Notes

Antimycotic Imidazoles. 5.[1] Synthesis and Antimycotic Properties of 1-[[2-Aryl-4-(arylalkyl)-1,3-dioxolan-2-yl]methyl]-1*H*-imidazoles

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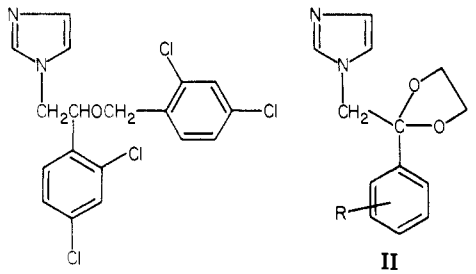
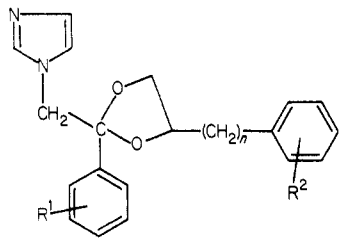
The synthesis of 1-[[2-aryl-4-(arylalkyl)-1,3-dioxolan-2-yl]methyl]-1*H*-imidazoles is described starting with phenylacetyl bromides or 1-(phenylacetyl)imidazoles. The compounds were generally obtained as cis/trans mixtures and found to be active in vitro against dermatophytes, yeasts, other fungi, and Gram-positive bacteria. Some also showed good activity against *Candida albicans* in vivo.

In 1969 the synthesis and antifungal spectrum of miconazole (I) were described.[2] This drug is now widely used



I

II

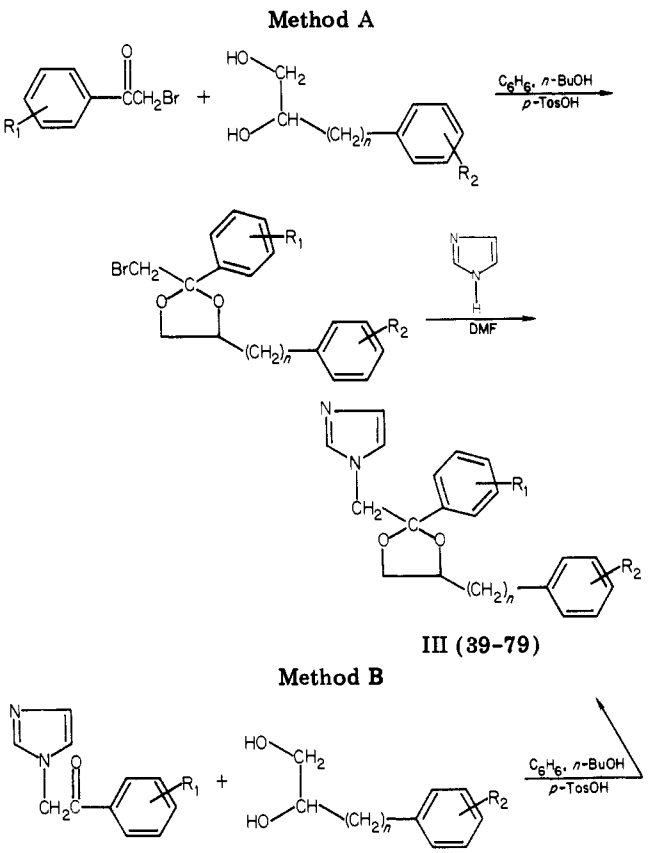


III

in topical and systemic treatment of fungal disease. In the same paper, mention was made of the cyclic ketals (II) of 1-(phenylacetyl)imidazoles, which showed only in vitro activity against dermatophytes. The present paper deals with the synthesis and antifungal properties of ketals of type III, which combine structural elements of both I and II. It was supposed that these compounds should have a better oral activity, as compared with the poorly resorbed miconazole, without loss of broad-spectrum in vitro activity.

Chemistry. The synthesis is outlined in Scheme I. The ω-(arylalkyl)-1,2-diols were prepared according to methods described in the literature.[3-15] Initial attempts to ketalize

Scheme I



phenylacetyl bromides with aryl-1,2-ethanediols, in the presence of catalytic amounts of *p*-toluenesulfonic acid (*p*-TosOH) in benzene with azeotropic removal of water, were unsuccessful. Although disappointingly low con-

(1) For part 4, see Heeres, J., Backx, L. J. J., Mostmans, J. H., and Van Cutsem, J., *J. Med. Chem.*, **22**, 1003 (1979).
(2) Godefroi, E. F., Heeres, J. Van Cutsem, J., and Janssen, P. A. J., *J. Med. Chem.*, **12**, 781 (1969).
(3) Bergkvist, T., *K. Fysiogr. Saellsk. Lund, Foerh.*, 18(2), 18 (1948); *Chem. Abstr.*, **44**, 1447*b* (1950).
(4) Neilson, D. G., Zakir, U., and Scrimgeour, C. M., *J. Chem. Soc. C*, 898 (1971).
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(8) Heeres, J., *Ger. Offen.* 2602770; *Chem. Abstr.*, **86**, P29811*b* (1977).
(9) Read, R. R., Lathrob, H., and Chandler, H. L., *J. Am. Chem. Soc.*, **49**, 3116 (1927).
(10) Heeres, J., U.S. Patent 4101666; *Chem. Abstr.*, **90**, P87453 (1979).
(11) Beasley, J. M., Petrow, V., Stephenson, O., and Wild, A. M., *J. Pharm. Pharmacol.*, 11, 36 (1959).
(12) Heeres, J., U.S. Patent 4101666; *Chem. Abstr.*, **90**, P23056*v* (1979).
(13) Karl Thomae G.m.b.H., French Patent 1445013; *Chem. Abstr.*, **68**, 21920*u* (1968).
(14) Bysouth, P. T., and Wild, A. M., *Ger. Offen.* 2036402; *Chem. Abstr.*, **74**, 87590*s* (1971).
(15) Steinbauer, E., and Prey, V., *Monatsh. Chem.*, **93**, 303 (1962).

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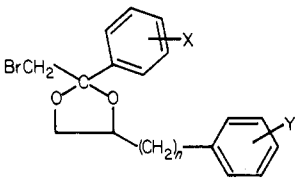
Table I



compd	X	Y	n	mp, °C	formula	crystn solv	yield,[a] %	GC[b]
1	H	4-Cl	0	63.9	$C_{16}H_{14}BrClO_2$		87	99.5
2	H	2,4-Cl_2	0		$C_{16}H_{13}BrCl_2O_2$		76 (calcd)	87.9
3	H	4-Br	0	71.3	$C_{16}H_{14}Br_2O_2$		68	98.5
4	2-Cl	4-Cl	0		$C_{16}H_{13}BrCl_2O_2$		73 (calcd)	75.3
5	2-Cl	2,4-Cl_2	0		$C_{16}H_{12}BrCl_3O_2$		72 (calcd)	83.6
6	2-Cl	4-Br	0		$C_{16}H_{13}Br_2ClO_2$		71 (calcd)	76.9
7	3-Cl	2,4-Cl_2	0		$C_{16}H_{12}BrCl_3O_2$		87 (calcd)	89.3
8	4-Cl	H	0	60	$C_{16}H_{14}BrClO_2$	MeOH	59	97.8
9	4-Cl	2-Cl	0		$C_{16}H_{13}BrCl_2O_2$		93 (calcd)	96
10	4-Cl	2,4-Cl_2	0	82.7	$C_{16}H_{12}BrCl_3O_2$	pet. ether	97	97.9
11	4-Cl	4-Br	0	80.5	$C_{16}H_{13}Br_2ClO_2$	MeOH	67	99.8
12	4-Cl	4-F	0		$C_{16}H_{13}BrClFO_2$		89 (calcd)	92.3
13	4-Cl	4-CH_3	0		$C_{17}H_{16}BrClO_2$		86 (calcd)	88
14	2,4-Cl_2	H	0		$C_{16}H_{13}BrCl_2O_2$		67 (calcd)	71
15	2,4-Cl_2	2-Cl	0		$C_{16}H_{12}BrCl_3O_2$		65 (calcd)	76.6
16	2,4-Cl_2	4-Cl	0		$C_{16}H_{12}BrCl_3O_2$		64 (calcd)	75.6
17	2,4-Cl_2	2,4-Cl_2	0		$C_{16}H_{11}BrCl_4O_2$		58 (calcd)	65.2
18	2,4-Cl_2	4-Br	0		$C_{16}H_{12}Br_2Cl_2O_2$		61 (calcd)	75.3
19	4-Br	H	0	70	$C_{16}H_{14}Br_2O_2$	MeOH	88	
20	4-Br	2-Cl	0		$C_{16}H_{13}Br_2ClO_2$		88 (calcd)	93.2
21	4-Br	4-Cl	0	101.3	$C_{16}H_{13}Br_2ClO_2$	pet. ether	90	
22	4-Br	2,4-Cl_2	0	99.9	$C_{16}H_{12}Br_2Cl_2O_2$	*i*-PrOH	86	97.2
23	4-Br	4-Br	0	96.8	$C_{16}H_{13}Br_3O_2$		86	98.3
24	4-Br	4-F	0		$C_{16}H_{13}Br_2FO_2$		84 (calcd)	87.5
25	4-Br	4-CH_3	0		$C_{17}H_{16}Br_2O_2$		88 (calcd)	89.5
26	4-CH_3	2-Cl	0		$C_{17}H_{16}BrClO_2$		78	99.5
27	4-CH_3	4-Cl	0	122	$C_{17}H_{16}BrClO_2$	MeOH	65	99.2
28	4-CH_3	2,4-Cl_2	0	89.5	$C_{17}H_{15}BrCl_2O_2$	MeOH	89	98.7
29	4-CH_3	4-Br	0	118.6	$C_{17}H_{16}Br_2O_2$	MeOH	54	98.8
30	4-CH_3O	4-Cl	0	115.6	$C_{17}H_{16}BrClO_3$	*n*-BuOH	44	99.4
31	2,4-Cl_2	H	1		$C_{17}H_{15}BrCl_2O_2$		73 (calcd)	73
32	2,4-Cl_2	4-CH_3	1		$C_{19}H_{19}BrCl_2O_2$		61 (calcd)	76.6
33	2,4-Cl_2	4-Cl	1		$C_{17}H_{14}BrCl_3O_2$		89 (calcd)	89.5
34	2,4-Cl_2	4-CH_3O	1		$C_{18}H_{17}BrCl_2O_3$		75 (calcd)	74.6
35	2,4-Cl_2	H	2		$C_{18}H_{17}BrCl_2O_2$		68 (calcd)	70
36	2,4-Cl_2	4-Cl	2		$C_{18}H_{16}BrCl_3O_2$		77 (calcd)	76.2
37	2,4-Cl_2	2,4-Cl_2	2		$C_{18}H_{15}BrCl_4O_2$		72 (calcd)	85
38	2,4-Cl_2	4-CH_3O	2		$C_{19}H_{19}BrCl_2O_3$		77 (calcd)	89

[a] Calculated yields are based on GC. [b] Gas chromatographic purity; sum of cis and trans isomers.

version to the desired ketal was seen (GLC analysis), the aryl-1,2-ethanediols disappeared very quickly, indicating a low stability in these reaction conditions. Without *p*-TosOH, no decomposition was observed. On the contrary, with arylalkyldiols moderate to good yields could be obtained. Modification of the ketalization procedure for phenylacetyl bromide with phenyl-1,2-ethanediol[16] as already described for 2,4-dichloroacetophenone with glycerol[1] in benzene/butanol finally gave high yields of the bromo ketals (Table I) as cis/trans mixtures. Bromo ketals derived from meta- and para-substituted phenylacetyl bromides were easily obtained. Preparation of ortho-substituted analogues required larger amounts of *p*-TosOH and larger reaction times, while yields were relatively lower. The bromo ketals, eventually purified by chromatography on silica gel, were coupled with a fivefold excess of imidazole in DMF at reflux. The title compounds (Table II), mostly cis/trans mixtures, were usually isolated as nitrate or ethanedioate salts (method A). Direct ketalization of the corresponding 1-(phenylacetyl)imidazoles with arylalkyl glycoles under the same reaction conditions (method B) constitutes an alternative preparation.

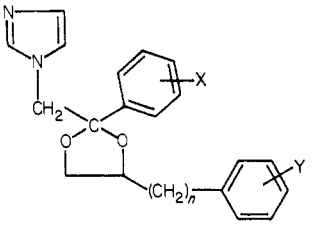
(16) Anteunis, M., and Becu, C., *Synthesis*, 23 (1974).

Biological Methods. The title compounds were tested against a large number of microorganisms. Preliminary in vitro experiments were conducted according to the method of Godefroi et al.[17] with the fungi *Microsporum canis* (*M.c.*), *Trychophyton 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.*), *Phialophora verrucosa* (*Ph.v.*), and with the Gram-positive bacteria *Erysipelothrix insidiosa*, *Staphyloccus hemolyticus*, and *Streptococcus pyogenes*.

In vivo, the compounds were tested in experimental vaginal candidosis of rats and in cutaneous candidosis of guinea pigs, following the methods described by Heeres[1] and Van Cutsem,[18] respectively. For oral treatment, the compounds were suspended in polyethylene glycol 200 and administered at 10 mg/kg daily dose levels for 14 consecutive days.

(17) Godefroi, E. F., Van Cutsem, J., Van der Eycken, C. A. M., and Janssen, P. A. J., *J. Med. Chem.*, **10**, 1160 (1967).
(18) Van Cutsem, J., and Thienpont, D., *Chemotherapy* **17**, 392 (1972).

Table II



compd	X	Y	n	mp, °C	formula	crystn solv	M_r	yield, %	anal.[a]
39	H	4-Cl	0	134.7	$C_{19}H_{17}ClN_2O_2 \cdot HNO_3$	MIK[b]/*i*-Pr_2O	403.8	70	C, H, N
40	H	2,4-Cl_2	0	163.8	$C_{19}H_{16}Cl_2N_2O_2 \cdot HNO_3$	MIK	438.3	40	C, H, N
41	H	4-Br	0	131.1	$C_{19}H_{17}BrN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	448.3	67	C, H, N
42	2-Cl	4-Cl	0	183.1	$C_{19}H_{16}Cl_2N_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	438.3	33	C, H, N
43	2-Cl	2,4-Cl_2	0	164.2	$C_{19}H_{15}Cl_3N_2O_2 \cdot HNO_3$	MIK/*i*-Pr_2O	472.7	55	C, H, N
44	2-Cl	4-Br	0	184.1	$C_{19}H_{16}BrClN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	482.7	18	C, H, N
45	3-Cl	2,4-Cl_2	0	165.4	$C_{19}H_{15}Cl_3N_2O_2 \cdot HNO_3$	*i*-PrOH/*i*-Pr_2O	472.7	32	C, H, N
46	4-Cl	H	0	153.2	$C_{19}H_{17}ClN_2O_2 \cdot HNO_3$	MIK	403.8	36	C, H, N
47	4-Cl	2-Cl	0	183.8	$C_{19}H_{16}Cl_2N_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	438.3	44	C, H, N
48	4-Cl	2,4-Cl_2	0	196.6	$C_{19}H_{15}Cl_3N_2O_2 \cdot HNO_3$	MeOH/*i*-Pr_2O	472.7	88	C, H, N
49	4-Cl	4-Br	0	145.2	$C_{19}H_{16}BrClN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	482.7	56	N, Cl + Br
50	4-Cl	4-F	0	163.2	$C_{19}H_{16}ClFN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	421.7	42	C, H, N
51	4-Cl	4-CH_3	0	144.3	$C_{20}H_{19}ClN_2O_2 \cdot HNO_3$	*i*-PrOH/*i*-Pr_2O	417.9	73	N, Cl
52	2,4-Cl_2	H	0	107.7	$C_{19}H_{16}Cl_2N_2O_2 \cdot 2C_2H_2O_4$	EtOAc	555.3	36	C, H, N
53	2,4-Cl_2	2-Cl	0	151.0	$C_{19}H_{15}Cl_3N_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	472.7	17	C, H, N
54	2,4-Cl_2	4-Cl	0	119.9	$C_{19}H_{15}Cl_3N_2O_2 \cdot C_2H_2O_4$	MIK	544.8	15	C, H, N
55	2,4-Cl_2	2,4-Cl_2	0	161.2	$C_{19}H_{14}Cl_4N_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	507.2	21	C, H, N
56	2,4-Cl_2	4-Br	0	141.9	$C_{19}H_{15}BrCl_2N_2O_2 \cdot HNO_3$	*i*-PrOH/*i*-Pr_2O	517.2	26	C, H, N
57	4-Br	H	0	156.5	$C_{19}H_{17}BrN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	448.3	65	C, H, N
58	4-Br	2-Cl	0	194.7	$C_{19}H_{16}BrClN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	482.7	53	N, Cl + Br
59	4-Br	4-Cl	0	152.6	$C_{19}H_{16}BrClN_2O_2 \cdot HNO_3$	MIK	482.7	55	C, H, N
60	4-Br	2,4-Cl_2	0	203.4	$C_{19}H_{15}BrCl_2N_2O_2 \cdot HNO_3$	MeOH/*i*-Pr_2O	517.7	48	C, H, N
61	4-Br	4-Br	0	144.3	$C_{19}H_{16}Br_2N_2O_2 \cdot HNO_3$	MeOH/*i*-Pr_2O	527.2	51	C, H, N
62	4-Br	4-F	0	179.3	$C_{19}H_{16}BrFN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	466.3	53	C, H, N
63	4-Br	4-CH_3	0	140.2	$C_{20}H_{19}BrN_2O_2 \cdot HNO_3$	*i*-PrOH/*i*-Pr_2O	462.3	35	Br, N
64	4-CH_3	2-Cl	0	207.5	$C_{20}H_{19}ClN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	417.9	45	C, H, N
65	4-CH_3	4-Cl	0	200.8	$C_{20}H_{19}ClN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	417.9	32	C, H, N
66	4-CH_3	2,4-Cl_2	0	193.6	$C_{20}H_{18}Cl_2N_2O_2 \cdot HNO_3$	MeOH/*i*-Pr_2O	452.3	42	C, H, N
67	4-CH_3	4-Br	0	210.5	$C_{20}H_{19}BrN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	462.3	38	C, H, N
68	4-CH_3O	4-Cl	0	196.3	$C_{20}H_{19}ClN_2O_2 \cdot HNO_3$	EtOH/*i*-Pr_2O	433.9	23	C, H, N
69	2,4-Cl_2	H	1	117.1	$C_{20}H_{18}Cl_2N_2O_2 \cdot 2C_2H_2O_4$	CH_3CN/*i*-Pr_2O	569.4	60	C, H, N
70	2,4-Cl_2	4-CH_3	1	123.1	$C_{21}H_{20}Cl_2N_2O_2 \cdot 1.5C_2H_2O_4$	MIK	538.4	32	N
71	2,4-Cl_2	4-F	1	153.1	$C_{20}H_{17}Cl_2FN_2O_2 \cdot 1.5C_2H_2O_4$	MIK	542.3	40	C, H, N
72	2,4-Cl_2	4-Cl	1	141.6	$C_{20}H_{17}Cl_3N_2O_2 \cdot 1.5C_2H_2O_4$	CH_3CN/*i*-Pr_2O	558.8	36	C, H, N
73	2,4-Cl_2	4-Br	1	128.8	$C_{20}H_{17}BrCl_2N_2O_2 \cdot 2C_2H_2O_4$	CH_3CN	648.3	36	C, H, N
74	2,4-Cl_2	4-CH_3O	1	94.2	$C_{21}H_{20}Cl_2N_2O_3 \cdot 2C_2H_2O_4$	MIK	599.4	34	N, Cl
75	2,4-Cl_2	4-Ph	1	116.8	$C_{26}H_{22}Cl_2N_2O_2 \cdot C_2H_2O_4$	MIK	645.4	39	N, Cl
76	2,4-Cl_2	H	2	117.8	$C_{21}H_{20}Cl_2N_2O_2 \cdot 1.5C_2H_2O_4$	MIK	538.4	50	N, Cl
77	2,4-Cl_2	4-Cl	2	131.9	$C_{21}H_{19}Cl_3N_2O_2 \cdot 2C_2H_2O_4$	MIK	617.8	27	C, H, N
78	2,4-Cl_2	4-CH_3O	2	130.7	$C_{22}H_{22}Cl_2N_2O_3 \cdot 1.5C_2H_2O_4$	EtOH/*i*-Pr_2O	568.4	18	C, H, N
79	2,4-Cl_2	4-Ph	2	143.9	$C_{27}H_{24}Cl_2N_2O_2 \cdot 0.5H_2O \cdot 1.5C_2H_2O_4$	CH_3CN/*i*-Pr_2O	623.5	32	C, H, N

[a] Unless otherwise stated, the analyses were within ±0.4% of the theoretical values. [b] MIK = $CH_3C(=O)CH_2CH(CH_3)_2$.

Results and Discussion

The test results, summarized in Table III, represent the lowest dose levels for total inhibition of fungal and bacterial growth. For most compounds a high in vitro activity against dermatophytes (1 μg/mL) was found, comparable to miconazole. In addition, compounds **47**, **63**, **70**, **72**, **73**, and **77** were also active against yeasts, other fungi, and Gram-positive bacteria; however, no activity was found against Gram-negative bacteria. In vitro and in vivo activity was poorly correlated. For example, in the vaginal candidosis model, **49** and **55** are the best compounds; however, **55** is devoid of any in vitro activity at 100 μg/mL against *C. albicans*. The same conclusion can be drawn for the cutaneous candidosis in guinea pig: although compounds **47**, **50**, **55**, **69**, and **72** are more potent than miconazole in this model, only **72** is active at 10 μg/mL against *C. albicans*. Lengthening of the alkyl chain (n = 0–2) has only minor effects on in vitro activity (**52**, **69**, **76** and **54**, **72**, **77**).

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 IR spectrometry (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).

Method A. 2-(Bromomethyl)-4-(2-chlorophenyl)-2-(4-chlorophenyl)-1,3-dioxolane (9). A solution of (4-chlorophenyl)acetyl bromide (23.4 g, 0.1 mol) and (2-chlorophenyl)-1,2-ethanediol (20.8 g, 0.12 mol) in benzene (400 mL) and 1-butanol (200 mL) was refluxed in the presence of *p*-TosOH·H_2O (1 g) with azeotropic removal of water. After completion, the solvents were evaporated in vacuo, leaving an oily residue, which was purified by chromatography over SiO_2 (eluent $CHCl_3$) to give 37.6 g (93%) of **9** (GC 96%).

Table III. Antifungal and Antibacterial Activities

	in vitro: lowest level of total inhibn[a,b]														in vivo[c,d]	
compd	*M.c.*	*T.m.*	*T.r.*	*Ph.v.*	*Cr.n.*	*C.tr.*	*C.a.*	*Muc.*	*A.f.*	*Sp.s.*	*Sapr.*	*E.ins.*	*Staph.*	*Strep.*	rat[e]	guinea pig[f]
39	<1	<1	<1	100	10	100	>100	100	10	10	100	1	100	1	0/2	1/2
40	10	<1	<1	100	10	>100	>100	100	10	10	100	10	10	1	0/2	0/2
41	<1	<1	<1	100	10	>100	100	100	10	10	100	1	>100	<1	0/2	0/2
42	<1	<1	<1	100	100	100	100	100	<1	10	10	<1	100	<1		
43	<1	<1	<1	100	<1	>100	>100	>100	<1	<1	10	1	10	<1	0/2	
44	<1	<1	<1	10	<1	10	100	10	<1	10	10	10	10	10		
45	100	10	<1	>100	100	100	100	100	100	10	100	10	100	<1	0/2	0/2
46	10	<1	<1	100	10	>100	100	100	10	10	100	1	10	<1		
47	10	<1	<1	100	10	>100	>100	100	100	>1	10	1	10	1	1/2	2/2
48	10	<1	<1	100	10	>100	100	100	100	10	100	1	10	<1	0/2	
49	<1	<1	<1	100	<1	10	10	10	<1	10	<1	<1	10	<1	2/2	0/2
50	<1	<1	<1	100	10	100	100	10	<1	10	100	100	>100	10	0/2	2/2
51	<1	<1	<1	100	<1	>100	100	100	<1	10	100	<1	100	<1	0/2	
52	<1	<1	<1	100	100	>100	100	100	<1	10	100	10	>100	10	0/2	
53	10	<1	<1	100	<1	100	100	100	100	10	100	<1	1	<1		
54	<1	<1	<1	100	<1	10	100	10	<1	10	100	1	10	1		1/2
55	10	<1	<1	100	<1	>100	>100	10	<1	10	100	<1	10	<1	2/2	
56	<1	<1	<1	100	<1	10	100	10	<1	10	100	1	10	1	0/2	3/4
57	<1	<1	<1	100	10	>100	100	100	100	100	100	10	100	<1	0/2	0/2
58	<1	<1	<1	100	<1	>100	100	10	100	10	100	<1	100	10	0/2	0/2
59	<1	<1	<1	100	100	100	>100	>100	10	10	100	1	100	1	0/2	0/2
60	10	10	<1	>100	>100	>100	>100	100	>100	100	>100	1	100	1		0/2
61	<1	<1	<1	100	<1	100	>100	10	<1	10	100	<1	10	<1	0/2	0/2
62	<1	<1	<1	100	10	100	100	<1	<1	10	100	10	100	<1	2/4	1/2
63	<1	10	<1	100	10	>100	10	10	<1	100	100	1	10	10	1/2	
64	10	<1	<1	100	100	>100	100	100	100	10	100	1	100	<1	1/2	0/2
65	<1	<1	<1	100	<1	100	>100	10	<1	10	100	<1	10	<1	0/2	0/2
66	10	<1	<1	100	10	>100	>100	100	100	10	100	<1	1	<1	0/2	0/2
67	<1	<1	<1	>100	>100	>100	>100	>100	<1	>100	10	<1	10	<1	0/2	0/2
68	<1	<1	10	100	>100	>100	>100	100	<1	10	100	10	100	10		0/2
69	<1	<1	<1	100	<1	10	100	10	<1	10	10	<1	10	10	0/2	2/2
70	<1	<1	<1	100	<1	>100	10	10	10	10	10	<1	<1	<1	0/2	
71	<1	<1	<1	100	10	100	100	<1	10	10	10	<1	10	10	0/2	
72	<1	<1	<1	100	1	10	10	10	10	10	100	<1	10	100	0/2	2/2
73	<1	<1	<1	100	<1	>100	10	<1	10	10	100	<1	10	<1	0/2	
74	<1	<1	<1	10	<1	100	>100	<1	<1	10	10	<1	100	<1	0/2	0/2
75	10	<1	<1	>100	100	>100	>100	>100	10	100	100	1	10	1	0/2	
76	<1	<1	<1	100	<1	10	100	10	<1	<1	100	<1	10	<1	0/2	
77	1	<1	1	100	<1	10	10	10	10	1	100	<1	10	<1	2/4	0/2
78	1	<1	<1	100	1	10	100	100	<1	10	100	<1	100	<1	2/4	0/2
79	<1	<1	<1	>100	10	>100	>100	>100	10	10	10	<1	100	<1	0/2	
mico-nazole	1	<1	<1	100	1	100	10	>100	10	1	10	<1	10	<1	0/6	4/13

[a] Figures proceeded by a greater than sign denote limited growth at 100 μg/mL. [b] Figures proceeded by a less than sign represent the lowest dose levels tested (μg/mL). [c] Dose = 10 mg/kg. [d] Ratio of animals cured/animals infected. [e] Vaginal candidosis by *C. albicans*. [f] Cutaneous candidosis by *C. albicans*.

1-[[4-(2-Chlorophenyl)-2-(4-chlorophenyl)-1,3-dioxolan-2-yl]methyl]-1*H*-imidazole Nitrate (47). A solution of 9 (37.6 g, 0.093 mol) in dry DMF (500 mL) was refluxed with imidazole (33.5 g, 0.5 mol) for 3 days. After cooling, the reaction mixture was diluted with water and extracted with ether. The organic layer was dried ($MgSO_4$), and the nitrate salt formed by the addition of a small excess of 65% HNO_3. The precipitated salt was filtered and recrystallized from EtOH/*i*-Pr_2O to yield 17.9 g (44%) of **47**, mp 183.3 °C.

Method B. *cis*- and *trans*-1-[[4-[(4-Bromophenyl)methyl]-2-(2,4-dichlorophenyl)-1,3-dioxolan-2-yl]methyl]-1*H*-imidazole Ethanedioate (73). A solution of 3-(4-bromophenyl)-1,2-propanediol (27.5 g, 0.12 mol), the *p*-toluenesulfonate of 1-[(2,4-dichlorophenyl)acetyl]imidazole (42.7 g, 0.1 mol), and *p*-TosOH·H_2O (3 g) in benzene (400 mL) and 1-butanol (200 mL) was refluxed with azeotropic removal of water. After completion, the solvent was evaporated in vacuo. The residue was dissolved in CH_2Cl_2 (300 mL), washed with 6 N NaOH solution, dried ($MgSO_4$), and filtered. After evaporation of the solvent, the residue was purified by column chromatography on SiO_2 (eluent $CHCl_3$/MeOH, 99:1). The resulting oily product was dissolved in CH_3CN/*i*-Pr_2O and a slight excess of oxalic acid was added. The formed precipitate was collected and recrystallized from CH_3CN to give 23.3 g (36%) of **73**, mp 128.8 °C.

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β-Adrenergic Blocking Agents. 21. *threo*-1-(Aryloxy)-3-(alkylamino)butan-2-ols

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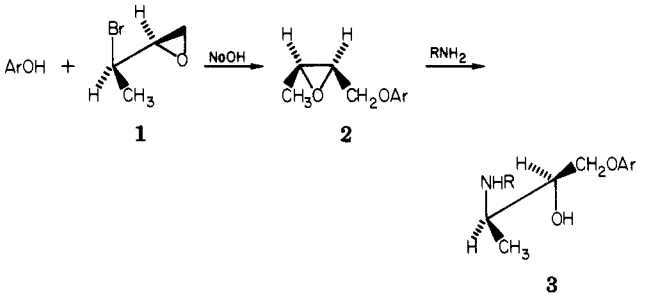
The synthesis and structure–activity relationships of a series of *threo*-1-(aryloxy)-3-(alkylamino)butan-2-ols are discussed. These compounds are less potent β-adrenoreceptor antagonists than the corresponding 1-(aryloxy)-3-(alkylamino)propan-2-ols. The data presented indicate that, unlike the arylethanolamine series, substitution of an alkyl group on the carbon atom α to the amino function on the oxypropanolamine side chain does not necessarily lead to enhanced vascular (β_2) selectivity.

Two structural features which are essential for a β-adrenergic receptor antagonist are an aromatic ring and an ethanolamine side chain. Crowther and Smith[1] showed that the introduction of an oxymethylene group between the aromatic ring and the ethanolamine side chain gave rise to even more potent β-adrenoreceptor antagonists. The effects on biological activity of introducing alkyl groups on the carbon atom α to the amino group in the ethanolamine series have been well documented.[2,3] However, with the exception of work by Howe[4] on propranolol analogues (mixtures of threo and erythro isomers) and a recent publication by Shtacher and co-workers,[5] little has been reported on the biological consequences of similar alkyl group substitutions in the (aryloxy)propanolamine series. The published biological work has been mainly devoted to studies on the threo α-methyl analogues of propranolol and practolol.[6,7] We report herein the synthesis of a series of *threo*-(aryloxy)butanolamines and discuss their structure–activity relationships.

Chemistry. The introduction of a methyl group α to the nitrogen atom on the side chain of an (aryloxy)-propanolamine gives rise to erythro and threo forms of the compound. We have developed a synthetic route which affords the erythro and threo isomers of the (aryloxy)butanolamines in a stereospecific manner.[8] The threo isomers are most conveniently prepared by the base-promoted reaction of the *threo*-oxirane **1** with the corresponding phenol (Scheme I). In practice, the *cis*-1-(aryloxy)-2,3-epoxybutanes formed were not purified but were characterized by NMR and reacted directly with the corresponding amine. A representative preparation is included under Experimental Section.

Pharmacology. β-Adrenoreceptor blocking potency was estimated in vivo using the previously described cat

Scheme I



preparation.[9] The results listed in Tables I–III are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg iv). The degree (percent) of blockade of the vasodepressor response at that dose level is also given. The relative potencies of these two systems give some indication of selectivity for

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