amount of insoluble material. The filtrate was evaporated in vacuo, and the residue was crystallized.

10-Methoxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (6). A solution of 3.53 g (0.01 mol) of **2a** in 100 mL of DMF containing 0.59 g (0.011 mol) of freshly prepared sodium methoxide was warmed on a steam bath for 5–10 min. After cooling to room temperature, the stirred solution was treated dropwise with 1.7 g (0.012 mol) of methyl iodide. The mixture was stirred at room temperature for 18 h, diluted with 100 mL of H_2O, and extracted with petroleum ether (bp 30–60 °C). The combined extracts were washed with H_2O, dried over sodium sulfate, and concentrated. The residue was purified by chromatography.

Compound **7** was prepared as above; **8** and **9** were obtained by using the appropriate bromides.

10-(Cyclopropylmethoxy)-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (10). A mixture of 4.95 g (0.014 mol) of **2a**, 0.96 g (0.02 mol) of NaH (50% suspension in oil), and 5 mL of DMF was heated, with stirring, at 80 °C for 2 h. The solution was allowed to cool and 0.5 g (0.003 mol) of KI and 1.81 g (0.02 mol) of cyclopropylmethyl chloride were added. The mixture was stirred at 80 °C for 3 h and then at room temperature overnight. To the mixture was added 75 mL of H_2O which was extracted with petroleum ether (bp 30–60 °C). The combined extracts were washed with H_2O, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by chromatography.

10-(3-Chloropropyloxy)-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine. A mixture of 7.06 g (0.02 mol) of **2a**, 1.01 g (0.024 mol) of NaH (57% suspension in oil), and 150 mL of DMF, under N_2, was warmed to effect solution. After cooling to room temperature, the stirred solution was treated dropwise with a solution of 3.77 g (0.024 mol) of 1-bromo-3-chloropropane in 5 mL of DMF. After stirring for 17 h, the mixture was diluted with H_2O and extracted with petroleum ether (bp 30–60 °C). The combined extracts were washed with H_2O, dried over sodium sulfate, and concentrated in vacuo. The residue was purified by chromatography using a Florisil column and $CHCl_3$. Anal. ($C_{26}H_{36}ClNO_2$) C, H, N.

5,5-Dimethyl-8-(1,2-dimethylheptyl)-10-(3-piperidinopropyloxy)-5*H*-[1]benzopyrano[4,3-*c*]pyridine (11). A mixture of 3.01 g (0.007 mol) of 10-(3-chloropropyloxy)-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine, 1.79 g (0.021 mol) of piperidine, 1.16 g (0.007 mol) of powdered KI, and 35 mL of 2-butanone was stirred and refluxed under N_2, for 42 h. The mixture was evaporated in vacuo, and the residue was triturated with H_2O and extracted with $CHCl_3$. The extracts were washed with H_2O, dried over sodium sulfate, and concentrated. The residue was purified by chromatography on a Florisil column using graded CH_3OH–$CHCl_3$ mixtures for elution. The dihydrochloride was prepared by passing HCl gas to the ether solution of the base, filtering, and recrystallizing.

Compound **12** was prepared in the same manner.

10-Hydroxy-5,5-dimethyl-8-(1,2-dimethylheptyl)-5*H*-[1]benzopyrano[4,3-*c*]pyridine *N*-Oxide (13a). A solution of 3.05 g (0.015 mol) of 85% *m*-chloroperbenzoic acid in 40 mL of $CHCl_3$ was added dropwise to a stirred, ice-cooled solution of 3.53 g (0.01 mol) of **2a** in 50 mL of $CHCl_3$. After stirring at room temperature for 72 h, the mixture was shaken twice with aqueous $NaHCO_3$, washed with H_2O, and dried over sodium sulfate. After removal of the solvent, the residue was crystallized.

Compound **13b** was similarly prepared.

Acknowledgment. The microanalyses were done by Ms. J. Hood, NMR spectra under the direction of Dr. R. Egan, and IR spectra under Mr. W. Washburn. Pharmacological testing was done by Mr. D. Ebert, Mr. F. Will, Ms. P. Morse, and Mr. W. Jochimsen.

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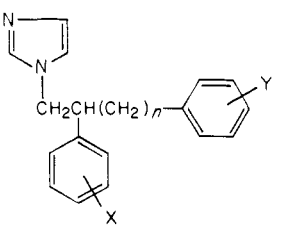
Antimycotic Imidazoles. 2. Synthesis and Antimycotic Properties of 1-[2-(Arylalkyl)-2-phenylethyl]-1*H*-imidazoles

Jan Heeres,* Jozef H. Mostmans, and Jan Van Cutsem

Janssen Pharmaceutica, Research Laboratoria, B-2340 Beerse, Belgium. *Received February 15, 1977*

Synthesis of 1-[2-(arylalkyl)-2-phenylethyl]-1*H*-imidazoles was accomplished starting from the corresponding phenylacetonitriles. Via successive alkylation, conversion to the corresponding ester, and sodium borohydride–lithium iodide reduction, β-phenylalcanols were obtained. These alcohols were mesylated and then refluxed with imidazole in dimethylformamide to yield the title compounds, which were active in vitro against dermatophytes, yeasts, other fungi, and gram-positive bacteria. Some were also active in vivo against *Candida albicans*.

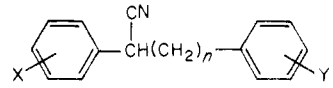
In a previous paper[1] the synthesis and antimycotic activity was described of a series of 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles. The present paper deals with the antimycotic activity of the analogous 1-[2-(arylalkyl)-2-phenylethyl]-1*H*-imidazoles (I). This class of compounds was synthesized by the same pathway described before.[1] In this case also the use of DMF–PhH mixtures prevented the formation of bis-alkylated phenylacetonitriles. Sterically hindered phenylacetonitriles in this case also had to be converted to the corresponding esters by a two-step pathway via the carboxylic acid (Scheme I). The new compounds are summarized in Tables I–V. The title compounds were tested against a large number of microorganisms by the procedure described by Godefroi et al.[2]



I

Fungi used in preliminary in vitro experiments are

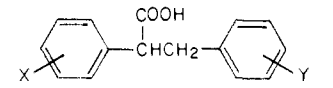
Table I



Compd	X	Y	n	Formula	Mp, °C	Yield, %	Crystn solvent	GC	Analyses[g]
1	2-CH_3	2,4-Cl_2	1	$C_{16}H_{13}Cl_2N$	98.2	77	MeOH		C, H, N, Cl
2	2-CH_3	2,6-Cl_2	1	$C_{16}H_{13}Cl_2N$	108.4	55	MeOH		Cl
3	2-CH_3	4-Cl	1	$C_{16}H_{14}ClN$[a]		78			Cl
4	2-Cl	2,4-Cl_2	1	$C_{15}H_{10}Cl_3N$	99.4	68	EtOH		C, H, N, Cl
5	2-Cl	2,6-Cl_2	1	$C_{15}H_{10}Cl_3N$	110	84	EtOH		Cl
6	2-Cl	2-Cl	1	$C_{15}H_{11}Cl_2N$	80.7	32	MeOH		N
7	2-Cl	4-Cl	1	$C_{15}H_{11}Cl_2N$[b]		73			Cl[d]
8	2-Br	2,4-Cl_2	1	$C_{15}H_{10}BrCl_2N$	92	71			C, H, N
9	2-Br	4-Cl	1	$C_{15}H_{11}BrClN$	77.1	78			Cl + Br
10	2,6-Cl_2	2,4-Cl_2	1	$C_{15}H_9Cl_4N$	125.7	99	*n*-BuOH		C, H, N, Cl
11	2,6-Cl_2	4-Cl	1	$C_{15}H_{10}Cl_3N$	97	75	MeOH-H_2O		C, H, N, Cl
12	4-Cl	2-Cl	1	$C_{15}H_{11}Cl_2N$	89.8	51	EtOH-H_2O		Cl
13	4-Cl	2,4-Cl_2	1	$C_{15}H_{10}Cl_3N$	60.0	26	EtOH-H_2O		Cl
14	4-Cl	2,6-Cl_2	1	$C_{15}H_{10}Cl_3N$[c]	116.3	82	EtOH		C, H, N
15	2,4-Cl_2	2-Cl	1	$C_{15}H_{10}Cl_3N$	89.8	42	*i*-PrOH		C, H, N
16	2,4-Cl_2	4-Cl	1	$C_{15}H_{10}Cl_3N$	97.0	64	MeOH		C, H, N, Cl
17	2,4-Cl_2	2,4-Cl_2	1	$C_{15}H_9Cl_4N$	108.5	85	*i*-PrOH		C, H, N, Cl
18	2,4-Cl_2	2,6-Cl_2	1	$C_{15}H_9Cl_4N$	105.1	74	*n*-Bu_2O		C, H, N, Cl
19	2,4-Cl_2	4-Br	1	$C_{15}H_{10}BrCl_2N$	105.1	44	EtOH		C, H, N[e]
20	2,4-Cl_2	H	1	$C_{15}H_{11}Cl_2N$	64.4	68	MeOH-H_2O		Cl[f]
21	2,4-Cl_2	4-OCH_3	1	$C_{16}H_{13}Cl_2NO$	76.7	60	EtOH		C, H, N, Cl
22	2,4-Cl_2	H	2	$C_{16}H_{13}Cl_2N$		65		96	Cl
23	2,4-Cl_2	4-Cl	2	$C_{16}H_{12}Cl_3N$		55		98	
24	2,4-Cl_2	4-OCH_3	2	$C_{17}H_{15}Cl_2NO$		58		97.4	
25	2,4-Cl_2	4-Br	2	$C_{16}H_{12}BrCl_2N$		61		92	
26	2,4-Cl_2	2-Cl	2	$C_{16}H_{12}Cl_3N$		100		97	
27	2,4-Cl_2	2,4-Cl_2	2	$C_{16}H_{11}Cl_4N$		100		96	

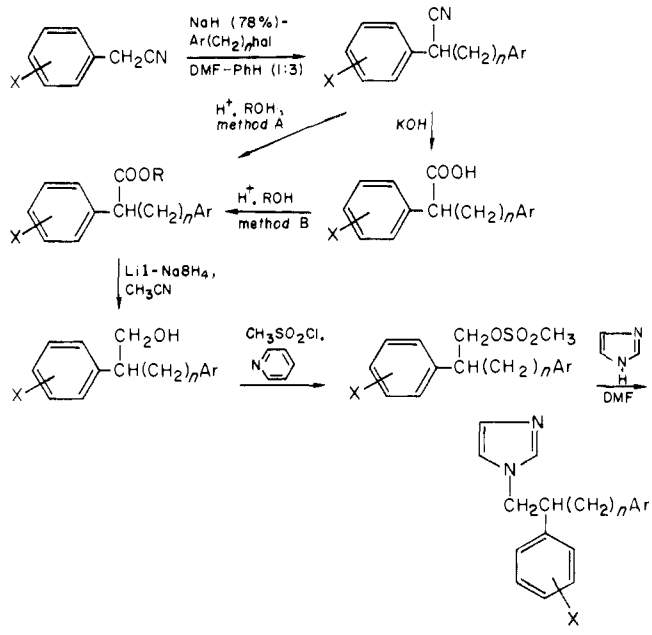
[a] Bp 155-160 °C (0.05 mm). [b] Bp 145-150 °C (0.05 mm). [c] Bp 180-185 °C (0.05 mm). [d] Cl: calcd, 25.68; found, 25.22. [e] N: calcd, 3.95; found, 3.25. [f] Cl: calcd, 25.68; found, 25.23. [g] Unless otherwise stated analyses are within 0.4% of theoretical values for elements indicated by symbols.

Table II



Compd	X	Y	Formula	Mp, °C	Method	Yield, %	Crystn solvent	Analyses
28	2,6-Cl_2	4-Cl	$C_{15}H_{11}Cl_3O_2$	157.4	B	78	EtOH-H_2O	C, H, Cl
29	2,6-Cl_2	2,4-Cl_2	$C_{15}H_{10}Cl_4O_2$	220.2	B	62	EtOH	C, H, Cl

Scheme I



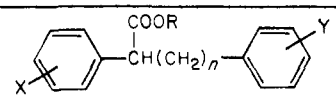
Microsporum canis (*M.c.*), *Trichophyton mentagrophytes* (*T.m.*), *Trichophyton rubrum* (*T.r.*), *Cryptococcus neoformans* (*Cr.n.*), *Candida tropicalis* (*C.tr.*), *Candida albicans* (*C.a.*), *Mucor species* (*Muc.*), *Aspergillus fumigatus* (*A.f.*), *Sporothrix schenckii* (*Sp.s.*), *Saprolegnia species* (*Sapr.*), and *Phialophora verrucosa* (*Ph.v.*). Included are also gram-positive bacteria *Erysipelothrix insidiosa*, *Staphylococcus hemolyticus*, and *Streptococcus pyogenes*.

In vivo experiments are conducted according to the method of Van Cutsem and Thienpont[3] using adult guinea pigs weighing more than 700 g, infected topically with *C. albicans*. For oral treatment, the compounds were suspended in PEG 200 and administered at daily dose levels of 10 mg/kg body weight for 14 days.

Results and Discussion

The test results summarized in Table VI indicate the lowest dose levels for total inhibition of fungal and bacterial growth. Most of the compounds were highly active against dermatophytes (1 μg/mL), some showing also good activity against yeasts, other fungi, and gram-positive bacteria. However, activity against gram-negative bacteria was not found, even at the highest dose levels tested. Optimal activity in vitro is found for compounds **90–92**,

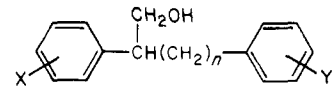
Table III



Compd	X	Y	n	R	Formula	Method	Mp, °C	Yield, %	GLC, %
30	2-CH_3	2,4-Cl_2	1	CH_3	$C_{17}H_{16}Cl_2O_2$	A		100	96
31	2-CH_3	2,6-Cl_2	1	CH_3	$C_{17}H_{16}Cl_2O_2$	A		90	97.6
32	2-CH_3	4-Cl	1	CH_3	$C_{17}H_{17}ClO_2$	A		91	97.7
33	2-Cl	2,4-Cl_2	1	CH_3	$C_{16}H_{13}Cl_3O_2$[a]	A	67.9	95	98.5
34	2-Cl	2,6-Cl_2	1	CH_3	$C_{16}H_{13}Cl_3O_2$	A		99	98.8
35	2-Cl	2-Cl	1	CH_3	$C_{16}H_{14}Cl_2O_2$	A		96	96.7
36	2-Cl	4-Cl	1	CH_3	$C_{16}C_{14}Cl_2O_2$	A		92	97.8
37	2-Br	2,4-Cl_2	1	CH_3	$C_{16}H_{13}BrCl_2O_2$	A	86.8	89	100
38	2-Br	4-Cl	1	CH_3	$C_{16}H_{14}BrClO_2$	A		91	100
39	2,6-Cl_2	2,4-Cl_2	1	CH_3	$C_{16}H_{12}Cl_4O_2$[b]	B	115.1	97	99.5
40	2,6-Cl_2	4-Cl	1	CH_3	$C_{16}H_{13}Cl_3O_2$[c]	B	67.6	95	99.6
41	4-Cl	2-Cl	1	C_2H_5	$C_{17}H_{16}Cl_2O_2$	A		91	97.5
42	4-Cl	2,4-Cl_2	1	C_2H_5	$C_{17}H_{15}Cl_3O_2$	A		93	96.5
43	4-Cl	2,6-Cl_2	1	C_2H_5	$C_{17}H_{15}Cl_3O_2$[d]	A	83.4	88	98.7
44	2,4-Cl_2	2-Cl	1	CH_3	$C_{16}H_{13}Cl_3O_2$	A		98	97.0
45	2,4-Cl_2	4-Cl	1	C_2H_5	$C_{17}H_{15}Cl_3O_2$	A		96	95.6
46	2,4-Cl_2	2,4-Cl_2	1	C_2H_5	$C_{17}H_{14}Cl_4O_2$	A		97	96.8
47	2,4-Cl_2	2,6-Cl_2	1	C_2H_5	$C_{17}H_{14}Cl_4O_2$	A		96	97.4
48	2,4-Cl_2	4-Br	1	CH_3	$C_{16}H_{13}BrCl_2O_2$	A		100	96.5
49	2,4-Cl_2	H	1	CH_3	$C_{16}H_{14}Cl_2O_2$	A		94	95.6
50	2,4-Cl_2	4-OCH_3	1	CH_3	$C_{17}H_{16}Cl_2O_3$	A		100	97.1
51	2,4-Cl_2	H	2	CH_3	$C_{17}H_{16}Cl_2O_2$	A		96	94
52	2,4-Cl_2	4-Cl	2	CH_3	$C_{17}H_{15}Cl_3O_2$	A		96	92
53	2,4-Cl_2	4-OCH_3	2	CH_3	$C_{18}H_{18}Cl_2O_3$	A		100	90
54	2,4-Cl_2	4-Br	2	CH_3	$C_{17}H_{15}BrCl_2O_2$	A		94	99
55	2,4-Cl_2	2-Cl	2	CH_3	$C_{17}H_{15}Cl_3O_2$	A		97	95
56	2,4-Cl_2	2,4-Cl_2	2	CH_3	$C_{17}H_{14}Cl_4O_2$	A		92	93

[a] Crystallization solvent: MeOH; [b] MeOH; [c] petroleum ether; [d] EtOH.

Table IV



Compd	X	Y	n	Formula	Yield, %	GLC, %
57	2-CH_3	2,4-Cl_2	1	$C_{16}H_{16}Cl_2O$	100	96.1
58	2-CH_3	2,6-Cl_2	1	$C_{16}H_{16}Cl_2O$	99	97.5
59	2-CH_3	4-Cl	1	$C_{16}H_{17}ClO$	100	95.4
60	2-Cl	2,4-Cl_2	1	$C_{15}H_{13}Cl_3O$	98	96.2
61	2-Cl	2,6-Cl_2	1	$C_{15}H_{13}Cl_3O$[a]	97	99.2
62	2-Cl	2-Cl	1	$C_{15}H_{14}Cl_2O$	69	99.2
63	2-Cl	4-Cl	1	$C_{15}H_{14}Cl_2O$[b]	76	98.9
64	2-Br	2,4-Cl_2	1	$C_{15}H_{13}BrCl_2O$	71	95.9
65	2-Br	4-Cl	1	$C_{15}H_{11}BrClO$[c]	98	98.0
66	2,6-Cl_2	2,4-Cl_2	1	$C_{15}H_{12}Cl_4O$	96	97.4
67	2,6-Cl_2	4-Cl	1	$C_{15}H_{13}Cl_3O$	97	96.7
68	4-Cl	2-Cl	1	$C_{15}H_{14}Cl_2O$	91	96.1
69	4-Cl	2,4-Cl_2	1	$C_{15}H_{13}Cl_3O$	92	95.1
70	4-Cl	2,6-Cl_2	1	$C_{15}H_{13}Cl_3O$	96	96.1
71	2,4-Cl_2	2-Cl	1	$C_{15}H_{13}Cl_3O$	79	95.1
72	2,4-Cl_2	4-Cl	1	$C_{15}H_{13}Cl_3O$	87	96.2
73	2,4-Cl_2	2,4-Cl_2	1	$C_{15}H_{12}Cl_4O$	77	97.1
74	2,4-Cl_2	2,6-Cl_2	1	$C_{15}H_{12}Cl_4O$	98	96.5
75	2,4-Cl_2	4-Br	1	$C_{15}H_{13}BrCl_2O$	95	95.6
76	2,4-Cl_2	H	1	$C_{15}H_{14}Cl_2O$	95	96.2
77	2,4-Cl_2	4-OCH_3	1	$C_{16}H_{16}Cl_2O_2$	70	97.0
78	2,4-Cl_2	H	2	$C_{16}H_{16}Cl_2O$	97	95
79	2,4-Cl_2	4-Cl	2	$C_{16}H_{15}Cl_3O$	100	94
80	2,4-Cl_2	4-OCH_3	2	$C_{17}H_{18}Cl_2O_2$	87	92
81	2,4-Cl_2	4-Br	2	$C_{16}H_{15}BrCl_2O$	92	90
82	2,4-Cl_2	2-Cl	2	$C_{16}H_{15}Cl_3O$	95	91
83	2,4-Cl_2	2,4-Cl_2	2	$C_{16}H_{14}Cl_4O$	100	95

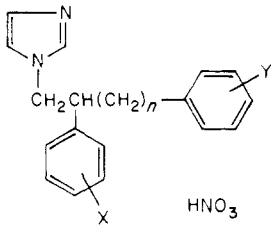
[a] Mp 76.9 °C (*n*-hexane). [b] Mp 79.6 °C (*n*-hexane). [c] Mp 75.8 °C (*n*-hexane).

100, **102**, **104**, **106**, and **109**, chain length (n = 1 or 2) having no influence on potency. In vitro results do not correlate with in vivo results as indicated by compounds **88**, **90**, **96–98**, **101**, and **108** which have a marked effect on *Candida* dermatomycosis in guinea pigs.

Experimental Section

Melting points were measured with a "Mettler FP 1" melting point apparatus and are uncorrected. All title compounds were routinely checked for their structure by UV and/or IR spec-

Table V



Compd	X	Y	n	Formula	Mp, °C[a]	Yield, %	Analyses[b]
84	2-CH_3	2,4-Cl_2	1	$C_{19}H_{18}Cl_2N_2 \cdot HNO_3$	136.8 (A)	59	N, Cl
85	2-CH_3	2,6-Cl_2	1	$C_{19}H_{18}Cl_2N_2 \cdot HNO_3$	202.7 (B)	34	N
86	2-CH_3	4-Cl	1	$C_{19}H_{19}ClN_2 \cdot HNO_3$	120.5 (C)	26	N, Cl
87	2-Cl	2,4-Cl_2	1	$C_{18}H_{15}Cl_3N_2 \cdot HNO_3$	142.7 (A)	67	C, H, N, Cl
88	2-Cl	2,6-Cl_2	1	$C_{18}H_{15}Cl_3N_2 \cdot HNO_3$	180.1 (A)	42	C, H, N
89	2-Cl	2-Cl	1	$C_{18}H_{16}Cl_2N_2 \cdot HNO_3$	149.9 (A)	35	C, H, N, Cl
90	2-Cl	4-Cl	1	$C_{18}H_{16}Cl_2N_2 \cdot HNO_3$	127.6 (A)	50	C, H, N, Cl
91	2-Br	2,4-Cl_2	1	$C_{18}H_{15}BrCl_2N_2 \cdot HNO_3$	135.9 (D)	50	C, H, N
92	2-Br	4-Cl	1	$C_{18}H_{16}BrClN_2 \cdot HNO_3$	123.0 (D)	55	C, H, N
93	2,6-Cl_2	4-Cl	1	$C_{18}H_{15}Cl_3N_2 \cdot HNO_3$	138 (A)	32	C, H, N
94	2,6-Cl_2	2,4-Cl_2	1	$C_{18}H_{14}Cl_4N_2 \cdot HNO_3$	191.1 (E)	42	C, H, N
95	4-Cl	2-Cl	1	$C_{18}H_{16}Cl_2N_2 \cdot HNO_3$	152 (E)	48	C, H, N
96	4-Cl	2,4-Cl_2	1	$C_{18}H_{15}Cl_3N_2 \cdot HNO_3$	143.7 (E)	29	C, H, N
97	4-Cl	2,6-Cl_2	1	$C_{18}H_{15}Cl_3N_2 \cdot HNO_3$	171.2 (B)	58	C, H, N
98	2,4-Cl_2	2-Cl	1	$C_{18}H_{15}Cl_3N_2 \cdot HNO_3$	156.1 (D)	45	C, H, N
99	2,4-Cl_2	4-Cl	1	$C_{18}H_{15}Cl_3N_2 \cdot HNO_3$	150.7 (A)	54	C, H, N
100	2,4-Cl_2	2,4-Cl_2	1	$C_{18}H_{14}Cl_4N_2 \cdot HNO_3$	147.3 (D)	57	C, H, N
101	2,4-Cl_2	2,6-Cl_2	1	$C_{18}H_{14}Cl_4N_2 \cdot HNO_3$	161.0 (E)	42	Cl
102	2,4-Cl_2	4-Br	1	$C_{18}H_{15}BrCl_2N_2 \cdot HNO_3$	150.5 (A)	53	C, H, N[c]
103	2,4-Cl_2	H	1	$C_{18}H_{16}Cl_2N_2 \cdot HNO_3$	146.7 (A)	50	C, H
104	2,4-Cl_2	4-OCH_3	1	$C_{19}H_{18}Cl_2N_2O \cdot HNO_3$	147.7 (A)	61	C, H, N
105	2,4-Cl_2	H	2	$C_{19}H_{18}Cl_2N_2 \cdot HNO_3$	136.7 (A)	48	C, H, N
106	2,4-Cl_2	4-Cl	2	$C_{19}H_{17}Cl_3N_2 \cdot HNO_3$	121.8 (D)	34	C, H, N
107	2,4-Cl_2	4-OCH_3	2	$C_{20}H_{20}Cl_2N_2O \cdot HNO_3$	119.0 (E)	18	C, H, N
108	2,4-Cl_2	4-Br	2	$C_{19}H_{17}BrCl_2N_2 \cdot HNO_3$	115.0 (D)	43	C, H, N
109	2,4-Cl_2	2-Cl	2	$C_{19}H_{17}Cl_3N_2 \cdot HNO_3$	186.7 (E)	35	C, H, N
110	2,4-Cl_2	2,4-Cl_2	2	$C_{19}H_{16}Cl_4N_2 \cdot HNO_3$	130.9 (E)	23	C, H, N

[a] Recrystallization solvents in parentheses: A, EtOH–*i*-Pr_2O; B, EtOH; C, MeCO-*i*-Bu; D, *i*-PrOH–*i*-Pr_2O; E, MeOH–*i*-Pr_2O. [b] Unless otherwise stated the analyses are within 0.4% of the theoretical values. [c] N: calcd, 8.88; found, 8.25.

trometry (UV, Beckman DK-2A; IR, Perkin-Elmer 421 or 225). Where indicated GC was measured with a gas chromatograph Varian 2100 (column 2 m, 3% OV-17).

4-Chloro-α-(2-chlorophenyl)benzenepropanenitrile (7). To a suspension of NaH (78%) dispersion (6.8 g, 0.22 mol) in a DMF (200 mL)–PhH (400 mL) mixture, 2-chlorobenzeneacetonitrile (30.3 g, 0.2 mol) was added. After stirring and cooling on ice under N_2 for 1 h, 4-chlorobenzyl chloride (32.8 g, 0.22 mol) was added dropwise, and stirring was continued for an additional 30 min. The reaction mixture was diluted with H_2O and extracted with *i*-Pr_2O. After drying ($MgSO_4$), the organic layer was evaporated in vacuo and the residue distilled to yield 40.3 g (73%) of **7**: bp 145–150 °C (0.05 mm).

Methyl 4-Chloro-α-(2-chlorophenyl)benzenepropanoate (36). To MeOH (150 mL), saturated with HCl gas at 0 °C, **7** (37.5 g, 0.136 mol) was added. The mixture was stirred and refluxed overnight. After cooling, the solution was diluted with H_2O and extracted with *i*-Pr_2O. The organic layer was dried ($MgSO_4$) and evaporated in vacuo leaving 38.7 g (92%) of **36** as an oil (GC 97.8%).

4-Chloro-α-(2,6-dichlorophenyl)benzenepropanoic Acid (28). To ethylene glycol (200 mL), containing KOH (13.0 g, 0.20 mol), **11** (43.1 g, 0.14 mol) was added. The mixture was refluxed for 48 h. After cooling, the reaction mixture was diluted with H_2O and acidified (HCl). Extraction with CH_2Cl_2, drying ($MgSO_4$) the organic phase, and stripping off the solvent in vacuo afforded 34.7 g (75%) of a solid, mp 156 °C. Recrystallization of 3.0 g from EtOH–H_2O gave 2.5 g of pure **28**, mp 157.4 °C.

Methyl 4-Chloro-α-(2,6-dichlorophenyl)benzenepropanoate (40). To MeOH (150 mL), saturated with HCl gas at 0 °C, **28** (31.7 g, 0.096 mol) was added. The mixture was refluxed with stirring overnight. After cooling, the solution was diluted with H_2O and extracted with *i*-Pr_2O. The organic phase was washed with a 5% $NaHCO_3$ solution, dried ($MgSO_4$), and evaporated in vacuo, leaving 31.3 g (95%) of a solid, mp 66 °C. Recrystallization of 3.0 g from petroleum ether (bp 60–80 °C) gave 2.6 g of **40**, mp 67.4 °C.

4-Chloro-β-(2-chlorophenyl)benzenepropanol (63). A solution of **36** (38.7 g, 0.125 mol) in CH_3CN (100 mL) was added to a mixture of $NaBH_4$ (10 g, 0.252 mol) and $LiI \cdot 2H_2O$ (32 g, 0.19 mol) in CH_3CN (100 mL). The reaction mixture was refluxed and stirred overnight, cooled, acidified (HCl), diluted with H_2O, and extracted with *i*-Pr_2O. After drying ($MgSO_4$) the organic layer and evaporation of the solvent 26.7 g (76%) of a solid, mp 77 °C, was obtained (GC 98.9%). Recrystallization of 3.0 g from *n*-hexane gave 2.1 g of **63**, mp 79.6 °C.

1-[2-(2-Chlorophenyl)-4-chlorophenylpropyl]-1*H*-imidazole (90). To a solution of **63** (23.7 g, 0.084 mol) in pyridine (100 mL), methanesulfonyl chloride (11.5 g, 0.10 mol) was added dropwise over a period of 10 min, while cooling on ice. The reaction mixture was stirred overnight. Then H_2O was added and the mixture was extracted with *i*-Pr_2O. The organic layer was washed with diluted HCl solution, dried ($MgSO_4$), and evaporated in vacuo. The oily residue (29.1 g, 0.08 mol) was refluxed overnight with a fivefold excess of imidazole (27.5 g, 0.405 mol) in DMF (150 mL). After cooling and diluting with H_2O, the mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo. To the oily residue, dissolved in Et_2O, a slight excess of HNO_3 (65% solution in H_2O) was added after which the nitrate salt crystallized. The solid was filtered and recrystallized from a mixture of EtOH–*i*-Pr_2O, yielding 16.5 g (50%) of **90**, mp 127.6 °C.

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Table VI. Antifungal and Antibacterial Activities

Compd	In vitro, lowest level of total inhibition[a,b]														In vivo[c,d]
	M.c.	*T.m.*	*T.r.*	*Cr.n.*	*C.tr.*	*C.a.*	*Muc.*	*A.f.*	*Sp.s.*	*Sapr.*	*Ph.v.*	*E.ins.*	*Staph.*	*Strep.*	
84	10	<1	<1	10	100	100	10	10	10	100	100	1	10	10	
85	10	<1	<1	100	>100	>100	100	100	100	100	100	<1	10	<1	
86	10	<1	10	10	>100	>100	100	100	100	100	100	1	10	<1	
87	10	<1	<1	<1	>100	100	100	100	10	100	100	10	100	<1	0/2
88	<1	<1	<1	10	>100	100	>100	10	10	100	100	1	1	<1	1/2
89	10	<1	<1	<1	>100	100	100	10	10	100	100	1	100	<1	0/2
90	10	<1	<1	<1	>100	10	100	100	10	100	100	1	100	1	2/2
91	10	<1	<1	<1	100	10	10	10	10	100	100	<1	<1	10	0/2
92	100	<1	<1	<1	>100	10	100	100	10	100	100	<1	10	1	
93	<1	<1	<1	100	>100	100	>100	100	100	100	100	<1	100	<1	0/2
94	10	10	<1	10	>100	>100	100	100	10	100	>100	1	10	<1	0/2
95	10	<1	<1	<1	100	100	10	100	100	100	100	1	10	10	0/4
96	10	<1	<1	<1	100	100	100	100	10	100	100	<1	10	1	1/2[e]
97	10	<1	10	<1	>100	>100	10	100	10	100	100	<1	10	<1	2/4
98	10	<1	<1	<1	<1	100	100	100	<1	10	10	<1	10	<1	1/5
99	10	<1	<1	<1	100	100	100	100	10	<1	100	<1	10	<1	0/4
100	10	<1	<1	<1	10	10	100	100	<1	100	100	<1	10	<1	0/3
101	10	<1	<1	<1	100	100	100	100	<1	100	100	1	100	1	1/2[e]
102	10	<1	<1	<1	10	10	10	100	10	100	10	<1	10	<1	0/2
103	10	<1	<1	<1	10	100	100	100	10	10	10	<1	10	<1	0/2
104	100	<1	<1	<1	10	10	10	100	10	100	10	1	10	1	0/2
105	10	<1	<1	<1	>100	100	100	100	10	10	10	<1	1	<1	0/1
106	10	<1	<1	<1	10	10	100	100	<1	10	10	<1	1	<1	0/2
107	10	<1	<1	<1	>100	>100	100	100	10	10	10	<1	1	<1	0/2
108	10	<1	<1	<1	10	>100	>100	100	10	10	100	<1	10	<1	2/4
109	10	<1	<1	<1	>100	10	100	100	<1	100	100	<1	1	1	
110	10	<1	<1	<1	>100	>100	>100	100	10	100	>100	<1	100	<1	0/2
Miconazole	1	<1	<1	1	100	10	>100	10	1	10	100	<1	10	<1	4/13

[a] Figures proceeded by ">" denote 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. [e] Dose, 40 mg/kg po.

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References and Notes

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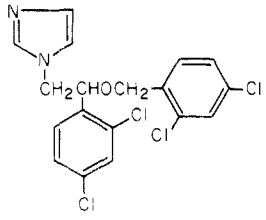
Antimycotic Imidazoles. 3. Synthesis and Antimycotic Properties of 1-[2-(Aryloxyalkyl)-2-phenylethyl]-1*H*-imidazoles

Jan Heeres,* Leo J. J. Backx, and Jan Van Cutsem

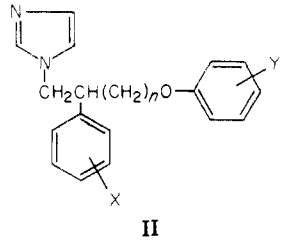
Janssen Pharmaceutica, Research Laboratoria, B-2340 Beerse, Belgium. *Received February 15, 1977*

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



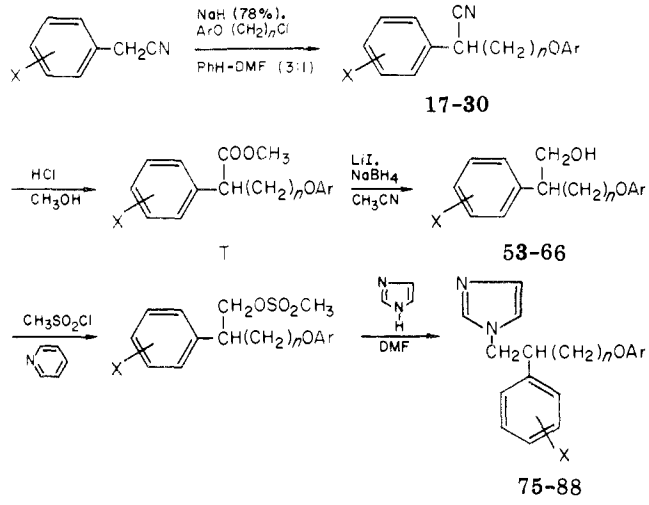
II

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).

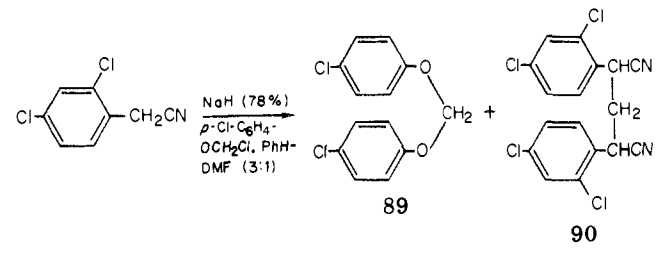
Phenols were alkylated with phenacyl bromides in refluxing acetone in the presence of K_2CO_3 giving α-phenoxy ketones **1–8** (Table I). Methylenation of these ketones with triphenylphosphonium methylide, generated in situ from $[Ph_3PCH_3]^+Br^-$ and NaH in anhydrous Me_2SO, afforded the olefins **9–16** (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