Methyl N-Acetyl-7(*S*)-chloro-7-deoxylincosaminide (7).—Acylation of 1 g of methyl 7(*S*)-chloro-7-deoxylincosaminide (**4**) with Ac_2O in MeOH gave after recrystallization from EtOAc–Skellysolve B[18] 930 mg of **7**, mp 174–176°. The rotation was +290° (MeOH). *Anal.* ($C_{21}H_{39}ClO_5NS$) C, H, Cl, N.

Solvolysis of Methyl N-Acetyl-7(*S*)-chloro-7-deoxythiolincosaminide (7).—A solution of 2.0 g of **7** in 80 ml of H_2O was heated at reflux for 5.5 hr. Tlc ($CHCl_3$–MeOH, 4:1) showed the gradual disappearance of **7**, with two slower spots gradually increasing in concentration. The solution was lyophilized. The residue was chromatographed over silica gel using $CHCl_3$–MeOH (4:1) for elution. A fraction of 110 mg, identified by tlc as **7**, was eluted in the early fractions. This was followed by a 155-mg and a 1.06-g fraction, respectively. Crystallization of the major fraction from MeOH gave 470 mg of crude **8**, mp 222–226°. Recrystallization afforded 360 mg of crystals, mp 255–258°, whose infrared spectrum was identical with a known sample of **8**.[4] In another experiment, a fraction similar to the 155-mg fraction from above gave a product, mp 178–182°, whose infrared spectrum was very similar to that of **8** suggesting the 7(*S*) isomer.

Attempted Solvolysis of Methyl N-Trifluoroacetyl-7(*S*)-chloro-7-deoxythiolincosaminide (6).—A solution of 500 mg of **6** in 30 ml of H_2O was heated under reflux for 18 hr. Tlc ($CHCl_3$–MeOH, 6:1) indicated chiefly unreacted **6**, and also a small amount of a slower moving spot, but no 7-hydroxy compound **5**. When worked up as above 220 mg of recovered **6** and 55 mg of a more polar oil which resisted crystallization were obtained. Crystallization from *i*-PrOH afforded 110 mg of **6**, mp 72–81°. Ir data confirmed the identity of **6**.

1′-Carbobenzoxy-1′-demethylclindamycin (*cis-trans*) (10, R = *n*-C_3H_7).—1-Carbobenzoxy-4-(*cis* and *trans*)-*n*-propyl-L-proline[6] (2.33 g) was dissolved in 150 ml of MeCN containing 1.12 ml of Et_3N. The solution was cooled to 0° and 1.18 ml of isobutyl chloroformate added. After 10 min at 0°, a solution of 2.17 g of **4** in 40 ml of MeCN and 40 ml of H_2O was added. The mixture was stirred for 2 hr at ambient temperature and the MeCN distilled *in vacuo* to yield crystals which were collected by filtration. The yield of **10**, mp 180–183°, was 3.56 g. Recrystallization (EtOH) raised the melting point to 189–192°. *Anal.* ($C_{25}H_{37}ClN_2O_7S$) C, H, Cl, N.

1-Carbobenzoxy-1′-demethylclindamycin (14).—1′-Demethyllincomycin hydrochloride (428 mg) was treated with carbobenzyloxy chloride[19] to yield 500 mg of **14**, mp 152–165°. Recrystallization (EtOAc–H_2O) gave 350 mg of **14**, mp 173–177°. Two recrystallizations from the same solvent afforded crystals, mp 176–178°, $[\alpha]D$ +109°. *Anal.* ($C_{33}H_{48}N_2O_9S$) C, H, N.

1′-Demethylclindamycin (*cis* and *trans*) Hydrochloride (11b).—A solution of 22.9 g of **10** was dissolved in 500 ml of MeOH and 6 g of 10% Pd–C was added. Hydrogenolysis and crystallization was as previously described.[2] The yield of **11b**, mp 218–223° dec, was 15.8 g (80.2%). Recrystallization (ArMe–H_2O) afforded 10.7 g of **11b**, mp 228–254° dec, $[\alpha]D$ +159° (H_2O). Further dilution with AcMe gave 2.95 g of second crop crystals, mp 226–230° dec.

1′-Demethyl-4′-depropyl-4′-pentylclindamycin (11e).—Triphenylphosphine (22 g) in 400 ml of MeCN was treated with 5.68 g of Cl_2 to produce a colorless solution of $(C_6H_5)_3PCl_2$. To this solution 4 g of 1′-demethyl-4′-depropyl-4′-pentyllincomycin hydrochloride (**12**)[6] was added. After stirring at 26° for 18 hr, 15 ml of MeOH was added and the solvent distilled *in vacuo*. The residue was shaken with 250 ml of EtOAc–Et_2O (1:1) and filtered. The residue (13.7 g) was partitioned between H_2O and EtOAc and the product was recovered from the aqueous solution by lyophilizing. This residue of 8.5 g was further purified by chromatography over silica gel using $CHCl_3$–MeOH (4:1) for elution. The major fraction of 2.09 g was dissolved in ArMe and acidified with HCl to give analytically pure **11e**, mp 222–223°. *Anal.* ($C_{19}H_{36}Cl_2N_2O_5S$) C, H, N, S.

1′-Demethylclindamycin Hydrochloride (11c). Method A.—1′-Demethyllincomycin hydrochloride (**3**) (1.72 g) was chlorinated as above to give hydrochloride **11c**, mp 212–216°, weighing 0.75 g (40.8%). Recrystallization (ArMe–H_2O) gave 550 mg of hydrochloride, mp 217–221° dec, $[\alpha]D$ +155° (H_2O). *Anal.* ($C_{17}H_{32}Cl_2N_2O_5S$) C, H, N, S.

Method B.—One gram of **14** was chlorinated and subjected to hydrogenolysis; after chromatography it gave 103 mg of **11c**. This product was converted to its crystalline hydrochloride and identified on the basis of tlc data. It melted at 227–229° and weighed 95 mg.

Acknowledgment.—The authors are indebted to Dr. D. J. Mason and C. Lewis for antibacterial and antimalarial testing and to R. J. Reid for technical assistance.

(18) A saturated hydrocarbon fraction, bp 60–71°, Skelly Oil Co., Kansas City, Mo.

(19) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 2, John Wiley and Sons, Inc., N. Y., 1961, p 891.

The Preparation and Antimycotic Properties of Derivatives of 1-Phenethylimidazole

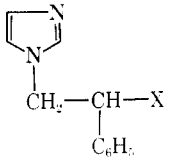
ERIK F. GODEFROI, JAN HEERES, JAN VAN CUTSEM, AND PAUL A. J. JANSSEN

Research Laboratoria, Janssen Pharmaceutica n.v., Beerse, Belgium

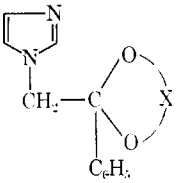
Received April 7, 1969

The synthesis of a large number of β-substituted 1-phenethylimidazoles is described. Many appropriately N-substituted 1-(β-aminophenethyl)imidazoles and cyclic ketals derived from 2-(1-imidazolyl)acetophenones were quite active against dermatophytes. However, 1-(β-benzyloxyphenethyl)imidazoles displayed potent, broad-spectrum activity, not only against dermatophytes but also against yeast cells (*Candida albicans*) and gram-positive bacteria.

For some years interest in our laboratories has been directed toward the synthesis and biological evaluation of imidazole derivatives.[1,2] As part of this program we prepared a series of 1-phenethylimidazoles, when it became apparent that certain O- and N-substituted derivatives of α-phenylimidazole-1-ethanol (A, X = OH) and 1-(β-aminophenethyl)imidazole (A, X = NH_2), respectively, displayed outstanding and broad-spectrum antimycotic activity. This observation



A, X = OH, NH_2



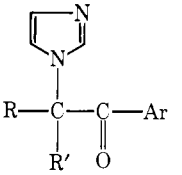
B, X = alkylene

(1) E. F. Godefroi, P. A. J. Janssen, C. A. M. Van der Eycken, A. H. M. T. Van Heertum, and C. J. E. Niemegeers, *J. Med. Chem.*, **8**, 220 (1965).

(2) E. F. Godefroi, J. van Cutsem, C. A. M. Van der Eycken, and P. A. J. Janssen, *ibid.*, **10**, 1160 (1967).

TABLE I

2-(1-IMIDAZOLYL)ACETOPHENONES



Compd	R	R′	Ar	Method	Yield, %	Mp, °C	Formula	Analyses
1	H	H	5-Chloro-2-thienyl	A	69	160–162	$C_9H_7ClN_2OS \cdot HNO_3$	C, H
2	H	H	2-Thienyl	B	23	136–138	$C_9H_8N_2OS \cdot HNO_3$	C, H, N
3	H	H	2,4-$Cl_2C_6H_3$	B	71	169–170	$C_{11}H_8Cl_2N_2O \cdot HNO_3$	C, H, N
4	H	H	*p*-BrC_6H_4	B	46	167–168	$C_{11}H_9BrN_2O$	C, H, N
5	H	H	*o*-ClC_6H_4	B	69	179–180	$C_{11}H_9ClN_2O \cdot HNO_3$	C, H
6	H	H	*p*-ClC_6H_4	A	77	160–161	$C_{11}H_9ClN_2O$	
						228–229	$C_{11}H_9ClN_2O \cdot HCl$	C, H, N
7	H	H	*p*-FC_6H_4	B	58	154–156	$C_{11}H_9FN_2O$	C, H, N
8	H	H	C_6H_5	A	62	117–118	$C_{11}H_{10}N_2O$[a]	C, H, N
9	CH_3	H	C_6H_5	A	80	139–140	$C_{12}H_{12}N_2O \cdot HNO_3$	C, H
10	H	H	*o*-$CH_3C_6H_4$	B	57	167–168	$C_{12}H_{12}N_2O \cdot HNO_3$	C, H
11	H	H	*p*-$CH_3C_6H_4$	B	59	136–138	$C_{12}H_{12}N_2O$	C, H
12	H	H	*o*-$CH_3OC_6H_4$	B	49	220–221	$C_{12}H_{12}N_2O_2 \cdot HCl$	C, H, N
13	H	H	*p*-$CH_3OC_6H_4$	B	77	171–172	$C_{12}H_{12}N_2O_2 \cdot HNO_3$	C, H, N
14	CH_3	CH_3	C_6H_5	B	45	167–168	$C_{13}H_{14}N_2O \cdot HNO_3$	C, H, N

prompted an expansion of our synthetic efforts, encompassing a large number of derivatives of A in order to investigate the structure–activity relationships governing this class of compounds. Moreover, during the course of this work it was found that many cyclic ketals derived from 2-(1-imidazolyl)acetophenone, *i.e.*, type B, showed significant biological activity. In the present paper we wish to report the synthesis and antimycotic and antibacterial properties of compounds derived from and related to A and B.

Chemistry.—The 2-(1-imidazolyl)acetophenones (compounds **1–14**, Table I), required as starting materials, were prepared by the reaction of the aryl bromoalkyl ketones with excess imidazole in MeCN or DMF at room temperature (method A). The literature method[3] for preparing **8** in alcohol was tried but was unsatisfactory as it led primarily to quaternary salts. Our method was subsequently simplified by brominating the prerequisite acetophenone followed by treatment of the crude reaction mixture with a fivefold excess of imidazole (method B).

The reaction of α-bromopropiophenone with imidazole furnished **9** in 68% yield. Its authenticity was established by its identity to the methylation product of the anion of **8** [hexamethylphosphoramide (HMPA)/NaH]. Compound **14** was prepared by successive treatment of isobutyrophenone with Br_2 and imidazole.

α-Arylimidazole-1-ethanols, shown in Table II, were obtained by three methods. Compound A (X = OH) was produced conveniently and directly by the base-catalyzed reaction of imidazole and styrene oxide, but commercial inaccessibility of substituted aromatic epoxides made extension of this method unpractical. $NaBH_4$ reduction of the ketones gave the desired alcohols in excellent yields (method C). Previous experience[4] had shown that the imidazole anion was most advantageously alkylated in a dipolar aprotic solvent such as DMF. Therefore sodium imidazole was treated with α-bromomethyl-*p*-chlorobenzyl alcohol in DMF, giving **19** in 83% yield (method D). This method also allowed for the preparation of tertiary alcohols **22** and **24**, since the prerequisite chlorohydrins are accessible from the reaction of chloroacetone and Grignard reagents.[5]

When the oxime of **8** was hydrogenated in the presence of Raney Ni, compound A (X = NH_2) was obtained. Schemes involving catalytic reductions precluded preparation of halogenated derivatives, so that attention was focussed on treatment of the ketones with a variety of amines to yield the corresponding imines. Reduction of the latter by $NaBH_4$ gave amines **28–54** (see Table III). Performing the reduction at 5–25° was found to be essential, as even at these temperatures the reaction was at times accompanied by formation of dibenzylamines. Elevated temperatures promoted this side reaction.

The sodium salts of alcohols **15–27** reacted smoothly with benzyl chlorides in DMF, THF, or HMPA, most favorable results being obtained with the latter at 5–25°. The resultant ethers are listed in Table IV. Nitrophenyl ethers **56** and **57** were obtained by treatment of the appropriate alcohol anions with *p*-nitrofluorobenzene or 2,4-dinitrochlorobenzene. Chemical reduction (Fe–aqueous NH_4Cl) furnished amine **58**.

Initial efforts to ketalize **8** by conventional procedures were unsatisfactory, due to unacceptably low conversions. Attention was therefore turned to the direct alkylation of sodium imidazole with 2-bromomethyl-2-aryldioxolanes and the corresponding 1,3-dioxanes in DMF. Some of the dioxolanes had already been prepared by Patel and Oneto.[6]

Our own approach was prompted by work of Garbish,[7] and consisted of brominating acetophenones in the appropriate 1,2- or 1,3-diol. This gave **96–114** in fair to good yields. Oftentimes ketalization had to be

(3) German Patent 488,681 (1954); F. K. Beilstein, "Handbuch der Organischen Chemie," Vol. 23 (II), p 37.

(4) E. F. Godefroi, *J. Org. Chem.*, **33**, 860 (1968).

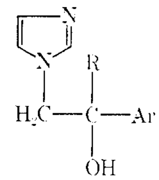
(5) M. S. Malinovskii and A. G. Yudasina, *Zh. Obshch. Khim.*, **30**, 1831 (1960); *Chem. Abstr.*, **55**, 7341 (1961).

(6) A. R. Patel and J. F. Oneto, *J. Pharm. Sci.*, **52**, 588 (1963).

(7) E. W. Garbish, Jr., *J. Org. Chem.*, **30**, 2109 (1965).

Table II

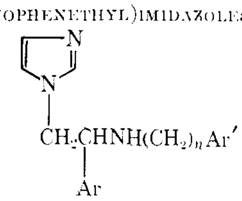
α-Arylimidazole-1-ethanols



Compd	R	Ar	Method	Yield, %	Mp, °C	Formula	Analyses
15	H	5-Chloro-2-thienyl	C	85	136–137	$C_9H_9ClN_2OS$	C, H, N
16	H	2,4-$Cl_2C_6H_3$	C	78	134–135	$C_{11}H_{10}Cl_2N_2O$	C, H, N
17	H	p-BrC_6H_4	C	87	191–192	$C_{11}H_{11}BrN_2O$	C, H, N
18	H	o-ClC_6H_4	C	84	99–100	$C_{11}H_{11}ClN_2O$	C, H
19	H	p-ClC_6H_4	C	99	183–184	$C_{11}H_{11}ClN_2O$	C, H, N
			D	83			
20	H	p-FC_6H_4	C	96	148–149	$C_{11}H_{11}FN_2O$	C, H, N
21	H	C_6H_5		39	149–150	$C_{11}H_{12}N_2O$	C, H, N
22	CH_3	p-ClC_6H_4	D	81	139–140	$C_{12}H_{13}ClN_2O$	C, H, N
23	H	o-$CH_3C_6H_4$	C	83	131–132	$C_{12}H_{14}N_2O\cdot HNO_3$	C, H, N
24	CH_3	C_6H_5	D	75	121–122	$C_{12}H_{14}N_2O$	C, H, N
25	H	p-$CH_3C_6H_4$	C	90	156–157	$C_{12}H_{14}N_2O$	C, H, N
26	H	o-$CH_3OC_6H_4$	C	89	173–174	$C_{12}H_{14}N_2O_2\cdot HCl$	C, H, N
27		Imidazol-1-yl-$C(CH_3)CH(OH)C_6H_5$	C	79	129–130	$C_{13}H_{16}N_2O$	C, H, N

Table III

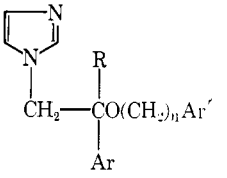
N-Substituted 1-(β-Aminophenethyl)imidazoles and Related Compounds



Compd	n	Ar	Ar′	Mp, °C	Formula	Analyses
28	1	2-Thienyl	p-ClC_6H_4	248–250	$C_{16}H_{16}ClN_3S\cdot 2HCl$	C, H, N
29	0	p-ClC_6H_4	C_6H_5	180–181	$C_{17}H_{16}ClN_3\cdot 2HCl$	C, H
30	0	C_6H_5	C_6H_5	176–178	$C_{17}H_{17}N_3\cdot 2HCl$	C, H, N
31	1	p-FC_6H_4	o-ClC_6H_4	211–212	$C_{18}H_{17}ClFN_3\cdot 2HNO_3$	C, H, N
32	1	p-FC_6H_4	p-ClC_6H_4	210–211	$C_{18}H_{17}ClFN_3\cdot 2HNO_3$	C, H
33	1	p-ClC_6H_4	o-ClC_6H_4	194–195	$C_{18}H_{17}Cl_2N_3\cdot 2HNO_3$	C, H, N
34	1	C_6H_5	p-ClC_6H_4	263–264	$C_{18}H_{18}ClN_3\cdot 2HCl$	C, H, N
35	1	C_6H_5	o-ClC_6H_4	254–256	$C_{18}H_{18}ClN_3\cdot 2HCl$	C, H, N
36	1	p-FC_6H_4	C_6H_5	218–219	$C_{18}H_{18}FN_3\cdot 2HNO_3$	C, H, N
37	1	C_6H_5	C_6H_5	253–255	$C_{18}H_{19}N_3\cdot 2HCl$	C, H
38	2	p-ClC_6H_4	C_6H_5	147–148	$C_{19}H_{20}ClN_3\cdot 2HNO_3$	C, H
39	1	p-ClC_6H_4	p-$CH_3C_6H_4$	270–274	$C_{19}H_{20}ClN_3\cdot 2HCl$	C, H
40	1	p-$CH_3C_6H_4$	p-ClC_6H_4	256–258	$C_{19}H_{20}ClN_3\cdot 2HCl$	C, H
41	1	p-ClC_6H_4	p-$CH_3OC_6H_4$	237–238	$C_{19}H_{20}ClN_3O\cdot 2HCl$	C, H, N
42	2	p-FC_6H_4	C_6H_5	153–154	$C_{19}H_{20}FN_3\cdot 2HNO_3$	C, H, N
43	1	p-FC_6H_4	p-$CH_3C_6H_4$	223–224	$C_{19}H_{20}FN_3\cdot 2HNO_3$	C, H
44	1	p-FC_6H_4	p-$CH_3OC_6H_4$	168–170	$C_{19}H_{20}FN_3O\cdot 2HNO_3$	C, H, N
45	1	C_6H_5	p-$CH_3C_6H_4$	261–263	$C_{19}H_{21}N_3\cdot 2HCl$	C, H, N
46	2	C_6H_5	C_6H_5	166–167	$C_{19}H_{21}N_3\cdot 2HNO_3$	C, H
47	1	C_6H_5	p-$CH_3OC_6H_4$	252–253	$C_{19}H_{21}N_3O\cdot 2HCl$	C, H
48	2	p-$CH_3C_6H_4$	C_6H_5	155–156	$C_{19}H_{23}N_3\cdot 2HNO_3$	C, H, N
49	1	p-$CH_3C_6H_4$	p-$CH_3OC_6H_4$	245–247	$C_{20}H_{23}N_3O\cdot 2HCl$	C, H, N
50	1-Im-CH—CHNHCH$_2$-p-ClC$_6$H$_4$ CH$_3$ C$_6$H$_5$			256–257	$C_{19}H_{20}ClN_3\cdot 2HCl$	C, H, N
51	1-Im-CH—CHNHCH$_2$C$_6$H$_5$ CH$_3$ C$_6$H$_5$			251–252	$C_{19}H_{21}N_3\cdot 2HCl$	C, H
52	1-Im-CH$_2$CHNHCHC$_6$H$_5$ C$_6$H$_5$ CH$_3$			165–169	$C_{19}H_{21}N_3\cdot 2HNO_3$	C, H, N
53	1-Im-CH$_2$CHNH-1-tetralyl p-ClC$_6$H$_4$			198–199	$C_{21}H_{22}ClN_3\cdot 2HCl\cdot 3H_2O$	C, H, N
54	1-Im-CH$_2$CHNH-1-tetralyl C$_6$H$_5$			139–140	$C_{21}H_{23}N_3\cdot 2HNO_3$	C, H, N

TABLE IV

ETHERS DERIVED FROM α-ARYLIMIDAZOLE-1-ETHANOLS



Compd	n	R	Ar	Ar′	Mp, °C	Formula	Analyses
55	1	H	5-Chloro-2-thienyl	*o*-ClC_6H_4	125–126	$C_{16}H_{14}Cl_2N_2OS \cdot HNO_3$	C, H
56	0	H	2,4-$Cl_2C_6H_3$	2,4-$(NO_2)_2C_6H_3$	167–168	$C_{17}H_{12}Cl_2N_4O_5 \cdot HNO_3$	C, H
57	0	H	2,4-$Cl_2C_6H_3$	*p*-$NO_2C_6H_4$	169–170	$C_{17}H_{13}Cl_2N_3O_3 \cdot HNO_3$	C, H
58	0	H	2,4-$Cl_2C_6H_3$	*p*-$NH_2C_6H_4$	95–96	$C_{17}H_{15}Cl_2N_3O$	C, H, N
59	1	H	2,4-$Cl_2C_6H_3$	2,4-$Cl_2C_6H_3$	184–185	$C_{18}H_{14}Cl_4N_2O \cdot HNO_3$	C, H, N
60	1	H	2,4-$Cl_2C_6H_3$	2,6-$Cl_2C_6H_3$	182–183	$C_{18}H_{14}Cl_4N_2O \cdot HNO_3$	C, H, N
61	1	H	*p*-FC_6H_4	2,4-$Cl_2C_6H_3$	120–121	$C_{18}H_{15}Cl_2FN_2O \cdot HNO_3$	C, H, N
62	1	H	2,4-$Cl_2C_6H_3$	*p*-FC_6H_4	139–140	$C_{18}H_{15}Cl_2FN_2O \cdot HNO_3$	C, H, N
63	1	H	2,4-$Cl_2C_6H_3$	*o*-FC_6H_4	147–148	$C_{18}H_{15}Cl_2FN_2O \cdot HNO_3$	C, H, N
64	1	H	2,4-$Cl_2C_6H_3$	*o*-ClC_6H_4	151–152	$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$	C, H, N
65	1	H	*p*-ClC_6H_4	2,6-$Cl_2C_6H_3$	144–145	$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$	C, H, N
66	1	H	2,4-$Cl_2C_6H_3$	*p*-ClC_6H_4	164–165	$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$	C, H, N
67	1	H	*p*-ClC_6H_4	2,4-$Cl_2C_6H_3$	119–120	$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$	C, H
68	1	H	*o*-ClC_6H_4	2,4-$Cl_2C_6H_3$	127–128	$C_{18}H_{15}Cl_3N_2O \cdot HNO_3$	C, H
69	1	H	*p*-BrC_6H_4	*o*-ClC_6H_4	124–125	$C_{18}H_{16}BrClN_2O \cdot HNO_3$	C, H, N
70	1	H	*p*-BrC_6H_4	*p*-ClC_6H_4	160–161	$C_{18}H_{16}BrClN_2O \cdot HNO_3$	C, H, N
71	1	H	*p*-FC_6H_4	*p*-ClC_6H_4	122–123	$C_{18}H_{16}ClFN_2O \cdot HNO_3$	C, H, N
72	1	H	*p*-FC_6H_4	*o*-ClC_6H_4	95–96	$C_{18}H_{16}ClFN_2O \cdot HNO_3$	C, H, N
73	1	H	*o*-ClC_6H_4	*o*-ClC_6	161–162	$C_{18}H_{16}Cl_2N_2O \cdot HNO_3$	C, H, N
74	1	H	*p*-ClC_6H_4	*o*-ClC_6H_3	125–126	$C_{18}H_{16}Cl_2N_2O \cdot HNO_3$	C, H, N
75	1	H	*o*-ClC_6H_4	*p*-ClC_6H_4	129–130	$C_{18}H_{16}Cl_2N_2O \cdot HNO_3$	C, H, N
76	1	H	*p*-ClC_6H_4	*p*-ClC_6H_4	154–155	$C_{18}H_{16}Cl_2N_2O \cdot HNO_3$	C, H, N
77	1	H	C_6H_5	*p*-ClC_6H_4	136–137	$C_{18}H_{17}ClN_2O \cdot HNO_3$	C, H, N
78	1	H	C_6H_5	C_6H_5	90–91	$C_{18}H_{18}N_2O \cdot HNO_3$	C, H, N
79	1	CH_3	*p*-ClC_6H_4	2,4-$Cl_2C_6H_3$	167–168	$C_{19}H_{17}Cl_3N_2O \cdot HNO_3$	C, H, N
80	1	H	*p*-$CH_3C_6H_4$	2,4-$Cl_2C_6H_3$	129–130	$C_{19}H_{18}Cl_2N_2O \cdot HNO_3$	C, H, N
81	1	H	*o*-$CH_3C_6H_4$	2,4-$Cl_2C_6H_3$	138–139	$C_{19}H_{18}Cl_2N_2O \cdot HNO_3$	C, H
82	1	CH_3	C_6H_5	2,4-$Cl_2C_6H_3$	187–188	$C_{19}H_{18}Cl_2N_2O \cdot HNO_3$	C, H
83	1	CH_3	*p*-ClC_6H_4	*p*-ClC_6H_4	172–173	$C_{19}H_{18}Cl_2N_2O \cdot HNO_3$	C, H, N
84	1	H	2,4-$Cl_2C_6H_3$	*o*-$CH_3C_6H_4$	124–125	$C_{19}H_{18}Cl_2N_2O \cdot HNO_3$	C, H
85	1	H	*o*-$CH_3C_6H_4$	2,4-$Cl_2C_6H_3$	131–132	$C_{19}H_{18}Cl_2N_2O_2 \cdot HNO_3$	C, H, N
86	1	H	2,4-$Cl_2C_6H_3$	*m*-$CH_3OC_6H_4$	114–115	$C_{19}H_{18}Cl_2N_2O_2 \cdot HNO_3$	C, H, N
87	1	H	2,4-$Cl_2C_6H_3$	*p*-$CH_3OC_6H_4$	149–150	$C_{19}H_{18}Cl_2N_2O_2 \cdot HNO_3$	C, H
88	1	H	*p*-ClC_6H_4	*o*-$CH_3C_6H_4$	135–136	$C_{19}H_{19}ClN_2O \cdot HNO_3$	C, H, N
89	1	H	*p*-$CH_3C_6H_4$	*o*-ClC_6H_4	125–126	$C_{19}H_{19}ClN_2O \cdot HNO_3$	C, H, N
90	1	H	*o*-$CH_3C_6H_4$	*o*-ClC_6H_4	166–167	$C_{19}H_{19}ClN_2O \cdot HNO_3$	C, H, N
91	1	CH_3	C_6H_5	*p*-ClC_6H_4	172–173	$C_{19}H_{19}ClN_2O \cdot HNO_3$	C, H, N
92	1	H	*o*-$CH_3C_6H_4$	*p*-ClC_6H_4	125–126	$C_{19}H_{19}ClN_2O \cdot HNO_3$	C, H, N
93	1	H	*p*-$CH_3C_6H_4$	*p*-ClC_6H_4	122–123	$C_{19}H_{19}ClN_2O \cdot HNO_3$	C, H, N
94	1	H	*o*-$CH_3OC_6H_4$	*o*-ClC_6H_4	160–161	$C_{19}H_{19}ClN_2O \cdot HNO_3$	C, H, N
95	1-Im-$C(CH_3)_2CHOCH_2C_6H_4$-*p*-Cl C_6H_5				Bp 190–200 (0.4 mm)	$C_{20}H_{21}ClN_2O$	C, H

driven to completion by azeotropic removal of H_2O with C_6H_6 (method E), but this was unnecessary for **101**, **103**, **104**, and **105**, which crystallized out of the crude bromination mixture (method F). All bromides were then treated with sodium imidazole in DMF to furnish ketals **115–134** which were best isolated as *nitrate salts.* A compilation of ketals is offered in Table V.

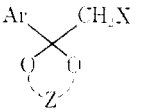
Biological Results.—All compounds described were tested against an array of microorganisms according to the method described earlier.[2] The *in vitro* assays were conducted primarily on *Aspergillus fumigatus*, on the yeast *Candida albicans*, the dermatophytes *Microsporum canis*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes*, the gram-positive bacteria *Eryso-pelotrix insidiosa* and *Staphylococcus hemolyticus*, and on the gram-negative *Escherichia coli*.

The test results are given in Tables VI–VIII and have been recorded as the lowest dose levels causing total inhibition of the substrates' growth. For comparative purposes etonam, tolnaftate, griseofulvin, diamthazole, and nystatine were assayed concurrently with our compounds and these test results have been included in Table VIII.

The amines shown in Table VI were found to be moderately active against dermatophytes, but essentially inactive against yeasts and bacteria. The poor activity of the parent compound **37** was somewhat improved by phenyl substitution and the highest potency was achieved by introduction of *para* substituents (**32**,

TABLE V

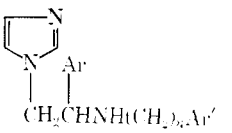
2,2-DISUBSTITUTED DIOXOLANES AND 1,3-DIOXANES



Compd	Ar	X	Z	Method	Bp (mm) or mp, °C	Formula	Analyses
96	2-Thienyl	Br	$(CH_2)_2$	E	90–95 (0.6)	$C_8H_9BrO_2S$	C, H
97	2,3,4-$Cl_3C_6H_2$	Br	$(CH_2)_2$	E	58–59	$C_{10}H_8BrCl_3O_2$	C, H
98	2,5-$Cl_2C_6H_3$	Br	$(CH_2)_2$	E	60–61	$C_{10}H_9BrCl_2O_2$	C, H
99	*o*-ClC_6H_4	Br	$(CH_2)_2$	E	125–130 (0.8)	$C_{10}H_{10}BrClO_2$	C, H
100	*m*-ClC_6H_4	Br	$(CH_2)_2$	E	39–40	$C_{10}H_{10}BrClO_2$	C, H
101	*p*-ClC_6H_4	Br	$(CH_2)_2$	F	61–62	$C_{10}H_{10}BrClO_2$	
102	*p*-FC_6H_4	Br	$(CH_2)_2$	E	48–49	$C_{10}H_{10}BrFO_2$	C, H
103	*p*-$NO_2C_6H_4$	Br	$(CH_2)_2$	F	130–131	$C_{10}H_{10}BrNO_4$[b]	
104	*p*-BrC_6H_4	Br	$(CH_2)_2$	F	78–80	$C_{10}H_{10}Br_2O_2$[c]	
105	C_6H_5	Br	$(CH_2)_2$	F	60–61	$C_{10}H_{11}Br_2O_2$[a]	
106	*p*-ClC_6H_4	Br	$(CH_2)_3$	E	75–76	$C_{11}H_{12}BrClO_2$[c]	
107	*p*-FC_6H_4	Br	$(CH_2)_3$	E	50–51	$C_{11}H_{12}BrFO_2$	C, H
108	*o*-$CH_3C_6H_4$	Br	$(CH_2)_2$	E	44–45	$C_{11}H_{13}BrO_2$	C, H
109	*m*-$CH_3C_6H_4$	Br	$(CH_2)_2$	E	58–59	$C_{11}H_{13}BrO_2$	C, H
110	*p*-$CH_3C_6H_4$	Br	$(CH_2)_2$	E	135–137 (2.5)	$C_{11}H_{13}BrO_2$	C, H
111	*o*-$CH_3OC_6H_4$	Br	$(CH_2)_2$	E	102–105	$C_{11}H_{13}BrO_3$	C, H
112	*m*-$CH_3OC_6H_4$	Br	$(CH_2)_2$	E	60–61	$C_{11}H_{13}BrO_3$	C, H
113	*p*-$CH_3OC_6H_4$	Br	$(CH_2)_2$	E	71–72	$C_{11}H_{13}BrO_3$[c]	C, H
114	*p*-ClC_6H_4	Br	$CH(CH_3)CH(CH_3)$	E	65–66	$C_{12}H_{14}BrClO_2$	C, H
115	2-Thienyl	1-Im	$(CH_2)_2$		163–164	$C_{11}H_{12}N_2O_2S \cdot HNO_3$	C, H
116	2,3,4-$Cl_3C_6H_2$	1-Im	$(CH_2)_2$		195–196	$C_{13}H_{11}Cl_3N_2O_2 \cdot HNO_3$	C, H, N
117	2,5-$Cl_2C_6H_3$	1-Im	$(CH_2)_2$		185–186	$C_{13}H_{12}Cl_2N_2O_2 \cdot HNO_3$	C, H
118	*p*-BrC_6H_4	1-Im	$(CH_2)_2$		212–213	$C_{13}H_{13}BrN_2O_2 \cdot HNO_3$	C, H, N
119	*o*-ClC_6H_4	1-Im	$(CH_2)_2$		207–208	$C_{13}H_{13}ClN_2O_2 \cdot HNO_3$	C, H, N
120	*m*-ClC_6H_4	1-Im	$(CH_2)_2$		174–175	$C_{13}H_{13}ClN_2O_2 \cdot HNO_3$	C, H, N
121	*p*-ClC_6H_4	1-Im	$(CH_2)_2$		199–200	$C_{13}H_{13}ClN_2O_2 \cdot HNO_3$	C, H
122	*p*-FC_6H_4	1-Im	$(CH_2)_2$		197–198	$C_{13}H_{13}FN_2O_2 \cdot HNO_3$	C, H, N
123	*p*-$NO_2C_6H_4$	1-Im	$(CH_2)_2$		189–191	$C_{13}H_{13}N_3O_3 \cdot HNO_3$	C, H, N
124	C_6H_5	1-Im	$(CH_2)_2$		77–78	$C_{13}H_{14}N_2O_2$	C, H
125	*p*-ClC_6H_4	1-Im	$(CH_2)_3$		205–206	$C_{14}H_{15}ClN_2O_2 \cdot HNO_3$	C, H
126	*p*-FC_6H_4	1-Im	$(CH_2)_3$		194–195	$C_{14}H_{15}FN_2O_2 \cdot HNO_3$	C, H, N
127	*o*-$CH_3C_6H_4$	1-Im	$(CH_2)_2$		218–219	$C_{14}H_{16}N_2O_2 \cdot HNO_3$	C, H
128	*m*-$CH_3C_6H_4$	1-Im	$(CH_2)_2$		161–162	$C_{14}H_{16}N_2O_2 \cdot HNO_3$	C, H
129	*p*-$CH_3C_6H_4$	1-Im	$(CH_2)_2$		186–187	$C_{14}H_{16}N_2O_2 \cdot HNO_3$	C, H
130	*o*-$CH_3OC_6H_4$	1-Im	$(CH_2)_2$		158–159	$C_{14}H_{16}N_2O_3 \cdot HNO_3$	C, H, N
131	*m*-$CH_3OC_6H_4$	1-Im	$(CH_2)_2$		161–162	$C_{14}H_{16}N_2O_3 \cdot HNO_3$	C, H
132	*p*-$CH_3OC_6H_4$	1-Im	$(CH_2)_2$		213–214	$C_{14}H_{16}N_2O_3 \cdot HNO_3$	C, H, N
133	*p*-ClC_6H_4	1-Im	$CH(CH_3)CH(CH_3)$		199–200	$C_{15}H_{17}ClN_2O_2 \cdot HNO_3$	C, H, N
134	*p*-ClC_6H_4	1-Im	$CH(CH_3)CH_2$		195–196	$C_{12}H_{13}ClN_2O_2 \cdot HNO_3$	C, H, N

TABLE VI

ANTIFUNGAL ACTIVITIES

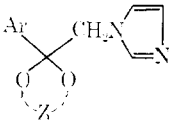


Compd[a]	Lowest level of complete inhibition,[b,c] μg/ml		
	M. canis	*T. mentagrophytes*	*T. rubrum*
30	X	X	X
50, 56, 57, 51, 52	X	100	100
33, 35, 41–44, 46, 49, 53, 54	100	100	100
31, 38, 45, 47, 48	100	10	100
32	100	100	10
28, 29	100	10	10
40, 50	10	10	10
54	10	<1	10

[a] The symbol "X" denotes partial growth at 100 μg/ml. [b] Figures preceded by "<" represent the lowest dose levels tested. [c] For structures, see Table III.

TABLE VII

ANTIFUNGAL ACTIVITIES

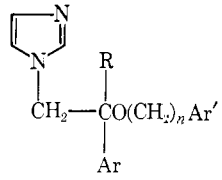


Compd[a]	Lowest level of complete inhibition,[b,c] μg/ml		
	M. canis	*T. mentagrophytes*	*T. rubrum*
131	X	X	X
115, 125, 124, 126, 129, 130, 132	100	100	100
120, 127, 128	100	10	100
118, 122, 125, 133	100	10	10
117, 119, 121, 134	10	10	10
116	10	10	<1

[a] The symbol "X" denotes partial growth at 100 μg/ml. [b] Figures preceded by "<" represent the lowest dose levels tested. [c] For structures, see Table V.

TABLE VIII

ANTIFUNGAL AND ANTIBACTERIAL ACTIVITIES



	Lowest level of total inhib.[a,b] μg/ml						
Compd[c]	*C. albicans*	*M. canis*	*T. mentagrophytes*	*T. rubrum*	*A. fumigatus*	*E. insidiosa*	*S. hemolyticus*
56	x	x	100	100	10	100	x
58	x	100	100	100	10	x	x
78	x	100	10	10	100	10	10
82	x	100	10	10	x	10	100
79	x	10	10	10	100	10	10
90	x	10	<1	<1	100	10	10
94	x	10	<1	<1	10	10	10
92	x	<1	<1	<1	<1	10	10
74	100	100	10	10	100	10	10
80	100	100	10	10	100	10	100
83	100	100	10	10	100	10	100
88	100	100	10	10	100	10	10
89	100	100	10	10	100	10	10
72	100	100	10	<1	100	10	10
81	100	10	10	<1	10	10	10
95	100	10	10	10	10	10	10
87	100	10	10	10	100	10	100
86	100	10	10	10	100	10	10
69	100	10	10	10	100	10	10
63	100	10	10	10	100	10	10
62	100	10	10	10	10	10	10
57	100	10	10	10	100	10	x
55	100	10	<1	<1	100	0.1	10
61	100	10	<1	<1	10	0.1	100
73	100	10	<1	<1	<1	10	10
77	100	10	<1	<1	10	10	10
91	100	10	<1	<1	100	10	10
93	100	10	<1	<1	10	10	10
60	100	<1	0.1	0.1	10	0.1	<1
84	100	10	0.1	0.1	10	0.1	<1
64	100	10	0.1	0.1	10	0.1	10
68	100	<1	<1	<1	<1	10	10
85	100	<1	<1	<1	<1	10	100
71	100	<1	<1	<1	10	10	10
75	100	<1	0.1	0.1	<1	0.1	10
66	100	0.1	0.01	0.1	<1	0.01	<1
65	10	100	10	10	100	0.1	01
59	10	<1	0.1	<1	10	0.01	0.01
67	10	10	<1	0.1	10	0.1	10
70	10	<1	0.1	0.1	<1	0.01	10
76	10	<1	0.1	0.1	10	0.1	<1
Etonamte	x	100	10	<1	x	x	x
Tolnaftae	x	x	10	<1	x	x	x
Griseofnlvin	x	10	10	10	x	x	x
Asterol	x	100	100	100	x	x	x
Nystatin	33	333	333	333	333		

[a] The symbol "x" denotes partial growth at 100 μg/ml. [b] Figures preceded by "<" represent the lowest dose levels tested. [c] For structures, see Table IV.

34 and **40**). Alterations in the most promising compound **34** are permissible; these include replacement of phenyl by thienyl (**28**) or aliphatic homologation (**50**).

Ketals (Table VII) were also active against dermatophytes but not against yeasts or bacteria. Aromatic substitution increased inhibitory activity against dermatophytes (*e.g.*, **124** *vs.* **117**, **119**, **121**). Modification of the dioxolan ring, such as ring enlargement (**125** and **126**) or methyl homologation (**133** and **134**), was permissible.

The ethers offered in Table VIII comprised by far the most interesting group. Not only were some members of this series highly active against dermatophytes, effecting total inhibition at dose levels as low as 0.01 μg/ml, but they also exhibited excellent activity against *C. albicans* and against gram-positive bacteria. They were essentially inactive against *E. coli*. The activity against the yeast cells is particularly noteworthy, as few of the currently available antimycotic agents are effective against such infections. Our

synthetic program was thereafter guided primarily by the anti *C. albicans* activity, with dermatophyte and bacterial inhibition playing an ancillary but, nonetheless, very desirable role.

The unsubstituted parent compound (**78**) was comparable in activity to the corresponding amines and ketals. However, whereas phenyl substitution in these latter types resulted in only moderately increased activity, incorporation of similar substituents in the ethers led to vastly enhanced potency. Compound **76** totally inhibited *C. albicans* at 10 μg/ml. whereas **78** was effective only at ±1000 μg/ml.

Highest potency was observed for combinations of *para* and *ortho-para* substituents, as exemplified by **59**, **65**, **67**, **70**, and **76**. Compounds bearing *ortho* substituents only, *e.g.*, **73**, **90**, and **94**, were generally less active. Ethers derived from tertiary alcohols, such as **79**, **82**, **83**, and **91**, also showed diminished activity.

It appears therefore that the ethers described above constitute a novel class of broad-spectrum antimycotic agents, which, moreover, are also highly active against gram-positive bacteria. Our *in vivo* test results will be reported elsewhere. The most promising candidates are undergoing clinical evaluation.

Experimental Section[8]

4′-Chloro-2-(1-imidazolyl)acetophenone (6) (Method A).—To a slurry of 350 g (5.2 moles) of imidazole in 250 ml of DMF at 5° was added portionwise and with stirring 234 g (1.0 mole) of 4′-chloro-2-bromoacetophenone while keeping the temperature below 15°. The solution was then stirred on ice for an additional 2 hr after which it was poured onto 5 l. of H_2O/l. of C_6H_6. The product was filtered off, washed with C_6H_6, and sucked as dry as possible. Adhering H_2O was best removed by means of azeotropic distillation with 1.5 l. of PhMe. When all H_2O had been removed, the hot solution was filtered to remove traces of quaternized material. Cooling, filtration, and washing with Et_2O gave 170 g (77%) of product, mp 155–157°. Recrystallization (MeCN) gave mp 160–160.5°.

2′-Chloro-2-(1-imidazolyl)acetophenone Nitrate (5) (Method B).—Br_2 (160 g, 1.0 mole) was added dropwise to a solution of 155 g (1.0 mole) of 2′-chloroacetophenone in 400 ml of Et_2O/200 ml of dioxane. The bromination was initiated at room temperature and was then carried through at 5–10°. Upon completion of the addition, 350 g (5.2 moles) of imidazole in 500 ml of MeOH was introduced with cooling. After 18 hr, 1.2 l. of H_2O was added and the product was extracted into $CHCl_3$. Successive additions of 1 l. of AcMe and excess HNO_3 to the organic phase gave 194 g (69%) of **5**, mp ~175°. Recrystallization (95% EtOH) gave platelets, mp 179–180°.

2-(1-Imidazolyl)propiophenone Nitrate (9).—A mixture of 9.3 g (0.05 mole) of **8**, 2.5 g (0.052 mole) of 50% NaH dispersion, and 25 ml of HMPA was stirred at 5–10° for 1 hr, and then at 45° for another hr. To the recooled mixture was added 8 g (0.057 mole) of MeI, and the reaction was allowed to proceed for 18 hr at room temperature. Addition of H_2O, extraction of the basic fraction with Et_2O, and introduction of HNO_3 to the dried organic phase gave 7.2 g (55%) of product after recrystallization (MeOH–AcMe–*i*-Pr_2O), mp 139–140°. This material was in all respects identical with the product obtained from 2-bromopropiophenone and imidazole (method A).

α-Phenylimidazole-1-ethanol[3] (21).—A solution of 140 g (2.05 moles) of imidazole in 500 ml of absolute EtOH containing 8 ml of C_5H_5N was brought to ~75°, when 240 g (2.0 moles) of styrene oxide was introduced dropwise at such a rate that the temperature remained at 80–85°. Upon completion of the exothermic reaction, the temperature was allowed to drop to 50°. Approximately 300 ml of *i*-Pr_2O was added and the mixture was poured into 1 l. of H_2O. Cooling, filtration, and washing (CH_3COCH_3, Et_2O) gave 147 g (39%) of off-white product, mp 149–150°.

α-(*o*-Methoxyphenyl)imidazole-1-ethanol Hydrochloride (26) (Method C).—A 12-g portion of $NaBH_4$ (0.30 mole) was added portionwise to a solution of 110 g (0.52 mole) of **12** in 500 ml of MeOH at 5–10°. After 1 hr the mixture was refluxed for an additional 1 hr, after which 400 ml of solvent was taken off and replaced with 400 ml of H_2O. Acidification (HCl), refluxing (15 min), and basification then gave 98 g of solid product. The HCl salt (95% EtOH–AcMe–*i*-Pr_2O) had mp 173–174°.

α-(*p*-Chlorophenyl)imidazole-1-ethanol (19) (Method D). To a solution of 25.3 g (1.1 g-atoms) of Na in 500 ml of MeOH was added 75 g (1.1 moles) of imidazole in 100 ml of MeOH. The solvent was taken off until the internal temperature reached 85°, and 500 ml of DMF was then introduced. Solvents were again removed until the internal temperature reached 125°. A solution of 203 g (0.86 mole) of α-bromomethyl-*p*-chlorobenzyl alcohol in 250 ml of C_6H_6 was introduced at such a rate that solvents distilled off at 100–125° (internal temperature). The heat source was removed and stirring was continued for 10 min; DMF (250 ml), H_2O (500 ml), and 1 g of $NaBH_4$ were added at this point, the latter serving to decolorize the mixture. Addition of more H_2O to the cloud point at 100° initiated crystallization. The product was filtered off, washed with H_2O then Et_2O, and dried; yield 156 g (83%), mp 185.5–184°.

2-(1-Imidazolyl)acetophenone Oxime.—A solution of 55 g (0.295 mole) of **8**, 29.9 g (0.435 mole) of $NH_2OH \cdot HCl$, and 300 ml of 95% EtOH was brought to pH 11 with 15 *N* NaOH. After refluxing for 3 hr, the solvent was removed, H_2O was added, and trace impurities were filtered off. The filtrate was then rendered acid to congo red and basified with $NaHCO_3$. Cooling, filtration, and recrystallization (*i*-PrOH–*i*-Pr_2O) gave 45 g (76%) of product, mp 165–166°. *Anal.* ($C_{11}H_{11}N_3O$) C, H.

1-(β-Aminophenethyl)imidazole Dihydrochloride (A, X = NH_2).—A mixture of 44 g (0.22 mole) of the above oxime in 250 ml of 95% EtOH containing ~50 g of Raney Ni was hydrogenated at an initial pressure of 3.5 kg/cm². Upon completion of the H_2 uptake (36 hr) the catalyst was removed and the solvent was evaporated. Distillation of the residue gave 31 g (70%) of amine, bp 172–175° (0.2 mm). The 2HCl salt, recrystallized (95% EtOH–AcMe), had mp 234–236°. *Anal.* ($C_{11}H_{13}N_3 \cdot 2HCl$) C, H, N.

1-(β-Benzylaminophenethyl)imidazole Dihydrochloride (37). A solution of 37.2 g (0.20 mole) of **8**, 23 g (0.215 mole) of benzylamine, 1.0 g of *p*-toluenesulfonic acid (TSA), and 150 ml of PhMe was refluxed with azeotropic H_2O removal for 3 hr. The solvent was evaporated and replaced with 150 ml of MeOH. To the ice-cold solution was added portionwise 3.0 g (0.075 mole) of $NaBH_4$, whereupon the mixture was stirred overnight. H_2O (200 ml) was then added, the pH was brought to 8 (concentrated HCl), and 200 ml of solvent was taken off. The mixture was made strongly acid and then refluxed for 15 min. Cooling caused deposition of solid by-product, which was filtered off. Basification of the filtrate, extraction of the product into C_6H_6, drying of the organic phase, and solvent removal left an oily base. An alcoholic solution of the latter, upon treatment with *i*-PrOH HCl gave 43 g (62%) of product, mp 245–248°.

1-[β-(*p*-Chlorobenzyloxy)phenethyl]imidazole Nitrate (77). Compound **21** (80 g, 0.425 mole) in 250 ml of HMPA was introduced dropwise into a slurry of 22 g (0.46 mole) of NaH dispersion in 100 ml of HMPA (containing antifoam) at 5–10° and was stirred till H_2 evolution ceased. The mixture was then warmed to 50° for 1 hr. To the recooled mixture was added, portionwise, 80 g (0.50 mole) of α,*p*-dichlorotoluene, while keeping the temperature below 25°. After 1 hr at 25° and then 1 hr at 45°, H_2O was added and the product was extracted into Et_2O. Addition of a slight excess of HNO_3 to the organic phase gave the product, which after filtration and trituration (50% Et_2O–AcMe) had mp 132–134°, yield 132 g (82%).

1-[β-(*p*-Nitrophenoxy)-2,4-dichlorophenethyl]imidazole Nitrate (57). To an H_2O-free mixture of DMF–C_6H_6 (50:25 ml) containing 3.4 g (0.07 mole) of 50% NaH dispersion, was added 8.7 g (0.031 mole) of **16**. Stirring was continued till H_2 evolution ceased, whereupon 5.0 g of MnO_2 and 8.0 g of *p*-nitrofluorobenzene were introduced while cooling the mixture on ice. After 3 hr at room temperature, the solids were removed by filtration through Hyflow. The filtrate was then diluted with H_2O and extracted with C_6H_6. Drying and stripping of the organic phase left a residual oil, which was taken up in CH_3COCH_3 and treated

[8] Melting points (taken on a Fisher-Johns block) and boiling points are uncorrected. Analyses are given in the tables. Analytical results therein pertain to those elements whose values fall within ±0.4% of the theoretical values.

with a slight excess of HNO_3. Filtration of the product (8.0 g) and recrystallization (MeOH–*i*-Pr_2O) gave 5.2 g, mp 169–170°.

1-[β-(*p*-Aminophenoxy)-2,4-dichlorophenethyl]imidazole (58).—A 20-g (0.053 mole) portion of **57** (base) was added to a refluxing mixture of 13.5 g of Fe dust, 10.6 g of NH_4Cl, and 150 ml of H_2O. Refluxing was continued for 6 hr. To the cooled mixture was added 100 ml of CH_2Cl_2, and solids were removed by filtration. Stripping of the dried organic phase left crude product, furnishing 10.0 g of amine after recrystallization from *i*-Pr_2O; mp 95–96°.

2-(Bromomethyl)-2-(*p*-chlorophenyl)dioxolane[6] (10) (Method F).—Br_2 (320 g, 2.0 moles) was introduced dropwise to a solution of 310 g (2.0 moles) of 4′-chloroacetophenone in 600 ml of ethylene glycol at 75°. The colorless mixture was subsequently stirred for 1 hr at 5°. The crude filtered product was taken up in 1 l. of CH_2Cl_2 and washed with dilute NaOH. Drying, removal of solvent, and recrystallization of the residue from MeOH gave 465 g (84%) of the product, mp 61–62°.

2-(Bromomethyl)-2-(*m*-methoxyphenyl)dioxolane (112) (Method E).—3′-Methoxyacetophenone (150 g, 1.0 mole) in Et_2O–dioxane (400:200 ml) was brominated [160 g (1.0 mole) of Br_2] at 5°. To the decolorized mixture was added 250 ml of ethylene glycol, whereupon solvents were removed till the temperature reached 150°. The solution was cooled, 1 l. of C_6H_6 and 5 g TSA were added, and H_2O was removed azeotropically for 18 hr. Washing of the solution with dilute NaOH, drying of the C_6H_6 phase, and removal of the solvent left crude product; this was purified by distillation over 10 g of K_2CO_3, giving 120 g of product, bp 145–155° (1.4 mm). The distillate solidified on standing and was triturated with *i*-PrOH to give 102 g of material, mp 60–61°.

1-[2-(*p*-Chlorophenyl)-1,3-dioxolan-2-ylmethyl]imidazole Nitrate (121).—To a solution of sodium imidazole (1.5 moles) in 500 ml of DMF (see preparation of **19**) was added 277 g (1.0 mole) of **101**, whereupon the solution was kept at 140–145° for 4 hr. Dilution of the mixture with H_2O and subsequent cooling caused deposition of the product base. This was filtered off, dissolved in AcMe–*i*-Pr_2O, and treated with a slight excess of HNO_3, giving 290 g (88%) of product, mp 199–200°.

Acknowledgment.—We thank the "Instituut tot Aanmoediging van het Wetenschappelijk Onderzoek in Nijverheid en Landbouw" for financial support. Analytical determinations were performed by Messrs. A. Sels and W. Verkest. It gives the senior author great pleasure to thank Dr. A. E. F. Chandler for helpful suggestions in the preparation of the manuscript.

Imidoylureas. A New Class of Anthelmintics

GUY D. DIANA, ALLEN YARINSKY, ETHEL S. ZALAY, DICRAN A. BERBERIAN, AND SAMUEL SCHALIT

Sterling-Winthrop Research Institute, Rensselaer, New York

Received March 13, 1969

A series of imidoylureas have been synthesized and examined for antihookworm activity in dogs. Among the various types prepared, the alkylimidoyl-substituted phenylureas were found most active, and 1-(*p*-chlorophenyl)-3-pentanimidoylurea was selected as the compound of choice, effective in a single dose of 10 mg/kg.

It has been estimated that more than one-fourth of the world's human population is infected with one or more intestinal nematodes.[1] The consequences of severe and widespread infections with the hookworms *Ancylostoma duodenale* and/or *Necator americanus* are well documented.[2–4] Because remedies currently employed in the treatment of these infections leave much to be desired we have been engaged in the synthesis of compounds with potential antihookworm properties.

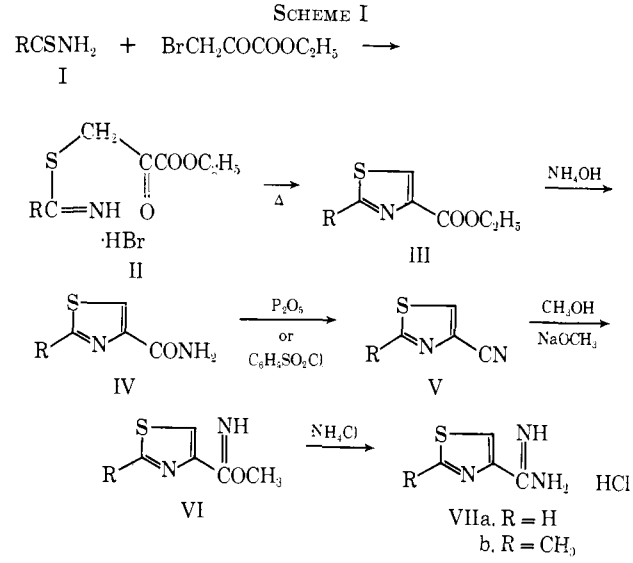
In the course of screening compounds in dogs against *Ancylostoma caninum* and/or *Uncinaria stenocephala*, it was discovered that a series of imidoylureas of the general formula, $R_1C(=NR_2)NHCONR_3R_4$, and related structures exhibited interesting activity.

Chemistry.—All of the compounds in Table I with the exception of **24** and **25** were prepared by treatment of equivalent amounts of the appropriate amidine hydrochloride and isocyanate in acetone or chloroform in the presence of a base such as Et_3N or Na in acetone.

$$R_1C(=NR_2)NH_2\cdot HCl \xrightarrow[\text{base}]{R_3N=CO} R_1C(=NR_2)NHCONR_4R_3$$

The synthesis of compounds **33** and **34** was initiated from the thioamide[5] I which was treated with ethyl

SCHEME I



bromopyruvate to produce the keto ester II (Scheme I). The latter was not isolated but immediately converted to the thiazole III.[6] Compound III was converted to the amide IV[7] by treatment with NH_4OH, and IV was then dehydrated to the nitrile V.[8] In the case of IV (R = CH_3), dehydration was achieved with benzenesulfonyl chloride[9] in 65% yield. However, under these

(1) (a) N. R. Stoll, *J. Parasitol.*, **33**, 1 (1947); (b) WHO Chronicle, Vol. 22, World Health Organization, Geneva, 1968, p 289.

(2) P. C. Beaver, Public Health Papers No. 10, World Health Organization, Geneva, 1961.

(3) E. C. Faust and P. F. Russell, "Clinical Parasitology," C. F. Craig and E. C. Faust, Ed., Lea and Febiger, Philadelphia, Pa., 1964.

(4) M. Roche and M. Layrisse, *Am. J. Trop. Med. Hyg.*, **15**, 1032 (1966).

(5) H. Erlenmeyer and K. Menzi, *Helv. Chim. Acta*, **31**, 2065 (1948).

(6) M. Erne, F. Ramirez, and A. Burger, *ibid.*, **38**, 143 (1955).

(7) H. Erlenmeyer and C. J. Morel, *ibid.*, **28**, 362 (1945).

(8) R. Menassé, B. Prijs, and H. Erlenmeyer, *ibid.*, **40**, 554 (1957).

(9) C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 (1955).