mixture was evaporated to dryness, water was added, and the product was extracted into heptane. The extract was acidified with ethereal HCl, and the precipitate was collected and recrystallized twice from MeOH–EtOAc to give 20.0 g of **38** with the properties listed in Table I.

In the same manner, XVIIId was allowed to react with piperidine or diallylamine (reaction times 72 and 24 h, respectively) to give **39** and **40**, respectively. Compound **40** was chromatographically purified from an alumina column, eluted with CH_2Cl_2.

9-(4-Chlorobenzylidene)-3,6-bis[2-[diethylamino(ethyl)-thio]]-9*H*-xanthene Dihydrochloride (42). An ethereal solution of **10** [free base, prepared from 14.5 g (0.0273 mol) of the dihydrochloride salt] was added to *p*-chlorobenzylmagnesium chloride [prepared from 17.6 g (0.109 mol) of *p*-chlorobenzyl chloride] in Et_2O and the mixture was refluxed for 5 h. Ammonium chloride solution was added to decompose the Grignard complex and the ether phase was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness. The residue could not be induced to crystallize. It was redissolved in Et_2O and extracted with 2 N HCl. The solution was made alkaline with 2 N NaOH and was extracted with Et_2O. The extract was dried ($MgSO_4$) and acidified with ethereal HCl. The precipitate was collected and was recrystallized twice from MeOH–EtOAc to give 8.3 g (48%) of **42** (Table I).

Reaction of **4** with 4-chlorobenzylmagnesium chloride followed by the same purification procedure as described for **42** gave **41** (Table I). Dehydration of the intermediate carbinols occurred under the conditions described. There was no evidence to indicate the presence of such intermediates in either **41** or **42**.

9-(4-Chlorobenzyl)-3,6-bis[2-(diethylamino)ethoxy]-9*H*-xanthen-9-ol (43). An ethereal solution of 10.7 g (0.025 mol) of **5** was added to 4-chlorobenzylmagnesium chloride [prepared from 16.1 g (0.1 mol) of 4-chlorobenzyl chloride] in Et_2O and the mixture was refluxed for 4 h. Ammonium chloride solution and some $CHCl_3$ were added and the organic phase was separated, dried ($MgSO_4$), and evaporated to dryness. The residue was recrystallized twice from hexane to give 4.2 g of **43** (Table I).

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References and Notes

(1) Presented in part at the 13th National Medicinal Chemistry Symposium, American Chemical Society, Iowa City, Iowa, June 1972.
(2) W. L. Albrecht, R. W. Fleming, S. W. Horgan, B. A. Deck, J. W. Hoffman, and G. D. Mayer, *J. Med. Chem.*, 17, 1150 (1974) (paper **6**).
(3) A. D. Sill, W. L. Albrecht, E. R. Andrews, R. W. Fleming, S. W. Horgan, E. M. Roberts, and F. W. Sweet, *J. Med. Chem.*, **16**, 240 (1973) (paper 1).
(4) W. L. Albrecht, E. R. Andrews, R. W. Fleming, J. M Grisar, S. W. Horgan, A. D. Sill, F. W. Sweet, and D. L. Wenstrup, Abstracts, 160th National Meeting of the Americal Chemical Society, Chicago, Ill., Sept 1970), MEDI 18.
(5) E. R. Andrews, R. W. Fleming, J. M. Grisar, J. C. Kihm, D. L. Wenstrup, and G. D. Mayer, *J. Med. Chem.*, 17, 882 (1974) (paper 2).
(6) R. F. Krueger and G. D. Mayer, Science, **169**, 1213 (1970).
(7) G. D. Mayer and R. F. Krueger, *Science*, **169**, 1214 (1970).
(8) W. L. Albrecht, R. W. Fleming, S. W. Horgan, J. C. Kihm, and G. D. Mayer, *J. Med. Chem.*, 17, 886 (1974) (paper 3).
(9) A. D. Sill, E. R. Andrews, F. W. Sweet, J. W. Hoffman, P. L. Tiernan, J. M. Grisar, R. W. Fleming, and G. D. Mayer, *J. Med. Chem.*, 17, 965 (1974) (paper **5**).
(10) T. Sengoku, *J. Pharm. Soc. Jpn.*, **53**, 962 (1933); *Chem. Abstr.*, **29**, 5445 (1935).
(11) Ng. D. Xuong and Ng. Ph. Buu-Hoi, *J. Chem. Soc.*, 3741 (1952).
(12) C. Liebermann and M. Zsuffa, *Ber.*, **44**, 852 (1911).
(13) R. Meyer and A. Conzetti, *Ber.*, **30**, **969** (1897); **32**, 2103 (1899).
(14) W. Wenner, *Justus Liebigs Ann. Chem.*, **607**, 121 (1957).
(15) M. S. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).
(16) R. W. Fleming, A. D. Sill, and F. W. Sweet, U.S. Patent 3576865 (1971); *Chem. Abstr.*, **73**, 3705 (1970).
(17) R. F. Krueger, G. D. Mayer, K. P. Camyre, and S. Yoshimura, paper presented at the 11th Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N.J., Oct 1971.
(18) G. D. Mayer, unpublished results, Merrell-National Laboratories, 1972.

Synthesis and Antimycotic Properties of 1-(2-Alkyl-2-phenylethyl)-1*H*-imidazoles

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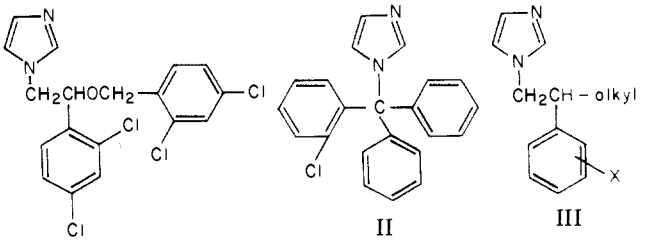
The synthesis of 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles was accomplished starting from the corresponding phenylacetonitriles. Via alkylation, esterification, and sodium borohydride reduction—in the presence of lithium iodide—β-phenylalcanols were obtained. Mesylation of these alcohols and refluxing with imidazole in dimethylformamide furnished title compounds, which were active in vitro against dermatophytes, yeasts, other fungi, and gram-positive bacteria and in vivo as well as in vitro against *Candida albicans*.

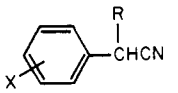
Substances containing the imidazole nucleus are known for their antimycotic activity. Miconazole[1] (I) and clotrimazole[2] (II) are among them, displaying a marked, broad-spectrum activity, not only against dermatophytes but also against yeasts (e.g., *Candida albicans*) and gram-positive bacteria. In the present paper we wish to report the synthesis and chemotherapeutic activity of a number of 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles (III).



I II III

Chemistry. The synthesis, starting from substituted phenylacetonitriles, is outlined in Scheme I. Monoalkylation of the phenylacetonitrile with an appropriate alkyl halide was performed via the carbanion, generated

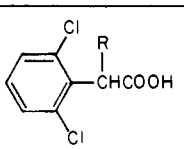
Table I. α-Alkylbenzeneacetonitriles



Compd	X	R	Method	Yield, %	Formula	GC[h]	Solvent	Bp (mm), °C
1	2-Cl	n-C_3H_7	A	66	$C_{11}H_{12}ClN$[a,e]	99.5	Me_2SO	76-77 (0.05)
2	2-Cl	n-C_4H_9	A	65	$C_{12}H_{14}ClN$[f]	99.5	Me_2SO	88-90 (0.05)
3	2-Cl	n-C_5H_{11}	A	63	$C_{13}H_{16}ClN$[f]	98.2	Me_2SO	104-106 (0.05)
4	2-Cl	n-C_6H_{13}	A	68	$C_{14}H_{18}ClN$	97	DMF	110-113 (0.05)
5	2-Cl	n-C_7H_{15}	A	50	$C_{15}H_{20}ClN$	97.6	DMF	120-123 (0.05)
6	2-Cl	n-C_8H_{17}	A	76	$C_{16}H_{22}ClN$[b]	97	DMF	125-133 (0.05)
7	2-Br	n-C_4H_9	A	65	$C_{12}H_{14}BrN$	90.2	DMF	98-103 (0.1)
8	2-Br	n-C_5H_{11}	A	68	$C_{13}H_{16}BrN$	98.4	DMF	108-109 (0.1)
9	2-Br	n-C_6H_{13}	A	71	$C_{14}H_{18}BrN$	97.2	DMF	118-122 (0.1)
10	2-Br	n-C_7H_{15}	A	75	$C_{15}H_{20}BrN$	96.5	DMF	123-128 (0.1)
11	2-Br	n-C_8H_{17}	A	73	$C_{16}H_{22}BrN$	97	DMF	135-140 (0.1)
12	4-F	CH_3			C_9H_8FN[c]			
13	4-F	n-C_3H_7	A	56	$C_{11}H_{12}FN$	82.4	DMF	80-83 (0.4)
14	4-F	n-C_4H_9	A	57.6	$C_{12}H_{14}FN$	89.9	DMF	75-85 (0.1)
15	4-F	n-C_5H_{11}	A	51	$C_{13}H_{16}FN$	84	DMF	85-93 (0.1)
16	4-F	n-C_6H_{13}	A	66	$C_{14}H_{18}FN$	94	DMF	100-106 (0.05)
17	4-F	n-C_7H_{15}	A	63.8	$C_{15}H_{20}FN$	96.7	DMF	110-115 (0.05)
18	4-F	n-C_8H_{17}	A	66	$C_{16}H_{22}FN$	96.8	DMF	125-130 (0.05)
19	4-Cl	CH_3			C_9H_8ClN[c]			
20	4-Cl	n-C_3H_7	B	57	$C_{11}H_{12}ClN$	77	DMF-PhH	80-85 (0.05)
21	4-Cl	n-C_4H_9	B	57	$C_{12}H_{14}ClN$[a]	89	DMF-PhH	87-93 (0.05)
22	4-Cl	n-C_5H_{11}	B	30	$C_{13}H_{16}ClN$	91.5	DMF-PhH	95-98 (0.01)
23	4-Cl	n-C_6H_{13}	B	65	$C_{14}H_{18}ClN$	94.2	DMF-PhH	118-124 (0.01)
24	4-Cl	n-C_7H_{15}	B	74	$C_{15}H_{20}ClN$	97.8	DMF-PhH	125-132 (0.1)
25	4-Cl	n-C_8H_{17}	B	58	$C_{16}H_{22}ClN$[b]	95	DMF-PhH	140-150 (0.15)
26	4-Br	n-C_4H_9	B	68	$C_{12}H_{14}BrN$	87.3	DMF-PhH	116-125 (0.2)
27	4-Br	n-C_5H_{11}	B	46	$C_{13}H_{16}BrN$	95.3	DMF-PhH	112-118 (0.05)
28	4-Br	n-C_6H_{13}	B	44	$C_{14}H_{18}BrN$	93.7	DMF-PhH	123-128 (0.1)
29	4-Br	n-C_7H_{15}	B	70	$C_{15}H_{20}BrN$	93.7	DMF-PhH	125-135 (0.1)
30	4-Br	n-C_8H_{17}	B	39	$C_{16}H_{22}BrN$	86.1	DMF-PhH	135-145 (0.15)
31	2,4-Cl_2	C_2H_5	A	69	$C_{10}H_9Cl_2N$[d]	95.2	Me_2SO	88-91 (0.1)
32	2,4-Cl_2	n-C_3H_7	A	72	$C_{11}H_{11}Cl_2N$[d]	97	Me_2SO	108-111 (0.2)
33	2,4-Cl_2	n-C_4H_9	A	67	$C_{12}H_{13}Cl_2N$	96.1	Me_2SO	101-104 (0.05)
34	2,4-Cl_2	i-C_4H_9	A	51.6	$C_{12}H_{13}Cl_2N$	96	Me_2SO	101-108 (0.1)
35	2,4-Cl_2	$CH_3CH_2CH(CH_3)$-	A	51.6	$C_{12}H_{13}Cl_2N$	98.6	Me_2SO	106-108 (0.1)
36	2,4-Cl_2	n-C_5H_{11}	A	62	$C_{13}H_{15}Cl_2N$	97.6	Me_2SO	115-117 (0.05)
37	2,4-Cl_2	i-C_5H_{11}	A	61	$C_{13}H_{15}Cl_2N$	91.3	DMF	107-112 (0.05)
38	2,4-Cl_2	n-C_6H_{13}	A	70	$C_{14}H_{17}Cl_2N$	95.6	Me_2SO	129-132 (0.1)
39	2,4-Cl_2	n-C_7H_{15}	A	69.5	$C_{15}H_{19}Cl_2N$	95.4	Me_2SO	138-141 (0.2)
40	2,4-Cl_2	n-C_8H_{17}	A	72	$C_{16}H_{21}Cl_2N$[e]	98.5	Me_2SO	147-149 (0.05)
41	2,6-Cl_2	n-C_4H_9	A	50	$C_{12}H_{13}Cl_2N$[g]	97.4	Me_2SO	118-122 (0.3)
42	2,6-Cl_2	n-C_5H_{11}	A	98	$C_{13}H_{15}Cl_2N$	95.7	DMF	120-135 (0.05)
43	2,6-Cl_2	n-C_6H_{13}	A	96	$C_{14}H_{17}Cl_2N$	97.1	DMF	128-132 (0.05)
44	2,6-Cl_2	n-C_7H_{15}	A	86	$C_{15}H_{19}Cl_2N$	95.8	DMF	133-135 (0.05)
45	2,6-Cl_2	n-C_8H_{17}	A	100	$C_{16}H_{21}Cl_2N$	90	DMF	145-149 (0.05)
46	2,4-Br_2	n-C_4H_9	B	66	$C_{12}H_{13}Br_2N$	97.4	DMF	124-126 (0.05)

[a] J. A. Faust, L. S. Yee, and M. Sahyun, *J. Org. Chem.*, 26, 4045 (1961), gave (1) bp 103-110° (1.3 mm) and (2) bp 126-129° (1.1 mm). [b] S. Miyano and N. Abe, *ibid.*, 36, 2948 (1971), gave (1) bp 157-162° (2 mm) and (2) 165-170° (2 mm). [c] Obtained from Aldrich, Europe. [d] *Chem. Abstr.*, 62, 16141 (1965); Netherlands Appl. 6408190 (Shell Internationale Research) to N. V. Maatschappij gave (1) bp 105° (0.6 mm) and (2) bp 111-112° (0.6 mm). [e] Analyzed for C, H, and N. Analyzed for Cl. [g] Analyzed for N. [h] Percent purity as determined by gas chromatography. All compounds are used without further purification.

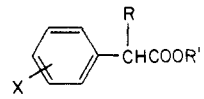
Table II. α-Alkyl-2,6-dichlorobenzeneacetic Acids



Compd	R	Method	Yield, %	Formula	Mp, °C	Analyses[a]	Recrystn solvent
47	n-C_4H_9	D	75	$C_{12}H_{14}Cl_2O_2$	132.3	C, H, Cl	Pet. ether
48	n-C_5H_{11}	D	87	$C_{13}H_{16}Cl_2O_2$	108	Cl	CH_3OH-H_2O
49	n-C_6H_{13}	D	88	$C_{14}H_{18}Cl_2O_2$	87.1	Cl	CH_3OH-H_2O
50	n-C_7H_{15}	D	85	$C_{15}H_{20}Cl_2O_2$	107.5	Cl	CH_3OH-H_2O
51	n-C_8H_{17}	D	72	$C_{16}H_{22}Cl_2O_2$	109.4	Cl	CH_3OH-H_2O

[a] Unless otherwise stated the analyses are within ±0.4% of the theoretical values.

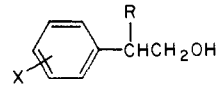
Table III. Esters Derived from α-Alkylbenzeneacetic Acids



Compd	X	R	R'	Method	Yield, %	Formula	GC[b]
52	2-Cl	n-C_3H_7	CH_3	C	95	$C_{12}H_{15}ClO_2$	96
53	2-Cl	n-C_4H_9	CH_3	C	97	$C_{13}H_{17}ClO_2$	90
54	2-Cl	n-C_5H_{11}	CH_3	C	99	$C_{14}H_{19}ClO_2$	97.3
55	2-Cl	n-C_6H_{13}	CH_3	C	100	$C_{15}H_{21}ClO_2$	96
56	2-Cl	n-C_7H_{15}	CH_3	C	92	$C_{16}H_{23}ClO_2$	92.4
57	2-Cl	nC_8H_{17}	CH_3	C	97.8	$C_{17}H_{25}ClO_2$	95.7
58	2-Br	n-C_4H_9	CH_3	C	97	$C_{13}H_{17}BrO_2$	87.6
59	2-Br	n-C_5H_{11}	CH_3	C	98	$C_{14}H_{19}BrO_2$	97.2
60	2-Br	n-C_6H_{13}	CH_3	C	99	$C_{15}H_{21}BrO_2$	96.8
61	2-Br	n-C_7H_{15}	CH_3	C	94	$C_{16}H_{23}BrO_2$	95.6
62	2-Br	n-C_8H_{17}	CH_3	C	96	$C_{17}H_{25}BrO_2$	97.6
63	4-F	CH_3	C_2H_5	C	98	$C_{11}H_{13}FO_2$	96.9
64	4-F	n-C_3H_7	CH_3	C	99	$C_{12}H_{15}FO_2$	80.2
65	4-F	n-C_4H_9	CH_3	C	93	$C_{13}H_{17}FO_2$	84.8
66	4-F	n-C_5H_{11}	CH_3	C	100	$C_{14}H_{19}FO_2$	87
67	4-F	n-C_6H_{13}	CH_3	C	98.8	$C_{15}H_{21}FO_2$	92.2
68	4-F	n-C_7H_{15}	CH_3	C	100	$C_{16}H_{23}FO_2$	96.3
69	4-F	n-C_8H_{17}	CH_3	C	96.7	$C_{17}H_{25}FO_2$	91.2
70	4-Cl	CH_3	C_2H_5	C	87	$C_{11}H_{13}ClO_2$	88
71	4-Cl	n-C_3H_7	CH_3	C	100	$C_{12}H_{15}ClO_2$	74.6
72	4-Cl	n-C_4H_9	CH_3	C	100	$C_{13}H_{17}ClO_2$	93.4
73	4-Cl	n-C_5H_{11}	CH_3	C	100	$C_{14}H_{19}ClO_2$	92.7
74	4-Cl	n-C_6H_{13}	CH_3	C	97.7	$C_{15}H_{21}ClO_2$	81
75	4-Cl	n-C_7H_{15}	CH_3	C	99	$C_{16}H_{23}ClO_2$	96.7
76	4-Cl	n-C_8H_{17}	CH_3	C	100	$C_{17}H_{25}ClO_2$	94.7
77	4-Br	n-C_4H_9	CH_3	C	97	$C_{13}H_{17}BrO_2$	85.1
78	4-Br	n-C_5H_{11}	CH_3	C	100	$C_{14}H_{19}BrO_2$	94.8
79	4-Br	n-C_6H_{13}	CH_3	C	96	$C_{15}H_{21}BrO_2$	92.9
80	4-Br	n-C_7H_{15}	CH_3	C	94	$C_{16}H_{23}BrO_2$	93.6
81	4-Br	n-C_8H_{17}	CH_3	C	91	$C_{17}H_{25}BrO_2$	86.4
82	2,4-Cl_2	C_2H_5	CH_3	C	96	$C_{11}H_{12}Cl_2O_2$	97.4
83	2,4-Cl_2	n-C_3H_7	CH_3	C	99	$C_{12}H_{14}Cl_2O_2$	98.7
84	2,4-Cl_2	n-C_4H_9	CH_3	C	97.7	$C_{13}H_{16}Cl_2O_2$	89.5
85	2,4-Cl_2	i-C_4H_9	CH_3	C	96.2	$C_{13}H_{16}Cl_2O_2$	93.3
86	2,4-Cl_2	$CH_3CH_2CH(CH_3)$-	CH_3	D	83	$C_{13}H_{16}Cl_2O_2$	91.6
87	2,4-Cl_2	n-C_5H_{11}	CH_3	C	99	$C_{14}H_{18}Cl_2O_2$	98.2
88	2,4-Cl_2	i-C_5H_{11}	CH_3	C	96	$C_{14}H_{18}Cl_2O_2$	84
89	2,4-Cl_2	n-C_6H_{13}	CH_3	C	96.5	$C_{15}H_{20}Cl_2O_2$	96.4
90	2,4-Cl_2	n-C_7H_{15}	CH_3	C	93.7	$C_{16}H_{22}Cl_2O_2$	95.2
91	2,4-Cl_2	n-C_8H_{17}	CH_3	C	97.8	$C_{17}H_{24}Cl_2O_2$	96.9
92	2,6-Cl_2	n-C_4H_9	CH_3	D	86.3	$C_{13}H_{16}Cl_2O_2$[a]	97
93	2,6-Cl_2	n-C_5H_{11}	CH_3	D	83.6	$C_{14}H_{18}Cl_2O_2$[a]	97.6
94	2,6-Cl_2	n-C_6H_{13}	CH_3	D	93	$C_{15}H_{20}Cl_2O_2$[a]	98
95	2,6-Cl_2	n-C_7H_{15}	CH_3	D	93	$C_{16}H_{22}Cl_2O_2$	90.1
96	2,6-Cl_2	n-C_8H_{17}	CH_3	D	91	$C_{17}H_{24}Cl_2O_2$	100
97	2,4-Br_2	n-C_4H_9	CH_3	C	68	$C_{13}H_{16}Br_2O_2$	88.4

[a] Analyzed for Cl. [b] Percent purity as determined by gas chromatography. All compounds are used without further purification.

Table IV. 2-Alkyl-2-phenylethanols



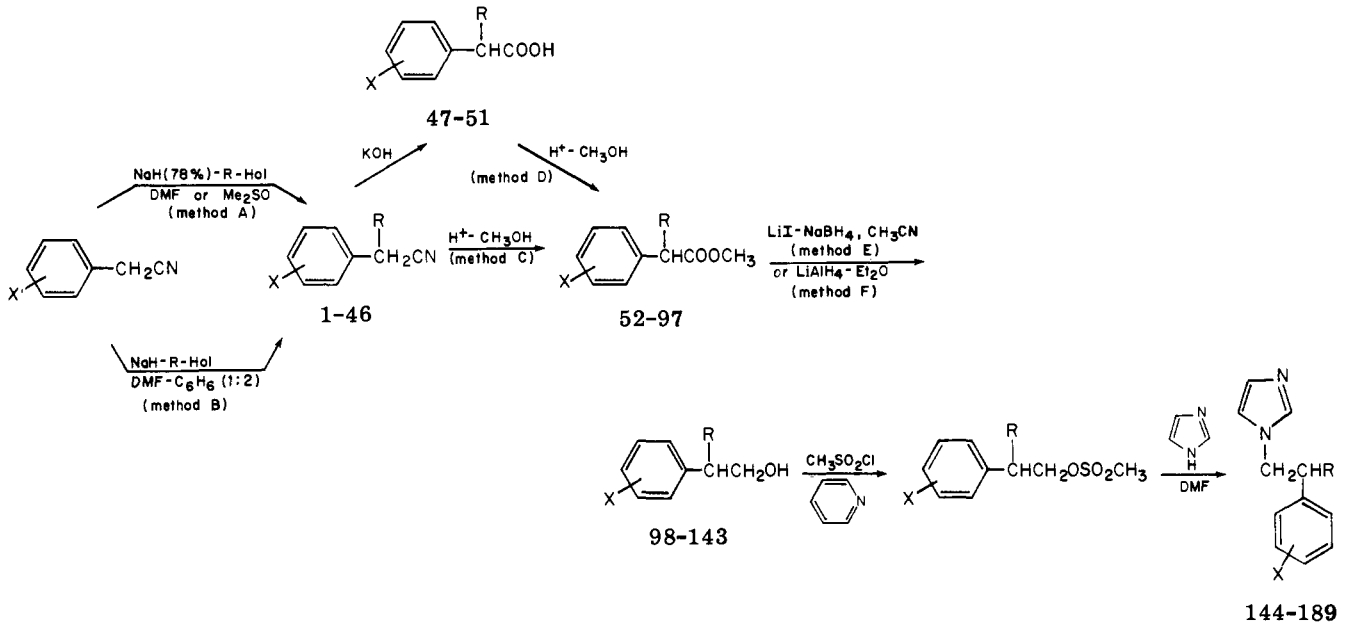
Compd	X	R	Method	Yield, %	Formula	GC[d]
98	2-Cl	n-C_3H_7	E	69	$C_{11}H_{15}ClO$	96
99	2-Cl	n-C_4H_9	E	98.7	$C_{12}H_{17}ClO$	89.9
100	2-Cl	n-C_5H_{11}	E	64.7	$C_{13}H_{19}ClO$	95.5
101	2-Cl	n-C_6H_{13}	E	91	$C_{14}H_{21}ClO$	95.3
102	2-Cl	n-C_7H_{15}	E	94	$C_{15}H_{23}ClO$	86
103	2-Cl	n-C_8H_{17}	E	93	$C_{16}H_{25}ClO$	90.4
104	2-Br	n-C_4H_9	E	100	$C_{12}H_{17}BrO$	89.2
105	2-Br	n-C_5H_{11}	E	91	$C_{13}H_{19}BrO$	96.9
106	2-Br	n-C_6H_{13}	E	95	$C_{14}H_{21}BrO$	94.2
107	2-Br	n-C_7H_{15}	E	100	$C_{15}H_{23}BrO$	89.4
108	2-Br	n-C_8H_{17}	E	100	$C_{16}H_{25}BrO$	93.7
109	4-F	CH_3	E	65	$C_9H_{11}FO$	96.4
110	4-F	n-C_3H_7	E	75	$C_{11}H_{15}FO$	93
111	4-F	n-C_4H_9	E	76.6	$C_{12}H_{17}FO$	92

Table IV (*Continued*)

Compd	X	R	Method	Yield, %	Formula	GC[d]
112	4-F	n-C_5H_{11}	E	69.5	$C_{13}H_{19}FO$	95.4
113	4-F	n-C_6H_{13}	E	79.8	$C_{14}H_{21}FO$	95.4
114	4-F	n-C_7H_{15}	E	71.7	$C_{15}H_{23}FO$[a]	98
115	4-F	n-C_8H_{17}	E	66	$C_{16}H_{25}FO$	97.8
116	4-Cl	CH_3	E	71	$C_9H_{11}ClO$[b]	96.5
117	4-Cl	n-C_3H_7	E	50.8	$C_{11}H_{15}ClO$	78.9
118	4-Cl	n-C_4H_9	E	71	$C_{12}H_{17}ClO$[c]	94.5
119	4-Cl	n-C_5H_{11}	E	83	$C_{13}H_{19}ClO$	92.8
120	4-Cl	n-C_6H_{13}	E	65	$C_{14}H_{21}ClO$	89
121	4-Cl	n-C_7H_{15}	E	99	$C_{15}H_{23}ClO$	95.8
122	4-Cl	n-C_8H_{17}	E	93	$C_{16}H_{25}ClO$	95.9
123	4-Br	n-C_4H_9	E	96	$C_{12}H_{17}BrO$	84
124	4-Br	n-C_5H_{11}	E	99	$C_{13}H_{19}BrO$	90.2
125	4-Br	n-C_6H_{13}	E	93	$C_{14}H_{21}BrO$	90.4
126	4-Br	n-C_7H_{15}	E	99	$C_{15}H_{23}BrO$	91.2
127	4-Br	n-C_8H_{17}	E	95	$C_{16}H_{25}BrO$	86.7
128	2,4-Cl_2	C_2H_5	E	87.7	$C_{10}H_{12}Cl_2O$	97.2
129	2,4-Cl_2	n-C_3H_7	E	98	$C_{11}H_{14}Cl_2O$	71
130	2,4-Cl_2	n-C_4H_9	E	57.8	$C_{12}H_{16}Cl_2O$	88.5
131	2,4-Cl_2	i-C_4H_9	E	83	$C_{12}H_{16}Cl_2O$	89.4
132	2,4-Cl_2	$CH_3CH_2CH(CH_3)$-	E	98	$C_{12}H_{16}Cl_2O$	82.6
133	2,4-Cl_2	n-C_5H_{11}	E	88.9	$C_{13}H_{18}Cl_2O$	80.2
134	2,4-Cl_2	i-C_5H_{11}	E	93	$C_{13}H_{18}Cl_2O$	89.5
135	2,4-Cl_2	n-C_6H_{13}	E	56.5	$C_{14}H_{20}Cl_2O$	85.4
136	2,4-Cl_2	n-C_7H_{15}	E	59.9	$C_{15}H_{22}Cl_2O$	87.7
137	2,4-Cl_2	n-C_8H_{17}	E	61.7	$C_{16}H_{24}Cl_2O$	88.5
138	2,6-Cl_2	n-C_4H_9	F	87	$C_{12}H_{16}Cl_2O$	95.6
139	2,6-Cl_2	n-C_5H_{11}	F	84.4	$C_{13}H_{18}Cl_2O$	96.5
140	2,6-Cl_2	n-C_6H_{13}	F	88	$C_{14}H_{20}Cl_2O$	97
141	2,6-Cl_2	n-C_7H_{15}	F	76	$C_{15}H_{22}Cl_2O$	94.2
142	2,6-Cl_2	n-C_8H_{17}	F	71	$C_{16}H_{24}Cl_2O$	92
143	2,4-Br_2	n-C_4H_9	F	100	$C_{12}H_{16}Br_2O$	86.5

[a] Analyzed for C, H, and F. [b] Analyzed for Cl. [c] M. Kullko, *Can. J. Chem.*, 42, 2797 (1965), gave bp 158–160° (11 mm). [d] Percent purity as determined by gas chromatography. All compounds are used without further purification.

Scheme I



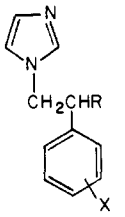
with NaH in DMF or Me_2SO (method A). For *p*-fluoro- and ortho-substituted phenylacetonitriles the monoalkylated products, contaminated with some bisalkylated material, were obtained in acceptable yields (Table I). However, under these reaction conditions, bisalkylation sometimes amounted to 50% for *p*-chloro- and *p*-bromophenylacetonitriles.

Fortunately, in these cases monoalkylation could be favored by the use of DMF–PhH (1:2) mixtures on the analogy of the method of Rossi et al.[3] (method B). Esterification of the nitriles was achieved directly by refluxing in methanol saturated with HCl (method C) or by a two-step pathway via the acids (method D). In the latter case the nitriles were saponified with KOH in ethylene glycol at 190 °C and the resulting acids (Table II) esterified with methanolic HCl in the usual way (Table III).

The esters were reduced either with sodium borohydride in the presence of LiI (method E) or with $LiAlH_4$ (method F), giving the desired alcohols in fair yields (Table IV). From these alcohols methanesulfonates were prepared with methanesulfonyl chloride in pyridine.

Most of these intermediate compounds were used without further purification. The methanesulfonates were refluxed with a fivefold excess of imidazole in DMF to give

Table V. 1-(2-Alkyl-2-phenylethyl)-1*H*-imidazoles



Compd	X	R	Yield, %	Formula	Mp, °C[a] (solvent)	Analyses[b]
144	2-Cl	*n*-C_3H_7	44	$C_{14}H_{17}ClN_2 \cdot HNO_3$	101.4 (A)	C, H, N, Cl
145	2-Cl	*n*-C_4H_9	26	$C_{15}H_{19}ClN_2 \cdot HNO_3$	118.8 (B)	C, H, N, Cl
146	2-Cl	*n*-C_5H_{11}	23	$C_{16}H_{21}ClN_2 \cdot HNO_3$	86.9 (B)	C, H, N, Cl
147	2-Cl	*n*-C_6H_{13}	48.6	$C_{17}H_{23}ClN_2 \cdot C_2H_2O_4$	133.0 (A)	C, H, N, Cl
148	2-Cl	*n*-C_7H_{15}	27	$C_{18}H_{25}ClN_2 \cdot C_2H_2O_4$	134.2 (A)	C, H, N, Cl
149	2-Cl	*n*-C_8H_{17}	54	$C_{19}H_{27}ClN_2 \cdot HNO_3$	70.3 (B)	C, H, N, Cl
150	2-Br	*n*-C_4H_9	49	$C_{15}H_{19}BrN_2 \cdot HNO_3$	107.8 (A)	C, H, N, Br
151	2-Br	*n*-C_5H_{11}	47	$C_{16}H_{21}BrN_2 \cdot HNO_3$	99.8 (A)	C, H, N, Br
152	2-Br	*n*-C_6H_{13}	56	$C_{17}H_{23}BrN_2 \cdot C_2H_2O_4$	128.1 (A)	C, H, N, Br
153	2-Br	*n*-C_7H_{15}	59	$C_{18}H_{25}BrN_2 \cdot C_2H_2O_4$	132.5 (A)	C, H, N, Br
154	2-Br	*n*-C_8H_{17}	62	$C_{19}H_{27}BrN_2 \cdot C_2H_2O_4$	133.3 (A)	C, H, N, Br
155	4-F	CH_3	59	$C_{12}H_{13}FN_2 \cdot HNO_3$	91.5 (A)	C, H, N
156	4-F	*n*-C_3H_7	48	$C_{14}H_{17}FN_2 \cdot HNO_3$	108.3 (A)	C, H, N
157	4-F	*n*-C_4H_9	56.7	$C_{15}H_{19}FN_2 \cdot HNO_3$	112.6 (A)	C, H, N
158	4-F	*n*-C_5H_{11}	56	$C_{16}H_{21}FN_2 \cdot HNO_3$	116.7 (A)	C, H, N
159	4-F	*n*-C_6H_{13}	64	$C_{17}H_{23}FN_2 \cdot HNO_3$	123.5 (A)	C, H, N
160	4-F	*n*-C_7H_{15}	51.7	$C_{18}H_{25}FN_2 \cdot HNO_3$	110.1 (A)	C, H, N
161	4-F	*n*-C_8H_{17}	61	$C_{19}H_{27}FN_2 \cdot HNO_3$	118.8 (A)	C, H, N
162	4-Cl	CH_3	57	$C_{12}H_{13}ClN_2 \cdot HNO_3$	81.2 (A)	C, H, N, Cl
163	4-Cl	*n*-C_3H_7	45	$C_{14}H_{17}ClN_2 \cdot HNO_3$	118 (A)	C, H, N
164	4-Cl	*n*-C_4H_9	51	$C_{15}H_{19}ClN_2 \cdot HNO_3$	96.1 (A)	C, H, N
165	4-Cl	*n*-C_5H_{11}	56	$C_{16}H_{21}ClN_2 \cdot HNO_3$	116 (A)	Cl
166	4-Cl	*n*-C_6H_{13}	56	$C_{17}H_{23}ClN_2 \cdot HNO_3$	122 (A)	Cl
167	4-Cl	*n*-C_7H_{15}	61	$C_{18}H_{25}ClN_2 \cdot HNO_3$	105.8 (A)	C, H, N, Cl
168	4-Cl	*n*-C_8H_{17}	62	$C_{19}H_{27}ClN_2 \cdot HNO_3$	111.1 (A)	C, H, N, Cl
169	4-Br	*n*-C_4H_9	30	$C_{15}H_{19}BrN_2 \cdot HNO_3$	113.4 (C)	C, H, N, Br
170	4-Br	*n*-C_5H_{11}	43	$C_{16}H_{21}BrN_2 \cdot HNO_3$	100.6 (A)	C, H, N, Br
171	4-Br	*n*-C_6H_{13}	45	$C_{17}H_{23}BrN_2 \cdot HNO_3$	101.9 (A)	C, H, N, Br
172	4-Br	*n*-C_7H_{15}	54	$C_{18}H_{25}BrN_2 \cdot HNO_3$	92.5 (A)	C, H, Br
173	4-Br	*n*-C_8H_{17}	42	$C_{19}H_{27}BrN_2 \cdot HNO_3$	95.3 (A)	C, H, N, Br
174	2,4-Cl_2	C_2H_5	44	$C_{13}H_{14}Cl_2N_2 \cdot HNO_3$	121.1 (D)	C, H, N, Cl
175	2,4-Cl_2	*n*-C_3H_7	40	$C_{14}H_{16}Cl_2N_2 \cdot HNO_3$	142.6 (D)	C, H, N, Cl
176	2,4-Cl_2	*n*-C_4H_9	49	$C_{15}H_{18}Cl_2N_2 \cdot HNO_3$	140 (A)	C, H, N, Cl
177	2,4-Cl_2	*i*-C_4H_9	55	$C_{15}H_{18}Cl_2N_2 \cdot HNO_3$	148.8 (A)	C, H, N, Cl
178	2,4-Cl_2	$CH_3CH_2CH(CH_3)$-	37	$C_{15}H_{18}Cl_2N_2 \cdot HNO_3$	160.6 (A)	C, H, N, Cl
179	2,4-Cl_2	*n*-C_5H_{11}	37.5	$C_{16}H_{20}Cl_2N_2 \cdot HNO_3$	116.7 (A)	C, H, N, Cl
180	2,4-Cl_2	*i*-C_5H_{11}	54	$C_{16}H_{20}Cl_2N_2 \cdot HNO_3$	146 (A)	C, H, N, Cl
181	2,4-Cl_2	*n*-C_6H_{13}	36.8	$C_{17}H_{22}Cl_2N_2 \cdot HNO_3$	90.7 (B)	C, H, N, Cl
182	2,4-Cl_2	*n*-C_7H_{15}	38.8	$C_{18}H_{24}Cl_2N_2 \cdot HNO_3$	91.2 (B)	C, H, N, Cl
183	2,4-Cl_2	*n*-C_8H_{17}	48.3	$C_{19}H_{26}Cl_2N_2 \cdot HNO_3$	82.9 (B)	C, H, N, Cl
184	2,6-Cl_2	*n*-C_4H_9	48	$C_{15}H_{18}Cl_2N_2 \cdot HNO_3$	119 (A)	C, H, N, Cl
185	2,6-Cl_2	*n*-C_5H_{11}	46	$C_{16}H_{20}Cl_2N_2 \cdot HNO_3$	102.6 (A)	C, H, N, Cl
186	2,6-Cl_2	*n*-C_6H_{13}	54	$C_{17}H_{22}Cl_2N_2 \cdot HNO_3$	81.5 (A)	C, H, N, Cl
187	2,6-Cl_2	*n*-C_7H_{15}	43	$C_{18}H_{24}Cl_2N_2 \cdot C_2H_2O_4$	92.1 (A)	C, H, N, Cl
188	2,6-Cl_2	*n*-C_8H_{17}	48	$C_{19}H_{26}Cl_2N_2 \cdot 1.5C_2H_2O_4$	92 (B)	C, H, N, Cl
189	2,4-Br_2	*n*-C_4H_9	58	$C_{15}H_{18}Br_2N_2 \cdot HNO_3$	142.8 (A)	C, H, N, Br

[a] Recrystallization solvents: A, *i*-PrOH–*i*-Pr_2O; B, MeC(=O)-*i*-Bu–*i*-Pr_2O; C, MeC(=O)-*i*-Bu; D, *i*-PrOH. [b] Unless otherwise stated the analyses are within ±0.4% of the theoretical values.

the desired 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles, isolated as nitrates or ethanedioates (Table V).

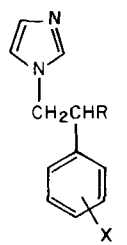
Biological Results. The title compounds were tested against a large number of microorganisms according to the procedure described by Godefroi et al.[4] Preliminary in vitro experiments were conducted on the following fungi: *Microsporum canis* (*M.c.*), *Trichophyton mentagrophytes* (*T.m.*), *Trichophyton rubrum* (*T.r.*), *Cryptococcus neoformans* (*Cr.n.*), *Candida tropicalis* (*C.tr.*), *Candida albicans* (*C.a.*), *Mucor species* (*Muc.*), *Aspergillus fumigatus* (*A.f.*), *Sporotrix schenckii* (*Sp.s.*), *Saprolegnia species* (*Sapr.*), *Phialophora verrucosa* (*Ph.v.*), and the gram-positive bacteria *Erysipelotrix insidiosa*, *Staphylococcus hemolyticus*, and *Streptococcus pyogenes*.

According to the method, described by Van Cutsem and Thienpont[5], 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 of body weight.

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 of them showing also excellent activity against yeasts, other fungi, and gram-positive bacteria. However, even at the highest dose levels tested, no activity was found against gram-negative bacteria. Ortho–para disubstitution on the phenyl ring seems to be favorable as exemplified by compounds **176**, **179–183**, and **189**. For significant broad-spectrum activity

Table VI. Antifungal and Antibacterial Activities



Compd	Lowest level of total inhibition,[a,b] iv													Iv cutaneous candidosis by *C.a.* in guinea pigs[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.*	
144	<1	<1	<1	100	>100	>100	>100	10	100	10	100	100	>100	100	0/2
145	<1	<1	<1	100	100	100	>100	10	10	10	100	10	100	10	
146	10	<1	<1	10	100	>100	>100	10	10	100	100	100	100	100	0/2
147	10	<1	<1	<1	>100	10	10	10	<1	10	100	<1	<1	<1	4/4
148	10	<1	<1	10	>100	100	10	100	<1	10	100	<1	10	<1	0/2
149	10	<1	<1	10	>100	10	100	100	<1	10	100	<1	10	<1	0/2
150	<1	<1	<1	10	10	100	100	10	10	10	100	10	100	<1	
151	<1	<1	<1	10	10	10	100	10	10	10	10	10	>100	10	
152	10	<1	<1	10	100	10	10	100	10	10	100	<1	>100	<1	
153	10	<1	<1	<1	>100	>100	10	100	10	10	100	<1	10	<1	
154	10	<1	<1	10	>100	>100	100	100	10	10	100	<1	10	<1	0/2
155	100	10	100	100	>100	>100	>100	100	100	100	100	>100	>100	>100	
156	10	<1	<1	10	>100	100	100	10	100	100	100	10	100	10	0/2
157	10	<1	<1	<1	10	100	100	10	10	100	100	10	100	10	0/2
158	10	<1	<1	10	>100	100	100	100	10	100	100	10	100	<1	2/2
159	10	<10	<10	<10	100	100	100	100	<10	100	100	<10	<10	<10	0/2
160	10	10	<1	<1	>100	10	100	100	10	100	100	<1	100	<1	0/2
161	10	<1	<1	<1	>100	10	10	100	10	10	100	<1	10	<1	0/2
162	100	10	100	10	>100	>100	>100	100	100	>100	100	>100	>100	100	
163	10	<1	<1	10	>100	100	100	10	100	100	100	10	100	10	0/2
164	10	<1	<1	<1	10	100	100	10	10	100	100	10	100	10	0/2
165	10	<1	<1	10	>100	100	100	100	10	100	100	10	100	<1	0/2
166	10	<1	<1	<1	>100	100	10	100	10	100	100	<1	10	<1	0/2
167	10	<1	<1	<1	>100	10	10	100	10	100	100	<1	10	<1	0/2
168	10	<1	<1	<1	>100	10	10	100	10	10	10	<1	10	<1	0/2
169	<1	<1	<1	<1	10	100	10	10	10	10	100	<1	100	<1	0/2
170	10	<1	<1	<1	10	100	100	100	10	100	100	<1	10	<1	1/2
171	10	<1	<1	<1	100	10	100	100	10	100	100	<1	10	<1	0/2
172	10	<1	<1	<1	>100	10	100	>100	10	100	100	<1	10	<1	0/2
173	100	<1	10	>100	>100	10	100	>100	10	100	100	<1	10	<1	0/2
174	10	<1	<1	<1	100	100	100	<1	10	10	10	10	>100	10	0/2
175	<1	<1	<1	<1	100	>100	>100	10	10	<1	10	<1	100	<1	1/2

176	<1	<1	<1	<1	10	10	>100	10	10	10	10	<1	100	<1	6/7
177	10	<1	<1	<1	100	100	100	10	10	10	100	10	100	<1	0/2
178	<10	<10	<10	<10	<10	100	100	<10	100	<10	<10	100	100	<10	0/2
179	10	<1	10	<1	100	10	100	10	10	10	10	<1	10	<1	1/2
180	<1	<1	<1	<1	10	10	10	10	10	10	100	<1	10	<1	
181	10	<1	<1	<1	10	10	10	100	<1	10	10	<1	10	<1	1/2
182	10	<1	<1	<1	>100	10	100	100	10	10	100	<1	10	<1	0/2
183	10	<1	<1	<1	>100	10	10	100	10	10	100	<1	10	<1	3/5
184	<1	<1	<1	100	100	100	100	10	10	100	100	<1	100	<1	
185	<1	<1	<1	100	100	10	100	10	<1	100	100	<1	10	10	0/2
186	<1	<1	<1	10	>100	10	100	10	<1	100	100	<1	100	<1	0/2
187	10	<1	<1	100	>100	10	100	10	<1	100	100	<1	10	<1	1/2
188	100	<1	10	100	>100	>100	10	100	10	100	100	<1	10	<1	
189	<1	<1	<1	<1	10	10	100	<1	10	10	10	<1	10	10	0/1
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] Dose, 10 mg/kg po. [d] Ratio of animals cured/animals infected.

the alkyl chain should contain at least four carbon atoms as demonstrated by compounds **147**, **149**, **151**, **152**, **160**, **161**, **167**, **168**, **171–173**, **176**, **179–183**, **185–187**, and **189**.

The in vitro results are confirmed by in vivo experiments, as shown by compounds **147**, **158**, **170**, **175**, **176**, **179**, **181**, **183**, and **187**, which have a marked effect on *Candida* dermatomycosis in guinea pigs.

It appears that 1-(2-alkyl-2-phenylethyl)-1*H*-imidazoles constitute a novel class of broad-spectrum antimycotic agents, being moreover also highly active against gram-positive bacteria.

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 spectrometry (uv, Beckman DK-2A; ir, Perkin-Elmer 421 or 225). Where indicated GC was measured with a gas chromatograph Varian 2100 (columm 2 m, 3% OV-17).

α-Butyl-2,4-dichlorobenzeneacetonitrile (33, Method A). To a suspension of NaH (78%) (6.8 g, 0.22 mol) dispersion in DMF (250 ml), 2,4-dichlorobenzeneacetonitrile (37.2 g, 0.20 mol) was added. After stirring and cooling on ice under N_2 for 1 h, *n*-butyl bromide (27.4 g, 0.2 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 oily residue distilled in vacuo to yield 32.5 g (67%) of **33**: bp 101–104 °C (0.05 mm).

4-Chloro-α-propylbenzeneacetonitrile (20, Method B). To a suspension of NaH (78%) (6.8 g, 0.22 mol) dispersion in a mixture of DMF (125 ml)–PhH (250 ml), 4-chlorobenzeneacetonitrile (30.3 g, 0.20 mol) was added. After stirring and cooling on ice under N_2 for 1 h, *n*-propyl bromide (24.6 g, 0.20 mol) was added dropwise and stirring was continued for 30 min. Water was added and the mixture was extracted with *i*-Pr_2O. The organic layer was dried ($MgSO_4$) and evaporated in vacuo. The oily residue was distilled in vacuo giving 22 g (57%) of **20**: bp 80–85 °C (0.05 mm).

Methyl α-Butyl-2,4-dichlorobenzeneacetate (84, Method C). To CH_3OH (150 ml), saturated with HCl gas at 0 °C, **33** (32.5 g, 0.134 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 layer was dried ($MgSO_4$) and evaporated in vacuo, leaving 36 g (97.7%) of **84** as an oil (GC 89.5%).

α-Butyl-2,6-dichlorobenzeneacetic Acid (47, Method D). To ethylene glycol (200 ml), containing KOH (13 g, 0.20 mol) and H_2O (5 ml), **41** (21.5 g, 0.089 mol) was added. The mixture was refluxed for 1 week. After cooling the reaction mixture was diluted with H_2O and acidified (HCl). Extraction with $CHCl_3$, drying ($MgSO_4$) the organic phase, and stripping off the solvent in vacuo afforded a solid: 17.5 g (75%); mp 130 °C. Recrystallization from petroleum ether gave 14.5 g (62%) of **47**: mp 132 °C.

Methyl α-Butyl-2,6-dichlorobenzeneacetate (92). To CH_3OH (100 ml), saturated with HCl gas at 0 °C, **47** (14.5 g, 0.056 mol) was added. The mixture was refluxed with stirring overnight. After cooling, the reaction mixture was diluted with H_2O and extracted with *i*-Pr_2O. Drying ($MgSO_4$) the organic phase and evaporation in vacuo afforded 13 g (87%) of **92** (GC 97%).

β-Butyl-2,4-dichlorobenzeneethanol (130, Method E). A solution of **84** (36 g, 0.126 mol) in CH_3CN (75 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 (50 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 30 g (97%) of **130** was obtained (GC 88%).

β-Butyl-2,6-dichlorobenzeneethanol (138, Method F). A solution of **92** (13 g, 0.047 mol) in ether (50 ml) was added dropwise to ether (200 ml), containing $LiAlH_4$ (1.8 g, 0.047 mol), while cooling on ice. After stirring overnight, the reaction mixture was decomposed by addition of 50% NaOH (2 ml) and H_2O (2 ml). After filtration and evaporation of the solvent 10 g (87%) of **138**

was obtained (GC 95.6%).

1-(2-Butyl-2,4-dichlorophenylethyl)-1*H*-imidazole (176). To a solution of **130** (18 g, 0.073 mol) in pyridine (50 ml), methanesulfonyl chloride (9.7 g, 0.085 mol) was added dropwise over a period of 10 min, while cooling on ice. The reaction mixture was stirred for 3 h. Then H_2O was added and the mixture extracted with *i*-Pr_2O. The organic layer was washed with diluted HCl solution, dried ($MgSO_4$), and evaporated in vacuo. The oily residue (21.5 g, 0.066 mol) was refluxed overnight with a fivefold excess of imidazole (22 g, 0.33 mol) in DMF (200 ml). After cooling and dilution with H_2O, the mixture was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), stirred with SiO_2, filtered, and evaporated in vacuo. The oily residue was dissolved in *i*-Pr_2O, and after addition of a slight excess of HNO_3, 65% solution in water, the nitrate salt crystallized. The solid was filtered and recrystallized from a mixture of *i*-PrOH–*i*-Pr_2O yielding 11.7 g (49%) of **176**: mp 140 °C.

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References and Notes

(1) E. F. Godefroi, J. Heeres, J. Van Cutsem, and P. A. J. Janssen, *J. Med. Chem.*, 12, 784 (1969).
(2) K. H. Buchel, W. Draber, E. Regel, and M. Plempel, *Arzneim.-Forsch.*, 22, 1260 (1972).
(3) A. Rossi, L. H. Werner, W. L. Bencze, and G. de Stevens, U.S. Appl. Nov 4, 1963 (Ciba Ltd.); *Chem. Abstr.*, 65, P2272*d* (1965).
(4) E. F. Godefroi, J. Van Cutsem, C. A. M. van der Eycken, and P. A. J. Janssen, *J. Med. Chem.*, 10, 1160 (1967).
(5) J. Van Cutsem and D. Thienpont, *Chemotherapy*, 17, 392 (1972).

Stereochemical Studies on Medicinal Agents. 20.[1] Absolute Configuration and Analgetic Potency of α-Promedol[2] Enantiomers. The Role of the C-4 Chiral Center in Conferring Stereoselectivity in Axial- and Equatorial-Phenyl Prodine Congeners

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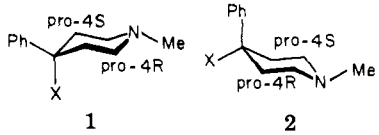
Optical antipodes of the axial phenyl analgetic, α-promedol hydrochloride (**3**), were prepared and the absolute stereochemistry was determined by relating one of the enantiomers to its γ diastereomer having the 2*S*,4*S*,5*R* configuration. The analgetic potency of (+)-(2*R*,4*S*,5*S*)-**3** is 20 times that of morphine, while its enantiomer, (–)-(2*S*,4*R*,5*R*)-**3**, is inactive at 50 mg/kg. These results are in accord with prior reports which indicate that substitution of a 3- or 5-alkyl group on the pro-4*S* enantiotopic edge of the piperidine ring leads to enantiomers which have greater potency than those substituted in an identical position on the pro-4*R* edge. This, coupled with the fact that the torsion angle between the axial phenyl group and piperidine ring in (+)-**3** is of the same sign as its equatorial congeners, suggests that the C(3)–C(4)–C(5) moiety and its substituents at C(4) are located in a similar chiral environment on the receptor. In contrast, the C(2)–N–C(6) portion of the axial and equatorial molecules does not bind in the same receptor environment, and it is suggested that different modes of interaction in the prodine series arise from different orientations of this moiety.

The concept that many enzymes can distinguish between the pro-*R* and pro-*S* enantiotopic edges of substrates containing an sp^3 prochiral center has been recognized for nearly 30 years.[3,4] Although this phenomenon, which is usually referred to as the "Ogston effect" after its original proponent,[5] has considerable precedent in enzymatic reactions, until recently[6] it had not been discussed in connection with nonenzymatic interaction between drugs and receptors.

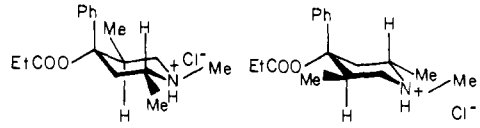
Over the past several years we have investigated[1,6-11] this phenomenon with 4-phenylpiperidine analgetics because meperidine (**1a**) and its reversed esters (**1b**) possess enantiotopic edges (pro-4*R* and pro-4*S*) and are known to interact with receptors that have a high degree of antipodal stereoselectivity.[12] These studies have demonstrated that analgetic receptors are capable of distinguishing between the enantiotopic edges of the piperidine ring, and it has been pointed out that the sign of the torsion angle between the phenyl group and piperidine ring is also correlated with analgetic potency.



1 **2**

X = OCOEt or COOEt

All of these investigations[6-11] have dealt with 4-phenylpiperidines in which the phenyl group is situated in an equatorial preferred conformation. However, there is no report pertaining to the role of the Ogston effect among members of this series containing an axially oriented aromatic group (**2**). Such studies not only should provide information on the stereostructure–activity relationship between equatorial and axial 4-phenylpiperidines but, in addition, might establish whether or not there is a correlation between members of the above series and structures related to morphine. In this report we describe the preparation, absolute configuration, and biological evaluation of enantiomers of α-promedol (**3**),[2,13-15] a highly potent analgetic whose phenyl group resides preferentially in the axial conformation.[12,16-18]



2*R*,4*S*,5*S* (+)-**3** 2*S*,4*R*,5*R* (–)-**3**

Chemistry. Synthesis of a diastereomeric mixture of promedol alcohols was accomplished by the method described previously.[10] The α isomer, (±)-**4**, constitutes ~5% of the mixture and was isolated by preparative GLC