(C_6H_5)$	206–207	50	MeOH	C	$C_{29}H_{29}ClF_3N_7O$	or	100	88
										sc	100	35
29	4-Cl	6-CF_3	OCH_3	NHC_2H_5	187–189	22	MeCN	C	$C_{22}H_{23}ClF_3N_7O$	or	100	100
										or	25	92
										or	3	81
										sc	100	*h*
										sc	25	100
										sc	6	92
30	4-Cl	6-CF_3	OCH_3	$N(CH_2)_4$	201–205	29	EtOAc/MeOH/Et_3N[l]	C	$C_{24}H_{25}ClF_3N_7O\cdot 0.3H_2O$	or	50[e]	100
										or	12[e]	100
										or	3	99
										or	0.5	100
31	4-OCH_3	6-CF_3	OH	$N(C_2H_5)_2$	178–179	43	MeCN	C	$C_{24}H_{28}F_3N_7O_2$	or	100	95
										or	25	100
										or	3	2
										sc	100	95
32	4-OCH_3	6-CF_3	OCH_3	$N(C_2H_5)_2$	208–210	51	MeCN	C	$C_{25}H_{30}F_3N_7O_2$	or	25	100
										or	3	0
										sc	100	100

33	4-CF_3	6-CF_3	OH	$N(CH_3)_2$	223–225	52	MeCN	C	$C_{22}H_{21}F_6N_7O$	or	25	100
										or	3	54
										sc	100	*h*
34	4-CF_3	6-CF_3	OH	$N(C_2H_5)_2$	202–204	68	MeCN	C	$C_{22}H_{25}F_6N_7O$	or	100	100
										or	25	100
										or	3	98
										or	0.5	22
										sc	100	100
35	4-CF_3	6-CF_3	OH	$N[(CH_2)_2]_2NCH_3$	214–218	46	MeCN	C	$C_{25}H_{26}F_6N_8O$	or	100	100
										or	25	40
										or	3	5
										sc	200[e]	96
36	4-CF_3	6-CF_3	OCH_3	NHC_2H_5	187–190	26	EtOAc	C	$C_{23}H_{23}F_6N_7O \cdot 0.3H_2O$	or	100	100
										or	25	100
										or	3	30
										sc	100	100
37	4-CF_3	6-CF_3	OCH_3	$N(C_2H_5)_2$	215–216	62	MeCN	C	$C_{25}H_{27}F_6N_7O$	or	100	100
										or	25	100
										or	3	73
										sc	100	100
38	4-CF_3	6-CF_3	$OCH_2C_6H_5$	$N(C_2H_5)_2$	193–196	61	MeCN	C	$C_{31}H_{31}F_6N_7O$	or	100	100
										or	25	100
										or	3	0
										sc	100	100
39	4-OC_6H_5	6-CF_3	OH	$N(CH_3)_2$	220–221	37	MeCN	C	$C_{27}H_{26}F_3N_7O_2$	sc	100	12
40	4-OC_6H_5	6-CF_3	OH	$N(C_2H_5)_2$	204–205	40	MeCN	C	$C_{29}H_{30}F_3N_7O_2$	or	100	9
										sc	100	3
41	4-OC_6H_5	6-CF_3	OH	$N[(CH_2)_2]_2NCH_3$	219–220	39	MeCN	C	$C_{30}H_{31}F_3N_8O_2 \cdot 0.3H_2O$	sc	100	8
42	4-OC_6H_5	6-CF_3	OCH_3	NHC_2H_5	215–218	36	EtOH	C	$C_{28}H_{28}F_3N_7O_2$	sc	100	0
43	4-OC_6H_5	6-CF_3	OCH_3	$N(C_2H_5)_2$	196–197	57	MeCN	C	$C_{30}H_{32}F_3N_7O_2$	or	100	*h*
										or	25	27
										sc	100	0
44	4-OC_6H_5	6-CF_3	$OCH_2C_6H_5$	$N(C_2H_5)_2$	149–152	28	MeCN	C	$C_{36}H_{36}F_3N_7O_2$	or	100	22
										sc	100	0
45	4-COC_6H_5	6-CF_3	OH	$N(CH_3)_2$	225–226	38	MeCN	C	$C_{28}H_{36}F_3N_7O_2$	or	25	32
										or	3	−22
										sc	100	100
46	4-COC_6H_5	6-CF_3	OH	$N(C_2H_5)_2$	193–195	45	MeCN	C	$C_{30}H_{30}F_3N_7O_2$	or	100	6
										sc	100	6
47	4-COC_6H_5	6-CF_3	OH	$N[(CH_2)_2]_2NCH_3$	231–233	30	MeCN	C	$C_{31}H_{31}F_3N_8O_2 \cdot 0.2H_2O$	sc	100	8
48	4-COC_6H_5	6-CF_3	OCH_3	NHC_2H_5	168–171	30	MeCN	C	$C_{29}H_{28}F_3N_7O_2$	sc	100	0
49	4-COC_6H_5	6-CF_3	OCH_3	$N(C_2H_5)_2$	181–183	52	MeCN	C	$C_{31}H_{32}F_3N_7O$	or	100	16
										sc	100	19
50	4-COC_6H_5	6-CF_3	$OCH_2C_6H_5$	$N(C_2H_5)_2$	179–181	62	MeCN	C	$C_{37}H_{36}F_3N_7O_2$	or	100	27
										sc	100	0
51	3,4-Cl_2	6-CF_3	H	$N(C_2H_5)_2$	167–169	53	EtOAc	C	$C_{23}H_{24}Cl_2F_3N_7$	or	100[e]	100
										or	25	100
										or	3	83
52	3,4-Cl_2	6-CF_3	OH	NHC_2H_5	207–210	34	EtOAc	C	$C_{21}H_{20}Cl_2F_3N_7O \cdot 0.3H_2O$	or	25	100
										or	3	97
										or	0.5	97
										sc	100	100
										sc	25	100

Table III (*Continued*)

no.	X	R_1, R_2	R_3	$NR_4R_5(R_6)$[a]	mp, °C	yield purified, %	purifcn solvent	procedure	formula[b]	antifilarial activity: route	dose[c]	% reduction[d] of live worms
53	3,4-Cl_2	6-CF_3	OH	$NHCH_2CH(CH_3)_2$	217–219	26	MeCN	C	$C_{23}H_{24}Cl_2F_3N_7O$	or	100[e]	100
										or	25	100
										or	3	35
54	3,4-Cl_2	6-CF_3	OH	$NHCH_2CH(CH_2)_5$	217–218	33	EtOAc	C	$C_{26}H_{28}Cl_2F_3N_7O$	sc	100	4
55	3,4-Cl_2	6-CF_3	OH	$N(CH_3)_2$	228–230	33	EtOAc	C	$C_{21}H_{20}Cl_2F_3N_7O$	or	100[e]	100
										or	25	100
										or	3	90
										or	0.5	100
56	3,4-Cl_2	6-CF_3	OH	$N(CH_3)C_2H_5$	213–216	75	MeCN	C	$C_{22}H_{22}Cl_2F_3N_7O$	or	25	100
										or	3	97
										or	0.5	100
										sc	100	100
										sc	25	100
57	3,4-Cl_2	6-CF_3	OH	$N(CH_2)_4$	219–221	28	MeCN/EtOAc	A	$C_{23}H_{22}Cl_2F_3N_7O\cdot 0.3H_2O$	or	100[e]	100
										or	25	100
										or	3	59
58	3,4-Cl_2	6-CF_3	OH	$N[(CH_2)_2]_2NCH_3$	244–246	36	$CHCl_3/Et_2O$	A	$C_{24}H_{25}Cl_2F_3N_8O\cdot 0.4H_2O$	or	400	100
										or	200	100
										or	100[e]	100
										or	25	100
										or	3	0
										sc	400	99
										sc	200	*h*
59	3,4-Cl_2	6-CF_3	OH	$N[(CH_2)_2]_2NCO_2C_2H_5$	229–230	46	EtOH	A	$C_{26}H_{27}Cl_2F_3N_8O$	sc	100	31
60	3,4-Cl_2	6-CF_3	OCH_3	$N(CH_3)_2$	222–223	47	EtOH	A	$C_{22}H_{22}Cl_2F_3N_7O$	or	100	100
										or	25	100
										or	3	*h*
										or	3	100
										sc	100	100
61	3,4-Cl_2	6-CF_3	OC_2H_5	$N(C_2H_5)_2$	169	58	Et_2O	A	$C_{25}H_{28}Cl_2F_3N_7O\cdot 0.1H_2O$	or	100[e]	100
										or	25	100
										or	3	21
62	3,4-Cl_2	6-CF_3	$OCH(CH_3)_2$	$N(C_2H_5)_2$	183–186	32	MeCN	A	$C_{26}H_{30}Cl_2F_3N_7O$	or	100	100
										or	25	100
										or	3	11
										sc	100	100
63	3,4-Cl_2	6-CF_3	$OCH_2C_6H_5$	$N(C_2H_5)_2$	188–190	64	cyclohexane	A	$C_{30}H_{30}Cl_2F_3N_7O$	or	100[e]	100
										or	25	100
										or	3	52
64	3,4-Cl_2	6-C_6H_5	OH	$N(C_2H_5)_2$	231 dec	11	DMF/MeOH	A	$C_{28}H_{29}Cl_2N_7O\cdot 0.2C_3H_7NO$	or	100[e]	47
										sc	100[e]	53
65	3,4-Cl_2	6-C_6H_5	OCH_3	NHC_2H_5	215–218	65	toluene	B	$C_{27}H_{27}Cl_2N_7O$	sc	100	0
66	3,4-Cl_2	6-C_6H_5	OC_2H_5	$N(C_2H_5)_2$	211–214	22	DMF/MeCN	B	$C_{30}H_{33}Cl_2N_7O\cdot 0.2H_2O$	or	25	78
										or	3	15
										sc	100	*h*
67	3,4-Cl_2	5,6-$(CH_2)_4$	OH	$N(C_2H_5)_2$	189–194	33	EtOH	A	$C_{26}H_{31}Cl_2N_7O$	sc	100	0
68	3,4-Cl_2	5,6-$(CH_2)_4$	OCH_3	NHC_2H_5	>270	58	EtOH	A	$C_{25}H_{29}Cl_2N_7O\cdot 2HCl\cdot 0.2H_2O$	sc	100	*h*
										sc	25	69

69	**3,4-Cl_2**	**5,6-$(CH_2)_4$**	**OC_2H_5**	**$N(C_2H_5)_2$**	**212–215**	**54**	**MeOH**	**A**	**$C_{28}H_{35}Cl_2N_7O$[i]**	or	100	*h*
										or	25	54
										sc	100	0
IV										or	25	100
										or	3	100
										sc	100[e]	100
										sc	25	100
XIa										or	100	*h*
										sc	100	0
										sc	100	68
XIb										or	600	66[j]
diethylcarbamazine (I)										sc	100	100
										sc	50	89[k]
suramin										or	100	98
amodiaquin (II)										or	25	71
										sc	100	100
										sc	25	61
										or	100	72
mebendazole (III)										sc	25	100
										sc	6.25	100
										sc	1.56	97

[a] Unless otherwise noted, R_6 = H. [b] Analyzed for C, H, N, and H_2O where necessary. [c] Milligrams per kilogram per day for 5 days. [d] Percent reduction of live adult worms at necropsy relative to sham-dosed controls. Unless otherwise noted, results are averages for three animals. [e] Five animals were used. [f] The ^1H NMR spectrum confirmed the presence of *n*-heptane. [g] Four animals were used. [h] Two or more animals died prematurely considered to be drug toxicity. [i] C: calcd, 60.42; found, 59.96. [j] Average for three tests. [k] Average for ten tests. [l] 75:25:1.

precipitate that accumulated was collected, and the filtrate was treated with an additional 0.2 equiv of ethyl 4,4,4-trifluoro-3-oxobutanoate. After the mixture was stirred at room temperature for 48 h, a second crop of product was collected. Compounds **3**, **4**, and **7** were recrystallized from DMF after triturating in hot MeOH.

Procedure B. To a mixture of 10.0 g (0.051 mol) of 4-aminobenzophenone and 10.8 g (0.051 mol) of [4-hydroxy-6-(trifluoromethyl)-2-pyrimidinyl]cyanamide sodium salt[35] was added a mixture of 51 mL of 2-ethoxyethanol, 4.4 mL of concentrated HCl, and 13 mL of H_2O. The solution was heated under reflux for 23 h and allowed to cool to room temperature. The precipitate that accumulated was collected, triturated in boiling MeOH, and dried in vacuo to give 14.3 g (70%) of *N*-(4-benzoylphenyl)-*N'*-[4-hydroxy-6-(trifluoromethyl)-2-pyrimidinyl]guanidine (**6**), mp 279 °C.

Preparation of *N*-[4-[[4-Alkoxy-3-[(dialkylamino)methyl]phenyl]amino]-2-pyrimidinyl]-*N'*-phenylguanidines X (Compounds 20–69, Table III). Procedure C. A mixture of 20.0 g (0.55 mol) of *N*-[4-hydroxy-6-(trifluoromethyl)-2-pyrimidinyl]-*N'*-[4-(trifluoromethyl)phenyl]guanidine and 80 mL of $POCl_3$ was heated under reflux for 2 h and added dropwise to a mixture of 1.5 L of H_2O and 6 mL of concentrated HCl cooled to 5 °C. The precipitate that accumulated was collected and dried to give 23.6 g (83%) of *N*-[4-chloro-6-(trifluoromethyl)-2-pyrimidinyl]-*N'*-[4-(trifluoromethyl)phenyl]guanidine hydrochloride phosphate. A mixture of 5.8 g (0.011 mol) of this material and 3.6 g (0.013 mol) of 4-amino-2-[(diethylamino)methyl]phenol dihydrochloride[21] in 80 mL of EtOH was heated under reflux for 20 h, treated with an additional 0.5 g (0.0019 mol) of 4-amino-2-[(diethylamino)methyl]phenol dihydrochloride, heated under reflux for an additional 20 h, and poured into a mixture of 1.8 L of H_2O and 25 mL of NH_4OH. The precipitate that accumulated was collected, washed with H_2O, dried, and recrystallized from CH_3CN to give 4.1 g (68%) of *N*-[4-[[3-[(diethylamino)methyl]-4-hydroxyphenyl]amino]-6-(trifluoromethyl)-2-pyrimidinyl]-*N'*-[4-(trifluoromethyl)phenyl]guanidine (**34**), mp 202–204 °C.

The condensations between the chloropyrimidines and the benzenamines forming compounds **21**, **24**, **35**, **41**, **47**, and **60** were treated with an excess of Et_3N to achieve solutions, and the condensations leading to compounds **52**, **60**, **61**, **64**, **67**, and **68** were run in DMF for solubility reasons. Compound **68** precipitated from the reaction mixture as the dihydrochloride and was collected and recrystallized. The purification of compound **28** required chromatography [SiO_2, eluting with $CHCl_3$/MeOH (9:1)].

Procedure D. A mixture of 5.8 g (0.011 mol) of *N*-(4-chloro-6-phenyl-2-pyrimidinyl)-*N'*-(3,4-dichlorophenyl)guanidine hydrochloride phosphate [prepared by chlorination of *N*-(3,4-dichlorophenyl)-*N'*-(4-hydroxy-6-phenyl-2-pyrimidinyl)guanidine with $POCl_3$ utilizing the procedure described in procedure C above] and 3.3 g (0.013 mol) of 5-amino-*N*-ethyl-2-methoxybenzenemethanamine dihydrochloride in 110 mL of pyridine was heated under reflux for 1.5 h, allowed to cool to ambient temperature, and filtered. The gummy residue remaining in the reaction vessel was combined with the solid that had been collected, and the mass was first washed with H_2O and then suspended in H_2O and treated with 2 N NH_4OH. The resulting solid was collected, dissolved in hot $CHCl_3$, treated with decolorizing charcoal, and filtered, and the filtrate was treated with 3 volumes of petroleum ether. The precipitate that resulted was dried and recrystallized from toluene to give 3.8 g (65%) of *N*-(3,4-dichlorophenyl)-*N'*-[4-[[3-[(ethylamino)methyl]-4-methoxyphenyl]amino]-6-phenyl-2-pyrimidinyl]guanidine (**65**), mp 215–218 °C.

Phenols and Benzenemethanamines. The following were prepared according to the cited literature: 4-amino-2-[(diethylamino)methyl]phenol and 4-amino-2-[[(2-methylpropyl)amino]methyl]phenol, ref 21; 4-amino-2-(1-pyrrolidinylmethyl)phenol and 4-amino-2-[(4-methyl-1-piperazinyl)methyl]phenol, ref 36; 5-amino-*N*-ethyl-2-methoxybenzenemethanamine, 4-methoxy-3-[(4-methyl-1-piperazinyl)methyl]benzenamine, and 4-methoxy-3-(1-pyrrolidinylmethyl)benzenamine, ref 15; 5-

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amino-*N,N*-diethyl-2-methoxybenzenemethanamine, ref 37; and 5-amino-*N,N*-diethylbenzenemethanamine, ref 38.

Procedure E. To a solution of 30.0 g (0.15 mol) of 2-(chloromethyl)-1-methoxy-4-nitrobenzene[21] in 250 mL of THF was added a mixture of 84.5 g (0.75 mol) of 40% aqueous dimethylamine and 250 mL of THF. The reaction mixture was stirred under reflux for 20 h, and the THF was removed in vacuo. The aqueous residue was treated with a mixture of 500 mL of H_2O, 75 mL of 2 N NaOH, and 300 mL of $CHCl_3$. The layers were separated, and the aqueous phase was extracted twice with $CHCl_3$. The extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give 31.4 g (99.6%) of 2-methoxy-*N,N*-dimethyl-4-nitrobenzenemethanamine as a light yellow oil, which was shown to be homogeneous by VPC. Anal. ($C_{10}H_{14}N_2O_3 \cdot 0.2H_2O$) C, H, N, H_2O.

A solution of the above benzenemethanamine (31.2 g, 0.15 mol) in 250 mL of *i*-PrOH was hydrogenated at 27 °C and an initial pressure of 51 psi over 3.0 g of Raney nickel. The reaction mixture was filtered into 65 mL of *i*-PrOH saturated with HCl gas. The mixture was stirred for 0.5 h, and the precipitate that accumulated was collected and dried in vacuo to give 34.0 g (91%) of 5-amino-2-methoxy-*N,N*-diethylbenzenemethanamine dihydrochloride (**11**), mp 265 °C dec.

Related compounds were prepared similarly with the following modifications: The reaction mixture for 2-[[(cyclohexylmethyl)amino]methyl]-4-nitrophenol was filtered to remove 1-cyclohexylmethanamine hydrochloride, and the filtrate was concentrated in vacuo to dryness. Crystallization of the residue from EtOAc/MeOH (20:1) provided the product in 44% yield, mp 158–159 °C. The reaction mixture to provide 2-[(ethylamino)methyl]-4-nitrophenol was concentrated in vacuo to dryness, and the residue was crystallized from DMF to give a 68% yield of the product, mp 208–210 °C. The reaction mixture from 4-[(2-hydroxy-5-nitrophenyl)methyl]-1-piperazinecarboxylic acid was filtered to remove 1-piperazinecarboxylic acid hydrochloride, and the filtrate was concentrated in vacuo to dryness. The residue was taken up in 1.5 L of 2 N NaOH, extracted four times with $CHCl_3$ to remove unreacted 1-piperazinecarboxylic acid, and neutralized (pH 7) with concentrated HCl. The mixture was extracted four times with $CHCl_3$, and the extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to dryness to provide 55.8 g of the product as a yellow oil, which was used without further purification.

Procedure F. A suspension of 151.2 g (1.0 mol) of *N*-(4-hydroxyphenyl)acetamide in 335 mL of anhydrous EtOH was treated successively with 45.1 g (1.0 mol) of anhydrous dimethylamine and 30.0 g (1.0 mol) of paraformaldehyde and heated under reflux for 1.5 h. TLC indicated that the reaction was incomplete; therefore, an additional 13.5 g (0.3 mol) of dimethylamine and 9.0 g (0.3 mol) of paraformaldehyde were added, and heating under reflux was resumed for 1.5 h. The mixture was chilled, treated with an excess of *i*-PrOH saturated with gaseous HCl, and allowed to stand at 0 °C for 24 h. The precipitate that formed was collected and dried in vacuo to provide 118.9 g (57%) of 4-(acetylamino)-2-[(dimethylamino)methyl]-phenol hydrochloride, mp 221–225 °C. A solution of 30.0 g (0.14 mol) of the above phenol in 70 mL of 20% HCl was heated under reflux for 70 min and concentrated to dryness in vacuo. The residue was coevaporated twice with EtOH and recrystallized from MeOH. The precipitate was pulverized, suspended in Et_2O, and collected. This was repeated three times to give 29.8 g (78%) of 4-amino-2-[(dimethylamino)methyl]phenol dihydrochloride (**10**), mp 232–236 °C dec.

Procedure G. To a solution of 25.0 g (0.11 mol) of 4-(acetylamino)-2-[(diethylamino)methyl]phenol[21] in 380 mL of DMF was added a suspension of 2.7 g (0.11 mol) of NaH (prepared by washing 5.4 g of a 50% oil dispersion of NaH twice with *n*-hexane) in DMF. The mixture was heated at 55–60 °C for 20 min, and 18.9 g (0.11 mol) of benzyl bromide was added via syringe. The reaction was heated to 100 °C, allowed to cool to 50 °C, and poured into 3 L of H_2O. The resulting suspension was stirred for 1 h, and the solid was collected and dried to give 31.5 g (91%) of *N*-[3-[(diethylamino)methyl]-4-(phenylmethoxy)phenyl]acetamide, mp 122–124 °C.

A mixture of 29.3 g (0.090 mol) of the above acetamide and 15.0 g of KOH in 150 mL of MeOH was heated at 100 °C for 26 h in a steel bomb. The reaction mixture was poured into 1.5 L of H_2O and extracted three times with $CHCl_3$. The extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to dryness. The residue was dissolved in a minimum amount of *i*-PrOH, treated with 15 mL of *i*-PrOH saturated with gaseous HCl, and poured into 850 mL of Et_2O. A gum separated, which crystallized on standing to give 21.5 g (67%) of 5-amino-*N,N*-diethyl-2-(phenylmethoxy)benzenemethanamine hydrochloride (**16**), mp 153–156 °C.

Compounds **14** and **15** were prepared by alkylation as above with diethyl sulfate and 2-iodopropane, respectively, followed by hydrolysis as described above for compound **10**.

Procedure H. A solution of 67.4 g (0.31 mol) of 5-nitro-[1,1′-biphenyl]-2-ol[25] in 170 mL of MeOH and 340 mL of THF was hydrogenated at 24 °C and an initial pressure of 51 psi over 3.0 g of Raney nickel. The reaction mixture was filtered into 35 mL of Ac_2O, heated on a steam bath for 15 min, and concentrated to dryness in vacuo. Crystallization of the residue from toluene gave 68.6 g (96%) of *N*-[6-hydroxy[1,1′-biphenyl]-3-yl]acetamide, mp 155.5–157 °C. A mixture of 30.0 g (0.13 mol) of the above acetamide, 12.8 g (0.16 mol) of a 37% aqueous formaldehyde solution, and 11.6 g (0.16 mol) of diethylamine in 100 mL of EtOH was heated in a steel bomb on a steam bath for 4.5 h. The reaction mixture was treated with an additional 3.8 g (0.053 mol) of diethylamine and 4.3 g (0.053 mol) of 37% aqueous formaldehyde solution and then heated on a steam bath for an additional 3 h. The solution was concentrated in vacuo to dryness, and the residue was chromatographed over 1 kg of silica gel, eluting with a $CHCl_3$/MeOH (9:1) mixture. Combination of the appropriate fractions and concentration to dryness in vacuo furnished 44.7 g of *N*-[5-[(diethylamino)methyl]-6-hydroxy[1,1′-biphenyl]-3-yl]acetamide as a brown oil. A solution of this oil and 500 mL of 6 N HCl was heated under reflux for 3 h, concentrated in vacuo to dryness, and coevaporated three times with EtOH to give 5-amino-3-[(diethylamino)methyl][1,1′-biphenyl]-2-ol dihydrochloride as an oil. Spectral data on this material were consistent with its structure, and it was homogeneous upon TLC evaluation. It was used in subsequent reactions without further purification.

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Angiotensin Converting Enzyme Inhibitors: N-Substituted Monocyclic and Bicyclic Amino Acid Derivatives

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The synthesis of *N*-(3-mercaptopropionyl)-*N*-arylglycines (**14a–x**), -*N*-arylalanines (**15a,b**), -*N*-cycloalkylglycines (**16a–k**), and -1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (**17a-d**), -1,2,3,4-tetrahydroquinoline-2-carboxylic acids (**18a–f**), and -indoline-2-carboxylic acids (**19a–k**) is described. In vitro inhibition of angiotensin converting enzyme (ACE) is reported for each compound, and the structure–activity relationship for each series is discussed. The in vivo inhibition of ACE and antihypertensive effects of representative compounds from each series are discussed. The most potent compound, **19d**, had an in vitro ACE IC_{50} of 2.6×10^{-9} M and lowered blood pressure in spontaneous hypertensive rats 85 mm at a dose of 10 mg/kg po.

Since the discovery[1] of the angiotensin converting enzyme (ACE) inhibitor 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline (captopril) and its use as an effective antihypertensive agent for essential and renal hypertension,[2] several papers have appeared describing a variety of analogues.[3] We have investigated the effect of replacing the proline portion of captopril with various N-substituted amino acids. In this report we describe the preparation and structure–activity relationship for a series of *N*-arylglycines,[4] *N*-arylalanines, *N*-cycloalkylglycines,[4,5] 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids,[6] 1,2,3,4-tetrahydroquinoline-2-carboxylic acids[6d,7] and indoline-2-carboxylic acids.[6d,8]

Chemistry. The desired compounds were obtained as shown in Scheme I. Amino esters **1–6** were transformed to amides **8–13** by treatment with acid chloride **7** in the presence of anhydrous potassium carbonate. Alkaline hydrolysis of **8–13** (R^5 = CH_3) led to the final products **14–24** (Table I).

The starting amino esters **1** or **2** required for **14** or **15** were prepared by alkylation of substituted anilines with ethyl chloroacetate or methyl 2-bromopropionate at 100 °C for 4–48 h in the presence of sodium acetate.[9] Amino esters **3** were obtained by reductive amination of aldehydes or ketones with glycine ethyl ester and sodium cyanoborohydride. Amino esters **4** were generated by cyclization of phenylalanine or substituted phenylalanine with formalin and hydrochloric acid,[10] followed by esterification. Amino esters **5** were synthesized from the corresponding quinaldic esters by hydrogenation at atmospheric pressure

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