and Mr. L. Cornwell for helpful suggestions in the preparation of this manuscript.

References and Notes

(1) J. Heeres, L. J. J. Backx, and J. Van Cutsem, *J. Med. Chem.*, 19, 1148 (1976).
(2) E. F. Godefroi, J. Van Cutsem, C. A. M. Van der Eycken, and P. A. J. Janssen, *J. Med. Chem.*, 10, 1160 (1967).
(3) J. Van Cutsem and D. Thienpont, *Chemotherapy*, 17, 392 (1972).

Antimycotic Imidazoles. 3. Synthesis and Antimycotic Properties of 1-[2-(Aryloxyalkyl)-2-phenylethyl]-1*H*-imidazoles

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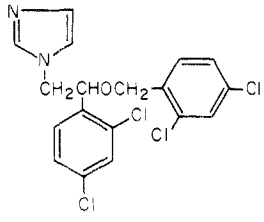
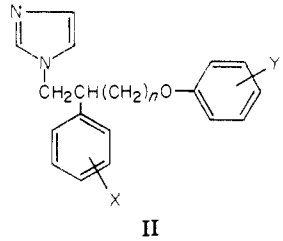
The synthesis and biological activity of a series of 1-[2-(aryloxyalkyl)-2-phenylethyl]-1*H*-imidazoles are described. These compounds are structurally related with Miconazole.

In previous reports,[1] the synthesis and antifungal effects of a large number of 2-substituted 2-phenylethyl-1*H*-imidazoles were described. One of these compounds, Miconazole (I), displays a marked broad-spectrum antimycotic activity and is now widely used as an antifungal drug. The aim of this paper is to describe the synthesis and antimycotic properties of a series of 1-[2-(aryloxyalkyl)-2-phenylethyl]-1*H*-imidazoles (II), which are structurally related to Miconazole.



I



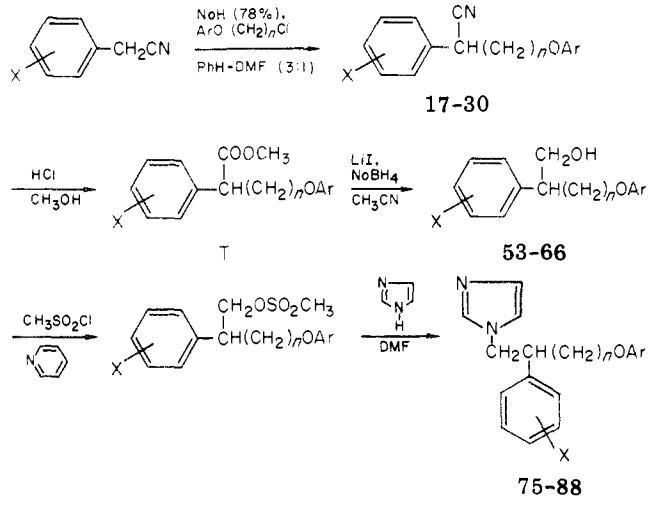
II

Chemistry. Compounds with $n > 1$ were synthesized by the method described before.[1b] The reaction sequence starting from arylacetonitriles and ω-phenoxyalkyl halides is outlined in Scheme I. On attempted alkylation of 2,4-dichlorophenylacetonitrile with 4-chlorophenyl chloromethyl ether, however, only bis(4-chlorophenoxy)methane (**89**) and 2,4-bis(2,4-dichlorophenyl)pentanedinitrile (**90**) were obtained (Scheme II). In order to prepare the title compounds with $n = 1$ another synthetic pathway was worked out (Scheme III).

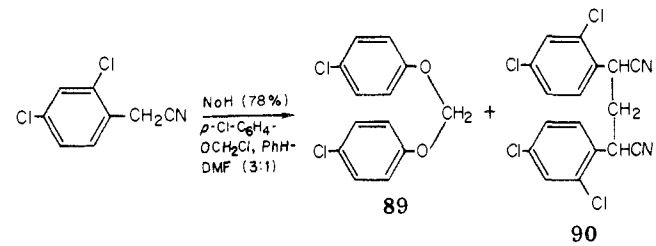
Phenols were alkylated with phenacyl bromides in refluxing acetone in the presence of K_2CO_3 giving α-phenoxy ketones **1–8** (Table I). Methylenation of these ketones with triphenylphosphonium methylide, generated in situ from $[Ph_3PCH_3]^+Br^-$ and NaH in anhydrous Me_2SO, afforded the olefins **9–16** (Table II) in fair yields. Hydroboration and subsequent oxidation gave alcohols **45–52** (Table V). The latter were converted to the mesylates which were reacted with imidazole in the usual way[1b] giving the desired compounds (Table VI). Most of the intermediates were used without further purification. The imidazole derivatives were isolated as nitrates or ethanedioates.

Methods. The title compounds were tested against a large number of microorganisms according to the procedure described by Godefroi et al.[2] Preliminary in vitro experiments were conducted on the following fungi: *Microsporum canis* (*M.c.*), *Trichophyton mentagrophytes* (*T.m.*), *Trichophyton rubrum* (*T.r.*), *Cryptococcus neoformans* (*Cr.n.*), *Candida tropicalis* (*C.tr.*), *Candida albicans* (*C.a.*), *Mucor species* (*Muc.*), *Aspergillus fumigatus* (*A.f.*), *Sporothrix schenkii* (*Sp.s.*), *Saprolegnia species* (*Sapr.*), *Phialophora verrucosa* (*Ph.v.*); and the gram-positive bacteria *Erysipelothrix insidiosa*, *Staphylococcus hemolyticus*, and *Streptococcus pyogenes*. According to

Scheme I. $n > 1$



Scheme II



Scheme III

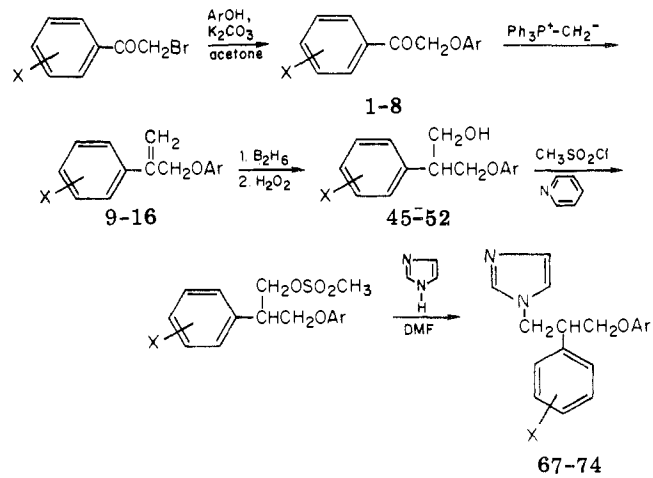
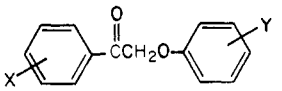


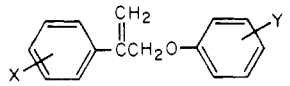
Table I



No.	X	Y	Formula	Mp, °C	Yield, %	Analyses[a]	Crystn solvent
1	2,4-Cl_2	4-Cl	$C_{14}H_9Cl_3O_2$	94.5	30	Cl	*i*-Pr_2O
2	2,4-Cl_2	4-Br	$C_{14}H_9BrCl_2O_2$	105.4	68	Cl + Br	CH_3OH
3	2,4-Cl_2	2,4-Cl_2	$C_{14}H_8Cl_4O_2$	100.6	63	Cl	*i*-PrOH
4	4-Cl	2-Cl	$C_{14}H_{10}Cl_2O_2$	108.5	67	Cl	*i*-Pr_2O
5	2,4-Cl_2	2-Cl	$C_{14}H_9Cl_3O_2$	86.7	63	Cl	CH_3OH
6	4-Cl	4-Cl	$C_{14}H_{10}Cl_2O_2$	140	76		*b*
7	4-Cl	2,4-Cl_2	$C_{14}H_9Cl_3O_2$	103.4	90	Cl	CH_3OH[c]
8	4-Br	4-Cl	$C_{14}H_{10}BrClO$	133.1	84	Cl + Br	CH_3OH

[a] Unless otherwise stated the analyses are within ±0.4% of the theoretical values for elements indicated by symbols. [b] E. B. Knot (Kodak Ltd.), British Patent 738 197 (Oct 12, 1955); *Chem. Abstr.*, 52, 942*gh* (1958). [c] Cl: calcd, 33.71; found, 33.30.

Table II



No.	X	Y	Formula	Yield, %	Analyses,[a] GC
9	2,4-Cl_2	4-Cl	$C_{15}H_{11}Cl_3O$	82	80
10	2,4-Cl_2	4-Br	$C_{15}H_{11}BrCl_2O$	79	95
11	2,4-Cl_2	2,4-Cl_2	$C_{15}H_{10}Cl_4O$	54	84
12	4-Cl	2-Cl	$C_{15}H_{12}Cl_2O$	67	87
13	2,4-Cl_2	2-Cl	$C_{15}H_{11}Cl_3O$	80	75
14	4-Cl	4-Cl	$C_{15}H_{12}Cl_2O$	85	89
15	4-Cl	2,4-Cl_2	$C_{15}H_{11}Cl_3O$	62	85
16	4-Br	4-Cl	$C_{15}H_{12}BrClO$	78	83

[a] Percent purity as determined by gas chromatography.

the method described by Van Cutsem and Thienpont,[3] in vivo experiments were conducted with adult guinea pigs weighing more than 700 g, infected with *C. albicans*. For oral treatment, the compounds were suspended in polyethylene glycol 200 and administered at daily dose levels of 10 mg/kg body weight.

Results and Discussion

The test results are summarized in Table VII. They represent the lowest dose levels for total inhibition of fungal and bacterial growth and indicate a high activity against dermatophytes (1 μg/mL) for most of the compounds. Some of them show also excellent activity against yeasts, other fungi, and gram-positive bacteria. However, even at the highest dose levels tested, no activity against gram-negative bacteria was noticed.

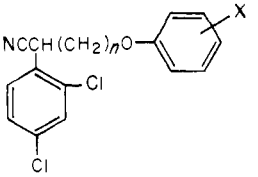
Chain length has practically no effect on potency against dermatophytes (see compounds **69**, **72**, **84**, and **88**) or yeasts (see compounds **67**, **73**, **76**, **77**, **80**, and **87**). Some of the title compounds are also active in vivo against *Candida* dermatomycosis in guinea pigs (see compounds **72**, **76**, **80**, **81**, **82**, and **83**). Both in vitro and in vivo activities do, however, not correlate.

Experimental Section

Melting points were measured on a "Mettler FP 1" melting point apparatus and are uncorrected. All title compounds were routinely checked for their structure by UV and/or IR spectrometry (UV, Beckman DK-2A; IR, Perkin-Elmer 421 or 225). Where indicated GC was measured with a Varian 2100 (column 2 m, 3% OV-17).

2-(4-Bromophenoxy)-1-(2,4-dichlorophenyl)ethanone (2). A solution of 4-bromophenol (17.3 g, 0.1 mol) and 2,4-dichlorophenacyl bromide (27 g, 0.1 mol) in 100 mL of acetone was added dropwise over a period of 15 min to a stirred suspension of K_2CO_3 (14 g, 0.1 mol) in 100 mL of acetone. The mixture was stirred and refluxed for 2 h, cooled, and poured into H_2O. The solid product was recrystallized from MeOH to give 24.5 g (68%) of **2**, mp 105.4 °C.

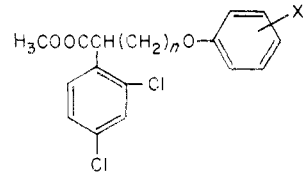
Table III



No.	X	*n*	Formula	Mp, °C	Yield, %	Crystn solvent	Analyses[a]	GC[b]
17	H	2	$C_{16}H_{13}Cl_2NO$	*c*	61			97
18	4-F	2	$C_{16}H_{12}Cl_2FNO$	58.9	48	EtOH	C, H, N	
19	4-Cl	2	$C_{16}H_{12}Cl_3NO$	*d*	66			95.6
20	2-Cl	2	$C_{16}H_{12}Cl_3NO$	94.4	74	EtOH	Cl	
21	2-Br	2	$C_{16}H_{12}BrCl_2NO$	97.2	94	EtOH	N, Cl + Br	
22	4-Br	2	$C_{16}H_{12}BrCl_2NO$	73.2	98	EtOH	C, H, N	
23	4-OCH_3	2	$C_{17}H_{15}Cl_2NO_2$	56.0	45	EtOH	C, H, N	
24	2,4-Cl_2	2	$C_{16}H_{11}Cl_4NO$	68.7	82	CH_3OH	Cl	
25	H	3	$C_{17}H_{15}Cl_2NO$	63.7	74	EtOH	C, H, N	
26	4-F	3	$C_{17}H_{14}Cl_2FNO$	86.1	83	EtOH	C, H, N	
27	4-Cl	3	$C_{17}H_{14}Cl_3NO$	83.3	81	EtOH	C, H, N	
28	4-Br	3	$C_{17}H_{14}BrCl_2NO$	70.5	76	EtOH	Cl + Br	
29	4-OCH_3	3	$C_{18}H_{17}Cl_2NO_2$	61.0	84	CH_3OH	Cl	98.4
30	2-Br	3	$C_{17}H_{14}BrCl_2NO$	61.2	70	CH_3OH	Cl + Br	99.7

[a] Unless otherwise stated the analyses are within ±0.4% of the theoretical values for elements indicated by symbols. [b] Percent purity as determined by gas chromatography. [c] Bp 180–185 °C (0.05 mm). [d] Bp 183–190 °C (0.05 mm).

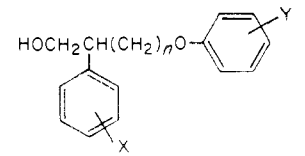
Table IV



No.	X	n	Formula	Mp, °C[a]	Yield, %	Analyses[b]	GC[c]
31	H	2	$C_{17}H_{16}Cl_2O_3$		98		96.5
32	4-F	2	$C_{17}H_{15}Cl_2FO_3$		95	Cl	98.4
33	4-Cl	2	$C_{17}H_{15}Cl_3O_3$		95		95.6
34	2-Cl	2	$C_{17}H_{15}Cl_3O_3$		98	Cl	99.5
35	2-Br	2	$C_{17}H_{15}BrCl_2O_3$		87	Cl + Br	99.6
36	4-Br	2	$C_{17}H_{15}BrCl_2O_3$		85		95.8
37	4-OCH_3	2	$C_{18}H_{18}Cl_2O_4$	52.2	100	Cl	
38	2,4-Cl_2	2	$C_{17}H_{14}Cl_4O_3$	55.1	97	Cl[d]	98.8
39	H	3	$C_{18}H_{18}Cl_2O_3$		93		94.8
40	4-F	3	$C_{18}H_{17}Cl_2FO_3$		97	Cl	99.7
41	4-Cl	3	$C_{18}H_{17}Cl_3O_3$		92	Cl	98.2
42	4-Br	3	$C_{18}H_{17}BrCl_2O_3$		98	Cl + Br	98
43	4-OCH_3	3	$C_{19}H_{20}Cl_2O_4$		95	Cl	99.4
44	2-Br	3	$C_{18}H_{17}BrCl_2O_3$		87		95.1

[a] Recrystallization solvent *n*-hexane. [b] Unless otherwise stated the analyses are within ±0.4% of the theoretical values for elements indicated by symbols. [c] Percent purity as determined by gas chromatography. [d] Cl: calcd, 34.75; found, 34.19.

Table V



No.	X	Y	n	Formula	Yield, %	Analyses, GC[a]
45	2,4-Cl_2	4-Cl	1	$C_{15}H_{13}Cl_3O_2$	31	87.9
46	2,4-Cl_2	4-Br	1	$C_{15}H_{13}BrCl_2O_2$	30	97.1
47	2,4-Cl_2	2,4-Cl_2	1	$C_{15}H_{12}Cl_4O_2$	52	89.5
48	4-Cl	2-Cl	1	$C_{15}H_{14}Cl_2O_2$	86	89.7
49	2,4-Cl_2	2-Cl	1	$C_{15}H_{13}Cl_3O_2$	38	89
50	4-Cl	4-Cl	1	$C_{15}H_{14}Cl_2O_2$	89	84
51	4-Cl	2,4-Cl_2	1	$C_{15}H_{13}Cl_3O_2$	59	92.5
52	4-Br	4-Cl	1	$C_{15}H_{14}BrClO_2$	89	96
53	2,4-Cl_2	H	2	$C_{16}H_{16}Cl_2O_2$	99	95.4
54	2,4-Cl_2	4-F	2	$C_{16}H_{15}Cl_2FO_2$	92	97.1
55	2,4-Cl_2	4-Cl	2	$C_{16}H_{15}Cl_3O_2$	62	96.3
56	2,4-Cl_2	2-Cl	2	$C_{16}H_{15}Cl_3O_2$	97	95.6
57	2,4-Cl_2	2-Br	2	$C_{16}H_{15}BrCl_2O_2$	98	97.5
58	2,4-Cl_2	4-Br	2	$C_{16}H_{15}BrCl_2O_2$	89	96.4
59	2,4-Cl_2	4-OCH_3	2	$C_{17}H_{18}Cl_2O_3$	92	97.1
60	2,4-Cl_2	2,4-Cl_2	2	$C_{16}H_{14}Cl_4O_2$	99	95.1
61	2,4-Cl_2	H	3	$C_{17}H_{18}Cl_2O_2$	63	92.3
62	2,4-Cl_2	4-F	3	$C_{17}H_{17}Cl_2FO_2$	93	97.8
63	2,4-Cl_2	4-Cl	3	$C_{17}H_{17}Cl_3O_2$	98	97.2
64	2,4-Cl_2	4-Br	3	$C_{17}H_{17}BrCl_2O_2$	98	93.5
65	2,4-Cl_2	4-OCH_3	3	$C_{18}H_{20}Cl_2O_3$	99	96
66	2,4-Cl_2	2-Br	3	$C_{17}H_{17}BrCl_2O_2$	96	99

[a] Percent purity as determined by gas chromatography.

Compounds 1 and 3–8 were synthesized in an analogous manner (Table I).

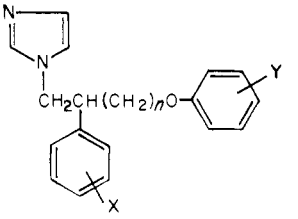
1-[1-(4-Bromophenoxymethyl)ethenyl]-2,4-dichlorobenzene (10). To a suspension of NaH 78% dispersion (3 g, 0.095 mol) in 100 mL of anhydrous Me_2SO, methyltriphenylphosphonium bromide (35 g, 0.098 mol) was added. After stirring under N_2 at 50 °C for 1 h, H_2 evolution was complete and a solution of **2** (23.5 g, 0.065 mol) in 20 mL of Me_2SO was added dropwise over a period of 10 min. The mixture was stirred at 50 °C for an additional 3 h and at room temperature overnight. It was then diluted with H_2O and extracted with *i*-Pr_2O. After drying ($MgSO_4$) and evaporating the organic layer, an oily residue was left, which was chromatographed over SiO_2 with $CHCl_3$ to afford 18.5 g (79%) of **10** (GC 95.3%).

Compounds **9** and 11–16, were prepared in an analogous manner (Table II).

β-(4-Bromophenoxymethyl)-2,4-dichlorobenzeneethanol (46). A solution of **10** (18.5 g, 0.052 mol) in 250 mL of THF was treated with B_2H_6 (B_2H_6 was generated in situ from anhydrous $NaBH_4$ and BF_3-Et_2O at 50 °C) (0.0275 mol). Stirring was continued for 30 min at 50 °C. After cooling the mixture, it was treated with 6 mL of 10 N NaOH for 10 min whereupon a solution of 50 mL of H_2O_2 (42%, 2.1 g, 0.062 mol) was added. The solution was stirred for 2 h and then diluted with H_2O and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and the solvent evaporated. The oily residue was chromatographed over SiO_2 with $CHCl_3$ as the eluent yielding 6 g (30%) of **46** (GC 97%). Compounds **45** and **47–52** were prepared in the same way (Table V).

1-[3-(4-Bromophenoxy)-2-(2,4-dichlorophenyl)propyl]-1*H*-imidazole Nitrate (68). To a solution of **46** (6 g, 0.016 mol) in 30 mL of pyridine, methanesulfonyl chloride (1.3 mL, 0.017

Table VI



No.	X	Y	n	Formula	Mp, °C	Crystn solvent[a]	Yield, %	Analyses[b]
67	4-Cl	2,4-Cl_2	1	$C_{18}H_{15}Cl_3N_2O\cdot HNO_3$	139.9	A	40	C, H, N
68	2,4-Cl_2	4-Br	1	$C_{18}H_{15}BrCl_2N_2O\cdot HNO_3$	119.3	B	59	H
69	2,4-Cl_2	2,4-Cl_2	1	$C_{18}H_{14}Cl_4N_2O\cdot HNO_3$	145.6	B	29	C, H, N
70	4-Cl	2-Cl	1	$C_{18}H_{16}Cl_2N_2O\cdot HNO_3$	151.8	B	26	C, H, N
71	2,4-Cl_2	2-Cl	1	$C_{18}H_{15}Cl_3N_2O\cdot HNO_3$	168.7	A	48	C, H, N
72	4-Cl	4-Cl	1	$C_{18}H_{16}Cl_2N_2O\cdot HNO_3$	131.2	B	48	C, H, N
73	2,4-Cl_2	4-Cl	1	$C_{18}H_{15}Cl_3N_2O\cdot HNO_3$	111.3	B	40	C, H, N
74	4-Br	4-Cl	1	$C_{18}H_{16}BrClN_2O\cdot HNO_3$	144.4	A	35	C, H, N
75	2,4-Cl_2	H	2	$C_{19}H_{18}Cl_2N_2O\cdot C_2H_2O_4$	145.0	C	43	C, H, N
76	2,4-Cl_2	4-F	2	$C_{19}H_{17}Cl_2FN_2O\cdot C_2H_2O_4$	104.7	C	57	C, H, N
77	2,4-Cl_2	4-Cl	2	$C_{19}H_{17}Cl_3N_2O\cdot HNO_3$	97.0	B	62	C, H, N
78	2,4-Cl_2	2-Cl	2	$C_{19}H_{17}Cl_3N_2O\cdot 2C_2H_2O_4$	123.2	D	56	H, Cl
79	2,4-Cl_2	2-Br	2	$C_{19}H_{17}BrCl_2N_2O\cdot 2C_2H_2O_4$	114.2	D	56	C, H, N
80	2,4-Cl_2	4-Br	2	$C_{19}H_{17}BrCl_2N_2O\cdot HNO_3$	72.3	E	41	N
81	2,4-Cl_2	4-OCH_3	2	$C_{20}H_{20}Cl_2N_2O\cdot HNO_3$	134.9	E	41	Cl
82	2,4-Cl_2	2,4-Cl_2	2	$C_{19}H_{16}Cl_4N_2O\cdot 2C_2H_2O_4$	139.5	D	54	C, H, N
83	2,4-Cl_2	H	3	$C_{20}H_{20}Cl_2N_2O\cdot 1.5C_2H_2O_4$	106.8	A	33	C, H, N
84	2,4-Cl_2	4-F	3	$C_{20}H_{19}Cl_2FN_2O\cdot C_2H_2O_4$	103.8	B	50	C, H, N
85	2,4-Cl_2	4-Cl	3	$C_{20}H_{19}Cl_3N_2O\cdot C_2H_2O_4$	133.1	D	69	C, H, N
86	2,4-Cl_2	4-Br	3	$C_{20}H_{19}BrCl_2N_2O\cdot C_2H_2O_4$	122.2	D	81	C, H
87	2,4-Cl_2	4-OCH_3	3	$C_{21}H_{22}Cl_2N_2O_2\cdot C_2H_2O_4$	126.8	E	28	N
88	2,4-Cl_2	2-Br	3	$C_{20}H_{19}BrCl_2N_2O\cdot C_2H_2O_4$	145.4	F	39	N

[a] A, *i*-PrOH; B, *i*-PrOH-*i*-Pr_2O; C, EtOH-*i*-Pr_2O; D, *i*-BuCOMe; E, *i*-BuCOMe-*i*-Pr_2O; F, CH_3CN-*i*-Pr_2O. [b] Unless otherwise stated the analyses are within ±0.4% of the theoretical values.

Table VII. Antifungal and Antibacterial Activities

	In vitro, lowest level of total inhibition[a,b]													In vivo[c,d]
Compd	*M.c.*	*T.m.*	*T.r.*	*Cr.n.*	*C.tr.*	*C.a.*	*Muc.*	*A.f.*	*Sp.s.*	*Sapr.*	*Ph.v.*	*E.ins.*	*Staph.*	*Strep.*	
67	10	<1	<1	<1	>100	10	>100	100	10	>100	100	1	10	<1	
68	<1	<1	<1	<1	>100	100	100	100	100	100	100	<1	10	<1	
69	<1	<1	<1	<1	>100	>100	>100	>100	<1	>100	100	<1	1	<1	
70	100	<1	10	<1	>100	100	100	>100	10	>100	>100	1	10	1	
71	10	<1	<1	<1	>100	100	>100	100	10	100	100	<1	1	<1	
72	<1	<1	<1	<1	>100	>100	10	100	10	100	100	1	10	<1	1/2
73	10	<1	<1	<1	>100	10	100	10	10	100	10	<1	10	<1	
74	10	<1	<1	10	>100	100	>100	100	10	>100	100	<1	10	<1	
75	10	<1	<1	<1	100	10	100	100	10	100	100	1	10	1	0/2
76	10	<1	<1	<1	>100	10	100	100	10	10	100	<1	10	1	2/2
77	10	<1	<1	<1	>100	10	10	100	10	10	100	<1	1	<1	
78	10	<1	<1	<1	>100	>100	>100	>100	10	100	100	<1	1	<1	0/2
79	100	<1	<1	<1	>100	>100	>100	>100	10	100	100	<1	10	<1	
80	<10	<10	<10	<10	100	<10	100	100	<10	<10	<10	<10	100	<10	1/2
81	10	<1	<1	<1	>100	100	100	100	10	<1	10	<1	10	<1	1/2
82	10	<1	<1	<1	>100	100	100	100	100	100	100	<1	1	<1	2/2
83	10	<1	<1	<1	>100	>100	>100	10	<1	10	10	<1	10	<1	1/2
84	<1	<1	<1	<1	>100	>100	>100	100	<1	10	100	1	10	1	
85	10	<1	<1	10	>100	>100	>100	100	<1	10	100	<1	1	<1	0/2
86	100	<1	10	10	>100	>100	>100	>100	100	100	100	<1	10	<1	0/2
87	10	<1	<1	<1	>100	10	100	10	<1	<1	10	<1	100	<1	
88	<1	<1	<1	<1	>100	100	>100	100	10	100	100	<1	10	<1	
Miconazole	1	<1	<1	1	100	10	>100	10	1	10	100	<1	10	<1	4/13

[a] Figures proceeded by ">" denoted partial growth at 100 μg/mL. [b] Figures proceeded by "<" represent the lowest dose levels tested (μg/mL). [c] Oral treatment (10 mg/kg) of cutaneous candidosis by *C. albicans* in guinea pigs. [d] Ratio of animals cured/animals infected.

mol) was added. The mixture was stirred at room temperature for 3 h, decomposed with water, and extracted with ether (three times). The organic layer was successively washed with diluted HCl solution and with water and dried ($MgSO_4$) and the solvent evaporated to yield 7.3 g (100%) of an oily residue. The latter was dissolved in 100 mL of DMF and imidazole (5.4 g, 0.08 mol) was added. This solution was stirred at 100 °C for 48 h. After cooling the mixture was poured into water and extracted with Et_2O (three times). The ethereal layer was washed and dried ($MgSO_4$) and the solvent evaporated. The residue was dissolved in *i*-PrOH and the nitrate salt was formed by addition of HNO_3 (65%). The salt was precipitated with *i*-Pr_2O and recrystallized from an *i*-PrOH–*i*-Pr_2O mixture to yield 4.6 g (58.8%) of pure **68**, mp 119.3 °C.

Bis(4-chlorophenoxy)methane (89) and 2,4-Bis(2,4-dichlorophenyl)pentanedinitrile (90). To a solution of 2,4-

dichlorophenylacetonitrile (18.5 g, 0.1 mol) in a mixture of DMF–benzene (50 mL/150 mL), NaH (78%, 3.2 g, 0.1 mol) dispersion was added portionwise under N_2 atmosphere. After stirring for 1 h the mixture was cooled to 0 °C and 4-chlorophenoxymethyl chloride (17.7 g, 0.1 mol) was added over a period of 1 h. The mixture was stirred at room temperature for 2 h and then poured into H_2O and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was triturated with MeOH giving a solid which was recrystallized from EtOH yielding 11 g (57%) of **90**, mp 172.8 °C.

The methanolic solution was evaporated in vacuo and the resultant residue crystallized from *n*-hexane to yield 5 g (37%) of **89**, mp 70 °C (lit.[4] 70–70.5 °C).

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4-Substituted Semicarbazones of Mono- and Dichlorobenzaldehydes as Antihypertensive Agents

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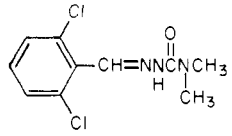
Twelve 4-substituted semicarbazone derivatives of *o*- and *p*-chloro- as well as 2,6-dichlorobenzaldehyde were synthesized and investigated for antihypertensive activity in spontaneously hypertensive rats. Several of the compounds synthesized (viz. **1**, **6**, **7**, and **15**) exhibited potent antihypertensive effects when orally administered. The same compounds were not hypotensive in the normotensive dog.

Several clinically effective antihypertensive drugs such as clonidine, guanabenz, guanoxabenz, and BS 100/141 possess a common molecular structural feature: a 2,6-dichlorobenzene moiety to which a basic nitrogen side chain is attached.[1]

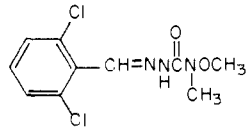
In the course of our investigation into the potential antihypertensive activity of various 2,6-dichlorobenzaldehyde derivatives, we observed that semicarbazone **1** was a potent (5.0 mg/kg) antihypertensive agent when orally administered to spontaneously hypertensive rats[2] (SHR).



1

Further evaluation of **1** revealed it to be free of adverse side effects, such as ataxia, sedation, agitation, or tachycardia, at 10 or 5 mg/kg in the SHR. Semicarbazone **1** was toxic at 100 mg/kg in SHR due to a general depression of cardiovascular function.

Examination of the literature revealed that **2**, a close analogue of **1**, was claimed to be a potent antihypertensive agent with low toxicity.[3] These observations prompted

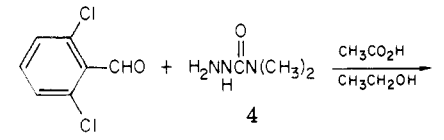


2

the synthesis of 11 related semicarbazones of **1** and the investigation of their antihypertensive activity.

Chemistry. The desired congeners of **1** were synthesized by two known general methods.[4] Method A involved the acid-catalyzed condensation of a chlorobenzaldehyde with a 4-methyl or dimethyl semicarbazide[5] to yield the semicarbazone. For example, **3** treated with **4** gave **1**. Method B involved the reaction of an amine (bp

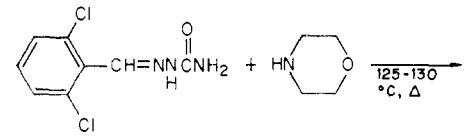
method A



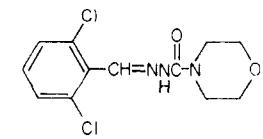
3 **4**

≥120 °C) with 2,6-dichlorobenzaldehyde semicarbazone[6] at 125–130 °C to yield the desired 4-substituted semicarbazone. For example, **5** treated with excess morpholine gave **6**. Table I lists the 12 synthesized semicarbazones and their method of preparation.

method B



5



6

Biological Methods and Results. The semicarbazones were administered orally in two doses of 100 mg/kg each to spontaneously hypertensive rats (SHR). The second dose was given 24 h after the first dose. The mean arterial blood pressure (MABP) was measured at 4 h after the second dosing. All determinations were made in restrained, conscious animals by direct femoral puncture.[2]